Optimal exposures of ceftazidime predict the probability of microbiological and clinical outcome in the treatment of nosocomial pneumonia

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Objectives: The %T>MIC of ceftazidime has been shown to correlate with microbiological outcome of Gram-negative bacteria (GNB) in preclinical studies. However, clinical data are still lacking. We explored the relationship of ceftazidime exposure and outcome in patients with nosocomial pneumonia using data from a recent randomized, double-blind Phase 3 clinical trial.

Patients and methods: Pharmacokinetic (PK) and demographic data from three clinical trials were used to construct a population PK model using non-linear mixed-effects modelling. Individual concentration–time curves and PK/pharmacodynamic indices were determined for individual patients. The MICs used in the analyses were the highest MICs for any GNB cultured at baseline or end of therapy.

Results: A two-compartment model best fit the data, with creatinine clearance as covariate on clearance and age on the central compartment. Classification and regression tree analysis showed a breakpoint value of 44.9% (P<0.0001) for GNB in 154 patients. The Emax model showed a good fit (R²=0.93). The benefit of adequate treatment increased from an eradication rate of 0.4848 at %T>MIC of 0% to 0.9971 at 100%. The EC50 was 46.8% and the EC 90 was 95.5% for %T>MIC. Exposure correlated significantly with both microbiological and clinical outcome at test-of-cure.

Conclusions: We conclude that exposures to ceftazidime predict microbiological as well as clinical outcome, and the %T>MIC required to result in a likely favourable outcome is 45% of the dosing interval. This value is similar to that observed in animal models and underscores the principle that adequate dosing can be predicted and is beneficial to patient care.

Keywords: pharmacokinetics, pharmacodynamics, effectivity, β-lactam antibiotics

Introduction

Ceftazidime is a third-generation cephalosporin primarily active against Gram-negative bacteria (GNB) and with a notable activity against Pseudomonas aeruginosa. Similar to other β-lactams, studies in animal models and in vitro pharmacokinetic (PK) models have shown that the duration of non-protein-bound plasma concentration above the MIC (%T>MIC) is the PK/pharmacodynamic (PD) index that best correlates with the drug-related response. In mouse infection models, a %T>MIC of 60%–65% of the dosing interval has been identified as the target for near-maximal bacterial killing, and a %T>MIC of 40% best predicted bacteriostasis at 24 h for cephalosporins.1–3 These %T>MIC values are often quoted as PD targets (PDTs) on which to base clinical breakpoints, and in general as targets to reach during therapy.4 However, whereas the PDTs in mice and humans have been shown to be of a similar magnitude for quinolones,5 confirmation of these targets in human infections is anecdotal at best for β-lactams. This may be due to a number of reasons. The first is that most clinical studies with β-lactams were performed decades ago, and at that time data collection to perform PK/PD analyses was not customary. Second, calculations of %T>MIC for individual patients are cumbersome. A third important aspect is the fact that many

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infections are often polymicrobial (i.e. at least more than one bacterial isolate or species is cultured from the site of infection) and it is not always clear which MIC to use in calculations, as opposed to a number of studies with quinolones quoted earlier. For instance, in the study of Bhavnani et al., showing that there was a relationship between the fAUC/MIC ratio and clinical as well as microbiological response in patients with community-acquired pneumonia, they looked at pneumococci only. Finally, the measure of outcome as well as the timing is not always clear or rational. In most trials, clinical cure at the test-of-cure (TOC) visit and the microbiological cure at the TOC visit have been used as an outcome measure. However, the TOC visit is often days if not weeks after treatment and colonization during the post-treatment period may lead to misinterpretation of the results. In addition, cultures at the TOC visit are often taken in a small number of patients. Microbiological effect is then deduced from clinical cure or other specific definitions, leading to possibly biased conclusions.

In the present study, using data obtained during a clinical trial involving ceftazidime as part of treatment for nosocomial pneumonia (NP), including ventilator-associated pneumonia (VAP), we made an attempt to address the issues stated above. We defined a measure of microbiological outcome based on actual treatment, and determined PK/PD indices in each individual patient by building a population PK model to correlate exposures in individual patients with various measures of outcome.

**Patients and methods**

**Trial, dataset and treatment**

This is a retrospective cohort study of a clinical trial conducted between 2005 and 2007 to compare the efficacy of ceftobiprole with a combination of ceftazidime and linezolid for the treatment of NP, including VAP. This was a randomized, double-blind, multicentre Phase 3 study involving 781 subjects in the USA (trial database NCT00210964), of which all data recorded in the trial database were provided to us. The main exclusion criteria were pregnancy, hypersensitivity to any relative anti-infective and any form of dialysis. See the Supplementary data (available at JAC Online) for the exact criteria. Included subjects were randomly assigned to treatment centrally in a 1:1 ratio to ceftobiprole (500 mg every 8 h, 2 h iv infusion) or linezolid (600 mg every 12 h, 1 h iv infusion) plus ceftazidime (2 g every 8 h, 2 h iv infusion) or linezolid (600 mg every 12 h, 1 h iv infusion) plus ceftazidime (2 g every 8 h, 2 h iv infusion) for 7–14 days. Subjects were stratified by infection type (NP and VAP) and by APACHE II scores (scores of 8–19 and 20–25, respectively). Subjects who had VAP were further stratified by time to randomization after onset of mechanical ventilation (<5 or ≥5 days of ventilation). An independent data monitoring committee was established to monitor data on an ongoing basis. Combination therapy (levofloxacin, amikacin or gentamicin) was permitted in subjects at risk for pseudomonal infections. Subjects were evaluated before the start of therapy [baseline (BL)], during therapy and at the end of therapy (EOT), performed within 24 h after last administration of the study drug. A TOC evaluation was done 7–14 days after the EOT visit.

In the current analysis we did not exclude any patient and all patients received ceftazidime following the protocol.

**Microbiology**

Cultures were taken at BL, EOT and if possible at the TOC visit. Microbiological procedures were conducted according to local practice. Duplicate isolates from all assessments were stored and shipped to a central laboratory (Eurofins Inc., Chantilly, VA, USA) for pathogen identification and antimicrobial susceptibility testing using broth microdilution. Suitable specimens for ventilated subjects included bronchoscopy with bronchoalveolar lavage/protected-brush sampling or transtracheal/endotracheal aspiration and for unventilated patients by deep expectoration or nasotracheal aspiration. Subsequently, the samples were processed following standard laboratory procedures. Subjects with insufficient or unsuitable specimens should have had the specimen repeated within 24 h of randomization. In cases of clinical failure, new cultures were attempted. Only central laboratory-derived data were used in the analyses.

**Population PK model**

PK data for ceftazidime in three studies were used. One was performed in healthy volunteers, the second in intensive care unit (ICU) patients and the third dataset was obtained from the NP study. For the latter, PK sampling was conducted at selected sites and consisted of seven 3 mL blood samples for each subject, including some elderly subjects (>65 years). Population PK parameters were estimated by means of non-linear mixed-effects modelling (NONMEM) (see the Supplementary data, available at JAC Online).

**Calculation of individual PK parameter estimates and PK/PD indices for GNB**

For patients with at least one serum sample, individual PK parameters were estimated by NONMEM. For patients without individual NONMEM estimates, parameter values were estimated using covariates as determined in the population PK model. Subsequently PD indices %fT > MIC, fAUC/ fMIC, fT >MIC, T >MIC and fCmax/MIC were calculated for each individual patient using the KinFun106 program (Medimatics, Maastricht, The Netherlands) in two ways. The first was by taking the highest MIC for the GNB cultured at BL. The second one was by first determination of the GNB with the highest MIC value at the EOT, and subsequently taking the GNB with the highest MIC value for either BL or EOT. Because of the limited number of cultures at the TOC visit, MICs for bacteria cultured at the TOC visit were not used in the analyses. The PK/PD index values were then determined for the highest MIC for the GNB as defined above, at BL, EOT or a combination. Steady state was assumed for calculations. Protein binding of 10% was used.

**Treatment outcome**

Various measures of outcome were used. The first measure was eradication of GNB at the EOT and was defined as follows. If any GNB was cultured at the EOT, the treatment was considered to have failed and was therefore independent of a positive or negative culture at BL. The analysis was performed for all patients in the intent to treat (ITT) population. At the TOC visit both the microbiological eradication and clinical cure as well as clinically evaluable (CE) and microbiologically evaluable (ME) were used as defined in the original study protocol (see the Supplementary data, available at JAC Online).

**Statistical analysis**

PK/PD indices were correlated with microbiological outcome at the EOT for all patients. For correlations of exposures with outcome at the TOC visit, because of the definitions used in the trial, the ME population was studied for microbiological outcome and the CE population for clinical outcome.

Classification and regression tree (CART) analysis to differentiate between lower and higher response rates and logistic regression were performed using SAS JMP software version 9.02 or SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).
Institute, Cary, NC, USA). Tests of significance for CART analysis were performed using the Fisher test (two-sided) as implemented in GraphPad Prism version 5.0 (GraphPad Software Inc., San Diego, CA, USA). The Emax model (GraphPad Prism) with variable slope was used to correlate exposure with response data.

## Results

### Patient population and demographics

The total NP trial database consisted of 390 individuals that were included in the study. The demographic data are shown in Table 1.

### Population PK model

A total of 89 individuals had information available for dosing times as well as concentrations and were included in the PK model. Of those, 75 individuals included were derived from the NP trial database, 8 individuals were volunteers and 6 individuals were ICU patients.

## Table 1. Demographic data of the individuals in the NP trial database

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients used in analysis using PK/PD indices (n=154)</th>
<th>Patients used in analysis with MIC (n=170)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number of patients</td>
<td>mean value</td>
</tr>
<tr>
<td>Age (years)</td>
<td>154</td>
<td>61.4</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>54/100</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>151</td>
<td>72.3</td>
</tr>
<tr>
<td>Height (m)</td>
<td>148</td>
<td>1.69</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>146</td>
<td>25.3</td>
</tr>
<tr>
<td>Infection type (VAP/non-VAP)</td>
<td>49/105</td>
<td></td>
</tr>
</tbody>
</table>

## Table 2. Population parameter estimates of the final ceftazidime PK model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard error</th>
<th>CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance (L/h)</td>
<td>6.47</td>
<td>0.0404</td>
<td>6.24</td>
</tr>
<tr>
<td>Volume of distribution of central compartment (V1) (L)</td>
<td>23.1</td>
<td>1.97</td>
<td>8.53</td>
</tr>
<tr>
<td>Volume of distribution of peripheral compartment (L)</td>
<td>6.77</td>
<td>0.81</td>
<td>12</td>
</tr>
<tr>
<td>Intercompartmental clearance (L/h)</td>
<td>3.38</td>
<td>0.608</td>
<td>18</td>
</tr>
<tr>
<td>Covariate creatinine clearance on clearance (L/h)</td>
<td>0.00208</td>
<td>8.87×10⁻⁴</td>
<td>42.6</td>
</tr>
<tr>
<td>Covariate age on V1 (Y)</td>
<td>0.0137</td>
<td>0.00122</td>
<td>8.91</td>
</tr>
<tr>
<td>Variability on clearance</td>
<td>0.305</td>
<td>0.0757</td>
<td>24.8</td>
</tr>
<tr>
<td>Variability on V1</td>
<td>0.326</td>
<td>0.111</td>
<td>34</td>
</tr>
<tr>
<td>Correlation between coefficients of variability</td>
<td>0.221</td>
<td>0.0675</td>
<td>30.5</td>
</tr>
<tr>
<td>Residual error 1</td>
<td>0.0762</td>
<td>0.0134</td>
<td>17.6</td>
</tr>
<tr>
<td>Residual error 2</td>
<td>2.13</td>
<td>0.748</td>
<td>35.1</td>
</tr>
</tbody>
</table>

A two-compartment model with a coefficient of variability on clearance and the central volume of distribution best described the data. Coefficients were correlated with each other and a combined error model best described the data. The model improved by including the creatinine clearance as a covariate on clearance and age as a covariate on the central volume of distribution. Results of the final model are shown in Table 2. Plots of the individual and population predicted concentrations versus observed concentrations are shown in Figure 1 with R²s of 0.85 and 0.51, respectively.

### Microbiology

Of the 390 patients in the NP trial database, 254 had a positive culture (65.1%) at BL. A total of 170 patients had at least one GNB in the BL and/or EOT cultures. Of these 170 patients, 57 patients had at least one Gram-positive species isolated besides the GNB in cultures at BL and/or EOT. From most patients with a positive culture with GNB, one or two isolates or species were isolated, but was up to seven different isolates/species in some patients. The different Gram-negative species with the highest MIC per culture with the numbers of times cultured from BL cultures and BL cultures in combination with EOT cultures are shown in Table 3. Of the ME patients at the TOC visit, 16 had a positive culture for GNB (P. aeruginosa, Acinetobacter baumannii, Klebsiella pneumoniae and 6 different species were found only once). Of these, the same microorganisms were found at the TOC and EOT in four cases. However, it should be realized that no cultures were obtained from a significant number of patients at the TOC visit.

### Exposure–response (PK/PD) analysis at EOT

The number of patients available for the exposure–response analysis is shown in the flow chart presented in Figure 2. PD analysis based on indices determined from MICs for GNB at BL were not significant, indicating no predictive value of the PK/PD index on microbiological outcome at the EOT, but the MIC did show significance (P=0.011). Table 4 shows the results of the CART analysis using the MIC and PK/PD indices based on the GNB with the highest MIC value for each patient at either BL or the EOT and a negative culture at the EOT (NCEOT) as the outcome parameter. For GNBs with an MIC value up to 2 mg/L, the probability of no positive culture of GNB was 95.7%, whereas for GNB with an MIC value >2 mg/L, this percentage was only 56.4%
All three PK/PD indices showed a significant relationship with outcome. The split value for \( \%fT \cdot \text{MIC} \) was 44.9%, with an eradication rate of 90.2% above that value, and only 50% below that value \((P<0.0001)\). Logistic regression was also performed and showed a significant relationship between the PK/PD index and NCEOT. For \( \%fT \cdot \text{MIC} \), this relationship is described as 
\[
\text{NCEOT} = -0.19591 + 0.03009 \times \%fT \cdot \text{MIC} 
\]
\((P<0.0001)\). Multiple logistic regression was also performed.

The following parameters were entered in the model: \( \%fT > \text{MIC} \), \( \text{fAUC} / \text{MIC} \), \( C_{\text{max}} / \text{MIC} \), APACHE II score, sex, body weight, white blood cell count, creatinine clearance, C-reactive protein and NP/VAP. Only \( \%fT > \text{MIC} \) and body weight remained as significant parameters.

The response rates in the eradication of GNB were plotted as a function of exposure with \( \%fT > \text{MIC} \) using an Emax model. The Emax model with variable slope was fitted to the data and the results are shown in Figure 3. A good fit was obtained for \( \%fT > \text{MIC} \) \((R^2=0.934)\), with an estimated BL eradication of 48.5% and >99% for the highest value for \( \%fT > \text{MIC} \). The EC_{50} and EC_{90} were 46.8% and 95.5%, respectively. The fit of \( \text{fAUC} / \text{MIC} \) was ambiguous. There was a relationship between the MIC as well as the \( fC_{\text{max}} / \text{MIC} \) and outcome \((R^2=0.810 \text{ for MIC and } R^2=0.834 \text{ for } fC_{\text{max}} / \text{MIC})\), but it was far less pronounced than with \( \%fT > \text{MIC} \).

### Exposure–response (PK/PD) analysis at TOC

Both microbiological outcome and clinical outcome at the TOC visit were correlated with exposures during treatment. Using CART analysis, microbiological eradication of GNB was significantly correlated with \( \%fT > \text{MIC} \) in the ME population \((n=95, P<0.0001)\), with a split value of 23.3%. Above this split value microbiological eradication was achieved in 71.6% of the evaluable patients, versus 25.0% in the patients with values below the split value. Logistic regression was also significant \((P<0.0001)\). CART analysis was also performed to determine the relationship between exposure and clinical cure. In the CE population, there was no significant correlation with PK/PD indices or MIC from

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**Table 3.** Gram-negative species with the highest MIC with the numbers of times cultured at BL or from BL and EOT cultures

<table>
<thead>
<tr>
<th>Gram-negative microorganism with highest MIC</th>
<th>BL cultures</th>
<th>BL or EOT cultures</th>
</tr>
</thead>
<tbody>
<tr>
<td>number</td>
<td>range of highest ceftazidime MIC (mg/L)</td>
<td>number</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>26</td>
<td>1–128</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>28</td>
<td>0.06–128</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>39</td>
<td>2–128</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>12</td>
<td>0.12–128</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>9</td>
<td>0.12–64</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>7</td>
<td>0.12–64</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>6</td>
<td>0.06–0.12</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>7</td>
<td>2–128</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>25</td>
<td>—</td>
</tr>
<tr>
<td>Total number of Gram-negatives</td>
<td>159</td>
<td>159</td>
</tr>
<tr>
<td>Total number of different species</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

Some patients had more than one microorganism with the same (highest) MIC. Only patients with Gram-negative microorganisms and PK data are included in the table.
BL pathogens. However, clinical outcome was significantly correlated with %\(f_T\)MIC for GNB based on BL and EOT, with a split value of 37.4\(\%\) (\(P = 0.0007\)). Of the patients with values for %\(f_T\)MIC above the split value, 78.9\% achieved clinical cure, whereas of the patients with %\(f_T\)MIC values below the split value, this was only 44.1\%, a difference of 34.8\%. After multiple logistic regression analysis using similar parameters as at the EOT (see above), only %\(f_T\)MIC remained in the model and confirmed these results (\(P = 0.0013\)).

Subgroup analysis

Because the trial was designed with strata of non-VAP and VAP, we also performed subgroup analyses. There were no significant differences between these two groups and the results were, in general, as described above within each of the subgroups. For %\(f_T\)MIC, the CART split values were 44.9\% in the ventilated patients and 52.6\% in unventilated patients and logistic regression was significant at \(P < 0.001\). Likewise, we explored whether the %\(f_T\)MIC value correlated with cure was dependent on the severity of disease as expressed by the APACHE II score. We did not find a significant interaction between APACHE II score and %\(f_T\)MIC in predicting outcome.

Discussion

Analysis of a large Phase 3 NP study showed that microbiological outcome at the EOT in patients treated with ceftazidime was significantly associated with exposure. A high probability of negative culture at the EOT was attained at values >44.9\% %\(f_T\)MIC in the ITT population. Moreover, there was a significant correlation between %\(f_T\)MIC during treatment and microbiological outcome as well as clinical outcome at the TOC visit.

Since ceftazidime is a drug that is primarily active against GNB, we performed the analysis with a focus on GNB only. However, all patients also received linezolid as a second drug to treat possible Gram-positive bacteria. These were not taken into consideration in this specific study. Nevertheless, we were able to show a highly significant effect of %\(f_T\)MIC during treatment on overall clinical outcome at the TOC visit. This indicates that, at least for a substantial number of patients, the...
relationship between adequate exposure during treatment for GNB is highly relevant for outcome.

To determine the correlation between exposure to ceftazidime and outcome we chose an alternative approach. Conventionally the effects of antimicrobial treatment are studied as microbiological cure of the microorganism(s) cultured at BL, at the TOC visit or, in some studies, at the EOT, and the outcome is correlated with drug dose or drug exposure. However, there are several disadvantages using a microbiological endpoint at the TOC visit. The first is that there is a time lapse between the EOT and the TOC visit. From a microbiological point of view, many events, including re-colonization, may take place that are not related to adequate exposure during therapy. The second is that often there are no cultures taken at the TOC visit, and microbiological eradication is deduced from the absence of clinical signs. In particular, in pneumonia this often happens, because samples are difficult to obtain. The microbiological outcome at the EOT is a more rational choice for evaluating antimicrobial eradication as a treatment outcome, and this has been used in a number of studies, in particular with pneumococci.\(^6,7\)

An initial challenge encountered in this study, and in many studies with the approach taken, is that multiple bacteria were cultured both at BL as well as at the EOT, with each of the bacteria having different MICs. To calculate the PK/PD indices, we used the highest MIC encountered, reasoning that outcome would be related to the bacteria with the lowest exposure, an approach taken before.\(^1^1\) In addition, we also took bacteria into account that were cultured at the EOT, since during antimicrobial treatment patients should not become colonized with pathogenic microorganisms in the lower respiratory tract. In that respect, culture results in pneumococcal pneumonia are more straightforward—the bacterium is eradicated or not at the EOT.

When compared with the use of cultures taken at the TOC visit, commonly used in such analyses, cultures at the EOT have several advantages for use as an endpoint. Healthy humans are continuously or temporarily colonized with various bacteria at most sites of the body and therefore cultures taken 2 weeks after the EOT might be positive with bacteria colonizing the respiratory tract. Furthermore, for a large number of patients, a culture 2 weeks after the EOT could not be obtained and therefore these data are difficult to use.

The split value for \%fT>MIC using CART analysis to differentiate between higher and lower rates of eradication was 44.9%, which is very close to the value for a static effect in mice for GNB.\(^3,12\) This further underlines the value of using models to predict antimicrobial effects in human treatment. Nevertheless, the split value found at the TOC was slightly different for microbiological cure. The reasons are similar to those mentioned.
above, in that microbiological eradication at the TOC visit may not be a good parameter for microbiological efficacy. This does not mean that this should not be evaluated—rebound effects may be present, or other unknown effects that need to be investigated. In contrast, the split value for clinical cure was of the same order of magnitude as at the EOT, i.e. 37.4%.

The results clearly show that the effect of treatment is not 100%. Even at very low exposures almost half the patient population is microbiologically cured. This may be for a variety of reasons, including other antibiotics that were allowed in some cases, the state of the disease, intubation and microbial eradication by the patient without antibiotics (immune system). This is a well-known phenomenon and indicates that the attributable cure of the antimicrobial is limited.6,13,14 However, we did observe a close relationship between exposure and cure, varying between close to 50% for microbiological eradication at the EOT and 34.8% for clinical cure at the TOC visit, and therefore a significant contribution to overall outcome. At exposures close to 100% for $T > \text{MIC}$, very few patients failed therapy with respect to microbiological eradication. Thus, although the split value of close to 40% optimally differentiates between a better and a worse outcome, higher exposures do contribute to overall effect. We extended our CART analyses to determine whether there were significant other splits, but none was significant (results not shown).

MIC alone did not predict outcome as well as PK/PD indices did, including exposure and the variation therein per patient. In Figure 3 there is significant scatter, in particular within the range of interest. Nevertheless, the number of patients within that range is relatively small, as indicated by the CART analyses. The figure also indicates that $\text{AUC}_{\text{max}}/\text{MIC}$ does not predict outcome as well as $\%T > \text{MIC}$ or $\text{AUC}/\text{MIC}$. Nevertheless, all three indices predict outcome, as indicated by CART analysis, which is probably due to strong co-linearity between the values. All patients received a similar dosing regimen, and there is therefore relatively little variation in exposure. However, a multiple logistic regression analysis with a forward and backward procedure to determine whether one index was more predictive than the other showed that $\%T > \text{MIC}$ was selected as the most significant index, both for microbiological eradication as well as for clinical cure.

We conclude that exposures to ceftazidime predict microbiological as well as clinical outcome, and the $\%T > \text{MIC}$ that is required to result in likely favourable outcome is $>45%$. This value is similar to that observed in animal models and underscores that adequate dosing regimens can be predicted and are beneficial to patient care.

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Transparency declarations

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Supplementary data

Supplementary data are available at JAC Online (http://jac.oxfordjournals.org/).

References