Ganciclovir-Resistant Cytomegalovirus Disease in Heart Transplant Recipients: The Dilemma of Donor-Positive/Recipient-Negative Serostatus

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(See the article by Li et al. on pages 439–47)

In the early days of heart transplantation, cytomegalovirus (CMV) disease was frequent and often severe. The development of strategies to prevent CMV disease has had a major beneficial effect [1, 2], but problems still remain. Traditionally, patients with donor-seropositive (D+)/recipient-seronegative (R−) status have had the highest risk of high viral loads, tissue-invasive disease, and ganciclovir resistance [3, 4]. These patients have also been the least likely to reap the benefits of CMV-prevention strategies. For example, in 1992, Merigan et al. [5] conducted a randomized trial of a 4-week regimen of intravenous ganciclovir regimen that showed a reduction in the incidence of symptomatic CMV disease from 46% to 9% in the recipient-seropositive (R+) group, whereas the D+/R− group experienced little, if any, reduction. However, because many organ donors are CMV seropositive, it has not been practical to match donors and recipients on the basis of CMV serostatus. Instead, intensified efforts have been applied to patients with D+/R− serostatus, including randomized trials devoted solely to such patients [6, 7].

In the current issue of Clinical Infectious Diseases, Li et al. [8] provide a significant contribution to the literature with their careful analysis of 274 patients who received heart transplants over a 10-year period, in which one cohort (n = 40) received prophylaxis with a 4-week course of intravenous ganciclovir, followed by oral acyclovir, and another, more recent cohort (n = 191) received oral ganciclovir for 3 months. Although it was not a randomized trial, the study yields information of considerable interest to the clinician. Limaye et al. [4] (from the same research group), in a landmark article in The Lancet from 2000, had already described ganciclovir-resistant CMV disease in kidney, liver, and pancreas transplant recipients who had received 3 months of oral ganciclovir prophylaxis. It is notable that, in the present study, the 4-week regimen of intravenous ganciclovir was associated with more cases of symptomatic CMV disease but with fewer cases of ganciclovir-resistant CMV disease. Although, at first, this may seem counterintuitive, it makes sense, because the 3-month oral ganciclovir regimen involves prolonged exposure to lower levels of drug. Because patients with D+/R− serostatus can develop high viral loads with rapid doubling times, exposure to subtherapeutic levels of the drug at those times of rapid viral replication can predispose to ganciclovir resistance [9].

In addition to demonstrating that ganciclovir resistance is still with us, the present study reminds us that the consequences are severe [8]. One of the 4 patients with ganciclovir-resistant CMV disease died, and although the other 3 survived, the average duration of CMV-related hospitalization was 66 days, compared with 6 days for patients with ganciclovir-susceptible CMV disease [8]. This underscores the fact that ganciclovir-resistant CMV syndromes are often protracted, and therapy is frequently associated with significant morbidity and even multiorgan failure [10]. The 2 drugs most frequently used (foscarnet and cidofovir) are both nephrotoxic; foscarnet therapy can lead to electrolyte disturbances and painful genitourinary ulcerations, whereas cidofovir is associated with myelotoxicity and, occasionally, uveitis and complete loss of intraocular pressure. Combination reduced-dose ganciclovir and foscarnet therapy was advocated by Mylonakis et al. [11], who reported excellent results for 6 patients; although this regimen represents an advancement, in my experience, it has
not always been successful. Leflunomide, an immunosuppressive agent with novel anti-CMV activity, has become part of the armamentarium for ganciclovir-resistant CMV disease [12], but prolonged use of this agent at the higher doses used for CMV therapy can be associated with hematologic and hepatic toxicity and peripheral neuropathy. Maribavir is a promising investigational drug with activity against ganciclovir-resistant strains of CMV [13], but it is not yet available on a compassionate use basis.

The difficulties inherent in treatment of ganciclovir-resistant CMV disease underscore the importance of preventing its occurrence. Preemptive therapy, for which an antiviral agent is administered only to persons who test positive for CMV viremia, has been advocated by Singh et al. [14] and others as less toxic, less costly, and less likely to lead to resistance, compared with prophylaxis. However, Limaye et al. [15] have demonstrated that resistance can occur in lung transplant recipients who receive preemptive therapy as well. Valganciclovir, which is more bioavailable than oral ganciclovir, was compared with oral ganciclovir in a randomized trial of 100 days of prophylaxis in 364 kidney, liver, heart, and pancreas transplant recipients with D+/R− serostatus [6]. Although the overall rates of viremia were similar at the end of 1 year, patients in the valganciclovir arm were less likely to have breakthrough viremia during the prophylaxis period, and no ganciclovir resistance occurred in the valganciclovir arm [16]. However, ganciclovir resistance has been reported during valganciclovir therapy in stem cell transplant recipients [17] and in HIV-infected persons [18]. It may be that any ganciclovir derivative may be associated with development of resistance if it used often enough in the presence of a driving force for a rapidly increasing viral load. Another option is a combined strategy that would use viral load monitoring and valganciclovir preemptive therapy after completion of prophylaxis to reduce the risk of late-onset CMV disease [19]. Although early results are promising, this strategy still needs to be tested in a randomized, controlled trial.

Although, in all likelihood, there will be less ganciclovir resistance in the era of valganciclovir, the work by Li et al. [8] is an important reminder that it is unlikely that this clinically vexing problem will be eliminated any time soon. In the future, trials of newer anti-CMV therapies and strategies ideally should incorporate monitoring of the viral load [20] and genotyping of breakthrough isolates to determine the impact on antiviral resistance.

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References