Research Article CODEN: IJPRNK ISSN: 2277-8713
Rama Gupta, IJPRBS, 2014; Volume 3(1): 286-296 IJPRBS

INTERNATIONAL JOURNAL OF
PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

NEWER ANTIMICROBIALS FOR GRAM POSITIVE ORGANISMS

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Accepted Date: 31/01/2014; Published Date: 27/02/2014

Abstract: Gram positive organisms entail colossal burden on patients and the health care system throughout the world. These organisms are a real test for the clinicians, particularly the organism with emerging and multiple drug resistance. Multiple drug resistant organisms fail to respond to standard first line antimicrobials and hence cannot be treated correctly using empirical treatment. The challenge for the clinician is not only to treat these infections but also to develop and follow certain strategic measures to control the emergence of wide spread resistance. Researchers are developing novel compounds as well as modifying currently available agents and also working on finding new targets for antimicrobials. Consequently new empirical treatment options for gram positive organisms can be formulated. Thus new agents such as Linezolid (Oxazolidinone) and Streptogramins (Quinupristin / dalfopristin) have been developed. FDA has approved the use of these drugs in resistant gram positive infections. In addition large numbers of chemically modified drugs are still in the various phases of development and are intended to be used against Gram positive infections. These drugs include various modified glycopeptides (Oritavancin, Teicoplanin etc); modified quinilones (Sparfloxacin, Grepafloxacin etc); macrolides (Dirithromycin) and tetracyclines (Glycylcyclines) etc.

Keywords: Therapeutics, Multi drug resistance, MRSA, VRE, VISA, Streptogramin and Linezolid.

PAPER-QR CODE

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Access Online On:

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How to Cite This Article:

Rama Gupta, IJPRBS, 2014; Volume 3(1): 286-296

INTRODUCTION

Infections due to gram positive organisms are a major health care problem as 30–40% of all the bacterial infections are caused by these organisms including, *Staphylococci, Enterococci, Pneumococcus,* and *Streptococci*. (1) The discovery of Penicillin by Alexander Fleming in 1944 was a major breakthrough in the development of antimicrobials and to combat these infectious diseases. Today, the lives of millions of the patients suffering from infections are saved that otherwise would have been lost because of antibiotics.

Unfortunately antibiotics are the most widely and indiscriminately used medication available today, particularly in the developing countries, resulting in appearance of multi drug resistant pathogens. Though a variety of antimicrobials are available today, drug resistance is not only prevailing but continues to expand its dimensions, with the emergence of resistance to newer antimicrobials. As a result the numbers of predictably effective antibiotics are decreasing day by day and a time may come when we land up in a situation without an alternative treatment left. Hence the arsenal of available antimicrobial agents has to be expanded further.

In 1960 first strain of *Staphylococcus aureus (S. aureus)* resistant to methicillin was reported. Methicillin resistance in *S. aureus* is mediated due to the presence of mecA genes which encodes for peripheral binding protein (PBP2a) with low affinity to all β–lactams hence mediating resistance not only to methicillin and other penicillins but also to all other β–lactams antibiotics including cephalosporins and carbepenams (2). Enterococci are upcoming major nosocomial pathogens because of emergence of vancomycin resistant enterococci (VRE) and are presenting a serious problem (3). Similarly Glycopeptides Intermediate *Staphylococcus aureus* (GISA) is posing a serious therapeutic challenge to the clinicians (4). This article reviews the newer antimicrobials available to be used as empiric therapy against multidrug resistant gram positive organisms.

Glycopeptides:

Vancomycin: Chemically this drug is a glycopeptide which was isolated in 1956 from *Streptomyces orientalis*.

Mode of Action: It inhibits bacterial cell wall synthesis by preventing cross linking of the cell wall peptidoglycan at the second stage of cell wall synthesis. Basically it forms a complex with D–alanyl–D–alanine precursors units for cell wall synthesis and thus inhibits peptidoglycan polymerase and transpeptidation reaction. Most of the other β–lactam antibiotics inhibit cell wall synthesis at the IIIrd phase of cell wall synthesis, hence there is no competition between vancomycin and other β–lactam antibiotic for binding site and also cross resistance between the drugs is not possible(5,6).

Antimicrobial Spectrum and Clinical indications: Vancomycin is bactericidal against most of the gram positive organisms including *Staphylococcus aureus* both Methicillin Sensitive (MSSA) & Methicillin Resistant (MRSA); coagulase negative *Staphylococci* (CONS); *Pneumococci* and *Viridans Streptococci. A*gainst *Enterococci* the drug is only bacteriostatic. Further, vancomycin is active against large number of other gram positive aerobic and anaerobic organisms including *Corynebacterium sp.; Bacillus sp; Clostridium difficile; Listeria monocytogenes; Lactobacilli; Actinomyces* and Anaerobic *Streptococci (3,7,8)*.

Clinically vancomycin has been recommended as a drug of choice for bacteremia, endocarditis, pneumonia, cellulitis and osteomyelitis caused by Methicillin resistant Coagulase negative and coagulase positive Staphylococcal infections. Vancomycin is also recommended for prophylactic use in patients who are allergic to penicillin and are undergoing invasive gastrointestinal procedures which may result into transient bacteremia leading to endocarditis.

Dosing: The recommended adult dose of vancomycin in a patient with normal renal function is 1 gram intravenously (I/V) every 12 hrs. Recommended I/V dosing schedule for pediatric patients vary according to the age and site of infection. In new born vancomycin is given at a dose of 15 mg / kg of body weight every 12 hrs for the first week of life and every 8 hrs in new born 8 -30 days of age; 10 mg / kg body weight every 6 hrs for older infants and children. Vancomycin can not be administered I/M because of severe pain at the injection site. Orally administered vancomycin is poorly adsorbed from gastro intestinal tract (GIT) (6, 9).

Adverse Effects: Rapid infusion of vancomycin may lead to Red Man syndrome which is due to immunologically mediated histamine release (10). Ototoxicity & nephrotoxicity can be seen with vancomycin but rare when used alone, however may be potentiated when vancomycin is administered along with amino-glycosides. Neutropenia may be seen when vancomycin therapy is prolonged (>14 days) but this is rare and reversible after the discontinuation of the drug. Skin rash and fever may occur in 4–5% of the patients (11, 12).

Resistance: Due to over usage of this drug selective pressure on the bacteria can be enormous and hence resistance to vancomycin needs a special reference. Vancomycin resistant enterococci (VRE) are increasing at an alarming rate and the established transfer of resistance from the enterococci to Staphylococci, though *in vitro*, is a matter of significant worry. There are two phenotypes of Enterococci showing resistance to Vancomycin, VanA & VanB. The Van A phenotype is plasmid encoded and simultaneously encodes for resistance to vancomycin and teicoplanin whereas Van B phenotype is chromosomally mediated and encodes resistance to vancomycin alone (3, 13).

The first case of decreased susceptibility of *S. aureus* towards vancomycin was reported in 1996 from Japan followed by reports from Michigan, New Jersey & Detroit in 1997 and yet another

from New York in 1998. All these vancomycin intermediately sensitive *S. aureus* (VISA) strains have MIC of 8 mg / L and the patients have previous history of treatment with Vancomycin. MRSA strains with reduced susceptibility to teicoplanin have also been reported from Europe, United States & SA, so the term Glycopeptides Intermediate *Staphylococcus aureus* (GISA) can be used as well. The mechanism of reduced susceptibility of *Staphylococcus aureus* to glycopeptides is still unclear but it seems not to be due to Van genes present in Enterococci (4, 14, and 15).

Teicoplanin is another glycopeptide antibiotic with good spectrum of antimicrobial activity against gram positive pathogens including *Staphylococcus aureus* both Methicillin Sensitive (MSSA) & Methicillin Resistant (MRSA) and Van B phenotype of VRE. Its mode of action and spectrum parallels the spectrum and activity of vancomycin. However its elimination half life is exceptionally long which allows once daily dosing of the drug via I/V or I/M route. In adults or elderly patients with normal renal functions, recommended dose is 400 mg I/V every 12 hours for first 3 doses followed by 200 mg I/V or I/M once daily. The drug can be used prophylactically in prosthetic joint implant surgery at the time of induction of anesthesia in a single dose of 400 mg I/V. Teicoplanin has excellent tissue penetration and low toxicity (16).

LY33328 (Oritavancin) and **LY 264826** are two another extensively studied glycopeptides which are structurally similar to Vancomycin. Both the glycopeptides has in vitro activity against vancomycin sensitive and vancomycin resistant enterococci and MRSA. The drugs also have a longer half life hence treatment duration can be reduced. However these drugs are not available for clinical use as more data has to be made available. These glycopeptides can play a significant role in the treatment of highly resistant organism, in future (17, 18).

Lipopeptide

Daptomycin is a lipopeptide which kills bacteria by disrupting the cell membrane. The action of daptomycin is concentration dependent and it is a bactericidal drug killing 99.9% of the bacteria tested within 6hrs. Daptomycin has proved to be more effective and potent, in *vitro*, than vancomycin and Linezolid against most of the gram positive isolates tested (19). The studies also confirm that daptomycin has in vitro activity against a variety of VS and VR strains of *Enterococci* as wells as all species of *Staphylococci* including Methicillin resistant coagulase negative Staphylococci and *Streptococci* including Penicillin susceptible, Penicillin intermediate & Penicillin Resistant *Streptococcus pneumoniae*. Hence it has a broad spectrum anti gram positive activity and is currently under phase III clinical trials (20).

Oxazolidinone

Linezolid chemically belongs to a new class of antibiotics i.e. Oxazolidinone.

Mode of Action: It inhibits protein synthesis by disrupting the interaction of f–Met-tRNA with the 50S ribosomal subunit at the time of formation of 70S complex. Hence inhibition of protein synthesis is at a much earlier step as compared to other protein synthesis inhibitors including chloramphenicol, clindamicin, aminoglycosides and macrolides.

Antimicrobial Spectrum and Clinical Indications: This drug is bacteriostatic against *Enterococci* and *Staphylococc*i (19), but it is bactericidal against most of the *Streptococci*. Linezolid is found to be effective against resistant gram positive organisms including MRSA, MRCons and vancomycin & Teicoplanin (Glycopeptides) intermediately resistant *S.aureus* (GISA) and VR E. feacium (21 - 23).

FDA has approved the use of linezolid in May 1999 for the treatment of community and hospital acquired pneumonia caused by *S. aureus* (Both MSSA and MRSA) or *Streptococcus pneumoniae* (Penicillin sensitive strains); complex skin and soft tissue infections caused by *S. aureus* (MSSA & MRSA), *Streptococcus pyogenes* and *Streptococcus aglactiae*; and bacteremia caused by Gram positive bacteria (24).

Dosing: As a completely synthetic oxazolidinone, linezolid has very good pharmacokinetics to be used for the treatment of life threatening infections in all parts of the world. Its high bioavailability (100%) in both the formulation i.e. IV / oral allows rapid conversion from intravenous to oral therapy, as soon as the patient is stable. Since the half life of the drug is approximately 5 hrs, the dosage for linezolid is 400/600 mg every 12 hrs for duration of 10 – 28 days using intravenous or oral route depending upon the condition of the patient. No dose adjustment is required for the patients with renal failure. Since 80% of the drug is eliminated during dialysis, it should be given post dialysis.

Adverse Effects: The drug has no interaction with the Cytochrome P450 metabolic pathway, so adverse drug interaction is uncommon. Only 2% of the patients been reported to have adverse reaction in clinical trials including rash, headache, diarrhea, nausea, vomiting, insomnia, constipation and fever. In addition thrombocytopenia has been reported in 2.4% of patients receiving linezolid. Myelosuppression (anemia, leucopenia and pancytopenia) the most adverse effect of linezolid has also been reported.

Linezolid is a reversible non selective inhibitor of monoamine oxidase A (MAO-A) and hence can present undesired side effects with adrenergic and serotonergic agents. Clinical data regarding the safety of the drug in children younger than 18 years of age, pregnant women and breast feeding mothers is scarce (16, 25).

Recently a novel 4 – substituted 1, 2, 3- triazole oxazolidinone has been found as a good replacement for the linezolid with reduced or no activity against MAO-A (26)

Quinupristin/dalfopristin:

Quinupristin/dalfopristin is the first formulation of a distinct class of antibiotics known as Streptogramins. It is a combination of two naturally occurring compound produced by *Streptomyces pristinaspirates*.

Mode of Action: The drugs act synergistically and inhibit protein synthesis by sequentially binding at two different sites on 50S ribosomes (27). Quinupristin and dalfopristin is available as a combination of 30% Quinupristin and 70% dalfopristin (W/W). Due to its synergistic nature, it is sometime bacteriostatic and some time bactericidal.

Antimicrobial Spectrum and Clinical Indications: FDA has approved the use of this combination against *S. aureus* (MSSA); *S.pyogenes*; vancomycin resistant *Enterococcus feacium*. However it is important to note that this synergistic drug is not active against *Enterococcus feacalis*. The drug is indicated for serious or life threatening infections associated with VRE (*E.feacium*); complicated/uncomplicated skin and skin structure infections caused by MSSA and *S. pyogenes (28, 29)*.

Dosing: Quinupristin and dalfopristin is administered parent rally and recommended dose is 7.5mg / Kg body weights every 8 – 12hrs. Half life of these drugs is almost similar i.e. 0.9 hrs and 0.7 hrs respectively. Tissue penetration is moderate with blister fluid concentration reaching 40% of the plasma concentration (16). However dose reduction is indicated in patients with hepatic failure but not in renal failure as it does not get eliminated during dialysis.

Adverse Effects: Adverse effects most commonly reported with the combination include nausea, vomiting diarrhea, rash, myalgia and arthralgia. Though reversible, myalgia and arthralgia were the adverse events which led to discontinuation of the therapy in approximately 50% of the affected patients. Pain and the inflammation at the injection site are quiet common but rarely required discontinuation of the treatment. Therefore in general the drug is safe with no reported nephrotoxicity, bone marrow suppression, ototoxicity or any other cardiovascular adverse effects. Quinupristin and dalfopristin significantly inhibit the biotranformation rate of enzyme Cytochrome P450 3 A4. As a result plasma concentration of some drugs, in particular cyclosporine was predicted to increase after the therapy hence need to be monitored (16, 30).

Flouriquinolones

The flouroquinolones (FQ), derivatives of nalidixic acid were first introduced in 1970s.

Mode of Action: Flouroquinolones inhibit bacterial DNA Gyrase activity hence interferes in DNA replication and are bactericidal. The newer FQ available for clinical use include levofloxacin, Sparfloxacin, trovafloxacin and grepafloxacin.

Sparfloxacin

Antimicrobial spectrum and clinical indications: It was introduced in 1996 and is structurally similar to ciprofloxacin but has greater Gram +ve activity specifically against *Streptococcus pneumoniae* strains highly resistant to oral penicillins. In addition sparfloxacin is also effective against *Staphylococcus aureus* (including penicillin resistant strains); coagulase negative *Staphylococci* (CONS); Gp.A *Streptococci* and *Cl. perfringens*. However this drug is not active against Methicillin resistant *Staphylococcus aureus* (MRSA), Methicillin & ciprofloxacin resistant *Staphylococcus aureus* (MRCRSA), Vancomycin resistant *Enterococci* (VRE), Methicillin resistant Coagulase Negative *Staphylococci* (MRCNS), Methicillin & ciprofloxacin resistant Coagulase Negative *Staphylococci* (MRCR CNS); Gp.B *Streptococci & S. viridans*. This drug is referred to as a respiratory quinolone because of its penetration into pulmonary fluids and tissue and also levels of Sparfloxacin in respiratory tissue is many fold greater than the serum levels

Dosing: Sparfloxacin has a half life of 16 – 20 hrs and >90% of it is absorbed from the GI tract, unaffected by food and reaches peak serum concentration in 4 – 5 hrs. Therefore this drug is available only as an oral medication and also this allows a dosing after every 24 hrs. The recommended dose is 400 mg on the first day; followed by 200 mg for 9 days thereafter. (31-34).

Levofloxacin

Antimicrobial spectrum and clinical indications: It is the L–isomer of D, L–Ofloxacin. Like sparfloxacin it is also considered one of the respiratory quinolones due to its excellent penetration into lung tissues. Among the Gram positive, the drug is active against *S. pneumoniae*; including penicillin resistant strains, *Enterococci & S. aureus* excluding VISA, MRSA, MRCR SA etc.

Dosing: The drug has relatively short half life, but 100% absorbed from GI tract with peak serum concentration reaching within 1 – 2 hrs. Recommended dose is 500 mg once a day for 7 – 14 days via oral route. However, the drug should be given empty stomach as food interferes with the absorption of the drug (33, 34).

Trovafloxacin

Antimicrobial spectrum and clinical indications: Like other newer FQs it has excellent Gram positive activity with the retention of native gram negative spectrum of native FQs. Gram positive spectrum of Trovafloxacin includes efficacy against Pneumococci including penicillin resistant strains, Methicillin sensitive as well as MRSA & MRCR SA. The activity of Trovafloxacin is variable against Enterococci and VRE and needs more data to be evaluated.

Dosing: Trovafloxacin is available both as an oral and IV medication. The recommended dosage is 300 mg of IV followed by 200 mg orally a day for 10 – 14 days. However recent data available shows the marked hepatotoxicity of this drug, therefore FDA has given specific recommendation for reserve use of trovafloxacin for the patient with serious life or limb threatening infections (16, 32).

Grepafloxacin also shows better activity against G +ve organisms specifically against *S. pneumoniae* including PCN resistant strains and can be given orally in a once daily dose of 400 – 600 mg for 10 – 14 days depending upon the site and severity of infection (16, 35).

Macrolides

Erythromycin is the prototype of macrolides class of antibiotics, which is a metabolic product of *Streptomyces erythereus*. There are at least four newer macrolides available including azithromycin, clarithromycin, dirithromycin and roxithromycin. Clarithromycin is the only newer macrolide which has improved activity against Gram positive organisms as compared to its prototype. The other three members are comparatively more effective against atypical organisms like M. pneumoniae, C. trachomatis, Borellia, Rickettisia, Legionella, Moraxella etc (16).

Mode of action: These drugs bind to 50S ribosomal subunit reversibly and inhibit protein synthesis.

Clarithromycin

Antimicrobial spectrum and clinical indications: It has three to four times more activity as compared to Erythromycin, against Gram positive organisms like *Staphylococci and* Streptococci including Penicillin resistant *S. pneumoniae*. FDA has approved the use of the drug for the treatment of Community acquired pneumonia (CAP), acute exacerbation of chronic bronchitis (AECB) and skin & soft tissue infections (SSIs).

Dosing: The drug is given at a dosage of 250 – 500 mg every 12hrs for 7 – 14days. The drug concentrates in lung, nasal, middle ear, skin and tonsillar tissue at a concentrations 2 – 6 times those achieved in serum (33).

Adverse effects: Clarithromycin weakly induces the Cytochrome P450 system, hence may potentiates the effect of drugs (theophyline, digoxin, terferidine. Carbamazipime etc.), which are metabolized by Cytochrome P 450 enzyme system. Clarithromycin is generally well tolerated, with lesser GI side effects than erythromycin. Like erythromycin leaves an unpleasant metallic taste in the mouth. Prolonged use of the drug in high dosage may cause hearing loss which is reversible (16, 33).

Other drugs under investigation

Tiglicycline, GAR – 936 a recent derivative of minocycline (tetracycline) has in vitro activity against multiresistant Gram positive species, a range atypical organism and some gram negative aerobes and few selected anaerobes. It is currently under Phase II clinical trials, intended for use against multiresistant gram positive organisms. Semi synthetic derivative of minocycline **(Glycylcycline CL329, 998)** and dimethyl deoxy tetracycline **(CL331, 002)** which are reported to be more active than Tiglicycline and glycopeptide respectively against MRSA are also currently under Phase II clinical trials. **SCH 27899** is an oligosaccharide everninomicin antibiotic found to be highly active against MRSA is also under investigation (9, 16).

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