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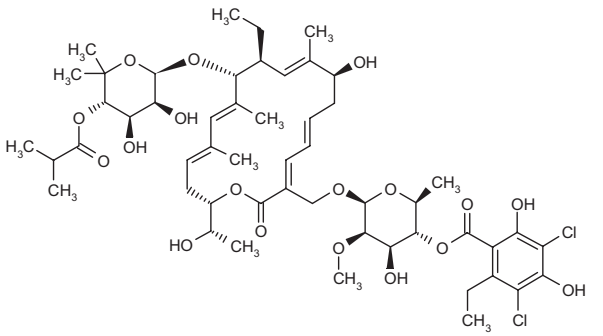
Tiacumicin B

Macrolide Antibiotic
Treatment of C. difficile-Associated Diarrhea

PAR-101
OPT-80

6-Deoxy-1-*O*-[(2*S*,8*R*,9*S*,12*S*)-17-[6-deoxy-4-*O*-(3,5-dichloro-2-ethyl-4,6-dihydroxybenzoyl)-2-*O*-methyl-β-L-mannopyranosyloxymethyl]-9-ethyl-12-hydroxy-2-[1(*S*)-hydroxyethyl]-5,7,11-trimethyl-18-oxooxacyclooctadeca-4,6,10,14,16-pentaen-8-yl]-4-*O*-isobutyryl-5-*C*-methyl-β-D-*lyxo*-hexopyranoside

3,5-Dichloro-2-ethyl-4,6-dihydroxybenzoic acid 4'-ester with (8*S*,11*S*,12*R*,18*S*)-3-(6-deoxy-2-*O*-methyl-β-L-mannopyranosyloxymethyl)-12-(6-deoxy-4-*O*-isobutyryl-5-*C*-methyl-β-D-*lyxo*-hexopyranosyloxy)-11-ethyl-8-hydroxy-18-[1(*S*)-hydroxyethyl]-9,13,15-trimethyloxacyclooctadeca-3,5,9,13,15-pentaen-2-one



$C_{52}H_{74}Cl_2O_{18}$
Mol wt: 1,058.0386

CAS: 056645-60-4

EN: 134139

Abstract

Tiacumicin B (OPT-80, PAR-101) is a macrolide antibiotic in phase III clinical trials for the treatment of *Clostridium difficile*-associated diarrhea (CDAD). *C. difficile* is responsible for 20% of antibiotic-associated diarrhea cases in hospitals. Current treatment requires that patients be taken off the offending antibiotic, followed by treatment with either vancomycin or metronidazole. Both of these antibiotics are effective at treating the infection, but the relapse rate is unacceptably high at 20-50%. Tiacumicin B is a narrow-spectrum antibiotic with good activity against clostridia and minimal activity against many other gut microflora. Specificity may be important for reducing the relapse rate seen with broad-spectrum antibiotics, because maintaining the natural balance of intestinal bacteria helps to provide resistance to re-colonization by pathogens. Initial clinical evaluation has shown tiacumicin B to be effective in the treatment of CDAD, with a relapse rate of only 5%.

Isolation

Tiacumicin B was isolated from cultures of the microorganism *Dactylosporangium auranticum* subsp. *hamdenensis* (AB 718C-41 NRRL 18085). A compound isolated from the culture of *Actinoplanes deccanensis* (ATCC 21983), designated lipiarmycin A3, has been shown to be identical to tiacumicin B. From the ethyl acetate extracts of the fermentation broths, as well as from acetone extracts of the mycelial mass, a mixture of active components was obtained, including the closely related tiacumicins A, B and C. Isolation of pure tiacumicin B is accomplished using chromatographic techniques, such as countercurrent chromatography (1-3).

Background

Clostridium difficile-associated diarrhea (CDAD) is a particular problem in hospitals and hospital-like institutions and *C. difficile* is responsible for about 20% of cases of nosocomial antibiotic-associated diarrhea. Greater use of broad-spectrum antibiotics in hospitals is associated with a rise in the incidence of this disease. Antibiotics disrupt the balance of normal intestinal microflora, which in turn allows toxigenic strains of *C. difficile* to take over, leading to diarrhea and in severe cases pseudomembranous colitis. Treatment involves discontinuation of the offending antibiotic followed by supportive therapy, often involving oral treatment with either vancomycin or metronidazole. These antibiotics are effective at treating the infection, and reduce the *C. difficile* counts in the intestine, but they are themselves relatively broad spectrum, and often exacerbate the conditions that allowed CDAD to develop in the first place; the relapse rate is between 20% and 50% (4-7). Other problems with these

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antibiotics include adverse effects in the case of metronidazole and the possible development of resistant enterococci and staphylococci in the case of vancomycin.

Tiacumicin B (OPT-80, PAR-101) is a narrow-spectrum antibiotic currently in phase III clinical trials for the treatment of CDAD. It is taken orally, is not absorbed across the intestinal wall into the bloodstream, and is specific to clostridia, enterococci and staphylococci but is generally inactive against other intestinal bacteria. These are seen as important properties because by allowing the normal gut flora to survive, this in turn provides resistance to re-colonization by the toxic *C. difficile* and potentially reduces the recurrence rate of CDAD.

One early report indicated that tiacumicin B (under the name lipiarmycin) inhibited initiation of RNA synthesis in *Bacillus subtilis* by the DNA-dependent RNA polymerase (8), but nothing else is known of its mechanism of action.

Preclinical Pharmacology

Early studies revealed that tiacumicin B was the most active antibacterial agent from a complex of 18-membered macrolide antibiotics designated the tiacumicins, with MIC values of < 0.78-50 μg/ml against a panel of Gram-positive aerobic bacteria (streptococci, staphylococci, *Micrococcus luteus* and *Enterococcus faecium* strains), and potent activity against a limited number of anaerobic bacteria, including *Clostridium perfringens* (9).

More recent studies demonstrated that tiacumicin B has potent and selective activity against clostridia, while not affecting other intestinal bacteria. MIC_{50} and MIC_{90} values against *C. difficile* are typically 0.125-0.25 μg/ml (range: 0.02-0.2 μg/ml) (10-14). These values are comparable or superior to those obtained for vancomycin and metronidazole. Ackerman *et al.* described lower MIC values for tiacumicin B, all strains being inhibited at concentrations of 0.0625 μg/ml or less (15). Tiacumicin B proved to be bactericidal against *C. difficile* and exhibited a long postantibiotic effect (PAE > 24 h) against this organism (10, 11).

Generally good activity was seen against most *Clostridium* species, with MIC values ranging from < 0.016 μg/ml to 0.25 μg/ml (12, 13) and from 0.06 μg/ml to 1024 μg/ml in other experiments (14). Tiacumicin B was less active than vancomycin or metronidazole against the *Bacteroides fragilis* group, with an MIC range of 64- > 128 μg/ml compared to > 16 and 0.25-16 μg/ml, respectively, for vancomycin and metronidazole (12-14). The data suggest that tiacumicin B, unlike the broader spectrum antibiotics, should not suppress the intestinal flora when taken orally and has the potential to maintain resistance to *C. difficile* colonization post-treatment.

The frequency of resistance to tiacumicin B is < 2.8×10^{-8} when tested at 4 and 8 times the MIC, comparable to that for vancomycin under the same conditions (10, 16). Tiacumicin B-resistant strains showed no cross-resistance with other antibiotics, but synergistic activity against *C. difficile* was seen only with rifampin (16). The activity of tiacumicin B against *C. difficile* was not influenced by inoculum size or cation concentration, but MICs increased with increasing pH (17).

In a hamster model of CDAD, oral administration of tiacumicin B provided complete protection even at the lowest dose of 0.2 mg/kg/day administered for 4 days. Relapse did not occur and all animals survived (n=8/group). In the same experiment, 6 of 8 control animals died within 10 days of the initial *C. difficile* infection, while vancomycin treatment showed a dose-dependent response, with the highest dose (5 mg/kg/day p.o.) extending the average survival to 16 days postinfection and 3 of 8 animals surviving to 35 days. All animals that died had diarrhea prior to death and evidence of *C. difficile* in the cecum, indicating a high rate of relapse after vancomycin treatment (10).

Pharmacokinetics

Swanson *et al.* reported that tiacumicin B was not absorbed into the sera 6 h after single oral doses of 25 mg/kg to hamsters. At this time point, the drug had accumulated in the cecum at 248 μg/g (10). These initial observations were supported by subsequent pharmacokinetic data from rats and monkey and from phase I and II clinical trials. Concentrations < 0.5 μg/ml were detected in rat and monkey plasma after doses of up to 90 mg/kg/day p.o. for 28 days; in contrast, a C_{max} of 2-7 μg/ml was detected in rats after 20 mg/kg i.v., with clearance from plasma within 10 min. The C_{max} in cynomolgus monkey plasma was 50-85 ng/ml after 30 mg/kg p.o. and 120-420 ng/ml after 90 mg/kg p.o. (18).

In a single-dose, double-blind, placebo-controlled phase I study, healthy volunteers were given escalating doses of 100/300 mg or 200/450 mg orally (n=8/group). Tiacumicin B could be detected only in the plasma of those receiving the highest dose, with a $t_{1/2}$ of 0.94-2.77 h (19). Subsequent phase Ib and IIa trials in patients with CDAD confirmed these results, with < 5 ng/ml detected in the plasma and urine of treated individuals. On the other hand, high fecal concentrations of the drug were observed, with up to 1433 μg/g at the 450-mg dose, > 10,000 times the MIC_{90} for *C. difficile* (20, 21).

Safety

Acute toxicity studies in mice indicated that the i.p. LD_{50} was > 500 mg/kg (10), and in rats the i.v. LD_{50} was approximately 200 mg/kg (18). No adverse events were seen in rats administered single oral doses of up to 1 g/kg or in rats and monkeys following repeated oral doses of up to 90 mg/kg. No genotoxicity was seen (18).

Clinical Studies

Forty-five patients with mild to moderate CDAD were enrolled in an open-label, dose-ranging phase IIa study and administered 50, 100 and 200 mg of tiacumicin B orally b.i.d. for 10 days. Two patients were transferred to conventional treatment after treatment failure. Of the 41

patients who completed the therapy, 2 (5%) had recurrence within the 6-week follow-up period. Tiacumicin B was well tolerated in all cases (20, 21). In a second study, 39 patients with CDAD were enrolled, 32 of whom were given the same regimen of tiacumicin B as described above, while 7 received 125 mg vancomycin q.i.d. for 10 days. The effect of the drug on fecal counts of *C. difficile* and *Bacteroides* spp. was monitored. At study entry, patients had mean counts of *C. difficile* of 6.8 ± 3.6 $\log_{10}$ CFU/g feces. At day 10 (with the exception of 1 patient on 50 mg tiacumicin B), mean counts were < 2 $\log_{10}$ CFU/g feces for both drugs. *Bacteroides* counts (taken as representative of normal fecal flora) were low in all patients upon study entry and were further reduced upon treatment with vancomycin, but not significantly altered after treatment with tiacumicin B at any of the doses tested (22, 23).

A phase II/III clinical trial started recruiting in April 2006 and is expected to enroll 664 patients, with completion scheduled for January 2008 (24).

Sources

Jointly developed by Optimer Pharmaceuticals, Inc. (US) and Par Pharmaceutical Companies, Inc. (US).

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