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Editorial

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A New Non-Traditional Antibacterial Agent that Promises to Overcome Antibiotic Resistance

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Abstract

Non-traditional antibacterials could be used as an alternative or complementary to, and synergistic with traditional antibacterial agents that are being pursued, and hold the potential to curb antimicrobial resistance. The Gamaleya Research Center of Epidemiology and Microbiology has developed an innovative broad-spectrum antibacterial drug designed for treatment and prevention of infections caused by antibiotic-resistant *Pseudomonas aeruginosa, Acinetobacter baumanii, Klebsiella pneumoniae, Escherichia coli, Chlamydia spp., Salmonella enterica*, including WHO critical priority carbapenem-resistant bacteria. After the completion of phase 2/3 clinical trials in patients with complicated UTIs, the drug was approved in April 2024 by the Ministry of Health of the Russian Federation according to the requirements of EEU and entered civil circulation in Russia. The target of the drug's action is the T3SS and flagellum, and the mechanism of action of Fluorothiazinone is associated with the specific suppression of toxin secretion, motility, intracellular survival, and biofilm formation. The unique effect on the target does not lead to bacterial death or selection of resistant variants, however, the multi-drug resistant bacteria show sensitivity to the drug.

Editorial

Development of innovative antibacterial drugs that will be effective against resistant bacteria and to which resistance does not develop is the most important task of modern medicine. According to the recent review by the WHO (2023 Antibacterial agents in clinical and preclinical development: an overview and analysis) development of direct-acting small molecule alternative antibacterial drugs and β-lactam/BLI combinations is drawing interest of researchers all around the world [1]. These alternatives are commonly known as non-traditional antibacterials. Their mechanism of prevention of infection or its treatment is direct or indirect inhibition of bacterial growth and virulence. Along with that, they boost the human immune system and contribute to changing and/or restoring a healthy microbiome. Non-traditional antibacterials could be used as an alternative to traditional antibacterial agents, complement them or work in a synergistic manner with them. Various implementations of these new drugs could be the key to restrain microbial resistance. More than 12 years ago, the Gamaleya Research Center of Epidemiology and Microbiology began to develop a non–traditional antibacterial drug based on a small molecule compound, an inhibitor of the type III secretion system (T3SS) and

flagella, which, after completing phase 2/3 clinical trials was approved in April 2024 by the Ministry of Health of the Russian Federation according to the requirements of the EEU. Fluorothiazinone, 300 mg tablet, is an innovative broad-spectrum antibacterial drug intended for treatment and prevention of infections caused by antibiotic-resistant *Pseudomonas aeruginosa, Acinetobacter baumanii, Klebsiella pneumoniae, Escherichia coli, Chlamydia spp., Salmonella enterica*, including critical priority pathogens defined by the WHO.

According to the mechanism of action, Fluorothiazinone specifically suppresses toxins secretion, motility, intracellular survival, and biofilm formation. The broad spectrum of the drug is determined by its target. The T3SS is the key virulence factor of the gram-negative bacteria, which determines their pathogenicity at different stages of interaction with the organism and, along with that, this system is not used by the normal microflora of the human. No resistance to Fluorothiazinone was detected, because unlike antibiotics, it does not affect the viability of bacteria, which fundamentally reduces selective pressure and selection of resistant variants. This has been shown experimentally: even with prolonged cultivation in the presence of the drug, resistant forms do not emerge, whereas under the same conditions forms resistant to antibiotics appear. Due to the specificity of its target, Flourothiazinone is effective against bacteria, regardless of whether they have genetic markers of resistance, including those associated with the efflux system. The efficacy of Fluorothiazinone against multidrug-resistant *Pseudomonas aeruginosa, Acinetobacter baumanii, Klebsiella pneumoniae, Escherichia coli* has been shown in experimental animal models **[2-5]**. Due to its pharmacological properties, Fluorothiazinone acts on extracellular and intracellular bacteria.

In clinical studies on healthy volunteers, a favorable level of tolerability has been shown at doses up to 2400 mg/day after a single dose and course taking **[6]**. Absence of direct antibacterial action of Flourothiazinone determines its advantage over antibiotics because no suppression of normal microflora was observed in healthy volunteers. Phase 2/3 clinical trials that studied the efficacy of Fluorothiazinone in patients with complicated UTIs were completed in January 2023. Clinical trials were conducted in 14 hospitals in different cities of Russia. This was the first implementation of the drug, therefore it was used as part of the complex therapy, 1200 mg/day of Fluorothiazinone and 2000 mg/day of Cefepime parenterally for 7 days. Upon completion, cure was achieved in almost all patients. However, 21 days after completion of the therapy in the group treated with the antibiotic and placebo, 55.2% of patients maintained the state of cure, and in the group treated with the antibiotic and Fluorothiazinone – 76,7%. After three months, 21,7% of patients in the group treated with the antibiotic and placebo had relapses, and in the group treated with the antibiotic and the experimental drug – 2.8% **[7]**.

For Fluorothiazinone, low potential for drug-drug interaction has been shown, therefore it can be used as part of a complex therapy with antibiotics, since neither synergistic nor suppressive interaction of Fluorothiazinone with antibiotics of different classes has been observed in infections in animal models. Wherein, Fluorothiazinone specifically inhibits the target present in pathogens regardless of whether they have resistance mechanisms. We have outlined a large program to expand indications for Fluorothiazinone. A clinical trial is planned for monotherapy of chronic prostatitis in men and chronic recurrent cystitis in women. This year, clinical trials that investigate the efficacy of Fluorothiazinone in prophylaxis of nosocomial infections caused by multidrug-resistant *Pseudomonas aeruginosa, Acinetobacter baumanii, Klebsiella pneumoniae, E. coli* are being completed (NCT06135350). The efficacy in prophylaxis of ventilator-associated pneumonia and catheter-associated UTIs will be studied. Fluorothiazinone is not a drug that competes with antibiotics. Its field of application is treatment when antibiotics are powerless. These areas are: infections caused by resistant bacteria; bacteria that hide intracellularly and create reservoirs for persistence so antibiotics do not act on them; cases when it is necessary to prevent infection without suppressing the normal microflora and developing resistance.

References

1. 2023 Antibacterial agents in clinical and preclinical development: an overview and analysis. ISBN. 2024;978-92-4-009400-0.
2. Tsarenko SV, Zigangirova NA, Soloveva AV, Bondareva NE, Koroleva EA, Sheremet AB, et al. A novel antivirulent compound fluorothiazinone inhibits Klebsiella pneumoniae biofilm in vitro and suppresses model pneumonia. J Antibiot (Tokyo). 2023;76(7):397-405.
3. Koroleva EA, Soloveva AV, Morgunova EY, Kapotina LN, Luyksaar SI, Luyksaar SV, et al. Fluorothiazinon inhibits the virulence factors of uropathogenic Escherichia coli involved in the development of urinary tract infection. J Antibiot (Tokyo). 2023;76(5):279-90.
4. Bondareva NE, Soloveva AV, Sheremet AB, Koroleva EA, Kapotina LN, Morgunova EY, et al. Preventative treatment with Fluorothiazinon suppressed Acinetobacter baumannii-associated septicemia in mice. J Antibiot (Tokyo). 2022;75(3):155-63.
5. Savitskii MV, Moskaleva NE, Brito AA, Zigangirova NA, Soloveva AV, Sheremet AB, et al. Pharmacokinetics, quorum-sensing signal molecules and tryptophan-related metabolomics of the novel anti-virulence drug Fluorothiazinon in a Pseudomonas aeruginosa-induced pneumonia murine model. J Pharm Biomed Anal. 2023;236:115739.
6. Baskhanova SN, Savitskii MV, Moskaleva NE, Samoylov VM, Lubenec NL, Luyksaar SI, et al. Development and validation of a quantitative determination method for fluorothiazinone in human blood plasma. Pharmaceut Chem J. 2024;57(11):1815-21.
7. Zigangirova NA, Lubenec NL, Beloborodov VB, Bondareva NE, Zakharov KA, Nelyubina SA, et al. A New “Non-Traditional” Antibacterial Drug Fluorothiazinone—Clinical Research in Patients with Complicated Urinary Tract Infections. Antibiotics (Basel). 2024;13(6):476.

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