



Brief Communication

Experience With Rituximab in Patients With Pemphigus Vulgaris and Hepatitis B

*Experiencia con rituximab en pacientes con pénfigo vulgar y hepatitis B*

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ABSTRACT

Rituximab is an anti-CD20 monoclonal antibody used as first-line therapy for moderate-to-severe pemphigus vulgaris.

For many years, it was contraindicated in patients with a past medical history of hepatitis B due to the risk of disease reactivation. However, it has recently been recognized that this infection should be considered a comorbidity requiring monitoring rather than an absolute contraindication.

Only a few publications in the dermatologic literature describe in detail the management of rituximab in patients with a history of hepatitis B.

We present two cases of pemphigus vulgaris in the setting of resolved hepatitis B infection who received antiviral prophylaxis and rituximab.

Introduction

Pemphigus vulgaris (PV) is a chronic autoimmune mucocutaneous blistering disease characterized by a relapsing course and severe clinical consequences. Systemic corticosteroids have historically been the cornerstone of therapy for this disease, leading to the prolonged use of high doses to achieve disease control and adding the consequent adverse effects to an already complex clinical condition.

In 2018, the *Food and Drug Administration* (FDA) approved the use of rituximab (RTX) for moderate-to-severe PV,¹ representing a paradigm shift in the treatment of this disease. Multiple studies have demonstrated that RTX allows corticosteroid tapering and achieves remission in most patients, producing a notable improvement in disease course and patients' quality of life.^{2–5} Thus, this monoclonal antibody has become a first-line therapy for moderate-to-severe PV.

Nevertheless, certain risks must be considered when administering this drug, including the reactivation of chronic or latent infections, among them viral hepatitis, particularly hepatitis B virus (HBV). Previously, a history of this viral infection was considered an absolute contraindication, but the increasing need for RTX has led clinicians to address these infectious challenges and establish management protocols.

Below we present 2 cases of PV with positive HBV serology consistent with resolved infection who received treatment with RTX under appropriate follow-up.

Case report # 1

A 48-year-old woman under follow-up for PV localized to the oral mucosa with a 2-year history (PDAI: 12) (Fig. 1). The patient received treatment with prednisone at an initial dose of 1 mg/kg/day combined with azathioprine (AZA) 2.5 mg/kg/day. During follow-up, an elevation of liver enzymes (three times the upper limit of normal) secondary to AZA was observed, leading to its discontinuation. In addition, as complications of prolonged steroid therapy, the patient developed diabetes and glaucoma. Therefore, due to persistent blistering lesions and the inability to taper corticosteroids, RTX administration was proposed as the therapeutic plan. Before initiating treatment, serologic tests were performed, revealing positive anti-core antibodies (anti-HBc), positive surface antibodies (anti-HBs), and negative surface antigen (HBsAg), consistent with resolved infection. Follow-up was initiated with hepatology and infectious diseases specialists, who requested viral load testing, which was undetectable (< 10 IU/mL). Prophylactic treatment with tenofovir 300 mg/day was started 15 days before RTX infusion and maintained for 18 months. RTX was initiated at the rheumatoid arthritis dosing regimen (1 g on day 0 and day 14). Subsequently, periodic monitoring of HBV viral load was performed, which remained negative. The patient sho-

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Fig. 1. Erosions on the lower labial mucosa.



Fig. 2. Erosions covered by adherent hemorrhagic crusts alternating with residual macules.

wed favorable clinical evolution with improvement of the dermatosis, allowing corticosteroid withdrawal (PDAI: 2).

Case report #2

A 43-year-old man with an 8-year history severe PV involving the oral mucosa (PDAI: 40) (Fig. 2) was referred from another institution, where he had received treatment with prednisone 1 mg/kg/day, dapsone 100 mg/day, and mycophenolate mofetil (MMF) 2 g/day without adequate disease control. Treatment with RTX at the rheumatoid arthritis dosing regimen was initiated.

Table 1

Complementary examinations prior to immunosuppression.

Complete blood count

Serologies

Hepatitis: HAV IgG, anti-HBc, HBsAg, anti-HBs, total anti-HCV.
 HIV (4th generation), HSV-1 and HSV-2, VZV, measles IgG, rubella IgG, CMV IgG, toxoplasmosis IgG, HTLV-1^a, Chagas disease.^a

Chest radiography

Tuberculin skin test; QuantiFERON-TB Gold.

Pregnancy test.

Gynecologic evaluation.

Dental evaluation.

Vaccines

Annual influenza vaccine, diphtheria–tetanus (DT) vaccine, 13-valent conjugate pneumococcal vaccine and 23-valent polysaccharide pneumococcal vaccine, hepatitis A and B vaccines, and COVID-19 vaccine.

^a According to regional epidemiology.

Baseline investigations were requested before starting treatment, revealing positive anti-HBc and anti-HBs serology, negative HBsAg, and undetectable viral load (< 10 IU/mL). These findings were interpreted as resolved infection.

Given the risk of viral reactivation, prophylactic treatment with entecavir 0.5 mg/day was initiated 15 days before the first RTX infusion and continued for 18 months thereafter. The hepatology service continued patient follow-up and observed that HBV viral load levels remained undetectable. Regarding his dermatosis, the patient evolved with complete remission of lesions (PDAI: 0).

Discussion

RTX is a chimeric IgG1 monoclonal antibody directed against the CD20 antigen, which is expressed on the surface of B lymphocytes (from the pre-B stage to mature B cells, but not on plasma cells), leading to B-cell depletion. Over the past few decades, it has been used for hematologic malignancies and autoimmune diseases, including PV, for which it has been considered a first-line therapy since 2018 for moderate and severe forms.⁶

Its efficacy has led to a change in the management of PV; therefore, it is of particular interest for dermatologists to be aware of the potential for reactivation of chronic and latent infections such as hepatitis B virus (HBV). These comorbidities represent a challenge in our specialty, and it is important to understand the recommended protocols for managing infectious scenarios.

In our experience, as well as in national and international clinical practice guidelines, screening should be performed prior to initiating RTX, including viral hepatitis serology⁷ (Table 1).

Hepatitis B virus

HBV infection may present as acute, chronic, or resolved infection (with resolution of the viral illness and development of immunity).

Even in resolved HBV infection, the virus has the particular characteristic of integrating its genome into the host DNA. In addition, circular DNA (cccDNA) is formed, which gives rise to virions. These are responsible for viral persistence in hepatocytes and the risk of reactivation in cases of immunosuppression.⁸

RTX is considered a high-risk agent because it has the potential to reactivate HBV in more than 10% of cases.⁹ This occurs due to RTX-induced depletion of B lymphocytes and the consequent dysregulation of T cells, which play a fundamental role in the cellular immune response against HBV.^{10,11} Therefore, screening for this infection must be performed before administration, and the correct interpretation of serologic results will determine the appropriate management strategy (Table 2).^{12,13}

In cases of resolved HBV infection, antiviral prophylaxis should be initiated at least 15 days before the first RTX infusion, and either tenofovir or entecavir may be used.

Table 2
Serologic interpretation of HBV and administration of RTX.

Anti-HBc (IgG)	Anti-HBs	HBsAg	Interpretation	Management
Negative	Negative	Negative	Susceptible patient	Vaccinate before RTX
Negative	Positive > 10	Negative	Vaccinated patient	Authorized to receive RTX
Positive	Positive (> 10)	Negative	Resolved HBV infection	Prophylactic treatment 15 days before initiation of RTX and monitoring of viral load, HBsAg, AST/ALT every 3 months
Positive	Negative	Positive	Chronic HBV	Antiviral treatment 15 days before initiation of RTX and monitoring of viral load, AST/ALT every 3 months
Positive	Negative	Negative	Possible occult HBV	Prophylactic treatment and vaccination
Negative	Negative	Positive	Acute HBV	RTX contraindicated. Risk of fulminant hepatitis

The risk of reactivation persists even after completion of RTX therapy; therefore, prophylaxis should be maintained for up to 18 months after the last dose. In addition, laboratory follow-up is required with viral load testing, HBsAg, and transaminase levels every 3 months until 12 months after completion of prophylaxis to evaluate signs of reactivation.^{14–16}

Another scenario to consider is the presence of reactive anti-HBc with negative anti-HBs and HBsAg, which may correspond to occult HBV infection. In such cases, and particularly when immunosuppression is anticipated, prophylaxis and vaccination should be indicated.

Cases of HBV reactivation following RTX administration have been reported in the literature, some of which progressed to fulminant hepatitis,¹⁷ highlighting the importance of meticulous monitoring and preventive measures before and during RTX therapy.

Conclusions

Currently, with the increasing indications for RTX and a better understanding of the pathogenesis of HBV, this infection—once considered an absolute contraindication—should instead be regarded as a comorbidity that requires careful monitoring and management.

It should be emphasized that interdisciplinary management and follow-up with hepatology and infectious diseases specialists are essential. It is important to develop protocols for dermatologists regarding the management of RTX in patients with a past medical history of HBV infection, which remains one of the most prevalent infections worldwide.

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Conflict of interest

The authors declare that they have no conflict of interest.

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