Enriching knowledge on adverse drug reactions from the patient perspective

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Colofon

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Chapter 1

General Introduction

Drug treatment and adverse drug reactions

Drug treatment is the most common intervention to prevent, treat and manage medical conditions, contributing considerably to improving medical outcomes and patient's functioning, wellbeing and survival. Around 11.5 million people in the Netherlands use at least one prescribed drug per year, comprising 65% of the population [1]. Even though drugs are important in managing various medical conditions, drug treatment can lead to the occurrence of adverse drug reactions (ADRs), which may increase morbidity and mortality [2, 3]. An ADR is defined by the World Health Organisation as a noxious and unintended response to a drug that occurs at normal doses [4]. It is unknown what proportion of patients using medication experience an ADR but studies in primary care have shown wide variation in frequency, ranging from 6% to 80% of patients [5]. Around 6% of hospitalisations worldwide are ADR related, while these are often preventable [6]. In addition, as the population continues to age, more individuals are suffering from chronic illnesses, leading to increased drug use and, as a result, occurrence of more ADRs [7].

Impact of ADRs

ADRs can have a big impact on patients health and wellbeing and have a significant impact on health outcomes, healthcare utilisation and healthcare costs [8-10]. To a patient, an ADR can have physical, social and psychological impact. Experiencing an ADR can make patients insecure about their medication which has an impact on treatment satisfaction, trust in healthcare, quality of life, self-efficacy and self-management [11-14]. As a consequence, ADRs can negatively affect medication adherence which may lead to decreased efficacy of treatment [15].

For healthcare professionals, recognising and treating ADRs can be challenging and time consuming. The drug causing the ADR may need dose adjustment or discontinuation after which another, often more expensive, treatment may be necessary [16, 17]. ADR treatment may involve prescribing additional drugs which induces polypharmacy and increases the risk of drug interactions and more ADRs. Such prescription cascades are often preventable [18].

Minimising the impact

To minimise their impact, it is essential to prevent ADRs if possible, recognise them when they occur and manage them quickly and adequately. Therefore relevant information should be available. To predict and prevent ADRs, information on specific patient characteristics and predisposing risk factors for their occurrence should be available [19]. To recognise ADRs, the patient and healthcare professionals should be alert and actively monitor for, and communicate about, symptoms indicative of potential ADRs [20]. This requires patients to be engaged in their treatment. As healthcare is evolving into more patient-centred care, the patient role is becoming more important [21]. Clinical practice is implementing shared decision making and patient-initiated care, with increasing medical self-measurement possibilities and self-management initiatives [22-24]. These are important developments that may contribute to recognising and managing ADRs more rapidly.

In addition, it is important to provide appropriate information to minimise the impact of ADRs. When an ADR occurs, accessible, comprehensive, reliable and relevant information is crucial for both patients and healthcare professionals to understand, manage and cope with the ADR so that it limits the effect on medication adherence and the patient's illness remains under control. Currently, patients' individual needs for drug information, particularly about ADRs, are not always met because patients also want information on aspects such as onset, duration and on how to avoid and reduce ADRs [25-28]. Therefore, the comprehensiveness, accessibility and understanding of medication information can and should be improved.

ADR information

Patients can find information about ADRs in a specific section in drug package leaflets. First, the most serious ADRs that require action are prominently listed. Furthermore, it contains a patient-friendly description of (symptoms of) ADRs listed by frequency [29, 30]. Only rarely, additional details on reversibility, time of onset and management strategies are provided.

For healthcare professionals, ADR information is listed in the summary of product characteristics (SmPC) in section 4.8 about undesirable effects. These documents can be found on the website of the national drug authority and include the types of ADRs that can occur and if known, a categorisation of the frequency of occurrence. The European Commission's guideline on SmPCs mentions that frequencies should be stated as accurately as possible as estimated from available data and if known, the timing of when ADRs occur can be indicated [31]. The guideline further mentions that additional information about reversibility, time of onset, severity, duration, mechanism of reaction, dose relationship, relationship with duration of exposure and risk factors can be described for selected individual ADRs that are serious and/or frequently occurring. However, there are no imperative rules for selecting these ADRs. In reality, such details are not available for most ADRs and furthermore, information in SmPCs is directed at healthcare professionals and does not contain patient-friendly descriptions.

Other sources that mention ADR information include various platforms or websites of professional or scientific associations, institutions or hospitals, which are often based on SmPCs. Dutch examples are Farmacotherapeutisch Kompas from the National Healthcare Institute, a website from the Royal Dutch Pharmacist Association (www.apotheek.nl), the website from the Netherlands Pharmacovigilance Centre Lareb (www.lareb.nl) and a tool built in pharmacy information systems to provide concise drug information for patients when a drug is dispensed, provided by Health Base, a centre providing pharmacotherapeutic content [32]. Other sources of information can be websites addressing patient experiences with ADRs or social media platforms. However, it can be challenging to judge the reliability of such sources.

Generating ADR information

Sources for ADR information in SmPCs and package leaflets can be clinical trials, post-authorisation safety studies including cohort studies and case reports, scientific literature and information from pharmacovigilance centres. Once a medicine is on the market, national authorities and pharmaceutical companies have legal pharmacovigilance obligations to monitor its safety. Pharmacovigilance is defined by the European Medicines Agency (EMA) as *the science and activities relating to detection, assessment, understanding and prevention of adverse effects or any other medicine related problem* [33].

The regulatory process of identifying new ADR information is known as signal detection, in which a safety signal is defined as: *Information on a new or known adverse event that is potentially caused by a medicine and that warrants further investigation* [33]. New aspects of a known association can include a change in frequency, distribution (e.g. gender, age and country), duration, severity or outcome of the ADR [34]. In reality, safety signals mainly concern new, previously unknown ADRs. Signal detection is an important task of national pharmacovigilance centres, with spontaneous reports often being the main data source. Spontaneous reports are suspected ADRs that are voluntarily reported by healthcare professionals and patients to pharmacovigilance centres through a dedicated form in a reporting system. Pharmacovigilance centres are often part of national drug authorities or work in close collaboration with national drug authorities. Assessment of spontaneous reports may lead to the detection of safety signals that serve as a first step in the identification of safety information. In addition to spontaneous reporting, pharmacovigilance centres may use other systems such as dedicated prospective studies. For instance, the Netherlands Pharmacovigilance Centre Lareb uses patient-reported questionnaires for prospectively monitoring medicines or vaccines [35].

National drug authorities evaluate safety signals for sufficient evidence and decide on regulatory actions. For European registered products, the Pharmacovigilance Risk Assessment Committee (PRAC) proposes recommendations for regulatory actions towards the European Commission, the Committee for Medicinal Products for Human Use of the EMA or national drug authorities [36]. Regulatory actions could entail, amongst others, an update of the SmPC and package leaflet and safety communication through various channels [37].

Patient-centred ADR information

Package leaflets and SmPCs rarely contain more details than just the nature and frequency of ADRs. To create better and in-depth ADR information, more patient-centred approaches to generate this information should be explored that also emphasise other aspects of ADRs, such as the (expected) course, including time to onset, duration and outcome, potential management strategies and their impact on patients [38, 39]. Such information can come directly from patients, as they are the ones experiencing an ADR and can better describe how it develops over time and affects their life than healthcare professionals [40]. The patient perspective on ADRs may be captured in spontaneous reports and other data sources using various available patient-reported questionnaires to identify ADRs in research and clinical practice [41]. Studies

using questionnaires and real-world data from patients have published details on the course of ADRs, including time to onset, frequency, persistence, recurring patterns, duration, outcome and management of ADRs [42-47]. Various studies have also reported information on the impact of ADRs on patients, such as the impact on the patient's well-being, ADR bother or tolerance, the impact on daily life, work impairment and impact on health-related quality of life [11, 12, 14, 42, 47-56]. Still, such information is not yet widely available. Pharmacovigilance centres can play an important role in collecting and combining such data and generating patient-centred information. For this, engaging patients in pharmacovigilance is an important step.

Patient engagement in Pharmacovigilance

Various initiatives have already been taken to improve patient-centredness in pharmacovigilance and incorporate the patient perspective [39, 57]. Patient-reported ADRs were allowed in the Dutch spontaneous reporting database in 2003 and new EU pharmacovigilance legislation in 2012 made the role of patients as stakeholders in pharmacovigilance more prominent, enabling patients to report ADRs to pharmacovigilance centres all over the European Union and introducing patient representatives as full member of the PRAC of the EMA [58, 59]. This has improved patient contribution to regulatory decision making and risk-benefit assessments of drugs and has led to a more prominent and visible position of the patient in pharmacovigilance. Patient-reported ADRs in spontaneous reporting databases have already been shown to contribute to detecting new ADRs [60, 61]. Even though these are important steps, more can be gained from engaging patients in pharmacovigilance.

Maximising the impact of patient engagement

As mentioned, pharmacovigilance centres can improve collecting and using patient-reported data to enrich knowledge on other aspects of ADRs that only patients can provide, and improve patient-centred information valuable for clinical practice, in addition to detecting new ADRs (**Figure 1**). Also, further engaging and stimulating patients to actively monitor their ADRs, for example with patient-reported questionnaires, may improve alertness and early detection which may improve management and adherence and ultimately reduce the impact of ADRs.

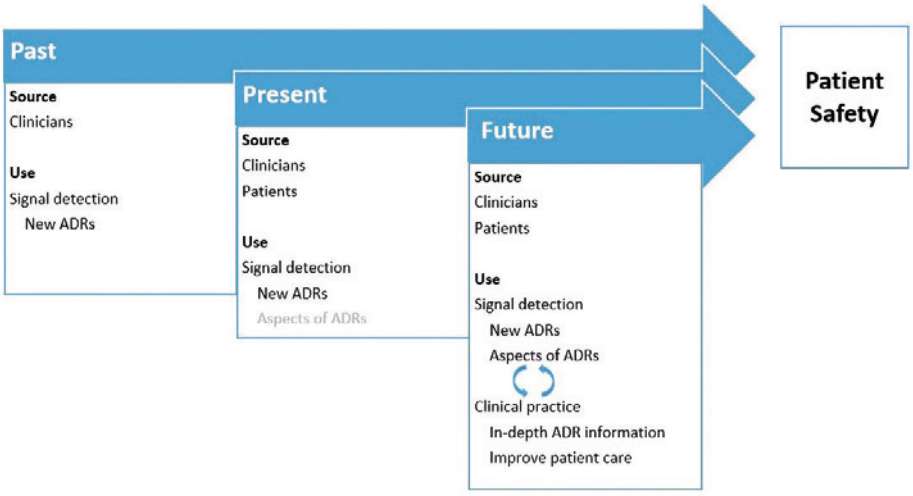

Figure 1. The past, present and future of data sources and what this data is used for and can be used for in pharmacovigilance

Another important step forward is integrating pharmacovigilance with clinical practice, as patient-reported ADR data can also be collected and directly used in clinical practice to improve patient care. An example is patient symptom monitoring using the *Patient-reported Outcome Version of the Common Terminology Criteria for Adverse Events* (PRO-CTCAE), which is increasingly being implemented in routine oncology practice [62, 63]. This PRO contains items on severity, frequency and interference of the ADR. PROs are health outcomes collected directly from patients using questionnaires. Use of such PROs has demonstrated benefits on communication, satisfaction, treatment adherence, symptom control, quality of life, hospital admissions and survival [64, 65]. Incorporating such PROs in the electronic health records of patients allows for detecting ADRs early and can alert clinicians for timely action when severe or worsening symptoms are reported [66, 67]. A Dutch example is a web application called 'BijKanker', which monitors ADRs experienced by cancer patients and also provides information and advice, the option to communicate with a healthcare professional and personal feedback of reported data showing the course of the patient's own ADRs [56]. This application is currently only used in research and not yet in routine clinical practice. Further steps need to be taken in combining patient-reported ADR data from PROs for research, regulatory purposes and pharmacovigilance, in order to improve and enrich ADR information for cancer patients [68, 69]. In this regard, it is important to consider that the amount of detail captured in ADR-related PROs varies widely and may be limited. Furthermore, developments in medical fields other than oncology are still sparse.

Patient engagement in detecting and monitoring ADRs in clinical practice and in pharmacovigilance is increasing. Enriching ADR knowledge with patient-reported data can maximise the benefits of patient engagement and enhance patient safety (**Figure 1**).

Aim and outline of this thesis

Currently, patient-reported ADR data is used mainly to detect new ADRs in pharmacovigilance while there is more potential for using the data, such as generating in-depth and patient-centred ADR information. Accordingly, pharmacovigilance centres can gain more in-depth knowledge and provide information about new and known ADRs to directly support clinical practice, as the Netherlands Pharmacovigilance Centre Lareb aims to do [58, 70, 71]. As patient-reported ADR data have not been widely used for this purpose, it is still unknown how this type of data can contribute to such knowledge and how this can be used in clinical practice. In order to assess the potential of patient-reported ADR data, this thesis aims to explore how systematically collecting such data can contribute to comprehensive and relevant information for patients and healthcare professionals to ultimately improve patient care.

Patients have been shown to provide detailed descriptions on course and burden of ADRs [40], and we investigated what type of insights into these aspects can be obtained from descriptions and experiences of patients. **Chapter 2** further explores how patients experience the burden of different ADRs. In **Chapter 3**, the course of ADRs as experienced by patients is described and classified into more in-depth elements of information. **Chapter 4** evaluates how details in descriptions of ADRs by patients can contribute to detecting new ADRs and aspects of these ADRs. **Chapter 5** explores how including the burden and course of symptoms from the patient perspective can contribute to discovering a potential new ADR. Finally, **Chapter 6** presents a general discussion and considers how these insights can be used in pharmacovigilance to enrich ADR knowledge, further engage patients and provide more in-depth information to minimise the impact of ADRs and to improve patient safety.

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Chapter 2

Burden of adverse drug reactions

Patient-Reported Burden of Adverse Drug Reactions Attributed to Biologics Used for Immune-Mediated Inflammatory Diseases

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ABSTRACT

Introduction: Although the burden of adverse drug reactions (ADRs) has significant impact on patients' quality of life, thorough knowledge about patients' perspectives on the burden of ADRs attributed to biologics is lacking.

Objectives:. This study was conducted to gain insight in patient burden of ADRs experienced with biologic use.

Methods: The Dutch Biologic Monitor is a prospective, multicentre, event monitoring cohort system including information collected by web-based questionnaires from patients using biologics, mainly for immune-mediated inflammatory diseases (IMIDs). Patients were asked to complete bimonthly questionnaires on used biologics, indication for the biologic, experienced ADRs, consequences of ADRs and burden on a five-point Likert type scale, ranging from 1 (no burden) to 5 (very high burden). We assessed potential factors associated with patient-reported burden of ADRs.

Results: A total of 1,355 patients completed 6,293 questionnaires between 1 January 2017 and 1 May 2019. Almost half of the patients (665 patients, 49%), of which 69% with rheumatic diseases and 31% with other diseases, collectively reported 1,720 unique ADRs. Infections and musculoskeletal complaints were the most burdensome ADRs and injection site reactions were the least burdensome. ADRs leading to healthcare professional contact were more burdensome than ADRs without healthcare professional contact. Smoking, respiratory and psychiatric comorbidities were associated with higher burden of ADRs. Crohn's disease, use of adalimumab and use of sulfasalazine as combination therapy were associated with lower burden of ADRs.

Conclusions: The patient perspective gives important insights in the burden of ADRs experienced with biologics. This information could be used by healthcare professionals to optimise treatment with biologics.

INTRODUCTION

Biological therapies have proven to be effective and safe, expanding the therapeutic armamentarium for a range of immune-mediated inflammatory diseases (IMIDs), including inflammatory rheumatic diseases, inflammatory skin diseases, and inflammatory bowel diseases. There is extensive knowledge on common adverse drug reactions (ADRs) of biologics, such as infections and injection site reactions. Most of this information is gathered from the perspective of the healthcare professional [1,2]. The healthcare professional's attention to biologic-induced ADRs is mainly focused on ADRs that require discontinuation of therapy or hospitalisation, such as respiratory and herpes zoster infections [3,4]. However, the patient perspective on ADRs may be rather focused on burden and quality of life [5]. It is important to realise this as ADRs may affect adherence [6]. Currently, there is a lack of knowledge about the patients' perspective on the burden of ADRs attributed to biologics and consequences these ADRs impose.

The Dutch National Pharmacovigilance Centre Lareb developed the Dutch Biologic Monitor, a system to collect and monitor patient-reported ADRs attributed to biologic treatment over time. It is a multicentre web-based cohort event monitoring system that follows patients using biologics mainly for IMIDs. Participating patients complete questionnaires about ADRs they attribute to the biologic treatment, including consequences and experienced burden [7].

The primary aim of this study was to gain insight in patient-experienced burden of ADRs that patients attributed to biologics, mainly prescribed for various IMIDs, in a multicentre longitudinal cohort. The secondary aim was to gain insight in demographic and clinical factors that are associated with the experienced burden of ADRs attributed to biologics. To our knowledge, this kind of study has not been conducted.

METHODS

The Dutch Biologic Monitor

The Dutch Biologic Monitor is a prospective cohort event monitoring model for patient-reported ADRs attributed to biologics [7]. Nine Dutch hospitals participated in the Dutch Biologic Monitor between January 1st, 2017 and May 1st, 2019. Patients using one of the monitored biologics, mainly for an IMID, were selected and invited to participate by healthcare professionals of the respective hospitals using consecutive sampling. Patients were eligible from eighteen years of age or older.

Recruitment strategies varied per hospital. Patients were either recruited via letters, during appointments with nurses and specialists, at the outpatient pharmacy or during infusion therapy at the ambulatory care unit. Participating patients were asked to complete a comprehensive web-based baseline questionnaire covering demographic information (gender, date of birth, weight, height, smoking), biologic, start date, indication for biologic therapy, combination

therapy, comorbidities at baseline and ADRs attributed to the biologics. Available options for biologics were the originator or, in case available, a biosimilar of abatacept, adalimumab, anakinra, brodalumab, canakinumab, certolizumab pegol, dupilumab, etanercept, golimumab, guselkumab, infliximab, ixekizumab, natalizumab, rituximab, sarilumab, secukinumab, tocilizumab, ustekinumab and vedolizumab. Rheumatoid arthritis (RA), psoriatic arthritis (PsA), psoriasis, axial spondyloarthropathy (SpA), ulcerative colitis (CU), Crohn's disease (CD) or other indications were the optional indications for biologic therapy in the questionnaires. Methotrexate, predniso(lo)ne, hydrocortisone, methylprednisolone, hydroxychloroquine, azathioprine, leflunomide, tioguanine, mercaptopurine, mesalazine, sulfasalazine, olsalazine, chloroquine or no combination therapy were the options for combination therapies. Respiratory disorder, cardiovascular disorder, hypercholesterolemia, psychiatric disorder, cancer, nervous system disorder, other comorbidities or no comorbidities were the options for comorbidities in the questionnaires. Multiple options could be selected for each of these variables. Patients were asked to report information about ADRs they attributed to the used biologic. This included the type of ADR, start and stop date, course, burden using a five-point Likert type scale ranging from 1 (no burden) to 5 (very high burden), contact with a healthcare professional, the type of healthcare professional, treatment or other actions taken by the healthcare professional and own action taken by the patient following the ADR. Patients could elaborate on the experienced burden in an open text field. Subsequent questionnaires during follow-up after baseline focused exclusively on drug use and ADRs and included identical questions on these topics. The baseline and subsequent questionnaire translated into English are presented in the supplementary material. Questionnaires were sent out bimonthly and patients received a reminder if they had not completed the questionnaire within 7 days and 14 days. No more questionnaires were sent in case the previous questionnaire had expired (after 21 days) or if the patient withdrew from the study. Patients could withdraw from the study at any time.

Data collection

Pharmacovigilance centre Lareb collected ADR reports as solicited reports from all questionnaires that were completed between January 1st, 2017 and May 1st, 2019. Reported ADRs were coded according to Medical Dictionary for Regulatory Activities (MedDRA®) terminology (version 21.0) [8] by qualified pharmacovigilance assessors. We included all reported ADRs in this study and assessed burden at the first time the patient reported the ADR. Long term or recurring ADRs with the same MedDRA® Preferred Term that were repeated by one patient in subsequent questionnaires were counted once. Multiple ADRs with different MedDRA® Preferred Terms reported by one patient were counted separately. ADRs regarding infections, skin reactions, musculoskeletal and gastrointestinal complaints were clustered as subtypes for separate analysis according to the corresponding MedDRA® default System Organ Class. Additionally, injection site reactions were clustered according to the MedDRA® Higher Level Group Term: Administration site reactions. We considered mean burden and use of care due to the clustered ADRs as indicators for the experienced burden. Use of care was specified as hospitalisation, healthcare professional contact and actions following the ADR.

Data analysis

Descriptive statistics were provided using equally weighted mean (± SD) values of the reported burden. We assessed differences in mean burden between variables with independent t-tests. Differences in ADR proportions were tested with Pearson Chi-Square tests. A p-value smaller than 0.05 was considered statistically significant. As our primary outcome measure, burden, was normally distributed (confirmed with a histogram of standardised residuals), multiple linear regression analysis was performed to assess potential variables associated with higher or lower burden. The variables gender, age, body mass index (BMI), smoking, biologic, duration of use, indication for biologic therapy, combination therapy, comorbidities at baseline and ADR subtype were included in the model following the enter method, in which all variables are entered simultaneously. A sensitivity analysis was conducted to account for missing data in case more than 5% of a variable was missing. Statistics were performed in IBM SPSS Statistics (version 22).

RESULTS

A total of 1,355 patients completed 6,293 questionnaires between January 1st, 2017 and May 1st, 2019 in the Dutch Biologic Monitor. Most patients (962 patients, 71%) used a biologic for an inflammatory rheumatic disease; 573 for RA (42%), 220 for PsA (16%), 137 for SpA (10%), 20 for PsA and SpA combined (1.5%) and 12 for RA and SpA combined (0.9%); and 29% used a biologic for other indications. Almost one third of the patients (31%) stopped participating in the Dutch Biologic Monitor after completing the first questionnaire. More than half of the patients (54%) were still participating after completing four questionnaires (six months of participation). After seven questionnaires (one year of participation) 36% of the patients were still participating. The participants covered 798 patient years in total with a mean of 7.1 months. Almost half of the patients (665 patients, 49%) reported an ADR. Most of these patients had inflammatory rheumatic diseases (461 patients, 69%) and 31% used a biologic for an inflammatory skin disease, an inflammatory bowel disease or another indication. The patients with an ADR collectively reported 1,720 unique ADRs during their participation. These patients covered 424 patient years (53%) in the Dutch Biologic Monitor, with a mean of 7.6 months. In total 55% of all reported ADRs were reported in the first questionnaire and 75% of all reported ADRs were reported in the first three questionnaires. See table 1 for demographics of the patients with ADRs.

Table 1. Demographics of patients in the Dutch Biologic Monitor who reported at least one adverse drug reaction.

Characteristics (N=665)	**N (%)**
Gender (Male)	222 (33%)
Age (years) (mean ± SD)	53 ± 13
Smoking	119 (18%)
BMI (kg/m^2) (mean ± SD)	25.9 ± 4.9
Biologic	
Adalimumab	235 (35%)
Etanercept	185 (28%)
Infliximab	66 (10%)
Tocilizumab	34 (5%)
Secukinumab	27 (4%)
Rituximab	25 (4%)
Ustekinumab	25 (4%)
Other biologics[a]	101 (15%)
Duration of biologic use at inclusion (months) (mean ± SD)	36.8 ± 45.5
Indication[b]	
Rheumatoid arthritis	291 (44%)
Psoriatic arthritis	100 (15%)
Crohn's disease	97 (15%)
Axial spondyloarthritis	86 (13%)
Ulcerative colitis	32 (5%)
Psoriasis	31 (5%)
Other indications[c]	64 (10%)
Patients with reported combination therapy at any time during participation	387 (58%)
Methotrexate	186 (28%)
Corticosteroids[d]	120 (18%)
Leflunomide	39 (6%)
Hydroxychloroquine	38 (6%)
Sulfasalazine	33 (5%)
Other combination therapy[e]	75 (11%)
Patients with reported comorbidities	374 (56%)
Cardiovascular disorder	168 (25%)
Hypercholesterolemia	101 (15%)
Respiratory disorder	83 (12%)
Psychiatric disorder	58 (9%)
Nervous system disorder	20 (3%)
Cancer	13 (2%)
Other comorbidity	146 (22%)

Table 1. Continued
BMI: body mass index, SD: standard deviation
[a] Other biologics include: certolizumab pegol (n=22), golimumab (n=20), vedolizumab (n=18), abatacept (n=16), anakinra (n=10), dupilumab (n=6), canakinumab (n=6), sarilumab (n=1), natalizumab (n=1), guselkumab (n=1)
[b] Patients could report more than one indication.
[c] Other indications include: uveitis (n=9), atopic eczema (n=6), vasculitis (n=4), hidradenitis (n=4), Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) (n=3), diverse (n=39)
[d] Corticosteroids include predniso(lo)ne (n=103), methylprednisolone (n=4), hydrocortisone (n=16)
[e] Other combination therapy includes: azathioprine (n=27), mesalazine (n=23), mercaptopurine (n=17), tioguanine (n=7). Olsalazine and chloroquine were not reported as combination therapy.

Reported ADRs

Out of 1,720 reported ADRs, 65% of the ADRs (1,116 ADRs) were included in the predefined ADR subtypes injection site reactions, infections, skin reactions, gastrointestinal complaints, musculoskeletal complaints and fatigue (Table 2). These ADRs were reported by 83% of the patients with an ADR (547 patients).

Musculoskeletal complaints were reported by 43 RA patients, 11 PsA patients and 8 SpA patients, accounting for 60% of patients with musculoskeletal complaints. Gastrointestinal complaints were reported by 22 patients with an inflammatory bowel disease, accounting for 21% of patients with gastrointestinal complaints. Skin reactions were reported by 9 psoriasis patients and 23 PsA patients, accounting for 20% of patients with skin reactions.

Burden of ADRs

The burden was reported for 1,689 ADRs, with a mean burden of 2.7 (SD ± 1.1) on a five-point Likert type scale. A healthcare professional was contacted for 932 ADRs (54%)(Table 2). Hospitalisation was reported by 29 patients (4%) following 32 ADRs (2%), including five infections, five cardiovascular reactions, four ADRs regarding benign or malignant tumours, two gastrointestinal complaints and two skin reactions. Patients experienced infections and musculoskeletal complaints as the most burdensome of all clustered ADRs (infections: 3.1 SD ± 1.1; musculoskeletal: 3.2 ± 0.9) and injection site reactions as the least burdensome (1.8 ± 0.8, $p<0.001$ for both comparisons). Patients reported the most healthcare professional contacts for infections (69% of all infections).

The mean burden of ADRs leading to a healthcare professional contact (3.0 ± 1.1) was higher compared to the mean burden of ADRs without healthcare professional contact (2.4 ± 0.9, $p<0.001$) (Table 3). The mean burden of ADRs leading to contact with a general practitioner was higher (3.4 ± 1.1) than the mean burden of ADRs leading to contact with a nurse (2.9 ± 1.2, $p<0.001$). Of all actions following an ADR, the mean burden was highest for ADRs leading to drug discontinuation (4.1 ± 0.9) and lowest for ADRs that were mentioned but for which no action was initiated (2.7 ± 1.1, $p<0.001$). Patients reported a higher than average burden for ADRs leading to hospitalisation (3.8 ± 1.2).

Table 2. Use of care and mean patient-reported burden following different adverse drug reaction subtypes.

	Total	Injection site reaction	Infection	Skin reaction	Gastro-intestinal complaints	Musculo-skeletal complaints	Fatigue[a]
Patients with ADRs, N (% of total patients with ADRs)[b]	665	172 (26%)	187 (28%)	157 (24%)	105 (16%)	103 (15%)	97 (15%)
ADRs, N (% of total ADRs)	1,720	256 (15%)	252 (15%)	219 (13%)	138 (8%)	151 (9%)	100 (6%)
ADRs leading to hospitalisation, N (% of no. of clustered ADR)	32	2 (1%)	5 (2%)	2 (1%)	2 (1%)	2 (1%)	1 (1%)
ADRs with healthcare professional contact, N (% of no. of clustered ADR)	932	89 (35%)	175 (69%)	133 (61%)	70 (51%)	76 (50%)	63 (63%)
Mean reported burden of ADRs ± SD	2.7 ± 1.1	1.8 ± 0.8	3.1 ± 1.1	2.7 ± 1.1	2.8 ± 1.1	3.2 ± 0.9	2.9 ± 1.0

Burden was measured on a scale from 1 (no burden) to 5 (very high burden)
ADR: adverse drug reaction, SD: standard deviation
[a] Fatigue includes MedDRA® Preferred Terms fatigue and asthenia
[b] Patients could report more than one adverse drug reaction

Table 3. Mean patient-reported burden following adverse drug reactions leading to different use of care.

N=1,689	Mean burden ± SD
Mean burden for all unique ADRs	2.7 ± 1.1
Without healthcare professional contact (n=757)	2.4 ± 0.9
With healthcare professional contact (n=932)	3.0 ± 1.1
Specialist doctor (n=627)	3.1 ± 1.2
General practitioner (n=377)	3.4 ± 1.1
Pharmacist (n=39)	3.2 ± 1.1
Nurse (n=239)	2.9 ± 1.2
Other healthcare professional[a] (n=27)	3.3 ± 0.8
ADRs with action by healthcare professional (n=932)	3.0 ± 1.1
Drug discontinuation (n=45)	4.2 ± 0.9
Dose adjustment (n=82)	3.4 ± 1.1
Switch to previous drug (n=8)	3.9 ± 1.1
ADR treatment (n=285)	3.2 ± 1.2
Mentioned but no action initiated (n=438)	2.7 ± 1.1
Referral to other healthcare professional[b] (n=61)	3.4 ± 1.1
Referral to hospital (n=42)	3.7 ± 1.1
Other action[c] (n=105)	3.4 ± 1.1
ADRs with hospitalisation (n=32)	3.8 ± 1.2
ADRs with action by patient (n=678)	3.0 ± 1.0

Use of care could consist of health care professional contacts, health care professional actions and own actions following adverse drug reactions. Patient-reported burden was measured on a scale ranging from 1 (no burden) to 5 (very high burden).
ADR: adverse drug reaction, SD: standard deviation.
[a] Other healthcare professionals include: dentist (n=16), physiotherapist (n=3), diverse (n=8)
[b] Referral to other healthcare professional includes: dermatologist (n=12), neurologist (n=6), ophthalmologist (n=4), otolaryngologist (n=3), diverse (n=36)
[c] Other actions by healthcare professional include: examination or laboratory test (n=28), diverse (n=77).
Patients described various explanations of the experienced burden, including ADRs leading to impaired ability of daily activities, anxiety and sleeping difficulties.

Factors associated with burden of ADRs

We assessed all demographic and clinical factors that were registered in the Dutch Biologic Monitor for an association with reported burden of ADRs and created a multivariable linear regression model (table 4). The residuals were normally distributed and the regression model predicted 20.2% of the variance ($F(39,1611) = 10.434$, $p<0.001$).

Table 4. Multiple regression model with patient characteristics associated with burden of adverse drug reactions

N=1,689 ADRs	Regression coefficient β [95%CI]
Gender (Male) (n=487)	0.072 [-0.045 to 0.189]
Age (years)	0.000 [-0.005 to 0.004]
Smoking (n=320)	**0.160 [0.025 to 0.295]**
BMI (kg/m²)	0.007 [-0.003 to 0.018]
Biologic	
Adalimumab (n=547)	-0.168 [-0.338 to 0.001]
Etanercept (n=415)	-0.085 [-0.264 to 0.093]
Infliximab (n=179)	0.154 [-0.078 to 0.387]
Tocilizumab (n=97)	-0.111 [-0.368 to 0.147]
Rituximab (n=77)	-0.018 [-0.289 to 0.254]
Ustekinumab (n=75)	-0.232 [-0.538 to 0.074]
Secukinumab (n=70)	-0.192 [-0.506 to 0.122]
Other biologic[a] (n=232)	Reference
Duration of biologic use (months)	0.001 [-0.001 to 0.002]
Indication	
RA (n=734)	-0.086 [-0.332 to 0.161]
CD (n=271)	**-0.271 [-0.535 to -0.007]**
PsA (n=240)	-0.158 [-0.404 to 0.087]
SpA (n=233)	0.065 [-0.168 to 0.299]
UC (n=89)	-0.291 [-0.662 to 0.079]
Psoriasis (n=66)	**-0.380 [-0.724 to -0.035]**
Other indication[b] (n=163)	-0.028 [-0.297 to 0.240]
Combination therapy	
Methotrexate (n=389)	-0.002 [-0.167 to 0.164]
Corticosteroids[c] (n=311)	-0.013 [-0.172 to 0.147]
Hydroxychloroquine (n=102)	0.009 [-0.215 to 0.233]
Leflunomide (n=89)	0.064 [-0.188 to 0.315]
Sulfasalazine (n=70)	**-0.354 [-0.629 to -0.080]**
Other combination therapy[d] (n=182)	-0.097 [-0.348 to 0.153]
No combination therapy (n=650)	0.064 [-0.106 to 0.234]
Comorbidities	
Cardiovascular disorder (n=420)	0.057 [-0.079 to 0.192]
Hypercholesterolemia (n=237)	**-0.177 [-0.339 to -0.014]**
Respiratory disorder (n=218)	**0.217 [0.055 to 0.379]**
Psychiatric disorder (n=157)	**0.368 [0.185 to 0.550]**
Nervous system disorder (n=40)	0.063 [-0.269 to 0.394]
Cancer (n=36)	-0.003 [-0.361 to 0.355]

Table 4. Continued

N=1,689 ADRs	Regression coefficient β [95%CI]
Other comorbidity (n=409)	**0.178 [0.046 to 0.310]**
No comorbidity (n=547)	-0.064 [-0.204 to 0.077]
Type of ADR	
Injection site reaction (n=252)	**-0.994 [-1.152 to -0.837]**
Infection (n=249)	**0.261 [0.108 to 0.414]**
Skin reaction (n=216)	-0.076 [-0.234 to 0.082]
Musculoskeletal complaint (n=146)	**0.396 [0.209 to 0.582]**
Gastrointestinal complaint (n=134)	-0.013 [-0.202 to 0.176]
Other ADR (n=692)	Reference

Results in bold indicate statistically significant outcomes. ADR adverse drug reaction, BMI body mass index, RA rheumatoid arthritis, CD Crohn's disease, PsA psoriatic arthritis, SpA axial spondyloarthropathy, UC ulcerative Colitis.

[a] Other biologics include: certolizumab pegol (n=54), golimumab (n=51), vedolizumab (n=40), abatacept (n=35), anakinra (n=22), canakinumab (n=12), dupilumab (n=14), sarilumab (n=2), natalizumab (n=2), guselkumab (n=4).

[b] Other indications include: uveitis (n=21), vasculitis (n=24), hidradenitis (n=10), Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) (n=9), atopic eczema (n=14), diverse (n=89).

[c] Corticosteroids include predniso(lo)ne (n=276), methylprednisolone (n=7), hydrocortisone (n=36).

[d] Other combination therapy includes: azathioprine (n=62), mesalazine (n=80), mercaptopurine (n=42), tioguanine (n=15)

A sensitivity analysis was performed since more than 5% of data was missing for combination therapy (6.5%) and comorbidities (11%). The regression analysis was repeated with these variables classified as 'no combination therapy' and 'no comorbidities'. Outcomes shifted statistically significant for adalimumab and hypercholesterolemia and did not change for other variables.

A higher burden of ADRs was associated with smoking (β: 0.161 [0.025 to 0.297]), a respiratory comorbidity (β: 0.248 [0.080 to 0.416]), psychiatric comorbidity (β: 0.397 [0.207 to 0.588]), other comorbidity (β: 0.211 [0.058 to 0.364]) and ADRs regarding infection (β: 0.258 [0.105 to 0.411]) and musculoskeletal complaints (β: 0.391 [0.205 to 0.577]). Infections were reported relatively more often than other ADRs by patients with respiratory comorbidities (25%, 54 ADRs) (figure 1). The proportion of respiratory infections in the population with respiratory comorbidities was not higher than the proportion of respiratory infections in the overall population (respiratory comorbidities: 44%; overall: 41%, p = 0.64). The mean burden of respiratory infections was not significantly higher in the population with respiratory comorbidities (3.4 ± 1.0) than in the rest of the population (3.0 ± 1.1, p = 0.061). No outstanding proportions of ADR subtypes were seen in ADRs experienced by smokers and patients with a psychiatric or other comorbidity. Relatively more patients with respiratory disorders or psychiatric disorders were smokers (respiratory: 24%, psychiatric: 33%) than in our overall population (18%).

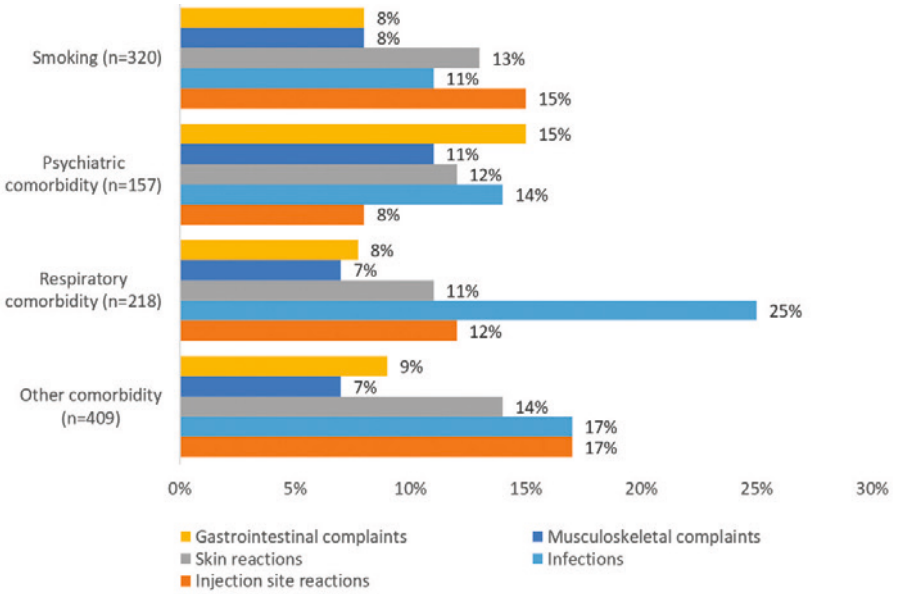

Figure. 1 Proportion of adverse drug reaction (ADR) subtypes for each factor that was associated with higher burden. The displayed ADRs account for 55% of the ADRs experienced by smoking patients, 61% of ADRs experienced patients with psychiatric comorbidity, 63% of ADRs experienced by patients with respiratory comorbidity and 64% of ADRs experienced by patients with other comorbidities.

A lower burden of ADRs was associated with Crohn's disease (β: -0.266 [-0.530 to -0.002]), psoriasis (β: -0.359 [-0.703 to -0.014]), hypercholesterolemia as comorbidity (β: -0.177 [-0.339 to -0.014]), combination therapy with sulfasalazine (β: -0.416 [-0.702 to -0.129]) and ADRs regarding injection site reactions (β: -0.991 [-1.148 to -0.833]). In the sensitivity analysis adalimumab use was associated with a lower burden of ADRs (β: -0.172 [-0.341 to -0.002]) and hypercholesterolemia was not associated with lower burden anymore (β: -0.153 [-0.321 to 0.015]). Relatively more injection site reactions than other ADRs were reported by patients with psoriasis and patients who used sulfasalazine as combination therapy (psoriasis: 23%, 15 ADRS; sulfasalazine: 29%, 20 ADRs) (Figure 2). No outstanding proportions of ADR subtypes were seen in ADRs experienced by patients with CD, hypercholesterolemia or patients using adalimumab. A total of 46 patients reporting 124 ADRs used adalimumab for CD (20% of adalimumab users; 47% of patients with CD) and 12 patients reporting 21 ADRs used adalimumab for psoriasis (5% of adalimumab users; 39% of patients with psoriasis). A total of 12 patients reporting 16 ADRs used adalimumab and had sulfasalazine as combination therapy (5% of adalimumab users; 36% of sulfasalazine users).

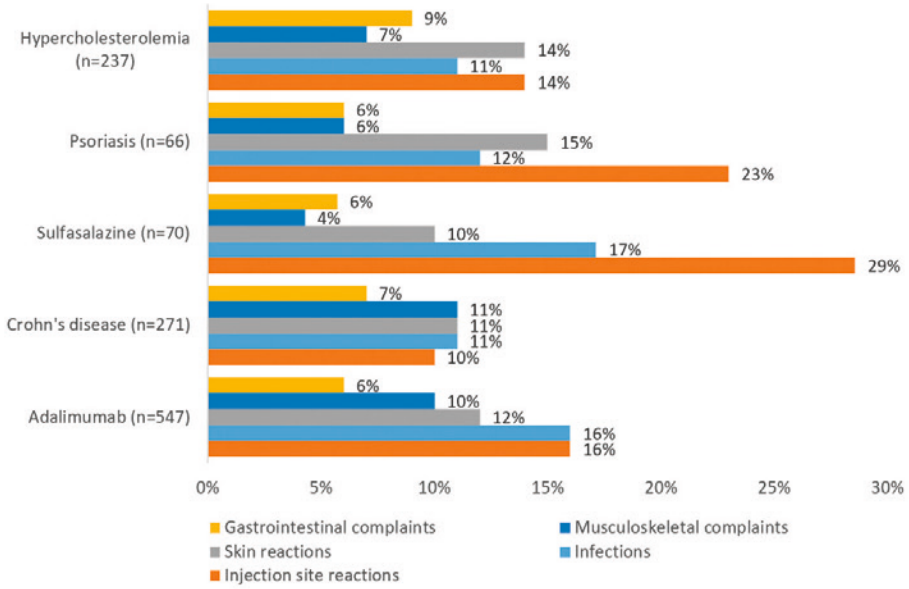

Figure. 2 Proportion of adverse drug reaction (ADR) subtypes for each factor that was associated with lower burden. The displayed ADRs account for 54% of ADRs experienced by patients with hypercholesterolemia, 62% of ADRs experienced by patients with psoriasis, 66% of ADRs experienced by patients using sulfasalazine as combination therapy, 50% of ADRs experienced by patients with Crohn's diseases and 59% of ADRs experienced by patients using adalimumab.

DISCUSSION

Patients in the Dutch Biologic Monitor consider infections and musculoskeletal complaints as the most burdensome ADRs and injection site reactions as the least burdensome ADRs. Furthermore, patients rated ADRs leading to drug discontinuation and hospitalisation with the highest burden score, which is in line with the perceived healthcare professional's focus on ADRs [3,4]. This study provides insight in the experienced burden of ADRs, including ADRs with other consequences than drug discontinuation and hospitalisation. ADRs leading to healthcare professional contact were regarded as more burdensome than ADRs which did not lead to healthcare professional contact. Presumably, a healthcare professional is contacted when the patient is worried about the ADR or believes that action needs to be taken. Infections often need treatment and patients are instructed to contact a healthcare professional when having signs and symptoms of infection, such as fever, explaining the high number of healthcare professional contacts for infections [9]. Although it is not surprising that ADRs leading to drug discontinuation, switch to a previously used drug, dose adjustment or hospitalisation are regarded as more burdensome than ADRs without these actions, the patient's perspective has not been systematically studied in a large population of patients before. Unfortunately, we cannot distinguish whether the characteristics of the ADRs or the actions that follow upon

the ADRs lead to the experienced burden. Both aspects should be considered when adjusting therapy due to experienced ADRs.

Some patient groups, such as patients with respiratory or psychiatric comorbidities, smokers and patients with ADRs regarding infections and musculoskeletal complaints, experienced their ADRs as more burdensome than other patients. A higher burden for patients with respiratory comorbidities could possibly be caused by the higher proportion of infections in this group. A closer look at the experienced infections showed that these were not respiratory tract infections in particular. This is in line with previous findings that asthma and chronic obstructive pulmonary disease are associated with an increased risk of infections in general [10,11]. Since these patients experience a combination of diseases, genetic predisposition for an increased risk of infections also cannot be ruled out. Negative thoughts are associated with numerous mental disorders and therefore patients with psychiatric problems might have a more negative approach and may experience the impact of ADRs as more challenging [12,13]. Even though the association between patient-reported burden of ADRs and drug withdrawal has not been investigated, it is remarkable that factors associated with higher burden in our study did not correspond with factors associated with increased biologic withdrawal in other studies, such as increasing age, female sex, rheumatoid arthritis and infliximab use [3,4,14,15].

We found that patients with Crohn's disease, psoriasis, use of sulfasalazine as combination therapy, injection site reactions, hypercholesterolemia and adalimumab use experienced their ADRs as less burdensome than other patients. Patients with sulfasalazine as combination therapy had a higher proportion of injection site reactions which are associated with lower burden. However, sulfasalazine was used more often in combination with etanercept than with adalimumab and was mainly used by RA patients. Since we cannot explain our findings, further research on the lower experienced burden with sulfasalazine as combination therapy may be indicated. To the best of our knowledge, factors associated with burden of ADRs have not been assessed before. Even though etanercept is suggested to be the safer tumor necrosis factor-α blocking agent in some studies assessing ADR occurrence in rheumatoid arthritis, the findings of this study suggest that ADRs patients attributed to adalimumab are experienced as less burdensome than ADRs attributed to other biologics, including etanercept [3,16].

A limitation of this study is that selection bias cannot be ruled out when asking patients to report information on ADRs. Patients that experience higher burden of ADRs may be more willing to participate. Furthermore, the causal relationship of patient-reported ADRs was not verified with the patient's practitioners. More than half of the patients reporting musculoskeletal complaints, used a biologic for an inflammatory rheumatic disease. Some of these complaints could possibly be related to the disease rather than the biologic drug. Even though the clinical confirmation of the reported ADRs is lacking, we consider patient reports as a strength since this is the patients' perspective on their drug use and unfiltered patient-reported ADR data is usually not systematically questioned or structurally available.

CONLUSION

This is the first study addressing patient perspectives on the burden of ADRs that patients experienced with biologic use. This information may advance healthcare professionals' understanding of patients perceptions of ADRs and the impact these ADRs impose. This may lead to more personalised treatment options, better adherence and finally better clinical outcomes.

Future research in different aspects of ADR burden, such as the time course of burden, can contribute to a better understanding of patient ADR experiences.

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SUPPLEMENTARY MATERIAL

Baseline and subsequent comprehensive web-based questionnaires from the Dutch Biologic Monitor. The original questionnaires are in Dutch. Side effects reappear in subsequent questionnaires if the side effect was reported in a previous questionnaire and is still current.

Baseline questionnaire

Questions in first questionnaire	Answer options	
Introduction		
How to complete this questionnaire? In this Monitor, the Netherlands Pharmacovigilance Centre Lareb is interested in biologic medicines. You can navigate through the questionnaire by using the "previous" and "next" buttons at the bottom of the page. Please do not use the buttons in the internet browser toolbar. This questionnaire consists of 5 steps. Mandatory questions have been marked with an asterisk (*). If you still have questions, please contact: Netherlands Pharmacovigilance Centre Lareb Goudsbloemvallei 7 5237 MH 's-Hertogenbosch Telephone no.: +31 73 - 64 69 700 (available on working days between 9 a.m. and 5 p.m.) E-mail: info@mijnbiologischmedicijn.nl		
Your medication		
Choose the biologic medicine you currently use *Select a medicine from the list*	Multiple choice	All in the Netherlands available brand names of the following biologics: Abatacept Adalimumab Anakinra Brodalumab Canakinumab Certolizumab pegol Dupilumab Etanercept Golimumab Guselkumab Infliximab Ixekizumab Natalizumab Rituximab Sarilumab Secukinumab Tocilizumab Ustekinumab Vedolizumab
When did you start using {{Survey medicine}}? *Please enter an estimated date if you are not sure about the exact date*	Date	
When was the last administration of this medicine? *Please enter an estimated date if you are not sure about the exact date*	Date	

Questions in first questionnaire	**Answer options**	
If biosimilar is chosen		
*For biosimilar: Have y*ou used {{Name original biologic}} previously?	Yes/no	
If yes: When did you start using {{Name original biologic}}?	Date	
What do you use the biological medicine for?	Multiple select	Rheumatoid arthritis
		Psoriasis
		Psoriatic arthritis
		Axial spondyloarthritis
		Colitis ulcerosa
		Crohn's disease
		Other: [open text]
What is the name of your treatment centre (hospital)?	Multiple choice	Participating hospitals or other: [open text]
Was the medicine last administered at the hospital or at home?	Hospital/at home	
Are you familiar with the batch number of {{Survey medicine}}? *It is visible on the packaging of the medicine. Below, you can upload a photo of the packaging.*	Yes: [open text] /no	
Do you have a photo of the packaging? Please upload the photo here. By uploading a photo, there is no need to retype the batch number. *upload your photo here (this should be a .jpg, .jpeg, or .png file).*	Photo upload	
Side effects		
Symptom or side effect? In this questionnaire, you will be asked about any side effect you may have experienced. We are interested in all side effects. Consider side effects during or shortly after administration (e.g. pain at the injection site or fever). You could also think of infections and a reduced effect of the medicine. You can also report complaints in case you are not sure whether it is caused by {{surveymedicine. Medicine}}. We also ask you to complete this questionnaire if you do not experience any side effects since this is important information as well		
Did you experience a side effect following the last administration of {{surveymedicine.Medicine}}? * *This could also be a side effect which started after administration of the medicine, but has already subsided. We are interested in all side effects. Consider also any side effects during or shortly after administration (e.g. pain at the injection site or fever). But also consider infections and a reduced effect of the medicine.*	Yes/no	
If yes: ***For each side effect***		

Questions in first questionnaire	**Answer options**	
Description of side effect Please enter one side effect in the column 'Description of side effect' text box. You may add multiple symptoms or side effects by clicking the 'Add side effect' button. Starting date Please enter a date when the side effect started. Have you forgotten when the side effect started? Or did the symptoms start gradually? If so, please enter an estimated date. How are things now? Please note the current status of the side effect.		
Description of side effect	Open text	
When did this side effect start?	Date	
Can you explain more about the side effect? For example: *- How often do you suffer from this side effect?* *- At what moment do you suffer from this side effect?* *- Is there a pattern?*	Open text	
Did you contact a healthcare provider about this side effect?	Yes/no	
If yes:		
With whom did you have contact?	Multiple select:	General practitioner
		Specialist doctor
		Nurse
		Pharmacist
		Other: [open text]
If yes:		
How was this side effect treated? *	Multiple select	Mentioned, but no action initiated
		Treatment
		Dose adjustment
		Drug discontinuation
		Referral to other health care professional
		Referral to hospital
		Switch to previous drug
		Other: [open text]
If option 1-7 was chosen: Here you can clarify your response	Open text	
If option 4 was chosen: When was {{surveymedicine. Medicine}} discontinued? * *Please enter an estimated date if you are not sure about the exact date*	Date	
Have you been you admitted to the hospital because of this side effect? *	Yes/no	
Did you do anything yourself about the side effect?	Yes: [open text]/no	

Questions in first questionnaire	Answer options	
What is the current status of the side effect? The side effect:	Multiple choice	is over
		is subsiding
		did not change
		is aggravating
If option 1 was chosen: When did you recover from the side effect? *Please enter an estimated date if you are not sure about the exact date*	Date	
What was the burden you experienced from this side effect?	Multiple choice	No burden
		Little burden
		Quite burdensome
		High burden
		Very high burden
Can you describe the experienced burden of the side effect?	Open text	
Other medication		
The medicines below are frequently used in combination with biologic medicines. Can you indicate whether you are currently using (one of) these agents?	Multiple select	I do not use any of these medicines
		Azathioprine
		Chloroquine
		Hydroxychloroquine
		Hydrocortisone
		Leflunomide
		Mercaptopurine
		Mesalazine
		Methotrexate
		Olsalazine
		Prednisone
		Prednisolone
		Sulfasalazine
		Tioguanine
		Methylprednisolone
General information		
Other diseases and general information The Netherlands Pharmacovigilance Centre Lareb is interested in side effects that occur during use of medicines used for an inflammatory disease (e.g. rheumatoid arthritis or psoriasis). Therefore it is important to know whether you have any other diseases.		

Questions in first questionnaire	**Answer options**	
Could you please indicate what other diseases you have?	Multiple select	No comorbidities
		Respiratory disorder
		Cardiovascular disorder
		Hypercholesterolemia
		Psychiatric disorder
		Cancer
		Nervous system disorder
		Other: [open text]
What is your length? *Please enter whole numbers*	[open] centimeter	
What is your weight? Please enter whole numbers	[0-500] kilogram	
How often do you smoke?	Multiple choice	Never
		Monthly
		Weekly
		Daily
How have you been informed about this Monitor biological medicines?	Multiple choice	In the pharmacy
		During consultation with nurse
		During consultation with specialist doctor
		At ambulatory care unit
		By letter
		By email
Conclusion		
Do you have a question, for example about a side effect? Ask your physician or pharmacist. If you have a specific question for the Netherlands Pharmacovigilance Centre Lareb, please send an e-mail to info@mijnbiologischmedicijn.nl. Do you have any remarks about this questionnaire? Please enter these below.	Open text	
Would you like to receive the results by e-mail following completion of this Monitor? *These can also be found on www.mijnbiologischmedicijn.nl.*	Yes/no	
If yes: Please state the desired e-mail address:		

Questions in first questionnaire	Answer options
Submit your questionnaire! By clicking submit, the questionnaire will be sent to us. We will send you an e-mail as soon as the next questionnaire is available to you. If you still have questions, please contact us. Netherlands Pharmacovigilance Centre Lareb Goudsbloemvallei 7 5237 MH 's-Hertogenbosch Telephone: +31 73 - 64 69 700 (available on working days between 9 a.m. and 5 p.m.) E-mail: info@mijnbiologischmedicijn.nl	
Download overview	
Thank you very much for your questionnaire! You have sent your first questionnaire of this Biologic Monitor to us. You may download the questionnaire below: Download questionnaire We will send you an e-mail when your next questionnaire is available. Use the top menu to log out of this website.	

Subsequent questionnaire

Questions in subsequent questionnaires	Answer options	
Your medication		
In case the biologic was discontinued in the previous questionnaire:		
In the previous questionnaire you indicated that {{surveymedicine.Medicine}} was discontinued		
Is {{surveymedicine.Medicine}} still discontinued? *	Yes/No	
In case the biologic was not discontinued in the previous questionnaire		
In the previous questionnaire you used {{surveymedicine.Medicine}}. The following questions are about use of {{surveymedicine.Medicine}}.		
Are you still using {{surveymedicine.Medicine}} ?*	Multiple choice	Yes, I have used the medicine in the last 2 months
		Yes, but I have not used the medicine in the last 2 months
		Yes, but from a different brand (manufacturer)
		No, I (temporarily) stopped using the medicine
		No, I stopped using this medicine but switched to another biologic medicine
In case the medicine was used in the last 2 months		
When was the last administration of this medicine? *Please enter an estimated date if you are not sure about the exact date*	Date	
In case of (temporary) discontinuation		
When did you stop using {{surveymedicine.Medicine}}? * *Please enter an estimated date if you are not sure about the exact date*	Date	
Why did you (temporarily) stop using {{surveymedicine.Medicine}}? *	Multiple choice	Because of one or more side effects
		Other reason: [open text]
Your new medication		
Choose the brand (manufacturer) of the medicine you currently use * *Select a medicine from the list*	Multiple choice	All in the Netherlands available brand names of the following biologics: Abatacept Adalimumab Anakinra Brodalumab Canakinumab Certolizumab pegol Dupilumab Etanercept Golimumab Guselkumab Infliximab

Questions in subsequent questionnaires	Answer options	
		Ixekizumab Natalizumab Rituximab Sarilumab Secukinumab Tocilizumab Ustekinumab Vedolizumab
When did you start using {{Survey medicine}}? *Please enter an estimated date if you are not sure about the exact date*	Date	
What is the name of your treatment centre (hospital)?	Multiple choice	Participating hospitals or other: [open text]
Was the medicine last administered at the hospital or at home?	Hospital/at home	
Are you familiar with the batch number of {{Survey medicine}}? *It is visible on the packaging of the medicine. Below, you can upload a photo of the packaging.*	Yes: [open text] /no	
Do you have a photo of the packaging? Please upload the photo here. By uploading a photo, there is no need to retype the batch number. *upload your photo here (this should be a .jpg, .jpeg, or .png file).*	Photo upload	
Side effects		
New side effect		
Did you experience a side effect following the last administration of {{surveymedicine.Medicine}}? * *This could also be a side effect which started after administration of the medicine, but has already subsided. We are interested in all side effects. Consider also any side effects during or shortly after administration (e.g. pain at the injection site or fever). But also consider infections and a reduced effect of the medicine.*	Yes/no	
All side effects (new and not recovered side effects in previous questionnaire)		
Description of side effect Please enter one side effect in the column 'Description of side effect' text box. You may add multiple symptoms or side effects by clicking the 'Add side effect' button. Starting date Please enter a date when the side effect started. Have you forgotten when the side effect started? Or did the symptoms start gradually? If so, please enter an estimated date. How are things now? Please note the current status of the side effect.		
Description of side effect	Open text	
When did this side effect start?	Date	

Questions in subsequent questionnaires	**Answer options**	
Can you explain more about the side effect? For example: *- How often do you suffer from this side effect?* *- At what moment do you suffer from this side effect?* *- Is there a pattern?*	Open text	
Did you contact a healthcare provider about this side effect?	Yes/no	
If yes:		
With whom did you have contact?	Multiple select:	General practitioner
		Specialist doctor
		Nurse
		Pharmacist
		Other: [open text]
If yes:		
How was this side effect treated? *	Multiple select	Mentioned, but no action initiated
		Treatment
		Dose adjustment
		Drug discontinuation
		Referral to other health care professional
		Referral to hospital
		Switch to previous drug
		Other: [open text]
If option 1-7 was chosen: Here you can clarify your response	Open text	
If option 4 was chosen: When was {{surveymedicine.Medicine}} discontinued? * *Please enter an estimated date if you are not sure about the exact date*	Date	
Have you been you admitted to the hospital because of this side effect? *	Yes/no	
Did you do anything yourself about the side effect?	Yes: [open text]/no	
What is the current status of the side effect? The side effect:	Multiple choice	is over
		is subsiding
		did not change
		is aggravating
If option 1 was chosen: When did you recover from the side effect? *Please enter an estimated date if you are not sure about the exact date*	Date	
What was the burden you experienced from this side effect?	Multiple choice	No burden

Questions in subsequent questionnaires	Answer options	
		Little burden
		Quite burdensome
		High burden
		Very high burden
Can you describe the experienced burden of the side effect?	Open text	
Other medication		
The medicines below are frequently used in combination with biologic medicines. Can you indicate whether you are currently using (one of) these agents?	Multiple select	I do not use any of these medicines
		Azathioprine
		Chloroquine
		Hydroxychloroquine
		Hydrocortisone
		Leflunomide
		Mercaptopurine
		Mesalazine
		Methotrexate
		Olsalazine
		Prednisone
		Prednisolone
		Sulfasalazine
		Tioguanine
		Methylprednisolone
Conclusion		
Do you have a question, for example about a side effect? Ask your physician or pharmacist. If you have a specific question for the Netherlands Pharmacovigilance Centre Lareb, please send an e-mail to info@mijnbiologischmedicijn.nl. Do you have any remarks about this questionnaire? Please enter these below.	Open text	
Submit your questionnaire! By clicking submit, the questionnaire will be sent to us. We will send you an e-mail as soon as the next questionnaire is available to you. If you still have questions, please contact us. Netherlands Pharmacovigilance Centre Lareb Goudsbloemvallei 7 5237 MH 's-Hertogenbosch Telephone: +31 73 - 64 69 700 (available on working days between 9 a.m. and 5 p.m.) E-mail: info@mijnbiologischmedicijn.nl		

Chapter 3

Course of adverse drug reactions

Development of a framework structuring themes in the course of adverse drug reactions from a patient's perspective

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ABSTRACT

Background There is a need for more extensive information about adverse drug reactions (ADRs) for patients than currently available, including information on the course of ADRs. Aspects characterising the course of adverse drug reactions (ADRs) from the patient perspective have not been identified before.

Objective To develop a framework based on common themes in the course of ADRs identified from patient descriptions in patient-reported ADRs.

Methods In this qualitative study, patient descriptions of the course of patient-reported ADRs were analysed by thematic analysis with an inductive approach using three different existing datasets containing patient-reported ADRs. Two datasets included patient-reported ADRs from cohort even monitoring of biologics and direct oral anticoagulants (DOACs) and one dataset included spontaneous reports from patients concerning medication for lower urinary tract symptoms (LUTS). A conceptual framework was developed from the identified main themes and subthemes .

Results Patient-reported data concerning 3,888 ADRs were analysed. Six main themes with multiple subthemes were identified from patient descriptions of the course of ADRs. Four themes were descriptive: frequency of an ADR episode, duration of an ADR episode, moment or period of ADR occurrence and development in intensity of the ADR. Two themes concerned factors influencing the course of ADRs: triggering factors and improving factors.

Conclusion The presented framework illustrates that patients describe extensive details on the course and timeframe of ADRs. The identified themes provide a basis for improving systematic data collection of more extensive details about ADRs from patients as a first step towards the provision of more comprehensive ADR information to patients.

INTRODUCTION

Although pharmacological interventions have a prominent role in the treatment of diseases, the use of drugs is also associated with adverse drug reactions (ADRs). These ADRs may impose burden and subsequently affect quality of life [1-3]. In addition, ADRs might reduce the effectiveness of therapy as the occurrence of ADRs is associated with reduced medication adherence and drug discontinuation [4].

Comprehensible patient education about ADRs is essential to collaboratively decide whether to start drug therapy, to recognise possible ADRs and to know what to do when ADRs occur [5]. Although ADR information is the most often sought drug information by patients, it is usually limited to the nature and frequency of ADRs in the package leaflet [6, 7]. However, several studies clearly demonstrate that patients' needs for ADR information are more extensive and include more detailed information about the course of ADRs such as time to onset, duration, information on whether the ADR resolves and management strategies [6, 8]. After all, especially for a patient it is not only relevant to know which ADR might occur, but also what to expect and how the ADR may develop over time [9, 10]. When more extensive information about the course of ADRs is available, patients can be better informed and supported according to their needs [5].

Although the European guideline on summary of product characteristics (SmPC) suggests including information on reversibility, time of onset, severity, duration, mechanism of the reaction, dose relationship, relationship with duration of exposure and risk factors in the section concerning descriptions of selected adverse reactions, these elements have not been assessed from a patient perspective [7]. Since ADRs influence drug adherence and effectiveness of therapy, addressing patients' information needs is essential while a framework covering important aspects of ADRs from the patient perspective is lacking. Data collection about ADRs from clinical trials, safety studies and spontaneous reporting systems has proven its value for signal detection, which mainly includes the nature and frequency of ADRs [11, 12]. Unfortunately, additional elements of ADRs as recommended by the European guideline are often not available and it remains challenging to include additional information about the course of ADRs in the SmPC or package leaflet if this information has not been systematically collected.

Patient-reported safety data are a valuable source for collecting extensive ADR information as this contains first-hand information about ADRs and includes details on the patient's experiences [13-18]. At the Netherlands Pharmacovigilance Centre Lareb, patient-reported safety data currently contains thorough descriptions with valuable information on the course of ADRs. These descriptions are unstructured and therefore challenging to analyse. The aim of this study was to create a framework based on the patient perspective on the course of ADRs by identifying common themes in the course of ADRs from patient descriptions in open-ended text fields using three existing representative datasets concerning ADRs reported by chronic disease patients. This framework might function as a foundation for improving systematic data collection on the course of ADRs from patients, for potentially categorizing the course

of specific ADRs in the future and eventually for including details about the course of ADRs in ADR information on a broader level than nature and frequency.

METHODS

Study Design

In this qualitative study, we created a framework including common themes in the course of ADRs from patient descriptions. We identified common themes in the course of ADRs by thematic analysis of patient descriptions from a restricted set of data, comprising three existing datasets with patient-reported ADRs. The datasets were selected as practical examples with variations in administration route and dosing schedule of the drugs for a representative selection. The datasets included ADRs reported through the spontaneous reporting system as well as cohort event monitoring [19].

Data sources

Dutch Biologic Monitor

The Dutch Biologic Monitor is a web-based questionnaire study following patients using a biologic for an immune-mediated inflammatory disease (IMID) [3, 20]. A total of 1382 patients from nine Dutch hospitals that were using a biologic participated between 1 January 2017 and 31 December 2020. The following biologics were included: abatacept, adalimumab, anakinra, brodalumab, canakinumab, certolizumab pegol, dupilumab, etanercept, golimumab, guselkumab, infliximab, ixekizumab, natalizumab, rituximab, sarilumab, secukinumab, tocilizumab, ustekinumab and vedolizumab. Participants completed comprehensive bimonthly web based questionnaires covering demographics, treatment information (IMID, used biologic, combination therapy and comorbidities) and ADR information.

In every questionnaire, patients were asked whether they experienced ADRs which they attributed to the used biologic. All ADRs had previously been coded according to the Medical Dictionary for Regulatory Activities (MedDRA®) by trained pharmacovigilance assessors [21]. For each ADR, a description of the ADR, a description of the course of the ADR, start and stop date of the ADR, and details on consequences and burden of the ADR were asked. If a patient had not recovered from an ADR when completing a questionnaire, these questions about the ADR were repeated in a subsequent questionnaire and thus longitudinal information on one ADR could be collected in multiple questionnaires. In all questionnaires, patients could comment on the course of the ADR in an open-ended text field, by answering the question (translated from Dutch): ‘Can you explain more about the ADR? For example, think of: How often do you experience this ADR? At what moments do you experience this ADR? Is there a pattern?’.

DOAC web-based questionnaires

A total of 1748 patients using rivaroxaban, apixaban, dabigatran or edoxaban completed four comprehensive questionnaires in 6 months between July 2012 and April 2017 in the DOAC web-based questionnaire study [22]. These questionnaires covered demographics, treatment information (DOAC, indication for use) and information about experienced ADRs. Patients were invited to participate by their pharmacist. All ADRs had previously been coded according to MedDRA® by trained pharmacovigilance assessors [21]. Patients could comment on the course of the ADR in an open-ended text field, by answering the question (translated from Dutch): 'Could you describe the course of this ADR?'.

Spontaneous reports tamsulosin, dutasteride, solifenacin

ADRs reported by patients using the spontaneous reporting system of the Netherlands Pharmacovigilance Centre Lareb can include details on the course of the ADR in open-ended text fields. All ADRs and indications for the drug had previously been coded according to MedDRA® by trained pharmacovigilance assessors [21]. All ADR reports reported by patients concerning lower urinary tract symptoms (LUTS) medication (tamsulosin, dutasteride or solifenacin) between 31 March 2003 and 3 March 2022 were included. This is since patient reporting was implemented to the spontaneous reporting system in 2003 [15].

Data collection

From the Dutch Biologic Monitor and DOAC web based questionnaires, all completed answers to the question about the course of ADRs were included for thematic analysis, including answers from follow-up questionnaires. From the spontaneous reports concerning LUTS medication, all information concerning the course of the ADR was extracted from open-ended text fields by a pharmacovigilance assessor (MS) and included for thematic analysis. We included all patient-reported ADRs from the three datasets and defined ADRs as all reported ADRs that patients attributed to their drug without verification of a causal relationship.

For all data sources, the researchers did not have any influence on the descriptions the patients provided as it concerned existing data. In all datasets multiple open-ended text fields could contain information about one ADR reported by one patient.

Data analysis

To develop a framework we analysed all patient-reported open text descriptions of the course of reported ADRs using thematic analysis [23]. Thematic analysis was separately conducted for the three datasets. At first, data from the Dutch Biologic Monitor were analysed by JvL and NJ (both trained pharmacovigilance assessors) with an inductive approach. Descriptions of the course of ADRs were systematically coded. In the first phase, the calibration phase, 200 open-ended text fields were separately coded by both assessors and discussed to reach agreement on the coding process. In the second phase, the control phase, 250 descriptions were double coded by both assessors for review, after which differences were discussed for consensus. Finally, the remaining open-ended text fields were divided and coded separately

by the two assessors. Codes were discussed in case of doubt. All codes were placed into categories following axial coding upon agreement by the two assessors out of which themes with corresponding subthemes were identified.

Subsequently, data from the other two datasets were analysed in the same manner. The DOAC dataset was analysed by JvL and AaK (a research student) and the LUTS medication dataset was analysed by MS (trained pharmacovigilance assessor) and KV (a research student). As themes had been identified from Dutch Biologic Monitor data first, themes and subthemes of DOACs and LUTS medication were identified with a deductive approach with the themes from the Dutch Biologic Monitor as a basis.

Finally, the identified themes and subthemes of the three datasets were discussed and adjusted with all assessors and combined into a framework after the remaining discrepancies were resolved [24]. The framework was visualised in an Ishikawa diagram which is a structured tool to illustrate and understand contributing factors leading to an effect [25].

RESULTS

Descriptions of the course of 3,888 ADRs in total were analysed from the three datasets, which included 2035 ADRs reported by 730 patients in the Dutch Biologic Monitor, 1149 ADRs reported by 627 patients from DOAC questionnaires and 704 ADRs from 373 spontaneous ADR reports concerning LUTS medication (Table 1, Table 2 and Supplementary material). A framework was created following thematic analysis including six themes in total. Four main themes with multiple subthemes concerned descriptive items of the course of ADRs (Figure 1):

1. Frequency of an ADR episode
2. Duration of an ADR episode
3. Moment or period of ADR occurrence
4. Development in intensity of ADR

Two main themes with multiple subthemes concerned factors influencing the course of ADRs:

1. Triggering factors
2. Improving factors

Patients described information covering multiple themes in many descriptions of the course of ADRs. All three datasets included descriptions of the course of ADRs concerning all six themes.

Table 1. Patient and treatment characteristics of patients reporting ADRs in the Dutch Biologic Monitor, the DOAC questionnaire study and spontaneous reports concerning LUTS medication.

Dutch Biologic Monitor		**DOAC questionnaires**		**LUTS spontaneous reports**	
Total N	730	**Total N**	627	**Total N**	373[a]
Age in years, mean ± SD	53.0 ± 13.7	**Age in years, mean ± SD**[b]	63 ± 12	**Age in years, mean ± SD**	65.9 ± 11.3
Female patients N (%)	473 (65)	**Female patients N (%)**	262 (42)	**Female patients N (%)**	0 (0)
Indication for drug N (%)		**Indication for drug N (%)**		**Indication for drug N (%)**	
Rheumatoid arthritis	309 (42)	Atrial fibrillation	252 (40)	Reproductive system and breast disorders (SOC)	162 (43)
Psoriatic arthritis	110 (15)	Thrombosis prophylaxis	197 (31)	Renal and urinary disorders (SOC)	162 (43)
Axial spondyloarthritis	94 (13)	Pulmonary embolism	87 (14)	Other	18 (5)
Crohn's disease	108 (15)	Deep vein thrombosis	55 (9)	Unknown	32 (9)
Ulcerative colitis	35 (5)	Thrombosis	33 (5)		
Psoriasis	33 (5)	Surgery	2 (0.3)		
Other	81 (11)	Unknown	1 (0.2)		
Drug N (%)		**Drug N (%)**		**Drug N (%)**	
Adalimumab	257 (35)	Rivaroxaban	262 (42)	Tamsulosin	286 (77)
Etanercept	197 (27)	Apixaban	167 (27)	Dutasteride	52 (14)
Infliximab	78 (11)	Dabigatran	115 (18)	Solifenacin	35 (9)
Tocilizumab	38 (5)	Edoxaban	83 (13)		
Ustekinumab	31 (4)				
Rituximab	29 (4)				
Secukinumab	28 (4)				
Certolizumab pegol	25 (3)				
Golimumab	21 (3)				
Vedolizumab	19 (3)				
Dupilumab	17 (2)				
Abatacept	17 (2)				
Other[c]	23 (3)				

ADR adverse drug reaction, DOAC direct oral anticoagulant, LUTS lower urinary tract symptoms, SD standard deviation, SOC System Organ Class. [a]It is not known whether the number of ADR reports represents the number of patients since multiple reports could have been submitted considering the same patient. Detected duplicate ADR reports were not included. [b]Age was unknown for 25 patients that completed the DOAC questionnaires. [c]Other biologics included: anakinra (10), canakinumab (7), sarilumab (3), natalizumab (2) and guselkumab (1)

Table 2. The reported adverse drug reactions for which the course was analysed in the Dutch Biologic Monitor, the DOAC questionnaire study and spontaneous reports concerning LUTS medication.

MedDRA® System Organ Class	Number of ADRs biologics N (%) n=2035	Number of ADRs DOACs N (%) n=1149	Number of ADRs LUTS medication N (%) n=704
Blood and lymphatic system disorders	14 (0.7)	0	2 (0.3)
Cardiac disorders	15 (0.7)	10 (0.9)	28 (4)
Congenital, familial and genetic disorders	1 (0.0)	0	0
Ear and labyrinth disorders	14 (0.7)	11 (1)	7 (1)
Endocrine disorders	3 (0.1)	1 (0.1)	1 (0.1)
Eye disorders	84 (4)	26 (2)	51 (7)
Gastrointestinal disorders	159 (8)	300 (26)	95 (13)
General disorders and administration site conditions	571 (28)	145 (13)	76 (11)
Hepatobiliary disorders	1 (0.0)	1 (0.1)	0
Immune system disorders	7 (0.3)	2 (0.2)	3 (0.4)
Infections and infestations	300 (15)	4 (0.3)	6 (0.9)
Injury, poisoning and procedural complications	9 (0.4)	2 (0.2)	5 (0.7)
Investigations	30 (1)	24 (2)	21 (3)
Metabolism and nutrition disorders	5 (0.2)	8 (0.7)	0
Musculoskeletal and connective tissue disorders	178 (9)	66 (6)	19 (3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	18 (0.9)	0	3 (0.4)
Nervous system disorders	134 (7)	226 (20)	133 (19)
Product issues	0	0	1 (0.1)
Psychiatric disorders	35 (2)	52 (5)	39 (6)
Renal and urinary disorders	8 (0.4)	20 (2)	20 (3)
Reproductive system and breast disorders	11 (0.5)	14 (1)	86 (12)
Respiratory, thoracic and mediastinal disorders	126 (6)	75 (7)	57 (8)
Skin and subcutaneous tissue disorders	264 (13)	102 (9)	39 (6)
Social circumstances	1 (0.0)	0	1 (0.1)
Vascular disorders	47 (2)	60 (5)	11 (2)

ADRs adverse drug reactions, DOACs direct oral anticoagulants, LUTS lower urinary tract symptoms, MedDRA Medical Dictionary for Regulatory Activities

Descriptive factors

Frequency of an ADR episode

Patients elaborated on the frequency of ADR episodes in five subthemes: once, first time, recurring with fixed pattern, changing pattern or without pattern. Recurring ADR episodes with a specific pattern were described as "*once a month*", *"three times a week",* "*often*" or "*sometimes*". Recurring ADR episodes with a changing pattern could be described as "*less often in the past months*" or "now *a few times a week. It used to be twice a day*". Recurring ADR episodes without pattern were described as "*It happened twice*" or "*irregular, sometimes not for a long time and sometimes a few days in a row*".

Duration of an ADR episode

Patients elaborated on the duration of an ADR episode in seven subthemes: a specific duration, short, long, constant, irregular, increasing or decreasing. Specific durations could be described in detail such as "*1.5 hours*" or less detail such as "*several days*". Short and long duration were described as "*it did not last long*" or "*long-lasting*". In case of a recurring ADR, patients elaborated on the duration of different ADR episodes. The duration of ADR episodes could be constant or irregular. An irregular duration was described as "*Sometimes it lasts a few days, sometimes it lasts two weeks"* or "*It depends from day to day".* The duration of ADR episodes could also decrease or increase, which could be described as "*It starts to last longer, already for 6 days now"* or *"the last time it improved after 1 week instead of 2 weeks".*

Moment or period of ADR occurrence

Patients elaborated on the moments or periods of ADR occurrence in five subthemes: spontaneous, seasonal, moment of the day, around drug administration and irregular. Descriptions of ADRs occurring in a specific season were described as ADRs occurring in winter, in summer or during "*sunny months*". Descriptions of moments of the day included specifications when an ADR episode usually occurs, such as "*only at night*", "*specifically in the morning*" or "*between 6pm and 8pm*". Patients experienced ADR episodes around the moment of drug administration in all three datasets. This included before, during or after administration, sometimes with a specific time relationship. This was described as "*directly after injection*", "*shortly after injection and a few days before injection*", "*1 to 2 hours after taking my pills*" or "*after every pill*".

Development in intensity of ADR

Patients elaborated on development in intensity of ADR in four subthemes: constant, aggravating, improving and variable. Patients described this as "*it is more intense than before*", "*varying intensity from day to day*", *"little change*" or "*gradual improvement*".

Influencing factors

Triggering factors

Patients described various factors that triggered the ADR or were involved in ADR aggravation. These factors were classified in eight subthemes: physical status, mental status, health status, external factors, nutrition, co-medication, the suspected drug and daily activities. Physical status included descriptions of physical activity or inactivity such as "*especially after sitting at a desk for a long time*" or "*after walking up the stairs*". Mental status mostly included stress and was described as "*it is worse in stressful situations*" or "*when I am nervous*". Health status included other diseases, allergies, a weakened immune system or injuries involved in ADR occurrence. This was described as "*it aggravated after having the flu*" or "*little wounds can evoke this*". External factors included weather circumstances such as "*in the sun and with warmer temperatures*". Nutrition as triggering factor included "*often after eating*" or "*food is of influence and plant-based proteins can aggravate it*". ADRs could be triggered by factors related to the suspected drug which included dose adjustments, switch in brand or method of administration, which could be described as "*it occurs more often when I inject in the belly than when I inject in the leg*". Factors related to co-medication included starting, stopping or adjustments in co-medication. Daily activities triggering an ADR could be described as "*carrying heavy bags with groceries*" or "*especially during driving*", social activities as "*gathering with groups of people at birthday parties*" and personal care as "*when combing or washing hair*".

Improving factors

Patients described various factors or actions that improved the ADR. Descriptions of these factors were classified in eight subthemes: physical status, mental status, selfcare, external factors, nutrition, co-medication, the suspected drug and treatment. Patients elaborated on physical status as an improving factor in descriptions such as: "*I started working out three times a week. That helped enormously*". Improvements in mental status which improved or resolved the ADR were often described, such as "*resting and monitoring my energy seems to help*". Examples of selfcare as improving action for ADRs were "*new glasses*" or "*the pain improved since I started wearing insoles*". External factors that improved an ADR were mostly weather or climate related, such as "*healthy air and healthy environment*". Patients described that adjustments in nutrition sometimes improved the ADR, such as "*it improves directly after eating*". Patients described improvements after adjustments in co-medication. ADR improvements were described because of discontinuing or adjusting the dose of the suspected drug but also switching in brand or adjustments in administration method such as "*cooling after injection*". Various treatment options were described to improve the ADR, such as treatment with medication or by a physiotherapist, a dentist, speech therapy or surgery.

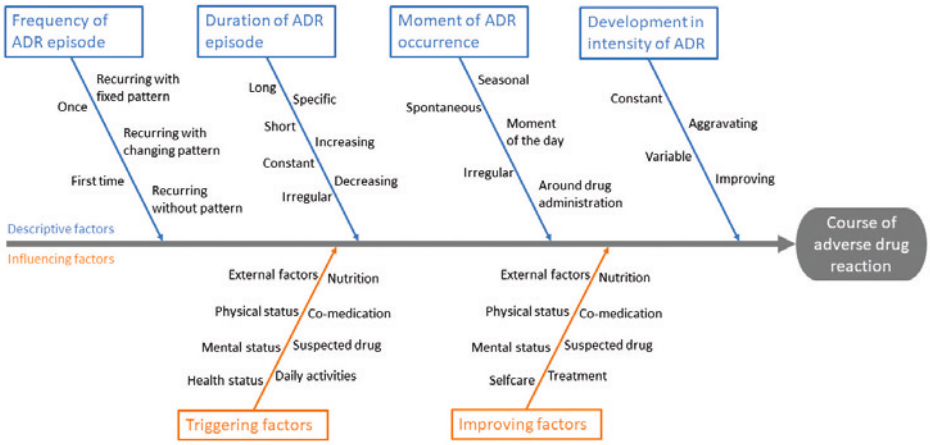

Figure 1. Framework with main themes and subthemes describing the course of ADRs as reported by patients

DISCUSSION

This qualitative study provides insights in the course of ADRs from the patient perspective. We found six themes in patient descriptions of the course of ADRs: the frequency of an ADR episode, the duration of an ADR episode, the moment of ADR occurrence, development in intensity of an ADR, triggering factors for ADR occurrence and improving factors. The identified common themes in the framework provide valuable insights in the type of information from the patient perspective on the development of ADRs in time, frequency and intensity and on factors influencing this development. Overall, the identified themes indicate that patients describe various details about the course of ADRs they experienced.

The identified themes include more extensive details than the available information in the package leaflet and, except for recurrence and a specific moment of occurrence, mostly resemble the previously described patients' needs for customizing ADR information as identified in a scoping review by Kusch et al.: frequency, severity, onset, duration and management and prevention strategies [6]. Patients described the duration and frequency of an ADR episode which indicates that one ADR may resolve and recur over time. Frequency of ADRs usually refers to the incidence of ADR occurrence in the exposed population rather than the frequency of recurring episodes of one type of ADR in one patient thus causing a difference in interpretation in the current study. Fluctuations in intensity are not commonly addressed, neither are specific moments an ADR may occur such as in a specific season or time of the day. However, seasonal variation in spontaneously reporting ADRs has been described before [26]. Temporal associations have also been described in a qualitative analysis of patient reports to the UK yellow card scheme [27]. The descriptions of subthemes influencing the ADR may provide valuable insights in the actions patients take or what patients avoid in order to deal with an ADR. This is potentially valuable information for other patients or healthcare professionals in clinical practice.

The current sources for collecting ADR information include clinical trials and post marketing drug safety surveillance, including spontaneous reporting systems and real world data sources such as registries and electronic health records [28-30]. Although the primary aim of post marketing surveillance is signal detection [11, 12], more information about ADRs can be acquired, especially from patients. Previous studies addressed that details such as impact on daily life can be captured in patient reports [15, 17, 27] and we now also present a framework with themes on the time course of ADRs as identified from patient reports. The themes concerning recurrence of ADR episodes and the moment of occurrence as described by patients in our study are not explicitly covered in the European guideline on SmPCs [7], the PRISMA checklist on reporting harms in systematic reviews [31] or the guideline for submitting adverse event reports for publication [32]. This suggests a discrepancy between patient and clinician or regulator's perspective regarding important aspects of the course of ADRs.

To our knowledge, this is the first study to systematically characterise common themes in the course of ADRs from the patient perspective. The identified themes show new aspects describing the course of ADRs which underlines the potential value of patient-reported data as a source to complement currently available ADR information. The themes could be included in tools for improving systematic collection of patient-reported ADR data in future studies. Consequently, if such data on the course of ADRs are structurally collected, the course of specific ADRs associated with specific drugs can potentially be categorised and defined. The derived information can eventually be provided to patients and healthcare professionals according to their individual needs [5, 6, 8]. In addition, our results indicate new leads to patterns in ADRs, such as specific moments an ADR might occur and factors influencing the ADR. This could be further explored in future research if this data is systematically collected.

Since we used three separately collected datasets including solicited as well as spontaneously reported ADR data, a limitation of this study is that the data was not collected in the same manner and the questionnaire or reporting form may have influenced the provided descriptions of the course of ADRs by patients. However, this is the first study to present common themes in the course of ADRs as described by patients in open-ended text fields and we believe this approach provides insights in elements of ADRs on a broader level than if data had been collected using an identical question, which increases generalisability. Although we characterised the course of ADRs associated with three different therapeutic groups with different dosing schedules and routes of administration and all three datasets contained elements describing the course of ADRs on all six themes, additional themes or subthemes may arise from data concerning other therapeutics such as topical or inhaled medication. This could be confirmed in future research. We also expect that the type of ADR plays a bigger role in the course of an ADR than the suspected drug, its route of administration or the underlying disease and in this study we included a substantial number of different ADRs. However, the generalisability of the presented themes should be investigated in future research to confirm if the presented themes contain universal elements that could be addressed for any ADR.

CONCLUSION

In conclusion, this study identified common themes from patient experiences on the development of ADRs in time. Our results illustrate that patients describe details on the course and timeframe of ADRs that are not easily identified from the healthcare professional's perspective. The presented themes can be used for improving systematic data collection on the course of ADRs from patients in order to potentially categorize the course of specific ADRs in the future. Ultimately, currently available ADR information may be enriched with details on the course of ADRs from the patient perspective.

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SUPPLEMENTARY MATERIAL

- Table 1. All included adverse drug reactions from the Dutch Biologic Monitor in MedDRA® Preferred Term.
- Table 2. All included adverse drug reactions from the direct oral anticoagulant questionnaires in MedDRA® Preferred Term.
- Table 3. All included adverse drug reactions of solifenacine, tamsulosin and dutasteride from spontaneous reports in MedDRA® Preferred Term

Table 1. All included adverse drug reactions from the Dutch Biologic Monitor in MedDRA® Preferred Term.

MedDRA Preferred Term	Number of reported ADRs	Number of serious ADRs[a]
Fatigue	110	1
Injection site pain	90	1
Headache	66	1
Injection site pruritus	58	
Arthralgia	51	
Pruritus	43	
Nasopharyngitis	42	1
Injection site erythema	38	
Injection site inflammation	37	
Injection site haematoma	34	
Nausea	32	
Therapeutic product effect decreased	31	1
Cystitis	27	
Cough	26	
Myalgia	24	1
Pneumonia	22	2
Diarrhoea	22	
Infection susceptibility increased	22	
Alopecia	20	
Eye inflammation	20	
Dizziness	19	
Influenza like illness	19	
Dry skin	18	
Eczema	18	
Haematoma	17	
Pain in extremity	17	
Pyrexia	17	1
Rash pruritic	17	
Dyspnoea	16	

Table 1. Continued

MedDRA Preferred Term	Number of reported ADRs	Number of serious ADRs[a]
Respiratory tract infection	16	1
Erythema	15	
Psoriasis	15	
Oropharyngeal pain	14	1
Herpes zoster	13	
Abdominal pain	13	
Malaise	12	
Rhinorrhoea	12	
Hot flush	12	
Vision blurred	11	
Hypertension	11	2
Palpitations	11	1
Sinusitis	11	
Rash	11	
Hyperhidrosis	10	
Rheumatoid arthritis	10	1
Depressed mood	10	
Oral herpes	9	
Muscle spasms	9	
Blepharitis	9	
Injection site irritation	9	
Impaired healing	9	
Aphthous ulcer	9	
Back pain	8	
Upper respiratory tract infection	8	1
Oedema peripheral	8	
Dermatitis	8	
Inflammation	8	
Abdominal discomfort	8	1
Weight increased	8	
Infection	7	2
Pharyngitis	7	
Injection site swelling	7	
Eye irritation	7	
Skin papilloma	7	
Abdominal pain upper	7	
Insomnia	7	
Photosensitivity reaction	6	

Table 1. Continued

MedDRA Preferred Term	Number of reported ADRs	Number of serious ADRs[a]
Skin infection	6	
Rash pustular	6	1
Gastrointestinal pain	6	
Asthenia	6	
Visual impairment	6	
Poor quality sleep	6	
Joint swelling	6	
Skin disorder	6	1
Lymphadenopathy	6	
Chills	6	
Pain	6	
Dry eye	6	
Musculoskeletal stiffness	6	
Nasal dryness	5	
Rash macular	5	
Paraesthesia	5	
Erysipelas	5	1
Tinnitus	5	
Injection site rash	5	
Dry mouth	5	
Disturbance in attention	5	
Productive cough	5	
Condition aggravated	5	1
Skin exfoliation	5	
Muscular weakness	5	
Vulvovaginal candidiasis	5	
Nasal congestion	5	
Restlessness	4	
Gastroenteritis	4	
Night sweats	4	
Erectile dysfunction	4	
Constipation	4	1
Eye pruritus	4	
Stomatitis	4	
Abdominal distension	4	
Urticaria	4	
Limb discomfort	4	
Pustule	4	

Table 1. Continued

MedDRA Preferred Term	Number of reported ADRs	Number of serious ADRs[a]
Feeling cold	4	
Respiratory tract irritation	4	
Feeling hot	4	
Rhinitis	4	
Musculoskeletal chest pain	4	
Influenza	4	
Fungal skin infection	4	
Arthritis	4	
White blood cell count decreased	3	1
Thirst	3	
Increased tendency to bruise	3	
Neuropathy peripheral	3	
Urinary tract infection	3	
Injection site induration	3	
Secretion discharge	3	
Blood cholesterol increased	3	
Somnolence	3	
Lichen sclerosus	3	1
Tremor	3	
Otitis media	3	
Dermatitis psoriasiform	3	
Infusion related reaction	3	
Chest pain	3	
Glossodynia	3	
Skin atrophy	3	
Paronychia	3	
Skin irritation	3	
Dysphonia	3	
Gait disturbance	3	
Hypersensitivity	3	
Nasal inflammation	3	
Pulpitis dental	3	
Upper respiratory tract congestion	3	
Injection site reaction	3	
Acne	3	
Diplopia	3	
Onychoclasis	3	
Oedema	3	

Table 1. Continued

MedDRA Preferred Term	Number of reported ADRs	Number of serious ADRs[a]
Nail discolouration	2	
Skin fragility	2	
Seasonal allergy	2	
Gingivitis	2	
Inflammation of wound	2	
Injection site haemorrhage	2	
Ear pruritus	2	
Fungal infection	2	
Skin cancer	2	1
Anal candidiasis	2	
Skin swelling	2	
Accommodation disorder	2	
Musculoskeletal pain	2	
Heart rate increased	2	
Nasal discomfort	2	
Onychomycosis	2	
Candida infection	2	
Oral blood blister	2	
Eyelids pruritus	2	
Oral candidiasis	2	
Memory impairment	2	
Oral fungal infection	2	
Muscle disorder	2	
Blood pressure fluctuation	2	
Squamous cell carcinoma	2	1
Herpes dermatitis	2	
Swelling face	2	
Hyperkeratosis	2	
Feeling jittery	2	
Blood triglycerides increased	2	
Chest discomfort	2	
Papule	2	
Vertigo	2	
Confusional state	2	
Injection site discomfort	2	
Furuncle	2	
Lung disorder	2	
Peripheral coldness	2	

Table 1. Continued

MedDRA Preferred Term	Number of reported ADRs	Number of serious ADRs[a]
Seborrhoeic dermatitis	2	
Peripheral swelling	2	
Basal cell carcinoma	2	
Pharyngeal swelling	2	
Dyspnoea exertional	2	
Dysgeusia	2	
Skin fissures	2	
Dyspepsia	2	
Ear infection	2	
Plantar fasciitis	2	
Ear pain	2	
Balance disorder	2	
Costochondritis	2	
Joint stiffness	2	
Staphylococcal infection	2	
Body temperature increased	2	
Sweating fever	2	
Hypoacusis	2	
Tension	2	
Hypoaesthesia	2	
Thyroid disorder	2	
Pyelonephritis	2	
Tooth disorder	2	
Hyposmia	2	
Conjunctivitis	2	
Bursitis	2	
Nasal crusting	2	
Anaemia	2	
Uveitis	2	1
Renal impairment	2	
Gingival bleeding	2	
Respiratory tract infection viral	2	
Vomiting	2	
Listless	2	
Localised infection	2	
Vulvovaginal mycotic infection	2	
Hordeolum	1	
Throat irritation	1	

Table 1. Continued

MedDRA Preferred Term	Number of reported ADRs	Number of serious ADRs[a]
Skin discomfort	1	
Exostosis	1	
Product administration error	1	
Iridocyclitis	1	
Cystitis-like symptom	1	
Weight decreased	1	1
Decreased appetite	1	
Eye allergy	1	
Urinary tract discomfort	1	
Eye disorder	1	
Pulmonary pain	1	
Eye infection bacterial	1	
Respiratory tract congestion	1	
Anal haemorrhage	1	
Sinus pain	1	
Juvenile idiopathic arthritis	1	
Arrhythmia	1	1
Koebner phenomenon	1	
Teeth brittle	1	
Libido decreased	1	
Tooth loss	1	
Dermatitis contact	1	
Bacterial rhinitis	1	
Ligament sprain	1	
Pruritus allergic	1	
Eye pain	1	
Histamine intolerance	1	
Lip dry	1	
Rash vesicular	1	
Coagulopathy	1	
Crohn's disease	1	
Liver function test abnormal	1	
Seborrhoea	1	
Eyelid margin crusting	1	
Skin bacterial infection	1	
Loose tooth	1	
Dacryocystitis	1	
Loss of libido	1	

Table 1. Continued

MedDRA Preferred Term	Number of reported ADRs	Number of serious ADRs[a]
Sneezing	1	
Low density lipoprotein increased	1	
Swelling	1	
Eyelid ptosis	1	
Cervix carcinoma	1	1
Lupus-like syndrome	1	
Enteritis	1	
Eyelid skin dryness	1	
Epicondylitis	1	
Lymphocyte count decreased	1	
Varicose vein	1	
Allergy to arthropod sting	1	
Vulval eczema	1	
Faeces hard	1	
Prostatic abscess	1	
Menopause	1	
Pulmonary embolism	1	1
Menorrhagia	1	
Pustular psoriasis	1	
Mental disorder	1	
Burning sensation	1	
Middle insomnia	1	
Anogenital warts	1	
Vulvovaginal dryness	1	
Respiratory disorder	1	
Vulvovaginal pruritus	1	
Respiratory tract infection fungal	1	
Mood swings	1	
Alcohol intolerance	1	
Mucosal dryness	1	
Rosacea	1	
Muscle discomfort	1	
Cytomegalovirus infection	1	
Anal incontinence	1	
Sjogren's syndrome	1	
Benign hepatic neoplasm	1	1
Ear congestion	1	
Febrile neutropenia	1	

Table 1. Continued

MedDRA Preferred Term	Number of reported ADRs	Number of serious ADRs[a]
Apnoeic attack	1	
Feeling abnormal	1	
Increased upper airway secretion	1	
Musculoskeletal discomfort	1	
Skin wrinkling	1	
Diarrhoea haemorrhagic	1	
Speech disorder	1	
Colitis microscopic	1	
Depressive symptom	1	
Birth mark	1	
Swelling of eyelid	1	
Colon cancer	1	1
Tendonitis	1	
Nail disorder	1	
Therapeutic response unexpected	1	1
Flank pain	1	
Tinea faciei	1	
Flatulence	1	
Tongue ulceration	1	
Folliculitis	1	
Enthesopathy	1	
Food poisoning	1	
Upper respiratory tract inflammation	1	1
Nasal herpes	1	
Asthma	1	
Frequent bowel movements	1	
Dermal cyst	1	
Nasal ulcer	1	
Vocal cord disorder	1	
Diverticulitis	1	
Injection site vesicles	1	
Blister	1	
Hepatic steatosis	1	
Nephrolithiasis	1	1
Dysmenorrhoea	1	
Nervousness	1	
Bone pain	1	
Neuralgia	1	

Table 1. Continued

MedDRA Preferred Term	Number of reported ADRs	Number of serious ADRs[a]
Pulmonary fibrosis	1	
Coordination abnormal	1	
Angular cheilitis	1	
Dizziness postural	1	
Hiccups	1	
Noninfective gingivitis	1	
Breath odour	1	
Ocular discomfort	1	
Rash erythematous	1	
Drug ineffective	1	
Rash papular	1	
Oedema mucosal	1	
Hyperaesthesia	1	
Coronary artery stenosis	1	1
Hyperaesthesia teeth	1	
Gastrointestinal disorder	1	
Respiratory symptom	1	
Chronic sinusitis	1	
Campylobacter infection	1	
Ophthalmic herpes simplex	1	
Anosmia	1	
Gastrointestinal viral infection	1	
Hypermobility syndrome	1	
Gastrooesophageal reflux disease	1	
Rheumatoid lung	1	1
Oral discomfort	1	
Cardiac failure	1	1
Genital infection fungal	1	
Hyperthyroidism	1	
Blood glucose fluctuation	1	
Hypertrichosis	1	
Oral mucosal blistering	1	
Sensitivity to weather change	1	
Oral pain	1	
Cellulitis	1	
Orchitis	1	
Dysuria	1	
Amnesia	1	

Table 1. Continued

MedDRA Preferred Term	Number of reported ADRs	Number of serious ADRs[a]
Skin burning sensation	1	
Osteitis	1	
Skin discolouration	1	
Dry throat	1	
Hypotension	1	
Overweight	1	
Impetigo	1	
Acne pustular	1	
Skin hyperpigmentation	1	
Gout	1	
Ear infection fungal	1	
Pain in jaw	1	
Abnormal dreams	1	
Palmar erythema	1	
Small fibre neuropathy	1	
Palmoplantar pustulosis	1	
Inflammation of lacrimal passage	1	
Body mass index increased	1	
Spontaneous haemorrhage	1	
Pancreatic carcinoma	1	1
Allergic respiratory symptom	1	
Groin pain	1	
Ejaculation failure	1	
Gynaecomastia	1	
Infusion site haematoma	1	
Paraesthesia oral	1	
Taste disorder	1	
Haematochezia	1	
Temperature intolerance	1	
Peau d'orange	1	
Infusion site pain	1	1
Periodontal disease	1	
Therapeutic product effect incomplete	1	
Anal pruritus	1	
Infusion site pustule	1	
Haemoglobin decreased	1	1
Infusion site rash	1	
Petechiae	1	

Table 1. Continued

MedDRA Preferred Term	Number of reported ADRs	Number of serious ADRs[a]
Tinea infection	1	
Pharyngeal cyst	1	
Tongue fungal infection	1	
Hair texture abnormal	1	
Arthropathy	1	
Angioedema	1	
Toothache	1	
Photophobia	1	
Ulcerative keratitis	1	
Dyshidrotic eczema	1	
Injection site hypersensitivity	1	
Plantar erythema	1	
Urethritis noninfective	1	
Heart rate irregular	1	
Epididymitis	1	
Body temperature fluctuation	1	
Atrial fibrillation	1	
Polyarthritis	1	
Vasculitis	1	
Polyneuropathy	1	
Viral infection	1	
Polyuria	1	
Allergy to animal	1	
Poor dental condition	1	
Anal fissure	1	
Hepatic enzyme increased	1	
Exercise tolerance decreased	1	
Post inflammatory pigmentation change	1	
Presyncope	1	
Migraine	1	
Chest wall abscess	1	
Migraine with aura	1	
Irritable bowel syndrome	1	
Wound	1	
Jaw disorder	1	
Joint effusion	1	

a. In the Dutch Biologic Monitor seriousness was only reported as hospitalisation

Table 2. All included adverse drug reactions from the direct oral anticoagulant questionnaires in MedDRA® Preferred Term.

MedDRA Preferred Term	Number of reported ADRs	Number of serious ADRs[a]
Dizziness	96	2
Headache	91	
Fatigue	90	3
Nausea	64	
Diarrhoea	45	
Pruritus	44	
Abdominal pain	41	1
Epistaxis	31	2
Haematoma	26	
Dyspnoea	23	
Dry mouth	18	
Bowel movement irregularity	18	
Heart rate irregular	18	1
Abdominal discomfort	17	
Dyspepsia	17	
Myalgia	16	
Constipation	15	
Insomnia	14	
Sleep disorder	14	
Muscle spasms	13	1
Menorrhagia	12	1
Rash	12	1
Oedema	11	1
Arthralgia	11	1
Abdominal distension	11	
Palpitations	10	
Paraesthesia	10	
Hyperhidrosis	9	
Haematochezia	9	2
Chest discomfort	9	1
Haematuria	9	
Tinnitus	9	
Haemorrhage	9	1
Feeling abnormal	8	
Flatulence	8	
Visual impairment	8	
Hot flush	8	

Table 2. Continued

MedDRA Preferred Term	Number of reported ADRs	Number of serious ADRs[a]
Limb discomfort	7	
Cough	7	
Peripheral coldness	6	
Decreased appetite	6	
Pain in extremity	6	1
Skin haemorrhage	5	
Gingival bleeding	5	
Somnolence	5	
Erythema	5	
Memory impairment	5	
Back pain	4	
Polyuria	4	
Dry skin	4	
Depressed mood	4	
Dysgeusia	4	
Abnormal dreams	4	
Impaired healing	4	1
Retching	3	
Vomiting	3	1
Eructation	3	
Photopsia	3	
Anxiety	3	
Haemoptysis	3	
Skin disorder	3	
Exercise tolerance decreased	3	
Listless	3	
Nervousness	3	
Hypoaesthesia	3	
Rash pruritic	3	
Respiratory disorder	3	
Hypertension	3	
Malaise	2	
Musculoskeletal stiffness	2	
Alopecia	2	
Dry eye	2	
Varicose vein	2	
Hypotension	2	
Faeces discoloured	2	

Table 2. Continued

MedDRA Preferred Term	Number of reported ADRs	Number of serious ADRs[a]
Oral discomfort	2	
Hunger	2	
Haemorrhage subcutaneous	2	
Urine odour abnormal	2	
Increased appetite	2	
Chromaturia	2	
Influenza like illness	2	
Restless legs syndrome	2	
Paraesthesia oral	2	
Rhinorrhoea	2	
Haemorrhoidal haemorrhage	2	
Mouth ulceration	2	
Weight increased	2	
Muscle twitching	2	
Haemorrhoids	2	
Tremor	2	
Joint swelling	2	
Urticaria	2	
Pyrexia	2	
Vision blurred	2	
Head discomfort	2	
Feeling hot	2	
Eye haemorrhage	2	
Yawning	2	
Eye swelling	1	
Confusional state	1	
Asthenopia	1	
Food allergy	1	
Secretion discharge	1	
Gait disturbance	1	
Thyroid pain	1	
Gastrointestinal disorder	1	
Herpes simplex	1	
Mental impairment	1	
Conjunctival haemorrhage	1	
Mood altered	1	
Eye pain	1	
Motion sickness	1	

Table 2. Continued

MedDRA Preferred Term	Number of reported ADRs	Number of serious ADRs[a]
Taste disorder	1	
Gastrointestinal haemorrhage	1	
Asthenia	1	
Muscle disorder	1	
Weight decreased	1	
General physical health deterioration	1	
Psoriasis	1	
Depression	1	
Renal disorder	1	
Muscular weakness	1	
Acne	1	
Gingival pain	1	
Skin discolouration	1	
Abnormal sensation in eye	1	
Inflammation	1	
Nail discolouration	1	
Swollen tongue	1	
Nasal congestion	1	
Therapeutic response unexpected	1	
Nasal discomfort	1	
Cystitis	1	
Nasopharyngitis	1	
Libido decreased	1	
Disturbance in attention	1	
Lip swelling	1	
Bleeding time prolonged	1	
Polymenorrhoea	1	
Night sweats	1	
Erectile dysfunction	1	
Nightmare	1	
Abulia	1	
Blepharospasm	1	
Hypersensitivity	1	
Oesophageal discomfort	1	
Renal impairment	1	
Oesophageal disorder	1	
Eye disorder	1	
Oesophageal pain	1	

Table 2. Continued

MedDRA Preferred Term	Number of reported ADRs	Number of serious ADRs[a]
Eye oedema	1	
Onychoclasis	1	
Sensation of foreign body	1	
Blister	1	
Skin discomfort	1	
Oral herpes	1	
Skin exfoliation	1	
Pain	1	
Skin wound	1	
Body temperature increased	1	
Coordination abnormal	1	
Pallor	1	
Syncope	1	
Anal fissure haemorrhage	1	
Tendon pain	1	
Burning sensation	1	
Thinking abnormal	1	
Anal haemorrhage	1	
Arthropod bite	1	
Ear haemorrhage	1	
Urinary incontinence	1	
Peripheral swelling	1	
Laryngospasm	1	
Petechiae	1	
Vasodilatation	1	
Pharyngeal haemorrhage	1	
Visual field defect	1	
Phlebitis	1	
Flushing	1	
Chest pain	1	
Liver disorder	1	
Platelet count decreased	1	
Intertrigo	1	
Intestinal haemorrhage	1	1

a. In the direct oral anticoagulant questionnaires seriousness was reported following CIOMS criteria [1]

1 CIOMS. Benefit-risk balance for marketed drugs: evaluating safety signals. Geneva: Council for International Organizations of Medical Sciences (CIOMS) Working Group IV; 1998. Available from https://cioms.ch/wp-content/uploads/2017/01/benefit-risk.pdf

Table 3. All included adverse drug reactions of solifenacine, tamsulosin and dutasteride from spontaneous reports in MedDRA® Preferred Term

MedDRA Preferred Term	Number of reported ADRs	Number of serious ADRs[a]
Dizziness	50	2
Therapeutic response unexpected	23	1
Syncope	21	6
Ejaculation failure	21	
Headache	20	1
Vision blurred	20	1
Erectile dysfunction	19	1
Constipation	17	1
Fatigue	17	1
Palpitations	14	1
Nasal congestion	13	
Ejaculation disorder	13	
Nausea	11	
Dry mouth	11	1
Dyspnoea	10	1
Pruritus	10	
Visual impairment	10	1
Epistaxis	8	
Depressed mood	7	1
Diarrhoea	7	
Libido decreased	7	
Abdominal pain upper	6	
Heart rate increased	6	
Asthenia	6	
Arthralgia	6	1
Rhinorrhoea	6	
Malaise	6	
Atrial fibrillation	6	2
Balance disorder	6	2
Somnolence	5	
Testicular pain	5	
Insomnia	5	
Rhinitis	5	
Rash	5	
Myalgia	5	1
Gynaecomastia	5	
Eye irritation	5	

Table 3. Continued

MedDRA Preferred Term	Number of reported ADRs	Number of serious ADRs[a]
Tinnitus	4	
Pollakiuria	4	
Retrograde ejaculation	4	
Dizziness postural	4	
Dyspepsia	4	
Dry eye	4	
Blood pressure decreased	4	1
Cough	4	1
Dysgeusia	4	
Abdominal discomfort	4	
Rash papular	3	1
Memory impairment	3	
Alopecia	3	
Abdominal pain	3	
Orthostatic hypotension	3	
Abdominal distension	3	
Hypersensitivity	3	2
Dysuria	3	
Tachycardia	3	1
Back pain	3	
Urticaria	3	
Feeling abnormal	3	
Presyncope	3	
Flatulence	3	
Rash pruritic	3	
Haematoma	3	
Hypotension	3	
Feeling cold	2	
Pyrexia	2	1
Penile swelling	2	
Abdominal pain lower	2	
Condition aggravated	2	
Dysphonia	2	
Blood glucose increased	2	
Heart rate irregular	2	
Fall	2	
Drug ineffective	2	
Anxiety	2	1

Table 3. Continued

MedDRA Preferred Term	Number of reported ADRs	Number of serious ADRs[a]
Hypogeusia	2	
Skin odour abnormal	2	
Arrhythmia	2	
Oral pain	2	
Dry throat	2	
Cataract	2	1
Loss of libido	2	
Polyuria	2	
Blood glucose decreased	2	1
Prostate cancer	2	2
Urinary retention	2	1
Ageusia	2	
Eructation	2	
Renal pain	2	
Nasal dryness	2	
Confusional state	2	1
Nervousness	2	1
Swelling	2	
Nipple pain	2	
Oedema peripheral	2	1
Testicular swelling	2	
Listless	2	
Tremor	2	
Parosmia	1	
Slow response to stimuli	1	
Chills	1	
Blood pressure systolic decreased	1	
Defaecation disorder	1	
Ejaculation delayed	1	
Aphonia	1	
Hirsutism	1	
Salivary hypersecretion	1	
Hyperhidrosis	1	
Blood pressure fluctuation	1	
Azoospermia	1	
Painful ejaculation	1	
Hypertension	1	
Penis disorder	1	

Table 3. Continued

MedDRA Preferred Term	Number of reported ADRs	Number of serious ADRs[a]
Hypertrichosis	1	
Anal incontinence	1	
Hyperventilation	1	
Restlessness	1	
Dry skin	1	
Sjogren's syndrome	1	1
Abnormal dreams	1	
Stomatitis	1	
Hypothyroidism	1	
Hallucination	1	
Immune thrombocytopenia	1	1
Pain	1	
Impaired gastric emptying	1	
Dysphagia	1	
Weight decreased	1	
Penile haemorrhage	1	
Increased upper airway secretion	1	
Pharyngeal swelling	1	
Inflammation	1	
Feeling jittery	1	
Bradycardia	1	
Chest pain	1	
Intraocular pressure increased	1	
Gastrooesophageal reflux disease	1	
Iris disorder	1	1
Gingival pain	1	
Irritability	1	
Sexual dysfunction	1	
Breast neoplasm	1	1
Skin exfoliation	1	
Disability	1	
Spermatozoa abnormal	1	
Loss of consciousness	1	1
Suspiciousness	1	
Anosmia	1	
Tachycardia paroxysmal	1	
Lymphadenopathy	1	
Dandruff	1	

Table 3. Continued

MedDRA Preferred Term	Number of reported ADRs	Number of serious ADRs[a]
Macular hole	1	
Tongue disorder	1	
Breast pain	1	
Pain in jaw	1	
Male orgasmic disorder	1	
Palatal swelling	1	
Erythema	1	
Paraesthesia	1	
Micturition urgency	1	
Penile discharge	1	
Toothache	1	
Device dislocation	1	
Urethral pain	1	
Peripheral swelling	1	
External ear disorder	1	
Chest discomfort	1	
Extrasystoles	1	
Posterior capsule opacification	1	
Altered state of consciousness	1	1
Procedural complication	1	1
Depression	1	
Prostatitis	1	
Vomiting projectile	1	
Floppy iris syndrome	1	
Breast tenderness	1	
Gastrointestinal pain	1	
Burning sensation	1	
Gingival bleeding	1	
Nasal discomfort	1	
Chromaturia	1	
Eye disorder	1	
Glaucoma	1	
Nasal mucosal disorder	1	
Sebaceous glands overactivity	1	
Nasal obstruction	1	
Sinus disorder	1	
Carpal tunnel syndrome	1	
Skin disorder	1	

Table 3. Continued

MedDRA Preferred Term	Number of reported ADRs	Number of serious ADRs[a]
Eye inflammation	1	
Glossitis	1	
Dyskinesia	1	
Aggression	1	1
Nocturia	1	
Spontaneous penile erection	1	
Ocular hyperaemia	1	
Suicidal ideation	1	
Oedema mucosal	1	
Glossodynia	1	
Eye pruritus	1	
Ear disorder	1	
Oligospermia	1	
Cystitis	1	
Oral discomfort	1	
Testis discomfort	1	
Oral mucosal blistering	1	
Throat irritation	1	
Facial pain	1	
Tongue discomfort	1	
Oropharyngeal pain	1	
Blood pressure increased	1	
Dermatitis bullous	1	
Migraine	1	
Urinary incontinence	1	
Miosis	1	
Urine odour abnormal	1	
Muscle contractions involuntary	1	
Vertigo	1	
Muscle fatigue	1	
Visual acuity reduced	1	
Muscle injury	1	
Vomiting	1	
Muscle spasms	1	
Derealisation	1	
Muscular weakness	1	
Incontinence	1	

a. In spontaneous reports seriousness was reported following CIOMS criteria [1]

Chapter 4

New adverse drug reactions

Chapter 4.1

Gastrointestinal adverse drug reaction profile of etanercept: real-world data from patients and healthcare professionals

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ABSTRACT

Objective: We aimed to describe the nature and frequency of gastrointestinal adverse drug reactions (GI-ADRs) of etanercept (ETN) using patient-reported and healthcare professional (HCP)-registered data and compared this frequency with the GI-ADR frequency of the widely used TNFα-inhibitor adalimumab (ADA).

Methods: Reported GI-ADRs of ETN for rheumatic diseases were collected from the Dutch Biologic Monitor and DREAM registries. We described the clinical course of GI-ADRs and compared the frequency with ADA in both data sources using a Fisher's exact test.

Results: Out of 416 patients using ETN for inflammatory rheumatic diseases in the Dutch Biologic Monitor, 25 patients (6%) reported 36 GI-ADRs. In the DREAM registries 11 GI-ADRs were registered for 9 patients (2.3%), out of 399 patients using ETN, with an incidence of 7.1 per 1000 patient years. Most GI-ADRs consisted of diarrhoea, nausea and abdominal pain. GI-ADRs led to ETN discontinuation in one patient (4%) and dose adjustment in four (16%) in the Dutch Biologic Monitor. Eight GI-ADRs (73%) led to ETN discontinuation in the DREAM registries. The frequency of GI-ADRs of ETN did not significantly differ from GI-ADRs of ADA in both data sources (Dutch Biologic Monitor: ETN 8.7% vs. ADA 5.3%, p=0.07; DREAM: ETN 2.8% vs. ADA 4.7%, p=0.16).

Conclusion: Most GI-ADRs associated with ETN concerned gastrointestinal symptoms. These ADRs may lead to dose adjustment or ETN discontinuation. The frequency of ETN associated GI-ADRs was comparable to the frequency of ADA associated GI-ADRs. Knowledge about these previously unknown ADRs can facilitate early recognition and improve patient communication.

INTRODUCTION

Etanercept (ETN) is a widely used biologic DMARD (bDMARD) for the treatment of various inflammatory rheumatic diseases such as rheumatoid arthritis and spondyloarthritis. The most common adverse drug reactions (ADRs) associated with ETN use are infections and injection site reactions (1, 2). While various gastrointestinal (GI-)ADRs such as nausea and abdominal pain are described in the European product label of other TNF-α inhibitors, such as adalimumab (ADA) and infliximab (IFX) (3, 4), these ADRS have seldom been described for ETN. Abdominal pain and nausea have been described as reason for ETN discontinuation in two children with juvenile idiopathic arthritis (5). Additionally, inflammatory bowel disease (IBD) has been demonstrated in patients with gastrointestinal complaints, such as diarrhoea or abdominal pain, while using ETN for an inflammatory rheumatic disease, mostly juvenile idiopathic arthritis (6-12).

Real world data provide a useful source of information for drug safety studies in post-marketing surveillance. Both the healthcare professional's (HCPs) and patient's perspective should be taken into account when assessing ADR reports because they may approach and experience the effects of ADRs differently (13, 14). In the Netherlands, patient-reported ADRs experienced with biologics are systematically collected in the Dutch Biologic Monitor, a multicentre web-based cohort event monitoring system. The Dutch Biologic Monitor was introduced by the Netherlands Pharmacovigilance Centre Lareb for collecting patient-reported information about ADRs that patients experience with biologics used for an immune-mediated inflammatory disease (13, 15). HCP-registered ADRs of biologics are also captured in the Dutch Rheumatoid Arthritis Monitoring (DREAM-RA) registry and the Dutch Registry for Spondyloarthritis (SpA-Net). The DREAM-RA and SpA-Net registries collect real-world data in participating hospitals on quality of care, including both clinical aspects and patient-reported outcomes, with the aim to monitor and evaluate safety and effectiveness of rheumatic treatment in daily clinical practice (16-18). All clinically verified ADRs that are captured in these registries are directly forwarded to Lareb (19).

Because little is known about the frequency and characteristics of GI-ADRs with ETN treatment, we aimed to describe the profile of GI-ADRs associated with ETN using the systematically collected patient-reported data from the Dutch Biologic Monitor and the HCP-registered and clinically verified data from the DREAM-RA and SpA-Net registries. Since ADA is the other most frequently used TNF-α inhibitor in the Netherlands, additionally, we also aimed to get an impression of the extent to which GI-ADRs occur with the use of ETN compared to those occurring with ADA in inflammatory rheumatic diseases.

METHODS

Study design

This observational study describes GI-ADRs from two data sources: GI-ADRs experienced with ETN by patients in the Dutch Biologic Monitor and HCP-registered and clinically verified GI-ADRs registered for ETN in the DREAM-RA and SpA-Net registries.

Dutch Biologic Monitor

The Dutch Biologic Monitor is a prospective cohort event monitoring system for patient-reported ADRs that they experienced with the use of biologics (13, 15). Nine Dutch hospitals participated in the Dutch Biologic Monitor between 1 January 2017 and 1 March 2020. Patients using one of the monitored biologics were consecutively invited to participate by HCPs of the respective hospitals. Patients were eligible for participation from eighteen years or older. Patients that had started using the biologic before they started participating in the Dutch Biologic Monitor were also eligible for participation.

Participating patients were asked to complete comprehensive web-based baseline questionnaires (https://www.mijnbiologischmedicijn.nl). The questionnaires included demographic information (gender, date of birth, weight, height, smoking), the biologic used, starting date, indication(s) for biologic therapy, combination therapy, comorbidities and ADRs experienced with biologics. Information on ADRs patients experienced with the used biologic included the type of ADR, start and stop date, course, burden using a five-point Likert-type scale ranging from 1 (no burden) to 5 (very high burden), contact about ADR with an HCP, the type of HCP, treatment or other actions taken by the HCP and own action taken by the patient following the ADR. Subsequent questionnaires after baseline focused exclusively on drug use (biologic and combination therapy) and follow-up of ADRs or new ADRs and included identical questions on these topics. Questionnaires were sent out bimonthly and patients received a reminder by e-mail if they had not completed the questionnaire within 7-14 days. Questionnaires expired after 21 days and no more questionnaires were sent after expiration. Questionnaires were sent out until patients stopped participating. Patients could withdraw from participation at any time. All participants received information about the study prior to participation and signed a digital informed consent form. The Dutch Biologic Monitor received a waiver for the Dutch Medical Research Involving Human Subjects Act (WMO) by the Medical Research Ethical Committee of Brabant (file number: NW2016-66). The Dutch Biologic Monitor was approved by the medical ethics committees of the participating hospitals.

DREAM registries

DREAM is a network of Dutch hospitals aiming to stimulate quality of care, efficient use of means and clinical research (19). The initiative started in 2003 with the DREAM-RA registry, a registry for monitoring all rheumatoid arthritis patients that started treatment with biologic DMARDs. The registry expanded from 2006 onwards with cohorts of early rheumatoid arthritis patients treated according to treat-to-target strategies (20-22). The SpA-Net registry started in

2016 with the systematic monitoring of patients with axial and/or peripheral SpA (17). SpA-Net is incorporated within the DREAM collaboration and both DREAM-RA and SpA-Net use a shared web-based data acquisition system (https://www.mijnreumacentrum.nl) to collect, store and use both HCP-reported clinical data and patient-reported outcomes. Upon patient inclusion in the registries, ADR history is registered retrospectively by the HCPs and new ADRs can be reported continuously by both HCPs and patients themselves. All patient-reported ADRs are systematically verified and scored by the respective HCP. All verified ADR reports in the DREAM-RA registry and all ADR reports leading to drug discontinuation in the SpA-Net registry are automatically forwarded to the Netherlands Pharmacovigilance Centre Lareb, beginning in December 2015. In addition, all ADRs that had been registered between 2003 and 2015 were retrospectively forwarded to Lareb (18). All patients had given written consent before inclusion in the registries, which included data assessments by Lareb. In the DREAM registries, no additional data, other than data collection in routine clinical practice, are collected. Therefore ethical approval was not required according to Dutch regulations.

The reports Lareb received from the registries include action taken with the drug following the ADR (dose adjustment, dose not changed or discontinuation) and the outcome of the ADR (recovered, recovered with sequel, recovering or not recovered). Seriousness of GI-ADRs in the registry reports was determined according to the Council for International Organizations of Medical Sciences (CIOMS) criteria (23). The criteria for serious reports are ADRs resulting in death, life threatening situations, (prolonged) hospitalization, persistent or significant disability or a congenital anomaly.

Data selection

All ADRs from both data sources were coded according to the Medical Dictionary for Regulatory Activities (MedDRA®) terminology by trained pharmacovigilance assessors (24). GI-ADRs were defined by MedDRA® System Organ Class 'Gastrointestinal disorders', excluding MedDRA® High Level Group Term 'Dental and gingival disorders'. All reported ADRs were explicitly attributed to the biologic by patients in the Dutch Biologic Monitor and by HCPs in the DREAM registries. Therefore, all reported GI-ADRs that were attributed to ETN used for inflammatory rheumatic diseases were selected. ADRs were selected at the MedDRA® Preferred Term (PT) level, which is the most distinctive descriptor within each System Organ Class. Patient-reported data was collected from the Dutch Biologic Monitor from 1 January 2017 until 1 March 2020. All DREAM-RA data forwarded to Lareb from patients from the rheumatology department of Medisch Spectrum Twente (Enschede, Netherlands) that participated from the onset in the DREAM-RA registry was used for analysis in the current study. For SpA-Net, all data from the rheumatology departments of both Medisch Spectrum Twente and Maastricht University Medical Center were used. The first registered GI-ADR with ETN in the DREAM registries occurred on 22 June 2004 and therefore, data from the DREAM-RA and SpA-Net registry collected from 22 June 2004 until 1 January 2020 were used.

Data analysis

Data from the Dutch Biologic Monitor (patient-reported) and DREAM registries (HCP-registered) were separately analysed and could not be compared due to differences in method, frequency of ADR assessment and registration of ADR details such as actions following the ADR. We calculated the incidence of GI-ADRs associated with ETN use in the registries as the number of reported GI-ADRs per total number of patient-years (PY) of ETN use in patients for whom start and stop dates of ETN were available. PY were calculated from the start date of ETN use until the start date of the GI-ADR or until 1 January 2020 in case no GI-ADR was reported. The incidence could not be calculated with Dutch Biologic Monitor data since we did not monitor all patients from start of ETN use.

Patient-reported GI-ADRs in the Dutch Biologic Monitor

We investigated the following GI-ADR characteristics using descriptive statistics for data from the Dutch Biologic Monitor: outcome of the ADR, action following the ADR, hospitalisation following the ADR, the reported ADR burden and Naranjo Probability Scale (25). The Naranjo Probability Scale is a quantitative tool for estimating the probability of an ADR and the likelihood that it is caused by the drug. The scale ranges from 0 (doubtful) to 10 (definite). We included the outcome of the ADR in the last completed questionnaire in the Dutch Biologic Monitor.

HCP registered GI-ADRs in the DREAM registries

We investigated the following characteristics using descriptive statistics for GI-ADRs in the DREAM registries: outcome of the ADR, action with ETN following the ADR, seriousness according to CIOMS criteria and Naranjo Probability Scale.

Frequency of GI-ADRs associated with ETN and ADA

The frequency of GI-ADRs associated with ETN was defined as the total number of unique GI-ADRs per total number of patients using ETN for inflammatory rheumatic diseases. Long term or recurring ADRs with the same MedDRA® PT reported for the same patient were counted once. The frequency of GI-ADRs reported for ETN was compared with the frequency of GI-ADRs reported for ADA used for inflammatory rheumatic diseases using a Fisher's exact test. We did not adjust for potential confounders since ADRs were explicitly attributed to the biologic by the patients. We compared GI-ADR frequency between ETN and ADA in patient reports from the Dutch Biologic Monitor and we compared GI-ADR frequency between ETN and ADA in HCP reports from the DREAM registries. Regarding the DREAM registries, we additionally compared the incidence of GI-ADRs per total number of PY between etanercept and ADA using a Chi-squared test. Statistical analysis was performed in IBM SPSS Statistics 22.

RESULTS

The Dutch Biologic Monitor included 416 patients using ETN for inflammatory rheumatic diseases and a total of 25 patients (6%) reported 36 GI-ADRs (Table 1). The DREAM registries included 399 patients using ETN for inflammatory rheumatic diseases, with 11 HCP-registered GI-ADRs in 9 patients (2.3%), with an incidence of 7.1 per 1000 PY. No GI-ADRs of etanercept concerning the same patient were reported in both the DREAM registries and the Dutch Biologic Monitor.

Table 1. Demographics and clinical characteristics of patients with GI-ADRs associated with etanercept for inflammatory rheumatic diseases in the Dutch Biologic Monitor and DREAM registries.

	Patients with GI-ADR in Dutch Biologic Monitor	**Patients with GI-ADR in DREAM registries**
Patients, n	25	9
Age, years, mean ± SD	57 ± 13	59 ± 8
Female sex	22 (88%)	7 (78%)
Indication		
Rheumatoid arthritis	19 (76%)	9 (100%)
Axial spondyloarthritis	3 (12%)	0
Psoriatic arthritis	6 (24%)	0
Combination therapy	18 (72%)	5 (56%)
Methotrexate	12 (48%)	2 (22%)
Corticosteroids[a]	1 (4%)	2 (22%)
Sulfasalazine	2 (8%)	2 (22%)
Hydroxychloroquine	3 (12%)	0
Leflunomide	1 (4%)	0

Values are expressed as n (%) unless otherwise indicated. [a] Dutch Biologic Monitor: prednisolone (1); DREAM Registries: prednisolone (1), triamcinolonacetonide used once (1). GI-ADR: Gastrointestinal adverse drug reaction, DREAM: Dutch Rheumatoid Arthritis Monitoring.

Patient-reported GI-ADRs in the Dutch Biologic Monitor

Most patient-reported GI-ADRs in the Dutch Biologic Monitor were gastrointestinal symptoms (Table 2). Diarrhoea, nausea and gastrointestinal or abdominal pain were the most frequently reported GI-ADRs. One patient reported Crohn's disease (CD) as ADR. In total, 10 reported GI-ADRs (28%) developed within one month after start with ETN. A pattern of recurring GI-ADRs after every ETN administration was described by 9 patients (36%) for 11 ADRs (31%), including 3 reports of nausea, 3 reports of diarrhoea and 5 reports of abdominal pain or discomfort. These ADRs developed within 1-3 days after each administration and patients recovered within several days. The Naranjo Probability Scale was probable in 2 GI-ADRs and possible in 34 GI-ADRs (Table 3). The probable ADRs were stomatitis and GI pain.

Table 2. The Medical Dictionary for Regulatory Activities (MedDRA) terminology Preferred Term (PT) of GI-ADRs associated with etanercept by patients (Dutch Biologic Monitor) and registered by healthcare professionals (DREAM registries) .

MedDRA PTs in Dutch Biologic Monitor (36 GI-ADRs)	MedDRA PTs in DREAM registries (11 GI-ADRs)
Nausea: 6	Diarrhoea: 5
Diarrhoea: 5	Nausea: 2
Gastrointestinal pain: 3	Abdominal pain: 1
Abdominal discomfort: 2	Abdominal discomfort: 1
Abdominal distension: 2	Constipation: 1
Abdominal pain upper: 2	Rectal spasm: 1
Aphthous ulcer: 2	
Dry mouth: 2	
Abdominal pain: 1	
Constipation: 1	
Anal pruritus: 1	
Flatulence: 1	
Crohn's disease: 1	
Enteritis: 1	
Angina bullosa haemorrhagica: 1	
Anal haemorrhage: 1	
Stomatitis: 1	
Glossodynia: 1	
Breath odor: 1	
Oral pain: 1	

GI-ADR: gastrointestinal adverse drug reaction. DREAM: Dutch Rheumatoid Arthritis Monitoring

Table 3. Profile of patient-reported GI-ADRs associated with etanercept in the Dutch Biologic Monitor

	GI-ADRs in the Dutch Biologic Monitor (36 ADRs)
Burden score[a] , mean ± SD	2.6 ± 0.8
No. of ADRs with contact HCP[b]	24 (67%)
Medical specialist	15 (63%)
General practitioner	14 (58%)
Nurse	7 (29%)
Pharmacist	2 (8%)
Other HCP[c]	6 (25%)
No. of ADRs with action by HCP	
Discontinuation	1 (4%)
Dose adjustment	4 (17%)
Treatment	8 (33%)
Referral to other HCP	7 (30%)

Table 3. Continued

	GI-ADRs in the Dutch Biologic Monitor (36 ADRs)
Mentioned, no action	11 (46%)
Other action[d]	3 (13%)
No. of ADRs with own action	23 (64%)
No. of ADRs with outcome	
Recovered	12 (33%)
Improving	8 (22%)
Not recovered	15 (42%)
Aggravating	1 (3%)
No. of ADRs leading to hospitalization[e]	2 (6%)
Naranjo Probability Scale	
Definite	0
Probable	2 (6%)
Possible	34 (94%)
Doubtful	0

Values are expressed as n (%) unless otherwise indicated. [a] 5-point Likert type scale. [b] Patients could report more than one HCP. [c] Contact with other HCPs: dental HCPs (dental hygienist or dentist): 5, nutritionist: 1. [d] Other actions: examination: 2, adjusted moment of administration: 1. [e] The 2 ADRs leading to hospitalisation were described by 1 patient. GI-ADR: gastrointestinal adverse drug reaction, HCP: healthcare professional

Actions following GI-ADRs

Hospitalisation was described by 1 patient following a combination of 2 included GI-ADRs: oral pain and breath odour. This patient also reported tooth disorder. No further information about hospitalisation was described and the exact cause of hospitalisation remains unclear. Patients in the Dutch Biologic Monitor contacted an HCP for 24 ADRs (67%), which was a medical specialist for 15 of these ADRs (63%, Table 3). HCP contact for ADRs included abdominal pains (n=5), diarrhoea (n=4), nausea (n=3) and oral issues (n=3).

Drug discontinuation

ETN discontinuation was reported by 1 patient that switched to ADA due to upper abdominal pain. The symptoms disappeared after switch. Prior to using ETN, this patient had used certolizumab pegol without experiencing GI-ADRs. Another patient with upper abdominal pain mentioned that ETN will be withdrawn in the future because of a combination of aggravating abdominal pain (a reported ADR) and aggravating rheumatic complaints (no ADR).

Dose adjustment

ETN dose adjustment was reported for 4 GI-ADRs by four patients: 2 reports of gastrointestinal pain, 1 of stomatitis and 1 of nausea. The ETN administration frequency was adjusted in 2 patients reporting gastrointestinal pain, which was effective for 1 patient. The patient for whom the adjusted frequency was not effective, was eventually referred to a gastroenterol-

ogist. The patient reporting stomatitis recovered after temporary withdrawal and treatment with unknown antibiotics. Stomatitis recurred after 2 years, and the patient recovered after 3 weeks following diet adjustments and improved oral hygiene. The patient with nausea recovered after adjusting the time of administration to the evening.

Treatment of GI-ADRs

Treatment of the ADR was reported for 8 GI-ADRs by 5 patients. A patient with gastrointestinal pain resulting in vomiting described effective treatment with metoclopramide and dose reduction of concomitant sulfasalazine (SSZ). A patient with diarrhoea described effective treatment with psyllium fibres. A patient with constipation and abdominal pain described effective treatment with laxatives and diet adjustments. A patient with rectal bleeding described improvement after using haemorrhoid ointment. A patient with breath odor, oral pain, and chest pain received dental treatment and was also effectively treated with pantoprazole since the general practitioner of this patient suspected an esophageal issue for the symptom of breath odor combined with chest pain.

Other information in patient reports

A total of 15 (60%) patients described that they acted on their own initiative following 23 GI-ADRs (64%). These actions varied from adjusting diet or improving dental care to altering injection time, changing injection site and trying different over-the-counter drugs.

A patient reporting nausea after every ETN and methotrexate (MTX) administration described improvement after MTX dose reduction, adjusting the order of administration and food intake in between administrating both drugs. Three patients described that they switched to another biologic during participation for other reasons than a GI-ADR. One of these patients recovered from nausea after switching to unknown therapy and a patient with oral blood blisters improved from this ADR after switching to rituximab. Another patient described improvement in diarrhoea after skipping an ETN dose for other reasons.

The patient reporting CD also reported oral aphthous ulcers as an ADR and mentions this was probably related to CD. CD was diagnosed 3 years after start with ETN. The patient switched to IFX and recovered from oral aphthous ulcers. CD improved after switch but the patient was not in full remission 1 year after switch.

Burden of GI-ADRs

The mean burden score of all 36 GI-ADRs was 2.6 (± SD 0.8) on a scale from 1 (no burden) to 5 (very high burden). Patients elucidated this GI-ADR burden score with various explanations, including affecting the mood and leading to insecurity, anxiety or a feeling of loss of control. Patients also described that GI-ADRs resulted in sleep disturbance or influenced daily life and lead to avoiding leaving the house.

HCP-registered GI-ADRs in the DREAM registries

Most GI-ADRs in the registries were general gastrointestinal symptoms, similar to the patient-reported GI-ADRs (Table 2). Out of 11 GI-ADRs, 5 GI-ADRs (45%) developed within 5 months after start. ETN was discontinued for 8 GI-ADRs in 6 patients (Table 4): diarrhoea (5 ADRs), nausea, constipation and abdominal pain. Patients recovered from the GI-ADR in 10 cases, including the GI-ADRs leading to ETN discontinuation. Three of these patients did not use combination therapy. The outcome of 1 ADR concerning rectal cramps, is unknown. Recurrence of nausea and diarrhoea was reported for 1 patient when ETN was later restarted. This patient used MTX concomitantly. In addition to ETN, MTX was also suspected to cause nausea in 1 patient. In 3 cases of diarrhoea the patient had experienced diarrhoea prior to ETN use with SSZ or with leflunomide (LEF). A patient with abdominal pain had collagenous colitis with variable activity which had been diagnosed before ETN was started. This patient later also experienced abdominal pain during use of LEF. It is unknown if the abdominal pain during ETN use was related to collagenous colitis.

The Naranjo Probability Scale was probable in 2 GI-ADRs and possible in 9 GI-ADRs. The probable ADRs were nausea and diarrhoea which recurred after rechallenge with ETN.

Table 4. Profile of HCP-reported GI-ADRs associated with etanercept

	GI-ADRs in DREAM registries (11 ADRs)
No. of ADRs with action taken	
Discontinuation	8 (73%)
Dose reduced	0
Dose not changed	3 (27%)
No. of ADRs with outcome	
Recovered	10 (91%)
Recovered with sequel	0
Recovering	0
Not recovered	0
Unknown	1 (9%)
No. of serious ADRs	0
Naranjo Probability Scale	
Definite	0
Probable	2 (18%)
Possible	9 (82%)
Doubtful	0

Values are expressed as n (%). ADR: adverse drug reaction; GI-ADR: gastrointestinal ADR; DREAM: Dutch Rheumatoid Arthritis Monitoring; HCP: healthcare professional.

Frequency of reported GI-ADRs associated with ETN and ADA

Patients reported GI-ADRs of ETN in the Dutch Biologic Monitor with a frequency of 8.7% and they reported GI-ADRs of ADA with a frequency of 5.3% (Table 5). The frequency of GI-ADRs associated with ETN in the DREAM registries was 2.8% and the frequency of GI-ADRs associated with ADA was 4.7%. The difference in frequency of GI-ADRs between ETN and ADA was not statistically significant in the Dutch Biologic Monitor (p=0.07) nor in the DREAM registries (p=0.16). The incidence of GI-ADRs attributed to ADA in the DREAM registries was 14.0 ADRs per 1000 PY. This was not statistically significantly different from 7.1 GI-ADRs per 1000 PY attributed to ETN (p = 0.09). One GI-ADR of ADA concerning the same patient was reported in both the DREAM registry as well as the Dutch Biologic Monitor.

Table 5. Frequency of patient-reported (Dutch Biologic Monitor) and HCP-reported (DREAM registries) GI-ADRs associated with ETN and ADA for inflammatory rheumatic diseases.

Patients	ETN	ADA	p
Dutch Biologic Monitor (n = 757 unique patients)	n = 416	n = 360	
	8.7% (36/416)	5.3% (19/360)	0.07
DREAM Registries (n = 724 unique patients)	n = 399	n = 486	
	2.8% (11/399)	4.7% (23/486)	0.16

ADA: adalimumab; DREAM: Dutch Rheumatoid Arthritis Monitoring; ETN: etanercept; GI-ADR: gastrointestinal adverse drug reactions; HCP: healthcare professional.

DISCUSSION

In this study we describe previously unknown gastrointestinal ADRs of ETN treatment for inflammatory rheumatic diseases. Both patient and HCP reports mostly concerned gastrointestinal symptoms such as diarrhoea, nausea and abdominal pain. Many reported GI-ADRs lead to ETN dose adjustment or discontinuation, HCP contact and treatment of the ADR.

We compared GI-ADR occurrence of ETN with ADA since both TNF-α inhibitors are widely used in the Netherlands and GI-ADRs are included in the European product label of ADA but not in that of etanercept (2, 4). This comparison provides an impression of the extent to which GI-ADRs were attributed to both TNF-α inhibitors and we found a similar frequency of GI-ADRs reported for ETN and ADA in both patient reports and HCP reports. This is remarkable since GI-ADRs had previously not been described in adults using ETN, except for several cases of IBD (6, 7, 26, 27). The high frequency of patient-reported GI-ADRs (8.7%) in relation to the frequency of HCP-reported GI-ADRs (2.8%) of ETN is also surprising because we did not observe a similar discordance with ADA. However, we could not directly compare data from the Dutch Biologic

Monitor with data from the DREAM registries due to differences in design. Since GI-ADRs are included in the European product label of ADA and are not included in the European product label of ETN, HCPs may recognise GI-ADRs more regularly with ADA treatment than with ETN treatment and therefore HCPs might not always attribute GI complaints to ETN.

The mechanism by which ETN may cause GI-ADRs remains unknown. ETN has been demonstrated to modify gut microbial communities, which could be involved in causing GI symptoms, even though these alterations in gut microbiota were beneficial for RA-associated gut dysbiosis (28). Some gastrointestinal complaints could also be symptoms of an infection. One patient reported CD which improved after switch to IFX. Even though the exact mechanism is uncertain, ETN may unmask underlying IBD in predisposed patients or induce IBD by increased inflammatory cytokine production (7, 27, 29). IBD as a possible ADR of ADA or IFX has also been suggested, but an increased risk has not been demonstrated in literature while an increased risk of IBD has been described for ETN (30, 31).

Despite a causality assessment of all GI-ADR reports, a limitation of this study is that we cannot confirm a causal relationship between ETN and the reported GI-ADRs. Although the included GI-ADRs were actively registered and verified by HCPs or were explicitly attributed as an ADR of ETN by patients, concomitant medication, an underlying infection or the underlying disease could have affected the reported complaints (32, 33). Twelve out of 26 patients (46%) in the Dutch Biologic Monitor and two out of nine patients (22%) in the DREAM registries used methotrexate as combination therapy, for which GI-ADRs are common (34). One patient described that the GI-ADR improved after dose reduction of methotrexate, which suggests a role of methotrexate in the occurrence of the GI-ADR in this specific case. In another reported GI-ADR, methotrexate was also suspected to cause the ADR in addition to ETN. However, 28% of the patients with GI-ADRs in the Dutch Biologic Monitor and 44% of the patients with GI-ADRs in the DREAM registries did not use combination therapy. Half of these patients in the DREAM registries recovered after ETN discontinuation which indicates a relationship between the use of ETN and the incurred GI complaints. Additionally, we found a probable or possible association for all GI-ADR reports of ETN using the Naranjo Probability Scale.

The results of this study contribute to unmasking the ADR profile of ETN by using real-world data, which included both patient-reported and clinically verified HCP-registered data. Including patient-reported data is a strength because the assessment of questionnaires with patient-reported data contributes to a better understanding of the patient's experience and consequences of these GI-ADRs. These patient-reported outcomes also provide us with more knowledge about the course of GI-ADRs. Patients, for example, reported a pattern of recurring GI-ADRs after every ETN administration – information which we did not capture in HCP reports and which may be valuable information for other or future ETN users. Therefore, systematically questioned patient-reported ADR experiences should be included more often in assessing the ADR profile of treatment options in inflammatory rheumatic diseases. Unfortunately, we were not able to compare GI-ADR frequencies between HCP-reported and patient-reported data

because of the differences in design between the two data sources. This would be a valuable comparison for future research. However, with our study we demonstrated that patient-reported data on ADRs can complement HCP-reported data.

We described the gastrointestinal ADR profile registered by both patients and HCPs. The described actions, course and burden by patients are considerable and clinicians should be alert towards GI-ADRs in patients using ETN. Knowledge about these previously unknown ADRs can facilitate early recognition and allow improved communication with patients. Not recognising ETN-associated GI-ADRs may delay ETN discontinuation or may initiate unnecessary treatment of GI complaints before switching to other, better tolerated treatment.

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Chapter 4.2

Hypoglycaemia following JAK inhibitor treatment in patients with diabetes

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Janus kinase inhibitors (JAKi) are effective drugs for the treatment of several immune-mediated inflammatory diseases and are increasingly prescribed.

The Netherlands Pharmacovigilance Centre Lareb received an adverse drug reaction (ADR) report of a potential glucose lowering effect in a 54-year-old male patient with diabetes mellitus type 1 (DM1) using baricitinib (4 mg daily) for rheumatoid arthritis (RA)[1]. Within two weeks after baricitinib initiation, this patient had to reduce the dosage of both insulin degludec (from 18 units to 14 units) and insulin aspart in order to prevent hypoglycaemia. Concomitant medication included methotrexate, tiotropium/olodaterol nebulizer and beclomethasone aerosol. When baricitinib was temporarily discontinued for 6 weeks due to a respiratory tract infection, the insulin dosages had to be increased, whereas insulin dosages needed to be reduced again after restarting baricitinib. The onset of glucose decrease shortly after initiation of JAKi treatment and recurrence after rechallenge with baricitinib suggests a causal relationship. Glucose lowering is not a labelled ADR and no warning for diabetic patients is mentioned in the European or FDA product information of baricitinib, tofacitinib, upadacitinib or filgotinib. A comparable case has been published concerning a 71-year-old female patient with RA that was complicated by systemic sclerosis and DM1[2]. This patient was resistant to multiple DMARDs but was successfully treated with baricitinib, with concomitant use of prednisolone for 3 weeks and methotrexate. In addition to improvements in RA and skin sclerosis, the required daily dose of insulin decreased from 17 to 11 units and did not increase for up to 1 year. The HbA1c level decreased from 7.4% to 6.4%.

To further investigate the development of hypoglycaemia as potential ADR of JAKi, we collected and analysed ADR reports of tofacitinib, baricitinib, upadacitinib and filgotinib with Medical Dictionary for Regulatory Activities Preferred Terms 'Hypoglycaemia' or 'Blood glucose decreased' from Eudravigilance, the European Medicines Agency pharmacovigilance database[3]. From initiation until 17 September 2021, Eudravigilance included 39,671 ADR reports concerning JAKi. Out of these, 43 reports concerned baricitinib, tofacitinib or upadactinib in patients with reported DM and/or with antidiabetic drugs as concomitant medication (Table 1). In nine out of 43 reports (21%) one or more other drugs were suspected to have contributed to the observed effect in addition to the JAKi, which included an antidiabetic in six cases, a corticosteroid in two cases and methotrexate in one case. Glucose levels after JAKi initiation were mentioned in 15 cases ranging from 1 mmol/L to 5.5 mmol/L or a decrease from reference levels of 0.5 mmol/L up to 4 mmol/L. In 15 cases the event occurred within one month after JAKi initiation. In eight cases, glycaemic control improved after discontinuation or dose reduction of the JAKi or antidiabetic drug. Reduced dosages of fast-acting as well as long-acting insulin were described with dose reductions up to 30%. These reports varied in their extent of documentation, especially with respect to other factors that could affect glucose levels and insulin requirement such as tapering of corticosteroids, concomitant medication such as methotrexate or other antidiabetics, disease activity and concurrent infections, which was not consistently reported. However, the time to onset, the required insulin dose reductions after

JAKi initiation and improvement after discontinuation suggest that JAKi may induce hypoglycaemia and may therefore reduce the need for antidiabetic medication in diabetic patients.

Table 1. Suspected adverse drug reaction (ADR) reports indicating hypoglycaemia in diabetic patients using a JAK inhibitor in the Eudravigilance database.

	Tofacitinib N (%)	**Baricitinib N (%)**	**Upadacitinib N (%)**
Number of reports	20 (100)	19 (100)	4 (100)
Mean age, years (range)	66.8 (56 – 83)	64.7 (48 – 80)	70.7 (65 – 74)
Female gender	17 (85)	14 (74)	4 (100)
Indication for JAKi			
Rheumatic disease	17 (85)	14 (74)	4 (100)
Unknown	2 (10)	3 (16)	-
Other[a]	1 (5)	2 (11)	-
Type of diabetes			
Diabetes mellitus type 1	3 (15)	6 (32)	1 (25)
Diabetes mellitus type 2	2 (10)	1 (5)	-
Not reported/type not specified	15 (75)	12 (63)	3 (75)
Reported ADR (MedDRA Term)[b]			
Hypoglycaemia	7 (35)	13 (68)	2 (50)
Decreased blood glucose	13 (65)	7 (37)	2 (50)
No. of drugs suspected to cause the reaction			
Only JAKi	13 (65)	18 (95)	3 (75)
JAKi and one other drug	5 (25)	1 (5)	-
JAKi and two other drugs	1 (5)	-	-
JAKi and three other drugs	1 (5)	-	-
JAKi and four other drugs	-	-	1 (25)
Concomitant medication			
Insulin	8 (40)	12 (63)	-
Other antidiabetic[c]	7 (35)	1 (5)	2 (50)
Methotrexate	4 (20)	1 (5)	1 (25)
Glucocorticoid	6 (30)	6 (32)	1 (25)
Other	11 (55)	10 (53)	3 (75)
Not reported	4 (20)	3 (16)	1 (25)
Reaction leading to hospitalisation	7 (35)	4 (21)	2 (50)
Time to onset after start JAKi:			
Within 1 month	8 (40)	6 (32)	1 (25)
2-6 Months	4 (20)	2 (11)	3 (75)
More than 6 months	2 (10)	-	-
Not reported	6 (30)	11 (58)	-

Table 1. Continued

	Tofacitinib N (%)	Baricitinib N (%)	Upadacitinib N (%)
Improvement after			
Drug withdrawal[d]	5 (25)	2 (11)	-
Dose adjustments[d]	1 (5)	1 (5)	-
Other[e]	3 (15)	4 (21)	3 (75)

There were no reports of filgotinib.
a. Tofacitinib: colitis ulcerative. Baricitinib: Neurodermatitis, COVID19.
b. In one case of baricitinib both hypoglycaemia and decreased blood glucose were reported
c. Tofacitinib: metformin: 3; glimepiride, pioglitazone and vildagliptin: 1; sitagliptin: 1; gliclazide, saxagliptin and metformin: 1; glimepiride and sitagliptin: 1. Baricitinib: Metformin: 1. Upadacitinib: pioglitazone, glipizide and metformin: 1, sitagliptin and glimepiride: 1.
d. Tofacitinib: Tofacitinib withdrawn: 2, tofacitinib and insulin withdrawn: 1, tofacitinib withdrawn and insulin dose reduced (units unknown): 1, sitagliptin withdrawn: 1. Baricitinib: Baricitinib withdrawn: 2, baricitinib dose reduced (unknown dosages): 1.
e. Tofacitinib: Tofacitinib dose not changed: 3. Baricitinib: Baricitinib dose not changed: 4. Updacatinib: Upadacitinib dose not changed: 2, action unknown: 1.
JAKi, Janus kinase inhibitors; MedDRA, Medical Dictionary for Regulatory Activities.

These findings may be explained by the role of the JAK/STAT-pathway in pancreatic islets. Previous studies showed evidence that the JAK1/2 and STAT1 pathway are involved in β-cell dysfunction in both DM1 and DM2[4, 5]. Cytokines involved in pancreatic β-cell apoptosis are dependent on JAK1/2-STAT1 activation as a response to other cytokines, such as interferon-γ (Figure 1). CXCL10 is a cytokine associated with β-cell apoptosis and is overexpressed in both DM1 and DM2[6]. Additionally, it has been demonstrated in preclinical models that DM can be reversed following JAKi treatment[7-9]. Consequently, the potential of repurposing JAKi for treatment of DM1/2 has been suggested and recently a phase 2 randomised placebo-controlled study investigating the efficacy of baricitinib in new onset DM1 has been started[2, 4, 7-10]. More detailed epidemiologic data or distinct pharmacologic studies that consider potential similarities and molecular differences of JAKi subtypes are needed to support our findings. Until the exact potential and risks of JAKi in DM1 and DM2 have been fully elucidated, physicians should be aware of the potential glucose lowering effect when starting a JAKi in diabetic patients.

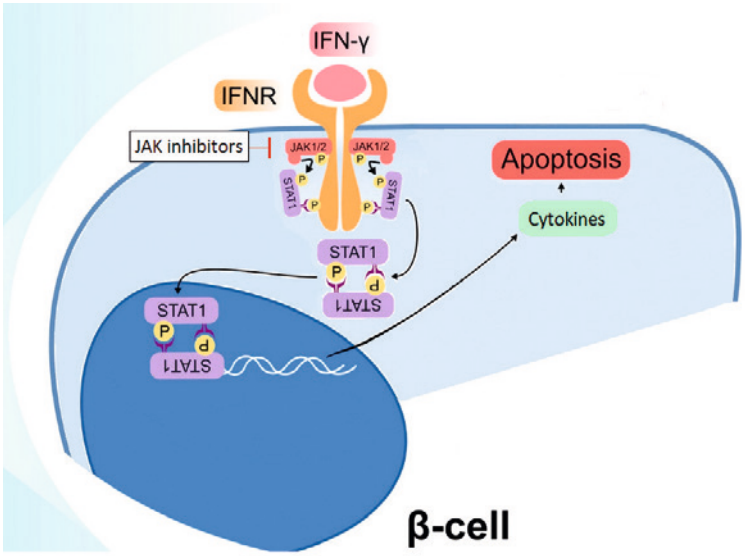

Figure 1. The JAK/STAT pathway involved in pancreatic β-cells, based on figure 4 of Gurzov et al;s work [5]. IFN-γ: Interferon-γ, IFNR: Interferon receptor, JAK: Janus kinase, STAT: Signal transducer and activator of transcription.

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Chapter 5

Course and burden of a potential new adverse drug reaction

Chapter 5.1

Recurring fatigue after biologic administration: patient-reported data from the Dutch Biologic Monitor

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ABSTRACT

Background Fatigue is a common problem in immune-mediated inflammatory disease (IMID) patients and it significantly impacts their quality of life.

Objectives In this study we describe the pattern and characteristics of fatigue as a patient-reported adverse drug reaction (ADR) of biologics and compared patient and treatment characteristics with patients reporting other ADRs or no ADRs.

Methods In this cohort event monitoring study, the description and characteristics of fatigue reported as a possible ADR in the Dutch Biologic Monitor were assessed and analysed for commonly recurring themes or patterns. Baseline and treatment characteristics of patients with fatigue and patients reporting other ADRs or no ADR were compared.

Results Out of 1382 participating patients, 108 patients (8%) reported fatigue as an ADR of a biologic. Almost half of these patients (50 patients, 46%) described episodes of fatigue during or shortly after biologic injection which often recurred following subsequent injections. Patients with fatigue were significantly younger than patients with other ADRs or patients without ADRs (median age for patients with fatigue: 52 years, patients with other ADRs: 56 years and patients without ADRs: 58 years), significantly more often smoked (25% vs 16% and 15%), used infliximab (22% vs 9% and 13%), rituximab (9% vs 3% and 1%) or vedolizumab (6% vs 2% and 1%) and significantly more often had Crohn's disease (28% vs 13% and 13%) and other comorbidities (31% vs 20% and 15%). Patients with fatigue significantly less frequently used etanercept (12% vs 29% and 34%) or had rheumatoid arthritis (30% vs 45% and 43%).

Conclusions IMID patients may experience fatigue as a postdosing effect of biologics.

INTRODUCTION

Patients with immune-mediated inflammatory diseases (IMIDs) frequently experience fatigue, which has a large impact on their quality of life [1,2]. The reported prevalence of fatigue in IMIDs varies from 19% to 72%, depending on IMID and disease status, compared to 9% to 25% in healthy adults [3]. It can be persistent and continuously present with sudden episodes of an overwhelming loss of energy and feeling exhausted[2,3]. Fatigue reduces the ability of physical and mental effort. Although fatigue is an important aspect of IMIDs, not all factors contributing to fatigue have been elucidated and treatment remains difficult.

It is well known that various factors may contribute to experiencing fatigue in patients with IMIDs, such as the disease itself and behavioral and psychological factors [3-7]. Multimorbidity, pain, depression and disability have been associated with fatigue in rheumatic diseases [3,4,8-10]. Anti-tumor necrosis factor (TNF) treatment as well as other biologic treatment have demonstrated improvements in fatigue in patients with rheumatoid arthritis and other IMIDs [11-17]. However, reducing disease activity alone is not always sufficient to improve fatigue. Rheumatoid arthritis patients that achieved remission using anti-TNF therapy may continue to report fatigue [18]. Conversely, an increased risk of fatigue has been described with anti-TNF therapy in inflammatory bowel disease, especially during long term treatment [19,20].

In a previous study we reported that 100 out of 1369 patients (7%) with IMIDs that participated in the prospective Dutch Biologic Monitor reported fatigue as an adverse drug reaction (ADR) of their biologic treatment [21-23]. Fatigue has previously been labelled as an ADR in the European Summary of Product Characeteristics (SmPC) only for infliximab, but not for other TNF-α inhibitors [24-28]. For interleukin inhibitors and other biologics used in IMIDs, fatigue has been labelled as an ADR in the European SmPCs of abatacept, brodalumab, canakinumab, rituximab, secukinumab, ustekinumab and vedolizumab [29-35]. Fatigue is mentioned as an adverse reaction in the FDA drug labels of infliximab, certolizumab pegol, brodalumab, ustekinumab, rituximab and vedolizumab [36-41]. Little is known about the pattern and characteristics of fatigue as an ADR of biologics. Because fatigue is a commonly reported complaint with IMIDs, it may remain unnoticed as an ADR or may, perhaps mistakenly, be attributed to the disease rather than biologic therapy. As patients with more severe disease are treated with more intensive therapies, including biologics, it may be challenging to distinguish the contribution of the underlying disease from the potential contribution of the biologic or other therapies. In this study we aimed to further understand fatigue as an ADR of biologics by assessing the pattern of the reported fatigue and the characteristics of the patients reporting fatigue in the Dutch Biologic Monitor. Therefore we aimed to 1) describe the pattern and characteristics of patient-reported fatigue and to 2) identify differences in baseline and treatment characteristics between patients reporting fatigue as a potential ADR and patients reporting other ADRs or no ADRs.

METHODS

Study design

An observational cohort event monitoring study of fatigue reported as an ADR of biologics in the Dutch Biologic Monitor.

Dutch Biologic Monitor

The Dutch Biologic Monitor is a prospective cohort event system for monitoring patient-reported ADRs attributed to biologics [21,22]. Nine Dutch hospitals participated in the Dutch Biologic Monitor. Between 1 January 2017 and 31 December 2020, consecutive patients using one of the monitored biologics, mainly for IMIDs, were invited to participate by the healthcare professionals (HCP) of the respective hospitals. Patients were eligible to participate from 18 years or older with access to internet and proficient in the Dutch language. Participating patients were asked to complete a comprehensive web-based baseline questionnaire covering demographic information (gender, date of birth, weight, height, smoking habits: daily, weekly, monthly or less, never), biologic, start date of the biologic, indication for the biologic, combination therapy, comorbidities at baseline and ADRs they attributed to the biologic (Table 1 in Supplementary Material). Multiple options could be selected for indication for biologic therapy, combination therapy and comorbidities. The originator or, when available, biosimilars of the biologics were included. Subsequent questionnaires after baseline focused exclusively on biologic use, combination therapy and ADRs and included identical questions on these topics. The baseline and subsequent questionnaire translated into English are presented in the supplementary material (Supplementary Material). Questionnaires were sent out bimonthly and patients received reminders if they had not completed the questionnaire within 7 days and 14 days. Patients could withdraw from the monitor at any time and no more questionnaires were sent in case the previous questionnaire had expired (after 21 days).

Ethical approval of the Dutch Biologic Monitor was waived for the Dutch Medical Research Involving Human Subjects Act (WMO) by the Medical Research Ethical Committee of Brabant, the Netherlands (NW2016-66). All participants received information about the Dutch Biologic Monitor prior to participation and signed a digital informed consent form.

ADR assessment

Patients were asked if they experienced any ADRs which they attributed to the biologic in each questionnaire. For each reported ADR, patients were asked for additional information. This included a description of the ADR using an open text field to reduce reporting bias, current status of the ADR (recovered, improving, aggravating, no change), start and stop date of the ADR if applicable, additional information about the ADR in an open text field, contact with an HCP, treatment or other actions taken by the HCP, self-initiated action by the patient following the ADR, the experienced ADR burden using a five-point Likert type scale ranging from 1 (no burden) to 5 (very high burden) and an explanation of the ADR burden using an open text field. In the open text field for additional information about the ADR, patients were asked

to further explain the ADR, which included the following suggested questions: how often do you experience this ADR, at which specific moments do you experience this ADR and is there a specific pattern [21]. ADRs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology (version 23.0) by trained pharmacovigilance assessors following standard practice [42].

Data collection

Fatigue as an ADR was defined as all reported ADRs with the MedDRA Preferred term (PT) Fatigue. We selected all questionnaires from patients reporting fatigue as a possible ADR of their biologic. Additionally, we selected questionnaires from patients reporting other ADRs on MedDRA PT level and questionnaires from patients reporting no ADRs.

Data analysis

To identify characteristics of the reported fatigue as an ADR of biologics, we assessed patient's descriptions of the course of fatigue in any questionnaire, the status of fatigue in the last completed questionnaire, HCP contact following fatigue in any questionnaire, treatment or other actions taken by the HCP in any questionnaire, self-initiated action reported in any questionnaire, hospitalization following fatigue in any questionnaire and the ADR burden of fatigue in all questionnaires. Since the course of ADRs was described by patients in open text fields, this was subjected to thematic analysis by Jvl and NJ for patterns or commonly recurring themes in the course of fatigue in different patients. Discrepancies were discussed for consensus. A causal association between the biologic and fatigue was assessed by applying the Naranjo Probability Scale in a case-by-case manner [43].

Baseline and treatment characteristics were compared between patients reporting fatigue as an ADR and patients who did not report fatigue as an ADR to investigate potential differences between these patients. Patients who did not report fatigue were divided in two groups: patients reporting other ADRs and patients reporting no ADR at all. The following baseline characteristics were included: age, gender, BMI, smoking status (ever or never) and comorbidities. The following treatment characteristics were included: biologic, indication for biologic and combination therapy. Differences between patients reporting fatigue and patients with other ADRs or no ADRs were analysed using Mann Whitney-U test for continuous variables that were not normally distributed or ordinal variables such as burden. Continuous normally distributed variables were analysed using independent t-tests. Categorical variables were analysed using Fisher's exact test. Normality was assessed with histograms and the Kolmogorov-Smirnov test. Statistical analyses were performed in IBM SPSS Statistics (version 22).

RESULTS

Out of 1382 consecutive participating patients in the Dutch Biologic Monitor, 730 patients (53%) reported 2035 unique ADRs they experienced with biologics. The most frequently reported ADR on MedDRA PT level was fatigue. In total, 108 patients (15%) out of 730 patients with ADRs reported fatigue (Table 1). All 108 patients reporting fatigue collectively completed a total of 813 questionnaires with a median of 5 completed questionnaires per patient (range: 1-24 questionnaires).

Table 1. Demographics of patients reporting fatigue as an adverse drug reaction of biologics

No. of patients	108 (100)
Age, years (median [IQR])	52 [39 – 63]
Female sex	66 (61)
Smoking	27 (25)
BMI, kg/m² (median [IQR])	25.4 [22.7-27.5]
Biologic[a]	
Adalimumab	30 (28)
Infliximab	24 (22)
Etanercept	13 (12)
Rituximab	10 (9)
Tocilizumab	8 (7)
Vedolizumab	6 (6)
Ustekinumab	6 (6)
Dupilumab	4 (4)
Abatacept	3 (3)
Certolizumab pegol	2 (2)
Anakinra	2 (2)
Secukinumab	1 (1)
Golimumab	1 (1)
Indication for biologic use	
Rheumatoid arthritis	32 (30)
Psoriatic arthritis	15 (14)
Axial spondyloarthritis	11 (10)
Crohn's disease	30 (28)
Ulcerative colitis	5 (5)
Psoriasis	6 (6)
Other indication	17 (16)

Table 1. Continued

Combination therapy	
Methotrexate	24 (22)
Corticosteroids[b]	21 (19)
Thiopurines[c]	12 (11)
Aminosalicylates[d]	9 (8)
Hydroxychloroquine	5 (5)
Leflunomide	2 (2)
No combination therapy	45 (42)
Comorbidities	
Cardiovascular disorder	23 (21)
Hypercholesterolaemia	15 (14)
Respiratory disorder	14 (13)
Psychiatric disorder	11 (10)
Nervous system disorder	3 (3)
Cancer	2 (2)
Other comorbidity	33 (31)
No comorbidity	30 (28)

Data are expressed as n (%) unless otherwise specified
BMI body mass index, IQR interquartile range, ADR adverse drug reaction
[a] One patient reported fatigue as an ADR of infliximab and adalimumab and one patient reported fatigue as an ADR of abatacept and rituximab
[b] Corticosteroids include predniso(lo)ne, hydrocortisone, methylprednisolone
[c] Thiopurines include azathioprine, mercaptopurine and thioguanine
[d] Aminosalicylates include sulfasalazine and mesalamine

Patterns of fatigue

Postdosing fatigue was a common theme in the patients' descriptions of the course of fatigue. Almost half (50 patients, 46%) of the 108 patients reporting fatigue as an ADR, described a pattern of fatigue specifically occurring during or shortly after administration of the biologic. Of these, 41 patients (82%) described that fatigue recurred following more than 1 injection. Almost all patients describing this postdosing fatigue, recovered or partially improved from fatigue within one week after biologic administration (48 out of 50 patients). Seven out of these 50 patients described that the severity of fatigue sometimes also increased in the week before biologic administration (Figure 1). Five patients specifically explained that they always experienced fatigue during their chronic disease but the fatigue was more severe shortly after the biologic administration.

No specific pattern was described by the 58 patients (54%) without the postdosing pattern. A common description of the course of fatigue in these patients was continuously or daily present fatigue, with variation in severity.

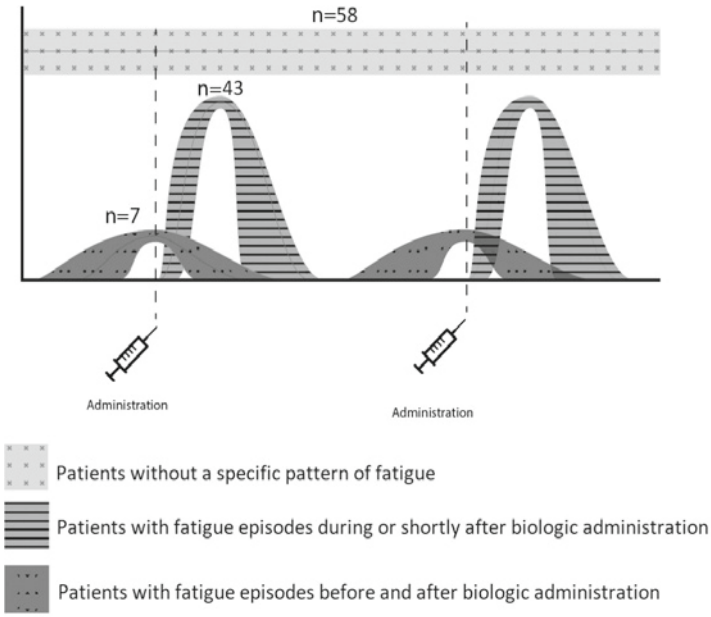

Figure 1. The described patterns in the course of fatigue as an adverse drug reaction of biologics

Consequences of fatigue

A total of 78 out of 108 patients (72%) reported HCP contact following fatigue, with dose adjustments in 13 patients (12%) and discontinuation in seven patients (6%) (Table 2). Four of the 13 patients describing dose adjustments experienced postdosing fatigue. In four cases this dose adjustment was a decrease in administration frequency and in five cases it was an increase in administration frequency. In nine patients, fatigue (temporarily) improved or resolved following the dose adjustment. The dose adjustment was not always initiated due to fatigue but could also have been due to other reasons than an ADR.

Table 2. Characteristics of patient-reported fatigue as an ADR of biologics (N=108)

No. of patients reporting HCP contact following fatigue	78 (72)
Specialist doctor	65 (60)
General practitioner	27 (25)
Nurse	35 (32)
Other	4 (4)
No. of patients who reported an HCP action	78 (72)
Discontinuation	7 (6)
Dose adjustment	13 (12)
Treatment	10 (9)
Referral	5 (5)

Table 2. Continued

Mentioned, no other action	39 (36)
Other[a]	17 (16)
No. of patients with status of 'fatigue' in last completed questionnaire	
Recovered	28 (26)
Improving	17 (16)
No change	54 (50)
Aggravating	9 (8)
No. of patients reporting fatigue and hospitalization	3 (3)
No. of patients reporting self-initiated action following fatigue	63 (58)
Naranjo score	
Doubtful	5 (5)
Possible	75 (70)
Probably	28 (26)
Certain	0 (0)
Mean ADR burden score ± SD	2.8 ± 0.9

Data are expressed as n (%) unless other specified.
ADR adverse drug reaction, HCP healthcare professional, SD standard deviation
[a] Other HCP actions: further examination, 6; adjusting concomitant therapy, 6; other therapy, 3

Seven patients reported (temporary) discontinuation of the biologic following fatigue, including two patients with postdosing fatigue. Five patients improved or recovered from fatigue after discontinuation, including two patients with postdosing fatigue. Three patients specifically mentioned that the biologic was discontinued because of one or more ADRs.

Ten patients (13%) reported that the fatigue was treated following HCP contact, including three patients with postdosing fatigue. Treatment was specified as iron infusion by two patients. The other patients did not further specify treatment. Four patients described improvements of fatigue after treatment, including one patient treated with iron supplementation and one patient with postdosing fatigue.

Three patients reported hospitalization following fatigue. In an explanation in an open text field, hospitalization was associated with other underlying problems in two patients. One patient described hospitalization for a liver procedure and one patient described hospitalization for a cardiac procedure. The third patient did not further explain the hospitalization.

The outcome of the Naranjo assessment was probable in 28 cases (26%) and possible in 75 cases (70%).

Burden of fatigue

The mean ADR burden of fatigue was 2.8 (SD 0.9) on a 5-point Likert type scale from 1 (no burden) to 5 (very high burden). The mean ADR burden experienced by patients with postdosing fatigue (2.6 ± 0.9) was lower than the mean ADR burden of fatigue in patients without this pattern (3.0 ± 1.0) (p<0.001). The mean ADR burden of fatigue (2.8 ± 0.9) was higher than the mean burden of other ADRs (2.4 ± 1.0) (p<0.001) (Table 3). Patients elucidated the experienced burden of fatigue with various explanations. Fatigue reduced quality of life, led to limitations in daily activities and affected work productivity and concentration. It also led to difficulties in combining and planning work with a social and personal life and to struggles in enjoying life. Moreover, patients explained that fatigue led to a depressed mood.

Patients reporting fatigue as an ADR compared with patients reporting other ADRs or no ADRs

The characteristics of patients reporting fatigue as an ADR compared with patients reporting other ADRs or no ADRs are summarized in Table 4. Patients reporting fatigue were younger and more frequently smoked. Patients reporting fatigue as an ADR more frequently used infliximab, rituximab or vedolizumab, more frequently had other comorbidities and more frequently used a biologic for Crohn's disease. Patients with fatigue less frequently used etanercept or less frequently used a biologic for rheumatoid arthritis than patients with other ADRs or patients without an ADR.

We also found differences between patients with fatigue and patients without ADRs. Patients with fatigue more frequently used tocilizumab, more frequently had a psychiatric comorbidity and less frequently used concomitant methotrexate. These differences were not found between patients with fatigue and patients with other ADRs.

Table 3. Characteristics of patients reporting fatigue as an ADR compared to patients with other ADRs and patients without ADRs

	Patients with fatigue	**Patients with other ADRs**	**p-value**	**Patients without ADR**	**p-value**
No. of patients	108 (100)	622 (100)		652 (100)	
Age, years (median [IQR])	52 [39 – 63]	56 [45 – 64]	0.02	58 [48 – 67]	<0.001
Female sex	66 (61)	407 (65)	0.39	331 (51)	0.05
Smoking	27 (25)	99 (16)	0.03	98 (15)	0.02
BMI, kg/m² (median [IQR])	25.4 [22.7-27.5]	25.1 [22.5 – 28.4]	0.83	25.8 [23.2 – 29.0]	0.11
Biologic					
Adalimumab	30 (28)	225 (36)	0.10	238 (37)	0.08
Infliximab	24 (22)	54 (9)	<0.001	82 (13)	0.01
Etanercept	13 (12)	180 (29)	<0.001	220 (34)	<0.001
Rituximab	10 (9)	19 (3)	0.01	5 (1)	<0.001
Tocilizumab	8 (7)	30 (5)	0.25	12 (2)	0.004

Table 3. Continued

	Patients with fatigue	Patients with other ADRs	p-value	Patients without ADR	p-value
Ustekinumab	6 (6)	25 (4)	0.44	33 (5)	0.81
Vedolizumab	6 (6)	12 (2)	0.04	7 (1)	0.01
Other	13 (12)	116 (19)	0.10	78 (12)	1.00
Indication					
Rheumatoid arthritis	32 (30)	277 (45)	0.004	279 (43)	0.01
Psoriatic arthritis	15 (14)	95 (15)	0.77	132 (20)	0.15
Axial spondyloarthritis	11 (10)	83 (13)	0.44	78 (12)	0.75
Crohn's disease	30 (28)	78 (13)	<0.001	86 (13)	<0.001
Ulcerative colitis	5 (5)	30 (5)	1.00	25 (4)	0.60
Psoriasis	6 (6)	27 (4)	0.61	50 (8)	0.55
Other indication	17 (16)	64 (10)	0.06	37 (6)	0.001
Combination therapy[a]					
Methotrexate	24 (22)	173 (28)	0.24	221 (34)	0.02
Corticosteroids[b]	21 (19)	111 (18)	0.69	93 (14)	0.19
Thiopurines[c]	12 (11)	45 (7)	0.17	58 (9)	0.47
Aminosalicylates[d]	9 (8)	51 (8)	1.00	39 (6)	0.39
Hydroxychloroquine	5 (5)	33 (5)	1.00	36 (6)	0.82
Leflunomide	2 (2)	42 (7)	0.05	23 (4)	0.56
No combination therapy	45 (42)	264 (42)	0.92	240 (37)	0.34
Comorbidity					
Cardiovascular disorder	23 (21)	155 (25)	0.47	162 (25)	0.47
Hypercholesterolaemia	15 (14)	93 (15)	0.88	117 (18)	0.34
Respiratory disorder	14 (13)	77 (12)	0.88	75 (12)	0.63
Psychiatric disorder	11 (10)	49 (8)	0.45	31 (5)	0.04
Nervous system disorder	3 (3)	19 (3)	1.00	19 (3)	1.00
Cancer	2 (2)	15 (2)	1.00	14 (2)	1.00
Other comorbidity	33 (31)	126 (20)	0.02	99 (15)	<0.001
No comorbidity	30 (28)	213 (34)	0.22	230 (35)	0.15
Mean burden score ± SD	2.8 ± 0.9	2.4 ± 1.0	<0.001		

Data are expressed as n (%) unless otherwise specified.
ADR: adverse drug reaction, BMI: body mass index, IQR: interquartile range, SD: standard deviation
[a] Combination therapy at the time of reporting the ADR for the first time. For the patients without ADRs the reported combination therapy at any time during participation was included.
[b] Corticosteroids include predniso(lo)ne, methylprednisoflone, hydrocortisone
[c] Thiopurines include azathioprine, thioguanine, mercaptopurine
[d] Aminosalicylates include mesalamine, sulfasalazine

DISCUSSION

In this study we investigated fatigue reported by patients as an ADR of biologics in the Dutch Biologic Monitor, a unique system for collecting patient-reported data on ADRs attributed to biologics. Fatigue was the most frequently reported ADR and patients included clear descriptions on the course and characteristics. This addresses the magnitude of patients experiencing fatigue as an ADR while fatigue is not a labelled ADR in the European product information of all biologics monitored in the Dutch Biologic Monitor [25-28,44].

Half of the patients described a similar pattern of recurring postdosing fatigue which resolved within one week after biologic administration. Although the pharmacological mechanism is not clear, this pattern substantiates a role of biologics in the manifestation of fatigue in these patients and supports fatigue as a potential ADR, comparable to the well-known gastrointestinal ADRs after methotrexate administration [45]. Treatment adjustments may decrease fatigue since some patients described improvements after discontinuation or dose adjustments. Some patients described increased fatigue in the week before biologic administration. In these patients, fatigue may be related to an increase in disease activity in the week before administration. This suggests that fatigue may sometimes emerge from a suboptimal biologic dose interval rather than an ADR. Improved fatigue after adjustments in concomitant drugs suggests that fatigue may sometimes be related to concomitantly used drugs rather than the biologic itself. Fatigue may also be a symptom of underlying medical problems which seemed apparent in some patients describing iron treatment. The different descriptions of the course of fatigue experienced by patients address the importance for HCPs to discuss and evaluate the course and characteristics with their patients and assess all potential factors contributing to fatigue to be able to optimize treatment and improve quality of life.

Patients reporting fatigue were younger and more frequently used a biologic for Crohn's disease. This is in line with a previous study addressing adverse symptoms with anti-TNF therapy in patients with inflammatory bowel disease and may suggest that patients with Crohn's disease more often experience fatigue during biologic use than patients with other IMIDs [19]. Patients with fatigue also more frequently used infliximab, rituximab or vedolizumab. These biologics are mostly administered intravenously, for which infusion related reactions are well known [46,47]. In these patients, fatigue could be a symptom of an infusion related reaction, similar to immediate adverse reactions following intravenous immunoglobulin administration [48]. In intravenously administered biologics, premedication, such as antihistamines or corticosteroids, may also play a role in the manifestation of fatigue [49]. It can also be postulated that immunogenicity might influence fatigue. However, we did not collect this data in the Dutch Biologic Monitor and as far as we know this association has not been described in previous studies [50,51]. Patients with fatigue more frequently smoked than patients with other or no ADRs and more frequently had psychiatric comorbidities than patients without ADRs. Smoking as well as psychiatric and depressive disorder have been associated with fatigue in IMIDs in previous studies, which is in line with our findings [52-56]. Even though this

does not support fatigue as an ADR of biologics, it does not exclude a role of biologics in the manifestation of fatigue and supports the notion that many factors may contribute to fatigue in IMID patients [3,7].

Interestingly, the mean ADR burden of fatigue was higher than the mean burden of other ADRs combined. The mean ADR burden of postdosing fatigue was lower than the mean ADR burden of fatigue without this specific pattern. Fatigue without this pattern implies the manifestation of chronic fatigue, which patients experienced as more burdensome. We cannot confirm these differences are clinically relevant as a standardised tool for measuring ADR burden is not available yet [57,58]. However, the differences were considered clinically relevant by the expert panel involved in the Dutch Biologic Monitor and this is supported by the descriptions patients provided explaining the significant impact that fatigue has on their lives. Given the challenges in improving patients' quality of life, HCPs should take the potential contribution of biologics into account.

Strengths of our study include the prospective nature of monitoring ADR information in a multicentre setting in patients using various biologics for different IMIDs which makes data on different IMIDs comparable. Assessing unfiltered patient-reported information on ADRs is a novelty and improves our understanding of the course of ADRs and the patient perspective on experiencing ADRs. A relationship was considered possible or probable in almost all cases following the widely used Naranjo assessment, although the reliability of this tool has been questioned [59,60]. Even though we cannot confirm a causal relationship between fatigue and biologics, the specific descriptions of a recurring postdosing pattern provide valuable information for HCPs. Because of the heterogeneity of the patients participating in the Dutch Biologic Monitor, we did not investigate risk factors for reporting fatigue as an ADR of biologics. The complexity of all factors involved in the manifestation of fatigue should be investigated in more detail for each biologic or group of biologics to better understand the contribution of different biologics in postdosing fatigue. The same applies to patient groups that may be more prone to suffer from fatigue as an ADR of biologics.

Although IMID patients frequently experience fatigue aside from biologics, a significant number of patients related fatigue to biologic use in this multicentre study that included a large number of patients with various IMIDs using a variety of biologics. This implies that a diverse group of patients associate fatigue with biologics across the Netherlands.

CONCLUSION

This is the first study to describe postdosing fatigue reported by patients as an ADR of various biologics for the treatment of IMIDs. Fatigue as an ADR of biologics may remain unrecognized or may automatically be attributed to the underlying disease. The specific recurring pattern after each administration suggests a contribution of biologics in the manifestation of fatigue.

Since fatigue has a significant burden on patients, this previously unknown knowledge may be helpful for HCPs in understanding the experienced fatigue by their patients and may assist in evaluating all possible factors contributing to fatigue. Distinguishing the relative contribution of underlying disease and treatment of the disease may be challenging. Evaluating the course of the symptoms may abate this challenge and may contribute to optimizing and personalizing biologic therapy to ultimately improve quality of life.

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SUPPLEMENTARY MATERIAL

Table 1. The included biologics, indications for biologic therapy, comorbidities and combination therapies in the Dutch Biologic Monitor

Biologic	Indication for biologic therapy	Comorbidities	Combination therapy
Abatacept	Rheumatoid arthritis	Respiratory disorder	Methotrexate
Adalimumab	Psoriatic arthritis	Cardiovascular disorder	Predniso(lo)ne
Anakinra	Axial spondyloarthritis	Hypercholesterolaemia	Hydrocortisone
Brodalumab	Psoriasis	Psychiatric disorder	Methylprednisolone
Canakinumab	Ulcerative colitis	Cancer	Hydroxychloroquine
Certolizumab pegol	Crohn's disease	Nervous system disorder	Leflunomide
Dupilumab	Other indication	Other comorbidity	Azathioprine
Etanercept		No comorbidity	Thioguanine
Golimumab			Mercaptopurine
Guselkumab			Mesalamine
Infliximab			Sulfasalazine
Ixekizumab			No combination therapy
Natalizumab			
Rituximab			
Sarilumab			
Secukinumab			
Tocilizumab			
Ustekinumab			
Vedolizumab			

Baseline and subsequent comprehensive web-based questionnaires from the Dutch Biologic Monitor. The original questionnaires are in Dutch. Side effects reappear in subsequent questionnaires if the side effect was reported in a previous questionnaire and is still current.

Baseline questionnaire

Questions in first questionnaire	Answer options	
Introduction		
How to complete this questionnaire? In this Monitor, the Netherlands Pharmacovigilance Centre Lareb is interested in biologic medicines. You can navigate through the questionnaire by using the "previous" and "next" buttons at the bottom of the page. Please do not use the buttons in the internet browser toolbar. This questionnaire consists of 5 steps. Mandatory questions have been marked with an asterisk (*). If you still have questions, please contact: Netherlands Pharmacovigilance Centre Lareb Goudsbloemvallei 7 5237 MH 's-Hertogenbosch Telephone no.: +31 73 - 64 69 700 (available on working days between 9 a.m. and 5 p.m.) E-mail: info@mijnbiologischmedicijn.nl		
Your medication		
Choose the biologic medicine you currently use *Select a medicine from the list*	Multiple choice	All in the Netherlands available brand names of the following biologics: Abatacept Adalimumab Anakinra Brodalumab Canakinumab Certolizumab pegol Dupilumab Etanercept Golimumab Guselkumab Infliximab Ixekizumab Natalizumab Rituximab Sarilumab Secukinumab Tocilizumab Ustekinumab Vedolizumab
When did you start using {{Survey medicine}}? *Please enter an estimated date if you are not sure about the exact date*	Date	
When was the last administration of this medicine? *Please enter an estimated date if you are not sure about the exact date*	Date	
If biosimilar is chosen		
For biosimilar: Have you used {{Name original biologic}} previously?	Yes/no	
If yes: When did you start using {{Name original biologic}}?	Date	
What do you use the biological medicine for?	Multiple select	Rheumatoid arthritis
		Psoriasis
		Psoriatic arthritis
		Axial spondyloarthritis
		Colitis ulcerosa

Baseline questionnaire

Questions in first questionnaire	Answer options	
		Crohn's disease
		Other: [open text]
What is the name of your treatment centre (hospital)?	Multiple choice	Participating hospitals or other: [open text]
Was the medicine last administered at the hospital or at home?	Hospital/at home	
Are you familiar with the batch number of {{Survey medicine}}? *It is visible on the packaging of the medicine. Below, you can upload a photo of the packaging.*	Yes: [open text] /no	
Do you have a photo of the packaging? Please upload the photo here. By uploading a photo, there is no need to retype the batch number. *upload your photo here (this should be a .jpg, .jpeg, or .png file).*	Photo upload	
Side effects		
Symptom or side effect? In this questionnaire, you will be asked about any side effect you may have experienced. We are interested in all side effects. Consider side effects during or shortly after administration (e.g. pain at the injection site or fever). You could also think of infections and a reduced effect of the medicine. You can also report complaints in case you are not sure whether it is caused by {{surveymedicine.Medicine}}. We also ask you to complete this questionnaire if you do not experience any side effects since this is important information as well		
Did you experience a side effect following the last administration of {{surveymedicine.Medicine}}? * *This could also be a side effect which started after administration of the medicine, but has already subsided. We are interested in all side effects. Consider also any side effects during or shortly after administration (e.g. pain at the injection site or fever). But also consider infections and a reduced effect of the medicine.*	Yes/no	
If yes: ***For each side effect***		
Description of side effect Please enter one side effect in the column 'Description of side effect' text box. You may add multiple symptoms or side effects by clicking the 'Add side effect' button. Starting date Please enter a date when the side effect started. Have you forgotten when the side effect started? Or did the symptoms start gradually? If so, please enter an estimated date. How are things now? Please note the current status of the side effect.		
Description of side effect	Open text	
When did this side effect start?	Date	
Can you explain more about the side effect? For example: *- How often do you suffer from this side effect?* *- At what moment do you suffer from this side effect?* *- Is there a pattern?*	Open text	
Did you contact a healthcare provider about this side effect?	Yes/no	

Baseline questionnaire

Questions in first questionnaire	Answer options	
If yes:		
With whom did you have contact?	Multiple select:	General practitioner
		Specialist doctor
		Nurse
		Pharmacist
		Other: [open text]
If yes:		
How was this side effect treated? *	Multiple select	Mentioned, but no action initiated
		Treatment
		Dose adjustment
		Drug discontinuation
		Referral to other health care professional
		Referral to hospital
		Switch to previous drug
		Other: [open text]
If option 1-7 was chosen: Here you can clarify your response	Open text	
If option 4 was chosen: When was {{surveymedicine. Medicine}} discontinued? * *Please enter an estimated date if you are not sure about the exact date*	Date	
Have you been you admitted to the hospital because of this side effect? *	Yes/no	
Did you do anything yourself about the side effect?	Yes: [open text]/no	
What is the current status of the side effect? The side effect:	Multiple choice	is over
		is subsiding
		did not change
		is aggravating
If option 1 was chosen: When did you recover from the side effect? *Please enter an estimated date if you are not sure about the exact date*	Date	
What was the burden you experienced from this side effect?	Multiple choice	No burden
		Little burden
		Quite burdensome
		High burden
		Very high burden
Can you describe the experienced burden of the side effect?	Open text	
Other medication		

Baseline questionnaire

Questions in first questionnaire	Answer options	
The medicines below are frequently used in combination with biologic medicines. Can you indicate whether you are currently using (one of) these agents?	Multiple select	I do not use any of these medicines
		Azathioprine
		Chloroquine
		Hydroxychloroquine
		Hydrocortisone
		Leflunomide
		Mercaptopurine
		Mesalazine
		Methotrexate
		Olsalazine
		Prednisone
		Prednisolone
		Sulfasalazine
		Tioguanine
		Methylprednisolone
General information		
Other diseases and general information The Netherlands Pharmacovigilance Centre Lareb is interested in side effects that occur during use of medicines used for an inflammatory disease (e.g. rheumatoid arthritis or psoriasis). Therefore it is important to know whether you have any other diseases.		
Could you please indicate what other diseases you have?	Multiple select	No comorbidities
		Respiratory disorder
		Cardiovascular disorder
		Hypercholesterolemia
		Psychiatric disorder
		Cancer
		Nervous system disorder
		Other: [open text]
What is your length? *Please enter whole numbers*	[open] centimeter	
What is your weight? Please enter whole numbers	[0-500] kilogram	
How often do you smoke?	Multiple choice	Never
		Monthly
		Weekly
		Daily
How have you been informed about this Monitor biological medicines?	Multiple choice	In the pharmacy

Baseline questionnaire

Questions in first questionnaire	Answer options	
		During consultation with nurse
		During consultation with specialist doctor
		At ambulatory care unit
		By letter
		By email
Conclusion		
Do you have a question, for example about a side effect? Ask your physician or pharmacist. If you have a specific question for the Netherlands Pharmacovigilance Centre Lareb, please send an e-mail to info@mijnbiologischmedicijn.nl. Do you have any remarks about this questionnaire? Please enter these below.	Open text	
Would you like to receive the results by e-mail following completion of this Monitor? *These can also be found on www.mijnbiologischmedicijn.nl.*	Yes/no	
If yes: Please state the desired e-mail address:		
Submit your questionnaire! By clicking submit, the questionnaire will be sent to us. We will send you an e-mail as soon as the next questionnaire is available to you. If you still have questions, please contact us. Netherlands Pharmacovigilance Centre Lareb Goudsbloemvallei 7 5237 MH 's-Hertogenbosch Telephone: +31 73 - 64 69 700 (available on working days between 9 a.m. and 5 p.m.) E-mail: info@mijnbiologischmedicijn.nl		
Download overview		
Thank you very much for your questionnaire! You have sent your first questionnaire of this Biologic Monitor to us. You may download the questionnaire below: Download questionnaire We will send you an e-mail when your next questionnaire is available. Use the top menu to log out of this website.		

Subsequent questionnaire

Questions in subsequent questionnaires	Answer options
Your medication	
In case the biologic was discontinued in the previous questionnaire:	
In the previous questionnaire you indicated that {{surveymedicine.Medicine}} was discontinued	
Is {{surveymedicine.Medicine}} still discontinued? *	Yes/No
In case the biologic was not discontinued in the previous questionnaire	

Subsequent questionnaire

Questions in subsequent questionnaires	Answer options	
In the previous questionnaire you used {{surveymedicine.Medicine}}. The following questions are about use of {{surveymedicine.Medicine}}.		
Are you still using {{surveymedicine.Medicine}} ?*	Multiple choice	Yes, I have used the medicine in the last 2 months
		Yes, but I have not used the medicine in the last 2 months
		Yes, but from a different brand (manufacturer)
		No, I (temporarily) stopped using the medicine
		No, I stopped using this medicine but switched to another biologic medicine
In case the medicine was used in the last 2 months		
When was the last administration of this medicine? *Please enter an estimated date if you are not sure about the exact date*	Date	
In case of (temporary) discontinuation		
When did you stop using {{surveymedicine.Medicine}}? * *Please enter an estimated date if you are not sure about the exact date*	Date	
Why did you (temporarily) stop using {{surveymedicine.Medicine}}? *	Multiple choice	Because of one or more side effects
		Other reason: [open text]
Your new medication		
Choose the brand (manufacturer) of the medicine you currently use * *Select a medicine from the list*	Multiple choice	All in the Netherlands available brand names of the following biologics: Abatacept Adalimumab Anakinra Brodalumab Canakinumab Certolizumab pegol Dupilumab Etanercept Golimumab Guselkumab Infliximab Ixekizumab Natalizumab Rituximab Sarilumab Secukinumab Tocilizumab Ustekinumab Vedolizumab
When did you start using {{Survey medicine}}? *Please enter an estimated date if you are not sure about the exact date*	Date	

Subsequent questionnaire

Questions in subsequent questionnaires	Answer options	
What is the name of your treatment centre (hospital)?	Multiple choice	Participating hospitals or other: [open text]
Was the medicine last administered at the hospital or at home?	Hospital/at home	
Are you familiar with the batch number of {{Survey medicine}}? *It is visible on the packaging of the medicine. Below, you can upload a photo of the packaging.*	Yes: [open text] /no	
Do you have a photo of the packaging? Please upload the photo here. By uploading a photo, there is no need to retype the batch number. *upload your photo here (this should be a .jpg, .jpeg, or .png file).*	Photo upload	
Side effects		
New side effect		
Did you experience a side effect following the last administration of {{surveymedicine.Medicine}}? * *This could also be a side effect which started after administration of the medicine, but has already subsided. We are interested in all side effects. Consider also any side effects during or shortly after administration (e.g. pain at the injection site or fever). But also consider infections and a reduced effect of the medicine.*	Yes/no	
All side effects (new and not recovered side effects in previous questionnaire)		
Description of side effect Please enter one side effect in the column 'Description of side effect' text box. You may add multiple symptoms or side effects by clicking the 'Add side effect' button. Starting date Please enter a date when the side effect started. Have you forgotten when the side effect started? Or did the symptoms start gradually? If so, please enter an estimated date. How are things now? Please note the current status of the side effect.		
Description of side effect	Open text	
When did this side effect start?	Date	
Can you explain more about the side effect? For example: *- How often do you suffer from this side effect?* *- At what moment do you suffer from this side effect?* *- Is there a pattern?*	Open text	
Did you contact a healthcare provider about this side effect?	Yes/no	
If yes:		
With whom did you have contact?	Multiple select:	General practitioner
		Specialist doctor
		Nurse
		Pharmacist
		Other: [open text]

Subsequent questionnaire

Questions in subsequent questionnaires	Answer options	
If yes:		
How was this side effect treated? *	Multiple select	Mentioned, but no action initiated
		Treatment
		Dose adjustment
		Drug discontinuation
		Referral to other health care professional
		Referral to hospital
		Switch to previous drug
		Other: [open text]
If option 1-7 was chosen: Here you can clarify your response	Open text	
If option 4 was chosen: When was {{surveymedicine. Medicine}} discontinued? * *Please enter an estimated date if you are not sure about the exact date*	Date	
Have you been you admitted to the hospital because of this side effect? *	Yes/no	
Did you do anything yourself about the side effect?	Yes: [open text]/no	
What is the current status of the side effect? The side effect:	Multiple choice	is over
		is subsiding
		did not change
		is aggravating
If option 1 was chosen: When did you recover from the side effect? *Please enter an estimated date if you are not sure about the exact date*	Date	
What was the burden you experienced from this side effect?	Multiple choice	No burden
		Little burden
		Quite burdensome
		High burden
		Very high burden
Can you describe the experienced burden of the side effect?	Open text	
Other medication		
The medicines below are frequently used in combination with biologic medicines. Can you indicate whether you are currently using (one of) these agents?	Multiple select	I do not use any of these medicines
		Azathioprine
		Chloroquine
		Hydroxychloroquine
		Hydrocortisone

Subsequent questionnaire

Questions in subsequent questionnaires	Answer options	
		Leflunomide
		Mercaptopurine
		Mesalazine
		Methotrexate
		Olsalazine
		Prednisone
		Prednisolone
		Sulfasalazine
		Tioguanine
		Methylprednisolone
Conclusion		
Do you have a question, for example about a side effect? Ask your physician or pharmacist. If you have a specific question for the Netherlands Pharmacovigilance Centre Lareb, please send an e-mail to info@mijnbiologischmedicijn.nl. Do you have any remarks about this questionnaire? Please enter these below.	Open text	
Submit your questionnaire! By clicking submit, the questionnaire will be sent to us. We will send you an e-mail as soon as the next questionnaire is available to you. If you still have questions, please contact us. Netherlands Pharmacovigilance Centre Lareb Goudsbloemvallei 7 5237 MH 's-Hertogenbosch Telephone: +31 73 - 64 69 700 (available on working days between 9 a.m. and 5 p.m.) E-mail: info@mijnbiologischmedicijn.nl		

Chapter 5.2

Fatigue patterns surrounding biologic disease-modifying antirheumatic drug injection in patients with an inflammatory rheumatic disease: an ecological momentary assessment study

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ABSTRACT

This study investigated severity, course and patterns of fatigue surrounding subcutaneous biological disease-modifying antirheumatic drug (bDMARD) injection in inflammatory rheumatic disease (IRD) patients using ecological momentary assessments and investigated self-reported adverse drug reactions (ADRs). In this prospective cohort study, IRD patients completed fatigue severity numeric rating scales (0-10) in web-based ecological momentary assessments in three waves of five days surrounding bDMARD injection. The course of fatigue was measured by the change in fatigue from pre-dosing to post-dosing scores and was classified as: worsening, improving or no clinically relevant change. A pattern was defined as a course of worsening, improving or no clinically relevant change in fatigue in at least two out of three waves for patients completing assessments across all three waves. ADRs could be reported on day five of each wave. In total 609 participants completed ecological momentary assessments surrounding 1541 bDMARD injections. Overall average fatigue severity across all three waves was 4.5 (±SD 2.4) and 78% experienced severe fatigue in at least one assessment. Of 398 patients completing all three waves, 61% had no clinically relevant change in fatigue in at least two out of three waves, 13% had a pattern of worsening fatigue and 18% had a pattern of improving fatigue. Of 398 patients, 36% had a consistent pattern in all three waves. IRD patients using a bDMARD may consistently experience specific fatigue patterns surrounding bDMARD administration. These patterns provide insights for clinical practice and could be used to inform patients properly.

INTRODUCTION

Fatigue is an important complaint in patients with inflammatory rheumatic diseases (IRDs) with half of the IRD patients experiencing severe fatigue, greatly impacting their quality of life [1, 2]. Fatigue can occur with an overwhelming intensity impacting daily lives on physical, cognitive, emotional and social level [3-5]. Fatigue is associated with increased healthcare use and considerable societal costs as a consequence [6]. While biological, physiological and psychosocial mechanisms have been implicated in fatigue, its exact pathogenesis remains unclear and the causes of fatigue are considered multifactorial [7, 8]. Prevalent fatigue is only weakly associated with disease activity and strongly associated with pain, poor sleep, obesity, lower aerobic condition and depression [4, 9]. So in general, especially in patients with low disease activity or remission, fatigue seems unrelated to the IRD.

Interestingly, fatigue has been reported and is labelled as an adverse drug reaction (ADR) of conventional and biological disease-modifying antirheumatic drugs, which are effective and essential therapeutic options for treating IRDs as recommended by the European Alliance of Associations for Rheumatology [9-14]. The relation between fatigue and bDMARDs appears contradictory. A review of 32 studies has demonstrated some improvement in fatigue in active rheumatoid arthritis (RA) following bDMARD treatment [15]. In contrast, some patients self-reported fatigue as an ADR of biologics in a cohort event monitoring study [16]. Out of 1,382 patients in this study, 8% spontaneously mentioned fatigue as an ADR with half of them (4% of 1,382 patients) describing it as a postdosing reaction. These patients experienced post-injection fatigue, often occurring within one day following injection, which typically resolved within a week but recurred after subsequent biologic injections. Although a pharmacological base for fatigue caused by bDMARDs seems unlikely, it is of interest to study this frequently mentioned complaint.

To date, fatigue fluctuations around bDMARD injection and postdosing fatigue shortly after injection have not been systematically described and, even though various treatment options for fatigue have been investigated, management of fatigue in IRD patients in general remains challenging and requires a tailored approach [9, 17]. Prospectively measuring the course of fatigue surrounding bDMARD injections as experienced by patients may substantiate and improve understanding and management of fatigue in IRDs. Therefore, this explorative study aimed to investigate and describe the severity and course of fatigue surrounding subcutaneous bDMARD injection in IRD patients using ecological momentary assessments and to describe self-reported adverse drug reactions (ADR) after bDMARD injection.

METHODS

Study design

This prospective cohort study utilized the fatigue severity numeric rating scale (NRS), the primary outcome, in web-based ecological momentary assessments to investigate fatigue severity, the course of fatigue surrounding an injection and patterns in the course of fatigue surrounding multiple injections in patients with IRDs. Self-reported ADRs were investigated as a secondary outcome. Ecological momentary assessments were scheduled in three waves of five days surrounding a bDMARD injection to assess intra-individual variation in patterns in the course of fatigue surrounding bDMARD injections.

Setting and participants

IRD patients using a subcutaneously administered bDMARD prescribed by a physician in the Sint Maartenskliniek, a specialised rheumatic disease centre in the Netherlands, were invited to participate in this study. Inclusion criteria were: 18 years or older and an active prescription for one of the following subcutaneous bDMARDs: abatacept, adalimumab, certolizumab pegol, etanercept, sarilumab or tocilizumab for a clinical diagnosis of rheumatoid arthritis, psoriatic arthritis, axial spondyloarthropathy, juvenile idiopathic arthritis or giant cell arteritis. These bDMARDs were selected based on their initial dosing frequency with an administration more often than once a month. Patients with a bi-weekly (etanercept 2x25 mg) dosing schedule were excluded to prevent overlapping assessments in different waves. Participants could withdraw from the study at any time.

Ethical considerations

The Dutch Medical Research Committee of East Netherlands (METC Oost-Nederland) exempted ethical approval on 3 May 2022 because this study was not subject to the Medical Research Involving Human Subjects Act (file number 2022-13752). This study was approved by the institutional review board of the Sint Maartenskliniek and all participants signed digital informed consent prior to participation. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data collection

From October 2022 to January 2023 patients were invited to participate by email through an online Personal Health Record (PHR) named Zorgdoc®. Zorgdoc® is also used by patients to order their bDMARDs from the outpatient pharmacy of the Sint Maartenskliniek. After log in patients could read study information and, if patients decided to participate they were asked to sign digital informed consent and to complete a baseline questionnaire in which the date of the upcoming bDMARD injection was registered. Multiple entries were not possible as patients were invited through their PHR.

The upcoming injection date was combined with the dosing schedule to automatically plan the study assessment schedule for each patient in the Zorgdoc® PHR. Participants received a

link by email every evening at 6.30 pm for five days in three waves, surrounding three bDMARD injections, to complete one to three web-based ecological momentary assessment items, comprising 15 assessments in total (Figure 1 and Supplementary Material). The assessment could be completed until 0.00 am that same evening. After completing an assessment, participants could not change the answers. All assessments included an end of day fatigue severity assessment. On day 1 and day 3 of each wave, participants were additionally asked to confirm or correct the planned injection date. On day 5 of the first and second wave, patients were additionally asked to confirm or correct the subsequent injection date. On day 5 of each wave, patients were additionally asked if they experienced any ADRs of the bDMARD. ADRs were coded using Preferred Terms of the Medical Dictionary for Regulatory Activities (MedDRA®) following standard pharmacovigilance practice by JvL [18]. The web-based ecological momentary assessments were pretested with five patients following the three-step test-interview [19] and pilot tested by three researchers (JV, VH and JvL) and by three patients.

The following demographic and clinical characteristics were collected from the electronic health records for each participant: age, sex, body mass index, diagnosis, disease activity from 3 months prior to participation until end of study period (DAS28 for rheumatoid arthritis and juvenile idiopathic arthritis, PASDAS for psoriatic arthritis, ASDAS and BASDAI for axial spondyloarthropathy), anti CCP status, rheumatoid factor (RF) status, bDMARD with dosing scheme and its start date, and combination therapy and dosing scheme.

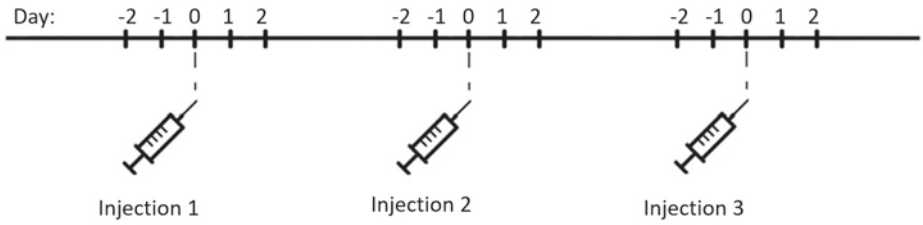

Figure 1. The schedule of ecological momentary assessments in three waves of five days surrounding a bDMARD injection.

Measures and data analysis

Study sample

The study sample was defined as the number of participants completing at least one pre-dosing and one post-dosing assessment in one wave. Descriptives of study variables were computed as proportions, means with standard deviation (SD) or medians with interquartile ranges (IQRs, 25° - 75° percentile), if appropriate. Data was analysed in R studio (version 4.3.0).

Severity of fatigue

Fatigue severity was measured using the fatigue NRS ("Please choose the number that shows your average level of fatigue today"), with 0 "no fatigue" to 10 "totally exhausted". The overall

severity of fatigue was measured by the proportion of patients with clinically relevant fatigue (NRS ≥ 2) and severe fatigue (NRS ≥ 5) in any assessment in any wave [20, 21].

Course of fatigue

To describe the course of fatigue surrounding a bDMARD injection, fatigue scores were examined for each wave completed by each patient. The mean of pre-dosing fatigue scores was compared with the mean of post-dosing fatigue scores in the same wave for all waves with at least one completed pre-dosing and post-dosing assessment. For each wave, the change in fatigue from pre-dosing to post-dosing was computed (mean post-dosing minus mean pre-dosing). Thereafter, the proportion of injections categorised into a clinically relevant change (i.e. worsening or improvement) or no clinically relevant change was calculated. An injection with a clinically relevant change was defined as 1.2 for worsening fatigue and -1.0 for improvement of fatigue, using average cut-off points for minimal clinically important difference (MCID) on the visual analogue scale in patients with rheumatoid arthritis [22].

For all patients completing a pre-dosing and post-dosing assessment in all three waves, patterns in the course of fatigue were investigated. Three distinct patterns were defined: a) clinically relevant improvement of mean fatigue in at least 2 out of 3 waves, the majority of bDMARD injections, b) clinically relevant worsening of mean fatigue in at least 2 out of 3 waves, or c) no clinically relevant change in mean fatigue in at least 2 out of 3 waves. These patterns were also stratified per bDMARD.

Self-reported ADRs

The type and frequency of ADRs reported on day 5 of each wave were assessed and described at MedDRA Preferred Term level. The frequency was expressed as the number of reported ADRs, the number of unique ADRs (counting one type of ADR reported by one patient once) and the number and proportion of patients reporting the ADR.

RESULTS

Out of 2,444 invited patients, 734 patients (30%) consented to participate, and 609 participants (83% of patients with consent) provided at least one pre-dosing and post-dosing fatigue score of a single wave (Table 1, Supplementary Table S1 and Figure 2). Most participants used adalimumab (52%) or etanercept (32%). A total of 398 participants (65%) completed at least one pre-dosing and post-dosing fatigue score of all three waves. At least one pre-dosing and post-dosing fatigue score was completed for 1541 waves in total, which is 84% of the theoretically possible number of 1827 waves completed by 609 patients.

Table 1. Baseline characteristics of participants that provided at least one pre-dosing and post-dosing fatigue score of a single wave.

	N (%)
Total	609 (100)
Female	384 (63)
Age, median years (IQR)	58 (48.5-66)
BMI, mean (SD)[a]	27.6 (5)
Rheumatic disease	
Rheumatoid arthritis	343 (56)
Psoriatic arthritis (mostly peripheral)	144 (24)
Radiographic axial spondyloarthropathy	96 (16)
Non-radiographic axial spondyloarthropathy	7 (1)
Psoriatic arthritis (mostly axial)	11 (2)
Juvenile idiopathic arthritis	4 (0.6)
Giant cell arteritis	4 (0.6)
Disease duration, median years (IQR) at baseline	8 (3-16)
Disease activity, median score (IQR) during study period	
DAS28 (n=275)	2.2 (1.6 – 3.0)
PASDAS (n=76)	3.0 (1.8 – 3.8)
ASDAS (n=62)	2.2 (1.7 – 3.0)
BASDAI (n=59)	3.8 (2.6 – 5.5)
Rheumatoid Factor positivity[b] (% of rheumatoid arthritis patients)	197 (57)
Anti-CCP positivity[c] (% of rheumatoid arthritis patients)	194 (57)
bDMARD	
Adalimumab	318 (52)
Etanercept	192 (32)
Tocilizumab	38 (6)
Abatacept	34 (6)
Certolizumab	16 (3)
Sarilumab	11 (2)
bDMARD treatment duration at baseline in months, median (IQR)	11 (8 – 47)
Other medication prescribed by rheumatologist[d]	
NSAID	285 (47)
Methotrexate	211 (35)
Corticosteroid	81 (13)
Leflunomide	47 (8)
Hydroxychloroquine	37 (6)
Sulfasalazine	26 (4)

a. BMI was unknown for 225 patients.
b. Rheumatoid factor was unknown for 32 rheumatoid arthritis patients.
c. Anti-CCP was unknown for 29 rheumatoid arthritis patients.
d. Other medication not prescribed by a rheumatologist is shown in Supplementary Table S1.

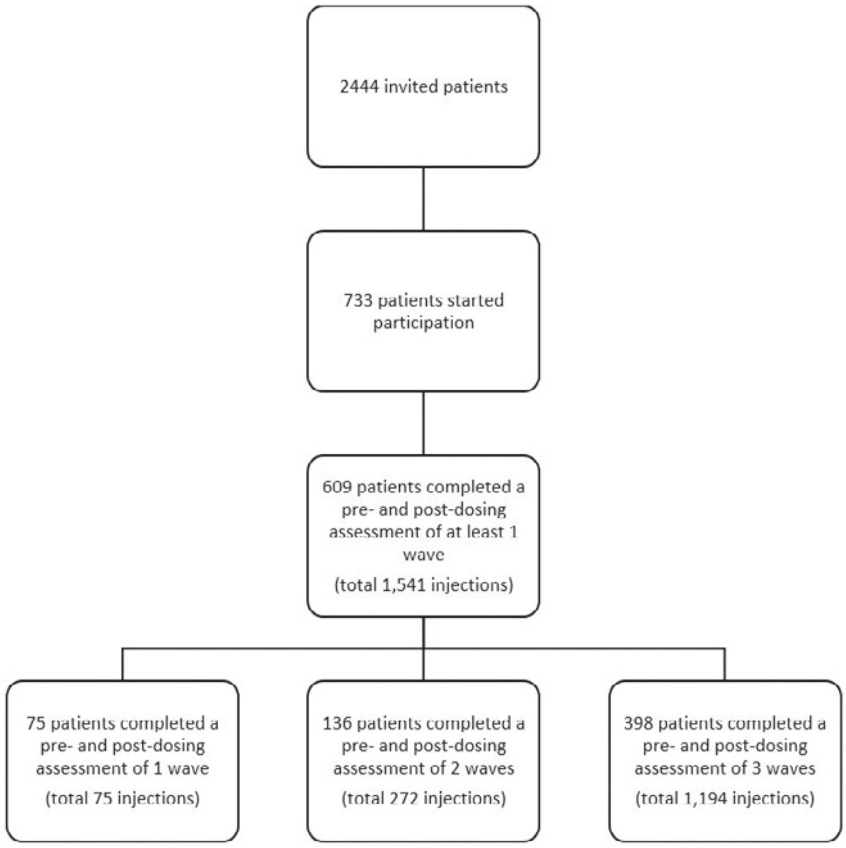

Figure 2. Flowchart of number of invited patients to number of patients completing ecological momentary assessments

Severity of fatigue

Overall mean fatigue severity across all three waves was 4.5 (±SD 2.4) (Supplementary Figure S1). Four hundred and fifty nine of 609 participants (75%) reported clinically relevant fatigue (NRS ≥2) in all completed assessments. A total of 477 patients (78%) reported severe fatigue (NRS ≥5) in at least one assessment and 145 patients (24%) reported severe fatigue in all completed assessments.

Course of fatigue (per injection wave)

Out of 1,541 injections, 17% (267 injections) were followed by worsening in fatigue, while 25% (378 injections) were followed by improvement in fatigue. No clinically relevant change in fatigue scores was observed following 58% (896 injections) of the administered injections (Figure 3).

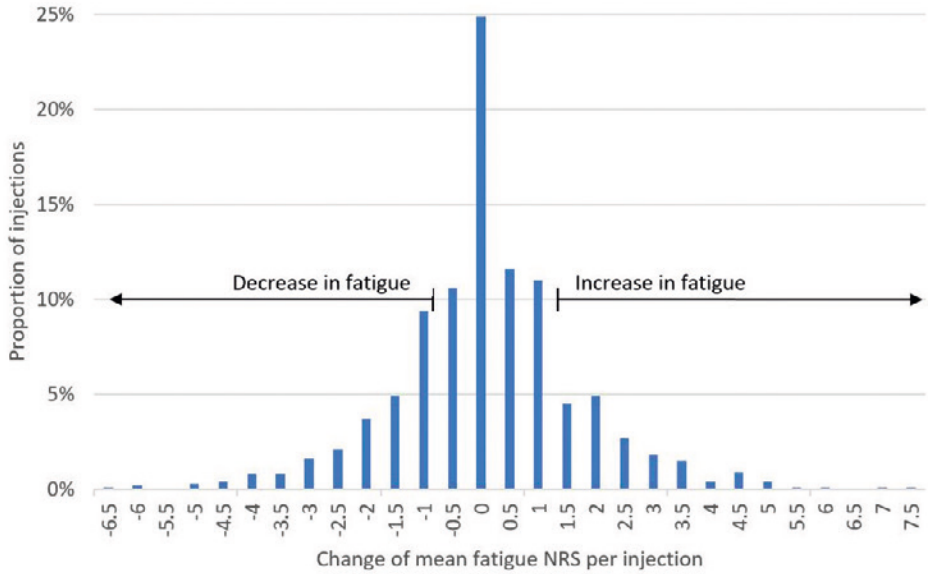

Figure 3. The change of fatigue per injection for all 1,541 injections.

Patterns in course of fatigue (per patient across three waves)

Of 398 patients completing all three waves, most patients (61%) had no clinically relevant change of fatigue, 13% had a pattern of worsening fatigue and 18% had a pattern of improving fatigue in the majority of injections (Figure 4). In total 145 patients (36%) had the same consistent pattern of fatigue around all three bDMARD injections. Four percent of the patients exhibited a consistent pattern of worsening fatigue following all three injections, while a similar consistent pattern of improvement of fatigue was observed in another 4% of the patients. A post-hoc analysis of 136 patients completing two waves in total showed a similar distribution of a consistent worsening pattern (7%) and consistent pattern of improvement (10%) of fatigue (Supplementary Figure S2).

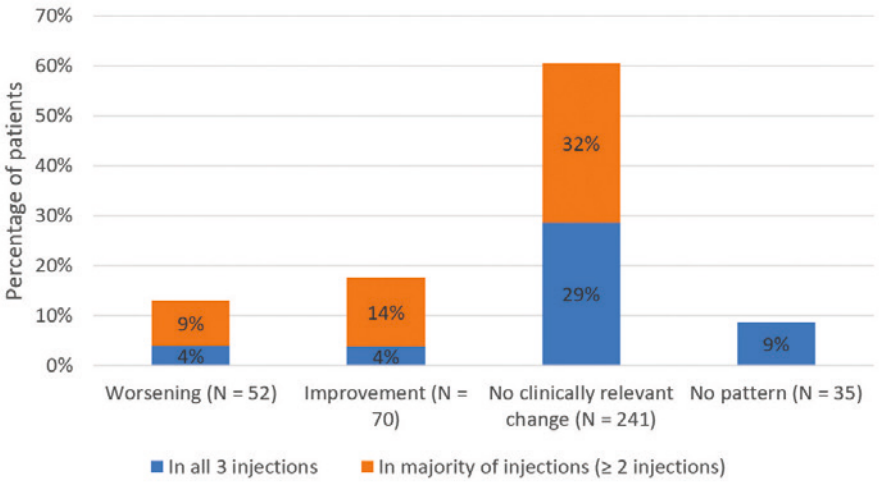

Figure 4. The proportion of patients with a pattern of worsening, improvement or no clinically relevant change of fatigue following bDMARD injection in the majority of injections, out of all patients completing all three waves (N=398).

The distribution of fatigue patterns for each bDMARD were similar to the overall distribution in patterns (Figure 5). Worsening of fatigue following the majority of injections varied between 8% to 12% and improvement of fatigue varied between 15% and 25% for the various bDMARDs. For each bDMARD, the majority of patients had no clinically relevant change of fatigue after injection, varying between 38% and 77%.

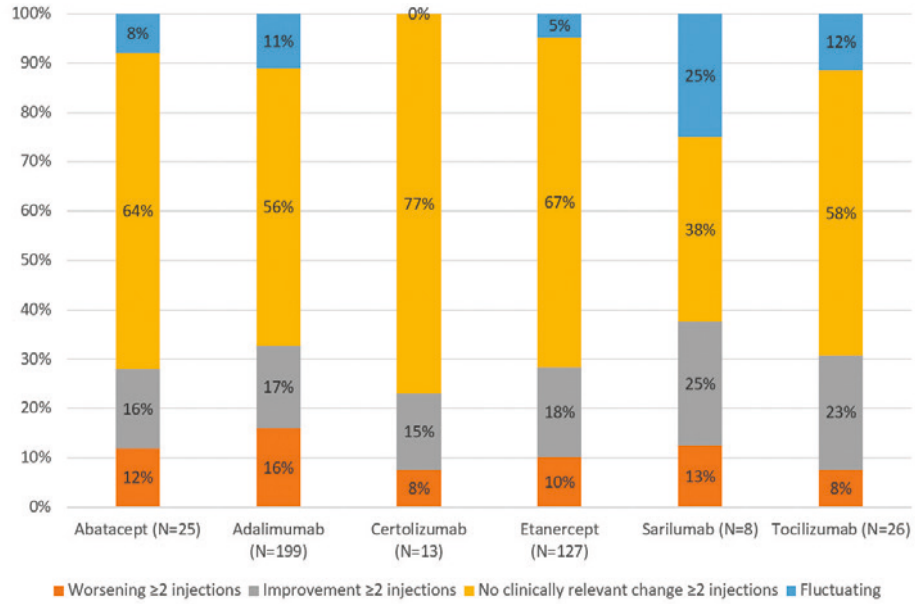

Figure 5. The proportion of patients with a pattern of worsening, improvement or no clinically relevant change of fatigue following bDMARD injection per bDMARD out of all patients completing three waves (N=398).

Self-reported ADRs

Out of 609 patients, 590 patients (97%) completed the last questionnaire (in which they were asked for ADRs) of at least one wave, comprising a total of 1423 injections. 148 patients (25%) reported at least one ADR following 248 injections (17%). In total, 402 ADRs and 320 unique ADRs were reported (Supplementary Table S2). The mean number of unique reported ADRs was 2.2 (SD 1.3) per patient, varying from 1 to 6 ADRs. The top 5 most reported ADRs was fatigue (reported 76 times by 51 patients, 9%), followed by headache (reported 35 times by 28 patients (5%)), injection site swelling (reported 19 times by 14 patients (2%)), nausea (reported 16 times by 12 patients (2%)) and injection site erythema (reported 16 times by 12 patients (2%)).

Of the 51 patients reporting fatigue as an ADR, a pattern of worsening fatigue following the majority of bDMARD injections was observed in 19 patients (37%), a pattern of no clinically relevant change in fatigue was observed in 11 patients (22%), a pattern of improving fatigue was observed in one patient (2%) and no specific pattern was measured in three patients (6%). The 17 remaining patients reporting fatigue as an ADR did not complete all three waves and patterns were not examined in these patients. However, 13 of these patients completed two waves and five of these patients had consistent worsening of fatigue following bDMARD injection in both waves.

DISCUSSION

This ecological momentary assessment study demonstrated the severity, course and specific patterns in course of fatigue surrounding subcutaneous bDMARD injection in IRD patients. In most patients, fatigue remained stable around bDMARD injection and more or less similar proportions of patients had an improving (18%) or worsening (13%) pattern following the majority of administered bDMARD injections administered during the study period. Overall fatigue severity was clinically relevant, addressing the significance of fatigue in this patient population in general. In addition to the quantified severity and course of fatigue, fatigue was the most frequently reported ADR and was reported by 9% of patients which comprised 37% (19/52) of the patients with a pattern of worsening fatigue following bDMARD injection.

As far as we know, individual fatigue patterns around bDMARD injection have not been quantified before. A study has demonstrated post-dosing fatigue patterns with methotrexate by quantifying patient-reported nausea and fatigue before and after administration [14]. In addition, distinct longitudinal fatigue trajectories have been identified before, despite minimal average changes on a group level [20]. Even though the cause of fatigue is known to be multifactorial and the pharmacological mechanism of bDMARD-associated fatigue remains unclear, fatigue is labelled as an ADR in the SmPC of various bDMARDs. We identified a similar proportion of patients reporting fatigue as an ADR in this study (9%) compared to the previous cohort event monitoring study (8%) [16]. In the previous study, 4% described fatigue as a post-dosing reaction which is similar to 3% (19/609) of patients with a worsening fatigue pattern following injection also reporting fatigue as an ADR in this study. Nevertheless, reporting methods of both studies differed and the current study did not aim to demonstrate an association between bDMARDs and fatigue. Furthermore, we demonstrate similar proportions of patients with improving and worsening fatigue.

Several explanations for different fatigue patterns around bDMARD injection can be considered. A pharmacological basis for fluctuations of fatigue around injection seems unlikely since time to peak drug concentrations of the various included bDMARDs do not align with the ecological momentary assessments two days after injection. Fatigue is prevalent in healthy people as well as in patients with chronic diseases and various individual day to day fluctuations of fatigue have been demonstrated [23, 24]. Fatigue fluctuations around injection could be related to patient expectations considering the effect of the injection. Patients know that they are injecting the drug, and this knowledge can be associated with positive or negative cognitions and emotions, leading to experiencing improvement or worsening of fatigue as a placebo or nocebo effect respectively [25]. Another explanation is that fatigue changes around use of medication occur by chance. Furthermore, studies investigating the effect of bDMARDs on fatigue are limited and a study evaluating the effect of biologic interventions on fatigue by pooling results of 32 studies concerning 9,946 bDMARD users demonstrated fatigue improvements after bDMARD initiation [15]. However, that study assessed fatigue on a group level and in active IRD patients, and did not assess individual fluctuations specifically around

injection. As the complexity of many factors involved in fatigue in IRD patients is well known, understanding fatigue fluctuations remains challenging.

As patients may experience different patterns, attention to individual fatigue patterns is recommended. Patients who mention a specific fatigue pattern in clinical practice could benefit from their healthcare professional's support in coping with fatigue. These patients could be informed that most patients do not experience specific patterns but that improving as well as worsening patterns have been reported. Overall, providing profound information about fatigue is important for all IRD patients in decreasing the burden of fatigue [17].

This study has some limitations. This was an exploratory study and to minimalize the administration burden for participations, fatigue was measured only in patients on open label subcutaneous bDMARDS, and for a short period of five days around injection. Therefore fluctuations in fatigue at times other than surrounding injection could not be investigated. Other variables potentially associated with fatigue such as sleep disturbances, pain, mood, disease perception and daily activities were not measured and could therefore not be taken into account [4, 9, 17]. Also, patients could only complete each ecological momentary assessment in the evening and not all assessments were completed which led to missing data. Nonetheless, the high proportion of patients completing at least one pre-dosing and one post-dosing assessment out of the total number of patients starting participation (83%, 609/734) addresses the dedication of these patients and the importance of fatigue in this population.

As this study is the first to explore and identify fatigue fluctuations surrounding bDMARD injection, future research should focus on how to manage these effects in clinical practice. In addition, other factors strongly associated with fatigue, such as obesity, depression, poor sleep and pain should be investigated in relation to fatigue patterns [4]. Since this is the first study quantifying fatigue fluctuations surrounding bDMARD administration and this study solely focused on IRD patients, it is unknown if similar patterns would be identified in other patient populations using bDMARDs, such as in dermatology or gastroenterology.

CONCLUSION

Previous research indicated that patients sometimes experience fatigue as an ADR of bDMARDs, specifically recurring around bDMARD injection. This study demonstrated that some patients experience consistent patterns in the course of fatigue following bDMARD injection and identified similar proportions of patients with a worsening and improving fatigue pattern. Since fatigue is a major issue for IRD patients, recognizing individual patterns and informing patients properly can contribute to fatigue management in clinical practice.

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SUPPLEMENTARY MATERIAL

Supplementary material 1. Baseline questionnaire and ecological momentary assessments (translated from Dutch)

Baseline questionnaire (text and questions translated from Dutch)

What day is the next injection of your biologic planned? [Calendar]

- *In case a date later than two days after completing the question is chosen:* You will receive the first questionnaire on (*date*). This is two days before your injection.
- *In case a date within two days after completing the question is chosen:* Your next injection is tomorrow or the day after tomorrow. That does not give us enough time to send you the first questionnaire (two days before injection). What day will you inject the next dose ? [Calendar without upcoming 2 days] → You will receive the first questionnaire on (*date*). This is two days before your next injection.

Ecological momentary assessments per wave (text and questions translated from Dutch)

Day 1

1. Is the next injection of your biologic the day after tomorrow (*day month*)? [Yes/No]

→ If yes:

a. Please choose the number that shows your average level of fatigue **today**:

No fatigue 0 1 2 3 4 5 6 7 8 9 10 Totally exhausted

→ If no:

b. Will you inject your biologic another day and if yes, when?
   i. **Yes** → [Calendar]
   - *If date at least 2 days later is chosen:* You will receive a new questionnaire on (*date*). This is two days before your next injection.
   - *If date within 2 days is chosen:* Your next injection is tomorrow or the day after tomorrow. That does not give us enough time to send you the first questionnaire (two days before injection). What day will you inject the next dose ? [Calendar without upcoming 2 days] → You will receive the first questionnaire on (*date*). This is two days before your next injection.

   ii. **I am not sure yet** → As the date of your next injection is unknown, we now presume (*date*) (*= 7 days after planned injection date of current wave*). This is one week later. You will receive the next questionnaire on (*date*) (*date = 7 days later / 5 days after planned injection date of current wave*]. If the presumed injection date is not correct, you can specify the new injection date in that questionnaire.

   iii. **No, I no longer use the biologic** → As you no longer use the biologic, your participation in this study will be discontinued. Thank you for participating.

Day 2

1. Please choose the number that shows your average level of fatigue **today**:

   No fatigue 0 1 2 3 4 5 6 7 8 9 10 Totally exhausted

Day 3

1. Did you inject your biologic today or will you inject your biologic today? [Yes/No]

→ *If No, assessments in this wave stop and questions for verifying the next:*

a. Will you inject your biologic another time and if yes, when?

i. **Yes** → [Calendar]

- *If date at least 2 days later is chosen:* You will receive the next questionnaire on *(Date two days before injection date)*
- *If date within 2 days is chosen:* Your next injection is tomorrow or the day after tomorrow. That does not give us enough time to send you the first questionnaire (two days before injection). What day will you inject the next dose ? [Calendar without upcoming 2 days] → You will receive a new questionnaire on (*date*). This is two days before your next injection.

ii. **I am not sure yet** → As the date of your next injection is unknown, we now presume (*date*) (*= 7 days later / 7 days after planned injection date of current wave*). This is one week later. You will receive the next questionnaire on (*date*) (*date = 5 days later / 5 days after planned injection date of current wave*). If the presumed injection date is not correct, you can specify the new injection date in that questionnaire.

iii. **No, I no longer use the biologic** → As you no longer use the biologic, your participation in this study will be discontinued. Thank you for participating.

→ *If yes:*

2. What time did you or will you inject your biologic? *[Time: 00:00 to 23:59]*
3. Please choose the number that shows your average level of fatigue **today**:

   No fatigue 0 1 2 3 4 5 6 7 8 9 10 Totally exhausted

Day 4

1. Please choose the number that shows your average level of fatigue **today**:

   No fatigue 0 1 2 3 4 5 6 7 8 9 10 Totally exhausted

Day 5 of first and second wave

1. Please choose the number that shows your average level of fatigue **today**:

   No fatigue 0 1 2 3 4 5 6 7 8 9 10 Totally exhausted

2. Did you experience a side effect of your biologic in the last two days? You may also describe your complaint if you are not sure your complaint is a side effect.
   - Yes, namely: [*Free text*]
   - No
3. Is it correct that the next injection of your biologic is on [*date = suggested injection date based on personal dosing frequency*]? [Yes/No]
   → *If yes*: You will receive the next questionnaire on (*date*). This is two days before your next injection.

   → If no:

a. Will you inject your biologic another time and if yes, when?
   - **Yes** → [Calendar]
   - **I am not sure yet** → As the date of your next injection is unknown, we now presume (*date*) *(= 7 days after planned injection date)*. This is one week later. You will receive the next questionnaire on (*date*) *(date = 5 days after planned injection date)*. If that injection date is not correct, you can specify the new injection date in that questionnaire.
   - **No, I no longer use the biologic** → As you no longer use the biologic, your participation in this study will be discontinued. Thank you for participating.

Day 5 of third wave

1. Please choose the number that shows your average level of fatigue **today**:

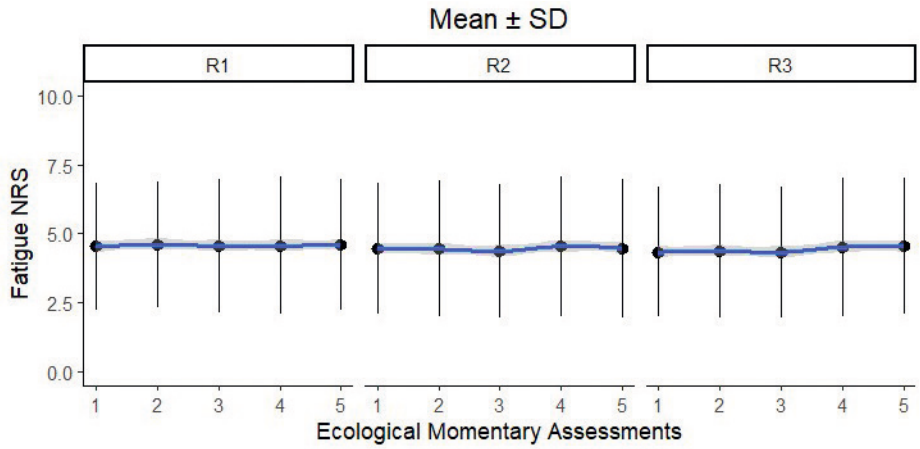
   No fatigue 0 1 2 3 4 5 6 7 8 9 10 Totally exhausted

2. Did you experience a side effect of your biologic in the last two days? You may also describe your complaint if you are not sure your complaint is a side effect.
   - Yes, namely: [*Free text*]
   - No

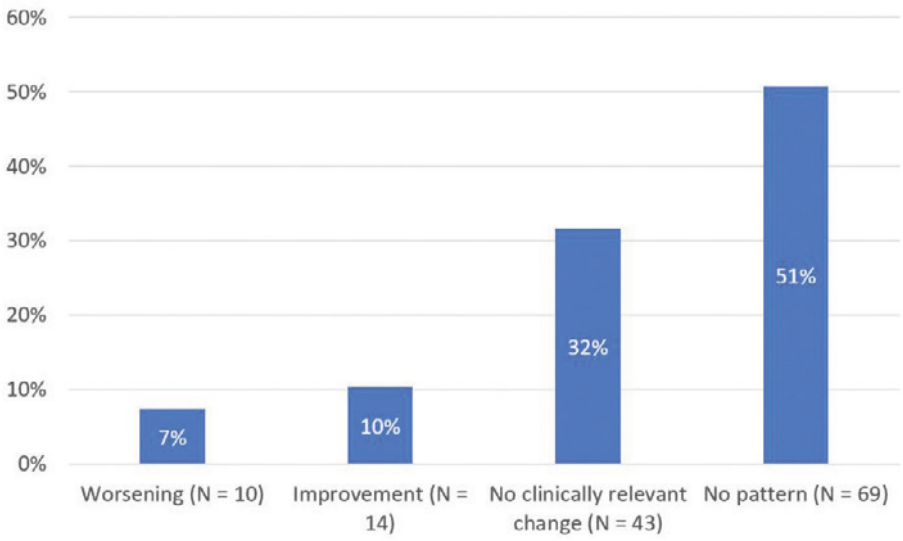
Supplementary Table S1. Medication used by participants not prescribed by a rheumatologist as registered in electronic health records classified according to the World Health Organisation Anatomical Therapeutic Chemical index.

Medication group	Anatomical Therapeutic Chemical code	N (%)
Drugs for acid related disorders	A02	317 (52)
Anti-emetics	A04	10 (2)
Drugs for constipation	A06	61 (10)
Drugs used in diabetes	A10	35 (6)
Antithrombotic agents	B01	90 (15)
Cardiovascular system drugs	C	255 (42)
Thyroid therapy	H03	25 (4)
Drugs for treatment of bone diseases	M05	42 (7)
Analgesics	N02	209 (34)
Antiepileptics	N03	11 (2)
Psycholeptics	N05	52 (9)
Antidepressants	N06A	52 (9)
Medication for obstructive airway diseases	R03	74 (12)
Antihistamines for systemic use	R06	74 (12)
Other	-	437 (72)

Supplementary Figure S1. The overall mean fatigue NRS scores and standard deviation of three waves, surrounding three bDMARD injections.



Supplementary Figure S2. The proportion of patients with worsening, improvement or no clinically relevant change of fatigue following bDMARD injection of patients completing two waves in total (N=136).



Supplementary Table S2. Reported adverse drug reactions two days after bDMARD injection according to Preferred Terms of the Medical Dictionary for Regulatory Activities (MedDRA)

Adverse drug reaction (MedDRA Preferred Terms)	Number of reported ADRs (Total 402)	Number of patients reporting the ADR (N= 590) N (%)
Total	**402**	**148 (25)**
Fatigue	76	51 (9)
Headache	35	28 (5)
Injection site swelling	19	14 (2)
Nausea	16	12 (2)
Injection site erythema	16	12 (2)
Pruritus	15	10 (2)
Injection site pruritus	14	11 (2)
Dizziness	9	6 (1)
Abdominal discomfort	9	7 (1)
Malaise	8	7 (1)
Injection site pain	7	7 (1)
Nasopharyngitis	6	4 (0.7)
Asthenia	6	6 (1)
Sleep disorder	6	6 (1)
Rash	6	5 (0.8)
Myalgia	6	6 (1)
Arthralgia	6	5 (0.8)

Supplementary Table S2. Continued

Adverse drug reaction (MedDRA Preferred Terms)	Number of reported ADRs (Total 402)	Number of patients reporting the ADR (N= 590) N (%)
Diarrhoea	6	5 (0.8)
Influenza like illness	6	4 (0.7)
Injection site haematoma	5	5 (0.7)
Pain in extremity	5	4 (0.7)
Somnolence	5	4 (0.7)
Emotional disorder	4	3 (0.5)
Erythema	4	3 (0.5)
Back pain	4	4 (0.7)
Alopecia	3	2 (0.3)
Pain	3	2 (0.3)
Dry skin	3	2 (0.3)
Abdominal pain	3	3 (0.5)
Inflammation	3	2 (0.3)
Injection site reaction	3	2 (0.3)
Restlessness	3	2 (0.3)
Insomnia	3	3 (0.5)
Musculoskeletal stiffness	3	3 (0.5)
Injection site warmth	3	2 (0.3)
Visual impairment	2	2 (0.3)
Odynophagia	2	1 (0.2)
Nasal congestion	2	2 (0.3)
Hypoaesthesia	2	2 (0.3)
Fungal infection	2	1 (0.2)
Dyspnoea	2	2 (0.3)
Weight increased	2	1 (0.2)
Injection site rash	2	2 (0.3)
Depressed mood	2	1 (0.2)
Dry mouth	2	1 (0.2)
Oral herpes	2	2 (0.3)
Listless	2	2 (0.3)
Dry eyes	2	2 (0.3)
Chills	2	2 (0.3)
Migraine	2	2 (0.3)
Muscle spasms	2	2 (0.3)
Drowsiness	1	1 (0.2)
Oral pain	1	1 (0.2)
Haematoma	1	1 (0.2)
Head discomfort	1	1 (0.2)

Supplementary Table S2. Continued

Adverse drug reaction (MedDRA Preferred Terms)	Number of reported ADRs (Total 402)	Number of patients reporting the ADR (N= 590) N (%)
Palpitations	1	1 (0.2)
Aphthous ulcer	1	1 (0.2)
Skin reaction	1	1 (0.2)
Chest pain	1	1 (0.2)
Injection related reaction	1	1 (0.2)
Ear pain	1	1 (0.2)
Flatulence	1	1 (0.2)
Feeling abnormal	1	1 (0.2)
Pharyngitis	1	1 (0.2)
Irritability	1	1 (0.2)
Restless legs syndrome	1	1 (0.2)
Joint stiffness	1	1 (0.2)
Gait disturbance	1	1 (0.2)
Hepatic pain	1	1 (0.2)
Night sweats	1	1 (0.2)
Glossitis	1	1 (0.2)
Abscess	1	1 (0.2)
Infection	1	1 (0.2)
Oropharyngeal pain	1	1 (0.2)
Infection susceptibility increased	1	1 (0.2)
Fluid retention	1	1 (0.2)
General physical health deterioration	1	1 (0.2)
Paraesthesia	1	1 (0.2)
Feeling cold	1	1 (0.2)
Flushing	1	1 (0.2)
Cough	1	1 (0.2)
Rash macular	1	1 (0.2)
Nail bed inflammation	1	1 (0.2)
Energy increased	1	1 (0.2)
Dysphonia	1	1 (0.2)
Injection site hypersensitivity	1	1 (0.2)
Arthritis	1	1 (0.2)
Vision blurred	1	1 (0.2)
Adverse drug reaction	1	1 (0.2)
Bloated feeling	1	1 (0.2)
Neck pain	1	1 (0.2)
Musculoskeletal discomfort	1	1 (0.2)

Chapter 6

General Discussion

Patient empowerment and patient-centred care are essential for better health outcomes and satisfaction with healthcare as it can improve communication between patients and healthcare professionals, improve treatment adherence and reduce healthcare costs [1]. Patient empowerment is defined by the World Health Organisation as '*a process through which people gain greater control over decisions and actions affecting their health*' and patient-centred care means that healthcare is tailored to patients' needs [2]. It seems self-evident that the patient also has an important role in the management of adverse drug reactions (ADRs) and in pharmacovigilance. Pharmacovigilance is defined as *the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem* [3]. After all, the patient is the one experiencing the ADR. However, it has not always been as obvious that the opinions and perspectives of patients play a crucial role in healthcare and the success of drug treatment. While many initiatives have increased patient engagement in pharmacovigilance, a paradigm shift is needed to transform pharmacovigilance into a more patient-centred practice [4, 5].

This thesis focuses on what we can learn from patients' ADR experiences and demonstrates its contribution to expanding knowledge of known and new ADRs. This general discussion will consider the studies of the thesis in a broader context by exploring how the insights gained can be applied to enhance pharmacovigilance methods. This may systematically enrich ADR knowledge in order to provide comprehensive and relevant information to patients and healthcare professionals and ultimately improve patient care. Finally, this general discussion will consider challenges and provide recommendations for future research.

A new perspective for pharmacovigilance

Pharmacovigilance historically focused primarily on detecting new, previously unknown ADRs, known as signal detection, but it should also aim to enrich knowledge about both new and known ADRs that is relevant for clinical practice [6]. The European Medicines Agency (EMA) defines a safety signal as *information on a new or known adverse event that is potentially caused by a medicine and that warrants further investigation* [3]. Until 2000, pharmacovigilance was defined as the detection, assessment and prevention of ADRs [7]. Since 2002 this definition also comprises the understanding of ADRs and has been expanded with other medicine-related problems [8]. Although pharmacovigilance methods have still not yet fully adapted to this newer definition, patient descriptions contain valuable information about the course of ADRs and the burden they impose. Knowledge about these aspects is valuable for both understanding and managing ADRs and is often not found in the descriptions of ADRs reported by healthcare professionals to pharmacovigilance centres [9]. As a result, such information is usually not available in the official product information or drug package leaflets as these documents mainly contain information on the nature and frequency of ADRs. Efforts should be made to supplement existing information with knowledge about new and known ADRs.

Incorporating aspects from patient-reported data in pharmacovigilance is an important development to make this effort [6, 10].

Identifying new ADRs

In **Chapter 4** and **Chapter 5** we demonstrate how patient-reported information can inform us about potential new ADRs. In **Chapter 4** we show how patients' descriptions contain details that can help identify these ADRs. We describe the gastrointestinal ADR profile of etanercept and decreased blood glucose levels as a potential ADR of JAK-inhibitors, which are both drugs used for immune-mediated inflammatory diseases. Patients attribute gastrointestinal complaints to etanercept, an association which had not previously been reported and which was thus not generally recognised by healthcare professionals. In line with previous studies, we demonstrate that patient-reported information can complement ADRs registered by healthcare professionals and can increase knowledge about previously unknown ADRs beyond just their nature and frequency [11, 12]. Combining all perspectives will thus lead to a more complete picture of the ADR profile of a drug.

In **Chapter 5** we investigate the patient-reported burden and course of fatigue as a potential ADR of biologics, drugs used for immune-mediated inflammatory diseases, and show that patients may experience specific patterns in fatigue. Knowledge of such patterns is valuable for clinical practice as it can be used to better inform and support patients in coping with this complaint and improve their quality of life.

New knowledge about ADRs

An example of new knowledge is the burden of ADRs experienced by patients, as explored in **Chapter 2**. Burden of ADRs from the patient perspective is not commonly addressed or taken into account in prescribing and evaluating drug treatment although it can negatively affect the quality of life and impair daily life [13, 14]. Patients and healthcare professionals perspectives on the burden of ADRs may differ and healthcare professionals tend to underestimate severity [15-18].

In **Chapter 3** we identify and classify information that patients provide on the course and timeframe of ADRs. We show how patients report details on duration, fluctuations in intensity, recurrence and patterns in recurrence, specific moments an ADR might occur or recur, like a specific moment of the day or a moment related to drug administration, and also factors triggering or improving the ADR. Generating and sharing such knowledge will contribute to meeting patients' information needs as topics related to the course are part of patients' desired information about ADRs [19].

Enhancing pharmacovigilance methods

Pharmacovigilance systems should become more patient-centred by adapting data collection methods and making better use of patient-reported data to expand knowledge that is valuable for clinical practice. More systematic data collection on aspects such as burden and course of ADRs, collecting longitudinal data in addition to spontaneous reporting and combining available data for analysis are important steps to generate such knowledge.

Systematic data collection

The spontaneous reporting system is still the most important source of information in pharmacovigilance. As spontaneous reporting forms were initially designed for regulatory purposes, these forms currently may not capture all aspects important to patients. To be able to expand knowledge on the course and burden of ADRs, this data should be systematically collected. Data in spontaneous reports have been standardised in ICH-E2B-R3 elements to enable collection and exchange of the data with the EMA and within the European Union [20]. Standardised ICH-E2B-R3 elements on the course of ADRs are currently restricted to time to onset, duration and outcome and should be expanded with aspects such as fluctuations, (patterns in) recurrence, moments of occurrence and factors triggering or improving the ADR, aspects which are mentioned by patients as we identified in **Chapter 3.** Standardised ICH-E2B-R3 elements related to the burden of an ADR can be labelled as serious according to the formal criteria: life threatening, causing or prolonging hospitalisation, disabling or incapacitating, leading to a birth defect, leading to death or other medically important conditions [21]. It should be noted that these seriousness criteria only partly reflect burden for a patient as it does not include social or psychological impact. In continuation of **Chapter 2** and as a step towards systematic data collection on burden of ADRs from patients themselves, we developed an instrument to systematically measure the burden using a seven item questionnaire for a better understanding of how an ADR is burdensome to a patient. It measures experienced ADR burden on seven domains that we identified from a wide range of patient descriptions: course of the ADR, appearance, medical treatment, daily life, fatigue, mental consequences and physical consequences [22]. This measurement instrument is currently being validated so that it can be widely used as a patient-reported outcome (PRO) in reporting forms as well as in clinical practice.

Adapting aspects of course and burden of ADRs in standardised data elements to better reflect the patient perspective will systematically expand knowledge obtained from the patient perspective in pharmacovigilance. Analysing and visualising such data can lead to knowledge about common ADRs that is currently scarcely available [23, 24]. It may also lead to more rapid identification of potential new ADRs as we explored in **Chapter 5**. Still, free text provides relevant insights into the details of an ADR, which are valuable for case-by-case analysis in detecting new ADRs and enhancing knowledge about known ADRs. Nevertheless, systems and methodology for collecting and assessing this information need further development [13, 25]. Especially when it concerns larger quantities of reports, open text data remains challenging

to analyse, even though the application of artificial intelligence such as Natural Language Processing is rapidly improving and may better facilitate this process in the near future [26].

Longitudinal data collection

Spontaneous reporting forms are designed to capture a momentary assessment and are less suitable to capture changes over time. Systematic ADR monitoring of patients reveals information about course and burden over time, including recurrence, fluctuations, (self)management, outcome and factors involved [23-25, 27]. In addition, systematic monitoring studies provide the possibility to gain knowledge about actual incidence of ADRs, specific patient characteristics and predisposing risk factors for their occurrence. Such knowledge is often not gained from spontaneous reports as these reports only concern patients with ADRs and monitoring studies also include patients without ADRs. The Netherlands Pharmacovigilance Centre Lareb has gained experience with several systematic monitoring studies on amongst others antidiabetic drugs, biologics, direct oral anticoagulants, medicinal cannabis and various vaccines [27-32].

Recently, the Netherlands Pharmacovigilance Centre Lareb developed the Dutch ADR Monitor. This a web-based cohort event monitoring infrastructure using online questionnaires for a more systematic approach to gather longitudinal information about course and burden of ADRs as experienced by patients with various chronic diseases [22]. This monitor includes the patient-reported outcome measure (PROM) on the burden and structured questions about the course of ADRs based on the findings in **Chapter 3.**

Systematic monitoring is currently not standard pharmacovigilance practice and needs further development and standardisation. Experience with international systematic monitoring has been gained in a European study actively monitoring patients' ADR experiences of COVID vaccines [33] but this approach could be further implemented internationally to enable data exchange and widely expand ADR knowledge.

Collaboration and combining ADR data

In addition to spontaneous reports and systematic monitoring, other existing data may contain information that can expand ADR knowledge, among which ADR data registered in routine practice like electronic health records or patient registries. This is also known as real-world data. An example of combining real-world data in pharmacovigilance is the Darwin EU project initiated by the EMA to provide timely and reliable evidence on the use, safety and effectiveness of medicines with 'big data' [34]. Furthermore, PROs used in studies and clinical practice may capture rich information from the patient perspective on ADRs [35]. Collaborating and connecting pharmacovigilance databases to other ADR data could facilitate better use of data [36, 37], as we explore in **Chapter 4.1** by combining data from systematic monitoring and a patient registry.

Thus, expanding standardised data elements of ADRs, implementing systematic monitoring, combining data from different sources, and collaborating with other healthcare systems provide opportunities for pharmacovigilance to make better use of data. Collaboration with healthcare systems also provides an opportunity to further integrate pharmacovigilance into clinical practice and facilitate data exchange [38]. With sufficient supporting data, patterns in specific ADRs can be identified and analysed so that big data can be used to create information valuable for the individual patient. Providing this information to patients and healthcare professionals in a comprehensible way can contribute to patient-centred care in clinical practice and improve ADR management.

Towards more tailored ADR information for patients

To engage patients in managing their ADRs, ADR information should be accessible, tailored to individual needs and comprehensible, taking differences in health literacy into account [39]. This means that ADR information should be tailored to a patient's information needs regarding content, the personal situation (context) and provided via the right channel at the right time.

Content of information

The content of currently available ADR information is insufficient and requires more aspects than only nature and frequency as mentioned in drug package leaflets. Additional information entails what to expect and what to do when an ADR occurs, and should include recurring patterns, duration, burden, specific moments it might occur or information on triggering factors or management strategies. The information provided to a patient should be personalised, depending on a patient's personal needs and should be trustworthy, up-to-date and should be similar across various channels distributing the information.

Context

Information should also be tailored according to the situation of the patient. This entails further specification in ADR occurrence or frequencies according to specific patient characteristics such as sex, condition, genetics or other predisposing risk factors. It also entails the amount of information a patient is able and willing to process and understand at once. These factors may differ for every individual.

Timing

The timing when a patient wants to receive or access information is important and might differ per individual. Some patients want information before they start using a drug, others only when an ADR occurs. A possibility for the latter could be to embed detailed, tailored information in patient therapy monitoring systems that provide information in the patient's personal environment as soon as an ADR is reported. A personal environment enables adjusting the information to the patient's individual wishes and contributes to individual patient care. Such

applications are currently under investigation in oncology for providing ADR information according to personal wishes at the right time [40-42].

Information distribution channels

According to patients' wishes related to content and context of desired information, the appropriate channel to receive or access information can vary. A channel is the medium through which information is provided, and it could be, for example, digital or printed, in text or with figures. The summary of product characteristics (SmPC) is currently the main and most frequently used document with ADR information. The drug package leaflet for patients is based on this SmPC.

Drug package leaflet

Expanding information in the drug package leaflet may be overwhelming and undesirable, as these documents are extensive and already difficult to understand [43-46]. All information combined in one package leaflet might not be in line with the patient's wishes and situation (content and context). Fear for ADRs is another hindering factor for reading package leaflets [47]. Broadening information for each individual ADR would take up more space in an already lengthy document. Besides, tailoring a package leaflet to individual needs would be a challenge as these documents contain information applicable to everyone. Potentially, the electronic product information the European Medicines Agency is currently developing, may allow for more tailored information in the future [48]. In addition, animated videos from '*Kijksluiter*', an initiative visualising information from package leaflets in a comprehensible way, decrease complexity of information and provide an opportunity to tailor information regarding content and context as videos can be adjusted for different patient groups [49].

Other information platforms

Different, synchronised platforms or tools for comprehensive tailored ADR information may be desired. Currently, various professional, patient or scientific organisations provide ADR information in the Netherlands. Examples are websites from the Royal Dutch Pharmacist Association, the Netherlands Pharmacovigilance Centre Lareb or 'Farmacotherapeutisch Kompas' from the National Healthcare Institute. Another example is a tool built in pharmacy information systems to provide concise drug information for patients when a drug is dispensed. This tool is provided by Health Base, a centre providing pharmacotherapeutic content [50]. Furthermore, various websites provide more extensive information for specific patient groups or within specific fields. Information about ADRs on websites from institutions and hospitals is often based on the SmPC uniformity is lacking and this information may not always be up-to-date. In addition, false or unreliable information may be distributed through various informal channels. Discrepancies and contradictions in information from different sources can be confusing for patients. A collaboration of stakeholders providing drug information in the Netherlands, known as G7, aims to synchronise the provision of independent drug information for healthcare professionals [51]. To distinguish reliable information, a quality mark assigned to trustworthy ADR information could provide clarity to patients. This quality mark could be coordinated

by the G7 collaboration and should be well-known and acknowledged and referred to by all national healthcare institutions and associations.

As the patient journey and the routing of care may differ in various fields, the channels for distributing ADR information should comply with the field. In oncology, a project aiming for one reliable ADR information source was recently initiated. The project involves cooperation of different stakeholders to provide uniform and up-to-date information from one source, www.bijwerkingenbijkanker.nl operated by the Netherlands Comprehensive Cancer Organisation IKNL [52]. For other fields, such an initiative could also be beneficial.

Exchanging patient experiences

A different and relatively new type of channel for providing ADR information is a 'PatientsLikeMe'-type platform where only patients provide content of information. The concept PatiensLikeMe originates from an online data-sharing platform developed in the USA where patients can share and compare experiences with those of others with similar conditions, drugs and ADRs (www.patientslikeme.com) [53, 54]. Many patients favour patients-like-me case studies as a way of presenting information, as demonstrated by an international survey among patients with neuroendocrine tumours [55]. The American PatientsLikeMe platform has already demonstrated various benefits for patients including improved outcomes, improved quality of life and perceived control over the disease and the possibility to ask and offer advice to patients with similar issues and social support [53, 54].

Such a platform based on patients' ADR experiences can be a valuable information source for patients, in line with rating and reviewing restaurants and hotels on recognised platforms. However, to ensure reliable information on such a platform, it should be adequately managed and regulated. In the Netherlands, patients can currently rate satisfaction with drugs and share and read personal experiences on several websites such as www.mijnmedicijn.nl and www.meldpuntmedicijnen.nl. On these websites, experiences can be shared through narratives but do not contain structured details of the ADR. To gain ADR knowledge from data on such a platform, patients should be able to share their own experiences in a standardised way so that elements such as course and burden can be included. This enables patients to track their own ADR experiences and compare these on an aggregated level with experiences from other patients, as illustrated in **Figure 1**.

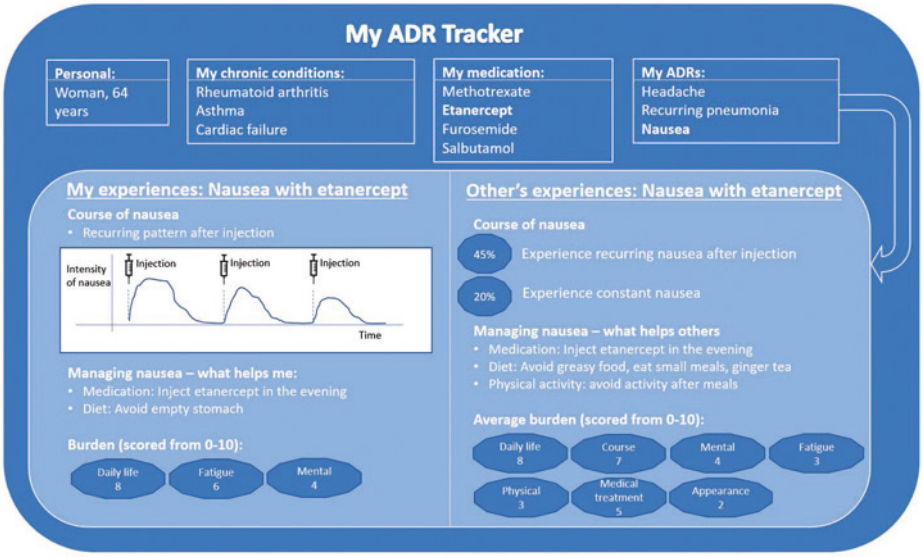


Figure 1. A suggestion for an adverse drug reaction tracking platform for patients to track their adverse drug reaction experiences and compare these with experiences from other patients. All information in this example is fictional. ADR: adverse drug reaction.

Further research should focus on patients' wishes and needs for reliable platforms for extensive, synchronised, up-to-date ADR information so that patients can be informed according to individual needs. These platforms should correspond to how different patients search for information, find and process information, taking into account personal wishes, health literacy and language proficiency. Connecting information platforms to existing healthcare systems would enable more efficient use in clinical practice [38].

Contribution to patient care

Enriching ADR knowledge with the patient perspective and providing more in-depth ADR information are pharmacovigilance activities that can improve ADR management and medication use when embedded in clinical practice. This could be accomplished by combining the pathways of pharmacovigilance activities, which have been outlined by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance [56], with the Chronic Care Model, as illustrated in **Figure 2** [57, 58]. The Chronic Care Model was developed to improve management of chronic illnesses by transforming routine care. According to this model, improvements in six interrelated elements are important for more informed, activated patients and prepared, proactive healthcare professionals to ultimately contribute to improved patient care:

- **Healthcare organisation:** Healthcare must be organised in a way that enables data exchange between pharmacovigilance centres and health records, ensuring data security and confidentiality.

- **Delivery system design** In-depth ADR information is important for a well-organised healthcare delivery system in order to deliver the information that is needed for proper ADR management.
- **Self-management support**: Self-monitoring of ADRs and providing ADR self-management opportunities will contribute to awareness and to patients taking control and recognising and managing their ADRs [59].
- **Decision support:** Treatment decisions tailored to the patient's situation can be improved when knowledge about occurrence and characteristics of ADRs and associated risk factors is expanded and implemented in shared decision support tools.
- **Clinical information systems**: ADR monitoring systems, establishing appropriate channels for ADR information and exchanging ADR data between healthcare systems and pharmacovigilance centres all contribute to improved use of medicines. Additionally, integrating patient ADR monitoring into clinical information systems enables healthcare professionals' awareness, feedback and involvement to get in contact about the ADR and allow for timely action if needed, to improve pharmacotherapy with a tailored approach.
- **Community resources**: Stimulating patients to discuss and report ADRs can be improved by healthcare professionals, patient associations and patients' caregivers and surroundings. A platform where patients can exchange ADR experiences may be a useful community resource.

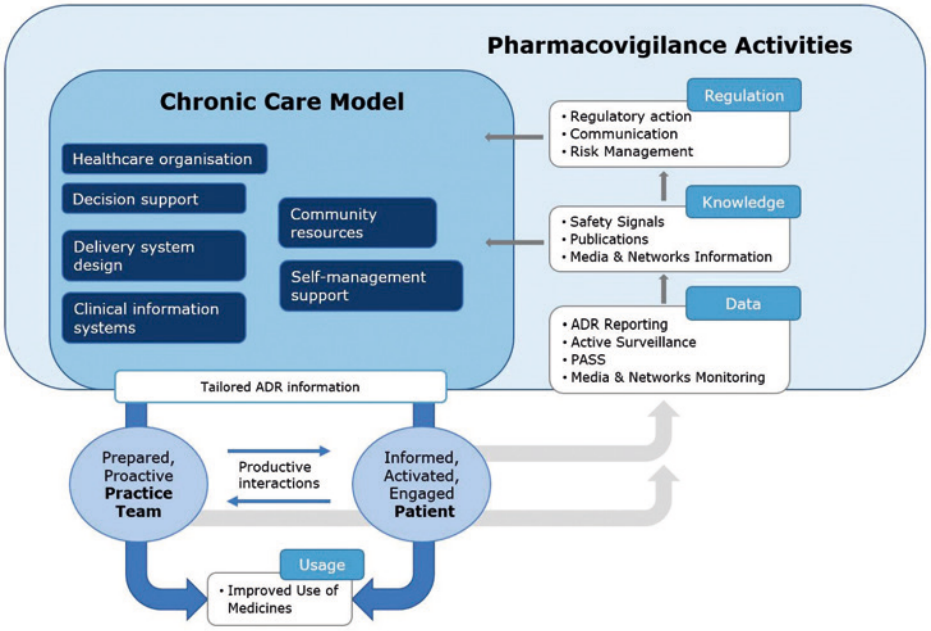


Figure 2. An illustration how pharmacovigilance activities can contribute to improving outcomes in the Chronic Care Model. ADR: adverse drug reaction. PASS: post-authorisation safety studies.

Challenges and Future research

Several challenges and recommendations for future research can be identified.

Challenges

Reliability of data

A challenge with ADR data from patients is that it is not always clinically verified and a causal relation is not always established. In fact, ADRs are often multifactorial and factors such as age, genetic predisposition and comorbidities may also play a role in their occurrence, making its identification extra complex [60]. In addition, distinguishing between an ADR and another condition is challenging and often remains unclear. Using patient-reported data in pharmacovigilance to gain knowledge about course and burden of ADRs is therefore challenging. A causality assessment is essential for determining the degree to which a reaction is linked to the drug, especially when identifying new ADRs. For common and well-known ADRs, expanding knowledge about course and burden is more feasible as more data becomes available. Richness of patient-reported data with aspects on course and burden of a potential new ADR may provide a new lead for further investigation, but a safety signal needs to be confirmed, just as the course of fatigue around biologic injections was a lead for further exploration in **Chapter 5**. Patterns in course of symptoms may reveal previously unknown issues or assumptions of patients not yet recognised by healthcare professionals, as was the case with fatigue with biologics. This information can subsequently be used to support or reassure patients about their symptoms, even when the symptom is not established as an ADR.

Embedding ADR monitoring systems for patients a in electronic health records, may increase reliability as it allows the patient and healthcare professional to get in contact about the potential ADR and discuss other possible causes before transferring the information to a pharmacovigilance centre.

Big data vs. the individual patient

Systematic data collection of elements as course and burden of ADRs enables quantification of such data that can be used to discover patterns. This step is valuable for expanding knowledge and may also help to identify risk factors for ADRs. Nonetheless, it is important to take the individual patient into account and not overgeneralise as every patient and ADR experience is unique. Individual differences and needs should be considered to create useful, tailored information for an individual patient.

Information applicable and accessible for everyone?

Providing accessible, comprehensible ADR information tailored to individual needs, taking differences in health literacy into account will be a challenge and requires further investigation. In the Netherlands, 36.4% of adults have insufficient or limited health literacy skills [61]. Health literacy is defined as '*the skills to gain access to, understand and use information to promote and*

maintain good health'. Therefore content, context and distribution channels of information should be designed according to the wishes and possibilities of people with different health literacy levels [61]. Also language and cultural differences should be taken into account.

Recommendations for future research

Implementing tailored ADR information

Future research should determine what ADR information should look like when more knowledge about course and burden of ADRs is available and how this can be personalised and should be presented so that it is useful for everyone according to individual needs and competencies. It is important to investigate how to implement this new type of information in clinical practice and regularly evaluate usefulness in order to contribute to shared decision making and improve patient care.

A quality mark for trustworthy ADR information

Feasibility and acceptability of a quality mark for trustworthy ADR information requires further investigation before this can be implemented.

Impact

When in-depth, tailored ADR information is available and implemented for use in clinical practice, research should focus on its contribution to shared-decision making, impact on treatment adherence and persistence, ADR management, burden and overall satisfaction with the available information.

Conclusion

This thesis demonstrated how information about ADRs provided by patients can enrich knowledge of known and new ADRs on a deeper level than only nature and frequency as currently available in drug package leaflets. As the aim of pharmacovigilance is to improve patient care and drug safety by minimising harm by medicines, it is time to maximise the impact of patient engagement and broaden the focus from detecting new ADRs to also expand knowledge and information about ADRs, to really contribute to minimising their impact and improve patient care. After all, we are doing this for the patient.

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Chapter 7

Samenvatting/Summary

Chapter 7.1

Nederlandse samenvatting

Achtergrond

Geneesmiddelen zijn waardevol om klachten bij ziekte te verminderen en soms zelfs een ziekte te remmen of te stoppen. Echter, bij gebruik van een geneesmiddel kunnen ook bijwerkingen optreden. Bijwerkingen zorgen niet alleen voor lichamelijke klachten, ze kunnen ook mentale klachten geven en impact hebben op sociaal functioneren. Daardoor kan de therapietrouw afnemen. Ook kan er een extra geneesmiddel worden voorgeschreven of er kan zelfs ziekenhuisopname nodig zijn om de bijwerking te behandelen. Door bijwerkingen hebben mensen meer zorg nodig waarmee de zorgkosten stijgen. Om de impact van bijwerkingen te beperken, is het belangrijk om ze zo mogelijk te voorkomen, en te herkennen, behandelen en onder controle te krijgen als een bijwerking optreedt. Daarvoor dient niet alleen de zorgverlener maar ook de patiënt voldoende geïnformeerd te worden. Echter, op dit moment wordt onvoldoende voldaan aan de behoefte van patiënten aan informatie over bijwerkingen.

De beschikbare informatie over bijwerkingen is afkomstig uit geneesmiddelonderzoek en van farmacovigilantie (geneesmiddelbewaking) centra. Farmacovigilantie is de wetenschap en activiteiten rond opsporing, beoordeling, kennis en preventie van mogelijke bijwerkingen of andere geneesmiddel-gerelateerde problemen. Farmacovigilantie centra houden zich bezig met het ontdekken van nieuwe informatie over bijwerkingen, wat met name neerkomt op het signaleren van 'nieuwe' bijwerkingen die nog niet in de bijsluiter van een geneesmiddel staan. In het verleden werd vooral data afkomstig van zorgverleners, zoals huisartsen en apothekers, gebruikt om nieuwe informatie over bijwerkingen te ontdekken. Tegenwoordig wordt ook informatie afkomstig van de patiënt gebruikt, die rijke details bevat. Daarmee kan informatie in de bijsluiter worden bijgewerkt.

Echter, in de bijsluiter staat vooral informatie over de aard van bijwerkingen en hoe vaak het voorkomt. Zelden staat er wat te verwachten is wanneer een bijwerking optreedt, of het over kan gaan, wat eraan gedaan kan worden en hoeveel impact het op patiënten kan hebben. Informatie over dergelijke, bredere aspecten van bijwerkingen is wenselijk om zorgverleners en patiënten meer inzicht te geven over bijwerkingen maar is nog nauwelijks beschikbaar.

Het is daarom zonde dat de details die patiënten geven over bijwerkingen vooral gebruikt worden om nieuwe bijwerkingen op te sporen. Immers, de informatie van patiënten kan ook gebruikt worden om nieuwe gebruikers te informeren over verwachtingen zoals het beloop, hoelang het kan duren of de impact die een bijwerking kan hebben. Farmacovigilantie centra zouden beter gebruik kunnen maken van het patiënten perspectief op bijwerkingen. In dit proefschrift is onderzocht hoe dit type data kennis over bijwerkingen kan verrijken om patiënten en zorgverleners van meer verdiepende en bruikbare informatie te voorzien die belangrijk is om de impact van bijwerkingen te beperken.

Belasting van bijwerkingen

Het eerste onderzoek van dit proefschrift in **hoofdstuk 2** beschrijft hoeveel last patiënten met chronische immuunziektes ervaren van bijwerkingen van biologische geneesmiddelen (geneesmiddelen die de afweer remmen). Hieruit blijkt dat infecties en spier- en botklachten het meest belastend zijn en injectieplaatsreacties het minst belastend. Ook bijwerkingen waarvoor contact met een zorgverlener nodig is en bijwerkingen waardoor met het geneesmiddel werd gestopt worden als belastend ervaren. Met meer inzicht in de last die bijwerkingen geven op het dagelijks leven, kunnen patiënten beter geholpen worden.

Beloop van bijwerkingen

In **hoofdstuk 3** is gekeken naar welke aspecten je moet kijken als je het beloop van bijwerkingen zou willen beschrijven. Op basis van patiëntbeschrijvingen zijn de volgende onderwerpen geïdentificeerd: frequentie van optreden (zoals eenmalig of terugkerende patronen), de duur van de bijwerking, ontwikkelingen in intensiteit, specifieke momenten dat een bijwerking optreedt en uitlokkende of verbeterende factoren. Door dergelijke aspecten van bijwerkingen beter in kaart te brengen kan er ook meer informatie over worden verstrekt.

Nieuwe bijwerkingen

Hoofdstuk 4 beschrijft hoe patiëntervaringen met bijwerkingen bijdragen aan het ontdekken van nieuwe bijwerkingen. In **hoofdstuk 4.1** is onderzocht hoe patiënten maagdarmklachten toeschrijven aan etanercept (een geneesmiddel dat de afweer remt). Deze mogelijke bijwerkingen werden eerder niet herkend door zorgverleners, maar leiden soms wel tot dosisreductie of stoppen met het geneesmiddel. In **hoofdstuk 4.2** wordt te lage bloedsuikerwaarden (hypoglykemie) als mogelijke nieuwe bijwerking beschreven bij JAK-remmers, een groep geneesmiddelen die worden gebruikt bij reuma. Een patiënt meldde dat hij na het gebruik van de JAK-remmer baricitinib te lage bloedsuikerwaarden opmerkte waardoor zijn geneesmiddelen voor diabetes moesten worden aangepast. In dit onderzoek is een reeks vergelijkbare meldingen aan farmacovigilantie centra in kaart gebracht en inmiddels wordt hiervoor gewaarschuwd in de bijsluiter.

Beloop en belasting van een potentiële nieuwe bijwerking

In **hoofdstuk 5** komen het beloop en de belasting van een potentiële nieuwe bijwerking samen. In **hoofdstuk 5.1** wordt beschreven hoe patiënten vermoeidheid ervaren als bijwerking van biologische geneesmiddelen, een klacht die door zorgverleners vaak niet als bijwerking van deze geneesmiddelen wordt beschouwd. De helft van de patiënten die denken dat vermoeidheid een bijwerking is, ervaart vermoeidheid volgens een specifiek patroon. Zo beschreven veel patiënten een toename in vermoeidheid tijdens of kort na de injectie, wat vaak na een volgende toediening terugkeert. In **hoofdstuk 5.2** zijn patronen in het beloop en de mate van vermoeidheid verder onderzocht bij een groter aantal patiënten door vermoeidheid te meten op de dagen rond de injectie met behulp van een vermoeidheidsscore. Bij de meeste mensen was er geen verandering in vermoeidheid na de injectie maar sommige mensen ervaarden structureel een verbetering in vermoeidheid na de injectie, terwijl andere patiënten steeds

na de injectie juist meer vermoeidheidsklachten hadden. Inzicht in dergelijke patronen is waardevol om patiënten goed te informeren.

Discussie

De onderzoeken in dit proefschrift laten de rijkheid aan informatie zien in patiënt-gerapporteerde bijwerkingen. In **hoofdstuk 6** wordt beschreven welke vervolgstappen nodig zijn om deze rijke informatie beter vast te leggen zodat waardevolle kennis voor de klinische praktijk kan worden uitgebreid om de impact van bijwerkingen op patiënten te verkleinen.

Om daar te komen moeten farmacovigilantie centra meer aandacht gaan besteden aan het verrijken van kennis over zowel nieuwe als bekende bijwerkingen. Daarvoor moeten aspecten over het beloop en de belasting van bijwerkingen systematisch worden uitgevraagd, in plaats van als vrije tekst zoals op dit moment nog veel gebeurt, zodat deze kennis makkelijker gegenereerd kan worden. Verder moeten de ervaringen van patiënten niet één keer maar meerdere keren achter elkaar opgevraagd worden waardoor waardevolle informatie over het beloop en de belasting van bijwerkingen in de tijd ontstaat. Als laatste is samenwerking met andere databronnen waar data over bijwerkingen wordt vastgelegd, zoals patiëntendossiers of andere zorgsystemen, een belangrijke stap om meer over bijwerkingen te kunnen leren. Dit laatste biedt ook een kans om farmacovigilantie meer te verankeren in bestaande zorgsystemen zodat data en nieuwe kennis makkelijker uitgewisseld kunnen worden. Dat versnelt ook het beschikbaar maken van nieuwe kennis voor direct gebruik in de praktijk.

Om de impact van bijwerkingen te verkleinen is het belangrijk dat beschikbare bijwerkingeninformatie toegankelijk en volledig is maar ook afgestemd op persoonlijke behoeften van de patiënt. Informatie moet daarom worden afgestemd op de inhoud, de situatie, timing en de manier waarop en wanneer een patiënt het wil ontvangen. Aan een bijsluiter zitten beperkingen, waardoor ook andere manieren om informatie bij de patiënt te krijgen moeten worden onderzocht. Een platform voor het uitwisselen en vergelijken van patiëntervaringen, inclusief het beloop en de belasting van bijwerkingen, kan bijvoorbeeld ook waardevol zijn.

Informatie over bijwerkingen afkomstig van patiënten kan kennis over bekende en nog onbekende bijwerkingen verrijken waarmee meer informatie beschikbaar kan komen dan er nu is. Het wordt tijd om patiënten echt bij farmacovigilantie te betrekken en om bruikbare informatie te creëren die de impact van bijwerkingen kan beperken.

Chapter 7.2

English summary

Background

Drug treatment is valuable to prevent, manage and cure medical conditions. Adverse drug reactions (ADRs) can occur with drug treatment. In addition to physical complaints, ADRs can have social and psychological impact on patients. This can negatively affect drug adherence, sometimes prescription an additional drug is prescribed and ADRs may even hospitalisation may be necessary to treat the ADR. This all affects healthcare utilisation and costs. To minimise the impact of ADRs, it is important to prevent them where possible and to recognise, treat and manage them when they occur. For that, relevant information for patients and healthcare professionals is important. Currently, patients' needs for information about ADRs are not sufficiently met.

Available ADR information comes from drug research and pharmacovigilance centres. Pharmacovigilance is defined as the science and activities relating to detection, assessment, understanding and prevention of adverse effects or any other medicine related problem. Pharmacovigilance centres monitor drug safety by detecting new information about ADRs, which mainly involves identifying 'new' ADRs that are not yet mentioned in the drug package leaflet. In the past, mainly data from healthcare professionals was used to detect new information about ADRs. Nowadays also information from patients is used, which contains rich details. With this information the package leaflet can be updated.

However, drug package leaflets mainly contain information about the nature and frequency of ADRs. Only rarely, they contain additional details on what to expect when an ADR occurs, if it can resolve, what to do about it and what impact it may have on patients. Information about such broader aspects of ADRs is rarely available but it is desirable to provide patients and healthcare professionals with better insights into ADRs.

Data from patients is mainly used to detect new ADRs while these rich data can also be used to inform other patients about expectations on the course or impact on daily life. Pharmacovigilance centres can therefore make better use of the patient perspective on ADRs. This thesis explores how this type of data can enrich knowledge about ADRs in order to provide useful and more in-depth information that is important to ultimately reduce the impact of ADRs.

Burden of adverse drug reactions

The study in **Chapter 2** provides insights into the burden of ADRs of biologics (which are immunosuppressant drugs) as experienced by patients with chronic immune diseases. Infections and muscle and bone-related ADRs are experienced as most burdensome and injection site reactions are least burdensome. ADRs that require contact with a healthcare professional and ADRs leading to drug discontinuation are also experienced as burdensome. With a deeper understanding of the impact that ADRs can have on daily life, patients can be supported better in clinical practice.

Course of adverse drug reactions

In **Chapter 3**, we investigated how patients describe the course of ADRs. We identified the following themes from a wide range of patient descriptions: frequency of ADR occurrence (such as once or with recurring patterns), the duration of ADR episodes, developments in intensity, specific moments an ADR occurs and triggering or improving factors. By identifying these aspects on the course of ADRs, more information can be provided in the future.

New adverse drug reactions

Chapter 4 evaluates how patient descriptions of ADRs contribute to detecting new ADRs. **Chapter 4.1** explored how patients attribute gastrointestinal complaints to etanercept, an immunosuppressant drug. These potential ADRs were generally not recognised by healthcare professionals but did sometimes lead to dose adjustments or drug discontinuation. **Chapter 4.2** outlines cases of low blood glucose levels as a new ADR of a group of drugs known as JAK-inhibitors. This was triggered by a clear description from a patient who experienced low blood glucose levels after starting with the JAK-inhibitor baricitinib, requiring dose adjustments of his antidiabetic drugs. A warning is now included in the package leaflet of baricitinib.

Course and burden of a potential new adverse drug reaction

Chapter 5 incorporates the course and burden in investigating a potential new ADR. **Chapter 5.1** describes how patients experience fatigue as an ADR of biologics, a complaint that healthcare professionals generally do not consider an ADR of biologics. Half of the patients suspecting fatigue as an ADR, describe a specific pattern of fatigue. Many of these patients experience an increase in fatigue during or shortly after injection, often recurring following subsequent injections. Patterns in the course of fatigue were further investigated in **Chapter 5.2** by measuring fatigue in rheumatic disease patients on the days surrounding the injection of their biologic using a numeric rating scale. Most patients did not experience a specific difference in fatigue following their biologic injections but some patients consistently experience an increase in fatigue after injection and other patients consistently experience an improvement in fatigue the days after injection. Insights into such patterns is valuable to better inform patients.

Discussion

The studies in this thesis demonstrate the richness of information in patient-reported ADRs. **Chapter 6** considers the steps that need to be taken to better collect and register this rich information, to enable expanding knowledge that can be used in clinical practice to minimise the impact of ADRs.

To achieve that, pharmacovigilance centres should pay more attention to enriching knowledge about new and known ADRs. Aspects as course and burden of ADRs should be systematically collected instead of using open text fields as is currently common practice. Furthermore, longitudinal data collection of patient experiences contributes to insights into the course and burden of ADRs over time. Finally, collaboration and combining pharmacovigilance data with

other ADR data sources, such as electronic health records or patient-reported outcomes, is an important step to learn more about ADRs. This also provides an opportunity for further integrating pharmacovigilance in existing healthcare systems which enables exchange of data and knowledge. This will facilitate faster availability of new ADR knowledge for direct use in clinical practice.

To minimise ADR impact it is important that ADR information is comprehensive, accessible and tailored to individual needs. Information should therefore be tailored to a patient's information needs regarding content, the personal situation and provided via the right way and at the right time. Drug package leaflets have limitations considering these aspects so other approaches should be explored. A platform for exchanging and comparing patient experiences that include course and burden of ADRs, could, for example, also be valuable for patients.

ADR information from patients can enrich knowledge about known and still unknown ADRs that can be used to provide more information than currently available. It is time to fully engage patients in pharmacovigilance and to provide useful information to patients and healthcare professionals to minimise the impact of ADRs.

Appendices

Research Data Management

Data sources

- In Chapter 2, Chapter 3, Chapter 4.1 and Chapter 5.1 data from the Dutch Biologic Monitor was used.
- In Chapter 3 and Chapter 4.2 adverse drug reaction reports were used from the databases of Pharmacovigilance centre Lareb and the European Medicines Agency (Eudravigilance). In Chapter 4.1 data from the DREAM registry was used that was reported to Pharmacovigilance centre Lareb, further referred to as Lareb.
- Chapter 5.2 is fully based on the results of research involving human participants.

Ethics and privacy

Ethics

A statement that the Dutch Biologic Monitor was not subject to the Dutch Medical Research Involving Human Subjects Act (WMO), was obtained from the recognized Medical Ethics Review Committee of Brabant (NW2016-66). The Monitor was also approved by the medical ethics committees of the associated hospitals. The studies based on existing Lareb and Eudravigilance data were conducted following guidelines on Good Pharmacovigilance Practice in accordance with relevant national and international legislation and regulations concerning pharmacovigilance data. In the DREAM registry, no additional data, other than data collection in routine clinical practice, are collected. Therefore, ethical approval was not required according to Dutch regulations. The registry was approved by the recognized Medical Ethics Review Committee 'METC Medisch Spectrum Twente' (P05-39). A statement that Chapter 5.2 was not subject to the Dutch Medical Research Involving Human Subjects Act (WMO), was obtained from the recognized Medical Ethics Review Committee 'METC Oost-Nederland' (2022-13752). The study was approved by the institutional review board of the Sint Maartenskliniek 'ToetsingsCommisie Reuma' (2022-1040).

Privacy

The privacy of the participants of the Dutch Biologic Monitor is warranted by encrypting personal information in a secured database. Directly identifiable data of the participants is only accessible in the admin of the survey software. Only appointed authorized personnel of Netherlands Pharmacovigilance Centre Lareb involved in the study can access the admin. Informed consent was obtained from all participants in the Dutch Biologic Monitor to collect and process their data for scientific research. The privacy of reporters to pharmacovigilance Centre Lareb is warranted by encrypting directly identifiable data in the database. Only appointed authorized personnel of Netherlands Pharmacovigilance Centre Lareb can access personal data. Informed consent to use the data for scientific research and share the reports without directly identifiable data with authorities for pharmacovigilance purposes is obtained from everyone submitting a report. Informed consent to publish the study in Chapter 4.2 was directly obtained

from the patient involved. The privacy of participants in the DREAM registry is warranted by pseudonymization. The pseudonymization key was only accessible to members of the project at Medisch Spectrum Twente. All patients had given written consent before inclusion in the registry, including data assessments by Lareb. The privacy of the participants in Chapter 5.2 was warranted by the use of pseudonymization. The pseudonymization key was stored on a secured network drive at the Sint Maartenskliniek that is only accessible to the members of the project that also have a treatment relationship with the patients. The pseudonymization key was stored separately from the research data. Informed consent was obtained from all participants to collect and process their data for this study prior to participation.

Data collection and storage

Data in the Dutch Biologic Monitor was collected using secured online questionnaires. The questionnaires were created in the Lareb Intensive Monitoring survey software. Participants could complete questionnaires in their secured personal account on a dedicated website for the study. This website was protected using a Secure Sockets Layers certificate and data was stored in an SQL database. Lareb reports are voluntarily reported to Lareb and are stored in a SQL database (PVreport) with a daily back-up. Adverse drug reaction data from the DREAM registry were collected from clinical data and patient-reported outcomes. Data was collected and stored using a shared Web-based data acquisition system (www.mijnreumacentrum.nl). Adverse drug reaction reports from the DREAM registry were included in the Lareb database and processed and stored in the same manner as Lareb reports. Data for Chapter 5.2 was obtained through an online survey system created in an online Personal Health Record (Zorgdoc) and partly extracted from electronic health records (Hix). Raw data was stored on the server of the research department at the Sint Maartenskliniek in .xlsx or .csv format. Pseudonomyzed data from this study were also stored at the Lareb server in .xlsx format.

Data sharing according to the FAIR principles

Findable and accessible

Data from the Dutch Biologic Monitor and Lareb reports, including reports from the DREAM registry, can be made available without directly identifiable data on reasonable request by contacting the corresponding author and after a collaboration agreement has been made to ensure data analyses and interpretation remain associated to Lareb. The Dutch Biologic Monitor and Lareb reports are listed in the metadatabase ‘Zorggegevens’. The Dutch Biologic Monitor does not follow a metadata standard, since the data is tailored and therefore cannot be coupled to other studies. Eudravigilance adverse drug reaction reports are accessible at https://www.adrreports.eu/ according to the European Medicines Agency’s (EMA) EudraVigilance Access Policy. The dataset from Chapter 5.2 can be made available on reasonable request by contacting the corresponding author.

Interoperable and reusable

Documentation for interpretability and R-scripts (where applicable) are saved with all datasets. Lareb registers data processing activities for Lareb reports, including reports from the DREAM registry, and Dutch Biologic Monitor data, in audit trails. This data is structured in standardised fields, including the Medical Dictionary for Regulatory Activities (MedDRA) for adverse drug reactions and classification of drugs according to the Anatomical Therapeutic Chemical (ATC) classification and the Dutch Drug database (G-standaard). Lareb reports will be saved as long as the data is of use for monitoring medication safety, as this is part of the responsibilities of Lareb according to legal requirements. Data from the Dutch Biologic Monitor is saved for maximally 15 years after the study end date. After this 15 year period, the data will be assessed to determine whether it is still useful for pharmacovigilance. The dataset from Chapter 5.2 is saved for 10 years at the Sint Maartenskliniek. Re-using the data for other research requires renewed permission by the patients as informed consent was only provided for the research objective of this study.

PhD Portfolio

PhD portfolio of Jette Annemarijn van Lint

Department: **Pharmacy**
PhD period: **2022-2025**
PhD Supervisor(s): **Prof. dr. B.J.F. van den Bemt, Prof. dr. H.E. Vonkeman, Prof. dr. E.P. van Puijenbroek**
PhD Co-supervisor(s): **Dr N.T. Jessurun**

Training activities	**Hours**
Courses	41.00
- EpidM Epidemiologisch onderzoek: basisprincipes (V10) (2021)	28.00
- Programming in R (2021)	18.00
- Statistical programming in R (2021)	36.00
- EpidM Principes van epidemiologische data-analyse (V20) (2022)	22.00
- EpidM Klinimetrie: het ontwikkelen en evalueren van meetinstrumenten (V40) (2022)	15.00
- RIHS - Introduction course for PhD candidates (2022)	52.00
- RU - Projectmanagement for PhD candidates (2022)	20.00
- RU - Analytic Storytelling (2023)	75.00
- RU - Effective Writing Strategies (2023)	20.00
- Radboudumc - Scientific integrity (2024)	36.00
- EpidM Regressietechnieken (V30) (2024)	
Seminars	
Conferences	28.00
- Annual European Congress of Rheumatology – poster presentation (2019)	16.00
- NVR Najaarsdagen – poster tour presentation (2019)	28.00
- Annual European Congress of Rheumatology – oral and poster presentation (2020)	28.00
- Annual European Congress of Rheumatology – poster presentation (2021)	8.00
- Congres Goed Gebruik Geneesmiddelen (2022)	28.00
- Annual European Congress of Rheumatology – poster tour presentation (2022)	8.00
- Post EULAR symposium – oral presentation (2022)	16.00
- Skin Inflammation & Psoriasis International Network Congress – oral and poster tour presentation (2022)	8.00
- Congres Goed Gebruik Geneesmiddelen – oral presentation (2023)	16.00
- ISoP Mid-Year Symposium - oral presentation (2023)	
Other	
Teaching activities	
Lecturing	
Supervision of internships / other	40
- Supervision student (HBO) 20 weeks parttime (2021-2022)	40
- Supervision student (HBO) 20 weeks parttime (2022)	56
- Supervision master student 6 months fulltime (2023)	40
- Supervision student (HBO) 20 weeks parttime (2024)	56
- Supervision master student 6 months fulltime (2024)	10
- Supervision master student 5 weeks fulltime (2024)	56
- Supervision master student 6 months fulltime (2025)	
Total	**845.00**

Curriculum vitae

Jette van Lint was born on 17 September 1991 in Utrecht and grew up in Breukelen. After completing bilingual VWO at RSG Broklede in 2009, she studied pharmacy at the Rijksuniversiteit Groningen. During her masters she conducted her masters research project about medication therapy management at the University of Minnesota in Minneapolis, USA. This resulted in her first peer-reviewed publication. She obtained her masters in Pharmacy in 2015. After graduating, she worked as a pharmacist for 2 years in Franciscus Vlietland hospital, Schiedam. As she realised that hospital pharmacy was fun but not everything, she started working as a clinical scientific assessor at the Netherlands pharmacovigilance centre Lareb in 's-Hertogenbosch. This was the perfect combination of exploring and learning about the effects drugs can have without having to deal with the logistics in daily pharmacy practice. At Lareb, she got involved in research with the Dutch Biologic Monitor project together with Naomi Jessurun, Leanne Kosse and the help of many students. This resulted in several publications and the start of this PhD trajectory. Some of the studies in this thesis have led to the successor of the Dutch Biologic Monitor: the Adverse Drug Reaction (ADR) Monitor (Bijwerkingmonitor), a currently ongoing project. After submitting this thesis, Jette started clinical pharmacology training in the Jeroen Bosch Hospital in 's-Hertogenbosch in April 2025.

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