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Prophylaxis with tenofovir in hepatitis-associated severe aplastic anemia treated with hematopoietic cell transplantation

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Hepatitis-associated severe aplastic anemia (HA-SAA) is a rare illness, characterized by the onset of pancytopenia with a hypoplastic bone marrow that usually occurs within 6 months after an increase in serum aminotransferases [1]. HA-SAA is diagnosed in 1–5% of newly diagnosed cases of SAA [1]. Different hepatotropic viruses have been associated with the disease, but no specific virus is detected in many cases. The exact pathophysiology is unknown, although immune destruction of hematopoietic stem cells is believed to be the underlying mechanism. Management of HA-SAA includes immunosuppression with anti-thymocyte globulin (ATG) and cyclosporine and allogeneic hematopoietic cell transplantation (allo-HCT) [1].

Patients undergoing allo-HCT who are receiving immunosuppressive treatment form a high-risk population for hepatitis B virus (HBV) reactivation, which can lead to life-threatening fulminant hepatitis [2, 3]. Therefore, it is recommended to use nucleotide analogs [i.e. entecavir, tenofovir disoproxil (TDF), tenofovir alafenamide] in the prevention of HBV reactivation and possible treatment of HBV infection after allo-HCT [2, 4, 5].

A meta-analysis comparing the efficacy of different drugs in the prophylaxis of HBV reactivation in patients undergoing HCT showed fewer events with entecavir than with lamivudine (1.9% vs. 11.5%). However, there is no data regarding telbivudine, adenofovir or tenofovir prophylaxis in HCT patients [6].

The aim of this report was to present a case of successful prophylaxis with TDF in a pediatric allo-HCT recipient.

A 14-year-old boy with hyperbilirubinemia and hypertransaminasemia, and negative serological and molecular markers of hepatotropic viruses [hepatitis A virus (HAV), HBV, hepatitis C virus (HCV), hepatitis E virus (HEV)], had a final diagnosis of auto-immune hepatitis (AIH) confirmed via biopsy. Two months later, severe thrombocytopenia followed by leukopenia, agranulocytosis and anemia with low reticulocytes were observed. Trepanobiopsy showed an aplastic bone marrow. Myelodysplastic syndrome (MDS), leukemias, Fanconi anemia and paroxysmal nocturnal hemoglobinuria were all excluded, and a diagnosis of hepatitis-associated severe aplastic anemia (HA-SAA) was made. The patient was treated with rabbit ATG, cyclosporine and steroids, but no response was achieved. He was qualified to allo-HCT from a matched unrelated donor (MUD).

Upon admission to the transplant center, the patient presented with jaundice, features of post-steroid Cushing's syndrome, and inflammatory anal lesions. Laboratory investigations revealed agranulocytosis, anemia, leukopenia, high C-reactive protein and procalcitonin, hyperbilirubinemia (predominantly direct hyperbilirubinemia caused either by drug–drug interactions or activation of autoimmunological process) and low levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP). Serological studies demonstrated the presence of hepatitis B core (anti-HBc) total and hepatitis B surface (anti-HBs) (447 IU/mL) antibodies, while anti-HBc-IgM, hepatitis B surface antigen

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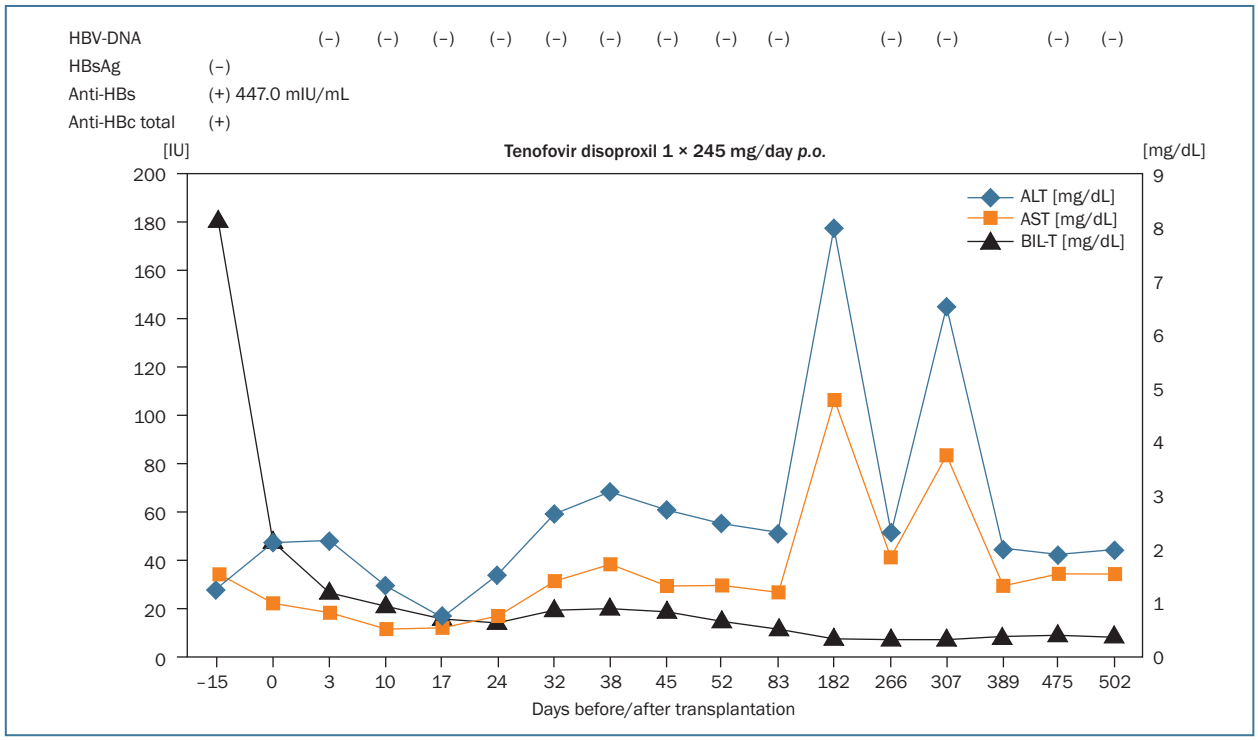

Figure 1. Timeline of prophylaxis with tenofovir; HBV DNA — hepatitis B virus DNA; HBsAg — hepatitis B surface antigen; anti-HBs — hepatitis B surface antibodies; anti-HBc — hepatitis B core antibodies; *p.o.* (Latin *per os*) — oral administration; ALT — alanine aminotransferase; AST — aspartate aminotransferase; BIL-T — total bilirubin

(HBsAg), HCV antibodies (anti-HCV), and human immunodeficiency virus antibodies (anti-HIV) were absent. In addition, HBV, HCV, and HIV were excluded by polymerase chain reaction (PCR). Considering the possible new contact with HBV and the high risk of HBV reactivation during immunosuppressive treatment, prophylactic administration of oral TDF was implemented, at a dose of 245 mg once daily from the start of conditioning chemotherapy (Figure 1). After treatment with antibiotics and prednisone (1 mg/kg/day), inflammatory markers and bilirubin levels rapidly decreased.

In the conditioning regimen, fludarabine (30 mg/m^2/day; days –6 to –3), cyclophosphamide (750 mg/m^2/day; days –6 to –3), and ATG (2.5 mg/kg/day; days –6 to –3) were used, with cyclosporine and methotrexate for GvHD prophylaxis. The patient was transplanted with peripheral blood hematopoietic stem cells (NC = 7.26 × 10^8 cells/kg, CD34+ = 4.52 × 10^6 cells/kg). Letermovir was used for cytomegalovirus (CMV) prophylaxis, as well as a standard anti-infective prophylaxis with acyclovir and trimethoprime/sulfamethoxazole. On day +5, rituximab was administered for prophylaxis of Epstein-Bárr virus (EBV)-related complications. Due to *Staphylococcus haemolyticus* sepsis, antibiotic therapy was intensified. Granulocyte-colony stimulating factor (G-CSF) was used to accelerate neutrophil recovery and the central line was replaced. At day +10, BK virus (BKV)-cystitis was diagnosed with no need for specific treatment. Neutrophil engraftment was observed on day +26, but a myelogram showed poor marrow cellularity with the need for frequent transfusions. For this reason, triple stimulation with filgrastim, darbopoetin alpha and eltrombopag was implemented, with success. On day +30, the patient was discharged home in overall good condition. No signs of GvHD were observed in the post-transplant period. The immunosuppressive therapy with cyclosporine was sustained for nine months. HBV-DNA was monitored weekly for the first two months, and then monthly for the next 18 months. Prophylaxis with oral TDF 245 mg/day was sustained throughout the entire period of immunosuppressive treatment and for the subsequent 12 months. During cessation of immunosuppression, a temporary increase of ALT/AST was observed. This was probably related to eltrombopag application. No HBV-DNA reactivation was observed.

The management of HA-SAA in the context of allo-HCT presents many challenges. The risk of reactivation of HBV infection depends on many factors: this risk is 5–8 times greater in patients with HBsAg(+) compared to HBsAg(–) in patients with detectable HBV-DNA and in patients without anti-HBs antibodies [7]. A meta-analysis of 55 studies, including 3,640 HBsAg(–)/anti-HBc(+) patients receiving immunosuppressive treatment, showed that the reactivation

rate was 10.9% in patients with hematological malignancies and 3.6% in patients with other diseases [8].

This is why preventing HBV reactivation in allo-HCT patients is critical. Our case shows that TDF at a dose of 245 mg/day was effective in this prophylactic strategy.

In conclusion, this case highlights the importance of prophylaxis of HBV infection in patients who are at high risk of HBV reactivation. This prophylaxis is cheap and easy and carries a low risk of adverse side effects.

Authors' contributions

KC — design of study; MP, AT, MRP, RD, KC — provision of clinical data; MP, AT, MRP, RD, KC — analysis of clinical data; MP, KC — literature search and analysis of data; MP, KC — writing manuscript. All authors — critical revision and final approval.

Conflict of interest

The authors declare no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

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