IJPPR
International Journal of Pharmacy & Pharmaceutical Research
An official Publication of Human Journals
ISSN 2349-7203

Human Journals
Review Article
December 2014 Vol.:2, Issue: 1

Tigecycline: A ray of hope for the resistant and complicated infections

IJPPR
International Journal of Pharmacy & Pharmaceutical Research
An official Publication of Human Journals
ISSN 2349-7203

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Submission: 28 November 2014
Accepted: 9 December 2014
Published: 25 December 2014

Keywords: Glycylcyclines, Tigecycline, Tetracycline resistance, Multi-drug resistance, Polymicrobial infections

ABSTRACT

Glycylcyclines, a novel class of antibacterial drugs are developed in response to the emergence of resistant organism. Tigecycline, the first-in-class glycylcycline antibiotics are being promoted for the treatment of complicated intra-abdominal and complicated dermatological infections in adults. Tigecycline's structure is similar to that of the tetracyclines but additional structural elements increase its potency and impede the mechanisms of bacterial resistance associated with the tetracycline's. The resistance profile will be the real key to tigecycline's market value. A high safety profile, with no observed effect on liver or kidney function, and a relatively convenient twice-daily dosing regimen that needs no adjustment in patients with impaired renal function, are also promising features. The present article reviews its current status for the treatment of notorious resistant and complicated infections and its market potential.

INTRODUCTION

In this current era of superbugs and bacterial resistance there is a pressing need for new antibiotics to combat the worsening problem to existing agents[1]. Severe life-threatening strains of bacteria such as Staphylococcus aureus which is one of the leading causes of hospital-acquired infections, are resistant to multiple antibiotics, even those that have historically been highly reliable, such as vancomycin are becoming increasingly widespread[1]. To restore activity against bacteria that have become to resistant to the previous generation of drugs[1] the approach for developing new antibiotics has been to modify existing class of drug. Glycylcyclines are newest class of antibacterial drugs, developed in response to the emergence of resistant organisms these are structurally related to tetracyclines and, like the tetracyclines, act through inhibition of protein translationin bacteria.[2–4] Glycylcycline activity is maintained in the presence of several resistance mechanisms that affect other classes of antimicrobial agents.[5] Tigecycline is the first member of the glycylcyclines, approved by the US FDA for the treatment of a range of bacterial infections in June 2005, developed to overcome the problems of resistance to earlier tetracyclines, although the development of second- and third-generation drugs in the major antibacterial classes, including penicillins, cephalosporins, macrolides and quinolones, have helped in keeping the antibiotic resistance at bay, success with this strategy is becoming much harder to achieve. Furthermore, agents in completely new classes have been very rare; only two such antibiotics, linezolid and daptomycin, have been introduced in the past four decades.

Basis of discovery

Discovered more than 50 years ago tetracycline antibiotics represented a significant advancement in the treatment of many Gram-positive and Gram-negative bacterial infections but their widespread and non rational use produced a high incidence of tetracycline resistance among many bacteria that led to tetracyclines being relegated to second- or third-line therapy. In an attempt to restore the potential of tetracyclines as broad-spectrum antibiotics, systematic searches for tetracycline analogues with activity against both tetracycline-susceptible and tetracycline-resistant organisms were performed in the early 1990.[2] These efforts led to the identification of the glycylcyclines, including tigecycline.[2–4]

Mechanism of action

Tigecycline acts by binding to the 30S ribosomal subunit of susceptible organisms,[2–5] interfering with the binding of tRNA to the mRNA-ribosome complex and subsequently preventing protein synthesis.[2–5] Tigecycline is not affected by major tetracycline resistance mechanisms because of the substitution at position 9.[2–5] The binding site of tigecycline and tetracycline is same but tigecycline binding is five times stronger and that helps overcome the tetracycline resistance.[2–5] The action of tigecycline is bacteriostatic in nature, which is due to its reversible interaction with the ribosome**.** It has been shown to have *in-vitro* and *in-vivo* activity (generally bacteriostatic) against a broad spectrum of bacterial pathogens, and no cross-resistance with other antibiotics has been observed,[2–5] providing a strong rationale for its clinical evaluation.

Clinical data

The potential of tigecycline for the treatment of complicated skin and skin-structure infections was evaluated in two randomized, double-blind, active-controlled studies involving more than 800 adults. Tigecycline (100 mg intravenous initial dose followed by 50 mg every 12 hours) was compared with vancomycin (1 g intravenously every 12 hours)/aztreonam (2 g intravenously every 12 hours) for 5–14 days. The primary efficacy endpoint was the clinical response at the test of cure (TOC) visit in the co-primary populations of the clinically evaluable (CE) and clinical modified intent-to-treat (cmITT) patients. The clinical cure rates for patients receiving tigecycline were 86.5% (CE) and 79.7% (cmITT) compared with 88.6% (CE) and 81.9% (cmITT) for patients receiving vancomycin/aztreonam[5]. Tigecycline was also assessed for the treatment of complicated intra-abdominal infections in two randomized, double-blind, active-controlled studies involving more than 1,000 adult patients. Tigecycline (100 mg intravenous initial dose followed by 50 mg every 12 hours) was compared with imipenem/cilastatin (500 mg intravenously every 6 hours) for 5–14 days. The primary efficacy endpoint was the clinical response at the TOC visits for the co-primary populations of the microbiologically evaluable (ME) and the microbiological modified intent-to-treat (m-mITT) patients. The clinical cure rates for patients receiving tigecycline were 86.1% (ME) and 80.2% (m-mITT), compared with 86.2% (ME) and 81.5% (m-mITT) for patients receiving imipenem/cilastatin.[5]

INDICATIONS

Tigecycline is approved for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below for patients 18 years of age and older: complicated skin and skin-structure infections caused by Escherichia coli, Enterococcus faecalis (vancomycin-susceptible isolates only), Staphylococcus aureus (methicillin-susceptible as well as resistant isolates), Streptococcus agalactiae, Streptococcus anginosus group, Streptococcus pyogenes and Bacteroides fragilis; and complicated intra-abdominal infections caused by Citrobacter freundii, Enterobacter cloacae, E. coli, Klebsiella oxytoca, Klebsiella pneumoniae, E. faecalis (vancomycin-susceptible isolates only), S. aureus (methicillin-susceptible isolates only), S. anginosus group B. fragilis, B. thetaiotaomicron, B. uniformis, B. vulgatus, Clostridium perfringens and Peptostreptococcus micros. Tigecycline has been shown to be active against most strains of the following microorganisms, both *in-vitro* and in clinical infections.

Gram-positive Aerobes: Enterococcus faecalis (vancomycin-susceptible isolates only), Staphylococcus aureus (methicillin-susceptible as well as resistant isolates, including isolates that bear molecular and virulence markers commonly associated with community-acquired MRSA including the SCCmec type IV element and the pvl gene), Streptococcus agalactiae, Streptococcus anginosus (includes S. anginosus, S .intermedius, S. constellatus), Streptococcus pyogenes, Streptococcus pneumoniae (penicillin-susceptible isolates).

Gram-negative Aerobes: Citrobacter freundii, Enterobacter cloacae, Escherichia coli (including ESBL producing strains), Haemophilus influenza, Klebsiella oxytoca, Klebsiella pneumoniae (including ESBL producing strains), Legionella pneumophila, Moraxella catarrhalis.

Anaerobic Bacteria: Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgates, Clostridium perfringens, Peptostreptococcus spp., Peptostreptococcus micros.

Atypical Bacteria: Chlamydia pneumonia, Mycoplasma pneumonia.

In vitro data are available for the following organisms, but their clinical significance is unknown. The in vitro minimum inhibitory concentrations (MIC) of 90% or more of these microorganisms were less than or equal to the susceptible breakpoint for tigecycline. However, the safety and

effectiveness of tigecycline in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram-positive Aerobes Enterococcus avium Enterococcus casseliflavus Enterococcus faecalis (vancomycin-resistant isolates) Enterococcus faecium (vancomycin-susceptible and -resistant isolates) Enterococcus gallinarum Listeria monocytogenes Staphylococcus epidermidis (methicillin-susceptible and -resistant isolates) Staphylococcus haemolyticus Streptococcus pneumoniae (penicillin-resistant isolates) Viridans group streptococci

Gram-negative Aerobes Acinetobacter calcoaceticus/baumannii complex Aeromonas hydrophila Citrobacter koseri Enterobacter aerogenes Haemophilus parainfluenzae Klebsiella pneumoniae (including AmpC producing strains) Pasteurella multocida Salmonella enterica ser. Enteritidis Salmonella enterica ser. Paratyphi Salmonella enterica ser. Typhi Salmonella enterica ser. Typhimurium Serratia marcescens Shigella boydii Shigella dysenteriae Shigella flexneri Shigella sonnei Stenotrophomonas maltophilia

Anaerobic Bacteria Bacteroides ovatus, Clostridium difficile, Peptostreptococcus spp., Porphyromonas spp., Prevotella spp.

Atypical Bacteria Mycobacterium abscessus, Mycobacterium chelonae, Mycobacterium fortuitum.

Resistant

Gram-negative Aerobes: *Pseudomonas aeruginosa* and *Proteeae* (*Proteus* spp., *Providencia* spp. and *Morganella* spp.)

Anaerobic bacteria: No naturally occurring species have been found to be inherently resistant to tigecycline.

RESISTANCE

No cross-resistance has been observed between tigecycline and other antibiotics caused by antibiotic-specific resistance mechanisms. Tigecycline is not affected by the major tetracycline resistance mechanism of ribosomal protection and is not affected by many efflux systems but acquired resistance to tigecycline has been demonstrated in several clinical isolates of

Enterobacteriaceae due to over expression of the AcrAB efflux system, a multi-drug efflux pump. In *in-vitro* studies, no antagonism has been observed between tigecycline and any other commonly used antibiotic class

SAFETY AND TOLERABILITY

The most frequently reported adverse effects associated with the use of tigecycline are nausea and vomiting. These adverse effects are dose limiting and are not diminished by a slowing of the rate of drug infusion.[6] There does not appear to be a relationship between nausea produced by tigecycline and serotonin release.[8] Subjects who were fed or received antiemetics at the time of administration had improved tolerability of tigecycline.[6-10] Older individuals (age, 75 years) and men also reported less nausea than did women and younger subjects.[8] In phase 3 clinical trials, nausea and vomiting occurred in 30% of older and male patients, and 20% of female and younger patients. Nausea as an adverse effect to tigecycline usually occurs in the first 1–2 days of treatment and is transient in most patients. The majority of cases of nausea and vomiting were reported to have been mild (patients were able to ingest food and water). In spite of these findings, close to 30% of patients with complicated skin/skin-structure infections received an antiemetic during tigecycline therapy. The overall discontinuation rate during tigecycline treatment was 5% and was most frequently associated with nausea (1.3%) and vomiting (1.0%).

There has been no clinically significant organ toxicity observed with tigecycline use during clinical trials. In dose-descending and multiple dose studies in healthy subjects (phase 1 investigations), no clinically relevant changes in laboratory parameters, blood pressure, or electrocardiogram intervals were observed[6-10] though transient elevations in alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase levels occurred in some test subjects. In a phase 2 clinical trial of 160 hospitalized patients with skin/skin-structure infections, there was 1 case of paresthesia and 1 case of allergy (itching) associated with tigecycline use.[11] Abnormal laboratory test results possibly related to tigecycline use were observed in only 9 patients, included an elevated serum transaminase level in 5, an elevated serum alkaline phosphatase level in 2, and an elevated blood urea nitrogen level in 1 patients respectively. A total of 1383 patients received tigecycline in multicenter, double-blind, randomized clinical trials (phase 3). No hematologic or serum chemistry abnormalities were associated with use of tigecycline in patients treated with tigecycline for skin/skin-structure

infections.[12] In patients with complicated intra-abdominal infections, few clinically important or unexpected changes in any routine hematologic or serum chemistry test results, vital signs, or electrocardiogram data were associated with tigecycline treatment.[13] None of the deaths in patients who received tigecycline were associated with an adverse drug effect; however, because tigecycline has been studied in <2000 patients, rare adverse events may have occurred without being documented during clinical investigations. Because of tigecycline's similarity to minocycline, potential adverse effects may include hepatitis, pancreatitis, vertigo, hearing loss, lupus erythematous–like syndrome, and hyperpigmentation. No safety data on long-term use of tigecycline have been published. Diarrhea was also reported in a significant number of patients (13%) in phase 3 clinical trials, but no tigecycline treated patient tested positive for C.difficile toxin or developed C.difficile–associated diarrhea. One case of C. difficile–associated diarrhea was reported from a phase 2 clinical trial of patients with complicated intra-abdominal infections.[14] Skin reactions with tetracyclines are not common but may be made manifest as pruritis, urticaria, and maculopapular rashes. Few cases of pancreatitis are reported. Cross-sensitization occurs with this class of antibiotics; therefore, anyone reporting an allergy to one of these agents should be considered hypersensitive to tigecycline.

DOSING

The recommended dosage of tigecycline for the treatment of complicated intra-abdominal and skin/skin-structure infections in adults is 100 mg iv initially, followed by 50 mg 12 hourly by intravenous infusion over 30-6- minutes for 5-14 days. Dosing guidelines in pediatric patients have not been established. Because of poor oral absorption qualities, tigecycline should not be given enterally. No dosage adjustment is necessary for renal or hepatic impairment unless the patient has severe hepatic dysfunction. Tigecycline is not a substrate, inhibitor, or inducer of common cytochrome P450 enzymes and is not highly protein bound therefore pharmacokinetic drug interactions will be uncommon with tigecycline. The concomitant use with warfarin can decrease the clearance of both of warfarin's isomers therefore careful monitoring of international normalized ratio(INR) is prudent while receiving tigecycline therapy . Tigecycline has a Pregnancy Category D label and should not be given to pregnant women.[15] When used in long-term care facilities or for outpatient parenteral antibiotic therapy, reconstituted tigecycline can be stored for 6 h at room temperature and up to 24 h if refrigerated.

Tigecycline appears to have low potentials for organ toxicity and drug-drug interactions. These properties, along with twice daily dosing and the lack of need to monitor renal function, make the use of this antibiotic relatively uncomplicated. One concern will be for patients who develop moderate-to-severe nausea and vomiting during tigecycline therapy. Antiemetics, such as metaclopramide and prochlorperazine, are effective in these patients, but they can add cost and potential adverse effects to patient care.

SUMMARY

Cinical studies suggest that Tigecycline could be one of the most useful antibiotic as empirical therapy for polymicrobial infections, especially in cases where deep tissue penetration is required or where multidrug-resistant pathogens are suspected. Though, tigecycline can be used in many infections, it is approved only for the treatment of serious and hospitalized patients of community acquired pneumonia, complicated skin and skin structure infections (but not diabetic foot), complicated intraabdominal infections caused by enterococci, anaerobes and Enterobacteriaceae. It is not recommended for hospital acquired/ ventilator associated chest infections, because in a comparative trial, all cause mortality was higher in tigecycline group than in the comparator group receiving other antibiotics. It is also not suitable for urinary tract infection, because only low concentrations are attained in urine.

Use in patients with beta-lactam or fluoroquinolone allergy or intolerance, in those with renal failure, or in those who are receiving numerous medications is also an important area where Tigecycline could be the answer. Tigecycline's lack of activity against P. aeruginosa and low serum concentrations will limit its use in some patient populations, such as those with neutropenic fever. Its potential for treating chronic infections in ambulatory care settings is an area currently under investigation. More clinical studies are needed to establish its role in multi-drug resistant infections.

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