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CASE AND RESEARCH LETTER

# [Translated article] Changes in Liver Viral Load in Hepatitis B Virus Infection During Treatment of Chronic Urticaria With Omalizumab: Is There a Pathophysiologic Relationship Between the 2 Diagnostic Entities?

## Cambios en la carga viral hepática del virus B durante el tratamiento de la urticaria crónica con omalizumab, ¿existe relación fisiopatológica entre ambas entidades?

*To the Editor,*

The relationship between urticaria and viral infections of the liver is controversial. Some authors have even recently proposed that serology testing for hepatitis B virus (HBV) and hepatitis C virus (HCV) infections in patients with chronic urticaria is not cost-effective.[1] Hepatitis infections, however, particularly those caused by HBV, are relatively common in patients with chronic urticaria, although no more common than in the general population.

A 46-year-old woman with celiac disease and chronic HBV infection was referred to our department for evaluation of a 4-year history of evanescent wheals and angioedema. Treatment with 4-fold doses of antihistamines did not achieve adequate control of the urticaria, with Urticaria Activity Scores over 7 days (UAS7) of more than 28 points. Additional tests showed immunoglobulin (Ig) levels above 200 IU/mL, normal D-dimer levels, and positive HBV serology (positive anti-HB core antibody, negative HB surface antigen) consistent with chronic HBV infection. The initial viral load was 5630 IU/mL. The patient was started on omalizumab 300 mg every 4 weeks. She responded after the first dose, reaching a UAS7 score of 0. At 6 months, the viral load had fallen to 900 IU/mL. Considering the favorable response, the treatment was discontinued after 4 months of an optimized regimen of omalizumab 300 mg every 6 weeks. The urticaria recurred, however, at 4 weeks (UAS7 > 28). Determination of viral load at 3 months showed an increase to 15 500 IU/mL. Omalizumab 300 mg every 6 weeks was restarted and again induced an early response, with a UAS7 score of less than 6 points. Three months after reinitiation of treatment, the viral load had again decreased to 630 IU/mL. The patient's urticaria is currently under complete control with omalizumab 300 mg every 6 weeks.

Urticaria and urticarial vasculitis are relatively common extrahepatic manifestations of HBV and HCV infections.[2] Little evidence is available on the relationship between viral hepatitis treatment and improvement of urticaria. Curative treatment of hepatitis C poses a rather different scenario to that observed with noncurative treatment of hepatitis B. Improvements in urticaria and urticarial vasculitis were described in a series of patients treated for HCV infection, but just 7 patients were studied.[3] The evidence in the case of HBV infection is limited to 16 patients, none of whom showed improvements in urticaria after chronic antiviral treatment. The above findings suggest that the presence of urticaria may not justify antiviral treatment in patients with urticaria and concomitant HBV infection. The different serologic profiles of HBV infection are shown in Table 1.

Despite the controversy surrounding the pathophysiologic relationship between urticaria and HBV infection, notable changes in viral load have been observed in relation to urticaria activity and treatment with omalizumab. Chicharro et al.[4] were the first authors to describe changes in load during omalizumab treatment, and to our knowledge, we are the second. It seems clear that the increases in load coincided with greater urticaria activity. Likewise, lower loads were observed in the presence of little or no urticaria activity. Although the effect may be causal, there are certain aspects that suggest a possible relationship between the 2 entities. On the one hand, it is known that omalizumab is capable of reducing plasma concentrations of IgE, possibly inducing polarization towards type 1 helper ($T_H1$) cells and increasing the release of interferon $\gamma$, whose antiviral properties are well known. On the other hand, increased production and release of a protein known as Fv has been detected in patients with chronic viral infections of the liver, mainly due to HBV.[5] Protein Fv acts as a superantigen. It interacts with the $V_H3$ domain of IgE, possibly activating

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**Table 1** Serologic Profiles of HBV Infection.

| HBsAg | Anti-HBc | HBsAb | Clinical situation | Treatment strategy |
|---|---|---|---|---|
| + | + (IgM) | – | Acute infection | Antiviral treatment for HBV |
| – | + (IgG)/– | + | Infection resolved | Antiviral treatment not needed; no risk of viral reactivation with immunosuppressants (e.g., cyclosporine) |
| +/– | IgG + | – | Chronic infection | Low risk of HBV reactivation; strict follow-up during treatment with immunosuppressants |
| – | – | + (>10 IU/mL) | Vaccinated patient | No risk of hepatitis; antibody determination to assess serologic status (revaccinate if necessary) |
| – | – | – | Patient not in contact with HBV or vaccinated (susceptible to infection) | Referral to preventive medicine to schedule vaccination before initiation of immunosuppressive treatment |

Abbreviations: (+) positive; (–) negative; anti-HBc, antibody against HBV core protein; HBsAb, antibody to HBV surface antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IgG, immunoglobulin G; IgM, immunoglobulin M.
Patients with chronic HBV infection and HBsAg positivity have a moderate risk of viral reactivation during treatment with cyclosporine. The risk in HBsAg-negative and HBsAb-positive patients is low to moderate.

mast cells and basophils and, as a result, triggering urticaria. In vitro studies have additionally shown that protein Fv is capable of directly activating basophils, increasing the secretion of interleukin 4, favouring polarization towards the $T_H2$ pathway, and stimulating the production of IgE by B cells and plasma cells.[6] This increase in IgE levels is particularly interesting considering that patients with elevated IgE respond better to omalizumab. Elevated levels of C5a[7] and C1q[8] deposits have also been detected in blood vessels in biopsy specimens taken from urticarial wheals, indicating a pathophysiologic link between urticaria and liver virus infection. Nonetheless, and despite the evidence available, it is difficult to establish a clear or direct relationship between the 2 entities.

The treatment of patients with viral infections of the liver and urticaria inadequately controlled with antihistamines and omalizumab also poses dilemmas. Although the immunosuppressive properties of cyclosporine are well known among dermatologists, this drug also has certain antiviral properties. Extreme caution must be exerted in patients with associated jaundice and a cholestatic pattern of liver injury, since interference with NTCP transporter activity[9] can cause fatal hepatitis. Cyclosporine, however, is not absolutely contraindicated in patients with chronic HBV infection, as long as HBsAg is negative. HBsAg-positive patients have a moderate risk of hepatitis reactivation, hence the recommendation to administer an antiviral together with cyclosporine. These patients require more rigorous blood testing than usual, as well as joint follow-up with the relevant hospital specialist.

In conclusion, there is a certain pathophysiologic relationship between chronic liver virus infections and urticaria, as well as a relationship between changes to viral load and changes to urticaria activity. Omalizumab can be considered a safe and effective treatment for patients with this complex profile, and cyclosporine can even be considered in refractory cases. Based on the limited evidence available, the presence of urticaria alone does not justify the use of antiviral treatment, although decisions should always be taken on a case-by-case basis.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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