Treatment of Vancomycin-Resistant Enterococcus faecium Infections with Quinupristin/Dalfopristin

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Clinicians caring for patients with vancomycin-resistant Enterococcus faecium (VREF) infections face severe constraints in the selection of treatment. Quinupristin/dalfopristin (Synercid) is active in vitro against VREF, with a MIC\textsubscript{90} of 1.0 \textmu g/mL. We investigated the clinical efficacy and safety of this agent in a multicenter, prospective, noncomparative, emergency-use study of 396 patients. Patients were included if they had signs and symptoms of active infection, including bacteremia of unknown origin, intra-abdominal infection, and skin and skin-structure infection, with no alternative antibiotic therapy available. The mean duration of treatment was 20 days (range, 4–40 days). The clinical response rate was 68.8% in the evaluable subset, and the overall response rate was 65.6%. The most common adverse events related to quinupristin/dalfopristin were arthralgias and myalgias. Related laboratory abnormalities were rare. In this severely ill patient population, quinupristin/dalfopristin was efficacious and demonstrated an acceptable safety profile in the treatment of VREF infection.

Quinupristin/dalfopristin (Synercid, Aventis Pharmaceuticals), a novel injectable streptogramin antibiotic, has a spectrum of in vitro activity against clinically relevant gram-positive organisms, including staphylococci, streptococci, and enterococci (except Enterococcus faecalis). Quinupristin/dalfopristin is active in vitro against vancomycin-resistant Enterococcus faecium (VREF), with a MIC\textsubscript{90} of 1.0 \textmu g/mL [1, 2].

The clinical development of this investigational antibiotic coincided with an increasing incidence of VREF infection worldwide and especially in the United States [3–5]. Although the enterococci are not especially virulent organisms, infection in immunocompromised patients causes substantial morbidity and mortality [6], and presents the clinician with severe constraints in antimicrobial treatment options. In light of the rising clinical importance of VREF infection, an emergency-use program was undertaken, starting in 1993, to provide quinupristin/dalfopristin to patients without other therapeutic options, and to evaluate the efficacy and safety of iv quinupristin/dalfopristin in the treatment of such infections. Results from an initial series of 396 patients treated in the emergency-use protocol have been published and demonstrate the efficacy and safety.
of this agent for VREF infection [7]. In this study, we report on a second large consecutive series of patients who were treated for VREF infection in the emergency-use protocol.

**METHODS**

**Study Design**

This prospective, multicenter, noncomparative study (IRV 398b) permitted inclusion of patients with infection caused by VREF and other gram-positive bacterial pathogens during the 8-month period from January 1996 through August 1996. Results for those patients with VREF infection are discussed here.

Patients were enrolled in ≥1 predefined indications on the basis of signs and symptoms consistent with guidelines of the Infectious Diseases Society of America and the European Society of Clinical Microbiology and Infectious Diseases [8, 9]. To be eligible, patients were to have signs and symptoms of active infection and no appropriate, approved, alternative antibiotic therapy (i.e., for all clinically appropriate antibiotics, the causative pathogen was resistant in vitro and/or the patient had documented intolerance or treatment failure). Proof of in vitro susceptibility of the VREF isolate to quinupristin/dalfopristin was not prospectively required for study enrollment, since the vast majority of VREF isolates are susceptible to quinupristin/dalfopristin and a delay in enrollment could have had a detrimental effect on outcome.

The recommended quinupristin/dalfopristin treatment regimen was administration of 7.5 mg/kg iv q8h for a duration judged appropriate by the investigator. A test-of-cure assessment was to be performed ~1–3 weeks following treatment discontinuation or at the end-of-treatment visit if the patient did not progress to follow-up. Adverse events were classified and recorded as described elsewhere [7].

**Microbiological Methods**

**Identification.** Bacterial isolates from enrolled patients were initially recovered, identified, tested for antimicrobial susceptibility, and stored at the local laboratory of the participating investigator. Available enterococcal strains subsequently were sent to the reference laboratory of one of the authors (R.C.M.), where bacterial colonies with the morphological appearance of enterococci on horse blood agar plates were identified by biochemical properties or gene probes, or both, as described elsewhere [7]. Probes for vanA and vanB were prepared from E. faecium 228 [10] and E. faecalis SF300, respectively, with use of primers described elsewhere [11].

**Dilution susceptibility studies.** Antimicrobial susceptibility of the isolates to quinupristin/dalfopristin and other potentially active antibiotics was performed by the agar dilution method [12], as described elsewhere [7].

**Antimicrobials.** Quinupristin/dalfopristin susceptibility test powder (30:70 ratio) was provided by Rhône-Poulenc Rorer Pharmaceuticals (now Aventis Pharmaceuticals), Teicoplanin and ciprofloxacin susceptibility test powders were the generous gifts of Hoechst Marion Roussel Research Institute (Hoechst Marion Roussel, now Aventis Pharmaceuticals) and Bayer Corporation, respectively. Other agents were purchased from Sigma Chemical Company.

**Assessment of Efficacy Outcomes**

**Clinical efficacy responses.** The response of the patient to study drug treatment was determined by the investigator. Clinical outcomes were defined as “cure,” “improvement,” “failure,” or “indeterminate,” as defined elsewhere [7]. The “clinical response rate” in the all-treated population was defined as the number of patients in the cure and improvement categories, divided by the number of patients in all outcome categories combined (cure + improvement + failure + indeterminate). For the evaluable population, the indeterminate responses were not included in the denominator.

**Bacteriologic efficacy responses.** The bacteriologic response for a VREF isolate for each indication, including blood if the patient was bacteremic, was determined by a steering committee, and one of the following outcomes was assigned: “eradication,” “presumed eradication,” “persistence,” “presumed persistence,” or “indeterminate,” as defined elsewhere [7]. The category of presumed eradication was assigned when no test-of-cure culture of a specimen from the infection site was available but the patient’s clinical response was cure or improvement. It should be noted that, depending on the infection site, it might be clinically inappropriate to obtain a culture specimen at this stage.

The “by-patient bacteriologic response” (hereafter referred to as “bacteriologic response”) was derived from the combination of the bacteriologic responses for the primary infection site(s) and the blood, if applicable. The “bacteriologic response rate” was defined as the number of patients in whom there was eradication or presumed eradication of VREF, divided by the number of patients in all bacteriologic outcome categories combined (eradication + presumed eradication + persistence + presumed persistence + indeterminate). The “overall response” was derived from the combination of the clinical and bacteriologic responses, with success defined as a clinical response of cure or improvement and a bacteriologic response of eradication or presumed eradication. The “overall response rate” was defined as the number of patients with a response of success divided by the number of patients with a response of success, failure, or indeterminate. For the evaluable population, the indeterminate responses were not included in the denominator.

**Patient Populations and Definitions of Infection**

The patient populations were defined as follows. The “all-treated population” included all patients who received at least
1 dose of quinupristin/dalfopristin and had at least one isolate of VREF recovered. The “evaluable population” included that subset of the clinically evaluable patient population for whom the bacteriologic evaluability criteria were met. Criteria for assessment of clinical and bacteriologic evaluability were as described elsewhere [7].

“Superinfection” was defined in the all-treated population as the isolation of a new gram-positive pathogen at or before the test-of-cure assessment (including end of treatment for failure), from the same site(s) sampled at baseline, provided the patient’s clinical response was failure. Investigator narrative summaries were used for this determination.

**Emerging Resistance to Quinupristin/Dalfopristin**

When available, sequential isolates were tested in the central laboratory for emerging resistance to quinupristin/dalfopristin, defined as a >4-fold increase in MIC to greater than or equal to the resistance breakpoint of 4 µg/mL.

**Statistical Methods**

A 2-tailed 95% CI was calculated for each of the efficacy outcome variables by population, with the exception of the superinfection rate. Quantitative data are given as mean ± SD unless otherwise indicated.

**RESULTS**

**Population description.** A total of 396 patients with infection caused by VREF were enrolled and comprised the all-treated group. Enrollment included 371 patients in the United States, 22 in the United Kingdom, 2 in Israel, and 1 in Sweden. The mean age was ~52 years, and 15 patients were <18 years of age. There was a modest preponderance of males (54.5%), and the majority were white (73%). Of these 396 patients, 377 were treated for a single indication. Bacteremia of unknown origin was the most common indication (n = 119), followed by intra-abdominal infection (n = 115), skin and skin-structure infection (n = 47), urinary tract infection (n = 40), and central-catheter–related bacteremia (n = 38). Less frequent indications included bone and joint, endocardial and nonendocardial, endovascular, deep wound, respiratory tract, and miscellaneous infections. Two patients had three indications and 17 patients had 2 indications. The distribution of demographic, medical history, and prognostic risk factors was similar across all populations.

The patients in both the all-treated and evaluable populations were substantially ill, with a high prevalence of bacteremia at enrollment. In the all-treated population, the most common underlying medical conditions were renal failure (n = 164), polymicrobial infection (n = 117), diabetes mellitus (n = 91), transplantation (n = 91), leukemia (n = 77), other oncologic disorders (n = 75), dialysis (n = 65), and requirement of mechanical ventilation (n = 64).

As determined by the reference laboratory, most tested baseline isolates were multidrug-resistant, with substantial rates of resistance to ampicillin and doxycycline (table 1). However, the majority (87.6%) of VREF isolates were susceptible to chloramphenicol. The dominant glycopeptide resistance profile was the vanA genotype. Of the 136 isolates tested for susceptibility to quinupristin/dalfopristin, 135 (99.3%) had a MIC of ≤2.0 µg/mL, and for 125 isolates (91.9%) the MIC was ≤1.0 µg/mL.

In the all-treated population, the majority of patients (n = 307; 77.7%) received quinupristin/dalfopristin q8h, and the remaining patients for whom data were available received quinupristin/dalfopristin q12h. The mean dosage was 20.0 ± 4.1 mg/kg/d (range, 4–40 mg/kg/d). Dosing was similar in the evaluable population, except that treatment duration was slightly longer (18.7 ± 13 days, compared with 13.7 ± 11 days in the all-treated population).

**Efficacy.** The clinical response rate was 68.8% in the evaluable population and 51.0% in the all-treated population (figure 1), reflecting the presence of patients with indeterminate clinical and/or bacteriologic responses as failures in the denominator of the latter. There was a modest effect of underlying condition(s) on the clinical response rate. Patients with underlying liver disease or a dialysis requirement exhibited the

<table>
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<tr>
<th>Table 1. Susceptibility pattern at baseline, as determined by the reference laboratory.</th>
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<tr>
<td>Antimicrobial agent, pattern</td>
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<tr>
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<tr>
<td>Ampicillin</td>
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<tr>
<td>Resistant</td>
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<tr>
<td>Susceptible</td>
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<tr>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Resistant</td>
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<tr>
<td>Susceptible</td>
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<tr>
<td>Doxycycline</td>
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<tr>
<td>Resistant</td>
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<tr>
<td>Susceptible</td>
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<tr>
<td>Vancomycin</td>
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<td>Resistant</td>
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<td>van Genotype</td>
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<tr>
<td>vanA&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>vanB&lt;sup&gt;b&lt;/sup&gt;</td>
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*NOTE.* No. of isolates tested is denoted after virgule.

<sup>a</sup> vanA genotype: confers high-level resistance to vancomycin and teicoplanin.

<sup>b</sup> vanB genotype: confers high-level resistance to vancomycin but not to teicoplanin.
The level of leading to treatment discontinuation was an elevation in the patients' 1.8%). The most common laboratory adverse event leading to discontinuation of study participation were infrequent (7 peripheral venous intolerability. Laboratory adverse events leading to discontinuation of quinupristin/dalfopristin because of peripheral venous intolerability occurred, which was judged as related to quinupristin/dalfopristin in 21 (84.0%). A single patient discontinued receiving quinupristin/dalfopristin because of peripheral venous intolerability. Laboratory adverse events leading to discontinuation of study participation were infrequent (7 patients; 1.8%). The most common laboratory adverse event leading to treatment discontinuation was an elevation in the level of ≥1 liver enzymes (serum aspartate aminotransferase or bilirubin, which occurred in 6 patients (1.5%).

**Superinfection and emerging resistance.** Superinfection caused by gram-positive pathogens was documented in 11 patients in the all-treated population. The most common superinfecting organism was *E. faecalis* (6 patients), and *Enterococcus* species occurred in 2 patients, *Enterococcus avium* in 1 patient, and α-hemolytic streptococci in 1 patient. In 1 patient, both *Staphylococcus epidermidis* and *Enterococcus* species were recorded as the superinfecting organisms.

Emerging in vitro resistance of VREF to quinupristin/dalfopristin was observed in 5 patients. In each case, the quinupristin/dalfopristin MIC rose to 4.0 μg/mL, from a baseline value of 0.5 μg/mL (three patients) or 1.0 μg/mL (2 patients). Four cases were clinical failures, with persistence of VREF; however, one case was evaluated as a cure with presumed VREF eradication. Molecular typing of the paired (susceptible and resistant) VREF strains was not performed.

**DISCUSSION**

The presence of high-level resistance to vancomycin eliminates a valuable therapeutic option in the management of serious enterococcal infections. Resistance to glycopeptides in these organisms is caused by synthesis of modified bacterial cell-wall precursors that demonstrate decreased affinity for vancomycin and teicoplanin [13]. Isolates with resistance to high levels of vancomycin (MIC, ≥64 μg/mL) and of teicoplanin (MIC, ≥16 μg/mL) are categorized as phenotypic class A (VanA); this type of resistance is inducible and transferable. In contrast, organisms in phenotypic class B show intermediate resistance to vancomycin (MIC, 16–64 μg/mL) but are susceptible to tei-

**Table 2. Summary of clinical response by underlying condition.**

<table>
<thead>
<tr>
<th>Underlying condition</th>
<th>All-treated</th>
<th>Evaluable</th>
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<tbody>
<tr>
<td>Polymicrobial infection</td>
<td>62/117 (53.0)</td>
<td>26/39 (66.7)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>45/91 (49.5)</td>
<td>19/28 (67.9)</td>
</tr>
<tr>
<td>Transplantation</td>
<td>43/91 (47.3)</td>
<td>22/35 (62.9)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>34/77 (44.2)</td>
<td>12/22 (64.5)</td>
</tr>
<tr>
<td>Dialysis</td>
<td>21/65 (32.3)</td>
<td>10/20 (50.0)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>21/64 (32.8)</td>
<td>10/18 (55.6)</td>
</tr>
<tr>
<td>Chronic liver disease with cirrhosis</td>
<td>12/43 (27.9)</td>
<td>4/8 (50.0)</td>
</tr>
<tr>
<td>Neutropenia, &lt;500 cells/mm²</td>
<td>22/43 (51.2)</td>
<td>9/14 (64.3)</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>12/26 (46.2)</td>
<td>4/5 (80.0)</td>
</tr>
<tr>
<td>HIV infection</td>
<td>4/4 (100.0)</td>
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</table>

**NOTE.** Data are no. (%) of patients.

* Patients with indeterminate response included in denominator.
The first clinical isolates of VREF, described by Leclercq et al. [17] in France in 1988, were \textit{E. faecium} of the VanA phenotype. There are now also reports of the occurrence of infection and/or colonization due to VREF in the United Kingdom [18], Australia [19], Canada [20], and Sweden [21]. Since 1990, VREF has rapidly emerged as a nosocomial pathogen in the United States [22–24]. Prior parenteral antibiotic treatment appears to be a risk factor for nosocomial acquisition of VREF [25, 26]. Oral vancomycin seems a more important risk factor than iv vancomycin [27].

Although enterococci, including VREF, are not intrinsically highly virulent or pathogenic, increasing numbers of immunocompromised patients have provided an expanding ecological niche for these organisms. The role of such organisms in morbidity and mortality has been clearly demonstrated [28–31]. Edmond et al. [6] determined an attributable (direct) mortality due to VREF bacteremia of 37.0% (95% CI, 10.0%–64.0%). Other studies have confirmed the pathogenic role of VREF [32, 33].

Treatment options for VREF infection have been severely limited, although ciprofloxacin, chloramphenicol, novobiocin, and cell wall–active agents, alone or in combination, have all been used with some success. Most recently, linezolid, an oxazolidinone compound, has shown efficacy for vancomycin-resistant enterococcal infection [34] and is now approved by the US Food and Drug Administration for use against serious infections due to VREF.

Quinupristin/dalfopristin consists of a 30:70 ratio of 2 different streptogramin antibiotics that bind to separate sites on the bacterial ribosome and are active against a broad variety of multidrug-resistant gram-positive organisms [35]. Quinupristin/dalfopristin became commercially available in the United States in September 1999 for treatment of both VREF infection and complicated skin and skin-structure infection.

The efficacy and safety of quinupristin/dalfopristin for the treatment of VREF infection were assessed in this prospective, multicenter, noncomparative study. Even under the emergency-use conditions of this study, considerable numbers of patients were evaluable. Despite a high frequency of medically significant underlying diseases, the bacteriologic and overall response rates for patients in the more rigorously defined evaluable population were 68.0% and 65.6%, respectively. Consistent response rates were seen across indications, with the exception of intra-abdominal infection, for which the overall response rate in the evaluable population was 58.1%. The lower response in the intra-abdominal subset is consistent with observational case series of enterococcal infection in the pre–vancomycin-resistant era that characterized intra-abdominal infection as high-risk.

The observed response rates in the current series mirror those reported for the first 396 patients treated in the emergency-use program [7], for whom overall success rates of 51.5% and 65.4% were observed in the all-treated and bacteriologically evaluable populations, respectively. Using a historical control cohort in a homogeneous population of liver transplant patients, Linden et al. [36] reported that quinupristin/dalfopristin reduced VREF-associated mortality, defined as death within 1 week of VREF bacteremia or the finding of VREF infection at autopsy (5 deaths of 20 patients in the quinupristin/dalfopristin vs. 17 of 42 in the historical control group; \(P = .05\)). A favorable clinical response has been reported recently for 19 (83%) of 23 evaluable patients with serious underlying conditions who were treated with quinupristin/dalfopristin for VREF infections [37].

The antimicrobial spectrum of quinupristin/dalfopristin excludes \textit{E. faecalis}, as the MIC\textsubscript{90} for this organism is 16 \(\mu\)g/mL, well above the achievable serum concentrations of 11–12 \(\mu\)g/mL for quinupristin/dalfopristin [38]. Thus, \textit{E. faecalis} superinfection could be expected \textit{a priori} and was in fact documented in the current study [39, 40]. Emergence of resistance can occur during therapy with any antimicrobial and has been reported elsewhere with quinupristin/dalfopristin for VREF infection [41, 42]. The rate of emerging resistance in VREF was low when expressed as the number of evaluable patients (5 [4.0%] of 125 patients), although not all baseline and subsequent VREF isolates were tested for susceptibility in this series. Notably, a recent large-scale surveillance report (from the G-SMART study) showed that 96.1% of \textit{E. faecium} isolates from 55 medical centers in the United States were susceptible to quinupristin/dalfopristin (MIC\textsubscript{90}, 1 \(\mu\)g/mL) [43].
was characterized primarily by musculoskeletal and digestive system symptoms. The arthralgias and myalgias were unaccompanied by clinical or laboratory findings indicative of an inflammatory process and were reversible upon cessation of therapy, as were the digestive system events. Authors of other recent series of patients treated with quinupristin/dalfopristin have reported higher rates of myalgia/arthralgia (33%–47%) than observed in our series [37, 44]. In one of these series, myalgia/arthralgia was seen only in patients treated with 7.5 mg/kg q8h, not in those given 5 mg/kg q8h [37]. Assessment of the laboratory safety profile was confounded by the high severity of illness, but data from comparative studies suggest that the cardiac, renal, nervous, and hematopoietic systems are not predictable target organs for toxicity [45]. Elevations of total and conjugated bilirubin values have been observed [46, 47]; elevations of hepatic transaminase values occur less frequently.

In conclusion, in this severely ill population, quinupristin/dalfopristin demonstrated substantial efficacy and was generally well tolerated for the treatment of VREF infection. These data indicate that quinupristin/dalfopristin is an efficacious and safe antimicrobial option for the treatment of patients with serious VREF infection.

### STUDY GROUP PARTICIPANTS


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References


