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BAY 73-7388 is highly efficacious in animal models of intra-abdominal infections caused by a range of aerobic and anaerobic organisms, including VRE

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Objective: BAY 73-7388, a novel antibiotic compound from the aminomethylcycline class, has an antibacterial spectrum encompassing Gram-positive, Gram-negative and anaerobic bacteria, including those resistant to currently available antibiotics. The efficacy of BAY 73-7388 in four different mouse infection models with pathogens causing intra-abdominal infections was compared with that of vancomycin (VAN), linezolid (LIN), imipenem (IMI) and metronidazole (MTN).

Methods: For systemic infections (sepsis), enterococci (tetracycline (TET)-resistant *Enterococcus faecalis* or *Enterococcus faecium* VRE) were administered intraperitoneally, and i.v. treatment was started 30 min post-infection; survival of the infected mice until day 5 was used as read-out. In the pouch model using *Bacteroides fragilis* as infecting pathogen, therapeutic efficacy of BAY 73-7388 compared with MTN was determined as reduction of CFU. The mouse model of caecal ligation was used as a model for polymicrobial peritonitis after surgical intervention and 10 days survival used as read-out.

Results: In systemic infections with TET-resistant *E. faecalis* or *E. faecium* VRE, efficacy of BAY 73-7388 was superior to VAN or LIN: 100% survival was observed at 1 mg/kg BAY 73-7388, 10 mg/kg VAN and 3 mg/kg LIN. For the *E. faecium* septicaemia model, 100% survival was found at 15 mg/kg BAY 73-7388, while neither VAN nor LIN treatment resulted in 100% survival, even at 50 mg/kg, the highest dose tested. In the pouch model with *B. fragilis*, the CFU reduction caused by BAY 73-7388 was superior to MTN (CFU reduction >6 log compared with 4 log at 25 mg/kg, respectively). Therapy (2 × 10 mg/kg i.v. on day 1) of intra-abdominal infections and post-operative polymicrobial peritonitis with BAY 73-7388 showed increased survival compared with IMI or LIN (80 vs. 70 vs. 30%, respectively).

Conclusions: Against pathogens causing intra-abdominal infections (including VRE and TET-resistant strains), BAY 73-7388 demonstrated superior therapeutic efficacy compared with VAN, LIN, MTN or IMI.

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

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BAY 73-7388 IS HIGHLY EFFICACIOUS IN ANIMAL MODELS OF INTRA-ABDOMINAL INFECTIONS CAUSED BY A RANGE OF AEROBIC AND ANAEROBIC ORGANISMS, INCLUDING VRE

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Abstract

Objective:

BAY 73-7388, a novel antibiotic compound from the aminomethylcycline class, has an antibacterial spectrum encompassing gram-positive, gram-negative, and anaerobic bacteria, including those resistant to currently available antibiotics. The efficacy of BAY 73-7388 in 4 different mouse infection models with pathogens causing intra-abdominal infections was compared with that of vancomycin (VAN), linezolid (LZD), imipenem (IMI), and metronidazole (MTN).

Methods:

For systemic infections (sepsis), enterococci (tetracycline [TET]-resistant *Enterococcus faecalis*, VAN-resistant *Enterococcus faecium* [VRE]) were administered intraperitoneally, IV treatment was started 30 min postinfection, and survival of the infected mice until day 5 was monitored. In the pouch model using *Bacteroides fragilis* as infecting pathogen, therapeutic efficacy of BAY 73-7388 compared with MTN was determined as reduction of colony forming units (CFU).The mouse model of caecal ligation was used as a model for polymicrobial peritonitis after surgical intervention and 10-day survival was monitored.

Results:

In systemic infections with TET-resistant *E.faecalis* or *E.faecium* VRE,efficacy of BAY 73-7388 was superior to VAN or LZD: 100% survival was observed at 1 mg/kg BAY 73-7388, 10 mg/kg VAN, and 3 mg/kg LZD. For the *E.faecium* septicaemia model,100% survival was found at 15 mg/kg BAY 73-7388, while neither VAN nor LZD treatment resulted in 100% survival, even at 50 mg/kg, the highest dose tested. In the pouch model with *B.fragilis*, the CFU reduction caused by BAY 73-7388 was superior to MTN (CFU reduction >6 log compared with 4 log at 25 mg/kg, respectively).Therapy (2 x 10 mg/kg IV on day 1) of intra-abdominal infections and postoperative polymicrobial peritonitis with BAY 73-7388 showed increased survival compared with IMI or LZD (80% vs 70% vs 30%, respectively).

Conclusions:

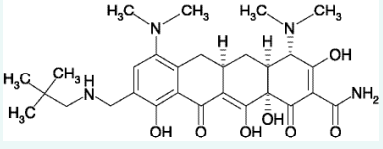
Against pathogens causing intra-abdominal infections (including VRE and TET-resistant strains), BAY 73-7388 demonstrated superior therapeutic efficacy compared with VAN, LZD, MTN, or IMI.

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

Introduction

BAY 73-7388 is the first compound selected from the novel class of amino-methylcyclines. BAY 73-7388 exhibits excellent activity against susceptible and resistant gram-positive and gram-negative pathogens as well as significant activity against anaerobic pathogens.

Structure of BAY 73-7388



The spectrum of BAY 73-7388 suggests a potential application for clinical management of serious intra-abdominal infections, which continue to be a significant cause of morbidity and mortality. To further evaluate the potential clinical usefulness of BAY 73-7388 in intra-abdominal infections, the efficacy of BAY 73-7388 in 4 different mouse infection models with pathogens causing intra-abdominal infections was determined in comparison with vancomycin (VAN),linezolid (LZD), imipenem (IMI), and metronidazole (MTN).

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), imipenem (MSD GmbH), and metronidazole (Sigma Chemical Co.).

All bacterial strains were taken from the culture collection of Bayer HealthCare AG, Germany. All strains were clinical isolates or from national strain collections.

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.

Systemic Infection

Overnight cultures of each microorganism were diluted and recultured such that the bacteria were in the early logarithmic phase of growth. Mice were inoculated intraperitoneally (IP) with a bacterial suspension in 5% mucin in physiological saline.The respective inocula are given in the descriptions below; in general, the inocula exceeded the LD_{100}. Treatment started at 30 min postinfection (PI), and survival was monitored over 5 days. 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.

Pouch Model

Pouches were formed by injecting 5 mL air and 0.5 mL 0.1% croton oil in olive oil into loose subcutaneous connective tissue of the backs of CFW1-mice weighing 18 to 22 g. After 72 h, most of the air was withdrawn and replaced by 1 mL of 0.25% agar in physiological NaCl. 48 h later, 0.5 mL of a suspension of *B.fragilis* (grown anaerobically in Columbia broth, logarithmic growth phase) was injected into the pouch. Antibiotic treatment was given IV at t = 0.5 h, 4 h, 24 h, and 32 h PI. At t = 48 h PI, samples of the pouch exudates were taken, and the viable bacterial load were then determined by plating diluted aliquots on agar.

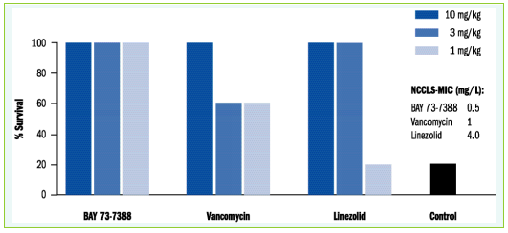
Caecal Ligation Model / Polymicrobial Peritonitis

For the model of postoperative or polymicrobial peritonitis, mice were anaesthetised and the peritoneum opened with a small cut.The caecum was taken out of the peritoneum without harming the surrounding intestine.A ligation was set at the proximal end of the caecum, and thereafter the ligated part punctured using an injection needle (21G). Then the ligated part of the intestine was put back in the peritoneum and the wound closed by tissue adhesive (Histoacryl,Aesculap, Tuttlingen, Germany). Survival of treated and nontreated mice was monitored daily until day 7 postinfection.

Results

Among animals infected with *E. faecalis* strain 27159 (tet^{Res}), efficacy of BAY 73-7388 was superior to that of VAN or LZD (Figure 1): 100% survival was observed at 1 mg/kg BAY 73-7388, 10 mg/kg VAN, and 3 mg/kg LZD.

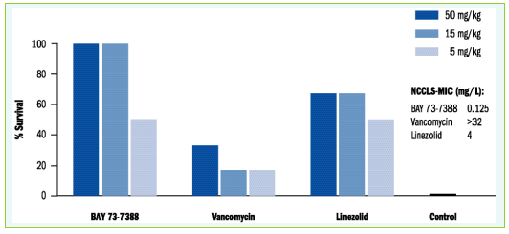
Figure 1. Efficacy in *E. faecalis* (tet^{Res}) mouse bacteremia model.



Infective dose 1.8 x 10^8 CFU/mouse of E. faecalis *strain 27159 in 5% mucin IP; treatment IV 30 min PI; data of n=6 mice per group at day 5 PI.*

In the neutropenic mouse model of vancomycin-resistant *E.faecium* bacteremia, 100% survival was found at 15 mg/kg BAY 73-7388, while neither VAN nor LZD treatment resulted in 100% survival, even at 50 mg/kg, the highest dose tested (Figure 2).

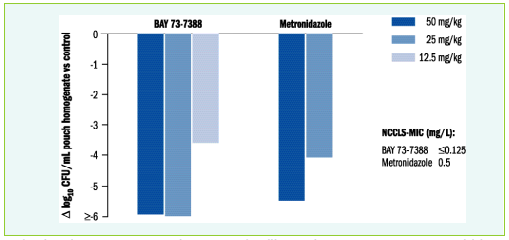
Figure 2. Efficacy in *E.faecium* VRE bacteremia model in neutropenic mice.



Infective dose 4.5 x 10^7 CFU/mouse of E. faecium *strain L4001 in 5% mucin IP; treatment IV 30 min PI; data of n=6 mice per group at day 5 PI.*

The results generated in the granuloma pouch model in mice are summarized in Figure 3.The reduction of *B.fragilis* cells caused by BAY 73-7388 was superior to that reached by MTN (CFU reduction >6 log compared with 4 log at 25 mg/kg, respectively).

Figure 3. Efficacy (IV) in the *B.fragilis* granuloma pouch model. Depicted are the reductions of viable bacterial load in the pouch exudates of antibiotic-treated mice as compared with untreated control animals.

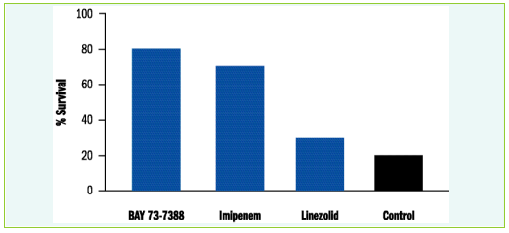


Infective dose 6 x 10^8 CFU/mouse B. fragilis *strain 06688; treatment IV bid PI; shown are the mean values of n=5 mice per group as determined at day 4 PI.*

The caecal ligation model has close parallels to the clinical setting, including the polymicrobial nature of the peritonitis and the pattern of remote organ failure. It has been reported that bacteremia (anaerobic and aerobic) rather than serum endotoxin is the pathogenic determinant (Mercer-Jones et al. *Br J Surg*. 1998;85:385-389).

Figure 4 shows the results which were obtained after intravenous antibiotic treatment (2 x 10 mg/kg IV on day 1). Therapy of postoperative polymicrobial peritonitis with BAY 73-7388 showed increased survival compared with IMI or LZD (80% vs 70% vs 30%, respectively).

Figure 4. Efficacy (IV) in mouse model of postoperative polymicrobial peritonitis.



Sepsis was induced by caecal ligation and puncture; treatment 10 mg/kg IV at t=4 h and 18 h postsurgery; shown are the data from n=10 mice per group.

Conclusions

BAY 73-7388 demonstrated superior therapeutic efficacy against pathogens causing intra-abdominal infections (including VRE and TET-resistant strains) compared with VAN, LZD, MTN, or IMI.

- In a mouse model of enterococcal (tet^{Res}, VRE) septicaemia, efficacy of BAY 73-7388 was superior to vancomycin or linezolid
- In a mouse model of anaerobic infection with *B.fragilis*, BAY 73-7388 shows higher potency than metronidazole
- In a polymicrobial peritonitis mouse model, BAY 73-7388 demonstrates superior efficacy compared with imipenem or linezolid

BAY 73-7388 is a promising agent for the treatment of intra-abdominal infections including those involving strains resistant to currently available antibiotics, eg, VRE.