Patients report fatigue as an adverse drug reaction of biologics

Jette van Lint, Tom Bakker, Jouke Ubbink, Martijn van Doorn, Phyllis Spuls, Sander Tas, Harald Vonkeman, Frank Hoentjen, Bart van den Bemt, Michael Nurmohamed, Eugene van Puijenbroek, Naomi Jessurun

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DISCLOSURE STATEMENT

- No conflicts of interest
- Taking pictures is ALLOWED during the full presentation

Background

- Fatigue is a well known symptom in many immune-mediated inflammatory diseases, including rheumatic diseases
- Fatigue was reported as an adverse drug reaction (ADR) of biologics in the Dutch Biologic Monitor

Van Lint JA, *et al*. *Drug Saf.* 2020
Kosse LJ, *et al. Rheumatol.* 2020

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Dutch Biologic Monitor

Prospective cohort event monitoring system for patient-reported ADRs attributed to biologics

- Comprehensive web-based questionnaires
- Patients were invited by healthcare professionals of 9 Dutch hospitals
- Inclusion criteria: use of a biologic, 18 years or older
- Started 1 Jan 2017, ongoing

Van Lint JA, *et al*. *Drug Saf.* 2020
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Dutch Biologic Monitor

Bimonthly questionnaires including follow-up

- Demographic information
- Biologic (e.g. adalimumab, etanercept, infliximab)
- Indication for biologic (e.g. RA, SpA, psoriatic arthritis, Crohn's disease, ulcerative colitis)
- Combination therapy (e.g. methotrexate, corticosteroids)
- Comorbidities (e.g. psychiatric, cardiovascular)
- For every experienced ADR: type and course of ADR, actions and consequences following ADR, experienced burden on a five-point Likert-type scale (5: very high burden)

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Objective

- To assess patient-reported fatigue as an ADR of biologics in the Dutch Biologic Monitor
- To investigate characteristics of patients that reported fatigue

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Methods

- All ADRs concerning fatigue reported between 1 Jan 2017 and 1 Nov 2019
- Comparison demographics/treatment characteristics:
  - Patients reporting fatigue as an ADR of biologics
  - Patients **not** reporting fatigue:
    - All patients reporting other ADRs
    - All patients reporting no ADRs
- Statistics: Mann Whitney U, independent t-test and Fisher's exact as appropriate

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Results

- Dutch Biologic Monitor: 1369 participants
  - 696 patients (51%) reported 1844 ADRs
- Fatigue attributed to biologics: 100 patients (7%)

	Patients with fatigue N(%)
Number of patients	100 (100%)
Age (years) (mean ± SD)	50.0 ± 14.6
Gender (Female)	59 (59%)
Smoking	25 (25%)
BMI (kg/m^2) (mean ± SD)	25.7 ± 4.4
ADR burden (mean ± SD)	2.9 ± 0.9

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Results

Out of 100 patient reporting fatigue as an ADR:

- Discussed with healthcare professional: 73%
- Consequences of biologic-associated fatigue:
  - Dose adjustments: 8%
  - Biologic discontinuation: 5%
- Pattern of recurring fatigue after each biologic administration: 48%
  - Recovery within one week: 88% (42 out of 48 patients)

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Results: patients that reported fatigue as ADR

	N	(%)
Number of patients	100	(100%)
Age (years) (mean ± SD)	50.0 ± 14.6	
Gender (Female)	59	(59%)
Smoking	25	(25%)
BMI (kg/m^2) (mean ± SD)	25.7 ± 4.4	
Mean burden of ADR ± SD	2.9 ± 0.9	
Biologics*		
Adalimumab	28	(28%)
Infliximab	22	(22%)
Etanercept	11	(11%)
Rituximab	9	(9%)
Tocilizumab	8	(8%)
Ustekinumab	6	(6%)
Vedolizumab	6	(6%)
Other	11	(11%)
Immune-mediated inflammatory diseases		
Rheumatoid arthritis	29	(29%)
Crohn's disease	29	(29%)
Psoriatic arthritis	15	(15%)
Axial spondyloarthritis	8	(8%)
Psoriasis	6	(6%)
Ulcerative colitis	5	(5%)
Other indication	16	(16%)

	N	(%)
Combination therapy		
Methotrexate	23	(23%)
Corticosteroids	22	(22%)
Thiopurines	12	(12%)
Hydroxychloroquine	5	(5%)
Leflunomide	2	(2%)
Sulfasalazine	3	(3%)
Mesalazine	4	(4%)
None	46	(46%)
Comorbidities		
Cardiovascular disorder	21	(21%)
Hypercholesterolaemia	13	(13%)
Respiratory disorder	12	(12%)
Psychiatric disorder	11	(11%)
Nervous system disorder	2	(2%)
Cancer	2	(2%)
Other	30	(30%)
None	27	(27%)

* One patient experienced fatigue as an ADR with 2 biologics (adalimumab and infliximab)

Fatigue vs. other ADRs

	Patients reporting fatigue N(%)		Patients reporting other ADRs N(%)		p-value*
Number of patients	100	(100%)	596	(100%)	
Age (years) (mean ± SD)	50.0 ± 14.6		53.4 ± 13.6		0.023
Smoking	25	(25%)	97	(16%)	0.046
Biologics					
Infliximab	22	(22%)	53	(9%)	<0.001
Etanercept	11	(11%)	177	(30%)	<0.001
Rituximab	9	(9%)	18	(3%)	0.009
Vedolizumab	6	(6%)	12	(2%)	0.033
Immune-mediated inflammatory diseases					
Rheumatoid arthritis	29	(29%)	270	(45%)	0.002
Crohn's disease	29	(29%)	77	(13%)	<0.001
Other indication	16	(16%)	53	(9%)	0.044
Comorbidities					
Other	30	(30%)	124	(21%)	0.050
ADR burden (mean ± SD)	2.9 ± 0.9		2.4 ± 1.1		<0.001

Patients with fatigue:

- Younger
- Smoked more often
- Used infliximab, rituximab or vedolizumab more often
- Used etanercept less often
- Had RA less often
- Had Crohn's disease more often
- higher ADR burden

* Statistics Mann Whitney U, independent t-test and Fisher's exact as appropriate. No statistically significant difference for: gender; BMI; biologics: adalimumab, tocilizumab, ustekinumab, other; indications: PsA, axSpA, ulcerative colitis, psoriasis; all combination therapy; comorbidities: cardiovascular, hypercholesterolemia, respiratory, psychiatric, nervous system, cancer, no comorbidity

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Fatigue vs. no ADR

	Patients reporting fatigue N(%)		Patients reporting no ADR N(%)		p-value
Number of patients	100	(100%)	673	(100%)	
Age (years) (mean ± SD)	50.0 ± 14.6		55.7 ± 14.2		<0.001
Smoking	25	(25%)	100	(15%)	0.013
Biologics					
Infliximab	22	(22%)	84	(12%)	0.018
Etanercept	11	(11%)	228	(34%)	<0.001
Rituximab	9	(9%)	6	(1%)	<0.001
Tocilizumab	8	(8%)	13	(2%)	0.003
Vedolizumab	6	(6%)	7	(1%)	0.003
Immune-mediated inflammatory diseases					
Rheumatoid arthritis	29	(29%)	272	(40%)	0.036
Crohn's disease	29	(29%)	88	(13%)	<0.001
Other indication	16	(16%)	39	(6%)	0.001
Combination therapies					
Methotrexate	23	(23%)	227	(34%)	0.039
Comorbidities					
Psychiatric disorder	11	(11%)	31	(5%)	0.016
Other	30	(30%)	102	(15%)	0.001

Patients with fatigue:

- Younger
- Smoked more often
- Used infliximab, rituximab, tocilizumab or vedolizumab more often
- Used etanercept less often
- Less often had RA
- More often had Crohn's disease
- Less often used MTX
- More often had psychiatric comorbidity

* Statistics independent t-test and Fisher's exact as appropriate. No statistically significant difference for: gender; BMI; biologics: adalimumab, ustekinumab, other; indications: PsA, axSpA, ulcerative colitis, psoriasis; all combination therapy; comorbidities: cardiovascular, hypercholesterolemia, respiratory, nervous system, cancer, no comorbidity

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Discussion

– Limitations
  - Lack of clinical confirmation of ADRs
  - Lack of disease charactistics

✓ Patient-reported data
  - Fill the gap in knowledge concerning ADRs and consequences of ADRs
  - Provides insights in patient experiences and can help clinicians in providing more personalised treatment options

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Conclusion

- Awareness of fatigue as a possible ADR is warranted since it can have significant burden
- Evaluating the course of complaints can help recognising fatigue as an ADR of biologics rather than a symptom of underlying disease

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Thank you for your attention!

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