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BBIL-5: An investigational new biotherapeutic for treating drug resistant S.aureus infections

S. Kandaswamy[1,*], K. Ella[2]

[1] *Bharat Biotech International Ltd., Hyderabad, Telengana, India*
[2] *Bharat Biotech International Ltd., Hyderabad, India*

Background: With development of resistance to new generation antibiotics, very few therapeutic options are left in the arsenal against *Staphylococcus aureus*. Virulence factors and resistant traits emerging in the hospital and in community acquired infections favor colonization and pathogenesis. BBIL-5 is a potent anti-*Staphylococcal* protein that kills *S.aureus* of any antibiotic resistance profile.

Methods & Materials: Minimum inhibitory concentration (MIC) of *S.aureus* clinical isolates to BBIL-5 was estimated by broth dilution method. Antibiotic susceptibility was determined by Stoke's method and by disk diffusion studies. Synergy with antibiotics was demonstrated by kill kinetics and *in vivo* in animal studies. Therapeutic dose regimen was established by infection with intraperitoneally administered 10^7-10^8 *S.aureus*, and subsequent treatment with BBIL-5 (doses in mg/Kg body weight). Pharmacokinetic/Pharmacodynamics (PK/PD) indices were determined for single and multiple doses administered intravenously in mice and rabbits. BBIL-5 concentration in PK studies and antibodies to the protein were estimated by ELISA. Recombinant production of BBIL-5 in *E.coli* and product development has been advanced to GMP. GLP pre-clinical toxicity studies are in progress.

Results: The MIC to BBIL-5 ranged from 2-32 ng/ml. No antibiotic cross resistance was observed. Standardized doses of BBIL-5 when administered intravenously in three bolus doses, q24h completely eradicated *S.aureus* infection in mice. A single therapeutic dose of the GMP product provided 2–3 Log reductions in colony forming units (CFU) of *S.aureus*. Synergy with beta lactams reduced the therapeutic dose to one-fifth of the standardized dose. AUC/MIC and Cmax/MIC were the pre-dominant PK/PD indices. A high ratio of Cmax/AUC and AUC/MIC positively improved the outcome in eradication of *S.aureus*. Pharmacokinetic profile in animals showed first order kinetics of elimination where C vs. t graph is not linear, but is a decaying exponential, while Log C vs. t graph is linear. Improved therapeutic efficacy against systemic *S.aureus* infections was achieved by reducing *kel* (elimination rate constant) by IV infusion. The protein was minimally immunogenic due to short circulating half-life. The GMP product was extensively characterized.

Conclusion: BBIL-5 is the first investigational biotherapeutic of its kind with demonstrated efficacy in treating multi-drug resistant *S.aureus infections.*

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In-vivo efficacy of a novel Leu-t-RNA synthatase inhibitor compound a against MDR Pseudomonas aeruginosa 1594965 in a foreign body associated urinary tract infection model

M. Kumar[1], M. Rao[2], T.K. Barman[2], M. Pandya[1], S. Dube[1], K.P. Purnapatre[3,*]

[1] *Daiichi Sankyo India Pharma Private Limited, Gurgaon, India*
[2] *Daiichi Sankyo India Pharma Private Limited, Gurgaon, Haryana, India*
[3] *Daiichi Sankyo India Pharma Private Limited, Gurgaon, India*

Background: *Pseudomonas aeruginosa* is one of the major pathogens causing morbidity and mortality in hospital acquired infections (HAI). MDR *P. aeruginosa* are resistant to 3 or more classes of antibiotics. In cUTI cases catheter associated infections are incurable by most of the antibiotics. Compound A a novel Leu-t-RNA synthetase inhibitor showed efficacy in mouse ascending urinary tract infection (AUTI) model against *P. aeruginosa* biofilms formed on urinary catheters.

Methods & Materials: In this study we established a mouse model of foreign body associated AUTI. A spiral polyethylene tube (PT) was placed transurethrally into bladder without surgical manipulation, followed by transurethral inoculation with *Pseudomonas aeruginosa* 1594965 (MDR) strain. Scanning electron microscopy (SEM) was done after 4h of inoculation of bacteria and bacterial counts were taken in kidneys, bladders and catheter pieces for respective samples. *In vivo* efficacy of Compound A was tested using this established model against *P. aeruginosa* 1594965(Compound A MIC: 1 μg/ml, meropenem MIC: 32 μg/ml). Compound A was tested at 30 and 220mg/kg SC q6h and meropenem was tested at human simulated dose of 60 mg/kg SC q6h. The treatment was initiated 4h post infection and continued daily for 7 days. Bacterial counts of placebo 4h, 7 days and 7 days treated group's samples of kidneys, bladders and catheters were calculated. Data was analysed using bacterial counts of each group and compared with those of 4 h placebo control group.

Results: SEM showed good establishment of biofilm in 4 h samples. In foreign body associated mouse infection model. LRS inhibitor Compound A at 30, 220 mg/kg SC q6h showed $\log_{10}$ difference of -2.38, -2.18 $\log_{10}$ CFU/kidney respectively compared to 4h placebo and meropenem at 60 mg/kg SC q6h was inefficacious. In bladders this log difference was -2.30, -1.21, -0.78 respectively. On catheter only Compound A at 220mg/kg SC q6h showed $\log_{10}$ difference of -1.59 $\log_{10}$CFU/ml. No efficacy was observed in remaining groups

Conclusion: Efficacy of Compound A in foreign body associated mouse AUTI infection model against MDR *Pseudomonas aeruginosa* 1594965 proves its efficacy on biofilm. These results warrant its further investigation in HAI associated *Pseudomonas aeruginosa* infections.

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