New and Investigational Antimicrobials for the Treatment of Severe Skin Infections

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Abstract: With increasing antibiotic resistance reported worldwide, there is a great interest in the development of new antibacterial agents for the treatment of severe skin and skin structure infections (SSSIs). SSSIs mainly involve Gram-positive pathogens. Although many of older antibiotics remain effective, new drug development remains crucial owing to the increase in drug resistance among the major Gram-positive pathogens. Since 1999 new antibacterial agents have entered the market or are being evaluated in clinical trials for the treatment of SSSIs. These agents have novel mechanism of action and sufficient improvements in potency to overcome resistance. Linezolid, quinupristin-dalfopristin, daptomycin and tigecycline have been approved by the FDA for the treatment of SSSIs. Other antimicrobials (dalbavancin, oritavancin, telavancin) are currently in clinical development for this indication. This review focuses on the chemistry, microbiology, pharmacology, clinical efficacy and safety of several novel antibacterial agents for the treatment of SSSIs.

Key Words: SSSIs, linezolid, quinupristin-dalfopristin, daptomycin, tigecycline, dalbavancin, oritavancin, telavancin.

INTRODUCTION

Gram-positive bacteria (e.g. Staphylococcus aureus, Streptococcus pyogenes and Streptococcus agalactiae) are the main cause of skin and skin structure infections (SSSIs) [1-3].

The terminology used for infections of skin and skin structures is often varied and confusing. SSSIs can be divided in uncomplicated (uSSSIs) or complicated (cSSSIs). USSSIs include such clinical entities as simple abscesses, impetigenous lesions, foruncles, and cellulitis. CSSSIs include soft tissue infections (STIs) such burns, major abscesses, infections of deeper soft tissues and other skin structure infections requiring significant surgical intervention along with antimicrobial drug therapy [2].

Antimicrobial resistance among Gram-positive bacteria has increased significantly during the last decade, with methicillin resistance among S. aureus [4-7]. Multiresistant bacteria (MRB) are involved in 1/5 of nosocomial infections and the 3/4 of the MRB are methicillin resistant S. aureus (MRSA) [8]. For many years, MRSA was considered a multi-drug-resistant pathogen associated with hospitals [9]. Recently, many studies have reported that MRSA is an emerging community-associated pathogen (CA-MRSA) [10, 11]. A recent study reported that skin and soft tissue infections (STIs) are more common in CA-MRSA cases than in nosocomial MRSA cases (75% versus 37%) [12]. The structural gene for methicillin resistance, mecA, encodes a novel penicillin binding protein (PBP)-2’, which has reduced affinity for all β-lactam agents [13]. For this reason, glycopeptide agents (vancomycin and teicoplanin) have been considered the only available antibiotics active against multidrug-resistant staphylococci. Subsequently, the first vancomycin-intermediately resistant S. aureus (VISA) isolate was identified in Japan in 1997 [14]. More recently clinical strains of MRSA with reduced susceptibility to vancomycin or more generally to glycopeptides, and referred as VISA or glycopeptide-intermediate S. aureus (GISA), have been reported in several countries [15-17]. However, the first clinical isolate of vancomycin resistant S. aureus (VRSA) was reported from United States in 2002 [18]. More recently VRSA strains have been reported from various parts of the world [19-22]. The emergence of antibiotic resistance among the pathogens most commonly associated with SSSIs (e.g. methicillin- and vancomycin-resistant S. aureus and macrolides-resistant S. pyogenes) has compromised treatment options and increased the incidence of treatment failure [3, 16, 23, 24]. The difficulty to treat the cSSSI caused from more resistant bacterial pathogens has created a need for different therapeutic agents. The response of the pharmaceutical industry is the development of new antibiotics which are highly active against these pathogens and have novel and diversified mechanisms of action. Newly approved options for the treatment of SSSIs include quinupristin-dalfopristin, linezolid and most recently daptomycin and tigecycline. This paper will review the potential role of novel FDA-approved investigational antimicrobial agents and will examine the status of some of those (dalbavancin, oritavancin, telavancin) that are currently under investigation. Table 1 provides information on the countries where these FDA licensed drugs are available with specific indications. Table 2 provides information about their pharmacological properties.

RECENT FDA-LICENSED ANTIMICROBIALS FOR TREATMENT OF SKIN INFECTIONS

Linezolid

Introduction

Linezolid is the first member of a new class of antibiot- ics, the oxazolidinones, which was developed for the treatment of infectious diseases caused by Gram-positive pathogens. Licensed by the FDA in the year 2000, the approved indications for linezolid use include the treatment of SSSIs,
caused by methicillin-susceptible *S. aureus* (MSSA) and MRSA, streptococci (*S. pyogenes* and *S. agalactiae*), in addition to other indications (e.g., nosocomial and community-acquired pneumonia and vancomycin-resistant *Enterococcus faecium* (VREF) infections) [25-27]. An additional indication approved in 2003 was for the treatment of diabetic foot infections caused by MSSA and MRSA [28].

**Chemistry and Mechanism of Action**

Linezolid, is a 3-(fluorophenil)-2-oxazolidinone [26]. Studies on its mechanism suggest that linezolid inhibits protein synthesis at a very early step, likely preceding the interaction of formyl-methionyl transfer RNA and the 30S ribosome with the initiator codon [29].

**In Vitro Susceptibility Testing**

*In vitro* studies have shown linezolid to be effective against many antibiotic resistant Gram-positive organisms, including MRSA, GISA and vancomycin-resistant enterococci (VRE) [30-33]. The linezolid susceptible breakpoints defined by FDA and Clinical Laboratory Standards Institute (CLSI), formerly National Committee for Clinical Laboratory Standards (NCCLS), are ≤ 2 μg/mL for *Enterococcus* spp., *Streptococcus pneumoniae* and other *Streptococcus* spp., and ≤ 4 μg/mL for *Staphylococcus* spp. [26]. Surveys have shown almost 100% susceptibility among staphylococci, including MRSA, enterococci and *S. pyogenes* [31, 34]. Tested against MRSA and MSSA strains collected from distinct part of the world, linezolid had MIC<sub>00</sub> ranging from 1-4 μg/mL [35, 36]. In a recent study, linezolid and several comparison Gram-positive focused agents were tested against 7971 Gram-positive isolates [37]. A total of 98% of linezolid MIC values were between 0.5 and 2 μg/mL. Linezolid resistance was detected in only 4 isolates (0.05%) [37]. No linezolid-resistant strains were detected from the 16 monitored nations participating in 2005, consistent with previously reported 2002-2004 results. Linezolid remained highly active against Gram-positive strains including MRSA (MIC<sub>90</sub>, 2 μg/mL) [38]. Linezolid is primarily a bacteriostatic against most susceptible organisms but has shown bactericidal activity against some strains of *S. pneumonia* [39].

**Mechanism of Resistance**

The only resistance mechanism described for linezolid is target modification. Most mutations defined in various species associated with linezolid resistance occur by guanosine to uracil substitution in the peptidyl transferase centre of 23S rRNA [40, 41]. These mutations were shown to decrease the oxazolidinone binding to the ribosome [42]. Studies into the mechanism of resistance have shown little evidence of spontaneous resistance development in *S. aureus* [43]. However, *in vivo* development of resistance to linezolid has been described for VREF and MRSA in patients who have received linezolid therapy [44-51]. Point mutations in the gene encoding for the 23S bacterial ribosome appear to be the mechanism in acquired resistance to linezolid in both enterococci and staphylococci [44, 52]. A recent study has demonstrated linezolid’s lack of cross-resistance with other protein synthesis inhibitors (including macrolides, chloramphenicol, lincomamides, aminoglycosides, streptogramins, tetracyclines) [53]. The ability of linezolid to circumvent multidrug-resistance is the result of its novel mechanism of action.

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Table 1. FDA Licensed Drugs for Treatment of Severe Skin and Skin Structure Infections<sup>a</sup>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
<th>Brand name</th>
<th>Countries</th>
</tr>
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<tbody>
<tr>
<td>Linezolid</td>
<td>cSSSIs and uSSSIs, nosocomial and community-acquired pneumonia, VREF infections (1999)</td>
<td>Zyvox</td>
<td>USA, Argentina, Brazil, Chile, Venezuela, UK, Ireland, Russia, Norway, Sweden, Finland, Denmark, Germany, Austria, Czech Republic, Switzerland, Belgium, France, Italy, Greece, Portugal, Spain, Israel, Singapore, Thailandia, Hong Kong, Malaysia, Australia, New Zeland, South Africa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zyvoxam, Linospan, Linox, Lizolid</td>
<td></td>
</tr>
<tr>
<td>Dalfopristin/Quinupristin</td>
<td>cSSSIs, VREF infections (1999)</td>
<td>Synercid</td>
<td>USA, Canada, Argentina, Mexico, Brazil, UK, Ireland, Sweden, Finland, Germany, Austria, Czech Republic, Hungary, France, Switzerland, Italy, Spain, Greece, Israel, Australia, New Zealand, South Africa</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>cSSSIs (2003)</td>
<td>Cubicin</td>
<td>USA, UK, Ireland, Island, Norway, Sweden, Finland, Estonia, Latvia, Lithuania, Poland, Danmark, Netherlands, Germany, Belgium, Luxembourg, Czech Republic, Slovakia, Hungary, Austria, Slovenia, Italy, France, Portugal, Greece, Malta, Cyprus, Israel</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>cSSSIs, complicated abdominal infections (2005)</td>
<td>Tygacil</td>
<td>USA, Chile, UK</td>
</tr>
</tbody>
</table>

<sup>a</sup>Micromedex, www.thomsonhc.com
Table 2. Pharmacokinetics of Linezolid, Quinupristin-Dalfopristin, Daptomycin and Tigecycline

<table>
<thead>
<tr>
<th></th>
<th>Linezolida</th>
<th>Dalfopristin/Quinupristinb</th>
<th>Daptomycinc</th>
<th>Tigecyclined</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage</strong></td>
<td>i.v. or p.o. (bioavailability 100%), 600 mg q12h (cSSSI), 400 mg q12h (uSSSI), 10mg/kg q8-12h (children)</td>
<td>i.v. 7.5 mg/kg q8 hr or q12 hr (at least 7 days for cSSSI)</td>
<td>4 mg/kg q12h</td>
<td>100 mg loading dose, then 50 mg q12h</td>
</tr>
<tr>
<td><strong>Protein binding %</strong></td>
<td>31</td>
<td>92</td>
<td>71-87</td>
<td></td>
</tr>
<tr>
<td><strong>Volume of distribution (L/kg)</strong></td>
<td>30-50</td>
<td>approximately 0.1</td>
<td>7-10</td>
<td></td>
</tr>
<tr>
<td><strong>Elimination half-life</strong></td>
<td>4.4 h</td>
<td>8-9 h</td>
<td>approximately 36 h</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>hepatic</td>
<td>not extensively metabolized</td>
<td>not extensively metabolized</td>
<td></td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>mainly renal</td>
<td>mainly renal</td>
<td>mainly renal</td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>gastrointestinal disturbances, myelosuppression, avoid in patients taking monoamine oxidase inhibitors</td>
<td>Infusione-site reactions, thrombophlebitis, arthralgia, myalgia</td>
<td>gastrointestinal disturbances, creatine kinase concentration elevations</td>
<td>gastrointestinal disturbances</td>
</tr>
</tbody>
</table>

a[26, 54, 62]; b[86, 92]; c[128]; d[132, 149, 150].

**Pharmacokinetics**

A major advantage of linezolid is that it is available in both oral and parenteral formulations. Linezolid is rapidly and extensively adsorbed after oral administration, reaching the maximum plasma concentration (C_{max}) within 1-2 h and having an average bioavailability of 100% [26]. Plasma protein binding has been estimated to be 31%. The drug has a steady-state volume of distribution of about 30-50 L with adequate to good tissue penetration into skin blister fluids, bone, muscle, fat, alveolar cells, lung extracellular lining fluid and cerebrospinal fluid [54]. For doses in the range of 100 to 400 mg, proportional increases in the area under the plasma concentration-time curve (AUC) and C_{max} have been observed [54]. Concomitant administration of food significantly reduced the C_{max} of linezolid although the AUC was not affected [32]. Linezolid is primarily metabolized by oxidation of the morpholine ring, which forms two inactive metabolites: aminoethoxyacetic acid metabolite (A) and hydroxymethyl glycine metabolite (B). Linezolid is predominantly excreted renally, with 80-85% found in the urine (30% parent compound, 40% metabolite A, and 10% metabolite B), 7-12% in feces [55, 56].

Pharmacokinetic parameters of linezolid in adults are not altered by hepatic or renal dysfunction, age or sex to an extent requiring dose adjustment [57].

**Clinical Studies**

There is considerable clinical experience with the use of linezolid in SSTIs in phase II and III clinical trials. In a randomized, double-blind study, the efficacy and the safety of linezolid and oxacillin-dicloxacillin in patients with SSTIs were compared [58]. A total of 826 hospitalized adult patients were randomized to receive 600 mg of linezolid intravenously (i.v.) every 12 hours (q12h) or oxacillin 2 g i.v. q6h; following sufficient clinical improvement, patients were switched to the respective oral agents (linezolid 600 mg orally q12h or dicloxacillin 500 mg orally q6h). Concomitant aztreonam therapy was added when necessary. Most common etiologic agents were *S. aureus, S. pyogenes* and *S. agalactiae* [58]. In the intent-to-treat (ITT) population, the clinical cure rates at test-of-cure (TOC) visit were comparable in the two treatment groups, with 279 of 400 (69.8%) linezolid-treated patients and 272 of 419 (64.9%) oxacillin-dicloxacillin-treated patients achieving a clinical cure in the linezolid and oxacillin-dicloxacillin groups, respectively. In the clinically evaluable (CE) subset of patients there was 90% rate of cure in the linezolid group versus 85% in the oxacillin-dicloxacillin group. Microbiological success was similar (88% vs. 86%). Both agents were well tolerated [58]. In comparative trials, linezolid was equally effective as vancomycin in patients with SSTIs caused by MRSA and has also demonstrated efficacy in patients with SSTIs caused by VRE [59]. In the treatment of MRSA caused infections the efficacy of linezolid was also evaluated in a randomized, open-label comparison with vancomycin [25]. At the TOC visit, among evaluable patients with MRSA, there was no statistical difference between the 2 treatment groups with respect to clinical cure rates (73.2% of patients in the linezolid group and 73.1% in the vancomycin group) or micro-
biological success rates (58.9% in the linezolid group and 63.2% in the vancomycin group). Both regimens were well tolerated with similar rates of adverse events [25].

Recently, a randomized, controlled, multicenter study compared vancomycin and linezolid for the treatment of cSSSIs with MRSA as a leading pathogen [27]. Patients were randomized (1:1) to receive linezolid (600 mg) q12h either i.v. or orally, or vancomycin (1 g q12h i.v.). In the ITT population, 92.2% and 88.5% of patients treated with linezolid and vancomycin, respectively, were clinically cured at the TOC visit. Linezolid outcomes (88.6%) were superior to vancomycin outcomes (66.9%) at the TOC visit for patients with MRSA infections. This study showed that linezolid therapy is well tolerated, equivalent to vancomycin in treating cSSSIs, and more effective than vancomycin in the treatment of cSSSIs due to MRSA [27].

**Adverse Events**

Linezolid seems to be well tolerated [60]. The most frequently adverse events (AEs) reported with linezolid were diarrhea (incidence across studies 2.8%-11%), headache (0.5%-11.3%), and nausea (3.4%-9.6%) [26]. Less common AEs included tongue discoloration and fungal infections [26, 61]. Thrombocytopenia and a slight increased risk for anemia were evident at ≥2 weeks of linezolid treatment. Hematologic abnormalities were consistent with mild, reversible, duration-dependent myelosuppression [62]. Due to an occurrence of myelosuppressive events, it is advisable to monitor blood cell counts weekly in patients with underlying hematologic abnormalities or lower baseline values especially when treatment with linezolid exceeds 14 days. Concerns have recently been raised about linezolid possibly inducing different types of neuropathies when administered for several months [63, 64].

**Drug Interaction**

The oral absorption of linezolid is not affected by the presence of antacids [65]. Physical incompatibilities resulted when linezolid was administered with some drugs (e.g., amphotericin B, ceftiraxone, diazepam), so the recommendation is to administer it separately. Linezolid is a reversible nonsclective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for an interaction with adrenergic and serotoninergic agents. Patients receiving linezolid need to avoid ingestion of large amounts of foods or beverages with high tyramine content [60].

**Dosage**

The recommended dose of linezolid i.v. or orally is 600mg q12h for cSSSIs. However, uSSSI, can be treated successfully with 400mg q12h. The parenteral drug product should be administered by i.v. infusion over a period of 30 to 120 minutes. No dose adjustment is necessary when switching from i.v. to oral therapy [60]. The maximum dosage for infants and children is 10mg/kg q8-12h. The duration of the treatment for skin infections is 10-14 days. Considering the high oral bioavailability of linezolid which distinguishes it from vancomycin, the patients treated with linezolid for cSSSIs can reduce i.v. therapy or take a full course of oral therapy. The ease of switching patients from i.v. to oral linezolid, enables patients to be discharged from hospital while continuing the same treatment, thus reducing the costs of hospitalization and the costs associated with home infusion [59, 66-69].

**QUINUPRISTIN-DALFOPRISTIN**

**Introduction**

Quinupristin-dalfopristin was the first injectable streptogramin antibiotic approved in the USA for VREF bacteremia and cSSSIs caused by MRSA or *S. pyogenes* [70-72]. In the last few years, growing clinical evidence has indicated that quinupristin-dalfopristin may be a useful antimicrobial alternative for the treatment of various serious infections caused by Gram-positive bacteria in patients who failed or were intolerant of vancomycin therapy [73-75].

**Chemistry and Mechanism of Action**

Quinupristin-dalfopristin belongs to the streptogramins family. Dalfopristin is a derivative of a group A streptogramin and quinupristin is a derivative of a group B streptogramin. These two water-soluble streptogramins have been combined in a commercially available injectable form 30:70 (w/w) [71, 73]. Individually, quinupristin and dalfopristin demonstrate only modest *in vitro* bactericidal activity. However, the combination of these antibiotics commonly produces *in vitro* bactericidal activity 8 to 16 times higher than the sum of each individual component’s activity against many Gram-positive organisms [76].

Quinupristin and dalfopristin act synergically and bind irreversibly on the 50S ribosome to inhibit early and late phase protein synthesis. In particular, quinupristin blocks binding of aminoacyl-tRNA complexes to the ribosome whilst dalfopristin inhibits peptide bond formation and distorts the ribosome, promoting the binding of quinupristin. Consequently, incomplete peptide chains are released. The compromised transfer RNA interrupts protein synthesis, resulting in cell death [77].

**In Vitro Susceptibility Testing**

Quinupristin-dalfopristin has an excellent *in vitro* activity against Gram-positive organisms most frequently encountered in SSSIs, including *S. aureus* and *S. pyogenes*. The criteria of the NCCLS (at present CLSI) for susceptibility, intermediate susceptibility, and resistance to quinupristin-dalfopristin are ≤1, 2, and ≥4 μg/mL, respectively [78]. MIC₉₀ for most staphylococci, streptococci, pneumococci and *E. fecium* are from 0.25 to 2 μg/mL [77, 79]. Furthermore, quinupristin-dalfopristin has an activity against most methicillin-, lincosamide- and erythromycin-resistant strains of coagulase-negative staphylococci (CoNS) and *S. aureus* (MIC₉₀ 0.5 and 1 μg/mL, respectively) [80]. The drug is also active (MIC₉₀ ≤1 μg/mL) against glycopeptide-resistant *S. aureus* [77]. Several studies have shown that the species *Enterococcus fecalis* has intrinsic resistance to this compound [81,82].

**Mechanism of Resistance**

Resistance to streptogramins occurs by at least three mechanisms: a) target modification that provides resistance to macrolides, lincosamides and streptogramin B and is conferred by the erm genes (as dalfopristin is a streptogramin A,
which susceptibility to quinupristin-dalfopristin is not affected by this mechanism; b) drug-modification confers resistance to streptogramin A and is provided by genes vatD and vatE encode acetyltransferases; and c) an efflux mechanism mediated by an adenosine triphosphate-binding protein caused by the expression of the lsa gene that explains the intrinsic resistance *E. faecalis* [83, 84].

Resistance to quinupristin-dalfopristin was expected to be a rare event. However, according to the SENTRY Antimicrobial Surveillance Program Report on Gram-positive organisms causing bloodstream infections, the resistance of *E. faecium* to this antibiotic went from 0% in 1997 to 16% in 1999 (12.6% intermediate-resistant and 3.8% resistant) [85].

Cross-resistance has not been reported between quinupristin-dalfopristin and glycopeptide, quinolone or β-lactam antimicrobials [80].

**Pharmacokinetics**

The drug has minimal oral absorption and is administered only i.v. Studies have demonstrated a linear correlation between the quinupristin-dalfopristin dose and AUC across a wide range of doses in healthy volunteers. i.v. administration of 9 or 10 doses of quinupristin-dalfopristin ranging from 1.4 to 29.3 mg/kg has yielded peak plasma concentrations of quinupristin ranging from 0.61 to 19.93 μg/mL and of dalfopristin ranging from 0.54 to 6.9 μg/mL [86]. The manufacturer’s recommended i.v. dose of quinupristin-dalfopristin in adults is 7.5 mg/kg given over 60 minutes every 8–12h; this has consistently produced total Cmax of ~11 to 12 μg/mL, based on combined peak concentrations of quinupristin (3.2 ± 0.67 μg/mL), dalfopristin (7.96 ± 1.30 μg/mL), and their major metabolites [71, 86].

Both quinupristin and dalfopristin undergo hepatic metabolism. Quinupristin has two primary active metabolites, and dalfopristin has a single major active metabolite [71]. The metabolites exert antibacterial activity similar to that of the parent compounds [87]. The parent drug and major metabolites are eliminated primarily by fecal excretion (75%), with a small portion of unchanged quinupristin and dalfopristin (15%–19%) eliminated renally [77].

The elimination half-lives of both quinupristin and dalfopristin range from 0.7 to 1.53 hours [88]. The results of a pharmacokinetic study in patients with advanced liver disease and cirrhosis suggested that no pharmacokinetic alterations occurred in either parent drug, despite marked increases in the AUC of the drugs’ individual metabolites [89]. However, no increase in AEs has been reported in patients with hepatic impairment [71]. In patients with renal impairment (creatinine clearance of < 30 mL/min), a 30% increase in the combined AUC of quinupristin-dalfopristin and their metabolites has been observed, but the manufacturer has not set guidelines for dosage reduction [71]. Finally, patients receiving continuous ambulatory peritoneal dialysis (CAPD) showed no significant alterations in the clearance of quinupristin-dalfopristin or the drugs’ metabolites [90].

**Clinical Studies**

Two randomized, open-label trials compared the efficacy and safety of quinupristin-dalfopristin versus standard comparators (cefoxitin, oxacillin, and vancomycin) in hospitalized patients with severe Gram-positive SSSIs. These investigations (one USA and one international trial) of virtually identical design enrolled a total of 893 patients (450 quinupristin-dalfopristin, 443 comparator) [91]. Patients treated with cefazolin, oxacillin, or vancomycin were combined in a single group for comparison with quinupristin-dalfopristin. The duration of antibiotic use ranged from 3 to 14 days. *S. aureus* was the most frequently isolated pathogen in both treatment groups and polymicrobial infection was more common in the quinupristin-dalfopristin group than in the comparator group. In the USA trial, patients were randomized to receive i.v. quinupristin-dalfopristin 7.5 mg/kg q12h or a comparator regimen of i.v. oxacillin 2 g q6h or vancomycin 1 g q12h. In the international trial, patients were randomized to receive i.v. quinupristin-dalfopristin 7.5 mg/kg q12h, cefazolin 1 g q8h, or vancomycin 1 g q12h. Unlike the USA trial, the international trial allowed the addition of aztreonam to either quinupristin-dalfopristin or comparator therapy [91]. The clinical success rate in the CE population was equivalent between the two treatment groups (68.2% quinupristin-dalfopristin, 70.7% comparator) despite a shorter mean duration of treatment for quinupristin-dalfopristin patients. In the bacteriologically evaluable population, by-patient and by-pathogen bacteriological eradication rates were lower for quinupristin-dalfopristin (65.8% and 66.6%, respectively) than for comparator regimens (72.7% and 77.7%, respectively). The lower bacteriological response rates in the quinupristin-dalfopristin group were, in part, due to a higher rate of polymicrobial infections the higher the incidence of patients classified as clinical failure, a category that included premature discontinuation of treatment because of local venous AEs. The bacteriological eradication rate for quinupristin-dalfopristin was higher in monomicrobial infections than in polymicrobial infections (72.6% versus 63.3%, respectively), whereas the corresponding rate for the comparator regimens was lower for monomicrobial infections than polymicrobial infections (70.8% versus 83.1%). The systemic tolerability of both treatment regimens was qualitatively similar. A higher rate of drug-related venous AEs was reported for quinupristin-dalfopristin (66.2%) than for comparator regimen (28.4%). Premature discontinuation of study drug was primarily due to adverse clinical events for quinupristin-dalfopristin (19.1%), whereas the most common reason for discontinuation among those receiving the comparator regimens was treatment failure (11.5%) [91].

**Adverse Events**

The most frequently reported adverse effects with administration of quinupristin-dalfopristin (7.5 mg/kg i.v. q8h to q12h) were infusion-site reactions (e.g. inflammation, pain, and edema), thrombophlebitis and other infusion-site events. A deep catheter is usually required because this antibiotic causes severe irritation when given by peripheral vein. Administration through a central venous line is requested. Arthralgia, myalgia, nausea, diarrhea, vomiting, and rash are the most common systemic effects related to the drug. Arthralgia and myalgia have been reported to occur in about 10% of quinupristin-dalfopristin-treated patients in non-comparative studies [92]. Although the mechanism of these AEs is unknown, they tend to be dose-related and reversible
after drug discontinuation. These AEs are more likely to occur in patients with chronic liver disease and those who have received a liver transplant or are receiving cyclosporine or mycophenolate [93]. Furthermore, elevations in liver enzymes, increases in total and direct bilirubin, thrombocytopenia and decreases in hemoglobin have also been reported [71, 92].

**Interactions**

Inhibits cytochrome P4503A4-mediated metabolism of drugs including midazolam, nifedipine, terfenadine and cyclosporin. Therefore, plasma drug monitoring and/or dosage reduction of these agents is prudent. However, concomitant administration of drugs that can prolong the electrocardiographic QTc interval should be avoided [71, 87, 92]. Limited experience with concomitant quinupristin-dalfopristin and cyclosporine has demonstrated a 2-fold increase in cyclosporine levels within 2 to 5 days of concomitant use [94].

**Dosage and Compatibility**

The recommended dosage of quinupristin-dalfopristin for cSSSIs is 7.5 mg/kg given i.v. q12. The recommended minimum duration for the treatment of cSSSI is seven days [71]. The dosage of quinupristin-dalfopristin does not have to be adjusted in elderly patients or patients with renal impairment. Limited clinical data are available on the use of the drug in patients with hepatic disease, but a dosage reduction may be required in patients with cirrhosis [71]. Quinupristin-dalfopristin is available in a single 500 mg vial. The recommended infusion volume and duration is 250 mL given over 60 minutes. Specific care should be taken to avoid saline and heparin flushes immediately before and after the drug administration. The manufacturer recommends that i.v. tubing be flushed with 5% glucose solution before and after infusion of quinupristin-dalfopristin. There are currently limited data concerning the compatibility of other drugs with quinupristin-dalfopristin [95].

**DAPTOMYCIN**

**Introduction**

Daptomycin is the first in a new class of cyclic lipopeptide agents derived from the fermentation of a strain of *Streptomyces roseosporus* [89]. The drug has been in clinical use in the USA since 2003 for treatment of cSSSI, caused by susceptible strains of the following Gram-positive organisms: *S. aureus* including MRSA, *S. pyogenes*, *S. agalactiae*, *Streptococcus dysgalactiae* subspecies *equisimilis* and *E. faecalis* (vancomycin-susceptible strains only) [96-99].

**Chemistry and Mechanism of Action**

Daptomycin is a cyclic lipopeptide comprising 13 amino acids with a water-soluble hydrophilic core and a lipophilic tail [97, 100]. This structure is a key to its novel mode of action [101]. The lipophilic tail of daptomycin binds irreversibly to the cell membrane of Gram-positive bacteria via a calcium-dependent process [100, 101]. Calcium ions promote deeper insertion of daptomycin into the membrane by bridging the residual negatively charged aminoacids on daptomycin and the negatively charged phospholipids that are found in the cytoplasmic membrane of bacteria [102]. The proposed mechanism of action of daptomycin is believed to involve a multistep process in which membrane potential dissipation and the efflux of potassium out of the exposed bacterial cells, is the major event [100, 101]. This is followed by arrest of DNA, RNA and protein synthesis resulting in bacterial cell death. It seems possible that the collapse of the electrochemical gradient caused from the daptomycin would interfere with membrane-associated processes including synthesis of cell wall components, energetics and cell division [103].

**In Vitro Susceptibility Testing**

Daptomycin showed in vitro activity against a wide range of aerobic and anaerobic Gram-positive bacteria including multidrug-resistant strains [30, 104-107]. A daptomycin susceptible breakpoint is ≤1 μg/mL for staphylococci and β-hemolytic streptococci, whereas ≤4 μg/mL for enterococci, as recently approved by CLSI [108]. The MIC₉₀ values for daptomycin against MSSA and MRSA isolates were ≤1 μg/mL [106, 107, 109-112]. Daptomycin demonstrated potency against the recently isolated VRSA as well as linezolid and quinupristin-dalfopristin-resistant *S. aureus* and *E. faecium* [107, 111, 113, 114]. In addition numerous GISA isolates were susceptible to daptomycin with MIC, of 0.13-1.0 μg/mL [30, 113]. Furthermore, daptomycin is also effective against a variety of streptococcal groups such as the β-hemolytic streptococci including *S. pyogenes* and *S. agalactiae* as well as other *Streptococcus* spp. [104, 114, 115]. Daptomycin has shown potent bactericidal activity in vitro. The bactericidal effect of daptomycin is rapid-greater than 99.9% of MRSA and MSSA bacteria die in less than 1 hour post treatment [116, 117]. Drug synergy with daptomycin has been described in vitro with aminoglycosides and rifampicin antibiotics [118, 119]. Antagonism between daptomycin and other antibiotics has not been seen [120]. A concentration-dependent post-antibiotic effect (PAE) has also been observed with daptomycin, lasting up to 6.3 and 6.7 h against *S. aureus* and *E. faecalis*, respectively, at clinically achievable concentrations [121].

**Mechanism of Resistance**

Daptomycin’s mechanism of action targets the cell membrane of Gram-positive bacteria, which typically has a relatively slow rate of inheriting resistance compared, for example, with agents targeting ribosomal RNA [100]. In vitro studies have shown a lack of propensity for spontaneous resistant mutants to arise; no transferable resistance elements have been identified [122]. However, stable *S. aureus* mutants were isolated by both serial passage in liquid media and chemical mutagenesis [123]. The daptomycin MICs for these isolates were 8- to 32-fold higher than for the parental strain. The bacterial membrane potential was increased in three independent resistant isolates. The potential mechanism of resistance patterns supported an alteration of membrane potential, which causes reduced binding of daptomycin [122]. In a recent study Kaatz et al. assessed that reduced binding of daptomycin to its target correlates with its resistance, possibly as a result of the loss of a membrane protein "chaperone" with which daptomycin interacts [124]. More recently, reports of Gram-positive strains with reduced susceptibility...
to daptomycin arising during therapy have begun to appear [125, 126]. Because of daptomycin’s unique mechanism of action, the development of cross-resistance between daptomycin and other antimicrobial agents, such as glycopeptide or β-lactam antibiotics appears unlikely [127].

**Pharmacokinetics**

Daptomycin exhibits linear pharmacokinetics with minimal accumulation (~20%) in healthy volunteers at doses up to 6 mg/kg, becoming slightly nonlinear at doses of 8 mg/kg in the AUC [128]. Its half-life ranged between 8 and 9 h, permitting dosing once per day. Daptomycin exhibits approximately 92% binding to plasma proteins, specially albumin. The low volume of distribution (~0.1 L/kg) is due to its inability to cross cell membranes and its higher affinity for plasma proteins, as compared to tissue binding. Daptomycin is not extensively metabolized. It is excreted mainly in urine (78%), with approximately 50% of the active drug being recovered unchanged from urine within 24 h. A small proportion of daptomycin (6%) is also recovered in feces. Pharmacokinetics or moderate hepatic insufficiency proportion of daptomycin (6%) is also recovered in feces. Pharmacokinetics

**Clinical Studies**

Two phase III clinical studies have been performed in patients with cSSSIs [130]. Both studies were randomized and evaluator blinded to compare the safety and efficacy of daptomycin with that of currently used antibiotics. Each phase III study involved approximately 500 patients (total population 1092 patients) with cSSSIs, associated or potentially associated with Gram-positive bacteria, including abscesses, surgical and traumatic wound infections and infected diabetic foot ulcers. Daptomycin 4 mg/kg i.v. once-daily, administered as a 30-min infusion, was compared with vancomycin 1 g i.v. twice-daily, given as a 60-min infusion, or an oxacillin-class antibiotic (cloxacillin, flucloxacillin, oxacillin or nafcillin) 4–12 g i.v. once-daily, for 7–14 days. Aztreonam and/or metronidazole were added as deemed necessary. Daptomycin was demonstrated to be non-inferior to the comparator antibiotics, both in the individual and collective trials. For the combined ITT population (n = 1092) clinical success rates were 71.5% and 71.1% for daptomycin- and comparator-treated patients, respectively. Success rates in the CE population were 83.4% and 84.2%, respectively. Consistent efficacy, in terms of both clinical success and post-treatment relapse rates, was observed across predefined patient populations, Gram-positive species and all types of infection or infection sites. The duration of the treatment with daptomycin was shorter than with comparator antibiotics: the proportion of patients requiring only 4–7 days’ therapy was 63% with daptomycin, vs. 33% with comparator therapy. In both phase III cSSSIs trials, daptomycin was well-tolerated, with the frequency and distribution of AEs being similar for patients receiving daptomycin (n = 534) and those given comparator antibiotics (n = 558). Most AEs were considered unrelated to the study medication and were of mild or moderate intensity. One or more drug-related AEs occurred in 18% of daptomycin-treated patients and in 21% of patients treated with comparator agents [130].

**Adverse Events**

The most frequently experienced AEs in the phase III cSSSIs clinical trials were gastrointestinal disorders (e.g., constipation, nausea, diarrhea, injection site reactions, headache and rash). Treatment discontinuation due to AEs occurred for only 15 patients (2.8%) in the daptomycin group and 17 patients (2.8%) in the comparator group [130]. Given the potential for daptomycin-related muscle toxicity, as reported by Tally et al. creatine phosphokinase (CPK) levels were closely monitored in the phase III cSSSIs studies [130, 131]. Only 11 daptomycin-treated patients (2.1%) and 8 patients (1.4%) in the comparator group experienced muscle pain or weakness associated with CPK elevations, which resolved after the discontinuation of treatment with daptomycin. To date no drug-drug interactions are known.

**Dosage**

Daptomycin is only available as an i.v. agent. The recommended dosage for the treatment of cSSSIs is 4 mg/kg once q24h for patients with a creatinine clearance of ≥ 30 mL/min [97]. For patients with a creatinine clearance of < 30 mL/min, including patients receiving hemodialysis and CAPD, the recommended dosage is 4 mg/kg q48h [97, 129]. No dosage adjustment is recommended for patients with mild-to-moderate hepatic dysfunction [97].

**TIGECYCLINE**

**Introduction**

Tigecycline is the first of a new class of antimicrobials, the glycyclines, that was approved by FDA for the treatment of cSSSIs caused by resistant Gram-positive and Gram-negative bacteria on June 15, 2005 [132].

**Chemistry and Mechanism of Action**

Similar to tetracyclines, tigecycline contains the central four-ring carbocyclic skeleton, with a substitution of an N-alkyl-glycylamido group at the D-9 position [133]. This substitution enables a broader spectrum of antimicrobial activity over the tetracyclines and allows defense against efflux pump and ribosomal protection mechanisms that otherwise confer tetracycline resistance [134]. Tigecycline’s mechanism of action involves the inhibition of protein synthesis and cell growth in bacteria by reversible binding to A site of the 30S ribosomal subunit [134-137].

**In Vitro Susceptibility Testing**

Several reports have evaluated the in vitro activity of tigecycline against a wide range of bacterial pathogens commonly found in cSSSIs which includes MSSA, MRSA and VRE [138]. It has exhibited pronounced activity against pathogens that are susceptible and resistant to other antibiotics [113, 139-141]. Susceptibility breakpoint interpretations defined by FDA indicate that ≤ 0.5 μg/ml is considered susceptible for S. aureus, ≤ 0.25 μg/ml for Enterococcus faecalis (vancomycin-susceptible isolates only) and Streptococcus spp., and ≤ 0.4 μg/ml for anaerobes [132]. MIC<sub>90</sub> values for tigecycline were uniformly low for most isolates including MRSA and MSSA (MIC<sub>90</sub> 0.25-0.50 μg/mL for both groups). No evidence of resistance was observed [138, 142]. Tigecycline is primarily bacteriostatic rather than bacteri-
Tigecycline does not undergo extensive metabolism, but a have been found lower than serum concentrations vial fluid. Concentrations of tigecycline in skin blister fluid. Its elimination half-life is approximately 36 hours altered by age, gender, or severe renal disease unchanged drug in the urine bile and feces (59%). Another 22% of the drug is excreted as multidrug efflux proteins. Tigecycline appears to be a sub-
tides mirabilis, Pseudomonas aeruginosa as the cause of reduced susceptibility to tigecycline in Pro-
tactic effect at sub-MIC concentrations. Numerous tetracycline-resistant genes or tet(M) have been identified. Some tet, genes code for efflux, whereas others influence ribosomal protection. As mentioned previously, tigecycline appears to overcome these mechanisms of resistance because of steric hindrance due to a large substituent at D-9 position. Tigecycline has shown an activity against organisms with plasmids containing either efflux or ribosomal protection genes. This activity likely results from the inability of tigecycline to induce tetracycline efflux proteins or simply because the efflux pump is ineffective in transporting glycyclines out of the cell. In addition, the stronger binding affinity of tigecycline may interfere with the tet genes ability to bind effectively to the receptor and protect the ribosome. To date, attempts to create tigecycline resistant isolates in the laboratory using prolonged exposure to suboptimal concentrations of tigecycline have been unsuccessful. In a recent study, Hirata et al. have examined the activity of tigecycline against E. coli strains harbouring plasmids encoding multidrug transporter genes, acrAB, acrEF and bcr. Tigecycline MICs increased fourfold with strains producing these multidrug efflux proteins. Tigecycline appears to be a substrate of acrAB and acrEF which are resistance-modulation-division type multicomponent efflux transporters. Other reports have addressed the possibility of efflux pumps as the cause of reduced susceptibility to tigecycline in Proteus mirabilis, Pseudomonas aeruginosa and Escherichia coli. Tigecycline requires intravenous administration. Studies on healthy volunteers demonstrated that tigecycline exhibited linear pharmacokinetics after single doses (range, 12.5-300 mg) and multiple doses (range, 50-200 mg) q12h. Food increased the maximum tolerated single-dose from 100 to 200 mg, but the duration of infusion did not affect tolerability. After a 1-h infusion, Cmax and AUC were dose proportional. Tigecycline is highly protein bound (71%-87%) and has a large volume of distribution (7-10 L/kg). Concentrations of tigecycline in the gall bladder, lung and colon are higher than serum concentrations, while smaller increases were observed in the bone and synovial fluid. Concentrations of tigecycline in skin blister fluid have been found lower than serum concentrations. Tigecycline does not undergo extensive metabolism, but a slight amount is metabolized by liver glucuronidation. Its elimination half-life is approximately 36 hours. It is mainly excreted as unchanged drug and metabolites in the bile and feces (59%). Another 22% of the drug is excreted as unchanged drug in the urine. The pharmacokinetics of tigecycline in adults are not significantly altered by age, gender, or severe renal disease.

Clinical Studies

Clinical efficacy of tigecycline has been demonstrated in cSSSIs. Postier et al. conducted a multicenter, randomized, dose-ranging study to assess the clinical efficacy and the safety of two doses of tigecycline for the treatment of cSSSIs in 160 hospitalized patients. Patients received either 25 mg or 50 mg of tigecycline i.v. q12h for 7 to 14 days. Patients in the 25 mg group received a loading dose of 50 mg, and patients in the 50 mg group received a loading dose of 100 mg. At the end of therapy, 78% of CE patients in the 25 mg group and 85% of CE patients in the 50 mg group were considered cured. At the TOC visit, 67% of patients in the 25 mg group and 74% of patients in the 50 mg group were deemed clinically cured. At the end of therapy, bacterial eradication occurred in 62% of patients in the 25 mg group and 74% of patients in the 50 mg group. At the TOC visit bacterial eradication occurred in 56% of patients in the 25 mg group and 69% of patients in the 50 mg group.

Adverse events were similar in both doses groups, with nausea and vomiting being the most common events. Rare laboratory abnormalities, including elevated serum levels of transaminases, alkaline phosphatase and blood urea nitrogen and anemia also occurred. This dose-ranging study showed that a loading dose (100 mg), followed by 50 mg i.v. q12h of tigecycline had higher rates of cure.

Two large, randomized, multicenter, double-blind phase III studies have recently compared tigecycline monotherapy with the combination of vancomycin and aztreonam (V/A) [154, 155]. Patients received tigecycline 100 mg i.v. loading dose followed by 50 mg i.v. q12h. Vancomycin was given at a dose of 1 g q12h and could be adjusted based on renal function. Aztreonam was given at a dose of 2 g i.v. q12h and could be discontinued after 48 hours at the investigator's discretion. Treatment was continued for up to 14 days in 1057 hospitalized patients with SSSIS [154, 155].

The investigators assessed the clinical response in the clinical modified intent-to-treat (cmITT) and CE population at a predefined TOC visit after the end of treatment, as well as the microbiologic response at the TOC visit. In addition, safety was assessed by physical examination, laboratory analyses, and AEs reporting.

Both studies showed no significant differences between either regimen in terms of clinical cure or microbiologic eradication rates.

As reported by Breedt et al. clinical responses in the tigecycline and the combination V/A groups were similar in the cmITT population (84.3% vs. 86.9%) and in the CE population (89.7% vs. 94.4%) [154]. Microbiologic eradication occurred in 84.8% of the patients receiving tigecycline and in 93.2% of the patients receiving the combination V/A. The number of patients reporting AEs was similar in the two groups, with increased nausea and vomiting rates in tigecycline group and an increased incidence of rash and increases in alanine aminotransferase and aspartate aminotransferase levels in the combination V/A group.

Likewise Sacchidanand et al. reported that no significant differences were between either regimen in terms of clinical
cure or microbiologic eradication rates. At the TOC, cure rates were similar between tigecycline and V/A groups in the CE population (82.9% vs. 82.3%, respectively) and in the cITT population (75.5% vs. 76.9%, respectively) [155].

In the microbiologic evaluable population, eradication rates of selected isolates commonly associated with cSSSI were high in both treatment groups; for MRSA, eradication rates were 76.2% for the tigecycline group and 81.0% for the V/A group. Frequency of AEs similar between treatment groups, although patients receiving tigecycline had higher incidence of nausea, vomiting, dyspepsia and anorexia, while increases in alanine aminotransferase levels, pruritis and rash occurred significantly more often in V/A treated patients [155].

Adverse Events

AEs reported with tigecycline are similar to those associated with tetracycline class as a whole [132]. Clinical trials reported nausea and vomiting as the most important AEs that, however, do not appear to lead to discontinuation of treatment. These events are thought to be caused by an irritant effect of tigecycline on the gastric mucosa [154, 155]. Other AEs included dyspepsia, diarrhea, headache, insomnia, dizziness, pain, fever, and anorexia. Mild elevation in liver function parameters and blood urea nitrogen were also observed, but required no intervention [132, 142].

Interactions

Significant interaction has not been reported related to tigecycline. The pharmacokinetic and pharmacodynamic interactions between tigecycline and warfarin when administered concomitantly in healthy subjects have been assessed in an open-label, non-randomized two-period study. A trial was conducted with warfarin (single 25 mg dose), which demonstrated an increased Cmax of 38% (R-warfarin) and 43% (S-warfarin), with a corresponding increase in the AUC of 68% and 29%, respectively. There was no significant alteration in the coagulant profile of warfarin and warfarin administration did not alter the pharmacokinetic profile of tigecycline. Nevertheless it is suggested that anticogulant monitoring is required in patients receiving warfarin. Similar to tetracyclines, caution is also warranted in patients receiving concomitant oral contraceptives, since decreased contraception efficacy may be the result otherwise [132].

Dosage

The recommended dosage of tigecycline is 100 mg i.v. given as a loading dose, followed by 50 mg i.v. q12h administered as an infusion over 30-60 minutes [156].

ANTIMICROBIALS CURRENTLY IN CLINICAL DEVELOPMENT FOR TREATMENT OF SKIN INFECTIONS

Dalbavancin

Introduction

Dalbavancin is a novel glycopeptide antimicrobial currently in clinical development for the treatment of resistant Gram-positive organisms implicated in cSSSI [157].

Chemistry and Mechanism of Action

Dalbavancin is a semisynthetic lipoglycopeptide structurally related to teicoplanin. Differences from teicoplanin occur at apolipoproteins 1 and 3. Further differences occur with the number and positioning of the sugar moieties and chlorine molecules, as well as various methyl and hydroxyl groups [157]. Dalbavancin is similar to other glycopeptides in its mechanism of action, binding to the terminal alanyld-alanine of nascent peptidoglycan chains and thus interfering with bacterial cell wall biosynthesis and resulting in cell death [158].

In Vitro Susceptibility Testing

Dalbavancin studies showed a wide spectrum of activity against frequently isolated Gram-positive pathogens without regard to other resistance markers [159-161]. Dalbavancin most closely resembles teicoplanin in potency and spectrum; however, it is not more active than teicoplanin against VRE harboring the vanA phenotype of resistance to glycopeptides [162]. The excellent antistaphylococcal activity of dalbavancin includes MSSA, MRSA, VISA and CoNS [161, 163-166]. Dalbavancin and selected comparators were tested against 6339 recent clinical isolates from worldwide sites [163]. The 99% of MIC results were at ≤ 1 μg/mL S. aureus and CoNS were extremely susceptible to dalbavancin (MIC90, 0.06 μg/mL) despite resistance patterns to other agents. Dalbavancin was the most potent compound against vancomycin-susceptible E. faecalis and E. fectorium (MIC90, 0.06 and 0.12 μg/mL, respectively); however, VRE strains showed decreased dalbavancin susceptibility (MIC90, 4 or 8 μg/mL). All streptococcal isolates were inhibited at ≤ 0.25 μg/mL of dalbavancin [163]. Another international survey tested a total of 7765 Gram-positive isolates against dalbavancin and 10 comparators agents [167]. The level of dalbavancin potency was greater than that of vancomycin (8- to 32 fold), linezolid (16- to 64 fold), teicoplanin (64- to 128 fold), and quinupristin-dalfopristin (8- to 32 fold). Dalbavancin (MIC90, 0.03-0.06 μg/mL) was active against enterococci, except vanA resistance phenotypes [167]. Recently, dalbavancin exhibited greater potency in contrast to glycopeptides or lipopeptides, streptogramin combinations, and oxazolidinones against Gram-positive pathogens associated with SSSIs [168]. Dalbavancin (MIC90, 0.06-0.12 μg/mL) was comparable in spectrum, but superior in potency to vancomycin (MIC90, 1-2 μg/mL) against staphylococci. Dalbavancin MIC90 value against the tested streptococci was 0.03 μg/mL. Dalbavancin was more active against tested SSTI pathogens than comparator agents having complete susceptibility rates (100%) similar to vancomycin [168]. To date, attempts to produce stable mutants with decreased susceptibility to dalbavancin in the laboratory have been unsuccessful [169].

Pharmacokinetics

Dalbavancin is available only in an i.v. formulation. It has a significantly longer terminal half-life compared with that of the older glycopeptides [170]. Dalbavancin is highly protein bound (> 90%) and its terminal half-life in human subjects ranges from 149-250 hours [170, 171]. Such a pro-
longed half-life supports the use of weekly dosing intervals when treating susceptible infections.

Prolonged plasma concentrations above 20 µg/mL have been found after a single 1000 mg dose of dalbavancin even at one week after administration [171-173].

By using a rat model, concentrations of dalbavancin in skin have been found to be equal to or greater than those in plasma, demonstrating good penetration into the peripheral compartments, which is essential in treating SSTIs [174].

Dalbavancin is eliminated by both renal and non-renal routes [171]. It was excreted at 25-45.5% unchanged in urine, illustrating the need to consider non-renal elimination routes [171].

Clinical Studies

In a phase II investigation of dalbavancin treatment for SSSIs, a 2-dose regimen (1000-mg dose given on day 1 followed by a 500-mg dose given on day 8) appeared to be well tolerated and to be more effective for the treatment of SSSIs due to Gram-positive bacteria, compared with either a single dose of dalbavancin regimen (1100 mg given on day 1) or investigator chosen standard of care. Comparator agents used were primarily β-lactams, (ceftriaxone, cefazolin, piperacillin-tazobactam, and cephalexin) or vancomycin alone or in combination. Other comparators were linezolid and clindamycin [172]. S. aureus was the most prevalent species. The MIC₉₀ for the 25 baseline staphylococcal isolates was 0.12 µg/mL. Clinical success rates at the TOC visit were 94.1% among patients treated with 2 doses of dalbavancin, 61.5% among patients treated with 1 dose of dalbavancin, and 76.2% among patients treated with a standard-of-care regimen. All treatment regimens were well tolerated; drug-related AEs rates were similar across the 3 groups [172].

More recently a multicenter, double-blind, randomized, phase III trial compared dalbavancin with linezolid for cSSSIs in 854 adult patients [175]. The dalbavancin dosage was 1000 mg i.v. on day 1 followed by 500 mg on day 8 (571 patients). The linezolid dosage was 600 mg twice/day i.v. or orally for a total of 14 days (283 patients). Approximately 90% of all pathogens isolated were S. aureus, of which a relatively high percentage (51%) was MRSA. All other pathogens were streptococcal species. The primary outcome was clinical success at the TOC visit. In the CE population, 88.9% and 91.2% achieved clinical success in the dalbavancin and linezolid arms, respectively. Microbiologic success rates at the TOC visit were similar between groups (89.5% and 87.5% for dalbavancin and linezolid, respectively). Overall, AEs events were similar between groups (25.4% for dalbavancin, 32.2% for linezolid) and most commonly involved nausea or diarrhea for both groups [175].

Adverse Effects

A number of clinical trials have evaluated the efficacy and AEs events associated with dalbavancin. To date, AEs are mild and limited; the most common include pyrexia, headache, nausea, diarrhea or constipation, and oral candidiasis [171, 175]. Transient asymptomatic elevations of liver function tests occurred but did not require intervention [171, 175]. No clinically significant serum creatinine concentration abnormalities have been reported with the use of dalbavancin [171, 172, 175, 176].

Oritavancin

Introduction

Oritavancin is a novel glycopeptide currently being developed for the treatment of cSSSIs, including those caused by multidrug resistant Gram-positive pathogens [136].

Chemistry and Mechanism of Action

Oritavancin is an agent derived semi-synthetically from a precursor drug closely related to vancomycin. Although its mechanism of action is largely the same as that of vancomycin, there are sufficient differences such that it is active against vancomycin-resistant pathogens. Unlike vancomycin, oritavancin can dimerize (i.e., form paired associated molecules), leading to a cooperative interaction with the two stems of the growing peptidoglycan chain. The lipophilic side chain assists in membrane anchoring by hydrophobic interactions, stabilizing the dimer in the most favorable position. Also, evidence exists of another mechanism of action for oritavancin: inhibition of the transglycosylation step of cell-wall biosynthesis [177, 178].

In Vitro Susceptibility Testing

The antibacterial spectrum of oritavancin includes S. pyogenes, S. pneumoniae including penicillin-resistant isolates, staphylococci including MRSA and GISA, enterococci including VREF [179]. Most recently, oritavancin demonstrated extended activity against VRSA and enterococci [180, 181]. Oritavancin is not affected by the vanA, vanB and vanC-encoded alterations in the bacterial cell wall that impart vancomycin resistance [177]. Rapid bactericidal in vitro activity against most isolates of E. fecalis and E. fecium is a property of oritavancin that distinguishes it from vancomycin, ampicillin, linezolid, and quinupristin-dalfopristin [177, 182].

Pharmacokinetics

The plasma pharmacokinetics of oritavancin have been evaluated in several single- and multiple-dose clinical pharmacology studies [136, 183]. The most salient pharmacokinetic property of oritavancin is its prolonged retention in the organism. Oritavancin displayed linear pharmacokinetics and an exceptionally long half-life (about 6-8 days). The plasma concentrations after a single infusion declined in a multi-exponential manner over the 2-weeks [182-184]. The exceptionally long terminal half-life of oritavancin suggests the existence of storage sites within the organism. Studies in cultured macrophages indicate that the drug accumulates slowly in the lysosomes, from which its efflux is extremely slow [185].

Clinical Studies

An open-label, uncontrolled, study has evaluated the pharmacokinetic profile and the safety of single doses of oritavancin administered i.v. to healthy subjects [183]. The drug displayed linear pharmacokinetics for weight-based
doses ranging from 0.02 to 0.5 mg/kg of body weight. Oritavancin plasma concentrations after the end of infusion display a multieponential decline over a 2-week period. Oritavancin displayed a long plasma terminal half-life (approximately 8 days), suggesting the drug accumulation will occur after multiple dosing. Less than 5% and 1% of administered drug were recovered in the urine and feces, respectively, after 7 days. No clinically relevant changes in renal, hepatic and hematologic indices were observed [183].

Oritavancin has completed two phase III clinical trials for the treatment of cSSSIs [136]. Both studies compared 3-7 days of oritavancin (dosed with either 200 mg or 1.5 to 3 mg/kg once daily) to 3-7 days of vancomycin followed by oral cephalaxin to complete 10-14 days of therapy. There was no difference in efficacy between the groups.

To evaluate the disposition of oritavancin in skin structures, ortavacacin plasmatic levels were compared to those in the interstitial space fluids of soft tissue using a carfanide-induced blister fluid model [186]. Seventeen healthy male subjects received ortavacacin, but only 16 subjects were evaluated. Each subject (eight per dose group) received 200 mg of ortavacacin once a day for 3 days (group A) or 800 mg as one single dose (group B). Oritavacacin levels were found maximal in blister fluid 10 h after dosing and decreased to undetectable levels 100 to 150 h after the last dose. The main observation of study has concerned the residence time of ortavacacin in skin blister fluid. The most likely hypothesis involves macrophages, as ortavacacin has been shown to be concentrated in macrophages, which migrate to inflamed tissues [185]. Furthermore, after administration of ortavacacin at 200 mg once daily for 3 days or 800 mg as a single dose, blister fluid concentrations for total drug exceed the MIC\textsubscript{90} of ortavacacin against \textit{S. aureus}. Together, these findings support ortavacacin as a valid therapeutic modality for cSSSIs [186].

**TELVANCIN**

**Introduction**

Telavancin is a new glycopeptide antibacterial currently in phase III development for cSSSIs in the USA.

**Chemistry and Mechanism of Action**

It is a semisynthetic derivative of vancomycin. Like ortavacacin, telavancin possesses a hydrophobic side chain on the vancosamine sugar and a substituent on the cyclic peptidic core [187]. The antibacterial effects of telavancin, are mediated through multiple mechanisms. Telavancin interacts with D-Ala–D-Ala-containing peptidoglycan intermediates that lead to inhibition of the transglycosylation step of peptidoglycan during cell wall synthesis [188, 189]. The drug also affects bacterial membrane functions, dissipating the membrane potential and effecting changes in cell permeability that correlate with loss in bacterial cell viability. This multiple mechanism of action may be responsible for the low frequency of spontaneous resistance to telavancin [190].

**In Vitro Susceptibility Testing**

Telavancin displays rapid, bactericidal, concentration-dependent activity against clinically important Gram-positive aerobic pathogens, such as \textit{S. aureus} (MSSA, MRSA, VISA and VRSA) [188-192]. The MIC\textsubscript{90} for both MRSA and MSSA was reported to be 1 µg/mL for both strains [189].

**Pharmacokinetics**

Currently, there are limited pharmacokinetic data available for telavancin [193-195]. Telavancin is only available as i.v. formulation. The pharmacokinetic profile of telavancin in plasma and blister fluid was studied in healthy subjects [195, 196]. Following the administration of multiple ascending doses the steady state was achieved by 3 to 4 days [196]. Peak telavancin concentrations in skin blister fluid lagged behind peak concentrations in plasma, but in both plasma and blister fluid adequate drug concentrations are achieved [195]. The plasma elimination half-life in subjects with normal renal function is 7-9 h [196]. Telavancin has a prolonged PAE (4-6 h) and a concentration dependent bactericidal activity [189, 194, 196]. Telavancin is primarily eliminated unmodified in the urine, and dose adjustment is needed in patients with renal failure [196].

**Clinical Studies**

Recently two randomized, double-blind phase II trials (FAST and FAST2) have been conducted in patients with cSSSIs caused by Gram-positive bacteria, in which telavancin (7.5 or 10 mg/kg i.v. q24h) was compared with standard therapy (antistaphylococcal penicillin at 2 g q6h or vancomycin at 1 g q12h) [183, 184]. Results showed that clinical success rates were similar in all analysis population at TOC. In patients infected with MRSA, treatment with telavancin produced significantly higher bacterial eradication rates at TOC (92% vs. 68%) [184]. AE rates were also similar in the two treatment groups with mild and transient nausea, insomnia, headache and taste alterations occurring more commonly with telavancin treatment [194].

These studies indicate telavancin's potential role as a treatment alternative for cSSSIs caused by resistant Gram-positive pathogens.

**CONCLUSIONS**

Drug resistant Gram-positive bacteria are serious emerging problems in clinical practice because these organisms are common causes of a variety of SSSIs. Patients who have cSSSIs or whose infection is progressing despite empirical antibiotic therapy should be treated more aggressively and the treatment strategy must include agents with activity against resistant strains. Several new agents to combat these strains have been developed in recent years, linezolid, quinupristin-dalfopristin, daptomycin and tigecycline have already been approved by FDA for the treatment of SSSIs, whereas other agents like dalbavancin, ortavacacin, telavancin are still undergoing clinical trials. Treatment options are based on the antibacterial activity, resistance, pharmacokinetics, safety and cost. As a consequence, evaluation of new drugs is essential. Among new anti-Gram-positive molecules linezolid seems attractive because of its potential for wider use, being an agent active not only against MRSA, VISA and VRE but also against important community-acquired pathogens such as \textit{S. pyogenes} susceptible and resistant to macrolides. The availability of linezolid...
in i.v. and oral formulation provides an advantageous therapeutic approach for both outpatient and inpatient use. Thus, linezolid has the potential to reduce medical resource use through reducing the length of stay in hospital and reduced i.v. therapy, significantly lowering the treatment costs. Quinupristin-dalfopristin is an effective alternative for the treatment of hospitalized patients with cSSSIs due to quinupristin-dalfopristin susceptible Gram-positive organisms, including MRSA, erythromycin-resistant \textit{S. aureus} and VRE. In seriously ill patients with unresponsive infections and minimal other potential treatment options, it should be considered the treatment of choice. However, its efficacy should be weighed against possible adverse effects, tolerability and interactions before using this potent antibiotic.

Daptomycin also has significant evidence for its favorable clinical profile. Its bactericidal activity against both growing and stationary-phase organisms suggests potential utility in the treatment of deep-seated infections. Tigecycline is an alternative agent available for the treatment of resistant Gram-negative and Gram-positive infections, especially in patients with a history of penicillin allergy or other microbiological-related toxicities. Tigecycline is typically bacteriostatic, rather than bactericidal. It is rapidly distributed and has extensive tissue penetration. Among the new lipoglycopeptides promising compounds are dalbavancin, oritavancin and telavancin. They are currently in advanced stages of clinical development. Their most salient property is the clinical relevance of pharmacokinetic/pharmacodynamic parameters that may be very important factors in clinical success. Due to its prolonged half-life, dalbavancin can be administered i.v. once weekly. This weekly regimen offers advantages such as improved patient compliance and reduced resource utilization compared with more frequently dosed agents.

Due to the continuing trend of increased resistance among Gram-positive organisms, it is very important to continue the development of new antibiotics. In order to limit the spread of antibiotic resistant pathogens, current and new antibiotic agents must be used appropriately. The safety profile of new antimicrobials also needs to be further assessed, especially for those molecules that are retained for prolonged times in an organism. A better understanding of where these agents belong in therapy should become more evident over the next few years. In the meantime, it is important to limit their use for the treatment of resistant infections or infections that recur despite adequate treatment with glycopeptides.

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New and Investigational Antimicrobials for the Treatment of Invasive, Multidrug-Resistant Staphylococcus aureus Infections


