The efficacy of a computer alert programme for increasing HBV screening rates before starting immunosuppressive therapy

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Abstract

Background/Aim : **Hepatitis B Virus (HBV) screening before starting immunosuppressive treatment is of vital importance in order to prevent HBV reactivation and its associated clinical consequences. Despite all recommendations by international organizations, screening rates are far below desired. The aim of this study was to assess the efficacy of a computer alert programme 'HBVision' for increasing HBV screening rates.**

Material and Methods : **'HBVision' identifies patients at risk of HBV reactivation by specific ICD-10 codes and immunosuppressive medication reports and sends sequential alert messages to screen for HBsAg, anti-HBc IgG and consult a specialist if one of them is positive. The demographic variables, treatment protocols, HBV screening and consultation rates of oncology and hematology patients who started immunosuppressive treatments within one year before (control group) and after "HBVision" (study group) were retrospectively compared.**

Results : **HBsAg and anti-HBc IgG screening rates (68.6% and 13.1%, respectively) were significantly higher in the study group (n=602) compared to control group (n=815) (55% and 4.3%, respectively) (p<0.001, for both). Subgroup analysis revealed significant improvements in the screening rates of HBsAg (65.8%) and anti-HBc IgG (5.1%) in oncology patients (p<0.001), anti-HBc IgG (89.1%) in hematology patients (p<0.001).**

Conclusion : **The computer alert programme significantly increased HBV screening rates before starting immunosuppressive treatments, however the results were still below ideal. Additional efforts, such as modifying the computer programme according to feedbacks, are probably needed.** (Acta gastroenterol. belg., **2019**, 82, **279-284**).

Key words : Hepatitis B virus, screening, reactivation, immunosuppressive therapy, oncology, hematology

Introduction

Hepatitis B virus (HBV) reactivation is a well-known complication of immunosuppressive treatment. It is associated with a significant morbidity and mortality (1). Additionally, it may result in the interruption of immunosuppressive treatment, which may increase the morbidity and mortality related to progression of the underlying disease. Screening and starting once-daily oral prophylactic antiviral therapy in selected cases is significantly effective in reducing the risk of reactivation in both HBsAg-positive and HBsAg-negative/anti-HBc-positive patients (2,3).

International liver disease and oncology organisations produced various recommendations for HBV screening before starting immunosupressive treatment. European Association for the Study of the Liver (EASL) and Asian Pacific Association for the Study of the Liver (APASL) recommend HBV screening in all patients (4,5). The American Association for the Study of the Liver (AASLD) recommends screening in patients who have a high risk of infection (6). American Gastroenterological Association (AGA) and American Society of Clinical Oncology (ASCO) recommend screening in patients with a high risk of HBV infection or who will receive immunosuppressive agents with at least moderate or high risk of reactivation, respectively (7,8).

Despite these recommendations by the major international organizations, the screening rates are far below desired. A study among 10729 cancer patients in the United States revealed that only 16.7% of patients were screened for HBV infection before undergoing chemotherapy (9). Lack of awareness among physicians who prescribe immunosuppressive drugs is probably the most important reason of the suboptimal screening rates (10).

For this purpose, we designed a computer programme called "HBVision" which alerts the clinicians to screen for HBV and consult a specialist in those with a positive serology, before starting immunosuppressive treatment in order to prevent reactivation. The primary aim of the study was to evaluate the efficacy of the programme for increasing the HBV screening rates. Secondary aim was to evaluate the changes in the consultation rates to a specialist after the programme.

Material and methods

"HBVision" programme

"HBVision" is a computer programme which was primarily designed to alert the clinicians to screen for HBV before starting immunosuppressive treatment. It was uploaded to the operating system of our hospital in June 2016 after the clinical significance of HBV reactivation after immunosuppressive treatment was reviewed and a consensus was achieved at a local seminar attended by gastroenterology, infectious disease, oncology and

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hematology specialists. The programme identifies patients who are at risk of HBV reactivation by two ways. First, it identifies patients with specific ICD-10 codes, such as oncologic and hematologic malignancies, rheumatologic diseases, etc. who may require immunosuppressive treatments. Second, it identifies immunosuppressive medication reports. The specific ICD-10 codes and immunosuppressive agents were determined at a national consensus meeting attended by gastroenterology, infectious disease, oncology and hematology specialists. After identifying the patient at risk of HBV reactivation, the system sends the following message to the clinician : 'Screen for HBsAg and anti-HBc IgG in order to prevent HBV reactivation after immunosuppressive treatment'. If the clinician follows the suggestion and screens for HBV serology, the system automatically evaluates the results and sends a second message to the clinician in case of a positive HBsAg and/or anti-HBc IgG : 'The patient has a positive HBV serology. Consult a gastroenterology or infectious disease specialist to prevent reactivation'. If the clinician does not screen for HBV or consult the patient with a positive serology, the system sends an alert message each time the patient is admitted to the hospital (Figure-1)

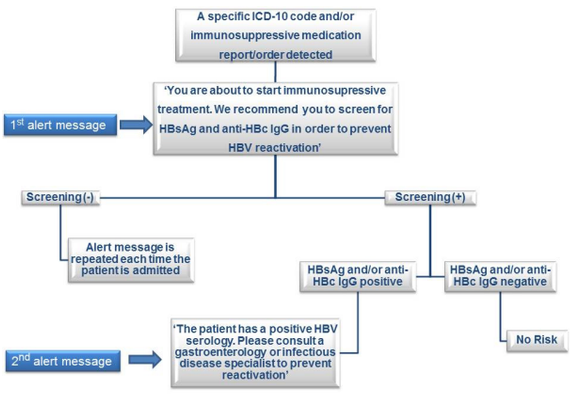

Figure 1. — Algorithm of HBV screening according to the "HBVision" programme.

"HBVision" programme was designed by a scientific advisory committee comprised of gastroenterology, infectious disease, oncology and hematology specialists. The committee was created to increase the awareness of clinicians to HBV reactivation after immunosuppressive treatment by coordinating local and national meetings and generate a consensus guideline on HBV reactivation during immunosuppressive treatment. The pilot programme started at Sakarya University Hospital and extended to 26 hospitals of Turkey within a year. The study was approved by the Institutional Review Board. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Study population

The study group (SG) included oncology and hematology patients who started immunosuppressive treatment within the year after alert programme. The demographic variables, diagnosis, immunosuppressive protocols and HBV screening rates of the study group were retrospectively determined and compared to a historical control group (CG) of oncology and hematology patients who started immunosuppressive treatment within the year before the alert programme. Additionally, the HBV screening rates were compared between subgroups which were classified according to the diagnosis of the patients and the immunosuppressive potency of the protocols. Finally, groups were compared with respect to the consultation rates to a gastroenterology or infectious disease specialist in patients with a positive HBV serology. The potency of the immunosuppressive agents were grouped according to the recommendations of AGA guideline in 2015 (7). Patients <18 years of age and those with a prior diagnosis of chronic HBV infection or hepatitis were excluded from the study.

Serological tests

Serum samples were tested for HBsAg and anti-HBc Ig G by using a fully automated Roche Modular E-170 (Roche Diagnostics ; Basel, Switzerland) ELISA instrument and kits.

Statistical analysis

Analyses were performed by using SPSS 22.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics (mean with standard deviation and simple proportions) were used to present relevant patient characteristics and serological results. Continuous variables were compared with Student's t test. Categorical variables were tested by the Chi-square test. Statistical significance was set at a p value of < 0.05.

Results

Clinical features of the study and control group

The study group included 628 patients who started immunosuppressive treatment within the year (median :178 days, range : 2-361 days) after alert programme. Control group included 829 patients. Twenty-six patients in the study group and 14 in the control group had a a prior diagnosis of chronic HBV infection or hepatitis and were excluded from the study. Clinical features of the study (n=602) and control groups (n=815) including the demographic variables, diagnosis and the immunosuppressive potency of the protocols are presented in Table 1. There was no statistically significant difference with respect to these parameters between the two groups.

Table 1. — **Clinical parameters of the study population including the demographic variables, diagnosis and the potency of the immunosuppressive agents**

	Control Group	Study Group	*p*
Total (n)	815	602	
Gender (M/F)	429/386	323/279	0,70
Age (Mean±SD)	60,6±12.8	60,4±12,2	0,72
Underlying diseases (n) **Oncologic malignancy** **Hematologic diseases (Total)** **Hematologic diseases (Lymphoma) Hematologic diseases (Other)**	 673 142 62 80	 547 55 24 31	*<0.001*
IS potency of the protocol (n) **Moderate** **High**	 761 54	 573 29	0.17

IS: Immunosuppressive

HBV screening rates before and after the alert programme

Out of 815 patients in the control group, 449 patients (55%) were screened for only HBsAg and 35 (4.3%) were screened for both HBsAg and anti-HBc IgG. In the study group, 413 patients (68.6%) were screened for only HBsAg and 79 (13.1%) were screened for both HBsAg and anti-HBc IgG. There was a significant improvement in the HBsAg and anti-HBc IgG screening rates after the alert system (p<0.001, for both).

Subgroup anaysis revealed that there was a significant improvement in the HBsAg and anti-HBc IgG screening rates in oncology patients (p<0.001) and anti-HBc IgG screening rates in hematology patients (p<0.001) after the alert system (Figure 2 A-E) Additionally, there was a significant improvement in the anti-HBc IgG screening rates in patients receiving moderately or highly potent immunosuppressive agents and HBsAg screening rates in patients receiving moderately potent immunosuppressive agents (p<0.001) (Figure 3 A-B).

Consultation rates in patients with a positive HBV serology

In the control group, 13 patients were HBsAg positive and 15 were isolated anti-HBc IgG positive. Among them, 9 HBsAg positive patients (69.2%) and 6 isolated

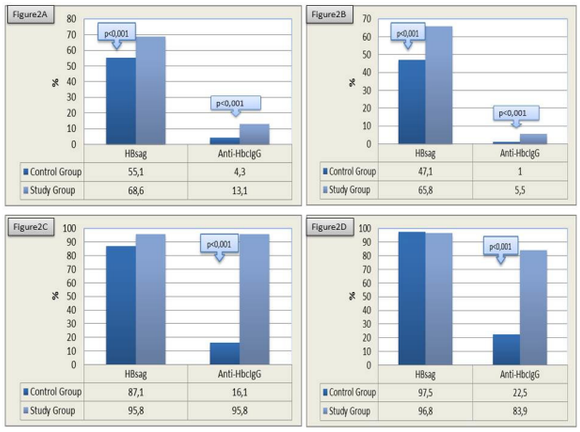

Figure 2. — The HBV screening rates. A : All patients ; B :Oncology patients ; C :Hematology (Lymphoma) patients ; D :Hematology (Non-Lymphoma) patients.

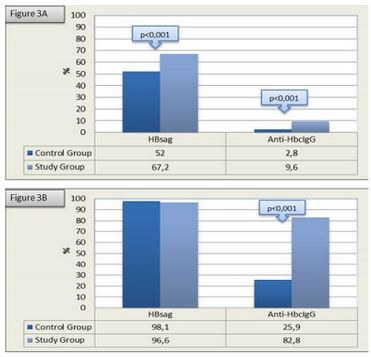

Figure 3. — The HBV screening rates according to the immunosuppressive potency of the protocols. A : Moderately potent immunosuppressive agents ; B : Highly potent immunosuppressive agents.

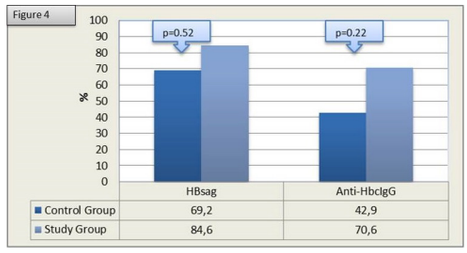

Figure 4. — The consultation rates of the patients with a positive HBV serology before and after the "HBVision" programme.

anti-HBc IgG positive patients (40%) were consulted to the gastroenterology or infectious disease specialists. In the study group, 26 patients were HBsAg positive and 35 were anti-HBc IgG positive. Among them, 22 HBsAg positive patients (84.6%) and 24 anti-HBc IgG positive patients (68.5%) were consulted (Figure 4). Overall, there was an increase in the consultation rates of patients with a positive HBV serology, from 52% to 75%, after the alert system (p=0.6).

Clinical outcomes of the study group

Twenty-two HBsAg positive patients in the study group were consulted to a specialist. Seventeen of them had a high (n=3) or moderate (n=14) risk of reactivation and received prophylactic antiviral treatment. Five

patients had a low risk of reactivation and were followed expectantly. None of the 22 patients experienced viral reactivation during a mean follow-up duration of 6,2 (1-12) months. Five patients died due to progression of their primary disease. Four HBsAg patients were not consulted to a specialist. Viral reactivation risk was high in 2, and moderate or low in 1 of them, each. Two patients in the high risk group experienced viral reactivation which led to interruption of chemotherapy for 1 and 2.5 months.
Twenty-four isolated anti-HBc IgG positive patients in the study group were consulted to a specialist. Twenty-three of them had a high (n=15) or moderate (n=8) risk of reactivation and received prophylactic antiviral treatment. One patient had a low risk of reactivation and was followed expectantly. None of the 24 patients experienced viral reactivation during a mean follow-up duration of 6,1(1-12) months. Eleven isolated anti-HBc IgG positive patients were not consulted to a specialist. Viral reactivation risk was high in 1, moderate in 4 and low in 6 of them. None of them experienced viral reactivation during a mean follow-up of 5,9(1-12) months. Five patients died due to progression of their primary disease.

Discussion

The present study showed that the computer alert programme was significantly effective in improving the HBV screening rates before starting cytotoxic immunosuppressive treatments. However, the final screening rates were still below ideal which highlights the importance of educational efforts to increase the awareness of the clinicians.

The use of immunosuppressive agents which may lead to reactivation of HBV has greatly expanded in recent years due to the increasing number of cancer patients and more frequent use of biological agents in various fields of medicine. However, HBV screening rates before starting immunosupressive agents are still suboptimal. Surveys of current oncology practices in the United States and Australia showed that less than 20% of the oncologists screened their patients for HBV before starting chemotherapy (11,12). An international survey of the membership of the AASLD revealed that among 188 patients who had HBV reactivation during cancer chemotherapy, HBV screening rate was 63% among patients with hematologic malignancies and 29% among those with solid tumors (13). In our study, HBsAg screening rate was 47% in patients with oncologic malignancies and % 93 in patients with hematologic malignancies. Although these rates were higher than those in the above-mentioned studies, given the intermediate endemicity of Turkey for HBV (4% HBsAg positivity and 30.6% anti-HBc IgG positivity), they were suboptimal and may lead to a higher risk for HBV reactivation and its consequences (14).

Reactivation of HBV can cause severe hepatitis, liver failure and even death. It may also lead to interruption of immunosuppressive treatment. Furthermore, antivirals are less effective at the time of reactivation (15). Therefore, every effort should be spent to improve the HBV screening rates in order to identify patients who may benefit from prophylactic antivirals and/or monitoring. There are several reasons of low HBV screening rates before starting immunosuppressives. Lack of awareness is probably the most important one. Uncertainity of guidelines in some special patient populations, heavy workload of clinicians, costs of testing, financial burden, unclear potential adverse effects of antivirals, fear of delay in chemotherapy due to consultation and start of antivirals are among the other reasons (16). Some measures can be taken to overcome these challenges. Multidisciplinary meetings may increase the awareness of clinicians and reassure them by increasing the communication between the departments. Computer alert systems may also increase the awareness of the clinicians and prevent overlooking HBV screening, especially in busy departments.

There are a few studies about the efficacy of computer alert systems on HBV screening rates prior to initiating immunosuppressive treatments. A study from Japan revealed that an alert system was significantly effective in increasing the screening rates for HBc antibody, HBs antibody and HBV DNA in patients receiving cancer chemotherapy (17). A study from Spain showed significant increases in the HBsAg (from 47% to 94%) and anti-HBc screening rates (from 29% to 85%) in patients receiving biologic agents (18). Our study also showed that alert system was significantly effective in improving screening rates for HBsAg and anti-HBc IgG in oncology patients and anti-HBc IgG rates in hematology patients. HBsAg screening rates were not significantly increased in our hematology patients possibly due to the high screening rates in the historical control group (93%). However, the final screening rates were still not ideal, especially in oncology patients and anti-HBc IgG screenings. We think that heavy workload of the clinicians and lack of awareness especially about the clinical significance of anti-HBc alone are the most important local factors playing role in the suboptimal final screening rates. Although a specialist evaluates patients with a positive HBV serology within a few days after consultation request, fear of delay in chemotherapy may also play a role. More effort is needed to increase the awareness and remove concerns of clinicians and emphasize the clinical significance of isolated anti-HBc IgG positivity.

Our alert system had some differences from the previous ones. The previous systems identified patients at risk of HBV reactivation when an immunosuppressive medication was prescribed. However, our system identifies both specific ICD-10 codes at the time of diagnosis and specific immunosuppressive medications at the time of prescription. This dual identification has some advantages. First, it helps us to early identify target population which spares time for serologic evaluations

and hence prevent possible delay of immunosuppressive treatments. Second, as the list of immunosuppressive agents grow day by day, the identification of specific ICD-10 codes functions as a double-check mechanism to prevent overlooking patients until the new agents were introduced to the alert system. Another difference was that it repeats the alert messages each time the patient is admitted to the responsible clinics. On the other hand, our alert system is relatively new and needs some modifications. One of them is to add short cuts to the serology and consultation orders on the alert page in order to decrease the work load of the clinicians. We also plan to automatise the serology order (HBsAg, anti-HBc IgG and anti-HBs) in order to increase the anti-HBc IgG screening rates. Another one is to send a reminder message to the consulting department if HBV DNA levels are waited to start prophylactic antivirals in patients with isolated anti-Hbc IgG positivity.

Screening and management of HBsAg-negative/anti-HBc-positive patients are more controversial. Some of the major international liver disease organisations recommend prophylactic antivirals in those with a positive HBV DNA or anticipating therapies with moderately or highly potent immunosuppressive agents (4,7). APASL recommends close monitoring and treatment in case of reactivation (5). On the other hand, ASCO recommends that clinicians can initiate antivirals before starting cancer therapies associated with a high risk of reactivation (8). The prevalence of HBsAg-negative/anti-HBc-positive patients are significantly higher than HBsAg positive patients, therefore the issue deserves serious consideration, especially in the eastern parts of the world. However, more robust data are needed to conclude about the management of this special patient population. An interesting finding of our study was that the oncologists were reluctant to screen for anti-HBc IgG compared to hematologists, even after the alert system (5.5% vs 89.1%, respectively). This may be due to more frequent use of highly potent chemotherapies in hematologic malignancies, such as lymphoma. Another reason may be the ASCO provisional clinical opinion in 2010, which stated that clinical significance of anti-HBc alone is unclear (8). Although the update of this provisional opinion clearly stated that screening for HBV infection should include both HBsAg and anti-HBc tests, awareness should be increased by multidisciplinary meetings (16). An automatized computer serology order can also prevent overlooking anti-HBc.

Another issue worth of mentioning is the suboptimal consultation rates to a specialist after a positive serology. Although the alert system significantly improved the consultation rates, 34% of patients with a positive HBV serology were not still consulted. We think that it may be possible to improve these rates by educational efforts. Periodic multidisciplinary seminars may help to develop the communication between the departments, inform the responsible clinicians about the clinical course of patients with a positive serology and highlight the importance of prophylaxis and at least monitoring, especially in the most overlooked group of patients with isolated anti-HBc IgG positivity.

Our study had some limitations. One of them was the absence of anti-HBs levels in the screening programme. Although the current guidelines suggest against using anti-HBs status to guide antiviral prophylaxis, it can be used to diagnose occult hepatitis B and may also give clues about the risk of HBV reactivation in isolated anti-HBc IgG positive patients (7,19). Our study was limited to the oncology and hematology patients because of the absence of rheumatology specialists at our center. We did not include patients with IBD, as they were managed by the doctors who conducted the study, which could lead to a bias. Although the consulted patients were monitored and/or treated with third-generation nucleos(t)ide analogues according to the current guidelines, we didn't provide information about the results of prophylactic treatments because they were out of concern of the study. In conclusion, the computer alert programme significantly increased HBV screening rates before starting immunosuppressive treatments. However, the results were still below ideal. Additional efforts, such as organising multidisciplinary seminars and upgrading the system according to feedbacks of the clinicians may help to optimize the screening rates.

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Conflict of interest

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Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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