New agents approved for treatment of acute staphylococcal skin infections

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Abstract

Vancomycin has been a predominant treatment for methicillin-resistant *Staphylococcus aureus* (MRSA) infections for decades. However, growing reservations about its efficacy led to an urgent need for new antibiotics effective against MRSA and other drug-resistant *Staphylococcus aureus* strains. This review covers three new anti-MRSA antibiotics that have been recently approved by the FDA: dalbavancin, oritavancin, and tedizolid. The mechanism of action, indications, antibacterial activity profile, microbial resistance, pharmacokinetics, clinical efficacy, adverse effects, interactions as well as available formulations and administration of each of these new antibiotics are described. Dalbavancin is a once-a-week, two-dose, long-acting intravenous bactericidal lipoglycopeptide antibiotic. Oritavancin, a lipoglycopeptide with bactericidal activity, was developed as a single-dose intravenous treatment for acute bacterial skin and skin-structure infections (ABSSSI), which offers simplifying treatment of infections. Tedizolid is an oxazolidinone-class bacteriostatic once-daily agent, available for intravenous as well as oral use. Increased ability to overcome bacterial resistance is the main therapeutic advantage of the novel agents over existing antibiotics.

Key words: acute bacterial skin, skin-structure infection, anti-bacterial agents, dalbavancin, oritavancin, tedizolid.

Antibacterial resistance is a growing global problem. At least 2 million people in the U.S. annually acquire serious infections with bacteria that are resistant to one or more antibacterial drugs. Approximately 23 000 people die because of drug-resistant infections [1]. The group of most widespread pathogenic bacteria includes *Staphylococcus aureus* (SA), one of the most important species developing resistance to chemotherapeutic agents. *Staphylococcus aureus* has become one of the major human pathogens causing life-threatening conditions in the 21st century. *Staphylococcus aureus* is a Gram-positive (G(+)) coccus. It is frequently found in the human respiratory tract and on the skin surface. *Staphylococcus aureus* is not always pathogenic, but infections due to methicillin-resistant *Staphylococcus aureus* (MRSA), representing up to 50% of all staphylococcal infections, are a particular challenge [2].

Staphylococcus aureus is a common cause of skin infections, respiratory diseases (e.g. sinusitis), as well as gastroenteritis. It can cause a range of conditions, from minor skin infections and abscesses to life-threat-

ening diseases such as pneumonia, endocarditis, osteomyelitis, meningitis, toxic shock syndrome, bacteremia, sepsis and potentially life-threatening skin and skin-structure infections (SSSIs). Pathogenic *S. aureus* strains developed several antibiotic-resistant forms (e.g. MRSA) in past decades; their emergence (particularly multi-drug resistant strains) is a worldwide medical problem. In addition, MRSA skin infections are increasingly common. Moreover, some community-acquired MRSA strains produce a deadly endotoxin called Panton-Valentine leukocidin. These strains cause skin and soft tissue necrotizing infections as well as severe necrotizing pneumonias [3]. SSSIs are estimated to represent more than 15 million infections [4] and 870 000 hospital admissions [5] per year in the United States. Hence, there is an urgent need for new antibiotics effective against MRSA and other drug-resistant SA strains.

Three new drugs, dalbavancin (Dalvance; Durata Therapeutics, U.S.) [6], oritavancin (Orbactiv; The Medicines Company, U.S.) [7], and tedizolid phosphate (Sivextro; Cubist Pharmaceuticals, U.S.) [8] were approved by the U.S. Food and Drug Administration (U.S. FDA) in 2014 for SA infections. These drugs are intended mainly to treat acute bacterial skin and skin-structure infections (ABSSSI) caused by MRSA and certain other types of bacteria. Dalbavancin, oritavancin, and tedizolid provide coverage of G(+) pathogens, including MRSA, with a simplified dosing regimen.

In Europe, the European Medicines Agency (EMA) granted a marketing authorization valid throughout the European Union for dalbavancin (under the name Xydalba; 500 mg powder for concentrate for solution for infusion) in February, 2015 [9]. In January, 2015, the EMA Committee for Medicinal Products for Human Use adopted a positive opinion, recommending the granting of a marketing authorization for the medicinal product Orbactiv (400 mg oritavancin powder, intended for the treatment of ABSSSI in adults) [10], as well as for the medicinal product Sivextro (200 mg tedizolid tablets), intended for the same indication [11].

Dalbavancin

Dalbavancin (formerly BI-387, BI-397, or MDL 63397), a long-acting intravenous (*i.v.*) bactericidal lipoglycopeptide antibiotic, is a teicoplanin-derived lipoglycopeptide. This once-a-week, two-dose antibiotic belongs to the same class as vancomycin, the most widely used antistaphylococcal chemotherapeutic.

Dalbavancin is approved in the U.S. for use in adults with ABSSSI from the following G(+) pathogens: *S. aureus* (including MRSA and methicillin-susceptible SA – MSSA), *Streptococcus pyogenes*, *S. agalactiae* and the *S. anginosus* group (including *S. anginosus*, *S. intermedius*, and *S. constellatus*) [12]. In the European Union, dalbavancin is indicated for the treatment of ABSSSI in adults [13].

Dalbavancin inhibits cell wall synthesis in G(+) bacteria. All Gram-negative bacteria are inherently resistant to dalbavancin. Apart from official indications, dalbavancin is also active against vancomycin-intermediate *S. aureus* (VISA) and heterogeneous VISA (hVISA) [14]. It also possesses *in vitro* activity against vancomycin-susceptible *Enterococcus faecium*, *Enterococcus faecalis*, and methicillin-resistant *Staphylococcus epidermidis* [15].

Microbial resistance

The drug has a low potential for the selection of resistant microorganisms. Resistance to dalbavancin in *Staphylococcus* spp. and *Enterococcus* spp. is mediated by VanA, a genotype that results in modification of the target peptide in the nascent cell wall [13]. Cross-resistance between dalbavancin and other classes of antibiotics was not seen in *in vitro* studies [13].

Pharmacokinetics

Dalbavancin has a prolonged half-life up to 8.5 days that facilitates once-a-week dosage [16, 17]. After intravenous injection of a single 1 g dose, serum dalbavancin concentrations stay above the minimum inhibitory concentration for MRSA for about 8 days [18]. The terminal half-life of dalbavancin is about 14 days. However, when the drug was given once a week for 8 weeks to healthy adults with normal renal functions, it did not accumulate [18]. Excretion is very slow; the drug is mainly excreted in the urine (33% unchanged, 12% metabolite) in 42 days and, to a lesser degree, in feces (20%) in 70 days. This can be important for patients who develop adverse reactions.

Clinical efficacy

Safety and efficacy of dalbavancin were evaluated in two double blind, non-inferiority phase III clinical trials, DISCOVER 1 and DISCOVER 2, with a total of 1312 (573/739) adults with ABSSSI [19]. These trials compared dalbavancin (1.0 g once on day 1 and 500 mg on day 8) to vancomycin (1.0 g or 15 mg/kg every 12 h for at least 3 days) followed by oral linezolid to complete a 10- to 14-day course. In both studies, the primary endpoint was no increase from baseline in the size of the infected area 48–72 h after starting treatment and a body temperature ≤ 37.6°C. Main DISCOVER 1 and DISCOVER 2 results are summarized in Table I. These results showed that dalbavancin was as effective as vancomycin for the treatment of ABSSSI [19, 20]. Clinical success rates were maintained at follow-up at days 26–30 [19].

Table I. Main DISCOVER 1 and DISCOVER 2 study results (primary endpoint[a] and sensitivity analysis[b] data) [19]

Trial name	Intervention	Total number of patients treated (*N*)	Cessation of lesion spread effect[a], % of patients treated (number/total number [*n*/*N*])	Reduction in lesion area effect[b], % of patients treated (number/total number [*n*/*N*])
DISCOVER 1	DAL	288	83.3 (240/288)	89.9 (259/288)
DISCOVER 1	VAN/LIN	285	81.8 (233/285)	90.9 (259/285)
DISCOVER 2	DAL	371	76.8 (285/371)	87.6 (325/371)
DISCOVER 2	VAN/LIN	368	78.3 (288/368)	85.9 (316/368)
Both trials	DAL	659	79.7 (525/659)	88.6 (584/659)
Both trials	VAN/LIN	653	79.8 (521/653)	88.1 (575/653)

DAL – dalbavancin, LIN – linezolid, VAN – vancomycin. [a]Effect of cessation of lesion spread is an element of primary composite end point. [b]The sensitivity analysis of the primary end point was the success rate, defined as a reduction in the infection area of at least 20% at 48 to 72 h after the initiation of therapy, in the intention-to-treat population.

Adverse effects

In phase II and III clinical trials (a total of 1778 patients treated with dalbavancin), the most common adverse reactions registered were nausea (5.5%), headache (4.7%), and diarrhea (4.4%) [12]. Rapid infusions can cause the hypersensitivity reaction of "red man syndrome". Slowing the infusion rate may prevent this reaction from recurring [13]. Rare but serious hypersensitivity reactions, including anaphylaxis, also have been reported; the long half-life of the drug can complicate it. Patients with a history of a hypersensitivity reaction to another glycopeptide (vancomycin, telavancin) may be at increased risk [18]. In clinical trials, some participants in the dalbavancin group had elevations in one of the liver enzyme tests [21]. Adverse effects (AE) were, however, less frequent with dalbavancin than older glycopeptides [22]. Unlike telavancin, dalbavancin did not prolong the time interval from the beginning of the QRS complex to the end of the T wave on an electrocardiogram that represents the time during which contraction of the ventricles occurs (QT interval) in *i.v.* doses up to 1500 mg [23].

Clostridium difficile is susceptible to dalbavancin [24], but treatment of *C. difficile* infections (CDIs) is not a licensed indication for dalbavancin currently. On the other hand, *C. difficile*-associated diarrhea (CDAD) has been reported with dalbavancin [12]. The CDAD must be considered in all patients who present with diarrhea following dalbavancin use, and all such persons must be thoroughly evaluated in order to begin appropriate treatment.

Drug interactions

No clinical drug-drug interaction studies have been conducted with dalbavancin. In *in vitro* studies, no antagonism has been observed between dalbavancin and some other essential antibiotics [13]. Nonclinical studies demonstrated that dalbavancin is not a substrate, inducer, or inhibitor of cytochrome P450 (CYP) isoenzymes. Drug-laboratory test interactions have not been reported [12, 13].

Formulation and administration

The drug is available in 500 mg single-use vials containing dalbavancin hydrochloride [12, 13]. Dalvance contains lactose as an excipient. Saline-based infusion solutions may cause precipitation and should not be used for reconstitution [12, 13].

Dalbavancin is administered in a two-dose *i.v.* regimen – 1000 mg on day one followed by 500 mg 1 week later. Both infusions should be given over 30 min. Patients with a creatinine clearance less than 30 ml/min require a dose adjustment – the first dose is 750 mg followed 1 week later by 375 mg [12, 13]. Patients receiving hemodialysis do not require a dose adjustment. No dose adjustment is necessary also for patients with mild hepatic impairment; no data exist with reference to patients with moderate or severe hepatic impairment.

In clinical trials, the efficacy and tolerability of dalbavancin were similar to a comparator drug regardless of age. The pharmacokinetic parameters of dalbavancin were not significantly altered with age [12].

Pregnancy and nursing

Dalbavancin is classified as pregnancy category C (no adequate human studies and some fetal toxicity in animals) [25]. The drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Dalbavancin is excreted in the milk of lactating rats; it is not known whether dalbavancin or its metabolite is excreted in human milk [25]. Therefore, caution should be used when dalbavancin is administered to a nursing woman.

Oritavancin

Oritavancin (LY-333328) is a semi-synthetic lipoglycopeptide that has concentration-dependent bactericidal activity [26]. This drug with potent activity against G(+) bacteria was developed as a single-dose treatment for ABSSSI. Gram-negative bacteria are resistant to oritavancin.

Oritavancin for injection (Orbactiv) is approved in the U.S. for the treatment of adult patients with ABSSSI caused by susceptible isolates of the following G(+) microorganisms: *S. aureus* (including MSSA and MRSA), *S. pyogenes*, *S. agalactiae*, *S. dysgalactiae*, *S. anginosus* group, as well as *E. faecalis* (vancomycin-susceptible isolates only) [27].

Oritavancin exerts its effects by way of three mechanisms of action – inhibition of transglycosylation, inhibition of transpeptidation, and cell membrane disruption [26, 28]. The first two mechanisms disrupt bacterial cell wall synthesis. The second mechanism distinguishes oritavancin from vancomycin and is responsible for oritavancin's activity against vancomycin-resistant bacterial strains. The third mechanism disrupts the bacterial membrane potential and increases membrane permeability, which finally results in rapid cell death [28]. The third mechanism is shared with telavancin but not vancomycin and confers activity against daptomycin non-susceptible organisms. In total, the three abovementioned mechanisms of action ensure activity of oritavancin against vancomycin-susceptible and vancomycin-resistant bacteria, as well as bactericidal activity against actively growing, stationary phase, and biofilm-producing Gram-positive bacteria.

Apart from official indications, oritavancin also has concentration-dependent activity against VISA, hVISA, and vancomycin-resistant SA (VRSA) strains [29]. Data from *in vitro* studies support oritavancin use in endocarditis and bacteremia, particularly as it has excellent intracellular bactericidal activity [30, 31].

Microbial resistance

In *in vitro* studies, resistance to oritavancin was observed in isolates of *S. aureus* and *E. faecalis*. Resistance to oritavancin was not observed in clinical studies until now [27].

Pharmacokinetics

At doses up to 1200 mg, the pharmacokinetics of oritavancin are linear. Oritavancin has a terminal half-life of approximately 245 h [32]. The long half-life allows for a single dose of drug [33]. Due to oritavancin's long half-life, effects of single drug administration persist for some days. This can be important for patients with adverse reactions, because the drug is not removable by hemodialysis [27, 34].

In vitro human liver microsome studies indicated that oritavancin is not metabolized. The drug is slowly excreted in feces and via the kidney [27].

Oritavancin has extensive tissue distribution [31, 35]. Therapeutic concentrations are achieved in skin structures and skin blister fluid [26]. The pharmacokinetics of oritavancin have not been investigated in the pediatric population [33].

Clinical efficacy

Safety and efficacy of oritavancin were evaluated in two randomized, double-blind, multicenter non-inferiority phase III clinical trials, SOLO I [36] and SOLO II [37], with a total of 1987 adults with ABSSSI (including 405 with proven MRSA infections). In these studies efficacy of ABSSSI treatment with oritavancin (n = 976) in a 1200 mg single dose was compared to efficacy of 7–10-day treatment with vancomycin (*i.v.* route, twice daily, 1.0 g or 15 mg/kg b.w.; n = 983). The results generally showed that oritavancin was as effective as vancomycin for the treatment of ABSSSI.

In the SOLO I trial (n = 954) three efficacy end points were set for non-inferiority [36]. The primary composite endpoint was defined as cessation of spreading (or reduction in lesion size), afebrile state, and no additional chemotherapeutics required 48 to 72 h after oritavancin administration. The secondary endpoints were investigator-assessed clinical cure 7 to 14 days after the end of treatment and a reduction in lesion size of 20% or greater 48–72 h after administration of the antibiotic. All three end points met the assumed non-inferiority margin (10 percentage points) for oritavancin vs. vancomycin. The results were as follows: primary end point 82.3% vs. 78.9%; investigator-assessed clinical cure 79.6% vs. 80.0%; and percentage of patients with a reduction in lesion area of 20% or greater 86.9% vs. 82.9%. Efficacy results measured according to type of pathogen, including MRSA, were similar in the two treatment groups. The frequency of AE was also similar (nausea was more common among patients treated with oritavancin). Thus, oritavancin was found to be non-inferior to vancomycin for all endpoints, including in the subset of patients with MRSA-proven infections [36].

In the SOLO II trial (n = 1019) [37], three efficacy endpoints were set for non-inferiority testing, the same as in the SOLO I trial. All three efficacy endpoints met the criterion of the 10% non-inferiority margin: the primary endpoint – 80.1% vs. 82.9%, the second – 82.7% vs. 80.5%, and third – 85.9% vs. 85.3%, for oritavancin and vancomycin, respectively. Efficacy outcomes measured according to type of pathogen, including MRSA, were similar in both treatment groups. The frequencies of adverse events also were similar between treat-

ment groups; in general, oritavancin was well tolerated [37].

Adverse effects

In the pooled SOLO I/II trials results, the most commonly encountered adverse reactions (≥ 3%) in patients receiving a single 1200 mg dose of oritavancin were headache, nausea, vomiting, limb and subcutaneous abscesses, as well as diarrhea. The same AE were most common in the vancomycin groups. Details concerning adverse events/effects in the SOLO I/II trials [27, 36, 37] are summarized in Table II.

Oritavancin did not cause prolongation of QT interval corrected for heart rate, even a supra-therapeutic 1600 mg dose in volunteers (n = 48) [26].

Existing data indicate the considerable potential of oritavancin for CDI treatment (potential indication only, currently not licensed) [31]. However, CDAD has been reported also with oritavancin [27]. *Clostridium difficile* infection must be considered in all patients who present with diarrhea following oritavancin administration. All such individuals must be thoroughly evaluated and adequately treated.

Drug interactions

In *in vitro* studies, oritavancin exhibits synergistic bactericidal activity in combination with gentamicin, rifampicin, or moxifloxacin against isolates of MSSA, with linezolid or gentamicin against isolates of hVISA, VISA, and VRSA, and with rifampin against isolates of VRSA. *In vitro* studies demonstrated no antagonism between oritavancin and gentamicin, moxifloxacin, rifampin or linezolid [27].

Oritavancin influences activity of certain cytochrome P450 enzymes. It is a nonspecific, weak inhibitor of some CYP isoforms (CYP2C9 and CYP2C19; warfarin and omeprazole metabolism inhibition, respectively) or its inducer (CYP3A4 and CYP2D6; midazolam and dextromethorphan metabolism induction, respectively) [27, 32]. Therefore, caution should be used when administering oritavancin concomitantly with drugs with a narrow therapeutic window that are metabolized mainly by one of the affected CYP enzymes (especially, patients should be closely monitored for bleeding if concomitantly receiving oritavancin and warfarin) [27, 32].

Use of unfractionated heparin sodium is contraindicated for 48 h after oritavancin administration (the false elevation of the activated partial thromboplastin time tests) [33]. In addition, results of the prothrombin time (PT) and international normalized ratio (INR) tests to determine proper dosage of warfarin are falsely prolonged – combination of oritavancin with warfarin may result in higher levels of warfarin and risk of bleeding. The effect on PT and INR remains for up to 24 h after

Table II. Adverse events/effects registered in ≥ 1.5% of individuals given oritavancin/vancomycin in the pooled SOLO I/II trials and drug discontinuation for AE [27, 36, 37]

Adverse event/effect	Oritavancin group, % of patients treated (number/total number [n/N])	Vancomycin group, % of patients treated (number/total number [n/N])
Nausea	9.9 (97/976)	10.5 (103/983)
Headache	7.1 (69/976)	6.7 (66/983)
Vomiting	4.6 (45/976)	4.7 (46/983)
Abscesses (limb and subcutaneous)	3.8 (37/976)	2.3 (23/983)
Diarrhea	3.7 (36/976)	3.4 (32/983)
Increased ALT levels	2.8 (27/976)	1.5 (15/983)
Dizziness	2.7 (26/976)	2.6 (26/983)
Infusion site phlebitis	2.5 (24/976)	1.5 (15/983)
Tachycardia	2.5 (24/976)	1.1 (11/983)
Infusion site reaction	1.9 (19/976)	3.5 (34/983)
Increased AST levels	1.8 (18/976)	1.5 (15/983)
SAR (total)	5.8 (57/976)	5.9 (58/983)
SAR – cellulitis	1.1 (11/976)	1.2 (12/983)
Drug discontinuation for AE[a,b]	3.7 (36/976)[a]	4.17 (41/983)[b]

AE – adverse events/effects, SAR – serious adverse reactions. [a]The most common reported reactions leading to discontinuation of oritavancin were cellulitis (4/976 patients, 0.4%) and osteomyelitis (3/976, 0.3%). [b]In the vancomycin group, adverse events that led to discontinuation of the study drug were hypersensitivity (5/983, 0.51%), cellulitis (5/983, 0.51%) as well as sepsis, bacterial skin infection, pruritus, and rash (2/983, 0.20% for each condition).

the oritavancin dose. Combined administration of oritavancin and warfarin renders the monitoring test for warfarin unreliable, and the levels of warfarin may be uncontrollably increased. However, oritavancin itself has no effect on the coagulation system [27, 38].

Formulation and administration

Oritavancin is administered intravenously, as a single-dose infusion of 1200 mg. Orbactiv contains oritavancin diphosphate in 400 mg sterile vials. Three Orbactiv 400 mg vials need to be reconstituted and diluted to prepare a single 1200 mg *i.v.* dose; aseptic technique should be used. The drug is administered over 3 h [27]. The drug should be given in one liter of 5% dextrose in sterile water. Normal saline cannot be used, as it is incompatible with oritavancin and may cause precipitation of the drug [27]. Dosage adjustment for patients with mild to severe renal (or mild to moderate liver) impairment is not required, and there are no adjustments in dosage for age, gender, race or weight [26].

No studies on safety and effectiveness of oritavancin in pediatric patients have been completed. Differences in responses between the elderly and younger patients have not been identified, but greater sensitivity of some older individuals cannot be ruled out.

Pregnancy and nursing

Oritavancin is classified in pregnancy category C. It is unknown whether oritavancin is excreted in human milk (caution should be exercised) [39].

Tedizolid

Tedizolid, the active moiety of the prodrug tedizolid phosphate (formerly torezolid, TR-701, DA-7157; active moiety TR-700), is an oxazolidinone-class bacteriostatic agent.

Tedizolid phosphate (Sivextro) is approved in the U.S. for the oral and intravenous treatment of ABSSSI caused by susceptible isolates of the following Gram-positive microorganisms [40]: *S. aureus* (including MRSA and MSSA isolates), *S. pyogenes*, *S. agalactiae*, *S. anginosus* group, as well as *E. faecalis*. Its *in vitro* potency is up to 16 times that of linezolid [16, 41]. The drug has been specifically designed to be active against linezolid-nonsusceptible *S. aureus* [41, 42].

As with linezolid, tedizolid inhibits bacterial protein synthesis by binding to the P site of the 50S ribosomal subunit of the bacterial ribosome [41], resulting in inhibition of protein synthesis. However, tedizolid presumably inhibits its synthesis also through an additional mechanism of action different from that of other oxazolidinone antibacterial drugs [16, 41]. Therefore, cross-resistance between tedizolid phosphate and other classes of antibacterial drugs is unlikely [43].

Apart from the above-mentioned strains, tedizolid is active *in vitro* against other Gram-positive pathogens, including *E. faecium* and coagulase-negative staphylococci. Tedizolid is also active *in vitro* against certain *Mycobacterium tuberculosis* strains resistant to isoniazid, rifampin, or both these drugs [44, 45]. Gram-negative bacteria are resistant to tedizolid.

Microbial resistance

Cross-resistance to tedizolid is generally displayed by microorganisms resistant to oxazolidinones via mutations in chromosomal genes encoding 23S subunit rRNA or ribosomal proteins. Spontaneous mutations responsible for reduced susceptibility to tedizolid occur *in vitro* at a frequency of about 10^{-10} [40].

Pharmacokinetics

Tedizolid phosphate is rapidly converted by endogenous phosphatases to tedizolid, the active agent, after administration [46]. T_{max} after administration of a single dose is about 1.1 h (intravenous route) or 2.5 h (oral route). Steady states are achieved within 3 days in both routes. The drug is mainly excreted in the feces (80%), and in lesser quantities (20%) via the kidney, both as an inactive metabolite. The terminal half-life of tedizolid is 12 h [18].

Clinical efficacy

Safety and efficacy of tedizolid were evaluated in two clinical, multicenter, double-blind, non-inferiority trials involving 1315 adults with ABSSSI named ESTABLISH-1 [47] and ESTABLISH-2 [48], comparing tedizolid 200 mg once daily for 6 days (plus 4 days of placebo) with linezolid 600 mg every 12 h for 10 days [49]. Patients in ESTABLISH-1 received oral therapy only; those in ESTABLISH-2 started with *i.v.* treatment for at least 1 day before being given the option to switch to the oral formulation. The primary endpoint in both trials was clinical response 48–72 h after the first dose. In the ESTABLISH-1 study (n = 649), tedizolid caused cessation of lesion spread in 79% of cases and reduction in lesion area in 78%. For linezolid analogical percentages were 79% and 76%. In the ESTABLISH-2 study (n = 666), tedizolid stopped lesion spread in 86% of cases and reduced lesion area in 85%, while administration of linezolid brought the same effect in 84% and 83% of cases, respectively. Clinical response rates were maintained 7–14 days after the end of therapy. These results showed that tedizolid was as effective as linezolid for the treatment of ABSSSI.

Adverse effects

The most common AE identified in the clinical trials were nausea (8%), headache (6%), diarrhea (4%), vomiting (3%), and dizziness (2%) [40]; similar reactions occurred in patients taking linezolid. In clinical trials, potentially significant decreases in platelet counts occurred in 2.3% of individuals taking tedizolid, compared to 4.9% of those who received linezolid. In an animal model of infection, the antibacterial activity of tedizolid phosphate was reduced in the absence of granulocytes (there is a lack of human data on safety and efficacy of tedizolid in patients with neutropenia). Therefore, alternative therapies should be considered when treating patients with neutropenia [43].

Tedizolid demonstrated relevant activity against *C. difficile* [50], but treatment of CDIs is not a licensed indication for tedizolid at present. On the other hand, CDAD has been reported with tedizolid phosphate [43]. All patients who present with diarrhea following tedizolid phosphate use must be thoroughly evaluated in order to begin appropriate treatment. Tedizolid has less gastrointestinal disturbance and myelotoxicity than pre-existing oxazolidinones [51, 52].

Drug interactions

In vitro drug combination studies with tedizolid and many essential chemotherapeutics demonstrate neither synergy nor antagonism [40]. *In vitro*, tedizolid weakly and reversibly inhibits monoamine oxidase. Tedizolid is not a substrate, inducer, or inhibitor of CYP enzymes [40].

Formulation and administration

Tedizolid is available for intravenous as well as oral use. There are 200 mg single-use vials and 200 mg tablets available. Sivextro vials for injection contain a lyophilized tedizolid phosphate powder for injection. The contents of the vial should be reconstituted using aseptic technique (first in sterile water for injection and then the solution must be further diluted in 0.9% NaCl) [40].

Recommended dosage for SSSIs is 200 mg administered either for 6 days orally once daily or as an *i.v.* infusion over 1 h (also once daily for 6 days) in patients 18 years of age or older. No dose adjustment is necessary for patients with liver or kidney impairment [46].

Available clinical trials have not identified differences in responses between the elderly and younger patients (insufficient numbers of subjects aged 65 and older). No substantial differences in pharmacokinetics were observed between elderly and younger subjects. Safety and effectiveness in patients below the age of 18 have not been established.

Pregnancy and nursing

Tedizolid is classified as category C in pregnancy [40]. Tedizolid is excreted in the breast milk of rats; it is not known whether the drug is excreted in human milk [53].

Conclusions

Dalbavancin, oritavancin, and tedizolid have been developed and evaluated for treatment of ABSSSI. These drugs offer simplified dosing regimens compared to other antibiotics that cover MRSA.

Dalbavancin has a long half-life [16, 17]. Hence, two required peripheral *i.v.* infusions at the clinic may, for instance, avoid the use of long-term PICC lines (a PICC line is a peripherally inserted central catheter – a long, slender, small, flexible tube that is inserted into a peripheral vein, typically in the upper arm) and home health services [54]. Use of dalbavancin in two doses 1 week apart may also allow outpatient treatment of some cases previously requiring hospitalization, providing a logistic advantage over vancomycin and daptomycin. However, the long half-life of dalbavancin also means that the effects of the drug administered once persist for some days. This can be important or even dangerous for patients who develop adverse reactions. Such patients or individuals who no longer need MRSA coverage will continue to be exposed to the antibiotic. This is an argument indicating that using previously available, lower cost antibiotics for ABSSSI may be a better choice in some cases.

Like dalbavancin, oritavancin also has a long half-life. Single dosing administration of oritavancin provides a small advantage over dalbavancin (two doses required), but a significant advantage over *i.v.* daptomycin and vancomycin (given once daily for 1–6 weeks and every 8–12 h, respectively [54]) in the case of individuals who require i.v. anti-MRSA therapy for ABSSSI. The advantage is that treatment of infections is simpler – e.g. the use of PICC lines and/or home infusions is avoided; it can lead to outpatient therapy after one infusion. Other potential advantages are the assurance of compliance, reduction of hospital-acquired infections, and patient satisfaction [33]. On the other hand, a long half-life of oritavancin causes that the effects of one drug administration persist for some days. This can be important (or dangerous) for patients with adverse reactions – hemodialysis is not effective in the case of this agent [34]. Persons who no longer need MRSA coverage will unnecessarily continue to be exposed to medication. This may be an argument for using pre-existing lower cost antibiotics for ABSSSI in some cases.

Tedizolid offers once-daily oxazolidinone dosing with high potency and reduced toxicity [22]. In an intravenous form it provides simpler dosing over daptomycin and vancomycin. As a tablet, it can be administered once daily (compared to twice daily with linezolid) [54]. Existence of both oral and intravenous formulation of tedizolid phosphate allows physicians flexibility in its use – e.g. to transition patients from *i.v.* to oral treatment as needed. The oral form offers the possibility of its use in outpatient settings, which could lower the requirement for expensive hospitalization [43].

Tedizolid is currently approved for treatment of ABSSSI only. However, non-purulent cases of ABSSSI are mostly not caused by MRSA and do not require MRSA coverage. In contrast, purulent skin infections are now caused predominantly by MRSA in many parts of the US [18]. Previously available, cheaper antibiotics with a good track record of treating non-purulent ABSSSI exist and can be used in such cases [54].

Dalbavancin, oritavancin, and tedizolid primarily offer improved ability to overcome bacterial resistance (there are no clinical reports of resistance to these drugs so far). The efficacy of dalbavancin and tedizolid for more dangerous infections (e.g. pneumonia, bacteremia) is still unknown, and their long-term safety has not been established [53]. However, alternative clinical indications for novel antibiotics licensed now for skin and soft tissue infection also exist. For dalbavancin prosthetic device infections, osteomyelitis and continuous ambulatory peritoneal dialysis (CAPD) peritonitis are proposed [55]. For oritavancin endocarditis, osteomyelitis, prosthetic joint infections (PJIs) and CAPD peritonitis are cited in the literature [55]. Tedizolid has potent activity against multidrug-resistant Gram-positive pathogens such as staphylococci, enterococci, and streptococci, including vancomycin-resistant enterococcal (VRE) and linezolid-resistant strains [56]. This is one reason why there is a longer list of potential indications for tedizolid – PJIs, osteomyelitis, other prosthetic device infections, pneumonia, infections caused by toxin producing organisms, pediatric Gram-positive infections and infections in patients with renal conditions [55]. All three drugs are taken into account as potential therapeutic options for VRE bacteremia, but no clinical data on their usage for VRE infections are available [57]. The above-mentioned potential clinical indications require further research and evidence.

The cost-benefit ratio for treating ABSSSI likely favors the pre-existing MRSA (and non-MRSA) chemotherapeutics. According to some authors, however, dalbavancin and oritavancin may constitute convenient and cost-effective treatments for ABSSSI [22]. The three new drugs discussed in this article are approved for use in adults only (no pediatric indications), but extension of indications can be expected. A single dose of dalbavancin (1000 mg/15 mg/kg b.w.; standard adult dose) was well tolerated in a phase I study in ten pediatric subjects aged 12–17 years [58].

Prevention of drug-resistant bacteria development is specifically required when new antibiotics are administered. Prescribing dalbavancin, oritavancin or tedizolid in the absence of a proven (or strongly suspected) bacterial infection or other appropriate indication increases the risk of development of resistant bacterial strains.

Conflict of interest

The authors declare no conflict of interest.

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