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PAH is an employee of Euro Nippon Kayaku, a branch of the mother company Nippon Kayaku, Tokyo, Japan, which provided the drug for this trial free of charge.
Treatment of SLE-GN with 15-DSG was approved by the local ethics committee.

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Autoimmune hepatitis associated with infliximab in a patient with psoriatic arthritis

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We read with interest the debate about liver toxicity of infliximab in psoriatic arthritis (PsA).[1 2] We describe the case of a 53 year old woman with a 4 year history of refractory PsA who developed transaminasitis during infliximab treatment.

CASE REPORT

Despite combination treatment (ciclosporin 300 mg/day, fluocortolone 10 mg/day, and methotrexate (MTX)15 mg/week intramuscularly), disease activity was still high, and intravenous infliximab at 3 mg/kg was administered initially at weeks 0, 2, 6, 14 and then every 6 weeks. Ciclosporin was withdrawn.

Within 3 weeks she improved, fluocortolone was gradually stopped while methotrexate (MTX) 20 mg/week intramuscularly, was continued. After the sixth infusion, she developed a mild transaminasitis and MTX, initially tapered, was stopped. After the eighth infusion transaminases continued to rise and in the absence of any other plausible cause, infliximab was withdrawn.

She was admitted to our department with persistently high values of aspartate aminotransferase and alanine aminotransferase and a flare of PsA.

The erythrocyte sedimentation rate was 30 mm/1st h, C reactive protein 170 mg/l, aspartate aminotransferase 143 IU (normal 5–40), alanine aminotransferase 234 IU (normal 5–55), anti-parietal cell antibodies and liver and kidney microsomal antigen were absent, and serology for hepatitis viruses, cytomegalovirus and Epstein-Barr virus, was negative. The new appearance of anti-dsDNA (IgG) 1/20 (indirect immunofluorescence on *Crithidia luciliae*), anti-smooth muscle antibodies (ASMA) 1/640 was observed, while the titre of antinuclear antibodies (ANA), previously present at a serum dilution of 1/80, increased to 1/160. Liver ultrasonography showed steatosis. A liver biopsy revealed intense and diffuse portal lymphoplasmacytic, granulocytic inflammatory infiltration and severe interface hepatitis. Mild periportal fibrosis was also evident (figs 1A and B). Fluocortolone 20 mg daily was started and the joints improved. Within a few months, transaminases declined and finally normalised; ANA remained positive, while anti-dsDNA and ASMA disappeared.

DISCUSSION

Feletar *et al* found a high incidence of liver toxicity in patients with PsA treated with infliximab,[1] even if, as Provenzano pointed out,[2] in some cases this association was debatable because of the concomitant use of MTX and the lack of exclusion of viral infections. In one of the largest studies on the use of infliximab in rheumatoid arthritis (RA),[3] no liver disease was recorded, but recently two possible cases of liver disease associated with infliximab use have been observed in Crohn's disease and PsA.[4 5] In our patient the chronological relationship between transaminasitis and treatment (fig 2), linked to the peculiar histology, is suggestive of autoimmune hepatitis induced by infliximab. The high titre of ASMA, notoriously associated with autoimmune hepatitis,[6] supports this hypothesis.

Our patient was concomitantly treated with MTX for almost 30 weeks. MTX can produce steatosis, fibrosis and, ultimately, cirrhosis; its hepatotoxicity in psoriasis is well known. A 2.5–5.0-fold increase in liver damage for psoriasis compared with RA has been reported.[7]

Moreover, patients with PsA seem more prone to liver toxicity during infliximab treatment than those with RA.[1] A dissimilar toxicity profile for disease modifying antirheumatic drugs in various diseases has been linked to differences in pathophysiology, genetic background, drinking behaviour, and age.

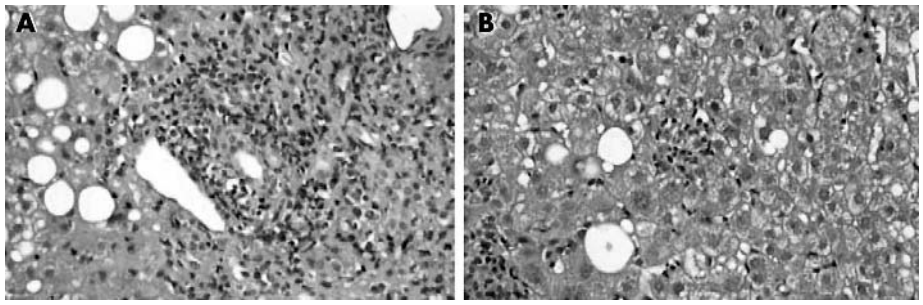

Figure 1 (A) A liver biopsy revealed intense and diffuse portal lymphoplasmacytic, granulocytic inflammatory infiltration and severe interface hepatitis; Diffuse macro-microvesicular steatosis (over 60% hepatocytes), intranuclear glycogen accumulation, and hyaline degeneration of hepatocytes (Mallory bodies) were also noted. Mild periportal fibrosis was evident with formation of incomplete septa and perisinusoidal and perivenular fibrosis. (B) Lobular evidence of confluent necrosis and inflammatory infiltrates.

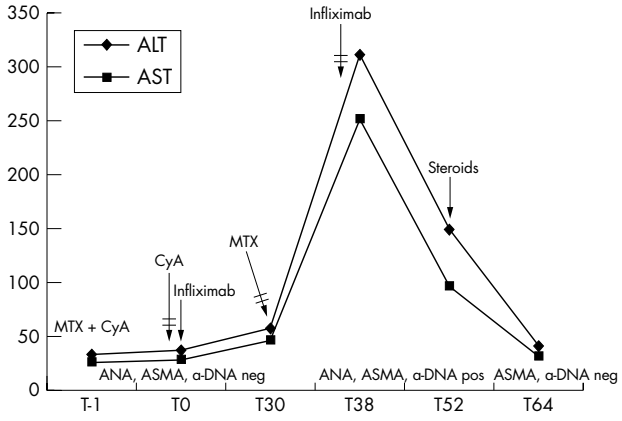

Figure 2 Chronological relationship between transaminasitis and infliximab in the patient. AST, aspartate aminotransferase; ALT, alanine aminotransferase; T, time in weeks; MTX, methotrexate; CyA, ciclosporin A; ANA, antinuclear antibodies; ASMA, anti-smooth muscle antibodies; a-DNA, anti-DNA antibodies.

However, our patient had received less than a third (900 mg in the past 4 years) of the cumulative dose known to be a risk for hepatic toxicity.[8] In this case, infliximab might have led to the acute damage—that is, severe portal inflammation and initial neoductulogenesis, whereas MTX might have been responsible for the chronic hepatic injury—that is, mild fibrosis and steatosis. The introduction of corticosteroids probably hastened liver recovery with subsequent normalisation of transaminases.

The appearance of autoantibodies, occasionally associated with mild and transitory autoimmune diseases, during anti-tumour necrosis factor α treatment has been documented[1 9] and reflects the complex relationship between tumour necrosis factor α blockage and autoimmunity. This report confirms the need to monitor liver enzymes carefully and perform liver biopsy, if necessary, not only in patients with PsA using combination treatment with MTX and infliximab but also for those using infliximab alone, especially in the presence of pre-existent serological signs of autoimmunity such as ANA. Such signs might be a risk factor for further development of clinical autoimmunity during infliximab treatment.

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