Risk of hepatitis B reactivation: From biologic therapies for psoriasis to immunosuppressive therapies for COVID-19 (Review)

LILIANA BAROIU[1,2*], LUCREȚIA ANGHEL[1,3*], ALIN LAURENȚIU TATU[1,4,5], ALINA VIORICA IANCU[6,7], CATERINA DUMITRU[7,8], ANA-CRISTINA LEȘE[9*], MIRUNA DRĂGĂNESCU[1,2], FLORENTINA NĂSTASE[10], ELENA NICULEȚ[5,11], SILVIA FOTEA[1,12], AUREL NECHITA[1,12], DOINA CARINA VOINESCU[1,3] and ANCA IOANA STEFANOPOL[5,13]

[1]Department of Clinical Medicine, Faculty of Medicine and Pharmacy, 'Dunărea de Jos' University, 800216 Galati; [2]Department of Infectious Diseases 'Sf. Cuv. Parascheva' Clinical Infectious Diseases Hospital, 800179 Galati; [3]Department of Internal Medicine, 'Sf. Apostol Andrei' County Emergency Clinical Hospital, 800578 Galati; [4]Department of Dermatology, 'Sf. Cuv. Parascheva' Clinical Infectious Diseases Hospital, 800179 Galati; [5]Multidisciplinary Integrated Center of Dermatological Interface Research, 'Dunărea de Jos' University, 800008 Galați; [6]Department of Morphological and Functional Sciences, Faculty of Medicine and Pharmacy, 'Dunărea de Jos' University, 800216 Galati; [7]Department of Laboratory Medicine, 'Sf. Cuv. Parascheva' Clinical Infectious Diseases Hospital, 800179 Galati; [8]Department of Pharmaceutical Sciences, Faculty of Medicine and Pharmacy, 'Dunărea de Jos' University, 800216 Galati; [9]Faculty of Visual Arts and Design, 'George Enescu' National University of Arts, 700451 Iasi; [10]Department of Neuropsychomotor Rehabilitation, 'Sf. Ioan' Clinical Hospital for Children, 800487 Galati; [11]Department of Pathological Anatomy, 'Sf. Apostol Andrei' County Emergency Clinical Hospital, 800578 Galati; Departments of [12]Pediatrics and [13]Surgery, 'Sf. Ioan' Clinical Hospital for Children, 800487 Galati, Romania

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Abstract. The cytokine storm from the evolution of severe cases of COVID-19, requiring strong immunosuppressive therapies, has raised the issue of reactivation of hepatitis B virus (HBV) infections in these patients. An analysis of the first observational studies in patients with COVID-19 and immunosuppressive therapy and HBV infection along with special clinical cases was presented, as well as personal experience on a series of cases (a group of 958 patients with COVID-19), compared with the analysis of studies performed on patients with HBV infection that underwent biological therapies for psoriasis and personal experience (a group of 81 psoriasis patients treated with biological therapies). Clinical studies have revealed that HBV reactivation in patients undergoing biological therapies for psoriasis, can be prevented with monitoring and treatment protocols and thus, these therapies have been demonstrated to be safe and effective. In COVID-19, immunosuppressive therapies are short-lived but in high doses, and the conclusions of clinical trials are contradictory, but there are published cases of HBV reactivation, which requires a unitary attitude in the prevention of HBV reactivation in these patients. An algorithm was presented for monitoring and treatment of HBV infection for patients with psoriasis treated with biological therapy and the conditions when this protocol can be used for patients with COVID-19 and immunosuppressive therapy.

Correspondence to: Dr Alina Viorica Iancu, Department of Morphological and Functional Sciences, Faculty of Medicine and Pharmacy, 'Dunărea de Jos' University, 35 A.I. Cuza Street, 800216 Galați, Romania
E-mail: iancualina.2003@yahoo.com

Dr Caterina Dumitru, Department of Pharmaceutical Sciences, Faculty of Medicine and Pharmacy, 'Dunărea de Jos' University, 35 A.I. Cuza Street, 800216 Galați, Romania
E-mail: dumitrukati@gmail.com

*Contributed equally

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1. Introduction

The COVID-19 pandemic has called into question the necessary drug-induced immune suppression in the hyperimmune response of the body and the possibility of reactivation of the hepatitis B virus (HBV) infection after these therapies. The cytokine storm of SARS-CoV-2 severe infection requires treatment with strong immunosuppressants (tocilizumab) or high doses of cortisone (1). Although these therapies are not needed for long periods of time, patients with chronic or latent HBV infection run the risk of reactivation of HBV during these therapies (2-5).

In severe forms of psoriasis, biological therapies have brought marked therapeutic successes in recent decades. The main estimated risk of these therapies was the development of severe infections during treatment or the reactivation of latent infections such as tuberculosis or HBV infection. The biological therapies have significantly improved the quality of life of psoriasis patients and are considered to be safer and more effective than traditional systemic drugs (6). The risk of reactivation of the HBV infection during these therapies depends on the status of this infection and the type of immunosuppressant used (7).

The aim of the present study was to compare the experience gained in monitoring immunosuppressive therapies in psoriasis with preliminary clinical observations in COVID-19 and to propose a strategy to monitor the risk of HBV reactivation and a prophylactic therapy scheme for patients, requiring immunosuppressive therapies, with severe forms of COVID-19 and HBV infection.

2. Literature review methodology

An updated narrative review of studies published between 2000 and 2021 in the current literature was performed, which were focused on the number of patients in whom the reactivation of chronic HBV infection was observed during various long-term immunosuppressive therapies from psoriasis and short-term immunosuppressive therapies from COVID-19. The testing protocols of patients for chronic HBV infection before starting immunosuppressive therapy and the patient profile at which antiviral prophylaxis for HBV was initiated were also monitored. Databases such as PubMed, Elsevier, Medline and ScienceDirect Freedom Collection were used, in the search for related articles, by introducing the terms: 'reactivation of hepatitis B and COVID-19' or 'Sars-CoV-2, reactivation of hepatitis B and psoriasis'.

3. Evolution of hepatitis B

Chronic HBV infection was responsible worldwide for approximately 257 million diseases (3.5% of the population) and 1.34 million deaths, in 2015, according to World Health Organization (8).

HBV infection can evolve to acute hepatitis, spontaneous viral clearance or chronic HBV infection. Clinical trials note approximately 23% of cases of acute viral hepatitis that achieve spontaneous viral clearance (6) with positive antibodies to hepatitis B core antigen (anti-HBc), in low titers, and without the presence of hepatitis B surface antigen (HBsAg). Acute forms of hepatitis with HBV evolve in 94-98% of adults and 10% of infected children in the first year of life, towards healing with negative HBV DNA and HBsAg with the appearance of antibodies to hepatitis B surface antigen (anti-HBs) and anti-HBc. A total of 2-6% of adults and 90% of children infected in the first year of life, progress to chronic persistence infection, with HBV DNA, HBsAg and total anti-HBc positive and will be monitored at 6 months and treated with specific antivirals in the case of HBV DNA with over 2,000 IU and minimum F1 fibrosis or A1 inflammation on Fibromax or over 7 kPa on Fibroscan (9,10).

HBV is a DNA virus that manages to graft its genome onto the genome of the host hepatocyte; HBV covalently closed circular DNA remains in the hepatocyte even in patients who manage to have spontaneous viral clearance and in those who remain on undetectable viremias in the blood, under antiviral therapies, which explains the occurrence of hepatic adenocarcinoma in patients with HBV infection, regardless of the degree of liver fibrosis and the possible reactivation of latent infection in case of immunosuppression. Reactivation of HBV may be an exacerbation of chronic hepatitis B or reactivation of previous HBV infection (11,12).

Patients with psoriasis treated with biologic therapy due to an immunocompromised status have an increased risk of reactivation of HBV infection and liver adenocarcinoma (13-16). Other therapies used for comorbidities or other concomitant infections, but also topically for psoriasis, can produce immediate or long-term liver damage (17-19).

Patients with severe forms of COVID-19 requiring immunosuppressive therapies are usually elderly, with multiple comorbidities, a compromised immune status through underlying pathology and severe viral disease, and thus a status that predisposes them to reactivation of HBV infection (20-22).

4. Therapeutic perspective for the prevention of HBV reactivation in patients using immunosuppressants

The perspective towards a patient with psoriasis who is about to start biological therapy, in order to prevent the reactivation of a latent HBV infection is the following (23-25): i) For HBV seronegative patients, the hepatitis B vaccine is indicated before starting biological therapy; ii) in patients with acute HBV infection and detectable HBV DNA in the serum, immunoglobulin M antibodies to hepatitis B core (anti-HBc IgM)-positive, elevated hepatic transaminases it is indicated to discontinue biological therapy for psoriasis or delay its onset by 6-12 months; iii) patients with chronic HBV infection, according to the Romanian protocol (December 2019), depending on the status of the infection will be monitored according to the protocols in Fig. 1; and iv) therapeutic options with nucleoside/nucleotide analogues (ANN) are: Entecavir 0.5 mg/daily, in adults and children weighing ≥32.6 kg and older than 3 years; or tenofovir 245 mg/daily, in adults and adolescents aged 12 to 18 years weighing ≥35 kg, and doses are adjusted for creatinine clearance.

All HBV-positive patients must be monitored at 6 months for liver adenocarcinoma with abdominal ultrasound and alpha-fetoprotein dosing.

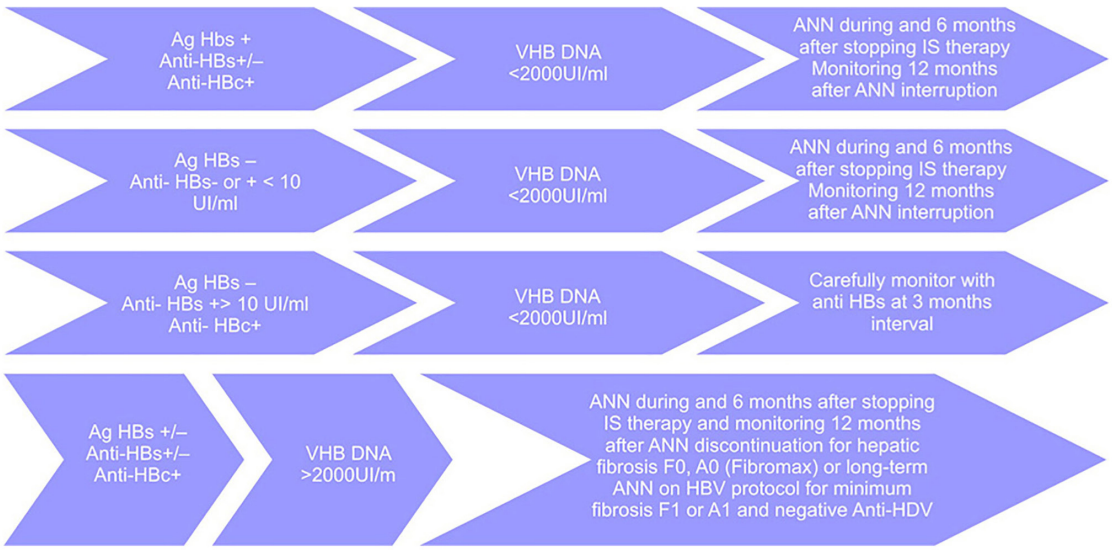

Figure 1. Scheme for monitoring and prophylactic treatment of reactivation of HBV infection in patients with immunosuppressive therapies.

5. Risk of reactivation of HBV in patients undergoing biological therapies for psoriasis

The risk of reactivation of the HBV during immunosuppressive therapies for psoriasis, is high risk (≥10%), moderate risk (1-10%) and low risk (<1%), depending on the presence or the absence of HBsAg and anti-HBc and the type of immunosuppressive therapy.

Depending on the serological status, this risk is: i) High, HBsAg-positive and HBV DNA >2,000 IU/ml; ii) medium, HBsAg-negative, anti-HBc IgG-positive and anti-HBs-negative; or low, HBsAg-negative, anti-HBc IgG-positive and anti-HBs-positive (7).

Depending on the type of biological therapy used in psoriasis, for both TNF-α inhibitors and other cytokine inhibitors this risk is medium (1-10%) (7).

A retrospective, observational study was performed on 81 patients (average age, 63 years; 83% males) admitted to the Dermatology Clinic of 'Sf. Cuv. Parascheva' Hospital of Infectious Diseases Galati and Braila Emergency County Hospital between June 1, 2016-1, 2020 with the diagnosis of moderate and severe forms of disseminated psoriasis, undergoing biological therapy in which HBV infection was monitored and treated prophylactically.

Criteria for inclusion in the study were: Adults with psoriasis, undergoing biological therapy; patients who signed informed consent for participation in the study, staff in full knowledge.

Exclusion criteria from the study were: Unconscious patients or inability to sign informed consent; patients who refused to participate in the study; pregnant or breastfeeding women; patients under 18 years, comedication contraindicated in psoriasis (for example beta blockers) (26).

Patients were monitored during the hospitalization period and every 3 months after discharge, they were evaluated in the hospital.

The treatment of the study group was: Of the 81 patients monitored for psoriasis, in biological therapies, 12 patients were treated with etanercept, 42 with adalimumab, 3 with infliximab, 5 with ixekizumab, 9 with secukinumab, 10 with ustekinumab. Of these, 6 patients (Table I) were detected with positive markers for HBV. The average age of these patients was 63 years, of which 83.33% were men, diagnosed with psoriasis between 1969 and 2016. They started immunosuppressive therapy between 2012 and 2019 with an average Psoriasis Area Severity Index (PASI) (27) of 32.9 and an average Dermatology Life Quality Index (DLQI) (28) of 22. All 6 patients were HBsAg-negative, anti-HBc positive, undetectable HBV DNA and anti-HDV negative. Anti-HBs in 2 patients was below 10 IU/l and they received prophylactic treatment with entecavir 0.5 mg per day and the other 4 patients with anti-HBs titers over 10 IU/l were monitored at 3 months.

All patients had a favorable evolution of dermatological lesions without reactivation of HBV infection.

The literature has noted cases between 1.14-34.3% of HBV reactivations in patients with psoriasis in biological therapies and a selection of 2 meta-analyses are presented (6,10): i) A meta-analysis from 2019, on 2,060 patients with psoriasis (3,562 episodes of treated disease) who received biological therapies between 2009 and 2018, of which 359 patients had HBV infection (561 treatment episodes), 88 therapeutic episodes were observed with HBV reactivations. Reactivations were more common in patients with chronic HBV infection than in those with occult HBV infection (34.3 vs. 3.2%, P=0.001). Patients who were HBsA-positive and hepatitis B envelope antigen (HBeAg)-positive were statistically the most prone to reactivation of HBV (6); ii) a meta-analysis from 2017, on 312 patients followed for a mean of 30.9 months, with psoriasis, treated with biological agents, observed 2 cases of HBV reactivation out of the 175 patients who were anti-HBc-positive and 8 reactivations in the 40 patients with chronic HBV infection (10).

Depending on the type of immunosuppressant used, clinical trials note small differences in the percentages of reactivation of the HBV infection. Among the TNF-α inhibitors (etanercept, infliximab, adalimumab and certolizumab), clinical trials note more HBV reactivations with infliximab and adalimumab than with etanercept (29-31). In our study, there were 3 patients treated with adalimumab and 2 patients treated with etanercept of which 2 patients with adalimumab

Table I. Characteristics of the patients with psoriasis and chronic infection with HBV.

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Sex	Male	Female	Male	Male	Male	Male
Age	58	71	69	60	63	57
The time of diagnosis of psoriasis	1992	1969	2000	1993	2016	1985
The date at the start of the IS therapy	03.2018	06.2019	06.2016	2014	12.2018	2012
PASI score at the start of IS therapy (35)	36.8	23.7	32	23.7	39.6	41.6
DLQI score at the start of IS therapy (36)	30	17	16	21	23	25
Special areas	Scalp, nails, palms, plants, genital, folds	Palms, plants	Scalp, nails	Scalp, plants	Palms, plants	Scalp, nails, palms, plants
Anti-HBc	Positive	Positive	Positive	Positive	Positive	Positive
HBs Ag	Negative	Negative	Negative	Negative	Negative	Negative
Anti-HBs	Below 2 UI/l	1,568-2,000 UI/l	58-64 UI/l	3 UI/l	124-362 UI/l	923-1,328 UI/l
HBV DNA undetectable	Yes	Yes	Yes	Yes	Yes	Yes
Anti-HDV	Negative	Negative	Negative	Negative	Negative	Negative
AST (U/l)	17.5	21.1	20.3	23	22	40.4
ALT (U/l)	25.5	26.5	18.5	34	23	48.5
IS therapy	Adalimumab	Adalimumab	Etanercept	Adalimumab	Secukinumab	Etanercept
HBV therapy	Entecavir 0.5 mg/day	Monitoring at 3 months	Monitoring at 3 months	Entecavir 0.5 mg/day	Monitoring at 3 months	Monitoring at 3 months
Favorable skin evolution	Yes	Yes	Yes	Yes	Yes	Yes

IS therapy, immunosuppressive therapy; Anti-HBc, core antibodies of the hepatitis B virus; HBsAg, surface antigen of the hepatitis B virus; HBV-DNA, hepatitis B genome; Anti-HDV, antibodies of the hepatitis D virus.

received prophylaxis with entecavir and the others were monitored once every 3 months. No patient experienced HBV reactivation.

A meta-analysis from 2017, on 187 cases of psoriasis treated with TNF-α inhibitors and chronic or occult HBV infections, monitored between 7.8 and 72 months, of which only 2 cases received prophylaxis with lamivudine or entecavir noted 3 HBV reactivations (9). In another study on 468 patients who were anti-HBc-positive and treated with infliximab, the HBV reactivation rate was 1.7% (29). In this group, HBsAg was present in 12.3% of patients.

A 2018 meta-analysis of 200 patients who received TNF-α inhibitors for psoriasis, who were followed for 24 weeks to 6 years, noted 3 patients with reactivated HBV (2 patients with DNA HBV-positive and one with HBsAg-positive and DNA HBV-negative), all without antiviral prophylactic treatment (7).

IL-12/IL-23 inhibitor is ustekinumab. IL-12 has an important role in triggering a cellular immune response against intracellular pathogens (32-34), so that IL-12 inhibitory therapies could contribute to HBV reactivation. A 2018 meta-analysis of 28 cases of psoriasis treated with ustekinumab that was undertaken between 4 months and 3 years, noted 3 cases that experienced HBV reactivation, inactive or occult carrier that did not receive antiviral prophylaxis (35).

IL-17 inhibitors include secukinumab, ixekizumab and brodalumab. A study of 46 patients treated with secukinumab, without prophylactic antiviral therapy, noted 7 (15.2%) patients with HBV reactivation (36). In our study there was one patient that was treated with secukinumab, which was monitored once every 3 months, that did not exhibit HBV reactivation.

Clinical trials of SPIRIT-P1 and SPIRIT-P2, performed on 1,118 patients with psoriasis that were treated with ixekizumab, noted discontinuation of therapy due to an HBV reactivation (37).

IL-23 inhibitors include guselkumab, tildrakizumab and risankizumab. Data were not found in the literature on HBV reactivation during the therapies with brodalumab and IL-23 inhibitors, but the guidelines recommend the same surveillance measures as for other biologic therapies (38).

6. Risk of reactivation of HBV in patients undergoing immunosuppressive therapies for severe forms of COVID-19

Severe cases of COVID-19 reveal an inadequate inflammatory response, with multiorgan damage whose common cause is a process of prothrombotic endotheliitis. The role of anti-inflammatory and immunomodulatory therapy is to stabilize this damaged endothelium (39,40). The recovery study shows that, in selected cases, corticosteroids save lives. The benefits were present only among patients who required a form of respiratory support, non-invasive or invasive, usually instituted after 7 days (1). Anti-cytokines represent a rescue therapy, off-label. The most commonly used agent is tocilizumab [humanized monoclonal antibody type IgG1, anti-human receptor for interleukin-6 (IL-6)] (41-43). Selection criteria for tocilizumab therapy are: IL-6 >40 pg/ml, D-dimers >1,500 ng/ml, ferritin >1,000 ng/ml, C-reactive protein >50 mg/l. Drug toxicity of tocilizumab treatment may increase liver enzymes and very rarely severe liver injury (44). In patients with rheumatoid arthritis, tocilizumab increases the risk of HBV reactivation (45,46).

A study of 12,997 patients with previous HBV exposure, who received systemic corticosteroid therapy, revealed that they had low risk of liver failure. Liver aggression is dependent on the dose of cortisone and its duration. Thus, alanine aminotransferase (ALT) elevation was observed starting from equivalent prednisone doses of 20-40 mg with a duration of administration of at least 7 days. The increase in ALT was progressive at administrations of 7-28 days and over 28 days. The study concluded that patients who were HBsAg-negative and anti-HBc-positive who received high doses of corticosteroids were at risk of a hepatitis flare and should be monitored frequently for early detection of hepatitis flares (47).

Direct aggression of SARS-COV-2 on the liver, which may add to the aggression caused by HBV, should also be considered. Liver damage in COVID-19 has been attributed to SARS-CoV-2 direct aggression, hypoxia caused by pneumonia, acute inflammatory damage and drug toxicity of COVID-19 therapy. SARS-CoV-2 direct aggression on the liver includes the direct cytopathic effect on hepatocytes and cholangiocytes, the effects of coagulopathy and endothelial aggression in small intrahepatic vessels (48-50).

Liver injury has been observed in 14-53% of the patients with COVID-19 (51-53). Abnormal hepatic biochemical tests in patients with COVID-19 were associated with increased disease severity and risk of mortality (54,55).

A meta-analysis of studies on pre-existing liver lesions, in COVID-19 estimated the pooled prevalence of HBV as 0.9% (56).

A meta-analysis of 28 studies that included 235 patients with COVID-19 and chronic HBV infection, with a mean age of 49.8 years, revealed a death rate of 6% and a transfer rate in intensive care of 14.1% for patients with HBV infection, statistically significantly higher than patients without this comorbidity (57).

A study of 3 patients who were HBsAg-positive and 69 patients who were HBsAg-negative and anti-HBc-positive, with severe forms of COVID-19 and treated with an immune modulator, revealed prophylaxis for HBV reactivation, as follows: HBsAg-positive patients received entecavir 0.5 mg/day for at least 6 months; those with only anti-HBc markers received entecavir 0.5 mg/day for 1 month (doses adjusted according to renal function); or did not receive antivirals and were closely monitored. They detected only two patients with positive HBV-DNA, who did not have entecavir prophylaxis. These patients were anti-HBs-negative, HBV-DNA-positive, below the limit of quantification and with normal ALT. The study noted low risk of HBV reactivation in patients with severe forms of COVID-19, treated with immunomodulators and resolved HBV infection. Monitoring of these patients at discharge is necessary, but if pandemic conditions do not allow it, a short course of entecavir may be helpful in preventing HBV reactivation in patients without anti-HBs (2,58).

Aldhaleei *et al* published the first case of HBV reactivation in a patient with severe COVID-19, specifically, a 36-year-old man who was HBsAg-positive, anti-HBc IgM-positive, HBeAg-negative, and antibodies to hepatitis B envelope antigen (anti-HBe)-positive, HBV-DNA 2,490 IU/ml, ALT 4,758 IU/l and mental disturbances, at admission. HBV

Table II. Demographic and clinical characteristics of the patients with COVID-19.

Characteristics	Total COVID-19 patients	Patients with chronic infection with HBV
Age (years)		
Minimum-maximum	0.083-97	32-64
Average	50.62	52.58 (P=0.6885)
95% CI	49.55-51.90	48.21-56.96
Female (%)	54.27	47.05 (P=0.7288)
BMI		
Minimum-maximum	14.42-58.59	21.16-37.87
Average	28.31	28.32 (P=1.0001)
95% CI	27.90-28.74	25.10-31.54
Charlson score (% patients)		
0	39.85	5.88 (P=0.0095)
(1-2)	33.15	64.70 (P=0.0135)
(3-4)	17.25	23.52 (P=0.7237)
(5-11)	9.72	5.88 (P=0.9067)
Hypertension (%)	28.91	0 (P=0.0188)
Diabetes (%)	11.58	0 (P=0.2691)
Obesity (%)	32.87	0 (P=0.009)
Cancer (%)	1.56	0 (P=0.6335)
Chronic respiratory diseases (%)	3.75	0 (P=0.8696)
Number of days of hospitalization		
Minimum-maximum	1-80	4-18
Average	11.00	10.29 (P=0.685)
95% CI	10.54-11.46	8.19-12.38
Curb 65 score (%)		
0	11.70	17.64 (P=0.7094)
1	60.61	76.47 (P=0.2815)
2	24.39	5.88 (P=0.1381)
3	3.28	0 (P=0.9476)
Unfavorable evolution (death or transfer to intensive care) (%)	4.38	11.76 (P=0.3876)

HBV, hepatitis B virus.

reactivation was interpreted in the context of immunosuppression caused by severe COVID-19 because the patient did not receive immunosuppressive therapy (3).

A study of 20 patients with COVID-19 and chronic HBV infection noted 3 cases of HBV reactivation and did not observe significant differences from the group without HBV infection in terms of increased liver transaminases and bilirubin (59).

A retrospective study including 72 patients diagnosed with COVID-19 and HBV carriers revealed that SARS-CoV-2 does not directly activate the HBV, and the risk of liver cell damage of HBV carriers with COVID-19 does not increase (60).

An observational, retrospective study was performed on 958 patients with COVID-19, hospitalized between March 1, 2020 to 30, 2021, at the Second Clinic of the Clinical Hospital of Infectious Diseases 'Sf. Cuv. Parascheva' Galati. Of these, 17 patients had a history of chronic infection with HBV. The statistical comparison (MedCalc v. 15.8) of the demographic, clinical and paraclinical characteristics of these two groups are presented in Table II. The group with chronic HBV infection did not statistically significantly differ from the total group with COVID-19, in terms of length of hospitalization or unfavorable evolution towards death or transfer to the intensive care. Of the 17 patients with chronic HBV infection, only 9 received systemic corticosteroid therapy between 5 and 13 days, no patient received tocilizumab, 10 patients had consistently elevated values of the transaminases, during hospitalization, and two patients required intensive care for severe forms of COVID-19. Patients were monitored for HBV reactivation, did not receive ANN therapy, and no cases of reactivation of chronic HBV infection were observed.

7. Conclusions

In our clinical experience and clinical studies, immunosuppressive therapies for patients with psoriasis, proved safe from the point of view of HBV infection reactivation if provided at

the initial screening of all patients for HBV infection, regardless of serological profile: HBsAg, anti-HBc IgG, anti-HBs and their monitoring and treatment according to Fig. 1.

Regarding the risk of reactivation of HBV in the severe acute episode of COVID-19, there are few clinical studies to monitor this situation. It has been revealed in clinical trials that liver damage worsens the prognosis of COVID-19 and that severe forms of COVID-19 can spontaneously reactivate HBV. The need for immunosuppressive therapies in severe forms of COVID-19 and evidence from clinical trials on other pathologies, that these therapies may reactivate HBV imposes special attention in monitoring patients with HBV infection and severe forms of COVID-19 and, if such monitoring is not possible, initiation of ANN prophylaxis, according to the protocol applicable to biological therapies in psoriasis.

More studies are indeed needed to fully evaluate the positive and adverse effects of ANN prophylaxis in patients with either long-term immunosuppressive therapies such as psoriasis or short-term as COVID-19 and the patient profile that requires this prophylaxis.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding authors on reasonable request.

Authors' contributions

LB and LA conceptualized the study, and prepared and wrote the original draft of the manuscript. The methodology, writing-review and editing of the manuscript, as well as software use were performed by ACL, AIS, ALT, and EN. Formal analysis was performed by AI, FN and CD. The investigation and data curation was performed by LB, SF and MD. The validation of data was performed by LB, AI, CD and DCV. The review was supervised by LB, ALT, AN and AIS. LB, ALT, MD confirm the authenticity of all the raw data. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of 'Sf. Cuv. Parascheva' Clinical Hospital of Infectious Diseases of Galati, Romania (Decisions no. 104, 105, date of approval: 30.12.2020). All patients signed informed consent to participate in this study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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