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Clinical Failure in Patients Receiving Outpatient Parenteral Antimicrobial Therapy (OPAT) with Vancomycin Compared to Daptomycin or Ceftaroline

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Abstract

Purpose: The purpose of this study was to determine if vancomycin therapy was associated with higher rates of clinical failure compared to those treated with daptomycin or ceftaroline therapy (DCT) in patients receiving outpatient parenteral antimicrobial therapy (OPAT). Methods: This was a retrospective, single center cohort study including patients who received ≥ 7 days of OPAT with vancomycin, ceftaroline, or daptomycin from 01/01/2009 through 03/31/2016 at the VA Saint Louis Healthcare System. The primary outcome was clinical failure, defined as a composite of acute kidney injury (AKI), creatinine phosphokinase elevations ≥ 500 units/L, adverse drug events necessitating a change in therapy, readmission due to recurrence of infection, or reinitiation of antibiotics after discontinuation. Multivariate logistic regression was used to evaluate independent risk factors for clinical failure. Results: A total of 125 patients were included in the analysis – 72 receiving vancomycin and 53 receiving DCT. Baseline characteristics between groups were similar, except patients in the DCT group had a greater mean serum creatinine and a higher rate of CKD at baseline; 1.53 vs 1.23 (p=0.032) and 35.9% vs. 19.4% (p=0.04) respectively. Forty three percent (31/72) of patients receiving vancomycin developed clinical failure compared to 54.7% (29/53) of DCT patients (p=0.197). Of the secondary outcomes analyzed, only readmission due to recurrence was significant between groups (vancomycin vs. DCT) – 13.8% vs. 30.2% (p=0.026). None of the factors included in the regression analyses were found to be significant. Conclusions: Vancomycin was not associated with an increased risk of clinical failure when compared to DCT in patients receiving OPAT.

Keywords: Anti-Infective Agents; Home Infusion Therapy; Methicillin-Resistant Staphylococcus Aureus; Outpatient Parenteral Antimicrobial Therapy

Introduction

Outpatient parenteral antimicrobial therapy (OPAT) has been identified as an effective method of administering intravenous (IV) antibiotics to patients without keeping them in a supervised health care setting [1]. In the United States approximately 250,000 patients per year receive OPAT with a stated goal of reducing inconvenience, avoiding exposure to nosocomial pathogens, and decreasing hospitalization costs [2]. With the advent of Affordable Care Act, it is likely that OPAT will remain an important method of delivering therapy in the US. Because of the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in the US, vancomycin has

been a mainstay of many OPAT regimens [3]. Vancomycin remains the drug-of-choice for treating most MRSA infections, although vancomycin therapy is not without complication [4]. Vancomycin has long been associated with the development of nephrotoxicity, occurring in up to 43% of patients, as well as other adverse drug reactions (ADR) [3,5,6]. Additionally, in a recent study 18% of all patients receiving OPAT (26.3% of which were treated with vancomycin) developed an ADR while on therapy [3].

Because of the high rate of ADRs in patients receiving OPAT, and particularly those treated with vancomycin, many clinicians seek out safer, yet equally effective therapies. Daptomycin, a cyclic lipopeptide, and ceftaroline, a cephalosporin with coverage against MRSA, are newer agents that may have lower ADR-rates than vancomycin; however, there is a lack of published data comparing the efficacy and safety of these two agents to vancomycin in an OPAT setting [5-7].

The VA St. Louis Health Care System has a robust OPAT service that requires all VA patients treated with OPAT to be seen and followed by the infectious diseases service. Since 2009 all patients discharged from the hospital on OPAT have their weekly laboratory data monitored by the infectious diseases clinical pharmacy team, and weekly progress notes are left in the computerized patient record system (CPRS). Clinical pharmacists are responsible for making any dose changes necessary and ensuring that each regimen is safe and effective. The clinical pharmacists also maintain an extensive database of all OPAT patients. The purpose of the present evaluation is to determine if OPAT with vancomycin is associated with higher rates of clinical failure compared to OPAT with daptomycin or ceftaroline.

Methods

This was a single center, retrospective cohort study. Data were collected via chart review of medical records from patients who received vancomycin, ceftaroline, or daptomycin from 01/01/2009 through 03/31/2016 via the OPAT program at the VA St. Louis Healthcare System. Patients were identified through pharmacy OPAT records. Patients met inclusion criteria if they were between the ages of 18 and 89 years old and received vancomycin, ceftaroline, or daptomycin as an outpatient. Patients were excluded if they had no follow-up note written by clinical pharmacy or no infectious disease clinic appointment while on therapy, received OPAT at a skilled nursing facility or long-term care facility, or received <14 days of IV antibiotics total or <7 days of IV antibiotics as an outpatient. Patients in the vancomycin group were excluded if they received greater than 5 days of ceftaroline or daptomycin while hospitalized. Patients in the daptomycin or ceftaroline group were excluded if they received greater than 5 days of vancomycin while hospitalized. The research protocol was approved by the VA St. Louis Healthcare System Institutional Review Board (IRB).

The primary outcome was a composite of clinical failure defined by the presence of any of the following: (1) readmission due to recurrence of infection at the same anatomical site within 6 months for osteomyelitis or septic arthritis, or within 2 weeks for all other infections, (2) re-initiation of antibiotics within 6 months of end of therapy for osteomyelitis or septic arthritis, or within 2 weeks for all other infections, (3) development of acute kidney injury (AKI) while on therapy (defined as an absolute increase of serum creatinine (SCr) of ≥ 0.3 mg/dL from therapy initiation) , (4) creatine phosphokinase (CPK) elevation greater than 500 units/L (regardless of symptoms) while on therapy, (5) any other adverse drug event necessitating a change in therapy. Each individual component of the composite endpoint was evaluated as secondary endpoints.

An additional secondary endpoint was to determine factors associated with clinical failure. Univariate analysis and multivariate logistic regression were utilized to identify if vancomycin was independently associated with increased rates of clinical failure in patients who received OPAT during the study period. The univariate model included treatment group (vancomycin versus daptomycin or ceftaroline), creatinine clearance (CrCl) (> or ≤ 50 mL/min), length of therapy (> or ≤28 days), age (< or ≥ 65), concomitant antibiotics, and the presence of comorbid conditions such as diabetes mellitus, peripheral vascular disease (PVD), chronic kidney disease (CKD), or immunocompromising conditions (defined as a severe combined primary immunodeficiency disorder identified on the patient's problem list, receiving cancer chemotherapy one month prior to OPAT initiation or at any point through the end of treatment, receiving immunosuppressive pharmacotherapy (with mycophenolate, cyclosporine, tacrolimus, sirolimus, everolimus, azathioprine, or 6-mercaptopurine) one month prior to OPAT initiation or at any point through the end of treatment, CD4 T-lymphocyte count <200 cells/mm^3 within one year prior to OPAT initiation or at any point during therapy, daily corticosteroid therapy with a dose ≥ 20mg of prednisone or equivalent for ≥14

days within one month prior to OPAT initiation or at any point during therapy, or receipt of adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, or rituximab one month prior to OPAT initiation or at any point during therapy).

Statistical Analysis

To achieve a power of 80%, assuming an overall treatment failure rate of 20% and a 15% difference between groups, with a two-sided α value of 5%, a sample size of 88 patients in each group was required. The primary outcome of clinical failure rates between treatment groups was determined via a Chi-squared test. Each individual component of the composite endpoint was evaluated as a secondary endpoint using a Chi-squared test. Descriptive statistics were used to characterize baseline characteristics of the cohort groups. Chi-squared tests were used for categorical variables and independent t-test or Wilcoxon-ranked sum test for continuous variables as appropriate. A univariate analysis and multivariate logistical regression were used to identify factors independently associated with clinical failure. All factors with a $p<0.2$ in the univariate model were included in the multivariate regression. Significance for the other variables was determined using a two-side alpha of 0.05. Statistical analysis was conducted using IBM-SPSS version 22.0 (IBM Corp., Armonk, NY).

Results

One hundred twenty-five patients were included in the final analysis, 72 receiving vancomycin and 53 receiving daptomycin or ceftaroline therapy (DCT). Baseline characteristics were similar between groups. However, patients in the DCT group had a greater mean SCr and a higher rate of CKD at baseline; 1.53 vs 1.23 (p=0.032) and 35.9% vs. 19.4% (p=0.04) respectively. Rates of diabetes mellitus, PVD, and immunocompromising conditions were not significantly different between groups. More patients in the vancomycin group were on an angiotensin converting enzyme (ACE) inhibitors and statins at baseline; 44% vs. 22% (p=0.030). See Table 1 for all characteristics.

Characteristics at Initiation	Vancomycin Therapy (N=72)	Daptomycin or Ceftaroline Therapy (N=53)	P-value
Age in years (mean (± SD))	62.8 (± 8.55)	60.2 (± 9.16)	0.097
Weight in kilograms (mean (± SD))	98.94 (± 26.62)	99.92 (± 28.19)	0.982
Comorbidities			
Diabetes [% (n)]	54.1 (39)	67.9 (36)	0.121
Peripheral Vascular Disease [% (n)]	33.3 (24)	28.3 (15)	0.548
Immunocompromised [% (n)]	9.7 (7)	11.3 (6)	0.772
Chronic Kidney Disease [% (n)]	19.4 (14)	35.8 (19)	0.04
Laboratory Parameters			
Serum Creatinine at initiation, mg/dL (mean (±SD))	1.23 (± 0.61)	1.53 (± 0.94)	0.032
Platelets, cells/mm3 (mean ± (SD))	259.2 K (± 110.4 K)	272.9 K (±118.1 K)	0.507
WBC[a], cells/mm3 (mean ± (SD))	10.4 K (± 5.6 K)	9.7 K (± 4.3 K)	0.477
Neutrophil % (mean ± (SD))	66.1 (±16.4)	66.2 (± 13.8)	0.972
Medications			
ACE[b] inhibitor [%(n)]	61.1 (44)	41.5 (22)	0.03
ARB[c] [%(n)]	4.2 (3)	11.3 (6)	0.126
Diuretic [%(n)]	48.6 (35)	41.5 (23)	0.563
NSAIDs[d] [%(n)]	19.4 (14)	7.5 (4)	0.074
Statins [%(n)]	61.1 (44)	41.5 (22)	0.03
Fibrates [%(n)]	4.2 (3)	1.9 (1)	0.637

Additional Antibiotic Therapy [%(n)]	76.4 (55)	73.6 (39)	0.898
Piperacillin/tazobactam [% (n)]	19.4 (14)	7.5 (4)	
Cefepime ± metronidazole [%(n)]	25 (18)	13.2(7)	
Ertapenem [%(n)]	9.7 (7)	20.7 (11)	
Duration of Therapy			
Duration of Outpatient Therapy, days (mean (± SD))	28.5 (± 15.1)	31.1 (± 14.9)	0.339
Total Duration of Therapy, days (mean)	35.8 (± 15.3)	37.9 (± 17.1)	0.473

Table 1: Baseline Characteristics.
[a]WBC: white blood cell count
[b]ACE: angiotensin converting enzyme
[c]ARG: angiotensin receptor blocker
[d]NSAID: non-steroidal anti-inflammatory drug

Thirty-six percent of patients (26/72) treated with vancomycin and 60% (32/53) treated with DCT had a polymicrobial culture; MRSA accounted for 47% (16/34) and 56.7% (17/30) of all staphylococci isolated in the vancomycin and DCT groups respectively. Please see Table 2 for selected causative organisms and indications for treatment.

Characteristics at Initiation	Vancomycin Therapy (N=72)	Daptomycin or Ceftaroline Therapy (N=53)
Causative Organism		
Staphylococcus cultured [% (n)]	47 (34)	57 (30)
MRSA[a] [% (n/N)]	47 (16/34)	56.7 (17/30)
Enterococcus cultured [% (n)]	14 (10)	34 (18)
Polymicrobial culture [% (n)]	36.1 (26)	60.3 (32)
Indication		
Osteomyelitis [% (n)]	40 (29)	62 (33)
SSSI[b] [% (n)]	28 (20)	6 (3)
Bacteremia [% (n)]	6 (4)	6 (3)
Joint infection [% (n)]	6 (4)	0 (0)
Pneumonia [% (n)]	6 (4)	0 (0)
UTI[c] [% (n)]	4 (3)	8 (4)
Other [% (n)]	10 (8)	19 (10)

Table 2: Causative Organisms and Indication.
[a]MRSA: methicillin-resistant Staphylococcus aureus
[b]SSSI: skin and skin structure infection
[c]UTI: urinary tract infection

Forty three percent (31/72) of patients receiving vancomycin had clinical failure compared to 54.7% (29/53) of patients receiving DCT ($p=0.197$). Forty-eight patients in the DCT group were treated with daptomycin and 52% (25/48) of those patients developed clinical failure. Four of the remaining 5 patients treated with ceftaroline (80%) had clinical failure; three experienced ADRs requiring therapy discontinuation and 2 required readmission. Amongst the secondary outcomes analyzed, only readmission due to recurrence was significant between groups (vancomycin vs. DCT) – 13.8% vs. 30.2% ($p=0.026$); (Table 3).

	Vancomycin Therapy (n=72)	Daptomycin or Ceftaroline Therapy (n=53)	P-Value
Clinical Failure [% (n)]	43 (31)	54.7 (29)	0.197
AKI[a] [% (n)]	33.3 (24)	24.5 (13)	0.287
CPK[b] >500 [% (n)]	0 (0)	5.6 (3)	xxx
Other ADRs[c] [% (n)]	4.2 (3)	9.4 (5)	0.282
Alkaline Phosphatase elevation to >1000 U/L, n	0	1	
Leukonepnia, n	2	0	
Neutropenia, n	0	3	
Rash, n	1	0	
Readmission [% (n)]	13.9 (10)	30.2 (16)	0.026
Antibiotic Reinitiation [% (n)]	9.7 (7)	18.9 (10)	0.14

Table 3: Rates of Clinical Failure Between Groups.
[a]AKI: acute kidney injury
[b]CPK: creatine phosphokinase
[c]ADRs: adverse drug reactions

Sixty-two percent of patients (10/16) with MRSA found on culture and treated with vancomycin developed clinical failure versus 47% (8/17) treated with DCT. One patient treated with daptomycin did develop rhabdomyolysis that necessitated discontinuation. In the univariate analysis, only choice of therapy met criteria for inclusion in the multivariate regression model (please see Table 4 for the complete univariate analysis). In the multivariate model, vancomycin therapy was associated with a non-significant trend towards decreased rates of clinical failure; OR: 0.71 (95% CI 0.33 – 1.52; p=0.37).

Variable	Clinical Failure	No Clinical Failure	P-value
Vancomycin Therapy [% (n)]	43 (31/72)	57 (41/72)	0.197
Age >65 [% (n)]	53 (26/49)	46.9 (23/49)	0.363
CrCl[a] >50 mL/min [% (n)]	47.8 (45/94)	52.1 (49/94)	0.96
Therapy >28 days, [%(n)]	51.2 (43/84)	48.8 (41/84)	0.307
Diabetes [%(n)]	45.3 (34/75)	54.7 (41/75)	0.465
CKD[b] [% (n)]	51.1 (17/33)	48.5 (16/33)	0.638
ACEi[c] [% (n/N)]	43.9 (29/66)	56.1 (37/66)	0.337
ARB[d] [% (n/N)]	66.7 (6/9)	33.3 (3/9)	0.31
NSAIDS[e] [% (n/N)]	38.9 (7/18)	61.1 (11/18)	0.403
Statins [% (n/N)]	45.4 (30/66)	54.5 (36/66)	0.547

Table 4: Univariate Analysi.
[a]CrCl: creatinine clearance
[b]CKD: chronic kidney disease
[c]ACEi: angiotensin converting enzyme inhibitor
[d]ARB: angiotensin receptor blocker
[e]NSAID: non-steroidal anti-inflammatory drugs

Discussion

In this single-center, retrospective analysis of patients discharged with vancomycin, ceftaroline, or daptomycin as a part of an OPAT regimen there was no difference in clinical failure between patients treated with vancomycin versus those treated with DCT. The patients treated with DCT had higher SCr at therapy initiation and higher rates of CKD at baseline. Patients treated with DCT did have a significantly higher rate of readmission compared to vancomycin treated patients. Thirty-three percent of vancomycin treated patients developed AKI, but this was not significantly different from the DCT comparator group.

In the subset of patient that grew MRSA on culture, DCT was associated with a 47% rate of clinical failure compared to 62.5% in patients treated with vancomycin. In our multivariate regression model vancomycin treatment was associated with a non-significant trend towards decreased rates of clinical failure (OR: 0.71; 95% CI 0.33-1.52).

Our results differ from those reported in in the study by Shrestha et al.[7] This was a retrospective, propensity-score matched cohort study that examined adverse event rates, healthcare intervention, and healthcare utilizations during home infusion therapy with daptomycin and vancomycin in the OPAT program at the Cleveland Clinic. The study included 476 patients treated with either daptomycin or vancomycin (119 patients in the daptomycin group were matched to 357 patients in the vancomycin group) with the median patient age being 56 years and a median OPAT duration of 19 days. Antimicrobial adverse event rates per 1000 OPAT days was 3.2 in the daptomycin group versus 7.7 in the vancomycin group (RR: 0.38; 95% CI 0.15-0.86; P=0.02). Additionally, antimicrobial intervention rates were 5.6 and 27.1 per 1000 OPAT days, respectively (RR 0.21; 95% CI 0.11–0.36; P<0.001). Readmissions for worsening infection or treatment complication were not significantly different between daptomycin (5%) and vancomycin (7%) [7].

Some notable differences between the current study and the evaluation completed by Shrestha, et al. [7] is that the median age of the patients involved in our study is greater (56 versus 61.5 years) and the duration of therapy was longer (19 versus 36.9 days). Additionally, Shrestha, et al. [7] did not report a baseline CKD for either population and, as previously stated, our DCT had a higher rate of CKD. Also, our evaluation involved patients treated with ceftaroline, not just vancomycin and daptomycin. While it is difficult to quantify severity or complexity in patients receiving treatment for these infections, it appears that, because our population was not randomized or matched, our DCT patients were more complex, possibly contributing to the difference in results.

More recently a study was conducted by Shrank, et al. [8] that evaluated patients discharged on either vancomycin or daptomycin OPAT from a large, tertiary care medical center. The primary outcome was change or early discontinuation of antibiotic therapy due to an ADR >7 days prior to the anticipated therapy end date. Nineteen percent of patient treated with vancomycin and 7.6% treated with daptomycin achieved the primary outcome (P<0.01). Hospital readmissions 30 days following OPAT completion were relatively high in both groups (30.3 % for vancomycin and 32% for daptomycin) but not significantly different (P=0.9). In multivariate regression vancomycin therapy was identified as an independent predictor of developing and ADR (aOR: 3.71; 95% CI 1.64-8.40) [8].

Patients here were treated with a mean duration of therapy similar to those in our cohort (34.8 days); however, 49.6% received treatment in a long-term care facility. In the authors multivariate logistic regression long-term care was found to be an independent predictor of not developing an ADR (aOR: 0.53; 95% CI 0.29-0.95; P=0.03). Additionally, most of the ADRs associated with vancomycin (22%) were classified as other hypersensitivity reactions [8]. The fact that nearly half of the patients in this study received treatment while a supervised setting make it difficult to extrapolate the results of this evaluation to patients receiving OPAT at home.

Our evaluation has several inherent limitations. The retrospective, non-randomized nature of the cohort means there is potential for selection bias, and it seems probable that our DCT patients were more complex than the vancomycin patients, as demonstrated by the higher rates of CKD and higher SCrs at initiation. Additionally, we did not report vancomycin levels, but this was done intentionally as all patients involved in this study were closely monitored by our clinical pharmacy infectious diseases service and trough goals are evaluated and acted upon twice weekly. Also, only 5 patients in our analysis received therapy with ceftaroline. Finally, our study was underpowered and could be subject to type II error.

Some of the strengths include the VA's robust record system and the fact that all patients included in the cohort received all OPAT-related care through the VA St. Louis. Additionally, all patients were continuously monitored by the clinical pharmacy infectious diseases service, ensuring that weekly labs were drawn and monitored closely for safety and efficacy. Finally, all patients in this cohort were receiving OPAT at home and not in a supervised, continually monitored setting.

In conclusion, to our knowledge, this study represents the first published data to investigate rates of clinical failure between patients receiving daptomycin or ceftaroline to vancomycin for OPAT. Our data is interesting in that it does not demonstrate a significant benefit in reduction of ADRs or readmissions amongst

patients treated with DCT; however, our study did not meet its stated power. While the sample size was small, there may have been a benefit for DCT in patients with confirmed MRSA infection. Additionally, while the number of patients was very small [5], ceftaroline was associated with a high rate of ADRs. Most patients in this study were receiving OPAT for OM, and both groups had complicated past medical histories. We believe this population reflects real-world OPAT experience in elderly patients with complicated medical histories. It may also demonstrate that vancomycin, even in populations at risk for ADRs, can safely be administered in the home setting with close monitoring and structured follow-up. Further evaluation should be considered, paying particular attention to outcomes in patients with confirmed MRSA infections.

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