

Safety and Pharmacokinetics of Exebacase in an Infant with Disseminated *Staphylococcus aureus* Infection

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Abstract

Exebacase, an anti-staphylococcal lysin produced from a bacteriophage-encoded gene, is a promising adjunctive therapy for severe methicillin-resistant *Staphylococcus aureus* infections. We describe the first infant to receive exebacase, dosing, and pharmacokinetics (PK). Exebacase may be safe and efficacious in children; however, further clinical trials are needed to optimize dosing.

Key words: Methicillin-resistant *Staphylococcus aureus*, exebacase, bacteriophage-derived therapy, endocarditis

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BACKGROUND

Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia causes significant morbidity and mortality.^{1,2} Intravenous antibiotics are the standard therapy for MRSA bacteremia and endocarditis^{3,4}; however, treatment is difficult due to limited drug penetration, adverse events, and emerging resistance.⁵ New therapies for MRSA bacteremia are greatly needed.

Lysin enzymes, which destroy the bacterial cell wall, are a novel add-on to antibacterial therapy for MRSA infections. Exebacase is a first-in-human anti-staphylococcal lysin recombinantly produced as a purified protein from a bacteriophage-encoded gene.^{6,7} In a recent randomized, double-blind, placebo-controlled international phase 2 study in adults, exebacase was well tolerated and showed preliminary efficacy.⁸ However, exebacase has not yet been studied in children. We present the first report of bacteriophage gene-derived lysin therapy use in an infant.

CASE PRESENTATION

A previously healthy 5-month-old male presented to Duke University Hospital for evaluation of jerking movements and inability to sit independently. Five days before presentation he had tactile fever, decreased oral intake, and rhinorrhea. Two weeks earlier, his mother noted an indurated area in his groin that spontaneously resolved. The infant was up-to-date on vaccinations and had no significant prenatal history.

He was admitted to the pediatric intensive care unit due to concern for neurologic instability. He had a body weight of 7.80 kg, length of 64 cm, body temperature of 36.8°C, blood pressure of 100/61 mm Hg, pulse rate of 149 beats/minute, respiratory rate of 32 breaths/minute, and peripheral oxygen saturation of 98% on room air. Pertinent physical examination findings included right-sided facial and right upper and lower extremity weakness, and red/purple discolorations and pinpoint white papules on bilateral heels. Initial laboratory results reported a white blood cell count of $27.8 \times 10^9/L$ with 72% segmented neutrophils, C-reactive protein of 39.96 mg/dL, and serum creatinine of 0.2 mg/dL. Electrolytes, hepatic enzymes, coagulation markers, hemoglobin, and platelets were all within normal range for age. A head computerized tomography scan noted left-sided subdural hemorrhage

and left-middle cerebral artery (MCA) infarct. Magnetic resonance imaging of the brain, head, and neck showed left hemispheric meningitis with associated subdural empyema, mycotic aneurysm, acute left MCA territory infarct, and a retropharyngeal abscess 3.6 cm in diameter with associated clival osteomyelitis.

Empirical antimicrobial treatment was started with vancomycin, ceftriaxone, metronidazole, and acyclovir. Within 12 hours of sample collection, MRSA—susceptible to vancomycin, trimethoprim-sulfamethoxazole, clindamycin, daptomycin, linezolid, and ceftaroline—was isolated from blood. He was urgently taken for operative drainage of the retropharyngeal abscess and left temporal subdural empyema. Intraoperative cultures from both abscesses isolated MRSA. On hospital day 2, a transthoracic echocardiogram showed a mobile echogenic mass (13 mm×7 mm) attached to the septal leaflet of the tricuspid valve with extension onto the right side of the membranous ventricular septum, confirming the diagnosis of endocarditis. Further imaging noted bilateral peripheral lung opacities suggestive of septic pulmonary emboli, but no additional evidence of end-organ MRSA disease. The patient had ongoing bacteremia and minimal clinical improvement, despite therapeutic dosing of vancomycin and linezolid. The timeline of antimicrobial therapy and surgical interventions is presented in Supplementary Figure 1.

We sought to hasten eradication of the bloodstream infection, sterilize the cardiac vegetation, and optimize the patient for future surgical intervention as the definitive therapy for endocarditis. We obtained an emergency use, single-patient US Food and Drug Administration investigational new drug application for exebacase. Caregivers consented to study drug dosing and participation in a pediatric pharmacokinetics (PK) protocol previously approved by the local institutional review board (NCT03481881) (Supplementary Figure 1). The patient received a one-time, 3 mg dose of exebacase on hospital day 7.

Blood cultures became sterile on hospital day 12. On hospital day 16, anticipating need for prolonged therapy, antibiotics were changed to daptomycin (12 mg/kg/dose daily) and ceftaroline (15 mg/kg/dose every 6 hours). He had ongoing clinical improvement and serial echocardiograms noted no evidence of vegetation or mass on hospital day 40, after nearly 6 weeks of therapy (Supplementary Figure 1). Immunologic work-up, including a neutrophil respiratory burst, complement levels, and an

immunoglobulin panel, were unremarkable; lymphocyte enumeration was notable for decreased B cells (CD19 8.2%, 178/mm³; CD20 8.3%, 181/mm³; CD40 8.3%, 181/mm³).

Study Drug Dosing and Pharmacokinetic Modeling

PK modeling and simulation were used to a) aid in dose selection prior to study drug administration and b) analyze the PK data from the infant. For dose selection, the analysis leveraged a previously developed population PK model including data from 72 adults (348 plasma concentrations) who received an intravenous dose of exebacase.⁹ The adult population PK model was a structural 3-compartment model with a systemic clearance (CL) estimate of 4.2 L/hr (relative standard error [RSE]=5.5%), V₁=4.5 L (RSE=8.2%), and volume of distribution (V_d)=20.2 L with creatinine clearance (CrCL) as a covariate for CL. This adult model was extrapolated using allometric scaling principles to predict infant exposures at different doses. Given the paucity of information on lysin PK in infants, a conservative allometric exponent (0.875) was used for the drug clearance parameters and predicted the expected (median) concentration profile for the infant using the following equations:

$$Cl_{infant} = Cl_{adult} \cdot (BW/79)^{0.875} \cdot (CrCl/46.5)^{0.388}$$
$$V_{infant} = V_{adult} \cdot (BW/79)$$

Where Cl_{adult} represents clearance parameters (central or intercompartmental clearance) for a typical adult; V_{adult} represents volume of distribution parameters (central or peripheral) for a typical adult; Cl_{infant} and V_{infant} represent the clearance and volume parameters for infant given the body weight (BW) in kilogram and $CrCl$ in mL/min. The model covariates were centered on median values observed in adults. The model predicted that a single dose of exebacase 3 mg (0.38 mg/kg) would achieve an area under the curve from time of administration to infinity (AUC_{inf}) of 2924 ng.hr/mL, consistent with exposures observed to be therapeutic in an average adult.

Following intravenous administration of 3 mg of exebacase over 2 hours, 3 blood samples were taken 38, 24, and 409 minutes after the end of the infusion. Exebacase was quantified in plasma samples (Charles River Laboratories, Senneville, QC, Canada) using a validated sandwich enzyme-

linked immunosorbent assay (ELISA). Exebacase was captured on maxisorb ELISA plate using a polyclonal rabbit antibody against exebacase and detected by a biotinylated human anti-exebacase bivalent Fab followed by a streptavidin-HRP conjugate (Jackson ImmunoResearch, West Grove, PA). TMB peroxidase substrate (SeraCare, Gaithersburg, MD) was applied to the plate, and absorbance at 450 nm was obtained with a SpectraMax plate reader (Molecular Devices, San Jose, CA). Exebacase concentrations were determined by interpolation from calibration standards.

For the PK analysis, the demographics, dosing, and drug concentration data for the infant were added to the PK analysis dataset and refitted to the population PK model that included allometric scaling. With this updated model and individual post-hoc PK parameter estimates, concentration-time profile over a 12-hour post-dose period for an infant was predicted (Figure 1). The calculated exebacase AUC_{0-inf} from this profile was 604 ng.hr/mL. All PK modeling and simulation was performed using NONMEM v7.1 and mrgSolve.

DISCUSSION

Exebacase is a new agent in development for treatment of serious MRSA infections.^{6,7} Exebacase, a first-in-class, non-antibiotic medication, targets the bacterial cell wall and works synergistically with antibiotic therapy. Adults treated with exebacase and antibiotics had decreased 30-day all-cause mortality (3.7% vs. 25.0% in the MRSA subgroup) compared with antibiotics alone.⁸

The patient in this report presented with a life-threatening MRSA infection with multi-organ involvement. Despite targeted therapy, optimized dosing, and attempts at source control, we did not achieve clearance of bacteremia with antibiotics alone. The median exebacase AUC_{0-inf} in this infant was nearly 5-fold lower than the value predicted from the allometric scaling of the adult model. Adult doses are designed to provide exebacase AUC_{0-inf} with a median of 1830 ng.hr/mL or higher to ensure the probability of target attainment approaches 100%.⁹ Pre-clinical models support a >60% probability of target attainment at exebacase AUC_{0-inf} of 525 ng.hr/mL.⁹ Therefore, the exposure in this infant may be within the efficacious range of exebacase; however, we cannot be certain until further studies in this population are conducted. If the data from this infant translate to other children, higher doses per mg of body weight may be required to achieve exposures similar to an average adult.

Reports evaluating pediatric scaling of adult PK models of lysin products to children are virtually non-existent. Factors that could influence a higher clearance in children could be an inherent higher catabolic activity for peptides and proteins or higher host immune response or interactions between phage products and antibiotics; however, there are no current data from adults or pre-clinical models to support this.¹⁰ Thus, allometric scaling based on body weight alone may not be sufficient when predicting dosing of these new therapeutics in children. Our findings underscore the need for PK clinical trials in this population.

This report represents a single patient, and it is difficult to know if clinical improvement was due to exebacase directly or the result of extended antibiotic therapy. Despite these limitations, exebacase is a novel agent that may be a beneficial adjunctive therapy for severe MRSA infections in children.

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NOTES

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RGG, CDH, and KRK have no disclosures to report.

CC is the Chief Medical Officer at ContraFect; reports Exebacase composition of matter patent and stock/stock options with ContraFect Corporation.

PG is a consultant for ContraFect.

VGF was the Overall Principal Investigator for the Exebacase Phase 2 trial and is the overall PI for the Phase 3 Exebacase trial. In addition, VGF reports personal fees from Durata, Novartis, Novadigm, Durata, Debiopharm, Genentech, Achaogen, Affinium, Medicines Co., Cerexa, Tetrphase, Trius, MedImmune, Bayer, Theravance, Basilea, Affinergy, Janssen, xBiotech, Contrafect, Regeneron, Basilea, Destiny, Advanced Liquid Logics, Genentech, NIH, Locus, Alergan, Contrafect, Pfizer, Karius, Medical Biosurfaces; Amphlphi Biosciences. Integrated Biotherapeutics; C3J, Armata,

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Figure Legends

Figure 1. Exebacase concentration-time profile.

Overlay of concentration-time profile in this patient (orange profile) compared with adults shown as median and 95% CI (blue solid line and shaded area).

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Figure 1

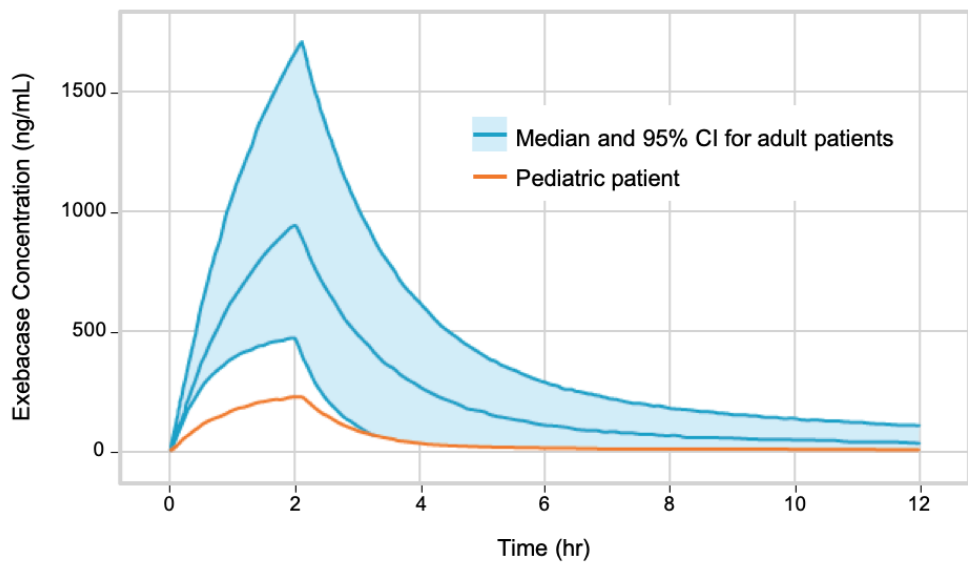


Figure 1: Exebacase concentration-time profile

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