

ORIGINAL ARTICLE

A Multicentre, Open label, Randomized, Comparative, Parallel Group, Active-controlled, Phase III Clinical Trial to Evaluate Safety and Efficacy of Arbekacin Sulphate Injection versus Vancomycin Injection in Patients Diagnosed with MRSA Infection

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Abstract

Background: Increasing resistance to currently available antimicrobials has led to the development of new agents. Arbekacin is aminoglycoside antibiotic currently used in Japan and Korea for the treatment of infections caused by multi-resistant bacteria including MRSA. Currently there is no published data available for use of Arbekacin in Indian patient population, thus the present study was conducted to evaluate the safety and efficacy of Arbekacin in Indian population.

Material and Methods: The study was a phase III, multi-centre, open-label, randomised comparative, active control study. Subjects with microbiologically confirmed MRSA infection were randomized in the study to receive either Arbekacin sulphate 200 mg OD or Vancomycin hydrochloride 1000 mg BD for a period of 7 to 14 days. The primary endpoint was to evaluate the overall cure rate i.e. Clinical and microbiological cure during the study.

Results: A total of 162 patients were randomized in 2 treatment groups (i.e. 81 patients in each group). Out of these microbiologically confirmed MRSA patients, 153 patients were admitted for SSTI while 9 patients were admitted for CAP. Overall cure rate of MRSA infection (clinical as well as microbiological cure) was comparable in both the treatment groups i.e. 97.5% (79/81) in Arbekacin group and 100 % (79/79) in Vancomycin group (p value: 0.159). Both Arbekacin and Vancomycin were well tolerated by the patients during the study period.

Conclusion: Arbekacin can be considered as safe and effective alternative to vancomycin in the management of MRSA infections.

negative Staphylococcus (VRCNS), as well as vancomycin-resistant *S. aureus* (VRSA) the use of vancomycin has to be reduced. Thus there is a need of alternative antibiotics effective against MRSA.⁴

Arbekacin, an aminoglycoside antibiotic was originally synthesized from dibekacin in 1973. It is primarily used for the treatment of infections caused by multi-resistant bacteria including MRSA. It has been registered and marketed in Japan since 1990 under the trade name Habekacin. Arbekacin is active in vitro against both gram-negative and gram-positive Aerobic bacteria, and it is refractory to hydrolysis by most aminoglycoside modifying enzymes produced by aerobic bacteria.⁵

Arbekacin is used in Japan and Korea for the treatment of patients infected with MRSA. In a study of comparing Vancomycin with Arbekacin in the treatment of infections caused by MRSA, bacterial and clinical efficacy of was comparable between 2 groups, however, complication rate was significantly higher in Vancomycin group as compared to Arbekacin group.⁶

Currently there is no published data available for use of Arbekacin in Indian patient population, thus the present study was conducted to evaluate

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) first emerged in 1961 and become one of the most important causes of nosocomial pathogenic infections.¹ In addition, Community acquired methicillin resistant *S. aureus* (CA-MRSA) has emerged over the past several years in most geographic regions. Prevalence of MRSA in India is also on higher side. In a clinical study to understand emerging trends of antimicrobial resistance among clinical isolates of *S. aureus* in India, overall MRSA prevalence was found as 42 per cent in 2008 and 40

per cent in 2009.² Another study from south India reported MRSA prevalence as 40-50%.³

Glycopeptides and linezolid continue to remain the mainstay for treatment for MRSA infections. With the emergence of Vancomycin-resistant Enterococcus (VRE), Vancomycin resistant coagulase-

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Table 1: Summary of demographic characteristics

	Arbekacin Group (N = 81)	Vancomycin Group (N = 81)	P value
Age Years (Mean + SD)	40.80 + 13.68	40.65 + 14.69	0.949
Weight Kg (Mean + SD)	60.10 + 11.50	65.37 + 11.39	0.071
Male/Female	45/36	59/22	0.022
H/O Type 2 DM n(%)	14 (17.3)	17 (21)	0.549
H/O COPD n(%)	01 (1.2)	01 (1.2)	1.000
H/O Surgery n(%)	03 (3.7)	4 (4.93)	0.699

DM: Diabetes Mellitus, COPD: Chronic obstructive pulmonary disorder

and compare the safety and efficacy of Arbekacin with Vancomycin in Indian patients diagnosed with MRSA infections.

Material and Methods

Study Design

The study was a multi-centre, open-label, randomised, comparative, active-controlled, phase III study conducted in patients diagnosed with MRSA infection. The study was conducted across 9 centres in India between February 2015 and February 2017. The study protocol was approved by office of Drug Controller General of India and Ethics Committees. The study was conducted in accordance with Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. Written informed consent was obtained from patients or their legally authorised representatives before initiation of any trial procedures.

Male and female patients between age group of 18 to 65 years with microbiologically confirmed diagnosis of MRSA, with normal Rinne and Weber test were included in the study. Clinical diagnosis of patients included post-operative wounds, pneumonia, skin and soft tissue infections such as infected ulcers, and deep abscess. Patients with history of allergy or serious adverse reaction to aminoglycoside or glycopeptide antibiotics, polymicrobial infections, serious infections like meningitis and endocarditis, impaired renal functions, comorbid conditions like severe congestive heart failure or uncontrolled diabetes and patients with abnormal otoscopic findings were excluded from the study.

The total duration of the study was approximately 22 months, including 21 months of enrolment period. For an individual patient, the maximum duration of the study was approximately 24 days. Each subject attended a total of

11 visits during the study. The treatment duration varied from minimum 7 days to maximum 14 days based on the investigator's discretion. Patient were treated with either Arbekacin Sulfate 200 mg Injection OD or Vancomycin hydrochloride 1000 mg injection BD both as IV infusion.

Endpoint Assessment

The primary efficacy endpoints in the study was overall cure rate which included both clinical and microbiological cure rates. Clinical cure rate was analysed at different time points such as at 3rd day of treatment, End of Treatment (EOT) and follow-up visit i.e. 7 (\pm 2) days after EOT. Clinical Cure was defined as resolution/reduction of baseline clinical sign and symptoms of MRSA infections as per investigator's discretion. Microbiological cure was defined as documented eradication, presumed eradication or colonization which was evaluated after 3 days of EOT. For microbiological evaluation, Blood and applicable culture i.e pus culture for SSTIs and sputum culture for pneumonia were performed at Test of Cure (TOC) visit.

Secondary efficacy endpoint was fever clearance time which was defined as no fever for continuous 24 hours without any antipyretic medication received during the study. For SSTI patients, clinical assessment of wound healing was performed at different time points including EOT and end of study (EOS). Vancouver Scar Scoring Scale was used in patients with SSTI for objective wound assessment whereas APACHE II Scoring system was used only for subjects presenting with pneumonia.

Safety and tolerability was evaluated by means of incidence of treatment emergent adverse events (TEAEs), laboratory tests (Complete blood count (CBC), Liver Function Test (Total bilirubin, ALT and AST), Renal Function Test (serum creatinine and

urinalysis) and Rinne/Weber test for hearing assessment.

Statistical Analysis

Categorical variables were compared using the Chi-square test or Fisher's exact test. Continuous variables were tested for normal distribution and compared using the unpaired t-test. Chi-square test, Fisher's exact test and t-test were analysed by using SPSS 19.0 (IBM Corp., NY, USA), and the P-value lower than 0.05 was defined as statistically significant.

Results

Demographic and Baseline Characteristics

A total of 357 patients were screened during the study, of which 162 patients were randomized in the 2 study groups in 1:1 ratio (81 each in Arbekacin and Vancomycin groups) and 195 patients were excluded of which majority were due to polymicrobial infection. Out of 162 randomised patients, 160 completed the study, while 2 patients withdrew consent for study participation and thus prematurely discontinued from the study. All demographics and baseline characteristics were comparable in both groups except for distribution of male and female patients (Table 1).

The most common type of MRSA infection was skin and soft tissue infections (SSTI) followed by CAP (community acquired pneumonia). Skin and Soft tissue infections (SSTI) presented as infection of deep soft tissue, deep ulcers and postoperative wounds. Distribution of various MRSA infections is shown in Table 2.

Efficacy Endpoint Assessment

Overall cure rate of MRSA infection (clinical as well as microbiological cure) was comparable in both the treatment groups across all the indications as shown in Table 3.

When endpoints were analysed separately for each indications i.e SSTI and Pneumonia, overall cure rate (clinical and microbiological cure) was comparable in both the treatment groups (Figure 1).

Fever clearance was evaluated in patients (n = 96) having fever at baseline. Median fever clearance time was lower in Arbekacin group (10 days) as compared to Vancomycin group (12 days) however the difference was not statistically significant. When fever

clearance was analysed at different time-points (Figure 2), 32 out of 49 (65.3 %) patients in Arbekacin group showed fever clearance in less than 10 days which was significantly lower than vancomycin group in which 16 out of 47 (34%) patients showed fever clearance (p value - 0.002).

Table 2: Distribution of MRSA Infection between two treatment groups

Category of MRSA infection	Arbekacin (N = 81)	Vancomycin (N = 81)
Pneumonia, n(%)	06 (7.4)	03 (3.7)
SSTI, n(%)	75 (92.6)	78 (96.3)
Post-operative infections, n	4	4
Infection of deeper soft tissue, n	60	63
Requiring significant surgical intervention (Infected ulcers and deep abscess), n	11	13

#One case had all 3 ailments of SSTI.

Patients presenting with SSTI were clinically evaluated for wound healing by means of characteristics like presence or absence of wound, redness, oedema and pus regular interval. Proportion of patients showing wound healing was comparable in both groups at each time-point as shown in Figure 3.

Vancouver scar score was objective parameter for evaluation of wound and scar apart from subjective evaluation of wound by investigators. The score

Table 3: Overall cure rate across all patients

Endpoint	Arbekacin (N = 81)	Vancomycin (N = 79)	P Value
Overall Cure Rate	79 (97.53%)	79 (100%)	0.159
Overall Clinical Cure Rate	79 (97.53%)	79 (100%)	0.159
Overall Microbiological Cure rate	79 (97.53%)	79 (100%)	0.159

was significantly improved in both treatment groups as compared with baseline, however, this improvement was comparable in both groups.

Patients with pneumonia were assessed with APACHE II score. Mean APACHE II score was reduced in both treatment groups at end of study, however the same was not statistically evaluable since the subject population in both the treatment groups was too low to apply any valid statistical test.

Safety Endpoint Assessment

A data safety monitoring board (DSMB) was established prior to start of the study. The board was consisting of independent members from relevant expertise (Intensivist, Chest Physician, Clinical Pharmacologist and Biostatistician). The DSMB periodically monitored and reviewed the cumulative safety data of the study, which included AEs, SAEs, and abnormal clinically significant laboratory investigations. During the course of the study, a total of 6 DSMB reviews were conducted during which the DSMB had recommended to continue the study without any modification.

Overall, 33 (20.37%) subjects reported 42 treatment emergent adverse events (TEAEs) as shown in Table 4. The proportion of mild, moderate, and severe TEAEs was comparable between the Arbekacin sulphate and Vancomycin groups. The majority of the AEs were not related to the study drug. In the Arbekacin group, the most common AEs reported during the study were elevated transaminases (5) and pyrexia (3), which were mild in intensity and not related to the drug. One severe event i.e. acute hepatocellular injury was reported which was possibly related to the drug. In the Vancomycin group, the most common AE reported during the study was elevated transaminases (3), which was mild in intensity and was not related to the drug. One severe event i.e. Pruritus was reported, which resolved on the same day without any treatment.

There was no clinically significant alteration of any laboratory parameter in patients who were administered arbekacin or vancomycin. Moreover, it was observed that patients in both the groups have shown decrease in their total leucocyte count and neutrophil

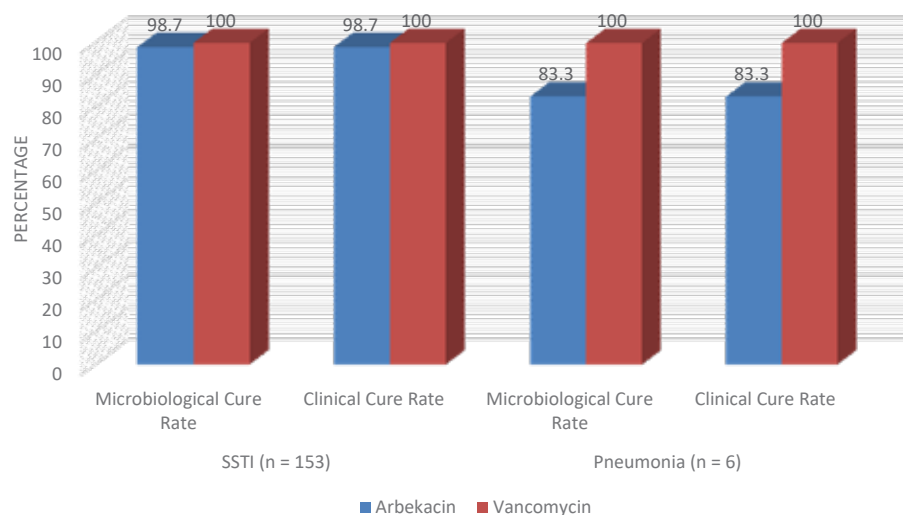


Fig. 1: Clinical microbiological cure rate in each indication

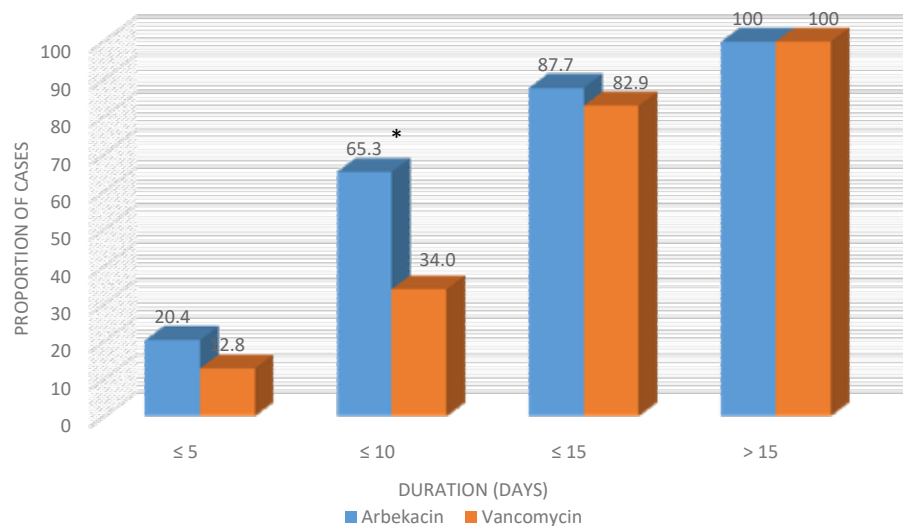
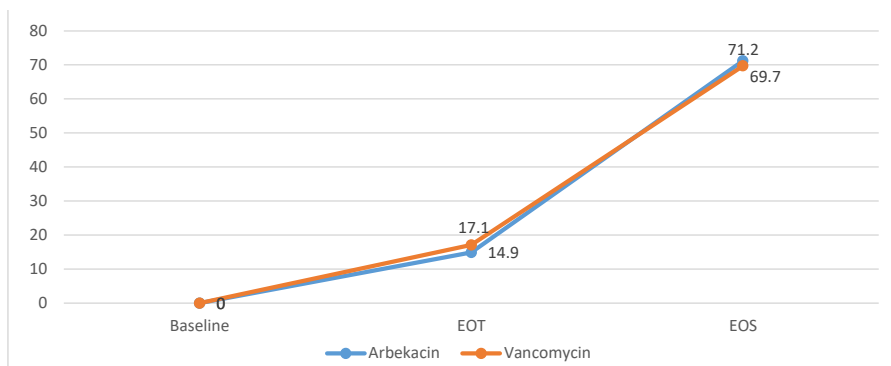


Fig. 2: Proportion of patients showing fever clearance at different time-points



EOT: End of treatment; EOS: End of Study

Fig. 3: Proportion of patients showing wound healing

count suggesting improvement in infection. Further none of the patients have shown any evidence of hearing impairment after the end of the study.

Discussion and Conclusion

Methicillin resistant *Staphylococcus aureus* (MRSA) is growing menace in India. The increasing use of antimicrobials and rampant use of these drugs is leading to drug resistance across the globe including India. There are specific drugs effective against MRSA like vancomycin, linezolid, and daptomycin. Most of the available therapies are associated with potential side effects or risk of drug resistance. Arbekacin is an aminoglycoside that is resistant to aminoglycoside inactivating enzymes produced by the bacteria thus has potential use in various resistant infections, has demonstrated efficacy against infections caused by MRSA.

The present phase III clinical study was conducted to compare the efficacy and safety of Arbekacin with the standard of treatment for MRSA i.e. vancomycin. The patients included in this study were hospitalized for the treatment of skin and soft tissue infection and community acquired pneumonia. Majority of the subjects included in the study had SSTI. The overall cure rate which included both clinical and microbiological cure was comparable in both treatment groups across both indications. The results are similar to an earlier study conducted by J.-H. Hwang group in a tertiary care hospital in Korea in patients with various MRSA infections.⁴ In another clinical study by the same group comparing arbekacin with vancomycin in 122 patients have shown similar results for clinical and microbiological

cure rates.⁶

In the current study, notable difference was found for rate of fever clearance in arbekacin group as compared to vancomycin group. Significant number of patients showed fever clearance during the initial 10 days of treatment in arbekacin group as compared to vancomycin group, indicating faster fever clearance in arbekacin group as compared to vancomycin group.

Patients with SSTI showed comparable rate of wound healing across both treatment groups. Various parameters of wound healings like redness, oedema and pus were found improved in both the treatment. Objective evaluation of scar also revealed comparable improvement of wound in both groups.

There was no serious adverse event reported in any of the patients. There was no statistically significant difference in the proportion of subjects experiencing AEs between the Arbekacin sulphate 200 mg OD and Vancomycin 1000 mg BD. The majority of the AEs were not related to the study drug. All TEAEs were resolved in both the treatment groups by the end of the study. The common AEs reported with arbekacin are elevated liver enzymes (5/24) and fever (3/24). These were mild in nature and not related to the drug. One case in Arbekacin group was found to have i.e. acute hepatocellular injury which was possibly related to the drug. In vancomycin group, the common AE reported during the study was elevated liver enzyme (3/18), which was mild in nature and was not related to the drug. Any None of the laboratory parameter were significantly altered in

Table 4: Overall summary of TEAEs

Description	Arbekacin	Vancomycin
	(N = 81) N (%)	(N = 81) N (%)
Patients in safety	81 (100)	81 (100)
Patients with atleast one AEs	19 (23.5)	14 (17.3)
Number of subjects who had a serious AE	0	0
Number of subjects who had an AE leading to death	0	0
Number of AEs by severity		
Total number of AEs	24	18
Mild AEs	17 (70.83)	15 (83.3)
Moderate AEs	6 (25)	2 (11.1)
Severe AEs	1 (4.16)	1 (5.6)

both treatment groups.

Thus, it can be concluded that arbekacin has comparable efficacy with vancomycin for treatment of MRSA infections in terms of clinical cure and microbiological cure rates. However, there was a significant difference in rate of fever clearance between two drugs. Arbekacin has shown faster resolution of fever as compared to vancomycin. There is no safety concern with arbekacin and the drug is found safe and well tolerated. It can be stated that arbekacin is an effective and safe alternative to vancomycin in the treatment of MRSA infection.

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