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Brincidofovir for Asymptomatic Adenovirus Viremia in Pediatric and Adult Allogeneic Hematopoietic Cell Transplant Recipients: A Randomized Placebo-Controlled Phase II Trial

Michael S. Grimley [1,*], Roy F. Chemaly [2], Janet A. Englund [3], Joanne Kurtzberg [4], Gregory Chittick [5], Thomas M. Brundage [5], Andrew Bae [5], Marion E. Morrison [5], Vinod K. Prasad [4]

[1] *Bone Marrow Transplant and Immune Deficiency, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio*
[2] *Department of Infectious Disease, Infection Control and Employee Health, The University of Texas MD Anderson Cancer Center, Houston, Texas*
[3] *Seattle Children's Hospital, Seattle, Washington*
[4] *Pediatric Blood and Marrow Transplant Program, Duke University Medical Center, Durham, North Carolina*
[5] *Chimerix, Durham, North Carolina*

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Adenovirus infection in immunocompromised patients contributes to significant morbidity and mortality, especially after allogeneic hematopoietic cell transplantation (HCT). Brincidofovir (BCV, CMX001) is an orally bioavailable lipid conjugate of cidofovir that has in vitro activity against adenoviruses and other double-stranded DNA viruses. This randomized placebo-controlled phase II trial evaluated pre-emptive treatment with BCV for the prevention of adenovirus disease in pediatric and adult allogeneic HCT recipients with asymptomatic adenovirus viremia. Allogeneic HCT recipients with adenovirus viremia were randomized 1:1:1 to receive oral BCV 100 mg (2 mg/kg if <50 kg) twice weekly (BIW), BCV 200 mg (4 mg/kg if <50 kg) once weekly (QW), or placebo for 6 to 12 weeks, followed by 4 weeks of post-treatment follow-up. For randomization, subjects were stratified by screening absolute lymphocyte count (<300 cells/mm^3 versus ≥300 cells/mm^3). Assignment to BCV or placebo was double blinded; dose frequency was unblinded. The primary endpoint was the proportion of subjects experiencing *treatment failure*, defined as either progression to probable or definitive adenovirus disease or confirmed increasing adenovirus viremia (≥1 $\log_{10}$ copies/mL) during randomized therapy. Between June 2011 and December 2012, 48 subjects were randomized to the BCV BIW (n = 14), BCV QW (n = 16), or placebo (n = 18) groups. The proportion of subjects with treatment failure in the BCV BIW group was 21% (odds ratio, .53; 95% confidence interval [CI], .11 to 2.71; $P = .45$), 38% (odds ratio, 1.23; 95% CI, .30 to 5.05, $P = .779$) in the BCV QW group, and 33% in the placebo group. All-cause mortality was lower in the BCV BIW (14%) and BCV QW groups (31%) relative to the placebo group (39%), but these differences were not statistically significant. After 1 week of therapy, 8 of 12 subjects (67%) randomized to BCV BIW had undetectable adenovirus viremia (<100 copies/mL), compared with 4 of 14 subjects (29%) randomized to BCV QW and 5 of 15 subjects (33%) randomized to placebo. In a post hoc analysis of subjects with viremia ≥1000 copies/mL at baseline, 6 of 7 BCV BIW subjects (86%) achieved undetectable viremia compared with 2 of 8 placebo subjects (25%; $P = .04$). Early treatment discontinuation because of adverse events was more common in subjects treated with BCV than with placebo. Diarrhea was the most common event in all groups (57% BCV BIW, 38% BCV QW, 28% placebo), but it led to treatment discontinuation in only 1 subject receiving BCV QW. Events diagnosed as acute graft-versus-host disease, primarily of the gastrointestinal tract, were more frequent in the BCV BIW group (50%) than in the BCV QW (25%) and placebo (17%) groups. There was no evidence of myelotoxicity or nephrotoxicity in BCV-treated subjects. The results of this trial confirm the antiviral activity of BCV against adenoviruses. Further investigation is ongoing to define the optimal treatment strategy for HCT recipients with serious adenovirus infection and disease.

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* Correspondence and reprint requests: Michael S. Grimley, MD, Bone Marrow Transplant and Immune Deficiency, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, MLC 11027, Cincinnati, OH 45229.
E-mail address: michael.grimley@cchmc.org (M.S. Grimley).

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INTRODUCTION

Adenoviruses cause a wide spectrum of disease in immunocompromised patients, ranging from asymptomatic viremia to severe disseminated disease, particularly before immune reconstitution in recipients of allogeneic hematopoietic stem cell transplantation (HCT). Although post-transplantation infection with adenoviruses, as detected in stool or nasopharyngeal wash, may remain asymptomatic in patients with rapid immune reconstitution, an array of factors can increase the risk for developing disseminated disease and mortality. The most consistent risk factors are frequently associated with delayed immune reconstitution, including cord blood and other unrelated donors, in vivo or ex vivo T cell depletion, graft-versus-host disease (GVHD), young recipient age, and higher adenovirus viremia in plasma [1-3]. The incidence of infection with adenoviruses in patients undergoing allogeneic HCT is estimated to be between 5% and 47% [4-11], with higher incidence in pediatric patients; most cases of serious disease occur in the first 100 days after transplantation [5,6,11]. Mortality rates of up to 26% are reported for untreated HCT recipients with symptomatic localized infection, and mortality rates of 80% or greater are reported for lower respiratory tract infections associated with disseminated disease [3,5,10-14].

There is no approved antiviral agent for the treatment of adenovirus infection. Current treatment strategies may include a reduction in immune suppression, if clinically possible, and/or the off-label use of intravenous gamma globulins or intravenous cidofovir (CDV) [10,15-17]. However, CDV is associated with significant dose-limiting nephrotoxicity in up to 50% of patients [12,18] as well as myelotoxicity. Brincidofovir (BCV, CMX001) is an orally bioavailable lipid conjugate of CDV that has more potent in vitro activity against adenoviruses and demonstrated reduction of viral replication in an established animal model, along with substantial reduction of adenovirus-related mortality [19]. In patients who were treated for serious infections with adenoviruses through emergency investigational new drug regulations in the United States, BCV reduced adenovirus viral load and reported cases had significant reductions in adenovirus-related symptoms and associated mortality [20,21]. Unlike CDV, BCV has not been associated with overt drug-related myelotoxicity or nephrotoxicity [22].

The pre-emptive use of appropriate antiviral therapy before symptomatic disease has demonstrated a substantial reduction in cytomegalovirus (CMV)-related disease and associated mortality in patients after HCT; such an approach could theoretically also improve outcomes in patients at risk for adenovirus disease. In this report, we describe the results from the AdV HALT trial (CMX001-202; NCT01241344), a randomized, placebo-controlled, multicenter, phase II study to evaluate the safety and efficacy of pre-emptive treatment with BCV for the prevention of adenovirus disease in pediatric and adult allogeneic HCT recipients.

MATERIALS AND METHODS

Subjects

Allogeneic HCT recipients who were between the ages of 3 months and 75 years, inclusive, and who had asymptomatic adenovirus viremia in plasma based on polymerase chain reaction (PCR) testing performed at the local virology laboratory and confirmed as ≥100 copies/mL by the designated central virology laboratory were enrolled into the study. To identify prospective subjects at centers that did not routinely conduct screening assessments for adenovirus viremia, subjects could be enrolled in a companion screening protocol, in which blood samples were collected weekly for the first 100 days after transplantation and were analyzed for adenovirus by PCR by the central virology laboratory. Subjects with possible, probable, or definitive adenovirus disease per protocol definitions (see Supplementary Table S1) were ineligible for the study. Additional exclusion criteria included elevated aminotransferases (>5 times upper limit of normal [ULN]), total bilirubin (≥2 times ULN), or conjugated bilirubin (≥1.5 times ULN); treatment with CDV, ribavirin, or leflunomide within 14 days of enrollment; human immunodeficiency virus infection; and suspected gastrointestinal (GI) GVHD that was not validated by a biopsy (ie, subjects with biopsy-proven GI GVHD could be enrolled). Each subject or legal guardian provided consent before participation in the study; assent was obtained from minors where required by institutional practices.

Study Design and Endpoints

The study protocol was approved by the institutional review board at each participating center. The study was conducted in accordance with recognized international scientific and ethical standards including but not limited to the International Conference on Harmonisation guideline for Good Clinical Practice and the original principles embodied in the Declaration of Helsinki. An independent data and safety monitoring board was convened to review unblinded study data on a periodic basis and to provide recommendations regarding the continued enrollment of the study.

Subjects were randomized 1:1:1 to BCV twice weekly (BIW), BCV once weekly (QW), or placebo. Assignment to BCV or placebo was double blinded; dose frequency was not blinded. The randomization schedule included stratification by the subject's absolute lymphocyte count (ALC) at screening (<300 cells/mm^3 or ≥300 cells/mm^3) and was implemented using an integrated voice/web response system. (The randomization schema is summarized in Supplementary Figure S1.) Adult subjects (≥18 years of age) randomized to a BCV cohort received either 100 mg BIW or 200 mg QW. Pediatric subjects (age <18 years) randomized to a BCV cohort received either 2 mg/kg BIW (maximum dose of 100 mg BIW) or 4 mg/kg QW (maximum dose 200 mg QW) as solution or suspension.

Subjects underwent safety and virology assessments on days 0, 3, 7, 10, 14, and 21 and then once each week thereafter for the duration of treatment. Subjects were on study treatment for at least 6 weeks but no more than 12 weeks, followed by 4 weeks of post-treatment follow-up. A *complete virologic response* was defined as confirmed adenovirus DNA PCR values <100 copies/mL (the limit of detection) reported by the central virology laboratory for 4 consecutive weeks. From week 6 and thereafter, subjects who had a negative or undetectable adenovirus viremia for 4 consecutive weeks were determined to have completed the treatment phase of the study. These subjects were discontinued from treatment and began 4 weeks of treatment-free follow-up.

Subjects who experienced an increased adenovirus viral load (≥1 $\log_{10}$ increase from baseline confirmed by 2 measurements performed 1 week apart) or who were considered to have developed probable or definitive adenovirus disease (see Supplementary Table S1 for detailed descriptions) at any time after initiating randomized treatment were offered open-label BCV 100 mg BIW (or 2 mg/kg BIW if <50 kg), regardless of how long they had been on randomized (blinded) study drug. In addition, after the implementation of a protocol amendment (in July 2012), open-label BCV BIW was also offered to subjects who developed probable or definitive adenovirus disease during prescreening or screening before initiating the randomized treatment. Subjects could receive up to 12 weeks of open-label BCV.

The primary efficacy endpoint was the proportion of subjects experiencing *treatment failure*, defined as progression to probable or definitive adenovirus disease (see Supplementary Table S1) or *increasing adenovirus viremia* during randomized therapy, defined as an increase from baseline by ≥1 $\log_{10}$, confirmed by a second measurement at least 1 week later and requiring discontinuation from randomized therapy. Secondary endpoints included the incidence of and time to progression to probable or definitive adenovirus disease and the incidence of and time to death (all cause) on treatment and to the end of the study.

Safety monitoring procedures, including physical examination, vital signs, the collection of blood and urine for clinic laboratory testing, and the recording of adverse events (AEs) and concomitant medications were performed before first study drug administration and at periodic intervals after the initiation of dosing. AE severity was graded according to the National Institutes of Health/National Cancer Institute Common Terminology Criteria for Adverse Events version 4.02. A program-wide safety monitoring and management plan developed following completion of a randomized, placebo-controlled study of BCV for the prevention of CMV in CMV-seropositive allogeneic HCT recipients [22] was implemented throughout the conduct of this study. The safety monitoring and management plan provided detailed methods for monitoring, characterizing, and managing GI symptoms or hepatic laboratory abnormalities that occurred while receiving BCV. For subjects with more than 1 GI AE or grade 2 diarrhea for more than 3 consecutive days, temporary interruption of study drug was considered. For subjects with grade 3 or higher GI AEs, study drug dosing interruption was mandated. After improvement of the grade 3 or higher signs and symptoms, study drug dosing was able to be resumed.