Drugs 2001; 61 (8): 1145-1150
0012-6667/01/0008-1145/$27.50/0

Valganciclovir

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Contents

Abstract

▲ Valganciclovir is a prodrug of ganciclovir which has been developed for the treatment of cytomegalovirus (CMV) retinitis in patients with AIDS.

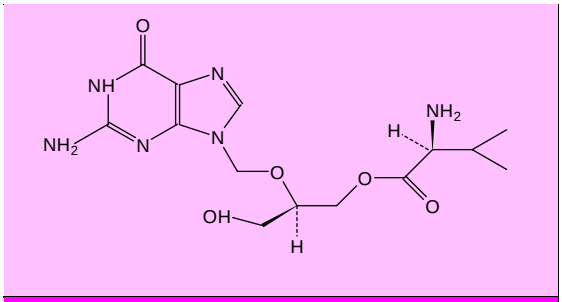
▲ Oral valganciclovir is rapidly absorbed and hydrolysed to ganciclovir. The oral bioavailability of ganciclovir after oral valganciclovir administration is high. Oral valganciclovir 900mg provides a daily exposure of ganciclovir comparable to that of intravenous ganciclovir 5 mg/kg.

▲ A single, randomised, nonblind study indicated that oral valganciclovir (900mg twice daily for 3 weeks then 900mg once daily) and intravenous ganciclovir (5 mg/kg twice daily for 3 weeks then 5 mg/kg once daily) were equally effective in the treatment of newly diagnosed CMV retinitis in 160 patients with AIDS.

▲ Valganciclovir appears to have a similar tolerability profile to intravenous ganciclovir during induction therapy in patients with AIDS and newly diagnosed CMV retinitis.

▲ During maintenance therapy with valganciclovir, the most commonly reported adverse events included neutropenia, anaemia, thrombocytopenia, gastrointestinal (including diarrhoea, nausea, vomiting and abdominal pain), fever, headache, insomnia, peripheral neuropathy, paraesthesia and retinal detachment.

Features and properties of valganciclovir	
Indication	
Cytomegalovirus retinitis in patients with AIDS	
Mechanism of action	
DNA polymerase inhibitor	
Dosage and administration	
Usual dosage in clinical trials	1800 mg/day for induction therapy then 900 mg/day for maintenance therapy
Route of administration	Oral
Frequency of administration	Twice daily for 3 weeks for induction therapy then once daily for maintenance therapy
Ganciclovir pharmacokinetic profile (875 mg/day for 3 days with food in CMV- and HIV-seropositive patients)	
Peak plasma concentration	6.1 mg/L
Time to peak plasma concentration	1.5h
Area under the plasma concentration-time curve	24.8 mg/L • h
Adverse events (reported during maintenance therapy)	
Most frequent	Diarrhoea, nausea, vomiting, abdominal pain, fever, neutropenia, anaemia, thrombocytopenia, headache, insomnia, peripheral neuropathy, paraesthesia and retinal detachment



Cytomegalovirus (CMV) infection is normally asymptomatic in immunocompetent individuals, but may result in a variety of clinical symptoms, including retinitis, in immunocompromised individuals. CMV retinitis is potentially a sight-threatening complication in patients with advanced HIV infection or in recipients of bone marrow or solid organ transplants. Patients with CMV retinitis may experience blurred or distorted vision, loss of central or peripheral visual fields, floaters or light flashes.[1]

Acute CMV infection can be controlled by a variety of options, including intravenous ganciclovir.[2] Intravenous ganciclovir treatment of CMV retinitis in patients with AIDS typically involves induction therapy followed by life-long maintenance therapy. Oral ganciclovir is also available and avoids the necessity of daily intravenous infusions. However, the low bioavailability of oral ganciclovir (approximately 6 to 9%)[3,4] has restricted its use to maintenance therapy only. The prodrug valganciclovir, an orally available monovalyl ester of ganciclovir, has been developed in an attempt to increase the bioavailability of ganciclovir, and to achieve a level of ganciclovir exposure similar to that achieved with intravenous administration.

1. Pharmacodynamic Profile

Valganciclovir is rapidly hydrolysed to ganciclovir by intracellular esterases in the mucosal cells of the gut,[5] and by hepatic esterases;[6] its pharmacodynamic properties are therefore those of the latter drug. The pharmacodynamic profile of ganciclovir based on previous reviews is briefly outlined below.[4,7]

- The anti-CMV activity of ganciclovir is primarily a result of inhibition of viral DNA synthesis by ganciclovir triphosphate (a product of phosphorylation of ganciclovir by viral and cellular enzymes). Ganciclovir triphosphate competes with deoxyguanosine triphosphate (dGTP) as a substrate for viral DNA polymerase. Reduced incorporation of dGTP, together with the incorporation of ganciclovir triphosphate into the growing chain of viral DNA, slows and/or prevents DNA chain extension, thus inhibiting viral replication.

- Ganciclovir is ≈26 times more potent than aciclovir against CMV *in vitro*. The concentration of ganciclovir required to achieve 50% viral inhibition (IC_{50}) ranged from 0.6 to 4.9 (mean 2.7) μmol/L.

- *In vitro* and *in vivo* studies have shown that ganciclovir inhibits the immune responses associated with CMV infection and/or graft rejection (reviewed by Noble and Faulds[7]). It has shown efficacy in numerous studies in animal models of CMV infection.

- Ganciclovir-resistant strains of CMV have been isolated from a small number of CMV-infected patients. These strains appear to have point mutations in a gene that encodes a protein kinase involved in the phosphorylation of ganciclovir and another that encodes viral DNA polymerase.

2. Pharmacokinetic Profile

The pharmacokinetic data discussed below are from 3 randomised, nonblind, crossover studies and involve patients who are CMV- and HIV-seropositive unless stated otherwise. In one of these studies, 18 patients received a single dose of oral valganciclovir 360mg, a single dose of oral ganciclovir 1000mg, and a single infusion of intravenous ganciclovir 5 mg/kg over 1 hour.[8] In a dose-ranging study, 39 patients received oral valganciclovir 450, 875, 1750 and 2625mg once daily for 3 days in the fed (n = 20) or fasted (n = 19) state.[9] The third study involved 28 liver transplant recipients who

received 3 single doses of oral ganciclovir 1000mg over 18 hours, single dose oral valganciclovir 450 and 900mg, and single infusion of intravenous ganciclovir 5 mg/kg over 1 hour.[10] A washout period of 3 to 7 days separated treatments in all studies.

- The absolute bioavailability of ganciclovir from oral valganciclovir is approximately 10-fold higher than that from oral ganciclovir.[8,10] The mean bioavailability of ganciclovir from single dose oral valganciclovir 360mg and single dose oral ganciclovir 1000mg was 60.9 and 5.6%.[8] The increased bioavailability of the prodrug is likely to be due to intestinal peptide transporters that recognise valganciclovir as a substrate.[5]

- Valganciclovir is rapidly absorbed and hydrolysed to ganciclovir. Oral valganciclovir 450, 875, 1750 and 2625mg once daily for 3 days produced mean valganciclovir maximum plasma concentration (C_{max}) values of 0.2, 0.3, 0.5 and 0.6 mg/L, respectively, after 1 to 1.5 hours in fed patients.[9] Ganciclovir C_{max} (3.3, 6.1, 11.2, and 15.4 mg/L, respectively) was reached ≈30 minutes after that for valganciclovir.[9] In liver transplant recipients, single dose oral valganciclovir 450 and 900mg produced valganciclovir C_{max} values of ≈0.1 and ≈0.2 mg/L after ≈2 hours and ganciclovir C_{max} values of 3.0 and 6.2 mg/L approximately 1 hour later.[10] Valganciclovir concentrations fell below the limit of quantitation in most patients within 3 to 4 hours, and were not measurable in any patient after 6 hours.

- Systemic exposure to valganciclovir was low in both CMV- and HIV-seropositive patients[9] and in liver transplant recipients,[10] with a mean valganciclovir area under the plasma concentration-time curve to 24 hours (AUC_{24h}) that was approximately 1 to 2% that of ganciclovir. After administration of valganciclovir 875mg with food, the mean valganciclovir AUC_{24h} was 0.39 mg/L · h compared with a mean ganciclovir AUC_{24h} of 24.8 mg/L · h.[9]

- Once daily oral valganciclovir achieved a daily exposure of ganciclovir similar to that produced by an intravenous dose of ganciclovir 5 mg/kg in CMV- and HIV-seropositive patients[9] and liver transplant recipients.[10] Linear regression analysis of data from CMV- and HIV-seropositive patients demonstrated that valganciclovir 900mg once daily for 3 days with food could produce a target ganciclovir AUC_{24h} value of 26 mg/L · h,[9] which is similar to a value of 22.1 mg/L · h obtained in 18 HIV- and CMV-seropositive patients treated with intravenous ganciclovir 5 mg/kg/day in a separate study.[3] In liver transplant recipients, the mean ganciclovir AUC_{24h} after single dose oral valganciclovir 900mg was similar to that produced by a single infusion of intravenous ganciclovir 5 mg/kg (41.7 *vs* 48.2 mg/L · h; fig. 1).[10] Ganciclovir AUC_{24h} values after single dose oral valganciclovir 450mg and 3 single doses of oral ganciclovir 1000mg over 18h were also similar (21.1 *vs* 20.7 mg/L · h; fig 1).

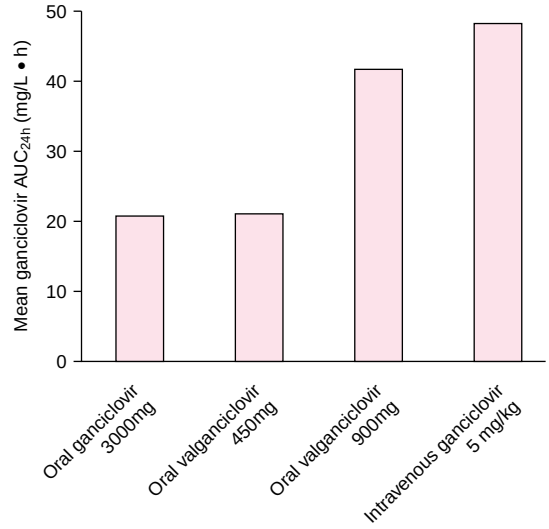


Fig. 1. Comparative drug exposure of oral ganciclovir, oral valganciclovir and intravenous ganciclovir in liver transplant recipients. In a nonblind, randomised, crossover study, mean ganciclovir area under the concentration-time curve to 24 hours (AUC_{24h}) was assessed in 28 liver transplant recipients.[10] Patients received 3 single doses of oral ganciclovir 1000mg over 18h, single dose oral valganciclovir 450 and 900mg, and a single oral infusion of intravenous ganciclovir 5 mg/kg over 1 hour, with a 3- to 7-day washout period between treatments.

• Administration of valganciclovir with food generally increased exposure to ganciclovir compared with administration in the fasted state. In patients receiving 3 days' treatment with oral valganciclovir 450 to 2625mg once daily, mean ganciclovir AUC_{24h} values were 23 to 57% higher in the fed than in the fasted state ($p < 0.001$); mean C_{max} values were also increased (by 6 to 25%) but this difference was not significant.[9]

• The terminal elimination half-life ($t_{½\beta}$) for ganciclovir in 18 CMV- and HIV-seropositive patients was similar after single dose oral valganciclovir 360mg and a single infusion of intravenous ganciclovir 5 mg/kg (3.7 and 3.7 hours) and shorter than that for single dose oral ganciclovir 1000mg (7 hours).[8] The longer $t_{½\beta}$ for ganciclovir (≈5 hours) after administration of single dose oral valganciclovir 450 and 900mg and intravenous ganciclovir 5 mg/kg to 28 liver transplant recipients probably reflects the use of immunosuppressive nephrotoxic drugs and the underlying disease.[10] This is also reflected in the higher ganciclovir AUC_{24h} values obtained in transplant recipients[10] compared with CMV- and HIV-seropositive patients[9] during treatment with similar doses of oral valganciclovir.

• In liver transplant recipients, renal clearance of ganciclovir was similar during single dose administration of oral valganciclovir 450 or 900mg, 3 single dose of oral ganciclovir 1000mg over 18h and a single 1-hour infusion of intravenous ganciclovir 5 mg/kg (126, 137, 137 and 125 L/h, respectively).[10]

3. Therapeutic Trials

The efficacy of valganciclovir as induction therapy in patients with newly diagnosed AIDS-related CMV retinitis has been evaluated in a single, randomised, nonblind comparison with intravenous ganciclovir (data presented as an abstract[11] and in the manufacturer's prescribing information[6]). Patients (n = 160) were randomised to receive oral valganciclovir 900mg twice daily for 3 weeks followed by 900mg once daily for 1 week, or intravenous ganciclovir 5 mg/kg twice daily for 3 weeks followed by 5 mg/kg once daily for 1 week. After week 4, all patients in the study continued ongoing maintenance treatment with valganciclovir 900mg once daily.[6] At baseline, $CD4^+$ cell count and highly active antiretroviral therapy (HAART) use were similar in each treatment group. The primary end-point of the induction therapy was photographically assessed CMV retinitis progression at week 4; secondary end-points included the time to progression of CMV retinitis and achievement of a prospectively defined 'satisfactory' response to therapy.

• The number of patients who experienced progression of CMV retinitis was similar with oral valganciclovir or intravenous ganciclovir therapy. In each treatment group, 10% of the patients progressed during the first 4 weeks of therapy (fig. 2).[11] The median time from randomisation to progression of CMV retinitis was longer in patients receiving induction and maintenance with oral valganciclovir than in those receiving intravenous ganciclovir induction then maintenance with oral valganciclovir (160 *vs* 125 days), whereas mean

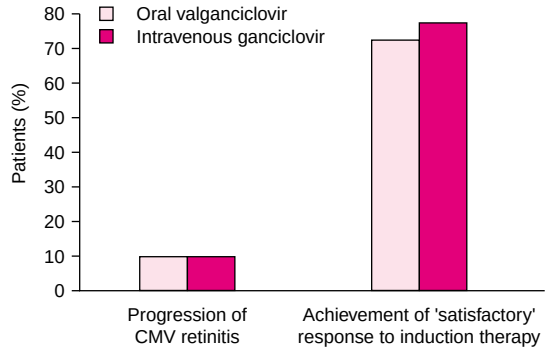


Fig. 2. Comparative efficacy of oral valganciclovir and intravenous ganciclovir as induction therapy. In a nonblind, randomised, parallel study, 160 patients with cytomegalovirus (CMV) retinitis and AIDS were treated with oral valganciclovir (900mg twice daily for 3 weeks followed by 900mg once daily for 1 week) or intravenous ganciclovir (5 mg/kg twice daily for 3 weeks followed by 5 mg/kg once daily for 1 week) .[11] Outcomes were assessed at 4 weeks; disease progression was the primary end-point.

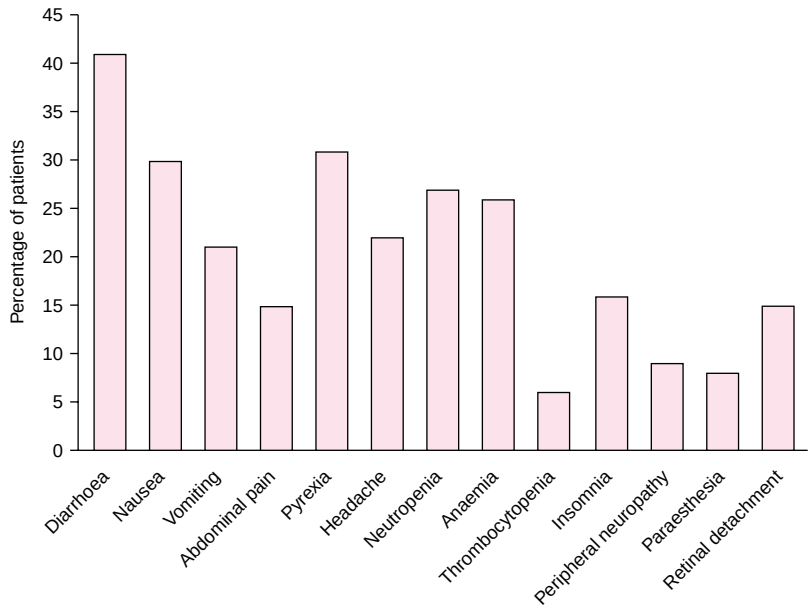


Fig. 3. Adverse events reported in 2 noncomparative trials in ô5% of patients (n = 370) treated with oral valganciclovir 900mg once daily as maintenance therapy.[6]

values were similar (226 *vs* 219 days) [statistical analyses not reported].[6]

- A 'satisfactory' response to induction therapy at 4 weeks was achieved in a similar proportion of oral valganciclovir and intravenous ganciclovir recipients (72 and 77%; fig. 2).[11]

- Analysis of subgroups according to $CD4^+$ cell count at baseline and week 4, increase in $CD4^+$ count, and HAART use confirmed that treatment response was similar in valganciclovir and ganciclovir recipients.

4. Tolerability

Since valganciclovir is a prodrug of ganciclovir, its tolerability profile should be similar to that of ganciclovir. The tolerability of ganciclovir as induction and maintenance therapy in patients with CMV retinitis and AIDS has been reviewed elsewhere.[12-14]

- The tolerability of oral valganciclovir as induction therapy was investigated in a randomised, nonblind trial in which 158 patients were evaluated for adverse events after randomisation to 4 weeks of therapy with oral valganciclovir (900mg twice daily for 3 weeks, then 900mg once daily for 1 week) or intravenous ganciclovir (5 mg/kg twice daily for 3 weeks, then 5 mg/kg once daily for 1 week).[6] Oral valganciclovir and intravenous ganciclovir recipients had similar tolerability profiles with the exception of catheter-related infection which occurred more frequently in intravenous ganciclovir recipients (11 *vs* 3%) [statistical analyses not reported]. Adverse events associated with oral valganciclovir versus intravenous ganciclovir included diarrhoea (16 *vs* 10%), neutropenia (11 *vs* 13%), nausea (8 *vs* 14%), headache (9 *vs* 5%), and anaemia (8% in both groups).

- Pooled tolerability data from 2 noncomparative trials involving 370 patients treated with oral valganciclovir 900mg once daily as maintenance

therapy are presented in figure 3.[6] Approximately 252 (68%) of the patients received oral valganciclovir for >9 months (maximum duration 36 months). The most commonly reported adverse events were gastrointestinal and haematological in nature. Increases in serum creatinine levels (>15 mg/L) occurred in 15% of oral valganciclovir recipients.

5. Valganciclovir: Current Status

Oral valganciclovir has been approved in the US for the treatment of CMV retinitis in patients with AIDS. It has shown similar efficacy to intravenous ganciclovir in a single, nonblind comparative trial in such patients. Trials investigating the efficacy of oral valganciclovir for the prevention of CMV disease in patients with solid organ transplants and bone marrow and stem cell transplants are ongoing.

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