

Leukopenia and thrombocytopenia induced by etanercept: two case reports and literature review

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ABSTRACT

Tumor necrosis factor-alpha (TNF-alpha) is a proinflammatory cytokine, and its excess can lead to severe consequences. Those effects are known to be antagonized by TNF-alpha inhibitors. Etanercept is a fusion protein that inhibits TNF-alpha action. As TNF-alpha regulation is related to cellular differentiation of various cellular types involved in immune response through expression of several other cytokines, it is possible that the use of its inhibitors may cause cytopenia. We report two cases of bicytopenia induced by etanercept. Both cases recovered after drug withdrawal. We discuss the need of introduction of routine laboratorial tests in patients using anti-TNF therapy, in order to identify possible hematological changes.

Keywords: biological products, neutropenia, leukopenia, thrombocytopenia, biological therapy.

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INTRODUCTION

Tumoral necrosis factor-alpha (TNF-alpha) is a proinflammatory cytokine synthesized by many different cellular types as a response to infectious or inflammatory stimuli. It has an adaptive role at immune response and wounds healing at physiologic levels. Its excess can lead to severe consequences. Its effects are known to be antagonized by TNF-alpha inhibitors: infliximab, etanercept, adalimumab, certolizumab and golimumab. Data has demonstrated that all antagonists are usually well tolerated.¹ The relationship between the TNF-alpha inhibitors and blood cells depletion is still unknown. TNF-alpha regulates proinflammatory cytokines, such as interleukins (IL-1, IL-6, IL-8) and granulocytes and macrophage colony stimulation factor (GM-CSF). As cytokines develop an important role at cell differentiation, it is conceivable that TNF-alpha blockage can lead to pancytopenia, by inhibiting the differentiation of the various cellular types (stopping different cellular strains'

differentiation).² Serious hematological reactions have been reported in patients treated with anti-TNF therapy,³ and leukopenia induced by etanercept is a potentially effect reported in clinical trials.⁴

We report two cases of patients who developed bicytopenia induced by etanercept, a TNF-alpha inhibitor, and completely recovered after drug withdrawal.

Case 1

EAM, female, caucasian, 54 years old. She had rheumatoid arthritis since 2002, with symmetrical involvement of hands, wrists, elbows, knees, and feet. Patient used methotrexate (MTX), sulfasalazine, prednisone, and leflunomide. In October 2008, she showed a significant worsening of arthritis, specially at her hands, wrists, elbows, and knees. The Disease Activity Score (DAS28) was 7.49 [12 swollen joints, 28 painful, Visual Analogical Scale 100, erythrocyte sedimentation rate (ESR) 22 mm]. Etanercept was started in December, at 25 mg subcutaneous (SC) twice a week.

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By that time, laboratory tests were hemoglobin 11.0 g/dL; hematocrit 32.9%; leukocytes 5,950/mm³; lymphocytes 1,490/mm³; neutrophils 3,576/mm³; platelets 187,000/mm³; glutamic-oxaloacetic transaminase (SGOT) and glutamic-pyruvic transaminase (SGPT) at normal levels; and C-reactive protein (CRP) 1.08 mg/dL (normal: 0.5 mg/dL).

In March 2009 the patient referred improvement of articular pain and noted small red lesions in the lower limbs. On physical examination, there were no swollen joints – only tenderness at the right metacarpophalangeal and wrists, and petechiae at lower limbs. Laboratory evaluation showed SGOT, SGPT, ESR, CRP, and creatinine at normal levels; hemoglobin 12.3 g/dL; hematocrit 35.6%; leukocytes 2,420/mm³; lymphocytes 1,016/mm³; neutrophils 1,432/mm³; and platelets 60,000/mm³.

Etanercept was discontinued due to the possibility of having induced leukopenia and thrombocytopenia. MTX and leflunomide were maintained at the same doses. Two weeks later, there was a complete disappearance of the skin lesions in lower limbs and recovery of the laboratorial tests: hemoglobin 12.3 g/dL; hematocrit 35.6%; leukocytes 3,410/mm³; lymphocytes 1,466/mm³; neutrophils 1,432/mm³; and platelets 88,000/mm³. In April 2009 the tests were: leukocytes 5,140/mm³; lymphocytes 1,644/mm³; neutrophils 3,392/mm³; and platelets 150,000/mm³.

Case 2

ABS, male, caucasian, 43 years old, in treatment for psoriasis since 1990. In 2003 he started having arthritis in his feet, hands and knees. Non-steroidal anti-inflammatory (NSAID) and MTX were prescribed. Methotrexate was suspended some weeks later due to gastric intolerance.

Patient started using sulfasalazine plus NSAID. He persisted with hands and knees arthritis and enthesitis of the left *pes anserinus*. Sulfasalazine was suspended due to gastric intolerance and palpitations. At that time, laboratory exams showed: hemoglobin 12.5 g/dL; hematocrit 38%; leukocytes 5,930/mm³; lymphocytes 2,134/mm³; neutrophils 2,965/mm³; and platelets 345,000/mm³. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT), ESR, creatinine and urine routine test were all normal. Because of the persistence of articular and skin problems, and contraindication of MTX and acicretin due to previous hepatic abnormalities, biological medication was indicated. In July 2006, etanercept was started, 25 mg SC twice a week, after negative tuberculosis screening. There was an improvement of the arthralgia with partial improvement of the arthritis and persistence of skin lesions. After the fourth etanercept dose, the patient showed: hemoglobin 13.4 g/dL; globular volume 41.7%; leukocytes 4,940/mm³; and platelets 145,000/mm³;

liver enzymes and bilirubins were normal. In February 2007 etanercept was suspended due to bicytopenia. Laboratory exams were: hemoglobin 14.6 mg/dL; hematocrit 42.2%; leukocytes 3,470/mm³; lymphocytes 2,255/mm³; neutrophils 694/mm³; and platelets 110,000/mm³. After two months there was a recovery of leucopenia (leukocytes 5,110/mm³ and neutrophils 2,961/mm³), and persistence of thrombocytopenia (87,000/mm³). A new exacerbation of his articular problems with worsening of his skin lesions happened after four months of etanercept stoppage. Blood count, eight months after biological medication suspension, has showed recovery of leukocytes and platelets' count, (leukocytes 4,780/mm³, with a normal differential count; and platelets 273,000/mm³).

DISCUSSION

We present two cases of patients who developed leukopenia and thrombocytopenia during their treatments with etanercept. In both, the temporal relationship between the drug administration and the subsequent development of neutropenia and between withdrawal of the drug and analytical improvement was clear. The causal relation between TNF-alpha blockade and neutropenia is still poorly understood. Some association between serum TNF-alpha and leukopenia has been described in patients with acute leukemia who have developed leukopenia induced by chemotherapy. The levels of serum TNF-alpha showed a further decrease when patients developed chemotherapy-induced leukopenia; and when leukopenic patients developed bacterial infections, serum concentrations of TNF-alpha increased. Interestingly, serum levels of TNF-alpha decreased when clinical signs of infection resolved during antibiotic therapy, but an increase occurred later in parallel with haematopoietic reconstitution.⁵

It is known that anti-TNF therapy may lead to inhibition of proinflammatory cytokines involved in bone marrow stem cell differentiation. Agranulocytosis and neutropenia have been described in patients using infliximab.⁶ Suppression of bone marrow has been reported in patients with pancytopenia or aplastic anemia after treatment with etanercept.³ A study of 130 patients on anti-TNF therapy showed a cytopenia rate of 12%, mainly leukopenia, and not associated with serious infections. These were transient changes, and myelograms were not necessary in those cases.⁷ Based on those cases we did not perform myelogram in our two patients.

The possibility that leukopenia induced by etanercept may be due to peripheral consumptions rather than a primary marrow disorder has been considered by Wenham et al.⁸ The authors have found normal bone marrow examinations in their

patients. The role of antibodies against leucocytes or other blood cell structures induced by anti-TNF-alpha therapy is not clear. For example, no association between antinuclear antibody and neutropenia in rheumatoid arthritis anti-TNF patients has been reported.⁹

Hematological complications due to etanercept use are rare, so full blood counts are not recommended.⁹ It is probable that, due to early drug discontinuation, no serious infections associated with neutrophil count decrease have been described. The incidence of cytopenia related to therapy with anti-TNF agents has already been reported in literature^{2,8-10} and most of them were considered light or moderate,⁷ although aplastic anemia has been described.¹¹ Our two patients have had moderated thrombocytopenia and leukopenia induced by etanercept; these changes were reversed with the discontinuation of the drug. Actually, although we had no major complications in both cases, not to reintroduce etanercept was a medical decision of our team.

The *Brazilian Society of Rheumatology* guidelines¹² have no recommendation related to hematological screening. As long as we know, hematological monitoring has not been usually recommended in other anti-TNF treatment guidelines. As many other authors, we believe that we are not alone in this recommendation.^{7,8}

CONCLUSION

Although in these two cases the hematological changes in patients using anti-TNF seem to be not severe, we suggest that routine blood cell count must be performed in order to identify hematological changes before and shortly after etanercept or other anti-TNF therapies have started. Myelograms are not necessary, and blood cell count is very cheap compared with other clinical laboratory tests and may prevent severe outcomes in patients, especially those who are using anti-TNF-alpha therapy.

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