Tigecycline – how powerful is it in the fight against antibiotic-resistant bacteria?

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Key words: *tigecycline; mechanism of action; in vitro and in vivo activity; resistance.*

Summary. *Tigecycline is a semisynthetic analogue of earlier tetracyclines and represents the first member of a novel class of antimicrobials – glycylcyclines – recently approved for clinical use. It is active against a broad range of gram-negative and gram-positive bacterial species including clinically important multidrug-resistant nosocomial and community-acquired bacterial pathogens. The exact molecular basis of tigecycline action is not clear at present, although similarly to the tetracyclines, it has been shown to inhibit the translation elongation step by binding to the ribosome 30S subunit and preventing aminoacylated tRNAs to accommodate in the ribosomal A site. Importantly, tigecycline overcomes the action of ribosomal protection proteins and is not a substrate for tetracycline efflux pumps of most bacteria – well-known and prevalent cellular mechanisms of microbial tetracycline resistance. The present review summarizes current knowledge on the molecular mechanism of the tigecycline action, antibacterial activity against various bacteria, clinical application, development of resistance to glycylcyclines.*

Introduction

Use of antimicrobial drugs over the last 60 years in medicine and veterinary has triggered a development of very efficient genetic and biochemical mechanisms within bacteria enabling them to live in the antibiotic-containing environments. In recent years, the emergence and spread of multidrug-resistant (MDR) pathogenic microorganisms, which possess exceptional risk to human health, have become a problem of special significance. The list of antibiotics available for efficient treatment of community-acquired and nosocomial infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus*, extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, carbapenemase-producing *Acinetobacter baumannii* became dramatically short. The availability of the effective antibacterials, which are active against a broad spectrum of antibiotic resistant gram-positive, gram-negative bacteria and anaerobic species, becomes of critical importance in the cases of serious bacterial infections, when empirical therapy often must be applied to avoid patient morbidity and mortality, and reduce the costs of healthcare.

Tigecycline is the first antimicrobial of glycylcycline class, recently approved for use in the clinical practice for the treatment of adult complicated skin and skin-structure infections (cSSSIs), complicated intra-abdominal infections (cIAIs), and community-acquired bacterial pneumonia (CABP) (1–2) and introduced during the past two decades into clinical practice (1).

Clinical and pharmacological studies of tigecycline are summarized recently in several comprehensive reviews including data on the large in vitro and clinical trials performed in number of countries worldwide (3–5). In the present work, we focused our attention on molecular basis of tigecycline action and on the issue of microbial resistance to glycylcyclines.

Glycylcycline structure and molecular basis of action

From the chemical point of view, glycylcyclines are related to tetracyclines, albeit constitute a new class of antibacterials (Fig. 1). Tigecycline (formerly GAR-936, Trademark: Tygacil®; Wyeth Pharmaceuticals, Inc., Philadelphia, PA, USA), the first member of the class, is a structural derivative of semisynthetic drug minocycline, differing from it by the long side chain at the 9 position of carbon atom (9-tert-butyl-glycylamido moiety) of the D ring of tetracyclic nucleus (Fig. 1). Search for more microbiologically active structural analogs of tetracycline in 1990s led to discovery of some derivatives of minocycline such as N, N-dimethylglycylamido (DMG) substituent at 9 position (DMG-MINO), which differently from other developed analogs was

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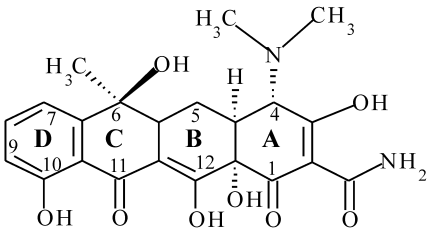

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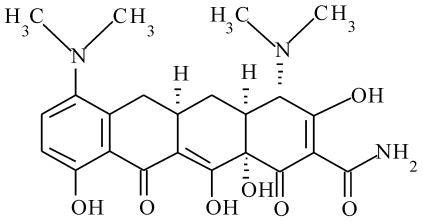

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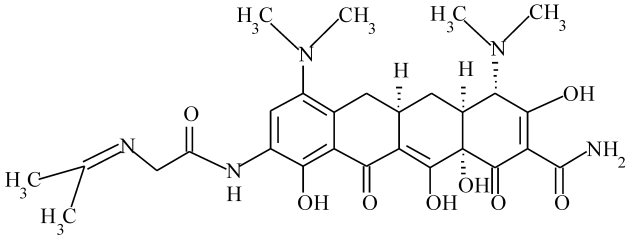
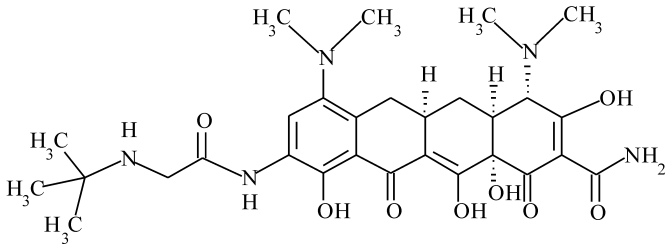


N, N-dimethylglycyclamido minocycline
(DMG-MINO)



Tigecycline

Fig. 1. Chemical structures of tetracycline derivatives and tigecycline

active in vitro not only against a wide range of tetracycline-susceptible bacteria but against those possessing known determinants of resistance to early tetracyclines (6). Further development of more efficient compounds led to discovery of GAR-963 in 1993, presently known as tigecycline (7) (Fig. 2). N-alkyl glycylamido side chain at the carbon 9 position equips tigecycline by several features, responsible for its biological activity: 1) increases lipid solubility of the drug; 2) creates a steric hindrance, which prevents tigecycline from the efflux out the cell by most membrane-bound efflux proteins; 3) increases affinity to the binding site of its cellular target – ribosome.

Tigecycline enters bacterial cell either through passive diffusion or active transport routes (Fig. 3). In the cytosol, similarly to tetracyclines and their structural analogs, it reversibly binds to ribosome 30S subunit and blocks bacterial growth by inhibition of protein biosynthesis (8–9). The effect is bacteriostatic rather than bactericidal in most bacteria. The inhibition of tigecycline-mediated translation is thought to be achieved, similarly to tetracyclines, through interfering with accommodation of aminoacyl-tRNA in the ribosomal A site, which precedes the peptidyl-transfer reaction (Fig. 3) (8–10). Notably, tigecycline binds 5 times stronger to the same ribosomal high-affinity site as compared to tetracycline, albeit in different orientation (8–10). Structural data of the tigecycline/ribosome complex are still lacking, although three dimensional structures of *T. thermophilus* ribosome 30S subunit with bound tetracycline, determined by x-ray crystallography, have shown that the high-affinity binding site 1 (Tet-1) is located between the head and the shoulder of the 30S subunit proximal to 16S rRNA helix 34 and A site (11). The oxygen atoms of the 16S rRNA phosphate backbone interact with the hydrophilic part of tetracycline through many hydrogen-bonding interactions and are additionally coordinated by Mg^{2+}, bound to tetracycline molecule. From structural data, tetracycline binding is proposed to create a steric hindrance, which prevents aminoacyl-tRNA from positioning (rotation)

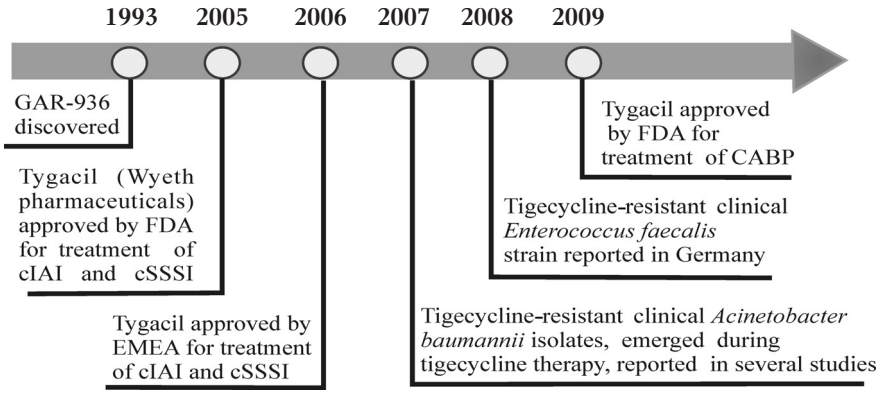


Fig. 2. Timetable of tigecycline (Tygacil) discovery, approval for clinical use, and reports on resistance

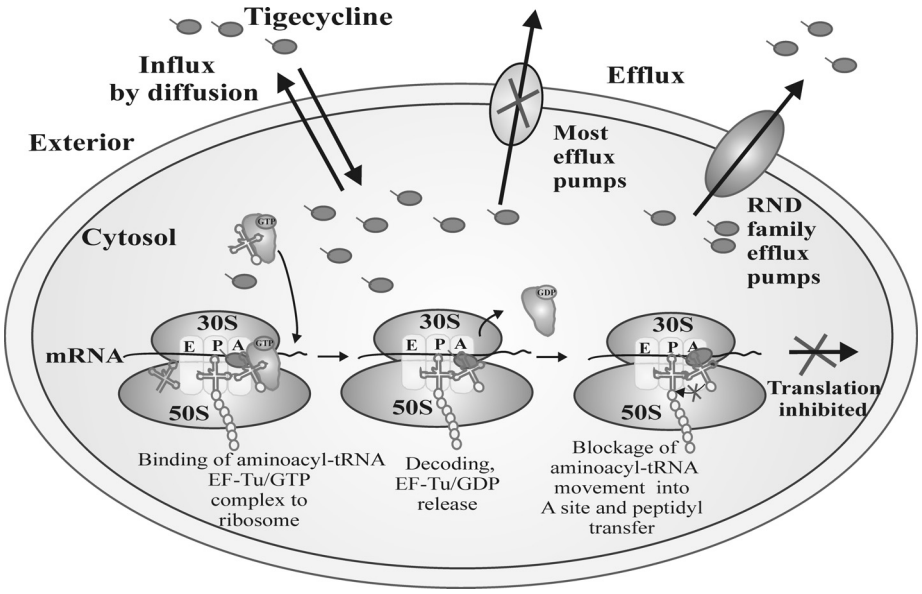


Fig. 3. Molecular mechanism of tigecycline action

Ribosome A (aminoacyl), P (peptidyl) and E (exit) sites, ribosome 30S and 50S subunits, messenger RNA (mRNA) aminoacyl-tRNA/EF-Tu complexes are shown.

in A site for peptidyl-transfer reaction (11). Similar mode of action has been proposed for tigecycline (Fig. 3). Notably, tetracycline binding appears do not interfere with earlier events of elongation cycle – the binding of aminoacyl-tRNA to the ribosome in a form of ternary complex with EF-Tu/GTP and the codon/anticodon (decoding) recognition-dependent ribosome-mediated GTP hydrolysis. Therefore, bound tetracycline prevents accommodation of aminoacyl-tRNA in the A site just after decoding and release of EF-Tu/GDP. The second tetracycline-binding site, Tet-5, is located in 30S subunit body, close to the 16S rRNA helix 44 and is proposed to participate in the mechanism of inhibition (11). Additionally, tetracycline has been crystallized in complex (1:1) with a modified form of *E. coli* EF-Tu-Mg-GDP suggesting another possible mode of action through its binding to EF-Tu (12). However, recent molecular dynamics simulations of ribosome 30S subunit have shown that Tet-1 site is, indeed, a predominant tetracycline binding site and thus steric interference is a major mechanism of tetracycline action (13). In a similar study, neither tetracycline nor tigecycline binding to EF-Tu has been shown to have a significant role in translation inhibition (14).

As it has been mentioned above, tigecycline is active against tetracycline-resistant bacterial strains (6). Tetracycline resistance in various bacteria is very common and is mediated through two most prevailing protein-based mechanisms: export of tetracyclines from the cell by the Tet efflux proteins (TetA-E, TetK) and protection of the ribosome from tetracycline binding by ribosomal protection proteins (TetO, TetM) (8). Large diversity of *tet* genes coding for both groups of proteins are known to function in tetracycline-resistant gram-negative and gram-positive bacteria either alone or in combinations (8). It is speculated that long side chain of tigecycline, most probably, prevents it from binding

to most efflux proteins and transport from the cell (15) (Fig. 3).

Ribosomal protection proteins show high similarity to translation elongation factors such as EF-G and EF-Tu and are members of GTPase protein superfamily (16). They bind to the binding site of elongation factors EF-G and EF-Tu in the 50S subunit, induce conformational changes of the ribosome, and release tetracycline from its inhibitory site in 30S subunit, thus eliminating a steric barrier for accommodation of aminoacyl-tRNA during elongation step of translation (16). It has been proposed that either higher affinity of tigecycline to Tet-1 binding site compared to tetracycline and its derivatives or its unique orientation, when bound to ribosome, could prevent tigecycline from dissociation via the action of ribosome protection proteins in tetracycline-resistant bacteria (10).

Importantly, tigecycline appears to overcome not only tetracycline resistance, but also most of other antibiotic resistance mechanisms known in bacteria, such as drug target modification, enzymatic degradation, DNA gyrase mutations. This makes tigecycline a promising antibacterial agent against a broad spectrum of clinically important antibiotic-resistant pathogens.

There are, however, some exceptions. Certain bacteria with clinical significance, such as *Pseudomonas aeruginosa*, *Proteus* spp., *Providencia* spp., and *Morganella* spp., have been reported to show intrinsic lowered susceptibility to tigecycline (17–19). Bacterial efflux pumps belonging to so-called resistance-nodulation-division (RND) family and conferring multidrug resistance phenotype appear to be responsible, at least in part, for the reduced tigecycline susceptibility of bacteria listed above (Fig. 3). These observations imply the most likely pathways for the emergence of efflux-mediated tigecycline resistance through mutations in transport proteins and/or their transcriptional regulators. The possible trends for development of resistance to tigecycline will be discussed below.

Tigecycline antibacterial activity in vitro

Recent reports on the global testing such as the Tigecycline Evaluation and Surveillance Trial (TEST Program) and other tigecycline studies conducted in a number of countries have shown in vitro susceptibility of large collection of isolates to tigecycline from community and nosocomial infections (20–22). In addition, cumulative data on the tigecycline activity against bacterial isolates in comparison with other antimicrobials have been recently presented (22). These studies have shown that tigecycline is active in vitro against various gram-positive and gram-negative bacteria including multidrug-resistant strains, aerobic, anaerobic bacteria, and atypical organisms. Tigecycline was demonstrated to be potent antibacterial drug against vancomycin-intermediate and vancomycin-resistant enterococci (VRE), MRSA, extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli*, *Klebsiella pneumoniae*, multidrug-resistant *Acinetobacter baumannii*, and penicillin-resistant *Streptococcus pneumoniae* (2–4, 20–22).

It must be noted that interpretive criteria for tigecycline susceptibility established by the U.S. Food and Drug Administration (FDA) and by the European Committee on Antimicrobial Susceptibility testing (EUCAST) differ for some clinically important bacteria, FDA breakpoints being higher than those estimated by EUCAST (1, 23). In addition, there are no definitive breakpoints for some nonfermenting pathogens yet.

Most studies use the broth microdilution method for the determination of microbiological activity of tigecycline according to the Clinical Laboratory Standards Institute (CLSI) recommendations (24). Some investigations have reported that several methodological aspects must be taken into consideration when performing susceptibility testing by this method. Petersen et al. (25) reported that use of the media, older than 12 h, might lead to the oxidation of tigecycline. Thus, partial loss of tigecycline activity could give falsely higher minimum inhibitory concentrations (MICs). Another recent study has shown that tigecycline MICs for *Enterobacter* species determined by the Etest are significantly higher that those determined by the broth microdilution method, and therefore strains determined as tigecycline nonsusceptible according to the Etest should be confirmed by the broth microdilution method (26).

Tigecycline MICs for gram-positive species are generally lower as compared to gram-negative bacteria. Thus, the MIC_{90} (MIC at which 90% of the isolates tested were inhibited) for most *Enterococcus fecalis* and *Enterococcus faecium* clinical isolates obtained in a series of studies was in a range of 0.12–0.25 mg/L. The MIC_{90} value for vancomycin-resistant strains of both species was 0.12 mg/L (20–22, 27–28).

Susceptibility ranges estimated for *S. aureus* were similar to those for *Enterococcus* spp. and varied from $\leqslant$0.125 to 0.5 mg/L (MIC_{90}) (20–22, 27–28). Similar tigecycline activity was estimated against MRSA isolates (MIC_{90}, 0.25–0.5 mg/L) (20–22, 27–28). Borbone et al. (27) showed that tigecycline was more active against MRSA and enterococci (MIC_{90}, 0.25 and 0.12 mg/L, respectively) as compared to linezolid (MIC_{90}, 2 mg/L) and quinupristin/dalfopristin (MIC_{90}, 0.5 and 2–4 mg/L, respectively).

Similarly, tigecycline MIC_{90} values for *Streptococcus pneumoniae* ranged from 0.06 mg/L to 0.5 mg/L.

The penicillin-resistant *S. pneumoniae* isolates also were highly susceptible to tigecycline (MIC_{90} range of 0.06–0.5 mg/L) (20–22, 27–28). Representative study published by Darabi et al. (29) showed that 98.4% of *S. pneumoniae* isolates were inhibited by tigecycline at the concentration of <0.12 mg/L, whereas 100% of penicillin-resistant *S. pneumoniae* were inhibited by this concentration.

Tigecycline susceptibility breakpoints for *Enterobacteriaceae*, defined by FDA and EUCAST, are 2 mg/L and 1 mg/L, respectively (1, 23). Numerous studies identified clinical *Escherichia coli* isolates as being the most tigecycline-susceptible among *Enterobacteriaceae*. Thus, tigecycline MIC_{90} for *E. coli* ranged from 0.25 mg/L to 0.5 mg/L including ESBL-producing strains (20–22, 28). Of ESBL-producers, 98.3% to 100% were found to be tigecycline-susceptible according to numerous studies (20–22, 28).

Tigecycline susceptibility breakpoint for most of *Klebsiella* spp., *Enterobacter* spp., *Serratia* spp. was MIC_{90} ⩽2 mg/L including ESBL-positive *K. pneumoniae* (20–22, 28).

Recent studies show, however, that some *E. cloacae*, *K. pneumoniae*, *S. marcescens* clinical isolates exhibit reduced susceptibility to tigecycline showing MIC_{90} of 4–8 mg/L (30). Emergence of *Enterobacteriaceae* strains with lowered susceptibility to tigecycline appears to be related to the constitutive expression of multidrug efflux systems (31–32).

Among gram-negative non-*Enterobacteriaceae*, *M. catarrhalis* (MIC_{90}, 0.5 mg/L), *S. maltophilla* (MIC_{90}, 2mg/L) (4), and *A. baumannii* (MIC_{90}, 1–2 mg/L) isolates demonstrated the highest susceptibility to tigecycline (20–22, 28). Tigecycline MIC_{90} values for *A. baumannii* were reported to be lowest of all antimicrobials tested including carbapenems (22, 28).

Tigecycline exhibited good activity in vitro against anaerobic species isolated from clinical samples. *Clostridium* spp., *Eubacterium lentum*, *Fusobacterium nucleatum*, *Peptostreptococcus micros*, *Porphyromonas* spp., *Prevotella* spp., *Propionibacterium acnes*, *Veillonella* spp. showed MIC_{90} ranging from 0.12 to 0.5 mg/L (33). Among anaerobes, *Bacteroides fragilis* and *Bacteroides fragilis* species exhibited the highest MIC_{90} values of 1–8 and 2–16 mg/L, respectively (34).

Tigecycline was shown to be potent antimicrobial in vitro against atypical pathogens such as *Mycoplasma pneumoniae*, *Legionella* spp., *Mycoplasma hominis, Chlamydia pneumoniae*, *Chlamydia trachomatis*, non-tuberculosis strains of *Mycobacterium* (reviewed in 3).

There is a group of pathogens, however, which exhibit reduced in vitro susceptibility to tigecycline. Thus, *P. aeruginosa* clinical isolates display high MIC_{90} values of 16 to ⩾32 mg/L; *P. mirabilis* and indole-positive *Proteeae* (*Proteus* spp., *Morganella* spp., *Providencia* spp.) show MIC_{90} of 2–8 mg/L (4, 20–22, 27–30, 35).

Tigecycline antibacterial activity in vivo, clinical use, pharmacodynamic and pharmacokinetic aspects

Clinical efficiency of tigecycline in the treatment of adult complicated skin and skin-structure infections and complicated intra-abdominal infections has been evaluated in several Phase 3, multicentered, randomized, double-blind studies (36–39). The clinical cure rates for tigecycline monotherapy were found to be similar to that of vancomycin-aztreonam combination for the treatment of cSSSIs (most of them were extensive cellulitis or surgery-requiring soft tissue infection), where methicillin-sensitive *Staphylococcus aureus* (MSSA) (cure rates, 88.8% and 90.8%, respectively) and MRSA were dominating pathogens (cure rates, 78.1% and 75.8%, respectively) (38). Similarly, tigecycline (585 patients) has been demonstrated to be noninferior to the imipenem-cilastatin combination (607 patients) for the treatment of cIAIs, 50% of which were complicated by appendicitis and 14% complicated by cholecystitis (39).

Tigecycline has been also evaluated in Phase 3, open-label, noncomparative study in the treatment of patients with selected serious infections caused by resistant gram-negative microbes (*Enterobacter* spp., *Acinetobacter baumannii*, *Klebsiella pneumoniae*). The clinical indications included cSSSIs, cIAIs, CABP, health care-associated pneumonia (HCAP) including ventilator-associated pneumonia (VAP), and bacteremia including catheter-related pneumonia (40).

Demonstration of the effectiveness and safety of tigecycline led to its approval by the FDA in 2005 for treatment of adult cSSSIs and cIAIs (Fig. 2). One year later, tigecycline was approved by the European Medicines Evaluation Agency (EMEA) for the same indications (2).

Several Phase 3 studies, in which tigecycline was compared with levofloxacin, as well as noncomparative clinical studies involving patients with CABP have also demonstrated drug efficacy (41–43). In 2009, tigecycline was approved by the U.S. FDA for treatment of CABP (Fig. 2) (44).

Based on the results of clinical studies, tigecycline is suggested as a suitable antimicrobial for the empirical monotherapy in the case of polymicrobial infections and where multidrug-resistant pathogens are involved (1).

Tigecycline (Tygacil) is administered intravenously (1). The recommended adult dose of tigecycline is 100 mg as a loading dose, then followed

by the doses of 50 mg every 12 hours. The recommended duration of the therapy is 5–14 days. Tigecycline has long terminal half life ($t_{1/2}$) yielding 42 hours and 27 hours after infusion of multiple 50-mg doses every 12 hours and a single 100-mg drug dose, respectively (45). Tigecycline exhibits high volume distribution ranging from 7.2 to 8.6 L/kg either after administration of a single dose or at multiple doses. It has excellent tissue penetration, and it was found to be distributed in various tissues (lungs, liver, heart, skin, meninges, bone) and body fluids of animals and humans. While highly potent for treatment of deeply infected tissues, tigecycline exhibits relatively low maximum plasma concentrations (C_{max}) of 0.8–1 mg/L (45). This raises some concerns about drug use for treatment of bloodstream infections caused by microorganisms with MIC values of $\geqslant$1 mg/L for tigecycline.

Tigecycline does not undergo extensive metabolism, and its major route of elimination is via biliary or fecal excretion as an unchanged drug. The secondary, albeit minor routes of elimination, are renal excretion and liver glucuronidation (45).

According to the reports from clinical trials, tigecycline was generally good tolerated. The major adverse effects reported were reversible nausea, diarrhea, vomiting at the initial phase (days 1–2) of administration (1).

Development of resistance to tigecycline

Recent reports on the results of surveillance trials show that tigecycline remained active against gram-positive and gram-negative bacteria since its introduction in 2005, whereas the proportion of strains resistant to its comparators, such as vancomycin-resistant *E. faecium*, fluoroquinolone and broad-spectrum β-lactam-resistant *Enterobacteriaceae*, has increased during the same period (46).

Nevertheless, the cases of emergence of tigecycline resistance in usually susceptible clinical bacterial isolates must be carefully examined as well as potential molecular mechanisms of such resistance investigated. Of concern is the recent report on the isolation of clinical tigecycline-resistant *E. faecalis* strain from the catheter urine sample of the patient who underwent intra-abdominal surgery and had treatment course with several antibiotics including tigecycline (44) (Fig. 2). The *E. faecalis* isolate showed MICs of 2 mg/L and 1 mg/L as determined by the Etest and microdilution methods, whereas MIC values for susceptible *E. faecalis* strain were 0.047 mg/L and 0.125 mg/L, respectively. Search for the mechanism, responsible for the reduced tigecycline susceptibility of *E. faecalis* isolate including altered expression of efflux pumps, tigecycline-modifying *tetX* gene (see below), 16S rRNA mutations, however, did not reveal possible target sites (44).

As it has been mentioned above, the most common basis of intrinsic tigecycline resistance observed in *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Morganella morganii* species is drug recognition and efflux by RND family transporters, which typically confer multidrug-resistant phenotype. Thus, up-regulation of the family members, efflux pumps AcrAB and MexAB-OprM, was demonstrated in clinical *Morganella morganii* and *Proteus mirabilis* strains with reduced tigecycline susceptibility (17–18). Overexpression of RND family members, *acrAB* and *acrEF*, has been already reported in clinical *E. coli*, *K. pneumoniae*, *E. cloacae* isolates with decreased susceptibility to tigecycline (31–32, 46, 47). In addition to this list, there are two tigecycline-resistant bloodstream *A. baumannii* isolates (MICs of 4 and 16 mg/L for tigecycline, respectively) recovered from patients who received tigecycline (Fig. 2). AdeABC transporter has been proposed to mediate drug resistance in these isolates (48). Notably, several other cases of tigecycline-resistant *A. baumannii* clinical isolates recovered from patients receiving treatment with tigecycline have been reported (49–50). In some cases, however, a rapid development of tigecycline resistance of this highly adaptable pathogen has been monitored. These observations, along with several earlier studies starting 2006, where the isolation of tigecycline-nonsusceptible MDR (including carbapenem-resistant) *A. baumannii* clinical strains is reported (see for review 50), alert the activity of tigecycline against *A. baumannii* might be limited at least for some clinical indications, e.g., bloodstream infections, where subtherapeutic levels of tigecycline might rapidly select resistance.

The most likely pathway of up-regulation of transporters in glycylcycline-susceptible bacteria is via mutations in genes coding either for protein regulators or protein components of efflux pumps. This was early demonstrated in two veterinary *Salmonella* spp. as well as in vitro generated laboratory strains with reduced susceptibility to glycylcyclines, which harbored mutations in efflux pump components TetA and TetB, respectively (51). As the rate of mutations was low and they only slightly decreased susceptibility of mutant strains to glycylcyclines, the minor role of such mutations in the development of resistance in clinical bacterial strains has been proposed. Nevertheless, more recently, mutations in *marA* and *ramA* genes, coding for transcription regulators and resulting in the overexpression of RND transporters, have been found to be responsible for decreased susceptibility of *E. coli* and *E. cloacae* clinical isolates to tigecycline (32, 47). Overexpression of *ramA* gene coding for a positive regulator of AcrAB in clinical *K. pneumoniae* isolates with reduced susceptibility to tigecycline has been recently linked to inactivating mutations in another gene,

homologous to *Salmonella* regulatory gene *ramR*, which is observed in tigecycline-resistant *Salmonella* strains (52). Authors propose that acquisition of mutations in *ramR* could lead to development of tigecycline-resistant phenotype through intermediate phenotypes (52).

Mutations in genes coding for transporters other than RND type, at least in part, were found to be responsible for elevated tigecycline MICs as it has been demonstrated by the selection of resistant MRSA mutants through the serial passage on the increasing concentrations of tigecycline. Subsequent transcription profiling has detected overexpression of *mepA* gene, coding for a novel single protein efflux pump belonging to multidrug and toxin extrusion (MATE) family (53).

At present, there is no evidence on the mutations of genes, coding for ribosome protection proteins of *tet* family (TetM, TetO, TetS), to be responsible for the reduced susceptibility to tigecycline. Overexpression of TetM protein, commonly observed in tetracycline-resistant strains, was not sufficient to render laboratory *S. aureus* strains to become tigecycline resistant (53).

Another known tetracycline-resistance mechanism based on the drug inactivation by modification enzyme TetX has been shown to be active in vitro using tigecycline as a substrate (54). Flavin-dependent monooxygenase TetX efficiently hydroxylates tetracycline and its derivatives at carbon 11 (Fig. 1), and an equivalent modification has been demonstrated for tigecycline (54). It has been proposed that modification results in a weakened ability of tetracycline to coordinate magnesium, which is critical for drug binding to the ribosome. The introduction of *tetX* copy into *E. coli* resulted in much smaller increase in tigecycline MICs as compared to other tetracyclines indicating that the effect of TetX-mediated cellular tigecycline modification is possibly still outcompeted by higher ribosome affinity of tigecycline leading to translation inhibition (54). So far, no tetracycline-resistant clinical isolates, harboring *tetX* gene, have been reported. Nevertheless, the shown susceptibility of tigecycline to enzyme-based modification extends the spectrum of possible mechanisms of resistance to glycylcycline, which might occur in vivo.

Knowing the enormous adaptability of microorganisms including the potency to develop antibiotic resistance, it is unlikely to expect it to be escaped with tigecycline, e.g. through further development pre-existing mechanisms of tetracycline resistance and/or acquiring new ones. The prudent use of tigecycline for therapeutic application hopefully will preserve its effectiveness against clinically important multidrug-resistant pathogens.

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Tigeciklinas. Kokio veiksmingumo ginklas kovoje su antibiotikams atspariomis bakterijomis?

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Raktažodžiai: tigeciklinas, veikimo mechanizmas, aktyvumas *in vitro* ir *in vivo,* atsparumas.

Santrauka. Tigeciklinas yra pusiau sintetinis tetraciklinų analogas, priskiriamas naujai glicilciklinų antibiotikų klasei, neseniai patvirtintas tam tikrų indikacijų infekcijoms gydyti JAV ir Europos Sąjungoje. Antibiotikas yra veiksmingas prieš daugelį gramneigiamų ir gramteigiamų bakterijų, tarp jų – prieš plintančius visuomenės ir hospitalinių infekcijų sukėlėjus, pasižyminčius dauginiu atsparumu antibiotikams. Tikslus tigeciklino molekulinis veikimo mechanizmas nepakankamai ištirtas. Manoma, kad tigeciklinas prisijungia prie bakterijų ribosomų 30S subvieneto toje pačioje prisijungimo vietoje kaip tetraciklinas ir slopina baltymų biosintezės (transliacijos) eigą, neleisdamas reakcijos substratui – aminoacil-tRNR tiksliai išsidėstyti ribosomos A centre peptidiniam ryšiui sudaryti. Pabrėžtina, kad tigeciklinas pasižymi gebėjimu prisijungti prie ribosomų ir yra aktyvus bakterijose, turinčiose gerai žinomus ir plačiai paplitusius atsparumo tetraciklinui molekulinius mechanizmus: apsauginius ribosomos baltymus, pašalinančius tetracikliną iš ribosomų, bei baltyminius siurblius, šalinančius tetracikliną iš ląstelių. Apžvalgoje apibendrinama naujausia informacija apie tigeciklino veikimo mechanizmą, vartojimą klinikoje, diskutuojama apie galimus atsparumo tigeciklinui atsiradimo kelius.

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