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BAY 73-7388, a novel aminomethylcycline, is highly active *in vivo* in a murine model of pneumococcal pneumonia

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Objectives: BAY 73-7388 is the first antibiotic compound from the novel class, the aminomethylcyclines. BAY 73-7388 is being investigated for the treatment of severe bacterial infections including those caused by strains resistant to current classes of antibiotics. The efficacy of BAY 73-7388 was compared with that of vancomycin (VAN) and linezolid (LIN) in a mouse model of pneumococcal pneumonia.

Methods: For lung infections, *Streptococcus pneumoniae* (strain L3 TV, Serotype 3) was administered intranasally to 5 mice per group, followed by i.v. antibiotic treatment bid over 2 days. The bacterial counts in the lungs on day 4 were used as read-out. Survival was monitored until day 4 post-infection.

Results: (a) CFU: Bacterial CFU in the lung at day 4 were lower with BAY 73-7388 and VAN in comparison with LIN therapy (reduction in CFU >6 log units at 1 mg/kg BAY 73-7388 vs. no reduction in CFU at the same doses of LIN). A 4.5 log unit CFU reduction was only obtained at a 10 mg/kg dose of LIN. (b) Survival assays: For BAY 73-7388 and VAN all mice survived at the three tested doses (1, 3 and 10 mg/kg). In contrast for LIN 0, 2, and 4 animals survived when tested at the same dose range.

Conclusions: Treatment with BAY 73-7388 is highly effective in an animal model of pneumococcal pneumonia.

(BAY 73-7388 was discovered by Paratek Pharmaceuticals, Inc., Boston, MA, and designated PTK 0796.)

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BAY 73-7388, A NOVEL AMINOMETHYLCYCLINE, IS HIGHLY ACTIVE IN VIVO IN A MURINE MODEL OF PNEUMOCOCCAL PNEUMONIA

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Abstract

Objectives:

BAY 73-7388 is the first antibiotic compound selected from the novel class, the aminomethylcyclines. BAY 73-7388 is under development for the treatment of severe bacterial infections including those caused by strains resistant to current classes of antibiotics.The efficacy of BAY 73-7388 was compared with that of vancomycin (VAN) and linezolid (LZD) in a mouse model of pneumococcal pneumonia.

Methods:

For lung infections, *Streptococcus pneumoniae* (strain L3 TV, Serotype 3) was administered intranasally to 5 mice per group, followed by IV antibiotic treatment bid over 2 days.The bacterial counts in the lungs on day 4 were used as read-out. Survival was monitored until day 4 postinfection; surviving mice were sacrificed and bacterial counts in the lung determined.

Results:

a) Colony forming units (CFU): Bacterial CFU in the lung at day 4 were lower with BAY 73-7388 and VAN in comparison with LZD therapy (reduction in CFU >6 log units at 1 mg/kg BAY 73-7388 vs no reduction in CFU at the same doses of LZD). A 4.5 log unit CFU reduction was only obtained at a 10 mg/kg dose of LZD.

b) Survival assays: For BAY 73-7388 and VAN all mice survived at the 3 tested doses (1, 3, and 10 mg/kg). In contrast, for LZD 0, 2, and 4 animals survived when tested at the same dose range.

Conclusions:

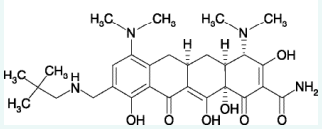
Treatment with BAY 73-7388 is highly effective in an animal model of pneumococcal pneumonia.

(BAY 73-7388 was discovered by Paratek Pharmaceuticals, Inc., Boston, MA, and designated PTK 0796.)

Introduction

Streptococcus pneumoniae is the most frequently isolated pathogen in community-acquired pneumonia and is a significant cause of mortality in humans. BAY 73-7388 is the first compound selected from the novel class of aminomethylcyclines and shows excellent *in vitro* activity against *S. pneumoniae,* including multidrug-resistant strains. We report here on the *in vivo* activity of BAY 73-7388 in comparison with VAN and LZD in an *in vivo* mouse model of acute pneumonia caused by pneumococci.

Structure of BAY 73-7388



Methods

The test compounds were obtained from the following sources: BAY 73-7388 (Paratek Pharmaceuticals,Inc.,Boston,MA),linezolid (Pharmacia GmbH), vancomycin (Lilly Deutschland GmbH).

The pneumococcal strain L3 TV (Serotype 3), a clinical isolate, was taken from the culture collection of Bayer HealthCare AG, Germany.

Female CFW-1 mice (18-20 g body weight) were used (Harlan-Winckelmann, Germany) for all experiments described.The animals were kept under conventional housing conditions.

Pneumococcal pneumonia

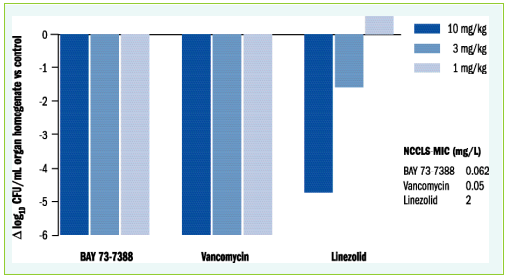
Isoflurane-anaesthetized mice were inoculated intranasally (IN) with 20 µL of physiological saline containing the infective dose of *S. pneumonia* strain L3 TV as indicated in the Figure legends. The animals were treated bid starting 2 h postinfection (PI).The survival and the bacterial counts in the lung were determined on day 4 PI. For determination of the viable bacterial load in the lungs, the lungs were removed aseptically and homogenised in a POTTER S homogeniser (B. Braun, Melsungen, Germany) in sterile saline. Diluted samples were spread on agar plates, and the CFUs were counted after overnight incubation.

Results

The therapeutic efficacy in the mouse model of pneumococcal pneumonia was measured by reduction of the CFUs in the lungs. With BAY 73-7388 and VAN, CFUs in the lung at day 4 were lower than with LZD therapy (reduction in CFU >6 log units at 1 mg/kg BAY 73-7388 vs no reduction in CFU at the same doses of LZD).A 4.5 log unit CFU reduction was only obtained at a 10 mg/kg dose of LZD (Figure 1). At 3 and 10 mg/kg, CFU values were below detection limit for BAY 73-7388 as well as for VAN (Figure 2).

For BAY 73-7388 and VAN, all mice survived at the 3 tested doses (1, 3, and 10 mg/kg) on day 4. In contrast, for LZD 0%, 40%, and 80%, respectively, survived when tested at the same dose range (Figure 3).

Figure 1. Efficacy in mouse model of pneumococcal pneumonia. Depicted are the differences in viable bacterial load in the lungs of antibiotic-treated mice as compared with untreated control animals.



Infective dose 9 x 10^5 CFU/mouse of S. pneumoniae strain L3 TV IN; treatment IV bid; data of n=5 mice per group at day 4 PI.

Figure 2. Efficacy in mouse model of pneumococcal pneumonia. Depicted are the viable bacterial loads in the lungs of single mice. For dead animals, CFUs were set to 10^9/mL lung homogenate.

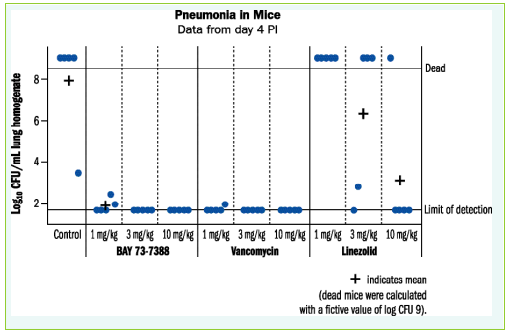
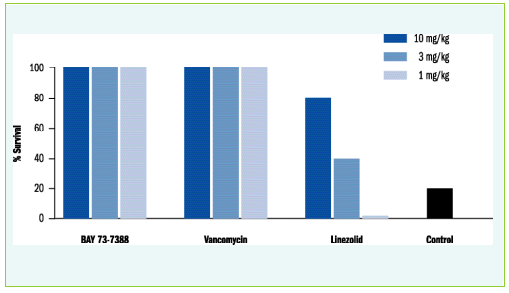


Figure 3. Efficacy in mouse model of pneumococcal pneumonia. Depicted are the percentages of survivors at day 4 PI.



Conclusions

- Treatment with BAY 73-7388 is highly effective in an animal model of pneumococcal pneumonia
- BAY 73-7388 demonstrated superior efficacy to linezolid as measured by reduction in CFU and survival