Treatment of Vancomycin-Resistant Enterococcal Infections in the Immunocompromised Host: Quinupristin-Dalfopristin in Combination with Minocycline

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Received 5 June 2000/Returned for modification 27 January 2001/Accepted 30 July 2001

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.

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 cancer patients with proven VRE infections were entered into the study. All subjects gave written informed consent to participate in the study, which was approved by our Institutional Review Board. VRE was isolated from at least one culture specimen from the site of infection from each patient. Infections were defined according to the criteria of the Centers for Disease Control and Prevention (2).

The patients’ histories and physical examinations were reviewed prior to entry into the study. Therapy was administered via a central venous catheter (CVC) in most patients. Liver function tests, including tests of bilirubin, alkaline phosphatase, alanine aminotransferase, and albumin, were performed on all patients in the week before therapy, midterm during therapy, and within 1 week after completion of therapy. Patients were monitored daily until the end of therapy and reevaluated 1 month after completion of therapy.

Microbiologic methods. Enterococci were identified initially in culture specimens based on colony morphology and Gram stain morphology. They were subcultured for final identification on Vitek GPI medium (BioMérieux Vitek, Hazelwood, Mo.). Testing of susceptibilities to various antibiotics was performed by the Kirby-Bauer disk diffusion method and the microdilution method in Mueller-Hinton broth according to the National Committee for Clinical Laboratory Standards (National Committee for Clinical Laboratory Standards, Subcommittee on Antimicrobial Susceptibility Testing, minutes of meeting, June 1998). Resistance to vancomycin was defined by a zone size of >16 mm by the Kirby Bauer method and by a MIC of >8 μg/ml by the microdilution method (National Committee for Clinical Laboratory Standards, minutes, June 1998). CVCs were cultured upon removal by the roller plate semiquantitative culture technique (6).

Definitions. The clinical and microbiological responses were defined as the resolution of all signs and symptoms related to the original infection and the eradication of VRE from the site of infection at the end of treatment. Relapse was defined as the return of signs and symptoms of infection and isolation of VRE from the site of infection within 1 month of follow-up from the end of treatment. Treatment failure was defined as no resolution or worsening of signs and symptoms of infection during treatment, coupled with persistent positive cultures for VRE. Neutropenia was defined as an absolute neutrophil count of <500 cells/mm³ and was considered persistent if it did not resolve during the course of therapy. VRE bacteremia was considered to be the primary cause of death if there were no other contributing causes. VRE infection was considered a contributing cause of death if other acute events could have contributed to the death.

Statistical analysis. Categorical variables were compared by the χ² test or the Fisher exact test. Statistical significance was defined as a P of <0.05. Fifty-six patients with VRE infection, 90% of whom had hematological malignancies, were included in the study, (Table 1). The mean age of the patients was 51 years (range, 7 to 86 years). The majority of patients (71%) had bacteremia. VREF accounted for 91% of the infections; E. faecalis and Enterococcus avium were each responsible for one infection. Three patients were infected with both E. faecium and E. faecalis.
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 every 8 h and MIN was administered at a dose of 100 mg every 8 h). According to William et al. (15), Or pure blood stem cell transplant.

There are reports to suggest that tetracyclines are effective 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-
tive studies should evaluate Q-D with and without MIN in immunocompromised cancer patients and compare its efficacy and safety to those of other available agents active against VRE, such as linezolid (8; M. C. Birmingham, C. R. Rayner, S. M. Flavin, A. K. Meagher, and J. J. Schentag. Abstr. 40th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 2238, p. 488, 2000).

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