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# LOOKING FOR THE NEW PREPARATIONS FOR ANTIBACTERIAL THERAPY III. NEW ANTIMICROBIAL AGENTS FROM THE QUINOLONES GROUP IN CLINICAL TRIALS

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## ABSTRACT

There is an essential need for searching for the new compounds effective in the treatment of infections caused by multidrug-resistant bacteria. This paper is the third part of a series associated with the exploration of new antibacterial agents and it discusses the compounds belonging to the group of quinolones and substances possessing a hybrid structure composed of the quinolone molecule and other compounds.
Eleven new substances at the stage of clinical trials are presented. Three of them belong to the group of non-fluorinated quinolone (nemonoxacin, ozenoxacin and KRP-AM1977X), while six are the quinolones containing fluorine atom at 6 position of the carbon atom in the quinoline ring (zabofloxacin, finafloxacin, delafloxacin, JNJ-Q2, WCK771 and KPI-10). The remaining two compounds possess a hybrid construction composed of the quinolone structure and other molecules (cadazolid and CBR-2092). There is a chance in the near future, that the presented compounds can extend the range of existing antibacterial drugs and provide an alternative to currently available medicinal products.

**Key words:** *novel antibiotics, quinolones, fluoroquinolones*

The presented article is a continuation of the series "Looking for the new preparations for antibacterial therapy", which discusses the new compounds introduced into the treatment of bacterial diseases in the twenty-first century, and those at the stage of clinical trials. The first part discusses the new antimicrobial agents that have received a marketing authorization (1), the second part of the series presents a group of new β-lactam antibiotics and β-lactamase inhibitors at the stage of clinical trials (2). This section presents new chemotherapeutic agents from the non-fluorinated quinolones group, fluoroquinolones and hybrid compounds containing molecule of quinolone in its structure. All of these compounds are currently at the stage of clinical trials.

## CHEMOTHERAPEUTICS FROM QUINOLONES GROUP

More than half a century has passed since the accidental invention of nalidixic acid, a by-product of the synthesis of the antimalarial drug - chloroquine and also the first representative of the group of quinolones (3). During this time, tens of thousands substances belonging to this group were synthesized, among them those possessing fluorine atom at the C-6 position exhibit the highest antibacterial activity. This modification caused the division of quinolones into four generations. The first generation consists of non-fluorinated compounds and the only fluoroquinolone - flumequine applicable in veterinary medicine. The next three generations possess fluorine atom, but they are differentiated by the spectrum of antibacterial activity. The second generation of quinolones is characterized by an increased activity against Gram-negative strains and atypical pathogens (*Mycoplasma pneumoniae*, *Legionella pneumophila* and Chlamydia), it is also effective against *Pseudomonas aeruginosa* and *Mycobacterium tuberculosis*. The third generation of fluoroquinolones has been used in the treatment of infections caused by Gram-positive bacteria, mainly streptococci and staphylococci, usually resistant to the second generation. The third generation of fluoroquinolones are more effective against atypical pathogens. Fourth generation of fluoroquinolones is characterized by an increased activity against anaerobic and atypical pathogens and also Gram-positive bacteria

(3). The quinolones effectiveness is caused by the presence of following groups: the carboxyl at C-3 position and the carbonyl at C-4, which are necessary to the transport of molecules into the bacteria cell, as well as to the formation of the complex of enzyme – DNA.

The quinolones are the only bactericidal group of compounds, whose mechanism of action involves the direct inhibition of the bacterial DNA synthesis. It occurs as a result of the inhibition of two bacterial enzymes: DNA gyrase (topoisomerase II) – responsible for negative helical supercoiling and DNA topoisomerase IV – separating nucleotide strands chain (4). Creation of an irreversible enzyme – DNA complex with chemotherapeutic causes the inhibition of the DNA replication process and rapid cell death. Despite the existence of two connection points, most quinolones has an affinity for only one of these enzymes. It is important that the recently synthesized fluoroquinolones (gemifloxacin and sitafloxacin) bind to both enzymes, making resistance difficult to increase.

There are several basic mechanisms of bacterial resistance to the chemotherapeutic agents from the quinolones group: i) mutations of genes encoding enzymes resulting in the loss of affinity of quinolone molecule to the enzyme connection point; ii) presence of membrane pumps systems actively removing the compound from the cell (efflux mechanism) (5), which can be activated by contact not only with the quinolone, but also with lipophilic compounds (eg. petroleum hydrocarbons), which indicates a significant contribution of environmental contamination to the development of this kind of resistance; iii) modification of the permeability of the outer membrane in Gram-negative bacteria by closing the porin channels.

Fluoroquinolones from the third and fourth generation form an effective treatment option with a wide spectrum of antimicrobial activity, favorable pharmacokinetics and large number of approved therapeutic indications. Nevertheless, it should be emphasized, that quinolones are used as a first-line drugs in exceptional clinical situations only (4,6). In general, quinolones are an alternative medicines, which can be used, when the applied therapy is ineffective or the use of first-line drugs is impossible or inadvisable.

Official registers and database of clinical trials were used as the main source of the information on the various phases of clinical trials of compounds described below (7).

## NEW COMPOUNDS FROM NON-FLUORINATED QUINOLONES GROUP

One non-fluorinated quinolone – garenoxacin (Japan - 2007) was introduced to the treatment over the past 10 years. Three new compounds: nemonoxacin, ozenoxacin and KRP-AM1977X are at the stage of clinical trials.

Nemonoxacin (TG-873870) exhibits a broad spectrum of antibacterial activity against Gram-positive bacteria, including penicillin-resistant and quinolone-resistant strains of *Streptococcus pneumoniae* (PRSP, *penicillin-resistant S. pneumoniae*), *Staphylococcus aureus* resistant to methicillin (MRSA, *methicillin-resistant S. aureus*) and registered quinolones and vancomycin-resistant enterococci (VRE). The lowest concentration of the antimicrobial agent inhibiting the visible growth of 90% microbial strains ($MIC_{90}$, *Minimal Inhibitory Concentration*) is 2 μg/mL against vancomycin-intermediate and vancomycin-resistant *S. aureus* (8). Nemonoxacin is also effective against the *Nocardia* sp. (9). The antibacterial activity of this compound is comparable to levofloxacin and moxifloxacin against Gram-negative rods. The advantage of nemonoxacin, when compared to other fluoroquinolones is reduced susceptibility to the development of resistance, because it requires no two, but three simultaneous mutations of different bacterial genes: *gyrA*, *gyrB* and *parC*. Chinese company TaiGen Biotechnology Co. Ltd. completed phase II of clinical trials for safety and efficacy of nemonoxacin in the treatment of diabetic foot infections. Currently, this chemotherapeutic agent is in the third phase of clinical trials in the treatment of community - acquired pneumonia (CAP). Based on the results of the study, it was found that nemonoxacin (at doses of 500 mg and 750 mg) administered orally, once daily displays the safety profile and efficacy comparable to the levofloxacin (500 mg) in the treatment of CAP.

Ozenoxacin (T-3912) is a chemotherapeutic agent possessing antibacterial activity against *S. aureus* isolates sensitive and resistant to methicillin and ofloxacin, *Staphylococcus epidermidis* including the strains resistant to ofloxacin, PRSP and *Propionibacterium acnes*. $MIC_{90}$ values against those pathogens are 4-16 000-fold lower in comparison to other fluoroquinolones such as nadifloxacin, ofloxacin, levofloxacin and antibiotics: clindamycin, erythromycin and gentamicin (10). According to the authors ozenoxacin is an effective quinolone for topical administration, which can be used to treat the complicated skin and soft-tissue infections and through its activity significantly reduce the time of treatment (10). What is essential, the mechanism of action of this chemotherapeutic compound is based on simultaneous affinity for both enzymes, DNA gyrase and topoisomerase IV. Ferrer Internacional S.A. conducts the phase III of clinical trials on efficacy and safety of ozenoxacin 1% cream versus placebo in the treatment of patients with non-bullous or bullous impetigo. The results of the phase II of the study revealed the efficacy, safety and tolerability of ozenoxacin in patients with

secondarily infected traumatic lesions. What is more, no photoallergic and phototoxic reactions or potential allergies have been observed.

The compound named KRP-AM1977X is a poorly understood substance with high efficacy against Gram-positive bacteria, including MRSA strains. The company Kyorin Pharmaceutical Co. Ltd. leads in Japan phase I of clinical trials on the application of this compound in oral administration. It is worth to mention, that the KRP-AM1977Y is an acronym determining the parenteral preparation formula, which is expected to be introduced into a phase I of clinical trials (11).

## NEW COMPOUNDS FROM FLUOROQUINOLONES

In the recent years seven compounds among the chemotherapeutic agents from fluoroquinolones group have received an approval for marketing authorization: balofloxacin (Korea - 2001), pazufloxacin (Japan - 2002), gemifloxacin (FDA - 2003) tosufloxacin (Japan - 2006 ), sitafloxacin (Japan - 2008), antofloxacin (China - 2009) and besifloxacin (FDA - 2009) (1). Currently, the following six compounds are undergoing clinical development: zabofloxacin, finafloxacin, delafloxacin, JNJ-Q2, WCK771 and KPI-10.

Antibacterial activity of zabofloxacin (DW-224a, PB-101) is higher in comparison with ciprofloxacin, moxifloxacin and gemifloxacin against Gram-positive strains, including MRSA, methicillin-resistant coagulase-negative staphylococci, *Streptococcus pyogenes* and *Enterococcus faecalis*. Particular efficacy against *S. pneumoniae* mostly isolated from patients with community-acquired pneumonia (16-fold greater than ciprofloxacin and moxifloxacin) should be noted. Although the zabofloxacin activity is a bit lower than the activity of other fluoroquinolones against microorganisms from the *Enterobacteriaceae* family, it still remains a very good efficacy against Gram-negative respiratory pathogens *Haemophilus influenzae* and *Moraxella catarrhalis* ($MIC_{90}$ = 0.008 μg/mL and 0.03 μg/mL) (12). The lowest concentration of the zabofloxacin inhibiting the visible growth of 50% microbial strains ($MIC_{50}$, *Minimal Inhibitory Concentration*) is 0.016 μg/mL against *Neisseria gonorrhoeae* and this is a value comparable to azithromycin, but 8-fold lower with respect to ciprofloxacin. Due to the double mechanism of binding of the molecule of zabofloxacin to the complex enzyme – DNA, the risk of development of bacterial resistance significantly decreases. The studies on the safety of DW-224a compound do not reveal any adverse effects on the central nervous system, cardiovascular system and respiratory system with the exception of possible impact on the prolonged QT interval in an electrocardiogram (13). Dong Wha Pharmaceutical Co. Ltd. conducts phase III of clinical trials evaluating the safety and efficacy of zabofloxacin (400 mg) following multiple oral administration in patients with acute bacterial exacerbations of chronic obstructive pulmonary disease. Unfortunately, the phase II of clinical trials led by IASO Pharma Inc. concerning the application of this compound in the treatment of community-acquired pneumonia with moderate intensity was suspended for financial reasons.

The feature that distinguishes finafloxacin (BAY35-3377) from other fluoroquinolones is a 4-8-fold increase in antibacterial activity at pH 6.0 compared to pH 7.4. Finafloxacin exhibits an optimum efficiency at acidic pH in the range 5.0-6.0. The MIC values in this pH range is 8-16-fold lower against *Escherichia coli* and *Klebsiella pneumoniae* strains, 4-8-fold lower against *S. aureus*, including MRSA and 2-4-fold lower against *Pseudomonas aeruginosa* in comparison to ciprofloxacin and levofloxacin (14). Finafloxacin causes also an effective eradication of *Helicobacter pylori* pathogens. The unique activity of this compound at low pH may contribute to its usage in the treatment of lesions located within the urinary tract, gastric mucosa or skin. It should be mentioned, that the efficiency of finafloxacin is also high against the sensitive and resistant to ciprofloxacin *Acinetobacter baumannii* strains causing opportunistic infections among hospitalized patients, especially those receiving intensive care (15). What is essential, during the study on the safety profile of this compound, any adverse reactions considered as typical for fluoroquinolones, such as electrocardiogram changes, neurotoxicity or hypoglycemia were not observed. In 2009, the Merlion Pharmaceuticals GmbH successfully completed two research projects at phase II of clinical trials. The first concerned an application of finafloxacin (400 mg) with amoxicillin (1000 mg) or esomeprazole (40 mg) in the treatment of *H. pylori* infections and the second project included an evaluation of the efficiency of finafloxacin (300 mg) in the treatment of uncomplicated urinary tract infections in the three-days therapy.

Delafloxacin (RX-3341, ABT-492) is a chemotherapeutic agent highly effective against Gram-positive bacteria, characterized by a weak acidic nature of the molecule. Due to this property, similar to finafloxacin, it can be successfully used for the treatment of *S. aureus* infections. It demonstrates a good tolerance in the acidic environment of pH 5.0-5.5 (16). The spectrum of antibacterial activity of delafloxacin includes sensitive and resistant to methicillin isolates of *S. aureus*. $MIC_{90}$ values are 0.008 μg/mL and 0.5 μg/mL respectively, which means that it is the one of the most efficient fluoroquinolones among those registered. Furthermore, *in vitro* studies indicate that delafloxacin is from 2 to 128-fold more effective against levofloxacin-resistant

strains of *S. pneumoniae* and *S. epidermidis* and from 4 to 16-fold more effective against ciprofloxacin-resistant isolates of *E. coli* and *K. pneumoniae*, in comparison to moxifloxacin, gemifloxacin and withdrawn form the market, due to toxicity: trovafloxacin and gatifloxacin. Unfortunately, delafloxacin does not have any activity against pathogens sensitive and resistant to registered quinolones: *Enterococcus faecium*, *E. faecalis*, *P. aeruginosa* and *Acinetobacter* genus (17). Rib-X Pharmaceuticals, Inc. completed phase II of clinical trials evaluating the usage of this compound in the treatment of acute bacterial skin and skin-structure infections (ABSSSI) in November 2011.

Compound named JNJ-Q2 (JNJ-32729463), as well as certain other fluoroquinolones, exhibits bactericidal activity against a broad spectrum of Gram-positive and Gram-negative bacteria. $MIC_{50}$ values are 0.008 μg/mL against methicillin-susceptible *S. aureus* and 0.12 μg/mL against MRSA. Pathogens were isolated from the patients with ABSSSI. The compound JNJ-Q2 shows a higher activity than moxifloxacin (16 times), levofloxacin and ciprofloxacin (at least 128 times) against *S. pneumoniae*. In case of Gram-negative bacteria, the values of $MIC_{50}$ for compound JNJ-Q2 are following: 0.004 μg/mL against *H. influenzae*, 0.015 μg/mL against *M. catarrhalis* (18) and 0.03 μg/mL against *N. gonorrhoeae* (19). As regards the mechanism of action of the compound JNJ-Q2, it also has an affinity for both enzymes at the same time, moreover preclinical studies have disclosed, it is not removed from the cells using efflux system. Phase II of clinical trials concerning the safety, efficacy and tolerance of JNJ-32729463 compound (250 mg) compared to linezolid in the treatment of patients with complicated skin and soft-tissue infections were completed in January 2011. However, phase II of clinical trials evaluating usage of this compound in the treatment of patients requiring hospitalization for community-acquired pneumonia were suspended. Insufficient number of participants included in the recruitment process was given as the official reason by marketing authorization holder; the proccess has no effect on the safety and efficacy of the product. Both projects involved the oral formula of the drug and were conducted by Furiex Pharmaceuticals, Inc.

The compound WCK771 is characterized by higher than registered fluoroquinolones, efficacy against resistant to methicillin and vancomycin strains of *S. aureus*, staphylococci resistant to currently available quinolones and anaerobic bacteria. $MIC_{50/90}$ values are 0.03 μg/mL and 1 μg/mL against hospital-acquired and community-acquired *S. aureus* isolates, respectively (20). In addition, the compound WCK771 exhibits *in vitro* and *in vivo* antibacterial activity similar to levofloxacin against *S. pneumoniae* sensitive to registered quinolones (21). Structurally, it exists as a hydrated salt of 2-amino-5-guanidinopentanoic acid (arginine) and the optical isomer *S* of nadifloxacin. Due to the fact, that the configuration *S* is primarily responsible for the antibacterial activity, WCK771 is 2 to 4-fold more effective than the racemic mixture of nadifloxacin. WCK771 in parenteral administration completed phase II of clinical trials for the treatment of MRSA infections led by Wockhardt Ltd. While, the compound described by acronym WCK2349 concerns an oral form of the this drug, which also completed phase II of clinical trials in the therapy of the same diseases like the previous form (22).

The compound KPI-10 (WQ-3813) is in the earliest stage of clinical trials among the other fluoroquinolones: phase I studies conducted by Kalidex Pharmaceuticals. As described compounds, the KPI-10 has an antibacterial activity against a broad spectrum of Gram-positive and Gram-negative bacteria including strains resistant to currently available chemotherapeutic agents from this group. Based on $MIC_{90}$ value analysis, it was observed that the compound is several times more effective against sensitive and resistant pathogens of *S. aureus*, *S. epidermidis*, *S. pneumoniae*, *S. pyogenes*, *Streptococcus agalactiae* and *E. faecalis*, but omitting *E. faecium* in comparison to levofloxacin, ciprofloxacin, moxifloxacin and gatifloxacin (23). KPI-10 also demonstrates improved efficacy against resistant to ciprofloxacin and penicillin *N. gonorrhoeae* strains *(*$MIC_{50/90}$ values = 0.06/0.12 μg/mL).

Kalidex Pharmaceuticals company informs about the excellent safety profile, favorable pharmacokinetics and efficacy of the compound KPI-10 in *in vivo* studies.

## ANTIBACTERIAL HYBRID COMPOUNDS CONTAINING THE QUINOLONE STRUCTURE

One of the recent achievements against multidrug-resistant bacteria is the development of hybrid chemotherapeutic agents, which consist of two compounds with different mechanisms of action, combined with each other.

Cadazolid (ACT-179811) is a hybrid of two pharmacophores from the oxazolidinones and quinolones group. A key element of the combination of these two pharmacophores was to ensure a proper combination of these structures, in order to obtain the optimum antimicrobial activity (24). The company Actelion Ltd. completed phase II of clinical trials concerning the efficacy and safety of the cadazolid in the therapy of *Clostridium difficile*-associated diarrhea in October 2012. The results of the study confirmed the good tolerance, efficacy and safety of twice daily administered oral formula of cadazolid.

The compound named CBR-2092 is a hybrid consisting of two pharmacophores from the rifamycins and quinolones group. It shows an antimicrobial activity of rifampicin due to the inhibition of RNA polymerase as well as an affinity for DNA gyrase and topoisomerase IV, so it is effective against strains resistant to rifampicin. Unfortunately, the CBR-2092 compound does not reveal any activity against pathogens resistant to currently available quinolones and also against Gram-negative bacteria (25). Based on the *in vivo* studies, 2M BioTech L.P. company leads phase I of clinical trials concerning the usage of this hybrid in the treatment of persistent staphylococcal infections. The probable reason for the lack of antibacterial activity of the hybrid compounds against Gram-negative bacteria is the reduced ability of passing through the outer membrane, resulting from the particle size. However, the undoubted advantage of hybrid compounds lies in creating extremely difficulties for microorganisms to induce mutations, which is the chance to stop a dangerous trend of increasing drug resistance.

## CONCLUSIONS

Chemotherapeutic agents from the quinolone group occupy an important position among the antimicrobial agents in the treatment of moderate to severe infections caused primarily by Gram-negative bacteria. For some diseases, such as pyelonephritis, gonorrhea and infections caused by *P. aeruginosa*, quinolone constitute drugs of choice, often replacing therapy by cephalosporins or aminoglycosides. There is no doubt that this is the most intensively expanding class of antibacterial agents. At least ten of these agents are currently at the stage of clinical trials and eight have been introduced to treatment in the recent 11 years.

Among such a large group of active substances – candidates for medicinal products, nemonoxacin with three points affinity to different bacterial enzymes, is worth mentioning, what is the source of reduced susceptibility to increasing resistance. Finafloxacin and delafloxacin - fluoroquinolones possessing high antimicrobial efficacy at low pH and successfully used to treat infections localized within the urinary tract, the gastric mucosa and skin, are also worth futher attention.

It is extremely difficult to find significant features distinguishing compounds aspiring to be introduced into the market as a medicinal products, because they are often at an early stage of clinical trials. Furthermore, pharmaceutical companies sponsoring the research indicate only on advantages of these compounds and the availability of scientific publications enabling verification of this information is frequently limited. However, these compounds represent an opportunity to inhibit resistance and undoubtedly hope for success against multidrug-resistance pathogens. At this point, we can just wait and hope for the development of research in the field of effective hybrid compounds and expect also successful results.

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