Agents in Development for Cytomegalovirus Infection
Summary and Table

Dene C. Peters and Richelle Paterson
Adis International Limited, Auckland, New Zealand

Adis Comment

All drugs appearing in the Adis Profile Summary table have been selected based on information contained in R&D Insight™, a proprietary product of Adis International. As the emphasis of Drugs in R&D is on the clinical potential of new drugs, selection of agents for full profile is based on the extensiveness of available data. Information on all drugs in clinical development, as identified from R&D Insight™, is included in the summary table. Information and/or profiles of agents in preclinical development may be included as appropriate.

The accompanying Profile Table contains the agents identified from Adis International’s R&D Insight™ database which are in clinical development for the prevention and/or treatment of cytomegalovirus (CMV) infections, including CMV retinitis. The features and properties of these agents are listed in the table according to their phase of development. Full profiles are provided for those agents that are in phase III or II of clinical development.

CMV infections occur most commonly in patients receiving immunosuppressive therapy after organ transplantation or in patients with AIDS, and many of the agents currently being trialed in patients with CMV infection are primarily under development as anti-HIV therapy. Two such agents are adefovir dipivoxil and valganciclovir, oral prodrugs of the currently available agents adefovir and ganciclovir, respectively. The convenience of once daily, oral administration of these agents should be helpful for patients already taking complicated HIV treatment regimens.

As discussed by Drs Akerele and Lightman, resistance to antiviral therapy occurs not infrequently. Clinical trial results to date indicate that the development of resistance with adefovir dipivoxil may not be a limiting factor with long term use. Glaxo Wellcome’s new agent benzimidavir, with its novel mechanism of action, may also prove useful in patients infected with strains resistant to currently available antiviral agents. Benzimidavir inhibits CMV DNA synthesis by an as yet undefined mechanism, and has shown in vitro activity against CMV 3- to 20-fold greater than ganciclovir, cidovir and lobucavir, and 100-fold greater than foscarnet.

Many novel approaches are also being trialed in patients with CMV infections or to prevent such infections. Two vaccines are currently in clinical development, both of which are directed toward CMV glycoprotein B (gpB). One is a live vaccine (Pasteur Mérieux Connaught) with the inherent risks of potential latency, reactivation and oncogenicity, and the other is an inert recombinant gpB subunit vaccine (Chiron) with the promise of avoiding these potential risks while retaining immunogenic capacity. Other novel approaches to therapy
include 2 agents that are being specifically trialed in patients with CMV retinitis, the human anti-CMV monoclonal antibody, sevirumab, and the antisense compound GEM 132 (Gene Expression Modulator 132). Sevirumab is directed toward a confirmational epitope of the viral envelope gpH and has shown promising results in patients with CMV retinitis when given as adjunctive therapy, although the optimal dose has yet to be determined. GEM 132 is comprised of the DNA sequence complementary to that of the intron-exon boundary between 2 genes required for CMV replication (UL-36 and UL-37), and both intravenous and intravitreal formulations are being developed.

Unfortunately, despite the range of approaches being investigated, there is overall a lack of agents under development for CMV infections, and CMV retinitis in particular.