Transient and Slight Thrombocytopaenia Induced by Etanercept During Treatment of Psoriatic Arthritis

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Sir,

Tumour necrosis factor-alpha (TNF-α) is a cytokine that has been implicated in the pathogenesis of several inflammatory diseases. Blocking TNF-α, via anti-TNF antibodies or soluble TNF-α receptor molecules, is a strategy currently employed in the treatment of patients with psoriasis or psoriatic arthritis. Etanercept is a fully soluble TNF receptor fusion protein that binds primarily to soluble TNF-α as well as TNF-β (lymphotoxin), thereby effectively blocking its physiological function (1). The possible development of side-effects during its use, including infections, demyelinating disease, lupus-like syndromes, congestive heart failure, malignancies and cytopaenias, have been described (2).

CASE REPORT

A 61-year-old man suffering from psoriatic arthritis for over 12 years was treated for about 10 years with methotrexate, which was stopped due to development of a toxic hepatopathy. He was also affected by a psychosis, which was treated with risperidone 1 mg/day with good control of his psychiatric symptoms. The patient took no other drugs. Baseline Psoriasis Area and Severity Index (PASI) and Ritchie index were 31.6 and 7, respectively. We started therapy with etanercept 25 mg subcutaneously twice a week and, before starting treatment, investigations including chest X-ray, complete blood count, urea, creatinine, transaminases, cholesterol, triglycerides, antinuclear antibody (ANA, anti ds-DNA, extractable nuclear antigens), antiphospholipid antibody (lupus anti-coagulant and anti-cardiolipin), tumour markers, haemoculture and urine culture had been performed; no significant aberrations were found. The Mantoux test was negative. Anti-citrulline antibody and rheumatoid factor was normal, while C-reactive protein (CRP) was 5.8 mg/l (normal value 0–5 mg/l). Complete blood count, hepatic and renal tests were repeated monthly during treatment with the biological drug. From the second month of therapy, with good control of skin and joint symptoms (PASI 14.3 and Ritchie index 4), we observed a decrease in platelet count (99×10^3/μl; baseline value 134×10^3/μl; reference value $130–450\times10^3$/μl), which achieved the minimal value at the third month of therapy (95×10^3/μl). In spite of the slight and asymptomatic thrombocytopaenia we decided to continue the treatment, and the platelet count was repeated every week. After the third month of therapy the platelet count gradually increased until the forth month, when the number of platelets recovered the initial value (130×10^3/μl) and maintained about the same value during the whole period of treatment. After 8 months of therapy, in complete remission of the disease (PASI 2.1 and Ritchie index 2), treatment was stopped and the patient was periodically examined. Six months after stopping treatment, the patient developed a relapse of psoriatic arthritis, with a PASI of 14 and Ritchie index of 5. Hence we decided to restart the therapy with etanercept subcutaneously, 25 mg twice a week; complete laboratory tests were performed and only an alteration in CRP (6 mg/l) was observed. After 2 months of therapy PASI was 6.4, Ritchie index 3 and a decrease in platelet count was again noted (98×10^3/μl) achieving the minimal value at the third month of treatment (94×10^3/μl). We decided to continue treatment, performing platelet count weekly. We observed a gradual improvement in the number of platelets achieving about the initial value (136×10^3/μl) after 4 months of therapy. The same value remained during the whole period of treatment (8 months). During both episodes of thrombocytopaenia, ANA, anti ds-DNA, ENA, IgG and IgM anti-cardiolipin antibody, LAC, anti-platelet antibody (plasma IIB/IIIA, plasma IA/IIA) were performed and no alterations were found.

DISCUSSION

Leucopaenia and thrombocytopaenia, although not common, are recognized side-effects of TNF-α blocking. In the literature some reports describe a decrease in platelet count during treatment with etanercept. Pathare et al. (3) described a case of severe thrombocytopaenia (38×10^3/μl), which occurred after 3 doses of etanercept; the platelet count improved 9 days after stopping the biological drug. Kuruvilla et al. (4) described a case of pancytopaenia with a severe thrombocytopaenia (33×10^3/μl) after 4 months of treatment with etanercept for rheumatoid arthritis; the platelet count improved 3 weeks after stopping the treatment. Furthermore, several cases of thrombocytopaenia induced by other anti TNF-α agents, such as infliximab and adalimumab, have been described (5–7).

The exact mechanism of thrombocytopaenia during treatment with TNF-α blockers is unclear. To our knowledge this is the first report of a transient, slight and asymptomatic thrombocytopaenia during treatment with etanercept. A gradual decrease in platelet count started between the second and third months of therapy and the number of platelets recovered to the initial value at the fourth month of treatment. A lupus-like syndrome, an anti-phospholipidic syndrome, or an autoimmune thrombocytopaenia, possible mechanisms of thrombocytopaenia during the treatment with biological drugs, were excluded due to absence of clinical and laboratory signs. In addition, a potential haematological toxicity induced by risperidone could have been considered, but our patient had had a stable blood count for over 15 years of therapy with this drug, and thrombocytopaenia appeared only after the administration of etaner-

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cept. We do not know the exact mechanism that led to thrombocytopaenia and why it occurred between the second and third months of treatment. We hypothesize that it is the expression of an idiosyncratic reaction in patients with a genetic predisposition. In fact TNF-α is not only a molecule that plays a pivotal role in inflammatory processes, but it also takes part in a complex and still not well understood cytokine network that controls haematopoiesis. Its role in the bone marrow is still debated. In fact TNF-α can elicit a stimulatory or inhibitory effect on the *in vitro* growth of haematopoietic progenitors depending on its concentration and on the type of cytokines interacting with it (stimulatory effect: G-CSF, CSF-1, Epo, SCF, Fl; inhibitory effect: GM-CSF and IL-3) (8).

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