Sir,

Infliximab, a chimeric monoclonal antibody directed against tumour necrosis factor (TNF-α) receptor, may be responsible for hepatic dysfunction ranging from minor anomalies in liver tests to, exceptionally, acute liver failure with transplantation or death (1, 2). We report here a new case of acute hepatitis after four infusions of infliximab in a patient with psoriasis. Drug withdrawal was followed by resolution of hepatic abnormalities. Etanercept was initiated with success without recurrence of hepatitis and with efficiency on psoriasis.

CASE REPORT

A 46-year-old woman with a history of severe psoriasis with joint involvement evolving since her adolescence had received various treatments in the past: corticosteroid ointments, psoralen ultraviolet A, systemic retinoids, sulphasalazine, methotrexate, etanercept, efalizumab and cyclosporin A. As all treatments proved ineffective, or were responsible for adverse effects, infliximab therapy was initiated in December 2007. Baseline findings included normal full blood count, kidney function and liver tests as well as negative antinuclear antibody and Mantoux tests. She received four infliximab infusions at a dose of 5 mg/kg (weeks 0, 2, 6, 14). Infusions were well tolerated and laboratory markers (full blood count, C-reactive protein, kidney and liver functions), performed before every infusion, were within normal ranges until the fourth infusion. Only gamma-glutamyl transferase (γ-GT) started to increase gradually and marginally above normal 12 days after the first infusion. Her cutaneous lesions of psoriasis improved after two infusions but arthralgias remained. She presented for her fifth infusion 2 months later (week 22) with a new blood test before treatment. Aspartate transferase (ASAT) increased to 210 IU/l (normal 5–34; six-fold above normal), alanine transferase (ALAT) increased to 369 IU/l (normal 5–45; eight-fold above normal), γ-GT was 128 IU/l (normal 9–36 IU/l) and bilirubin was 15 mg/l (normal 2–12 mg/l). Her psoriasis was almost cleared. Arthralgias affecting the hands and the feet persisted without arthritis. The rest of the physical examination was otherwise unremarkable; in particular there was no sign of hepatic failure. The patient denied any history of recent alcohol intake or of exposure to a new (hepatotoxic) treatment. Full blood count and renal function were not affected. Autoantibodies (anti-nuclear, anti-smooth muscle, anti-mitochondrial, and anti-liver/kidney microsomal antibodies), hepatitis A, B and C, herpes simplex virus, cytomegalovirus and Epstein-Barr virus blood screening and ferritin were negative or within normal ranges. Liver biopsy was not performed. Infliximab was withdrawn and liver function tests fell to normal limits within 6 weeks. One month after infliximab withdrawal, a psoriasis flare-up was observed. Therefore, etanercept was initiated again at a dose of 50 mg twice a week with monitoring of liver function, which remained within normal ranges during the first 3 months of follow-up. Psoriasis began to improve 3 weeks after initiating the treatment and is now in remission.

DISCUSSION

Infliximab is licensed for use in the management of rheumatoid arthritis, ankylosing spondylitis, Crohn’s disease, ulcerative colitis, psoriatic arthritis and moderate-to-severe cutaneous psoriasis. Minor anomalies in liver tests are not uncommon with anti-TNF-α antibodies (1). However, severe reactions have also been reported, such as jaundice, hepatitis, cholestasis, autoimmune hepatitis and acute liver failure. Severe hepatic reactions occurred between 2 weeks and more than one year after initiation of infliximab. Some cases may lead to liver transplantation or death (1, 2). United States Food and Drug Administration (FDA) post-marketing surveillance disclosed 134 spontaneous reports of liver failure associated with either infliximab or etanercept (3). Fifty of these were well documented and, among them, 7 cases (infliximab and etanercept) lacked another cause of liver failure, suggesting that TNF-α inhibitors may be responsible (3). Arguments in support of a correlation in the present case between hepatitis and infliximab include: (i) a normal baseline liver function test before initiation of infliximab; (ii) the occurrence of hepatitis after four infusions; (iii) the regression after drug withdrawal; and (iv) the absence of other identified cause of hepatitis. Hepatitis appearing during therapy with infliximab may have many causes: concomitant drugs such as methotrexate, infection such as hepatitis B (4) or C (5), malignant disease, or autoimmune hepatitis (6). In some cases, as in ours, no concomitant condition is found that may explain hepatitis apart from infliximab per se (7, 8). The mechanism of hepatitis induced by infliximab is unknown. A predisposed genetic back-
ground, the consumption of alcohol (9), the use of other hepatotoxic drug such as methotrexate may play a role. Moreover, in the specific case of autoimmune hepatitis, the TNF-α blockade interferes with the suppression of auto-reactive B-cell production (9). In our case, the absence of circulating autoimmune antibodies during hepatitis suggests an acute toxic hepatitis rather than an autoimmune reaction. In case of such a reaction, etanercept, a soluble TNF-α-receptor fusion protein, has been proposed as an alternative with efficiency (7–9) that supports a direct effect of infliximab on the liver rather than a class effect.

This case confirms that: (i) acute hepatitis is a rare, but sometimes life-threatening, adverse effect of infliximab. It may be underestimated in the absence of systematic liver function test monitoring. We therefore recommend that liver function tests should be monitored before and after any infusion of infliximab. (ii) The absence of cross-reactivity on liver function of etanercept, allows the maintenance of anti-TNF-α therapy in cases of infliximab-related hepatitis. On the contrary, adalimumab, a humanized monoclonal antibody against TNF-α, has a similar mechanism of action to that of infliximab; it is therefore not clear whether it can be proposed as an alternative in situations like the one described.

Conflict of interest

Dr Bessis has been employed as a consultant for Schering-Plough France and Wyeth Pharmaceuticals France. Drs Kluger, Girard and Guillot declare no conflict of interest. No financial support was received for this work.

REFERENCES