RHEUMATOLOGY

Letter to the Editor (Case report)

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Toxic drug-induced liver failure during therapy of rheumatoid arthritis with tocilizumab subcutaneously: a case report

Rheumatology key message

- Drug-induced liver failure under therapy with tocilizumab can occur even after years of treatment.

SIR, in RA, inflammation is regulated by a complex cytokine and chemokine network, of which TNF-α and IL-6 seem to be most relevant [1]. However, IL-6 is an important inducer of the acute phase response in the liver, modifying infection defence. Furthermore, it is a potent hepatocyte mitogen essential for liver regeneration [2].

Although MTX still remains the anchor drug, the outcome of patients with RA has dramatically changed with the advent of new therapeutic agents, such as tocilizumab, targeting the IL-6 receptor. Low disease activity and remission are now frequently achieved [3]. However, this highly effective treatment can cause liver damage, and patients at risk cannot be anticipated. Liver failure after years of treatment has not been reported so far.

The patient is a 51-year-old, Caucasian female who was diagnosed with anti-CCP-positive RA in 2008 and was started on different DMARDs during the course of the disease; MTX, among others. Owing to the poor clinical response, the treatment regimen was changed to a monotherapy of toxicilizumab i.v. in 2011. Before administration of tocilizumab her blood counts and biochemical data were all within the normal range, including liver and renal function tests. Clinical response was improved and the patient started on toxicilizumab, 162 mg s.c. once a week.

Five years later, routine laboratory controls demonstrated elevated liver enzymes in the 300–500 U/l range, and tocilizumab was discontinued. At this point, there was no history of potentially hepatotoxic drug intake, especially of no co-medication with any DMARD.

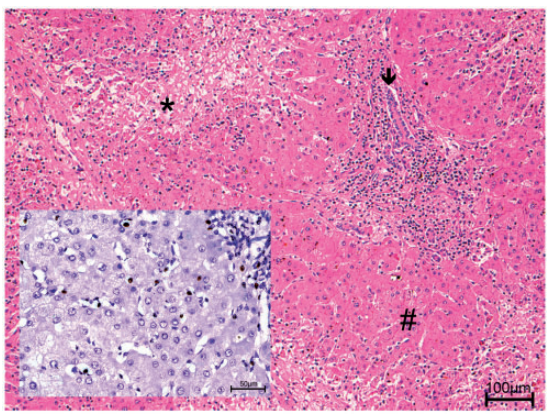
Three months later, the patient experienced increasing fatigue, and physical examination showed jaundice, with a serum bilirubin at 4.9 mg/dl. Repeat laboratory results showed a marked progress of the elevated liver enzymes [Aspartate Aminotransferase (AST) 1049 U/l, Alanine Aminotransferase (ALT) 1415 U/l]. A medical work-up at a community hospital excluded viral hepatitis, autoimmune hepatitis, haemochromatosis, Wilson's disease (supplementary Table S1, available at *Rheumatology* Online) and biliary obstruction as possible causes. A biopsy of the liver demonstrated a 30–50% hepatocyte necrosis, with no indication of pre-existing liver disease, notably no signs of haemosiderosis, fibrosis or steatosis. Liver enzymes persisted ~1000 U/l with continuously increasing bilirubin concentrations up to 15 mg/dl and a decreased liver function [International Normalized Ratio (INR) >2], leading to the patient's admission to our centre a month later. A limited course of CSs resulted in no significant change in laboratory results; instead, a continued deterioration of liver synthesis occurred (INR 4.1; bilirubin 24.8 mg/dl; factor V 17%).

The patient was transferred to the intensive care unit after becoming progressively somnolent with a mild flapping tremor, in addition to oliguria and hypernatraemia. At that point, the patient met four out of four King's College criteria for non-paracetamol drug-induced liver failure: age >40 years; S-bilirubin >17 mg/dl; onset of jaundice >7 days before encephalopathy; and INR >4. She was listed for high-urgency liver transplantation at Eurotransplant, and a donor liver was allocated 3 days after listing, followed by orthotopic liver transplantation. During surgery, the recipient liver appeared highly dystrophic, with a residual weight of only 528 g. Histological assessment revealed extensive liver necrosis, with ongoing cell death and a parenchyma remnant between 30 and 40% (Fig. 1). Around the necrotic areas, $CD68^+$ histiocytes were found. The CD3 count was low. Ki67 was expressed in < 1% of hepatocytes, thus eliminating hepatic regeneration. There were no signs of malignancy or pre-existing liver injury.

The graft was functioning well after surgery, and the patient could be transferred to a peripheral ward on post-operative day 9, where she made a full recovery.

Although the half-life of tocilizumab in blood samples is reported to be 11 days [4], liver injury in our patient

FIG. 1 Histology results



Liver section (Haematoxylin and Eosin stain) of the explanted liver with necrotic tissue (asterisks), remnant of intact liver tissue (hash) and a portal field with infiltration of lymphocytes (arrow). Section: immunohistochemistry of Ki67 in intact liver parenchyma showing proliferating lymphocytes; expression in hepatocytes is almost not detected.

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proceeded over a month after discontinuation of IL-6 receptor blockade, finally leading to liver failure, with no signs of proliferating hepatocytes. Elimination and metabolism of mAbs, such as tocilizumab, primarily takes place in the reticuloendothelial system [4]. Mild to moderate elevation of liver enzymes is reported in trials on tocilizumab in RA and occur in up to 35.7 (AST)–40.1% (ALT), but seem to be mostly temporary. Elevation of serum bilirubin appears less frequently, in up to 8.9% of patients treated with the IL-6 receptor antibody [5]. None of the randomized controlled trials or long-term extension studies on tocilizumab showed fulminant hepatic failure [5]. In daily routine, severe liver injury attributable to treatment with tocilizumab is a rare phenomenon, but has been reported occasionally [6].

Histological findings in drug-induced liver injury vary, but the degree of necrosis and presence of ductular reaction are correlated with liver transplantation and fatal outcome [7, 8]. Even in long-term treatment with tocilizumab, frequent monitoring of liver function tests is essential. Patients with persistently elevated liver enzymes and deteriorating liver function after discontinuation of tocilizumab should be referred to a centre with a liver transplant programme.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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