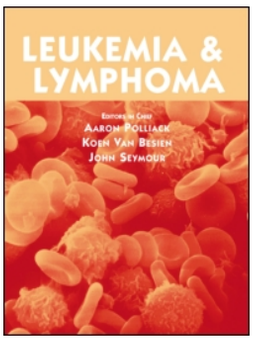

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LETTER TO THE EDITOR

Low risk of hepatitis B virus reactivation in patients with resolved infection and chronic myeloid leukemia treated with tyrosine kinase inhibitors

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The hepatitis B virus (HBV) infection is a crucial issue for the management of patients with hematological malignancies, who often receive treatments that suppress the immune system with a consequent increased risk of HBV reactivation. Thus, routine screening for the assessment of HBV serological status is mandatory, as effective antiviral therapies are available for the treatment of HBV infection.

According to the current guidelines, the universal prophylaxis with high genetic barrier drugs, such as entecavir or tenofovir, has a well-established efficacy in the prevention of HBV hepatitis in HBV surface antigen (HBsAg) positive patients.[1] However, the best strategy for the management of HBsAg negative patients with resolved HBV infection who are HBV core antibodies (antiHBc) positive with or without hepatitis B surface antibodies (antiHBs) positivity is less clear. During and after a profound suppression of the immune system, serum HBsAg detectability may be observed in these patients, usually associated with a decline of antiHBs when present at baseline, before immunosuppression; this has been defined as 'reverse seroconversion', and may lead to HBV infection reactivation, defined as the presence of significant HBV-DNA and alanine aminotransferase (ALT) serum levels above the normal upper limit, and eventually to HBV hepatitis, defined as ALT serum levels exceeding three times the upper limit of normal or an increase of more than 100 IU/L compared with the baseline, pre-chemotherapy, values.[2–4] In patients with hematological malignancies and resolved HBV infection, this risk has been reported to be as high as 12% during conventional chemotherapy, but it can rise to 14–50% in patients treated with hematopoietic stem cell transplantation,[5] or in patients treated with monoclonal anti-lymphocyte B and T (anti-CD20 and anti-CD52) antibodies.[3,6]

According to the current evidence-based guidelines of the American Gastroenterological Association,[7] the risk of HBV reverse seroconversion and reactivation in HBsAg negative/antiHBc positive patients treated with B-cells depleting agents (e.g. rituximab) is high (>10%); therefore, in these subjects antiviral prophylaxis with drugs presenting a high barrier to resistance is recommended. Conversely, this risk is considered moderate (1–10%) in patients treated with tumor necrosis factor alpha (TNF) inhibitors, with other cytokine or integrin inhibitors (e.g. vedolizumab), with high or moderate doses of daily corticosteroids for more than 4 weeks, with antracyclin derivatives, and with tyrosine kinase inhibitors (TKIs), such as imatinib, nilotinib, and dasatinib. In these cases, antiviral prophylaxis over monitoring is suggested, although the strength of recommendations is weak and derived from evidence of moderate quality due to the insufficient data published in these settings.[7,8] Indeed, few data about the occurrence of HBV reverse seroconversion in Western patients receiving TKIs for a long period are available.

We conducted a retrospective study to investigate the prevalence of resolved HBV infection and the incidence of HBV reactivation in a cohort of patients affected by chronic myeloid leukemia (CML) treated with TKIs in our Institution during the last 15 years. At the time of CML diagnosis, screening for HBsAg, HBeAg, antiHBe, antiHBc IgG and IgM, antiHBs, and HBV-DNA was performed in all patients using commercially available kits (COBAS Ampli Prep/COBAS TaqMan HBV test, Roche Diagnostics, Switzerland).

Patients with serum markers of resolved HBV infection (HBsAg negative, antiHBc positive with or without antiHBs, HBV-DNA negative) and antiHBs positive patients who had never been vaccinated and who had lost serum antiHBc were enrolled in the study. After the beginning of TKIs treatment, each patient underwent clinical evaluation at three-month intervals, or whenever necessary based on the course of the disease; HBV virological assessment and liver function tests, as well as routine

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laboratory examinations and specific CML monitoring tests, were also scheduled every three months.

Among 122 patients affected by CML and treated with oral TKIs, 11 patients (9%) presented serum markers of resolved HBV infection at the time of diagnosis. Patients' characteristics are shown in Table 1; 7 out of the 11 patients started treatment with imatinib at 400 mg/day, the other 4 with nilotinib at 600 mg/day.

In all cases, HBV-DNA serum levels were undetectable and HBsAg was negative (Table 1). AntiHBc was positive in 10/11 patients who had antiHBs positivity in 9/10 cases; one patient (n. 10), who had never been vaccinated had detectable antiHBs alone. None of the patients included in the study had serum HCV or HIV antibodies positivity. In only one patient (n.10), the serum ALT level was above the upper limit of normal before TKI treatment, whereas in the other cases no alteration was observed.

The median follow-up period was 45.8 months and was calculated from the treatment beginning to death or to the last visit. One patient died 11 months from the beginning of TKI therapy due to gastrointestinal bleeding caused by portal hypertension secondary to portal vein cavernomatosis. TKIs therapeutic regimen was changed in 3/11 patients due to molecular relapse; in particular, two patients were switched from imatinib to dasatinib after 42, and 46 months from the beginning of the first TKI administration, respectively (n. 6 and 8, Table 1); in the remaining patient (n. 2), after 9 months Imatinib was switched to Nilotinib but the TKI was changed two more times due the loss of response; in particular, this patient was switched to dasatinib and then to ponatinib.

None of the 11 patients underwent prophylactic antiviral treatment for HBV, and none of them experienced HBV reverse seroconversion or reactivation (Table 1). In particular, there was no case of HBsAg positivity or detectable serum HBV-DNA throughout the study period until the last follow-up visit. The serum ALT levels remained below the upper normal value during the follow-up, and returned within the normal range also in the patient who presented high ALT values before the beginning of TKI treatment. Finally, none lost antiHBc antibodies, and all patients with detectable antiHBs levels at baseline maintained stable antiHBs levels.

As a matter of fact, six cases of HBV hepatitis in HBsAg positive patients with CML treated with TKIs have been reported so far. Three cases of hepatitis flare successfully treated with entecavir included two patients on imatinib and another one receiving nilotinib [9]; in three other patients treated with imatinib, acute HBV hepatitis leading to irreversible liver function failure and death in one case [10] and to liver transplantation in the other two cases was described.[11,12] Although the real incidence of HBV reactivation in patients undergoing TKIs cannot be assessed, based on these case reports, it seems advisable to plan universal prophylaxis with high genetic

Table 1. Liver-related variables of patients with previous hepatitis B infection and chronic myeloid leukemia undergoing treatment with tyrosine kinase inhibitors.

							Baseline					Last visit				
PT	Age	TKI	TKI switch	Comorbidities	Death	OS (mo)	HBsAg	AntiHBc (IgG)	AntiHBs	HBV-DNA (IU/mL)	ALT (IU/L)	HBsAg	AntiHBc (IgG)	AntiHBs	HBV-DNA (IU/mL)	ALT (IU/L)
1	73	I	no	Chronic pancreatitis, arterial hypertension, diabetes	yes	11	neg	pos	neg	ND	20	neg	pos	neg	ND	11
2	61	I	N-D-P	Ischemic cardiomyopathy	no	158	neg	pos	pos	ND	18	neg	pos	pos	ND	14
3	73	I	no	Arterial hypertension, diabetes, renal insufficiency	no	71.5	neg	pos	pos	ND	25	neg	pos	pos	ND	32
4	65	I	no	Extrasystolic arrhythmia	no	133.8	neg	pos	pos	ND	32	neg	pos	pos	ND	34
5	51	N	no	–	no	37.7	neg	pos	pos	ND	25	neg	pos	pos	ND	53
6	82	I	D	Ischemic cardiomyopathy, aortic aneurysm, diverticular disease, benign prostatic hypertrophy	no	33.5	neg	pos	pos	ND	18	neg	pos	pos	ND	23
7	53	N	no	Uterine fibromatosis	no	42.5	neg	pos	pos	ND	5	neg	pos	pos	ND	33
8	78	I	D	Lymphoma, thymoma, diabetes, paroxysmal atrial fibrillation	no	48	neg	pos	pos	ND	18	neg	pos	pos	ND	38
9	67	N	no	Arterial hypertension	no	42.3	neg	pos	pos	ND	12	neg	pos	pos	ND	17
10	72	I	no	Ischemic cardiomyopathy, arterial hypertension, cerebrovascular disease, prostatic adenocarcinoma	no	91.3	neg	neg	pos	ND	153	neg	neg	pos	ND	40
11	37	N	no	–	no	12	neg	pos	pos	ND	19	neg	pos	pos	ND	20

PT: patient; TKI: tyrosine kinase inhibitor; I: imatinib; N: nilotinib; D: dasatinib; P: ponatinib; OS: overall survival; mo: months; HBsAg: HBV surface antigen; antiHBc: HBV core antibodies; antiHBs: HBV surface antibodies; HBV: hepatitis B virus; ND: not detectable; f-up: follow-up; ALT: alanine aminotransferase.

barrier antivirals in HBsAg positive patients with detectable serum HBV-DNA undergoing TKIs treatment, in order to prevent HBV reactivation and acute hepatitis.

A different virological scenario is that of patients with resolved HBV infection who are the object of the present study. Indeed, there are no consistent data in literature about the effect of TKIs on HBV reverse seroconversion. Only one case of reverse seroconversion has been recently reported in a 71-year-old woman with resolved HBV infection (HBsAg negative, antiHBc, and antiHBs positive) diagnosed with accelerated-phase CML. Serum HBV-DNA was not quantified at baseline, and the patient was initially treated with imatinib and subsequently switched to a small dose of dasatinib (20 mg/day). Three years after the beginning of dasatinib treatment a mild rise of serum ALT level was detected, HBsAg and HBeAg resulted positive and HBV-DNA was 6.9 $\log_{10}$ copies/mL. The patient was treated with lamivudine at standard dose achieving ALT normalization and HBV-DNA undetectability, then she was switched to entecavir 0.5 mg/day; dasatinib was also stopped, and the patient maintained major molecular response.[13] To our knowledge, the present study is the only case series published so far including patients with resolved HBV infection treated with TKIs for CML. No case of reactivation has been observed during the intense hepatological and hematological follow-up. As a point of strength of this study, all patients were tested pre-TKIs treatment and at three-month intervals for HBsAg, HBV-DNA, antiHBc, and antiHBs, thus ruling out possible transitory virological flares. It should be noted that 10 out of 11 patients in this series were antiHBs positive at baseline. The partial protective role of antiHBs against reverse seroconversion in patients with resolved HBV infection receiving immunosuppressive therapy has been shown in other series.[4,14,15]

In conclusion, our study, performed in a small cohort of patients, shows that the risk of HBV reactivation in patients with resolved HBV infection undergoing TKIs treatment is low especially if antiHBs is detectable in the serum. In these subjects, universal prophylaxis is probably not indicated, whereas ALT serum level, HBsAg, antiHBs, and HBV-DNA monitoring followed by immediate treatment in case of reverse seroconversion or HBV reactivation should be advised.

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