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Treatment of methicillin-resistant *Staphylococcus aureus* infections with quinupristin–dalfopristin in patients intolerant of or failing prior therapy

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Safety and efficacy of quinupristin–dalfopristin (an injectable streptogramin antibiotic) were evaluated in the treatment of a variety of infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) in patients either intolerant of or failing prior therapy. The influence of resistance phenotypes on treatment outcome was also assessed. This worldwide, multicentre, open-label, non-comparative, emergency-use clinical study enrolled patients with one or more of nine predefined, culture-confirmed infections with MRSA, who had no clinically appropriate alternative antibiotic therapy. The recommended quinupristin–dalfopristin dose was 7.5 mg/kg administered iv every 8 h for a duration judged appropriate by the investigator. There were no restrictions on prior or concomitant treatment with other antibiotics. Clinical, microbiological and laboratory assessments were performed at baseline, during study drug treatment, within 24 h after the last dose, and 7–21 days post-therapy. Ninety patients [age (mean ± S.D.) 57.4 ± 18.5 years] with significant underlying medical illnesses were treated at 63 centres in five countries. The most common indications were bone and joint infection (44.4% of patients) and skin and skin structure infection (16.7%). The mean (± S.D.) daily dose and treatment duration was 20.2 ± 2.9 mg/kg/day for 28.5 ± 22.3 days, most frequently administered every 8 h. The overall success rate (defined as a clinical outcome of either cure or improvement and a bacteriological outcome of eradication or presumed eradication) was 71.1% in the all-treated population (n = 90) and 66.7% in patients who were both clinically and bacteriologically evaluable (n = 27). Success rates for endocarditis, respiratory tract infection and bacteraemia of unknown source were below the population mean. The macrolide–lincosamide–streptogramin type B resistance phenotype did not appear to alter the response rate. The most common non-venous adverse events related to study medication were arthralgias (10.8%), myalgias (8.6%) and nausea (8.6%). Quinupristin–dalfopristin should be considered as a treatment option for infections caused by MRSA, especially in patients intolerant of or failing alternate therapy.

Introduction

The growing incidence and severity of infections due to Gram-positive pathogens at many institutions in the United States and elsewhere have presented clinicians with therapeutic dilemmas.[1–3] In particular, infections caused by *Staphylococcus aureus* account for a significant percentage of nosocomial infections, such as bacteraemia, pneumonia, and skin and skin structure infection.[1] While prevalence varies widely worldwide, a recent study of isolates obtained in the United States reports that 41.0–43.7% of *S. aureus* isolates are methicillin resistant (MRSA).[4] In addition, many strains of MRSA are resistant to all antibiotics except glycopeptides (vancomycin and teicoplanin).[4] Alternatives to glycopeptides are sometimes necessary due to intolerance or treatment failures. Furthermore, *S. aureus* with intermediate glycopeptide-resistance have now been documented in Europe, Japan and the USA.[5–8]

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Quinupristin–dalfopristin (Synercid), the first injectable streptogramin antibiotic, demonstrates *in vitro* activity against a variety of Gram-positive organisms including staphylococci, streptococci and enterococci (except *Enterococcus faecalis*).[4] In particular, quinupristin–dalfopristin is active *in vitro* against *S. aureus*, with an MIC_{90} of 1.0 mg/L.[4] Quinupristin–dalfopristin also demonstrates consistent *in vitro* activity against MRSA, and therefore has a potential role in the treatment of infections due to these organisms.[4,9–14] However, published reports on the treatment of staphylococcal infections with quinupristin–dalfopristin are few.

The primary objective of this study was to evaluate the efficacy and safety of quinupristin–dalfopristin for the treatment of infections caused by MRSA in patients participating in a worldwide emergency-use protocol. A secondary objective was to observe the influence of resistance phenotypes on treatment outcome.

Materials and methods

This study was approved by the Ethics Committee or Institutional Review Board at each participating institution, and forms part of a worldwide, multicentre, open-label, non-comparative, emergency-use programme.[15] Patients were eligible for treatment with quinupristin–dalfopristin in the emergency-use programme if their infection was caused by Gram-positive pathogens and they were not candidates for alternative therapy (defined as the absence of clinically appropriate therapeutic options owing to documented intolerance, absolute contraindication to, and/or documented treatment failure with all available clinically appropriate antibiotics). Patients were eligible for this study if they were diagnosed with culture-proven MRSA infection resulting in one or more of nine predefined indications for therapy, based on signs and symptoms consistent with guidelines of the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases.[16,17] Those with known hypersensitivity to streptogramin antibiotics (pristinamycin, virginiamycin or quinupristin–dalfopristin) were excluded. This study was conducted between 9 September 1996 and 1 June 1998.

Before any study-related procedures were carried out, written informed consent was obtained from each patient or his/her agents (except where exempted by local regulations). The recommended quinupristin–dalfopristin treatment regimen was 7.5 mg/kg iv every 8 h for a duration judged to be appropriate based on the severity of infection, the anatomical site involved, the comorbidities and the patient's initial response to treatment. Clinical and microbiological assessments were performed at baseline, during study drug treatment, within 24 h after the last study drug infusion (end-of-treatment visit) and 7–21 days post-treatment (test-of-cure visit). Clinical and laboratory adverse events judged to be related to treatment or that led to treatment discontinuation were recorded.

Pathogen identification and antimicrobial susceptibility to comparative antibiotics were determined by broth microdilution or agar macrodilution methods according to NCCLS guidelines[18] (for all centres in the USA), or locally defined susceptibility test methods. No central testing laboratory was used. *S. aureus* resistance to methicillin was defined as MIC $\geqslant$ 16 mg/L. The resistance phenotype of MRSA isolates to macrolide–lincosamide–streptogramin type B (MLS_B) antibiotics was inferred from their resistance to erythromycin and clindamycin as follows: MLS_B-susceptible (MLS_BS), susceptible to both erythromycin and clindamycin; MLS_B-inducibly resistant (MLS_BI), erythromycin resistant, clindamycin susceptible; MLS_B-constitutively resistant (MLS_BC), resistant to both erythromycin and clindamycin. The MIC breakpoints for resistance used were erythromycin $\geqslant$8 mg/L and clindamycin $\geqslant$4 mg/L. Baseline isolates were not routinely tested for susceptibility to quinupristin–dalfopristin.

Assessment of efficacy outcomes

The clinical response to quinupristin–dalfopristin was assessed for each infection at the test-of-cure assessment (or end-of-treatment if the patient did not progress to test-of-cure). Definitions were as follows. Cure: resolution of all signs and symptoms related to the original infection(s), with no new signs or symptoms; improvement: 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 (i) no resolution and no reduction of a majority of signs and symptoms, (ii) a worsening of one or more signs and symptoms, or (iii) new signs or symptoms associated with the original infection or a new infection; indeterminate: inability to assess the patient's signs and symptoms because of lack of information, or interference in the assessment by concomitant medical or surgical conditions. Indeterminate responses were classed as failures for the calculation of success rates in the all-treated population (see below), but were not included in the calculation for the evaluable population.

The bacteriological response of each isolate was determined by an internal steering committee, based on culture results obtained within 3 days before or after the day of the clinical response assessment, and was assigned as one of the following. Eradicated: culture obtained from original site(s) and no growth of MRSA; presumed eradicated: no culture obtained, but the clinical response was cure or improvement; persistence: culture obtained, growth of MRSA; presumed persistence: no culture obtained, but clinical response was failure; indeterminate: no culture obtained, and clinical response was indeterminate.

The by-patient bacteriological response was derived from the bacteriological responses for the primary infec-

tion site(s) and the blood, if applicable. In the case of multiple indications, the worst outcome was used. Bacteriological success was defined as a response of eradication or presumed eradication.

The overall response was defined as success if a clinical response of either cure or improvement together with a by-patient bacteriological response of eradicated or presumed eradicated were observed.

Assessment of evaluability

For a patient to be considered clinically evaluable, the following were required: (i) documented infection with MRSA isolated any time before, or within 2 days after, the start of quinupristin–dalfopristin therapy, and either documented treatment failure or intolerance to all other clinically appropriate antibiotics; and (ii) signs and symptoms of infection consistent with the specified indications. For bacteraemia of unknown source, two positive blood cultures obtained within 7 days before, or 2 days after, initiation of therapy were required; (iii) clinical response of cure, improvement or failure (i.e. not indeterminate); (iv) quinupristin–dalfopristin administration for $\geqslant$5 days; (v) mean quinupristin–dalfopristin daily dose of $\geqslant$15 mg/kg; (vi) not $\geqslant$10% of scheduled quinupristin–dalfopristin doses missed; (vii) no scheduled dose missed on three consecutive days; (viii) no more than one course of quinupristin–dalfopristin therapy during the study; (ix) test-of-cure assessment performed 3–21 days after the last dose of quinupristin–dalfopristin, or, for patients who discontinued study treatment, end-of-treatment assessment performed between 1 day before and 2 days after the last dose of quinupristin–dalfopristin.

For a patient to be bacteriologically evaluable, the following were required: (i) they must have been clinically evaluable; (ii) bacteriological specimens had to establish the diagnosis within the period from 96 h before starting treatment to day 2 of treatment; and (iii) test-of-cure procedures had to be completed such that the bacteriological response could be assessed, using cultures obtained within 3 days before or after the clinical response assessment.

Patient populations

The two patient populations were defined as follows. (i) All-treated population: all patients who received any amount of study medication and for whom data were available were included in the all-treated population. Each patient in the all-treated population also had at least one isolate of MRSA. Patients with indeterminate clinical and/or bacteriological responses were retained in the denominator as failures for the calculation of success rates for this population. (ii) Evaluable population: consisted of patients who met both the clinical and bacteriological evaluability criteria. All patients receiving study medication were eligible for safety analysis.

Superinfection. Superinfection was defined as a Gram-positive pathogen not present at baseline but present at the primary infection site at the test-of-cure assessment along with clinical evidence of continued infection. Some superinfecting organisms were tested for susceptibility to quinupristin–dalfopristin. NCCLS-approved interpretive criteria were not in place at the time of the study, so the provisional MIC breakpoint for resistance to quinupristin–dalfopristin of $\geqslant$4.0 mg/L was used.[19]

Statistical methods. Descriptive statistics were used to characterize the patient population, clinical response and incidence of adverse reactions. A two-tailed 95% confidence interval (CI) was calculated for the primary and selected secondary efficacy outcome variables. CIs were also derived for indications with 10 or more patients.

Results

Ninety-three patients were enrolled at 63 centres in five countries. Three patients were excluded from efficacy evaluation because of prior quinupristin–dalfopristin use, but were included in the safety evaluation. Seventy-one patients were treated in the United States. Other participating countries included Brazil (one patient), France (10 patients), Germany (five patients) and Italy (three patients). Patients in the all-treated population ranged from 13 to 96 years of age, with a mean age of 57.4 $\pm$ 18.5 (S.D.) years. There were more male (55.6%) than female patients, and the majority of patients were Caucasian (85.6%). Most patients had significant comorbidities (Table I), with hypertension, diabetes mellitus, ischaemic heart disease and renal dysfunction each present in >20% of patients. Antibiotic allergy or intolerance to prior therapy was observed in 63/90 (70.0%) of patients.

Of the 90 patients in the all-treated population, 27 were clinically and bacteriologically evaluable. The most common reasons for clinical non-evaluability were efficacy assessment deviations (52.3%), an indeterminate clinical response (25.0%) and poor medication compliance (13.6%). The reasons for bacteriological non-evaluability were lack of clinical evaluability (69.8%), and the baseline culture being collected outside the specified time window (30.2%). Twenty-four of the 27 evaluable patients were treated in the USA.

A descriptive summary of study drug administration is contained in Table II. Quinupristin–dalfopristin was administered every 8 h to the majority (76/90, 84.4%) of patients at a mean ($\pm$ S.D.) daily dose and duration of 20.2 $\pm$ 2.9 mg/kg for 28.5 $\pm$ 22.3 days. The duration of quinupristin–dalfopristin treatment varied for different infection sites. For those patients with bone and joint infection who completed the study, the mean duration of quinupristin–dalfopristin treatment was 45.2 $\pm$ 30.6 days, while the corresponding values for patients with skin and

Table I. Selected significant comorbidities of patients receiving quinupristin–dalfopristin for MRSA infections ($n = 90$)

Significant comorbidities	Number of patients (%)
Hypertension[a]	34 (38.2)
Diabetes mellitus[a]	25 (28.1)
Myocardial ischaemic disease[a]	24 (27.0)
Renal dysfunction (creatinine clearance <30 mL/min)	21 (23.3)
Anaemia[a]	19 (21.3)
Congestive heart failure[a]	17 (19.1)
Septicaemia[a]	17 (19.1)
Peripheral vascular disease[a]	16 (18.0)
Chronic lung disease[a]	14 (15.7)
Dialysis-dependent renal failure	7 (7.8)
Malnutrition	7 (7.8)
Mechanical ventilation	6 (6.7)
Chronic liver disease and cirrhosis	5 (5.6)
Neutrophils <500 cells/mm^3	4 (4.4)
Alcoholism	4 (4.4)
HIV disease	3 (3.3)
Leukaemia	2 (2.2)

[a]Based on data from 89 patients.

Table II. Treatment description of patients receiving quinupristin–dalfopristin for MRSA infections ($n = 90$)

Treatment	All-treated ($n = 90$)	Clinically and bacteriologically evaluable ($n = 27$)
Daily dose: mg/kg; mean ± S.D. (range)	20.2 ± 2.9[a] (11.1–27.2)	20.4 ± 2.9 (11.1–27.2)
Dosing frequency: number (%)		
every 8 h	76 (84.4)	20 (74.1)
every 12 h	11 (12.2)	5 (18.5)
unknown	3 (3.3)	2 (7.4)
Duration: days; mean ± S.D. (range)	28.5 ± 22.3 (2–173)	30.6 ± 32.3 (5–173)
Time between hospitalization and initiation of treatment: days; mean ± S.D. (range)	22.9 ± 29.2[a] (1–177)	20.0 ± 36.0[b] (1–177)

[a]Based on data from 88 patients.
[b]Based on data from 26 patients.

skin structure infection and respiratory tract infection were 24.7 ± 18.2 days and 18.2 ± 9.1 days, respectively. The mean interval from the date of hospitalization to the initiation of quinupristin–dalfopristin was *c.* 3 weeks.

Of the 27 clinically and bacteriologically evaluable patients, the majority (23/27, 85.2%) received one or more concomitant antimicrobials including ciprofloxacin (10 patients), vancomycin (eight), ceftazidime (six), metronidazole (four) and rifampicin (three). Macrolides, penicillins, tetracyclines and sulfonamides were used in a small percentage of patients. Concomitant antimicrobials were generally directed at comorbid infections, or (in the case of vancomycin or rifampicin) continued despite prior failure. In some cases, the pathogen responsible for the concomitant infection was identified, and these included *Escherichia coli* (two patients), *Serratia* spp. (two), *Pseudomonas aeruginosa* (one) and coagulase-negative staphylococcus (one).

Table III contains a description of the types of infections treated with quinupristin–dalfopristin in this trial. Bone

Table III. Clinical, bacteriological and overall responses of patients receiving quinupristin–dalfopristin for MRSA infections

	All-treated[a] (n = 90) [number[b] (%, 95% CI[c])]		Clinically and bacteriologically evaluable (n = 27) [number[b] (%, 95% CI[c])]		
Infection Type	clinical success[d]	overall success[e]	clinical success[d]	bacteriological success[f]	overall success[e]
Bone and joint	31/40 (77.5, 64.6–90.4)	31/40 (77.5, 64.6–90.4)	9/13 (69.2, 44.1–94.3)	9/13 (69.2, 44.1–94.3)	9/13 (69.2, 44.1–94.3)
Skin and skin structure	14/15 (93.3, 80.6–106.0)	13/15 (86.7, 69.5–103.9)	5/6	5/6	5/6
Endocarditis	6/11 (54.5, 25.1–83.9)	6/11 (54.5, 25.1–83.9)	0/2	0/2	0/2
Respiratory	7/10 (70.0, 41.6–98.4)	4/10 (40.0, 9.6–70.4)	4/6	2/6	2/6
Central catheter-related bacteraemia	4/6	4/6	1/1	1/1	1/1
Bacteraemia of unknown origin	3/5	3/5	–	–	–
Intra-abdominal	4/5	4/5	1/1	1/1	1/1
Intravascular	3/4	3/4	–	–	–
Other infection type	2/2	2/2	1/1	1/1	1/1
Urinary tract	1/1	1/1	–	–	–
Overall total	68/90 (75.6, 66.7–84.4)	64/90 (71.1, 61.7–80.5)	20/27 (74.1, 57.5–90.6)	18/27 (66.7, 48.9–84.4)	18/27 (66.7, 48.9–84.4)

[a]Patients with indeterminate response are included in the denominator as failures.
[b]Patients are counted more than once if they were treated for more than one indication, except in the overall total.
[c]Percent and confidence intervals not shown if denominator is <10.
[d]Defined as a clinical response of cure or improvement.
[e]Defined as a clinical response of cure or improvement and a by-patient bacteriological response of eradication or presumed eradication.
[f]By-patient response, defined as a bacteriological response of eradication or presumed eradication, combining responses for the primary infection site(s) and the blood, if appropriate.

and joint infections constituted 40/90 (44.4%) and 13/27 (48.1%) of the all-treated and clinically and bacteriologically evaluable patient populations, respectively. These included osteomyelitis (n = 24), prosthetic joint infection (6), septic arthritis (6) and post-surgical mediastinitis (4). Skin and skin structure infections made up 15/90 (16.7%) and 6/27 (22.2%) of patients in each population, respectively. Respiratory tract infections [10/90 (11.1%) and 6/27 (22.2%), respectively] included pneumonia (n = 8) and pleurisy (2). As previously stated, each patient required a baseline culture positive for MRSA to be included in the evaluation. *Staphylococcus epidermidis* and vancomycin-resistant *E. faecium* were also isolated as a causative pathogen in one patient each. MRSA bacteraemia was identified in 43 patients (47.8%) in the all-treated group. Of patients clinically and bacteriologically evaluable, MRSA was isolated from blood cultures of patients with bone and joint, respiratory tract, and skin and skin structure infections, central-catheter-related bacteraemia and endocarditis.

Response rates by population (clinical and bacteriological) are also described in Table III. The clinical success rate (cure or improvement) across all indications was 75.6 and 74.1% in the all-treated and clinically and bacteriologically evaluable populations, respectively. Clinical success rates in patients with bacteraemia were slightly less (70.5 and 55.6%, respectively). Overall success rates for all indications were 71.1 and 66.7%, respectively. The overall success rates appeared lower in patients with respiratory tract infection (40.0 and 33.3%, respectively) than their corresponding clinical success rates (70.0 and 66.7%, respectively). Patients with endocarditis also had a lower overall success rate in the all-treated patient population (54.4%), while neither of the two endocarditis patients who were bacteriologically evaluable had an overall favourable outcome.

The clinical responses were also determined for all-treated and evaluable patients according to resistance markers for MLS_B antibiotics, and are summarized in Table IV. Although numbers are small for two groups, the presence of the MLS_BC phenotype did not appear to affect the clinical response.

There were 24 (25.8%) deaths during the study, sepsis being the most common cause (11.8%). Twenty-seven (29.0%) patients reported clinical adverse events considered by the investigator to be possibly or probably related to quinupristin–dalfopristin (Table V). The most common related clinical adverse events were arthralgia (10.8%), myalgia (8.6%), nausea (8.6%) and rash (6.5%). Twenty patients (21.5%) discontinued treatment prematurely due to a related adverse clinical event. The incidence of infusion-related venous intolerance (including phlebitis) was not measured in this study, since patients generally received therapy by central venous access. Serious adverse laboratory events occurred in eight patients (8.6%). The most frequent serious adverse laboratory events associated with blood chemistry were abnormal blood creatinine (4.3%) and abnormal blood urea nitrogen (3.2%); the most frequent of those associated with haematology were abnormal haemoglobin (4.3%), haematocrit (3.2%), red blood cells (3.2%) and white blood cells (3.2%). None of the serious adverse laboratory events was considered by the investigator to be related to quinupristin–dalfopristin. Three patients discontinued due to adverse laboratory events, which in two cases were related to quinupristin–dalfopristin.

Superinfection involving a new Gram-positive pathogen occurred in five patients in the all-treated group. The superinfecting organisms were coagulase-negative staphylococci (two patients), *E. faecalis* (two), and both vancomycin-resistant *E. faecium* and *E. faecalis* (one). Two isolates were tested for susceptibility to quinupristin–dalfopristin. One coagulase-negative streptococcus isolate was found to be susceptible, and one *E. faecalis* isolate was resistant. However, the consequences of superinfection on the microbiological response of the initial infection could not be determined, since none of these patients was considered bacteriologically evaluable.

Table IV. Clinical response by resistance marker of patients receiving quinupristin–dalfopristin for MRSA infections

Resistance marker	All-treated (n = 90)[a]	Clinically and bacteriologically evaluable (n = 27)[a]
MLS_BS[b]	2/2 (100)	–
MLS_BI[c]	3/6 (50.0)	2/4 (50.0)
MLS_BC[d]	43/55 (78.2)	11/12 (91.7)
MLS not specified	20/27 (74.1)	7/11 (63.6)
Total	68/90 (75.6)	20/27 (74.1)

[a]Values given are number (%) of patients.
[b]Macrolide–lincosamide–streptogramin type B susceptible (MLS_BS).
[c]Macrolide–lincosamide–streptogramin type B inducibly resistant (MLS_BI).
[d]Macrolide–lincosamide–streptogramin type B constitutively resistant (MLS_BC).

Table V. Adverse clinical events[a] (incidence >2%) related[b] to administration of quinupristin–dalfopristin for MRSA infections (n = 93)

Adverse event	Incidence (n = 93)[c]	Leading to treatment discontinuation (n = 93)[c]
Arthralgia	10 (10.8)	2 (2.2)
Myalgia	8 (8.6)	3 (3.2)
Nausea	8 (8.6)	1 (1.1)
Rash	6 (6.5)	5 (5.4)
Vomiting	3 (3.2)	1 (1.1)
Anorexia	2 (2.2)	–
Facial oedema	2 (2.2)	1 (1.1)
Pain	2 (2.2)	–
Fever	2 (2.2)	3 (3.2)
Metabolic/nutritional disorder	2 (2.2)	–
Nervous system disorder	2 (2.2)	2 (2.2)
Pruritis	2 (2.2)	–
Total[d]	27 (29.0)	20 (21.5)

[a]Exclusive of venous events.
[b]Judged by the investigator to be possibly or probably related to quinupristin–dalfopristin treatment.
[c]Values given are number (%) of patients.
[d]Patients having one or more adverse event counted only once.

Discussion

MRSA poses an increasingly serious health care problem in many parts of the world. Several surveillance studies have shown an increase in the prevalence of methicillin resistance among *S. aureus* isolates, although there is considerable variation between countries.[20,21] Among more than 10 000 recent *S. aureus* isolates from across the United States and Canada, the incidence of oxacillin/methicillin resistance was 41.0–43.7%, depending upon susceptibility testing methods.[4]

Several studies have reported increased morbidity and mortality associated with MRSA compared to methicillin-susceptible *S. aureus* (MSSA) infections. For example, the European Prevalence of Infection in Intensive Care Study, involving >10 000 patients from 1417 intensive care units in 17 Western European countries, found that patients with MRSA infections were less likely to survive than those with MSSA.[22] For lower respiratory tract infections, the risk of mortality was three times higher in patients with MRSA compared with those with MSSA. A case–control study of *S. aureus* primary bacteraemia in the USA concluded that MRSA infection resulted in an approximately three-fold increase in direct costs compared with MSSA.[23] Many MRSA strains are resistant to all clinically available antibiotics with the exception of the glycopeptides vancomycin and teicoplanin. In cases of treatment failure or intolerance to these agents, few proven alternative therapeutic options are available.

The *in vitro* activity of quinupristin–dalfopristin has been studied extensively.[4,9–14] Jones and colleagues[4] examined its activity against 10 216 clinical isolates of MSSA and MRSA from the USA and Canada. The MIC_{50} and MIC_{90} reported for quinupristin–dalfopristin for MRSA were 0.5 and 1.0 mg/L, respectively, and did not differ significantly from those reported in methicillin-susceptible isolates. Over 99% of these isolates were considered to be susceptible to quinupristin–dalfopristin. Similar MIC_{50} and MIC_{90} values have been reported recently in a study of 251 MRSA isolates.[10] A worldwide evaluation of MRSA susceptibility to quinupristin–dalfopristin has shown *in vitro* resistance rates of <1%.[14] MRSA isolates with reduced susceptibility to vancomycin have also been reported to be susceptible to quinupristin–dalfopristin *in vitro*.[13,24]

Previously published data regarding the use of quinupristin–dalfopristin in the treatment of MRSA infections are limited. Successful outcomes were reported in three of nine patients with catheter-related bacteraemia caused by *S. aureus* in a phase II dose-finding trial of either 5 or 7.5 mg/kg quinupristin–dalfopristin administered every 8 h.[25] However, it was unclear from this report how many of these were MRSA. In a comparative study involving quinupristin–dalfopristin in the treatment of hospitalized patients with complicated skin and skin structure infections, only nine patients assigned to the quinupristin–dalfopristin treatment group had MRSA infection.[26] A bacteriological success rate of 77.8% was reported in these patients, with an overall response rate for all infections caused by *S. aureus* in this study of 70/109 (64.2%). The efficacy rate for quinupristin–dalfopristin in combination

with aztreonam for nosocomial pneumonia caused by MRSA was 6/20 (30.0%), compared with 8/18 (44.4%) for patients treated with a combination of vancomycin plus aztreonam.[27] However, these results should be interpreted cautiously because of the small number of patients. The bacteriological success rate for patients with *S. aureus* bacteraemia in global phase III studies of quinupristin–dalfopristin has been reported to be 8/14 (57.1%).[28]

In the present study, quinupristin–dalfopristin therapy was associated with a satisfactory overall response of 71% in the all-treated population and 67% in the evaluable population. Such response rates must be interpreted in light of the severity of illness, the high prevalence of significant comorbidities, and the study population which included only treatment failures or treatment-intolerant patients. Our experience is comparable to that previously reported for treatment with either vancomycin or teicoplanin. Average clinical response rates of *c.* 78% for vancomycin and teicoplanin were reported in a meta-analysis of 11 randomized trials, involving over 1000 patients, published between 1987 and 1995.[29] For those patients that could be identified as having deep-seated infection, including bone and joint infection, endocarditis and central catheter infection, the response rates were much lower than for the patient population as a whole (44% when vancomycin and teicoplanin results were combined). The highest clinical response rates in the present study were observed for patients with skin and skin structure infection, urinary tract infection, and 'other' infections. The clinical response rate for bacteraemic patients in the all-treated population was only slightly lower than that for the entire population. Lower success rates were documented for patients with endocarditis and bacteraemia of unknown source. For patients with endocarditis, only about half in the all-treated population were considered to be clinical successes. Furthermore, both of the bacteriologically evaluable patients with endocarditis were clinical failures. Published data regarding the successful use of quinupristin–dalfopristin in the treatment of MRSA endocarditis are limited to a single case report.[30] Our limited experience suggests that quinupristin–dalfopristin as monotherapy may not be able to consistently sterilize cardiac vegetations, but further data are needed.

The relatively long and highly variable interval between hospitalization and initiation of quinupristin–dalfopristin therapy in this study probably reflects both the nosocomial acquisition of infection and the initiation of quinupristin–dalfopristin therapy after one or more treatment failures with other antibacterial agents. The data regarding community-acquired as opposed to nosocomially acquired MRSA infections were not specifically collected in this study and thus cannot be addressed.

Response rates in our study were apparently not affected by MLS_B resistance phenotype, suggesting that the efficacy of quinupristin–dalfopristin was not significantly reduced by the presence of resistance to streptogramin type B antibiotics. This result is consistent with *in vitro* findings that the synergism between the two components of quinupristin–dalfopristin is retained for bacterial strains that show resistance to the quinupristin component on its own.[31] Although *S. aureus* strains with MLS_B resistance are still susceptible to quinupristin–dalfopristin, its bactericidal activity may be affected by the MLS_B resistance phenotype.[32] Quinupristin–dalfopristin has been reported to show reduced *in vitro* bactericidal activity against *S. aureus* strains that are constitutively resistant to macrolides (MLS_BC phenotype).[33] This finding might be significant for treating indications such as endocarditis when bactericidal activity is important. In recent *in vivo* rat models of endocarditis, optimized to closely simulate human pharmacokinetics, with erythromycin-resistant MRSA, combination therapy with quinupristin–dalfopristin plus cefepime and quinupristin–dalfopristin plus cefamandole was superior to either antibiotic alone,[34–36] but clinical data are not available.

The adverse event profile is similar to that reported in other quinupristin–dalfopristin emergency-use patients.[37] A substantial majority of the adverse events observed in the present study reflect the high severity of illness in the population studied. Adverse clinical events of note included nausea, arthralgia and myalgia. The aetiology of these arthralgias and myalgias is presently under investigation, but they are reversible upon treatment discontinuation. In earlier comparative trials of quinupristin–dalfopristin, a high proportion of patients receiving the drug via peripheral venous catheters experienced local adverse events, and administration by a central venous route has therefore been recommended.[37] Venous adverse events were not analysed in the present study because the great majority of patients received the study medication via a central catheter.

In summary, the data from this study indicate that quinupristin–dalfopristin is a therapeutic option for patients with certain MRSA infections, including strains with the MLS_BC phenotype. The presence of multiple comorbidities in many patients, combined with the mortality rate of 25.8% in the all-treated population, illustrates the severity of illness of the population treated. Furthermore, all patients had failed, or were judged not suitable for, alternative antibiotic therapy, and thus the response rates obtained under such circumstances for selected infections were excellent. Efficacy rates for skin and skin structure and for bone and joint infections were generally favourable. However, response rates were lower for patients with endocarditis, in which rapidly bactericidal therapy may be needed; the effectiveness of quinupristin–dalfopristin against MRSA strains of the MLS_BC phenotype for this important infection remains to be fully assessed. Combination antimicrobial therapy may prove necessary in endocarditis patients. Additional comparative clinical trials with vancomycin and newer classes of agents with activity against Gram-positive pathogens are needed

to further define the role and impact of quinupristin–dalfopristin in the treatment of MRSA infections.

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Appendix

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