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Evaluation of Ceftriaxone Plus Avibactam in an Intracellular Hollow Fiber Model of Tuberculosis: Implications for the Treatment of Disseminated and Meningeal Tuberculosis in Children

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Background: Ceftazidime-avibactam is an effective agent for the treatment of tuberculosis (TB) but requires frequent administration because of a short half-life. Due to a longer half-life, ceftriaxone could allow intermittent dosing.

Methods: First, we identified the MIC of ceftriaxone with 15 mg/L avibactam in 30 clinical *Mycobacterium tuberculosis* isolates. Next, 2 ceftriaxone exposure-effect studies in the intracellular hollow fiber model of TB (HFS-TB) that mimics disseminated disease in young children, were performed. Ceftriaxone was administered once or twice daily for 28 days to explore percentage of time that the concentration persisted above MIC ($\%T_{MIC}$) ranging from 0 to 100%. In a third HFS-TB experiment, the "double cephalosporin" regimen of ceftazidime-ceftriaxone-avibactam was examined and analyzed using Bliss Independence.

Conclusion: The MIC_{99} of the clinical strains was 32 mg/L, in the presence of 15 mg/L avibactam. Ceftriaxone $\%T_{MIC}$ <42 had no microbial effect in the HFS-TB, $\%T_{MIC}$ >54% demonstrated a 4.1 $\log_{10}$ colony-forming units per milliliter *M. tuberculosis* kill, while $\%T_{MIC}$ mediating E_{max} was 68%. The "double cephalosporin" combination was highly synergistic. Monte Carlo experiments of 10,000 subjects identified the optimal ceftriaxone dose as 100 mg/kg twice a day.

Conclusion: The combination of ceftriaxone-avibactam at 100 mg/kg could achieve E_{max} in >90% of children. The ceftriaxone potent activity *M. tuberculosis* could potentially shorten therapy in children with disseminated TB.

Key Words: hollow fiber model, cephalosporin, optimal dose, children, tuberculosis

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Drug-resistant *Mycobacterium tuberculosis* is a major global health emergency; drug resistance has already been reported to the newly developed tuberculosis (TB) drugs delamanid and bedaquiline.[1–7] Given the limited number of candidates in the TB drug pipeline, "repurposing" drugs already approved for other indications could be an important strategy to achieve global TB control.[8,9] Repurposed drugs have the advantage that post-licensure data on dosing and toxicities are already available. This makes them more "shovel ready" for use, especially in historically understudied populations, such as in children. Frequently, data on dosing and toxicity for children lag behind those in adults when new drugs are developed. Elsewhere we have shown that benzylpenicillin and ceftazidime, when used with avibactam, were highly effective against *M. tuberculosis*, despite the short half-life.[10,11] In the present study, we wanted to optimize ceftriaxone, which has been used throughout the world for over fifty years for the treatment of Gram-positive and Gram-negative infections and has a long half-life[10–13] for the treatment of TB.

Ceftriaxone, an aminothiazolyl-oxyimino cephalosporin, is more β-lactamase stable, with a half-life of 6–8 hours that could allow once-daily dosing in TB. Ceftriaxone has a good cerebrospinal fluid (CSF) to serum penetration ratios, which makes it useful for the treatment of TB meningitis, commonly encountered in young children with disseminated disease.[14–16] Ceftriaxone is also safe during pregnancy as well as for children and infants out of the neonatal period, suggesting that if efficacy against *M. tuberculosis* is demonstrated, it would be a useful drug in these neglected patient groups. In children <3 years, in whom there are higher rates of death and therapy failure, disseminated disease is predominantly intracellular.[17] Involvement of meninges, peritoneum and bone is more common than in older patients. Here, we examined the efficacy of ceftriaxone plus avibactam in the hollow fiber model of TB (HFS-TB).[10,11,18–20]

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MATERIALS AND METHODS

Bacterial Strain, Cell Lines and Supplies

The culture conditions and the growth medium for both *M. tuberculosis* ATCC #25177) and the THP-1 cells (ATCC TIB-202) were as reported previously.[10,11,20] We used our library of 30 clinical isolates [10 susceptible to rifampin and isoniazid and 20 multidrug-resistant (MDR; resistant to both rifampin and isoniazid] obtained from the Medical Research Council of South Africa. Hollow fiber cartridges were purchased from FiberCell (Frederick, MD), ceftriaxone from Baylor University Medical Center pharmacy and avibactam from BOC Sciences (Shirley, NY). The BACTEC 960 system and Mycobacteria Growth Indicator Tubes (MGIT) were purchased from Becton Dickinson (Franklin Lakes, NJ).

Ceftriaxone MIC Distribution and Concentration-Response Studies

First, we performed a concentration-response study to determine if avibactam monotherapy has any effect on the growth of *M. tuberculosis*. The experiment was performed with *M. tuberculosis* H37Ra using the avibactam concentrations of 0, 3.75, 7.5, 15 and 30 mg/L. Second, we used both MGIT and micro-broth dilution methods to identify ceftriaxone MICs for *M. tuberculosis* H37Ra laboratory strain, but only the micro-broth dilution method for the clinical isolates.[21] The ceftriaxone concentrations, in a 2-fold dilution series, ranged from 0.25 to 128 mg/L. MICs were performed with and without the addition of 15 mg/L avibactam for the laboratory strain, but with avibactam for all clinical strains. Third, ceftriaxone concentrations-response studies (with 15 mg/L avibactam) were performed using the same concentrations as in the MIC experiments. The cultures were incubated at 37ºC under shaking conditions for 7 days, followed by 10-fold serial dilutions and inoculation on Middlebrook 7H10 agar supplemented with 10% oelic acid, albumin, dextrose, catalase agar. Colony-forming units per milliliter (CFU/mL) were counted after 21 days of incubation at 37ºC. All experiments were performed twice.

Ceftriaxone Hollow Fiber System Model of Tuberculosis Studies

Using the intracellular HFS-TB model,[11,20,22] we performed 2 different ceftriaxone experiments to identify (1) the optimal ceftriaxone exposure and (2) the best dosing schedule, based on the ceftriaxone serum half-life of 5.8 ± 2.6 hours encountered in infants and children <2 years.[13,23] In the first HFS-TB experiment, we used avibactam at a constant concentration of 1 mg/L, described as the pharmacokinetics/pharmacodynamics (PK/PD) target for avibactam for Gram-negative bacilli in the ceftazidime-avibactam Food and Drug Administration approval document.[13] In the second HFS-TB experiment, avibactam was used at a concentration of 15 mg/L, which is the concentration achieved in children when given the standard dose of the ceftazidime-avibactam, as well as the optimal avibactam concentration we identified in our *in vitro* experiments and elsewhere.[11,24] The details of the THP-1 monocytes infection with *M. tuberculosis* and inoculation into the HFS-TB have been described in detail elsewhere.[20,22] The HFS-TB units were treated with either a once daily or twice daily dosing schedule to achieve the percentage of time that the concentration persisted above MIC ($\%T_{MIC}$) ranging from 0 to 100%. Each HFS-TB unit was repetitively sampled to measure the ceftriaxone concentration as well as for *M. tuberculosis* CFU counts, using the methods described in detail elsewhere.[11,20] A portion of the processed sample from the peripheral compartment of the HFS-TB was inoculated into MGIT tubes to determine the time-to-positivity (TTP) as a second readout for bacterial burden.

Ceftazidime-Avibactam as Source of β-Lactamase Inhibitor

Currently, avibactam is only commercially available as ceftazidime-avibactam,[24] and is thus the only available avibactam source for clinicians. To determine if there is synergy/antagonism/additivity between ceftriaxone-avibactam and ceftazidime-avibactam, ceftriaxone optimal exposure and ceftazidime-avibactam at optimal exposure of $\%T_{MIC} \geq 63\%$[11] were administered to HFS-TB units as either (1) "monotherapy" (with avibactam) or (2) a combination as ceftriaxone-ceftazidime-avibactam. Samples for drug concentrations and CFU at various times were processed as described above.

Drug Concentration Measurements

The ceftazidime and avibactam concentration assays have been reported previously.[11] We used a stable-isotope dilution liquid chromatography-electrospray ionization tandem mass spectrometry to measure ceftriaxone concentrations. The calibrators, controls and internal standards (ceftazidime-d5) were included in each analytical run for quantification. The lower limit of detection of the method was 0.05 mg/L with a 6.2% and 7.4% inter- and intra-day variation.

Pharmacokinetics/Pharmacodynamics Analysis

The observed drug concentrations were modeled using ADAPT 5 software.[25] Concentrations were analyzed using a 1-compartmental model with first-order rate absorption and elimination. The primary PK parameters were estimated using the maximum likelihood expectation-maximization algorithm and then used to calculate the secondary parameters such as half-life, peak concentration (C_{max}) and 24-hour area under the concentration-time curve (AUC_{0-24}) for each HFS-TB. We used the inhibitory sigmoid E_{max} model using $\%T_{MIC}$ versus *M. tuberculosis* burden, to estimate the PK/PD exposure associated with 50% (EC_{50}), or 80% (EC_{80}) or 90% (EC_{90}) of maximal bacterial kill (E_{max}). We also identified the PK/PD index linked to microbial kill using the same inhibitory sigmoid E_{max} model for CFU/mL versus exposure ($\%T_{MIC}$ or AUC_{0-24}/MIC or C_{max}/MIC) based on corrected Akaike Information Criteria (AIC) scores.[26] GraphPad Prism (v7) was used for graphing.

Bliss Independence versus Loewe Additivity

In our prior experiments evaluating the impact of ceftazidime-avibactam on *M. tuberculosis*, we found that ceftazidime has a different binding target (PonA1) from other beta-lactams and cephalosporins,[11] and the inhibitory sigmoid E_{max} dose-response curves of ceftazidime-avibactam are not parallel with those of ceftriaxone-avibactam. Based on this, we assumed that ceftriaxone and ceftazidime work on independent targets, and fulfil the criteria for noninteraction, hence Bliss Independence.[27,28] Thus, we utilized Bliss Independence for our modeling. Effect was measured as percentage change from day 0. Theoretical additivity (X_T) was calculated by adding the effect of ceftriaxone-avibactam "monotherapy" (A) to ceftazidime-avibactam "monotherapy" (B) on each sampling day. The observed effect (X_o) was the percentage change from day 0 in the ceftriaxone-ceftazidime-avibactam combination regimen. The combination index (X_I) is given by:

$$X_I = \frac{X_T - A * B}{X_o}. \quad (1)$$

Monte Carlo Experiments

We utilized Monte Carlo experiments (MCE) to identify the optimal ceftriaxone doses for use in children.[18,22,29–31] The

following PK parameter estimates were used in both subroutine PRIOR of ADAPT and the parameter files: plasma clearance of 0.051 ± 0.024 L/h/kg and a volume of distribution of 0.382 ± 0.129 L/kg for 50 mg/kg dose, and clearance of 0.055 ± 0.018 L/h/kg and a volume of distribution of 0.387 ± 0.056 L/kg for 75 and 100 mg/kg, based on Steele et al[23] Each dose was infused intravenously over 10 minutes. The ratio for the ceftriaxone CSF-to-plasma AUC in neonates and infants with meningitis of 17%, as reported by Martin et al, was used for meningitis.[32] In children <5 years, at a dose of 50 mg/kg, ceftriaxone protein binding in serum is 82% ± 8% while that in CSF during purulent meningitis is 9% ± 6% protein-bound, which is negligible.[33] Free drug ceftriaxone concentrations were used in the MCE; for CSF total ceftriaxone was assumed equivalent to free drug. The ceftriaxone MIC distribution used was from our 30 clinical isolates.

RESULTS

MIC and Concentration-Response in Test Tubes

Avibactam up to 30 mg/L concentration did not show any inhibitory effect on *M. tuberculosis* growth. Therefore, avibactam on its own does not kill *M. tuberculosis*. The ceftriaxone MIC for *M. tuberculosis* H37Ra was 16 mg/L without avibactam but fell by 2-tube dilutions to 4 mg/L in the presence of 15 mg/L avibactam. Therefore, we subsequently identified ceftriaxone MICs against 30 clinical isolates only in combination with 15 mg/L avibactam. The MIC range was 0.5–32 mg/L. The MIC_{50} and MIC_{90} were 4 mg/L and 32 mg/L, respectively. In the concentration-response studies, ceftriaxone EC_{50} was calculated as 2xMIC and effect was near maximal at 4xMIC, consistent with time-driven effect ($r^2 = 0.97$).[34]

Hollow Fiber Model of Tuberculosis Experiment with 1 mg/L Avibactam

In the first ceftriaxone HFS-TB examined ceftriaxone, with an avibactam constant infusion concentration of 1 mg/L, the time-kill curves showed an exposure-dependent lowering of bacterial burden compared with nontreated control. After initial microbial kill below day 0 (stasis) on day 3, there was therapy failure due to the rebound growth by day 7. The Inhibitory sigmoid E_{max} model showed highest r^2 on day 7 when the relationship was described by following equation:

$$\text{Effect} = \frac{5.41 - 1.07 * \left(\%T_{MIC}\right)^{1.0}}{19.90^{1.0} + \left(\%T_{MIC}\right)^{1.0}} \quad (2)$$

so that the EC_{50} was $\%T_{MIC} = 19.90$, and EC_{80} was calculated as $\%T_{MIC} = 79.60$ ($r^2 = 0.92$).

Hollow Fiber Model of Tuberculosis with 15 mg/L Avibactam for Exposure-effect and Dose Scheduling

The ADAPT model predicted versus the observed ceftriaxone concentrations (r^2 of 0.99) with once daily or twice daily dosing schedule are shown in Figure 1A and B. The ceftriaxone elimination rate constant (K_{el}) achieved in the HFS-TB extracellular compartments, reported as a "population" was 0.09 ± 0.02/h while the volume of distribution was 1.39 ± 0.21 L and half-life was 7.25 ± 1.54 hours. The corresponding intracellular concentrations are shown in Figure 1C. The K_{el} was 0.04 ± 0.02/h while volume of distribution was 0.62 ± 0.17 L and half-life of 11.41 ± 10.32 hours. Thus, clearance of ceftriaxone from intracellular compartment was slower.

Figure 2A shows the kill curves in the HFS-TB by these exposures, based on the TTP readout, while Figure 2B shows the kill curves based on the CFU/mL readout. Lower the TTP, higher the bacterial burden. Figure 2A and B shows that there was microbial kill below day 0 (stasis) by several doses and dosing schedules, and a much greater depth of kill, which was sustained for up to 21 days in some doses, with 15 mg/L avibactam compared with what was observed with 1 mg/L of avibactam.

Figure 3A–C shows the inhibitory sigmoid E_{max} model output for the TTP readout for each PK/PD index: C_{max}/MIC or AUC/MIC or $\%T_{MIC}$. On day 28, the AIC scores for C_{max}/MIC was 15.58, for AUC/MIC was 13.75, while that for $\%T_{MIC}$ was 8.61. Based on this the PK/PD parameter linked to effect was $\%T_{MIC}$. Figure 3D–F shows the model output for CFU/mL versus exposure. The same was apparent with the CFU/mL readout: on day 28, the AIC score for C_{max}/MIC was 18.12, for AUC/MIC was 14.34, while that for $\%T_{MIC}$ was 7.34. Based on this readout, the lowest AIC score was for $\%T_{MIC}$, which was chosen as the PK/PD index-linked to *M. tuberculosis* kill. The relationship between $\%T_{MIC}$ and *M. tuberculosis* burden on day 28, at the end of the experiment, was described by Equation #3:

$$\text{Effect} = \frac{8.06 - 3.08 * \left(\%T_{MIC}\right)^{7.61}}{50.67^{7.61} + \left(\%T_{MIC}\right)^{7.61}} \quad (3)$$

The EC_{50} $\%T_{MIC}$ was 50.7%, while the EC_{80} $\%T_{MIC}$ was 60% of dosing interval ($r^2 = 0.91$).

Hollow Fiber Model of Tuberculosis to Explore Double β-Lactam Strategy

Figure 4A–C shows that ceftriaxone-avibactam and ceftazidime-avibactam as "monotherapies" had identical kill curves by TTP (Fig. 4A) and CFU/mL (Fig. 4B). The figure also shows that the double β-lactam combination of ceftriaxone-ceftazidime-avibactam killed better than either cephalosporin "monotherapy". We calculated Bliss Independence for each day, and then an overall interaction factor (X_I) and 95% confidence intervals (CI) for all sampling days, and then an overall X_I, based on CFU/mL readout, with results shown in Figure 4C. When X_I and its 95% CI were less than zero, as shown in Figure 4C for days 7 onwards, then there was synergy because the effect observed for the ceftriaxone-ceftazidime-avibactam combination regimen was greater than expected from adding the effect of ceftriaxone-avibactam "monotherapy" to that of ceftazidime-avibactam "monotherapy". On day 3, X_I and it is 95% CI crossed zero, which means the observed effect was exactly the same as the effect of the sum of the 2 monotherapies so that on that day they were additive. Overall, when data for all the entire experiments were combined, the mean X_I was –0.81 (95% CI: –1.01 to –0.63), indicating synergy (Fig. 4C).

Monte Carlo Experiments

MCE of several different doses is shown in Fig. 5A and B. The PK parameter estimates and standard deviations in the MCE output were clearance of 0.05 ± 0.04 L/h and volume of 0.38 ± 0.22 L (half-life = 5.21 hours) in 5000 children, which are identical to the parameters in the domain of input, which is an internal validation step. For external validation, we compared the peak concentrations we identified in the MCE for children treated with 50 mg/kg of 232 ± 134 mg/L to those of 220 ± 64 mg/L observed in actual children in the clinic treated with the same dose, and 308 ± 1106 mg/L versus 295 ± 76 mg/L in children treated with 75/mg/kg.[13] This means our simulations represent the reality seen in clinical trials when it comes to drug concentrations. Target

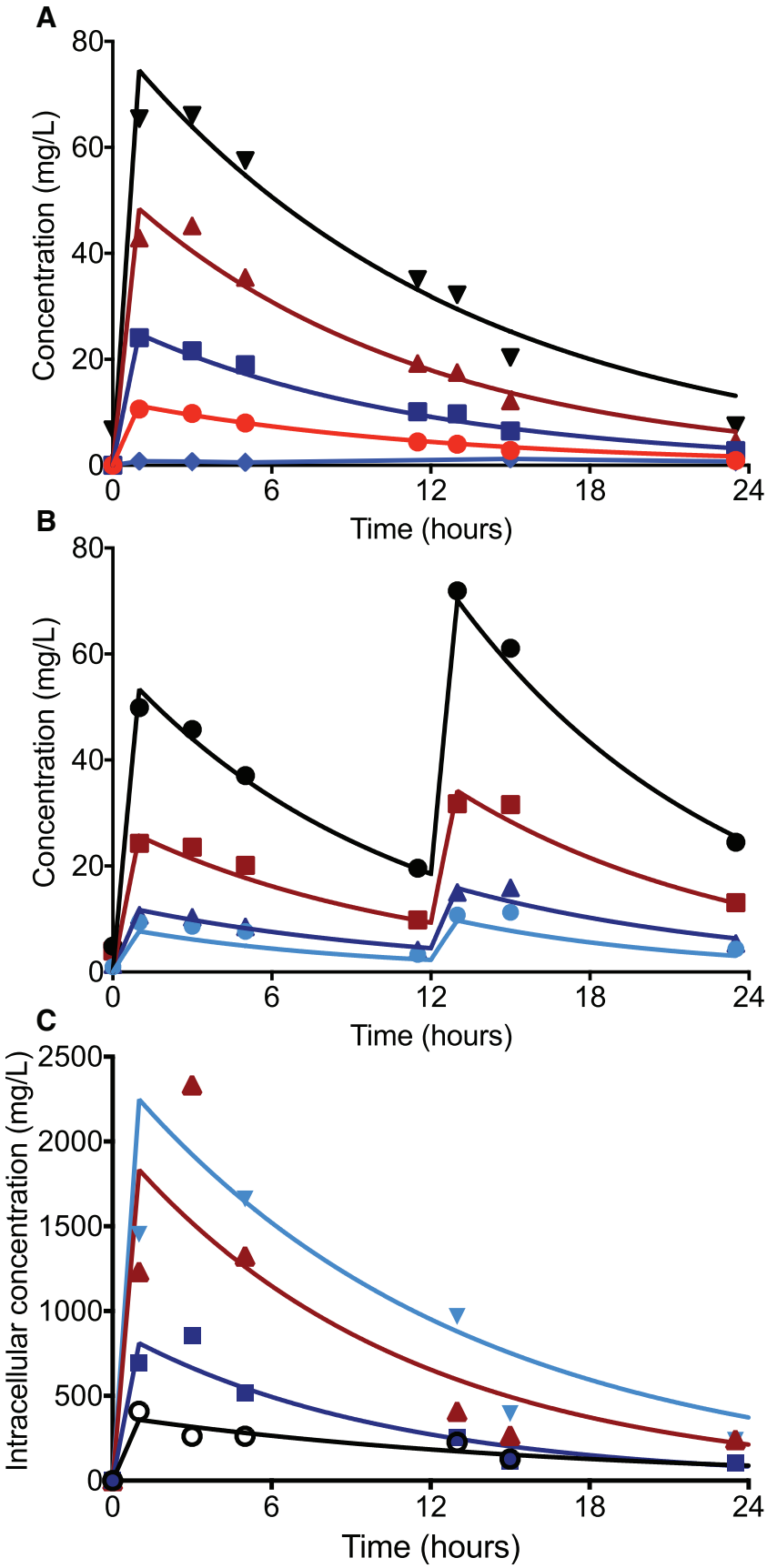

FIGURE 1. Ceftriaxone concentration-time profile in the HFS-TB. (A) Observed ceftriaxone concentrations versus ADAPT model-derived curves for the HFS-TB treated with a once-daily dosing schedule. (B) Observed ceftriaxone concentrations achieved in the central compartment of the HFS-TB with a twice-daily dosing schedule versus ADAPT model-derived curves. (C) Ceftriaxone concentration measured inside the THP-1 cells was multiple times higher than the concentration observed in the central compartment. The solid lines represent ADAPT PK model predicted ceftriaxone concentrations, and the symbols represent the observed concentration. HFS-TB indicates hollow fiber model of TB; TB, tuberculosis.

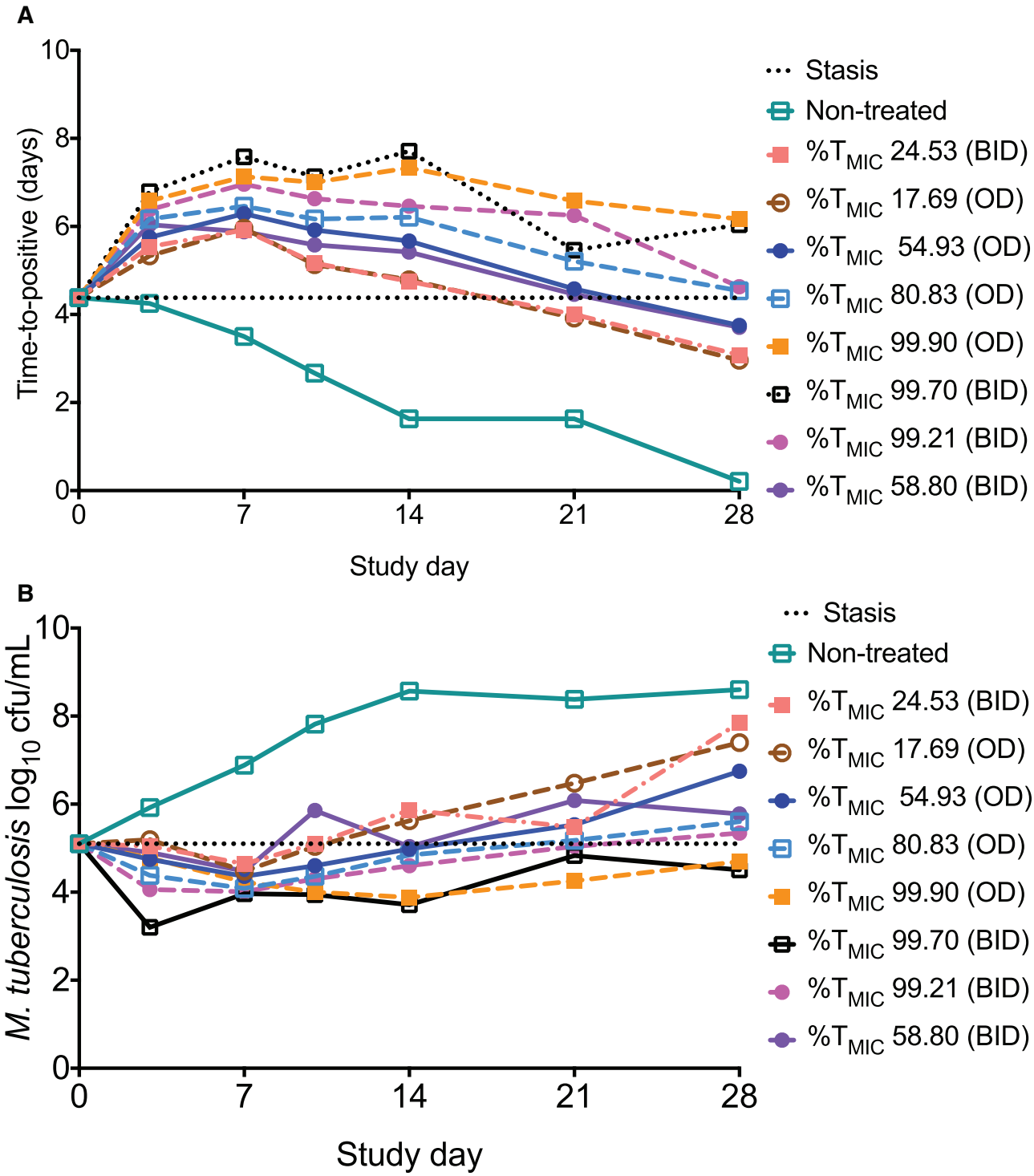

FIGURE 2. Ceftriaxone kill curves in the HFS-TB. (A) The TTP in the nontreated controls decreased from day 0 to day 28 indicating intracellular *M. tuberculosis* growth. In the ceftriaxone treated HFS-TB TTP was longer than the nontreated controls indicating inhibition of the intracellular *M. tuberculosis* growth. However, on days 21 and 28 the TTP was lower compared with day 14 showing regrowth. (B) Results of the CFU/mL readout confirmed the higher microbial kill with different ceftriaxone $\%T_{MIC}$ exposures with 15 mg/L avibactam, that sustained for longer durations of therapy. HFS-TB indicates hollow fiber model of TB; TTP, time-to-positive; TB, tuberculosis.

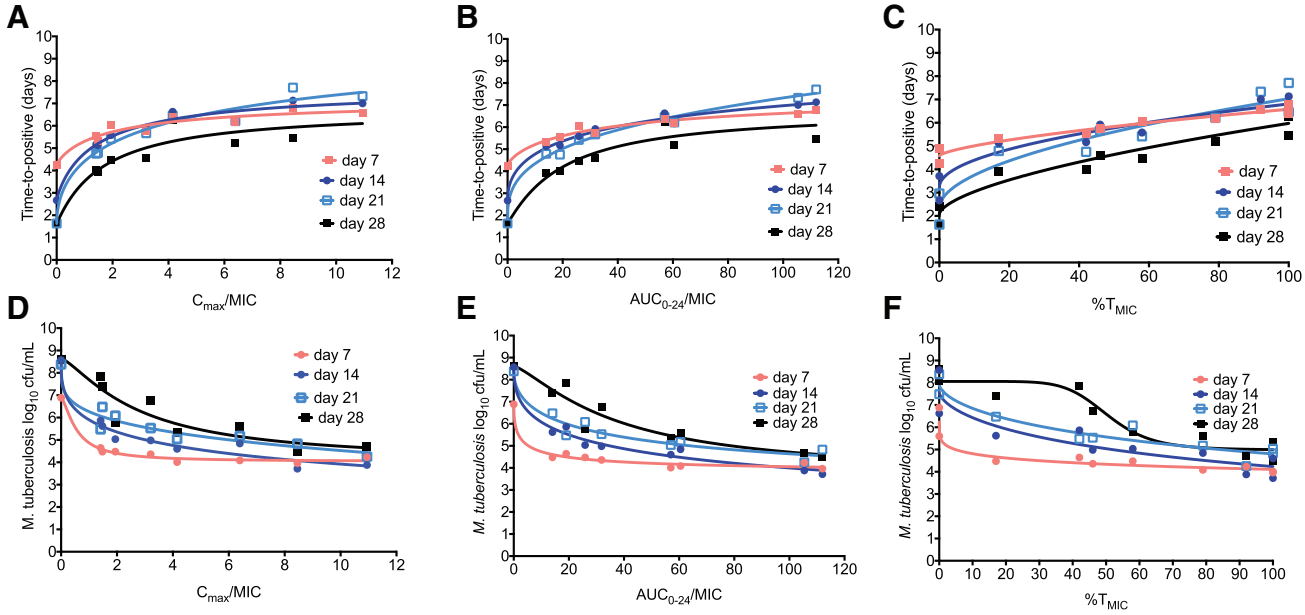

FIGURE 3. Ceftriaxone dose-response and PK/PD parameter linked to the efficacy in the HFS-TB. (A) TTP versus C_{max}/MIC, (B) TTP versus $AUC_{0\text{-}24}$/MIC and (C) TTP versus $\%T_{MIC}$ on different timepoints. The model fit line for %TMIC on day 14 is missing as it did not converge. Inhibitory Sigmoid E_{max} model results for (D) CFU/mL versus C_{max}/MIC, (E) $AUC_{0\text{-}24}$/MIC and (F) percentage of time ceftriaxone concentration in the HFS-TB persisted above the MIC. The results show that on day 28, both by the TTP and CFU/mL readouts, the $\%T_{MIC}$ showed the best Akaike Information Criteria score and therefore, identified as the PK/PD parameter linked to the ceftriaxone efficacy against *M. tuberculosis*. AUC indicates area under the concentration-time curve; HFS-TB, hollow fiber model of TB; PK/PD, pharmacokinetics/pharmacodynamics; TTP, time-to-positive.

attainment probabilities (TAP) to achieve $\%T_{MIC}$ of 60% for disseminated disease without meningitis are shown in Figure 5C. The cumulative fraction of response (CFR) over the entire MIC distribution for 50 mg/kg once a day was 46.8% while that for twice a day was 76.0%. The CFR for 75 mg/kg once a day was 55.9% while that for twice a day was 83.4%. For meningeal TB, the TAPs are shown in Figure 5D. The CFR for 50 mg/kg once a day was 43.6% while that for twice a day was 72.7%. The CFR for 75 mg/kg once a day was 52.6% while that for twice a day was 80.3%. Thus, 75 mg/kg twice a day would be the best dose; the PK/PD derived susceptibility breakpoint for this dose is >16 mg/L. A dose of 100 mg/kg once-a-day achieved a CFR of 69.37%, while twice a day achieved a CFR of 90% in disseminated TB. It is unclear if this larger dose would be tolerated by the children.

DISCUSSION

Here, first, we show that ceftriaxone has efficacy against *M. tuberculosis* even without avibactam, but the avibactam dramatically improved both potency and efficacy. We have found that *M. tuberculosis*'s natural resistance to cephalosporins is via degradation by BlaC (encoded by a lone gene) of the drug and that otherwise, *M. tuberculosis* has a cephalosporin binding target and even a benzylpenicillin binding target.[10,11,35] Avibactam is a particularly effective inhibitor of *M. tuberculosis* BlaC.[10,11,36] Thus, ceftriaxone, when used with a β-lactamase inhibitor would be effective in children and adults, with particular relevance to neglected populations including young children and pregnant women. For young children, who more commonly have disseminated intracellular TB than older patients, there could be additional benefits due to the high concentrations achieved intracellularly. Since ceftriaxone-avibactam was effective against both drug-susceptible and MDR-TB clinical strains, this highlights an important potential role in the treatment of drug-resistant TB.

Second, we found that microbial kill of *M. tuberculosis* by ceftriaxone-avibactam was linked to $\%T_{MIC}$, with an optimal target of 60% of dosing interval. This exposure target is very similar to observations of 50-70% identified with cephalosporins and Gram-negative bacteria. In the HFS-TB study that had suboptimal concentrations of avibactam, the EC_{80} target of $\%T_{MIC}$=80% was higher than with avibactam, consistent with improved potency. We did not isolate any ceftriaxone resistant *M. tuberculosis* subpopulations, thus the PK/PD parameter linked to resistance suppression remains unknown.

Third, our clinical trial simulations show that a dose of 100 mg/kg twice a day could achieve a CFR of >90% in both disseminated and meningeal TB. However, there could be adverse events of this high dose such as nephrolithiasis, cholestatic jaundice, neutropenia, hepatitis, eosinophilia, and so on.[13,37] The once a day dose of 100 mg achieved a CFR of 69.4%; this rate could be acceptable in combination therapy in which the ceftriaxone gets help from companion drugs and would have the virtue of more convenient dosing schedule in children and resource-limited settings. Otherwise, the dose of 100 mg/kg twice a day that could achieve CFR of 90% of the patients would be optimal, and for this dose, the susceptibility breakpoint was MIC >16 mg/L (32 mg/L).

Finally, we show that there is synergy between ceftazidime-avibactam and ceftriaxone; the commercially available preparation of ceftazidime-avibactam, therefore, can be used as a source of avibactam. However, given that the high cost associated with the commercially available ceftazidime-avibactam combination, there is a need to develop a ceftriaxone-avibactam combination. The oral formulations of ceftriaxone[38] and avibactam[39] are in the developmental stage and in future, this could potentially lead to a

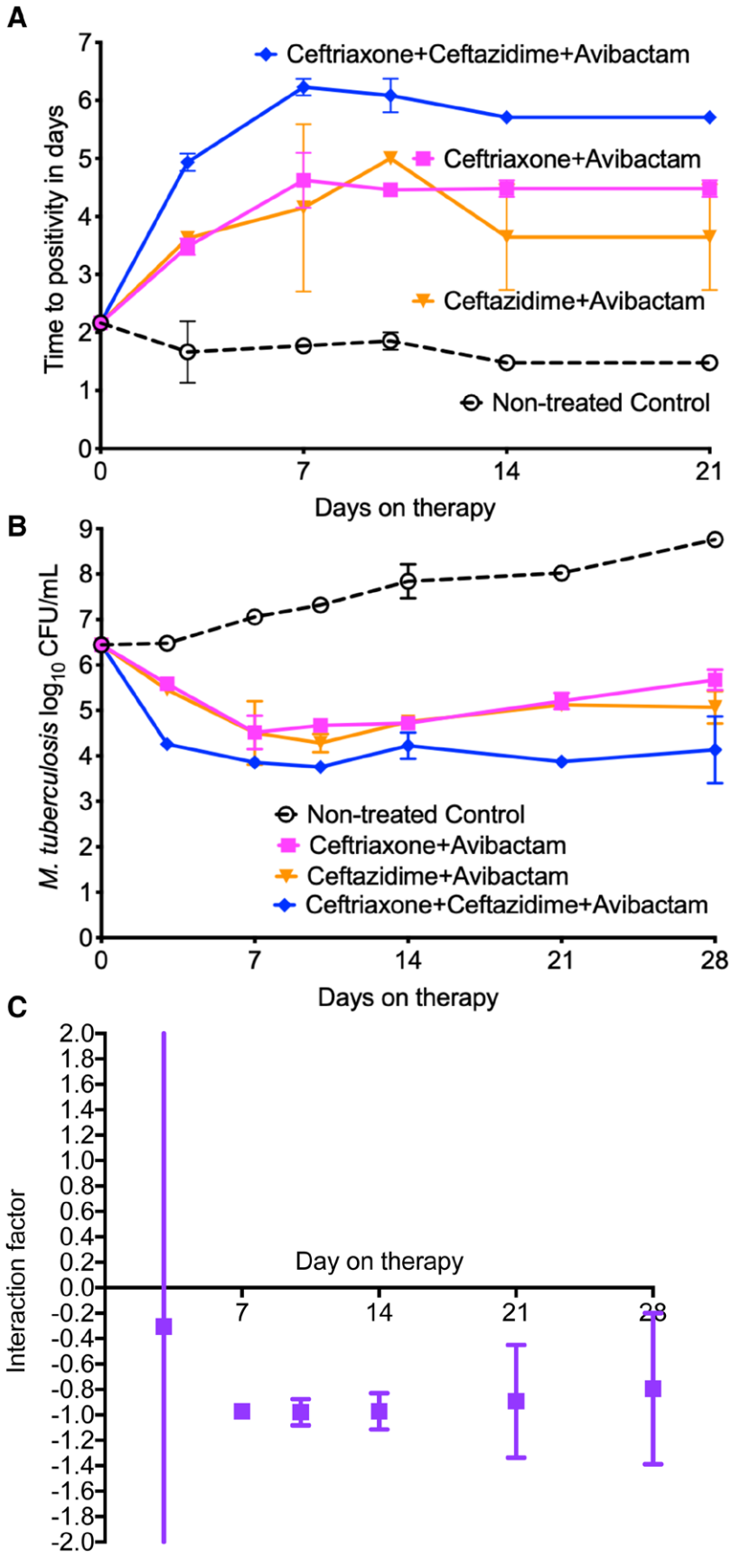

FIGURE 4. Ceftriaxone and synergy with ceftazidime-avibactam combination. (A) TTP for the nontreated control was lowest showing high bacterial burden. Both ceftriaxone-avibactam and ceftazidime-avibactam as monotherapy showed higher TTP compared with the nontreated controls indicating microbial kill. The TTP for the combination of ceftriaxone-ceftazidime-avibactam was highest showing lowest bacterial burden in terms of TTP, (B) The bacterial burden in the HFS-TB with monotherapy or dual therapy shown as CFU/mL, where the direction of the curves is opposite to the TTP. Similar to the TTP results, the ceftriaxone-ceftazidime-avibactam combination showed the best microbial kill, (C) Bliss Independence for each day was calculated based on the CFU/mL readouts. Shown in the figure is the overall interaction factor for each sampling day indicating that the dual β-lactam regimen was synergistic throughout the 28 days of the study. HFS-TB indicates hollow fiber model of TB; TTP, time-to-positivity; TB, tuberculosis.

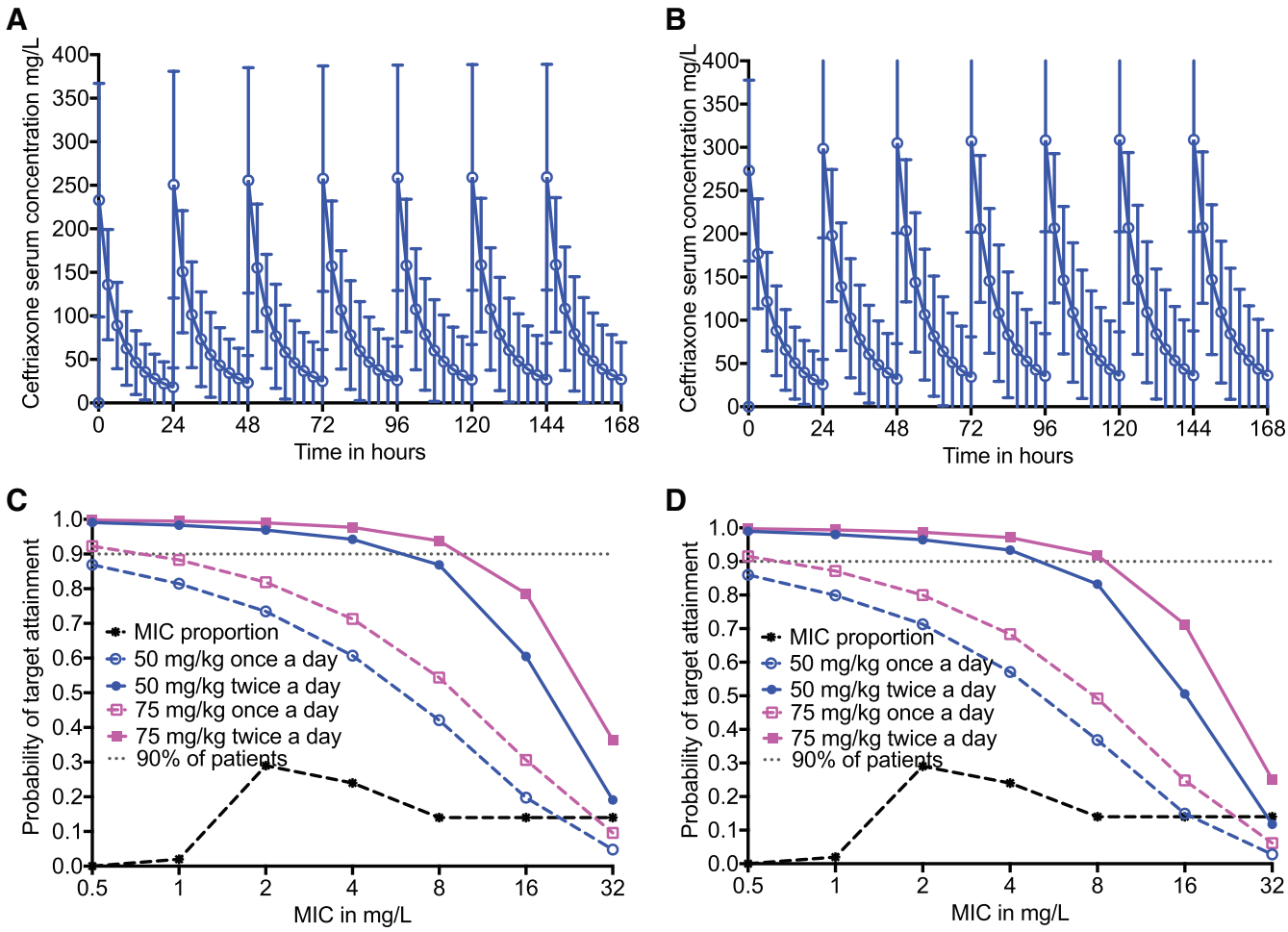

FIGURE 5. Monte Carlo experiments with different ceftriaxone doses. (A) Simulated concentration-time profiles in serum with the 50 mg/kg once daily dose revealed peak concentrations 259 ± 130 mg/L and AUC_{0-24} of 1097 ± 130 mg*h/L at steady state, similar to the peak of 220 ± 64 mg/L observed in children clinically treated and presented to the FDA.[13] (B) Simulated concentration-time profiles in serum with the 75 mg/kg once daily dose revealed peak concentrations 308 ± 1106 mg/L and AUC_{0-24} of 2531 ± 158 mg*h/L at steady state, similar to the peak of 295 ± 76 mg/L observed in children in the clinic. (C) Probability of target attainment for each of the 2 doses administered with either a once a day or twice a day schedule in children with disseminated disease. The once a day schedule achieves target in <90% of patients starting at MIC = 1 mg/L, while the twice a day dose extends the MIC range to a susceptibility breakpoint of ≥16 mg/L. (D) In the special case of disseminated TB that includes meningeal TB, the probability of target attainment is slightly worse at each dose, but the same MIC breakpoints are identified as in other disseminated diseases. AUC indicates the area under the concentration-time curve.

child-friendly oral combination. Similarly, exploring ceftriaxone in combination with amoxicillin-clavulanic acid for potential synergy may also present a more cost-effective treatment option.

In summary, we show that ceftriaxone could be used for the treatment of TB, including drug-resistant forms, the 100 mg/kg dose for children and adults with TB could achieve exposure-target in a large proportion of patients.

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