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Dalbavancin, a Second Generation Lipoglycopeptide is a New Addition to Therapy Armamentarium

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ABSTRACT

Gram-positive infections with widespread developing resistance have posed considerable challenges to the long stay of antimicrobials in the market. Also, there has been a dearth in the provision of a suitable antimicrobial to treat the evolving resistance. Dalbavancin a 2nd generation lipoglycopeptide has shown its activity against gram-positive and multidrug resistant isolates. Owing to a favorable pharmacokinetic profile and supporting evidence this drug moiety has been used as long-term therapy for various indications. These indications include infective endocarditis (IE), osteomyelitis, bloodstream infections, and prosthetic joint infections. However, it is approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) only for acute bacterial skin and skin structure infections (ABSSSIs). Dalbavancin can be a valuable alternative to daily in-hospital intravenous or outpatient antimicrobial regimens in the treatment of long-term Gram-positive infections and 'niche' but important indications. This systematic review demonstrates comparative microbiology, chemistry, in vitro susceptibility, pharmacokinetics, clinical efficacy, safety, tolerability, dosage, and administration of dalbavancin. Additionally, it highlights past, present, and upcoming evidence of real-world use of dalbavancin alone or in combination with different indications.

Keywords: Dalbavancin, Acute bacterial skin and skin structure infections, Gram-positive, Long-term, and pharmacokinetics.

LITERATURE REVIEW

Treatment of serious gram-positive infections presents multiple challenges. An improper treatment often results in prolonged hospitalization for intravenous administration. Prolonged hospitalization is typically unfavorable to patient preferences and potentially subjects patients to additional healthcare-associated complications. Additionally, the evolution in resistance of pathogens has challenged the positioning of current and upcoming antimicrobials. The most common infections frequently encountered in hospitals and communities worldwide, with high morbidity and mortality are due to methicillin-resistant Staphylococcus aureus (MRSA).

With the increasing modifications in the resistance pattern in microbes, the minimum inhibitory concentration (MICs) of the antimicrobials have been also moving towards to upper limits. This has perhaps led to an increase in the graph of morbidity and mortality. The prevalence of MRSA in India ranges from 40% to 70% especially

among S. aureus isolates, with differences seen between hospital and community settings.[1] MRSA prevalence in North India reports the highest percentage of 52.8%, followed by West India at 48.1%.[2]

Surprisingly, the ideal antibiotic for MRSA does not yet exist. Such agents should have the following properties: rapid bactericidal killing; exceptional tissue penetration; steady pharmacokinetics and pharmacodynamics that allow for predictable dosing; low potential for the development of resistance while on therapy; low side effect profile; and demonstrated clinical and microbiological efficacy.[3]

Currently, such an agent with these ideal properties is not available. Hence, some have backed combination therapy to bridge the gaps where each agent fails. Additionally, in India, satisfactory evidence of improved efficacy of newer agents against complicated MRSA infections in different designs of trials is lacking.[1]

Gram-positive infections, resistance and Adverse effects of the treatment options available in India

Methicillin-Susceptible S. aureus (MSSA)

For definitive treatment of MSSA bacteremia, 1st generation cephalosporins such as cefazolin, and semisynthetic anti-staphylococcal penicillins such as cloxacillin are considered the optimal antimicrobials. Also, for empirical treatment, Vancomycin can be initiated if the methicillin-resistant pattern of the suspected S. aureus infection is unknown.

Methicillin-resistant S. aureus (MRSA)

One of the most common causes of serious hospital-acquired infections is MRSA which can be clinically grouped as community-associated (CA-MRSA) or hospital/ healthcare-associated (HA-MRSA). India, reports high rates of MRSA 54.8% (ranging between 32% and 80% among the S. aureus pool) in clinical isolates from various studies.[4]

In this condition, Vancomycin remains the most essential drug for the treatment.[5] In addition, the Infectious Disease Society of America (IDSA) guideline considers other drugs like daptomycin to be another useful drug for invasive MRSA infections.[6] Whereas, telavancin, ceftaroline, and linezolid may be used for second-line therapy of MRSA.[7] The 2016 Indian infectious disease treatment guidelines recommend glycopeptides like vancomycin and teicoplanin as drugs of first choice for MRSA, linezolid for MRSA-induced SSTIs, and daptomycin for complicated SSTIs and bacteremia due to MRSA.[8]

There have been reports from various parts of India on resistance to MRSA with linezolid and to multiple antibiotics such as vancomycin and tigecycline (multidrug-resistant S. aureus, MRSA).[9]

Vancomycin Resistance in MRSA

IDSA guidelines recommend the usage of vancomycin alternatives such as a combination of high-dose daptomycin with another antibiotic including gentamicin, rifampicin, linezolid, trimethoprim-sulfamethoxazole (TMP-SMX), or a β-lactam, for the treatment of challenging infections like- vancomycin-intermediate S. aureus (VISA) and vancomycin-resistant S. aureus (VRSA).[10]

Antibiotic Resistance among Streptococcus pneumoniae

The prevalence of drug-resistant S. pneumoniae (DRSP) has been reported to be increasing in India. Hence, this development is compromising the management of pneumococcal infections. However, the clinical impact of the current levels of antibiotic resistance is still unclear. Some studies do highlight resistance of S. pneumoniae is highly prevalent with beta-lactams including cephalosporins, macrolides, clindamycin, tetracyclines, and penicillins.[11]

Quinolone Resistance in Gram-Positive Bacteria

Quinolones are considered to be an important part of antimicrobials for both

gram-negative and gram-positive infections. From the past evidence, resistance developed for quinolone has increased which is threatening the usefulness of this class of drugs. In endocarditis, the experience in the use of antimicrobials is limited to the use of ciprofloxacin plus rifampicin in intravenous drug users with right-sided Staphylococcus aureus endocarditis.[12]

Chronic and unconditional use have always led to some or the other results that as adverse drug reactions (ADRs). From the above overview of the antimicrobials used for gram-positive infections, there are some significant ADRs reported with drugs like- Vancomycin when used chronically cause nephrotoxicity, hypotension, hypersensitivity reactions; and Red man syndrome. Linezolid causes thrombocytopenia, optic neuropathy, peripheral neuropathy, and lactic acidosis. Daptomycin known to cause myopathy, rhabdomyolysis, eosinophilic pneumonia, anaphylactic hypersensitivity reactions. Tigecycline causes bone growth inhibition, teratogenicity, hepatic toxicity, and elevated liver enzymes. Clindamycin causes pseudomembranous colitis, thrombophlebitis, azotemia, and agranulocytosis. This has now on a high scale dragged healthcare providers to switch to new treatment therapies for better patient safety profile.

We know that the current therapies for gram-positive infections include glycopeptides - vancomycin, teicoplanin, and more recently telavancin, dalbavancin, and oritavancin. Cephalosporins - fifth generation ceftaroline and ceftobiprole, and glycylcycline tetracyclines - tigecycline. The lipopeptide - daptomycin, the oxazolidinones - linezolid, and, more recently, tedizolid.

Glycopeptides are one of the important members of the antibiotics family. This family includes the most commonly used molecule for severe infections, vancomycin. The use of vancomycin has been the mainstay in parenteral therapies for MRSA infections and has now led to the development of resistance to the highest MIC values also.[13]

Another glycopeptide which is slowly revealing its efficacy and now getting highlighted for gram-positive infections with reported better safety and efficacy profile, is Dalbavancin. This teicoplanin derivative possesses more potent in vitro activity than vancomycin or teicoplanin. Food and Drug Administration (FDA) in 2014 approved Dalbavancin and European Medicines Agency (EMA) in 2015.

Infectious disease specialists from the collaboration of the World Society of Emergency Surgery (WSES) and the Surgical Infection Society Europe (SIS-E) 2018 have shared some clinical practice recommendations, as intravenous antibiotics (dalbavancin; recommendation-1A) can be used for the management of MRSA skin and soft-tissue infections.[14]

Dalbavancin has been explored in uncomplicated and complicated skin and skin structure infections (SSSIs) in clinical trials and has demonstrated equivalent or superior (versus vancomycin only) efficacy versus comparators.[15]

Dalbavancin is currently only approved for treating acute bacterial skin and skin structure infections in adults and is administered intravenously (IV) in either a single dose regime - 1500 mg single infusion or a double dose regime- 1000 mg dose followed by 500 mg one week later.

In this article, we have compared dalbavancin with other antimicrobials and highlighted that it can be used efficiently in niche and other indications.

Chemistry

Dalbavancin is derived from the naturally occurring glycopeptide, which was isolated from Nonomuria species, through a 3 step process namely- esterification, amidation, and saponification.[16]

The molecular structure of Dalbavancin is designed in such a way that its antimicrobial activity is likely enhanced than the other glycopeptides. The antimicrobial property is due to its ability to enter bacterial

membranes with the C-terminal dimethyl-propylamine group. This group supports dalbavancin to be more free and flexible in the penetration of bacterial membranes. Additionally, the fatty acyl group adds value to the long plasma half-life and promotes binding to target sites efficiently with nonspecific protein binding.[17]

Pharmacodynamics and Pharmacokinetics

The antimicrobial activity of Dalbavancin is exerted in two distinct modes of action, 1st by inhibition of cell wall synthesis and an anchoring mechanism. This molecule compared with previous glycopeptide antibiotics, demonstrates improved antibacterial potency against Gram-positive organisms. Dalbavancin has a long half-life of approximately 1 week, which is longer in tissues like skin and bone than plasma. These factors enabled the development of single-dose or once-weekly dosing regimens to treat acute bacterial skin and skin structure infections (ABSSSI). Also, Dalbavancin exhibits dose-proportional pharmacokinetics and is highly protein-bound (93%). No dosage adjustment is required in mild to moderate renal dysfunction and patients on chronic hemodialysis. The recommended dose is reduced by 25% for patients with severe renal dysfunction (creatine clearance < 30 mL/min/1.73m^2).[18] Cojutti et al. findings supported by Dunne et al reported, that a two-dose regimen of dalbavancin 1500 mg on Day 1 and Day 8 produced efficacy against S. aureus for up to 5 weeks in bone joint infections (BJIs).[19,20]

Clinical Use

Dalbavancin can be a drug of choice in numerous gram-positive infections. Some evidence from the literature is collated below.

Dalbavancin in ABSSSI

Recently one Indian clinical trial highlighted significant success rates in the dalbavancin-treated group. Patients who received dalbavancin had a higher clinical success rate than those receiving telavancin. At the end of treatment on day 7, the percentage of patients with a systemic inflammatory response syndrome (SIRS) score of 0 was higher in the dalbavancin group (86%) compared to the telavancin group (81%).[21]

In the DALBITA study, dalbavancin demonstrated a success rate of >80%, with similar efficacy/safety in ABSSSI.[22]

Dalbavancin in Pulmonary Infections

Currently, there is limited data on Dalbavancin in the treatment of pneumonia. Another same class drug, Telavancin is used in MRSA pneumonia and the reported success rate is 81.8%. However, Telavancin is now infrequently used for this condition due to its risk of renal toxicity and drug interactions. Fortunately, Dalbavancin overtakes these limitations.

A recent study of Dalbavancin has demonstrated high potency (100.00% susceptibility) against S. aureus causing pneumonia in patients with and without cystic fibrosis.[23] Additionally, one case report highlighted in the literature suggested one-time dose of dalbavancin is effective in patients with recurrent MRSA-positive respiratory, sputum, or bronchoalveolar lavage (BAL) cultures. Although the use of and optimal dosing for MRSA pneumonia will require further investigation, but Dalbavancin can be an alternative in conditions with limited options and difficult-to-treat infections.[24]

Dalbavancin in Infective Endocarditis (IE)

IE is another infectious syndrome mostly caused by Gram-positive cocci that requires extended antimicrobial treatment. The most common infection is extracardiac foci, which require antimicrobials different from those mostly active in the bloodstream. These criteria suit the use of dalbavancin and has been proposed as an option for the treatment of staphylococcal IE, including patients who are allergic to penicillin.

IE generally occurs when bacteria from a distant body site, such as the mouth or skin, enter the bloodstream and subsequently attach to a heart valve defect or prosthesis. One of the most common causes of IE is S. aureus. IE is considered a setting as suitable as osteomyelitis to exploit the effects of dalbavancin.[25] Austrian Society for Infectious Disease and Tropical Medicine includes dalbavancin as an option for infective endocarditis (IE) in outpatient parenteral antibiotic therapy (OPAT) settings.[26]

Dalbavancin was shown to be highly active in vitro against the vast majority of 626 Gram-positive organisms causing IE collected in the SENTRY Program, 2007–2017, with very low MIC90 values. The first report of dalbavancin use as second-line treatment in IE came from a small single-center study of nine intravenous drug users (a vulnerable patient population with difficult intravascular access and poor treatment adherence) affected by S. aureus tricuspid valve IE (seven MRSA). Most patients had been treated with other molecules and had then mostly received a single 1000 mg dose of dalbavancin. Only one-third completed the predefined treatment course and clinical response was observed in five cases and was unknown in four.[27]

In a subsequent report, Tobudic et al. evaluated clinical outcomes and safety of dalbavancin as either primary or sequential treatment in 27 patients with IE, including native, prosthetic, and cardiovascular implantable electronic device (CIED) infections, due to staphylococci, streptococci, and enterococci. In this study, dalbavancin was mostly used in an outpatient (OPAT) setting and was given to most patients for ≥4 weeks, with eight patients receiving >8 weeks of therapy. The clinical success rate was 92.6%, with most patients experiencing no adverse events.[28]

In their multicentre clinical experience of real-life dalbavancin use in Gram-positive infections, Wunsch et al. included 25 cases of IE reporting a cure rate of >90%.[29]

In a recent case reported by Jones et al., dalbavancin was used for the treatment of Streptococcus pneumonia native tricuspid valve endocarditis in a man with a history of intravenous drug use, who had a long hospital course complicated by a CR-BSI by E. faecalis. The subject was not a candidate for OPAT and needed 14 more days of treatment, but he could be discharged with a 3-day supply of oral levofloxacin and a single dose of dalbavancin. This report outlines the successful use of dalbavancin in the treatment of complicated streptococcal IE and E. faecalis bacteremia.[30]

A case of dalbavancin failure to control bacteremia in a complex patient with MRSA IE has also been published. This panel is gaining experience with Dalbavancin in IE and overall believes it can be an option for selected patients, mostly to reduce hospital length of stay and costs.[31]

Dalbavancin in Osteomyelitis (OM)

OM is an infection of the bone with frequent serious consequences. It is not an uncommon disorder; infection at a distant body site may spread through the bloodstream into a bone, or an open fracture or surgery may expose the bone to infection.[32]

The study assessed the efficacy and safety of dalbavancin given as a two-dose regimen for OM; this study represents a large randomized comparative clinical trial in adult subjects with a first episode of OM defined by symptoms, radiological analysis, and elevated C-reactive protein (CRP). Patients were randomized to dalbavancin (1500 mg i.v. on Days 1 and 8) or standard-of-care osteomyelitis treatment, and clinical response was assessed at 21 days, 6 months, and 1 year. Clinical cure at Day 42 was seen in 65/67 (97%) and 7/8 (88%) patients, respectively, in the dalbavancin and standard of care groups in the clinically evaluable population. The clinical response was similar in the dalbavancin group at Day 21 (94%), 6 months, and 1 year (96%), with the conclusion that a two-dose regimen of weekly dalbavancin (3 g overall) is effective

for the treatment of the first episode of OM in adults, with good tolerability of this drug.[33]

In a case of bacteremia S. aureus vertebral OM, a common form of hematogenous osteomyelitis, Almangour et al. showed how multiple weekly dalbavancin infusions appeared to be safe, although unable to prevent infection recurrence.[34]

Dalbavancin in Prosthetic Joint Infection (PJI)

Anti-microbial therapy in PJI has always been challenging as most of the infections commonly involve gram-positive microbes. Considering dalbavancin to treat PJIs can suffice the need for the limiting treatment options.

Some of the studies extracted from the literature have shown a way for clinicians to consider this molecule to be worthy of its use. Buzón-Martín et al reported the effectiveness of dalbavancin in total hip arthroplasty infection (THAi) and total knee arthroplasty infection (TKAi) due to Staphylococcus spp. and Enterococcus spp. The rationale behind using this molecule in this indication was in each particular case, generally, because of the failure of other antibiotics, their toxicity, interactions, and/or unavailability of other orally administered choices.[35] Additionally, a total of 571 days of hospitalization were avoided by using dalbavancin, as an alternative to daptomycin, which requires prolonged hospitalization for daily intravenous administration.[23]

The studies for dalbavancin in PJIs throw light more for its use as a salvage therapy which is considered a safe and easy treatment for the management of outpatients. Most of the study reports claim the overall results as favorable in 68/93 cases (73.1%).[36]

Future Prospects

Even though there is a considerable impact of gram-negative infections all over the world, we cannot overlook the current and upcoming alarms arising from gram-positive infections. More significantly these infections are observed in healthcare and ICU settings. Difficult-to-treat infections like MRSA, VISA, VRSA, VRE, and other multidrug-resistant organisms have left treatment therapies on a toss. There is a need to strategically plan the treatment option for gram-positive infections. With the thorough literature survey, there are very few antimicrobials that can meet the entire criteria of gram-positive infections accompanied by other comorbidities.

Dalbavancin can be a promising drug to treat gram-positive infections owing to its convenient dosing, usage in multiple indications, and favorable safety profile. Considering its activity against Gram-positive cocci, including MDR strains, dalbavancin represents a potential alternative to daily IV antibiotic administration. Also, the hospital stay can be benefited by a reduction in prolonged hospitalization for patients with BJIs, IE, PJIs, and vascular graft infections (VGIs). This is of particular interest in the context of centers with a dearth of inpatient resources and where there is a necessity to improve patient flow through acute care hospitals. Dalbavancin could therefore be a useful addition to outpatient parenteral antimicrobial therapy (OPAT) services in these settings. Moreover, In Phase II and III clinical trials, dalbavancin was effective and well-tolerated for the treatment of skin and soft-tissue infections, catheter-related bloodstream infections, and skin and skin-structure infections. Also, the data captured from these trials show that dalbavancin's safety profile in terms of adverse events has been mild and limited; the most common being pyrexia, headache, and diarrhea. Despite the remarkable and favorable pharmacokinetic prolonged half-life (6-10 days) and once-weekly dosing, the use of this potent agent should be restricted to severe infections due to multidrug-resistant organisms to limit the risk of selection of resistance. It is active against Gram-positive aerobes and anaerobes, including resistant pathogens, except strains producing vanA-

mediated resistance. The extent to which dalbavancin will supersede vancomycin and whether it will be preferred over other newer agents such as linezolid in the next decade will be seen with its logistic use.

Declaration by Authors

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