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TEIXOBACTIN - A GAME CHANGER ANTIBIOTIC

Sahil Hussain, Neelam Yadav

Department of Pharmacy

Era's Lucknow Medical College & Hospital, Era University Sarfarazganj Lucknow, U.P., India-226003

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Address for correspondence

Dr. Neelam Yadav
Department of Pharmacy
Era's Lucknow Medical College & Hospital, Era University Lucknow-226003
Email: Yadava.neelam@gmail.com
Contact no: +91-

ABSTRACT

A team of scientist under the supervision of Kim Lewis from Northeastern University has discovered a novel antibiotic called Teixobactin, which kills the bacteria by inhibiting them from building their outer protein envelop. The bacterial resistance interference are key challenges to the global health. Teixobactin shows exceptional antibacterial activities against the range of pathogenic bacteria viz S. Aureus and Mycobacterium Tuberculosis. It is bactericidal and has many mode of operation, however it is one of the most important contribution in the modernization of medicine. However, the increase in Antibiotic resistance is at alarming rate and the ability of patient care through antibiotics is a challenge nowadays increment in Antibiotics resistance is among the top public health threats in the century 21". According to the Centers for Disease Control and Prevention (CDCP), around 23 thousand peoples die in every year in United States of America (USA) due to Antibiotic resistance. Whenever the patient is administered with an antibiotic the condition of the patient does not improve due to which more than 2 million people are sickened. The increase in Antibiotic resistance is much greater than the increase in epidemic diseases such as Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome (Al DS) or Ebola Virus Disease. The cost of human Antibiotic resistance crisis is estimated to be 300 million mortalities collectively by 2050. And it will also be the cause of declining graph of global economy of around $100 trillion. Production of new antibiotics in the 21" century seems to be difficult task to deal Teixobactin comes under new class of antibiotics. It is the first new antibiotic that is being isolated from bacteria after 30 years. After teixobactin's isolation from the soil full of bacteria, another novel class of antibiotics are discovered known as Malacidine, which was revealed later in 2018.

KEYWORDS: Teixobactin, Antibiotic, Staphylococcus aureus, Mycobacterium tuberculosis.

INTRODUCTION

There is an epidemic that is mentioned earlier and its spread to every continent, it's the epidemic of Antibiotic resistance. Overuse of antibiotics in both humans and livestock 80 per cent of antibiotics go to the animals that are consumed by humans has resulted in drug resistant strains of various microbes including mycobacterium tuberculosis and salmonella. In the last 3 decades no new antibiotics have come down the market. Some current drugs are in their fourth generation as pharmaceutical companies tweak existing medicines to gain time before the next resistant strain appears (1).

The era of totally drug resistant diseases maybe daunting a variant of tuberculosis in India that defies every method of treatment already exixts. The first truly new antibiotic Teixobactin was discovered in a laboratory but it orginates in the dirt. The journal Nature reports that scientists have figured out how to grow previously unculturable bacteria using an electronic isolation chip (1)(2).

They have reported they have isolated a new antibiotic Teixobactin which they claim has no detectable resistance. It works against organisms that have become hardened to standard standard antibiotics for Staphylococcus aureus and Mycobacterium tuberculosis. There are millions of uncultured bacteria that are yet to be grown and investigated.

Teixobactin is a polypeptide chain. This means it's a molecule composed of many peptides. The molecule has a backbone consisting of repeating N-C-C bonds that have groups hanging off them. Scientists use soil to find possible molecules to fight against dangerous organisms. These soil bacteria produce antibodies to fight off the introduced infectious bacteria. Researchers find these antibodies and identify the structure of the molecule. After finding the structure, they test the molecule against various forms of bacteria (3).

Teixobactin is a new class of antibiotic. It was discovered by cultivating bacteria in soil. It has exceptional lethal activity against Staphylococcus

aureus and Mycobacterium tuberculosis. It is an inhibitor of cell wall synthesis. It acts by binding to lipid II precursor of peptidoglycan. Although, same activity was seen in vancomycin but teixobactin binding to lipid precursor inhibits the production of peptidoglycan and leads to the lysis of vulnerable bacteria.

No resistant strain of S. aureus or M. tuberculosis was generated in vitro. Almost after 3 decades antimicrobial resistance is predicted for mortality than any carcinogen. To overcome this antimicrobial resistance (AMR) there is a need for the development of new antibiotics. Teixobactin is one of the antibiotics that is discovered and seems promising antibiotic (4).

Teixobactin kills Methicillin Resistant Staphylococcus Aureus (MRSA) and mycobacterium tuberculosis which contributed in infection of more than 10.4 million individual and also holds a record of 1.5 million deaths per year worldwide (4).

MECHANISM OF ACTION AND SYNTHESIS

Teixobactin inhibits the cell wall synthesis of bacteria. The development of resistance is low. It does not target enzymes but act on Lipid – II precursor of cell membrane which is responsible for cell wall synthesis of bacteria. The inhibition of cell wall takes place via various pathways which results in cell wall damage and necrosis (5)(6).

Teixobactin contains four D- amino acids namely D-Thr8, D-allo-Ile5, D-Gln4, and N-Me-D-Phe1 and very rarely L-allo-enduracididine amino acid. In the recent study Arg10 – texiobactin and other homologues such as SPPS on 2 – chlorotrityl chloride resin followed by Solution phase macrolactamization (SPM) to form amide bond Arg10 – Ile11 was synthesized.

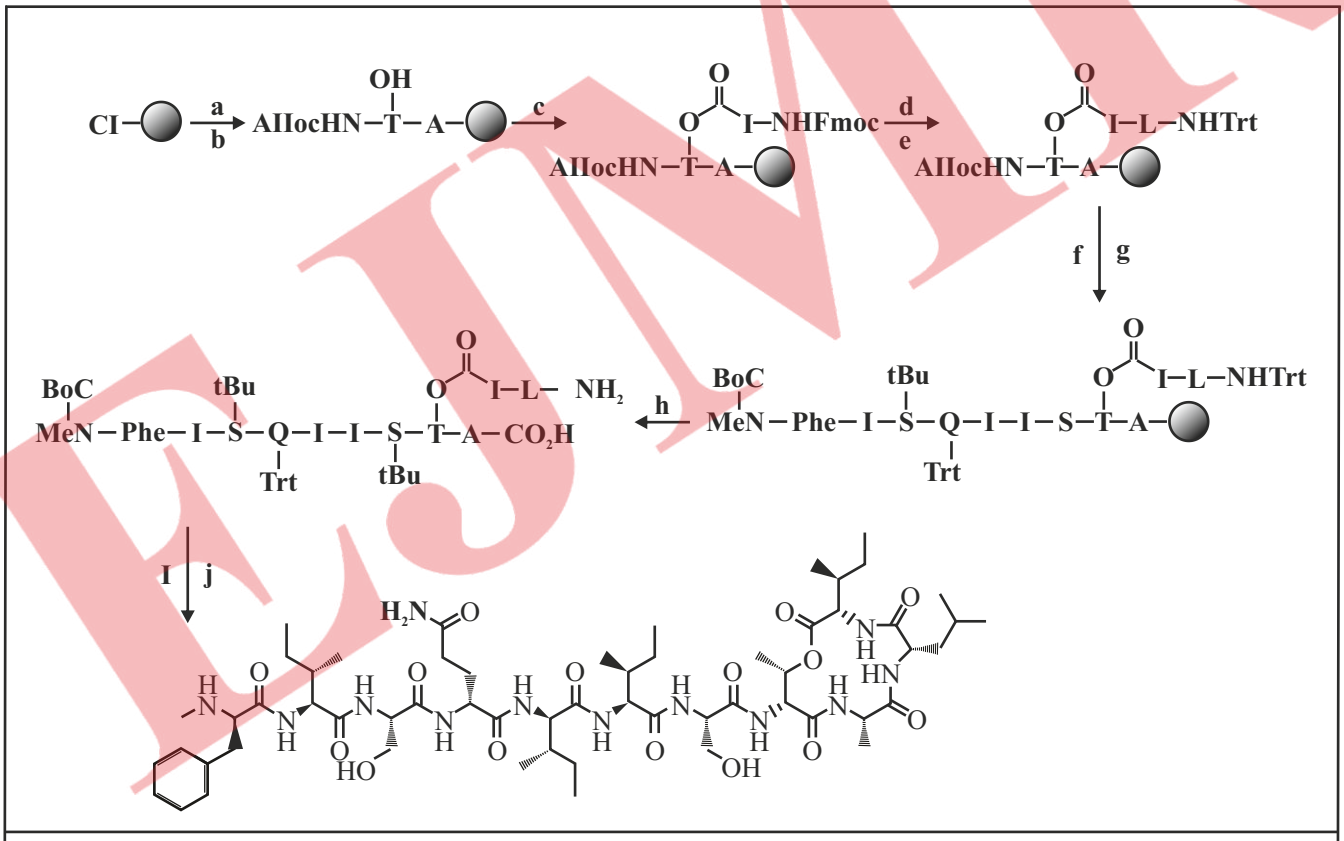

Fig. 1: Synthesis of Leu10-teixobactin Starting from 2-chlorotritylchloride Resin.

Fmoc protecting groups to construct all the bonds of amide was used and D – Thr8 was carried through the entire synthesis without protection of side chain. Synthesis started by attaching Fmoc – Arg (pbt) – OH to 2- chlorotrityl chloride resin (8)(9).

RESISTANC E AND MODE OF ACTION

Tanja Schneider at the University of Bonn and Loose Ling from NovoBiotic Pharmaceuticals demonstrated that teixobactin works by withholding two molecules Lipid – II which is used by the bacteria for making thick cell wall. It is also the precursor of peptidoglycan layer. Lipid – III stops their existing walls from breaking down. When teixobactin binds to the bacterial cell it inhibits the formation of thick layer around the bacterial cell (10)(11).

The same activity on other bacterial species was seen.

However, it does not work on ever bacteria many of them like E. coli, Salmonella and Helicobacter have different membrane around their cell and teixobactin has no effect on them.

To study the resistance of teixobactin, the Ling et.al kept the antibiotic with the pathogen for 25 days. The result showed no resistance to the infectious bacteria (12).

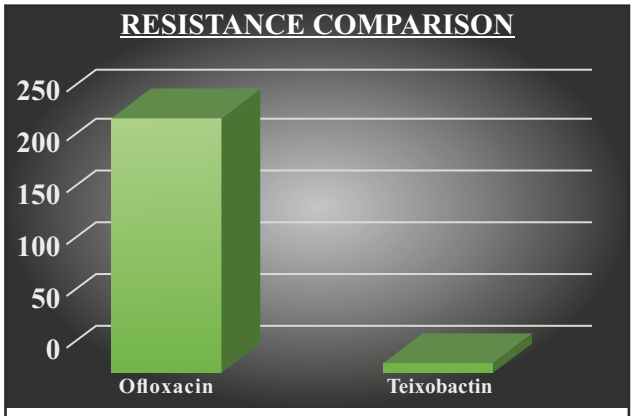

Fig. 2: Resistance of Ofloxacin was Developed 250 Times than Teixobactin

Same activity of existing antibiotic Vancomycin was seen it also works by sticking to Lipid – II. It took a long period of around 30 years to develop resistance and Lewis hope that teixobactin resistance will take longer to appear.

It basically targets Gram positive bacteria. It kills Methicillin – resistance Staphylococcus aureus (MRSA) and Mycobacterium tuberculosis. Scientists were unable to obtain mutants of S. aureus or M. tuberculosis resistant to teixobactin even when plating on media with a low dose (4 x MIC) of the compound. Serial passage of Staphylococcus aureus in the presence of sub-MIC levels of teixobactin over a period of 27 days failed to produce resistant mutants as well (12)(14).

MINIMUM INHIBITOR CONCENTRATION MIC

After the discovery of teixobactin, Ling et.al tested the drug against various pathogens and analyzed their MU. This test show's the smallest amount of antibiotic is needed so no infection appears. Ling et.al compared this antibiotic w ith another drug to compare its effectiveness and survivability. (16)(17)(19)

Pathogen	Teixobactin MIC (ug/mL)
S. Aureus (MSSA)	0.25
S. Aureus (MRSA)	0.25
Enterococcus Faecalis (VRE)	0.5

Tab. 1: Mic Activity of Teixobactin Against Various Pathogens

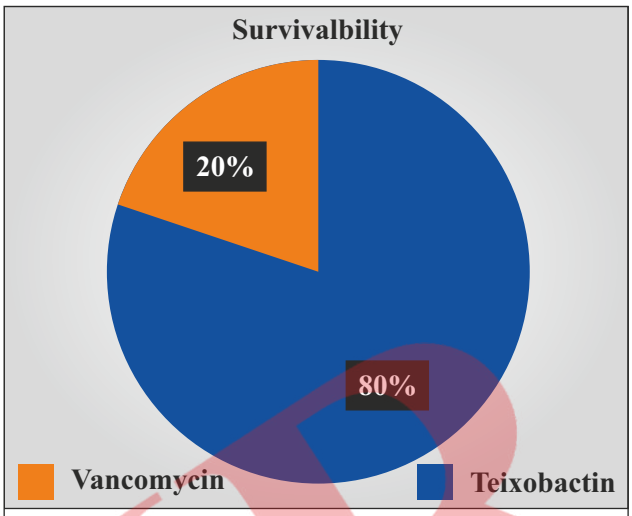

Fig. 3: Activity of Teixobactin Against Pathogenic Microorganism

Organism and genotype	Teixobactin MIC (ug ml^{-1})
S.aureus (MSSA)	0.25
S.aureus 10% serum	0.25
S.aureus (MRSA)	0.25
Enterococcus faecalis (VRE)	0.5
Enterococcus faecium (VRE)	0.5
Streptococcus pneumoniae (penicillin)	≤0.03
Streptococcus pyogenes	0.06
Streptococcus agalactiabe	0.12
Viricians group streptococci	0.12
B. anthracis	≤0.06
Clostridium clifficile	0.005
Propionibacterium acnes	0.08
M. tuberculosis H37Rv	0.125
Haernophilus influenzae	4
Moraxella catarrhalis	2
Escherichia coli	25
Escherichia coli (asmB1)	2.5
Pseudomonas aeruginosa	≥32
Klebsiella pneumoniae	≥32

Tab. 2: Activity of Teixobactin Against Resistant Bacteria.

CONCLUSION:

The excellenct activity of a new antibiotic molecule looks promising against the MRSA

Bacteria. No resistant strain was found in Staphylococcus aureus and other resistant bacteria. No new discovery in the field of antibiotics is done in last 3 decades so the new molecule of teixobactin obtained from the soil shows non reistant activity.

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