An overview of reports on Infliximab

Introduction

Infliximab (Remicade®) has been approved for marketing in the EU on 13 August 1999 for treatment of rheumatoid arthritis and Crohn's disease. Newly collected information on safety resulted in several updates of the indications for use by the EMEA, most recently on 17-1-2002:[1,2]

> *Rheumatoid arthritis. The reduction of signs and symptoms as well as the improvement in physical function in patients with active disease when the response to disease-modifying drugs, including methotrexate, has been inadequate. In this patient population a reduction in the rate of progression of joint damage, as measured by X-ray, has been demonstrated. Efficacy and safety have been demonstrated only in combination with methotrexate.*
>
> *Treatment of severe, active Crohn's disease in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies. Treatment of fistulising Crohn's disease in patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).*

Infliximab is a chimeric IgG1 monoclonal antibody against tumour necrosis factor a (TNFa). TNFa, which level is increased in joints of rheumatoid patients and colonic tissue of Crohn's disease patients, is a cytokine with multiple biological actions including mediation of inflammatory responses and modulation of the immune system. The most commonly encountered adverse reactions during treatment were upper respiratory infections, headache, nausea, sinusitis, rash, cough and acute infusion reactions. Contraindications include infections and moderate to severe heart failure[2]. Some concern about the appropriate implementation of the indications, contraindications, special warnings and precautions might be justified. Infliximab is considered an active agent with a clinically relevant benefit, but also with substantial risks.
The recent (public) attention for infliximab, the update of the EMEA public statement and the issued 'dear doctor letter' on 7-2-2002 are reasons for Lareb to give an overview of the reports it has received.

Reports

Up until 20-3-2002 Lareb received 24 spontaneous reports from health professionals representing 45 suspected adverse drug reactions (ADRs) on infliximab (see Table 1). Seventeen of these reports were classified as serious.

Table 1. Distribution of the reported ADRs associated with the use of infliximab

System Organ Class (MedDRA)	*n*
Blood and lymphatic system disorders	1
Cardiac disorders	2
Gastrointestinal disorders	4
General disorders and administration site conditions	8(5†)
Immune system disorders	1
Infections and infestations	7
Investigations	2
Metabolism and nutrition disorders	1
Musculoskeletal and connective tissue disorders	3
Neoplasm benign, malignant & unspecified	1
Nervous system disorders	3
Renal and urinary disorders	1
Reproductive system and breast disorders	1
Skin and subcutaneous tissue disorders	3
Vascular disorders	3

The ADRs in the most frequently reported system organ class are specified below.
The class 'general disorders' includes five deaths in rheumatoid arthritic patients (Table 2) due to sepsis (3), pneumonia (1), and cardiac failure (1), respectively. Other reactions were influenza-like symptoms, chills, malaise, and chest pain.
The reported infections include sepsis, endophthalmitis, lower respiratory-tract infection, bacterial infection, otitis media, meningitis, pneumonia, and pleuritis.
Gastrointestinal reactions were vomiting, nausea, stomatitis, and intestinal perforation.
In addition, two cases of clinical manifestation of systemic lupus erythematosus with anti DNA antibodies were reported. Cases of demyelinating disease or delayed hypersensitivity reactions were not reported to Lareb.

Table 2. Description of fatal ADRs probably associated with the use of infliximab

Patient, sex, age	Concomitant medication	Suspected fatal adverse drug reaction	Time to onset, last / first dose
I, F, 66	prednisone, paroxetine, simvastatine	Sepsis with streptococcus pyogenes (groep A)	1 day / 7 months
II, M, 82	digoxine, naproxen,temazepam	Agranulocytosis, fever, sepsis	14 days/ first infusion
III, M, 61	naproxen,ranitidine, prednisone	Cardiac failure, oesophagal haemorrhage and anaemia	8 weeks/4 months
IV, F, 71	methotrexate, prednisone	Pneumonia	24 days/ 38 days
V, M, 53	methotrexate, naproxen, prednisone, omeprazole, folic acid	Pleuritis, sepsis (pneumococ)	5 days/ 7 months

Other sources of information

SPC

Section 4.8 of the SPC mentions the pooled results of several clinical studies in which 771 patients were treated with infliximab and 192 patients with placebo. In these studies 57% of the infliximab patients versus 36% of the placebo patients reported ADRs. Most common were infusion-related reactions (dyspnoea, urticaria, headache).
In the clinical studies referred to in the SPC, infections were experienced by 32% of the patients treated with infliximab versus 22% of patients receiving placebos. In post-marketing spontaneous reporting infections are the most serious ADRs including tuberculosis[2].

Literature

Reviews on the efficacy and safety of anti-TNFα therapy in clinical studies reveal the same list of most frequent ADRs as referred to in the SPC[3-6]. Recently, the first case reports on demyelinating disease[7] and drug-induced systemic lupus erythematosis[8] were published.

Databases

The WHO database contained 1740 ADRs on infliximab on 1January 2002. ADRs that were disproportionately over-presented concerned the system organ classes general disorders, respiratory disorders, resistance mainly representing infections including tuberculosis and application site disorders.

Mechanism

The functions of TNFα in the modulation of the cellular immune response may explain the effects of inhibition of the bioactivity of TNFα on (opportunistic) infections. In addition, the relative TNFα

deficiency could be associated with the initiation of an autoimmune process with lupus-like symptoms[9] and antibody production against double-stranded DNA[4].

Conclusion

The reports on infliximab received by Lareb and the WHO show a spectrum of adverse reactions comparable to the reactions and contraindications mentioned in the latest SPC. Except for aggravated heart failure, all these reactions can be explained by the effects of anti-TNFα therapy and are described in literature. The number of reports at Lareb is not yet sufficient to carry out a statistical analysis of disproportionality.

References

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- The reported adverse reactions are covered by the SPC and seem to be related to anti-TNFα therapy