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LOOKING FOR NEW PREPARATIONS FOR ANTIBACTERIAL THERAPY IV. NEW ANTIMICROBIAL AGENTS FROM THE AMINOGLYCOSIDE, MACROLIDE AND TETRACYCLINE GROUPS IN CLINICAL TRIALS

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ABSTRACT

This paper is the fourth in a series on the search for new antibacterial therapies, and covers new compounds belonging to the aminoglycoside, macrolide and tetracycline groups of antibiotics.
The article describes eight new substances at the clinical trial stage of development. One of them is an aminoglycoside (plazomicin), four are macrolides, collectively known as ketolides (cethromycin, solithromycin, EDP-420 and EDP-788), and the remaining three are members of the tetracycline group (omadacycline, eravacycline, sarecycline). Despite the long-term and very expensive process of collecting documentation proving the efficacy of antimicrobial drugs, there is a possibility, that particular compounds find use as active ingredients of medicinal products allowing for the triumph over the clinically relevant, dangerous bacteria.

Keywords: *novel antibiotics, aminoglycosides, macrolides, tetracyclines*

The present article is a continuation of the series "Looking for new preparations for antibacterial therapy," discussing compounds introduced for the treatment of bacterial diseases in the twenty-first century, including those at the stage of clinical trials. The first part discusses new antibiotics and chemotherapeutics that have received marketing authorization (1), the second part of the series presents a group of β-lactam antibiotics and β-lactamase inhibitors at the stage of clinical trials (2), while the third part deals with new chemotherapeutic agents from the quinolone and fluoroquinolone groups and also describes hybrid compounds containing quinolone as part of their molecular structure (3). This section presents new antibacterial compounds belonging to the aminoglycoside, macrolide and tetracycline groups. Official registers and a database of clinical trials were used as the primary sources of information on the various phases of clinical trials of compounds described below (4).

NEW AMINOGLYCOSIDE COMPOUNDS

Along with the fluoroquinolones and β-lactams, aminoglycosides are a major group of antibiotics used to treat infections caused by Gram-negative bacteria. Despite bactericidal properties, a wide range of activity and synergism with other antibiotics, their position is not dominant, because of their potential adverse effects, such as ototoxicity, nephrotoxicity, cellular toxicity or neuromuscular blockade. There are three major bacterial resistance mechanisms toward the aminoglycoside group: (i) formation of enzymes that modify the antibiotic's structure (AMEs, *aminoglycoside-modifying enzymes*); (ii) reduction of the affinity of the 30S ribosomal subunit for its binding site by methyltransferase synthesis and (iii) disruption of the active transport mechanism for antibiotic transport into cells by changes in the permeability of the outer membrane or reduced activity of porin channels.

There have been no new aminoglycoside antibiotics over the past 10 years; however, plazomicin has now reached the clinical trial stage.

Plazomicin (ACHN-490, Achaogen) is considered the first representative of a new generation of aminoglycosides, the so-called neoglycosides. It is a semisynthetic derivative of sisomicin, an antimicrobial antibiotic with anticancer activity (5). The structural modifications introduced in plazomicin provide protection against a plethora of AMEs. It lacks the 3'- and

4'- hydroxyl groups, protecting it from the O-phosphotransferase APH(3') and O-nucleotidyltransferase ANT(4'); enzymes that generate resistance to amikacin. The hydroxyethyl substituent at the 6' position blocks N-acetyltransferase AAC(6'). Additionally, the introduction of the 4-amino-2-hydroxybutanoic acid (HABA) at the C-1 amino position provides protection from the AAC(3), ANT(2") and APH(2") AMEs (5). The one known enzyme that does decrease the activity of plazomicin is AAC(2')-I, produced by *Providencia stuartii* strains. Fortunately, the gene encoding this enzyme has not been transferred to other species of microorganisms (5).

Plazomicin activity remains unchanged regardless of the presence of AMEs produced by *Staphylococcus*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and family of *Enterobacteriaceae*. The lowest concentration of the antimicrobial agent inhibiting visible growth of 90% of microbial strains (MIC_{90}, *Minimal Inhibitory Concentration)* is less than 2 μg/mL against *Escherichia coli*, serine carbapenemases producing *Klebsiella pneumoniae*, multi-drug resistant (MDR) *Enterobacteriaceae* that produces metallo-β-lactamases, microorganisms from the *Acinetobacter* species and *Staphylococcus aureus* including strains resistant to methicillin (MRSA, methicillin-resistant *S. aureus*) (6). Plazomicin is resistant to the extended-spectrum β-lactamases (ESβL), chromosomal or plasmidic AmpC cephalosporinases, serine carbapenemases, and metallo-β-lactamases, as well as KPC carbapenemases (*Klebsiella pneumoniae* carbapenemases), which makes it an important alternative to carbapenems (5). However, its activity is considerably decreased by the strains producing NDM-1 metallo-β-lactamases (New Delhi metallo-β-lactamase 1) (7).

The combination of plazomicin with daptomycin is very favourable; the combination showed a greater than 2 $\log_{10}$ decrease in CFU/mL as compared with its most active constituent after 24 h. Plazomicin is effective against 46 of the 47 staphylococci strains, including MRSA and vancomycin-resistant *S. aureus*, which greatly broadens the spectrum of its activity (8). Moreover, plazomicin exhibits *in vivo* activity in a murine model of sepsis and neutropenia, demonstrating a linear concentration-dependent pharmacokinetic profile, characterized by an elimination-phase half-life of 3.4 and a volume of distribution at steady state of 0.22 L/kg (9).

Four stages of phase I clinical trials evaluating the safety, pharmacokinetics and tolerability of parenterally administered plazomicin in healthy volunteers and renally impaired subjects have been completed. In addition, both single and multiple dose safety studies evaluating the pharmacokinetics, lung penetration and the effect on QT/QTc interval of plazomicin, in a concentration range of 1 to 15 mg/kg, for up to 10 days have been completed (4). A phase II clinical trial on the safety, efficacy and pharmacokinetics of the compound in patients with complicated urinary tract infection and acute pyelonephritis was completed in April 2012. The phase III clinical trials assessing the efficacy of plazomicin compared with colistin in patients with bacteraemia or hospital acquired pneumonia due to carbapenem-resistant *Enterobacteriaceae* is currently recruiting participants. The number of observed adverse effects is relatively low. There have been no incidents of ototoxicity or nephrotoxicity during phase I and II clinical trials, only rare cases of tinnitus (9).

NEW MACROLIDE COMPOUNDS

Macrolides are a group of compounds composed of a large lactone ring, containing 14, 15 or 16 carbons, combined with a sugar molecule, usually cladinose and the aminosugar desosamine. The mechanism of action of macrolides is inhibition of mRNA translation and bacterial protein biosynthesis by reversible binding to peptidyltransferase within the 50S ribosome subunit. Macrolides exhibit activity especially against the Gram-positive cocci, staphylococci and streptococci, as well as intracellular pathogens from *Mycoplasma*, *Legionella* and *Chlamydia* species. One of the characteristic features of this group is a relatively simple and quick increase in resistance, which is usually crossover-resistance, particularly for the 14- and 15-membered compounds, and probably results from the widespread use of macrolides as first-line drugs in antibacterial therapy. The following mechanisms of resistance to macrolides were observed: (i) a constitutive or induced cross-resistance to all macrolides, lincosamides and streptogramin B (MLS_B resistance) involving the methylation of the ribosomal binding site by an *erythromycin resistance methylase* (*erm*) gene; (ii) efflux pump systems associated with the presence of membrane proteins, such as transporters type ABC (*ATP binding cassette*) occurring in staphylococci and pump systems type MFS (*major facilitator superfamily*) responsible for the resistance of *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae* and other streptococci and enterococci; (iii) enzymatic inactivation of macrolides by enzymes, including esterase, phosphotransferase and macrolide glycosyltransferase (10).

Ketolides are a group of compounds with a mechanism of action that is similar to the macrolides; however, they possess a spectrum of antibacterial activity extending to macrolide-resistant microorganisms. Regarding their chemical structure, ketolides contain a ketone group in place of the cladinose at the C-3 position and

also incorporate a carbamate side ring at C-11 and C-12. The undoubted advantage of this group is efficacy against macrolide-resistant bacteria. Ketolides do not induce MLS_B-resistance and are not removed from the cell by efflux pump systems.

Telithromycin is the only ketolide approved for the treatment (Ketek, tablets, Sanofi) by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA). Two of the three indications for use, acute bacterial sinusitis and acute exacerbations of chronic bronchitis, were withdrawn by the FDA in 2007 as a result of improper clinical trials (11). A compound with a slightly different structure, fidaxomicin, belonging to the macrocyclic group of antibiotics, was approved by the FDA and the EMA in 2011 (Dificlir, tablets, Astellas Pharma) for the treatment of diarrhoea caused by *Clostridium difficile* (1). Four new ketolides, cethromycin, solithromycin EDP-420 and EDP-788 (temporary names), are at the stage of clinical trials.

Cethromycin (ABT-773; Advanced Life Sciences) possesses antibacterial activity and a mechanism of action similar to telithromycin, but is distinguished by its favourable safety profile. It is a 3-keto-11,12-carbamic derivative of erythromycin A with a quinoline moiety attached in the O-6 position by an allyl group. Cethromycin exhibits better activity than the macrolides and fourth generation fluoroquinolones against streptococci and staphylococci, with regard to *S. pneumoniae* strains resistant to penicillin and macrolides, and *S. pyogenes* that produce methylase and possess an efflux system (12). Thanks to its antibacterial activity against *Bacillus anthracis* (13), cethromycin received orphan drug designation for the treatment of anthrax in 2007 (Restanza). The efficacy of this compound is similar to azithromycin, but it is better than erythromycin and clarithromycin against Gram-negative respiratory pathogens, including *Haemophilus influenzae* isolates producing β-lactamase and *Moraxella catarrhalis*. Thanks to its activity against *Francisella tularensis* and *Yersinia pestis*, cethromycin obtained orphan drug status for the treatment of tularemia and plague in 2009 (14).

Cethromycin exhibits a non-linear pharmacokinetic profile. Its maximum plasma concentration is reached two hours after oral administration and steady-state level is attained after four days of treatment. Cethromycin achieves high concentrations in respiratory tissues. Concentrations in bronchial mucosa, follicular fluid and alveolar macrophages are significantly higher than in plasma. As a result, the compound is intended for use in the treatment of respiratory tract infections. The compound is metabolized in the liver and excreted primarily in the faeces; 7% of the administered dose is eliminated in the urine, of which 90% is unchanged (15). The half-life of cethromycin is 4.8–5.0 hours. The advantage of cethromycin over telithromycin is the lack of hepatotoxicity.

Two stages of phase III clinical trials evaluating the safety and efficacy of cethromycin compared with clarithromycin for the treatment of mild to moderate community-acquired pneumonia have been completed (4). The compound was administered orally at a dose of 300 mg, once a day for seven days. During the study, there were no clinically significant adverse effects. The FDA refused to approve cethromycin in 2009 for the above indications and requested more data confirming the efficacy of the compound. After receiving this response, Advanced Life Sciences suspended its operations due to loss of liquidity. The patent for cethromycin expires in 2016 (16).

Solithromycin (CEM-101, OP-1068; Cempra Pharmaceuticals) is the first ketolide possessing fluorine in the lactone ring. The molecule possesses an 11,12-carbamate-butyl-[1,2,3]-triazolyl-aminophenyl side chain. The compound exhibits *in vitro* antimicrobial activity primarily against microorganisms responsible for acquired pneumonia: *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, methicillin-sensitive *S. aureus*. Its MIC_{90} values are equal to 0.03 μg/mL, 2 μg/mL, 0.12 μg/mL and 0.06 μg/mL for the previously stated pathogens, respectively. The disadvantage of solithromycin is its lack of efficacy against all strains of *S. aureus*, particularly those that demonstrate constitutive MLS_B resistance (17). Like cethromycin, telithromycin and other 16-ring macrolides, solithromycin is a weak inducer of resistance type MLS_B, so its use in the treatment of staphylococcal infections allows the selective assessment of constitutively expressed *erm* methyltransferase genes (18,19). Solithromycin demonstrates antimicrobial efficacy against cocci, β-hemolytic streptococci resistant to telithromycin and *Neisseria gonorrhoeae*, including strains resistant to azithromycin. Like telithromycin, but in a concentration at least 10-fold higher, solithromycin causes abnormal visual disorders and exacerbates the symptoms of myasthenia gravis (20). The half-life of the compound is 5.1–6.5 hours after a single oral dose of 400–800 mg.

Phase I clinical trials evaluating the pharmacokinetics and safety of solithromycin as an adjunctive therapy in the treatment of infections in adolescents aged 12–17 years was completed in September of 2014. The compound proved to be safe, even at a dose of 1600 mg. Furthermore, Cempra Pharmaceuticals completed two stages of phase II clinical trials, the first concerning the efficacy and safety of solithromycin compared with levofloxacin in patients with community-acquired pneumonia. The second stage covered the treatment of gonorrhoea in males and females. Cempra Pharmaceuticals is currently recruiting participants for a phase III clinical trial assessing the efficacy and safety of oral

solithromycin compared to intramuscular ceftriaxone plus oral azithromycin in the treatment of patients with gonorrhoea.

A phase III clinical trial of solithromycin compared with moxifloxacin in the treatment of adults with community-acquired bacterial pneumonia was completed at the end of 2014. To date, all solithromycin clinical trials used an oral dosage form; however, participants currently are being recruited to the next phase III study that will examine both oral and intravenous administration. The National Institute of Allergy and Infectious Diseases (NDAID) began recruiting participants for a phase I clinical trial evaluating blood, genitourinary and pharyngeal pharmacokinetics of solithromycin at a dose of 1000 mg orally. Cempra Pharmaceuticals also is recruiting for a phase I study assessing the pharmacokinetics and safety of the compound in children and adolescents ages 0–17 years. A study on the development of both intravenous and oral dosage forms intended for children is underway (20).

Entanta Pharmaceuticals is developing a new subclass of macrolide antibiotics, the bicyclolides. They are bicyclic macrolides with a bridging moiety usually consisting of three carbon atoms. Two compounds represented by the acronyms **EDP-420** and **EDP-788** were patented. Due to the structural modification consisting of the introduction of a heteroaryl oxime with a bridge at the C-6 and C-11 position of the lactone ring and conversion of the 9-keto group into an acetylamino, the first compound, EDP-420, acquired acid stability. The spectrum of antimicrobial activity is comparable to telithromycin and cethromycin; the compound is effective against multi-drug resistant strains of *S. pneumoniae,* including pathogens resistant to penicillin G and erythromycin. Currently, a phase II clinical trial for the efficacy, safety and tolerability of EDP-420 in comparison with telithromycin for the treatment of community-acquired bacterial pneumonia is ongoing (4).

Phase I clinical trials evaluating the efficacy, safety and tolerability of EDP-788 after administration of a single oral dose in healthy adult volunteers was completed in September of 2014. A study evaluating multiple oral doses will begin soon. Compound EDP-788 (prodrug EDP-322) shows efficacy mostly against Gram-positive strains with regard to MRSA (21). Its spectrum of antimicrobial activity also includes the macrolide-resistant isolates of *S. pneumoniae* and *S. pyogenes*.

NEW TETRACYCLINE COMPOUNDS

Tetracyclines are a group of antibiotics that gained very wide use after their introduction to the market in the 1950s, because of their range of activity. They lost their potential as a result of widespread usage and advertising encouraging their application without any restrictions. Early in the 1960s, information appeared about the rise of bacterial resistance to tetracyclines. Twenty years later, tetracycline resistance of Gram-positive pathogens causing respiratory tract infections reached 70% (22). Widespread use of tetracyclines, not only in human therapy, but also in veterinary medicine for rapid stimulation of animal weight gain, also contributed to this situation (23). The mechanism of action of tetracyclines is based on binding to the 30S ribosomal subunit and blocking the connection of aminoacyl-tRNA to the acceptor. In this way it prevents introduction of new amino acids to the nascent peptide chain, and promotes a bacteriostatic effect.

Several mechanisms of bacterial resistance to tetracyclines have been identified. The most common type is mediated by an active efflux pump system associated with the presence of membrane transporters type MFS, the next type, though considerably less common, involved protection of the ribosome binding site. In very rare cases, tetracycline resistance involves the existence of antibiotic inactivating enzymes. The genes *tet(M)* and *tet(O)* are responsible for the ribosomal protection mechanism, while chromosomal determinants of the system efflux are encoded by a family of genotypes, in particular, *tet(A)* and *tet(B)* for Gram-negative bacteria and *tet(K)* and *tet(L)* for Gram-positive bacteria (24). Tigecycline belongs to a new group of glycylcycline antibiotics, which is the third generation of tetracyclines introduced to the market (Tygacil, powder for solution for infusion, Wyeth Europe Ltd.) (1). Omadacycline, eravacycline and sarecycline are new members of this group and are at the clinical trial stage.

Omadacycline (PTK 0796, Paratek Pharmaceuticals) is a 9-aminomethylcycline, a semi-synthetic derivative of minocycline, possessing *in vitro* antibacterial activity against Gram-positive and Gram-negative bacteria, anaerobes and atypical pathogens. Furthermore, this compound demonstrates efficacy not only against strains resistant to tetracyclines, but also to other antibiotics such as methicillin, vancomycin, ciprofloxacin and erythromycin. The MIC_{90} values of omadacycline against MRSA, vancomycin-resistant enterococci (VRE), and β-hemolytic streptococci are 1 μg/mL, 0.25 μg/mL and 0.5 μg/mL, respectively, whereas against penicillin-resistant *Streptococcus pneumoniae* (PRSP) and *H. influenzae* the MIC_{90} values are equal to 0.25 μg/mL and 2 μg/mL (25). Omadacycline's broad spectrum of *in vitro* antibacterial activity has been confirmed *in vivo* in several infection models. The compound is effective regardless of the presence of mechanisms of resistance to tetracyclines, whether efflux systems or ribosomal protection determined by the presence of *tet(O)* genes. The efficacy of a single intravenous dose

of omadacycline against *S. pneumoniae*, *E. coli* and MRSA with *tet(M)* and *tet(K)* genes in a mouse model of intraperitoneal infection has been demonstrated. However, the compound does not exhibit activity against *P. aeruginosa* or *K. pneumoniae*.

The compound is available both intravenously and orally. It does not cause any adverse effects on the gastrointestinal tract, the most common ailment resulting from treatment with tetracyclines. Omadacycline binds strongly to plasma proteins in a concentration-dependent manner (minimum concentration = 0.1 μg/mL). This plasma-protein binding prolongs the half-life to 14 hours, resulting in a reduction of the daily dose, and thus has a positive effect on the safety profile (26).

Phase III clinical trials assessing the safety and efficacy of omadacycline compared with linezolid in the treatment of complicated skin and soft tissue infections were completed in May of 2010. Omadacycline was administered either orally at a dose of 150 mg, or intravenously at 100 mg. Paratek Pharmaceuticals started phase III clinical trials evaluating the safety and efficacy of the compound compared with linezolid in the treatment of acute bacterial skin and soft tissue infections in July 2015 (20). Both drugs were administered either by injection (omadacycline) or infusion (linezolid) and in tablet form. The intended date of completion of this phase is scheduled for October 2016.

Eravacycline (TP-434, Tetraphase Pharmaceuticals) is a fully synthetic compound that is distinguished from the rest of the tetracycline group by its unique structure. It contains two structural modifications of the D ring: a fluorine at the C-7 position and a pyrrolidinoacetamido group at the C-9 position, which ensure broad spectrum antibacterial activity. It is effective against multi-drug resistant aerobic and anaerobic Gram-positive and Gram-negative pathogens like *A. baumannii* (MIC_{90} = 2 μg/mL) and *Enterobacteriaceae*, along with *E. coli* (MIC_{90} = 0.5 μg/mL) and *K. pneumoniae* (MIC_{90} = 1 μg/mL) that produce β-lactamases with extended spectrum and resistant to carbapenems (27). Eravacycline does not exhibit activity against *P. aeruginosa* and *Burkholderia cenocepacia*. It was not observed to antagonise any other antibiotics effective against strains of these species. MIC_{90} values are below 0.12 μg/mL and 0.25 μg/mL against streptococci and MRSA. The biofilm of uropathogenic strains of *E. coli* also showed sensitivity to eravacycline (28). Its *in vitro* activity was also confirmed *in vivo* in several models of infection. Eravacycline demonstrates improved efficacy in comparison with linezolid in a mouse model of inflammation pneumonia caused by MRSA or MDR *S. pneumoniae* (29). Tetraphase Pharmaceuticals completed the four stages of phase I clinical trials for this compound. A phase I trial evaluating the safety and pharmacokinetics of this compound in patients who underwent bronchoscopy and bronchoalveolar lavage after receiving seven doses of 1.0 mg/kg i.v. TP-434 every 12 hours for four days was completed in April of 2013. A thorough phase I QT/QTc study to evaluate the effects of an intravenous infusion of eravacycline in comparison to moxifloxacin on cardiac repolarisation was completed in July 2013.

The last two stages of phase I clinical trials assessing the pharmacokinetics of the compound were completed in March and May 2014, and they included patients with impaired hepatic function and end stage renal disease, who were administered a dose of 1.5 mg/kg. Good tolerability and no serious adverse effects have been observed (30). Tetraphase Pharmaceuticals also has launched two stages of phase III clinical trials (4). The study on efficacy and safety of eravacycline compared with levofloxacin in complicated urinary tract infections is currently recruiting participants, whereas the second project will include ertapenem as a reference drug and therapy will involve patients with complicated intra-abdominal infections. All of the projects will use parenteral administration.

Sarecycline (WC-3035) is a compound that, compared with existing tetracyclines, exhibits superior antimicrobial properties, but a narrower spectrum of activity (31). It was developed through a collaboration between Paratek Pharmaceuticals and Actavis. Warner Chilcott completed phase II clinical trials evaluating safety and efficacy of sarecycline in 50 mg and 100 mg doses compared with placebo in the treatment of moderate to severe acne in April 2015. Recruitment for phase III clinical trials started in December of 2014 (4). Sarecycline is administered orally. The completion date is planned for November 2016. In addition, Paratek Pharmaceuticals indicates that sarecycline is also effective in the treatment of rosacea (32).

It is also worth mentioning the compound named **TP-271**. It is a fully synthetic fluorocycline possessing antibacterial activity *in vitro* and *in vivo* against MDR strains including respiratory isolates resistant to tetracyclines. TP-271 also is effective against the five isolates belonging to important biohazard agents: *Y. pestis*, *B. anthracis*, *F. tularensis*, *Burkholderia mallei* and *Burkholderia pseudomallei* (33). Tetraphase Pharmaceuticals announced that the compound is in the advanced preclinical stage and it is available in an oral and parenteral form (34).

CONCLUSIONS

Microorganism resistance to antibiotics and antimicrobial chemotherapeutics is spreading at an alarming rate and effects both the strains existing in a hospital and a community-acquired environment, thereby reducing

the arsenal of available medicinal products. This is a signal to search for and develop new effective compounds, which will become useful instruments in the fight against multidrug resistant isolates.

Independently of their classification, each compounds offers different advantages and disadvantages in regard to safety, pharmacokinetics profile and spectrum of activity. Among the discussed compounds, it is worthwhile to pay attention to plazomicin, which may be an important alternative to carbapenems and combined with other antibiotics it may have therapeutic success. However, the principle advantage of solithromycin is its safe pharmacokinetic profile that allows administration of the drug to children. Hopefully, thanks to its extremely broad spectrum of activity, efficacy, and a unique chemical structure, and despite the existing mechanisms of bacterial resistance, eravacycline will become a much better successor of the tetracycline group and its main representative, doxycycline.

Frequently, it is difficult to precisely verify information about new antibacterial agents at the stage of clinical trials due to limited access to information. All new compounds, regardless of which group of antibiotics they represent, are characterized by several superlatives on company websites. Therefore, it remains to be determined if the enthusiasm of pharmaceutical companies will prove to be justified.

REFERENCES

1. Karpiuk I, Tyski S. Looking for the new preparations for antibacterial therapy. I new antibiotics and chemotherapeutics on the market. Przegl Epidemiol 2012;66:567-73.
2. Karpiuk I, Tyski S. Looking for the new preparations for antibacterial therapy. II. Clinical trials; new β-lactam antibiotics and β-lactamase inhibitors. Przegl Epidemiol 2013;67:51-56.
3. Karpiuk I, Tyski S. Looking for the new preparations for antibacterial therapy. III. New antimicrobial agents from the quinolones group in clinical trials. Przegl Epidemiol 2013;67:455-460.
4. http://www.clinicaltrials.gov
5. Dougherty TJ, Pucci MJ. Antibiotic discovery and development. Springer Science+Business Media; 2012:244.
6. Armstrong ES, Miller GH. Combating evolution with intelligent design: the neoglycoside ACHN-490. Curr Opin Microbiol 2010;13:565-73.
7. Livermore DM, Mushtaq S, et al. Activity of aminoglycosides, including ACHN-490, against carbapenem-resistant Enterobacteriaceae isolates. J Antimicrob Chemother 2011;66:48-53.
8. Lin G, Ednie LM, et al. Antistaphylococcal activity of ACHN-490 tested alone and in combination with other agents by time-kill assay. Antimicrob Agents Chemother 2010;54:2258-61.
9. Cass RT, Brooks CD, et al. Pharmacokinetics and safety of single and multiple doses of ACHN-490 injection administered intravenously in healthy subjects. Antimicrob Agents Chemother 2011;55:5874-80.
10. Hryniewicz W, Mészáros J. Antybiotyki w profilaktyce i leczeniu zakażeń. Wyd. Lek. PZWL, Wyd. I, Warszawa 2001, 2002, str. 251.
11. FDA Safety Alerts For Human Medical Product http://www.fda.gov/downloads/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm154544.pdf
12. Shortridge VD, Zhong P, et al. Comparison of *in vitro* activities of ABT-773 and telithromycin against macrolide-susceptible and –resistant streptococci and staphylococci. Antimicrob Agents Chemother 2002;46:783-6.
13. Frean J, Klugman KP, et al. Susceptibility of *Bacillus anthracis* to eleven antimicrobial agents including novel fluoroquinolones and a ketolide. J Antimicrob Chemother 2003;52:297-9.
14. Mansour H, Chachine EB, et al. Cethromycin: a new ketolide antibiotic. New Drug Developments 2013;47:368-79.
15. Conte JE Jr, Golden JA, et al. Steady-state plasma and intrapulmonary pharmacokinetics and pharmacodynamics of cethromycin. Antimicrob Agents Chemother 2004;48:3508-15.
16. Cethromycin: A-195773, A-195773-0, A-1957730, Abbott-195773, ABT 773. Drugs R D 2007;8:95-102
17. Putnam SD, Sader HS, et al. Antimicrobial characterization of solithromycin (CEM-101), a novel fluoroketolide: activity against staphylococci and enterococci. Int J Antimicrob Agents 2011;37:39-45.
18. Schmitz FJ, Petridou J, et al. Molecular analysis of constitutively expressed *erm(C)* genes selected *in vitro* by incubation in the presence of the mininducers quinupristin, telithromycin, or ABT-773. Microb Drug Resist 2002;8:171-7.
19. Schmitz FJ, Petridou J, et al. Molecular characterization of ketolide-resistant *erm(A)* – carrying *Staphylococcus aureus* isolates selected *in vitro* by telithromycin, ABT-773, quinupristin and clindamycin. J Antimicrob Chemother 2002;49:611-17.
20. Sutcliffe J. Antibiotics in development targeting protein synthesis. Ann N Y Acad Sci 2011;1241:122-52.
21. Souza Mendez C, Souza Antunes AM. Pipeline of known chemical classes of antibiotics. Antibiotics 2013;2:500-34.
22. Garrod LP, Lambert HP, et al. Antybiotyko- i chemioterapia. PZWL, Warszawa 1983.
23. Heth DA, Bird HR. Growth response of chicks to antibiotics from 1950–1961. Poult Sci. 1962;41:755–60.
24. Chopra I, Roberts M. Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance. Microbiol Mol Biol Rev 2001;65:232-60.
25. Macone AB, Caruso BK, et al. *In vitro* and *in vivo* antibacterial activities of omadacycline, a novel aminomethylcycline. Antimicrob Agents Chemother 2014;58:1127-35.
26. Chaturvedi P, Esposito C, et al. *In vitro* assessment of plasma protein binding and metabolic stability of PTK

0796. Abstr. F-760 in Proceedings of the 43rd Annual ICAAC, September 14-17. Chicago, IL, Stany Zjednoczone.
27. Sutcliffe J, O'Brien W, et al. *In vitro* activity of fluorocycline TP-434 against panels of recent bacterial clinical isolates. Abstr. F1-2158 in Proceedings of the 50th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, September 12-15. Boston, MA, Stany Zjednoczone.
28. Grossman TH, O'Brien W, et al. Eravacycline (TP-434) is active *in vitro* against biofilms formed by uropathogenic *Escherichia coli*. Antimicrob Agents Chemother 2015;59:2446-9.
29. Murphy T, Slee A, et al. TP-434 is highly efficacious in animal models of infection, Abstr. F1-2161 in Proceedings of the 50th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, September 12-15. Boston, MA, Stany Zjednoczone.
30. Pucci MJ, Bush K. Investigational antimicrobial agents of 2013. Clin Microbiol Rev 2013;26:792-820.
31. http://www.paratekpharm.com/content/pipeline/sarecycline.htm
32. Paratek Pharmaceuticals, Late stage, "Best-in-class" antibiotics novel tetracycline chemistry. http://www.abingworth-advisory-board.com/perch/resources/presentations/paratek-presentation-24th-september-2014.pdf
33. Grossman T, Hunt D, et al. TP-271, a novel oral fluorocycline for community-acquried respiratory and biothreat pathogens. Abstr. F1-2156 in Proceedings of the 50th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, September 12-15, 2015. Boston, MA, Stany Zjednoczone.
34. http://tphase.com/pipeline/overview

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