Quinupristin/dalfopristin: the first available macrolide-lincosamide-streptogramin antibiotic

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Quinupristin/dalfopristin (Synercid, Rhone-Poulenc Rorer, Collegeville, Penn) is a member of the macrolide-lincosamide-streptogramin class of antibiotics. This new drug is a combination of 2 products derived from pristinamycin. The product is provided as a 30:70 ratio of quinupristin (pristinamycin I A, a group B streptogramin) and dalfopristin (pristinamycin II A, a group A streptogramin) (1, 2).

The agent was approved by the US Food and Drug Administration in the second quarter of 1998 and is now available from the manufacturer. The delay was due in part to the complicated and time-consuming manufacturing process that takes place in 4 different manufacturing facilities worldwide and requires approximately 9 months to complete (3). Quinupristin/dalfopristin received approval for use in adults for the treatment of infections caused by susceptible strains of vancomycin-resistant *Enterococcus faecium* (VREF) and for the treatment of complicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible) or *Streptococcus pyogenes* (4).

PHARMACOLOGY

The genus *Streptomyces* produces 2 streptogramins, A and B. Each type inhibits bacterial cell growth and is classified as a bacteriostatic agent. It is thought that group A streptogramins, such as dalfopristin, block substrate attachment to both the acceptor site and the donor site of the peptidyl transferase catalytic center, thereby inhibiting the elongation phase of ribosomal replication of gram-positive organisms. It has been further speculated that group B streptogramins, such as quinupristin, block peptide bond synthesis, which prevents the extension of polypeptide chains and promotes the detachment of incomplete protein chains. When combined, the 2 agents provide a synergistic effect that can be bactericidal in nature (5). Synergism is thought to occur as a result of conformational changes in the 50S ribosomal subunit created when the group A compounds attach. In addition, group A streptogramins exert their effects in the early stages of protein synthesis, whereas group B streptogramins are active in the later stages (6, 7).

Cell division of most gram-positive organisms halts when the combination is added to broth mixtures containing susceptible pathogens. Because the drug cannot permeate gram-negative cell wall structures, most bacteria of this type are resistant to this combination antibiotic preparation (5).

PHARMACOKINETICS

Rat, monkey, and human models were used to elucidate the pharmacokinetic parameters of quinupristin, dalfopristin, and a combination of the 2 agents. Oral absorption is minimal, and thus the combination preparation is given as an intravenous infusion. When administered as a 1-hour infusion to healthy volunteers, the maximum blood concentration ($C_{\max}$) of quinupristin/dalfopristin ranged from 0.95 mg/L to 24.2 mg/L. The combination exhibited a linear relationship between dose and $C_{\max}$; at higher doses, the drug was present up to 6 hours after the infusion was completed (8–10).

The drug is distributed extensively to tissues and penetrates well in the liver, kidney, spleen, blood, bone marrow, salivary glands, adrenals, and the intestinal contents. Protein binding is thought to be 11% for quinupristin and 26% for dalfopristin. Metabolism of quinupristin was not observed in the models tested. Dalfopristin metabolized extensively to an active component in the liver via glutathione conjugation. The plasma half-life is thought to be 0.1 to 1.5 hours. A postantibiotic effect was anticipated with this drug and has been confirmed in vitro by various researchers. This phenomenon could explain how a drug with a relatively short half-life can provide bactericidal effects when administered every 8 to 12 hours. Elimination occurs mainly in the bile and feces and, to a lesser extent, in the urine (8–10).

SPECTRUM OF ACTIVITY AND RESISTANCE

Quinupristin/dalfopristin has shown bacteriocidal activity against methicillin-susceptible strains of *Staphylococcus aureus* and against *Streptococcus pyogenes*. The drug has displayed only bacteriostatic activity against vancomycin-resistant and multi-drug-resistant strains of *E. faecium* (4). Aeschlimann and Rybak speculate that a bactericidal effect would be exhibited by quinupristin/dalfopristin against *E. faecium* based on their research conducted in vitro; however, this has not been confirmed clinically (8). Susceptibility testing with this agent has also confirmed in vitro activity against *Corynebacterium jeikeium*, methicillin-resistant *Staphylococcus aureus*, methicillin-resistant *Staphylococcus epidermidis*, and *Streptococcus agalactiae*; however, this activity cannot be translated to an appropriate clinical application due

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to the lack of prospective trials in situations involving these pathogens (8). Additionally, the drug has not demonstrated activity against *E. faecalis* (4, 8–16).

Minimum inhibitory concentration (MIC) breakpoints for *E. faecium*, *Staphylococcus* spp., and *Streptococcus* spp. (excluding *Streptococcus pneumoniae*) have been established using standardized techniques and are as follows: ≤ 1.0 $\mu\text{g/mL}$ interpreted as susceptible, 2.0 $\mu\text{g/mL}$ interpreted as intermediate, and ≥ 4.0 $\mu\text{g/mL}$ interpreted as resistant (8–16).

The emergence of resistant pathogens has been cited in the literature. Chow et al report the development of a resistant *E. faecium* sample after a 10-day course of therapy with quinupristin/dalfopristin (17). The organism was isolated from a blood culture that was drawn 7 days after the end of therapy. The organism was originally considered sensitive but at that point in time was determined to be resistant.

ADVERSE EFFECTS AND TOXICITIES

A safety evaluation was conducted as part of the project coordinated by the Synercid Skin and Skin Structure Infection Group (18). All patients who received at least 1 dose of drug were included in this portion of the study's evaluation. Reportable adverse events were classified to describe the likelihood that the drug was the causative agent (probable, possible, remote, or none) and the severity of the event (mild, moderate, or severe).

Results were reported separately for venous as opposed to all other clinical adverse events. Venous events were defined as atrophy, edema, hemorrhage, hypersensitivity, inflammation, thrombophlebitis, or pain at the site of infusion. The reported adverse event rate was 63% for those receiving quinupristin/dalfopristin and 54% for those receiving infusion of the comparator drug. Most adverse events from either group were classified as mild to moderate in severity. Events that could probably or possibly be linked to drug administration for either group that occurred $\geq 2\%$ of the time were tabulated. Nausea (6%), vomiting (4%), rash (3%), pain (3%), and pruritus (3%) were reported for patients receiving study drug. Statistical significance was seen for occurrences of nausea, vomiting, and pain compared with administration of comparator drug ($P \leq 0.05$). When considering adverse venous events, the occurrence rate was 66% for study drug vs 28% for comparator drug, which was also a statistically significant finding. Injection site pain and inflammation were the most commonly reported venous events and were classified as moderate to severe in nature. Further, the discontinuation of therapy due to an adverse venous event was higher for the quinupristin/dalfopristin group than for the comparator drug, 12% vs 2%, respectively.

Arthralgias and myalgias have been reported in patients receiving quinupristin/dalfopristin therapy. Reactions of this type were sometimes severe enough to require discontinuation of therapy.

The manufacturer's package insert suggests increasing the volume of final diluent as a possible way to alleviate problems associated with venous irritation. Inserting a central venous catheter or peripherally inserting a central catheter is suggested as an alternative as well. One final recommendation is to alter the infusion frequency to every 12 hours as a method to decrease the incidence of infusion-related adverse events (4, 19).

DRUG INTERACTIONS

Because quinupristin/dalfopristin significantly inhibits the cytochrome P450 3A4 isoenzyme, the potential for drug interactions is high. A formal study designed to test quinupristin/dalfopristin against drugs metabolized via this common pathway has not been conducted to date but is warranted. Published anecdotal reports are lacking as well (4).

DOSAGE

Quinupristin/dalfopristin is available only as an injectable formulation, with each single-use vial providing a total of 500 mg of active drug (quinupristin, 150 mg; dalfopristin, 350 mg). The reconstituted vial is compatible only in dextrose solutions and cannot be administered with saline-containing solutions of any kind. Subsequent line flushes must be made with saline-free solutions as well. Unopened vials of drug require refrigeration, and reconstituted vials should be used within 30 minutes. When mixed in a dextrose solution for infusion, the drug is stable for 5 hours at room temperature and 54 hours when refrigerated (2, 4).

The recommended dosage for patients with documented VREF is 7.5 mg/kg given by intravenous infusion over a 60-minute period, repeated every 8 hours until the infection has been eradicated and/or clinical symptoms have resolved. For the treatment of complicated skin and skin structure infections, the manufacturer's dosage recommendation is 7.5 mg/kg every 12 hours, for a minimum of 7 days. No dosage adjustments are necessary for elderly patients or patients with renal dysfunction. Dosage reductions for patients with hepatic cirrhosis are likely to be needed; however, specific recommendations are not available at this time (2, 4).

CLINICAL EFFICACY

Vancomycin-resistant *E. faecium*

To date, no published results of comparative trials in the treatment of VREF with quinupristin/dalfopristin are available. Linden et al provide a description of compassionate-use experiences compared with historical treatment of VREF infections at their facility (20). Twenty patients received the study drug. To be included in the compassionate-use protocol, an adult man or nonpregnant woman had to have a positive culture growing *E. faecium* that displayed a vancomycin MIC > 8 mg/L resistant to all other appropriate agents and a quinupristin/dalfopristin MIC ≤ 2 mg/L. Additionally, the patient had to have 2 or more of the following: temperature $> 38^\circ\text{C}$ (100.4°F), white blood count $> 10 \times 10^3/\mu\text{L}$ (or left shift), heart rate > 100 beats/minute, respiratory rate > 20 breaths/minute or on a ventilator, blood pressure < 90 mm Hg or on vasopressor therapy, or an altered mental status. Patients received 7.5 mg/kg of study drug every 8 hours (20).

All patients had received prior antimicrobial therapy for at least 3 days when the study drug was initiated. Seven of the 20 quinupristin/dalfopristin patients were eventually discharged from the hospital; however, overall mortality was high in both groups. Sixty-five percent of the study-treated patients and 52% of the control patients died during the follow-up period. Undisputed clinical failure was documented in 25% of the patients who received the study drug. The authors of the report conclude that the lack of bactericidal activity limits the drug's application in situations where complete pathogen eradication is required.

Moellering et al summarize their experience with quinupristin/dalfopristin administered as part of a compassionate-use protocol (21). Inclusion criteria were consistent with those described above. Criteria were established to define which patient's data would be included in the clinical cure evaluations. These criteria mandated validation of VREF and defined parameters for the percentage of missed doses of study drug that were considered acceptable.

There were 193 patients who met the criteria for inclusion in the clinically evaluable portion of the data analysis. As can be seen from the data compiled in the *Table*, patients with deep wound infections, urinary tract infections, central catheter-related bacteremia, or bone and joint infections were most likely to benefit from therapy with the study drug.

It is unclear why patients from this study group responded better than those discussed previously. Perhaps it was the types of infections and severity of illnesses that were being treated in this group of patients compared with those in the earlier compassionate-use studies. This study identified the emergence of resistance to quinupristin/dalfopristin therapy over the course of the treatment period.

Complicated skin and skin structure infections

Data from 2 separate open-label trials, conducted at various sites worldwide, were analyzed and reported in a single publication. Both studies were phase III comparative trials designed to evaluate safety, efficacy, and tolerance of quinupristin/dalfopristin (18).

The first study was conducted at 40 sites in the USA and Puerto Rico. Enrollment and randomization of hospitalized adult patients with presumed complicated gram-positive skin or skin structure infections were conducted between February 1995 and April 1996. Criteria for enrollment included collection of a specimen for culture prior to initiation of either study drug or control drug. Patients with liver or kidney dysfunction (calculated creatinine clearance <30 mL/min) were excluded from the study. Additionally, those who were pregnant, those whose infection would require extensive surgical intervention, those who were immunosuppressed, and those who had received any other investigational agent within 30 days were excluded from the study patient population.

Patients assigned to the study drug received quinupristin/dalfopristin, 7.5 mg/kg, as a 1-hour infusion every 12 hours for 3 to 14 days. Those patients assigned to the control group received either oxacillin (2 grams every 6 hours) or vancomycin (1 gram every 12 hours) for 3 to 14 days. Vancomycin dosing adjustments were made in response to therapeutic blood level monitoring. The selection of control drug was determined by each site's investigators based on local susceptibility patterns. Study patients could receive concomitant antibacterial agents provided that they did not have in vitro activity against gram-positive pathogens.

Debridement and drainage were allowed, as well as wound cleaning, according to each hospital's local practice. Baseline clinical and microbiological assessments were made on day 4, at the end of the course of drug therapy, and 14 to 28 days after treatment completion.

The second study was conducted at 89 centers worldwide, including the USA, and ran from June 1995 to July 1996 (18).

Table. Percentage of success rates for the treatment of infections caused by vancomycin-resistant *E. faecium* classified by infection type*

Type of infection	No. of clinically evaluable infections	Success rate (%)
Deep wound infection	3	100
Central catheter-related bacteremia	14	85.7
Bone and joint infection	6	83.3
Urinary tract infection	23	82.6
Skin and skin structure infection	21	76.2
Respiratory tract infection	4	75
Intra-abdominal infection	68	64.7
Bacteremia of unknown origin	36	64.7
Intravascular infection, excluding endocarditis	3	33.3
Endocarditis	5	20

*Compiled from Moellering et al (21).

Enrollment and randomization were identical to those in the first study. The control drug in this study consisted of either cefazolin (1 gram every 8 hours) or vancomycin (1 gram every 12 hours), each for 3 to 14 days. Again, the choice was at the discretion of each center's investigator.

From both studies, a total of 450 patients received the study drug and 443 received a control drug regimen. From that population, 289 study patients and 273 control patients satisfied the specified criteria and were included in the clinical response analysis. Contrary to how the study was designed, these data were then reported for each trial separately. Regardless of this inconsistent method, a lower rate of clinical success was seen in the quinupristin/dalfopristin group compared with the control group (68% vs 71% in trial 1, 65% vs 68% in trial 2, study vs control drug, respectively). Success rates for treatment of polymicrobial infections accounted for the largest disparity between treatment regimens (57%, study group; 78%, comparator group). Quinupristin/dalfopristin provided equivalent coverage for monomicrobial infections overall. However, in trial 1, the quinupristin/dalfopristin treatment group did not perform as well against *Staphylococcus aureus*, whether the infection was monomicrobial or polymicrobial.

Authors cite 2 issues of study design as probable factors contributing to the outcomes of the 2 trials. First, the prohibition of concomitant use of agents with gram-positive activity was not considered to reflect actual clinical practice. Second, patients who experienced adverse effects of study drug and were therefore discontinued from the trial were considered clinical failures.

ECONOMIC ISSUES

The acquisition cost for each 500-mg vial is \$85.07. The dose for a 70-kg (156 lb) patient would be 525 mg, necessitating the use of 2 vials per dose. The total daily cost of therapy with this agent would be \$340 to \$510.

SUMMARY

Pathogens resistant to traditionally effective antimicrobial agents continue to pose a tremendous challenge in the treatment of infectious disease. The development of a new class of drugs that is effective against the evolution of multiresistant strains of gram-positive organisms is critical for the eradication of their corresponding life-threatening infections. The introduction of the macrolide-lincosamide-streptogramin class was met with eager acceptance; however, delays in production of the first agent, quinupristin/dalfopristin (Synercid), allowed the clinical evaluations of the product to identify limitations to its application.

Approved indications include the treatment of vancomycin-resistant *E. faecium* and the treatment of complicated skin and skin structure infections caused by *Staphylococcus aureus* and *Streptococcus pyogenes*. In vitro studies confirming the agent's spectrum are numerous; however, published controlled comparative trials are scarce. Most noteworthy is the need for comparative trials for the treatment of VREF infections. Additionally, the drug provides no coverage for *E. faecalis* infections, which are more prevalent at Baylor University Medical Center than those involving *E. faecium*.

Information on the side effects associated with the use of this drug causes concern, and many patients receiving the agent under compassionate-use protocols discontinued the drug due to adverse events. Arthralgia and myalgia pain was noted in patients receiving the drug at our facility. The pain was not relieved with the administration of analgesic medications and often resulted in discontinuation of the drug.

Limitations on the compatibility of the drug in solution pose tremendous challenges with administration of the drug. Because the reconstituted vial is only compatible in dextrose solutions, it cannot be administered with saline-containing solutions of any kind. Subsequent line flushes must be accomplished with saline-free solutions, which are not currently available.

Regardless, the agent will be needed to provide an option when traditional therapy has failed. Reports of resistance to this agent have already been cited in the literature, mandating that restrictions be placed on its use. The following are the only situations in which the agent should be used:

1. Clinically significant, documented, vancomycin-resistant *E. faecium* infections
2. Clinically significant, documented, methicillin-resistant *Staphylococcus* spp. infections that are not treatable with any other agent
3. Drug MIC ≤ 1.0 $\mu\text{g/mL}$ against the documented pathogen or MIC ≥ 1.0 $\mu\text{g/mL}$ if drug is used as a part of a combination drug regimen

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