105

Twice-Weekly Brincidofovir (CMX001) Shows Promising Antiviral Activity in Immunocompromised Transplant Recipients with Asymptomatic Adenovirus Viremia

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Background: Adenovirus (AdV) infection causes morbidity and mortality in immunocompromised patients, particularly in pediatric patients. There is no approved therapy for the prevention, preemption or treatment of AdV infection. Brincidofovir (BCV, CMX001), an orally bioavailable broad-spectrum nucleotide analog, has demonstrated *in vitro* potency against all AdV species tested, including those most often associated with severe disease. Two recent clinical trials initiated brincidofovir twice weekly (BIW) in transplant recipients who presented with AdV viremia and no evidence of end-organ AdV disease.

Methods: Study 202 was a randomized, placebo-controlled trial that evaluated BCV as preemptive treatment of asymptomatic adenoviremia in hematopoietic cell transplant (HCT) recipients. Study 350 was an open-label, expanded access trial in immunocompromised patients with no alternative therapeutic intervention. Adult subjects were treated with BCV 100 mg BIW; pediatric subjects were treated with BCV 2 mg/kg BIW. AdV viremia was monitored weekly. Antiviral responses and mortality results are reported.

Results: A total of 26 subjects in Study 202 (n=14) and Study 350 (n=12) received BCV BIW based on AdV viremia at screening. Subjects ranged from 7 months to 68 years of age and all but one were HCT recipients. AdV was detected at the central laboratory in 21 subjects at the time of first dose. Baseline viremia (BL) ranged from 100 (the lower limit of detection for the assay, LLOD) to 2.2 x 10^7 copies/mL (median 3700). AdV viremia decreased to ≤LLOD for 67% (14 of 21) subjects within the first week of therapy; an additional 4 subjects (18 of 21, 86%) reached ≤LLOD at some time during treatment. High levels of AdV viremia (>1000 c/mL) detected in 14 subjects decreased to ≤LLOD in 79% (11 of 14) within a median of 9 days of BCV, and with a mean decrease of 1.8 $\log_{10}$c/mL. Observed all-cause mortality during a median 8 weeks (range 3 to 47) of follow-up was 15% (4 of 26). Two of the 4 subjects who died had undetectable AdV viremia at the time of death.

Conclusions: High risk transplant patients receiving twice-weekly brincidofovir had rapid decline in their AdV viremia, with limited progression to all-cause mortality. BCV is a promising therapy for AdV and further study is warranted.

106

Brincidofovir (CMX001) Is Well Tolerated in Highly Immunocompromised Pediatric Patients

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Background: Brincidofovir (BCV, CMX001) is a Phase 3 broad-spectrum antiviral in development for the prevention of dsDNA viral infections in immunocompromised patients. Since pediatric patients pose unique toxicity challenges and dsDNA viral infections are common in this age group, we undertook an analysis of the collective safety experience in pediatric subjects receiving BCV.

Methods: All pediatric subjects (<18 years) received oral BCV weekly or twice-weekly under EINDs, in the open-label expanded access Study 350, and in placebo-controlled Study 202 for the preemptive treatment of adenovirus (AdV) infection. In Study 202, BCV was administered with food and guidance on the management of gastrointestinal (GI) disturbances was provided to the investigators.

Results: 147 pediatric subjects (median 7 years, range 3 months to 17 years) received a median of 7 weeks of BCV (range 1 to 44), with 45 subjects receiving at least 10 weeks of 4 mg/kg/week. Subjects were predominantly hematopoietic cell transplant (HCT) recipients. Consistent with data from adult immunocompromised subjects, the most frequently reported adverse events (AEs) were GI disturbances, with diarrhea of any grade reported in 48% of subjects in Study 202 and 43% in Study 350 and EINDs. Grade 3/4 diarrhea was reported in 13% (Study 202) and 12% (Study 350) of subjects. Less than 10% of subjects across Studies 202 and 350 discontinued BCV for GI symptoms. Transient increases in ALT were reported in 4% (Study 202) and 12% (Study 350 and EINDs) of subjects, predominantly <5x ULN (grade 2) and not requiring discontinuation of BCV. In Study 202, the incidence of GI and ALT events leading to study drug discontinuation was not higher in the BCV group than in the placebo group, although the interpretation of these data is limited by the small sample size. Based on treatment emergent laboratory abnormalities, no indications of renal toxicity or hematologic toxicity including neutropenia were observed, including subjects who received higher BCV dose or longer durations of treatment.

Conclusions: A review of data from pediatric subjects treated with brincidofovir did not indicate any previously unidentified safety signals. In these subjects, as in adults, there was no indication of hematologic or renal toxicity. The safety and tolerability profile in adults and pediatric patients to date support the continued development of brincidofovir as prevention for dsDNA viral diseases.

107

Robust Vaccine Responses in Double-Unit Cord Blood Transplantation (CBT) Recipients Despite Lack of Transfer of Memory T and B Cells

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Introduction: CBT is now associated with comparable disease-free survival to that of adult donor transplantation. However, given CB grafts lack memory T & B cells, the ability of CBT recipients to respond to vaccines is of great interest.

Methods: We analyzed the proportion of surviving double-unit CBT recipients undergoing vaccination & their responses (seroconversion or >3x rise in titers) to primary series vaccines (tetanus, diphtheria, pertussis, H. influenzae, polio & pneumococcus). Pneumococcal response was defined as