The New Antitubercular Drugs SQ109 and TMC207 Act Synergistically In Vitro to Kill M. tuberculosis

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BACKGROUND

A number of initiatives to discover and develop new therapeutic agents that not only cure TB but also shorten the duration of treatment are ongoing (5, 13). SQ109 and TMC207 are among new drugs being developed for therapy of TB, and both are currently in human efficacy trials. SQ109 is a novel diamine derivative of the diarylquinoline class of antimicrobial drugs. TMC207, highly specific for biosynthesis, although the exact site of action is not known (7). TMC207 (also known as R207910) is a derivative of the diarylquinoline class of antimicrobial drugs. TMC207 is highly specific for biosynthesis, although the exact site of action is not yet known.

PURPOSE AND HYPOTHESIS

To determine the in vitro interactions of SQ109 and TMC207, with and without Rif, for killing of MTB.

MATERIALS AND METHODS

MIC determination: MIC (µg/ml) of SQ109, TMC207 and Rif against H37Rv was determined by broth dilution method. MIC results were calculated as mean of duplicate experiments.

RESULTS

Table 1: Concentration of drug alone and in combination

Table 2: Interaction between SQ109, TMC207 and Rif in 3-drug combinations

Table 3: Time-dependent activities of drug alone or in combination

Table 4: Time-kill activities of drug alone or in combination

CONCLUSIONS

Four clinical trials of two- and three-drug combinations using SQ109, TMC207 and Rif, the combination SQ109-TMC207 was synergistic against the drug susceptible laboratory strain of MTB (H37Rv) or additive against the two clinical isolates of MTB. On the other hand, the combination TMC207-Rif combination was additive against both. Addition of Rif to the SQ109-TMC207 combination did not significantly improve the activity of the two drugs.

TMC207-SQ109-Rif combination killed MTB faster as determined by both BLU and GGI estimations, and both methods were more sensitive than CFU determination. The apparent increased rate of killing by TMC207 in fluorescence assays could be due to depletion of ATP by the drug. Since BLU depends on the amount of ATP within the bacteria, minor changes in the ATP levels in the bacteria reflect the BLU levels in the sample.

Increased rate of killing by the SQ109-TMC207-Rif combination was also evident in BACTEC, which is the gold standard for susceptibility testing to MTB.

SQ109 combined with TMC207 enhanced the PAE of TMC207.

In macrophages, TMC207 was more effective at killing MTB than SQ109 or Rif. In combination, SQ109-TMC207 was superior to either TMC207-Rif or SQ109-Rif. It is of utmost importance to determine whether SQ109-TMC207 combination shows improved activity in vivo.

BIBLIOGRAPHY