International Journal of Antimicrobial Agents ■■ (2018) ■■–■■

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Surveillance of tigecycline activity tested against clinical isolates from a global (North America, Europe, Latin America and Asia-Pacific) collection (2016)

Michael A. Pfaller [a,b], Michael D. Huband [a], Jennifer M. Streit [a], Robert K. Flamm [a], Helio S. Sader [a,*]

[a] JMI Laboratories, Inc., 345 Beaver Kreek Centre, Suite A, North Liberty, IA 52317, USA
[b] University of Iowa, Iowa City, Iowa, USA

ARTICLE INFO

Article history:
Received 16 October 2017
Accepted 14 January 2018
Editor: P. Tulkins

Keywords:
Antimicrobial resistance
Staphylococcus aureus
MRSA
VRE
Enterobacteriaceae
CRE

ABSTRACT

Tigecycline and comparators were tested by the reference broth microdilution method against 33 348 non-duplicate bacterial isolates collected prospectively in 2016 from medical centres in the Asia-Pacific (3443 isolates), Europe (13 530 isolates), Latin America (3327 isolates) and the USA (13 048 isolates). Among 7098 *Staphylococcus aureus* isolates tested, >99.9% were inhibited by ≤0.5 mg/L tigecycline ($MIC_{50/90}$, 0.06/0.12 mg/L), including >99.9% of methicillin-resistant *S. aureus* and 100.0% of methicillin-susceptible *S. aureus*. Tigecycline was slightly more active against *Enterococcus faecium* ($MIC_{50/90}$, 0.03/0.06 mg/L) compared with *Enterococcus faecalis* ($MIC_{50/90}$, 0.06/0.12 mg/L) and its activity was not adversely affected by vancomycin resistance when tested against these organisms. Tigecycline potency was comparable for *Streptococcus pneumoniae* ($MIC_{50/90}$, 0.03/0.06 mg/L), viridans group streptococci ($MIC_{50/90}$, 0.03/0.06 mg/L) and β-haemolytic streptococci ($MIC_{50/90}$, 0.06/0.06 mg/L) regardless of species and penicillin susceptibility. Tigecycline was active against Enterobacteriaceae ($MIC_{50/90}$, 0.25/1 mg/L; 97.8% inhibited at ≤2 mg/L) but was slightly less active against Enterobacteriaceae isolates expressing resistant phenotypes: carbapenem-resistant Enterobacteriaceae ($MIC_{50/90}$, 0.5/2 mg/L; 98.0% susceptible); multidrug-resistant ($MIC_{50/90}$, 0.5/2 mg/L; 93.1% susceptible); and extensively drug-resistant ($MIC_{50/90}$, 0.5/4 mg/L; 87.8% susceptible). Tigecycline inhibited 74.4% of 888 *Acinetobacter baumannii* isolates at ≤2 mg/L ($MIC_{50/90}$, 2/4 mg/L) and demonstrated good in vitro activity against *Stenotrophomonas maltophilia* ($MIC_{50/90}$, 1/2 mg/L; 90.6% inhibited at ≤2 mg/L) Tigecycline was active against *Haemophilus influenzae* ($MIC_{50/90}$, 0.12/0.25 mg/L) regardless of β-lactamase status. Tigecycline represents an important treatment option for resistant Gram-negative and Gram-positive bacterial infections.

1. Introduction

Antimicrobial resistance (AMR) is a serious problem, with multidrug-resistant (MDR) strains, i.e. strains resistant to at least three classes of agents, both of Gram-positive cocci (GPC) and Gram-negative bacilli (GNB) impacting medical progress in most regions of the world [1]. Collecting AMR surveillance data is an essential approach to define the scope of the resistance problem and to develop interventions that improve appropriate use of antibiotics and decrease the resistance selection pressure [1,2]. Another important effort is to understand the mechanisms of resistance, whereby bacteria avoid the effects of antibiotics, and to use this information to develop new agents, or to modify older agents, that retain potent activity against the key target pathogens [3–5]. AMR reduces the potential efficacy of commonly used antimicrobial agents that include tetracyclines, fluoroquinolones and third-generation cephalosporins, highlighting the clinical importance of newer antimicrobial agents such as the glycylcyclines [6–11].

Tetracyclines are broad-spectrum agents with activity against GPC and GNB as well as intracellular *Chlamydia*, *Mycoplasma* and *Rickettsia* and protozoan and helminthic parasites [12]. Tetracyclines have been used extensively in clinical and veterinary medicine, in agriculture and for a variety of non-infectious conditions (e.g. acne) for many years [12,13]. Broadly using tetracyclines has resulted in the emergence of tetracycline-resistant bacteria and has limited the use of the older members of this class (tetracycline, doxycycline and minocycline) in treating bacterial diseases [12,13]. A great deal is known about resistance mechanisms that bacterial strains have developed to the tetracyclines. Genes encoding efflux pumps and ribosomal protection proteins have been described both in GPC and

* Corresponding author. JMI Laboratories, Inc., 345 Beaver Kreek Centre, Suite A, North Liberty, IA 52317, USA.
E-mail address: helio-sader@jmilabs.com (H.S. Sader).

https://doi.org/10.1016/j.ijantimicag.2018.01.006
0924-8579/

GNB and confer resistance to tetracycline, doxycycline and minocycline [12–15].

Tigecycline is a semisynthetic derivative of minocycline and is the first member of the novel class of glycylcyclines [7–11]. Similar to the older tetracyclines (doxycycline, minocycline and tetracycline), tigecycline binds to the 30S ribosomal subunit of target GPC and GNB with resultant inhibition of protein synthesis [10,11]. Notably, tigecycline remains active both against ribosomal protection and efflux tetracycline resistance genes [7,9–11]. Tigecycline also maintains its activity against difficult-to-treat MDR pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE) and Enterobacteriaceae strains that express resistant phenotypes, including extended-spectrum β-lactamases (ESBLs) and carbapenemases, in addition to MDR strains of *Acinetobacter* spp. and *Stenotrophomonas maltophilia* [7–11]. Tigecycline does not have useful activity against *Pseudomonas aeruginosa* [11]. Tigecycline was approved by the US Food and Drug Administration (FDA) in 2005 for acute bacterial skin and skin-structure infections (ABSSSIs) and complicated intra-abdominal infections (cIAIs) and in 2009 to treat community-acquired bacterial pneumonia [16,17].

In the present study, the antimicrobial activity of tigecycline was evaluated in a longitudinal SENTRY Surveillance Program against isolates of GPC and GNB collected in 2016 from individual medical centres in the Asia-Pacific region (APAC), Europe (EU), Latin America (LA) and North America (USA only). Resistant subsets for most of the pathogen groups were evaluated and included in the analysis.

2. Materials and methods

A total of 33 348 non-duplicate bacterial isolates were collected prospectively in 2016 from medical centres located in the APAC region (17 sites; 3443 isolates), EU (40 sites; 13 530 isolates), LA (17 sites; 3327 isolates) and the USA (30 sites; 13 048 isolates). Organisms were isolated from hospitalised patients with bloodstream infection (BSI) (9021 isolates), community-acquired respiratory tract infection (3138 isolates), pneumonia in hospitalised patients (7266 isolates), ABSSSI (7962 isolates), cIAI (1476 isolates), urinary tract infection (3161 isolates) and other types of infection (1324 isolates). Isolates were identified to species level at each participating medical centre and all identifications were confirmed by the monitoring laboratory (JMI Laboratories, North Liberty, IA) using a VITEK®2 system (bioMérieux, Hazelwood, MO) or matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF/MS) (Bruker, Billerica, MA) when necessary.

Minimum inhibitory concentrations (MICs) were determined by the monitoring laboratory (JMI Laboratories) using the reference Clinical and Laboratory Standards Institute (CLSI) broth microdilution method [18]. Susceptibility testing for tigecycline for 2016 surveillance was done with frozen-form broth microdilution MIC panels prepared at JMI Laboratories. Each batch of panels was tested against the appropriate CLSI quality control organisms in triplicate, and all MICs were within the established testing range [19]. Further quality of results was assured by concurrently testing CLSI quality control organisms (*S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Streptococcus pneumoniae* ATCC 49619, *Escherichia coli* ATCC 25922 and *Haemophilus influenzae* ATCC 49247) on each day of testing. Quality control and interpretation of results were performed in accordance with CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2016 guidelines [19,20]. Tigecycline MIC breakpoints were those in the FDA-approved package insert [16]. The tigecycline breakpoints established by the FDA for *S. aureus* (≤0.5 mg/L for susceptible), *E. faecalis* (≤0.25 mg/L for S) and Enterobacteriaceae (≤2/≥8 mg/L for susceptible/resistant) were also applied to coagulase-negative staphylococci (CoNS), *Enterococcus faecium* and *Acinetobacter baumannii*/*S. maltophilia*, respectively, for comparison purposes only [21]. VRE was defined as a vancomycin MIC > 16 mg/L (resistant by CLSI and EUCAST criteria) [19,20]. Carbapenem-resistant Enterobacteriaceae (CRE) isolates were resistant to one or more of the carbapenems (meropenem, doripenem or imipenem; *Proteus mirabilis* and indole-positive Proteae were not included due to intrinsically elevated MICs [19]. MDR, extensively drug-resistant (XDR) and pandrug-resistant (PDR) bacteria were classified as such per recently recommended guidelines [22] using the following antimicrobial class representative agents and CLSI interpretive criteria [19]: ceftriaxone (≥2 mg/L); meropenem (≥2 mg/L); piperacillin/tazobactam (≥32/4 mg/L); levofloxacin (≥4 mg/L); gentamicin (≥8 mg/L); tigecycline (≥4 mg/L); and colistin (≥4 mg/L). Classifications were based on the following recommended parameters: MDR, non-susceptible to at least one agent in three or more antimicrobial classes; XDR, non-susceptible to at least one agent in all but two or fewer antimicrobial classes; and PDR, non-susceptible to all antimicrobial classes [22].

3. Results and discussion

The 33 348 isolates tested included 7098 *S. aureus*, 1577 CoNS, 891 *E. faecalis*, 481 *E. faecium*, 1872 *S. pneumoniae*, 596 viridans group streptococci (VGS), 1351 β-haemolytic streptococci (BHS), 12 869 Enterobacteriaceae (including 5554 *E. coli*, 3521 *Klebsiella* spp. isolates, 1526 *Enterobacter* spp. isolates, 491 *Citrobacter* spp. isolates, 775 *Proteus* spp. isolates, 631 *Serratia* spp. isolates, 265 *Morganella morganii* isolates and 106 *Providencia* spp. isolates), 888 *A. baumannii*, 478 *S. maltophilia* and 1286 *H. influenzae* isolates (Table 1).

The frequency of key resistant phenotypes included 2501 (35.2%) MRSA isolates, 208 (43.2%) vancomycin-resistant *E. faecium* isolates, 346 (2.7%) CRE isolates, 2033 (15.8%) MDR Enterobacteriaceae isolates and 384 (3.0%) XDR Enterobacteriaceae isolates; there were only 3 PDR Enterobacteriaceae isolates. The frequency of the resistant phenotypes varied by geographic region and infection type (Table 2). The highest frequencies of MRSA and VRE were seen in isolates from the USA and the lowest frequencies were seen in isolates from EU, regardless of infection type. Conversely, the lowest frequencies of CRE, MDR and XDR phenotypes of Enterobacteriaceae were seen in the USA and high rates of these resistant GNB were detected in EU and LA. The highest rates of CRE, MDR and XDR Enterobacteriaceae in the APAC region were seen in ABSSSI isolates (Table 2).

MIC distributions for each organism or organism group from the 104 participating medical centres are shown in Table 1. Tigecycline was very active when tested against *S. aureus* isolates (7098 isolates tested; $MIC_{50/90}$, 0.06/0.12 mg/L), with 7097 isolates (>99.9%) inhibited by ≤0.5 mg/L tigecycline (MIC range, ≤0.015–1 mg/L), including 100.0% of methicillin-susceptible *S. aureus* and >99.9% of MRSA isolates (Table 1). All CoNS isolates were susceptible to tigecycline at ≤0.5 mg/L ($MIC_{50/90}$, 0.06/0.25 mg/L).

Tigecycline was slightly more active against *E. faecium* ($MIC_{50/90}$, 0.03/0.06 mg/L) compared with *E. faecalis* ($MIC_{50/90}$, 0.06/0.12 mg/L) and its activity was not adversely affected by vancomycin resistance when tested against these organisms (Table 1). The potency of tigecycline was comparable for *S. pneumoniae* ($MIC_{50/90}$, 0.03/0.06 mg/L), VGS ($MIC_{50/90}$, 0.03/0.06 mg/L) and BHS ($MIC_{50/90}$, 0.06/0.06 mg/L) regardless of species and penicillin susceptibility (Table 1). All streptococci isolates were inhibited by ≤0.25 mg/L tigecycline.

Tigecycline was active against 12 869 Enterobacteriaceae isolates ($MIC_{50/90}$, 0.25/1 mg/L; 97.8% inhibited at ≤2 mg/L) (Table 1). Tigecycline was slightly less active against Enterobacteriaceae isolates expressing resistant phenotypes: CRE ($MIC_{50/90}$, 0.5/2 mg/L; 98.0% susceptible); MDR ($MIC_{50/90}$, 0.5/2 mg/L; 93.1% susceptible); and XDR ($MIC_{50/90}$, 0.5/4 mg/L; 87.8% susceptible) (Table 1). Among the 12 isolates of Enterobacteriaceae that were resistant to tigecycline

Please cite this article in press as: Michael A. Pfaller, Michael D. Huband, Jennifer M. Streit, Robert K. Flamm, Helio S. Sader, Surveillance of tigecycline activity tested against clinical isolates from a global (North America, Europe, Latin America and Asia-Pacific) collection (2018), International Journal of Antimicrobial Agents (2018), doi: 10.1016/j.ijantimicag.2018.01.006