Tygacil® (Tigecycline IV) MOA
Animation Script v 6

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Overview

These two videos will comprise five minutes of 3-D animation. The first video covers the mechanisms of several classes of antimicrobial agents and the development of resistance to these agents. The second video captures the key messaging that Tygacil® is unique because of its structure, expanded broad-spectrum activity and ability to overcome the issue of resistance currently seen in other classes of antimicrobials.

Video I: Mechanism of Disease

In the United States, hospital-acquired infections afflict nearly 2 million patients, and many of these infections show resistance to common antibiotics. The focus on resistance has increased in recent years as these types of infections are now also originating in the community.

Factors such as overuse and misuse of antibiotics, lapses in infection control and proficiency of bacterial adaptation, have contributed to the prevalence of resistant infections. When compared to susceptible infections, studies suggest that there is a substantial increase in mortality, morbidity, and cost for patients with antibiotic-resistant infections. Accurate diagnosis and appropriate treatment are critical.

To understand the evolution of bacterial resistance, we turn to the evolution of antibiotics. Over the decades, several classes of antibiotic agents have leveraged the biology of the bacterial cell to arrest or hinder its growth. Common sites of action in both gram-negative and gram-positive bacteria are the cell wall, DNA, and ribosomes.

The beta-lactams, a class of drugs which include penicillins, carbapenems, cephalosporins, and beta-lactam/beta-lactamase inhibitor combinations (or BLICs), interfere with the synthesis of the bacterial cell wall through two mechanisms.
Beta-lactams inhibit the cell wall enzyme transpeptidase and inhibit penicillin-binding proteins, causing the lysis of the cell wall. Some bacteria have adapted to produce enzymes - beta-lactamases and extended spectrum beta-lactamases – which hydrolyze the core beta-lactam ring, inactivating the antibiotic.

Fluoroquinolones are synthetic broad spectrum antibiotics which inhibit two enzymes necessary for DNA replication, recombination and repair. Inhibition of either enzyme arrests DNA replication, killing the bacteria. Resistance to fluoroquinolones arises either as a result of mutations which alter the target enzymes or by creating a decoy protein that binds to the drug so it cannot inhibit the target enzymes.

Tetracyclines are broad-spectrum antibiotics active against gram-negative and gram-positive bacteria, which bind to bacterial ribosomes and interrupt protein synthesis. Bacteria have overcome this mechanism of action through two methods of resistance, efflux pumps and ribosomal protection. Efflux pumps remove the antibiotic from the cell. Ribosomal protection mechanisms reduce the affinity of the ribosome for tetracyclines, preventing efficient drug binding.

Video II: TYGACIL MOA

Tetracycline resistance prompted the development of the glycylcyclines. TYGACIL, or tigecycline, was specifically designed to circumvent key bacterial resistance mechanisms. TYGACIL is a glycylcycline and is structurally similar to tetracycline, but with a key substitution that enables it to bind to ribosomes in a unique manner.

Similarly to tetracyclines, TYGACIL binds to and blocks the site on the ribosome that normally accommodates an incoming amino acid. This binding results in the inhibition of protein synthesis needed for growth. However, TYGACIL binds to the ribosome at additional sites and with five times greater affinity compared to tetracyclines. *In vitro* data suggests that TYGACIL's structure and points of contact on the ribosome may confer the ability to overcome tetracycline resistance mechanisms.

TYGACIL is not affected by ribosomal protection, tetracycline efflux pumps, target-site modifications or enzyme target changes. **[text on screen:** In some bacteria, tigecycline resistance has been associated with multi-drug resistant efflux pumps.] TYGACIL, as glycylcycline, is not a beta-lactam and therefore is not affected by beta-lactamases, including ESBLs and KPCs.

~~Overusing antibiotics can drive resistance.~~ TYGACIL offers a different mechanism of action that, within its indications, represents an alternative therapeutic option to ~~help relieve pressure off many of the classes known to be driving current resistant trends.~~

INDICATION & IMPORTANT SAFETY INFORMATION

Indications

TYGACIL® (tigecycline) is indicated for the treatment of adults with:

- Complicated skin and skin structure infections caused by *Escherichia coli, Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae, Streptococcus anginosus* grp. (includes *S. anginosus, S. intermedius,* and *S. constellatus*),*Streptococcus pyogenes*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Bacteroides fragilis*
- Complicated intra-abdominal infections caused by *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus anginosus* grp. (includes *S. anginosus, S. intermedius*, and *S. constellatus*), *Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Clostridium perfringens*, and *Peptostreptococcus micros*
- Community-acquired bacterial pneumonia caused by *Streptococcus pneumoniae* (penicillin-susceptible isolates), including cases with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative isolates), and*Legionella pneumophila*

Important Safety Information

- TYGACIL is contraindicated in patients with known hypersensitivity to tigecycline
- Anaphylaxis/anaphylactoid reactions have been reported with nearly all antibacterial agents, including tigecycline, and may be life-threatening. TYGACIL should be administered with caution in patients with known hypersensitivity to tetracycline-class antibiotics
- Isolated cases of significant hepatic dysfunction and hepatic failure have been reported in patients being treated with tigecycline. Some of these patients were receiving multiple concomitant medications. Patients who develop abnormal liver function tests during tigecycline therapy should be monitored for evidence of worsening hepatic function. Adverse events may occur after the drug has been discontinued
- The safety and efficacy of TYGACIL in patients with hospital-acquired pneumonia have not been established
- **An increase in all-cause mortality has been observed across phase 3 and 4 clinical studies in TYGACIL-treated patients versus comparator-treated patients. The cause of this increase has not been established. This increase in all-cause mortality should be considered when selecting among treatment options**
- **TYGACIL may cause fetal harm when administered to a pregnant woman**
- **The use of TYGACIL during tooth development may cause permanent discoloration of the teeth.**TYGACIL should not be used during tooth development unless other drugs are not likely to be effective or are contraindicated
- Acute pancreatitis, including fatal cases, has occurred in association with tigecycline treatment. Consideration should be given to the cessation of the treatment with tigecycline in cases suspected of having developed pancreatitis
- *Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including TYGACIL, and may range in severity from mild diarrhea to fatal colitis
- Monotherapy should be used with caution in patients with clinically apparent intestinal perforation
- TYGACIL is structurally similar to tetracycline-class antibiotics and may have similar adverse effects. Such effects may include: photosensitivity, pseudotumor cerebri, and anti-anabolic action (which has led to increased BUN, azotemia, acidosis, and hyperphosphatemia). As with tetracyclines, pancreatitis has been reported with the use of TYGACIL
- To reduce the development of drug-resistant bacteria and maintain the effectiveness of TYGACIL and other antibacterial drugs, TYGACIL should be used only to treat infections proven or strongly suspected to be caused by susceptible bacteria. As with other antibacterial drugs, use of TYGACIL may result in overgrowth of non-susceptible organisms, including fungi

- The most common adverse reactions (incidence >5%) are nausea, vomiting, diarrhea, abdominal pain, headache, and increased SGPT
- Prothrombin time or other suitable anticoagulant test should be monitored if TYGACIL is administered with warfarin
- Concurrent use of antibacterial drugs with oral contraceptives may render oral contraceptives less effective
- The safety and effectiveness of TYGACIL in patients below age 18 and lactating women have not been established

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