Etanercept-induced hypertriglyceridemia during the treatment of recurrent aphthous stomatitis

Sir,

Tumor necrosis factor alpha (TNF-α) is known to play an important role in the lipid homeostasis.[1] However, the effects of TNF-α inhibition on circulating lipids remain controversial.[2] In this regard, a case of hypertriglyceridemia (HTG) associated with the soluble TNF-α receptor etanercept in a patient with psoriasis has recently been reported.[3] The HTG was also described in psoriasis patients following treatment with the anti-TNF-α monoclonal antibodies, such as infliximab[4] and adalimumab.[5] We report a new case of etanercept-induced HTG during treatment of recurrent aphthous stomatitis (RAS). A 34-year-old non-obese man presented with a 15-year history of recalcitrant recurrent aphthous stomatitis (RAS). Eight to ten new recurrent lesions occurred every 2 weeks. They healed without scarring in approximately 12 days. They were very painful (subjective pain severity of 8; scale, 1-10) and caused dysphagia. Treatment with topical and systemic corticosteroids only yielded slight improvement of symptoms. Previous treatments, such as tetracyclines, acyclovir, sulfones, colchicines, and thalidomide, had to be discontinued due to lack of efficacy or intolerance. Different conditions that may present with RAS such as Behçet´s disease, gastrointestinal disorders, nutritional deficiencies, human immunodeficiency virus, and herpes simplex virus infection were excluded. In February 2010, he started the treatment with etanercept (25 mg twice weekly). Before the onset of this therapy, complete laboratory studies such as lipid profile and chest X-ray did not show abnormalities. The tuberculin skin test shows negative. Significant clinical improvement was observed after 4 weeks of etanercept therapy. However, a routine blood test revealed high triglyceride (TG) levels (291 mg/dl; normal <200). After eight weeks of treatment, the TG levels rose to 529 mg/dl; high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterols were within normal ranges. There was no family history of hyperlipidemia, diabetes, or other predisposing factors known to influence lipid metabolism.

Taken together, etanercept was considered as a potential-triggering factor for HTG and, because of that, this drug was discontinued. One month after etanercept withdrawal, the TG levels returned to the normal range. However, two months later the etanercept was reintroduced because of a new relapse. Four weeks later, high plasma TG level (852 mg/dl) were observed. Despite having very high TG levels the patient declined discontinuation of etanercept because of the improvement of the RAS. Consequently, gemfibrozil therapy (900 mg/daily) was started, leading to a remarkable decrease in TG levels. There are a number of reasons to consider that HTG in our patient was caused by etanercept, namely, (i) the close temporal relationship between the initiation of etanercept and the onset of HTG, (ii) its resolution following etanercept withdrawal, and (iii) the new increase of TG when etanercept therapy was reintroduced. To our knowledge, this is the first report of HTG associated with etanercept in a non-psoriatic patient. We also want to emphasize the efficacy of etanercept in the treatment of RAS, which has scarcely been documented in the literature.[6] The TNF-α acts on lipoprotein metabolism by increasing LDL and TG.[1,5] However, the effects of TNF-α blockers on lipids are unclear. Several studies have shown improvement in the lipid pattern with decrease of TG and increase of HDL serum levels. However, a trend toward an atherogenic profile following treatment with anti-TNF-α antibodies has also been described.[1,2,5] Garces *et al*. have reported a lower atherogenic lipid profile in etanercept-treated patients than in infliximab-treated patients.[7] These authors reported that after 1 year of treatment with etanercept, there was a significant increase in HDL and no significant changes in total cholesterol or LDL levels. Furthermore, improvement in TG levels was observed after etanercept use.[7] The different effect on lipid profile of etanercept and other anti-TNF-α were proposed to be related to an additional blockage of lymphotoxin-α mediated by etanercept, leading to a less pro-atherogenic profile.[7] Nevertheless, our patient developed an HTG following treatment with this drug. The reasons for our findings are unknown. With respect to this, it is important to keep in mind that etanercept may have effects on other cytokines involved in the lipid homeostasis. With respect to this, both α- and γ-interferons increase the TG levels.[8] Interestingly, an up-regulation of both α- and γ-interferons has been disclosed in patients treated with etanercept.[9,10] Therefore, it is possible that in predisposed individuals etanercept might lead to an over-production of some cytokines that can alter

the lipid metabolism and increase the serum TG. In summary, lipid profile should be closely monitored during anti-TNF-α therapy. When TG levels exceed 400 mg/dl, drugs aim to lower TG should be added to prevent further complications.

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