Letters to the Editor

Syndrome and toxic epidermal necrolysis have occasionally been reported.[1]

Only a few previous cases of drug reaction with eosinophilia and systemic symptoms syndrome have been reported following exposure to a calcium channel blocker. Diltiazem was the most frequently incriminated calcium channel blocker agent.[3] The onset of the eruption occurred 2–10 days after starting diltiazem. Liver involvement occurred in the majority of the cases. Recently, Moriya et al.[4] presented a case of drug reaction with eosinophilia and systemic symptoms syndrome, which occurred 19 months after initiating azelnidipine and verapamil hydrochloride, which appears to be a very long delay in the onset of the syndrome.

Our patient's symptoms started 3 weeks after lercanidipine initiation. It was classified as a definitive case of drug reaction with eosinophilia and systemic symptoms according to the RegiSCAR scoring system.[5] According to the Naranjo probability scale, the adverse drug reaction was considered probable.[6]

In conclusion, lercanidipine can be added to the list of drugs known to induce drug reaction with eosinophilia and systemic symptoms syndrome.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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Safety of ustekinumab in severe psoriasis with chronic hepatitis B

Sir,

Biologics are an important option for treating severe psoriasis that has failed conventional therapies. Biologics include specific monoclonal antibodies against tumor necrosis factors-alpha and monoclonal antibodies against the p40 subunit of interleukin 12 and interleukin 23 (ustekinumab).

Biologics carry a risk of infection due to their immunosuppressive action making screening for infection mandatory before their use. In patients with Hepatitis B and C, continuous and careful monitoring is required on account of a higher predisposition to
infections and the reactivation and aggravation of pre-existing conditions.

We report a case of 56-year-old male diagnosed with plaque psoriasis in 1973. Prior to reporting to our hospital, he was treated with oral methotrexate for 7 years and oral acitretin for 2 years, both of which were discontinued because of side effects. At presentation the psoriasis area and severity index (PASI) score was 22.9. Due to the lack of clinical improvement with prior medication, we started oral cyclosporine in the dose of 3.6 mg/kg. Investigations revealed heterogeneous liver texture on ultrasound, positive hepatitis B surface antigen, positive anti-hepatitis B core IgG, negative anti-hepatitis B surface, negative hepatitis B e antigen and viral load of 4.910 UI/ml (3.69 log) consistent with the diagnosis of chronic hepatitis B infection.

The patient was treated with entecavir, 0.5 mg/day orally by the gastroenterologist.

When the use of cyclosporine approached its allowable limit (24 months) but psoriasis persisted with a PASI score of 6.6, we chose to start ustekinumab with an induction dose of 45 mg followed by a second dose of 45 mg. 30 days after the first dose in May 2012. The patient attained excellent psoriasis control and has been maintaining a PASI score of around 1.8 with a maintenance dose of ustekinumab, 45 mg every 12 weeks. No side effects were observed. In addition, after starting entecavir, the hepatitis B viral load became undetectable and continued to be undetectable in annual viral load tests from December 2011.

Ustekinumab is a human monoclonal antibody against interleukin-12 and interleukin-23. However, this medication may predispose to viral infections or to the reactivation of latent infections.[1,2] The connection between biological treatments and reactivation of hepatitis B infection has been frequently reported. Screening for hepatitis B is recommended for all patients before biological therapy.[3]

It is known that hepatitis B virus is integrated into the host genome and can persist indefinitely in the hepatocyte nuclei as covalently closed circular DNA. This material serves as a model for hepatitis B virus genome replication facilitating future virus reactivations whenever immune control is interrupted.[4]

Patients who have chronic hepatitis B, identified as hepatitis B surface antigen positive usually require treatment with antiviral therapy when the disease is active. Antiviral therapy can be started 1–2 weeks before immunobiological therapy and maintained for at least 6 months after the immunosuppressive treatment is discontinued.[3,5]

The most complicated group consists of patients with cured infections. They are identified by negative hepatitis B surface antigen and positive antihepatitis B core. In these cases though the risk is low if reactivation of infection occurs, it might be catastrophic. If the viral load is detectable, antiviral treatment should be considered. If undetected, viral load should be monitored every 1–3 months.[2]

Several mechanisms have been proposed for reactivation of hepatitis B virus in patients treated with ustekinumab. Inhibition of interleukin-12 prevents the differentiation of T helper cells, the activation of CD8 cytotoxic T cells and the production of interferon resulting in intracellular replication of the residual hepatitis B virus. Inhibition of interleukin-23 suppresses the differentiation of Th-17 cells affecting the ability of B cells to proliferate and to produce antihepatitis B surface antibodies. In addition, interleukin-12 blockade leads to an increase in the levels of regulatory T cells which may adversely affect the production of antibodies. Furthermore, antigen-presenting cells, nitric oxide and growth factor (transforming growth factor) also appear to be involved in the onset of infection.[1]

A review of literature shows that there are some data concerning the use of ustekinumab in this type of patient. Navarro et al. published a retrospective and multicenter study of five patients diagnosed with chronic hepatitis B who were treated with immunobiological agents and concomitant antiviral therapy. One patient received ustekinumab along with entecavir for 5 months without disease reactivation.

Steglich et al. reported a patient with severe psoriasis with positive anti-hepatitis B core, positive antihepatitis B surface antigen and undetectable viral load. The patient was treated with lamivudine and ustekinumab for 3 years without hepatitis B virus reactivation during follow-up.

Koskinas et al. reported a case of hepatitis B virus reactivation in a patient with negative hepatitis B surface antigen and positive anti-hepatitis B surface, caused by the administration of ustekinumab, after 16 months of treatment.
The use of ustekinumab in patients with hepatitis B infection is controversial. Our patient is still under therapy with ustekinumab along with entecavir. His viral load indices remain negative and there are no other indications of viral reactivation. The patient has been subjected to periodic evaluation, undergoing liver function tests quarterly.

Considering the cases reported in literature to date, the drug does not appear to have an impact on acute immunity in hepatitis B although it is not yet possible to draw a definite conclusion about the role of ustekinumab in host immunity against hepatitis B virus. The drug has been used in our patient for 39 months until now, safely.

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Conflicts of interest
There are no conflicts of interest.

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