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REVIEW ARTICLE

Maribavir in the Treatment of Cytomegalovirus Infections that are Resistant and/or Refractory in Transplant Recipients

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ABSTRACT

Objectives: This scoping review aims to gather data and map the available evidence on the efficacy and safety of maribavir (MBV) in transplant patients with resistant and/or refractory CMV infection. **Methods:** This is a scoping review conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines. The databases searched were MEDLINE, Scopus, Embase, Web of Science, and LILACS. The search used the keywords "Maribavir," "Cytomegalovirus," "Resistance," and "Transplantation," along with their synonyms and appropriate Boolean operators. **Results:** A total of 640 articles were retrieved in the literature search, of which 11 were included in the review. Phase 3 clinical trials showed that MBV is more effective and safer than conventional antivirals, with higher rates of viral clearance and a lower incidence of toxicities such as nephrotoxicity and myelotoxicity. Virological response rates to MBV ranged from 21% to 90%, with greater efficacy observed at week 8 compared to conventional therapies. Recurrences occurred in 20.8% to 40% of cases, mainly associated with high initial viral load. **Conclusion:** MBV stands out as an effective therapeutic option with a more favorable safety profile. Despite its demonstrated benefits, the emergence of resistance and viral recurrences remains an ongoing challenge. Further studies are needed to assess its impact on long-term clinical outcomes and to optimize management strategies, especially in specific patient subgroups.

Descriptors: Antivirals; Cytomegalovirus Infections; Transplantation.

Maribavir no Tratamento de Infecções por Citomegalovírus Resistentes e/ou Refratários em Pacientes Transplantados

RESUMO

Objetivos: Esta revisão de escopo tem como objetivo reunir dados e mapear as evidências disponíveis sobre a eficácia e segurança do maribavir (MBV) em pacientes transplantados com infecção por citomegalovírus (CMV) resistente e/ou refratária. **Métodos:** Trata-se de uma revisão de escopo seguindo as diretrizes do Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR). As bases de dados utilizadas na busca foram MEDLINE, Scopus, Embase, Web of Science e LILACS. A busca foi realizada utilizando as palavras-chave "Maribavir", "Cytomegalovirus", "Resistance", e "Transplantation", bem como seus sinônimos e operadores booleanos correspondentes **Resultados:** Ao todo, 640 artigos foram encontrados na busca bibliográfica; desses, 11 foram incluídos na revisão. Ensaios clínicos de fase 3 demonstraram que o MBV é mais eficaz e seguro que antivirais convencionais, com maior taxa de eliminação viral e menor incidência de toxicidades, como nefrotoxicidade e mielotoxicidade. As taxas de resposta virológica ao MBV variaram de 21% a 90%, com maior eficácia na 8ª semana em comparação às terapias convencionais. Recidivas ocorreram em 20,8% a 40% dos casos, associadas principalmente à alta carga viral inicial. **Conclusão:** O MBV se destaca como opção terapêutica eficaz e com perfil de segurança mais favorável. Apesar dos benefícios demonstrados, a emergência de resistência e as recidivas virais permanecem como desafios. São necessários estudos adicionais para avaliar seu impacto em desfechos clínicos de longo prazo e aprimorar estratégias de manejo, especialmente em subgrupos específicos de pacientes.

Descritores: Antivirais; Infecções por Citomegalovírus; Transplante.

INTRODUCTION

Cytomegalovirus (CMV), a member of the *Herpesviridae* family, is a widespread virus with a prevalence of over 90% in developing countries. Transmission occurs through bodily fluids such as saliva, urine, blood, breast milk, semen, and cervicovaginal secretions, and can also occur vertically (transplacentally), through transfusions, and through organ transplants[1].

In immunocompetent individuals, it usually causes asymptomatic or mild infections, but it can remain latent in the body. In immunocompromised patients, specifically in solid organ or hematopoietic stem cell transplant recipients, CMV is a common opportunistic infection associated with serious complications such as graft failure and increased mortality[2,3]. In these cases, the infection may result from viral reactivation, graft transmission, or primary infection acquired after transplantation. CMV infection in transplant patients represents a significant clinical challenge, resulting in increased morbidity, prolonged hospitalizations, and increased use of hospital resources[4]. Furthermore, the virus can act as an immunomodulatory factor, favoring secondary infections and graft rejection, which further worsens the prognosis[5]. Given the complexity of the immune response in these patients, active viral surveillance and antiviral prophylaxis are frequently adopted strategies, although not consistently effective.

Standard treatment involves antivirals such as ganciclovir and foscarnet (FOS), but resistance or refractoriness (R/R) to treatment has become an increasing challenge[6]. Resistance refers to the presence of genetic mutations in the virus that reduce or nullify the effectiveness of antivirals, even when administered appropriately. Refractoriness, on the other hand, is characterized by the failure of clinical and/or virological response to treatment despite the absence of known resistance mutations. It may be related to host factors such as severe immunosuppression or inadequate pharmacokinetics. Mutations in viral genes such as UL97 and UL54 are associated with resistance to these therapies, limiting therapeutic options and increasing the risk of adverse outcomes[7]. Furthermore, significant side effects such as nephrotoxicity and myelosuppression contribute to early discontinuation of treatment or the need for dose adjustments.

Maribavir (MBV), a UL97 kinase inhibitor, emerges as a promising alternative, with efficacy against resistant strains and a better safety profile[8]. Its mechanism of action differs from traditional antivirals, allowing it to be used even in cases of cross-resistance. Recent studies show that MBV is generally well tolerated, with milder adverse events and rarely associated with hematologic or renal toxicity[9].

Therefore, this scoping review aims to map the available evidence on the efficacy and safety of MBV in transplant patients with R/R CMV infection. Outcomes such as mortality, graft failure, adverse events, toxicity, response to treatment, and viral resistance will be analyzed.

METHODS

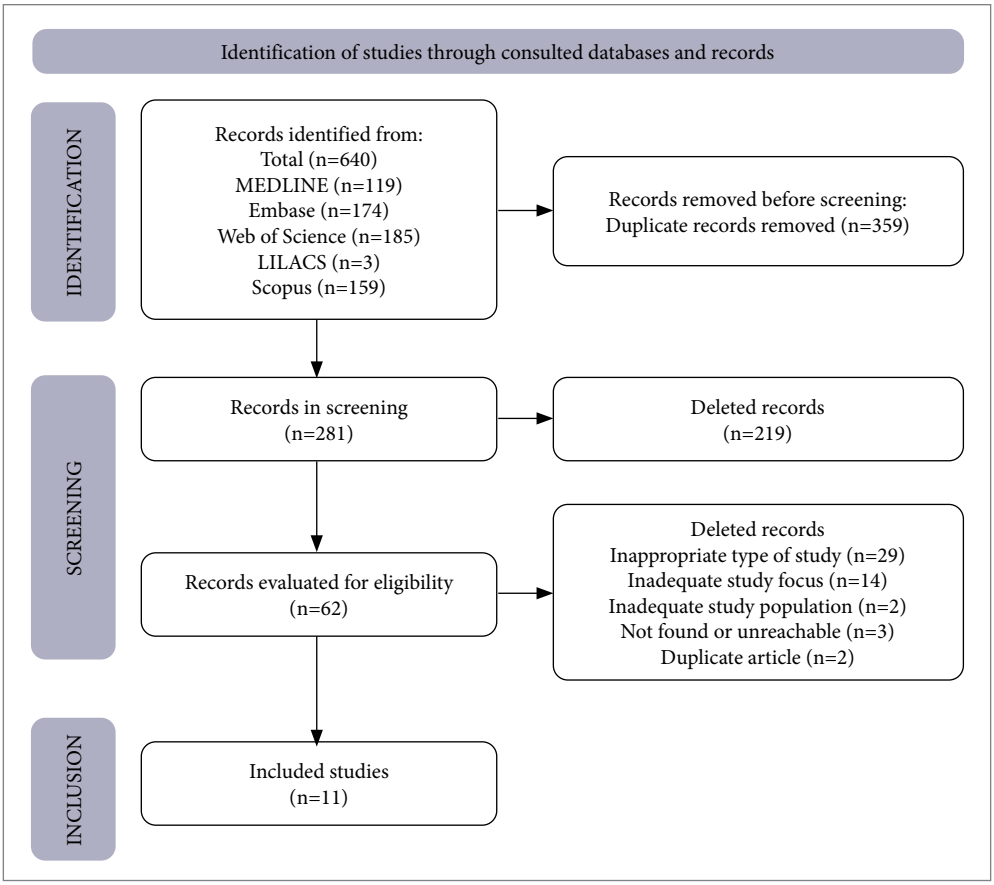
This is a scoping review carried out according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) checklist[10]. To construct the research problem, the acronym PCC (Population, Concept, and Context) was used, as recommended by the Joanna Briggs Institute, to identify the main elements that guide this scoping review[11]. In this context, P was assigned to transplant patients with refractory CMV infection, with or without antiviral resistance; C was assigned to evaluation of the efficacy and safety of MBV use in treatment; and C was assigned to post-transplant CMV infection, excluding prophylactic use and first-line treatment. Thus, the research question was formulated: "What is the available evidence on the efficacy and safety of MBV use in the treatment of refractory cytomegalovirus infections, with or without resistance, in transplant patients?"

The review included articles that evaluated the efficacy and safety of MBV in transplant patients, whether solid organ or hematopoietic stem cell recipients, with refractory CMV infection, with or without resistance. Eligible articles were published from January 2015 to April 2025, written in any language, and reviewed independently by two reviewers, with a third person responsible for resolving any conflicts. Randomized clinical trials (phase 2 or 3), cross-sectional studies, case-control studies, as well as retrospective and prospective cohorts. Those addressing the use of MBV in immunocompromised non-transplant patients, as well as its use in first-line or prophylactic treatment settings, were excluded. Clinical case series, case reports, opinion pieces, narrative reviews, systematic reviews, and other scoping reviews that did not fit the theoretical framework of this study were also disregarded. The search for relevant studies was carried out in April 2025 in the following databases: MEDLINE (via PubMed), Embase, Web of Science, LILACS, and Scopus.

The study team developed the search strategy, and no other complementary search methods were used. The same team subsequently analyzed all studies found. The search strategy used in the PubMed search engine and adapted for each of the databases mentioned above was ("Maribavir" OR "livtencity" OR "Benzimidazole riboside" OR "1263W94" OR "GW1263" OR

"GW257406X") AND ("Cytomegalovirus" OR "CMV" OR "HCMV" OR "human herpesvirus 5" OR "Herpesvirus type 5" OR "HHV-5" OR "HHV5") AND ("Resistance" OR "Resistant" OR "refractory" OR "failure" OR "unresponsive" OR "persistence" OR "persistent " OR "recurrence" OR "Recurrent" OR "escape") AND ("transplant" OR "Transplantation" OR "transplanted" OR "Graft" OR "grafting" OR "recipient" OR "recipients" OR "SOT").

The selection of evidence sources was conducted with the help of the Rayyan platform (Qatar Computing Research Institute)12. Initially, 640 articles were found, from which duplicates were removed, resulting in 281 unique studies. These were divided and analyzed by two reviewers in a double-blind manner, considering the title and abstract. A third supervisor resolved eligibility conflicts. As a result, 62 articles were selected for full reading, of which 11 fully met the inclusion criteria and were incorporated into the review, as demonstrated in the PRISMA study screening diagram (Fig. 1).



Source: Elaborated by the authors.

Figure 1. PRISMA diagram of study screening.

For data extraction, a table was developed with the following categories: author and year, study design, sample, objective, methodology, results, and outcome. The 62 pre-selected articles were reanalyzed and discussed by the team until the final 11 studies were selected. The following data were extracted from the studies: identification data (author's name and year of publication), methodological characteristics (study type, design, and clinical phase, when applicable), and sample information (transplant type, total number of participants, and relevant clinical characteristics). Information on the MBV dose used, treatment duration, clinical indication (refractory or resistant infection, or prophylactic use), presence of concomitant therapies, and other methodological aspects was also recorded. The primary outcomes evaluated were virological response rate, time to viral load conversion, occurrence of relapse, treatment failure, mortality, adverse events, side effects, treatment discontinuation rates, and information on antiviral resistance. When the data were not clearly described in the articles, inferences were made according to the context, duly recorded during extraction.

Finally, the selected articles were organized into a descriptive table that included the respective authors, study design, sample, and a summary of the objective, methodology, results, and outcomes. A total of 11 studies were included. Two arms of the same phase 3 randomized clinical trial were identified and analyzed separately for their samples and results to avoid redundancy in data interpretation. The primary data summarized included mortality, viremia clearance, adverse effects, and recurrence, with an

emphasis on the efficacy of MBV compared to conventional therapies. The tabular presentation of the evidence allowed mapping and comparing the efficacy and safety of MBV considering different samples and methodologies.

RESULTS

Eleven sources of evidence were used to compile the final sample for this scoping review, predominantly published in the United States of America (USA) from 2019 to 2025, with a greater number in the last 2 years. Regarding the type of study, a predominance of phase 3 randomized clinical trials (n = 5) was identified[8,13-16], followed by retrospective cohort studies (n = 5)[3,17-20] and a phase 2, double-blind, randomized clinical trial[21], with evaluation of different MBV dosages. Phase 3 clinical trials were mainly open-label and multicenter[8,13-15], also including specific subanalyses, such as the SOLSTICE study[13], that analyzed patients with refractory CMV infection with or without resistance after solid organ transplantation (SOT). Retrospective cohort studies included both single-center observational analyses[17,19,20] as well as clinical experiences, aimed at evaluating outcomes such as therapeutic efficacy, viral resolution, adverse events, and antiviral resistance.

These analyses examined groups previously exposed to MBV, comparing clinical outcomes with or without alternative therapy. The study populations in all sources consisted of transplant patients (whether solid organ or hematopoietic stem cell transplant) who developed R/R CMV infection, with or without genotypic resistance to standard therapies. The variability of methodological designs contributed to a broad mapping of the available evidence, providing insights into the practical and experimental application of MBV in different clinical settings.

The main methodological characteristics of the included studies are presented briefly in Table 1, allowing a structured view of the study designs, clinical contexts, interventions, and outcomes evaluated.

Table 1. Summary of included studies.

Author	Study design	Sample	Objective	Methodology	Results	Outcome
Bassel et al.[3]	Retrospective cohort study	One hundred nine transplant recipients (68 SOT and 41 HSCT) with refractory CMV infection, with or without resistance, were randomized to the MBV arm in the SOLSTICE phase 3 clinical trial.	To evaluate mortality and graft status in transplant patients with refractory or resistant CMV infection after MBV treatment.	Retrospective review of medical records of patients enrolled in the MBV arm of the SOLSTICE clinical trial, followed for 52 weeks (20 weeks of study + 32 weeks of review).	Overall mortality of 15.6% at 52 weeks. Overall survival of 0.84. In SOT: 0.96 (4.4% deaths); in HSCT: 0.65 (34.1% deaths). There was no new graft loss or retransplantation.	The mortality rate observed with the use of MBV was lower than that previously described with conventional therapies, indicating a possible clinical advantage of MBV in this population.
Papanicolaou et al.[21]	Randomized, double-blind, phase 2 clinical trial	120 transplant patients (HSCT or SOT) ≥ 12 years of age with refractory or resistant CMV infection and plasma CMV DNA ≥ 1,000 copies/mL	To evaluate the efficacy and safety of different doses of MBV in transplant patients with R/R CMV infection.	Patients were randomized (1:1:1) to receive MBV 400 mg, 800 mg, or 1,200 mg twice daily for up to 24 weeks. Adverse events were also assessed.	Eighty patients (67%) achieved undetectable CMV DNA within 6 weeks (70% for 400 mg, 63% for 800 mg, 68% for 1,200 mg); 25 patients experienced recurrent infection; 13 developed resistance to MBV; 34% discontinued treatment due to adverse effects, 17 due to CMV infection. Dysgeusia was the most common adverse event (65%). Mortality during the study was 27%, with four deaths related to CMV.	MBV ≥ 400 mg twice daily demonstrated activity against R/R CMV infections in transplant patients, with no new safety concerns.
Ni et al.[17]	Single-center, retrospective cohort study	Thirteen solid organ transplant recipients (lung, heart, liver, kidney, and multiorgan) with 15 episodes of R/R CMV infection treated with MBV from June 2020 to October 2022 at Duke University Hospital. The median age was 57 years at the start of treatment.	To evaluate the real-world experience of using MBV to treat R/R CMV infection in SOT recipients.	Retrospective collection of clinical data, including transplant history, immunosuppression, MBV treatment details, viral resistance, viral load, renal function, and clinical outcomes. Viral success was defined as sustained viral clearance and failure as non-clearance or relapse. Descriptive analysis.	40% (6/15) of episodes achieved sustained viral clearance; 47% (7/15) presented treatment failure due to emerging resistance or early viral relapse; 33% of successful cases had relapse; dysgeusia in 85% of patients, without interruptions due to adverse effects; renal function remained stable; higher initial viral load associated with failure/relapse.	MBV had a virological response in 40% of episodes in high-risk patients, but with a high rate of failure and relapse (47%), indicating the need for careful monitoring and optimization of clinical use for this population.

Continue...

Table 1. Continuation...

Author	Study design	Sample	Objective	Methodology	Results	Outcome
Beechar et al.[18]	Retrospective observational cohort study	10 kidney transplant recipients treated with MBV for R/R CMV DNAemia/ disease from 2021 to 2023.	To describe the real-world experience with MBV for R/R CMV after kidney transplantation.	Review of medical records, viral load analysis, treatment regimens, resistance testing and immunosuppression.	5/10 (50%) achieved durable virological suppression; 2/5 (40%) had recurrence of low-level DNAemia; 2/3 (66.7%) of patients without virological suppression had resistance-associated mutations.	MBV was effective for many patients, especially with mycophenolate reduction; resistance and recurrence were detected in some cases, recommending constant surveillance.
Ogawa et al.[19]	Single-center retrospective cohort study	54 episodes of CMV infection (27 in the MBV group and 27 in the FOS group), adult transplant patients (solid organs and hematopoietic cells).	To compare the efficacy and safety of MBV compared to FOS in the treatment of R/R CMV infection in transplant recipients.	A review of electronic medical records of patients treated with MBV or FOS from 2019 to 2024 was performed. Patients under 18 years of age, those with therapy lasting less than 72 hours, and cases of off-label use were excluded. The analysis included demographic data, immunosuppressive profile, viral response, toxicity, and genetic resistance.	Infection resolution rate: 74% (MBV) vs. 66.7% (FOS); median time to clearance: 23 days (MBV) vs. 16 days (FOS); resistance to MBV in 18.5% vs. FOS in 11.1%; adverse effects: dysgeusia (25.9%) with MBV, nausea, headache, genital ulcers and mainly electrolyte disturbances and renal dysfunction (85.2%) with FOS ($p < 0.001$); mortality: 22.2% in the MBV group and 29.6% in the FOS group (no significant difference). In both groups, CMV was a contributing factor in some deaths.	MBV was effective and well tolerated in the treatment of CMV infection, with a success rate similar to that of FOS, but with fewer adverse effects and no nephrotoxicity or electrolyte disturbances. The risk of resistance and virological failure was comparable between groups, as was mortality. With a better safety and tolerability profile, MBV emerges as an attractive alternative, especially for patients with intolerance or risk factors for conventional therapies.
Avery et al.[8]	Randomized, open-label, phase 3, multicenter clinical trial	352 transplant patients (235 MBV; 117), aged ≥ 12 years. Overall, 256 patients (73%) completed the study [MBV, 199 (84.7%); Investigational Treatment, 58 (49.6%)], and 22 patients received MBV as salvage therapy.	To compare the efficacy and safety of MBV vs. Investigational Treatment for the treatment of refractory CMV infection in patients receiving solid organs and hematopoietic cells.	Open-label, multicenter study with patients randomized 2:1 to MBV 400 mg twice daily or investigator-assigned therapy (Investigational Treatment: VGCV/ ganciclovir, FOS, or cidofovir) for 8 weeks, with 12 weeks of follow-up.	The rate of patients achieving confirmed clearance of CMV viremia at week 8 was higher in the MBV group (55.7%, 131/235) compared to the Investigational Treatment group (22.9%, 28/117). 18.7% of patients for MBV achieved clearance and symptom control by week 16, while 10.3% of Investigational Treatment achieved this endpoint. There was greater clearance of viremia in patients with baseline genotypic resistance to MBV compared to Investigational Treatment [MBV (62.8%) vs. Investigational Treatment (20.3%)]. In patients with refractory (non-resistant) viremia, MBV was superior to Investigational Treatment (43.8% vs. 32.4%). The rate of at least one adverse effect was 97.4% for MBV and 91.4% for Investigational Treatment. Fewer patients discontinued treatments due to the adverse impacts in the MBV group (13.2%) compared to TDP (31.9%). Mortality: MBV 11.5% vs. IAT 11.1%.	MBV was superior to TDI (ganciclovir, VGCV, FOS, or cidofovir) for eliminating CMV viremia at week 8. The treatment discontinuation rate was lower in the MBV group than in the TDI group. The MBV group had a lower frequency of neutropenia and leukopenia compared with VGCV/ ganciclovir (9.4% vs. 33.9%) and lower hypocalcemia and acute kidney injury compared with FOS (acute kidney injury: 8.5% vs. 21.3%). Dysgeusia was the most commonly reported adverse effect in the MBV group (37.2%), and nausea, vomiting, and diarrhea were similar between groups.
Daher et al.[20]	Retrospective observational, single-center study	Thirteen patients [11 hematopoietic stem cell transplant (HSCT) recipients and two with hematologic malignancies] were treated with MBV.	To describe the initial clinical experience with MBV in patients with refractory or resistant CMV infection after HSCT or with hematologic malignancy.	Retrospective chart review of patients treated with MBV from November 2021 to December 2022. Clinical characteristics and outcomes of CMV infection were collected.	69% of patients had resolution of CMV infection—one case of emerging resistance to MBV (*UL97 C480F* mutation). Dysgeusia occurred in six patients, without requiring treatment discontinuation.	MBV is effective and safe in the real world for the treatment of R/R CMV in HSCT recipients and patients with hematologic malignancies, despite challenges such as resistance and high viral load.

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Table 1. Continuation...

Author	Study design	Sample	Objective	Methodology	Results	Outcome
Blumberg et al.[13]	Phase 3, randomized, open-label, multicenter study	Subgroup of 232 SOT recipients with refractory CMV infection, drawn from the total SOLSTICE study population (which also included hematopoietic cell transplant recipients).	To evaluate the efficacy and safety of MBV compared to IAT in SOT recipients with refractory CMV infection, with or without genotypic resistance.	Patients were randomized (2:1) to MBV 400 mg twice daily or IAT for 8 weeks, with 12 weeks of follow-up. Primary outcome: confirmed clearance of CMV viremia by week 8. Assessment of adverse events, graft rejection, changes in immunosuppression, and emerging treatment resistance.	Higher viremia clearance rate at week 8 with MBV (55.6% vs. 26.1%). Beneficial in all types of SOT, with significant benefits for the kidneys and lungs. Shorter median time to negative test with MBV (25 vs. 30 days). Lower incidence of neutropenia (0% vs. 14.5%) and acute kidney injury (2.8% vs. 13%). Dysgeusia is more common with MBV (43.7%). Emerging resistance in 28% of those treated with MBV.	MBV demonstrated superior efficacy to IAT and a better safety profile, notably with lower hematologic and renal toxicity. It has proven to be a promising alternative for the treatment of R/R CMV in transplant recipients, especially kidney and lung transplant recipients.
Chou et al.[14]	Randomized, phase 3, open-label, multicenter clinical trial	350 recipients of TOS or hematopoietic cells with CMV infection resistant or refractory to treatment with standard therapy. MBV 234 and IAT 116.	To evaluate the use of MBV and possible resistance to this drug compared with IAT in patients receiving SOT or hematopoietic cells with resistant or refractory CMV infection.	Baseline and post-treatment plasma samples were tested for resistance-conferring mutations in the viral genes *UL97, UL54*, and *UL27* for 8 weeks, and 350 patients who received at least one dose of MBV (234) or IAT (116) were considered. Among those who received IAT, the investigator-assigned drug was FOS (n = 47), ganciclovir (n = 28), VGCV (n = 28), FOS combined with ganciclovir or VGCV (n = 7), or cidofovir (n = 6).	At baseline, genotypic testing revealed resistance to ganciclovir, FOS, or cidofovir in 56% of patients receiving MBV and 68% receiving IAT. Of these, 63% (MBV) and 21% (IAT) responded to treatment. The MBV resistance mutations detected at baseline were *UL27 L193F* (n = 1) and *UL97 F342Y* (n = 3). After treatment, emergent MBV resistance mutations were detected in 60 (26%) patients randomized to MBV. The most common MBV resistance mutations were *UL97 T409M* (n = 34), *H411Y* (n = 26), and *C480F* (n = 21), first detected 26 to 130 days (median 56) after starting MBV treatment.	Baseline resistance to MBV was rare. Resistance to standard CMV antivirals did not impede response to MBV treatment. Nevertheless, the rebound in plasma CMV DNA during MBV treatment strongly suggests the emergence of drug resistance.
Papanicolaou et al.[15]	Phase 3, double-blind, randomized, multicenter study	Patients with asymptomatic first infection after hematopoietic cell transplantation were divided into two groups: 273 treated with MBV and 274 with VGCV.	To test whether MBV is more effective than VGCV for post-HCT CMV infections, especially in cases of neutropenia.	Patients were stratified and randomized 1:1. Two hundred seventy-three patients initially received 400 mg of MBV twice daily, and 274 received a dose adjusted for renal clearance over the same 8-week period, with 12 weeks of follow-up.	Of the randomized patients, 215 (77.9%) and 217 (78.3%) who received MBV and VGCV, respectively, completed the study. The median time on study was 141 days in each treatment arm (range: MBV, 1-307 days; VGCV, 1-351 days). Adverse events were the most frequent reason for early treatment discontinuation.	Although the non-inferiority of MBV compared to VGCV did not occur as a primary outcome, according to the pre-established non-inferiority margin, MBV demonstrated comparable elimination of CMV viremia during post-treatment follow-up, with fewer interruptions due to neutropenia.
Chou et al.[16]	Phase 3 randomized clinical trial	547 patients with early CMV infection after hematopoietic cell transplantation, treated with MBV (n = 273) or VGCV (n = 274) for ≥ 21 days.	To compare the emergence of resistance mutations to MBV and ganciclovir in patients with CMV infection after transplantation undergoing treatment with one of the two antivirals.	Genotyping by Sanger sequencing of the *CMV UL27, UL54* and *UL97* genes; phenotyping by genetic recombination to assess drug susceptibility; analysis of virological response and emergence of mutations in patients with detectable post-treatment viremia.	Emergent resistance to MBV was observed in 10% of patients (n = 24), while to ganciclovir it occurred in 2.5% (n = 6); the *UL97 G343A* mutation conferred significant cross-resistance; 74% of patients with MBV resistance responded to alternative therapy.	MBV has demonstrated a higher rate and rapidity of resistance emergence compared to VGCV, but mutations generally do not confer cross-resistance with ganciclovir, allowing subsequent effective treatment; early genotyping is essential to guide appropriate therapeutic switching.

Source: Elaborated by the authors. All papers were published in the USA.

The efficacy of MBV in the treatment of R/R CMV with or without recurrence had an average of 68% within 6 weeks[21]. In a comparative study with FOS, MBV obtained the highest infection resolution rate, with 7.3 percentage points above[19]. The rate of patients who achieved elimination of CMV viremia at week 8 was higher in the MBV group (55.7 to 63%) compared to the Investigational Treatment group (21 to 26.1%)[8,13,14]. The percentage of recurrent infections, that is, cases with an initially favorable response to treatment that evolved with viral recurrence, varied from 20.8% to 40%[17,18,21]. An association between a higher initial viral load and recurrence of infection was observed[17].

Regarding graft status during MBV treatment, good clinical and functional conditions were observed, with no cases of chronic loss during the study period, indicating a positive outcome regarding the viability and maintenance of the transplanted tissue. However, acute rejection occurred in some recipients in both groups [MBV 6.3% vs. investigator-assigned treatment (IAT) 5.8%][13]. The mortality rate of transplant recipients treated with MBV ranged from 11.5% to 27%. Total mortality was 15.6% in solid organ transplants (4.4%) and 34.1% in hematopoietic cell transplants[3], in addition to an overall rate of 27% during the study[21]. The mortality rate of MBV compared to FOS was 22.2% and 29.6%, respectively[19]. However, a slightly higher mortality rate was also observed for MBV (11.5%) compared to Investigational Treatment (11.1%)[8].

Most studies highlighted the presence of adverse effects associated with MBV, among which dysgeusia was predominant and varied between 25.9%, 46.1%, 65% and 85% of patients[17,19-21]. Acute kidney injury was presented with less predominance and with a percentage rate equivalent to 2.8%[13]. The occurrence of neutropenia among the adverse effects of MBV was equivalent to 0%[13], and the rate of occurrence of at least one adverse effect of MBV was 97.4%[8]. Treatment discontinuation due to adverse effects varied across studies. Adverse events were found to be the leading cause of treatment discontinuation[15], with a rate of 34% of patients[21]. There was also no need to interrupt treatment in the face of adverse effects on MBV[17,20]. Furthermore, there was a lower rate of treatment discontinuation with MBV (13.2%) compared to Investigational Treatment (31.9%)[8].

Studies have compared treatment with MBV versus FOS, and success rates were similar[19]. The infection resolution rate was slightly higher with MBV (MBV 74% vs. FOS 66.7%), although viral clearance time was shorter with FOS (FOS 16 days vs. MBV 23 days)[19]. However, resistance development was higher in the MBV group (18.5%) compared to the FOS group (11.1%)[19]. Mortality was lower among patients treated with MBV (22.2%) compared to those who received FOS (29.6%)[19]. Regarding adverse effects, the MBV group had a better safety profile, with only 25.9% of patients experiencing adverse events, compared to 85.2% in the FOS group[19]. Lower hypocalcemia was also observed in patients treated with MBV and a lower incidence of acute kidney injury; 8.5% of the sample treated with MBV presented this adverse effect, compared to 21.3% for those treated with FOS[8].

Studies have investigated the efficacy and safety of MBV compared to Investigational Treatment. MBV demonstrated greater efficacy in eliminating viremia in the 8th week of the trial.[8,13]. Furthermore, it presented a favorable safety profile, with a low incidence of acute kidney injury (MBV 2.8% to 8.5% vs. Investigational Treatment 13% to 21.3%) and neutropenia/leukopenia (MBV 0% to 9.4% vs. Investigational Treatment 14% to 33.9%), although there was a high occurrence of dysgeusia (37.2% to 43.7%)[8,13]. Although the incidence of adverse effects was slightly higher with the use of MBV (97.4% vs. Investigational Treatment 91.4%), these events were primarily minor, resulting in fewer treatment discontinuations for this reason[8]. Some gastrointestinal adverse effects, such as nausea, vomiting, and diarrhea, occurred similarly in both groups[8].

MBV was compared to valganciclovir (VGCV) in terms of adverse effects and resistance rate, and showed a lower incidence of neutropenia compared to VGCV, with a rate of 9.4% of the sample for patients treated with MBV and 33.9% for VGCV/ganciclovir[8]. However, it was also reported that MBV did not meet the non-inferiority criterion for the primary outcome[15]. Regarding the emergence of resistance, a higher resistance rate was observed in the MBV group (10%) compared to VGCV (2.5%)[16]. Furthermore, adverse events were the main reason for early discontinuation in both groups. Despite this, MBV demonstrated a more favorable safety profile, with less hematologic toxicity.

Different doses of MBV showed different efficacies, among which the dose of 400 mg twice daily demonstrated superiority, with 70% of patients in this group presenting undetectable CMV DNA within 6 weeks, compared to the doses of 800 mg (63%) and 1,200 mg (68%)[21]. The median time required for CMV DNA to become negative with the use of MBV compared to traditional therapies was 23 and 25 days for MBV, compared to 16 and 30 days for the other medications, respectively[13,19]. The development of resistance to MBV has been observed in several studies, which have highlighted genetic mutations in the UL97 gene, with emphasis on the C480F, T40M and H411Y variants[14,20]. The frequency of resistance to MBV varied between studies, with resistance mutation rates of 18,5%[19], 10%[16] and 26%[14]. Two-thirds (66.7%) of patients without virological response had mutations associated with resistance[18]. Treatment failure or early relapse was reported in 47% of episodes, often linked to viral resistance[17]. Finally, emerging resistance was identified in 10.8% to 28% of the sample during treatment[13,21], which reinforces the need for continuous genotypic monitoring and therapeutic adjustments in the face of the possibility of antiviral resistance.

Mutations associated with MBV resistance have been reported in various studies. With minimal cross-resistance with first-line anti-CMV agents, MBV has a unique mechanism of action unless specific mutations occur in UL97, such as C480F and F342, which result in resistance to both MBV and ganciclovir. Two patients have been reported with resistant CMV infections before initiation

of MBV treatment: one with the CMV UL97 H520Q mutation, which indicates resistance to ganciclovir but not to MBV, and the other with the UL56 C325Y mutation, which determines resistance to letermovir. Furthermore, two of the five patients undergoing resistance testing showed detectable mutations in UL97. On day 64 of MBV treatment, one of these patients developed a C480F mutation, demonstrating high-grade resistance to MBV and low-grade resistance to ganciclovir. This patient had received ganciclovir twice during the 6 months of MBV treatment; however, his MBV resistance test was negative before treatment began. The other patient, on day 3 of MBV treatment, developed a UL97 polymorphism of uncertain significance; nevertheless, he continued MBV treatment and experienced elimination due to CMV viremia[20].

DISCUSSION

This scoping review synthesized the available evidence on the use of MBV in the treatment of R/R CMV infections in transplant patients. The included studies generally demonstrated that MBV has significant antiviral activity against R/R CMV, a favorable safety profile, and the potential to replace conventional therapies associated with high toxicity, especially nephrotoxicity and myelotoxicity. The randomized phase 3 clinical trials[8,13-15] demonstrated superiority of MBV over conventional antiviral treatments, such as ganciclovir, VGCV, FOS, and cidofovir, in controlling CMV viremia in patients with refractory infection.

The confirmed viral clearance rate was significantly higher in the MBV-treated groups, especially among those with baseline genotypic resistance mutations, reinforcing its efficacy against viruses resistant to standard antivirals. The safety profile of MBV was consistently more favorable, notably with a lower incidence of neutropenia, acute kidney injury, and electrolyte disturbances compared to standard therapies[8,13,19]. Dysgeusia was the most frequently reported adverse event, but it rarely resulted in treatment discontinuation. In contrast, observational and real-world studies[17,18,20] pointed to relatively high rates of therapeutic failure, early relapse, and emergence of resistance, particularly in patients with a high initial viral load or extensive prior exposure to antivirals.

These findings highlight the importance of virological monitoring and genotyping to guide early interventions, such as immunosuppression adjustments or therapy changes. The emergence of specific mutations in the UL97, UL27, and UL54 genes during MBV use has been described, with particular emphasis on mutations such as UL97 T409M, H411Y, and C480F, which are frequently associated with virological failure[14,16]. Given this scenario, clinical management should be based on strategies that combine early diagnosis and rapid therapeutic adjustments. Genotyping of the UL97 and UL54 genes is essential to confirm the resistance profile and guide treatment changes, as these mutations confer loss of response to MBV. Furthermore, the recommendation is to replace MBV with alternative antivirals, such as FOS or, in specific situations, cidofovir, although the latter presents greater limitations due to the risk of nephrotoxicity. It is important to emphasize that the combination with ganciclovir or VGCV should be avoided due to the pharmacodynamic antagonism between these agents[8,21]. Additionally, controlled reduction of immunosuppression, therapies with specific T lymphocytes, and the use of letermovir as secondary prophylaxis to prevent relapses are recommended.

Some articles suggest that most of these mutations do not confer significant cross-resistance with ganciclovir, allowing, in some cases, therapeutic rescue with conventional antivirals[14,16], while another states that there may be cross-resistance to ganciclovir and VGCV, with a higher prevalence in the UL97 gene and a lower prevalence in the UL54 gene[21]. Patient subgroups, such as kidney and lung transplant recipients, demonstrated more pronounced clinical benefit[13], while evidence on use in patients with hematologic malignancies remains limited[20]. Furthermore, the use of MBV in asymptomatic infection after hematopoietic cell transplantation was evaluated, with results indicating a lower rate of discontinuation due to neutropenia, although without evidence of superiority in relation to VGCV[15]. Data on the impact of MBV on long-term clinical outcomes, such as graft rejection, quality of life, and overall survival, are still scarce. Although lower mortality associated with the drug has been reported, the data come from retrospective analyses, which require caution in interpreting the results[3].

Despite the relevant findings, this review has some limitations that are worth highlighting. The primary concern is the heterogeneity of the included studies, which range from randomized clinical trials to retrospective and observational studies, hindering direct comparisons and compromising the accuracy of the analysis of results. Furthermore, despite the importance of aspects such as long-term quality of life, particularly related to overall survival, graft rejection, and treatment costs, this information was not documented in the analyzed articles, as they were limited to outcomes occurring only during the study period.

Therefore, it is essential that new studies be developed or these patients reanalyzed to support the use of this drug further. Another weakness was the lack of critical analysis of potential conflicts of interest in the reviewed primary studies.

CONCLUSION

This scoping review sought to map the available evidence on the efficacy and safety of MBV in the treatment of R/R CMV infections in transplant patients. The 11 included studies, predominantly randomized clinical trials and retrospective cohort studies, indicate that MBV is an effective therapeutic option, with virological response rates ranging from 21% to 90% (mean of 63%). In direct comparisons, MBV demonstrated superiority over FOS and investigator-designated therapies in viremia elimination and safety.

In terms of safety, MBV presented a more favorable profile, with a lower incidence of serious adverse events, such as acute kidney injury and neutropenia, compared to traditional antivirals. Although dysgeusia was a common adverse effect, the events were predominantly minor, resulting in lower treatment discontinuation rates. The mortality rate among patients treated with MBV ranged from 11.5% to 27%, influenced by the type of transplant and comparators. However, the review also highlighted significant challenges, such as the development of resistance to MBV, mainly associated with mutations in the UL97 gene, and the occurrence of recurrent infections. These findings reinforce the need for continued genotypic surveillance and strategies to manage relapse.

In summary, MBV represents a significant advance in the management of R/R CMV infections in transplant patients, offering a more effective and tolerable option compared to existing therapies. However, future studies are needed to monitor resistance and manage relapses.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

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DATA AVAILABILITY STATEMENT

Data will be available upon request.

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