Infections with vancomycin-resistant enterococci (VRE), especially Enterococcus faecium (VREF), have emerged as a significant problem among hospitalized patients. The occurrence of VRE infections in neutropenic patients is also disconcerting because most agents used as therapy, such as chloramphenicol, are only bacteriostatic and hence not usually effective in neutropenic patients (12).

Quinupristin-dalfopristin (Q-D) is a new antimicrobial agent of the streptogramin class that is active against most gram-positive organisms, except Enterococcus faecalis (3). The combination of Q-D plus doxycycline was found to be synergistic against VRE isolates (7). We therefore initiated a compassionate-use open trial of Q-D with minocycline (MIN) for the therapy of VRE infections in cancer patients to determine its efficacy and tolerability.

Patients. Between February 1994 and November 1998, 56 oncology patients infected with vancomycin-resistant enterococci (VRE) were treated with quinupristin-dalfopristin (Q-D) plus minocycline (MIN). Infections included bacteremia, urinary tract infection, pneumonia, and wound infection. The response rate was 68%, and the most frequent adverse event was arthralgia or myalgia (36%). Q-D–MIN is effective for VRE infection in cancer patients but is associated with a substantial frequency of arthralgia or myalgia.
Q-D was administered at a dose of 7.5 mg/kg of body weight every 8 h and MIN was administered at a dose of 100 mg every 12 h, both for a period ranging from 2 to 52 days (mean, 12 days). All patients who responded did so both clinically and microbiologically, with an overall response rate to Q-D–MIN of 68% (38 of 56 patients). The response rates for the 40 neutropenic patients and the 16 nonneutropenic patients were similar (65 versus 75%, P = 0.47). Of the patients that responded, the relapse rate was 15% (4 of 26) for neutropenic patients and 25% (3 of 12) for nonneutropenic patients (P = 0.65). The response rate for the patients with persistent neutropenia during the treatment course (21 patients) was 57%, while the response rate for the 35 patients who were nonneutropenic or recovered their neutrophil count was 74% (P = 0.18).

Twenty-six (65%) of the 40 patients with bacteremia, 7 of the 8 patients with urinary tract infections, 2 of the 3 patients with pneumonia, and 3 of the 5 patients with infections at other sites responded. Of the 34 primary bacteremia patients for whom stool culture was done, 16 (47%) were colonized. Only four patients were considered to have CVC-related VRE bacteremia. Three were neutropenic and responded to therapy and catheter removal, whereas one patient who was not neutropenic failed to respond. In this latter patient, the catheter was exchanged over a guide wire, which may account for the failure.

Most of the organisms causing infection were fully susceptible to Q-D (86%) and/or MIN (82%). Five organisms had intermediate susceptibility to Q-D, and three were resistant. Eight organisms had only intermediate susceptibility to MIN, and two were resistant.

The response rate for the 39 patients with infections caused by organisms susceptible to both Q-D and MIN was 69% compared to 63% for the 16 patients with infections caused by organisms susceptible to only one drug (Table 2). One patient with *E. faecalis* bacteremia responded to the combination of Q-D–MIN even though the organism was resistant to Q-D but susceptible to MIN. All three patients with mixed *E. faecium*-*E. faecalis* bacteremia responded to the combination therapy.

Myalgia and arthralgia were reported in 20 patients (36%), 17 of whom had leukemia. Other toxicities were abnormalities in liver function tests of four patients (7%), leukopenia in three (5%), and phlebitis in one (2%). A total of 41 patients died during the course of the study. VRE infection was considered the primary cause of death in 4 patients (7%) and was a contributing cause of death in another 13 (23%).

**Efficacy of Q-D.** Although Q-D is highly active in vitro against VREF, clinical studies have shown that when used alone it is associated with limited efficacy in immunocompromised patients (1). Wood et al. reported an overall response rate of 49% to Q-D among 65 patients of whom 38% were neutropenic and 35% had leukemia (C. A. Wood, E. A. Blumberg, A. E. Fuchs, A. Molvani, and H. D. Mandler, Program Abstr. 36th Annu. Meet. Infect. Dis. Soc. Am. 1998, abstr. 606 Fr, p. 190, 1998). In another report, Wood et al. reported a 14% rate of emergence of resistance to Q-D, which was associated with clinical and bacteriologic failure (C. A. Wood, E. A. Blumberg, A. E. Fuchs, A. Molvani, H. D. Mandler, J. Smith-Davis, and A. I. Hartstein, Program Abstr. 36th Annu. Meet. 1998, abstr. 607 Fr, p. 190, 1998).

A clinical and microbiological cure in response to the combination of Q-D–MIN was noted in our study at a frequency of 65% in neutropenic patients, including those with associated VRE bloodstream infections. Since the response rate in neutropenic febrile patients with bacteremia is reportedly lower than that of nonneutropenic patients with bacteremia (13), this response rate of 65% in a patient population consisting mostly of leukemia and bone marrow transplant patients seems favorable. In addition, there was no evidence of emergence of resistance to either Q-D or MIN among those patients with recurrence of the VRE infection. Nevertheless, in the absence of a control group, valid comparisons to prior studies are difficult and should be made with great caution.

There are reports to suggest that tetracyclines are effective for the treatment of VREF and that outcome could be improved by their addition to Q-D (4, 5, 7, 9, 11, 14). In our study, the addition of MIN may have improved the outcome in those patients with VRE infections resistant to Q-D. Future prospec-
Occurrence of adverse events. Myalgia and arthralgia were the leading adverse events associated with the use of Q-D and MIN in our study, occurring at a frequency of 36%. In a large prospective study of 396 patients treated with Q-D for VREF infection, arthralgia and myalgia occurred at a rate of 6.6 and 9.1%, respectively (10). However, the cohort was mostly non-oncological, with only 19% of the patients having underlying malignancies. In another study of 65 patients treated with Q-D, arthralgia and myalgia occurred at a rate of 26% and were found to be significantly associated with leukemia as a risk factor (H. D. Mandler, E. A. Blumberg, A. E. Fuchs, A. Molvani, and C. A. Wood, Abstr. 36th Annu. Meet. Infect. Dis. Soc. Am. 1998, abstr. 608 Fr, p. 190, 1998). In our study, of the 20 patients who had arthralgia and myalgia, 17 had leukemia. It is possible that cancer patients, particularly those with leukemia, are more prone to arthralgia and myalgia.

A combination of Q-D at 7.5 mg/kg every 8 h, and MIN at 100 mg every 12 h administered intravenously was found to be efficacious in the treatment of VRE infections in cancer patients. The efficacy was maintained in neutropenic patients with VREF bloodstream infections. Arthralgia or myalgia was reported in more than one-third of the patients but resolved upon completion of therapy.

Q-D was furnished by Aventis Pharmaceuticals (formerly Rhone-Poulenc Rorer) for this study.

REFERENCES