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Human Metabolism of the Drug Candidate PBTZ169

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Abstract : PBTZ169 is novel drug candidate with high efficacy in animals models, and its combination treatment of PBTZ169 with BDQ and pyrazinamide was shown to be more efficacious than the standard treatment for tuberculosis in a mouse model. The target of PBTZ169 is famous DprE1, an essential enzyme in cell wall biosynthesis. The crystal structure of the DprE1-PBTZ169 complex reveals formation of a semimercaptal adduct with Cys387 in the active site and explains the irreversible inactivation of the enzyme. Furthermore, this drug candidate demonstrated during preclinical research 'drug like' properties what made it an attractive drug candidate to treat tuberculosis in humans. During first clinical trials several cohorts of the healthy volunteers were treated by the single doses of PBTZ169 as well as two weeks repeated treatment was chosen for two maximal doses. As expected PBTZ169 was well tolerated, and no significant toxicity effects were observed during the trials. The study of the metabolism shown that human metabolism of PBTZ169 is very different from microbial or animals compound transformation. So main pathway of microbial, mice and less rats metabolism connected with reduction processes, but human metabolism mainly connected with oxidation processes. Due to this difference we observed several metabolites of PBTZ169 in humans with antitubercular activity, and now we can conclude that animal antituberculosis activity of PBTZ169 is a result not only activity of the drug itself, but it is a result of the sum activity of the drug and its metabolites. Direct antimicrobial plasma activity was studied, and such activity was observed for 24 hours after human treatment for some doses. This data gets high chance for good efficacy of PBTZ169 in human for treatment TB infection. Second phase of clinical trials was started summer of 2017 and continues to the present day. Available data will be presented.

Keywords : clinical trials, DprE1, PBTZ169, metabolism
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