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The efficacy and safety of quinupristin/dalfopristin for the treatment of infections caused by vancomycin-resistant *Enterococcus faecium*

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A progressive increase in the incidence of vancomycin resistance in strains of *Enterococcus faecium* (VREF) has severely constrained treatment options for patients with infection caused by this emerging pathogen. Quinupristin/dalfopristin (Synercid), the first injectable streptogramin antibiotic, is active *in vitro* against VREF, with an MIC_{90} of 1.0 mg/L. We studied the clinical efficacy and safety of quinupristin/dalfopristin in the treatment of VREF infection. Two prospective studies were conducted simultaneously. The first enrolled only patients with VREF infection; the second included patients with infection caused by other Gram-positive bacterial pathogens in addition to VREF. Patients were enrolled if they had signs and symptoms of active infection and no appropriate alternative antibiotic therapy. The recommended treatment regimen of quinupristin/dalfopristin was 7.5 mg/kg iv every 8 h for a duration judged appropriate by the investigator. A total of 396 patients with VREF infection were enrolled. The most frequent indications for treatment included intra-abdominal infection, bacteraemia of unknown origin, urinary tract infection, catheter-related bacteraemia, and skin and skin structure infection. This patient population had a high prevalence of severe underlying illness, including a history of diabetes mellitus, transplantation, mechanical ventilation, dialysis, chronic liver disease with cirrhosis and oncological disorders. The mean (± S.D.) duration of treatment was 14.5 ± 10.7 days (range: 1–108). The majority of patients (82.1%) were treated every 8 h, as assessed on day 2 of treatment, while 15.9% were treated every 12 h. The clinical success rate was 73.6% [142/193 clinically evaluable patients; 95% confidence interval (CI): 67.4%, 79.8%], the bacteriological success rate 70.5% (110/156 bacteriologically evaluable patients; 95% CI: 63.4%, 77.7%) and the overall success (both clinical and bacteriological success) rate 65.8% (102/156 bacteriologically evaluable patients; 95% CI: 57.9%, 72.9%). VREF bacteraemia at entry, mechanical ventilation and laparotomy were associated with a worse outcome. Quinupristin/dalfopristin was generally well tolerated. The most common systemic adverse events related to treatment were arthralgias (9.1%) and myalgias (6.6%). Related laboratory abnormalities were infrequent. In these severely ill patients with VREF infection and no other clinically appropriate therapeutic alternatives, quinupristin/dalfopristin demonstrated substantial efficacy and a good nervous system, cardiovascular, gastrointestinal, renal and hepatic tolerability.

Introduction

The development of resistance to antimicrobial agents is a problem which is assuming increasing importance. There is no organism or class of antibiotics which has not in some way been involved in the growing epidemic of antimicrobial resistance. Among the organisms causing the greatest problems in developed countries at the present time is a

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variety of multiply resistant Gram-positive cocci including methicillin-resistant staphylococci and penicillin-resistant pneumococci.

Vancomycin-resistant *Enterococcus faecium* (VREF) are a particular public health concern. These organisms were first described in Europe in the mid-1980s[1] and, shortly thereafter, began to cause serious problems in the USA,[2] where 47% of all *E. faecium* are now resistant to vancomycin. Moreover, VREF are often cross-resistant to penicillin, ampicillin and numerous other antimicrobial agents. It is not uncommon to encounter infections due to *E. faecium* that are resistant to all currently available antimicrobial agents.[3–5]

In the presence of multidrug resistance in VREF, in-vitro studies have sought to identify effective combinations of antibiotics. Unfortunately, until now, no single available antibiotic or combination of available antibiotics has been consistently bacteriostatic or bactericidal.[6–8] Furthermore, because of the multiple resistance phenotype often encountered in *E. faecium*, there is currently no standard therapy for these highly resistant organisms. Chloramphenicol, the one antibiotic to which VREF are most often susceptible *in vitro*, has been tried, but has not been proven truly effective in this setting.[9,10] Moreover, the recent discovery of efflux pumps for chloramphenicol in enterococci casts further doubt on its clinical utility.[11] Case studies include that by Feldman *et al.*[12] who observed increased survival among patients treated with rifampin, doxycycline or gentamicin if their organism was susceptible; a lower mortality was seen in patients receiving at least one active antimicrobial compared with those who received no drugs exhibiting in-vitro activity against VREF. Therapy with cell wall-active agents, e.g. imipenem–cilastatin, ampicillin/sulbactam or vancomycin (one or more of each) in combination with gentamicin, has been reported rarely, but the numbers of patients are small and the success rates variable.[13–15] Novobiocin has also been utilized infrequently to treat infection and/or colonization, but availability and adverse events limit its usefulness.[16,17]

Even though enterococci are not particularly virulent organisms, VREF are causing major problems in transplant patients, neutropenic patients and other patients with impaired host defences.[18] Accordingly, there is an urgent need to discover new antimicrobial agents with efficacy against these organisms.

Quinupristin/dalfopristin (Synercid) is a novel parenteral antimicrobial agent which consists of two different streptogramin antibiotics (quinupristin and dalfopristin) that bind to separate sites on the bacterial ribosome and have activity against a broad variety of multiply resistant Gram-positive cocci, including *Staphylococcus aureus* and *Staphylococcus epidermidis* (including methicillin-resistant strains), *E. faecium* (including vancomycin-resistant strains), *Streptococcus pneumoniae* (including penicillin-resistant strains) and other streptococci.[19,20] When the organism is susceptible to both streptogramins, the action of quinupristin/dalfopristin is commonly a bactericidal one. However, for enterococci harbouring genes that encode the MLS_B type of resistance, quinupristin/dalfopristin remains active, but for many strains is bacteriostatic rather than bactericidal.[21]

As presented in the current report, this new agent has been subjected to extensive clinical testing in patients infected with VREF. Because many of the organisms involved in this study were resistant to all clinically available agents, it was impossible to include a comparison group. It is, therefore, an open-label, non-comparative study. This article summarizes the initial clinical results for quinupristin/dalfopristin treatment of VREF infections.

Materials and methods

Study design

Two prospective emergency-use studies were conducted simultaneously. The first study enrolled only patients with VREF infection at pre-selected investigative sites in the USA with a documented high prevalence of VREF; the second study, which permitted inclusion of patients with infection caused by both VREF and other Gram-positive bacterial pathogens, was conducted worldwide to allow availability of quinupristin/dalfopristin on an urgent basis to eligible patients. For each study, appropriate Ethics Committee regulations were followed.

Patients were enrolled into one or more predefined indications (e.g. skin and skin structure infection) consistent with guidelines of the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases.[22,23] Patients were enrolled if they had signs and symptoms of active infection, isolation of a pathogen presumed to be susceptible to quinupristin/dalfopristin and no appropriate 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. Candidate patients were not excluded based on severity of underlying illness, impending death or infection site. The recommended quinupristin/dalfopristin treatment regimen was 7.5 mg/kg iv every 8 h for a duration judged appropriate by the investigator. A test-of-cure assessment was to be performed approximately 1–3 weeks after treatment discontinuation or at the end-of-treatment visit if the patient did not progress to follow-up.

Adverse events that were judged as either serious (e.g. life-threatening, caused or prolonged hospitalization, resulted in death) or related (possibly or probably) to treatment by the investigator were recorded, as were those that led to treatment discontinuation or were associated with venous intolerability. Laboratory test parameters indicating an adverse event that was serious or led to treatment discontinuation were ascertained in both studies.

APACHE II score data were collected in the first, but not the second study;[24] calculation of the score was based on data available at study entry.

Microbiology

Organisms. Bacterial strains isolated from patients were identified, tested for antimicrobial susceptibility and stored at the local laboratory of the participating investigator. Available enterococcal strains were sent subsequently to the reference laboratory of one of the authors (R. C. Moellering), where bacterial colonies with the morphological appearance of enterococci on horse blood agar plates were identified by biochemical properties or by gene probes, or both. Biochemical identification employed the API 20 Strep system (bioMérieux Vitek, Inc., Hazelwood, MI, USA). Pigment production, motility and β-lactamase production were assessed as previously described.[25–27] A probe for the *aac(6′)-Ii* gene which is specific to *E. faecium*[28,29] was also used for identification. Probes for *van*A and *van*B were prepared from *E. faecium* 228[30] and *E. faecalis* SF300, respectively, using primers described previously.[31]

Antibiotic susceptibility testing. Antimicrobial susceptibility of the isolates to quinupristin/dalfopristin and other potentially active antibiotics was determined by the agar dilution method.[32] Quality control strains and ranges approved by the National Committee for Clinical Laboratory Standards were utilized for all susceptibility testing. Screening for vancomycin resistance (6 mg/L) was performed on Synergy Quad plates (Remel, Lenexa, KS, USA) according to the manufacturer's recommendations, spotting 10 μL of a bacterial suspension (0.5 McFarland) on to the surface of each quadrant.[33]

Antibiotics. Quinupristin/dalfopristin susceptibility test powder (30:70 ratio) was provided by Rhône-Poulenc Rorer Pharmaceuticals, Inc., Collegeville, PA, USA. Teicoplanin and ciprofloxacin susceptibility test powders were the generous gifts of Hoechst Marion Roussel Research Institute, Hoechst Marion Roussel, Inc., Cincinnati, OH, USA and Bayer Corp., West Haven, CT, USA, respectively. Other agents were purchased from Sigma Chemical Co., St Louis, MI, USA.

Assessment of efficacy outcomes

Efficacy responses. The clinical response of the patient to quinupristin/dalfopristin treatment was assessed by the investigator as *cure* (resolution of all signs and symptoms relating to the original infection(s), with no new signs or symptoms); *improved* (in patients not cured, resolution or reduction of the majority of signs and symptoms relating to the original infection, with no new or worsened signs or symptoms); *failure* (either (a) no resolution and no reduction of a majority of signs and symptoms, or (b) worsening of one or more signs and symptoms, or (c) new symptoms or signs associated with the original infection(s) or a new infection); or *indeterminate* (inability to assess the signs and symptoms due to lack of information, or interference of the assessment due to concomitant medical/surgical condition(s)). The clinical success rate as presented in this paper for the 'all-treated' population (see below) reflects the sum (cure + improved) divided by (cure + improved + failure + indeterminate), i.e. indeterminate responses are considered as failures. For the evaluable populations, the indeterminate responses are not included in the calculation.

The bacteriological response of each VREF isolate for each indication was determined by a steering committee. All cultures, other than those of faeces, were assessed during a period of ±3 calendar days around the date of the clinical response assessment, and one of the following outcomes was assigned: *eradicated* (culture obtained and no growth of VREF), *presumed eradicated* (no culture obtained, but the clinical response was cure or improved), *persistence* (culture obtained, growth of VREF), *presumed persistence* (no culture obtained, clinical response of failure) or *indeterminate*.

The by-patient bacteriological response (hereinafter, 'bacteriological response') was derived from the bacteriological responses for the primary infection site(s) and the blood, if applicable. The bacteriological success rate for the all-treated population reflects the sum (eradicated + presumed eradicated) divided by (eradicated + presumed eradicated + persistence + presumed persistence + indeterminate), i.e. indeterminate responses are considered as failures. For the evaluable populations, the indeterminate responses are not included in the calculation.

The overall response was derived from the combination of the clinical and bacteriological responses. The overall success rate for the all-treated population reflects the number of patients with a clinical response of cured or improved plus a bacteriological response of eradicated or presumed eradicated, divided by the total number of patients, including those with indeterminate responses. For the evaluable populations, the indeterminate responses are not included in the calculation.

The by-pathogen (combining blood and site), by-indication and by-patient bacteriological responses as well as the overall response were programmatically derived.

Assessment of evaluability

For a patient to be considered clinically evaluable the following were required.

(i) Signs and symptoms of infection; for the bacteraemia of unknown origin indication, ⩾2 sets of blood cultures had to reveal growth of VREF within the 7 days prior to initiation of quinupristin/dalfopristin therapy, without reversion of subsequent cultures to no growth pre-therapy.

(ii) Clinical response of cure, improved or failure (i.e. not 'indeterminate').
(iii) Test-of-cure assessment performed 3–21 days after the last dose of quinupristin/dalfopristin.
(iv) No concomitant medical condition confounding the evaluation of clinical response.
(v) Quinupristin/dalfopristin administration of >5 days' duration.
(vi) Not more than 10% scheduled quinupristin/dalfopristin doses missed.
(vii) No scheduled dose missed on each of ⩾3 consecutive days.
(viii) Mean quinupristin/dalfopristin daily dose of ⩾15 mg/kg.

Requirements for bacteriological evaluability included the following.

(i) A pathogen isolated within the 96 h before starting treatment or up to day 2 of treatment. For patients whose infection site was difficult to culture and in whom spontaneous reversion to a culture-negative status was unlikely, e.g. bone and joint infection, cultures obtained up to 1 week before treatment were accepted.
(ii) In patients receiving concomitant chloramphenicol and/or doxycycline, the *E. faecium* isolate must have been resistant *in vitro* to these agents. If in-vitro resistance was not documented, then the drug(s) could not have been administered for more than 20% of quinupristin/dalfopristin dosing days. A similar restriction was applied to exposure to these treatments if received after quinupristin/dalfopristin therapy but before the test-of-cure assessment.

Patient populations

The patient populations were defined as follows.

(i) All-treated population—all patients who received at least one dose of quinupristin/dalfopristin; in this study, each patient in the all-treated population also had at least one isolate of VREF. For this population, patients with indeterminate clinical and/or bacteriological responses were retained in the denominator as failures for the calculation of success rates.
(ii) Clinically evaluable population—patients who met the clinical evaluability criteria.
(iii) Bacteriologically evaluable population—subset of the clinically evaluable patient population, including only those patients for whom the bacteriological evaluability criteria were met.

Superinfection. Superinfection was determined 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. Emerging resistance was defined as a ⩾4-fold increase in mean inhibitory concentration (MIC) to greater than or equal to the tentative resistance breakpoint of 4.0 mg/L.

Statistical methods. Results of these two contemporaneous studies were combined for analysis because the enrolment criteria for VREF infection, the recommended treatment regimen, and the primary efficacy and evaluability assessments were identical. No formal inferential testing was performed; 95% CIs were constructed around point estimates of the primary efficacy outcomes by population. Since many factors analysed in unifactor analyses were covariates, logistic regression analyses were performed on the dependent variables of clinical success and overall success in the clinically evaluable population.[34] In these exploratory models, demographic, medical history, bacteriological, quinupristin/dalfopristin dosing regimen and concomitant antibiotic administration explanatory factors were tested, using $P = 0.10$ for entry into the model.

Results

Population description

A total of 467 patients were enrolled in the two studies. Of these, 396 patients had infection caused by VREF: 250 in the first study and 146 in the second. Enrolment included 383 patients in the USA, 12 in the UK and one in Germany. The mean age was 53.4 ± 16.8 (standard deviation (S.D.)) years (range: 7.5 weeks to 89 years), with eight patients being <8 years of age. The majority were male (59.3%) and a substantial majority were Caucasian (71.5%), versus black (18.9%) or other (9.6%). Of the 396 patients, 392 were treated for a single indication, intra-abdominal infection being the most common (Table I). The distribution of demographic characteristics, prior medical conditions and poor prognostic risk factors was similar across all populations. The numbers of patients in the evaluable populations were smaller, in some cases substantially so, reflecting the application of strict evaluability criteria.

The patients in both the clinically and bacteriologically evaluable populations were seriously ill with a high prevalence of bacteraemia at study entry, diabetes mellitus, dialysis, leukaemia, malnutrition, requirement for mechanical ventilation, leucopenia (absolute leucocyte count <500/mm^3) and transplantation. In addition, 16.2% of patients had an underlying oncological disorder. This severity of illness is reflected in the relatively high mean

Table I. Indication by patient population at baseline

Indication[a]	Population: number (%) of patients		
	all-treated (n = 396)	clinically evaluable (n = 193)	bacteriologically evaluable (n = 156)
Intra-abdominal infection	135 (33.8)	68 (35.2)	56 (32.1)
Bacteraemia of unknown origin	113 (28.2)	36 (18.7)	27 (17.3)
Urinary tract infection	35 (8.8)	23 (11.9)	18 (9.3)
Central catheter-related bacteraemia	32 (8.0)	14 (7.3)	12 (7.7)
Skin and skin structure infection	31 (7.8)	21 (10.9)	18 (9.3)
Bone and joint infection	13 (3.3)	6 (3.1)	6 (3.8)
Endocarditis	9 (2.3)	5 (2.6)	4 (2.6)
Respiratory tract infection	9 (2.3)	4 (2.1)	2 (1.3)
Deep wound infection	4 (1.0)	3 (1.6)	3 (1.9)
Intravascular infection (not endocarditis)	3 (0.8)	3 (1.6)	3 (1.9)
Other infection	16 (4.0)	11 (5.7)	8 (5.1)

[a]Four patients had two indications as follows: urinary tract infection plus central catheter-related bacteraemia; intra-abdominal infection plus skin and skin structure infection; bone and joint infection plus skin and skin structure infection; and central catheter-related bacteraemia plus endocarditis.

Table II. Susceptibility pattern at baseline determined by the reference laboratory

Antimicrobial agent	Population: % of baseline isolates susceptible (number susceptible/number tested)	
	all-treated	bacteriologically evaluable
Quinupristin/dalfopristin[a]	98.6 (287/291)	97.5 (115/118)
Ampicillin	0.0 (0/291)	0.0 (0/118)
Chloramphenicol	92.1 (280/304)	93.4 (114/118)
Doxycycline	46.0 (134/291)	44.9 (53/130)
Vancomycin	0.0 (0/330)	0.0 (0/130)

[a]Minimum inhibitory concentration ⩽2.0 mg/L.

APACHE II score (18.2 ± 7.7), as performed in the first study. Approximately 13% of evaluable patients had an APACHE score of greater than 25 and approximately 40% had scores between 16 and 25. Furthermore, the crude mortality rate in study patients was 52.6%.

The number of baseline isolates for which susceptibility testing results were available varied by antibiotic due to technical factors. All tested baseline isolates were multi-drug resistant, with rates of in-vitro resistance to ampicillin and doxycycline of 100% and 54%, respectively (Table II). The majority were susceptible to chloramphenicol. For 287 (98.6%) of the 291 isolates tested for susceptibility to quinupristin/dalfopristin, the MIC was 2.0 mg/L or less; 274 (94.2%) had an MIC < 1.0 mg/L. The majority of isolates tested (217 of 293, 74.1%) were of the VanA phenotype, indicating resistance to teicoplanin as well as vancomycin.

The majority (82.1%) of patients in the all-treated population received quinupristin/dalfopristin every 8 h, as assessed on day 2 of treatment, while 15.9% were treated every 12 h; for the remaining 2.0%, the day 2 treatment regimen was not ascertained. Treatment duration was 14.5 ± 10.7 days, with a mean daily dose of 20.3 ± 3.6 mg/kg.

Efficacy

Clinical success rates were in excess of 70% in both evaluable populations (Table III). Success rates were higher in the evaluable populations than in the all-treated population, reflecting the consideration of patients with indeterminate clinical and/or bacteriological responses as failures in the latter. There was no apparent impact of underlying condition on the clinical success rate, except for a lower

Table III. Clinical, bacteriological and overall success rates by population

Outcome parameter	Population: number (%) patients		
	all-treated[a] (n = 396)	clinically evaluable (n = 193)	bacteriologically evaluable (n = 156)
Clinical success[b]	219 (55.3)	142 (73.6)	110 (70.5)
95% CI[c]	(50.4%, 60.2%)	(67.4%, 79.8%)	(63.4%, 77.7%)
Bacteriological success[b]	241 (60.9)	ND	110 (70.5)
95% CI[c]	(56.1%, 65.7%)		(63.4%, 77.7%)
Overall success[b]	204 (51.5)	ND	102 (65.4)
95% CI[c]	(46.6%, 56.4%)		(57.9%, 72.9%)

[a]Patients with indeterminate response included as failures.
[b]Definitions given in Materials and methods.
[c]CI, confidence interval.
ND, not done.

Table IV. Overall success rates[a] by population by indication

Indication	Population: number (%) of patients		
	all-treated[b] (n = 396)	clinically evaluable (n = 193)	bacteriologically evaluable (n = 156)
Intra-abdominal infection	53/135 (39.3)	44/68 (64.7)	33/56 (58.9)
Bacteraemia of unknown origin	58/113 (51.3)	22/36 (61.1)	14/27 (51.9)
Urinary tract infection	24/35 (68.6)	19/23 (82.6)	16/18 (88.9)
Central catheter-related bacteraemia	23/32 (71.9)	12/14 (85.7)	10/12 (83.3)
Skin and skin structure infection	19/31 (61.3)	16/21 (76.2)	13/18 (72.2)
Bone and joint infection	7/13 (53.8)	5/6 (83.3)	5/6 (83.3)
Endocarditis	4/9 (44.4)	1/5 (20.0)	1/4 (25.0)
Respiratory tract infection	4/9 (44.4)	3/4 (75.0)	1/2 (50.0)
Deep wound infection	4/4 (100.0)	3/3 (100.0)	3/3 (100.0)
Intravascular infection (not endocarditis)	1/3 (33.3)	1/3 (33.3)	1/3 (33.3)
Other infection	10/16 (62.5)	8/11 (72.7)	6/8 (75.0)

[a]Definition given in Materials and methods.
[b]Patients with indeterminate response included in denominator.

rate in bacteriologically evaluable patients receiving mechanical ventilation (50.0%) and those with leucopenia (53.8%) or leukaemia (55.0%). For patients in the first study, the clinical success rate was inversely related to the APACHE II score. Patient outcome data were consistent with in-vitro susceptibility profiles, in that response rates were comparable for isolates with a quinupristin/dalfopristin MIC of $<$1.0, 1.0 or 2.0 mg/L, but slightly lower for those with an MIC $\geq$ 4.0 mg/L.

The overall success rate in the bacteriologically evaluable population was lower (65.4%). The overall success rate varied by indication, with somewhat lower rates observed in the intra-abdominal (58.9%) and bacteraemia of unknown origin (51.9%) indications and higher rates in the urinary tract infection (88.9%), central catheter-related bacteraemia (83.3%) and skin and skin structure infection (72.2%) indications (Table IV). One of four patients with VREF endocarditis in the bacteriologically evaluable population was a success; a higher success rate (4 of 9) was seen in the all-treated population, but three of these patients with favourable responses were excluded from the evaluable populations because of confounding conditions, e.g. other concomitant or post-treatment therapies.

Logistic regression analyses

Explanatory factors tested in the models were as follows: age, gender, race, study, quinupristin/dalfopristin dose fre-

quency (every 12 h or every 8 h), quinupristin/dalfopristin relative mean daily dose in mg/kg, diabetes mellitus, dialysis, liver insufficiency, renal insufficiency, immune deficiency, malnutrition, leucopenia, transplantation, laparotomy, mechanical ventilation, polymicrobial infection, presence of VREF bacteraemia at study entry, indication: intra-abdominal infection, and concomitant administration of ampicillin, chloramphenicol, doxycycline or vancomycin.

Four statistically significant explanatory factors were associated with clinical failure: presence of VREF bacteraemia at study entry (odds ratio (OR): 0.20; $P = 0.0001$), mechanical ventilation (OR: 0.26; $P = 0.0013$), age >75 years (OR: 0.34; $P = 0.0563$) and the concomitant administration of chloramphenicol (OR: 0.40; $P = 0.0784$). Three statistically significant explanatory factors were identified for overall failure: presence of VREF bacteraemia at entry (OR: 0.25; $P = 0.0001$), mechanical ventilation (OR: 0.32; $P = 0.0032$) and laparotomy (OR: 0.40; $P = 0.0617$).

Safety

Arthralgia, without objective signs of articular pathology, and myalgia were the related adverse events most frequently reported and also most frequently leading to discontinuation of treatment (Table V). These symptoms could occur separately or in combination; they were reversible following cessation of therapy. Gastrointestinal adverse events and rash were also documented. The majority of the 396 patients received therapy exclusively via a central venous catheter. Of 101 patients receiving at least one infusion of quinupristin/dalfopristin via a peripherally inserted iv line, 47 (46.5%) experienced local venous intolerability (e.g. pain, burning, inflammation, thrombophlebitis); in 35 (34.9%) cases this was judged to be related to quinupristin/dalfopristin. Quinupristin/dalfopristin was discontinued in only one patient due to peripheral venous intolerability. Related laboratory adverse events leading to study discontinuation were infrequent, occurring in five patients (1.3%); these 13 events were increases in alkaline phosphatase (three), SGOT (two) and SGPT, γ-glutamine transferase (GGT and lactate dehydrogenase (LDH) (one each), as well as decreases in platelets, sodium, haemoglobin, haematocrit and RBC count (one each).

Superinfection and emerging resistance

Superinfection caused by Gram-positive pathogens was documented in 22 patients. Sixteen of these patients had superinfection with *Enterococcus faecalis*, an organism generally not lying within the spectrum of activity of quinupristin/dalfopristin. Emerging resistance *in vitro* to quinupristin/dalfopristin occurred in six patients in the bacteriologically evaluable population, as reflected by four- to eight-fold increases in the baseline MIC to a value of 4.0 mg/L or, in one case, 8.0 mg/L. Of six strain pairs in these patients, five had the same molecular typing results and one exhibited differing types. Four of the patients with isolates showing emerging resistance had intra-abdominal infection as the indication for treatment; four had clinical and/or bacteriological evidence of treatment failure at the test-of-cure assessment.

Discussion

Quinupristin/dalfopristin was tested in a very seriously ill group of patients with a variety of VREF infections, representative of the clinical spectrum of disease currently caused by this organism. The overall success rate was excellent, given the prognosis and underlying disease in these patients. Success rates of approximately 65–70% were achieved in the evaluable population, even in patients with the highest APACHE II scores. In addition, many patients

Table V. Related[a] adverse events (all-treated population)

Adverse events related[a] to study drug	Number (%) of patients	
	most frequent (>1.0%) ($n = 396$)	leading to treatment discontinuation ($n = 396$)
Arthralgia	36 (9.1)	13 (3.3)
Myalgia	26 (6.6)	11 (2.8)
Nausea	13 (3.3)	4 (1.9)
Pain	10 (2.5)	1 (0.4)
Asthenia	6 (1.5)	1 (0.4)
Rash	6 (1.5)	1 (0.4)
Vomiting	6 (1.5)	2 (1.1)
Diarrhoea	5 (1.3)	0 (0.0)
Pruritus	5 (1.3)	0 (0.0)

[a]Related adverse events are those judged possibly or probably related to study drug.

had failed previous antimicrobial therapy, and a number ultimately died of their underlying disease(s). Success rates were lower in more difficult-to-treat infections, such as endocarditis and intra-abdominal infection, the latter often occurring in the most compromised patients, e.g. liver transplant recipients. Higher rates were achieved for urinary tract infection, central catheter-related bacteraemia, and skin and skin structure infection.

Our analysis also identified prognostic factors for failure of therapy, such as bacteraemia at entry, requirement for mechanical ventilation or laparotomy. These markers of poor prognosis are biologically plausible, and could well be encountered with any pathogen, not just VREF. Of note, concomitant therapy with chloramphenicol was associated with clinical failure. Antagonism at the bacterial ribosome could be invoked as a putative mechanism, but other in-vitro data suggest the possibility of additive or even synergic effects of chloramphenicol and doxycycline with quinupristin/dalfopristin,[35,36] so the clinical implications of this observation are unclear.

The current study represents the largest to date assessing a single therapeutic intervention for VREF infection. Ideally, we would have preferred to have conducted a randomized trial of quinupristin/dalfopristin versus a suitable control antibiotic or antibiotic combination. However, in the large majority of cases, there was no other viable therapeutic option. The drug which exhibited the greatest apparent in-vitro activity against VREF in this study was chloramphenicol, which has uncertain efficacy in enterococcal infections. Indeed, the design of these studies was driven by the fact that no medical consensus existed as to an appropriate comparator regimen and that using a placebo control would have been unethical. Assessment of results with quinupristin/dalfopristin in relation to a historical control cohort has been scientifically justifiable in a homogeneous population such as liver transplant recipients[37] but was not justified in the setting of this broad programme.[38]

Despite the open-label, non-comparative design of this study, the weight of data indicates that quinupristin/dalfopristin was effective against serious, life-threatening VREF infections. Although spontaneous remission of VREF infection, including catheter-related bacteraemia, can occur,[39] this pathogen clearly causes morbidity and mortality if left untreated.[40–44] Indeed, there were even clearly documented clinical failures of quinupristin/dalfopristin. Some of these may have been related to the presence of undrained focal collections or abscesses and some (e.g. in cases of endocarditis) to the fact that quinupristin/dalfopristin is bacteriostatic to modestly bactericidal against many isolates of *E. faecium*.[21]

In several cases, resistance to quinupristin/dalfopristin appeared to emerge during treatment.[45] The mechanism of resistance in these strains has not been determined, but in no instances did highly resistant strains emerge. The increase in MICs of quinupristin/dalfopristin in this setting was in the four- to eight-fold range, generally to an MIC of 4.0 mg/L. The incidence of Gram-positive superinfections in this study was modest, although it was interesting to note that superinfection with *E. faecalis* occurred most frequently, confirming the lack of efficacy of quinupristin/dalfopristin against this species of enterococcus.[46]

The overall tolerability of quinupristin/dalfopristin was good, but it did produce a significant incidence of phlebitis when given by peripheral vein, and it would appear optimal to give the drug via a central line if that option is available. Myalgias and/or arthralgias occurred in approximately 10% of patients in this study.[47] In all cases these side-effects were reversible upon discontinuing the drug. Assessment of the laboratory safety profile was confounded by the severity of illness, but data from comparative studies suggest that the renal, nervous and haematopoietic systems are not predictable target organs for toxicity.[48] Elevations of total and conjugated bilirubin have been documented in these same studies, but they are generally not accompanied by elevations of hepatic transaminases, suggesting an absence of hepatocellular injury.[48,49]

In summary, quinupristin/dalfopristin is the first new agent with consistent in-vitro activity against multiresistant VREF. Its efficacy and safety in patients with various VREF infections have now been confirmed in this multicentre, open-label trial. While alternative agents with activity against enterococci are on the horizon (e.g. linezolid, everninomycin, clinafloxacin[50–53]), the clinical efficacy of quinupristin/dalfopristin against VREF infections demonstrated in this study represents a significant step forward in our battle against antimicrobial resistance.

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