Background: MGB-BP-3 is a new class of antibacterial that binds selectively to the Minor Groove of DNA and has shown strong in vitro antibacterial activity against aerobic Gram-positive bacteria, including susceptible and resistant Streptococci, Staphylococci, and Enterococci. This study assessed the in vivo pharmacokinetics (PK) and pharmacodynamics (PD) of MGB-BP-3.

Methods: The murine thigh infection model was used to investigate the ED50 and the PD of MGB-BP-3. Naïve mice were rendered neutropenic, inoculated intramuscularly with 10^7 CFU of S. pyogenes, S. pneumoniae or MRSA, and treated IV with 100 mg/kg MGB-BP-3, after which, concentration-time curves were generated. The PD of MGB-BP-3 was investigated following single or multiple dosing, ranging from 20 - 100 mg/kg. The tissue samples were incubated on agar plates, and colony counts were determined at 24 h. In vivo efficacy of optimal dosing was verified in the murine pneumonia model with S. pneumoniae.

Results: The ED50 of MGB-BP-3 was determined to 62 mg/kg, 50 mg/kg and 51 mg/kg respectively for S. pyogenes, S. pneumoniae and MRSA in the thigh infection model. Fractionated dosing studies revealed that efficacy against S. pneumoniae and MRSA correlated equally well to T-MIC and AUC24/MIC at an assumed protein binding of 80%. 90% of max efficacy against MRSA was estimated to be reached at AUC24/MIC = 288 h, and against S. pneumoniae at AUC24/MIC = 263 h. The most potent effect of MGB-BP-3 against S. pneumoniae was observed when dosing mice once 40 mg/kg, resulting in a 5.1 log10 reduction of bacterial load compared to vehicle treatment, whereas 4 x 20 mg/kg resulted in a 2.1 log10 reduction. Similar dosing scenarios, 4 x 20 mg/kg, 4 x 40 mg/kg and 3 x 60 mg/kg, resulted in a potent effect in the pneumonia model with 2.1, 2.3 and 2.7 log10 reduction of bacterial load respectively, compared to the vehicle.

Conclusion: MGB-BP-3 showed a potent antibacterial in vivo effect against S. pneumoniae and MRSA in experimental infection models. Efficacy correlated to T-MIC and AUC24/MIC.

ABSTRACT

In Vivo Antimicrobial Activity of MGB-BP-3, a New Class of Antibacterial Agent, in Murine Infection Models

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INTRODUCTION

MGB-BP-3 is a new class of antibacterial, belonging to the DNA Minor Groove Binder group, that has very strong antibacterial activity against all susceptible and multi-resistant Gram-positive pathogens tested, including methicillin-resistant and susceptible Staphylococcus species, pathogenic Streptococcus species, Vancomycin-Resistant and susceptible Enterococcus and Clostridium difficile.

MGB-BP-3 was originally developed by scientists at the University of Strathclyde. It has the architecture of a typical minor groove binder and is based upon the structure of naturally occurring product, Distamycin (Figure 1). Its oral formulation is currently in a clinical Phase I study for the treatment of C. difficile infections, and its intravenous formulation is in the final stages of preclinical development for the treatment of hospital acquired Gram-positive infections.

In this group of experiments, we investigated in vivo activity of MGB-BP-3 against Streptococcal and Staphylococcal/bacteria in various mouse infection models. The aim was to quantitate MGB-BP-3's antibacterial activity in live organisms and assess the correlation between activity and plasma concentrations.

METHODS

Assessment of pharmacokinetic profile of MGB-BP-3: Mice were injected IV with a single dose of MGB-BP-3 in the range 20 - 100 mg/kg. Blood samples were collected from 15 minutes to 24 h after injection. Plasma concentrations were quantified using an optimised and validated HPLC method.

Assessment of Minimum Inhibitory Concentration (MIC) for S. pneumoniae and S. aureus: The MIC of MGB-BP-3 against S. aureus (MRSA) and S. pneumoniae was determined by using a broth micro dilution method in accordance with CLSI guidelines. The tested range was 0.031 - 32 μg/mL.

Quantification of the antibacterial effect of MGB-BP-3 in mouse thigh model: Assessment of efficacy of MGB-BP-3 against S. pneumoniae and S. aureus (MRSA) in the murine neutropenic thigh infection model was investigated following IV administration. Mice were then inoculated intracutaneously with 10^7 CFU of S. pneumoniae or MRSA suspension in the left thigh. Mice were treated with a single or fractionated IV dose of MGB-BP-3 at 10-100 mg/kg or vehicle over approximately 1 min, 1h post infection. The positive control for S. pneumoniae was subcutaneous penicillin, and IV vancomycin for MRSA and S. pyogenes. The colony counts in thighs were determined at 1h for vehicle, 6h for S. pyogenes, and 24h for S. pneumoniae post infection for MGB-BP-3.

PK/PD modelling to identify the optimal dosing regimen: The purpose of this study was to select, by means of mathematical modeling, a set of suitable MGB-BP-3 dosing regimens to obtain optimal separation of the PK/PD indices for future pharmacodynamic studies with MRSA and S. pneumoniae. Pharmacokinetic indices (Cmax, AUC24 and terminal elimination half-life t1/2) were determined by non-compartmental modelling with the windowSTIM program in the PPKSim software package [2]. A linear-two-compartment model (Figure 2) was fitted to concentration-time data. The pharmacokinetic indices were then calculated by simulation of a selected dosage regimen with the fitted compartment model. The NPAG population parameter estimation program [3, 4] was used to fit the compartment model.

RESULTS

The pharmacokinetics of MGB-BP-3 in mice showed a rapid initial redistribution followed by slow elimination. There was substantial between-subject variability.

The concentration-activity profile of MGB-BP-3 showed dose dependent activity against S. pyogenes, S. pneumoniae and S. aureus (MRSA) in mouse thigh model (Figure 3).

The ED50 of MGB-BP-3 in the thigh infection model against S. pneumoniae was determined to 62 mg/kg, 50 mg/kg and 51 mg/kg respectively for S. pyogenes, S. pneumoniae and MRSA in the thigh infection model. Fractionated dosing studies revealed that efficacy against S. pneumoniae and MRSA correlated equally well to T-MIC and AUC24/MIC at an assumed protein binding of 80%. 90% of max efficacy against MRSA was estimated to be reached at AUC24/MIC = 288 h, and against S. pneumoniae at AUC24/MIC = 263 h. The most potent effect of MGB-BP-3 against S. pneumoniae was observed when dosing mice once 40 mg/kg, resulting in a 5.1 log10 reduction of bacterial load compared to vehicle treatment, whereas 4 x 20 mg/kg resulted in a 2.1 log10 reduction. Similar dosing scenarios, 4 x 20 mg/kg, 4 x 40 mg/kg and 3 x 60 mg/kg, resulted in a potent effect in the pneumonia model with 2.1, 2.3 and 2.7 log10 reduction of bacterial load respectively, compared to the vehicle.

The colony counts in lungs were determined at the start of treatment and 24 h after the start of treatment.

CONCLUSION

• MGB-BP-3 pharmaco kinetic profile showed a rapid initial redistribution followed by slow elimination. The half-life was in the range of 6 to 12 hours.

• MGB-BP-3 showed high activity against Streptococcus pyogenes, Streptococcus pneumoniae strains, and Staphylococcus aureus (MRSA) in the mouse thigh model.

• PK/PD modelling showed that T-MIC and AUC24/MIC are highly correlated with efficacy of MGB-BP-3.

• The accurate assessment of plasma protein binding will allow inclusion of this parameter into the calculation of the PK/PD relationship and selection of a suitable MGB-BP-3 dosing regimen for future pharmacodynamic studies.

• MGB-BP-3 showed high activity in the mouse pneumonia disease model.

REFERENCES

2. PPKSim homepage; http://www.pakosim.dk