Efalizumab-induced Lupus-like Syndrome

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Accepted October 22, 2007.

Sir,

Psoriasis is an inflammatory, immune-mediated, chronic skin disease that affects quality of life. Many therapies have been used with variable efficacy and safety. Biological therapies have recently been approved for the treatment of psoriasis and their use is increasing. Nevertheless, these medications are not always safe and immunologically induced side-effects should systematically be taken into account.

We report here the case of a patient who developed a lupus-like syndrome after being treated with efalizumab for severe psoriasis resistant to several previous therapies.

CASE REPORT

A 58-year-old woman presented with a long history of severe psoriasis. She had received several systemic treatments, including retinoids, methotrexate, cyclosporine, and psoralen and ultraviolet A therapy, with various levels of toxicity and efficacy. In 2003, while she was receiving topical treatments (topical steroids and topical vitamin D3 analogues) for her psoriasis, a type I auto-immune hepatitis was diagnosed. She was then treated with oral corticosteroids, azathioprine and, finally, mycophenolate mofetil because of its activity against psoriasis. At the beginning, a favourable evolution of psoriasis was observed with prednisolone (10 mg/day) and mycophenolate mofetil (1.5–2 g/day). However, in April 2005, she developed a severe recurrence of her psoriasis and efalizumab (0.8 ml once a week) was proposed. Before starting treatment, mycophenolate mofetil was replaced by azathioprine. At this time, her ALT and AST values were 37 and 40 UI/l, respectively. A rapid cutaneous improvement was observed after commencing efalizumab (Raptiva®, Serono, Geneva, Switzerland) treatment, but a few months later the patient developed right hypochondrium pain, asthenia, enthesitis, inflammatory polyarthralgia, dyspnoea and pericarditis. Laboratory parameters showed a cytolytic and cholestatic hepatitis (ALT = 129 (normal: < 32 UI/l), AST = 54 (< 32 UI/l), PAL = 192 (35–104 UI/l), γGTP = 469 (5–36 UI/l)), a major oligoclonal gammapathy (IgG = 49 (6.82–12.66 g/l)), and auto-immune disorders with positive serum nuclear antibodies (1/1280 with speckled pattern), anti-double-stranded DNA > 1000 and positive anti-Sm antibodies. Smooth muscle, anti-liver/kidney microsomal (LKM)-1, anti-mitochondrial and anti-SCA antibodies were negative. A cholecystectomy was performed because of persistent abdominal pain associated with persistent liver enzyme elevation. Liver biopsy showed neither significant activity nor fibrosis. Abdominal pain and biological liver abnormalities persisted after cholecystectomy. At this time, the patient was still being treated with efalizumab, corticosteroids (10 mg/day) and azathioprine (150 mg/day).

Differential diagnoses were considered, such as atypical lymphoma, primary lupus erythematosus flare-up and drug-induced lupus. The thoraco-abdominal-pelvic computerized tomography scan, positron emission tomography scan, and myelogram were not contributory for the diagnosis of lymphoma or myelodysplasic syndromes. A lupus-like syndrome was considered more likely because of the combination of polyarthralgia, hepatitis, pericarditis and immunological disorders. Efalizumab was stopped and a combination of cyclosporine (150 mg twice a day) and corticosteroids (0.5 mg/kg/day) was introduced to treat autoimmune hepatitis and prevent the rebound flare of psoriasis that is usually observed. Fifteen days after efalizumab withdrawal, clinical symptoms started to disappear without flare of psoriasis, and laboratory tests normalized. Clinical results had been obtained before the delay of efficacy of cyclosporine. A lupus-like syndrome induced by efalizumab was the most probable diagnosis in view of the combination of compatible clinical symptoms, immunological abnormalities and spontaneous clinical improvement following drug withdrawal. Six months later, the patient is still in complete remission and corticosteroids have been decreased to 20 mg/day. Psoriasis was stabilized with only minor skin lesions on the back, trunk and scalp. Topical treatment was sufficient.

DISCUSSION

Efalizumab is a humanized monoclonal IgG1 antibody targeted against the CD11a site of leukocyte function-associated antigen-1 (LFA-1), which is the predominant integrin expressed on T cells. It normally binds to intercellular adhesion molecule-1 (ICAM-1) expressed on antigen-presenting cells, endothelial cells and keratinocytes. In this way, efalizumab prevents LFA-1 from binding ICAM-1 and inhibits several important steps in psoriasis pathogenesis including initial T-cell activation, T-cell trafficking and migration to the skin, T-cell

 ISSN 0001-5555
doi: 10.2340/00015555-0393

reactivation and T-cell interaction with keratinocytes (1). This drug is indicated for the treatment of moderate to severe cutaneous psoriasis. Hyperlymphocytosis is usual and reversible after drug withdrawal. Some cases of lymphoma have been reported to the manufacturer (Serono, data on file) and one case has been published (2). One case of drug-induced lupus-like syndrome has been published, but with skin involvement only (3). To our knowledge, our case is the first one developing with a systemic disease.

Spontaneous clinical improvement after efalizumab withdrawal supports a relationship between efalizumab and the lupus-like syndrome. Several drug-induced lupus-like syndromes have been reported in the literature, with over 40 medications incriminated, such as anti-arythmic, anti-hypertensive, anti-psychotic, antibiotic (isoniazid, cycline, nitrofurantoin), anti-convulsant, anti-thyroid, anti-inflammatory drugs, and others (4). It has also been described with biologic drugs (TNF-α antagonists, adalimumab, infliximab, etanercept), α-interferon and other cytokines (5, 6). However, this adverse event is rare. The drugs posing most risk are procainamide and hydralazine. The probability of developing a lupus-like disease for the remaining drugs is much lower, less than 1%.

The pathogenesis of drug-induced lupus-like syndrome is not known. Several mechanisms for the induction of an autoimmune process have been discussed: hapten hypothesis, increased immunogenicity of autoantigens by drug interaction, pharmacogenetic factors, such as acetylation phenomena, HLA haplotype, cross-reacting autoantibodies between drug and autoantigens (7). The autoimmune hepatitis in this patient, diagnosed in 2003, was perhaps a first sign of a lupus-like reaction, and efalizumab probably promoted the immunological disorder. Efalizumab action in pathologies other than psoriasis is unclear, and this drug has also been reported to be an alternative treatment in lupus erythematous (8, 9). Lupus is T-cell mediated inflammatory disease and efalizumab has T-cell modulator effects, which can play a role in disease evolution. Similarly, it has been observed that anti-TNF-α treatment could be a treatment for systemic lupus (10) even though it is known that such therapy can induce lupus-like syndromes (11–13). These paradoxical effects are well known concerning psoriasis and anti-TNF-α treatment (14).

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