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DELPAZOLID A NOVEL DEVELOPMENT IN THE TREATMENT OF PULMONARY TUBERCULOSIS

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ABSTRACT

The objective of the review paper is to discuss the biology and chemistry of oxazolidinone, a novel class of synthetic antibiotics now being used in medicine. Five-membered heterocyclic ring oxazolidinone has a variety of biological uses in medicinal chemistry. In terms of drug discovery, 2-oxazolidinone is the most studied compound. Delpazolid, a brand-new oxazolidinone, was created which is used for the treatment of Tuberculosis. Delpazolid's safety, tolerability, and pharmacokinetics have been assessed in a phase 1 clinical research, which found that, even after three weeks of repeated treatment, it did not produce adverse effects like myelosuppression. Delpazolid shows better activity with lesser adverse effect than previous available drug for the treatment of TB. Delpazolid exhibits in vitro action against Mycobacterium TB and other Gram-positive bacteria. In patients with pulmonary tuberculosis (TB), this study assessed the bactericidal efficacy, safety, and pharmacokinetics of delpazolid.

Keywords: Oxazolidinone, Tuberculosis, Linezolid, Delpazolid.

I. INTRODUCTION

The word antibiotic was first introduced in 1941 by Selman Waksman to indicate any small molecule produced by a microbe capable of counteracting the growth of other microbes. In the years between 1940 and 1960, a period known as the antibiotic golden age, penicillin, streptomycin, tetracycline and chloramphenicol were developed. However, the evolution of bacterial resistance has made these antibiotics and many other successors largely ineffective. According to the WHO (World Health Organization) definition, antimicrobial resistance refers to change in microorganisms (viruses, bacteria, parasites and fungi) which make the drugs used to treat the infections they have caused in effective. Such resistance to a wide variety of infectious agents is a major global health concern and the rapid spread of multidrug-resistant bacteria is alarming . In recent years, bacterial resistance to first-line drugs has reached very high percentages and, unfortunately, resistance to second- and third-line drugs has also become quite common. Of particular concern are the multidrug-resistant and cross-resistant strains , including methicillin-resistant Staphylococcus aureus (MRSA), which is responsible for traditional treatment failure, high mortality rate and prolonged hospital stays. Treatment of infections due to Gram-positive strains has become a challenge for clinicians. Dissemination of drug resistance among these strains has left few options for management of infections with Gram positive bacteria. Staphylococci, with acquired multi-drug resistance associated with methicillin resistance, cause a major problem especially in hospital but also in community acquired infections. Worldwide colonization of hospitals with such strains complicates treatment of nosocomial infections. Recent isolation of vancomycin intermediate, and latterly vancomycin-resistant Staphylococcus aureus (VRSA) carrying the vanA gene, has increased the gravity of this problem, threatening to take away the most valuable treatment option, in staphylococci, namely glycopeptides. The spread of other multi-drug resistant Gram-positive bacteria including enterococci and pneumococci, which have growing levels of penicillin and vancomycin resistance, respectively, along with resistance to other current medications, highlights the need for novel infection-treating options.

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II. METHODOLOGY

1. OXAZOLIDINONE

Oxazolidinones are a recent class of synthetic antibiotics with a chemical structure characterized by a basic nucleus of 2-oxazolidone active against a wide spectrum of multidrug-resistant Gram-positive bacteria (GPB), namely vancomycin-resistant Enterococcus (VRE), MRSA and Mycobacterium tuberculosis (MTB). Oxazolidinones bind to the 50S ribosomal subunit, inhibiting the biosynthesis of bacterial proteins. The first oxazolidinone clinically available was Linezolid (LNZ), discovered in 1996 and approved in 2000 for clinical use by the FDA (U.S. Food and Drug Administration). The first oxazolidinones developed by EI DuPont de Nemours & Co. Inc. in 1978, were synthesized because of their activity against certain plant pathogens. Nine years later, in 1987, two antibacterial oxazolidinones, DuP 721 and DuP 105, were synthesized as antibacterial against human pathogens. However, because of their toxicity, the development of these antibacterial was stopped. Upjohn Laboratories (latterly Pharmacia and now Pfizer) continued to study oxazolidinones and in 1996 developed two nontoxic derivatives of these drugs, a morpholine derivative linezolid {U-100766 (S)-N-[[3-(3-fluoro - 4 - morpholinylphenyl) - 2- oxo-5-oxazolidinyl] methyl] acetamide}, and a piperazine derivative eperezolid {U-100592 (S)-N-[[3-[3-fluoro-4-[N-1- (4-hydroxyacetyl) piperazinyl]phenyl]-2-oxo-5-oxazolidinyl] methyl] acetamide}.

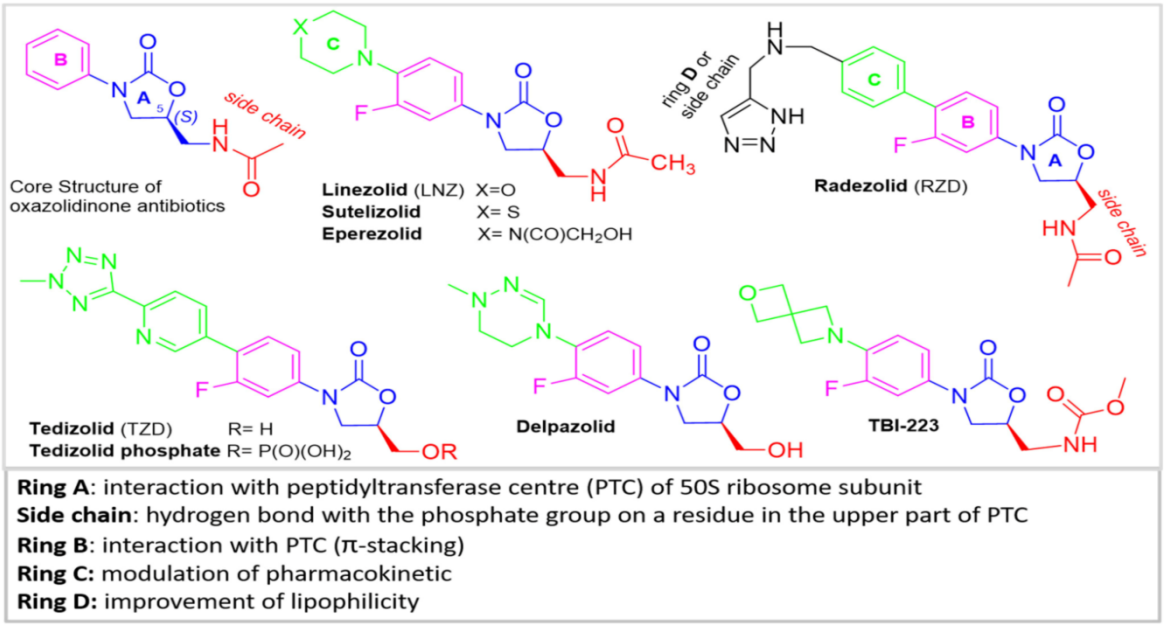

Figure 1: shows the basic chemical makeup of oxazolidinone antibiotics as well as the molecular makeup of their most important derivatives, including Linezolid, Sutezolid, Eperezolid, Delpazolid, Tedizolid, Tedizolid phosphate, Radezolid, and TBI-223. Brief explanation of chemical groups that enhance pharmacokinetics and those necessary for binding to the peptidyltransferase center (PTC).

Chemistry: Oxazolidinones are a type of five-membered heterocyclic compounds that have use in both organic and pharmaceutical chemistry. They contain both a nitrogen and an oxygen atom in their structure. The early SAR studies discovered the first non-toxic oxazolidinones (such LNZ and Eperezolid) as well as the crucial structural elements necessary for their biological action. The oxazolidone ring (ring B) with the S configuration of substituent at C5 and the acylaminomethyl group connected to C5 and the N-aryl substituent make up the pharmacophoric core specifically. Biological activity is increased by the meta-fluoro substitution on the B ring, while the antibacterial range is broadened by the para-substitution.

2. MECHANISM ACTION OF OXAZOLIDINONE

2.1 Protein synthesis:

RNAs are wrapped in proteins to form the bacterial ribosome's two subunits, 30S and 50S. 30S is made up of 16S rRNA and 21 proteins (S1-S21), whereas 50S is made up of 5S and 23S rRNAs and 36 proteins (L1-L36). These two units combine to start the synthesis of proteins and separate after it is finished. Ribosomal

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component 30S first forms a complex with mRNA, the genetic code for the protein to be synthesized, and fmet-tRNA, which carries the first amino acid, methionine, as well as GTP, which supplies energy for the synthesis, and three initiation factors, IF1-3. The 70S ribosome, which is prepared to begin protein synthesis, is created when this initiation complex combines with ribosomal subunit 50S. As of right now, the ribosome is carrying fmet-tRNA at the P site (peptidyl site), and the A site (amino acid site) is free. In a complex with Ef-Tu (elongation factor) and GTP, the tRNA that transports the amino acid for the second codon of the mRNA attaches to the A site. The peptidyl transferase cente at subunit 50S is where the amino acids transported by the tRNAs are situated. The tRNAs are connected to the mRNA by codon/anticodon action. With GTP and an elongation factor (EF-Tu), the aminoacyl-tRNA is in a complex. The peptide at the P site is released from tRNA at the peptidyl transferase center and binds to the amino acid at the A site during this contraction motion, which is caused by the energy produced by GTP and causes substantial conformational changes in the ribosome. The EF-G-GTP complex releases energy that causes the ribosome to advance on the mRNA by one codon (translocation), causing the tRNA that released its peptide (deacylated tRNA) to move to the E site, the tRNA with peptide to move to the P site, and the A site to become free for the subsequent tRNA with the amino acid to be added. The protein synthesis is continued till the end of this elongation stage. (Fig.2)

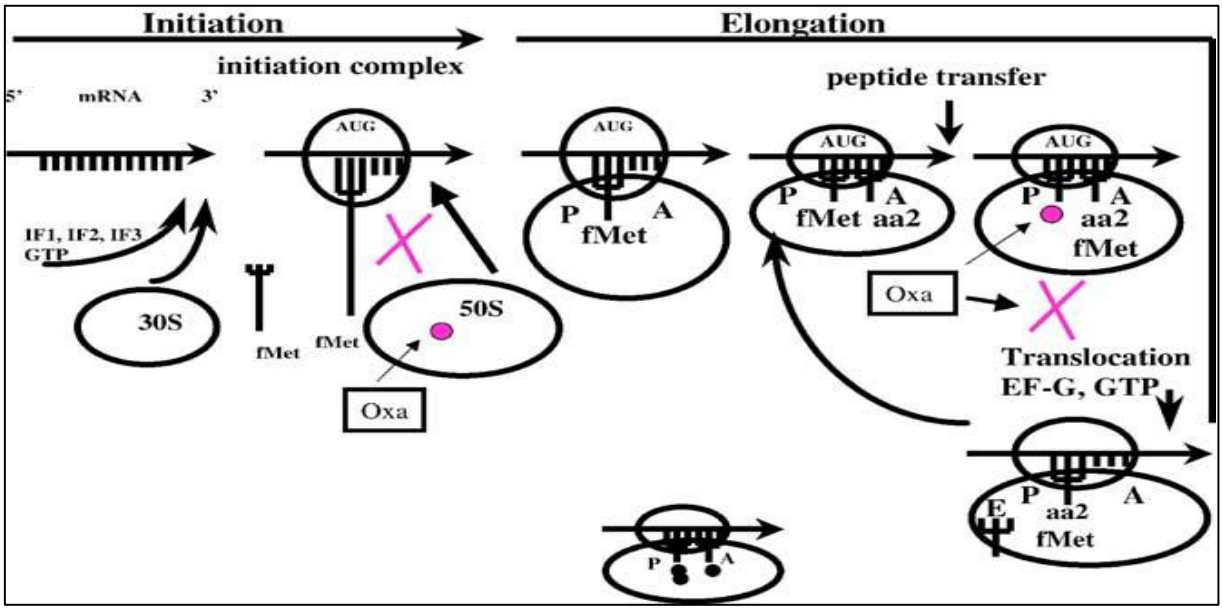

Fig 2. Bacterial protein synthesis and oxazolidinones method of action. To create the 70S mature ribosome and kick off protein synthesis, ribosomal subunit 30S interacts to ribosomal subunit 50S in a complex comprising initiation factors, mRNA, and fMet-tRNA. This assemblage is not possible in the presence of oxazolidinone, which binds to the P site at the 50S ribosomal subunit. Additionally, oxazolidinone binds to mature 70S ribosomes, which prevents translocation.

2.2 MOA of Oxazolidinone

By attaching to the 50S ribosomal subunit's P site, oxyazolidinones prevent the production of new proteins. The activity of oxazolidinone is unaffected by resistance to other protein synthesis inhibitors, however there have been a few isolated occurrences of oxazolidinone resistance that have been linked to treatment-related 23S rRNA changes. Despite having a binding site on 50S, oxazolidinones are believed to prevent the development of the initiation complex, which is made up of the 30S subunit, fMet-tRNA, mRNA, GTP, and initiation factors 1-3. Oxazolidinones have recently been found to prevent fMet-tRNA from binding to the P site. The effect of oxazolidinones binding to 50S is inhibition of 70S formation. If the 70S is already formed, binding of oxazolidinones inhibits translocation of the peptide chain to P site from A site, during formation of the peptide bond. Even though the binding sites overlap, the mechanism of action of oxazolidinones is different from all existing protein synthesis inhibitors. The main action of oxazolidinones is by binding P site, inhibition of initiation complex and also translocation of peptidyl-tRNA from A site to P site (Fig.2).

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3.TUBERCULOSIS :

Tuberculosis is an infectious disease which is caused by a bacteria Mycobacterium tuberculosis. The ninth-leading cause of death worldwide, tuberculosis (TB), has been around for millennia and affects roughly 10 million people annually. Latent TB is present in around 1.7 billion people, or 23% of the world's population. To meet the global TB targets outlined in the Sustainable Development Goals and the End TB Strategy, new findings in the field of TB research and development are crucial. Following extensive research and development, recently discovered TB medicines have recently received approval. Anti-tuberculosis activity of oxazolidinones was also confirmed with some new oxazolidinones.

4. LINEZOLID:

Oxazolidinones are a new class of antibiotics and linezolid are the first oxazolidinone available. Linezolid's activity range includes Gram-positive bacteria, while its effectiveness against Gram-negative bacteria is restricted. Linezolid also shows action against the Streptococcus pneumoniae, regardless of its resistance to other antimicrobials, including macrolides, -lactams and quinolones. The FDA has authorized the use of linezolid, the sole oxazolidinone currently on the market, to treat difficult skin infections brought on by methicillin-resistant S. (MRSA), nosocomial pneumonia brought on by MRSA, concurrent bacteraemia linked to enterococcus faecium that is vancomycin-resistant, and concurrent bacteraemia linked to penicillin-resistant S. pneumonia caused community-acquired pneumonia. Therapeutic treatments based on Linezolid improved the outcomes of several drug-resistant infections, including TB; however, long-term side effects such as reversible myelosuppression, potentially irreversible optic neuropathy and peripheral neuropathy are often correlated to its prolonged administration. To overcome these critical issues, different derivatives with improved safety and tolerability were approved by local regulatory agencies or are under development for diseases that require long-term therapy.

5. DELPAZOLID:

Delpazolid (or LCB01-0371) is a new oxazolidinone antitubercular agent. LegoChem Biosciences (Daejeon, Korea) is a company that creates effective and secure medications utilizing legochemistry technology, which permits the modification of chemicals by attaching and detaching molecules using Lego-style building pieces. Delpazolid a derivative of oxazolidinone, is the first candidate antibiotic substance identified by LegoChem Biosciences. A comparative study of in vitro activity of delpazolid and linezolid against MDR-TB and XDR TB isolates showed that the two oxazolidinones have comparable activity with only 2.9% of these drug-resistant strains showing resistance to Delpazolid. Delpazolid is an antibiotic that works against M. tuberculosis and other Gram-positive bacteria (MRSA, VRE). For the treatment of Gram-positive (MRSA, VRE) bacteremia, it is currently undergoing a Phase 2 clinical trial for oral (PO) administration and a Phase 1 trial for intravenous (IV) administration. The main scaffold of delpazolid was covered with cyclic amidrazone blocks.

6. In vitro Study(s):

The Clinical and Laboratory Standards Institute (CLSI) (3)'s 2-fold agar dilution method was used to calculate in vitro MICs. The MHA (Mueller-Hinton Agar) medium was used to evaluate facultative and aerobic organisms. On Mueller-Hinton agar with 5% defibrinated sheep blood as a supplement, Streptococcus pneumoniae, Streptococcus pyogenes, and Moraxella catarrhalis were cultivated (Hanil Komed Ltd., Sungnam City, Republic of Korea). For Haemophilus influenzae, Mueller-Hinton agar supplemented with 3% Fildes enrichment (Oxoid Ltd., Basingstoke, Hampshire, England) was utilized. On plates with the proper medication concentration, bacteria (104 to 105 CFU) were observed. 18 hours of incubation at 35°C on plates were used to check for growth. The MIC was defined as the lowest quantity that prevented any growth on agar plates, regardless of the presence of a single colony or a faint haze caused by the inoculum.

7. In vivo Study(s):

It was shown that LCB01-0371 has in vivo action against systemic infections in mice brought on by S. aureus giorgio (MSSA), S. aureus p125 (MRSA), Enterococcus faecalis u810, S. pneumoniae ATCC 6305, and Haemophilus influenzae hd2. The systemic infection model was carried out using male ICR mice that were four weeks old and weighed 18 to 22 g (Daehan Bio Link Co., Ltd., Eum-sung Gun, Republic of Korea). They were kept in animal rooms with a humidity level of 55% 20% and a temperature of 23 2°C. In order to test for

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infection, Mueller-Hinton agar medium (Difco) was cultured for 18 hours at 37°C. Muller-Hinton agar medium for S. pneumoniae was enhanced with 5% defibrinated sheep blood.

8. PHASE 1 STUDY(s):

Phase 1 study was conducted in two phases that is phase 1A and phase 1B. Healthy male subjects between the ages of 20 and 45 years were eligible to participate in the study. They were screened over a 28-day period before study initiation. The design of this trial was two-by-two crossover, randomized, open-label, single-dose. Eight people each were included in each of the groups, for a total of 32 subjects in the study. In phase 1a of a phase 1 clinical trial to assess its safety, 64 participants were split into eight groups, with six receiving delpazolid and two receiving a placebo. Each group had a 7-day washout period. The present study consisted of 2 parts: a BID, multiple-dose escalating study (400-1600 mg; 200- mg tablet or 400-mg tablet) and a single-dose study (800 mg; 400-mg tablet) of LCB01-0371.

i) Phase 1A study(s):

Sr.no	Dose of LCB01-0371 or placebo (Study design: Double blind, randomized, placebo control)	Number of subject administered LCB01-0371	Number of subject administered placebo
1	PO 400mg BID LCB01-0371 (400mg)	6	2
2	PO 800mg BID LCB01-0371 (200mg)	6	2
3	PO 1200mg BID LCB01-0371 (200mg)	6	2
4	PO 1600mg BID LCB01-0371 (400mg)	6	2

A double-blind, placebo-controlled, multiple-dose escalation study was the initial component of the investigation. It was done to assess the multiple-dose oral LCB01-0371's pharmacokinetic and pharmacodynamic characteristics, safety profile, and tolerability. During a 7-day dosing period with subsequent follow-up, each individual received a BID dosage of LCB01-0371 or a placebo at 4 doses (400, 800, 1200, and 1600 mg). The remaining doses, LCB01-0371 400 mg and 1600 mg, were given as 400 mg tablets, while LCB01-0371 800 mg and 1200 mg were given as 200 mg tablets. Only mildadverse events were observed up to 2400 mg

ii) Phase 1B study(s): The second part of the study phase 1B was an open-label, single-dose study in which LCB01-0371 800 mg was administered to 6 subjects as a novel 400-mg tablet formulation to compare the pharmacokinetic characteristics between this formulation and a 200-mg tablet.

9. Safety:

Delpazolid's safety is one of its main benefits. In a phase 1 clinical trial to assess its safety, 64 participants were split into eight groups, six of them received delpazolid, and the other two received a placebo. The review represented the initial double-blind, random human trial of delpazolid. Delpazolid was given in increments of 50 mg up to 3200 mg in order to deliver single-ascending-doses (SADs). Up to 2400 mg, very minor side effects were seen. Adverse effects involving the gastrointestinal (GI) tract were reported after taking 3200 mg of delpazolid. Volunteers in the 3200 mg dosage group were required to consume 16 200 mg delpazolid pills all at once, which led to severe GI tract reactions. The most common side effect of Delpazolid is headache.

10. Delpazolid activity against TB compare to Linezolid :

Gram-positive bacteria were the main topic of studies on the early stages of delpazolid formation. Delpazolid's effectiveness against Gram-positive bacteria was comparable to or slightly superior than that of linezolid. For instance, in investigations on systemic infection in animals, infections of the soft tissues, the lungs, and the thighs Delpazolid outperformed linezolid in mouse model studies (data not shown). An in vitro susceptibility test for M. tuberculosis H37Rv was performed to assess the efficacy of delpazolid in treating tuberculosis. The

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minimum inhibitory concentration (MIC) for M. tuberculosis H37Rv was comparable to that of delpazolid compared to linezolid, whereas the minimum bactericidal concentration was more than four times lower with delpazolid.

Drug activities/ Resistance rate	Delpazolid	Linezolid
MIC value for M. tuberculosis H37Rv (μg/mL)	0.5	0.5
MBC99 value for M. tuberculosis H37Rv (μg/mL)	>16	4
MDR-TB MIC90 (μg/mL)	1	0.5
XDR-TB MIC90 (μg/mL)	0.25	1
ECOFFs (epidemiological cuto_ values) (μg/mL)	1.0	2.0
Resistant rate of MDR-TB (%)	6.7	0.8
Resistant rate of XDR-TB (%)	4.2	4.2

III. CONCLUSION

In this review we concluded that Delpazolid shows better effect with lesser side effects. In summary, the oral administration of LCB01-0371 at BID doses up to 1200 mg for 7 days straight was safe and well tolerated. In the dose range studied, the pharmacokinetic characteristics did not show dose proportionality and showed a minor drug buildup. Rapid serum inhibitory and bactericidal activity against widespread gram-positive pathogens were provided by LCB01-0371. The findings of this study support testing a continuous BID regimen for this antibacterial agent's future development. Under fed and fasting conditions, the total systemic exposure to 800 mg of LCB01-0371 was comparable. This demonstrated that LCB01-0371's effectiveness is based on AUC and that it can be taken regardless of diet. The phase 1 trial showed that myelosuppression might be decreased, and the phase 2a data suggested that delpazolid could take the place of linezolid as a TB treatment and shorten the duration of the course of therapy.

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