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A Study on Antibiotic Drug against Super Bug

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ABSTRACT: This review will focus on Dalbavancin's effectiveness against MRSA.Vancomycin has long been considered the drug of choice for the treatment of MRSA recently various vancomycin-resistant Staphylococcus aureus strain was reported in countries like Japan and US.Dalbavancin is used to treat acute bacterial skin and skin structure infections (ABSSSI) in adults. Dalbavancin differs from vancomycin in structure giving it a novel pharmacokinetic profile with a longer half-life.In various clinical trials, patients showed more success when treated withdalbavancin than vancomycin. It is an interesting option for 'difficult-to-treat infections' caused by susceptible gram-positive microorganisms due to its half-life of 14.4 days, high bone penetration and optimal safety.Increasing antibiotic resistance in the hospital environment has increased the demand for more effective antibiotics making it an attractive sector for new antibacterial agents. As a potential successor to vancomycin, dalbavancin appears well placed to succeed.

Key Words: Staphylococcus aureus, Dalbavancin, Vancomycin, ABSSSI.

I. BACKGROUND:

The development of glycopeptide-resistant pathogens was initially identified in the late 1980s, when vancomycin-resistant enterococci (VRE) first emerged in hospitals. More recently in 1995, Staphylococcus aureus strains with increased vancomycin minimum inhibitory concentrations (MICs) were reported in the USA. Soon after, a heterogeneous vancomycin-intermediate Staphylococcus aureus (VISA) strain was identified in Japan in 1996. In 2002, the first vancomycin-resistant Staphylococcus aureus (VRSA) strain was reported in the USA. To date, there have been six VRSA isolates reported worldwide. Vancomycin has long been considered the drug of choice for the treatment of MRSA infections. Its modest efficacy, coupled with increasing reports of treatment failures as a result of elevated vancomycin MICs seen in a proportionally greater number of isolates, has made it increasingly important to find an alternative agent that is effective in the treatment of resistant Gram-positive infections.

II. INTRODUCTION:

SUPER BUG-Staphylococcus aureus is a gram-positive bacterium that frequently colonises the skin and nostrils of healthy humans. However, S.aureus is also an opportunistic microorganism involved in infections of both community and healthcare origin. Besides being a common cause of skin, soft tissue and bone infections, it is one of the leading causes of bloodstream infections. S. aureus acquires resistance to meticillin and some other beta-lactam agents through expression of the exogenous mecA.

Dalbavancin is a lipoglycopeptide antibiotic. It demonstrated potent activity against several gram-positive bacteria, including methicillin-resistant Staphylococcus aureus. Dalbavancin works by binding to the D-alanyl-D-alanine terminus of the stem pentapeptide peptidoglycan, which interferes cell wall synthesis.

Dalbavancin is not active against gram-negative bacteria; therefore, combination therapy may be clinically indicated if the ABSSSI is polymicrobial and includes a suspected or documented gram-negative pathogen. [19]

Mechanism of action: Dalbavancin has a spectrum and mechanism of action similar to vancomycin, a naturally formed glycopeptide antimicrobial. The bactericidal action of dalbavancin results primarily from inhibition of cell-wall biosynthesis. Specifically, dalbavancin prevents incorporation of

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N-acetylmuramic acid (NAM)- and N-acetylglucosamine (NAG)-peptide subunits from being incorporated into the peptidoglycan matrix; which forms the major structural component of Gram-positive cell walls. The large hydrophilic molecule is able to form hydrogen bond interactions with the terminal D-alanyl-D-alanine moieties of the NAM/NAG-peptides, which is normally a five-point interaction . Binding of dalbavancin to the D-Ala-D-Ala prevents the incorporation of the NAM/NAG-peptide subunits into the peptidoglycan matrix. In addition, dalbavancin alters bacterial-cell-membrane permeability and RNA synthesis. [20]

Pharmacokinetics:

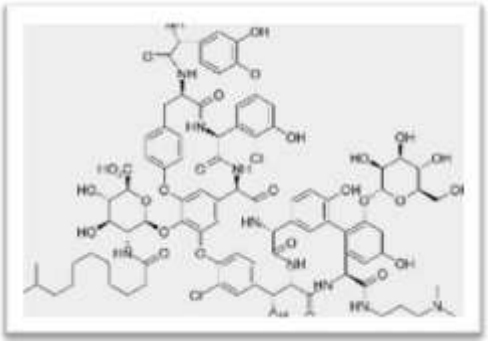
Absorption: In healthy subjects, dalbavancin increased proportionally to dose following single intravenous (IV) dalbavancin doses ranging from 140 mg to 1500 mg, indicating linear pharmacokinetics. [19]

Protein binding: Dalbavancin is reversibly bound to human plasma proteins, primarily to albumin. The plasma protein binding of dalbavancin is 93% and is not altered as a function of drug concentration, renal insufficiency, or hepatic insufficiency.[19]

Metabolism: Dalbavancin is not a substrate, inhibitor, or inducer of CYP450 isoenzymes. Subsequently, metabolites have not been observed in significant amounts in human plasma. The metabolites hydroxy-dalbavancin and mannosyl aglycone have been detected in urine (< 25% of administered dose) . The metabolic pathways responsible for producing these metabolites have not been identified. Hydroxy-dalbavancin and mannosyl aglycone show significantly less antibacterial activity compared to dalbavancin. [19]

Route of elimination: Following administration of a single 1000 mg dose in healthy subjects, an average of 33% of the administered dalbavancin dose was excreted in urine as unchanged dalbavancin and approximately 12% of the administered dose was excreted in urine as the metabolite hydroxy-dalbavancin through 42 days post-dose. Approximately 20% of the administered dose was excreted in feces through 70 days post-dose. [19]

Dosage: The recommended dosage is 1500 mg, Dalbavancin should be administered over 30 minutes by intravenous infusion. adverse reactions in patients were nausea (5.5%), headache (4.7%), and diarrhoea (4.4%).



Dalbavancin is not compatible with normal saline, and should be diluted in dextrose 5% water to a concentration between 1 and 5 mg/mL [1].

It has a favourable pharmacokinetic profile since the drug is not a substrate, inducer or inhibitor of cytochrome P450 enzymesand half-life of 170–210 h, which makes the once-weekly dosing optimal with no drug monitoring requirement.

Clinical trials that informed its approval demonstrated that a two-dose regimen of IV 1000 mg administered on day 1 followed by 500 mg on day 8 was non-inferior to standard-of-care (SOC) antibacterial agents such as vancomycin and linezolid [13,14,16]. The pharmacokinetic (PK) and pharmacodynamic (PD) parameters of dalbavancin suggest that its time-dependent and prolonged and persistent antibacterial effects allow for larger doses to be given early in treatment and enhance its duration of action [17,18].

Drug-drug interaction: Antagonism was not observed between dalbavancin and any of the nine antimicrobials tested (clindamycin, daptomycin, gentamicin, levofloxacin, linezolid, oxacillin, quinupristin/dalfopristin, rifampin and vancomycin). [4]

Dalbavancin has not been well-studied in pregnant women. Human dosages given to pregnant rats or rabbits (15mg/kg/day, 1.2 and 0.7 times the human dose on an exposure basis, respectively) have not demonstrated evidence ofembryo or fetal toxicity.It has been shown to be excreted in the milk of lactating rats. Because dalbavancin has poor oral bioavailability, it is not likely to reach the bloodstream of the infant or cause any adverse effects in breastfed infants.

Side effects: clinical trials for the use of dalbavancin in ABSSSI showed that it was generally well tolerated, demonstrating that the majority of adverse effects were designated as mild

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or moderate. The most common reported were rash, headache, nausea, vomiting, and diarrhea.[12,13,14] Adverse events occurred in 3/101 patients. One patient with multiple allergies in her medical history developed dyspnea and arterial hypertension during the second administration of dalbavancin, therefore the infusion was immediately stopped.[22]

III. RESEARCH AND DISCUSSION:

Dalbavancin differs from vancomycin with a structural modification of the lipophilic side chain, which enhances its binding affinity to the cell membrane and prolongs its half-life.

Analysis of 51 clinically evaluable patients demonstrated clinical success in 16 of 17 (94%) patients treated with two doses of dalbavancin, eight of 13 (62%) treated with one dose of dalbavancin, and 16 of 21 (76%) patients treated with the comparator.[5]

Dalbavancin exhibits linear, dose-dependent pharmacokinetics, peak serum concentration was achieved within 30–60 minutes and reaching steady state concentrations after 3 days when administered to healthy adult volunteers .[1]

In a study, Raad et al conducted a Phase II, open-label, randomized, multicentre clinical trial evaluating dalbavancin vs. vancomycin[21] in adult patients with catheter-related bloodstream infections (CR-BSIs). Dalbavancin was administered as a 1000 mg intravenous loading dose, followed by a 500 mg intravenous dose 1 week later and compared with a 14-day course of intravenous vancomycin at 1000 mg twice daily. Infected patients who received weekly dalbavancin had an overall success rate that was significantly higher than that of those who received vancomycin. Adverse events and laboratory abnormalities were generally mild and were comparable for the 2 drugs. [2]

Data has become available suggesting that it may also have a role in the treatment of other sources of infection, most notably osteomyelitis and endocarditis. [7,8,9,10]

A study conducted by Jones et al. analysed 64,815 isolates from 2011 to 2013 from a surveillance study collection in an effort to demonstrate that using vancomycin susceptibility to infer dalbavancin susceptibility is an appropriate practice. [11]

dalbavancin has been studied for off-label uses in the treatment of osteomyelitis, infective endocarditis, prosthetic joint infections, and catheter-associated bacteremia. [15]

The use of dalbavancin has major significance for antimicrobial stewardship programmes (ASPs), reducing the length of hospital stay improves patient quality of life and mobility and eliminates discomfort and complications associated with intravenous catheters; specifically, it decreases the risk for non-infectious and infectious catheter-associated AEs ,the risk of colonisation and disease by multidrug-resistant bacteria.[23,24,25,26]

IV. CONCLUSION:

Data suggests that dalbavancin use as first-line treatment should be implemented especially in ABSSSI, without any concomitant treatment when possible, and as an outpatient or emergency department regimen in order to reduce hospitalization rates and costs. In OTA, despite excellent available data for bone infections, more experience and efficacy studies on larger populations are needed, especially in prosthetic joint infections, endocarditis, and complicated bacteremia where dalbavancin could really change the paradigm of maintenance therapy According to the data, dalbavancin is currently placed as second-line and/or association therapy also in ABSSSI, somehow thwarting its potency and favorable pharmacokinetic properties. Should dalbavancin efficacy in difficult-to-treat infections be confirmed in randomized controlled trials, the current off-label use of dalbavancin could be enhanced at the advantage of patients' and antimicrobial stewardship's perspective.

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