

Reactivation of Hepatitis Virus B Infection in a Patient With Rheumatoid Arthritis After Treatment With Rituximab[☆]

Reactivación del virus de la hepatitis B en un paciente con artritis reumatoide tras el tratamiento con rituximab

To the editor:

The reactivation of hepatitis B virus (HBV) infection is defined as an increase in HBV replication in a patient with an inactive or resolved hepatitis (usually accompanied by increased serum transaminase levels). Most reported cases have occurred in patients with hematologic malignancies after chemotherapy.^{1–3} Recently, there have been reports of HBV reactivation in patients with rheumatoid arthritis after treatment with biological therapies such as rituximab (RTX)^{4,5} (Table 1). Although most cases of HBV reactivation have occurred in patients with serology indicating chronic HBV infection, patients with resolved HBV infection can develop this complication.⁵

We report the case of a 77 year old patient with a history of seropositive and erosive rheumatoid arthritis of 12 years of evolution, receiving the first cycle of RTX in February 2008. Serology for HBV in 2001 was HBsAg negative and anti-HBc positive, compatible with resolved hepatitis B. The patient received methotrexate from 2002 to 2004 and the treatment was stopped by the appearance of oral ulcers. In 2005, treatment was started with infliximab 3 mg/kg every 8 weeks with good response; after one year of treatment, the patient presented a lack of response in March 2006 and it was suspended due to multiple episodes of lung infections and switched to etanercept 50 mg weekly. From 2005 to 2008, serum levels of ALT transaminase (GPT) and AST (GOT), remained stable, but new virus serology was not requested. Due to poor control of symptoms (disease activity score [DAS] 28 joints 6.43) the patient

was treated with RTX (2×1000) in February 2008. He received the second cycle of RTX in August 2008. After treatment, the DAS 28 was 3.79, but in July 2009 the patient had anicteric hepatitis with ALT (GPT) 555 U/L, AST (GOT) 349 U/l, GGT 81 U/l, total bilirubin 0.7 mg/dl and HBsAg+, HBeAg+, albumin 35 mg/dl, 70% TP, 99 000 platelets/mm³ and HBV DNA was >8 log U/ml (virus genotype was A). This data indicated the presence of a reactivation of chronic hepatitis B with a moderate degree of hepatocellular failure. At this point the patient quickly was sent to the hepatologist and began treatment with entecavir. After one month of therapy, HBV was DNA down to 5.4 log U/ml. Five months later HBV-DNA was only 1.74 U/ml (3.24 log U/ml), but remained positive until February 2011. The biochemical response was faster, with normalization of transaminases after only 8 months of therapy.

HBV reactivation after immunosuppressive treatment is a serious adverse effect which can be identified and prevented. There have been various guidelines and recommendations but the management of HBV occult infection with only anti-HBc positivity remains unclear today.^{6,7} The consensus on RTX use in rheumatoid arthritis recommends monitoring of transaminases and/or HBV DNA⁸ in patients without active HBV with HBsAg negative but anti-HBc-positive antibodies, as in our patient. In patients who had increased levels of HBV DNA during therapy with RTX, one should consider associating antiretroviral therapy. The exact mechanism of HBV reactivation is unknown and although it is not a very common complication, there have been cases of fulminant hepatitis that were seen even after 6 months of cessation of therapy with RTX.⁹ Prophylactic treatment with antiretroviral therapy significantly reduces the incidence of HBV reactivation after treatment with RTX.¹⁰ In conclusion, strict monitoring should follow liver biochemistry, HBsAg, HBV-DNA in the anti-HBc positive and HBsAg negative patients during and 6 months after treatment with RTX.

Table 1
Previous Cases of HBV Reactivation in RA Patients Following Treatment With RTX.

Reference	Patient	Treatment	No. cycles RTX	HBV serology before RTX	HBV serology after RTX	Antiretroviral therapy	Evolution
Pyrpasopoulou et al. ¹	F 56 RA	Only RTX	1	HBsAg+ HBeAg+ HBeAb– HBV DNA>9.6×10 ² U/ml Normal serum transaminases treatment with lamivudine	HBsAg+ HBeAg+ HBV DNA>1.1×10 ⁸ U/ml ASAT 110 U/l ALT 150 U/l	Tenofovir and lamivudine	10 months later HBV load was 46 U/ml
Ghrénassia et al. ⁵	M 78 RA and mantle cell lymphoma	RTX+prednisone 10 mg/day	4	HBsAg HBcAb+normal serum transaminases	HBsAg +HBeAg+ HBV DNA>7 log U/ml ASAT 177 U/l ALT 421 U/l	Entecavir	6 months later HBV load was undetectable
Case	M 77 RA	RTX+prednisone 15 mg/day	2	HBsAg HBcAb+normal serum transaminases	HBsAg+ HBeAg+ HBV DNA>8 log U/ml ASAT 349 U/l ALT 555 U/l	Entecavir	18 months later HBV load was undetectable

F: female, M: male.

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Frequency of Gout According to the Perception of Physicians in México[☆]

Frecuencia de la gota según la percepción de los médicos en México

To the Editor:

Prevalence studies may underestimate the frequency of some chronic diseases such as gout, as they are asymptomatic for long periods of time; several articles have reported that osteoarthritis (OA) and rheumatoid arthritis (RA) are the most prevalent rheumatic diseases.^{1–3} In an epidemiological study in our country, in which the COPCORD methodology was used, a prevalence of 10.5% and 1.6% for OA and RA was reported, respectively, whereas the prevalence of gout in this report was 0.3%.⁴ Reports of incidence in other countries suggest that gout is the most common inflammatory joint disease, in contrast to some studies that indicate other methodology.^{5,6} In our country, there is no epidemiological data on the incidence of various rheumatic diseases, but we have the perception that some of them are more common than others.

With this in mind, we interviewed 111 doctors, asking them the number of persons among their “known”-first-or second-degree family members, political family and friends, who had the diagnosis of OA, fibromyalgia (FM), RA, lupus erythematosus (SLE), ankylosing spondylitis (AS) or gout. Statistical analysis was performed using descriptive statistics.

The physicians who responded to the survey were 57 men/54 women, 45 (40.5%) medical residents, mainly of internal medicine (17), rheumatology (5) and gastroenterology (4); 37 (33.3%) were medical specialists, of which 29.7% saw musculoskeletal diseases, 70.3% are internists or related subspecialists (9 internists, 2 endocrinologists and 2 geriatricians); finally, 24 (21.6%) were general practitioners and 5 (4.5%) family physicians, with a mean age ± standard deviation 30.9 ± 6.7 years. As perceived by the respondents, 85.5% had at least one family member/friend with

one of the diseases mentioned. Each respondent had, on average, 4.3 ± 7.2 (median 2) family/friends with one of the diagnoses. As expected, OA was the most common rheumatic disease followed by gout, RA, FM, SLE and AS (Fig. 1).

The respondents knew 1.3 times more patients with gout among family and friends than someone diagnosed with RA; in addition, we found that there were 1.38, 1.7 and 3.75 times more patients with gout than those observed with FM, SLE and AS, respectively.

The reported differences in the frequency of gout are related to the methodology, the type of study and the approach to diagnosis. It is also possible that these differences are related to the characteristics of the disease, since, unlike the OA and RA, gout has episodic clinical manifestations and may remain asymptomatic for long periods of time. In the various studies, the diagnosis is established variably, either by patient self-report, clinical databases and drug use, evaluation by a family doctor, internist or rheumatologist. Sometimes the diagnosis can be challenging for primary care physicians; the preliminary criteria of the American College of Rheumatology⁷ have been evaluated in several studies and have shown great limitations.^{8,9}

There are at least 5 proposals for the clinical diagnosis of gout, including 2 very recent,^{10,11} but both have some controversial points¹² and these are taken as the basis for a multicenter, multinational study being done in order to propose clinical criteria for the

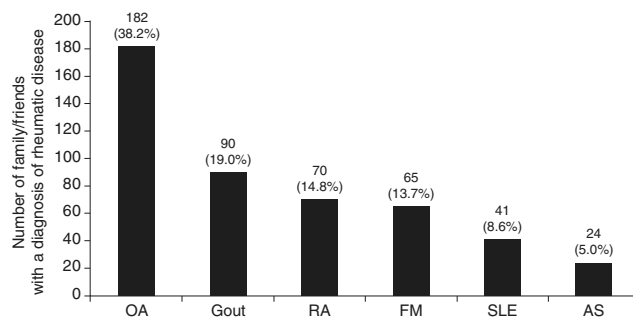


Fig. 1. Frequency of rheumatic diseases as perceived by physicians. OA (osteoarthritis), RA (rheumatoid arthritis), FM (fibromyalgia), SLE (systemic lupus erythematosus) and AS (ankylosing spondylitis).

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