Ramoplanin: A Promising Treatment Option for Clostridium difficile–Associated Diarrhea and Vancomycin-Resistant Enterococcus

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INTRODUCTION
The emergence of resistant pathogens, along with a lack of novel antimicrobial agents in the pharmaceutical pipeline, is becoming a growing problem in treating nosocomial infections. Among hospitalized patients, Clostridium difficile–associated disease (CDAD) is the leading cause of infectious diarrhea, with more than 400,000 cases reported per year in the U.S.\(^1\)-\(^9\) The incidence of CDAD is estimated to be 3.4 to 8.4 cases per 1,000 hospital admissions.\(^1\),\(^1\)\(^0\)

Another nosocomial pathogen that has emerged in the last 15 years is vancomycin-resistant Enterococcus (VRE). More than 25% of enterococci specimens obtained for culture from intensive-care units (ICUs) in the U.S. are resistant to vancomycin. CDAD and VRE infections are associated with significant morbidity and mortality.\(^1\),\(^1\)\(^2\)

Treatment of CDAD with proven efficacy is limited to oral formulations of metronidazole (Flagyl, Pfizer) and vancomycin (Vancocin, ViroPharma), with extensive literature to support their use. Metronidazole is recommended as the drug of choice by the Infectious Disease Society of America, the Centers for Disease Control and Prevention, and the Society for Hospital Epidemiology of America, even though the Food and Drug Administration (FDA) has not approved it for this indication.\(^1\)\(^3\)-\(^1\)\(^5\) On the other hand, oral vancomycin (approved for the treatment of enterocolitis caused by Staphylococcus aureus and antibiotic-associated pseudomembranous colitis caused by C. difficile) is considered a second-line agent.\(^1\)\(^6\)-\(^1\)\(^8\) The theory behind this recommendation is that oral vancomycin therapy increases colonization rates with VRE.\(^1\)\(^7\)

Both metronidazole and vancomycin are still considered to be equally efficacious, with treatment success rates of more than 90%; however, metronidazole failure has been documented in clinical practice in the treatment of CDAD.\(^1\)\(^9\)-\(^2\)\(^1\) Limited data are available with other agents that have been used to treat CDAD, including oral bacitracin, oral nitazoxanide (Alinia, Romark Laboratories), intravenous immunoglobulin (IVIG), intracolonic vancomycin, cholestyramine (Questran, Par), and teicoplanin and fusidic acid (which are not available in the U.S).\(^2\)\(^2\)-\(^2\)\(^9\)

Colonization with VRE typically develops in hospitalized patients, in residents of long-term care facilities, in critically ill patients, and in patients receiving prolonged courses of broad-spectrum antibiotics. Depending on various risk factors, colonization can subsequently lead to urinary tract infections, intra-abdominal infections, catheter infections, or wound infections.\(^1\)\(^1\)-\(^1\)\(^2\) Treatment of VRE colonization is not routinely practiced or recommended, because no available pharmacological agents effectively eradicate it.

Therapeutic options for active VRE infection are quinupristin/dalfopristin (Synercid, Monarch), linezolid (Zyvox, Pfizer), and daptomycin (Cubicin, Cubist).\(^1\)\(^1\),\(^1\)\(^2\),\(^3\)\(^0\)

Linezolid is the only approved agent for the treatment of VRE infection. Unlike quinupristin/dalfopristin and daptomycin, it is available in both IV and oral formulations.\(^3\) However, overuse of linezolid is a major concern, because linezolid-resistant enterococci (LRE) were isolated at the Mayo Clinic in 2001.\(^1\)\(^2\)

A potentially useful agent in the pharmaceutical pipeline is ramoplanin, a novel nonabsorbed, glycolipodepsipeptide antibiotic that has shown activity in vitro and in vivo against VRE and C. difficile.\(^3\)\(^1\)-\(^3\)\(^5\) Currently in phase 3 of development by Oscient Pharmaceuticals, the compound was first isolated in 1984 and was derived through fermentation of Actinoplanes spp.\(^3\)\(^0\),\(^3\)\(^4\),\(^3\)\(^6\),\(^3\)\(^7\)

Figure 1 illustrates the chemical structure of ramoplanin.

PHARMACOLOGY AND MECHANISM OF ACTION\(^3\)\(^6\),\(^3\)\(^8\),\(^3\)\(^9\)

Ramoplanin exerts its effects by preventing the formation of peptidoglycan, an essential part of the bacterial cell wall. The preceding steps involve the formation of peptidoglycan by the enzymatic conversion of lipid I to lipid II by MurG, resulting in the final polymerization with the cross-linking of lipid II. Initially, it was thought that ramoplanin blocked peptidoglycan biosynthesis by inhibiting the MurG-catalyzed conversion of lipid I to lipid II. However, further studies have shown that ramoplanin binds directly to...
were 1,043 mcg/g with 200 mg and 2,032 mcg/g with 400 mg. The mean minimum fecal concentrations were 467 mcg/g with 200 mg and 765 mcg/g with 400 mg.

The study authors concluded that ramoplanin was not absorbed by the human gastrointestinal (GI) tract and that it was excreted in the feces at a rate of 100%. Because the drug is not absorbed and is excreted exclusively in the feces, no renal or hepatic excretion data are available.

In a study by de Lalla et al., the non-absorbability and high fecal concentrations of ramoplanin were also demonstrated. A 200-mg single dose of ramoplanin was given to six healthy male volunteers. The mean maximum fecal concentration after a single dose of ramoplanin was 389.2 ± 211.2 mcg/g (range, 184.7–712.1 mcg/g). Ramoplanin was undetectable in urine and plasma.

CLINICAL TRIALS
C. difficile–Associated Disease: Ramoplanin vs. Vancomycin (Pullman et al.)

In a phase 2, randomized, parallel-group, multicenter, open-label trial, Pullman et al. compared two different doses of ramoplanin with vancomycin in the treatment of CDAD. The primary endpoint was a clinical response to treatment. Clinical responses were classified as complete, partial, or failure or recurrence, as assessed on day 10 of treatment, at seven to 14 days after the end of treatment, and at 21 to 28 days after the end of treatment:

- A “complete response” was defined as the resolution of all baseline signs and symptoms in conjunction with the passage of formed stools.
- A “partial response” was defined as improved or resolved baseline signs and symptoms, the presence of loose or semi-formed stools, a negative stool assay for toxin, and no further requirement for CDAD therapy.
- “Failure” or “recurrence” was defined as persistence, progression, or a return of baseline symptoms; administration of a non-study antibiotic owing to its lack of efficacy.
surgical intervention resulting from disease progression; or premature withdrawal from the treatment period because of a lack of efficacy or death attributable to CDAD.

- “Clinically cured” referred to either a complete or a partial response.

Safety was evaluated for all patients receiving at least one dose of the study medication. The assessment was based on a combination of physical findings, laboratory values, diagnostic testing, and patients’ subjective reporting of symptoms. Inclusion and exclusion criteria were extensive.

Eighty-six patients were assigned, in a blinded fashion, into one of three groups: 28 received ramoplanin 200 mg orally twice daily, 29 received ramoplanin 400 mg orally twice daily, and 29 received vancomycin 125 mg orally four times daily. All doses were given for 10 days.

Seventy-eight patients were included in the final efficacy analysis. Clinical cure was achieved on day 10 of treatment in 83% of the ramoplanin 200-mg patients, in 85% of the ramoplanin 400-mg group, and in 86% of the vancomycin group.

The safety assessment is summarized later under “Safety and Adverse Events” on this page.

Because the cure rates for vancomycin were not consistent with the available literature, the Pullman investigators could not determine the non-inferiority of ramoplanin. The data suggested that ramoplanin was equally efficacious to vancomycin with a similar incidence of adverse drug effects (ADEs). A larger non-inferiority trial is necessary to further elucidate ramoplanin’s role in treating CDAD.

Vancomycin-Resistant Enterococcus: Ramoplanin vs. Placebo (Wong et al.)

In a phase 2, randomized, double-blind, placebo-controlled multicenter study, Wong et al. compared two different doses of ramoplanin with placebo in the ability to suppress GI colonization with VRE. The primary endpoint was recovery of VRE from rectal specimens on days 7, 14, and 21 after the initiation of treatment.

To be eligible, patients had to have VRE colonization or infection and had to be at least 18 years of age. Females were required to be using effective contraception and had to be surgically sterile or postmenopausal. Exclusion criteria consisted of:

- active diarrhea at the time of screening.
- a history of intestinal motility disorders.
- intra-abdominal surgery resulting in stagnation of bowel contents or blind-loop syndrome.
- previous anaphylactic reactions to antimicrobial medications.
- clinically apparent gastric ulcers.
- any condition that precluded assessment by serial rectal specimen swabs.
- the use of any other investigational drug for 30 days or less before enrollment.

The investigators screened 128 patients; 68 patients were initially enrolled, and 56 patients completed the full 21-day duration of the study. Of the 68 patients, 24 received placebo, 23 received ramoplanin 100 mg orally twice daily, and 21 received ramoplanin 400 mg orally twice daily for seven days. Four patients from each arm withdrew from the study.

Of the 56 patients who completed the seven days of therapy and returned for follow-up, five patients (25%) in the placebo group, four patients (21%) receiving ramoplanin 100 mg twice daily (p = 0.770), and five patients (29%) receiving ramoplanin 400 mg twice daily (p = 0.763) were free of VRE on day 21.

The interim analyses performed on days seven and 14 showed significantly lower VRE colonization rates among treated patients. The results are summarized in Table 1.

Although patients were receiving ramoplanin therapy, the rate of colonization by VRE was considered to be significantly less than that associated with placebo. However, after therapy was discontinued, VRE colonization rates returned to levels similar to those in patients treated with placebo. Ramoplanin therapy in this setting may have a pivotal role in decreasing colonization rates among patients at high risk for disseminated VRE infections. Further studies are required to determine ramoplanin’s efficacy in this patient population.

SAFETY AND ADVERSE EVENTS

Safety was assessed in both phase 2 studies just summarized.

The Pullman Study

In the CDAD study, which compared ramoplanin 200 mg twice daily, ramoplanin 400 mg twice daily, and vancomycin 125 mg orally every six hours, the most common ADEs were nausea (in 22.8%), vomiting (in 14.1%), and diarrhea (in 10.5%). Serious ADEs were reported for 10 patients receiving ramoplanin 200 mg, for 20 patients treated with ramoplanin 400 mg, and for 15 subjects receiving vancomycin.

Serious ADEs associated with ramoplanin 200 mg included two reports of deep-vein thrombosis (DVT) and C. difficile colitis and one report each of respiratory failure, sepsis, aortic stenosis, anemia, mucosal inflammation, and acute renal failure.

For the ramoplanin 400-mg arm, there were three reports of respiratory failure; two GI hemorrhages; and one report each of aspiration, hypoxia, gastric ulcer hemorrhage, ileus, pancreatitis, proctitis, obstruction of the small intestine, vomiting, C. difficile colitis, sepsis, anemia, pectoris, unstable anina, and cholelithiasis.

In the vancomycin group, serious ADEs included two reports of ascites and C. difficile colitis and one report each of respiratory failure, aspiration, hypoxia, GI hemorrhage, DVT, aortic stenosis, cardiac failure, cardiogenic shock, mul-

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**Table 1 Percentage of Patients Free from VRE Infection with Ramoplanin vs. Placebo**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0%</td>
<td>10%</td>
<td>25%</td>
</tr>
<tr>
<td>Ramoplanin 100 mg</td>
<td>81% (P &lt; 0.001)</td>
<td>29% (P = 0.134)</td>
<td>21% (P = 0.770)</td>
</tr>
<tr>
<td>Ramoplanin 400 mg</td>
<td>90% (P &lt; 0.001)</td>
<td>41% (P = 0.028)</td>
<td>29% (P = 0.763)</td>
</tr>
</tbody>
</table>

VRE = vancomycin-resistant Enterococcus.

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tiple-organ failure, pyrexia, and sickle cell anemia with crisis.

The mortality rate was similar among the three arms, and no deaths were attributed to the medications being studied.

The Wong Study

In the study comparing placebo with ramoplanin 100 or 400 mg twice daily for suppressing VRE, five patients had ADEs possibly relating to ramoplanin. Three cases of diarrhea, two cases of abdominal pain, two cases of dyspepsia, one case of flatulence, and one case of nausea were reported. C. difficile was observed in one patient receiving placebo.

During the study, three patients receiving ramoplanin 100 mg and one patient receiving placebo died. At the end of the study, four placebo patients died, three patients receiving 100 mg died, and one patient receiving 400 mg died. The investigators concluded that ramoplanin therapy had not contributed to any of the deaths.

DRUG INTERACTIONS

Specific drug–drug interactions associated with ramoplanin therapy are under investigation. To date, no significant drug interactions have been reported, and available data are limited. Given that 100% of ramoplanin is excreted in the feces, it is possible that a drug interaction would arise when agents given concomitantly with ramoplanin have similar elimination routes. It appears unlikely that ramoplanin interacts with other agents that are exclusively metabolized heptatically or eliminated renally.

CONTRAINDICATIONS, PRECAUTIONS, AND WARNINGS

Information about possible contraindications or precautions to be taken with ramoplanin in certain patient populations is incomplete. We can hypothesize that because ramoplanin is eliminated via the feces, it might be contraindicated or prescribed with caution for patients with bowel dysfunction (e.g., Crohn’s disease, ileus, intestinal obstruction, gastric outlet, inflammatory bowel disease, or malabsorption syndromes). Further studies are needed.

DOSAGE AND ADMINISTRATION

On the basis of phase 2 studies, the ramoplanin dose may be either 200 or 400 mg orally twice daily. The recommended dosage may vary, depending on the indication for treating either CDAD or VRE.

The optimal duration of therapy for the phase 2 study of CDAD was 10 days, with suppression of GI VRE colonization observed at seven days. Typically, a 10- to 14-day course of therapy for CDAD is considered the standard duration of therapy when metronidazole or vancomycin is used as the gold standard of treatment. Therefore, ramoplanin would probably be recommended for the same duration of treatment.

Because no agents are yet available for suppressing GI VRE colonization, the duration of treatment cannot be predicted. The effective doses and treatment durations for both indications are expected to be determined in the larger phase 3 studies.

FUTURE RESEARCH

In December 2005, Oscient and the FDA agreed to a Special Protocol Assessment for the continued development of ramoplanin. It was agreed that there would be two phase 3 trials, with one trial comparing ramoplanin with vancomycin and each trial enrolling approximately 500 patients with CDAD.

Several agents in the pharmaceutical pipeline for the treatment of CDAD also seem promising. A monoclonal antibody to toxin A and toxin B (Medarex, Inc.) and benzazoxinorifamycin (Rifalazil, ActivBiotics) are currently in phase 2 clinical trials. A toxoid vaccine (Acambis) is being studied in phase 1 trials.

Agents in phase 3 trials include OPT-80 (Optimer Pharmaceuticals) and tolevamer (Genzyme). OPT-80, a macrocycle antibiotic under development, has shown in vivo activity against C. difficile.44 Tolevamer is a non-antibiotic polymer that noncovalently binds C. difficile toxins A and B, thereby neutralizing these toxins. Data for tolevamer are limited to phase 2 trials.45

CONCLUSION

From the available phase 1 and 2 data, ramoplanin appears to be a promising option for treating CDAD and suppressing GI VRE colonization. Phase 3 studies are needed to further elucidate the appropriate dosing for this medication as well as its side-effect profile, contraindications, precautions, and drug interactions.

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