R E V I E W

# Valganciclovir in the treatment of cytomegalovirus retinitis in HIV-infected patients

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**Abstract:** Oral valganciclovir is a new and highly efficacious alternative to the chronic administration of ganciclovir in the treatment of cytomegalovirus (CMV) retinitis in HIV-infected patients. In addition to its excellent bioavailability and favorable pharmacokinetic profile, valganciclovir has also proved cost effective and is the most widely used drug in the armamentarium for the treatment of CMV retinitis. Valganciclovir is a prodrug of ganciclovir, the erstwhile commonly used therapy. In March 2001, the US Food and Drug Administration approved valganciclovir for the induction and maintenance treatment of CMV disease, including CMV retinitis. Valganciclvoir has compared favorably with both oral and intravenous treatments for induction and maintenance therapy with ganciclovir. The reduced pill burden and the ease of oral administration has helped avoid the risks associated with intravenous therapy. The most serious adverse event is neutropenia, which makes the patient susceptible to infections. In the current review, we have compiled all the available evidence-based information on valganciclovir.

**Keywords:** CMV retinitis, ganciclovir, valganciclovir

## Introduction

Cytomegalovirus (CMV) retinitis is the leading cause of visual impairment in patients with human immunodeficiency virus (HIV), and typically occurs in HIV-positive individuals with CD4 count below 50 cells/mm$^3$.[1–3] Historically, the most utilized antiviral agent has been ganciclovir, which was initially licensed as an intravenous agent. In an attempt to make an oral preparation with convenient dosing that has the safety profile, efficacy and bioavailability comparable to ganciclovir, the prodrug was developed.[4,5] Valganciclovir, the valine ester of ganciclovir, was the first systemic agent found to be as effective as intravenous ganciclovir, and is the oral prodrug of the popular anti-CMV drug ganciclovir. Valganciclovir has answered the great need of patients with CMV retinitis for an injection free medication in the induction and maintenance phases of therapy.[5,6] In this review we highlight the pharmacokinetics and pharmacodynamics of valganciclovir and address the issues of clinical trials and related studies. We also discuss valganciclovir drug interactions, drug economics and efficacy as a substitute to intravenous ganciclovir.

With the advent of highly active anti-retroviral therapy (HAART), the prevalence of CMV retinitis has drastically decreased by 75%–90% from a pre-HAART era prevalence of 30% or more in people with advanced AIDS.[7] Of the patients having access to HAART, the prevalence is now less than 5%.[8] Nevertheless, CMV retinitis still remains the chief vision threatening infection in HIV infected patients.[9] Untreated retinitis typically progresses and can lead to the development of atrophic retinal holes and subsequent retinal detachment. Approximately 15% of patients develop retinal

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detachment even before the treatment is initiated.[10,11] Thus CMV retinitis is thought to profoundly affect ocular morbidity, and quality of life, unless timely treatment is instituted. Valganciclovir hydrochloride (Valcyte®; Hoffmann-La Roche Inc., Nutley, NJ, USA) is an US Food and Drug Administration (FDA)-approved antiviral medication for the treatment of CMV disease that has revolutionized the treatment of CMV retinitis. Studies WV 15376 and WV 15705 were the two pivotal studies that established the bioequivalence, efficacy, and safety of oral valganciclovir in comparison with oral and intravenous ganciclovir. These studies formed the basis for clinical use of oral valganciclovir and have played an important role in the drug development. In this review we have compiled all the information on valganciclovir available from PubMed and results from a Google search from December 1996 to June 2009. The information was also derived from clinical trials, case reports, abstracts and previous reviews. Additional references were obtained from the bibliographic data of published review articles. The valganciclovir package insert also provided useful information. The two pivotal studies are described in detail below.

## Pharmacokinetics

Valganciclovir hydrochloride is a hydrochloride salt of the L-valyl ester of ganciclovir. It is a prodrug of ganciclovir. Upon absorption, it is extensively and rapidly hydrolyzed into the active forms of ganciclovir, which is a mixture of two diastereomers, by hepatic and gut esterases. Hence the pharmacokinetics of oral valganciclovir is essentially the same as that of intravenous ganciclovir.[12] Treatment with valganciclovir/ganciclovir typically stabilizes retinal lesions in two to four weeks, and frequently there is a complete response in one month. Ganciclovir (intravenous) treatment of CMV retinitis is associated with clearing of CMV viremia and CMV DNA from the buffy coat of the infected blood in 7–8 days.[13]

Protein binding of valganciclovir has not been established due to rapid and extensive conversion of oral valganciclovir to ganciclovir. Kidneys excrete valganciclovir as ganciclovir, both by glomerular filtration and active tubular secretion. Hence the plasma level of ganciclovir and thus terminal half-life is increased in patients with renal impairment.[14] Pharmacokinetic parameters are described in Table 1.

## Bioavailability

Oral valganciclovir at the standard dose of 900 mg once a day produces a daily systemic exposure which is 1.7-fold greater than that attained with oral ganciclovir at the standard dose of 1000 mg three times daily. In addition, the area under

**Table 1** Pharmacokinetics of valganciclovir[22]

| Feature | Valganciclovir | Intravenous ganciclovir | Ganciclovir capsules |
|---|---|---|---|
| Dosage | 900 mg qd with food | 5 mg/kg once daily | 1000 mg tid with food |
| Plasma half-life (hours) | 4.08 | 2.9 | 4.4[20] |
| $AUC_{24}$ µg.h/mL | 29.1 ± 9.7 | 26.5 ± 5.9 | 12–19.2 |
| Oral Bioavailability (%) | 60[4] | Not applicable | 6[24] |

**Abbreviations:** qd, once a day; tid, three times daily; AUC, area under curve.

curve at 24 hours/drug exposure (AUC24) of valganciclovir increased from 24% to 56% when compared from fed state to the fasting state.[6] As a result, valganciclovir has greater CMV-suppressing ability than ganciclovir.[15]

The absolute bioavailability of oral valganciclovir is approximately 60%,[16] which is 10 times higher than ganciclovir bioavailability after oral administration.[17] The peptide-mediated active transport of valganciclovir due to the presence of valine moiety explains its increased bioavailability.[17–19] A dose of 900 mg/day of valganciclovir produces a daily exposure equivalent to the 5 mg/day daily intravenous dose of ganciclovir.[6,17] Oral ganciclovir was developed as an initial attempt to provide a more convenient therapeutic regimen for ganciclovir (Cytovene®; Roche Laboratories), but was found to have low and variable bioavailability (6%–9%) compared to oral valganciclovir (60%). In clinical trials oral ganciclovir was found to be inferior to intravenous ganciclovir for the induction phase, as it reached a subtherapeutic serum level.[20,21] It was however approved by the FDA for maintenance phase therapy of CMV retinitis.

## Mechanism of action

Ganciclovir is the only metabolite of valganciclovir and it undergoes no further metabolism. Intracellular phosphorylation of ganciclovir forms ganciclovir triphosphate, which is the most active form. Ganciclovir triphosphate inhibits viral DNA synthesis by competing with deoxyguanosine. This prevents the incorporation of deoxyguanosine into elongating viral DNA, thus terminating DNA synthesis, chiefly of the group of herpes viruses. Ganciclovir monophosphate formed after the release of pyrophosphate is also incorporated into the growing viral DNA chain further slowing the process of replication.[22]

## Clinical trials

Based on the equivalent pharmacokinetic profile and AUC24 of oral valganciclovir compared to the conventional intravenous ganciclovir, Hoffmann-La Roche applied for FDA

approval in 1997.[12] The initial FDA application was not approved based on the pharmacokinetics alone. Roche was asked to complete another randomized controlled trial demonstrating the equivalence between the two drugs for the induction therapy of CMV retinitis.[5]

## Study WV 15376

Unlike a traditional head-to-head study, this pivotal trial, Study WV 15376,[5,22] was a noninferiority study designed to prove that oral valganciclovir was not 10% worse than intravenous ganciclovir. The study enrolled 160 patients with newly diagnosed CMV retinitis; 80 of them received induction therapy with intravenous ganciclovir 5 mg/kg for three weeks and the remaining 80 received induction therapy with oral valganciclovir 900 mg twice daily for three weeks. The patients were followed with the same therapy once daily for one week. All patients were then placed on maintenance treatment with oral valganciclovir 900 mg once daily. Retinal photographs were obtained at baseline visit and then week two and week four and evaluated by masked reviewers. Although most patients had zone-3 retinitis, 24% in each arm had zone-1 retinitis. The mean CD4 cell count at baseline was 54 cells/mm$^3$ in the intravenous ganciclovir arm, and 58 cells/mm$^3$ in the oral valganciclovir arm. The median HIV RNA at baseline was 4.9 log10 copies/mL in the intravenous ganciclovir arm, and 4.8 log10 copies/mL

in the oral valganciclovir arm. This registrational study is summarized in Table 2.

The primary efficacy end point of the study was the progression of retinitis during the first four weeks of the therapy. Analysis of the primary endpoint revealed that seven patients (10%) in each treatment arm had progression of retinitis after four weeks as determined by the masked reviewer. The secondary efficacy end point was the time to CMV retinitis progression. This was not significantly different between the two groups (219 days in the ganciclovir arm and 226 days in the valganciclovir arm). Of importance, the mean time to progression of CMV retinitis in this trial conducted during the HAART era was substantially longer than the times observed in studies before the introduction of HAART (approximately 70 days). No significant difference in serious adverse events between the two drugs was noted in the study except for the increased catheter related infectious complications in intravenous ganciclovir group.[23]

## Study WV 15705

Study WV 15705[24] enrolled 212 patients who received maintenance treatment with oral valganciclovir for CMV retinitis. Patients who were receiving intravenous ganciclovir for maintenance treatment of CMV retinitis were eligible for enrollment. The results of the study established the safety profile of oral valganciclovir in AIDS patients with

**Table 2** Summary of the valganciclovir registrational study WV 15376[22]

| | |
|---|---|
| Total number of patients enrolled and randomized to either arms | 160 |
| Number of patients completing the study | 146 |
| Induction therapy | Oral valganciclovir arm: 900 mg bid for three weeks followed by 900 mg once daily for one week. |
| | Intravenous ganciclovir arm: 5 mg/kg bid for three weeks followed by 5 mg/kg once daily for one week. |
| Maintenance therapy | All patients were given the maintenance therapy of valganciclovir of 900 mg once daily. |
| Primary endpoint of the study | Progression of CMV retinitis within four weeks of initiation of treatment determined as growth of lesion ≥750 μm or a new retinitis lesion measuring ≥750 μm in diameter. |
| Secondary endpoint of the study | Secondary outcome measures included the achievement of a satisfactory response to induction treatment during the first four weeks, as determined by analysis of retinal photographs. A satisfactory response was achieved when all of the following criteria were met: no movement of a lesion border by 1500 μm or more and no development of a new lesion 1500 μm or more in diameter between base line and week 4, no movement of a lesion border by 750 μm or more and no development of a new lesion 750 μm or more in diameter between week 2 and week 4, no increase in retinitis activity between week 2 and week 4, and a decrease in retinitis activity between base line and week 4 by at least two steps on the six-step activity scale. |
| Bioavailability of valganciclovir | 60%, about 10-fold higher than the oral ganciclovir. |
| Outcomes of the study | 10% of patients in each arm showed progression of retinitis after four weeks. 77% of patients in the intravenous ganciclovir arm and 72% of patients in the oral valganciclovir showed no progression. |
| Adverse events | Seven patients suffered retinal detachment during the first four weeks of the study.[5] Twenty percent of participants experienced grade 3–4 adverse events by week 4. |

**Abbreviation:** bid, twice a day.

CMV retinitis. Due to the low number of clinical events it was not possible to calculate the mean time to CMV retinitis progression. The mean treatment duration was 779 days. No significant difference in adverse reactions particularly hematological abnormalities were noted between the two treatment arms as seen in Table 3.[24]

More than 30% of patients had diarrhea, nausea, and fever.[4–6] More than 20% of patients experienced candidiasis, headache, dermatitis, neutropenia, anemia, insomnia, cough, vomiting and fatigue. 19% experienced progression of CMV retinitis during the study. Patients with CMV retinitis progression needed multiple cycles of induction and maintenance therapy. Of the 113 patients who entered the study with unilateral retinitis, 10 (8.8%) developed CMV retinitis in the previously unaffected eye. Adverse reactions are summarized in Table 3.

## Administration and dosage

Valganciclovir is available as 496.3 mg film-coated tablets of valganciclovir hydrochloride corresponding to 450 mg of valganciclovir. It is stored between 15–30 °C. Valganciclovir administration with food maximizes its bioavailability. Fatty foods significantly increase the bioavailability. The tablets are not to be broken or crushed because of its potential teratogenic and carcinogenic property in humans. Valganciclovir tablet is not a one-to-one substitute for ganciclovir capsules. As the bioavailability of oral valganciclovir is significantly higher than the ganciclovir capsules, patients turning from ganciclovir capsules to oral valganciclovir should be warned of possible over dosage if they take more than the prescribed valganciclovir.[22] The treatment regimen is summarized in Table 4.

Patients on oral valganciclovir therapy must undergo complete ophthalmic evaluations periodically. This serves as the basis to judge the recovery of retinitis with treatment. Complete blood count with total and differential counts, serum creatinine levels 2–3 times a week during the induction phase,

**Table 3** Adverse reactions (%) noted in study WV 15705[22]

| Adverse reaction | Valganciclovir | Intravenous ganciclovir |
|---|---|---|
| Diarrhea | 16 | 10 |
| Nausea | 8 | 14 |
| Anemia | 8 | 8 |
| Neutropenia (Neutrophil count <1000/mm³) | 11 | 13 |
| Headache | 9 | 5 |
| Cathether-related infections | 3 | 11 |

**Table 4** Treatment regimen

| Induction therapy | 900 mg (two 450 mg tablets) bid with food for 21 days. |
|---|---|
| Maintenance therapy | 900 mg (two 450 mg tablets) qd with food. |

**Abbreviations:** qd, once a day; bid, twice a day.

and once a week during maintenance therapy is recommended to identify any hematological adverse events.[22]

Treatment of CMV retinitis with oral valganciclovir is suppressive but not curative.[8] Valganciclovir profoundly suppresses viral replication, but does not eradicate the virus itself. Cessation of oral Valganciclovir therapy in a profoundly immunosuppressed person results in reactivation of CMV viral replication. Therefore maintenance therapy is essential in the successful management of CMV retinitis if the patient's immune function remains poor. Recent reports from the US Public Health Service (USPHS) advises discontinuation of maintenance oral valganciclovir in a patient on HAART therapy with quiescent CMV retinitis having CD4 count persistently greater than 100–150 cells/mm³ for at least six months, backed by cautious clinical, immunological and ophthalmological monitoring.[25,26] Maintenance therapy is reconsidered if the CD4 count falls below 100–150 cells/mm³ or the patient develops other signs of HIV progression.[27]

On September 12, 2003, valganciclovir was also approved for the prevention of CMV disease in kidney,[28] heart, lung,[29] liver,[17] and pancreas transplant recipients.[16] This was based on the results of the clinical trial, PV 16000, in which oral valganciclovir decreased the incidence of CMV disease, including CMV syndrome and tissue-invasive disease in the first six months after transplantation.[22] Valganciclovir is currently being investigated for its efficacy in prevention and treatment of CMV end-organ disease in HIV infected patients, congenital and neonatal CMV disease and in preventing CMV disease in stem cell transplant recipients.

## Alternative therapies

Approved alternative therapies for the treatment of CMV retinitis in addition to intravenous ganciclovir and oral ganciclovir include the ganciclovir intravitreal implant, intravenous foscarnet (Foscavir®; AstraZeneca, Wilmington, DE, USA) and intravenous cidofovir (Vistide®; Gilead, Foster City, CA, USA).[22] For CMV retinitis, resistant to ganciclovir, the commonly used alternative drugs are foscarnet and cidofovir. With the exception of the study comparing oral valganciclovir to intravenous ganciclovir, there exists no head-to-head study between valganciclovir and any other drugs used in patients with CMV. Foscarnet and cidofovir act by directly inhibiting CMV DNA polymerases. They are considered second-line

drugs in the management of CMV retinitis because of their associated adverse effects discussed in Table 5.

## Gancicloivir implant

Intraocular sustained-release ganciclovir implants (Vitrasert®; Chiron Vision, Irvine, CA, USA) with a release rate of 1 µg/hour of ganciclovir and intravitreal injections of ganciclovir have been very effective in treating CMV retinitis.[5,30,31] In the pivotal trial, patients treated with the ganciclovir implant had a mean time to CMV retinitis reactivation of 220 days compared to 70 days for patients treated with intravenous gancicloivir.[30] The risk of CMV retinitis becoming bilateral was 50% at six months with the sustained-release implant alone. However biopsy confirmed the development of visceral CMV disease in 31% of patients indicating lack of protection from systemic CMV disease with the intraocular implant alone. Given that CMV retinitis is the ocular manifestation of a systemic infection, local therapy by itself must be given with awareness of systemic risks. In general, when local intraocular therapy is administered, it is done so in combination with systemic therapy typically oral valganciclovir.

## Intravenous foscarnet

A direct comparison of ganciclovir and foscarnet was conducted in an open-label, randomized, multicenter clinical trial sponsored by Studies of Ocular Complications of AIDS Research Group (SOCA) in patients with AIDS and CMV. In the ganciclovir group, induction therapy with intravenous ganciclovir sodium at 5 mg/kg twice a day for two weeks was followed by maintenance therapy of 5 mg/kg per day. In the foscarnet group, induction therapy with intravenous foscarnet sodium at 90 mg/kg twice a day for two weeks was followed by maintenance therapy of 120 mg/kg per day. Retinitis progression, visual acuity, visual fields, mortality

and morbidity were the outcome parameters. The mortality rate was significantly different between the two groups. Median survival times were 8.5 months for the ganciclovir group and 12.6 months for the foscarnet group. The median times to retinitis progression were similar between groups (53 days for foscarnet and 47 days for ganciclovir), and no significant difference was detected in visual acuity outcomes and visual field loss (29° per month for foscarnet and 31° per month for ganciclovir), and retinal area involvement on fundus photographs.[32]

## Intravenous cidofovir

The SOCA sponsored HPMPC (cidofovir) Peripheral Cytomegalovirus Retinitis Trial suggested the effectiveness of both high-dose and low-dose cidofovir in controlling CMV retinitis when given as intravenous infusions intermittently. This was a multicenter, randomized, and controlled trial evaluating the role of intravenous cidofovir as a treatment for CMV retinitis. Sixty-four AIDS patients with small, peripheral, untreated CMV retinitis were enrolled for the study. These patients were assigned to one of three groups as described here: the deferral group, in which cidofovir treatment was withheld until CMV retinitis was found progressive; the low-dose cidofovir group received cidofovir, 5 mg/kg of body weight once a week for two weeks, then maintenance therapy with cidofovir, 3 mg/kg of body weight once every two weeks; or the third treatment group of high-dose cidofovir receiving 5 mg/kg of cidofovir once a week for two weeks followed by maintenance therapy of cidofovir, 5 mg/kg once every two weeks. Concomitant administration of cidofovir with probenecid, adequate hydration, intermittent dosing and monitoring for proteinuria was found to minimize associated nephrotoxicity of cidofovir. In the low-dose cidofovir group, the median time to retinitis progression was 64 days and it

**Table 5** Alternative therapies for CMV disease[15]

| Parameter | Ganciclovir[9] | Valganciclovir[22] | Cidofovir | Foscarnet[44] |
|---|---|---|---|---|
| Induction therapy | IV 5 mg/kg for two weeks | 900 mg bid for three weeks | 5 mg/kg weekly for two weeks | IV 60 mg/kg tid for two weeks |
| Maintenance therapy | IV 5 mg/kg qd | 900 mg qd | IV 5 mg/kg every two weeks | IV 30 mg/kg tid |
| Advantages | Systemic therapy, oral therapy, long acting implants available | Systemic therapy, oral therapy, low pill burden, convenient dosing | Systemic therapy, least expensive, suppresses exacerbations | Systemic therapy |
| Adverse effects | Myelosuppressant, large pill burden, Intravenous regimen and infusion related problems, if orally- poor bioavailability | Myelosuppressant | Nephrotoxic, Co-administration with probenicid | Nephrotoxic, electrolyte imbalance, intravenous regimen and infusion-related problems |

**Abbreviations:** IV, intravenous; qd, once a day; bid, twice a day; tid, three times a day.

was 21 days in the deferral group. In the high-dose group, the median time to progression was not reached at all. In conclusion, both high- and low-dose intravenous cidofovir delayed the progression of CMV retinitis effectively.[33]

## Combination therapy of intravenous ganciclovir and foscarnet

In the SOCA-CMV Retinitis Retreatment Trial, for the relapsed retinitis, the combination of intravenous ganciclovir and foscarnet was found to be more effective than either drug alone. Combination of ganciclovir sodium at 5 mg/kg per day and foscarnet sodium at 90 mg/kg per day was the treatment regimen in the study. Combination therapy was found to be the most effective regimen in controlling retinitis progression, as evaluated by the centralized Fundus Photograph Reading Center in a masked fashion. The median times to retinitis progression were 1.3 months, 2.0 months, and 4.3 months in the foscarnet group, ganciclovir group, and combination therapy group, respectively. Quality-of-life parameters were found to be best with the combination therapy compared to the monotherapy groups of ganciclovir and foscarnet.[33] However, infusion times and systemic side effects are significant, and in the HAART era, this treatment approach is rarely utilized.

## Combination of ganciclovir implant and oral ganciclovir with intravenous cidofovir

*In vitro* data suggest that combination therapies are synergistic in inhibiting viral replication. Therefore, the combination of daily oral ganciclovir and intermittent intravenous cidofovir was thought to be an attractive therapy for relapsed disease as both these act in synergy to control the systemic and ocular CMV disease.

The Ganciclovir-Cidofovir CMV Retinitis Trial (GCCRT) was a randomized, multicenter clinical trial aimed at comparing the regimen of the ganciclovir implant plus oral ganciclovir to one of intravenous cidofovir for the treatment of CMV retinitis. Sixty-one patients with AIDS and CMV retinitis were randomized either to the regimen of the ganciclovir implant plus oral ganciclovir, 1 gm three times daily, or intravenous cidofovir, 5 mg/kg once a week for two weeks, followed by 5 mg/kg every other week. The results were as follows: Ocular outcomes were similar between the two groups, with retinitis progression occurring at a rate of 0.67 per person-year in the ganciclovir group, 0.71 per person-year in the cidofovir group, and a 15-letter loss of visual acuity occurring at a rate of 0.78 per person-year

in the ganciclovir group and 0.47 per person-year in the cidofovir group. Vitreous hemorrhage associated with the surgical procedure of placing the implant was noted in the ganciclovir implant group (0.13 per person-year) with no cases in the cidofovir group. Conversely, uveitis occurred more frequently in the cidofovir group (0.35 per person-year) than in the ganciclovir group (0.09 per person-year). Mortality rates were not different between groups (0.41 per person-year for ganciclovir and 0.49 per person-year for cidofovir). Nephrotoxicity, the main systemic side effect of cidofovir was significantly more common in the cidofovir group (0.48 per person-year) compared to the ganciclovir group (0.18 per person-year).[34]

## Advantages of systemic therapy with valganciclovir

1. Systemic treatment with oral ganciclovir reduced the incidence of systemic CMV disease.[35] The effectiveness of systemic ganciclovir is emphasized by the fact that there is an increase of 22%–35% in the incidence of new CMV retinitis in the untreated contralateral eye with intraocular treatment alone.[36]
2. The convenient administration of valganciclovir has resulted in better patient compliance as suggested in a study by Claxton.[37]
3. In a study with oral ganciclovir, it has been found to prevent CMV disease in patients with HIV infection and CD4 count of lesser than 100 cells/mm³. Hence, oral valganciclovir/ganciclovir holds promise in preventing CMV disease in patients with HIV infection.[38]
4. Systemic treatment reduces mortality.[13]

## Resistance to valganciclovir

Viral resistance to ganciclovir has been noted with prolonged treatment in patients with CMV retinitis and was first reported in 1989. Ganciclovir resistance has been attributed to the mutations in protein kinase gene UL97 and polymerase gene UL54.[22] The incidence of ganciclovir resistance in valganciclovir therapy is similar to that in intravenous ganciclovir therapy. Patients showing poor clinical response but with persistent viral excretion are considered to have developed resistance to ganciclovir. In a study involving 72 immunocompromised patients with HIV and CMV retinitis, 20% of patients who failed to respond to valganciclovir were found to have nine different resistant strains of CMV.[39] All these patients failed to phosphorylate ganciclovir. Surprisingly in some patients, valganciclovir resistance was noticed without any prior exposure to ganciclovir. In another study, genotypic

resistance to ganciclovir was found in 9.4% of patients after 182 days of therapy.[40]

## Mutation in viral protein kinase gene UL97

Deletion of four amino acids in a highly conserved region of viral protein kinase results in a mutation of UL97, viral protein kinase gene. These viral mutants fail to phosphorylate ganciclovir efficiently and this is the main cause for CMV resistance to ganciclovir.[22]

## Mutation in viral polymerase gene UL54

Mutation in viral polymerase gene UL54 has resulted in cross-resistance with other antiviral drugs acting on viral DNA polymerase such as cidofovir and foscarnet.[22] This leads to reduced incorporation of the drug into the CMV DNA strand.

## Drug interactions

No drug–drug *in vivo* interaction has been studied with valganciclovir. Valganciclovir is rapidly and extensively converted to ganciclovir and hence the same drug interactions with ganciclovir are seen with valganciclovir.[22] The important drug interactions are discussed in Table 6.

## Adverse effects
### General

The common adverse events reported during maintenance therapy are diarrhea, nausea, vomiting, abdominal pain, fever, headache, insomnia, tremors, peripheral neuropathy, seizures, confusion, paresthesia, hallucinations, graft rejection, constipation, back pain, high blood pressure and retinal detachment.[22,23]

## Myelosuppressant

Less than 5% patients had serious adverse reactions such as pancytopenia and aplastic anemia.[22,41]

## Teratogenic

Valganciclovir is a FDA pregnancy category-C drug with reproductive toxicity similar to ganciclovir. Common teratogenic abnormalities reported in animal models include cleft palate, hydrocephaly, microphthalmos and brachygnathia. Adequate contraception is advised to women of reproductive potential on valganciclovir.[22]

## Carcinogenic

Although there is no human study to prove the carcinogenesis of valganciclovir, patients are warned to consider it a potential carcinogenic.

## Anti-fertility

It causes azoospermia in animals due to direct cessation of spermatogenesis, without affecting testicular endocrine functioning. Suppressed fertility is reported in females in a different animal study.[22]

## Special precautions
### Pediatric and geriatric population

The effects of valganciclovir on pediatric and geriatric population have not been studied. Caution is to be exercised while using valganciclovir in the elderly keeping in mind the increased frequency of impaired renal, hepatic and cardiac function in them.

### Nursing mothers

It is not known whether ganciclovir is secreted in human milk. Nursing mothers are instructed not to breast-feed if

**Table 6** Valganciclovir drug interactions[22]

| Valganciclovir interactions with | Drug interactions | Comments |
|---|---|---|
| Zidovudine | Myelosuppression | This calls for reduction in valganciclovir dosage or substitution with a different antiretroviral drug. |
| Didanosine | Paradoxical decline in the CD4 cell counts, despite persistent suppression of viral load | The probable explanation is the inhibition of purine nucleoside phosphorylase by ganciclovir and its prodrug valganciclovir. |
| Mycophenolate mofetil[22] | Myelosuppression | Granulocytopenia reversed with granulocyte-colony stimulating factor |
| Probenecid[22] | Reduces renal clearance and increases plasma concentration | Close monitoring advised |
| Imipenem/cilastatin | Induces convulsions | No human studies done |
| Stavudine/zalcitabine/trimethoprim[22] | No untoward effects reported | |
| Nephrotoxic drugs such as aminoglycosides, cisplatin, tacrolimus and amphotericin B[12] | Increased nephrotoxicity | Avoidance or cautious administration is advised |

they are on valganciclovir. The Centers for Disease Control also recommend HIV-infected mothers not to breast feed their infants to avoid postnatal transmission of HIV.

## Contraindications

Valganciclovir is contraindicated in patients with ganciclovir hypersensitivity. It is contraindicated in patients with absolute neutrophil count less than 500/mm³, platelet count less than 25,000/mm³ or the hemoglobin less than 8 g/dL.[22,42]

Valganciclovir is not advised in patients on hemodialysis or in those with creatinine clearance below 10 ml/minute, as the optimal daily dosage is less than 450 mg. There is no study regarding the effects of peritoneal dialysis on the excretion of valganciclovir.[14]

## Drug economics

Oral valganciclovir is an efficient and advantageous substitute for ganciclovir in many ways. It is an effective alternative to intravenous ganciclovir[43] in induction and maintenance therapy of CMV retinitis in HIV patients, and is found to achieve significantly higher systemic levels than oral ganciclovir. Based on the wholesale prices in the United States, a two-week induction therapy with intravenous ganciclovir costs US$1,583, while oral valganciclovir costs US$2,136. For maintenance treatment, intravenous ganciclovir costs US$57 each day, and oral valganciclovir costs US$76 each day.

Valganciclovir is cost and time effective as it eliminates the expenses involved in hospitalization, intravenous, or indwelling catheterizations and nursing care associated with the use of parenteral ganciclovir, foscarnet or cidofovir.[15,38,44] Long-term intravenous therapy predisposes the patient to the risk of catheter-related complications such as thrombophlebitis, intravenous line infection and sepsis.[45] Although valganciclovir is more expensive per pill than ganciclovir, the costs are comparable with intravenous ganciclovir taking into account the cost of parenteral administration.[42] Valganciclovir has overcome the large pill burden of oral ganciclovir and has improved treatment adherence. Roche has agreed to offer valganciclovir at a price of US$1800 for two weeks in developing countries of Africa and Asia, after negotiations with Médecins Sans Frontières's (MSF) Access to Essential Medicines Campaign.[11]

## Conclusions

Valganciclovir is a relatively safe, highly bioavailable oral form of ganciclovir that has greatly enhanced the efficacy of preventive and maintenance treatment regimens for CMV retinitis in AIDS patients. Valganciclovir is the only drug with bioavailability equivalent to the intravenous ganciclovir and is indicated for the treatment of serious vision and life-threatening CMV infections.[5] Valganciclovir in AIDS patients has been shown to be highly effective for the induction and maintenance of CMV disease, and has significantly improved quality of life for patients with this disease as it has eliminated the need for chronic indwelling catheterization and chronic intravenous therapy for people with CMV retinitis.

## Disclosures

The authors report no conflicts of interest in this work.

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