IDWeek 2015
#786

Dalbavancin: A Nationwide Outpatient Experience in Physician Office Infusion Centers (POICs)

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Abstract, revised

Background: Dalbavancin (DAL), a long-acting lipoglycopeptide, was recently approved for the treatment of acute bacterial skin and skin structure infections caused by susceptible gram-positive bacteria. With weekly administration, this agent may be beneficial for use in outpatient parenteral antimicrobial therapy (OPAT). We report clinical experience of OPAT use of DAL.
Methods: A multi-center, retrospective database review was conducted of all patients (pts) receiving DAL in 16 POICs from July 2014 through March 2015. Demographics, therapy characteristics, microbiology, adverse events (AEs), clinical outcomes and recurrences were evaluated.
Results: DAL was administered to 105 pts with 57 (54%) males and an overall mean age of 62 ± 16 years. Predominant diagnoses were cellulitis (45%), abscess (28%), osteomyelitis (12%), diabetic foot infection (11%) and implanted prosthetic device infection (4%). Forty nine pts (47%) had DAL therapy initiated in the POIC and 56 pts (53%) received DAL following hospitalization. Fifty-five pts (53%) received other intravenous antibiotics (IVABs) prior to treatment with DAL for a median of 5 days. Eighty seven pts (83%) received 2 doses of DAL, one week apart. Six pts (6%) received more than 2 doses. Infusions were administered by peripheral intravenous catheter in 84 pts (80%). Among 81 pts with available cultures, methicillin-resistant *S. aureus* was the most frequent pathogen (48%). Overall clinical success was reported in 88 of 105 pts (84%) with 52% cured and 32% improving. Reasons for failure included disease exacerbation in 6 pts (6%) and serious adverse events causing discontinuation of DAL in 10 pts (9%). Of these, 9 of 10 pts had hypersensitivity reactions following the first dose, the majority (67%) occurring in pts receiving other IVABs prior to DAL. Mild to moderate AEs were reported in 20 pts (19%), most commonly diarrhea (n=10), nausea (n=4), dizziness (n=4) and infusion site reactions (n=3). Disease recurrences within 60 days post DAL occurred in 7 of 82 evaluable pts (9%).
Conclusion: OPAT use of DAL in a physician office setting appears to be safe and effective. AEs were notable, including those requiring DAL discontinuation. The use of DAL may offer added safety and potential cost reductions in this setting due to avoidance of central line catheters. Additional studies are warranted.

Introduction

DAL is a lipoglycopeptide approved for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible gram-positive bacteria.[1] It has been shown to be non-inferior to intravenous vancomycin followed with oral linezolid and has potent activity against a large majority of drug resistant *S. aureus* strains.[2] An advantage of DAL is its long half life which allows for once weekly dosing with a recommended 2 dose regimen consisting of 1000 mg followed by 500 mg one week later. This decreases treatment burden on pts and facilitates use in OPAT.

Currently, data in the literature are scarce regarding the real-world clinical use of DAL. The purpose of this study is to report a nationwide clinical experience of outpatient DAL use in a POIC setting.

Methods

A multi-center retrospective database and chart review was conducted to identify pts who received DAL at 16 POICs nationally from July 2014 through March 2015. Data collected included pt demographics, all treatment parameters including prior therapy, microbiology, regimen, AEs, clinical outcomes and recurrences.

- Descriptive statistics (mean, median) were used for demographics, microbiology, regimen, and outcome data.
- AEs were compared to clinical trial data using Chi-squared test to determine statistical significance with $p < 0.05$.
- Clinical outcomes were evaluated for all pts who completed therapy as follows:
  - Cured: resolution of signs/symptoms and no further treatment needed
  - Improved: partial resolution of signs/symptoms, continued oral antibiotics
  - Failed: new or worsening of signs/symptoms
- Success rate (%) was defined as (cured + improved)/(total no. of pts)/100%.
- Pts were followed for up to 60 days after end of DAL treatment

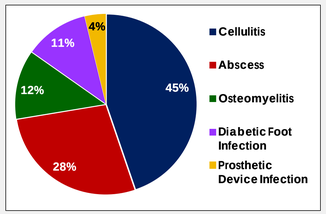
Results

Demographics

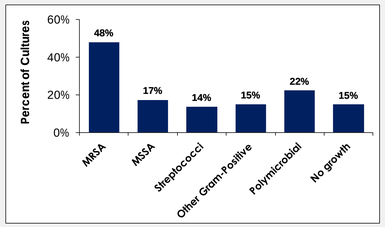
Characteristics (n=105)	No. (%)
Gender, male	57 (54%)
Age (years)	
Mean (range)	62 (19-92)
≥65	48 (46%)
Comorbidities	
Hypertension	58 (55%)
Cardiovascular disease	49 (47%)
Obesity	43 (41%)
Diabetes mellitus	39 (37%)
Arthritis	35 (33%)
History of cellulitis	33 (31%)
Neoplasm	27 (26%)
Psychiatric disorder	18 (17%)
Endocrine disorder	16 (15%)
Gastrointestinal disorder	16 (15%)
Location Prior to Therapy	
Home/POIC	49 (47%)
Antibiotic Use Prior to DAL	
Antibiotic naïve	13 (12%)
IVAB naïve	50 (48%)

- 78 pts (74%) had 3 or more comorbidities.

Infection Classification

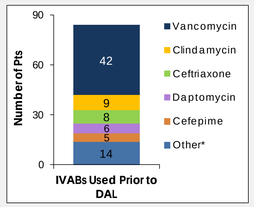


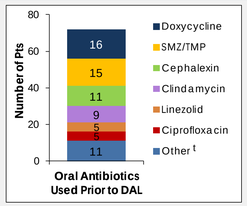
Microbiology



- Other gram-positive included unspecified *S. aureus* (10%), coagulase-negative staphylococci (4%), enterococci (1%)
- 23% (n=24) pts had no culture data available

Antibiotic Treatment Prior to DAL

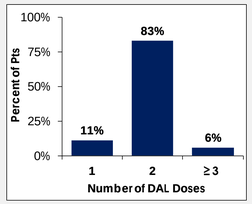




*; piperacillin/tazobactam, ampicillin/sulbactam, linezolid, ceftaroline, cefazolin, meropenem, aztreonam, penicillin; †; amoxicillin/clavulanate, cefadroxil, azithromycin, levofloxacin, minocycline, rifampin

- 88% (n=92) received either oral or IV antibiotics for treatment of infection prior to initiation of DAL
  - 53% (n=55) received IVAB prior to DAL for a median of 5 days
  - 34% (n=36) received only oral antibiotics prior to DAL
- 24% (n=25) received both oral and IV antibiotics prior to DAL

DAL Treatment Regimen



- 12 (11%) pts received only 1 DAL dose:
  - 9 pts with serious AEs
  - 2 improved pts able to discontinue 2nd dose
  - 1 hospitalized pt for reasons unrelated to therapy
- Peripheral intravenous catheters were utilized in 84 pts (80%)

Adverse Events

Treatment-Related AEs	POIC Study n=105 No. (%)	DISCOVER 1&2[1] n=652 No. (%)	P Value
Diarrhea	10 (9.5)	8 (1.2)	<0.0001*
Hypersensitivity reaction	9 (8.6)	1 (0.2)	<0.0001*
Rash	7 (6.7)	10 (1.5)	0.003*
Pruritis	5 (4.8)	6 (0.9)	0.007*
Dizziness	4 (3.8)	8 (1.2)	0.116
Nausea	4 (3.8)	27(4.1)	0.903
Fatigue	3 (2.9)	-	-
Pyrexia	3 (2.9)	8 (1.2)	0.359
Infusion Site Reaction	2 (1.9)	9 (1.4)	0.966
C. difficile-associated diarrhea	1 (0.9)	-	-
Pts with any AE	30 (28)	80 (12)	<0.0001*
Total No. of AEs†	48 (46)	139 (21)	<0.0001*
AEs leading to drug discontinuation	10 (9.5)	14 (2.1)	0.0002*

*; statistically significant (p<0.05) using Chi-squared test; †; includes all other reported treatment-related AEs

- 50% (15/30) of pts with adverse events had drug or latex allergies

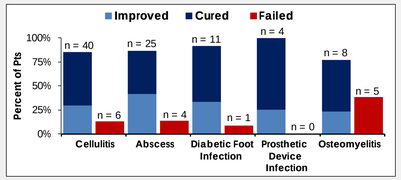
Adverse Events Requiring DAL Discontinuation

Pt	Reason	Onset	Prior Antibiotics	Outcome
1*	Dyspnea	Immediate	Oral doxycycline	Treated in POIC, symptoms (sx) resolved
2	Urticaria	Immediate	IV vancomycin, oral	Treated in POIC, sx
3	Dyspnea, urticaria	2 hrs post infusion	IV vancomycin	Pt hospitalized, sx resolved
4	Anaphylaxis	2 hrs post	Oral antibiotic	ED visit, treated and
5	Anaphylaxis	2 hrs post infusion	IV vancomycin, IV cefepime, oral	Treated in POIC, sx resolved
6*	Urticaria	several hrs	Oral ciprofloxacin	Pt lost to follow-up
7	Urticaria	several hrs	IV vancomycin, oral linezolid	Treated, sx resolved
8*	Urticaria	several days	IV vancomycin	Treated in POIC, sx
9*	Urticaria, fever	several days	IV vancomycin, IV cefepime	Treated, sx resolved in 10 d
10*	Severe GI distress	several days	Oral SMZ/TMP	Sx resolved

* Pt with allergies to other drugs prior to DAL therapy

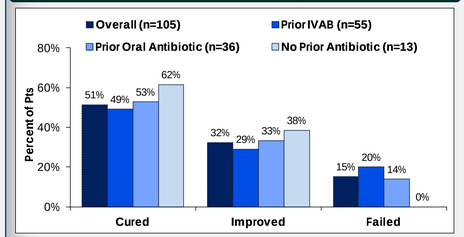
Clinical Outcomes by Infection Classification

- Overall clinical success was reported in 84% (88/105) of pts with 52% (54/105) cured and 32% (34/105) improved



- 15% failed, with 10 of the 16 failures attributable to AEs
- 25 pts (24%) were continued on oral antibiotics

Outcomes by Prior Treatment History



- 1 pt receiving IVAB prior to DAL was lost to follow-up.

Infection Recurrence Within 60 Days

60-Day Recurrence (n=82)	No. (%)
No recurrence	75 (91)
Recurrence	7 (9)

Discussion

This retrospective study described the outpatient use of DAL in POICs.

- Almost half of pts (47%) initiated therapy in the POIC. DAL was used as a first-line therapy in 13 pts (12%) naïve to antibiotics.
- DAL was successfully used in treating a variety of infections in the POIC.
- DAL was used successfully to treat prosthetic joint infections and osteomyelitis. Data on these diagnosis may provide background for further studies.
- Incidence of overall and certain AEs was significantly higher in this study than previously reported in clinical trials.[1] Possible contributing factors include: 88% of pts were antibiotic non-naïve, 15% of pts with AEs reported prior drug or latex allergies and 27% of pts were treated for diagnoses other than ABSSI.
- Further investigation into the incidence of serious adverse events and hypersensitivity reactions is warranted. Characterizing those patients at higher risk will be beneficial for broader use of long-acting lipoglycopeptides.
- DAL demonstrated an overall clinical success rate of 84%, with a 52% cure rate and 32% improved status. Among infection classes, cellulitis had the highest success rate (87%) and osteomyelitis had the lowest rate (62%). Success rates did not differ significantly in antibiotic naïve vs. non-naïve pts.
- Overall 60-day recurrence rate was low at 9% among evaluable pts.

Conclusions

- With once-weekly administration and strong bactericidal activity against MRSA, DAL can be an effective treatment option in the outpatient setting, particularly for patients who are not candidates for daily infusions or for self-administration of IV antibiotics.
- AEs were notable, with a higher rate of serious events than previously reported. Patients previously treated with IVABs and those with drug allergies may predispose pts to DAL adverse events and hypersensitivity. This study would suggest that close management of AEs during treatment is necessary for successful outcomes.
- Further real-world studies can help establish DAL's place in therapy and provide additional information on safety parameters.

References

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We acknowledge the assistance of Alex Ng, PharmD and Jason Xu in this study.