VIRAL B AND C HEPATITIS IN RHEUMATIC PATIENTS UNDER BIOLOGICAL THERAPY

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VIRAL B AND C HEPATITIS IN RHEUMATIC PATIENTS UNDER BIOLOGICAL THERAPY (Abstract): Both rheumatic immune-inflammatory diseases and viral hepatitis represent important health problems worldwide. Modern therapies with biological and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) have revolutionized the management of immune-inflammatory diseases. However, these therapies have a strong immunosuppressive impact, patients being at risk of reactivation of viral hepatitis. The aim of this study was to assess the prevalence and the risk of reactivation of B and C hepatitis (HBV, HCV) in rheumatic patients who are treated with b/tsDMARDs for rheumatoid arthritis (RA) and ankylosing spondylitis (AS). **Material and methods:** We retrospectively analyzed all patients with RA and AS receiving b/tsDMARDs therapies in the Rheumatology department over a one-year period. Serological screening for HBV infection (HBsAg, anti-HBc, anti-HBs) and HCV antibodies was performed in all patients. For each patient we reviewed the diagnosis, demographic data, type of the treatment, HBV and HCV serology, viral infection treatment. **Results:** There were 132 patients diagnosed with RA and 90 patients diagnosed with AS receiving therapy with bDMARDs or tsDMARDs. 65 of the patients with RA (49.24%) and 32 of those with AS (35.55%) presented changes in viral markers. Both in the group of patients with RA and those with AS, approximately 10% of patients showed previous B vaccination. Only 2.27% of the patients with RA and 1.11% of those with AS presented chronic B infection. Most of the patients (36.36% RA, 24.44% AS) had resolved B infection. Inactive HCV infection was found in 2.25% of total number of patients. A percentage of 12.12% among those with RA and 3.33% of those with AS received treatment with Entecavir/Tenofovir. There were no cases of hepatitis reactivation. **Conclusions:** Viral B infection has a high prevalence in patients with RA and AS. Screening for chronic viral B and C infections should be done in all patients with autoimmune rheumatic diseases. Treatment with nucleotide/nucleoside analogs is effective in preventing HBV flare regardless of the type of b/tsDMARDs. All patients with viral C infection should be treated with direct-acting antivirals. **Keywords:** VIRAL HEPATITIS, RHEUMATOID ARTHRITIS, ANKYLOSING SPONDILITIS, BIOLOGICAL THERAPY.

Both rheumatic immune-inflammatory diseases and viral hepatitis represent important health problems worldwide. Chronic hepatitis B (HBV) and C virus (HCV) infection are major causes of morbidity and mortality, leading to cirrhosis, hepatocellular carcinoma, and liver transplantation (1). The prevalence of hepatitis varies between populations, and even in areas with low endemic levels it is necessary to identify those whose current or previous infection could influence their clinical outcome (2). It is estimated that approximately 1 in 3 individuals in this world may have been exposed to HBV infection (3,4), and 110 million persons are HCV antibody-positive, with 80 million viremic HCV infection (5).

The treatment of patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS) is aimed at relieving symptoms, improving physical function and quality of life, and preventing structural damage (6). Pharmacological options include (6,7):

- conventional synthetic (cs) disease-modifying antirheumatic drugs (DMARDs) such as Methotrexate, Leflunomide, Sulfasalazine;
- biological (b) DMARDs, including tumor necrosis factor (TNF) inhibitors (Adalimumab, Etanercept, Infliximab, Certolizumab, Golimumab), T-cell stimulation modulators (Abatacept), interleukin-6 (IL-6) receptor antagonists (Tocilizumab), interleukin-1 (IL-1) inhibitors (Anakinra) , interleukin-17 (IL-17) inhibitors (Secukinumab) and anti-CD20 antibodies (Rituximab);
- targeted synthetic (ts) DMARDs, such as Janus kinase (JAK) inhibitors (Tofacitinib, Baricitinib and Upadacitinib).

The new therapies (b/ts DMARDs) have revolutionized the management of rheumatic immunoinflammatory diseases. However, these therapies have a strong immunosuppressive impact. Patients receiving this treatment have the risk of reactivation of viral hepatitis - especially reactivation of HBV infection (HBVr) (8, 9). Recent guidelines advice to perform a complete hepatitis status screening before starting biologic therapy (2, 8, 10). This involves testing for four serological components of hepatitis infection: hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc) and hepatitis C antibody (HCV) (2). HBsAg indicates the presence of acute or chronic hepatitis B infection, anti-HBc antibodies may be present in acute, chronic or resolved infection, anti-HBs antibody may indicate resolved infection, or vaccination if found alone (2,11). Before the initiation of biological therapy, antiviral therapy is recommended for positive HbsAg patients, while for negative HbsAg, positive anti-HBc patients recommendations of the guidelines are not uniform, varying between monitoring and treatment. Anti-HBV drugs with a high resistance barrier, such as entecavir or tenofovir, should be preferred over low-barrier agents such as lamivudine (12).

Although all rheumatologists should be aware that the immunosuppression associated with b/tsDMARDs can provoke HBVr, with a significant morbidity and mortality of susceptible patients, screening and treatment practices for B and C viral infections are extremely varied worldwide (13). In addition, the risk of reactivation of viral infections under new b/tsDMARDs other than anti-TNF agents is incompletely known.

The aim of this study was to assess the prevalence and the risk of reactivation of B and C hepatitis in rheumatic patients who are treated with b/tsDMARDs for RA and AS.

MATERIAL AND METHODS

Study design and patients

We retrospectively analyzed all patients with RA and AS receiving b/tsDMARDs therapies in the Rheumatology department (a tertiary referral care center), over a one-year period, between 1st September 2021 and 1st September 2022. Data among these patients were screened from the first b/tsDMARDs administration to the last visit to our hospital. Data were collected from the Romanian Registry of Rheumatic Diseases. This study was performed in accordance with the ethical principles of the Declaration of Helsinki. All patients have signed inform consent before therapy initiation.

Diagnosis of RA and AS

Diagnosis of chronic rheumatic diseases was established according to criteria recommended by international guidelines. The diagnosis of RA was based on the 1987 American College of Rheumatology criteria (14) or 2010 American College of Rheumatology/European League Against Rheumatism collaborative initiative (ACR/EULAR) classification criteria (15). The diagnosis of AS was established according to the modified New York 1984 criteria (16).

Diagnosis of HBV and HCV infections

Serological screening for HBV infection (HBsAg, anti-HBc, anti-HBs) and HCV antibodies was performed in all patients. Based on the results of the screening tests, patients were categorized to the following groups:

1. Non-modified serological markers (HBsAg-, anti-HBc-, anti-HBs-, anti-HCV);
2. Previous B vaccination (HBsAg-, anti-HBc-, anti-HBs+);
3. Chronic B infection (HBsAg+, anti-HBc+, anti-HBs-);
4. Resolved HBV infection (HBsAg-, anti-HBc+, anti-HBs±);
5. HCV infection (anti-HCV+).

According to the Romanian protocol for the treatment of viral B infection in patients under immunosuppressive treatment (17), all patients with positive HBsAg, as well as those with negative HBsAg, positive anti-HBc and anti-HBs <10 mIU/mL received prophylactic treatment with nucleoside/nucleotide analogues (Entecavir/ Tenofovir).

Data collection. For each patient we reviewed the diagnosis, demographic data, type of the treatment, HBV and HCV serology, viral infection treatment.

RESULTS

Baseline characteristics of the patients

There were 132 patients diagnosed with RA and 90 patients diagnosed with AS receiving therapy with bDMARDs or tsDMARDs. In the group of patients with RA, the majority were female, and the average age was 62.68 years. In the group of patients with AS, the majority were male, the average age being lower than in the group of patients with RA. We note that patients with AS mostly received anti-TNFα treatment (according to the Romanian treatment protocol), only 4.44% being treated with anti-IL-17. In the group of patients with RA, the majority received anti-IL-6 treatment, followed by those with anti-TNFα, but also with JAK-kinase inhibitors in a close percentage (tab. I).

TABLE I.
Baseline characteristics of the study group

Parameter	RA (n=132)	AS (n=90)	Total (n=222)
Sex M	34 (25.75%)	66 (73.33%)	100 (45.04%)
F	98 (74.24%)	24 (26.66%)	122 (54.95%)
Medium age	62.68±9.42	51.15±14.31	58.84±12.53
Treatment			
Anti-TNF	41 (31.06%)	86 (95.55%)	127 (57.20%)
Infliximab	4 (3.03%)	9 (10%)	13 (5.85%)
Adalimumab	15 (11.36%)	33 (36.66%)	48 (21.62%)
Etanercept	16 (12.12%)	28 (31.11%)	44 (19.81%)
Certolizumab	2 (1.51%)	5 (5.55%)	7 (3.15%)
Golimumab	4 (3.03%)	11 (12.22%)	15 (6.75%)
Anti-interleukins	47 (35.60%)	4 (4.44%)	51 (22.97%)
Tocilizumab	47 (35.60%)	-	47 (21.17%)
Secukinumab	-	4 (4.44%)	4 (1.80%)
JAK inhibitors	38(28.78%)		38 (17.11%)
Tofacitinib	17 (12.87%)	-	17 (7.65%)
Baricitinib	16 (12.12%)	-	16 (7.20%)
Upadacitinib	5 (3.78%)	-	5 (2.25%)
Anti-B-cell agents			
Rituximab	6 (4.54%)	-	6 (2.70%)

The presence of markers of B and C viral infections

65 of the patients with RA (49.24%) and 32 of those with AS (35.55%) presented changes in viral markers. Both in the group of patients with RA and those with AS, more than half did not show any change in viral markers. Regarding vaccination, both in the group of patients with RA and those with AS, approximately 10% of patients (13 of those with RA and 9 of those with AS) showed positive anti-HBs antibodies, these being considered subjects immunized by vaccination.

Most of those who presented changes in the serological markers were those with resolved HBV infection (48 patients with RA and 22 patients with AS). Among them, in the case of patients with RA, 35 subjects (26.51% of total number of patients) presented anti-HBc+ and anti-HBs+, meaning spontaneous seroconversion. They did not require prophylactic treatment. 13 patients (9.84% of total number of patients) presented only anti-HBc+, without protective titer of anti-HBs antibodies. All these patients received treatment with Entecavir/ Tenofovir. In the case of patients with AS, approximately 20% of total number of subjects presented spontaneous seroconversion, with protective titer of anti-HBs. Two patients showed anti-HBc+, anti-HBs- and they also received treatment with Entecavir.

Only two of the patients with RA and one patient with AS presented HBsAg+, anti-HBc+, anti-HBs-, these being classified as patients with chronic B infection. These patients also received antiviral treatment with NAs resulting a total of 16 patients among those with RA (12.12%) and 3 (3.33%) of those with AS being treated with Entecavir / Tenofovir.

Among the patients with RA, 4 subjects

showed positive anti-HCV, 2 of them associated with resolved HBV infection, one with chronic B infection, and one with no changes in serology for hepatitis B. Also, one patient with AS associated inactive HBV + HCV infection. All five patients had sustained virologic response to HCV treatment (tab. II).

TABLE II.

The presence of markers of B and C viral infections

Type of viral infection	RA	AS	Total
Non-modified serological markers (HBsAg-, anti-HBc-, anti-HBs-, anti-HCV-)	67 (50.75%)	58 (64.44%)	125 (56.30%)
Previous B vaccination (HBsAg-, anti-HBc-, anti-HBs+)	13 (9.84%)	9 (10%)	22(9.90%)
Chronic B infection (HBsAg+, anti-HBc+, anti-HBs-)	3 (2.27%)	1(1.11%)	4 (1.80%)
Resolved HBV infection (HBsAg-, anti-HBc+, anti-HBs±)	48 (36.36%)	22 (24.44%)	70 (31.53%)
HCV infection (anti-HCV+)	4 (3.03%)	1 (1.11%)	5 (2.25%)

Viral infection reactivation

Among the patients with chronic B infection, half were treated with anti-TNFα and half with JAK-inhibitors. Most of the patients with resolved HBV infection were treated with anti-TNFα (47.14%), followed by anti-IL-6 treatment (34.28%) and JAK-inhibitors treatment (12.85%). Among the patients with HCV infection, 80% were under anti-TNFα treatment and one patient under JAK-inhibitors treatment (tab. III).

There was no case of hepatitis reactivation during the follow-up period.

TABLE III.

Relationship between the type of treatment followed and the B and C infection markers.

Type of treatment	Chronic B infection	Resolved HBV infection	HCV infection
Anti-TNFα	2 (50%)	33 (47.14%)	4 (80%)
Anti-IL-6	0 (0%)	24 (34.28%)	0 (0%)
Anti IL-17	0 (0%)	1 (1.42%)	0 (0%)
JAK-inhibitors	2 (50%)	9 (12.85%)	1 (20%)
Anti-CD20 antibodies	0 (0%)	3 (4.28%)	0 (0%)

DISCUSSION

Chronic viral hepatitis B and C represent a real public health problem. Despite the fact that they can be asymptomatic for many years, they have the potential to progress to liver cirrhosis, hepatocarcinoma and death. In immune rheumatic diseases, such as RA and AS, there is an increased risk of activation of viral infections as a result of immunosuppressive treatment.

It is considered that HBV and HCV infection have the same prevalence in rheumatic diseases patients as in the general population. In these patients the prevalence of positive HBsAg is estimated at 3-3.5%, past HBV infection between 13-50% and anti-HCV positive 1.2% (18,19). The prevalence data from our study (HBsAg was found in 1.80% of the patients, past HBV infection in 31.53% and anti-HCV positive in 2.25% of the patients) are similar to the data from the literature. In our study, we recorded a higher prevalence of HBV infection markers in patients with RA com-

pared to those with AS, a fact also reported in other studies in the literature (20). Most patients had the profile of negative HBsAg/positive anti-HBc/positive anti-HBs; only 4 patients had positive HBsAg. It should be mentioned that in Romania the complete screening of HBV infection (HBsAg, anti-HBc, anti-HBs) is mandatory for all patients who initiate b/tsDMARDs. In the USA, for example, only 1/3 of the patients of the national Rheumatology Informatics System for Effectiveness (RISE) registry have the full screening done (21). In Mohareb's study (22), only 29% of the patients who initiated tocilizumab and 24% of those who initiated tofacitinib had complete screening for HBV infection.

There is evidence regarding the risk of reactivation of viral B infection under biological therapy (23,24). The reactivation rate of HBV infection in patients with rheumatological diseases seems to be lower compared to data from oncology or hematology: only 1.4% in the meta-analysis performed by Moghoofei (25). However, in patients with B viral infection treated with anti-TNF agents, who did not receive prophylactic antiviral therapy, reactivation of HBV infection occurred in up to 75% of patients (19). The risk of reactivation of HBV infection is much lower in HBsAg negative/anti-HBc positive patients: 1.7% in Lee meta-analysis (26).

In Romania, the protocol of the National Health Insurance House (17) stipulates that all patients who initiate immunosuppressive therapy or chemotherapy should be screened for markers of HBV infection. All HBsAg - positive or anti-HBc positive subjects (without positive anti-HBs) will initiate therapy with nucleotide/nucleoside analogues during immunosuppressive therapy and 6 months after stopping it. Patients with negative HBsAg, positive anti-HBc and positive anti-HBs (> 10 mIU/mL) will be closely monitored at 3 months. Following the national protocol, all HBsAg positive or anti-HBc positive patients (without anti-HBs positive antibodies) benefited from prophylactic antiviral treatment with Entecavir or Tenofovir before starting b/tsDMARDs. During the studied period, we did not register a single case of reactivation of the B viral infection. Many authors have shown that the prophylactic treatment with analogues is effective for preventing HBV flare both in HBsAg positive and in anti-HBc positive patients (23). The lack of reactivation of viral B infection in our study is explained by the prophylactic treatment of all patients with HBV markers, including those with negative HBsAg, which is different from most other countries. Current practice in most countries involves - in the case of patients with resolved HBV infection - only monitoring without initiation of antiviral treatment (27).

Data from the literature regarding the risk of reactivation of HBV infection under the new biological and targeted synthetic therapies are poor, given that HBV positive patients were excluded from the pivotal studies. Rituximab, an anti-CD20 agent, is known from oncology-hematology for the increased risk of reactivation of viral B infection. In rheumatic diseases this risk seems to be lower (2%) (19). The data on Abatacept, interleukin inhibitors and oral targeted therapies (JAK inhibitors) regarding the risk of HBV reactivation come from small, retrospective studies or case reports. Lin's meta-analysis (28) showed the same risk of reactivation of HBV infection regardless of the type of b/tsDMARDs used: anti-TNF, other biological, non-biological therapies. It is generally accepted that the risk and management of patients is similar in the new b/tsDMARDs therapies to that of anti-

TNF agents. A significant proportion of patients included in our study were treated with non-anti-TNF biological agents and JAK inhibitors. Our study showed that prophylaxis with nucleoside/nucleotide agents is also effective in the case of these new therapies in RA and AS.

According to the Romanian protocol, patients with anti-HBs over 10 mIU/mL did not initiate prophylactic treatment with nucleotide/nucleoside analogs. Indeed, data from the literature reveal a low risk of HBV reactivation in patients with positive anti-HBs, directly proportional to their titer (29,30). However, Tien's study (31) demonstrated that there is still a low risk of HBV reactivation in patients with low anti-HBs titers (<100 mIU/mL), which explains the monitoring of these patients. The loss of anti-HBs in patients with rheumatic diseases under treatment with b/tsDMARDs is greater in patients who associate chronic kidney disease (32).

We note a small percentage of patients vaccinated against B virus (9.90%). This revealed deficiencies in the management of these patients. An explanation can be the increased average age of the studied group, taking into account that in Romania mandatory B vaccination at birth only started in 1996. In Romania, a country with a high prevalence of viral hepatitis B, ideally all patients with RA and AS should be screened for markers of HBV infection, right from diagnosis. If they are negative, the complete vaccination schedule is indicated.

Regarding the C virus, there are no special recommendations related to immunosuppressive therapy, the risk of reactivation of the viral infection being reduced. In Patel's study (33), RA and HCV patients had higher rheumatic disease activity scores and were more likely to be treated with cortisone or biologics. Considering the hepatotoxicity potential of b/tsDMARDs, treatment with direct-acting antivirals is ideally recommended before starting immuno-suppressive treatment. Some recent data in the literature suggest improvement in RA activity scores after achieving a sustained viral response in patients with C virus treated with direct-acting antivirals (34). Italian group for the Study and Management of the Infections in patients with Rheumatic diseases (36) recommends screening for HCV infection and treatment with direct-acting antivirals for all patients, ideally before starting treatment with DMARDs. Anti-TNF agents can be administered concurrently with DAA therapy. In the case of patients in whom viral eradication cannot be done, DMARD therapy is not contraindicated, but liver function must be carefully monitored. In our studied group there were only 5 cases of viral C infection, all 5 having sustained viral response after oral antiviral treatment.

The limitations of our study are the short follow-up period (one year), the retrospective nature and the lack of evaluation of all parameters related to the viral infection (viremia level, hepatic fibrosis staging). However, it is a study conducted in a tertiary rheumatology center, which included a large number of patients, brought new epidemiological data (unknown in Romania), and analyzed patients with various biological and JAK inhibitors.

CONCLUSIONS

Viral B infection has a high prevalence in patients with RA and AS, most patients being negative HBsAg, positive anti-HBc, positive anti-HBs. Screening for chronic viral B and C infections should be done in all patients with autoimmune rheumatic diseases, right from the moment of diagnosis. Treatment with nucleotide / nucleoside

analogs is effective in preventing HBV flare regardless of the type of b/tsDMARDs. All patients with viral C infection should be treated with direct-acting antivirals. Additional efforts are needed so that all patients with autoimmune rheumatic diseases, likely to receive immunosuppressive treatment throughout their lives, should be vaccinated against the B virus.

CONFLICT OF INTEREST AND FUNDING

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