Efficacy and safety of abatacept in a patient with rheumatoid arthritis and concomitant *Staphylococcus aureus* osteomyelitis

Sirs,

Infectious adverse events represent a widely exposed issue in rheumatoid arthritis patients (RA), especially in those with a long-standing disease (1). Their higher risk of encountering infective complications may be explained by both the long-term use of immusuppressive agents, mainly glucocorticoids (2, 3), and the intrinsic attitude of RA patients to infections (1). Accordingly, up to 40% of patients complaining with septic arthritis have a previous diagnosis of RA (1).

Also, osteomyelitis is not unlikely in these patients (1) and many cases involving foot bones have been reported over time (4-6). Beyond antibiotics, therapy may also include foot amputation, and immunosuppression employing is a hazard in such cases. We herein report a RA patient complicated with foot osteomyelitis and successfully treated with the cytotoxic T lymphocyte antigen 4-immunoglobulin abatacept without dampening infection resolution.

In September 2014, a 67-year-old Caucasian woman with a 13-year RA history referred to our Unit for multiple swelling joints mainly affecting the first and second metacarpophalangeal joints bilaterally, wrists, proximal interphalangeal joints and the right shoulder. Disease Activity Score in 28 Joints (DAS28), Simple Disease Activity Index (SDAI), Patient Global Visual Analogue Scale (PG-VAS) were 5.82, 26.8 and 4.9, respectively. The patient was also affected with type 2 diabetes mellitus.

During the past years of active disease, the patient had been administered with methotrexate (dosage unknown), leflunomide (20 mg/day), adalimumab (40 mg every 14 days), etanercept (50 mg weekly), certolizumab (200 mg/month) and anakinra (100 mg/day). All these treatment approaches either proved to be ineffective or underwent a loss of efficacy over time. As a result, on July 2013 tocilizumab (8 mg/kg every 30 days) treatment was started, but Staphylococcus Aureus osteomyelitis involving proximal phalange of hallux (Fig. 1) occurred after the third administration as a fistulous rheumatoid nodule complication. For this reason, tocilizumab was discontinued and non-steroidal anti-inflammatory drugs (NSAIDs), leflunomide, low-dosage corticosteroids and several antibiotics were employed during the following year. Nevertheless, RA disease control was not achieved and osteomyelitis was not eradicated. Therefore, the patient was referred to our Rheumatology Unit and because of the high disease activity, abatacept treatment was started. Abatacept induced a striking amelioration within few weeks from the start of treatment and at 6-month follow up DAS28, SDAI, and PG-VAS were 2.39, 1.6 and 12, respectively. Meanwhile, levofloxacin was administered at the posology of 500 mg daily for 75 days. During abatacept treatment, osteomyelitis resolved after 5 months. Afterwards, the rheumatoid nodule fistula was surgically treated applying lyophilised dermis followed by skin graft.

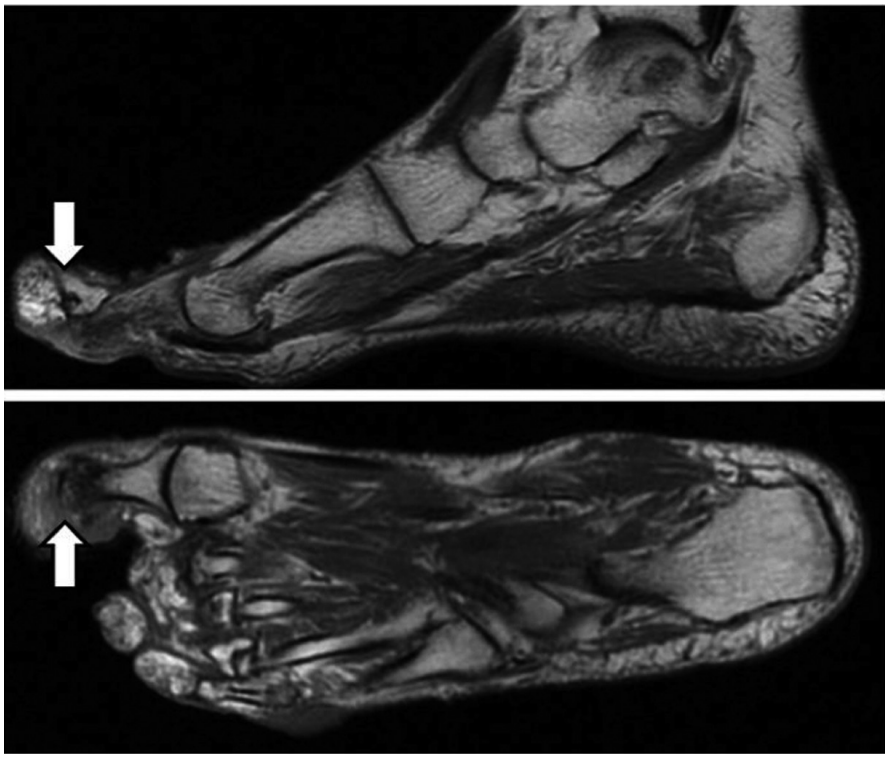

Fig. 1. Shows osteitis of the proximal phalanx of the first finger, with oedema of the surrounding soft tissues.

Patients affected by RA show a high risk of infections, which may be increased during biologic therapy (7), especially when anti-TNF agents are administered (8). In particular, bone represents a site of high-risk infection with a rate ratio for osteomyelitis amounting to 10.63 compared to non-RA subjects (1). *Staphylococcus aureus* is by far the most prevalent causative microorganism (9), and diabetes mellitus figures as a major risk factor for infections (1).

Although knowledge about the clear mechanism of action is still increasing (10), abatacept inhibits immune response mostly by preventing T cell activation (11). However, abatacept long-term safety profile has been reported to be consistent and satisfactory along with sustained clinical benefits and non-progressive joint structural damage (12-16). In particular, infective risk was relatively low and negligible among patients treated with abatacept when compared to other drug-related adverse events (7, 12). Nevertheless, also severe infectious have been described (17). Nasopharynigitis, sinusitis, pneumonia, and vulvovaginal infections represent the most frequently reported abatacept-related infections, while more severe infective events included bronchopneumonia, acute diverticulitis, pelvic inflammatory disease, and haemophilus pneumonia (13).

In our patient, we administered abatacept as monotherapy with the aim of controlling a very active RA without interfering with osteomylelitis healing under antibiotic treatment. In any case, a close biochemical and radiological monitoring during the subsequent 6-month follow-up allowed keeping track of osteomyelitis. In this patient, abatacept use led to a complete RA disease control on a hand and was not complicated by osteomyelitis worsening on the other. Furthermore, the simultaneous levofloxacin treatment allowed osteomyelitis resolution followed by a successful surgical approach aimed at repairing the fistula.

Noteworthy, osteomyelitis occurring during abatacept administration has also been reported (17) and caution is always necessary in such cases. However, according to our experience and under close clinical monitoring, abatacept may be a feasible therapeutic option in patients with osteomyelitis and active RA not controlled on corticosteroids, NSAIDs and disease-modifying antirheumatic drugs.

J. Sota[1]
A. Vitale[1]
G. Lopalco[2]
F. Iannone[2]
M. Galeazzi[1]
L. Cantarini[1]

Letters to the Editors

[1]Research Center of Systemic Autoinflammatory Diseases and Behçet's Disease Clinic, Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Siena, Italy; [2]Interdisciplinary Department of Medicine, Rheumatology Unit, Policlinico of Bari, Italy.

Address correspondence to:
Luca Cantarini, MD PhD,
Rheumatology Unit, Department of Medical Sciences, Surgery and Neurosciences,
University of Siena, Policlinico Le Scotte,
Viale Bracci 1, 53100 Siena, Italy.
E-mail: cantariniluca@hotmail.com

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