Necrotizing fasciitis in a rheumatoid arthritis patient treated with tocilizumab

Sirs, Necrotizing fasciitis (NF) is a severe infectious disease affecting the subcutaneous tissue associated with considerable mortality (70–80%). Tocilizumab is a humanized anti-IL-6 receptor antibody that has recently been approved for the treatment of RA and other inflammatory joint diseases. The most important serious adverse events (SAEs) reported during treatment with tocilizumab are infectious complications [1, 2].

A 59-year-old woman presented at the emergency room with severe pain in the right axillary line just next to her right breast of 6 h duration without any other complaints. She denied recent trauma. Her past medical history mentioned Hashimoto’s hypothyroidism, cerebrovascular ischaemia, and since 2009 she has been treated for IgM RF, anti-citrullinated protein-positive RA. Previously she was treated with MTX, HCQ, adalimumab and etanercept, which were discontinued because of lack of efficacy. Two months before presentation she was started on tocilizumab monotherapy (800 mg i.v. every 4 weeks). She did not have CS as a background therapy.

Physical examination did not reveal any abnormalities except for an area of skin in the right axillary line that was tender when touched, without any discoloration. The right arm had normal strength and showed no neurological or vascular abnormalities. Initial investigations showed a normal CRP level and leucocyte count $9.1 \times 10^9/L$. Chest X-ray and electrocardiogram were normal. She was started on diclofenac and acetaminophen under suspicion of myalgia or bursitis, and went home. However, because of increasing excruciating pain, she presented again several hours later. In contrast, physical examination then showed a very tender small red spot next to her right breast. A CT scan was performed to exclude pulmonary embolism, aortic dissection or abscess, which showed suspicion of extended infection, possibly NF with diffuse infiltration, axillary nodes, and thickened and less circumscribed muscles. Because of severe sepsis, assumed with streptococcus, treatment with gentamicin, penicillin and clindamycin was started and because of the ongoing, progressive (septic) shock she went for surgery. Surgical debridement of the pectoralis major, pectoralis minor and latissimus dorsi muscles was performed. Cultures showed group A Streptococcus (pyogenes) species. Diagnosis of NF was confirmed and she was treated for 11 days with penicillin and clindamycin and she received IVIG. Due to severe sepsis she was also treated with hydrocortisone from Day 6 to Day 10 of her admission according to protocol. Due to disease progression, surgical debridement was repeated (total of three), where additional tissue was removed. During her stay at the intensive-care unit she developed multi-organ failure and had several severe infectious complications, which finally resulted in her death. This report describes the first case of NF in an RA patient treated with tocilizumab. It is difficult to determine if the development of NF in this patient is attributable to treatment with tocilizumab. Treatment with immunosuppressive drugs is known to be associated with development of NF. Previous treatment with other DMARDs might be a confounding factor in our patient. Serious infections are the most frequent SAEs seen with tocilizumab treatment. Most commonly reported infections are pneumonia and cellulitis [1, 2]. The pathogens in cellulitis are the β-haemolytic streptococci. It is unknown if the reported increased risk of cellulitis with β-haemolytic streptococci also implies an increased risk of severe group A streptococci infections such as in NF. The case described underlines the need for post-marketing surveillance and collection of data on adverse events in treated populations. [We reported this case to The Netherlands Pharmacovigilance Centre (www.lareb.nl).]

Case reports of NF in RA patients on other immunosuppressive drugs such as anti-TNF-α treatment [3–5] and steroids [6] have been published. Although serious infections are a well-known side effect associated with treatment with biologicals, the numbers in which these SAEs are seen are quite low [7] and occur more in the first 6 months after initiation of treatment [8].

At initial presentation our patient showed little signs of a serious infection. This might be explained by her treatment with tocilizumab, as tocilizumab can suppress acute-phase reactions and symptoms of a severe infection might be masked. Although in our patient the diagnosis of NF was made timely and treatment with antibiotics and surgical debridement was readily performed, suppression of acute-phase reaction and related symptoms may lead to a delay in treatment resulting in a more severe sepsis. Also, in patients treated with immunosuppressive drugs the disease course can be more severe. Even after the drug is stopped it can have long-lasting immunosuppressive effects as the half-life of tocilizumab is 8–14 days. Furthermore, it is not known how long it takes before IL-6 receptors regain adequate function after tocilizumab is discontinued. Although it is difficult to determine whether there is an association between tocilizumab treatment and development of NF in this patient, this is the first reported case. We believe that in the post-marketing surveillance it is
important to report such serious infections and we want to highlight the possibility of such a serious infection in a patient with only mild symptoms treated with tocilizumab.

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**Marleen G. H. van de Sande**¹ and **Eline R. van Slobbe-Bijlsma**¹

¹Intensive Care Unit, Tergooiziekenhuizen, Hilversum, The Netherlands.

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Correspondence to: Marleen G. H. van de Sande, Intensive Care Unit, Tergooiziekenhuizen, van Riebeekweg 212, 1213 XZ, Hilversum, The Netherlands.
E-mail: mvandesande@tergooiziekenhuizen.nl

**References**


