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BAY 73-7388 demonstrates greater activity than linezolid in a range of murine models of skin and soft tissue infection

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BAY 73-7388 is a novel antibiotic compound being developed for the treatment of severe bacterial infections. It 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 infections, including those resistant to currently available antibiotics. The efficacy of BAY 73-7388 in different mouse models of skin and soft tissue infection (SSTI) was compared with that of vancomycin (VAN) and linezolid (LIN).

Methods: Two mouse models were employed to determine the efficacy of BAY 73-7388: (1) infected abscess model (induced by implantation and subsequent infection of Gelfoam (TM)) and (2) infected thigh muscle model in neutropenic mice. *Staphylococcus aureus* strain DSM11823 (MSSA) was used to infect the respective structures in the skin and soft tissues. Infected abscess bearing mice were treated i.v. bid for 2 days, while thigh muscle infection model mice were treated s.c. 30 min post-infection. CFU reduction of infected tissues and bacterial load in different organs (spread from the infection site) were used as read-out for therapeutic efficacy.

Results: As measured by reduction of bacterial load, therapy of infected abscesses with BAY 73-7388 (CFU reduction >4 log units at 10 mg/kg) was superior to VAN and LIN (no reduction in bacterial load). Furthermore, BAY 73-7388 reduced the overall bacterial load in spleen, liver, lung and heart. In the reduction of organ load, BAY 73-7388 was as efficacious as VAN or LIN. In the mouse thigh muscle infection model, BAY 73-7388 proved to be as least as effective as VAN (2 log CFU reduction) and superior to LIN, which demonstrated no efficacy at the same dose (0.5 log CFU increase).

Conclusions: BAY 73-7388 was clearly more potent than LIN and VAN in the infected abscess model, and more potent than LIN and at least as effective as VAN in the thigh wound model.

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

BAY 73-7388 DEMONSTRATES GREATER ACTIVITY THAN LINEZOLID IN A RANGE OF MURINE MODELS OF SKIN AND SOFT TISSUE INFECTION

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Abstract

Objectives:

BAY 73-7388 is a novel antibiotic compound being developed for the treatment of severe bacterial infections. It is the first compound selected from the novel class of aminomethylcyclines and was designed to meet the increasing need for additional therapies for treatment of infections, particularly those resistant to currently available antibiotics. The efficacy of BAY 73-7388 in different mouse models of skin and soft tissue infection was compared with that of vancomycin (VAN) and linezolid (LZD).

Methods:

Two mouse models were employed to determine the efficacy of BAY 73-7388: 1) infected abscess model (induced by implantation and subsequent infection of Gelfoam®) and 2) infected thigh muscle model in neutropenic mice. The infecting strain in both models was *Staphylococcus aureus* DSM11823 (MSSA). Infected abscess bearing mice were treated IV bid for 2 days, while thigh muscle infection model mice were treated SC 30 min postinfection. Therapeutic efficacy was assessed by CFU reduction of infected tissues and bacterial load in different organs spread from the infection site.

Results:

As measured by reduction of bacterial load, therapy of infected abscesses with BAY 73-7388 (CFU reduction >4 log units at 10 mg/kg) was superior to VAN and LZD (no reduction in bacterial load). Furthermore, BAY 73-7388 reduced the overall bacterial load in spleen, liver, lung, and heart. In the reduction of organ load, BAY 73-7388 was as efficacious as VAN or LZD. In the mouse thigh muscle infection model, BAY 73-7388 proved to be at least as effective as VAN (2 log CFU reduction) and superior to LZD, which demonstrated no efficacy at the same dose (0.5 log CFU increase).

Conclusions:

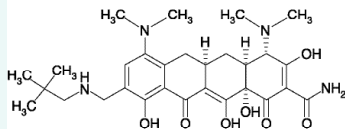
BAY 73-7388 was clearly more potent than LZD and VAN in the infected abscess model, and was more potent than LZD and at least as effective as VAN in the thigh wound model.

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

Introduction

BAY 73-7388 is a novel antibiotic compound being developed for the treatment of severe bacterial infections. It is the first compound selected from the novel class of aminomethylcyclines and was designed to meet the increasing need for additional therapies for infections, particularly those resistant to currently available antibiotics.

Structure of BAY 73-7388



Skin and soft tissue infections (STTI) are among the most frequent hospital infections, and are often caused by multiresistant gram-positive pathogens. These pathogens continue to be a significant cause of serious disease.

BAY 73-7388 shows potent activity against a range of clinically prevalent organisms, including gram-positive organisms resistant to currently available classes of antibiotics. To investigate the potential of BAY 73-7388 in the treatment of STTI, the *in vivo* activity of BAY 73-7388 in two *Staphylococcus aureus* STTI mouse models (including a model designed to mimic infected abscesses) was determined in comparison to vancomycin (VAN) and linezolid (LZD).

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 *S. aureus* strain employed in these studies is a clinical isolate (MSSA) from the culture collection of Bayer HealthCare AG, Germany, deposited at the DSM strain collection, Braunschweig, Germany, with the number DSM 11823.

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

Staphylococcal Abscess Model

A collagen Gelfoam® (Pharmacia & Upjohn, Kalamazoo, USA) was cut into pieces of ca. 1 x 1 cm and incubated overnight in sterile PBS, pH 7.4. Gelfoam® pieces were implanted subcutaneously on the backs of the mice. After 3 to 4 days, abscess-like fibrotic capsules had formed around the implanted material. The mice were infected by injection of 50 µL of a suspension of *S. aureus* into the implanted Gelfoam® (Figure 1). Previous experiments had shown that this results in a colonization of the implanted material and subsequent spread of the bacteria to different organs, leading to a colonization of those organs. Antibiotic treatment was administered bid, starting 2 h after the infection of the Gelfoam® implants. Two days after termination of treatment, the Gelfoam® implants and organs were removed for determination of the bacterial cell counts.

Staphylococcal Thigh Muscle Infection in Neutropenic Mice

Mice were rendered neutropenic by two intraperitoneal injections of cyclophosphamide 4 days (150 mg/kg) and 1 day (100 mg/kg) prior to infection. Under light anaesthesia with CO₂, the animals were infected intramuscularly (IM) by injecting 0.1 mL of a suspension of *S. aureus* (log growth phase) into the thigh muscle of the right hind leg at t = 0 h. Antibiotic treatment was administered subcutaneously at t = 0.5 h postinfection (PI). For assessment of the therapeutic effects, the infected muscles were removed and homogenized 24 h PI and diluted samples were spread on agar plates for CFU determination.

Results

Figure 1. Mouse model of infected staphylococcal abscess. A collagen Gelfoam® was implanted subcutaneously on the back of mice. Four days after implantation, the Gelfoams® were surrounded by a fibrotic capsule and showed beginning vascularization. At that time, Gelfoams® were infected by *S. aureus*, which colonized the implanted material and caused the formation of an abscess-like structure. Systemic bacterial spread from this infection site resulted subsequently in the colonization of various organs.

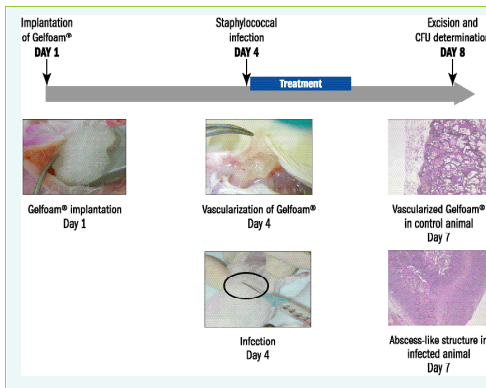
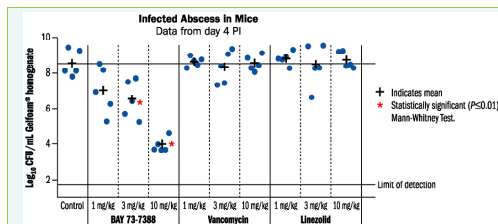
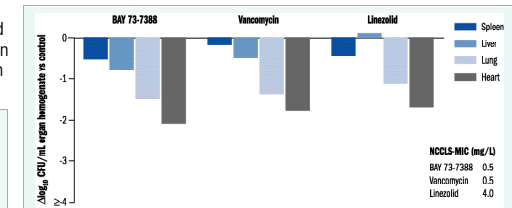


Figure 2. Efficacy in the *S. aureus* mouse abscess model. Depicted are the reductions of viable bacterial load in the Gelfoam® implants at day 4 after infection as compared with untreated control animals.



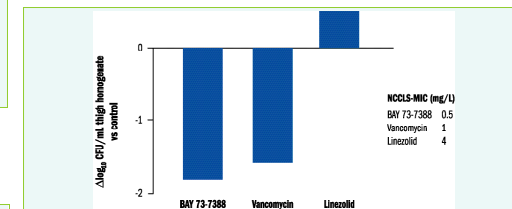
Infective dose 3.5×10^5 CFU/mouse of *S. aureus* DSM 11823; treatment with 1 to 10 mg/kg IV bid starting 2 h PI of the Gelfoam®. Values of n=5 mice per group are depicted; each dot represents a single animal.

Figure 3. Efficacy in the treatment of systemic bacterial spread from the primary infection site in the *S. aureus* mouse abscess model. Depicted are the reductions of viable bacterial load in several organs at day 4 after infection as compared with untreated control animals.



Infective dose 3.5×10^5 CFU/mouse of *S. aureus* DSM 11823; treatment 10 mg/kg IV bid starting 2 h PI of the Gelfoam®. Depicted values represent means of n=5 mice per group ($\Delta \log_{10}$ CFU ≥ 4 means reduction below the detection limit).

Figure 4. Efficacy in *S. aureus* thigh muscle infection model in neutropenic mice. Depicted are the reductions of viable bacterial load in the thigh muscle homogenates from antibiotic-treated mice as compared with untreated control animals.



Infective dose 2×10^6 CFU/mouse of *S. aureus* DSM 11823 IM; treatment 25 mg/kg SC 0.5 h PI; depicted are the mean values of n=5 mice per group at 24 h PI.

The therapeutic efficacy of BAY 73-7388 in two models of staphylococcal STTI was compared to that of VAN and LZD. The results obtained in the *S. aureus*-infected abscess model are summarized in Figures 2 and 3. On day 4 PI, BAY 73-7388 (at 3 mg/kg) had caused a significant reduction of the bacterial loads in the Gelfoam® implants by about 4 log units, whereas VAN and LZD failed to reduce the bacterial counts in the Gelfoam® even at 10 mg/kg. All three compounds reduced the CFU in the periphery to the same extent, with only minor differences. In the *S. aureus* thigh muscle infection model (Figure 4) a clear ranking in efficacy was observed. BAY 73-7388 was found to be at least as effective as VAN (2 log CFU reduction at 25 mg/kg) and superior to LZD (no therapeutic efficacy at the same dose).

Conclusions

- BAY 73-7388 was clearly more potent than LZD and VAN in the infected abscess model, and more potent than LZD, and at least as effective as VAN in the thigh wound model.
- BAY 73-7388 is a promising agent for treatment of STTI, including infections caused by isolates resistant to current classes of antibiotics.