Tigecycline: what is it, and where should it be used?

David M. Livermore*

Antibiotic Resistance Monitoring & Reference Laboratory, Centre for Infections, Health Protection Agency, 61 Colindale Avenue, London NW9 5HT, UK

Tigecycline is the first glyyclycline to be launched and is one of the very few new antimicrobials with activity against Gram-negative bacteria. It evades acquired efflux and target-mediated resistance to classical tetracyclines, but not chromosomal efflux in Proteae and Pseudomonas. C\textsubscript{max} is low, but tissue penetration is excellent and the compound has shown equivalence to imipenem/cilastatin in intra-abdominal infection and to vancomycin plus aztreonam in skin and skin structure infection. Tigecycline may prove particularly useful for treatment of surgical wound infections, where both gut organisms and MRSA are likely pathogens. It is also likely to find a role in the treatment of infections due to multiresistant pathogens, including Acinetobacter spp. and ESBL producers, as well as MRSA and enterococci.

Keywords: tetracyclines, glyyclyclines, GAR-936

Tigecycline (Wyeth, formerly GAR-936), was licensed by the USA’s Food and Drug Administration in June 2005. It is the first glyyclycline to be launched and the first new tetracycline analogue since minocycline over 30 years ago. It is also unique among the small raft of anti-MRSA and anti-enterococcal drugs now reaching the market because it additionally has substantial anti-Gram-negative activity, encompassing not only most Enterobacteriaceae, but also—at least in vitro—multiresistant Acinetobacter baumannii. Whilst many microbiologists and clinicians viscerally feel tetracyclines are not ‘powerful’ antibiotics in the way of β-lactams, aminoglycosides and quinolones, it is striking that tigecycline showed equivalence to imipenem in intra-abdominal infections and to vancomycin plus aztreonam in skin and skin structure infections. Such successes imply that the old prejudices about tetracyclines may be inappropriate for tigecycline, or unduly pessimistic for tetracyclines and glyyclyclines as a whole.

Research into glyyclyclines began at Lederle in the early 1990s, when it was realized that addition of a modified glycylamido- to carbon 1 of the D ring (Figure 1) allowed both efflux and ribosomal type resistances to be overcome. Two N,N-dimethylglycylamido- derivatives were progressed initially, but neither proved suitable for pharmaceutical development and progress stalled until Wyeth, who bought Lederle in 1994, decided to progress the t-butylglycylamido derivative of minocycline. This is the compound now being launched as tigecycline.

Tigecycline evades the Tet(A-E) efflux pumps, which account for most acquired resistance to tetracycline and minocycline in Enterobacteriaceae and Acinetobacter spp. The Tet(K) pumps, which occur widely in staphylococci conferring resistance to tetracycline though not minocycline or doxycycline. In addition, tigecycline binds to bacterial ribosomes that have been modified by the Tet(M) protein, a mechanism that compromises all available tetracyclines, and which is frequent in Gram-positive cocci and Neisseria spp. Evasion of Tet(M) is probably because tigecycline attaches to the ribosome in a different orientation from classical tetracyclines. Tigecycline remains vulnerable to the chromosomally-encoded multidrug efflux pumps of Proteae, and Pseudomonas aeruginosa, and to Tet(X), a tetracycline-degrading mono-oxygenase found, albeit rarely, in Bacteroides spp.

The compound’s antibacterial spectrum reflects this evasion of acquired resistance along with its continued vulnerability to chromosomally-mediated efflux in Pseudomonas and Proteae: MIC distributions for Enterobacteriaceae species are unimodal with only a slight positive skew: typical values are ~0.12 to 0.25 mg/L for Escherichia coli and 0.5–1 mg/L for Klebsiella, Enterobacter and Citrobacter spp., with fewer than 2% of isolates of these latter species having MICs >2 mg/L. Acinetobacter spp. are mostly susceptible at 0.5–2 mg/L and Bacteroides spp. at 1–8 mg/L, whilst MICs for Proteae are mostly 2–8 mg/L and those for P. aeruginosa are 8–32 mg/L. Tigecycline MICs for enterococci, staphylococci, and streptococci are mostly 0.06–0.25 mg/L, again with little or no skew to the distribution. MIC values vary a little with the medium, being about a dilution lower in Iso-Sensitest media than Mueller–Hinton broth; whether this will impact on susceptibility categorizations will depend on the breakpoints ultimately adopted by the CLSI and EUCAST, but it seems unlikely to be a source of major discrepancies. Like classical tetracyclines, tigecycline is prone to oxidation, and MIC values, particularly for the most susceptible isolates, may be raised if the drug is added to broth that has become...
pneumonias are in progress and, if positive, will form the basis of a licence extension. Trials in urinary tract infections were abandoned on pre-completion review, because excretion proved to be largely biliary, with limited urinary recovery of the active drug. In addition, there are ongoing trials against infections caused by specific multiresistant pathogens, along with an extensive compassionate-use programme. The main side effect, seen in 24.4% of patients in the intra-abdominal infection studies and 34.5% 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 III studies was under 1.5%.5–8 As with classical tetracyclines, use in children and women who are (or may be) pregnant is to be avoided owing to potential effects on bone development.

The big question now is how to deploy tigecycline. The most attractive on-label application seems—to this author—to be in surgical wound infections, particularly following abdominal surgery, where the likely pathogens include MRSA (except in Scandinavia and the Netherlands) as well as Enterobacteriaceae, staphylococci and anaerobes.23 No other single agent covers this spectrum and combination regimens, whilst arguably more flexible, add cost and complexity. Wider empirical use in skin and skin structure infections also seems reasonable, especially in settings where either or both MRSA and Gram-negative pathogens are likely. There is less obvious immediate need in those intra-abdominal infections that are likely to involve only the gut flora itself and not MRSA, where β-lactamase inhibitor combinations, cephalosporin/metronidazole or carbapenem treatments remain highly effective in the great majority of cases. Nevertheless, tigecycline would be a reasonable alternative in penicillin-allergic patients, and is likely to become increasingly attractive as extended-spectrum β-lactamases (ESBLs) become more widely disseminated among the endogenous gut Enterobacteriaceae that seed these infections. ESBLs, and particularly the CTX-M types, are now spreading rapidly in many countries, including the UK.24 Recent studies around York and in Shropshire found ESBL-positive Enterobacteriaceae in 2–2.5% of stool specimens from diarrhoeal outpatients and up to 4.5% of those from inpatients.25,26 Most ESBL-producing E. coli in the UK have the CTX-M-15 enzyme and are multiresistant to quinolones, aminoglycosides and (owing to simultaneous production of OXA-1 enzyme) to β-lactamase inhibitor combinations, leaving only the carbapenems and tigecycline as reliably active,24 along with a few agents with limited application, notably fosfomycin and nitrofurantoin. At present, though, the major site for infections with ESBL producers remains the urinary tract, a setting where tigecycline is not an obvious first choice owing to its biliary excretion profile.

Acinetobacter spp. are another group of multiresistant pathogens where tigecycline’s activity is exciting much interest, especially as growing numbers of isolates of the genus are resistant even to carbapenems owing to production of OXA carbapenemase or, more rarely, metallo-β-lactamases.27 Currently, three carbapenemase-producing A. baumannii strains are prevalent in multiple hospitals in and around London,28 two with both OXA-23 and OXA-51-like carbapenemases and the third with only an OXA-51-like enzyme. Producers of these and other OXA carbapenemases are being widely reported elsewhere in Europe, South America and East Asia, with OXA-24 enzyme prevalent in Iberia and metallo-carbapenemases more frequent in the Far East.27 In the USA, the proportion of Acinetobacter isolates resistant or intermediate resistant to imipenem rose from 6.3% in 1999
to 11.4% in 2001, though the prevalent mechanisms remain undefined. Many carbapenemase-producing A. baumannii isolates are resistant to all available agents except polymyxins, drugs with significant toxicity and poor penetration to respiratory secretions (though this might be overcome with nebulized colistin). Tigecycline, which is active against most carbapenemase-producing strains at ≤2 mg/L,4 may be a useful alternative to polymyxins. A few positive case reports have begun to appear29 and there is also a report of successful use of doxycycline and minocycline in six of seven cases of ventilator-associated Acinetobacter pneumonia, supporting the concept of using tetracyclines in this setting.30 Nevertheless, systematic study is needed to assess the relative merits of tigecycline versus polymyxins in infections due to multiresistant acinetobacters.

Last, tigecycline will certainly be used as microbiologically-directed therapy of infections due to multiresistant Gram-positive pathogens, including MRSA and vancomycin-resistant enterococci, and a key challenge is to determine when to prefer tigecycline as against old and new glycopeptides, linezolid, daptomycin, and (in the future) ceftobiprole. There is growing evidence that linezolid is superior to vancomycin versus MRSA31,32 but, as yet, there is no comparison among the various new agents, including tigecycline.

In short, tigecycline is among the more unique recent additions to the armamentarium and its achievements in clinical trials should lead us to rethink the status of tetracycline derivatives. Aside from empirical usage in wound infections where either or both MRSA and Enterobacteriaceae are likely, tigecycline should have a role in directed treatment of infections due to ESBL producers, pan-resistant Acinetobacter spp. and multiresistant Gram-positive cocci. Needless to say, its propensity to select resistance needs to be monitored closely and it is disturbing that in vitro-selected mutations of tet(A), enabled efflux of glyyclcyclines;33 also that there were five instances of emerging resistance during the Phase III trials, two with K. pneumoniae and one each with Enterobacter cloacae, Morganella morganii and A. baumannii, all apparently associated with up-regulation of chromosomally-mediated efflux pumps (Wyeth, data on file). Moreover, this reference laboratory is also investigating several tigecycline non-susceptible (MIC, 4–16 mg/L) A. baumannii from London, and particular attention needs to be addressed to any potential for selection of resistance in this notoriously adaptable species. Whether or not significant resistance threats ultimately do emerge (and experience shows that they usually do!), it is excellent news to have a new agent with increased activity against Gram-negative as well as Gram-positive bacteria. Few others will come this decade.

References


Leading article
Leading article


