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DAPTOMYCIN IN THE TREATMENT OF VANCOMYCIN-RESISTANT *ENTEROCOCCUS FAECIUM* BACTEREMIA IN NEUTROPENIC PATIENTS

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Abstract

Objective—Vancomycin resistant enterococcal (VRE) blood stream infection (BSI) in neutropenic patients is associated with poor outcome. We report our experience in treating VRE BSI in febrile, neutropenic patients with daptomycin, a recently licensed lipopeptide with bactericidal activity against VRE.

Patients and Methods—Patients with fever, neutropenia and VRE BSI were treated with more than one dose of daptomycin (either 6 mg/kg/day or 4 mg/kg/day) in an open label, emergency-use trial. Patients were then assessed for clinical and microbiological cures and survival. MIC's of isolates to daptomycin were determined.

Results—Nine febrile, neutropenic patients with VRE BSI received daptomycin. Four of 9 courses (44%) had clinical and/or microbiologic cure. Two of the 5 who failed cure died within 3 days of initiation of daptomycin. Five subjects survived to 30 days after the onset of BSI.

Conclusions—Use of daptomycin in neutropenic patients with VRE BSI deserves further study as a treatment for VRE BSI in neutropenic patients.

Keywords

daptomycin; VRE BSI; neutropenia

INTRODUCTION

We and others have shown that vancomycin resistant enterococcal (VRE) blood stream infection (BSI) is difficult to treat in the setting of hematologic malignancy, fever and neutropenia and/or hematopoietic stem cell transplantation (HSCT) and is an independent risk factor for death (1-3). At Tufts-New England Medical Center, VRE accounts for 10% of all blood isolates in hematopoietic stem cell transplantation recipients with BSI and is an

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independent risk factor for mortality [D. Poutsiaka, manuscript in preparation]. Historically such patients have very high in-hospital mortality and suppression of BSI has been difficult.

Daptomycin, a novel lipopeptide with bactericidal activity against VRE (4-6) was licensed in 2003 by the Food and Drug Adminstration (FDA) and in 2006 by the European Medicines Agency for the treatment of skin and soft tissue infections at a dose of 4 mg/kg/day and in 2006 by the FDA for the treatment of Staphylococcus aureus blood stream infections (BSI) and right-sided endocarditis at a dose of 6 mg/kg/day. However, there are limited data on the efficacy of daptomycin in the treatment of vancomycin-resistant enterococcal BSI. As part of an open label emergency use trial, we sought to assess the outcomes of neutropenic patients, including those undergoing HSCT, with VRE BSI treated with daptomycin.

PATIENTS AND METHODS

Patients

All patients receiving daptomycin resided on the Bone Marrow Transplant Units of the two participating institutions (Tufts-New England Medical Center, Boston Massachusetts and the University of Iowa Hospital, Iowa City, Iowa) from 2000 to 2002. After meeting entry criteria (see below), patients were enrolled in one of two open label emergency use protocols of daptomycin for the treatment of BSI with gram positive organisms. Inclusion criteria were ability to provide a signed and dated consent form, age of at least 18 years, if of childbearing age, a negative pregnancy test and the use of appropriate contraception, presence of neutropenia (absolute neutrophil count of less than $500/mm^3$) and inability to receive linezolid due to neutropenia, as judged independently by the patient's care providers. Exclusion criteria were weight greater than 150 kg or less than 50 kg; pregnancy or lactation; preexisting condition associated with rhabdomyolysis; creatine phosphokinase 2.5 times greater than the upper limit of normal; central nervous system or pulmonary infection as the source of BSI; serious allergic or other adverse effect due to daptomycin; and exposure to any other investigational agent other than daptomycin in the prior 30 days. Creatine phosphokinase was measured at least weekly during daptomycin administration. Bacteremia was defined as the isolation of VRE from two or more blood cultures (7). Cultures were obtained through central venous catheters or by venupuncture in response to an indication of infection, usually fever. Data were collected in a prospective fashion. Informed consent was obtained. This protocol was approved by the Institutional Review Boards of the respective institutions.

Vancomycin minimal inhibitory concentrations (MIC) were determined by broth dilution (5). Ampicillin MIC were determined by the Vitek automated system (bioMerieux, Inc, Durham, NC). Daptomycin MIC were determined by broth microdilution using Mueller-Hinton broth containing calcium chloride, final concentration, 50 micrograms/ml (5).

Daptomycin Administration

Daptomycin was administered using one of two dosing regimens according to the open label emergency use protocol as determined by the sponsor: Protocol A: 4 milligrams (mg)mg/kg iv every 24 hours or Protocol B: initial loading dose of 6 mg/kg intravenously, followed by 3 mg/kg iv every 12 hours or 6 mg/kg iv every 24 hours. When necessary, doses were adjusted for renal insufficiency.

Outcomes

Patients were observed for 30 days after the onset of VRE bacteremia for the following outcomes: *clinical cure*: Resolution of signs and symptoms of infection after discontinuation of daptomycin without recurrence for the duration of the 30 day observation period ; *microbiologic cure*: lack of positive blood cultures for VRE at least 12 days after cessation of

daptomycin; *microbiologic failure*: positive blood cultures obtained on therapy necessitating a change in treatment, or positive blood cultures obtained after discontinuation of therapy; *death*.

RESULTS

Results

Nine patients with neutropenia and one episode each of VRE BSI were assessed in this study. All blood isolates but one were *Enterococcus faecium*. Vancomycin-resistant *E. faecalis* was isolated from the blood of Subject 8. The source of bacteremia was unknown for all patients, except subject 3 who had subclavian vein septic thrombophlebitis. Table 1 displays clinical characteristics of the patients, details of the treatment schedule and microbiological data. All isolates of VRE were susceptible to daptomycin and resistant to ampicillin (median MIC 128 ug/ml, range 64-128 ug/ml). Two subjects with normal renal function (subjects 5 and 6) received 4 mg/kg/day of daptomycin per protocol of the sponsor. The remaining subjects were involved in the protocol specifying a dose of 6 mg/kg/day, which was reduced in the event of renal impairment (subjects 2, 3, 8 and 9).

Analyzed in an intention-to-treat approach, 44% of patients (four of nine) experienced cures. Two patients died 3 days after the initiation of daptomycin. In this intention-to-treat analysis, they are considered microbiological and clinical failures. All other patients received at least 9 days of daptomycin. Of 9 patients who underwent daptomycin therapy, four (44%) experienced microbiological and clinical cures after a median follow-up period of 16 days (range, 14-21 days) after the cessation of daptomycin. Of the three patients who survived more than 3 days after the initiation of daptomycin and experienced microbiological failure, two did so within one day of cessation of daptomycin. Those two patients had received daptomycin at doses adjusted for renal failure. Isolates from subjects 2, 3 and 9 obtained after the failure of daptomycin therapy had the following MIC's to daptomycin: subject 2: 2-4 ug/ml, subject 3: 2 ug/ml, subject 9: 2 ug/ml. These are identical or similar to the MIC's obtained prior to treatment (Table 1). Several blood cultures obtained from subject 8, deemed a daptomycin failure because of death 3 days after the initiation of daptomycin, remained negative after the initiation of daptomycin. Data on isolates from the remaining subject experiencing failure (subject 7) were not available.

All patients with microbiological and clinical cure were alive at 30 days after the onset of VRE BSI, as was one patient with treatment failure (five of nine, or 56%). Two subjects, both with treatment failure, died after cessation of daptomycin but within 30 days of the onset of VRE bacteremia. One (subject 3) was found to have subclavian vein thrombosis and the presence of gram positive cocci within the thrombus at autopsy. Of note, of the 4 patients receiving doses of daptomycin adjusted down from the 6 mg/kg/day dose due to renal failure, 3 died. Daptomycin was well tolerated in that no patient experienced an elevation in creatine phosphokinase.

DISCUSSION

VRE infection, including BSI, is an important infection in immunocompromised persons, including recipients of solid organ transplantation and those with fever and neutropenia (1,2, 8,9). This report illustrates the high rate of death in neutropenic patients with VRE BSI which has also been observed in other types of patients such as liver transplant recipients and hospitalized patients in general (9,10) In addition, this report describes, as others have, cases in which daptomycin was used to treat VRE bacteremia (11).

There is disagreement in the literature as to whether or not VRE BSI is a cause of death or associated with other factors that are the true cause of death. However, one recent study of febrile, neutropenic patients and one recent meta-analysis of varied patient populations, demonstrated an increased mortality due to VRE BSI (1,12). In another study, the attributable mortality of VRE BSI was calculated to be 23% in a population of patients in a tertiary care hospital (10). Our earlier study demonstrated a two-fold increase in mortality in patients with VRE infection compared to those with vancomycin-sensitive enterococcal infection, and showed that inappropriate therapy was a risk factor for death (3). This implies that infection with VRE contributed to death and that early appropriate therapy might be beneficial.

Daptomycin-associated microbiological and clinical cure rates for VRE BSI suggested by our observations might be improved upon by using a different dose of daptomycin or using daptomycin in combination with other antimicrobial agents. For example, the combination of daptomycin and gentamicin exhibited synergistic *in vitro* killing of enterococci, including VRE, and was more effective in the treatment of experimental enterococcal pyelonephritis and VRE endocarditis (13). In addition, daptomycin in combination with other antimicrobial agents has exhibited synergistic *in vitro* killing of enterococci, including VRE (14-17).

Prior to the introduction of agents active against VRE, a factor cited as a potential contributor to the excess mortality associated with VRE BSI was the lack of adequate therapy (9). However, in a recent study of the use of linezolid in treating resistant Gram-positive infections in neutropenic patients, where 83% of infections were caused by VRE and the site of 90% of infections was BSI, the clinical and microbiological cure rates in an intention-to-treat analysis were 57% and 45% respectively and the overall mortality rate was 67% (18). Similarly, in a study of the use of quinupristin-dalfopristin in treating VRE infections, of which 49% were BSI of unknown origin, 51% of neutropenic patients had a favorable clinical response, although the proportion of neutropenic patients with BSI was not available (19). The current study suggests that there might be a role for daptomycin in treating VRE BSI in this population of very compromised patients especially since daptomycin is a bactericidal agent, as opposed to the bacteriostatic agents, linezolid and quinupristin-dalfopristin. However, one important issue to recognize in the use of daptomycin is resistance to VRE, including that arising during therapy (20,21). This has been observed with other antibiotics, including linezolid (22-24). In the current study, the MIC's of isolates obtained at treatment failure were identical or similar to the MIC's of isolates obtained before the initiation of treatment. From this very limited data set, it is not possible to draw any conclusions about the development of resistance to daptomycin while on therapy.

This small observational study has a number of limitations. There are few patients included in the cohort, thus removing our ability to confidently estimate the efficacy of or analyze factors that might contribute to the success or failure of daptomycin therapy for VRE bacteremia. Another limitation is the variation in the dosing of daptomycin. This study was performed before the licensing of daptomycin in the United States and Europe and as part of two emergency treatment protocols that specified the dosing of daptomycin. Most subjects were treated with 6 mg/kg/day unless there was adjustment for renal failure. However, there were two subjects who were treated with a dose of 4 mg/kg, in the absence of adjustment for renal failure, a dose now considered inadequate for the treatment of gram positive bacteremia. In addition, it is unclear if the deaths of the 3 patients receiving renal dosing of daptomycin were due to the infection, inadequate dosing of daptomycin or other factors. Despite these limitations, we have shown that it is possible to successfully treat VRE bacteremia in neutropenic patients with daptomycin. Future studies of daptomycin, alone or in combination with other agents, will be necessary to further explore the use of this novel agent in the treatment of resistant gram positive infections including VRE, in neutropenic hosts.

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Table 1

Patient Characteristics

Subject	Age (Years)	Sex	Underlying Disease	Dose of daptomycin[1] (Protocol Designation)	Creatinine Clearance (Estimated)	Renal Dosing	Duration (days)	Central Catheter Removed?	MIC (ug/ml)	Micro Cure	Clinical Cure	Status 30 days after onset of bacteremia
1	49	M	AML, allogeneic HSCT	6 mg/kg once then 3 mg/kg every 12 hours (B)	> 70 cc/min	No	16	Y	0.5	Yes	Yes	Survived
2	70	M	AML	Course 1: 6 mg/kg once then 2.25 mg/kg every 18 hours. Course 2 (4 days after course 1): 6 mg/kg once then 2.25 mg/kg every 18 hours then 4 mg/kg every 24 hours (B)	20 cc/min	Yes	Course 1: 14 days Course 2: 15 days	Y	2-4	No	No	Survived
3	50	F	AML, allogeneic HSCT	6 mg/kg once then 4.5 mg/kg every 36 hours (B)	32 cc/min	Yes	10	Y	2	No	No	Died
4	66	M	AML	6 mg/kg every 24 hours (B)	> 70 cc/min	No	14	Y	2	Yes	Yes	Survived
5	61	M	MDS progressed to AML	4 mg/kg every 24 hours (A)	> 70 cc/min	No	14	--[2]	4	Yes	Yes	Survived
6	25	M	AML, allogeneic HSCT	4 mg/kg every 24 hours (A)	> 70 cc/min	No	10	N	2	Yes	Yes	Survived
7	58	F	AML, allogeneic HSCT	6 mg/kg once then 3 mg/kg every 12 hours (B)	> 70 cc/min	No	9	N	1	No	No	Died
8	38	M	AML, autologous HSCT	4 mg/kg every 24 hours (B)	<10 cc/min	Yes	3	NA[3]	2	No[4]	No[4]	Died
9	59	M	Lymphoma, CLL, allogeneic HSCT	6 mg/kg once then 4.5 mg/kg every 36 hours (B)	56 cc/min	Yes	3	NA[3]	2	No[4]	No[4]	Died

Abbreviations: M: male; F: female; AML: acute myelogenous leukemia; HSCT: hematopoietic stem cell transplantation; MDS: myelodysplastic syndrome; CLL: chronic lymphocytic leukemia; NA: not applicable.

[1] Subjects 5 and 6 were entered into Protocol A, which specified per the sponsor a dose of daptomycin of 4 mg/kg/day (normal renal function). All other subjects were entered into Protocol B, which specified a dose of 6 mg/kg/day, for normal renal function, with adjustments for impairment of renal function.

[2] Not applicable.

[3] Data not available.

[4] Died 3 days after the initiation of daptomycin.