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Letermovir use in children after hematopoietic cell transplantation: summary of reported data

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Abstract

Introduction: Letermovir (LMV) is approved for primary prophylaxis of cytomegalovirus infection (CMVi) in CMV-seropositive adult patients undergoing allogeneic hematopoietic stem cell transplantation. However, it is not registered for CMVi pre-emptive treatment, CMVi secondary prophylaxis, or the treatment of CMV disease. There is very limited data regarding LMV's use in pediatric patients, as it has not been approved so far as any kind of treatment in children, with its use remaining off label. The aim of this study was to summarize reported data on the efficacy and safety of LMV in pediatric patients.

Material and methods: Studies and case reports regarding LMV's use in pediatric patients were searched in PubMed.

Results: Overall, nine reports that fulfilled the search criteria, published between 2019 and 2022, were found and analyzed. The total number of cases involved in research was 46 with patient age ranging from 2–19 years; one child was counted twice due to another transplant.

The most common serostatus of donor/recipient was D+/R+ (47%), followed by D–/R+ (42%), then D+/R– (2%), and then unknown (9%). Most patients had received the transplant from a matched unrelated donor (40%). There were 47 incidents of LMV administration as CMV management strategy. The analyzed patients received LMV as primary prophylaxis (74%), secondary prophylaxis (15%), pre-emptive therapy (6%), or treatment of CMV disease (4%). One patient received LMV as a treatment and then as a secondary prophylaxis. In 44/46 (95.6%) cases, no symptomatic CMVi occurred during LMV administration, with only transient CMV DNA-emia present on rare occasions.

Conclusion: The use of LMV is safe in pediatric patients.

Key words: letermovir, children, transplantation, CMV

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Introduction

Cytomegalovirus infection (CMVi) is one of the most severe complications for immunosuppressed patients undergoing hematopoietic stem cell transplantation (HSCT). Its harmful effect comprises both direct and indirect toxicity. Direct toxicity is the result of ongoing infection, while indirect toxicity concerns the immunological effects of the virus and the side effects of the used drugs [1, 2]. CMV infection is associated with higher non-relapse mortality (NRM) and all-cause mortality [3]. CMV reactivation happens in up to 70% of CMV-seropositive recipients (R+) [4, 5]. The most

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common clinical manifestations of CMVi in HSCT patients include pneumonia, hepatitis, enteritis, retinitis and bone marrow suppression. Moreover, CMVi increases the risk of life-threatening secondary bacterial and fungal infections as well as graft-versus-host disease (GvHD) development and graft failure [2, 6, 7]. Documented high risk factors of CMVi include: CMV-seronegative donor/recipient, CMV positive serostatus (D–/R+) [odds ratio (OR) = 11.0], grade 3–4 of acute GvHD (aGVDH) (OR = 5.4), and unrelated (OR = 6.0) and mismatched donors (OR = 4.2) [8, 9]. Furthermore, older age, male sex and nonwhite/nonblack race are non-modifiable risk factors in pediatric patients [10]. Pharmacological strategies to prevent CMV infections include prophylaxis and preemptive therapy. Prophylaxis is based on the administration of antiviral drugs to prevent infection, whereas preemptive therapy requires repetitive screening assay and treating asymptomatic, infected patients [2].

Before the letermovir (LMV) era, gancyclovir (GCV), valgancyclovir (VGC) and foscarnet (FOS) were used as a preemptive therapy, but not prophylaxis due to their myelo- and nephrotoxicity [2–4, 7, 10, 11]. LMV, which is devoid of these side effects, became a new treatment strategy in adults. LMV inhibits CMV by disrupting the viral terminase. Studies on LMV used as primary prophylaxis proved its high efficacy at reducing the incidence of CMV disease and the number of deaths caused by CMVi [2–7, 11]. In 2017, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved LMV for primary prophylaxis in CMV-seropositive adult patients undergoing allogeneic HSCT (allo-HSCT) [2–8, 10, 11]. However, it was not registered for CMVi preemptive treatment, CMVi secondary prophylaxis, or the treatment of CMV disease [2, 3, 7]. There is very limited data regarding LMV's use in pediatric patients as it has not been approved so far as any kind of treatment in children, with its use remaining off label [1–8, 10–12]. The aim of this study was to summarize reported data on the efficacy and safety of LMV in pediatric patients.

Material and methods

Studies and case reports regarding LMV use in pediatric patients were searched in PubMed. Searched queries included 'letermovir' AND 'child*'; 'letermovir' AND 'pediatr*'. The following data was retrieved from these reports: number of patients treated with LMV, gender, underlying disease, serostatus, type of transplantation, CMV treatment before LMV, type of CMV management, treatment outcome, dosage of LMV, and the initiation and duration of treatment.

Based on published reports, we used the term 'breakthrough symptomatic CMVi' during LMV administration to denote the presence of viral DNAemia in a patient with symptoms in a case of primary/secondary prophylaxis and preemptive therapy. We considered it also as ongoing symptomatic CMVi unsuccessfully treated with LMV.

Results

We found nine reports that fulfilled the search criteria, published between 2019 and 2022 (Table I) [1, 4–8, 10–12]. The total number of cases involved in research was 46, with the patients' ages ranging from 2 to 19 years. Out of 43 children with a known gender, 22 (51%) were male. In the vast majority of patients, the underlying hematological disease was acute lymphoblastic leukemia or acute myeloid leukemia. All but one child had undergone HSCT at some point, with the only exception being the case of a 2-year-old girl suffering from medulloblastoma complicated by refractory CMVi. One patient had had two allo-HSCTs, and thus was considered to be two cases.

The most common serostatus was D+/R+ (21/45; 47%), followed by D–/R+ (19/45; 42%), then D+/R– (1/45; 2%), and four were unknown (9%). Most patients had received the transplant from a matched unrelated donor (MUD; 18/45; 40%).

There were 47 courses of LMV administration as CMV management strategy. Analyzed patients received LMV as primary prophylaxis (35/47; 74%), secondary prophylaxis (7/47; 15%), pre-emptive therapy (3/47; 6%), or CMVi treatment (2/47; 4%). One patient received LMV as a treatment and then as a secondary prophylaxis.

In 8/9 analyzed reports, the same dose of LMV in children >30 kg body weight (b.w.) was provided as in adults i.e. 240 mg/day [intravenous/*per os* (iv/*po*)] with concomitant cyclosporine and 480 mg (iv/*po*) per day without cyclosporine. In all studies with patients <30 kg b.w., the dose of LMV was 120 mg/day with concomitant cyclosporine and 240 mg/day without cyclosporine. This was regardless of the type of CMV management (i.e. primary/secondary prophylaxis or treatment). In a case described by Pérez Marín et al. [11], initially 7 mg/kg b.w. of LMV was administered once a day with an escalation to 24 mg/kg twice a day due to lack of efficacy of the lower dosage. It is however worth noting that when used as CMVi treatment method, LMV was (in both found cases) administered concomitant to foscarnet (FOS). 10/46 (22%) patients received other anti-CMV treatment before switching to LMV.

The use of LMV was safe in pediatric patients. The incidence of adverse effects occurring due to LMV administration in children was inconclusive, so we the authors considered different ones. Most common were nausea, vomiting and transient liver function impairment. The latter, however, cannot be fully associated with LMV toxicity as patients simultaneously took other hepatotoxic drugs (e.g. mycophenolate mofetil). The same applies to the enteritis described by Kilgore et al., being difficult to differentiate between LMV-induced, progressive GvHD or effects of ongoing CMV colitis [7].

Overall, in 44/46 (95.6%) cases, no symptomatic CMVi occurred during LMV administration, with only transient CMV DNA-emia present on rare occasions.

Table I. Summary of reported cases of use of letermovir (LMV) in children

Author	Patients	Sex	Median age; range	CMV management	Serostatus of CMV	HLA match	Breakthrough symptomatic CMVi during LMV administration
Styczyński et al. [1]	5	1 M, 1 F 3 N/A	N/A	2 × PP 3 × SP	2 × (D+/R+) 3 × N/A	1 × MUD 1 × MMRD 3 × N/A	0/5
Cheng et al. [8]	4	3 M, 1 F	16,1 (9.2–17.8)	4 × PP	4 × D–/R+	2 × MRD 1 × MUD 1 × MMUD	0/4
Richert-Przygonska et al. [6]	13	6 M, 7 F	13,2 (7.1–16.9)	12 × PP 1 × SP	8 × (D+/R+) 5 × (D–/R+)	4 × MRD 8 × MUD 1 × haplo	0/13
Strenger et al. [12]	2	2 M, 0 F	8.8 (6–11.5)	2 × PET	2 × (D+/R+)	2 × MRD	0/2
Pérez Marín et al. [11]	1	0 M, 1 F	2	1 × TOC	–	–	1.1
Kuhn et al. [10]	9	4 M, 5 F	14 (4–19)	7 × PP 2 × SP	5 × (D+/R+) 1 × (D+/R–) 2 × (D–/R+) 1 × N/A	1 × MRD 5 × MUD 3 × haplo	0/9[b]
Chiereghin et al. [5]	1	1 M, 0 F	17	1 × PET	1 × (D–/R+)	1 × MMUD	0/1
Kilgore et al. [7]	1	0 M, 1 F	14	1 × TOC/SP	1 × (D–/R+)	1 × DUBT	1/1[c]
Daukshus et al. [4]	10[a]	5 M, 5 F	15.2 (10–17.6)	10 × PP	6 × (D–/R+) 4 × (D+/R+)	2 × MRD 3 × MUD 5 × MMUD	0/10
Total	46	22 M (47.8%) 21 F (45.7%) 3 N/A (6.5%)	Range (2–19)	35 × PP (74.5%) 7 × SP (14.9%) 2 × TOC (4.3%) 3 × PET (6.4%)	21 × (D+/R+) (46.7%) 19 × (D–/R+) (42.2%) 1 × (D+/R–) (2.2%) 4 × N/A (8.9%)	11 × MRD (24.4%) 1 × MMRD (2.2%) 18 × MUD (40.0%) 7 × MMUD (15.6%) 4 × haplo (8.9%) 1 × DUCBT (2.2%) 3 × N/A (6.7%)	2/46 (4.3%)

[a]One patient had two hematopoietic cell transplantatios and is counted as two; [b]one patient had CMV DNA-emia of 467 IU/mL and had LMV discontinued in favor of valgancyclovir; [c]LMV was used concomitant to foscarnet for cytomegalovirus infection (CMVi) treatments, which was successful. Then LMV was used in monotherapy as secondary prophylaxis and patient developed symptomatic cytomegalovirus (CMV) after 2.5 months; HLA — human lymphocyte antigen; M — male; F — female; N/A — not available; PP — primary prophylaxis; SP — secondary prophylaxis; D — donor; + — seropositive of CMV; R — recipient; MUD — matched unrelated donor; MMRD — mismatched related donor; – — seronegative of CMV; MRD — matched related donor; haplo — haploidentical transplant; PET — preemptive therapy; TOC — treatment of CMVi; MMUD — mismatched unrelated donor; DUCBT — double umbilical cord blood transplant

Primary prophylaxis

Primary prophylaxis was the most common use for LMV in CMV management strategy in the analyzed reports (35/47; 74.5%). Out of 29 cases with known LMV initiation time, the median was day +1. In three cases, LMV administration was started prior to allo-HSCT procedure. Two children had switched to LMV for primary prophylaxis because of gancyclovir/valgancyclovir (GCV/VGC) intolerance, thus they only started administration of LMV on days +83 and +84. No patient developed symptomatic CMVi. One child, in the work by Kuhn et al., developed viral load of 467 IU/ /mL which resulted in discontinuation of LMV in favor of VGC [10]. This patient was cured and remained asymptomatic. It remains unknown whether the patient would have developed symptomatic CMVi, had it not been for the switch of treatment.

Secondary prophylaxis

LMV was used as secondary prophylaxis in seven cases (7/47; 14.9%) following successful treatment with GCV/ /VGC. In 6/7 cases (85.7%) no symptomatic CMVi was observed. A girl described in the work by Kilgore et al. [7] received LMV as secondary prophylaxis after successful CMV treatment with a combination of iv FOS and LMV, and 2.5 months after the resolution of her initial CMV-DNAemia, this patient presented with symptomatic CMVi. Further tests revealed *UL56* mutation (R369S) which conferred LMV resistance. Therapy was changed to concomitant GCV and FOS which resulted in a decrease of CMV-DNAemia.

Pre-emptive therapy

There were three cases of LMV use as pre-emptive therapy in our research (3/47; 6.4%). The median initiation time was day +120 (range: +11 to +203) with median treatment duration of 24 days (range 10–57). None of the cases included administration of LMV as first line treatment. Patients had their primary pharmacotherapy switched after intolerance (1/3; 33.3%) or refractory high CMV-DNA-emia (2/3; 66.7%). All children (3/3; 100%) became CMV negative after LMV was initiated in monotherapy (time range: 1 week–42 days).

Treatment of CMV

In 2/47 cases (4.3%), LMV was administered with concomitant FOS as CMVi treatment due to a lack of response to standard therapy. In one case described by Perez Marin et al., therapy was unsuccessful and the patient died due to a massive subdural hemorrhage, although the viral load was reduced from 360,000 copies/mL to 4,300 copies/mL [11]. The same combination of antivirals, as described by Kilgore et al., was successful in overcoming CMVi [7]. FOS was withdrawn and secondary prophylaxis with oral LMV in monotherapy was initiated.

Discussion

The use of LMV in prophylaxis of CMV infection in patients after allo-HSCT has changed the paradigm of prevention of this infection, and will hopefully contribute to decreases in other infections and complications [1–3, 13, 14]. In this paper, we have summarized all publications on LMV use in off-label indications in pediatric populations available on PubMed. Despite increased interest in the use of LMV, there is still limited data regarding this issue. In 44/46 (95.6%) cases, no symptomatic CMVi occurred during LMV administration, with only transient CMV DNA-emia present on rare occasions. One patient with symptomatic CMV received LMV as a treatment option which failed to decrease viral load to undetectable levels. A second one developed symptomatic CMVi during secondary prophylaxis which was preceded by successful treatment with LMV. This patient however developed LMV resistance.

Although a daily dose of LMV in children is not established yet, patients >30 kg b.w. in 8/9 analyzed publications were provided the same treatment as adults (240 mg with/480 mg *po*/iv without cyclosporine per day); for <30 kg b.w., the dosage was halved. This resulted in no severe side effects. Nevertheless, due to the absence of data about pharmacokinetics of LMV in pediatric population, selecting dosage should be done with caution [8].

Only two papers included control groups in the methodology, with Cheng et al. noting a trend towards delay in platelet engraftment in the LMV group ($p = 0.088$) [8]. However, this was not the case for Richert-Przygońska ($p = 0.452$) [6]. It is difficult to draw statistically significant conclusions considering the small sizes of both LMV and control groups in these papers. Nonetheless, they support the promising effect LMV can bring to CMV prophylaxis among pediatric patients.

The presented data suggests high effectiveness and safety regarding the use of LMV for CMVi prophylaxis in immunosuppressed children. There is not enough information regarding its use in pre-emptive therapy, because it was not utilized as the first line treatment in any of the cases. A similar scenario occurred with analysis of treatment of ongoing CMV, where a combination of LMV and FOS was once successful and once was not. However, the complexity of these two cases, and the use of polytherapy prior to LMV administration, makes it difficult to evaluate LMV for this indication.

More data about LMV effectiveness and safety in pediatric populations will be available after the much-anticipated outcome of a currently ongoing study (MK-8228-030) (Clinical-Trials.gov identifier NCT03940586) [4, 10].

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Authors' contributions

KC, JS — design of study. All authors — analysis of clinical data. TS, JS — literature search and analysis of data. TS, JS — 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; uniform requirements for manuscripts submitted to biomedical journals.

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