POTENT ACTIVITY OF A NOVEL GYRASE INHIBITOR (SPR719/SPR720) IN VITRO AND IN A PROLONGED ACUTE MYCOBACTERIUM ABSCESSUS MOUSE MODEL OF INFECTION

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ABSTRACT

Background: Mycobacterium abscessus, a fast-growing mycobacterial species, has emerged in recent years as an important opportunistic pathogen increasingly responsible for morbidity with extremely limited therapeutic options available. Here we evaluate the in vitro and in vivo activity of SPR719 and its phosphate prodrug, SPR720, against M. abscessus 103 in a prolonged acute SCID mouse model of M. abscessus infection.

Methods: MIC testing was performed by microbroth dilution method using cation adjusted Mueller Hinton broth, consistent with CLSI methodology against clinical strains of M. abscessus. Spleen efficacy of SCID female mice inoculated an acute SCID mouse model of M. abscessus infection was used (n=5). Two groups were treated on days 1 and 17 infected control. Findings support the further advancement of SPR720 for the treatment of nontuberculosis mycobacterial disease.

INTRODUCTION

• Infections caused by nontuberculosis mycobacteria (NTM) are increasing in prevalence due to improved recognition and diagnosis.
• NTM infections are generally difficult to treat since these organisms are resistant to most of the antibiotic drugs and therefore new agents are needed.
• M. avium complex (MAC) and M. abscessus are the most common species isolated in Europe and the USA.
• M. abscessus is a rapidly growing mycobacterium (RGM) that has recently emerged as an important opportunistic pathogen.
• Here we evaluate the in vitro and in vivo activity of SPR719 and its phosphate prodrug, SPR720, against M. abscessus 103 in a prolonged acute SCID mouse model of M. abscessus infection.

RESULTS

• SPR719 was more potent than CLR or AMK against M. abscessus 103.
• No significant weight loss or clinical observations in the lungs, spleen, and liver were noted for any of the SPR720 treated groups.
• CLR served as a positive control in the acute infection model and behaved as expected.
• SPR720 at 100 mg/kg q24h demonstrated the greatest reduction in bacterial burden in the lung, spleen, and liver (p<0.0001) compared to the day 17 control.

METHODS

• MIC testing of SPR719 was performed by microbroth dilution using cation adjusted Mueller Hinton broth, consistent with M24-A2 CLSI methodology.
• To test efficacy, SCID mice were infected using M. abscessus subcut bollet 103 via tail vein injection as described previously.
• SPR720 or clarithromycin treatment initiated on day 2 and continued for 16 days with mice sacrificed 24 h after the last dose.

CONCLUSIONS

• The novel gyrase inhibitor displayed potent activity in vitro against strains of M. abscessus.
• SPR720 treatment significantly reduced the bacterial burden in the lungs, spleens and livers of SCID mice infected with strains of M. abscessus.
• These findings support the further development of SPR720 for the treatment of NTM infections.

REFERENCES

1. CLSI (2011) M34-A2