Anakinra long-term efficacy and safety in the management of Schnitzler's syndrome and latent tuberculosis infection

Sirs,

We read with great interest the article by Migkos *et al*. presenting the case of a tuberculous pyomyositis in an 85-year-old rheumatoid arthritis patient treated with the interleukin (IL)-1 receptor antagonist anakinra (ANK) and corticosteroids for 11 years (1). Hence he was hospitalised due to fever (up to 39°C) together with redness, swelling and induration on the lateral side of the thigh. Multifocal opacities in the upper lung fields were found by a chest x-ray and diagnosis of *Mycobacterium tuberculosis* (Mtb) infection was established by cultures of the fluid from thigh and bronchoalveolar lavage. The beginning of anti-Mtb treatment induced a prompt amelioration of symptoms.

Although it cannot be excluded that ANK might have favoured the occurrence of Mtb infection, we would like to point out the safety of IL-1 inhibition, from this viewpoint. Indeed, although the magnitude of the risk of Mtb infection associated with ANK is unknown and although it is unclear whether this effect is modified by the concomitant use of corticosteroids, the reported rates of development of Mtb disease in patients treated with ANK have been usually very low. In this regard, we report herein a 58-year-old female patient with Schnitzler's syndrome (SchS), and concomitant latent tuberculosis infection (LTBI), successfully managed with anakinra without the occurrence of any adverse event.

Our patient was admitted to our Unit for a 3-year history of recurring episodes of high fever (up to 40°C) lasting several weeks and occurring up to six times a year. In addition, she also showed intense fatigue, chronic non-pruritic urticaria and arthralgia mainly involving the shoulders, hips, and knees that significantly impaired her quality of life. Laboratory investigations performed upon admission revealed highly increased inflammatory markers as well as a monoclonal immunoglobulin M (IgM) gammopathy associated to a kappa light chain. Antinuclear antibodies and Bence Jones proteins were absent, while examination of the peripheral blood smear and chest x-ray gave normal results. A full investigation for infectious diseases showed a QuantiFERON test >10 IU/mL (n.v <0.2), disclosing a LTBI. A skin biopsy was also performed showed histological features consistent with urticarial dermatitis, while ultrasonography detected synovitis in wrists and shoulders. Based on the clinical and laboratory findings, the patient was diagnosed with SchS (2). Over the following months a combination therapy with high-dose oral prednisone (up to 25 mg/daily) and methotrexate (15 mg/weekly) was administered, without obtaining any clinical amelioration. Considering the beneficial effects derived from IL-1 inhibition in SchS we decided to administer anakinra and a prophylactic therapy with isoniazid (300 mg/die) for treating LTBI was given. Unfortunately, 10 days after the start of treatment, she developed severe haemolytic anaemia and several blood transfusions were required. Isoniazid therapy was promptly interrupted. Few months later, anakinra at a dose of 100 mg/day was started without administering any antituberculosis medication. The patient experienced a prompt clinical amelioration, furthermore, acute phase reactants rapidly dropped to normal levels. Prednisone was gradually tapered up to 5 mg/daily. From here onwards, chest radiograph and routinary checks for infectious disease were performed respectively every three months and monthly, without any sign of LTBI reactivation. Notably, the disease flares following the start of anakinra were managed by temporarily increasing its dosage even up 200 mg/day. At the 18-month follow-up, the patient was symptom-free and no adverse events occurred.

Mtb infection still represents a major international public health problem, being approximately one third of the world's population infected with this bacterium (3). Tumour necrosis factor (TNF)-α is a crucial cytokine in the control of Mtb proliferation and granuloma formation and stability, condition known as latent tuberculosis (4). Conversely, IL-1α but not IL-1β seems to have a crucial role against Mtb, but IL-1 neutralisation has not proven an overall major susceptibility effect during reactivation of latent tuberculosis in mouse models (5). However, although the most recent evidences suggest that anti-IL1 agents represent an effective therapeutic choice for a wide number of inflammatory disorders (6), clinical data on the risk of tuberculosis reactivation in long-term anti-IL-1 treatment are still sparse. With regard to SchS, a French two-year nationwide survey focusing on anakinra effectiveness and safety profile in twenty-nine patients highlighted six severe infectious events during follow-up, but no case of tuberculosis reactivation was referred (7). Similarly, a 24-month observational multicentre study aimed at evaluating anti-IL-1 treatment in thirty patients with Behçet's disease (8) along with other similar studies (9-10) confirm the trend that IL-1 targeting agents have a favourable profile with regard to tuberculosis reactivation risk.

In conclusion, our aim is here to provide additional data on anakinra safety in the management of patients with concomitant LTBI, even when anakinra is administered at high dose and without any LTBI prophylactic therapy. Therefore, in agreement with Migkos *et al*. we consider it critical to perform screening test for LTBI and when positive, adequate anti-Mtb therapy before starting biologic treatment, but we also believe that IL-1 blockers might be a safe therapeutic option, especially in those geographical areas where tuberculosis still represents a social concern (11).

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