Eur J Clin Pharmacol (2011) 67:213–214
DOI 10.1007/s00228-010-0915-1

LETTER TO THE EDITORS

Is exogenous administration of IL-1ra (anakinra) likely to induce severe depression?

Annie Pierre Jonville-Bera · Jean-Louis Guilmot · Gilles Aspe · Elisabeth Autret-Leca · Julie Magnant

Received: 17 September 2010 / Accepted: 27 September 2010 / Published online: 13 October 2010

Sirs:

Anakinra is approved for rheumatoid arthritis, but it is also effective in patients with adult-onset Still's disease. We present here what is, to the best of our knowledge, the first reported case of depression related to anakinra use.

A 43-year-old man had been diagnosed with Still's disease 18 months previously based on chronic fever up to 39°C, chronic inflammatory arthralgias, myalgias, major inflammatory biological syndrome (C-reactive protein 200–300 mg/L, fibrinogen 9 g/L, and neutrophils 20 to 30.10^9/L), and the exclusion of any other diseases. Blood cultures, tests for infectious agents, antinuclear antibodies, and antineutrophil cytoplasmic antibodies, and skin tests for tuberculosis were negative. The patient had no medical history of other diseases or medical conditions. The initial treatment regimen of prednisolone (1 mg/kg/day) dramatically improved the symptoms, but with lowering of the dose to 0.5 mg/kg/day, arthralgias and myalgias reappeared. Despite the introduction of methotrexate (20 mg weekly), the dose of prednisolone could not be lowered below 20 mg daily. The patient's general status remained characterized by disabling pain. One year following the initial diagnosis, treatment with anakinra was initiated (100 mg subcutaneous daily), and the arthralgias and myalgias promptly disappeared. Prednisolone was progressively reduced to 8 mg daily and methotrexate to 10 mg weekly.

Six weeks after the initiation of anakinra treatment, the patient complained of depressive symptoms. Two months later, the clinical and biological signs of the disease were under control, but the depressive symptoms had worsened. The patient was unable to work and was hospitalized in a psychiatric inpatient unit due to a major depressive disorder with suicidal ideation. As the patient had no personal or family history of depressive symptoms and no recent psychological trauma, a pharmacological cause was suspected.

Anakinra, the last drug introduced prior to the depressive disorder, was discontinued, and the patient was treated with cyamemazine (75 mg/day for 3 days), clonazepam (8 mg/day), and citalopram (20 mg/day). Within a few days, the depressive symptoms improved, allowing for a reduction in psychiatric treatment after 1 week. Anakinra was not reintroduced as a treatment, and the depressive symptoms did not recur following clonazepam and citalopram cessation.

This case report suggests a "probable" link between depression and anakinra, as there was a temporal relationship between the beginning of anakinra treatment and the onset of depressive symptoms, as well as between the discontinuation of anakinra and the regression of depressive symptoms. It should be noted that the depressive symptoms did not recur following the withdrawal of psychotropic drugs. The role of metothrexate can be excluded because its dosage had been reduced prior to the onset of the patient's depression and because the depressive symptoms improved

A. P. Jonville-Bera (✉) · E. Autret-Leca
Regional Drug Monitoring Centre, Clinical Pharmacology Unit,
University Hospital CHRU Tours,
2 Boulevard Tonnellé,
37044 Tours, France
e-mail: jonville-bera@chu-tours.fr

J.-L. Guilmot · J. Magnant
Internal Medicine B Unit, University Hospital, CHRU de Tours,
37044 Tours, France

J.-L. Guilmot · E. Autret-Leca
François Rabelais University,
37032 Tours, France

G. Aspe
Psychiatric Unit, Clinic of Vontes Chamgaul,
37320 Esvres, France

despite the continuation of methotrexate treatment. The role of prednisolone can also be ruled out as depressive symptoms improved despite the continuation of this treatment.

A literature search did not reveal any case report of depression related to anakinra use. However, in one case of Crohn's disease worsened by anakinra [1], the patient also reported depressive symptoms that disappeared after discontinuation of the anakinra therapy. Anakinra, a recombinant human interleukin-1 receptor antagonist (IL-1ra), acts as an IL-1 inhibitor. A significant association has been found between high serum IL-1ra levels and depression in several studies [2], and a significant positive relationship between serum IL-1ra level and the severity of depression has been demonstrated in others [3], as documented by a higher risk of developing depressive symptoms over time in patients with high serum IL-1ra levels [4]. This cytokine may alter the activity of IDO (indoleamine 2,3-dioxygenase), a tryptophan-metabolizing enzyme, thereby inducing changes in brain serotonin levels [5]. A decrease in serotonin levels induced by IL-1ra could account for anakinra-related depression.

This first case report of anakinra-associated depression underlines the need for the physician to be aware of this new side effect as it requires rapid anakinra cessation.

Conflicts of interest None

References

1. Carter JD, Valeriano J, Vasey FB (2003) Crohn disease worsened by Anakinra administration. J Clin Rheumatol 9(4):276–277
2. Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E, Neels H (1997) Increased serum Il-6 and Il-1 receptor antagonist concentrations in major depression and treatment resistant depression. Cytokine 9(11):853–858
3. Maes M, Vandoolaeghe E, Ranjan R, Bosmans E, Bergmans R, Desnyder R (1995) Increased serum interleukin-1-receptor-antagonist concentrations in major depression. J Affect Disord 36(1–2):29–36
4. Milaneschi Y, Corsi A, Penninx B, Bandinelli S, Guralnik J, Ferrucci L (2009) Interleukin-1 receptor antagonist and incident depressive symptoms over 6 years in older persons: The InCHIANTI study. Biol Psychiatry 65(11):973–978
5. Myint AM, Kim YK (2003) Cytokine-serotonin interactions through indoleamine 2, 3-dixygenase: a neurodegenerative hypothesis of depression. Med Hypoth 61(5–6):519–525