Ramoplanin: a novel antimicrobial agent with the potential to prevent vancomycin-resistant enterococcal infection in high-risk patients

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The prevention of vancomycin-resistant Enterococcus (VRE) colonization and infection continues to be a high priority for clinicians. An oral antimicrobial agent that reduces or eliminates VRE gastrointestinal colonization could be useful for preventing VRE infection in selected patients. Ramoplanin, a glycolipodepsipeptide, is the first in a new class of antimicrobials. It has excellent in vitro activity against vancomycin-resistant Enterococcus faecium and Enterococcus faecalis. It is orally administered, and not absorbed systemically. In clinical trials, VRE gastrointestinal colonization was reduced to undetectable levels in 80–90% of patients during receipt of ramoplanin. A randomized, double-blinded, placebo-controlled multicentre study is currently being conducted to determine whether ramoplanin will prevent VRE bloodstream infection in oncology patients who are neutropenic due to treatment for a haematological malignancy or a bone marrow/stem cell transplant.

Introduction

For 15 years, vancomycin-resistant enterococci (VRE) have posed a serious challenge to clinicians. When vancomycin resistance was first identified in Enterococcus faecium, only a few antimicrobial agents were found to be active in vitro against VRE, and these only on an inconsistent basis. Even for those drugs that showed activity in vitro, there was little clinical experience in treating patients infected with this multiply antimicrobial-resistant microorganism. In addition, there was great concern that the vancomycin resistance determinant present in vancomycin-resistant E. faecium would spread to the more virulent pathogen, Staphylococcus aureus. These issues, in conjunction with the rapid increase in vancomycin resistance among enterococcal isolates throughout the USA, led the Hospital Infection Control Practices Advisory Committee of the Centers for Disease Control and Prevention to issue recommendations targeted specifically at vancomycin resistance. The clinical impact of VRE, and the epidemiology, treatment and prevention of VRE infection have been studied extensively. The articles in this supplement by Drs Kauffman, Patel, and Drs Goossens, Jabes, Privitera & Courvalin, provide comprehensive reviews of these subjects. Although two recently licensed antimicrobial agents, quinupristin/dalfopristin and linezolid, are now available for treatment of VRE infections, emerging resistance to these drugs indicate that the treatment of VRE infection will continue to present ongoing challenges.

Prevention of VRE infection remains a high priority. VRE gastrointestinal colonization usually precedes or is present concurrently with VRE infection and is much more frequent than VRE infection (see Kauffman, this supplement, and Patel, this supplement). VRE infection occurs mostly in specific high-risk populations, such as oncology patients, transplant recipients and critically ill patients. Gastrointestinal colonization of patients is probably the principal reservoir of VRE in hospitals. To date, efforts to decolonize the gastrointestinal tract of VRE using oral antimicrobial agents have been unsuccessful (see Kauffman, this supplement). Presumably, the best strategy for preventing VRE infection is to prevent VRE gastrointestinal colonization. Reducing the number of VRE-colonized patients may be more important than ever, given the recent emergence of vancomycin-resistant S. aureus in which the vancomycin resistance determinant was the vanA gene, present in VRE.

In the hospital setting, prevention of VRE gastrointestinal colonization is achievable by adherence to contact precautions, which focus on reducing VRE transmission to patients from healthcare workers’ hands, contaminated...
clothing or equipment. Patients may be less susceptible to VRE gastrointestinal colonization if they are not exposed to particular antimicrobial agents, such as third-generation cephalosporins or antimicrobials with anti-anaerobe activity. In Belgium, a decrease in the rate of VRE gastrointestinal colonization among hospitalized and haemodialysis patients may have been related to the ban on avoparcin, a glycopeptide used in animal feed (see Goossens, this supplement).

While the prevention of VRE infection by reducing overall VRE colonization rates is an effective strategy, it is also labour intensive, particularly in hospitals where VRE is endemic and many patients are VRE colonized. An oral antimicrobial agent that could reduce or eliminate VRE gastrointestinal colonization in selected patients at high risk of VRE infection could be a useful adjunct to the prevention of VRE gastrointestinal colonization.

An ideal agent for decolonizing the gastrointestinal tract of VRE should have a number of distinct characteristics: it should be safe and well tolerated by patients at high risk of VRE infection; it should have a narrow spectrum of antimicrobial activity; it should display a low potential for development of resistance; it should be unlikely to lead to cross resistance with antimicrobial agents used to treat VRE or other infections; and it should be orally administered and not systemically absorbed. Ramoplanin, a new oral antimicrobial agent with in vitro and in vivo activity against VRE, may have the potential to serve as an agent for decolonizing the gastrointestinal tract of VRE, and perhaps prevent VRE infection in high-risk patients by reducing VRE gastrointestinal colonization.

Ramoplanin: a glycolipodepsipeptide

Ramoplanin is the first in a new class of antimicrobials to reach clinical trials. It is a glycolipodepsipeptide produced by the fermentation of Actinoplanes spp. (Figure 1). Ramoplanin inhibits bacterial cell wall biosynthesis by interfering with peptidoglycan production. Ramoplanin blocks bacterial cell wall biosynthesis by interfering with peptidoglycan production. Ramoplanin inhibits the N-acetylglicosaminytransferase-catalysed conversion of lipid intermediate I to lipid intermediate II, a step that occurs before the transglycosylation and transpeptidation reactions. Ramoplanin’s mechanism of action is distinct from that of glycopeptides. Unlike glycopeptides, ramoplanin does not complex with the D-Ala–D-Ala sequence of cell wall precursors.

In vitro activity

Ramoplanin is highly active against Gram-positive aerobic and anaerobic bacteria. MIC<sub>90</sub>s of ramoplanin for vancomycin-susceptible and vancomycin-resistant E. faecium and Enterococcus faecalis are 0.5 mg/L. Vancomycin-resistant enterococci are susceptible to ramoplanin, regardless of whether the VRE isolate is resistant to teicoplanin. In time–kill studies, ramoplanin is bactericidal against vancomycin-resistant E. faecium and E. faecalis. The potential for the development of ramoplanin resistance was evaluated in studies in which cultures of vancomycin-susceptible and vancomycin-resistant E. faecium were exposed to subinhibitory concentrations of ramoplanin. The MICs for the isolates remained unchanged. Ramoplanin is also active in vitro against most Gram-positive aerobic and anaerobic bacteria, including Clostridium difficile (MIC<sub>90</sub> 0.25–0.5 mg/L) (Table 1).

Human studies

A Phase I multiple-dose study in 24 healthy male volunteers demonstrated that ramoplanin was well tolerated and not absorbed following oral doses of 200 mg, 400 mg or 800 mg, administered twice daily for 10 consecutive days (data on file, Genome Therapeutics Corporation, Waltham, MA, USA). In this study, the mean faecal concentrations of ramoplanin on day 3 and day 10 were 827 mg/kg and 949 mg/kg for the 200 mg dose, 1742 mg/kg and 1417 mg/kg for the 400 mg dose, and 1901 mg/kg and 2647 mg/kg for the 800 mg dose. Ramoplanin was detectable in faeces for up to 4 days after the last dose. In addition, a single-dose study of ramoplanin (200 mg) given to six patients with pseudomembranous colitis and C. difficile cytotoxin in stools, did not demonstrate
Ramoplanin: potential prevention of VRE infection

A Phase II randomized, double-blinded, placebo-controlled, multicentre study evaluated the safety and efficacy of oral ramoplanin versus placebo for the suppression of VRE gastrointestinal colonization in 68 patients. This was a three-arm study. Participants received either ramoplanin 100 mg, ramoplanin 400 mg or placebo, twice daily for 7 days and were evaluated for VRE gastrointestinal colonization on the last day of treatment, and 7 and 14 days after treatment.

Table 1. *In vitro* activity of ramoplanin against Gram-positive and Gram-negative aerobic and anaerobic bacteria

<table>
<thead>
<tr>
<th>Organism</th>
<th>No. of isolates</th>
<th>Ramoplanin MIC&lt;sub&gt;90&lt;/sub&gt; (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. faecium</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vancomycin-susceptible&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12</td>
<td>0.5</td>
</tr>
<tr>
<td>vancomycin-resistant&lt;sup&gt;a&lt;/sup&gt;</td>
<td>31</td>
<td>0.5</td>
</tr>
<tr>
<td><em>E. faecalis</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vancomycin-susceptible&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15</td>
<td>0.5</td>
</tr>
<tr>
<td>vancomycin-resistant&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12</td>
<td>0.5</td>
</tr>
<tr>
<td><em>Leuconostoc</em>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Lactobacillus</em>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14</td>
<td>0.125</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>oxacillin-susceptible&lt;sup&gt;b&lt;/sup&gt;</td>
<td>140</td>
<td>0.5</td>
</tr>
<tr>
<td>oxacillin-resistant&lt;sup&gt;b&lt;/sup&gt;</td>
<td>100</td>
<td>0.25</td>
</tr>
<tr>
<td><em>Streptococcus</em>, β-haemolytic&lt;sup&gt;b&lt;/sup&gt;</td>
<td>60&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.06</td>
</tr>
<tr>
<td><em>Streptococcus bovis</em>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10</td>
<td>0.12</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20</td>
<td>≤0.03</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10</td>
<td>0.06</td>
</tr>
<tr>
<td><em>Bacillus</em>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Corynebacterium jeikeium</em>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td><em>Gram-negative bacteria</em>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>39&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&gt;16</td>
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<tr>
<td><em>C. difficile</em>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>18</td>
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<tr>
<td><em>Actinomyces</em>&lt;sup&gt;e&lt;/sup&gt;</td>
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<td><em>Bifidobacterium</em>&lt;sup&gt;e&lt;/sup&gt;</td>
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<td><em>Clostridium cadaveris</em>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>10</td>
<td>0.125</td>
</tr>
<tr>
<td><em>Clostridium clostridioforme</em>&lt;sup&gt;e&lt;/sup&gt;</td>
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<td><em>Clostridium innocuum</em>&lt;sup&gt;e&lt;/sup&gt;</td>
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<tr>
<td><em>Clostridium paraputrificum–tertium group</em>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>10</td>
<td>0.125</td>
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<td><em>Clostridium perfingens</em>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>11</td>
<td>0.06</td>
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<tr>
<td><em>Clostridium ramosum</em>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>15</td>
<td>0.06</td>
</tr>
<tr>
<td><em>Eubacterium lentum</em>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>17</td>
<td>0.25</td>
</tr>
<tr>
<td><em>Eubacterium group spp.</em>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>31</td>
<td>0.125</td>
</tr>
<tr>
<td><em>Peptostreptococcus asaccharolyticus</em>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>10</td>
<td>0.25</td>
</tr>
<tr>
<td><em>Peptostreptococcus magnus–micros group</em>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>14</td>
<td>0.125</td>
</tr>
<tr>
<td><em>Peptostreptococcus spp.</em>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>13</td>
<td>0.125</td>
</tr>
<tr>
<td><em>Propionibacterium</em>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>15</td>
<td>0.25</td>
</tr>
<tr>
<td><em>Bacteroides fragilis group</em>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>17</td>
<td>&gt;256</td>
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<tr>
<td><em>Fusobacterium–Veillonella</em>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>15</td>
<td>&gt;256</td>
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<tr>
<td><em>Porphyromonas asaccharolytica</em>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>10</td>
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<tr>
<td><em>Prevotella</em>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>12</td>
<td>128</td>
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</table>

*aMIC as obtained from Collins et al.\textsuperscript{12}*
*bMIC as obtained from Jones & Barry.\textsuperscript{11}*
*cIncludes two strains each of *Acinetobacter calcoaceticus*, *Moraxella catarrhalis*, *Citrobacter diversus*, *Citrobacter freundii*, *Enterobacter aerogenes*, *Enterobacter agglomerans*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Morganella morgani*, *Providencia rettgeri*, *Providencia stuartii*, *Salmonella enteritidis*, *Serratia marcescens*, *Shigella sonnei* and *Yersinia enterocolitica*, and one strain of *Klebsiella oxytoca*.

dMCs as obtained from Citron et al.\textsuperscript{15}*

any gastrointestinal absorption of ramoplanin (data on file, Genome Therapeutics Corporation).\textsuperscript{16}

A Phase II randomized, double-blinded, placebo-controlled, multicentre study evaluated the safety and efficacy of oral ramoplanin versus placebo for the suppression of VRE gastrointestinal colonization in 68 patients.\textsuperscript{17} This was a three-arm study. Participants received either ramoplanin 100 mg, ramoplanin 400 mg or placebo, twice daily for 7 days and were evaluated for VRE gastrointestinal colonization on the last day of treatment, and 7 and 14 days after treatment.
Gastrointestinal colonization with VRE was detected by a rectal swab culture. Of the 68 participants, 41 were hospitalized patients, 19 were long-term care facility patients and eight were outpatients. On the last day of treatment, VRE gastrointestinal colonization was below the limit of detection in 17 of 21 patients receiving ramoplanin 100 mg, 18 of 20 patients receiving ramoplanin 400 mg and 0 of 20 patients receiving placebo. These results were statistically significant ($P < 0.001$). This effect was not well sustained following treatment. Fifteen of 19 patients receiving ramoplanin 100 mg, 12 of 17 patients receiving ramoplanin 400 mg and 15 of 20 patients receiving placebo had VRE gastrointestinal colonization detectable 14 days after the end of treatment. The MIC$_{90}$s of ramoplanin for VRE isolates following treatment were unchanged compared with the MIC$_{90}$s for pre-treatment isolates. Ramoplanin was well tolerated and the occurrence of adverse events was similar across all three groups. Five patients (four ramoplanin recipients and one placebo recipient) had adverse events that were considered possibly related to study drug. These events were diarrhea (in three patients), abdominal pain (in two patients), dyspepsia (in one patient), flatulence (in one patient), nausea (in one patient) and C. difficile (noted only in the patient receiving placebo). Baden et al. evaluated the VRE isolates from the Phase II study to determine whether the VRE isolate before treatment was genotypically related to the VRE isolate recovered from the patient following treatment. The relatedness of isolates was determined by pulsed field gel electrophoresis. VRE isolates recovered after treatment were clonally related to the pre-treatment isolate in 60% of patients receiving ramoplanin 100 mg, 53% of patients receiving ramoplanin 400 mg and 74% of patients receiving placebo. These data suggest that 40–50% of patients receiving ramoplanin may have acquired a new strain of VRE following ramoplanin treatment. The six ramoplanin-treated patients who did not demonstrate clearance of VRE gastrointestinal colonization during treatment all had VRE isolates that were genotypically related to the pre-treatment isolate. Of note, in this study, in ramoplanin-treated patients, receipt of antimicrobial agents with anti-anaerobic activity was associated with positive VRE rectal swab cultures on the last day of treatment, and the absence of antimicrobial agents with anti-anaerobic activity was associated with negative VRE rectal swab cultures.

Currently, a randomized, double-blinded, placebo-controlled, multicentre study is being conducted to determine whether ramoplanin will prevent VRE bloodstream infection in oncology patients with VRE gastrointestinal colonization who are neutropenic due either to treatment for a haematological malignancy or to a bone marrow/stem cell transplant. This study is intended to enrol 950 patients at ∼50 sites in the USA. Although the primary endpoint of the study is VRE bloodstream infection, the study will also assess the effect of ramoplanin on the occurrence of bloodstream infection due to any Gram-positive, Gram-negative or fungal pathogen, and on the occurrence of C. difficile-associated diarrhea.

In summary, ramoplanin has several of the features of an ideal agent for decolonizing the gastrointestinal tract of VRE. It is orally administered and does not appear to be systemically absorbed. It has a mechanism of action that is distinct from that of other antimicrobial agents. In a limited experience it appears to have a low potential for the development of resistance, and it is safe. The spectrum of antimicrobial activity of ramoplanin is clearly broader than activity only against VRE. It is active against many Gram-positive aerobic and anaerobic bacteria, including C. difficile. The Phase III trial will determine whether there is a beneficial effect associated with the use of this relatively broad-spectrum Gram-positive antimicrobial agent. The prevention and treatment of VRE infection will certainly continue to be a complex challenge for clinicians. Whether ramoplanin may have a role in the prevention of VRE infection in high-risk patients remains to be determined.

**Acknowledgements**

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**References**


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