TEIXOBACTIN: AN ANTIBIOTIC WITH UNDETECTABLE RESISTANCE

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ABSTRACT
Irrational use of antibiotics cause resistance to available antibiotics. The threat is serious because there will be multi-drug resistance across the globe with no antibiotics to withstand it. The situation demands discovery of newer antibiotics against bacterial machinery. Therefore, Teixobactin, 11-amino acid peptide antibiotic extracted from gram negative bacteria—Eleftheria Terrae is promising. This antibiotic acts by forming a complex with precursors of peptidoglycan and teichoic acids of the cell wall of gram positive bacteria. It has potent bactericidal activity against gram positive pathogens (Including MDR strains) with MIC 0.5ug per ml or less. (1,3)

KEYWORDS
Teixobactin, Eleftheria Terrae, MRSA, VRE.


INTRODUCTION
Researchers are now turning to nature in quest of find out new antibiotics i.e looking at the deepest of oceans or the driest of deserts or the inside of insects. Consequently, they have succeeded in creating a new class of antibiotics which can deal with pathogens that are becoming resistant to the present lot of antibiotics in use. So the antibiotic called “Teixobactin” was isolated by screening the previously unculturable organisms present in a sample of soil from a grassy field. (1,2)

An extract from a new species of β-proteobacteria provisionally named Eleftheria terrae showed good antibacterial activity. The molecule which we named Teixobactin is an unusual depsipeptide which contains enduracible methylphenylalaine and four amino acids. The properties of this compound suggests a path towards developing antibiotics that are likely to avoid development of resistance. (3)

Biosynthesis and Spectrum
Teixobactin is synthesized in Eleftheria terrae by nonribosomal peptide synthetase Txo1 and Txo2 (Encoded by genes txo1 and txo2). It is potent in-vitro against most gram positive bacteria including S. aureus, Enterococci, M tuberculosis, Clostridium difficile, Bacillus anthracis and also in vivo methicillin-resistant aureus (MRSA), streptococcal pneumonia.

It also shows good activity against strains of E. Coli with a defective outer membrane permeability barrier. It is more robust against mutation of the target pathogens because of its unusual antibiotic mechanism of binding to less mutable fatty molecules rather than binding to relatively mutable proteins in the bacterial cell. (1,3)

Pharmacodynamic Properties
Teixobactin inhibits bacterial cell wall synthesis primarily acting by binding to lipid β-precursor to peptidoglycan and lipid III-precursor of cell wall teichoic acid leading to lysis of vulnerable bacteria. So there is excellent bactericidal activity. This is similar to the mechanism of action of Vancomycin.

Teixobactin forms a complex by binding to lipid I, II, and III by and incubating 2 nmol of each purified precursor with 2 to 4 n mol of Teixobactin for 30 min at room temperature. Teixobactin and control compounds like vancomycin/lasmocin were incubated with human liver microsome at 37°C to determine their effect on five major Cytochrome p450s. (1,3)

Clinical Trial and Resistance
Teixobactin’s dual mode of action and binding to non-peptide regions suggest that resistance will be very difficult to develop. In the Laboratory, Teixobactin was effective at combating some notoriously difficult bacteria. It is only on two years on human trial but needs for confirmation over the course of five or six years.

It shows potent killing against a broad panel of bacterial pathogen including MRSA and vancomycin resistant enterococci (VRE). Uncultured organisms have recently been reported to produce interesting compound with new structures/mode of action such as Lasmocin (An inhibitor of essential mycobacterial protease) and Teixobactin (New cell wall inhibitor).

Resistance has not been developed to this compound suggesting that the target is not a protein. Resistance to vancomycin was identified almost 40 years after the drug’s discovery which is believed that self-resistance vector from vancomycin producing bacteria was captured by pathogenic bacteria through horizontal gene transfer. Although resistance to Teixobactin was difficult to manufacture in lab, resistance could eventually emerge in the same manner vancomycin resistance emerged, through horizontal gene transfer.
As E. terrae is gram negative it does not carry genes for resistance like vancomycin producing bacteria, the genes for resistance would likely come from other soil bacteria.\(^{(1,3)}\)

**Pharmacokinetic Properties.**\(^{(1,3)}\)

The mean plasma concentration of Teixobactin after a single iv injection of 20mg per kg Teixobactin. Few Pharmacokinetic parameters are highlighted as initial. Con (27.2ug/ml); AUC to last (57.8ug-hr/ml); T1/2 (4.7hr) Total Cl (6.9ml/hr); Total Cl (5.8ml/min/kg); Vol. of distribution (47ml) Vss (9.7ml); Last time point (24hr); Oral route is preferred than parenteral route.

**Adverse drug events and clinical uses.**\(^{(1,3)}\)

- Mammalian cytotoxicity; Haemolytic activity; Complex formation of Teixobactin
- Life threatening blood and lung infections with staphylococcus aureus and streptococcus pneumoniae; infections of heart, prostate, urinary tract and abdomen with enterococcus; Infections with vancomycin resistance enterococcus(VRE); infections with MRSA.

**REFERENCES**