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Dalbavancin in Comparison with Vancomycin Followed by Linezolid in The Treatment of Acute Bacterial Skin and Skin Structure Infections

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Abstract

Background: *Novel antimicrobial agents are needed for the treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSIs) due to reported treatment failures and meagre clinical outcomes. Dalbavancin offers an alternative to glycopeptides such as vancomycin in combating resistant gram-positive bacterial pathogens and for use in the outpatient setting. This non-inferiority study aims evaluate the efficacy and safety of dalbavancin in comparison with vancomycin followed by linezolid in the treatment of patients with ABSSSIs.*

Materials and Methods: *After the informed consent procedure, patients were randomized to receive Group 1 - intravenous dalbavancin first dose of 1000 mg on Day 1 followed by next dose of 500 mg on Day 8 and Group 2 - intravenous vancomycin 1000 mg or 15 mg/kg twice daily for 3 to 14 days and switched to oral linezolid 600 mg administered every 12 hours upon investigator's discretion. The primary endpoint was early clinical response at 72hrs post study drug initiation. Secondary endpoints include clinical status at the end of treatment visit and follow up visit, resolution of local signs of infection, resolution of fever, patient's pain assessment, patient's microbiological response, and adverse event and serious adverse event assessment.*

Results: *A total of 256 patients have completed the study. Majority of them had fever at baseline (85.1% in Group – 1 and 84.1% in Group – 2). Early clinical response was found in 84.4% in Group – 1 and 83.5% in Group – 2 with a non-inferiority margin of 8.2%. All the secondary endpoints have shown non-inferiority of dalbavancin. No serious adverse event (death) occurred during the study.*

Conclusion: *With its most unique feature of once weekly dosing which provides opportunities for increased adherence and fewer hospitalizations, it is easy to conclude that Dalbavancin is a better alternative to vancomycin followed by oral linezolid.*

Keywords: *ABSSSI, Dalbavancin, antibiotics*

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I. Introduction

Acute bacterial skin and skin structure infections (ABSSSIs) are infections of the skin and surrounding tissues and are significant global healthcare burdens causing substantial morbidity both in inpatient and outpatient settings [1-3]. Common clinical presentations of ABSSSIs include skin lesions with redness, induration, and oedema, as well as report of pain and significant discomfort by the affected individuals. In the recent past, the United States Food and Drug Administration (FDA) have defined ABSSSIs as bacterial infection of the skin with a minimum lesion area of at least 75 cm^2. The incidence and severity of disease has increased in recent years, in parallel with the emergence of community-acquired methicillin-resistant Staphylococcus aureus (CA- MRSA) [1, 2, 4].

The 2016 Indian Infectious disease treatment guidelines recommended intravenous (IV) antimicrobial agents for the treatment of suspected severe MRSA which include vancomycin, teicoplanin, daptomycin, linezolid, telavancin, or ceftobiprole. The glycopeptides antibiotics vancomycin and teicoplanin are drugs of first choice for MRSA, linezolid for MRSA-induced SSTIs, and daptomycin for complicated SSTIs and bacteraemia due to MRSA [5]. Ceftobiprole is a "5th generation" cephalosporin and it also has activity against gram-positive bacteria, including MRSA [6].

Vancomycin has been the mainstay of antibacterial therapy for severe infections caused by resistant Gram-positive organisms, including MRSA. [7-9]. Though the overall prevalence of these isolates remains low, infections caused by vancomycin-resistant strains are concerning due to high rates of treatment failure and poor clinical outcomes [4, 10-12]. Therefore, novel antimicrobial agents are needed for the treatment of ABSSSIs.

Dalbavancin offers an alternative to glycopeptides such as vancomycin in combating resistant gram-positive bacterial pathogens and for use in the outpatient setting [13]. Dalbavancin's high-protein binding and prolonged half-life allow for easily and consistently attainable therapeutic levels. Even with extensive protein binding, the free serum levels are adequate to provide excellent tissue penetration. Several clinical trials have demonstrated its tolerability, efficacy, and noninferiority compared to standard therapy for ABSSSI. Dalbavancin's most unique feature is its once weekly dosing which provides opportunities for increased adherence and fewer hospitalizations for complicated ABSSSI.

As vancomycin has been proposed as the treatment of choice for patients with a MRSA skin and skin structure infections [14], this phase III open label, non-inferiority study was planned to evaluate the efficacy and

safety of dalbavancin in comparison with comparator regimen (vancomycin followed by linezolid) for the treatment of patients with Acute Bacterial Skin and Skin Structure Infections (ABSSSIs).

II. Methodology

Study design and study population

This study was a Multi-centre, Phase III, Randomized, Open label, Parallel group, Non-inferiority study to evaluate the efficacy and safety of dalbavancin versus vancomycin followed by possible switch to linezolid for the treatment of patients with ABSSSIs caused by gram +ve/ mixed bacteria. The DCGI and all institutional ethics committees at 16 trial sites gave their approval to the protocol and other documents, which was then registered in the Clinical Trial Registry of India (CTRI/2020/02/023409). The Good Clinical Practice recommendations and the principles of the Declaration of Helsinki were followed during the study's execution.

Patient recruitment

Informed consent was given to the patients before getting enrolled in the study. Eligible subjects were randomly assigned to one of the two study groups in 1:1 ratio. A total of 256 patients were enrolled in this study. We included male/female patients with 18 - 65 years of age who were willing to consent and who require hospitalization or already hospitalized patients with diagnosis of ABSSSIs who can comply with the study procedures. Additionally, ABSSSIs characterized by major cutaneous abscess that requires surgical incision and drainage or surgical site/traumatic wound infection occurred within 30 days of surgery/trauma and cellulitis each associated with pus accompanied by erythema, oedema and/or induration and with total affected area involves at least 75cm^2 of erythema and alternatively involves the central face and is associated with an area of erythema of at least 50 cm^2. Patients with at least two local signs and symptoms of ABSSSIs in addition to erythema that include purulent drainage/discharge, fluctuance, heat/localized warmth, tenderness to palpitation and swelling/induration were considered. Patients with minimum 3 days of intravenous therapy who had at least one systemic signs of infections, including an elevated body temperature ≥ 38°C/100.4°F as measured by the patient/caregiver or investigator within 24 hours of baseline and/or with white blood cell count greater than 12,000 cells/mm3 were considered.

Patients who had exclusive gram-negative bacterial infections or fungal infections alone/in combination of bacterial pathogen were excluded. Patients with any contra-indication to dalbavancin, vancomycin, linezolid, or any other study required drug or participation in any other study within 30 days were excluded. Patients with sustained shock (systolic blood pressure <90 mm Hg for more than 2 hours despite adequate fluid resuscitation, with evidence of hypoperfusion, or need for sympathomimetic agents), estimated creatinine clearance less than 50 ml/min, evidence of meningitis, necrotizing fasciitis, gas gangrene, gangrene, septic arthritis, osteomyelitis, endovascular infection, such as clinical and/or echocardiographic evidence of endocarditis or septic thrombophlebitis, venous catheter entry site infection, infections of perirectal abscess or a decubitus ulcer, infections with infected device even if the device is removed, and ABSSSIs as a result of sustained full or partial thickness burns were excluded. Additionally, patients who had received antibiotic within 14 days prior to randomization, infection involving a limb with evidence of critical ischemia, superficial/simple cellulitis/erysipelas, impetiginous lesion, furuncle, or simple abscess that only requires surgical drainage for cure, patients who were placed in a hyperbaric chamber as an adjunctive therapy for ABSSSIs, known or suspected human immunodeficiency virus (HIV) infected patients , more than 2 surgical interventions for ABSSSIs, medical conditions with chronic inflammation, absolute neutrophil count less than 500 cells/mm^3, with a recent bone marrow transplant (in post-transplant hospital stay), received oral steroids > 20 mg prednisolone per day (or equivalent), received immunosuppressant drugs after organ transplantation, and life expectancy less than 3 months with rapid fatal illness were excluded. Patients with other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate and female patients who were breast-feeding, pregnant or intended to become pregnant during the study were also excluded.

Study interventions

Eligible subjects were randomly assigned to one of the two study groups in 1:1 ratio.

- Group 1 (n=128): Received intravenous dalbavancin, first dose of 1000 mg on Day 1 followed by next dose of 500 mg on Day 8.
- Group 2 (n=128): Received intravenous vancomycin 1000 mg or 15 mg/kg twice daily for 3 to 14 days. Investigators had the option of switching patients in the comparator regimen from IV vancomycin to oral linezolid 600 mg administered every 12 hours.

In Group 2, following at least 72 hours of vancomycin treatment (i.e., 6 doses), patients were switched from the IV vancomycin to oral linezolid therapy on investigator's discretion.

Study procedure

All patients were made to undergo the screening procedure to determine whether they are meeting the required inclusion and exclusion criteria. All patients were hospitalized for at least 3 days. After this, hospitalization would be continued depending on patient condition and as decided by the Investigator. Discharged patients in Group 1 were required to visit study site on Day 8 to receive second dose of Dalbavancin and for study related assessment. Discharged patients in Group 2 were required to visit study site on Day 8 for study related assessment. After the last dose of study drug, all patients in Group 1 and Group 2 had to visit the study site for End of Treatment (EOT) visit on Day 14 and for safety follow up visit on Day 28 ± 2.

Assessments

The primary endpoint was to assess early clinical response at 72 hours post study drug initiation. A clinical responder was defined as both no increase in the lesion area of the erythema associated with the infection as compared to baseline and a temperature of 37.6°C or lower at two consecutive readings performed 6 hours apart with no intervening temperature >37.6°C at 72 hours. A non-clinical responder was defined as increase in lesion area, a temperature >37.6°C or initiated with a new systemic antibacterial gram +ve / mixed strain activity within 72 hours. Patients with missing data for lesion size or temperature were also considered as a non-clinical responder. Clinical response success or failure was determined on the basis of the above criteria after the treatment was completed.

Secondary endpoints include clinical status at EOT visit (Day 14), clinical status at follow-up visit (Day 28 ± 2) defined as success or failure based on the decrease/increase in lesion size, lower/higher temperature than 37.6°C, absence/presence of local signs of fluctuance and localized heat/warmth, reduction/worsening of local signs of tenderness to palpation and swelling/indurations to mild, absence/presence of purulent drainage or considered as failure only when patient got new systemic antibacterial treatment or if surgical intervention was required (unless pre-planned as a non-drug therapy). Resolution of local signs of infection, resolution of fever for those with fever at baseline, patient's assessment of pain, adverse Event (AE), patient's microbiological response to therapy (i.e., eradication, presumed eradication, persistence and presumed persistence), and serious adverse event (SAE) assessment. A microbiologic success was defined as eradication or presumed eradication whereas a failure was defined as persistence or presumed persistence.

Statistical analysis

All baseline summary statistics were obtained on the Intent to Treat (ITT), Per Protocol (PP) and Safety populations. The descriptive statistics like mean, median, standard deviation, minimum and maximum were obtained for all continuous/real variables, while frequencies and percentages were obtained for the categorical/nominal variables. All efficacy analyses were presented for ITT and PP populations. The mean of continuous parameters was tested for significance of difference between group using t-test for independent samples, while parameters on nominal scale was compared using Pearson's Chi-square test or Fisher's exact test.

The average change in the lesion area of patients in two groups were compared at each time point using t-test for independent samples and the change in area were evaluated across times (visits) using repeated measure analysis of variance (ANOVA). The temperature for each patient was coded as binary data and compared at each time point (visit) between groups using Pearson's Chi-square test and compared across times using Friedman ANOVA. The secondary endpoint i.e., clinical status was compared between two treatment groups at end of treatment and safety follow up visit. The comparison of success among patients between two groups were carried out using Pearson's Chi-square test. Also, the significance of difference in success rates across time (visits) was evaluated using Friedman ANOVA. Moreover, the additional efficacy endpoints like resolution of local signs of infection, fever and pain assessment, microbiology data were compared between and within groups using appropriate non-parametric tests. The intra-group comparison before and after treatment was performed using Friedman ANOVA, while the inter-group comparison was performed using Wilcoxon rank sum test. AEs were summarized by treatment group, severity, and relationship with the study drug. Listings were presented for all AEs and SAEs as well as those events that led to discontinuation from the study.

III. Results

A total of 256 patients have completed the study with 128 patients in each group. 390 patients been screened and 131 has screen failed. 3 patients had discontinued after screening but before first dose **(Figure 1)**. The mean (SD) age was 47.05 (10.50) years in Group 1 and 45.76 (11.48) years in Group 2. Males in both the groups were 80.5% and 79.7% respectively. Common comorbidities include fever (85.1% in Group 1 and 84.1% in Group 2) followed by Type 2 diabetes (14.8% in Group 1 and 10.9% in Group 2) **(Table 1)**.

Overall, 84.4% of patients were found to be responders at 72Hrs in Group 1 and 83.5% in Group 2 with p value of >0.99 with non-inferiority margin of 8.2% **(Figure 2)**.

In Group 1, clinical status at EOT (Day 14) was found to be 100% success for 4 out of 5 parameters and 1.6% clinical failure in one parameter and 99.2% success and 0.8% failure for 4 out of 5 parameters and 1.6% failure in one parameter with a p value of >0.99 **(Table 2)**. Clinical status at follow-up visit (Day 28) was found to be 100% success for all the parameters in both the groups. Complete resolution of local signs of infection at Day 14 was found to be 94.5% in Group 1 and 96.1% in Group 2 with a p value of >0.99.

Mean (SD) changes from baseline pain score was -2.02 (±1.46) on Day 3 and -4.72 (±1.99) on Day 14 in Group 1, whereas -2.18 (±1.21) on Day 3 and -4.81 (±1.83) on Day 14 in Group 2. Presumed eradication at Day 14 was observed in 98.4% patients in Group 1 and 96.8% patients in Group 2.

Total 76 adverse events were reported, out of which 43 were in Group - 1 and 33 in Group - 2. 71 adverse events were of mild in nature and 5 adverse events were of moderate. All the 76 adverse events were 'not related' to the study drug. No serious adverse event occurred during the study.

IV. Discussion

Current study results are endorsed by significant clinical efficacy and safety in both the groups with respect to end points. Thus, once-weekly IV Dalbavancin was non-inferior to twice-daily IV Vancomycin followed by oral Linezolid.

Early clinical response at 72hrs has no increase in the lesion area or the fever with similar response in both the groups conferring clinical relevance to the statistical conclusion of noninferiority for the primary end point. Similar results observed in DISCOVER 1 and DISCOVER 2 trials, with clinical response at 72hrs were 79.7% and 79.8% in both the groups [15].

Clinical status at all the endpoints (at 72hrs, day 14 and day 28) were comparable between both the groups. Almost similar results found with resolution of local signs of infection and fever in both the groups with a p value of >0.99 indicating the non-inferiority of dalbavancin. Noticeable trend of reduction in pain score from day 3 to day 14 was observed in both the groups. Similarly, comparable microbiological responses with presumed eradication observed in both the groups.

Though patients treated with Group 2 had lesser AEs than those of Group 1, considering the point that they were unrelated to the study treatment, dalbavancin did not produce any deleterious effects and appears to have an acceptable safety profile.

V. Conclusion

The results of these trials showed the non-inferiority of dalbavancin administered once weekly as compared with vancomycin–linezolid administered twice daily for the treatment of ABSSSIs. With its most unique feature of once weekly dosing which provides opportunities for increased adherence and fewer hospitalizations, it is easy to conclude that Dalbavancin is a better alternative to vancomycin followed by oral linezolid.

List of Abbreviations

ABSSSIs	Acute Bacterial Skin and Skin Structure Infections
AE	Adverse Event
CA	Community-acquired
DCGI	Drug Controller General of India
EC	Ethics Committee
EOT	End of Treatment
GCP	Good Clinical Practice
IV	Intravenous
MRSA	Methicillin-Resistant *Staphylococcus aureus*
NI	Non-Inferior
SAE	Serious Adverse Event

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Tables/Figures

Figure 1: Patient's Disposition

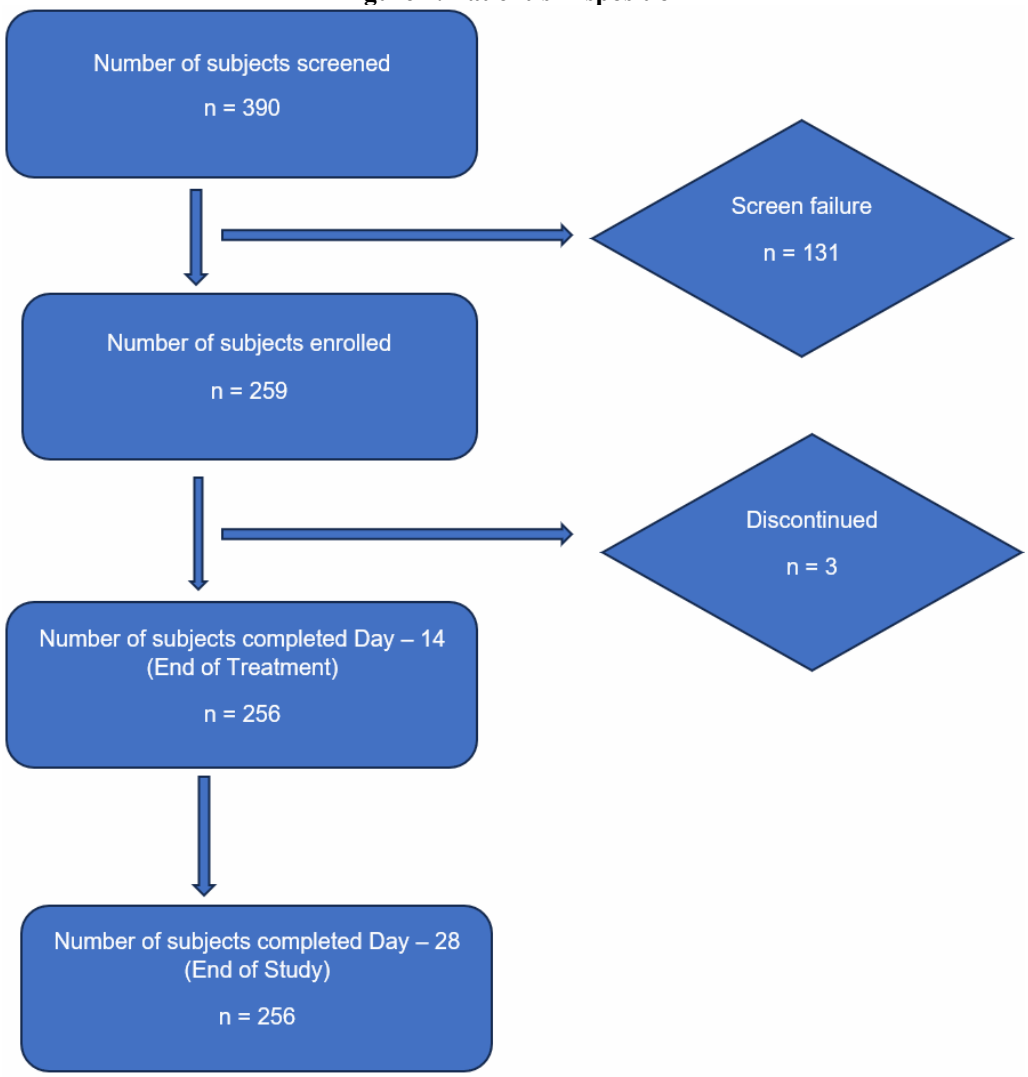

Figure 2: Early Clinical Response at 72 hours post study drug initiation

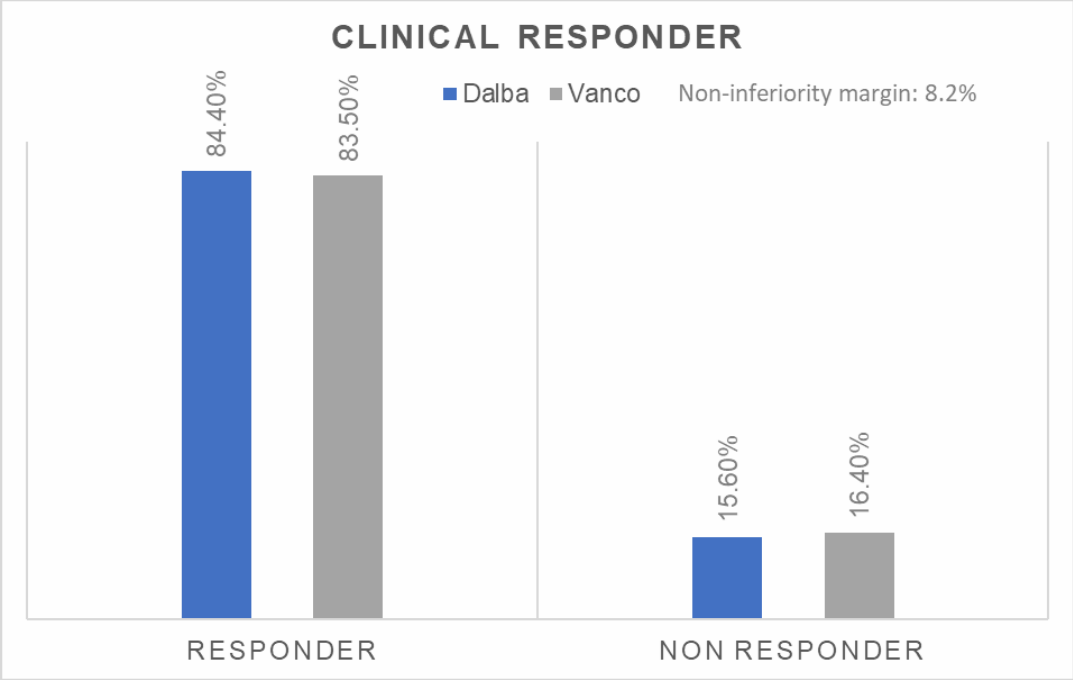

Table 1: Demographics and other Baseline Parameters

Parameters	Dalbavancin (N=128) n (%)	Comparator Regimen (N=128) n (%)
Age (years)		
N	128	128
Mean	47.05	45.76
SD	10.50	11.48
Median	48.00	46.00
Min; Max	(21.00, 64.00)	(19.00, 63.00)
Sex, n (%)		
Male	103 (80.5)	102 (79.7)
Female	25 (19.5)	26 (20.3)
Medical/Surgical History		
Abdominal wall repair surgery	1 (0.8)	0
Cataract Surgery	0	1 (0.8)
Fever	109 (85.1)	101 (84.1)
Hypertension	1 (0.8)	7 (5.4)
Suturing of traumatic wound	1 (0.8)	0
Type 2 Diabetes	19 (14.8)	14 (10.9)
Abdominal wall repair surgery	1 (0.8)	0

Table 2: Demographics and other Baseline Parameters

Parameters	Response	Dalbavancin (N=128) n (%)	Comparator Regimen (N=128) n (%)	P-value
End of Treatment Visit (Day 14)				
The local signs of fluctuance and localized heat warmth are absent?	No	0	1 (0.8%)	>0.9999
	Yes	128 (100%)	127 (99.2%)	
The local signs of tenderness to palpation and swelling indurations are reduced to mild?	No	0	1 (0.8%)	>0.9999
	Yes	128 (100%)	127 (99.2%)	
The patient's lesion size is decreased from baseline?	No	0	1 (0.8%)	>0.9999
	Yes	128 (100%)	127 (99.2%)	

The patient's temperature is = 37.6°C (by any measurement method)?	No	0	1 (0.8%)	>0.9999
	Yes	128 (100%)	127 (99.2%)	
The purulent drainage is turns to non-purulent compared to baseline in patients with a wound infection?	No	2 (1.6%)	2 (1.6%)	>0.9999
	Yes	122 (94.5%)	123 (96.1%)	
Missing		4 (3.1%)	3 (2.3%)	