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Lack of HBV reactivation among patients receiving immunomodulatory drugs in Egyptian cohort who underwent either close monitoring or Preemptive treatment.

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ABSTRACT

Background: HBV reactivation is a preventable disease with high incidence among immunosuppressed. This can be attributed to either HBV virus widespread in the community or an inadequate assessment of HBV status prior to the start of the drug therapy.

Materials and strategies: A prospective cohort study included 200 patients with various autoimmune diseases prior to initiation of their immunosuppressives, with a 1 year follow up. Baseline liver biochemicals and HBV virology status were recorded for all patients, and they were arranged into 4 groups (Group A, previously vaccinated; Group B, HBV naïve; Group C, HBV disease and Group D, isolated HBV core). Group A was offered only follow-up, Group B were offered HBV immunization with follow up, and Groups C and D were offered either preemptive therapy or follow-up according to their risk of reactivation.

Results: The mean age was 26.5 years (22-34), 58.5% (117 patients) were female, 41.5% (83 patients) were male, our study group included 85 patients with IBD (54 patients with ulcerative colitis and 31 patients with Crohn's disease), 54 patients with SLE, 41 patients with Bechet's disease, 4 patients with rheumatoid arthritis and 16 patients with a variety of other autoimmune diseases. 93.5 % of patients have low risk for reactivation (as HBV status and the commenced drug), 3.5 % were moderate and only 3 % were at high risk. Group A included 43.5% (87 patients). Group B included 47.5 % (95 patients), group C was 4.50% (9 patients) and group D was 4.50% (9 patients). After 1 year follow up, Elevated liver enzymes were found in 10.3%, 20%, 66.7%, 44.4% of patients in group A, B, C and D respectively, pulse steroid therapy and positive HBsAg were the highest predictable values for elevated liver enzymes; However, no patients showed HBVr.

Conclusion: Monitoring with a proper assessment is needed for all patients prior to starting immunosuppressives or immunomodulatory drug therapy, there was a low prevalence of HBV among our cohort owing to the effective immunization programs**.** A close screen with no treatment is seen in HBV core positive patients who are prescribed moderate risk immunosuppressives; HBV core routine screening may be suggested for high-risk immunosuppressives only. HBV vaccine is essential prior to the immunosuppressives and HBsAb titre may not be impacted by the immune system or immunosuppressive medication**.** Preemptive therapy for HBsAg-positive patients on high-risk immunosuppressives is needed. However, longer follow-up studies with a larger sample size may be required.

Keywords: HBV, HBVr, Vaccine, Autoimmune, Immunosuppressives, Preemptive treatment.

INTRODUCTION

Autoimmune diseases are among the most common disorders in both rheumatological and gastrointestinal practice. High doses and prolonged duration of immunosuppressives are very common in the management of many of those diseases, like autoimmune hepatitis, inflammatory bowel diseases, systemic lupus, Behcet's disease, and others [1].

The natural course of hepatitis B virus (HBV) infection is determined through the interplay between viral replication and the host's immune response. HBV remains integrated in the host genome due to the CCC DNA, and there is a risk of reactivation with viral flare and liver injury when the host immune response is reduced, as in immunosuppressive therapy or after organ transplantation.[2]

Prior to initiating immunosuppressive therapy, patients should be tested for an evidence of hepatitis B virus (HBV) infection; for adults receiving glucocorticoids alone it is recommended to screen on those who will receive doses of prednisone 20 mg/day for at least four weeks. This approach is supported by several guideline panels.[3]

Assessment of HBV status should include HBsAg, HBV core antibody total, and IgM; all patients who are HBsAg positive should have baseline HBV DNA levels measured. Baseline HBV DNA testing should also be considered in patients who are HBsAg negative and anti-HBc positive (e.g., those at moderate or high risk of reactivation).[4]

The estimated risk of reactivation is based upon a combination of the patient's HBV serologic status as well as the type of immunosuppressive therapy. The American Gastroenterological Association (AGA) and the American Association for the Study of Liver Diseases (AASLD) have attempted to categorize the level of the risk for HBV reactivation among individuals receiving certain immunosuppressive agents.[5]

High-risk Patients are at >20% risk of reactivation if they are HBsAg positive and are going to receive anti-CD20 therapy (i.e., rituximab) or undergo hematopoietic cell transplantation or are going to receive high-dose glucocorticoids (e.g., 20 mg/day for at least four weeks) or the anti-CD52 agent, alemtuzumab while moderate-risk patients are at a 1-10% risk of reactivation if they have HBsAg positivity and are receiving anti-TNF or anti-rejection therapy for solid organ transplants, or if they are HBsAg negative and anti-HBc positive and are receiving anti-CD20 therapy or hematopoietic cell transplantation.[6]

Patients with HBsAg-positive individuals are considered at low risk if they received methotrexate or azathioprine. Most patients with HBV reactivation are asymptomatic, and the only manifestation is an increase in the HBV DNA level. The diagnosis is a detectable HBV DNA level when they previously had been undetectable, a 10- to 100-fold increase in HBV DNA, or seroconversion (when a patient previously HBsAg negative or anti-HBc positive becomes HBsAg positive) is required for diagnosis.[7]

Close monitoring of HBV biomarkers and liver profiles, early treatment, and preemptive therapy in those with a very high to high risk of reactivation is recommended. Close monitoring or preemptive therapy may be required in those with a moderate risk of reactivation based on clinical judgment [8,9,10].

Unfortunately, HBV reactivation in immunosuppressive settings is one of the most frequently overlooked agenda items for most physicians, and many patients may present with a flare of liver functions during therapy; careful risk assessment and standardization of the management plan are thus critical.

PATIENTS &METHODS

Study population. The aim of this prospective study was to evaluate Hepatitis B viral status before initiation and during the immune-modulating drug therapy. We enrolled 250 patients in the study from the Endemic Hepatology and Gastroenterology and Rheumatology and Rehabilitation departments. Five patients died from disease activities and 45 patients lost their follow up.

A patient was eligible to study if they were an adult (age 18–80 years). Small doses or duration of steroids (< 7.5 mg or less than 3 months) as well as chronic HBV infection on Nucleoside analogue inhibitors or interferons were excluded. In addition, all patients with HCV or HIV-coinfection and all patients with chronic decompensated liver diseases were excluded from our study cohort.

All patients were categorized and underwent follow up plan according to figure 1.

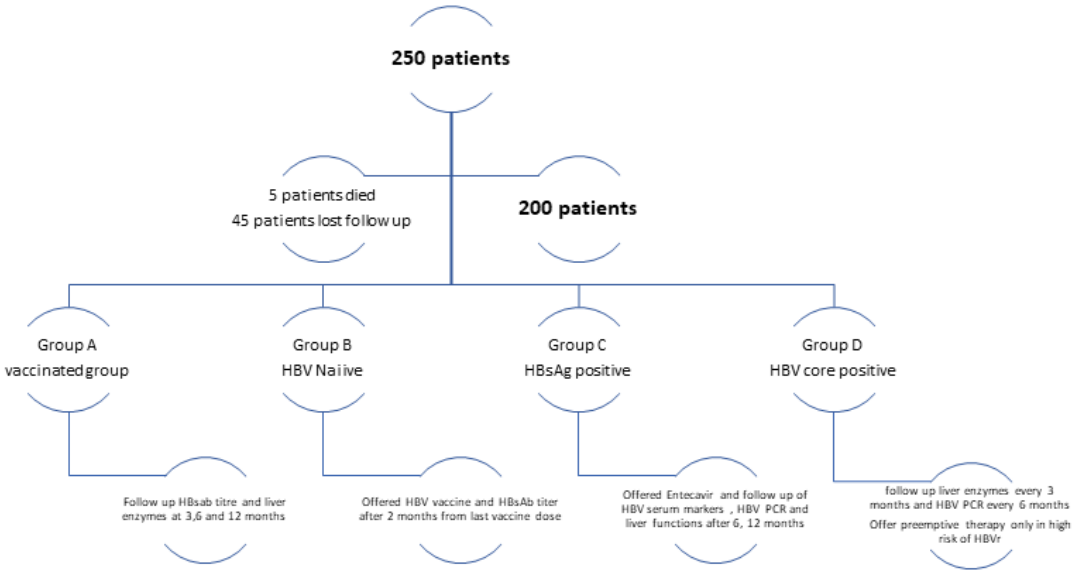

Figure 1. Patients' enrollment and management plan

Statistical Analysis. The sample size was calculated by using (PASS 11, NCSS, LLC, Kaysville, Utah, USA) software. Data were analyzed using IBM SPSS advanced statistics (Statistical Package for Social Sciences), version 24 (SPSS Inc., Chicago, IL). Numerical data were described as mean and standard deviation, median, and range. Data were explored for normality using the Kolmogorov-Smirnov test and the Shapiro-Wilk test. Comparisons between 2 groups for normally distributed numeric variables were done using the independent t test, while for non-normally distributed numeric variables, they were done using the Mann-Whitney test. Categorical data were described as numbers and percentages, and comparisons were done by the chi-square test or Fisher exact as appropriate. Logistic regression was used to estimate factors affecting depression; all significant variables in univariate analysis were entered into the model. A p-value less than or equal to 0.05 was considered statistically significant. All tests were two-tailed.

RESULTS

In our study, only 200 patients were eligible and completed the follow up management plan, 83 (41.5 %) were males and 117 (58.5%) were females, 80.5% patients were living in urban areas while only 5 % had associated comorbidities in the form of either Diabetes or Hypertension. Initial Abdominal Ultrasonographic findings for all patients revealed 3 % of the studied population had a bright parenchymal liver texture.

Our studied patients were classified according to the disease type in to IBD patients (42.5 %) and other various autoimmune diseases (57.5%) (figure 2)

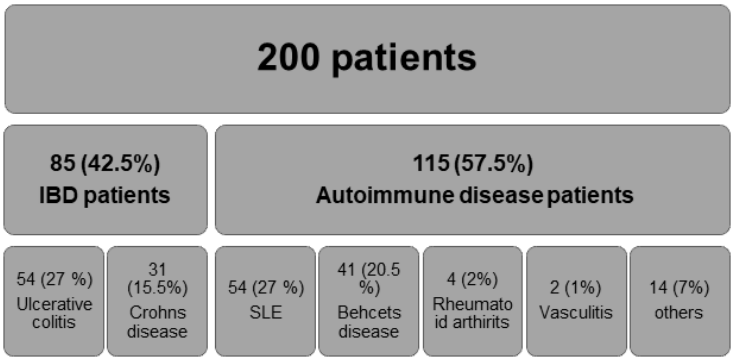

Figure 2. Different autoimmune diseases of the studied patients.

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Initial HBV assessment of our patients (as shown in figure 3) revealed that 87 (43.5%) patients were from Group A (positive HBsAb, vaccinated), 95 (47%) were Group B (HBV naive), 4.5 % of the cases were HBV infected and 4.5 % were isolated HBV core positive correlating to group C and D respectively.

In a comparison between various groups regarding demographic data, baseline HBV status and the commenced immunosuppressives as shown in (table 1), Steroids were the most prescribed immunosuppressives in group C (HBV infection), while biological therapy was prescribed in 24.4 %, 32.3 %, 11.1 %, 33.3 % of group A (HBV vaccinated), B (Non vaccinated), C (HBV infection) and group D (isolated HBV core IgG positive) respectively.

Table 1. Demographics & therapeutic regimens used in different studied groups.

	Group A (vaccinated) n=87(%)	Group B (non-vaccinated) n=95(%)	Group C (HBV infection) n=9(%)	Group D (Isolated HBV core) n=9(%)
Male	32(37.6)	42(43.3)	5(55.6)	4(44.4)
Female	53(62.4)	55(56.7)	4(44.4)	5(55.6)
Urban	71(83.5)	76(78.4)	7(77.8)	7(77.8)
Rural	14(16.5)	21(21.6)	2(22.2)	2(22.2)
Comorbidities	2(2.4)	5(6.0)	2(22.2)	1(11.1)
Nonsmoking	70(82.4)	75(77.3)	8(88.9)	7(77.8)
Smoking	15(17.6)	22(22.7)	1(11.1)	2(22.2)
Biological therapy	21(24.7)	32(33.0)	1(11.1)	3(33.3)
Azathioprine	27(31.8)	39(40.2)	3(33.3)	3(33.3)
Cyclophosphamide	32(37.6)	39(40.2)	4(44.4)	5(55.6)
Aminoacylates	14(16.5)	16(16.5)	1(11.1)	0(.0)
Rituximab	0(.0)	2(2.1)	0(.0)	0(.0)
Cyclosporine	2(2.4)	2(2.1)	0(.0)	0(.0)
Oral Steroids	16(18.8)	21(21.6)	7(77.8)	3(33.3)
Pulse IV steroids	0(.0)	3(3.1)	2(22.2)	0(.0)
Hydroxychloroquine	0(.0)	1(1.0)	2(22.2)	1(11.1)

Hepatitis B virus reactivation's risk based on HBV virology status and the prescribed immunosuppressives. It showed that 187 patients (93.5 %) have low risk for reactivation, 7 patients (3.5 %) were moderate and only 6 patients (3 %) were at high risk. Preemptive therapy in the form of Entecavir 0.5 mg was prescribed before initiation of the immunosuppressive therapy for 9 patients of the group C (4.5%).

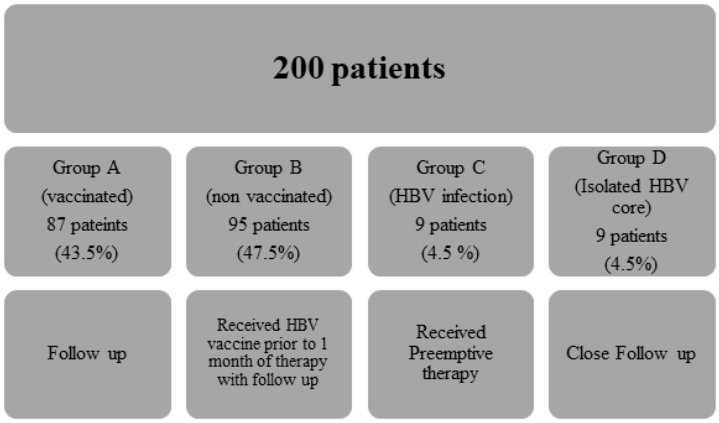

Figure 3. Group classification and interventions during follow up

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During our 3, 6 and 12 months follow up protocol as shown in (figure 3), alterations in liver functions, HBs Ab titre and HBV PCR were shown table 5 with most of fluctuations in liver biochemical profile were non-HBV related (as evidenced by negative HBV PCR and negative HBsAg) and all were related to either disease activity, drugs, or sepsis related complications. However, no patients documented any evidence of HBVr at the end of the one year follow up study project. (Table 2)

Table 2. HBV outcome status and preemptive therapy in different groups follow up.

		Group A (Vaccinated) n=87(%)	Group B (Non-Vaccinated) n=95(%)	Group C (HBV infection) n=9(%)	Group D (HBV core IgG) n=9(%)
Preemptive therapy		0(.0)	0(.0)	9(100.0)	0(.0)
Risk of HBV reactivation	**High**	0	0	6(66.7)	0
	Low	87(100.0)	95(100.0)	2(22.2)	3(33.3)
	Mod	0	0	1(11.1)	6(66.7)
HBsAg (base line)		0(.0)	0(.0)	9(100.0)	0(.0)
HBsAg (6 months)		0(.0)	0(.0)	9(.0)	0(.0)
HBsAg 1 year		0(.0)	0(.0)	9(100.0)	0(.0)
HBcore IgG (base line)		0(.0)	0(.0)	0(.0)	9(100.0)
HBcore IgG 1 year		0(.0)	0(.0)	0(.0)	9(100.0)
HBsAb titre (base line)		227.7±166.2	12.5±101.4	0.8±1	2.8±3.2
HBsAb titre (3rd month)		236.4±303	265.9±322	5±3	8.4±1.1
HBsAb titre (6th month)		285.3±346	344.9±341.1	1.5±4	6.3±6.1
HBsAb titre 1 year		182.4±269.5	352.4±361	0.2±1	4±2.9
HBV PCR level (IU/ml) (base line)		NA	NA	16983.3±29819.9	0±0
HBV PCR level (IU/ml) (6th month)		NA	NA	7900±14821.1	0±0
HBV PCR (IU/ml) level 1 year		NA	NA	503.3±899.3	0±0
Biochemical elevation of transaminases (1.5 folds IU/L)		9(10.3%)	19(20%)	6(66.7%)	4(44.4%)
HBV reactivation		0(0%)	0(0%)	0(0%)	0(0%)

In a multivariate logistic regression showing factors independently associated with elevated liver functions in our study cohort, Group C (HBV infection group), group D (isolated HBV core group) and using pulse steroids were the most common risk factors for elevated liver functions with OR (12.02, 6.85 and 10.95 respectively) with 95 % confidence interval and these elevations (more than one half folds of transaminases) were not related to HBV reactivation.

Table 3. Multivariate Logistic regression analysis for risk factors correlated with elevation of transaminases in studied cohort.

					95% C.I.for OR	
	B	**S.E.**	**p value**	**OR**	**Lower**	**Upper**
Groups(C)	2.487	0.836	0.003	12.02	2.34	61.87
Groups(D)	1.925	0.768	0.012	6.85	1.52	30.89
Pulse steroids	2.393	1.201	0.046	10.95	1.04	115.32
Constant	-2.339	0.373	0	0.10		

DISCUSSION

There is emerging evidence suggesting that the actual number of individuals presenting with HBV reactivation (HBVr) following commencement of treatment with immunosuppressive agents is increasing. This can be attributed to an increase in

the prevalence of positive HBV serology in the population in tandem with a rise in the licensed clinical indications for potent immunosuppression, including but not limited to malignancies, inflammatory bowel disease (IBD), and autoimmune disorders, as well as to the emergence of new agents that account for HBV reactivation.[11]

The current study aimed to assess Hepatitis B virus status in the context of immune-modulatory drug therapy on 200 eligible patients with various autoimmune diseases (85 IBD patients and 115 autoimmunity-related rheumatological diseases) prior to the start of immunosuppressive therapy.

The initial HBV assessment of our patients prior to starting immunosuppressive therapy showed a low prevalence of HBV, with HBsAg positivity in only 4.5 percent (1 percent for IBD patients and 7 percent for autoimmune rheumatological disorders) and HBV core positivity in 4.5 percent of our studied population (3.5 percent for IBD and 4.5 percent for autoimmune rheumatological disease), and this result was slightly comparable to a Chinese study.[12]

Despite many guidelines' recommendations, many people still lag in HBV screening in immunosuppressive settings, with only 14-20% receiving screening [13]. In Our study, we included a full HBV virology panel prior to the commencement of immunosuppressive therapy and during the follow-up period. It should be mentioned that we noticed 43.5 percent of our study cohort were adequately previously immunized with protective antibody titers > 10 IU/L with a higher incidence compared to the recent study done in Italy by Canzoni M et al. (2020), in which only 3% were immunized prior to commencement of immunosuppressives, and this may reflect the adequacy of childhood vaccination. [14]

Interestingly, 47.5% of patients who were HBV naive and received HBV vaccine according to the standard protocol regimen of 0, 3, and 6 monthly doses showed adequate HBsAb titre responses that were sustained for 3 months after the last vaccine dose and at the end of study as well, suggesting that a booster dose or a short vaccination schedule may not be required, although further studies are recommended. We also noticed that 43.5 percent of patients who were previously vaccinated with an adequate HBsAb titre showed no evidence of HBV infection during our 1-year study period. Follow-up confirming Cholongitas E et al.'s meta-analysis of HBVr in patients with resolved HBV infection showed that the total pooled rate of HBV reactivation risk was lower in immunosuppressed patients with positive anti-HBs (5.2% versus 17.0%; RR: 0.29) .[15]

There is a considerable heterogeneity in the approaches that various professional medical societies have taken to address the issue of screening for hepatitis B prior to starting immunosuppressive therapies.[16] In our study, we have noticed that all HBc-positive patients weren't prescribed any preemptive therapy, and no one showed HBV after the end of the study period. Screening of anti-HBc in highly endemic areas, especially in resource-limited countries, may not be a cost-effective strategy and requires further studies[17].

CONCLUSION

In our current study, we aim to assess Hepatitis B virus status in the setting of immune-modulatory drug therapy. An initial HBV assessment of our patients prior to starting immunosuppressive therapy showed a low prevalence of HBV, with HBsAg positivity in only 4.5 percent and HBV core positivity in 4.5 percent of our studied population. Vaccinated HBV-naive patients responded well to standard doses of HBV vaccine. Preemptive therapy may be needed for all HBsAg-positive patients, irrespective of their risk of HBV reactivation; none of our patient groups showed any signs of HBVr during our 1-year follow-up protocol of management.

AUTHOR CONTRIBUTION:

Ismail Anwar: writing – editing and review, visualization, supervision**, Mahmoud Essam** validation, formal analysis, writing original draft**,** data curation**, Mohamed Said** writing – editing and review, visualization, supervision**, Eman Hamza** writing – editing and review, supervision**, Hatem El Eleishi:** methodology, **Hany Shehab, Ahmed Bahaa, Mohammed B.Hashem, Mohamed Negm:** Integrated clinical and research center for intestinal disorders team included during patient collection . All authors read and approved the final manuscript.

Conflict of interest: None

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Ethical approval : This study was approved by the Ethics Committee of Cairo University Hospital number (MD-195-2020). and carried out in accordance with the Helsinki Declaration. The purpose and methods of the study were explained to all participants. Written informed consent was obtained from each participant prior to enrollment.

Abbreviations:

HBV, Hepatitis B virus; HBVr, Hepatitis B virus reactivation; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; PCR, Polymerase chain reaction; HBcAb, Hepatitis B core antibody total; HBsAg, Hepatitis B surface antigen; DNA, Deoxyribonucleic acid; ULN, upper limit of normal; SLE, Systemic lupus erythematosus; IBD, Inflammatory bowel disease.

Highlights:

- HBV assessment in the status of immunosuppressives and immunomodulatory drug therapy
- Risk Stratification of HBV among immunosuppressives
- HBV vaccination versus Preemptive therapy versus close monitoring during follow up

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