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. Valganciclovir 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/mm3.1–3 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
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. 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 theuffy coat of the infected blood in 7–8 days.

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

The absolute bioavailability of oral valganciclovir is approximately 60%, which is 10 times higher than ganciclovir bioavailability after oral administration. The peptide-mediated active transport of valganciclovir due to the presence of valine moiety explains its increased bioavailability. A dose of 900 mg/day of valganciclovir produces a daily exposure equivalent to the 5 mg/day daily intravenous dose of ganciclovir. 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. 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.

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

### Table 1 Pharmacokinetics of valganciclovir

<table>
<thead>
<tr>
<th>Feature</th>
<th>Valganciclovir</th>
<th>Intravenous ganciclovir</th>
<th>Ganciclovir capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage</td>
<td>900 mg qd</td>
<td>5 mg/kg</td>
<td>1000 mg tid</td>
</tr>
<tr>
<td>Plasma half-life (hours)</td>
<td>4.08</td>
<td>2.9</td>
<td>4.4</td>
</tr>
<tr>
<td>AUC_{24} µg.h/mL</td>
<td>29.1 ± 9.7</td>
<td>26.5 ± 5.9</td>
<td>12–19.2</td>
</tr>
<tr>
<td>Oral Bioavailability (%)</td>
<td>60%</td>
<td>Not applicable</td>
<td>6%</td>
</tr>
</tbody>
</table>

Abbreviations: qd, once a day; tid, three times daily; AUC, area under curve.
approval in 1997. 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.

**Study WV 15376**

Unlike a traditional head-to-head study, this pivotal trial, Study WV 15376, 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 every two weeks 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/mm³ in the intravenous ganciclovir arm, and 58 cells/mm³ 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 endpoint 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 endpoint 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.

**Study WV 15705**

Study WV 15705 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>
<thead>
<tr>
<th>Table 2 Summary of the valganciclovir registrational study WV 15376</th>
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<tbody>
<tr>
<td>Total number of patients enrolled and randomized to either arms</td>
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<tr>
<td>Number of patients completing the study</td>
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<tr>
<td>Induction therapy</td>
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<tr>
<td>Maintenance therapy</td>
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<tr>
<td>Primary endpoint of the study</td>
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<tr>
<td>Secondary endpoint of the study</td>
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<tr>
<td>Bioavailability of valganciclovir</td>
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<tr>
<td>Outcomes of the study</td>
</tr>
<tr>
<td>Adverse events</td>
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</tbody>
</table>

**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 overdose 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, and once a week during maintenance therapy is recommended to identify any hematological adverse events.22

T able 3 Adverse reactions (%) noted in study WV 1570522

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Valganciclovir</th>
<th>Intravenous ganciclovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Anemia</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Neutropenia (Neutrophil count &lt;1000/mm³)</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Headache</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Cathether-related infections</td>
<td>3</td>
<td>11</td>
</tr>
</tbody>
</table>

The treatment regimen is summarized in Table 4.

<table>
<thead>
<tr>
<th>Table 4 Treatment regimen</th>
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<tbody>
<tr>
<td>Induction therapy 900 mg (two 450 mg tablets) bid with food for 21 days.</td>
</tr>
<tr>
<td>Maintenance therapy 900 mg (two 450 mg tablets) qd with food.</td>
</tr>
</tbody>
</table>

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

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.

**Ganciclovir 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 ganci-
clovir 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 intra-
venous ganciclovir.\(^10\) 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 manifes-
tation 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 combina-

**Intravenous foscarnet**

A direct comparison of ganciclovir and foscarnet was con-
ducted 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 treat-
ment 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 cidofo-

<table>
<thead>
<tr>
<th>Table 5 Alternative therapies for CMV disease(^15)</th>
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<tr>
<td><strong>Parameter</strong></td>
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<tr>
<td>Induction therapy</td>
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<td>Maintenance therapy</td>
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<tr>
<td>Advantages</td>
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<tr>
<td>Adverse effects</td>
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**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 immuno-compromised 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.
resistance to ganciclovir was found in 9.4% of patients after 182 days of therapy.\textsuperscript{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.\textsuperscript{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.\textsuperscript{22} This leads to reduced incorporation of the drug into the CMV DNA strand.

**Drug interactions**

No drug–drug \textit{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.\textsuperscript{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.\textsuperscript{22,23}

**Myelosuppressant**

Less than 5\% patients had serious adverse reactions such as pancytopenia and aplastic anemia.\textsuperscript{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.\textsuperscript{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 function. Suppressed fertility is reported in females in a different animal study.\textsuperscript{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>
<thead>
<tr>
<th>Table 6 Valganciclovir drug interactions\textsuperscript{22}</th>
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<tr>
<td><strong>Valganciclovir interactions with</strong></td>
</tr>
<tr>
<td>Zidovudine</td>
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<tr>
<td>Didanosine</td>
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<tr>
<td>Mycophenolate mofetil\textsuperscript{22}</td>
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<tr>
<td>Probenecid\textsuperscript{22}</td>
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<tr>
<td>Imipenem/cilastatin</td>
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<tr>
<td>Stavudine/zalcitabine/trimethoprim\textsuperscript{22}</td>
</tr>
<tr>
<td>Nephrotoxic drugs such as aminoglycosides, cisplatin, tacrolimus and amphotericin B\textsuperscript{22}</td>
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they are on valganciclovir. The Centers for Disease Control also recommend HIV-infected mothers not to breastfeed 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 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, foscarin 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.³ 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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