Combination Activity and Emerging Resistance Profile of Brincidofovir in CMV Prevention and Treatment

S. Foster[1], D. Selleseth[1], M. Prichard[2], T. Brundage[1], H. Momméja-Marin[1], R. Lanier[1]

[1]Chimerix, Inc., Durham, NC;
[2]University of Alabama, Birmingham, AL.

Abstract:

Background:
Brincidofovir (CMX001, BCV) is an in vitro broad-spectrum oral antiviral in Phase 3 development for prevention of cytomegalovirus (CMV) in hematopoietic cell transplantation. BCV is converted intracellularly to cidofovir (CDV) diphosphate which is an alternative substrate inhibitor of the CMV DNA polymerase (UL54). The combination activity and resistance profile of BCV were evaluated in vitro and in two completed clinical trials; Study 201enrolled CMV antiviral naïve subjects and Study 350 enrolled antiviral therapy experienced patients.

Methods:
Combination activity was assessed using a matrix of drug dilutions and viral load was quantified by real time PCR. Passaging used CMV AD169 and HFF cells cultured in increasing amounts of BCV for 10 months; plaque reduction assays were used to assess phenotypic resistance. Clinical samples from the Phase 2 CMV prevention dose escalation study (Study 201) and the expanded access for treatment of refractory CMV (Study 350) were sequenced at Viracor-IBT using CMV Antiviral Resistance Test 5600.

Results:
In vitro combination activity studies with acyclovir or ganciclovir (GCV) and BCV showed additive to synergistic activity against CMV and no evidence of antagonism. BCV selected a unique mutation (D542E) in UL54 associated with slower replication and resistance to BCV and CDV, but no cross-resistance to GCV or foscarnet. In Study 201 (N=171), no known resistance associated mutations (RAMs) were detected and all polymorphisms tested had a sensitive phenotype. In Study 350 baseline genotyping revealed UL54 CDV/GCV RAMs in 2 subjects and UL97 GCV RAMs in 18 subjects; 39 subjects had no CDV or GCV RAMs detected. Neither subject with UL54 CDV RAMs had plasma CMV values <200 copies/mL at the time of last on-therapy specimen while 44% (8 of 18 and 17 of 39, respectively) of subjects with prior UL97 GCV RAMs or no prior RAMs detected reached 200 copies or less.

Conclusions:
Use of CMV antivirals leading to UL54 RAMs may compromise the antiviral activity of BCV. By contrast, first line use of BCV for prevention may preserve subsequent therapeutic options. Combination therapy may be desirable in heavily pretreated subjects, especially those with CMV UL54 mutations associated with antiviral resistance, and should be explored further