INTRODUCTION

Acute bacterial skin and skin structure infections (ABSSIs), defined as a bacterial infections of the skin with a lesion size area of at least 75 cm², are leading cause of hospital admission and ambulatory care visit worldwide [1, 2]. In the last years, several observational studies have shown a substantial increase in the incidence of hospital outpatient and emergency department visits. In a three-year study period from 2009 to 2011, Ray et al. found that the incidence of clinically-diagnosed skin infections was nearly 500 episodes per 10,000 person-years. The majority (63%) of these infections were cellulitis and skin abscesses and *Staphylococcus aureus* was by far the most common pathogen [3]. More recently, in a large five-year study period from 2005 to 2010, Miller et al. found that skin and soft tissue infection (SSTI) incidence remained relatively unchanged from 47.9 [95% confidence interval (CI) 47.8 to 48.1] cases per 1,000 person-years in 2005 to 48.5 cases (95% CI 48.3 to 48.6) per 1,000 person-years in 2010. Most infections (95%) were treated in the ambulatory setting and most (60%) were categorized as abscesses or cellulitis [4]. Overall, *S. aureus* is the leading cause of ABSSIs, and community- and hospital-acquired methicillin-resistant *S. aureus* (CA- and HA-MRSA, respectively) account for many of these infections [5-8]. Moreover, MRSA is frequently associated with a poor clinical outcome, inappropriate treatment, and longer duration treatment compared to methicillin-susceptible *S. aureus* [9-12]. Although there are many agents for the treatment of ABSSIs, including those due to MRSA, there are still concerns on the optimal management of these infections [13, 14]. The purpose of this paper is to review the available data on dalbavancin (DAL) for the treatment of ABSSSI.

Mechanism of action and in vitro activity

DAL, formerly BI-397, was discovered in 1996. It is synthesized from a fermentation product of the actinomycete *Nonomuria* spp. DAL, like other glycopeptides, inhibits transglycosylation by binding to the terminal d-alanyl-d-alanine residues of peptidoglycan precursors [15]. DAL has a similar spectrum of in vitro activity to the other glycopeptides, but it is more potent than vancomycin or teicoplanin [15]. DAL demonstrates in vitro activity against *S. aureus* (including MRSA strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group (including *S. anginosus*, *S. intermedius*, *S. constellatus*) [16, 17]. It demonstrates a minimum inhibitory concentration value generally below or at 0.06 mg/L for staphylococci and streptococci. DAL has a reduced susceptibility against heterogeneous vancomycin-intermediate *S. aureus* (hVISA) and VISA strains, whereas vancomycin-resistant *S. aureus* (VRSA) strains are resistant [18, 19]. Against enterococci, DAL possesses higher MIC values than it does against...
other Gram-positive species. It maintains activity against strains of vancomycin-resistant enterococci (VRE) expressing \textit{vanB} and \textit{vanC} gene products but it is inactive against VRE expressing \textit{vanA} [19, 20].

**Pharmacokinetics**
DAL administered intravenously exhibits linear dose-related pharmacokinetics [21]. DAL has a \(\beta\) half-life of \(>8\) days \((\sim 200\) hours\) and a terminal half-life of \(>14\) days \((\sim 346\) hours\), allowing for clinical safety and efficacy assessment using a once-weekly dosing regimen of \(1000\) mg on day 1 and \(500\) mg on day 8 [22]. The extended half-life of DAL is largely due to extensive, reversible binding to serum albumin, estimated to be roughly \(95\%\) [23]. The volume of distribution is \(0.52\) L/kg, with an area under the curve of \(3194.2\) L/mg/h and total plasma clearance of \(6.3\) mL/kg/h (24). DAL is not extensively metabolized. Approximately \(33\%\) of the total dose is excreted in the urine [21].

**Dosage**
The proposed clinical dosing regimen of DAL for the treatment of ABSSSI is \(1000\) mg given intravenously followed one week later by \(500\) mg. Dose adjustments are not required for patients with mild or moderate renal impairment (creatinine clearance \(\geq 30\) to \(79\) mL/min) and for patients receiving regularly scheduled haemodialysis \((3\) times/week\), whilst in those with chronic renal impairment whose creatinine clearance is \(<30\) mL/min and in those who no receiving regularly scheduled haemodialysis, the recommended once-weekly dose regimen for DAL should be reduced to \(750\) mg followed one week later by \(375\) mg. No dose adjustment of DAL is recommended for patients with mild hepatic impairment (Child-Pugh A), whereas caution should be exercised in those with moderate or severe hepatic impairment (Child-Pugh B and C) as no data are available to determine appropriate dosing [25].

**Clinical efficacy**
In a randomized, controlled, open-label, phase II proof-of-concept trial (VER001-5 study), adults patients with an SSTI due to Gram-positive bacteria were randomly assigned to 1 of 3 groups: 1-dose DAL (a single \(1100\)-mg dose of DAL administered intravenously as a single dose), 2-dose DAL (1 intravenous dose of \(1000\) mg of DAL, followed by a second intravenous dose of \(500\) mg 1 week later, or a comparator regimen (determined by the investigator before randomization). Similar success rates at both end of therapy (EOT) and follow-up assessments (day 24 for 1-dose DAL group, day 34 for 2-dose DAL group, and 2 weeks after the last dose for comparator regimen group) were found in all populations. The clinical success at EOT in the intention-to-treat (ITT) population was achieved in \(15\) of \(20\) (\(75\%)\) patients in 1-dose DAL group, \(19\) of \(21\) (\(91\%)\) patients in 2-dose DAL group, and in \(17\) of \(21\) (\(81\%)\) patients in comparator group, respectively. Similarly, the clinical success at EOT in the clinically evaluable (CE) population was achieved in \(13\) of \(16\) (\(81\%)\) patients in 1-dose DAL group, in \(16\) of \(17\) (\(94\%)\) patients in 2-dose DAL group, and in \(17\) of \(21\) (\(81\%)\) patients in comparator group, respectively. Clinical success rates at the follow-up visit for patients infected due to MRSA were \(80\%\) (4 of 5 patients) for 2-dose DAL group, \(50\%\) (3 of 6 patients) for 1-dose DAL group, and \(50\%\) (1 of 2 patients) for the comparator group. The overall microbiologic success rates at follow-up visit against \textit{S. aureus} were \(90\%\) (9 of 10 patients) for 2-dose DAL group, \(50\%\) (5 of 10 patients) for 1-dose DAL group, and \(60\%\) (6 of 10 patients) for the comparator group [26]. In a randomised, double-blind, phase III trial (VER001-9 study), patients with complicated SSTIs (cSSTIs) were randomized to receive DAL (\(1000\) mg given intravenously on day 1 and \(500\) mg given intravenously on day 8) or linezolid (\(600\) mg given intravenously or intravenously/orally every 12 h for 14 days). Eight hundred fifty-four patients with cSSTIs received treatment under this protocol. Of the 854 treated patients, \(700\) (\(82\%)\) were CE at the EOT visit, and \(660\) (\(77\%)\) were CE at the test-of-cure (TOC) visit (14±2 days after completion of treatment with the study medication). The clinical and microbiological success at the EOT visit in the CE population was achieved \(92.3\%\) and \(87.6\%\) \textit{versus} \(94.2\%\) and \(90.2\%\) in the DAL group and in the linezolid group, respectively. Similarly, the clinical and microbiological success at the TOC visit in the CE population was achieved \(88.9\%\) and \(89.5\%\) \textit{versus} \(91.2\%\) and \(87.5\%\) in the DAL group and in the linezolid group, respectively. MRSA eradication rates at the TOC visit (eradicated or presumed eradicated) were \(91\%\) and \(89\%\) for the DAL and linezolid groups, respectively [27].
recently, two multicentre, randomised, double-blind, phase III trials (DISCOVER 1 and DISCOVER 2; ClinicalTrials.gov numbers, NCT01339091 and NCT01431339) examined the non-inferiority of DAL at a dose of 1000 mg intravenously on day 1 followed by 500 mg intravenously on day 8 versus vancomycin at a dose of 1000 mg (or 15 mg/Kg) intravenously every 12 hours for at least 3 days, with an option to switch to oral linezolid, at a dose of 600 mg every 12 hours, to complete 10 to 14 days of therapy in adults with ABSSSI. Pooled results of the DISCOVER trials showed that the success rate at 48 to 72 hours after the initiation of therapy [early clinical evaluation (ECE)] in the ITT population [79.7% versus 79.8%; absolute difference (AD) -0.1%, 95% CI -4.5% to 4.2%], the decrease in lesion area by ≥20% from baseline at ECE in the ITT population [88.6% versus 88.1%; AD 0.6%, 95% CI -2.9% to 4.1%], and the success rate at the EOT in the CE population [90.7% versus 92.1%; AD -1.5, 95% CI -4.8% to 1.9%] were similar for DAL group and comparator group. Similarly, no significant differences between DAL and comparator among patients with infection due to MRSA (89.2% versus 96.0%, respectively) or MSSA (91.5% versus 92.9%, respectively) were observed at the EOT in the CE population. Moreover, no significant differences between the groups according to systemic inflammatory response syndrome (SIRS) status at baseline were observed. Clinical success according to infection type (cellulitis, major abscess, and traumatic wound or surgical-site infection) were similar for DAL group and comparator group [28].

**Efficacy in elderly patients**

It is well documented that more than 70% of elderly patients have at least one skin problem owing to multiple factors [29, 30]. Although limited by small numbers, in the DISCOVER’s trials, no substantial differences between DAL and comparator were observed in ≥65 years old patients at ECE in the ITT population [32/37 (86.5%) vs. 33/43 (76.7%); AD 9.7%, 95%CI -8.1 to 26.8 in DISCOVER 1 and 57/70 (81.4%) vs. 66/81 (81.5%); AD -0.1, 95%CI -13.0 to 12.4 in DISCOVER 2, respectively] [31]. In this population, no dose adjustment is necessary.

**Clinical safety**

DAL appears to be well tolerated in animal studies, phase I, II and III clinical trials [32]. In VER001-5 study, all treatment regimens were well tolerated and drug-related adverse reaction rates were similar across the 3 groups. Specifically, drug-related adverse events were reported in 11 (55%) patients of 1-dose DAL group, 10 (48%) patients of 2-dose DAL group, and 12 (57%) patients who received comparator regimens. However, there were no discontinuations due to adverse event in the DAL groups [26]. In VER001-9 study, adverse events were reported in 56% of patients in the DAL group and in 61% in the linezolid group. Overall, adverse events were categorized as mild or moderate. Adverse events related to treatment were more frequent in the linezolid group (32.2%) than in the DAL group (25.4%). In the experimental group, the most common adverse event related to treatment were nausea (3.2%), diarrhoea (2.5%), headache (1.9%), vomiting (1.9%), and rash (1.8%). Elevation of blood lactate dehydrogenase level was observed in 1.9% of DAL-treated patients compared to 1.8% of linezolid-treated patients [27]. In the DISCOVER’s trials, the number of patients that reported adverse events and the number of adverse events per patient in the DAL group were lower than those of vancomycin/linezolid group (32.8% versus 37.9%, P=0.05 and 540 versus 645, P=0.05; respectively). Overall, no significant differences between DAL and comparator among patients with treatment-related adverse event were observed (12.3% versus 13.7%, P=0.45; respectively). The most common treatment-related adverse events in the DAL and vancomycin/linezolid groups were nausea (2.5% versus 2.9%, P=0.62; respectively), diarrhoea (0.8% versus 2.5%, P=0.02; respectively), and pruritus (0.6% versus 2.3%, P=0.01; respectively). An infusion site-related reaction was found in 9 (1.4%) patients in the DAL group and 11 (1.7%) patients in the comparator group. Serious adverse events treatment-related were observed in 2 (0.3%) patients and 4 (0.6%) patients in the DAL and vancomycin/linezolid groups, respectively (P=0.41) [28].

**Other potential indications**

DAL was compared to vancomycin in the treatment of catheter-related bloodstream infections (CR-BSIs) in a phase II, open-label, randomized, controlled, multicenter study. The combined microbiological and clinical success at EOT visit in the microbiologically evaluable ITT population (micro-ITT) was achieved in 21 of 23 (91.3%) pa-
tients in DAL group and in 18 of 28 (64.3%) patients in comparator group, respectively. Similarly, the overall response at TOC visit in the micro-ITT population was achieved in 20 of 23 (87.0%) patients in DAL group and in 14 of 28 (50.0%) patients in comparator group, respectively [33]. Finally, the prolonged half-life and the promising bone penetration suggest that DAL might be useful in the management of patients with bone and joint infections, including prosthetic joint infection and osteomyelitis [34-36]. More recently, in a recent rabbit model of experimental sternal osteomyelitis with mediastinitis due to MRSA, DAL has proved superior to treatment with saline and similar to treatment with vancomycin [37].

**CONCLUSION**

DAL is a recent addition to the antibiotic armamentarium against Gram-positive microorganisms, including multi-resistant staphylococci. Overall, DAL demonstrated comparable efficacy and safety to comparator regimens in the treatment of ABSSSIs. The long-life of DAL is very attractive for the management of patients with ABSSSI in both the in-patient and out-patient settings, potentially reducing the length of hospital stay or avoiding hospital admission, with cost savings.

**Keywords:** acute bacterial skin and skin structure infections, MRSA, dalbavancin.

**SUMMARY**

Dalbavancin is a novel parenteral lipoglycopeptide antibiotic approved for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) in adults. Dalbavancin is highly active against common Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA). Dalbavancin has a prolonged half-life that allows for once weekly dosing. Phase III trials have demonstrated non-inferiority compared with vancomycin/linezolid in the treatment of ABSSSIs, including those sustained by MRSA.

**REFERENCES**


