Effect of quinupristin/dalfopristin on the outcome of vancomycin-resistant Enterococcus faecium bacteraemia: comparison with a control cohort

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Serious infection with vancomycin-resistant Enterococcus faecium (VREF) strains has no proven effective antimicrobial therapy. We compared the clinical and bacteriological outcomes of 20 patients with VREF bacteraemia treated with quinupristin/dalfopristin (RP 59500), an investigational streptogramin, with a historical cohort of 42 patients with VREF bacteraemia treated with other agents. Quinupristin/dalfopristin demonstrated in-vitro bacteriostatic activity against all 20 initial VREF blood isolates (MIC range 0.03–0.50 mg/L) by macrobroth dilution. The clinical characteristics of both groups were comparable for major outcome-dependent variables. There were five cases of recurrent VREF bacteraemia in the quinupristin/dalfopristin-treated cohort and 21 in the controls ($P = 0.11$); persistence of VREF at the primary site was found in six and 18 of the evaluable patients with follow-up cultures in these two cohorts ($P = 0.06$). In-hospital mortality was high in both groups: 65% in the quinupristin/dalfopristin group and 52% in the control group; however, VREF-associated mortality was significantly lower in the quinupristin/dalfopristin group (five and 17 respectively; $P = 0.05$). Follow-up susceptibility testing of five VREF isolates in the quinupristin/dalfopristin group did not demonstrate resistance to quinupristin/dalfopristin. Quinupristin/dalfopristin may be a useful agent for the therapy of serious VREF infection. Further clinical investigations are warranted to confirm or refute its clinical efficacy.

Introduction

The rapid emergence of strains of Enterococcus faecium with high-level resistance to vancomycin (VREF) has created a serious therapeutic void in the management of enterococcal infection. As for vancomycin-susceptible enterococci, serious infection with VREF strains frequently occurs in debilitated or immunocompromised hosts with significant underlying disease. Several recent series report an increase in the attributable morbidity and mortality due to vancomycin-resistant enterococcal infection in both medical and surgical patients. At present there are no antimicrobial agents with proven in-vivo efficacy for serious VREF infection. Several investigators have reported the use of approved antimicrobial agents including novobiocin, chloramphenicol or triple combination therapy with ampicillin, vancomycin and gentamicin. However, these trials included only a small number of patients, lacked any control data, and have not been confirmed by others. Teicoplanin may be effective against vancomycin-resistant enterococci with the VanB phenotype but the development of resistance during therapy may severely limit the efficacy of this agent.

Quinupristin/dalfopristin (RP 59500) is a novel investigational antibiotic which belongs to the streptogramin family. It has a wide spectrum of activity against Gram-positive bacteria including coagulase-negative staphylococci, Staphylococcus aureus (including methicillin-resistant strains) and Streptococcus pneumoniae. Quinupristin/dalfopristin was previously reported to be successful in the treatment of VREF peritonitis in patients on peritoneal dialysis but clinical experience remains very limited.
limited for this organism. We report the first series where quinupristin/dalfopristin was used to treat serious infection complicated by VREF bacteraemia.

Materials and methods

Description of VREF outbreak

Strains of E. faecium with high-level resistance to both vancomycin and teicoplanin were first isolated at the University of Pittsburgh Medical Center in November 1990. VREF-colonized and VREF-infected patients were predominantly on the liver transplant service and in the intensive care units. Macrobath antibiotic susceptibility testing demonstrated the following MICs: vancomycin (>64 mg/L), teicoplanin (>8 mg/L), ampicillin (>128 mg/L), ciprofloxacin (2-4 mg/L). High level (1,000 mg/L) gentamicin resistance was variable and 8-lactamase was not detected. Strain typing with field-inverted gel electrophoresis and Southern blotting demonstrated the presence of two dominant VREF clones during the first 18 months of the outbreak. A nalysis with a vanA oligonucleotide probe demonstrated hybridization with chromosomal, but not plasmid DNA.

Microbiological methods

Blood cultures were obtained by venepuncture with 10–15 mL inoculated into BA CTEC 460 6A (aerobic) and 16T (anaerobic) bottles (Becton-Dickinson, Towson, M.D., USA) from January 1991 to June 1992. After June, 1992 the blood culture system was converted to BacT/alert (Organon Teknika, Durham, NC, USA). Enterococci were identified by growth on sheep blood agar, bile–asculin agar, and in 6.5% sodium chloride, growth at 45°C, lack of gas production from glucose, and hydrolysis of L-pyroglutamyl-8-naphthylamide. Differentiation of enterococcal species was performed with arginine hydrolysis, motility and carbohydrate fermentation.

A ntibiotic susceptibility testing of non-blood isolates was performed by disc diffusion using Mueller-Hinton agar. MIC determinations were performed for all blood isolates and selected non-blood isolates by macrobroth dilution with standard breakpoints.

Since no definitive susceptibility breakpoint exists for quinupristin/dalfopristin, macrobroth MIC testing was performed over the quinupristin/dalfopristin concentration range of 0.03–16 mg/L. MICs of ≤2 mg/L were considered to indicate susceptibility for the purposes of this study since achievable peak plasma concentrations are in the range of 4–5 mg/L with conventional dosing.

High-level gentamicin resistance (>500 mg/L) was determined in Mueller-Hinton or brain-heart infusion broth agar plates using established methods. Nitrocefyn discs (Cefinase; BBL Microbiology Systems, Cockeysville, M D, USA) were used for 8-lactamase detection.

Quinupristin/dalfopristin compassionate use protocol for VREF infection

Quinupristin/dalfopristin became available in December 1993 under an IRB-approved compassionate use protocol for serious VREF infection. Inclusion criteria for study entry included the following: general criteria: age > 18 years, male or non-pregnant female and provision of informed consent; microbiological criteria: bacteraemia with E. faecium with a vancomycin MIC > 8 mg/L, teicoplanin MIC > 8 mg/L, in-vitro resistance to all other appropriate agents, and quinupristin/dalfopristin MIC ≤ 2 mg/L; clinical criteria included two or more of the following systemic signs of infection: temperature > 38°C, white blood cell count > 10,000/mm³ or a leftward shift in the differential count, heart rate > 100/min, respiratory rate > 20/min or mechanical ventilator dependence, blood pressure < 90 mm Hg or dependence on vaso pressor agents, or an altered mental status.

Quinupristin/dalfopristin was administered intravenously in a dose of 7.5 mg/kg every 8 h via a central or peripheral venous catheter. Each patient was followed with close consultation between the principal investigator and the primary physician team. The duration of quinupristin/dalfopristin therapy was individualized based on the initial severity of the VREF infection, clinical response and bacteriological response. The selection of other antibiotic therapy or non-antimicrobial therapy directed against the VREF infection was left to the discretion of the primary physician team. Repeat blood cultures were performed at 24 and 48 h until they showed no growth, or thereafter whenever clinically indicated. Cultures from other sites were obtained only at the discretion of the primary physician team. Repeat MIC determinations were performed for clinically significant VREF isolates during quinupristin/dalfopristin therapy and in the early post-therapy period.

The following laboratory tests were obtained at baseline and at least every 2–3 days during therapy: leucocyte count and differential, platelet count, serum BUN and creatinine, aspartate transaminase, alanine transaminase, g-glutamyl transpeptidase and the total and direct serum bilirubin.

Control cohort with VREF bacteraemia

All patients with VREF bacteraemia before the availability of quinupristin/dalfopristin (January 1991–December 1993) were considered the historical control cohort. A computerized database on these patients was prospectively maintained and included demographic, clinical and microbiological data.

Study definitions

Study definitions were as follows. Shock: sustained systolic arterial blood pressure < 90 mm Hg or requirement for
Quinupristin/dalfopristin for VREF bacteraemia

Vasopressor agents to maintain a systolic blood pressure of > 90 mm Hg. Renal failure: serum creatinine > 2.0 mg/dL or requirement for haemodialysis. Hepatic failure: serum bilirubin > 3.0 mg/dL and prothrombin time > 15 s, or biopsy evidence of cirrhosis or necrosis. VREF bacteraemia: isolation of VREF from two or more blood culture sets or one blood culture set with a documented primary source of VREF infection. Recurrent VREF bacteraemia: two or more days of VREF bacteraemia. VREF-associated mortality: death within one week of a positive blood culture, or microbiological evidence of active VREF infection at death or autopsy.

Statistical analysis

A analysis of proportions were compared using either Fisher’s exact test or the chi-square method depending on the sample size. Sample means for continuous variables were compared using Student’s t-test or the Wilcoxon rank-sum test depending on sample distribution. A two-tailed P value of <0.05 was considered significant.

Results

The first patient received quinupristin/dalfopristin at our centre in November 1993. During the subsequent 14 months (November 1993–December 1994), quinupristin/dalfopristin was administered to 32 patients with serious VREF infection who met the inclusion criteria. Twenty patients in this group had VREF bacteraemia and are further analysed here. Patients in the control group had one or more episodes of VREF bacteraemia between March, 1991 and February, 1994. Two control patients were offered quinupristin/dalfopristin (after it became available in November, 1993) but refused their consent. The median duration of quinupristin/dalfopristin therapy was 18 days (range 5–43 days). Median clinical follow-up from the initial bacteraemic episode to hospital discharge or death was 28 days in the quinupristin/dalfopristin cohort (range 5–144 days) and 20 days (range 1–174 days) in the control cohort. No patients were lost to follow-up.

Clinical and bacteriological characteristics

The clinical characteristics of the quinupristin/dalfopristin and control groups are shown in Table I. There were no significant differences for the major features we analysed. Both groups consisted predominantly of solid organ recipients, resided in the ICU at the time of VREF bacteraemia and had comparable rates of organ failure (shock, respiratory, renal, hepatic) at the time of the first episode of VREF bacteraemia.

The primary sites of VREF infection are summarised in Table II. The dominant site of VREF infection was intra-abdominal in both groups; quinupristin/dalfopristin, 14 (70%) and control, 32 (76%). VREF bacteraemia was present without a known primary source in three quinupristin/dalfopristin-treated patients and seven patients in the control group. At the time of the initial bacteraemic episode, VREF was the sole blood isolate in the majority of cases; 15 (75%) in the quinupristin/dalfopristin group and 36 (88%) in the control group. The frequency of other blood and tissue pathogens is demonstrated in Table III. The incidence of polymicrobial infection at the primary site was more frequent in the quinupristin/dalfopristin group but this difference was not statistically significant; 11 (55%) vs 16 (38%), P = 0.32.

The MICs for all the initial and repeat-tested blood isolates in the quinupristin/dalfopristin-treated group are summarized in Table IV. The observed MIC range of 0.12–0.50 mg/L for all 20 blood isolates was well below the peak achievable serum concentration of quinupristin/dalfopristin (4 mg/L). However, MBC testing did not demonstrate any bactericidal activity up to a maximum quinupristin/dalfopristin concentration of 16 mg/L.

Table I. Clinical features of quinupristin/dalfopristin and control groups at the time of the first episode of VREF bacteraemia

<table>
<thead>
<tr>
<th></th>
<th>Quinupristin/dalfopristin (n = 20)</th>
<th>Control (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>42.1</td>
<td>46.1</td>
</tr>
<tr>
<td>Gender (% males)</td>
<td>60</td>
<td>71</td>
</tr>
<tr>
<td>Hospital LOS (days)</td>
<td>35</td>
<td>31</td>
</tr>
<tr>
<td>ICU</td>
<td>18</td>
<td>37</td>
</tr>
<tr>
<td>Transplant recipient</td>
<td>17</td>
<td>35</td>
</tr>
<tr>
<td>Shock(^a)</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td>Renal failure(^a)</td>
<td>15</td>
<td>23</td>
</tr>
<tr>
<td>Hepatic failure(^a)</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

\(^a\)See text for definitions used.

M LOS, median length of stay; ICU, present in intensive care unit at time of VREF bacteraemia

Table II. Primary sites of VREF infection

<table>
<thead>
<tr>
<th></th>
<th>Quinupristin/dalfopristin (n = 20)</th>
<th>Control (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-abdominal</td>
<td>14</td>
<td>32</td>
</tr>
<tr>
<td>Urological</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pleural space</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Septic phlebitis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>
Antimicrobial and surgical interventions

Table V summarizes the empirical and definitive antimicrobial therapy which was administered from the first episode of VREF bacteraemia throughout the 28 day follow-up period. All patients received one or more antimicrobial agents for a minimum of 3 days. The distribution of antimicrobial agent use was similar with the significant exception that vancomycin was used more frequently in the control group (35 vs 9, \( P = 0.005 \)). Based on macrobroth susceptibility testing, a number of control patients also received antimicrobial therapy directed specifically at VREF; 11 patients received oral novobiocin (mean duration = 18 days, range 10–37 days) and another three received intravenous doxycycline (mean = 8 days, range 5–10 days).

Surgical interventions

The majority of patients in both groups underwent one or more surgical or percutaneous drainage procedures. Percutaneous drainage was unsuccessful and required subsequent surgical intervention in three quinupristin/dalfopristin-treated patients and seven control patients respectively. Multiple exploratory laparotomies were performed to correct technical surgical problems or for therapeutic abdominal irrigation in those patients with peritonitis or loculated and infected collections.

Clinical and bacteriological outcome

The clinical and bacteriological outcomes are shown in Table VI. There were 21 (50\%) and five (25\%) recurrent episodes of VREF bacteraemia in the control cohort and quinupristin/dalfopristin group, respectively (\( P = 0.11 \)). One quinupristin/dalfopristin-treated patient with 6 days of VREF bacteraemia was neutropenic due to bone marrow aplasia, probably drug-induced. Two control patients with multiple episodes of VREF bacteraemia were eventually diagnosed as having enterococcal endocarditis. The MICs of the VREF blood isolates on therapy are shown in Table IV.
Quinupristin/dalfopristin for VREF bacteraemia

Table V. Antimicrobial and other therapeutic interventions

|                     | Quinupristin/dalfopristin (n = 20) | Control (n = 42) | P  
|---------------------|-----------------------------------|-----------------|-----
| A antimicrobial agent | int | int | int |
| vancomycin          | 9    | 35   | 0.005 |
| β-lactam            | 10   | 16   |     |
| aminoglycoside      | 10   | 26   |     |
| clindamycin         | 2    | 6    |     |
| ciprofloxacin       | 6    | 25   |     |
| novobiocin          | 0    | 11   |     |
| doxycycline         | 0    | 3    |     |
| Other interventions |       |      |     |
| percutaneous drainage| 4    | 7    |     |
| surgical drainage* | 14   | 22   |     |
| retransplantation   | 1    | 3    |     |

*Only vancomycin use had a P value of <0.05.

*Exploratory laparotomy for drainage of abscess, haematoma or abdominal irrigation.

Table VI. Clinical and bacteriological outcomes

|                     | Quinupristin/dalfopristin (n = 20) | Control (n = 42) | P  
|---------------------|-----------------------------------|-----------------|-----
| Recurrent bacteraemia | 5    | 21   | 0.11 |
| Primary site* (no. patients) | 6 (14) | 18 (23) | 0.06 |
| In-hospital mortality | 13   | 22   | 0.50 |
| VREF-associated mortality | 5    | 17   | 0.05 |

*Isolation of VREF > 10 days after initial bacteraemia.

in Table IV. Blood isolates from two patients showed an increase in the quinupristin/dalfopristin MIC to 2.0 mg/L though this was still below the achievable peak serum level. In those patients with follow-up cultures beyond 7 days (14 quinupristin/dalfopristin-treated patients and 23 control patients), VREF was isolated from the primary site in six (42%) of the quinupristin/dalfopristin cohort and 18 (78%) of the controls (P = 0.06). Overall mortality was high in both cohorts; 13 (65%) quinupristin/dalfopristin-treated patients and 22 (52%) controls died in the follow-up period. The median duration from the first episode of VREF bacteraemia to death was 19 days in the quinupristin/dalfopristin group and 11 days in the controls; however, this was not statistically significant (P = 0.36). Notably, when only patients with in-hospital mortality were analysed, death was less likely to be VREF-associated in the quinupristin/dalfopristin-treated group: five (36%) vs 17 (79%); P = 0.05. The causes of the eight deaths not associated with VREF in the quinupristin/dalfopristin group included five due to sepsis from a non-enterococcal pathogen, and three due to allograft liver failure. Seven quinupristin/dalfopristin-treated patients completed their course of therapy and were eventually discharged from the hospital.

Discussion

The data presented in our study demonstrate that quinupristin/dalfopristin may have a potential role in the treatment of serious VREF infection. The mix of clinical and bacteriological outcomes in our series is similar to the patterns described in recent series of patients with bacteraemia due to vancomycin-susceptible or -resistant enterococci.12,13 The diverse range of outcomes after enterococcal bacteraemia is associated with the serious nature of chronic underlying disease(s), unresponsive acute conditions (e.g. visceral perforation, sepsis, multi-system organ failure), and co-infection with non-enterococcal pathogens. The dominant effect of these co-morbidities is also illustrated by several other series of cases of enterococcal bacteraemia which have failed to show a benefit from anti-enterococcal therapy.14-16 For these reasons it was of paramount importance to compare
the quinupristin/dalfopristin-treated cohort with an appropriate control population with VREF bacteraemia to determine the effects of quinupristin/dalfopristin.

Both groups were similar with respect to the relevant demographic, aetiological and illness-severity factors which have potential prognostic value. VREF bacteraemia was predominantly monomicrobial in both groups: 75% and 86% in the quinupristin/dalfopristin and control groups, respectively. This observation probably reflects the intensity of selective antibiotic pressure in both groups. In our study population, VREF infection originated from a post-surgical condition and or required further surgical interventions. Thus, quinupristin/dalfopristin was used as a therapeutic adjunct combined with single or multiple invasive therapies in the majority of cases. The bacteriological effects of quinupristin/dalfopristin occurred both in the bloodstream and at the primary site of infection as lower rates of both recurrent bacteraemia and persistent isolation of VREF at the primary site in comparison to the control group. It can be argued that the rates of refractory VREF infection are also influenced by several other important variables. Firstly, the timing and adequacy of percutaneous or open surgical drainage could strongly affect the bacteriological outcomes with or without effective antibiotic therapy. Since our control patients were historical (from a time before the availability of quinupristin/dalfopristin), the promptness and adequacy of surgical management of VREF infection may have improved over time, thus favouring patients in the quinupristin/dalfopristin group. Secondly, the concomitant use of VREF-selective antibiotics may promote the persistence of VREF colonization or infection. This effect may have been present in our study comparison as the historical control cohort had a significantly higher frequency of vancomycin use. With these confounding factors in mind, quinupristin/dalfopristin therapy was associated with a significantly lower incidence of VREF-associated mortality despite the high overall mortality rates in both groups. Frank clinical failure was seen in five quinupristin/dalfopristin-treated patients. Notably, one failure occurred, in a patient with refractory neutropenia following drug-induced bone marrow suppression. The lack of bactericidal activity with quinupristin/dalfopristin may compromise its clinical and bacteriological efficacy in neutropenia and other conditions where bactericidal activity is required for bacterial eradication. However, satisfactory outcomes have been reported in other challenging clinical conditions. Quinupristin/dalfopristin therapy achieved microbiological and clinical cure in a patient with VREF prosthetic valve endocarditis, an 8-month old infant with ventriculitis due to a VREF-infected central nervous system shunt and three cases of VREF peritonitis due to peritoneal dialysis catheter infection.

Several other investigators have documented in-vitro activity of quinupristin/dalfopristin against both Van A and Van B phenotypes of E. faecium. The rise in quinupristin/dalfopristin MIC to 1–2 mg/L in VREF isolates obtained on therapy raises the possibility that frank resistance to quinupristin/dalfopristin could develop in some strains. De novo resistance amongst E. faecium strains has been reported previously, although there are no reports of resistance developing in previously quinupristin/dalfopristin-susceptible VREF strains. The clinical relevance of the rise in MIC to sub-breakpoint levels is unclear at the present time. These strains and other similar phenotypes are currently being analysed by several other laboratories to ascertain both their resistance mechanisms and clinical behaviour in several animal models.

These clinical results are promising, but should be considered as preliminary data and thus interpreted with caution. The large number of confounding variables in patients with VREF bacteremia makes a definitive evaluation of antimicrobial efficacy problematic in such a relatively small series. A large prospective multicentre clinical trial in which the clinical and bacteriological outcomes in a diverse spectrum of quinupristin/dalfopristin-treated patients with serious VREF infection were studied was recently completed (F. Bompart, personal communication). The data obtained from this larger population should help to confirm or refute the clinical efficacy of quinupristin/dalfopristin for the management of serious VREF infection.

A cknowledgement

This work was presented as a poster at the Third International Conference on the Macrolides, Azalides and Streptogramins, Lisbon, Portugal, 1996.

R eferences


