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HBV reactivation in immunosuppressed patients

M. Maresca, E. Scibilia, M.R. Guglielmino, R. Bruno, L. Trovato[1], S. Oliveri[1], M.C. Tedesco, M. Gussio, F. Benanti, B. Cacopardo

Division of Infectious Diseases, Department of Clinical and Experimental Medicine, Garibaldi Nesima Hospital, University of Catania, Catania, Italy

[1]Department of Biomedical and Biotechnological Sciences, University of Catania, Laboratory Analysis Unit, A.O.U. "Policlinico-Vittorio Emanuele", Catania, Italy

ABSTRACT:

— ***Background:*** Reactivation of hepatitis B virus (HBV) is an important complication of immunosuppressive therapies. The aim of our study was to retrospectively evaluate the clinical and epidemiological features, as well as the outcome, of a cohort of patients with HBV infection undergoing immunosuppressive therapy in the period between January 2009 and November 2013.

— ***Patients and Methods:*** We evaluated the clinical and epidemiological characteristics of two groups of patients: 45 patients were identified as HBV positive before immunosuppression and, therefore, treated with antiviral prophylaxis or therapy (Group A). 22 patients were identified as HBV-positive during or after immunosuppression (Group B)

— ***Results****:* We evaluated 67 patients: 43 males (64.2%) and 24 females (35.8%), median age 62 (interquartile range 48-68) years. 61 patients were Italian (91%), 4 Chinese (5.9%) and 2 Romanian (2.9%). Hematologic malignancies were the most common diseases in both groups (73% in group A and 50% in group B, respectively). HBV reactivation occurred only in patients who were not treated by either prophylaxis or therapy. They all required anti-HBV therapy, which led to HBV suppression in all cases.

— ***Conclusions:*** Our work emphasizes the importance of HBV screening and eventually prophylaxis/therapy in patients undergoing immunosuppressive therapies to prevent potential reactivations and even fatal consequences.

— ***Key words:*** Hepatitis B virus, HBV, Reactivation, Steroids, Immunosuppression.

INTRODUCTION

Hepatitis B virus (HBV) reactivation is characterized by the sudden reappearance or increase of HBV DNA in patients with a history of HBV infection (active, inactive, resolved)[1-11]. It may occur either spontaneously or after an immunodeficiency[3].

During immunosuppression/chemotherapy, HBV reactivation can occur in two different stages: either during the treatment (in relation to the intense immunological suppression which is associated with a strong viral replication), or after the end of the therapy, during the immune reconstitution phase.

Reactivation of HBV induced by chemotherapy has been known for years. In 1975, Galbraith et al. already observed that, in order to prevent HBV-related fulminant hepatitis due to the suspension of cytotoxic therapy, it was necessary to evaluate the presence of HBsAg, to follow patients after the end of the therapy and to treat the initial elevations of transaminases with steroids[2].

Such events have been observed in patients receiving chemotherapy (especially when combined with steroids), chemoembolization for hepatocellular carcinoma, immunosuppressive therapy with rituximab for lymphoma or infliximab, other anti-tumor necrosis factor (TNF) and steroids or immunosuppressants for inflammatory bowel

Corresponding Author: Mauro Maresca, MD; e-mail salmare@hotmail.com

diseases, skin diseases or rheumatoid arthritis[6-10]. The treatment with any immunosuppressive agent can lead to reactivation of HBV, with the reappearance of the necroinflammatory active disease in inactive HBsAg carriers, or in subjects that achieved the resolution of the disease (as documented by the presence of anti-HBs in serum)[1,11]. Typically, HBV DNA becomes detectable during immunosuppression, then transaminases increase after the suspension of the drug and the rebound of the immunological response. Acute hepatitis can lead to the chronicization of the disease or acute liver failure. For the reactivation of the liver disease it is often required to reduce drug dose or stop chemotherapy. Reactivation of HBV infection is more common among patients positive for HBsAg (72%) but may also occur in individuals who are anti-HBc positive (20%). The predictors of reactivation are: HBV DNA level prior to the beginning of chemotherapy, HBV serological markers, the type of malignancy, the levels of immunosuppression and the type of drugs used[1,10-11].

In oncology, the prevalence of HBsAg positivity ranges from 5.3% (in Europe) to 12% (in China). In these patients, the frequency of reactivation varies from 20% to 56%, and it is related to the use of steroids, anthracyclines and 5-fluorouracil. In hematologic tumors, the frequency of reactivation seems to be higher than in other cancers, depending on the length and the severity of immunosuppression. Indeed, the risk of reactivation is 21-67% (median 50%), with an average mortality of 20%. The risk appears to be increased by the use of monoclonal antibodies (anti-CD20, anti-CD52), with the possibility of reactivation of hepatitis even 12-36 months after the last dose of the monoclonal antibody, not only in the carriers, but also in the anti-HBc positive ones. A similar risk exists in the allogenic bone marrow transplantation (BMT), because the immunosuppressive effect during the conditioning phase is particularly strong and it is amplified by the subsequent anti-rejection therapy, for which the possibility of reactivation of hepatitis exists for the entire phase of immune reconstitution (in some cases up to 1-2 years after transplantation)[1-6,11].

This important clinical event led the attention of several experts and medical societies to developed guidelines to help specialists in the management of these complex population[4,5].

The aim of our study was to retrospectively evaluate the clinical and epidemiological features, as well as the outcomes, of a cohort of patients with HBV infection undergoing immunosuppression.

PATIENTS AND METHODS

Our retrospective observational study evaluated all medical records of patients with evidence of HBV infection that underwent immunosuppressive therapy, or scheduled to receive it, between January 2009 and November 2013.

We considered all patients with at least one clinical evaluation for immunosuppressive therapy (monoclonal antibodies, antimetabolites, antitumor antibiotics, hydrazine derivates, selective inhibitors) or steroids. Subjects with negative HBV markers were excluded.

For each patient we checked the following parameters at baseline: sex, age, nationality, the disease that required immunosuppression, immunosuppressive therapy, HBV markers, the level of serum HBV DNA, antiviral drugs used for prophylaxis or therapy, any follow-up strategies. Furthermore, we evaluated HBV DNA and HBV markers during and after our prophylactic/therapeutic program.

We also evaluated the clinical and epidemiological characteristics of two groups of patients: 45 patients were identified as HBV positive before the beginning of immunosuppression and, therefore, treated with antiviral prophylaxis or therapy (Group A). 22 patients were identified as HBV positive during or after immunosuppression (Group B).

RESULTS

We evaluated 67 patients: 43 males (64.2%) and 24 females (35.8%), median age 62 (interquartile range (IQR) 48-68) years. 61 patients were Italian (91%), 4 Chinese (5.9%) and 2 Romanian (2.9%).

This is the list of diseases that led to the immunosuppressive treatment: 29 non-Hodgkin's lymphomas; 4 Hodgkin's lymphomas; 7 multiple myeloma; 4 rheumatoid arthritis; 2 hairy cell leukemia; 2 Crohn's diseases; 2 rectal ulcerative colitis; 2 chronic lymphocytic leukemias; 3 acute myeloid leukemias; 1 idiopathic myelofibrosis; 1 immune thrombocytopenic purpura; 1 anaplastic lymphoma; 1 autoimmune thyroiditis; 1 COPD; 1 breast cancer; 2 colon-rectal cancer; 1 psoriatic arthropathy; 1 idiopathic arthritis and 1 ankylosing spondylitis (Figures 1, 2).

Monoclonal antibodies were used in 34% of the subjects, steroids in 27%, antimetabolite drugs in 6%, antitumor antibiotics in 9%, selective inhibitors in 7%, classic immunosuppressive drugs in 1%. 14% received bone marrow transplantation, only 2% underwent ABVD protocol (doxorubicin, vinblastine, dacarbazine, bleomycin).

Patients were divided into two groups: 45 Patients were identified as HBV-positive before the beginning of immunosuppression and, therefore, treated with antiviral prophylaxis or therapy (Group A). 22 Patients identified as HBV positive during or after immunosuppression (Group B).

In Group A, 24 patients were anti-HBs positive with undetectable HBV DNA; 6 were HBsAg negative and anti-HBc positive with undetectable HBV-DNA; 15 patients were HBsAg positive with mean HBV DNA of 15.319.489. In this group, 37 patients underwent HBV prophylaxis; 7 patients started therapy for chronic HBV-related active hepatitis; a single patient was managed with simple follow up (monthly for transaminases and quarterly for quantitative HBV DNA) (Figure 3).

The drugs used for prophylaxis were: lamivudine (in 34 patients), entecavir (1 patient) and tenofovir (2 patients). Among group A patients, 5 were treated with entecavir and 2 with Tenofovir.

No HBV reactivation was observed in this group.

Only one case of lamivudine resistance occurred: the patient affected by NHL and subjected to prophylaxis with LAM showed a viral load rebound that led the antiviral treatment to be replaced by tenofovir. A patient with multiple myeloma, HBsAg-positive at baseline, and treated with entecavir, showed serum conversion to anti-HBs.

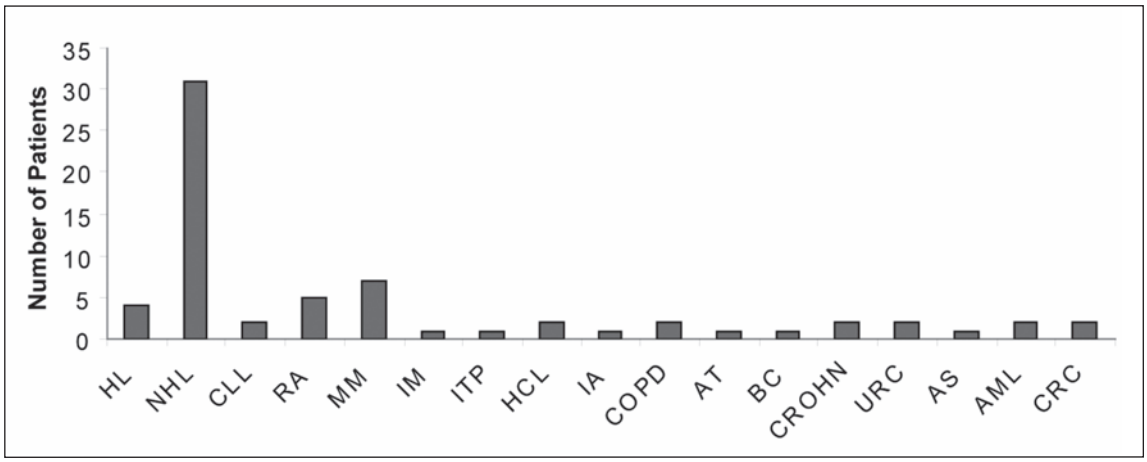

Figure 1. Individual diseases: Hodgkin's lymphomas (HL); non-Hodgkin's lymphomas (NHL); multiple myelomas (MM); rheumatoid arthritis (RA); hairy cell leukemia (HCL); Crohn's diseases; rectal ulcerative colitises (UC); chronic lymphocytic leukemias (CLL); acute myeloid leukemias (AML); idiopathic myelofibrosis (IM); immune thrombocytopenic purpura (ITP); anaplastic lymphoma (AL); autoimmune thyroiditis (AT); COPD; breast cancer (BC); colon-rectal cancer (CRC); psoriatic arthropathy (PA); idiopathic arthritis (IA); ankylosing spondylitis (AS).

Group B included 22 patients: 4 HBsAg negative and anti-HBc positive, mean HBV DNA 4,530,000; 16 HBsAg positive and anti-HBc positive, mean HBV-DNA 4,107,247; 2 patients HBs and anti-HBc positive, HBV DNA undetectable.

All 22 patients showed HBV reactivation. Reactivations were distributed as follows: 5 in anti-Hbc positive patients (3 affected by NHL, one of them treated with rituximab, 2 with a bone marrow transplant); 2 patients with immune disorders, RA and Crohn's disease, both treated with high-dose infliximab and Steroids; 2 in HBs and Anti-HBc subjects, both affected with MM and LH, respectively treated with bortezomib + steroids and bone marrow transplantation.

Finally, 15 reactivations were observed in patients positive for HBsAg and anti-HBc: 1 in a patient with MM, who underwent bone marrow transplantation; 4 cases of NHL (2 treated with rituximab and 2 with bone marrow transplantation); 1 HL with bone marrow transplantation; 1 AML with transplantation; 2 URC treated with high-dose steroids; 1 reactivation in a patient affected by Crohn's disease in steroid therapy; 1 reactivation in a patient with autoimmune thyroiditis in steroid therapy; 1 reactivation in a patient affected by psoriatic arthritis treated with cyclosporine and steroids; 1 reactivation in a subject with ankylosing spondylitis treated with infliximab (Figures 4, 5).

All reactivations occurred during immunosuppression and none during immune reconstitution.

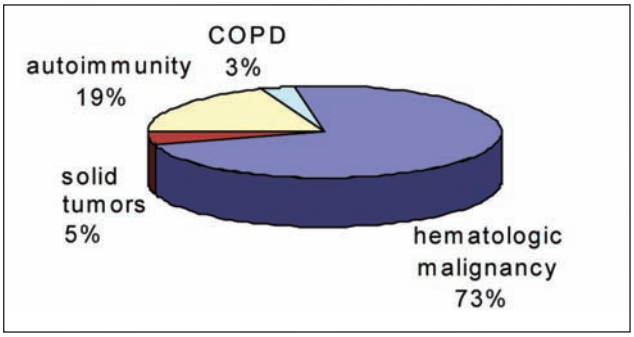

Figure 2. This figure shows the distribution of diseases in the study population: 73% of the patients were affected by hematologic malignancy; 19% by autoimmune diseases; 5% by solid tumors; 3% by COPD.

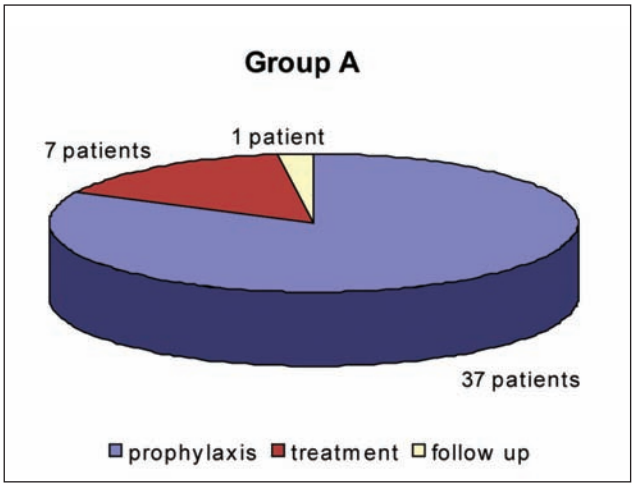

Figure 3. Distribution of treatment, prophylaxis and follow-up in Group A patients.

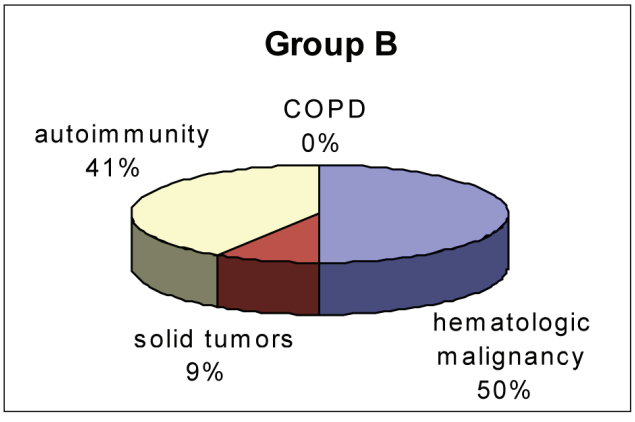

Figure 4. Disease distribution in Group B: haematologic malignancy and solid tumors were the most common diseases in the patients of Group B.

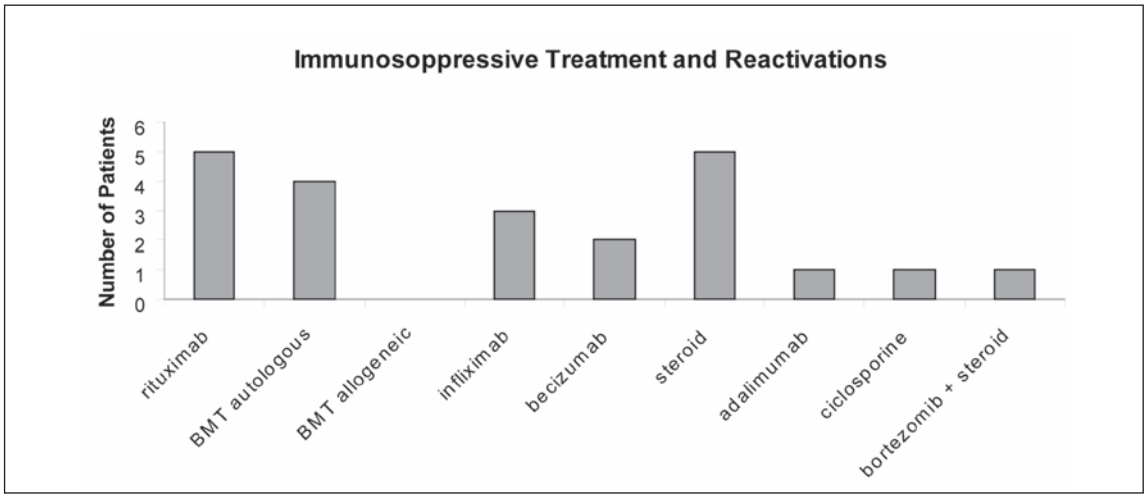

Figure 5. This figure shows the immunosuppressive agents responsible of HBV reactivations in Group B: 5 patients received rituximab; 4 patients were treated with autologous BMT; 3 patients received infliximab; 2 bevacizumab; 5 steroid; 1 adalimumab; 1 ciclosporine; 1 patient was treated with bortezomib plus steroids.

Mean HBV DNA at reactivation was 3,879,929 copies/ml, while the average value of ALT was 546 IU/ml. Finally, 4 patients were treated with lamivudine, 9 with entecavir, 6 with tenofovir and 3 with telbivudine (Figure 6).

One of the reactivations was observed in a HBsAg, anti-HBc positive patient, suffering from MM, who underwent allogeneic bone marrow transplantation: the reactivation occurred 4 years after the transplant, while the patient was subjected to steroid therapy and selective inhibitors for chronic graft. A woman, that was anti-HBc, HBsAg positive, reactivated HBV during immunosuppressive therapy for MM. She was under antiviral therapy with TDF and developed anti-HBs antibodies. An anti-HBs anti-HBc positive patient, affected by Hodgkin's disease, and who received autologous bone marrow transplantation, experienced HBV reactivation.

CONCLUSIONS

Reactivation of HBV in patients that receive immunosuppressive therapy is a relevant clinical event because of prolonged life expectancy, treatment of oncologic and autoimmune disorders and the development of new generations of immunosuppressive drugs. Moreover, HBV has a very high worldwide prevalence[1,3-4].

In our study, we had noticed that reactivation of HBV during immunosuppression was relatively common and far from being negligible. In particular, reactivation occurred in all patients that were not treated with either prophylaxis or therapy. On the other hand, it did not occur in patients under anti-HBV prophylaxis or treatment.

Finally, it should be noticed that in our series all the reactivations occurred during the immunosuppressive treatment. Nevertheless, in the literature reactivations have been described even during immune reconstitution. Thus, the cessation of immunosuppressive therapy should not coincide with the discontinuation of prophylaxis or follow-up.

CONCLUSIONS

We believe that extensive screening tests for all those diseases that may reactivate during the course of immunosuppression should be mandatory. The prevention of disease reactivation, hence the clinical consequences, morbidity and mortality, in these patients is of critical importance and needs to be emphasized to non-infectious diseases specialists.

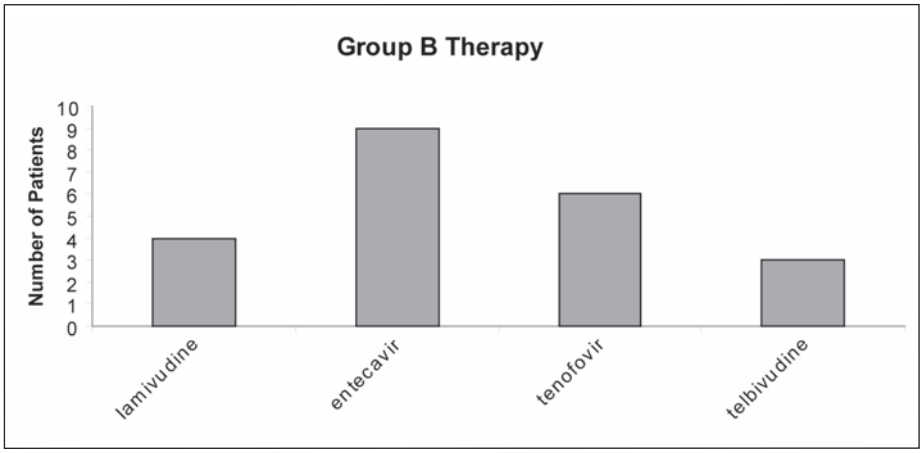

Figure 6. Anti-HBV treatments used in patients with reactivations.

CONFLICT OF INTERESTS:
The Authors declare that they have no conflict of interests.

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