

Fatal DRESS syndrome under tocilizumab treatment for seronegative polyarthritis

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Clinical Implications

- The anti-IL-6 receptor monoclonal antibody tocilizumab has been reported to be effective in the treatment of rheumatoid arthritis and giant cell arteritis and is likely to be increasingly prescribed in the future. Clinicians should be aware of tocilizumab-induced drug rash with eosinophilia and systemic symptom syndrome with possible critical liver failure.

TO THE EDITOR:

Drug rash with eosinophilia and systemic symptoms (DRESS) is one of the most severe delayed drug allergic reactions associated with a high mortality estimated from 1.7% to 10%.¹ This syndrome is characterized by multiple organ failure. Culprit drugs are mostly antiepileptics, sulfonamides, and allopurinol. The anti-IL-6 receptor monoclonal antibody tocilizumab (TCZ) has been reported efficient in rheumatoid arthritis and giant cell arteritis.² We report herein the first case of fatal DRESS syndrome after TCZ use.

A 69-year-old woman had seronegative polyarthritis. Because of multiple treatment failure including methotrexate, corticosteroids, and monoclonal anti-TNF- α antibodies (adalimumab and infliximab), TCZ was started in March 2016. In July 2016 (3 weeks after TCZ third infusion), the patient had generalized maculopapular exanthema covering 60% of her body surface area without facial edema or clinical lymphadenopathy (Figure 1) associated with fever (102.2°F), eosinophilia (baseline 555/mm³, maximum 1000/mm³ = 12.4% of leucocytes) and grade 3 hepatitis (peak ALT 511/AST 296 UI/mL; Palc 1774 UI/mL; GammaGT 5240 UI/mL; and bilirubin 561 μ mol/L).¹ No other drugs were started before the skin rash. Herpes virus viral load (human herpes virus 6, 7, Epstein-Barr virus, cytomegalovirus [CMV]) and other viruses (HIV, hepatitis A, B, C, E) were negative. Skin and liver histology analyses were consistent with DRESS showing cellular infiltration made of activated and atypical lymphocytes with eosinophils only in the skin. TCZ-induced DRESS syndrome was diagnosed with a Kardaun score at 6.³ High-dose steroids were started (2 mg/kg and then 4 mg/kg) without improvement of liver symptoms (bilirubin level = 564 mg/L [N = 20]). In August 2016, the patient's condition did not improve with features of reactive hemophagocytic syndrome: pancytopenia (neutropenia: 0.05 g/L [N > 1500]; anemia: 6.5 g/dL [N > 12 g/dL]; lymphopenia: 0.05 g/L [N > 2 g/L]; hypertriglyceridemia: 6.6 mmol/L [N < 1.70]; hyperferritinemia:

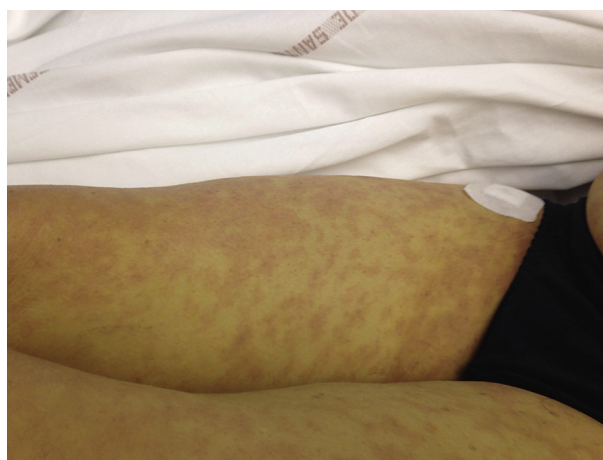


FIGURE 1. Generalized exanthema during drug rash with eosinophilia and systemic symptom syndrome.

10,949 μ g/L [N < 252]; high lacticodeshydrogenase level: 789 UI/L [N < 246]), and histological features of hemophagocytic syndrome on a second liver biopsy and on bone marrow analysis. CMV blood virus load showed at this time 61,000 copies/mL. Valganciclovir therapy was started in association with steroids with effect on CMV viral load but no improvement on hepatitis. Liver failure did not improve despite liver dialysis, employed to avoid the accumulation of toxins not cleared by the failing liver. The patient died in November 2016 before liver transplantation could be discussed.

Our case is the first reported case of DRESS under TCZ treatment. One case of TCZ-induced eosinophilia has already been reported.⁴ The severity of acute liver injury in this case could be explained by different mechanisms, Drug-induced liver injury associated with TCZ treatment has been linked to the activation of apoptotic pathways in the liver (caspase 3 activation as demonstrated by the expression of cleaved caspase 3 on hepatocytes). In this case, TCZ is blocking antiapoptotic signals such as nuclear factor- κ B and phosphatidylinositol 3 kinase-Akt, which could favor prolonged hepatocyte apoptosis.⁵ The long blood half-life of TCZ could increase the hypersensitivity reaction as previously suggested in patients with DRESS caused by allopurinol where delayed oxypurinol clearance is associated with severity of the disease.⁶ It is known that liver injury in DRESS is often very severe and steroid resistant, as recently published in a series of 16 patients with an overall mortality of 40%.⁷ CMV infection is a classical late complication of DRESS (at least 4-5 weeks after the disease onset) and is associated with decreased blood cell counts (neutropenia, thrombocytopenia) and poor prognosis.⁸ The absence of viral inclusions in the liver of our patient was strong evidence for DRESS imputability in the liver toxicity. Finally, clinicians should be aware of TCZ-induced DRESS syndrome with possible critical liver failure.

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No funding was received for this work.

Conflicts of interest: B. S. Benoit declares no relevant conflicts of interest. M. Gerfaud-Valentin has received travel support from Alexion and Novartis. P. Seve is on the boards for Abbvie and Novartis; has received consultancy fees from Abbvie; has received research support from the French Health Ministry; has received lecture fees from Abbvie, Pfizer, and SOBI; and has received travel support from Abbvie, Actelion, and GlaxoSmithKline.

Received for publication April 9, 2017; revised June 27, 2017; accepted for publication August 1, 2017.

Available online November 7, 2017.

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2213-2198

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<https://doi.org/10.1016/j.jaip.2017.08.041>

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