Pharmacodynamics of a New Streptogramin, XRP 2868, in Murine Thigh and Lung Infection Models

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XRP 2868 is a new streptogramin antibiotic with broad-spectrum activity against gram-positive cocci. We used the neutropenic murine thigh and lung infection models to characterize the time course of antimicrobial activity of XRP 2868 and determine which pharmacokinetic/pharmacodynamic (PK/PD) parameter and magnitude best correlated with efficacy. Serum levels following four two- to fourfold-escalating single-dose levels of XRP 2868 were measured by liquid chromatography mass spectrometry assay. In vivo postantibiotic effects (PAEs) were determined after doses of 2.5, 10, and 40 mg/kg. Mice had 106.8 to 107.4 CFU/thigh of strains of Streptococcus pneumoniae ATCC 10813 or Staphylococcus aureus ATCC 29213 at the start of therapy when treated for 24 h with 2.5 to 640 mg/kg/day of XRP 2868 fractionated for 3-, 6-, 12-, and 24-h dosing regimens. Nonlinear regression analysis was used to determine which PK/PD parameter best correlated with CFU/thigh at 24 h. Pharmacokinetic studies exhibited peak dose values of 0.03 to 0.07, area under the concentration-time curve (AUC) dose values of 0.02 to 0.07, and half-lives of 0.35 to 1.27 h. XRP 2868 produced in vivo PAEs of 0.5 to 3.4 h with S. pneumoniae strain ATCC 10813 and −1.5 to 10.7 h with S. aureus strain ATCC 29213. The 24-h AUC/MIC was the PK/PD parameter that best correlated with efficacy. In subsequent studies, we used the neutropenic murine thigh infection model to determine if the magnitude of the AUC/MIC needed for the efficacy of XRP 2868 varied among pathogens (including resistant strains). Mice had 106.1 to 107.8 CFU/thigh of four isolates of S. aureus (three meticillin-susceptible and one meticillin-resistant strain) and nine isolates of S. pneumoniae (one penicillin-susceptible, four penicillin-intermediate, and four penicillin-resistant strains) when treated for 24 h with 0.16 to 640 mg/kg of XRP 2868 every 6 h. A sigmoid dose-response model was used to estimate the doses (mg/kg/24 h) required to achieve a net bacteriostatic affect over 24 h. MICS ranged from 0.06 to 0.25 μg/ml. The 24-h AUC/MICs for each static dose (20.7 to 252 mg/kg/day) varied from 3 to 70. Mean 24-h AUC/MICs ± standard deviations (SDs) for S. pneumoniae and S. aureus isolates were 14 ± 10 and 31 ± 16, respectively. Beta-lactam and macrolide resistance did not alter the magnitude of AUC/MIC required for efficacy.

Streptogramins are naturally occurring antibiotics that act on the 50S ribosome. XRP 2868 is a new oral streptogramin that is comprised of a mixture of 70% RPR 132552A and 30% RPR 202868. XRP 2868 has been shown to exhibit broad and potent in vitro activity against gram-positive aerobic, fastidious gram-negative, and anerobic bacteria. Similar to other streptogramins, XRP 2868 has enhanced potency against gram-positive cocci including multiple-drug-resistant Streptococcus pneumoniae (8, 11). This novel compound is in early clinical development for the treatment of respiratory tract and skin infections.

The goals of our experiments were to characterize the in vivo time course antimicrobial activity of XRP 2868 and determine the pharmacokinetic/pharmacodynamic (PK/PD) parameter and parameter magnitude predictive of efficacy.

MATERIALS AND METHODS

Bacteria, media, and antibiotic. Nine strains of Streptococcus pneumoniae with variable resistance to penicillin (one penicillin-susceptible, four penicillin-intermediate, and four penicillin-resistant S. pneumoniae strains) were used. Six of the strains were also macrolide resistant. Four strains of Staphylococcus aureus (three methicillin-susceptible and one methicillin-resistant S. aureus strains) were also used for these experiments. Organisms were grown, subcultured, and quantified in Mueller-Hinton broth (Difco Laboratories, Detroit, MI) and Mueller-Hinton agar (Difco Laboratories, Detroit, MI) for all organisms except S. pneumoniae. Sheep blood agar plates (Remel, Milwaukee, WI) were utilized for S. pneumoniae. XRP 2868 was supplied by Aventis.

In vitro susceptibility studies. The MICs of XRP 2868, penicillin, methicillin, and erythromycin for the various isolates were determined by standard Clinical Laboratory Standards Institute microdilution methods.

Murine infection model. Animals were maintained in accordance with the American Association for Accreditation of Laboratory Animal Care criteria. All animal studies were approved by the Animal Research Committee of the William S. Middleton Memorial VA Hospital.

Six-week-old, specific-pathogen-free, female ICR/Swiss mice weighing 23 to 27 g were used for all studies (Harlan Sprague-Dawley, Indianapolis, IN). Mice were rendered neutropenic (neutrophils, <100/mm3) by injecting them with cyclophosphamide (Mead Johnson Pharmaceuticals, Evansville, IN) ipretaperically 4 days (150 mg/kg) and 1 day (100 mg/kg) before thigh infection. Previous studies have shown that this regimen produces neutropenia in this model for 5 days. Broth cultures of freshly plated bacteria were grown to logarithmic phase overnight to an absorbance at 580 nm of 0.3 (Spectronic 88; Bausch and Lomb, Rochester, NY). After a 1:10 dilution into fresh Mueller-Hinton broth, bacterial counts of the inoculum ranged from 106 to 109 CFU/ml. Thigh infections with each of the isolates were produced by injection of 0.1 ml of inoculum into the thighs of halothane-anesthetized mice 2 h before therapy with XRP 2868.

Murine lung infection model. Stationary-phase broth cultures of S. pneumoniae strain ATCC 10813 or S. aureus strain ATCC 29213 were obtained by overnight incubation. Cultures were centrifuged at 10,000 × g for 20 min and washed twice in 0.9% saline before being resuspended in saline. Diffuse pneum-
monia in mice was induced by an intranasal inoculation of 50 µl of 10^8 CFU/ml inoculum. Antimicrobial therapy was initiated 2 h after the infection procedure.

Drug pharmacokinetics. Single-dose serum pharmacokinetic studies were performed in thigh-infected mice given oral doses (0.2 ml/dose) of XRP 2868 (10, 40, 80, and 160 mg/kg). For each of the doses and time points examined, three mice were sampled by cardiac puncture. Sampling time intervals ranged from 0.25 to 16 h over a period of 24 h. Samples were then centrifuged for 5 min at 10,000 × g, and serum was removed and frozen at −80°C until assay. Serum XRP 2868 concentrations were determined by an liquid chromatography mass spectrometry assay was 20 ng/ml. Assay variation was less than 7.8%. Pharmacokinetic constants, including elimination half-life, area under the concentration-time curve (AUC), and peak level were calculated using a non-compartmental model. Protein binding in the serum of neutropenic infected mice was performed using ultrafiltration methods (6).

Treatment protocols. (i) In vivo PAE. Two hours after infection with S. pneumoniae strain ATCC 10813 or S. aureus strain ATCC 29213, neutropenic mice were treated with single oral doses of XRP 2868 (2.5, 10, or 40 mg/kg). Groups of two treated and untreated control mice each were sacrificed at sampling intervals ranging from 1 to 6 h. Control growth was determined at seven sampling times over 24 h. The treated groups were sampled nine times over 24 h. The intervals ranging from 1 to 6 h. Control growth was determined at seven sampling times over 24 h. The treated groups were sampled nine times over 24 h. The mice were sacrificed every 6 h were utilized to treat groups ranging from 1 to 6 h.

(ii) PK/PD parameter determination. Neutropenic mice were infected with a strain of either penicillin-susceptible S. pneumoniae ATCC 10813 or methicillin-susceptible S. aureus ATCC 29213. Treatment with XRP 2868 was initiated 2 h after infection. Groups of two mice were treated for 24 h with 20 different dosing regimens using twofold-increasing total doses divided into one, two, four, or eight doses. Total doses of XRP 2868 ranged 256-fold (2.5 to 640 mg/kg/24 h).

(iii) PK/PD parameter magnitude studies. Similar dosing studies using six fourfold-increasing XRP 2088 doses administered every 6 h were utilized to treat thigh-infected neutropenic animals with nine strains of S. pneumoniae (one penicillin-susceptible, four penicillin-intermediate, four penicillin-resistant) and six macrolide-resistant S. pneumoniae strains and four strains of S. aureus (three methicillin-susceptible and one methicillin-resistant strain). The XRP 2868 MICs for the organisms studied varied only fourfold. The total daily dose of XRP 2868 used in these studies varied from 0.625 to 2,560 mg/kg/day.

Data analysis. The results of these studies were analyzed using the sigmoid dose-effect model. The model, as follows, is derived from the Hill equation: $E = \frac{[E_{max} \times D^N][ED_{50}^N + D^N]}{E_{max} + D^N}$, where $E$ is the effect or, in this case, the log change in CFU per thigh between treated mice and untreated controls after the 24 h period of study, $E_{max}$ is the maximum effect, $D$ is the 24 h total dose, $ED_{50}$ is the dose required to achieve 50% of $E_{max}$, and $N$ is the slope of the dose-effect curve. The indices $E_{max}$, $ED_{50}$, and $N$ were calculated using nonlinear least-squares regression. The correlation between efficacy and each of the three PK/PD parameters (T>MIC, AUC/MIC, peak/MIC) studied was determined by nonlinear least-squares multivariate regression (SigmaStat; Jandel Scientific Software, San Rafael, CA). The coefficient of determination, or $R^2$, was used to estimate the variance that could be due to regression with each of the PK/PD parameters.

We utilized the 24-h static dose as well as the doses necessary to achieve both the 1 and 2 log_{10} reduction in colony counts compared to numbers at the start of therapy to compare the impact of the dosing interval on treatment efficacy. If these dose values remained similar among each of the dosing intervals, this would support the 24-h AUC/MIC as the predictive parameter. If the dose values increased as the dosing interval was lengthened, this would suggest that T>MIC is the predictive parameter. Lastly, if the dose values decreased as the dosing interval was increased, this would support peak/MIC as the pharmacodynamically important parameter.

To allow a comparison of the potency of XRP 2868 against a variety of organisms, we utilized the 24-h static dose. The magnitude of the PK/PD parameter associated with each endpoint dose was calculated from the following equation:

$$\log_{10} D = \log_{10}\left(\frac{E}{E_{max} - E}\right) + \log ED_{50}$$

where $E$ is the control growth for dose ($D$), $E$ is the control growth + 1 log for a $D$ of 1 log kill, and $E$ is the control + 2 log for a $D$ of 2 log kills. The significance

TABLE 1. In vitro susceptibility of XRP 2868, penicillin, methicillin, and erythromycin against S. pneumoniae and S. aureus

| Isolate          | XRP 2868 Penicillin | Methicillin | Erythromycin |
|------------------|--------------------|-------------|--------------|
| S. aureus Smith  | 0.06               | 0.25 NA     | NA           |
| S. aureus 25923  | 0.06               | 0.25 NA     | NA           |
| S. aureus 29213  | 0.06               | 0.5 NA      | NA           |
| MRSA*            | 0.25 NA >8 NA      |             |              |
| S. pneumoniae 1325 | 0.12              | 2.0 NA      | >8 (Erm)    |
| S. pneumoniae 1396 | 0.12              | 0.5 NA      | >8 (Erm)    |
| S. pneumoniae 1293 | 0.25              | 2.0 NA      | >8 (Erm)    |
| S. pneumoniae 1020 | 0.12              | 1.0 NA      | 2.0 (Mef)   |
| S. pneumoniae 49619 | 0.12             | 0.5 NA      | 0.06        |
| S. pneumoniae 1329 | 0.12              | 2.0 NA      | 8.0 (Mef)   |
| S. pneumoniae 1199 | 0.12              | 1.0 NA      | >8 (Erm)    |
| S. pneumoniae 673  | 0.12              | 8.0 NA      | 0.06        |
| S. pneumoniae 10813 | 0.25             | 0.008 NA    | 0.015       |

* MRSA, methicillin-resistant S. aureus.

b NA, not applicable.

FIG. 1. Serum XRP 2868 concentrations after administration of single doses of 10, 40, 80, and 160 mg/kg in neutropenic infected mice. Each symbol represents the mean ± standard deviation of the levels in the sera of three mice. 1/2, serum elimination half-life in hours; Cmax, peak serum level.
of differences among the various dosing endpoints was determined by using analysis of variance on ranks.

**RESULTS**

**In vitro susceptibility testing.** The MICs of XRP 2868, penicillin, methicillin, or erythromycin for the 13 study strains are shown in Table 1. XRP 2868 MICs varied fourfold (range, 0.06 to 0.25 μg/ml).

**Pharmacokinetics.** The time course of serum levels of XRP 2868 in infected neutropenic mice following oral doses of 10, 40, 80, and 160 mg/kg are shown in Fig. 1. Over the dose range studied, kinetics were nonlinear, with the elimination half-life increasing 3.6-fold with dose escalation. The elimination half-life ranged from 0.35 to 1.27 h. The AUC dose and peak dose values for the escalating single doses ranged from 0.02 to 0.07 and 0.03 to 0.07, respectively. XRP 2868 binding in mouse serum was 60 to 70% at drug concentrations of 12.8 and 128 μg/ml. This is similar to the degree of binding in other animal species and in human serum (John Lowther, Aventis, personal communication). Both free- and total drug levels are considered in pharmacokinetic calculations throughout this paper.

**In vivo PAE.** At the start of therapy, mice had 10^6.9 to 10^7.2 CFU/thigh of *S. pneumoniae* or *S. aureus*. Growth of 1 log 10 CFU/thigh in saline-treated animals occurred in 2.02 and 4.3 h in *S. pneumoniae*- and *S. aureus*-infected animals, respectively. Based upon the serum pharmacokinetic determinations, serum XRP 2868 levels following the single doses of 2.5, 10, and 40 mg/kg remained above the MIC for *S. pneumoniae* strain ATCC 10813 (MIC, 0.25 mg/liter) for 0, 0.40, and 1.1 h (0, 0.57 h based on free-drug levels), respectively. The times above the MIC for these doses against *S. aureus* strain ATCC 25923 (MIC, 0.06 mg/liter) were 0.40, 1.1, and 1.8 h (0, 0.60, and 1.3 h based on free-drug levels). The time-kill curves for both of the studies are shown in Fig. 2. Against *S. pneumoniae*, escalating doses produced free-drug PAEs ranging from 0.50 to 3.4 h. Study with *S. aureus* produced free-drug PAEs ranging...
from −1.5 to 10.7 h. No detectable drug carryover was observed in any of the treatment groups.

**PK/PD parameter determination.** At the start of therapy, mice had $8.4 \pm 0.15$ and $6.8 \pm 0.21 \log_{10}$ CFU/thigh of *S. pneumoniae* strain ATCC 10813 and *S. aureus* strain ATCC 29213, respectively. The organisms grew $2.3 \pm 0.2$ and $1.9 \pm 0.3 \log_{10}$ CFU/thigh after 24 h in untreated control mice, respectively. Escalating doses of XRP 2868 resulted in the concentration-dependent killing of both strains. The highest doses studied reduced organism burden from $4.1 \pm 0.1$ to $5.1 \pm 0.01$

### TABLE 2. Impact of dose fractionation on efficacy of a new streptogramin, XRP 2868, against *S. pneumoniae* and *S. aureus*

| Organism   | Dose endpoint | Total dose (mg/kg/24 h) (95% CI)* |
|------------|---------------|-----------------------------------|
|            |               | q3h      | q6h      | q12h     | q24h     |
| *S. pneumoniae* | Static dose  | 77 (22–133) | 112 (28–196) | 78 (71–83) | 81 (76–87) |
|             | 1 log         | 125 (34–212) | 225 (67–383) | 112 (105–119) | 115 (107–123) |
|             | 2 log         | 184 (30–318) | 475 (142–868) | 163 (153–173) | 175 (163–187) |
| *S. aureus* | Static dose   | 139 (118–160) | 80 (72–89) | 64 (50–78) | 39 (−0.75–77) |
|             | 1 log         | 199 (169–229) | 114 (101–127) | 100 (79–121) | 79 (−1.0–159) |
|             | 2 log         | 237 (217–310) | 163 (145–181) | 152 (120–182) | 154 (−3.0–311) |

* CI, confidence interval.
log\(_{10}\) CFU/thigh compared to numbers at the start of therapy. The dose-response relationship for the four dosing intervals against *S. pneumoniae* and *S. aureus* are shown in Fig. 3a and 3b, respectively. The curves were similar among each of the dosing intervals against both organisms. The dosing endpoints (standard deviations [SDs], 1- and 2-log kills) are presented in Table 2. At each of these endpoints, we did not observe a significant difference, as the dosing interval was lengthened from every 3 h to every 24 h. These analyses suggest that treatment efficacy was dependent upon dose level and independent of the dosing intervals studied.

The relationships between microbiologic effect and each of the pharmacodynamic parameters, 24-h AUC/MIC, percent time above the MIC, and peak/MIC against *S. pneumoniae* strain ATCC 10813 are shown in Fig. 4a. As with other streptogramin antibiotics, the strongest relationship was seen when results were correlated with the 24-h AUC/MIC ratio with an \(R^2\) value of 93%. Regression with both the %\(T>/MIC\) and peak/MIC result in slightly less strong relationships. The reasonable fit of the data with each of the PK/PD parameters is due to the interrelationships among each of the parameters. Consideration of bound or unbound drug levels did not appreciably impact the relationship between efficacy and %\(T>/MIC\) (data not shown). Similar analysis of study with *S. aureus* is shown in Fig. 4b and also established the strength of the correlation of 24-h AUC/MIC with efficacy (24-h AUC/MIC \(R^2 = 91\%\)). Here, also, consideration of both total and free-drug serum levels did not remarkably affect these relationships (data not shown).

**PK/PD magnitude determination.** Calculation of the doses necessary to achieve a static effect against multiple organisms is shown in Table 3. The growth curves of the nine pneumococcal and four staphylococcal strains in the thighs of control animals were relatively similar. At the start of therapy, mice had between 7.7 ± 0.81 (range, 6.1 to 7.8) \(\log_{10}\) CFU/thigh of pneumococci or *S. aureus*. The organisms grew 2.4 ± 0.44 \(\log_{10}\) CFU/thigh (range, 1.76 to 3.06) in untreated control mice. The maximal reduction in *S. pneumoniae* with XRP 2868-treated mice compared to untreated controls ranged from 1.8 ± 0.3 to 5.8 ± 0.4 \(\log_{10}\) CFU/thigh (mean, 4.1 ± 1.5). Somewhat less killing was observed against the *S. aureus* strains (mean, 2.9 ± 1.1 \(\log_{10}\) CFU/thigh).

Table 3 shows the 24-h dose and free-drug 24-h AUC/MIC ratios necessary to achieve a net static effect, and a 1- and 2-log\(_{10}\) reduction in organism burden. The 24-h AUC/MIC ratio associated with a static effect was relatively similar among all of

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**TABLE 3. Relationship between the streptogramin XRP 2868 MIC of *S. pneumoniae* and *S. aureus* and efficacy**

| Isolate     | MIC  | SD  | 24-h AUC/MIC | 1 Log reduction | 24-h AUC/MIC | 2 Log reduction | 24-h AUC/MIC |
|-------------|------|-----|--------------|----------------|--------------|----------------|--------------|
| *S. aureus* Smith | 0.06 | 20.7| 5.17         | 70.1           | 55.8         | 184            | 217          |
| *S. aureus* 25923 | 0.06 | 34.7| 21.3         | 62.3           | 38.7         | 112            | 69.3         |
| *S. aureus* 29213 | 0.06 | 84.8| 26.7         | 124            | 40           | 219            | 95.3         |
| MRSA\(^a\)   | 0.25 | 23.4| 2.92         |                 |              |                |              |

Mean ± SD  

\[40.9 ± 29\]  
\[14.0 ± 10\]  
\[85.4 ± 27\]  
\[44.8 ± 7.8\]  
\[172 ± 44.5\]  
\[127 ± 64\]

* MRSA, methicillin-resistant *S. aureus*.

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**FIG. 5. The relationship between the XRP 2868 free-drug 24-h AUC/MIC and efficacy against nine *S. pneumoniae* and four *S. aureus* isolates. Each symbol represents the mean datum per mouse from two thighs. \(R^2 = 95\%\).**
the organisms studied (means ± SDs, 24-h AUC/MIC ratios of 14 ± 10 for S. pneumoniae and 32 ± 16 for S. aureus). Penicillin and methicillin resistance did not alter the magnitude of the 24-h AUC/MIC ratio necessary for efficacy. Similarly, macrolide resistance due to both drug efflux and ErmB mutations did not impact the pharmacodynamic target.

The relationship between the 24-h free-drug AUC/MIC and efficacy against the two organism groups is demonstrated graphically in Fig. 5. The dose-response relationships were relatively strong, with a $R^2$ value of 95%.

Infection site and host immune status. The efficacy of XRP in mice infected at both the thigh and lung infection sites is shown in Fig. 6 and Table 4. A portion of the dose-response curve in both S. aureus- and S. pneumoniae-infected animals was shifted somewhat to the right in the thigh model, suggesting that less drug was required in the lung infection model. Indeed, the amount of XRP 2868 associated with a static effect was lower in the pneumonia model. However, the doses necessary to produce 1- and 2-log kills were not statistically different.

The impact of neutrophils on the in vivo efficacy of XRP is shown in Fig. 7 and Table 4. The dose-response curve is very slightly shifted to the right in the neutropenic model, suggesting that more drug was required in the immunocompromised mice. However, the differences were not statistically different. Maximal efficacy was similar in both models, with nearly a 4-log reduction in organism burden in the pneumococcal thigh-infected mice.

DISCUSSION

A variety of in vitro and in vivo studies have demonstrated that the streptogramins exhibit concentration-independent killing and produce prolonged postantibiotic effects with gram-positive organisms (1, 2, 3, 4, 10, 12, 13). The efficacy of antibiotics characterized by this pattern of activity is best correlated with the 24-h AUC/MIC PK/PD parameter. Indeed, prior animal infection models have identified the AUC/MIC ratio as the principal PK/PD parameter predictive of streptogramin efficacy (4, 7, 13).

The current studies characterized the in vivo pharmacodynamic activity of a new streptogramin, XRP 2868. Penicillin and macrolide resistance in S. pneumoniae and methicillin resistance in S. aureus had no impact upon the in vitro and in vivo potency of XRP 2868. The activity against ErmB isolates was similar from that identified for quinupristin-dalfopristin, for which in vivo activity was less than that anticipated based upon the MIC. Similar to studies with the streptogramin quinupristin-dalfopristin, the antimicrobial activity of this streptogramin was enhanced by escalating drug concentrations (2, 4, 10). The in vivo PAEs were of moderate duration against the S. pneu-
TABLE 4. Impact of infection site and neutrophils on efficacy of a new streptogramin, XRP 2868, against S. pneumoniae and S. aureus

| Infection site (organism) or mouse type | Efficacy (mg/kg/24 h) (range) |
|----------------------------------------|-------------------------------|
|                                        | Static dose  | 1-Log reduction | 2-Log reduction |
| Lung (S. aureus)                       | 49 (–24–123) | 142 (–71–353)   | 250 (–230–625)  |
| Thigh (S. aureus)                      | 211 (181–240) | 229 (197–261)   | 601 (517–684)   |
| Lung (S. pneumoniae)                   | 59 (–55–173)  | 246 (–223–713)  | NA              |
| Thigh (S. pneumoniae)                  | 200 (34–356)  | 237 (41–434)    | 358 (61–655)    |
| Normal                                 | 78 (13–140)   | 127 (21–233)    | 205 (33–377)    |
| Neutropenic                            | 135 (111–159) | 193 (159–227)   | 281 (231–331)   |

moniae and S. aureus isolates studied. One would predict that the AUC/MIC would be the PK/PD parameter that most strongly correlated with efficacy of XRP 2868, given this pattern of antimicrobial activity. Data from the current multiple-dosing regimen studies confirmed that the 24-h AUC/MIC is the best PK/PD predictor of efficacy of this new streptogramin.

The amount of XRP 2868 or parameter magnitude associated with in vivo efficacy was similar between the pneumococci and staphylococci examined. The mean total drug 24-h AUC/MICs associated with a net static effect ranged from near 15 to 32. The AUC/MIC targets associated with organism reductions of 1 and 2 log10 were 2.5- to 3.2-fold and 4- to 9-fold larger that those associated with a static effect, respectively. Protein binding in infected mice ranged from 60 to 70% and was similar to that in humans.

The current in vivo studies also examined outcome at two sites of infection to determine the impact of this variable on the magnitude of the pharmacodynamic target associated with efficacy. There was a trend toward enhanced activity in the lung compared to the thigh; however, the differences were not statistically significant. It is possible that this trend, in effect, could be due to elevated epithelial lining fluid concentrations of XRP 2868 relative to serum. We are unaware of epithelial lining fluid pharmacokinetic investigations with this or other streptogramins. The impact of one arm of the host immune system was similarly examined by utilizing mice with neutropenia and nonneutropenia. The neutrophils appeared to have minimal impact on the amount of drug needed for treatment efficacy of the streptogramin.

While XRP 2868 has not yet undergone extensive clinical investigation, the current studies suggest that the relationship between the pharmacokinetics of this streptogramin and efficacy is similar to quinupristin-dalfopristin. The 24-h AUC/MIC was the most important pharmacodynamic parameter for describing the in vivo activity. The 24-h AUC/MIC target associated with a net static effect was a value near 25. This pharmacodynamic target should be considered in the design of dosing regimens for clinical trials with this compound.

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