Utility of oral valganciclovir for the treatment of cytomegalovirus disease after renal transplantation

Original article Asberg A *et al.* (2007) Oral valganciclovir is noninferior to intravenous ganciclovir for the treatment of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* **7:** 2106–2113

SYNOPSIS

KEYWORDS cytomegalovirus, ganciclovir, renal transplantation, treatment, valganciclovir

BACKGROUND

Standard therapy for cytomegalovirus (CMV) disease in recipients of solid organ transplants comprises intravenous ganciclovir, which is costly and inconvenient to administer.

OBJECTIVE

To compare the efficacy and safety of intravenous ganciclovir with that of its orally administered prodrug, valganciclovir, for the treatment of CMV disease after solid organ transplantation.

DESIGN

This open-label, noninferiority trial ('VICTOR') enrolled adult solid organ transplant recipients from five continents who had CMV in their blood and symptoms consistent with CMV disease. Life-threatening CMV disease, resistance to ganciclovir, and Cockcroft–Gault-estimated creatinine clearance <10 ml/min were among the exclusion criteria.

INTERVENTION

Participants were randomized to receive induction treatment with either oral valganciclovir 900 mg twice daily or intravenous ganciclovir 5 mg/kg twice daily, for 21 days. After 21 days, patients in both groups underwent maintenance treatment with valganciclovir 900 mg/day for 28 days. Doses of both drugs were adjusted according to Cockcroft–Gault-estimated creatinine clearance. Use of other antiviral agents (such as aciclovir), interferons and CMV hyperimmune globulin was prohibited. CMV load was measured with a polymerase chain reaction assay at baseline, on days 3, 7, 10, 14, 17 and 21, and weekly thereafter until study end (49 days).

OUTCOME MEASURES

The primary end point was eradication of CMV viremia, defined as <600 virus copies per ml plasma, after 21 days. Secondary end points included the rate of clinical resolution of CMV disease and the rate of adverse events.

RESULTS

A total of 333 patients were screened between April 2004 and June 2006. Of the 321 patients who comprised the intention-to-treat population, 164 (122 kidney transplant recipients) had been randomized to receive valganciclovir and 157 (115 kidney transplant recipients) to receive ganciclovir. Clinical presentation of CMV disease, incidence of previous anti-CMV therapy, and baseline CMV serostatus were similar in the two groups. By day 21, CMV viremia had been eradicated in 45.1% (74) of the valganciclovir-treated patients and in 48.4% (76) of the ganciclovir-treated patients (95% CI for difference –14% to 8%); therefore, valganciclovir met the noninferiority criterion of achieving 50% eradication, within a range of –15%. Rates of viral eradication remained comparable for valganciclovir and ganciclovir at study end (67.1% [110 patients] and 70.1% [110 patients], respectively). Rates of clinical resolution were similar in the two groups at 21 days (77.4% [127 patients] for valganciclovir; 80.3% [126 patients] for ganciclovir) and at 49 days (85.4% [140 patients] and 84.1% [132 patients], respectively). The kinetics of viral eradication were also similar in the two groups, according to the per-protocol analysis. There were no differences in the rates of treatment discontinuation or adverse events between the groups.

CONCLUSION

Oral valganciclovir is not inferior to intravenous ganciclovir for the treatment of CMV disease in renal transplant recipients and has a similar adverse event profile.

COMMENTARY

David A Pegues

Over 75% of solid organ transplant recipients are at risk of the direct and indirect effects of CMV disease, which include viremia, tissue invasion, secondary bacterial and fungal infection, graft rejection and loss, and death.[1] The prevention and treatment of CMV disease in this setting has been recently reviewed.[2,3] Valganciclovir, the oral valine prodrug of ganciclovir, is effective for the primary prevention of CMV disease after solid organ transplantation.[4] Intravenous ganciclovir remains the standard treatment for CMV disease in solid organ transplant patients despite its need for long-term intravenous access, the inconvenience of administration, and the substantial cost of hospitalization. Although there are only limited data from small, nonrandomized trials, outpatient administration of oral valganciclovir has recently emerged as an alternative to intravenous ganciclovir for the management of CMV disease after solid organ transplantation, particularly for patients with low-level viremia (<10,000 copies/ml) or mild disease.

The results of the VICTOR study support the efficacy of oral valganciclovir and represent an important advance in the treatment of CMV disease after solid organ transplantation. In this large, randomized, multicenter trial, oral valganciclovir was found to have safety and efficacy comparable to that of intravenous ganciclovir for clearing CMV viremia and resolving clinical disease. Of those patients with known CMV serostatus, 24% were seronegative and had a seropositive donor; furthermore, a substantial proportion (46%) of patients had tissue-invasive infection. Both of these groups are at increased risk of severe complications, and typically receive intravenous ganciclovir for CMV disease.[1] Despite the inclusion of such patients in the study, baseline viral load was the only predictor of viral suppression. The primary outcome—suppression of CMV viremia after 3 weeks of induction therapy—was achieved in only 45–48% of patients, a response rate similar to that (46.9–50%) in a recent historically controlled trial that compared oral valganciclovir with intravenous ganciclovir in solid organ transplant patients.[5] The median viral load half-lives in the VICTOR trial (11.5 days for valganciclovir and 10.4 days for ganciclovir) were, however, longer than that reported in a recent observational study of pre-emptive valganciclovir therapy.[6] These findings emphasize the need for at least weekly monitoring of blood viral load in patients receiving treatment for CMV disease, and the fact that suppression of viremia rather than arbitrary cutoff points (e.g. 14 or 21 days) should be used to guide the duration of therapy.

The results of the VICTOR trial provide important information for clinicians, but questions remain to be answered. Pediatric patients and those with severe CMV disease were excluded, and the impact on virologic response of reducing immunosuppression was not compared between the two groups. A formal economic analysis that included the administrative costs of the two therapies and the cost of medical care would have been useful, as the pharmacy acquisition price of intravenous ganciclovir in the US (US$47.50 per 10 ml vial of 500 mg) is less than that of valganciclovir ($61.50 for two 450 mg capsules). Until further information is available, kidney transplant recipients with high CMV viral loads (e.g. >500,000 copies/ml) or severe tissue-invasive disease, and those who fail to achieve a reduction in viral load after 7 or more days of oral valganciclovir treatment, should probably be treated with intravenous ganciclovir. Other patients should receive valganciclovir until viremia is eradicated.

References

1 Fishman JA *et al.* (2007) Cytomegalovirus in transplantation—challenging the status quo. *Clin Transplant* **21:** 149–158
2 [No authors listed] (2004) Cytomegalovirus. *Am J Transplant* **4 (Suppl 10):** S51–S58
3 Preiksaitis JK *et al.* (2005) Canadian society of transplantation consensus workshop on cytomegalovirus management in solid organ transplantation final report. *Am J Transplant* **5:** 218–227
4 Paya C *et al.* (2004) Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* **4:** 611–620
5 Humar A *et al.* (2005) A prospective assessment of valganciclovir for the treatment of cytomegalovirus infection and disease in transplant recipients. *J Infect Dis* **192:** 1154–1157
6 Mattes FM *et al.* (2005) Kinetics of cytomegalovirus load decrease in solid-organ transplant recipients after preemptive therapy with valganciclovir. *J Infect Dis* **191:** 89–92

DA Pegues is a Professor of Clinical Medicine and Hospital Epidemiologist at the David Geffen School of Medicine at UCLA, Los Angeles, CA, USA.

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Competing interests
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Correspondence
David Geffen School of Medicine at UCLA
Division of Infectious Diseases
37-121 CHS
10833 Le Conte Avenue
Los Angeles
CA 90095-1688
USA
dpegues@mednet.ucla.edu

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PRACTICE POINT
Renal transplant recipients with CMV disease should be given oral valganciclovir until viremia is eradicated, unless they have a high viral load or severe tissue-invasive disease, or their viral load fails to decrease after ≥7 days of treatment