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Successful treatment of pritelivir in an immunocompromised pediatric patient with refractory/resistant HSV-1 infection: a first report with therapeutic drug monitoring

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Research Article

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Abstract

Management of refractory and resistant (R/R) Herpes Simplex Virus (HSV-1) infections in hematopoietic stem cell transplant (HSCT) recipients remains challenging. Literature on pritelivir's efficacy in pediatric patients is scarce.

We successfully treated a 7-year-old HSCT recipient with pritelivir for an (R/R) HSV-1 infection and performed therapeutic drug monitoring.

Introduction

Herpes simplex virus 1 (HSV-1) infection is one of the most prevalent viral infections affecting hematopoietic stem cell transplant (HSCT) pediatric recipients. Acyclovir/valacyclovir are the gold standard prophylaxis [1]. Their use may be extended if a severe immune deficiency persists, exposing to a risk of emergence of viral resistance of up to 36% in some cohorts of HSCT adults recipients [2, 3]. Resistant and refractory (R/R) HSV-1 infections represent also a growing clinical concern in pediatric HSCT recipients [4]. Because of the risk of nephrotoxicity associated with the use of foscarnet and cidofovir, novel second-line antiviral options with better safety profile are urgently needed. Pritelivir, a novel oral helicase-primase inhibitor, has recently demonstrated good clinical tolerance and superior efficacy compared with investigator's choice therapy in immunocompromised adults with R/R HSV-1 [5]. We describe a 7-year-old male undergoing HSCT who developed a R/R HSV-1 mucocutaneous infection following graft rejection and was successfully treated with pritelivir.

Case presentation

A 7- year-old male with Fanconi anemia underwent haploidentic HSCT with TCR alpha/beta depletion in december 2025 for moderate aplastic anemia. On day 9 after HSCT, he developed HSV1-related oral mucositis, which required a switch from valacyclovir prophylactic dosage (PD) to curative acyclovir (See Fig. 1 for the timeline). This episode resolved completely following a 2-week course of intravenous acyclovir and valaciclovir PD was resumed. The patient presented a fever with aplasia following macrophage activation syndrome which was treated with corticosteroids (2 mg/kg/day). Full recipient chimerism was confirmed on blood and bone marrow samples performed 26 days after the HSCT, indicating a graft rejection. On day 38 after the first HSCT, the patient proceeded to a second HSCT from a cord blood donor, following a regimen comprising rituximab, 2 Gy total body irradiation, cyclophosphamide, alemtuzumab, and fludarabine. HSV1-related genital phlyctenules appeared 4 days before the second HSCT leading to resumption of intravenous acyclovir. On day 2 after the second HSCT, the patient experienced a relapse of oropharyngeal lesions with positive HSV1 PCR in oral and blood samples ((4.5 $\log_{10}$ and 3.1 $\log_{10}$ DNA copies/mL, respectively). The worsening of oral mucositis associated with fever 5 days after acyclovir initiation prompted acyclovir pharmacokinetic monitoring (0.27 mg/L) and genotypic resistance testing of HSV. This test revealed a deletion at position 1065 in the *UL23* gene, conferring resistance to acyclovir. No resistance-associated mutations were detected in the

UL30 gene. Further microbiological testing showed no evidence of superinfection. Based on these results, acyclovir was switched to foscarnet (40 mg/kg/12h, later increased to 60 mg/kg/12h because of worsening lesions). Due to the progression of extensive oral mucositis (Fig. 2A) and probable drug-related toxicity (severe hypokalemia), foscarnet was switched to cidofovir, without clinical benefit after the first injection. Thirteen days after the diagnosis of acyclovir-resistant HSV-1, pritelivir (2 mg/kg a day following a loading dose of 8 mg/kg on day 1) was initiated under expanded access approval and was accompanied by a second injection of cidofovir. Pritelivir was administered as an oral suspension in water prepared from the film-coated tablets via a nasogastric tube. This rescue therapy was associated with a dramatic improvement in HSV1-related oral mucositis (Fig. 2B), resolution of fever, and a significant reduction in pain intensity from day 5 following its initiation. Due to the lack of dosing recommendations for pediatric use of pritelivir, therapeutic drug monitoring (TDM) was performed, including trough and peak plasma concentrations (12.6 mg/L and 14.7 mg/L, respectively). The patient received two additional doses of cidofovir for concomitant adenovirus viremia. Neutrophils engraftment occurred 33 days after the second HSCT. After 6 weeks of pritelivir therapy, the patient was discharged on valaciclovir prophylaxis. One month after pritelivir discontinuation, the patient experienced oral mucositis relapse related to the same strain of acyclovir-resistant HSV. Pritelivir was resumed after a 2-week course of foscarnet and led to clinical improvement. The patient was still receiving pritelivir in july 2026 and did not experience any drug-associated side effects.

Discussion

We reported the first pediatric patient who was successfully treated with pritelivir using a TDM of the novel antiviral. The decision to pursue compassionate use of pritelivir was made by a multidisciplinary team—including pediatricians, infectious disease specialists, virologists, and pharmacologists—and was informed. In pediatric HSCT recipients, only two cases have been reported and no TDM was performed for these patients even though the unsuitable formulation used would justify it [6]. Both patients were male, aged sixteen months, and had refractory disseminated HSV diseases with proven resistance to acyclovir for the first child and acyclovir and foscarnet for the second individual. The first patient experienced clinical progression despite pritelivir and died from HSV-associated acute respiratory distress syndrome. The second patient responded to a 28-day course of pritelivir but presented a refractory respiratory relapse with resistant HSV, leading to death. The recurrence of HSV-1 infections following pritelivir discontinuation, is consistent with our case and with observations of Serris *et al* about HSCT adult patients experiencing R/R HSV-2 infections, emphasizes the need to assess which antiviral drug can be used for long-term prophylaxis in these patients [7].

In addition, pritelivir targets the viral proteins UL5 and UL52, which are not affected by either thymidine kinase or DNA polymerase mutations, unlike acyclovir and foscarnet [8, 9]. In the PRIOH-1 trial, which included 101 immunocompromised adult patients with refractory HSV1 infections, pritelivir demonstrated clinically meaningful superiority in lesion healing up to 28 days of treatment, compared with foscarnet or cidofovir [5]. Because pritelivir is currently available as an oral formulation, administration may be challenging in children with severe mucositis. However, the TDM performed in our

patient confirmed a good oral bioavailibility of pritelivir even if the tablets were given via the nasogastric tube. Although the pritelivir were above the expected range (2.7–4.3 mg/L and 4.7–8.1 respectively), no dose adjustment was made due to the good tolerance [10].

In addition, the clinical failure associated with foscarnet was not explained by genotypic resistance test and may be related to the profound immunosuppression. Indeed, the sequential impact of TCR α/β-depleted first HSCT, graft failure, steroid use, and re-conditioning resulted in deep and persistent T-cell lymphopenia in this patient with underlying aplastic anemia. Therefore, reducing immunosuppression was not feasible in our patient due to the high risk of GVHD associated with the second HSCT.

Regarding the antiviral treatment duration, even though no guidelines are available, some experts recommend continuing pritelivir until complete clinical regression, for a maximum of 6 weeks [3, 8]. In our patient, the 6-week course of pritelivir was associated with clinical relapse 1 month after treatment discontinuation. This high risk of relapse in HSCT patients may be related to the prolonged alteration of HSV-specific T-cell response as shown by the interferon gamma release assay [11]. For instance, our patient had TCD4 lymphopenia (146/mm3). Besides, pritelivir seems to have a high genetic barrier to resistance as highlighted by only one resistance case in the PRIOH-1 trial [5].Therefore, given its safety profile, pritelivir could be an interesting candidate as long-term prophylaxis in HSCT pediatric recipients dealing with R/R HSV infections [12].

While this single observation should be interpreted with caution, it supports further evaluation of pritelivir as a potential therapeutic option for refractory or resistant HSV infections in highly immunocompromised pediatric patients. Clinical studies are needed to assess its safety, pharmacokinetics, and efficacy in children under 16 years of age.

Figure titles and legends

Figure 1: Timeline of the patient

This timeline shows the clinical course of HSV-related oral mucositis and genital lesions, along with the different antiviral treatments used. It also describes the patient's lymphocytes subpopulations counts at day 116 after the first allogeneic stem cell transplant.

Figure 2: Clinical evolution of the patient’s oral mucositis

Ten days after foscarnet initiation, the patient experienced a progression of extensive oral mucositis (Fig. 2A).

Pritelivir was associated with a dramatic improvement in HSV1-related oral mucositis from day 5 following its initiation (Fig. 2B).

Declarations

Author contributions

HBB analyzed the data and wrote the initial manuscript

AD, PS, VB,LP, MA,MS,HC, CG and SV took care of the patient, reviewed the manuscript, and provided edits and feedback

PF, GP, ML, CB, CZ, CS and LL reviewed the manuscript, and provided edits and feedback

Conflict of Interest

PF has received travel grants from Takeda for participation to international conferences. The other authors declare no conflict of interests.

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Ethical approval statement

Written informed consent has been given by the patient and retained by authors.

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Figures

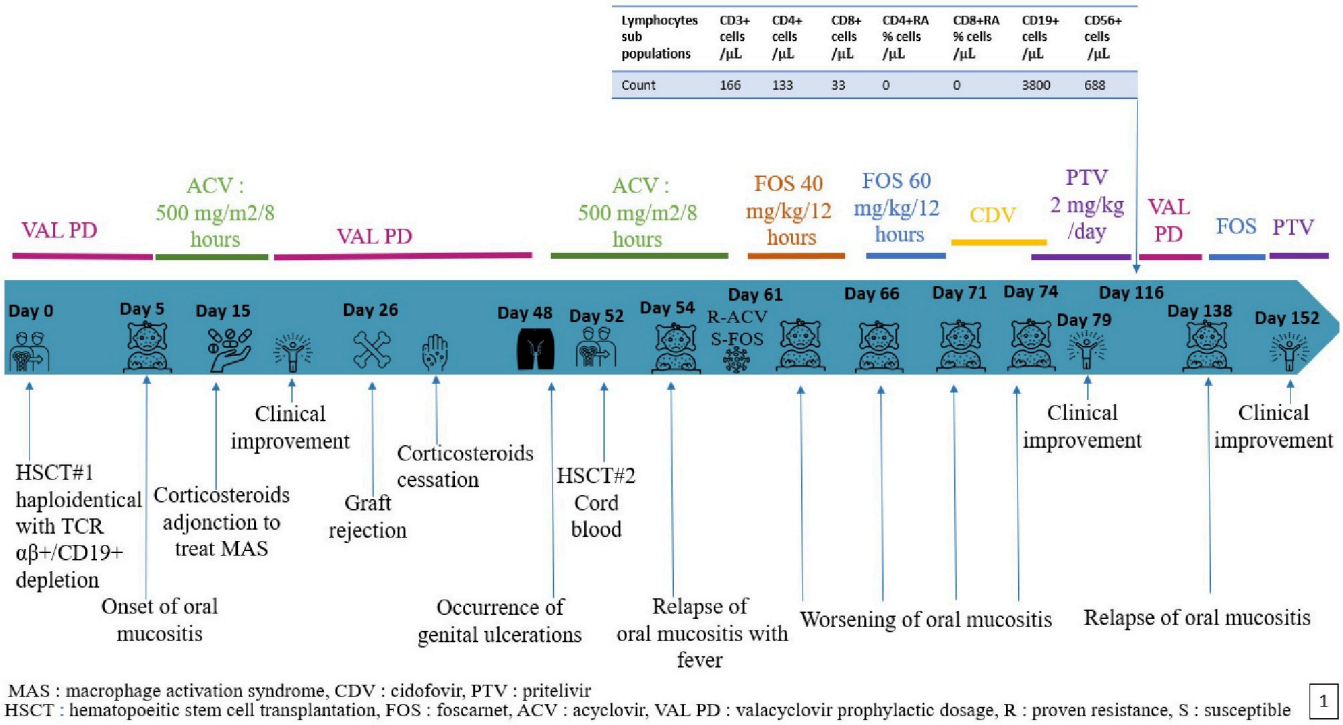


Figure 1

Timeline of the patient

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Figure 2

Clinical evolution of the patient’s oral mucositis

Ten days after foscarnet initiation, the patient experienced a progression of extensive oral mucositis (Figure 2A).

Pritelivir was associated with a dramatic improvement in HSV1-related oral mucositis from day 5 following its initiation (Figure 2B).