Valganciclovir for cytomegalovirus prevention and treatment

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Cytomegalovirus (CMV) continues to be an important cause of significant disease in various groups of immunocompromised hosts, including organ and hematopoietic stem cell transplant recipients and AIDS patients. Therapeutic and preventative strategies have been used in these patients to improve overall outcomes. Ganciclovir has traditionally been the first-line drug for the treatment and prevention of CMV. Valganciclovir is a prodrug of ganciclovir with enhanced oral bioavailability. Studies have shown that it is effective for the prevention of CMV disease in high-risk (donor seropositive/recipient seronegative) solid-organ transplant recipients. It is also as effective as intravenous ganciclovir for the treatment of CMV retinitis in AIDS patients. The side-effect profile is similar to ganciclovir. Treatment studies in solid-organ transplant recipients, evaluation in pediatric patients, and prevention studies in stem cell recipients are ongoing and will help define the full role of valganciclovir in immunocompromised hosts.

Keywords: AIDS, cytomegalovirus ganciclovir, organ transplant, valganciclovir

Cytomegalovirus in immunosuppressed patients

Cytomegalovirus (CMV) infection remains an important cause of morbidity and occasional mortality in immunocompromised patients. HIV-1-infected patients who have a CD4 count of less than 100 cells/mm^3, and especially those with CD4 counts of less than 50 cells/mm^3, are at a significantly increased risk of CMV disease [1]. In these patients, CMV retinitis is the most common manifestation of CMV disease. In contrast, retinitis is quite uncommon in solid-organ transplant (SOT) and hematopoietic stem-cell transplant (HSCT) recipients. With the availability of potent antiretroviral therapy for HIV, the incidence of CMV retinitis has decreased significantly [2,3]. In organ transplantation, CMV infection is commonly defined as evidence of viral replication regardless of symptoms. Some patients with infection may go on to develop symptomatic CMV disease, which may include either the viral syndrome or tissue-invasive disease [4–6]. Viral syndrome presents with fever, malaise, with or without leucopenia, thrombocytopenia and abnormal liver enzymes [7]. Without CMV prophylaxis, CMV disease usually occurs in the first 3 months post-transplant. However, with prophylaxis, disease is often delayed to as far out as 1 year or longer post-transplant [8]. In organ-transplant recipients, CMV disease has a predilection to involve the allograft. This may be a reflection of poor local immune responses within the allograft [6]. In HSCT recipients, the most common manifestations of CMV disease are CMV pneumonitis and gastrointestinal disease [9].

There is now considerable epidemiologic evidence to suggest that CMV also has an immunomodulatory effect in transplant recipients. CMV disease is an independent risk factor for bacteremia, invasive fungal infection and Epstein–Barr virus (EBV)-related post-transplant lymphoproliferative disease (PTLD) [10]. CMV probably also plays a part in acute and chronic allograft injury and rejection [11]. There is evidence to suggest that CMV contributes to the development of chronic graft vasculopathy, resulting in lesions such as chronic allograft nephropathy, bronchiolitis obliterans (lung transplant) and accelerated coronary artery disease (heart transplant) [11].

Risk factors for CMV have been relatively well defined in transplant recipients. The pretransplant donor and recipient CMV serostatus is very useful for stratifying the risk of CMV after transplant. In solid-organ transplant, if the donor is seropositive (D+) and the recipient is seronegative (R-) pretransplant, the risk of disease is highest since these patients lack pre-existing immunity to CMV [6]. Recipients who are seropositive pretransplant have an intermediate risk of developing CMV. In HSCT recipients, CMV infection is more common in transplant settings where the recipient is seropositive prior to transplant [9]. In particular, CMV D-/R+ HSCT recipients lack CMV immunity in association with the transplanted immune system and are predisposed to CMV disease. The net state of immunosuppression is another important risk factor for CMV. This includes the type

of immunosuppressive medications, dose, timing and duration. Some medications in particular, such as antilymphocyte antibodies, are associated with a high incidence of CMV disease. The type of organ transplant also influences the risk of CMV disease. This may be due to differing degrees of immunosuppression, or other factors within the graft, such as the latent viral load. For example, lung and intestinal transplant recipients are at considerably higher risk of CMV disease compared with liver and kidney-transplant recipients [4,6].

Several strategies have been developed to prevent CMV disease. In the treatment of AIDS, oral ganciclovir has been successfully used in patients with low CD4 counts to prevent the development of CMV disease [12]. In organ and stem cell transplant patients, one of two strategies is commonly employed: universal prophylaxis or pre-emptive therapy. In universal prophylaxis, an antiviral drug (such as intravenous or oral ganciclovir or valganciclovir) is administered to all patients at risk or selected high-risk patients (e.g. D+/R-) for a period of time post-transplant to prevent CMV disease. In pre-emptive therapy, patients are monitored at regular intervals for CMV reactivation with a sensitive laboratory test such as PCR. Patients with early evidence of reactivation are then targeted with pre-emptive antiviral therapy in order to prevent symptomatic disease. Both strategies have their benefits and disadvantages [13].

Overview of the market

In addition to valganciclovir, other drugs currently available for systemic CMV infections include oral and intravenous ganciclovir, intravenous foscarnet and intravenous cidofovir. Also, acyclovir and valacyclovir have been assessed for CMV prophylaxis. In addition, fomiversen is approved for intravitreal treatment of CMV retinitis. Investigational drugs include leflunomide and maribavir [14,15]. Oral and intravenous ganciclovir have been well studied in different populations. Ganciclovir has been shown to be effective for prophylaxis and treatment of CMV in AIDS patients, SOT recipients and HSCT recipients. For treatment, intravenous ganciclovir is generally given at a dose of 10 mg/kg/day in two divided doses adjusted for renal function. In patients with AIDS-associated CMV retinitis, induction therapy is usually administered for 3 weeks and is followed by maintenance therapy (for intravenous ganciclovir, this is at 5 mg/kd/day or oral ganciclovir at 1 g three-times daily adjusted for renal function), which is usually either lifelong or until immune reconstitution can be established with highly active antiretroviral therapy (HAART) [16]. For treatment of CMV disease in organ-transplant recipients, induction therapy is usually of 2 to 4 weeks' duration and is based on clinical and virologic response [6]. Secondary prophylaxis may be administered but in general, only short courses are required. Intravenous ganciclovir has also been shown to be effective for primary prophylaxis in high risk organ and stem cell recipients [4,9]. Disadvantages include the inconvenience of prolonged intravenous therapy and the risk for catheter-related complications.

Oral ganciclovir has been shown to be useful for prophylaxis in most SOT populations and AIDS patients. In patients with CMV retinitis, after induction therapy with intravenous ganciclovir, oral ganciclovir has been shown to be effective for maintenance therapy [16]. Similarly, oral ganciclovir decreased the incidence of CMV retinitis when used for primary prophylaxis in AIDS patients at high risk of CMV disease [12]. In SOT, the efficacy of oral ganciclovir for the prevention of CMV disease has also been demonstrated. In a randomized placebo-controlled trial, oral ganciclovir for 3 months post-transplant was effective in preventing CMV disease in liver transplant recipients when compared with placebo [17]. The primary limitation of oral ganciclovir is its low bioavailability, which is estimated to be about 6%, necessitating high doses (1 g three-times daily) when used for prophylaxis. Also, because of its limited oral bioavailability, oral ganciclovir cannot be used for the treatment of CMV disease.

Other drugs with activity against CMV include foscarnet and cidofovir [18]. Foscarnet is a pyrophosphate analog that directly inhibits CMV DNA polymerase. Cidofovir is a nucleotide analog of deoxycytidine monophosphate that inhibits viral DNA synthesis. Both foscarnet and cidofovir have significant potential toxicities, especially nephrotoxicity, which limit their usefulness in many immunosuppressed patients.

Acyclovir has been evaluated in numerous studies for CMV prophylaxis. Compared with ganciclovir, acyclovir has poor *in vitro* activity against CMV. While some trials have demonstrated modest efficacy [19], others have suggested only a limited benefit, especially in high-risk D+/R- subgroups [4,6]. Trials comparing acyclovir with ganciclovir have demonstrated lower efficacy rates for acyclovir [20]. Valacyclovir, a prodrug of acyclovir, has also been evaluated for prophylaxis against CMV. In a randomized controlled trial in

kidney-transplant recipients, valacyclovir was superior to placebo for the prevention of CMV disease in both high- and moderate-risk patients [21]. Interestingly, valacyclovir was also associated with a decreased incidence of acute rejection in this trial. Valacyclovir has also been shown to be superior to oral acyclovir for CMV prophylaxis in HSCT recipients [22]. No direct randomized controlled trials comparing valacNSyclovir and valganciclovir have been published.

Valganciclovir is an oral prodrug of ganciclovir with improved oral bioavailability. This allows more convenient once- or twice-daily dosing, or in some settings, allows patients to avoid intravenous therapy.

Introduction to the compound

Chemistry

Valganciclovir is an L-valyl ester salt of ganciclovir, that is, it is a prodrug of ganciclovir [5,23]. The addition of the L-amino acid valine to the 2-hydroxyl group of the nucleoside results in significantly improved oral bioavailability. Ganciclovir is a synthetic analog of 2´-deoxyguanosine, an inhibitor of herpes virus replication. The chemical structures of valganciclovir and ganciclovir are shown in Figure 1.

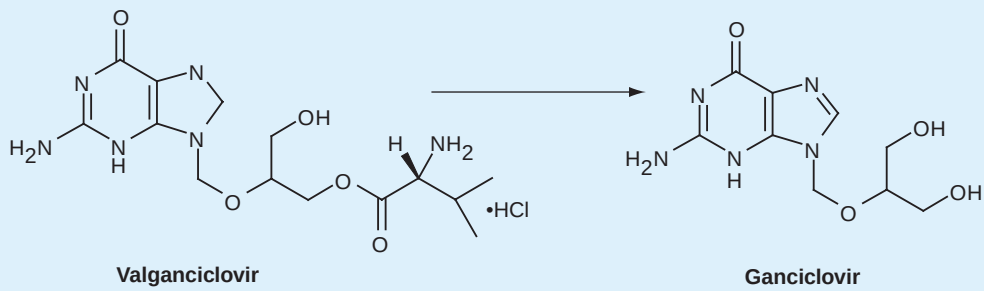
Pharmacodynamics & mechanism of action

After absorption, valganciclovir is rapidly metabolized in the intestinal wall and liver to ganciclovir [23]. In CMV-infected cells, CMV viral protein kinase, encoded by the UL97 gene, phosphorylates ganciclovir to ganciclovir monophosphate. Cellular enzymes further phosphorylate ganciclovir to the active compound, ganciclovir triphosphate. This inhibits viral DNA synthesis by competitive inhibition of incorporation of deoxyguanosine triphosphate into viral DNA. Incorporation of ganciclovir triphosphate into viral DNA also results in chain termination. Gancicloivr triphosphate has an intracellular half-life of approximately 18 h in CMV-infected cells [24].

Pharmacokinetics & metabolism

The absolute bioavailability of ganciclovir from valganciclovir is approximately 60% [23]. The high affinity to PEPT1, an intestinal peptide transporter, results in the high bioavailability of ganciclovir from valganciclovir [25]. Absorption is improved with food [26]. The route of elimination is by renal excretion through glomerular filtration and active tubular secretion. In a study of 44 patients, including patients with HIV and those with renal impairment, the elimination half-life ($T_{1/2}$) of ganciclovir was longer in patients with renal failure than healthy controls (68.1 vs. 3.5 h) [27]. Therefore, the dose of valganciclovir must be adjusted based on renal function. No differences in pharmacokinetics were observed between HIV-positive patients and healthy subjects. Pescovitz and colleagues studied the pharmacokinetics of valganciclovir, and oral and intravenous ganciclovir in 28 liver transplant recipients [28]. The exposure of 450 mg of valganciclovir (20.56 µg.h/ml) was comparable to oral ganciclovir 1 g three-times daily (20.15 µg.h/ml) and the exposure of 900 mg of valganciclovir (42.69 µg.h/ml) was found to be comparable to that of intravenous ganciclovir 5 mg/kg (47.61 µg.h/ml) [21]. Based on the population pharmacokinetic evaluation from the PV16000 trial in heart, kidney and liver recipients, the mean systemic exposure to ganciclovir was 1.7-fold higher following administration of 900 mg of valganciclovir once daily versus 1 g of oral ganciclovir three-times daily [8,23]. These data indicate that 450 mg of valganciclovir once daily may provide less drug exposure than 1 g three-times daily of oral ganciclovir.

Figure 1. Valganciclovir and its conversion to ganciclovir.



Clinical efficacy

Valganciclovir has been evaluated for a number of indications. While its use is primarily related to CMV, the indications can be divided into those for prevention and those for treatment. The drug has been evaluated in two major populations: intravenous-positive patients and SOT recipients. Studies are also ongoing in hematopoietic stem cell-transplant recipients.

Valganciclovir in intravenous patients

In HIV-positive patients, valganciclovir has been assessed primarily for treatment of CMV retinitis and subsequent maintenance therapy. The pivotal Phase III treatment trial was a large multicenter randomized controlled trial comparing intravenous ganciclovir and oral valganciclovir for the induction of treatment of CMV retinitis in HIV-positive patients [29]. In this trial, AIDS patients with CMV retinitis were randomized to receive therapeutic-dose valganciclovir (900 mg twice daily) versus intravenous ganciclovir (5 mg/kg twice daily) for 3 weeks of induction therapy and then 1 week of maintenance-dose therapy. At the end of 4 weeks, all patients received valganciclovir 900 mg once daily for maintenance therapy. This trial was powered to demonstrate noninferiority with a lower 95% confidence interval for the difference in proportions that was greater than -0.25. A total of 141 patients were evaluable for the primary end point of photoprogression. The incidence of progression of CMV retinitis during the first 4 weeks was 10% in the intravenous ganciclovir arm versus 9.9% in the oral valganciclovir arm. The rate of adequate response to induction therapy was 77% in the intravenous ganciclovir arm and 71.9% in the valganciclovir arm (p = nonsignificant [NS]). The median time-to-progression of retinitis was 125 days in the intravenous ganciclovir arm and 160 days in the valganciclovir arm. This trial confirmed that oral valganciclovir was as effective as intravenous ganciclovir for induction therapy of CMV retinitis in AIDS patients. Based on this study, valganciclovir also appeared useful for maintenance therapy after induction. Valganciclovir is currently also being assessed for primary CMV prevention in high-risk AIDS patients.

Valganciclovir in solid-organ transplant recipients

Recently, the pivotal study comparing oral ganciclovir with valganciclovir for CMV prophylaxis in high-risk CMV D+/R- SOT recipients was published [8]. This was a randomized, double-blinded, prospective study that evaluated antiviral prophylaxis in 364 CMV D+/R- transplant recipients. Transplant types included liver, kidney, heart and kidney–pancreas. Notably, lung transplant recipients were excluded from this study. Patients were randomized to receive either 900 mg of oral valganciclovir once daily versus 1000 mg of oral ganciclovir three-times daily until 100 days post-transplant. The incidence of CMV viremia, and symptomatic disease was assessed out to 6 and 12 months post-transplant. This trial was designed to demonstrate noninferiority with a power of 90% or more.

By 6 months, CMV disease occurred in 12.1% in the valganciclovir arm versus 15.2% in the ganciclovir arm (p = NS). By 12 months, the incidence of CMV disease was 17.2 and 18.4%, respectively (p = NS). As part of this study, CMV viral loads were also measured at regular intervals post-transplant. The incidence of detectable viremia (>400 copies/ml) was low while patients were receiving antiviral prophylaxis (up to day 100) and was lower with valganciclovir (2.5%) versus oral ganciclovir (10.4%) (p = 0.001). However, at 6 and 12 months the incidence of detectable viremia was similar in the two arms and very high (48.5% valganciclovir, 48.8% ganciclovir by 12 months).

Important differences among organ transplant subgroups were observed in this study. For example, in kidney-transplant recipients, the incidence of CMV disease by 6 months was 6% in the valganciclovir arm versus 23% in the oral ganciclovir arm. In contrast, in liver recipients, the incidence of disease was 19 versus 12%, respectively. In particular, in a subgroup analysis, there appeared to be a higher incidence of tissue-invasive CMV disease in liver-transplant recipients given valganciclovir prophylaxis (14 vs. 3%). The results of this subgroup analysis are controversial, and further data are needed in liver-transplant recipients. However, as a result, the US Food and Drug Administration (FDA) did not approve valganciclovir for prophylaxis in liver-transplant recipients.

Other studies in solid-organ transplant

Akalin and colleagues retrospectively analyzed 129 kidney and/or pancreas recipients receiving either standard dose oral ganciclovir or reduced dose valganciclovir (450 mg once daily) [30]. The overall incidence of CMV disease at 1 year was 14% and comparable in those receiving valganciclovir or oral ganciclovir. D+/R- and use of thymoglobulin were risk factors for CMV disease. The use of lower doses of valganciclovir, which seems to have been effective in this study, may be

due to reduced creatinine clearances commonly seen in renal-transplant recipients leading to adequate systemic exposure to ganciclovir.

In a retrospective review of 88 kidney and/or pancreas-transplant recipients [31], valganciclovir prophylaxis resulted in a CMV disease rate of 5.7%. Disease occurred exclusively in patients who were D+/R- and in those who received prophylaxis for less than 100 days post-transplant. Ciancio and colleagues retrospectively assessed the efficacy of 3 months' prophylaxis with valganciclovir in 161 kidney and/or pancreas transplant patients [32]. Mean follow up was 440 days. Only one patient developed CMV infection, which occurred at 120 days post-transplantation.

Recently, Zamora and colleagues evaluated valganciclovir prophylaxis in lung-transplant recipients. All patients received an initial course of intravenous ganciclovir for a minimum of 30 days and CMV immunoglobulin [33]. Patients then received prophylaxis with valganciclovir to either 180, 270 or 365 days post-transplant. The incidence of CMV disease was significantly lower compared with a historical control group that received acyclovir after the initial course of intravenous ganciclovir (2.2 vs. 20%). In addition, longer courses of prophylaxis were associated with less CMV disease.

Cytomegalovirus treatment in solid-organ transplant recipients

Fewer data are available concerning the use of valganciclovir for the treatment of CMV infection or for treatment of established disease in SOT recipients, although studies are ongoing. Data from single-center studies suggests that valganciclovir may be a safe alternative for the treatment of CMV infection and disease in selected individuals. Mattes and colleagues treated 22 patients (15 liver and seven kidney) with CMV viremia with oral valganciclovir (900 mg twice daily) and compared viral kinetics with 23 patients who received intravenous ganciclovir at standard treatment doses [34]. Viral load half-life and median time to resolution of viremia was similar in patients who received intravenous ganciclovir and those that received valganciclovir [34].

Valganciclovir in stem cell recipients

There is less published data on the use of valganciclovir in the HSCT transplant population, as there is a greater concern about potential myelosuppression. However, intravenous ganciclovir has proven very useful in both pre-emptive and prophylactic strategies for the prevention of CMV disease in this patient population. In patients with concomitant graft-versus-host disease of the gut, absorption of valganciclovir could theoretically be impaired although unpublished pharmacokinetic data suggest adequate absorption. Several small and large studies are ongoing to assess valganciclovir for prophylaxis and pre-emptive use in this patient population.

Ganciclovir resistance

Ganciclovir resistance is an important problem in the treatment of patients with CMV disease. Ganciclovir resistance usually occurs due to mutations in the CMV UL97 gene, which encodes the protein kinase that phosphorylates ganciclovir. These mutants remain sensitive to foscarnet and cidofovir. Occasionally, mutations may arise in the UL54 gene, which encodes the CMV DNA polymerase. Such mutants may have crossresistance to alternative therapies [18]. Oral ganciclovir with its low bioavailability may promote ganciclovir resistance [35]. Theoretically, valganciclovir should be less likely to promote resistance. In the PV16000 study, in patients with CMV disease, no resistance was observed in the valganciclovir arm versus 2/33 (6.1%) in the ganciclovir arm [36]. From the AIDS clinical trial, in 148 patients on maintenance valganciclovir the cumulative percentages of patients with UL97-mutant viruses at 3, 6, 12 and 18 months was 2.2, 6.5, 12.8 and 15.3%, respectively (a rate similar to that reported with intravenous ganciclovir) [37].

American Society of Transplantation guidelines

Recently, the American Society of Transplantation published a set of guidelines regarding CMV prophylaxis and treatment in SOT recipients [6]. The guidelines propose that oral valganciclovir is an option for prophylaxis in all organ-transplant recipients (including lung) deemed to be at risk for CMV with the possible exception of liver-transplant recipients (see FDA caution above). The guidelines note that some experts still use and recommend valganciclovir for liver recipients as well. The guidelines also recommend either intravenous ganciclovir or valganciclovir for use in pre-emptive strategies, although further studies are need in this area.

Safety & tolerability

The safety and tolerability data for valganciclovir are shown in Table 1. Since valganciclovir is rapidly converted to ganciclovir, the side effects are similar to those seen with intravenous or oral ganciclovir.

Table 1. Adverse effects associated with valganciclovir use in solid-organ transplant and AIDS patients.

Adverse event with valganciclovir	Organ transplant study (PV16000)	AIDS retinitis studies
Hematologic	Leukopenia (14%) vs. 7% with oral ganciclovir; neutropenia (8%) vs. 3% with oral ganciclovir; anemia (12%)	Neutropenia (27%); anemia (26%), thrombocytopenia (6%)
Gastrointestinal symptoms	Diarrhea (30%); nausea (23%), abdominal pain (16%); similar to oral ganciclovir	Diarrhea (41%), nausea (30%), vomiting (21%), abdominal pain (15%)
Neurologic symptoms	Headache (22%), insomnia (20%), tremors (28%), paresthesia (5%); similar to oral ganciclovir; peripheral neuropathy not reported	Headache (22%), dizziness (11%), insomnia (16%), depression (11%), paresthesia (8%); peripheral neuropathy (9%) – more likely if on hydroxyurea
Miscellaneous	Pyrexia (13%), fatigue (13%), back pain (20%), thrombocytopenia (5%), increased creatinine (7%)	Pyrexia (31%), fatigue (21%), dermatitis (22%), retinal detachment (15%), sinusitis (12%)

In animal studies, ganciclovir is mutagenic and carcinogenic and therefore valganciclovir should be considered a potential teratogen and carcinogen [23]. Women of childbearing potential should use effective contraception during treatment. Men should use barrier contraception until 90 days following treatment [23].

The most common side effects of valganciclovir reported from trials in AIDS patients, which were considered related to valganciclovir included neutropenia, anemia, diarrhea, and nausea [23,29,38]. In the SOT trial (PV16000), the most frequently associated adverse events that were considered related to valganciclovir included leukopenia and neutropenia, diarrhea, and nausea [8,23]. Importantly, leukopenia and neutropenia were more common with valganciclovir than oral ganciclovir. This probably reflects increased systemic exposure to ganciclovir in the valganciclovir treated patients. Other potential adverse events include neurologic symptoms (such as headaches, paresthesias, insomnia, peripheral neuropathy, tremor, and seizures), gastrointestinal symptoms, back pain, pyrexia and thrombocytopenia.

Regulatory affairs

Valganciclovir is currently approved for several indications, although important differences exist in different countries. In North America and Europe, valganciclovir is approved for the treatment of CMV retinitis in patients with AIDS and for use in subsequent maintenance therapy. For solid-organ and stem cell transplantation, valganciclovir is not approved for therapy of CMV disease. In heart, kidney, and kidney–pancreas transplant recipients, valganciclovir is approved for CMV prophylaxis in patients at risk for CMV. Due to the finding of a higher incidence of tissue invasive disease in the liver subgroup in the PV16000 study, the FDA did not approve valganciclovir for use in liver-transplant recipients. In contrast, however, approval for use in liver as well as lung transplant recipients was granted in Europe and Canada.

Expert opinion

Valganciclovir hydrochloride is a prodrug of ganciclovir with significantly improved oral bioavailability. Its development represents a significant advance in the available armamentarium for treatment and prevention of CMV disease in immunocompromised patients. Well-designed studies have demonstrated similar efficacy to intravenous ganciclovir for treatment and subsequent maintenance therapy of CMV retinitis in AIDS patients. For CMV prevention, it is an effective alternative to oral ganciclovir prophylaxis in high-risk SOT recipients. Preliminary and pharmacokinetic data suggest it will also likely be useful for treatment of CMV disease in organ transplant recipients. Valganciclovir offers more convenient once or twice daily oral dosing and may avoid the logistic and other side effects of prolonged intravenous dosing. Since the drug is rapidly converted to ganciclovir, it shares many

Highlights

- Valganciclovir is a prodrug of ganciclovir with improved oral bioavailability compared with oral ganciclovir.
- Valganciclovir is approved for induction and maintenance therapy of cytomegalovirus (CMV) retinitis in AIDS patients.
- Valganciclovir is approved for CMV prophylaxis in high-risk organ-transplant recipients (see text regarding issue of liver-transplant recipients).
- Valganciclovir is being evaluated for prophylaxis and pre-emptive therapy in hematopoietic stem cell transplant (HSCT) recipients and will likely prove useful in this population.
- Valganciclovir is being evaluated for pre-emptive therapy and treatment of CMV disease in solid-organ transplant recipients and will likely prove useful for these indications.
- The major side effects of valganciclovir are myelosuppression, gastrointestinal toxicity and nervous system toxicity.

of the same adverse effects as intravenous or oral ganciclovir. Particular care must be taken to monitor white blood cell and hemoglobin counts while on valganciclovir.

Outlook

Over the next 5 to 10 years, we will undoubtedly see new developments in the treatment and management of CMV in immunosuppressed patients. First, with respect to valganciclovir, ongoing studies are expected to clarify its role in the treatment of CMV disease in solid-organ transplant recipients and its role in prevention of CMV in HSCT recipients. Hopefully, the issue regarding a possible increase in tissue invasive disease in liver-transplant recipients receiving valganciclovir prophylaxis will also be clarified by further studies.

CMV infection and disease will probably also continue to change. New antiretroviral regimens for HIV therapy, and new immunosuppression drugs for organ and stem cell recipients will continue to modify the disease presentations and risk factors in these patient populations. Widespread use of prophylaxis and more potent immunosuppression may also result in increasing ganciclovir-resistance rates. Finally, new therapies for the treatment and prevention of CMV will be further developed and will hopefully provide useful alternatives to the current limited armamentarium against CMV.

Information resources

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