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Superior efficacy of BAY 73-7388, a novel aminomethylcycline, compared with linezolid and vancomycin in murine sepsis caused by susceptible or multiresistant staphylococci

H. Broetz-Oesterhelt, R. Endermann, C.H. Ladel, H. Labischinski
Wuppertal, D

Objective: BAY 73-7388 is the first compound selected from the novel class of aminomethylcyclines and was designed to meet an increasingly significant need for additional therapies for treatment of bacterial infections, including those resistant to currently available antibiotics. The increasing frequency of multi-resistant staphylococci is of particular concern in the clinical setting. Therefore, the efficacy of BAY 73-7388 was compared with that of vancomycin (VAN) and linezolid (LIN) in different mouse models of staphylococcal infection.

Methods: Murine sepsis was used to determine the efficacy of BAY 73-7388 compared with VAN and LIN. For systemic infections, *Staphylococcus aureus* MSSA/quinolone-resistant MRSA and *Staphylococcus epidermidis* (MRSE, TET-resistant) were administered intraperitoneally, and i.v. treatment was started 30 min post-infection. Survival of the infected mice was monitored until day 5. For the investigation in immunocompromised animals, mice were rendered neutropenic by two injections of 150 and 100 mg/kg cyclophosphamide at days 4 and 1 prior to infection.

Results: In systemic infections with MSSA, BAY 73-7388 was more effective than VAN or LIN resulting in 100% survival at 0.3 mg/kg compared with 10 and 10 mg/kg, respectively. The efficacy of BAY 73-7388 therapy on systemic quinolone-resistant MRSA and MRSE infection was also pronounced (100% survival for quinolone-resistant MRSA at 3 mg/kg compared with >10 and >10 mg/kg, respectively; 100% survival for MRSE at 1 mg/kg compared with 10 and >10 mg/kg, respectively). Moreover, in neutropenic mice, BAY 73-7388 was the only curative agent (100% survival for BAY 73-7388 at 50 mg/kg). In contrast there was zero survival in the VAN and the LIN groups at the highest dosage tested, 50 mg/kg.

Conclusions: Treatment with BAY 73-7388 is highly effective in systemic staphylococcal infections (susceptible and multi-resistant strains) in mice, and is superior compared with LIN and VAN.

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

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SUPERIOR EFFICACY OF BAY 73-7388, A NOVEL AMINOMETHYLCYCLINE, COMPARED WITH LINEZOLID AND VANCOMYCIN IN MURINE SEPSIS CAUSED BY SUSCEPTIBLE OR MULTIRESISTANT STAPHYLOCOCCI

H. Broetz-Oesterhelt, R. Endermann, C.H. Ladel and H. Labischinski*

Bayer HealthCare AG, 42096, Wuppertal, Germany.

Abstract

Objective:

BAY 73-7388 is the first compound selected from the novel class of aminomethylcyclines and was designed to meet an increasing need for additional therapies for bacterial infections, including those resistant to currently available antibiotics. Multiresistant staphylococci are of particular concern in the clinical setting. Therefore, the efficacy of BAY 73-7388 was compared with that of vancomycin (VAN) and linezolid (LZD) in different mouse models of staphylococcal infection.

Methods:

Murine sepsis was used to compare the efficacy of BAY 73-7388 with VAN and LZD. For systemic infections, *Staphylococcus aureus* (MSSA), methicillin- and quinolone-resistant *Staphylococcus aureus* (MQRSA), and methicillin-resistant *Staphylococcus epidermidis* (MRSE) were administered intraperitoneally, and IV treatment was started 30 min postinfection. Survival of the infected mice was monitored until day 5. For the investigation in immunocompromised animals, mice were rendered neutropenic by 2 injections of 150 and 100 mg/kg cyclophosphamide at days 4 and 1 prior to infection.

Results:

In systemic infections with MSSA, BAY 73-7388 was more effective than VAN or LZD, resulting in 100% survival at 0.3 mg/kg compared with 10 mg/kg for VAN and LZD. The efficacy of BAY 73-7388 therapy on systemic MQRSA and MRSE infection was also pronounced (100% survival for MQRSA at 3 mg/kg compared with >10 mg/kg for VAN and LZD; 100% survival for MRSE at 1 mg/kg compared with 10 mg/kg and >10 mg/kg for VAN and LZD, respectively). Moreover, in neutropenic mice, BAY 73-7388 was the only curative agent (100% survival for BAY 73-7388 at 50 mg/kg). In contrast, there was 60% survival in the VAN and the LZD groups at the highest dosage tested, 50 mg/kg.

Conclusions:

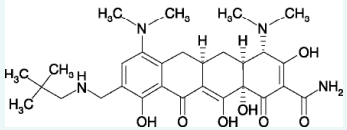
Treatment with BAY 73-7388 is highly effective in systemic staphylococcal infections (susceptible and multiresistant strains) in mice and is superior compared with LZD and VAN.

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

Introduction

Staphylococci (coagulase-positive as well as coagulase-negative) are the most frequently isolated gram-positive pathogens in the hospital setting. The high prevalence of multiresistant isolates (MRSA/MRSE, GISA) in many countries poses additional problems, and novel treatment options are urgently needed. BAY 73-7388 is the first compound selected from the novel class of aminomethylcyclines which was designed to provide potent activity against a range of clinically relevant pathogens including susceptible and resistant gram-positive pathogens.

Structure of BAY 73-7388



To further evaluate the potential clinical usefulness of BAY 73-7388 in infections caused by *Staphylococcus spp.*, the efficacy of BAY 73-7388 in different mouse models of staphylococcal infections in immunocompetent and neutropenic mice was determined.

Methods

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

The MSSA and MQRSA strains are clinical isolates from the culture collection of Bayer HealthCare AG, Germany, deposited at the DSM strain collection, Braunschweig, Germany, with the numbers DSM 11823 and DSM 11822, respectively. The MRSE strain was obtained through the Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA) supported under NIAID/NIH contract No. N01-AI95359, NARSA designation of the isolate: NRS 101.

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

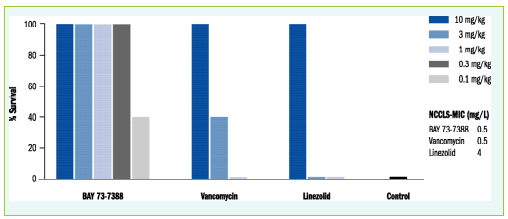
Staphylococcal Infections

Overnight cultures of each microorganism were subcultured in broth and incubated until the early phase of exponential growth was reached. The cultures were then diluted with physiological saline containing 5% mucin. The dilution was such that the desired inoculum was finally contained in 0.25 mL, and then used for IP infection of the mice or rats. In general, bacterial challenges were chosen which exceeded the previously determined lethal infective doses. At 30 min postinfection (PI), the animals received a single dose of antibiotic treatment (as indicated in the figure legends).Survival was monitored over a period of 5 days PI. For the neutropenic mouse model, the animals were rendered neutropenic by 2 IP injections of cyclophosphamide 4 days (150 mg/kg) and 1 day (100 mg/kg) prior to infection.

Results

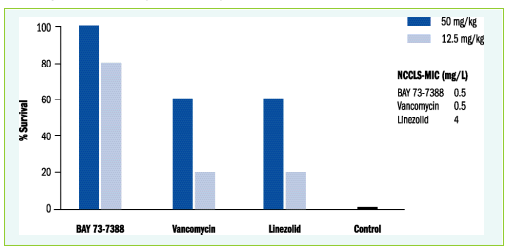
The therapeutic efficacy of BAY 73-7388 in mouse models of staphylococcal bacteremia was compared with that of VAN and LZD. In a systemic infection with MSSA, the efficacy of BAY 73-7388 was superior to that of VAN or LZD resulting in 100% survival at 0.3 mg/kg compared with 10 mg/kg for VAN or LZD (Figure 1). When neutropenic mice were systemically challenged with the same strain, BAY 73-7388 was the only curative agent (100% survival at 50 mg/kg), while both VAN and LZD yielded only 60% survival at 50 mg/kg (Figure 2). In the therapy of a systemic MQRSA, a single dose of 3 mg/kg of BAY 73-7388 completely protected the animals, while VAN and LZD showed only marginal therapeutic effects, even at 10 mg/kg (Figure 3). Moreover, the efficacy of BAY 73-7388 in an MRSE septicaemia was also pronounced. 1 mg/kg of BAY 73-7388 completely protected the animals, compared with 10 mg/kg for VAN and >10 mg/kg for LZD (Figure 4).

Figure 1. Efficacy in the *S. aureus* mouse bacteremia model.The percentage of surviving animals on day 5 postinfection (PI) is depicted. While 0.3 mg/kg of BAY 73-7788 is sufficient for survival of all animals, 10 mg/kg of VAN or LZD are required for comparable therapeutic efficacy.



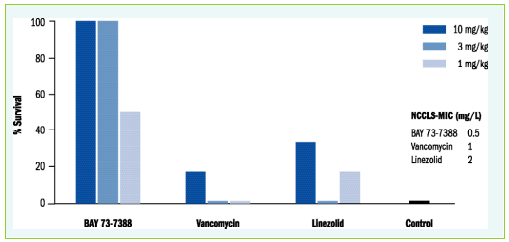
Infective dose 1.2 x 10⁶ CFU/mouse of S. aureus *DSM 11823 (MSSA) in 5% mucin IP; treatment IV 30 min PI; data of n=5 mice per group at day 5 PI.*

Figure 2. Efficacy in *S. aureus* bacteremia in neutropenic mice. The percentage of surviving animals on day 5 PI is depicted. BAY 73-7388 showed excellent activity in the therapy of neutropenic mice systemically infected with *S. aureus*.



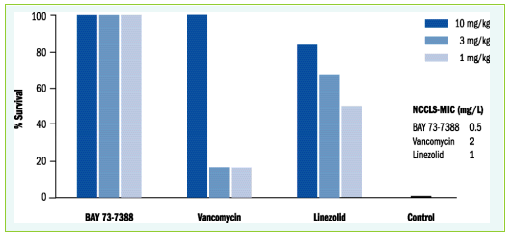
Infective dose 4 x 10⁶ CFU/mouse of S. aureus *DSM 11823 in 5% IP; treatment IV 0.5 h PI; data of n=5 mice per group at day 5 PI.*

Figure 3. Efficacy in MQRSA mouse bacteremia model.The percentage of surviving animals on day 5 PI is depicted. A single dose of 3 mg/kg of BAY 73-7388 completely protected the systemically infected animals, while VAN and LZD at up to 10 mg/kg showed only marginal therapeutic effects.



Infective dose 9 x 10⁶ CFU/mouse of S. aureus *DSM 11822 in 5% mucin IP; treatment IV 30 min PI; data of n=6 mice per group at day 5 PI.*

Figure 4. Efficacy in *S.epidermidis* MRSE mouse bacteremia model. The percentage of surviving animals on day 5 PI is depicted at 1 mg/kg BAY 73-7388, which completely protected the animals.



Infective dose 5 x 10⁶ CFU/mouse of S. epidermidis *strain NRS 101 in 5% mucin IP; treatment IV 0.5 h PI; data of n=6 mice per group at day 5 PI.*

Conclusions

- Treatment with the novel aminomethylcycline BAY 73-7388 is highly effective in murine models of staphylococcal infection.
- The efficacy of BAY 73-7388 is superior to linezolid and vancomycin in murine models of staphylococcal infection.
- The efficacy of BAY 73-7388 is not affected by resistance to other antibiotic classes, including methicillin.
- BAY 73-7388 is a promising agent for the treatment of staphylococcal infections, including those caused by MRSA.