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Glycylcyclines –The New Class of Antimicrobial

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Abstract

In an era of increasing antimicrobial resistance, there is a growing need for new antimicrobial agents with novel mechanisms of action, particularly for the management of serious nosocomial infections. Tigecycline is the first in a new class of antimicrobial agents, the glycylcyclines. Although structurally derived from minocycline, tigecycline has been modified to overcome common tetracycline-resistance mechanisms. Tigecycline has a broad spectrum of antibacterial activity, including activity against some multidrug resistant Gram-positive and Gram-negative pathogens. The safety and efficacy of tigecycline has been demonstrated in phase lll clinical trials. It is currently approved for the treatment of complicated skin and skin structure infections and complicated intra-abdominal infections in adult patients.

Keywords: tigecycline, tetracycline resistance, antimicrobial

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INTRODUCTION

The issue of antimicrobial resistance is gaining increased attention worldwide as resistant pathogens are growing at an alarming rate.[1] With emerging serious infections combined with significant increases in antimicrobial resistance of Gram-positive and Gram-negative pathogens, doctors are running out of effective antimicrobials and, particularly in the hospital setting, increasingly faced with the challenge of treating serious nosocomial infections caused by multidrug resistant bacteria.

Resistance in Gram-positive pathogens

Significant increases in methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococcus and multidrug- resistant Streptococcus pneumoniae have been reported.[1]

Resistance in Gram-negative pathogens

There appears to be a corresponding increase in resistant Gram-negative infections caused by extended-spectrum betalactamase (ESBL)-producing organisms such as Escherichia coli,

Klebsiella pneumoniae, fluoroquinolone-resistant and third-generation cephalosporin-resistant Pseudomonas aeruginosa and carbapenem-resistant Acinetobacter species.

This increasing resistance clearly depletes treatment options for serious infections and underscores the urgent need for new antibiotics with novel mechanisms of action and/or the ability to overcome mechanisms of resistance displayed by multidrug resistant pathogens.[2]

The development of the glycylcyclines

The emergence of tetracycline resistance prompted the development of the glycylcyclines, a new class of antimicrobials, which were designed to overcome bacterial mechanisms of tetracycline resistance, such as ribosomal protection and efflux pumps.[3]

Tigecycline is the first glycylcycline antimicrobial.[2] It is a semisynthetic agent, structurally derived from minocycline.[2] Tigecycline has been modified to provide a broad spectrum of antibacterial activity and an ability to overcome tetracycline-resistance mechanisms.[2] It is unique among the new anti-methicillin resistant Staphylococcus aureus and anti-enterococcal drugs now reaching the market in that it also has substantial anti- Gram-negative activity. Tigecycline has been approved for the treatment of complicated skin and skin structure infections and intra-abdominal infections in patients over 18 years of age.[1]

This article reviews the pharmacology, spectrum of activity, clinical efficacy, safety and place in therapy of tigecycline.

Pharmacology

Similar to the tetracyclines, the glycylcyclines comprise a central four-ring carbocyclic skeleton.[4] The substitution of a N-alkyl-glycylamido group on the D-9 position enables a broader spectrum of activity and protects against the development of resistance.[4]

Tigecycline is bacteriostatic in vitro.[4] Reports of bactericidal activity have been demonstrated against certain pathogens.[1] Tigecycline's mechanism of action involves the inhibition of protein synthesis by binding to the 30S ribosomal subunit, but it binds with five times higher affinity than the tetracyclines.[4]

Tigecycline has a post-antibiotic effect (PAE) ranging from 2-5 hours against Gram-negative bacteria to approximately 9 hours against S. pneumoniae.[4] No cross-resistance has been observed with other antibiotic classes.[4]

Tigecycline has a large volume of distribution and penetrates several tissues, including pulmonary, skin and intra-abdominal sites.[2] In contrast to classical tetracyclines, tigecycline can only be administered parenterally and the regimen used in clinical trials involved a 100 mg loading dose, followed by 50 mg twice daily. Intravenous infusions should be administered over 30 to 60 minutes every 12 hours.[5] The duration of therapy is usually 5 to 14 days.[4] Tigecycline is available as a 50 mg vial. It is reconstituted with normal saline or 5% dextrose and infused in 100 ml normal saline or ringer's lactate (maximum concentration 1 mg/ ml). Reconstituted solution may be stored at room temperature for up to 24 hours and at 2-8oC for up to 45 hours.[4,5]

Spectrum of activity

Tigecycline has potent in vitro activity against a wide range of Gram-positive, Gram-negative, anaerobic and atypical bacteria.[2] It is one of the few new antimicrobials with activity against Gram-negative bacteria (See Table 1).

Tigecycline also has good activity against many multidrug resistant pathogens, such as methicillin-resistant Staphylococcus aureus (MRSA), methicillin-resistant Staphylococcus epidermidis, vancomycin-resistant enterococcus (VRE), Acinetobacter baumannii, penicillin-resistant Streptococcus pneumoniae (PRSP) and tetracycline-, aminoglycoside-, carbapenem- and fluoroquinolone-resistant extended-spectrum beta-lactamase-producing Enterobacteriaceae[4]

Note: Tigecycline lacks significant activity against Pseudomonas spp., Proteus spp., and Providencia spp.[3]

Clinical efficacy

Tigecycline is currently indicated for the treatment of severe lifethreatening infections in adults, including complicated skin and skin structure infections (cSSIs) and complicated intra-abdominal infections (cIAI).[5] It has been found to be effective (but is not approved) for the treatment of community- as well as hospitalacquired and ventilator-associated pneumonia and bacteraemia and sepsis with shock.[4] Tigecycline also offers a new option for patients allergic to penicillins and cephalosporins.

Two pairs of phase lll clinical trials were undertaken for registration: one pair comparing tigecycline with imipenem plus cilastatin in intra-abdominal infections and the other pair comparing tigecycline with aztreonam plus vancomycin in skin and skin structure infections. Over 2850 patients were treated in these trials.

Complicated skin and skin structure infections

Tigecycline was found to be effective and well-tolerated in a phase ll trial conducted in adult patients with cSSI. The efficacy of tigecycline in the management of skin and skin structure infections was subsequently evaluated in two Phase lll, randomised, double-blind trials.[6]

Patients were eligible for inclusion in the trials if they were at least 18 years of age, hospitalised and had a complicated skin and skin structure infection involving deep soft tissue or requiring surgical intervention (e.g. cellulitis, wound infection, major abscesses, infected ulcers or burns) plus two signs of active infection. Deep tissue infection involving cellulitis was the most common diagnosis, many cases of which required surgical intervention.

Patients were randomised to receive tigecycline (100 mg loading dose followed by 50 mg twice daily) or vancomycin (1 g twice daily) plus aztreonam (2 g twice daily) for up to 14 days.[6]

The primary efficacy endpoint in these trials was clinical response, defined as ‘cure’ if the infection resolved and did not require additional antimicrobial therapy or ‘failure’ if the infection warranted additional antimicrobials or surgical intervention. Clinical cure was reported for 79.7% of patients in the tigecycline group versus 81.9% in the vancomycin-aztreonam group.[6]

Complicated intra-abdominal infections

Two phase lll clinical trials evaluating tigecycline in the treatment of complicated intra-abdominal infections have been conducted.[7] Patients were included if they had or would receive

a laparotomy, laparoscopy or percutaneous drainage of an intra-abdominal abscess and were suspected or known to have a complicated intra-abdominal infection. The most common complicated intra-abdominal infection encountered was complicated appendicitis.

Patients were randomised to receive either tigecycline (100 mg loading dose followed by 50 mg every 12 hours) or imipenemcilastatin (500 mg every 6 hours) for 5 to 14 days. The primary endpoint was clinical response which as designated as 'cure' (resolution of intra-abdominal infection), 'failure' (infection required additional antibiotic therapy or surgical or radiological intervention), death or withdrawal from study. Overall clinical cure rates were similar in both groups. Clinical cure rate was 86.7% for tigecycline versus 87.1% for imipenem-cilastatin.[7]

Table 1: In vitro antibacterial specturm of tigecycline[2,3,4]

Gram-positive	Gram-negative	Anaerobic	Atypical
• Staphylococcus aureus • Staphylococcus epidermidis • Streptococccus spp. • Enterococcus faecalis • Enterococcus faecium •Listeria monocytogenes	• Acinetobacter baumannii • Citrobacter freundii • Citrobacter koseri • Klebsiella oxytoca • Klebsiella pneumoniae • Aeromonas hydrophilia • Serratia marcescens • Enterobacteriaceae spp. • Enterobacter aerogenes • Haemophilus influenzae	• Bacteroides spp. • Clostridium perfringes • Clostridium difficile •Peptostreptococcus spp.	• Mycobacterium spp. • Chlamydia pneumoniae •Chlamydia trachomatis

Other clinical data

Additional studies comparing tigecycline with different antibiotics for complicated intra-abdominal infections, skin infections as well as for the treatment of other serious infections such as pneumonia have been and are being conducted, which may expand the clinical indications for tigecycline.

One international study tested tigecycline activity in bacterial pathogens collected from patients hospitalised in intensive care units. Aside from isolates of Pseudomonas aeruginosa, tigecycline showed potent activity against prevalent intensive care unit bacteria, including drug-resistant pathogens MRSA, VRE and A. baumannii.[2]

Adverse effects, precautions and drug interactions

Adverse effects that have been reported with tigecycline are similar to those associated with the tetracyclines.[3] The main side effect, seen in 24.4% of patients in the intra-abdominal infection studies and in 34.5% of patients in the skin and skin structure infection studies, was nausea, sometimes with vomiting. Although these frequencies are high, the severity was low and the overall treatment discontinuation rate for nausea in the phase lll studies was 1.5%.[8]

Tetracycline-related adverse effects may also occur, such as photosensitivity, pseudotumor cerebri, pancreatitis, and antianabolic reactions leading to azotemia, acidosis, increased blood urea nitrogen and hypophosphatemia. Interestingly, there have been no reports of C. difficile-associated diarrhea associated with tigecycline. It is thought that the reason for this may be due, in part, to tigecycline's potent activity against C. difficile. Tigecycline is contra-indicated in patients with known hypersensitivity to tetracyclines.

Isolated cases of significant hepatic dysfunction and hepatic failure have been reported in patients being treated with tigecycline. 5 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.

As with classical tetracyclines, use of tigecycline in children and during pregnancy is to be avoided due to the potential effects on bone development, such as permanent tooth discolouration, enamel hypoplasia and abnormalities in bone growth and skeletal development. [1,8] The use of tigecycline in patients less than 18 years of age is not recommended since no usage data are available.

Significant drug-drug interactions have not been reported with tigecycline. The drug is only moderately protein bound and is not affected by the cytochrome P450 isoenzyme system, potentially explaining the lack of drug interactions.

When co-administered with digoxin, tigecycline may decrease the Cmax of digoxin. However, no change in the area under the concentration-time curve (AUC) was observed.[1] When co administered with warfarin, tigecycline may increasethe Cmax of warfarin, with a corresponding increase in AUC. Although these changes did not result in significant changes in the International Normalised Ratio (INR), patients receiving warfarin should have their INR monitored routinely.

Similar to tetracyclines, decreased oral contraceptive efficacy may result in women receiving concomitant oral contraceptives.

Place in therapy

The big question is when to use tigecycline: It may prove particularly useful for treatment of surgical wound infections, particularly following abdominal surgery, where MRSA, Enterobacteriaceae, Streptococci and anaerobes are the most likely pathogens.[8] No other single antimicrobial agent covers this spectrum and combination regimens, while equally effective, add cost and complexity.[8]

It may be a reasonable alternative in penicillin-allergic patients. It is also likely to find a role in the treatment of infections due to multi-resistant pathogens, including Acinetobacter and ESBL producers, as well as MRSA and enterococci.[8]

CONCLUSION

Although the development of resistance to tigecycline and the new glycylcycline class of antimicrobials needs to be monitored closely, tigecycline provides clinicians with a new agent which has increased activity against Gram-negative as well as Gram-positive bacteria.[8] However, tigecycline should not be used as empiric therapy for Gram-negative infections because it lacks activity against Pseudomonas aeruginosa and Proteus species.

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