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Omadacycline, a Magic Antibiotics for Bacterial Infections

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Nowadays antibiotic resistance is a worldwide serious problem that mainly affects public health. Omadacycline is a unique antibiotic which has two available dosage forms such as intravenous (IV) and oral that development for community-acquired bacterial infectious disease treatment. It is a modified form of older tetracycline at C-9 aminomethyl substituent of 6-member core ring of tetracycline. Modification form shows its activity against efflux pump and ribosomal protein protection mechanism of tetracycline resistance. Generally, omadacycline is effective against methicillin-resistant *S. aureus* (MRSA), *Streptococcus pneumoniae*, vancomycin-resistant *Enterococcus* (VRE), *Legionella* and *Chlamydia* spp. Efficacy, safety and tolerability profile of omadacycline those compares with recent antibiotics shows that omadacycline is less resistant than others. One derivative from tetracycline derivatives is 9-neopentylaminomethylminocycline called omadacycline was discovered and ongoing phase III clinical experiments as a therapy for acute bacterial skin and skin structure infections (ABSSSI) as well as community-acquired bacterial pneumonia (CABP). Omadacycline seems to be a strong drug candidate for future promising new antibacterial agent that is effective against ABSSSI and CABP.

Key Words: Antibiotics, Omadacycline, Aminomethylcycline

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INTRODUCTION

Omadacycline a potent aminomethylcycline antibacterial agent is sensitive against Gram-positive as well as Gram-negative bacteria (1). There are two available dosage forms developed for novel antibiotic omadacycline, of them one is oral once daily and another is intravenous (IV) route (2). Tetracycline resistance is increasing day by day that's why it is urgent to develop new antibiotics that can counteract this type resistance (3). Efflux and ribosomal protection are two prime mechanism of tetracycline resistance (4). Our new antibiotic omadacycline has the ability to overcome these types of tetracycline resistance. It also to mentionable that omadacycline has demonsrated antimicrobial efficacy against aerobes, anaerobes and pathogens such as *Legionella* and *Chlamydia* spp. (5). Compare with linezolid omadacycline had shown its potency into phase II and phase III clinical studies performed for complicated skin and skin structure infections (cSSSI) (6).This new antibiotic also undergoing development to phase III clinical experiment for acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP) (1).

DISCOVERY AND STRUCTURE ACTIVITY RELATIONSHIP OF OMADACYCLINE

Compare with tetracycline only one difference is shows in omadacycline at in C-9 position (2). Omadacycline is an aminomethyl C-9 substituent antibiotic that is modified form of tetracycline (2). This form shows more antimicrobial potency which is also active against ribosomal protection proteins as well as efflux pump resistance mechanism (7, 8). *In vitro* potentiality of aminomethylcyclines was determined against Gram-positive bacteria. The minimum inhibitory concentration (MIC) of omadacycline was evaluated 0.06~2.0 mcg/ml (1). Omadacycline was discovered as a potent aminomethylcycline by structure activity relationship, which was established a unique group of new modified tetracycline antibiotics with potential antibacterial sensitivity against Gram-positive tetracycline resistant bacteria such as methicillin resistant *S. aureus* (MRSA) and vancomycin-resistant *enterococci* (VRE) (1). Due to presence of aminomethyl functional group, omadacycline is different from glycylcycline tetracyclines like tigecycline as well as eravacycline (9, 10).

MECHANISM OF ACTION OF OMADACYCLINE

The well-known mechanism of tetracycline is that inhibits the protein synthesis. Like a typical tetracycline, omadacycline also inhibits the protein synthesis of bacteria (4). Omadacycline shows its activity by binding with 70S ribosome of bacterial cell with a good affinity which can be compared to minocycline (4).This affinity is stronger than the affinity of tetracycline. In case of tetracycline there are two type of binding site one is high affinity another is low affinity binding site. There is competition between omadacycline and tetracycline for the binding to ribosome; it is difficult to distinguish to where the competition either at primary and/or at secondary sites (4). Compare with other tetracyclines like tetracycline, doxycycline, omadacycline has similarity with tigecycline is nearly similar to omadacycline but it is not affected by two prime resistance to tetracycline are efflux as well as ribosomal protection. Using MIC values *in vivo* studies in bacterial strains the ability of omadacycline was eastablished. From the MIC values, macromolecular synthesis and *in vitro* studies of protein translation we can assure that resistance mechanism present or not. It is still unknown how omadacycline can overcome efflux pump tetracycline resistance (4).

WAY TO OVERCOME THE TETRACYCLINE RESISTANCE

Ribosomal protection proteins and efflux pump are two main mechanism of tertracycline resistance (3). The main action of ribosomal protection proteins is altering the conformational change of ribosome that keeps away tetracycline from binding (11). Efflux protein produce from Gram-negative *tet*(B) gene that has the ability to bacterial resistance in case of tetracycline as well as minocycline, but aminomethylcyclines and glycylcyclines are not affected by efflux mechanism (3, 4). The Tet(M) and Tet(O) proteins are potential ribosomal protection proteins have almost similar characterized in case of omadacycline and tigecycline that can retain their effectiveness against above mentioned protein (3, 4). *In vitro* experiment of efficacy, omadacycline and other aminomethylcyclines were evaluated by using gram positive bacteria. The results have been shown that these drugs were effective against tetracycline resistance (4). Omadacycline has a great ability to inhibit cellular protein synthesis but no effect on DNA, RNA and peptide glycan synthesis (1). This ability is the parameter to indication of effectiveness for becoming bacterial resistant to antibacterial agents during therapy or over the life time of the antibiotic. Bacteria carrying these tetracycline resistance genes that conferring either efflux pump for tetracycline or ribosomal protection have remained susceptible to omadacycline (1).

IN VITRO AND *IN VIVO* STUDIES OF OMADACYCLINE

Numerous *in vitro* studies were performed for the effectiveness of omadacycline that has been established by using different types of bacteria (5).

From these *in vitro* studies it can be concluded that omadacycline is active against almost each and every types of pathogens which were already resistant tetracycline (5).

On the other hand *in vivo* stability of novel antibiotic omadacycline was determined in human microsomes and hepatocytes. More than 90% remain intact after incubation of omadacycline for 30 minutes. As the same way more than 86% remain intact after 1 day incubation. So we can say that this unique drug is rarely metabolized in any significant amount by using this result.

TRANSPORTER EFFECTS OF OMADACYCLINE

In vitro efficacy of omadacycline for drug-drug interactions were evaluated by using human drug transporter proteins. The activities of omadacycline is induce or inhibit were established by expressing human organic anion transporters1 or 3 (hOAT1 or hOAT3), organic cation transporter 2 (hOCT2), and organic anion transport polypeptide transporters OATP1B1 and OATP1B3 (1). Omadacycline shown its inhibitory effect on hOAT1, hOAT3, hOCT2, OATP1B1, and OATP1B3 was evaluated in HEK293 cells and inhibitory effect of BRCP, P-gp, and MRP2 by omadacycline was shown in T8, T0.3, and MDCKII cell lines (1). Measurement of level of mRNA in human hepatocytes had shown that induction of MRP2 as well as P-gp by this drug. Omadacycline neither inhibit P-gp, BRCP or MRP-2 nor induce P-gp or MRP-2 mRNA (1). Finally we can say that omadacycline rarely interact with specific human transporters as well as it is not an inducer or an inhibitor of P-gp (1).

CLINICAL PROFILE AND EFFICACY OF OMADACYCLINE

Phase II and phase III clinical studies were performed with omadacycline in cSSSI patients (6). cSSSI patients take 100 mg omadacycline in intravenous (I.V.) route once daily switch to another option of 200 mg omadacycline once daily by oral route (Phase II study) or 300 mg omadacycline once daily in oral route (Phase III study). In above cases it was compared with linezolid 600 mg omadacycline in I.V. route with switch to another option of 600 mg omadacycline two times daily for oral administration. Response of test of cure (TOC) and intent-to-treat population were measure with omadacycline was 88.3% and 75.9% with linezolid, finally we conclude that above drugs were active against MRSA infectious disease (6).

CLOSING REMARKS

Numerous clinical studies has evaluated that omadacycline is a unique antibiotic improved the spectrum against microbial infections. Omadacycline is a modified form of tetracycline that has the greater ability to improve the antimicrobial activity. It has the ability to overcome the tetracycline resistance such as efflux as well as ribosome protection. Oral bioavaility and less side effect carry additional benefit for treatment of different infectious disease with omadacycline. Compare with other respective drugs it also shows that omadacycline is more active well tolerable antibiotic. It has two available convenient route of administration such as oral and IV. Finally we can say that omadacycline is a promising new antibiotic that is active against ABSSSI and CABP.

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