1.1. Tocilizumab and necrotising fasciitis

Introduction

Tocilizumab (RoActemra®) binds specifically to both soluble and membrane-bound interleukin-6 (IL-6) receptors. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, monocytes and fibroblasts. IL-6 is involved in divers physiological processes such as T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of haemopoiesis. IL-6 has been implicated in the pathogenesis of several diseases including inflammatory diseases, osteoporosis and neoplasia [1].

Tocilizumab was granted marketing authorization on 16 January 2009 through a centralised procedure. The therapeutic indications include treatment of *moderate to severe active rheumatoid arthritis (RA)* in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) including tumour necrosis factor-α (TNF-α) inhibitors. It is also indicated for the treatment of *active systemic juvenile idiopathic arthritis* in patients two years of age and older who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. In both indications tocilizumab is used either as monotherapy (in case of intolerance to methotrexate (MTX) or where treatment with MTX is inappropriate) or in combination with MTX.

Other antagonists of interleukin (IL) receptors on the Dutch market are the monoclonal antibodies canakinumab (Ilaris®, 2009) an antagonist of the IL-1β receptor, and ustekinumab (Stelara®, 2009) an antagonist of the IL-12 and IL-23 receptor. Anakinra (Kineret®, 2001), a recombinant, non-glycosylated version of human IL-1 and rilonacept (Rilonacept Regeneron®, 2008), a dimeric fusion protein, are both antagonists of the IL-1α and IL–β receptor [2,3,4,5].

Necrotising fasciitis (NF) is a severe infectious disease affecting the subcutaneous tissue and is associated with considerable mortality between 70-80% [6]. Two types of necrotising fasciitis can be distinguished. The first type refers to a mixed infection with aerobic and anaerobic bacteria and occurs most commonly after surgical procedures and in patients with diabetes and peripheral vascular disease. A second type concerns necrotising fasciitis caused by a monomicrobial infection with group A *Streptococcus* [7]. Other predisposing conditions for NF include malignancy, alcohol abuse, and chronic liver and kidney diseases. The incidence of NF in adults has been reported to be 0.4 cases per 100.000 population while the incidence in children is 0.08 cases per 100.000 population [8,9]. The initial clinical picture of NF mimics that of cellulitis or erysipelas, including fever, pain, tenderness, swelling and erythema. The cardinal manifestations of NF are severe pain at onset out of proportion to local findings, haemorrhagic bullae and/or vital sign abnormality. Wong *et al.* identified six independent variables (elevated CRP level, increased White blood cell (WBC) count, low haemoglobin level, low sodium level, high creatinine level, and high glucose level) that can be used to differentiate NF from non-necrotising infections [10].

The current observation describes the possible association between tocilizumab and necrotising fasciitis.

Reports

On 7 April 2012, the database of the Netherlands Pharmacovigilance Centre Lareb contained three reports concerning NF associated with the use of tocilizumab, one case was reported by a rheumatologist and sent to Lareb by the marketing authorization holder (MAH) and one case was reported twice to Lareb: by a rheumatologist and by a pharmacist from the same hospital.

Information on the reported cases:

123332
This report from a rheumatologist, reported to Lareb by the MAH, concerns a female aged 41 to 50 years with necrotising fasciitis of her lower arm four months after start of the tocilizumab infusions. Concomittant medication were hydroxychloroquine, triamcinolone acetonide injection, etoricoxib tablets and tramadol. Past drug therapy was sulfasalazine, methotrexate, adalimumab, etanercept. The patient presented with a swollen right hand which was diagnosed as necrotising fasciitis due to a *Streptococcus* infection. The patient was surgically treated and received a skin transplant. The patient recovered, it is unknown of this was with or without sequel.

121923 and 121351
This report from a rheumatologist and a pharmacist concerns a female aged 51 to 60 years, with necrotising fasciitis following administration of tocilizumab for rheumatoid arthritis (800 mg once every 4 weeks) with a latency of 2 months after start. The drug tocilizumab was withdrawn. Concomitant medication was not reported. The rheumatologist reported that the patient recovered with sequel.

This case is published as a letter to the editor in 2012 in the medical journal Rheumatology [6]. Additional information from this article shows that the patient presented at the emergency room with severe pain in the right axillary line just next to her right breast of 6 hour duration without any other complaints. Previously she was treated with MTX, hydroxochloroquine, adalimumab and etanercept, which were discontinued because of lack of efficacy. Two months before presentation she started with tocilizumab monotherapy (800mg intra venous every 4 weeks). Initial investigations showed a normal CRP level and leucocyte count of $9.1*10^9$/l. She started with analgesics and went home. Because of increasing excruciating pain, she presented again several hours later. Physical examination then showed a very tender small red spot next to her right breast. At the time of diagnosis laboratory findings were normal (CRP, leucocytes) and the patient lacked fever. Treatment with antibiotics was started and because of the ongoing progressive septic shock she went for surgery. Surgical debridement was performed. Cultures showed group A *Streptococcus* pyogenes species and the diagnosis of NF was confirmed. During her stay at the intensive care unit she developed multi-organ failure, had several severe infectious complications and eventually died [6].

Other sources of information

SmPC,
The section 4.4 ‘special warnings and precautions for use’ of the SmPC of tocilizumab mentions serious and sometimes fatal infections which have been reported in patients receiving immunosuppressive agents including tocilizumab. Upper respiratory tract infections are described as very common adverse drug reactions (>10%) and cellulitis, pneumonia, oral herpes simplex and herpes zoster infections are described as common (1-10%) adverse drug reactions. Necrotising fasciitis (NF) is not described [1]. The SmPCs of mentioned IL

antagonists in the former paragraph all mention serious and sometimes fatal infections but none of them describes NF in particular [2,3,4,5].

Literature
Recently, two case reports of NF associated with tocilizumab were published in medical journals for rheumatologists (search terms: tocilizumab AND necrotising fasciitis). The first case was published as a letter to the editor in 2012 in the medical journal Rheumatology [6] and mentioned the case description above.

The second case report concerns a 65-year old female who had suffered from RA for 15 years. Despite various treatments with anti-rheumatic drugs, including methotrexate, sulfasalazine, tacrolimus and the TNF-α-inhibitors, infliximab and etanercept, the RA remained active. Treatment with tocilizumab was started (8 mg/kg once every 4 weeks). Two weeks after the 12th infusion of tocilizumab the patient came to the clinic complaining of painful swelling of her left forearm. She presented with a body temperature of 36.9°C, blood pressure 134/64 mmHg, and pulse 124 beats/min. Laboratory studies showed C-reactive protein (CRP) of 0.04 mg/dl, hemoglobin of 11.3 g/dl, and white blood cell (WBC) count of 5,300/µl. The serum creatine kinase level was not elevated at 46 IU/l. The patient was admitted to the hospital for treatment of her skin infection. Three hours after admission, her condition deteriorated and she went into shock with progression of purpura of her left forearm. An exploratory incision revealed marked necrosis and the patient was diagnosed as having NF due to *β-Streptococcus* group A. After surgical debridement, the patient's surgical wounds improved, and she recovered [11].

The authors of both publications emphasize the importance of recognising that tocilizumab may delay or mask both inflammatory laboratory findings and systemic symptoms, even in the event of life threatening infections such as NF.

Databases
On 7 April 2012, the database of the Netherlands Pharmacovigilance Centre Lareb contained three reports of NF (one duplicate) in association with tocilizumab. Because of this low number the Reporting Odds Ratio (ROR) was not calculated. Beside these reports the Lareb database contained six other reports of NF. NF was associated with the following medicines: etanercept (1), sulfasalazine (1), interferon-beta 1a (1), naproxen (1), temozolomide (1) and diclofenac (1).

The WHO database of the Uppsala Monitoring Centre contained three reports of NF associated with tocilizumab with a ROR of 33.8 (95% CI 10.9 – 105.3). Two of these reports originated from Australia, one is from the USA. The case from the USA (2011) concerns a female of unknown age and is reported by a physician, the patient died. One report from Australia (2011) concerns a 60 year old female and the other report (2012) concerns a male of unknown age. None of the reports mention the duration of treatment with tocilizumab. The WHO received more cases of NF associated with antagonism of proinflammatory cytokines. The findings are shown in table 1.

Table 1. Reports in the WHO-database of necrotising fasciitis associated with tocilizumab and other antagonists of proinflammatory cytokines (IL receptor antagonists and TNF-α receptor antagonists)

Drug	Number of reports	ROR (95% CI)
Tocilizumab	3	33.8 (10.9 – 105.3)
Anakinra	2	-
Rilonacept	-	-
Canakinumab	-	-
Ustekinumab	-	-
Etanercept	37	4.9 (3.5-6.9)
Infliximab	14	4.1 (2.4-7.0)
Adalimumab	23	4.1 (2.7-6.2)

On 4 April 2012, the Eudravigilance database contained six reports of NF in association with tocilizumab; the association is reported disproportionally (ROR = 11.2, 95% CI: 5.0 – 25.1). The reports concerned five females and one male with a median age of 60 years (range 46 – 74 years). In one case, the age was not reported. All reports were classified as serious, and the criteria for seriousness were a combination of “hospitalisation”, “life threatening” and “other”.

Prescription data
The GIP-database does not contain any prescription data of tocilizumab.

Mechanism
Tocilizumab has been shown to inhibit both soluble and membrane-bound IL-6 signalling. Antagonizing these processes with the administration of tocilizumab may interfere with immune response and allow serious and sometimes fatal infections.

Class effects
The Lareb database contains two cases of NF associated with interleukin antagonism and 1 case of NF with TNF-α inhibition (etanercept). The WHO received a total of five reports of NF associated with IL antagonism: three reports associated with tocilizumab and two reports associated with anakinra. Additionally, the WHO- database contains 37 reports of NF associated with the TNF-α-inhibitor etanercept, 14 reports of NF associated with infliximab, and 23 reports of NF associated with adalimumab. The associations, in case of more than three reports, are reported disproportionally.
The current findings support the association between receptor antagonism of proinflammatory cytokines and necrotising fasciitis.

Discussion

Lareb has received two cases of necrotising fasciitis associated with tocilizumab, the WHO received three cases (not including the cases in the Netherlands’ Pharmacovigilance Centre database). The Eudravigilance database contains six cases including the two cases from the Netherlands and one case from Australia. Based on the data from the databases there are eight identified cases of NF in association with tocilizumab. The association is reported disproportionally in the Eudravigilance database.

The available information indicates that both patients in the described cases had TNF-α antagonists in their past drug therapy. These therapies were stopped several months before the diagnosis of NF was made. As a result, it is not likely that these medicines contributed to the cause of NF in these patients.
In the SmPC of etanercept, a TNF-α antagonist, *Streptococcal* fasciitis is mentioned; in the SmPC of infliximab, another TNF-α antagonist it is not [12, 13]. In the SmPC of the TNF-α antagonist adalimumab, skin and soft tissue infections including NF, are mentioned as common adverse drug reactions with an incidence between 1 and 10% [14]. One of the reasons why there are so much more reports of NF associated with the TNF-α inhibitors might be that they are much longer on the market.
In the two published cases which are described in the literature section, the patients lack systemic symptoms (e.g. fever and malaise) and typical laboratory findings of NF on initial examination. This might be explained by the treatment with tocilizumab, as tocilizumab can suppress acute-phase reactions and symptoms of a severe infection might be masked [6, 11]. Although this is mentioned in the SmPC and in both patients the diagnosis of NF was made timely, suppression of acute-phase reaction and related symptoms may lead to a delay in treatment resulting in a more unfavorable outcome.

Conclusion

Lareb received two cases of necrotising fasciitis in association with tocilizumab. The association was supported by data from the WHO and Eudravigilance databases and literature. In the SmPCs, tocilizumab and other interleukin receptor antagonists are associated with serious and even fatal infections but not with NF in particular. The lack of systemic symptoms and typical laboratory findings makes it challenging to recognize these infections on initial examination. Drawing the attention to NF in the SmPC can prevent delays in diagnosis and should be considered.

- Consider to mention necrotising fasciitis in the SmPC of tocilizumab

References

1. European SmPC RoActemra®. (version date: 16-01-2009, access date: 16-04-2012) http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000955/WC500054890.pdf
2. European SmPC Ilaris®.(version date: 23-10-2009, access date: 16-04-2012) http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001109/WC500031680.pdf
3. European SmPC Stelara®. (version date:16-01-2009, access date: 16-04-2012) http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000958/WC500058513.pdf
4. European SmPC Kineret®. (version date: 20-03-2007, access date: 16-04-2012) http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000363/WC500042310.pdf
5. European SmPC Rilonacept Regeneron®. (version date: 23-10-2009, access date: 16-04-2012) http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001047/WC500026510.pdf
6. van de Sande MG, van Slobbe -Bijlsma ER. Necrotising fasciitis in a rheumatoid arthritis patient treated with tocilizumab. Rheumatology 51 (3):577-578, 2012.
7. Shimizu T, Tokuda Y. Necrotizing fasciitis. Intern Med. 2010;49(12):1051-7.
8. File TM, Tan JS, DiPersio JR. Group A streptococcal necrotising fasciitis. Diagnosing and treating the "flesh-eating bacteria syndrome". Cleve Clin J Med. 65 (5):241-249, 1998.
9. Fustes-Morales A, Gutierrez-Castrellon P, Duran-Mckinster C et al. Necrotising fasciitis: report of 39 pediatric cases. Arch Dermato 138 (7):893-899, 2002.

10. Wong CH, Khin LW, Heng KS, et al. The LRINEC score: a tool for distinguishing necrotising fasciitis from other soft tissue infections. Crit Care Med 32 (7):1535-1541, 2004.
11. Yoshida A, Ota T, Sasaoka S, et al. Necrotising fasciitis in a patient with rheumatoid arthritis treated with tocilizumab. Mod Rheumatol, Published online: 10 Aug 2011.
12. European SmPC Enbrel®. (version date: 03-02-2010, access date: 16-04-2012) http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000262/WC500027361.pdf
13. European SmPC Remicade®. (version date: 02-07-2009, access date: 16-04-2012) http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000240/WC500050888.pdf
14. European SmPC Humira®. (version date:08-09-2008, access date: 16-04-2012) http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000481/WC500050870.pdf

This signal has been raised on October 2012. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).