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Abstract (poster session)

TP-834, a novel IV and oral isoindoline-containing pentacycline, is highly efficacious in rodent models of pneumonia

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Objective: TP-834 is a novel fully synthetic pentacycline antibiotic with activity against MDR community-acquired respiratory pathogens. These studies evaluated the efficacy of TP-834 versus comparator antibiotics in various rodent lung infection models. Methods: Neutropenic (NP) mouse lung infection: BALB/c mice were challenged with either tetracycline-resistant tet(M) Streptococcus pneumoniae (SP) strain SP160 or tet(M) Staphylococcus aureus SA191. Mice were made NP by pre-treatment with cyclophosphamide and infected with either pathogen via intranasal administration. At 2 and 12 hrs post-infection, mice were dosed orally (PO) and intravenously (IV) with compound. At 24 hrs post-initiation of treatment, mice were euthanized and bacterial colony forming unit (CFU) reduction in lung was quantified by plating lung homogenates. Non-NP mouse lung infection: CD-1 mice were infected with SP SP514 via IN and dosed PO or IV with compound at 5, 24 and 36 hrs post-infection. At 48 hrs post- initiation of treatment, mice were euthanized and lung CFUs were quantified. Non-NP rat lung infection model: Sprague-Dawley rats were infected with Haemophilus influenzae HI551via intratracheal administration. At 5, 24, and 48 hrs rats were dosed PO with compound. At 72 hrs post-initiation of treatment, rats were euthanized and lung CFUs were quantified. Results: NP SA191 model: TP-834 dosed IV at 1, 5, and 10 mg/kg produced -0.45, -1.69, and -2.7 log CFU reductions in lung, respectively; linezolid (LZD) at 10 mg/kg produced a -1.29 log CFU reduction. TP-834 dosed PO at 12.5, 25, 50 and 100 mg/kg produced -1.41, -2.58, -2.58 and -2.9 log CFU reductions, respectively; LZD at 30 mg/kg produced a -2.62 log CFU reduction. NP SP160 model: TP-834 dosed IV at 1, 5, and 10 mg/kg produced -0.85, -2.26 and -3.07 log CFU reductions, respectively; LZD at 5 mg/kg produced no CFU reduction. TP-834 dosed PO at 15, 30, and 60 mg/kg produced -1.29, -1.55 and -2.34 log CFU reductions, respectively; LZD at 30 mg/kg produced a -2.5 log CFU reduction. Non-NP SP514 model: When dosed orally at 30 mg/kg, TP-834 and LZD produced -6.14 and -3.56 log CFU reductions, respectively. Non-NP HI551 model: Dosed 100 mg/kg PO and 25 mg/kg IV, TP-834 produced -2.93 and -3.4 log CFU reductions, respectively; azithromycin at 50 mg/kg PO produced a -6.24 log CFU reduction. Conclusion: TP-834 is highly efficacious in rodent lung infection models using IV and PO administration.