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Chapter 7

New Antituberculosis Drug FS-1

Rinat Islamov, Bahkytzhan Kerimzhanova and Alexander Ilin

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http://dx.doi.org/10.5772/intechopen.80795

Abstract

The new iodine complex (FS-1), including molecular iodine, which is coordinated by lithium, magnesium halides, and bioorganic ligands, possesses high bactericidal activity against various microorganisms, including *Mycobacterium* sp., *Staphylococcus aureus* MRSA and MSSA, *Escherichia coli*, *Pseudomonas aeruginosa*, etc. FS-1 has synergistic properties with a broad class of antibiotics. The experimental model of tuberculosis in guinea pigs caused by clinical multidrug-resistant strains of *Mycobacterium tuberculosis* shows antituberculosis, immunomodulatory, and anti-inflammatory activity. FS-1 is characterized by low acute toxicity and lack of genotoxicity and mutagenicity. FS-1 is well distributed to organs and tissues; its pharmacokinetics is linear. The maximum nontoxic dose is 100 mg/kg for rats after 28-day oral administration and 30 mg/kg for rabbits after 180-day oral administration.

Keywords: *Mycobacterium tuberculosis*, iodine, complex, antimicrobial activity, antimicrobial resistance, tuberculosis, antituberculosis drug, preclinical trials, toxicity

1. Introduction

Antimicrobial resistance (AMR) has long been recognized as a global problem [1, 2]. At that, the solution to this problem is complicated by the fact that as soon as a new antibiotic appears, it is immediately reported about resistance to it. For example, some isolates of *Pseudomonas aeruginosa* and *Burkholderia cenocepacia* showed intermediate resistance to a new antibiotic eravacycline as early as at the stage of clinical trials, although the antibiotic effectiveness is very high against other bacteria, including the multiresistant ones [3]. Sometimes this resistance can be natural, for example, to pyrazinamide in *Mycobacterium bovis* [4, 5]. A widely practiced method of reducing AMR, the cyclic and mixed use of antibiotics that belong to alternative classes, has proved to be ineffective [6].

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Pulmonary tuberculosis poses a particular problem. The global WHO report announced the number of new tuberculosis cases detected in 2015—2110.4 million, of which 480,000 new cases of multidrug-resistant tuberculosis (MDR-TB) and 7579 cases of extensively drug-resistant TB (XDR-TB). The greatest number of the disease cases is registered in six countries—India, Indonesia, China, Nigeria, Pakistan, and South Africa—60% of the worldwide incidence [7]. Despite the emergence of new antituberculosis drugs, the situation with high resistance of *M. tuberculosis* remains difficult [7, 8]. In this regard, the search and development of new anti-infectious drugs are extremely relevant.

Among the numerous substances with high antimicrobial activity, resistance to which was not detected or it remains at the minimum level, there are polymeric complexes of iodine [9, 10]. Iodine complexes have broad antimicrobial, anti-inflammatory, immunomodulatory, and antitumor activity [11–16]. Really interesting are nanocomposites with molecular iodine, which are superior in their antimicrobial activity to the widely known complex of polyvinylpyrrolidone and iodine (PVP-iodine) [17, 18]. The ability of molecular iodine to form complexes with a variety of properties and compositions with ligands of different nature makes it very promising to develop drugs based on iodine coordination compounds [19–24].

The new drug FS-1 relates to iodine coordination compounds with bioorganic ligands, magnesium, and lithium cations. The active center of FS-1 included α-dextrin helix with molecular iodine (I_2) that is coordinated with lithium halogenides and amide groups of protein component. Such a structure protects I_2 from interaction with bioorganic compounds after oral intake. Bioorganic compounds are only able to compete with I_2 in complexing if donor activity is greater as against amide groups [24–26].

The developed drug FS-1 possesses broad antimicrobial activity against antibiotic-resistant and antibiotic-susceptible Gram-positive and Gram-negative bacteria, mycobacteria, fungi, and viruses [27–33].

Both liquid and solid dosage forms of FS-1 were produced from the pharmaceutical development process [34]. Preclinical trials of the drug FS-1 were conducted according to the recommendations of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This chapter will present the major results from preclinical trials of the new drug FS-1, conducted in 2004–2014.

2. In vitro antimicrobial activity

The aim of these studies presented here was to assess the in vitro antimicrobial activity of FS-1. By using a serial dilution technique assay, the activities of FS-1 were tested against both on typified bacteria and on clinical isolates. **Table 1** shows a list of microorganisms that were used to examine the in vitro effectiveness of FS-1 [27–29, 33, 35, 36].

The minimum inhibitory concentration (MIC) was in the range of 0.02–0.3 mg/mL. At the same time, clinical isolates *M. tuberculosis* SCAID 187.0 (MDR); 562, 892, 535, and 722

Typified bacteria	Clinical isolates
M. tuberculosis H37Rv*	*M. tuberculosis* MS-115 (MDR), SCAID 187.0 (MDR); 562, 892, 535, and 722* (isoniazid-resistant); *M. bovis*** 2, 3, and 5; *M. avium* 780
	*Yersinia pestis****, *Bacillus anthracis****, *Brucella* sp.***
Staphylococcus aureus ATCC 6538-P B-RKM 0039, *S. aureus* ATCC 29213—oxacillin-susceptible strain (MSSA), *S. aureus* ATCC 43300—methicillin- and oxacillin-resistant (MRSA), *S. aureus* ATCC 29213, *S. aureus* ATCC 43300, *Escherichia coli* ATCC 25922, and ATCC BAA-196 and *Candida albicans* ATCC 18814	*S. aureus*****—114 MRSA and MSSA clinical isolates—*P. aeruginosa* № 4/32, *E. coli* O55 № 12, *C. albicans* 3/4

*Collections of microorganisms at the National Scientific Center for Pulmonology, Kazakhstan.

**At Kazakh Scientific Research Veterinary Institute.

***At Kazakh Scientific Center for Quarantine and Zoonotic Diseases.

****At Institute of Experimental Pathology and Parasitology, Bulgaria.

Table 1. List of bacteria and their characteristics used to examine antimicrobial activity of FS-1.

(isoniazid-resistant); and *M. bovis* 2, 3, and 5 showed the greatest susceptibility [36]. The MIC of FS-1 against *Y. pestis* and *B. anthracis* was 0.2 mg/mL [35].

FS-1 causes lysis of the bacterial cell, damaging the cell membrane [37]. A study on the membrane lytic activity of FS-1 on *M. smegmatis* by electron microscopy showed that the bacterial cell lysis occurs within 5–30 minutes at a concentration of FS-1 of 4 μg/mL. In addition, FS-1 inhibits DNA-dependent RNA polymerase (RNAP) of *M. tuberculosis* forming a complex between bacterial DNA and magnesium ion in RNAP [26].

Most bacterial diseases including tuberculosis are treated with a combination of multiple drugs in a regimen. Synergistic effects with existing drugs are valuable characteristics of a new drug candidate. FS-1 was tested in combination with antibiotics and various first and second antituberculosis drugs (ATBD). Synergy between drugs and FS-1 was determined by chequerboard in vitro [27]. Testing showed that synergy between FS-1 and antituberculosis drugs (ATBD) was observed against both on susceptibility and on multidrug resistance MTB. Among the cephalosporins, only cefamandole showed synergy with FS-1 against clinical isolates *S. aureus*. The index of fractional inhibitory concentration was 0.62 [27]. Thus, according to the results of testing, in vitro the FS-1 is an effective compound of a class of iodine coordination compounds.

3. In vivo antituberculosis activity

The most important stage of preclinical studies of new drugs is the evaluation of efficacy in animal models. There are various animal *M. tuberculosis* infection models. The most common are guinea pigs and mice. A classical guinea pig model of tuberculosis caused by highly

virulent clinical strains of *M. tuberculosis* MS-115 and SCAID 187.0 isolated from patients with MDR-TB was used in the study on the therapeutic effectiveness of FS-1 [8, 29, 38].

The efficacy result of the tuberculosis model showed that the FS-1 combination regimen reduced the bacterial load in comparison with standard therapy. A primary characteristic of the therapeutic activity of FS-1 was an increase in the effectiveness when combined with ATBD including isoniazid, rifampicin, pyrazinamide, cycloserine, protionamide, capreomycin, and amikacin [29, 30]. It was noted that in the treatment of tuberculosis in guinea pigs with FS-1 *M. tuberculosis* acquired susceptibility to first-line ATBD. Apparently this is due to the effect of FS-1 on the *M. tuberculosis* genome [30]. In the studies on other bacteria, *Streptococcus mutans* and *S. aureus* and *S. epidermidis*, iodine complexes have been shown to influence the transcription activity in microbial genome [39–41].

The therapeutic effect on the guinea pig body has also been noted. In particular, the exposure to FS-1 inhibits the development of inflammation in tuberculosis and increases the airiness of the lung parenchyma and permeability of capillaries [29]. This is due to the ability of iodine complexes to inhibit the production of NO and TNF-alpha and increase mucociliary clearance in the respiratory tract [15, 42]. In addition, combination therapy with FS-1 and ATBD reduces the incidence of adverse reactions and toxic effects of the drugs in animals [30].

In the studies presented here, the combination of FS-1 in MDR-TB animal models is significantly more effective than therapy only with ATBD.

4. Toxicity studies

The toxicity of FS-1 was examined in both liquid form and tablets [34, 43].

The median cytotoxic concentration (CC_{50}) of FS-1 on the MDCK cells exceeds 5 mg/mL [44]. In vitro and in vivo genotoxicity and mutagenic potential of FS-1 were examined in mice with Ames test, micronucleus, and comet assays. According to the results from the studies, FS-1 does not induce gene mutations or chromosomal abnormalities [45, 46].

Acute toxicity study of FS-1 liquid dosage form was carried out after intravenous administration to rodents, mice (CD-1), and rats (Wistar) [47]. The median lethal dose (LD_{50}) was 65 mg/kg in mice and 100 mg/kg in rats. After the administration of FS-1, the following signs were observed in animals: exophthalmos, piloerection, impaired motor coordination, paroxysmal convulsions of lower limbs, bradycardia, and tachypnea. Death occurred within 24 hours after the administration of FS-1. Necropsy revealed a disturbance of blood circulation in the heart, liver, and kidneys and pulmonary edema in dead animals. Microscopic examination showed plethora and inflammatory infiltration in the lungs, liver, and kidneys and diapedesis hemorrhages in the myocardium. At the same time, there were no changes in the thyroid gland [47].

After oral administration of FS-1 liquid form to rats (Wistar), LD_{50} was not achieved. The maximum administered dose of FS-1 was 466 mg/kg. The minimal dose of FS-1 did not cause damage to the mucous membrane of the gastrointestinal tract (GIT). Medium and high doses

provoked minimal damage to the gastric mucosa. Histological examination of thyroid gland did not reveal the pathological changes [47].

Toxicokinetics (TK) of FS-1 liquid form was examined in male and female rats after single oral administration at doses of 233, 116, and 30 mg/kg [48]. The content of FS-1 was measured in the blood, heart, lungs, liver, kidneys, and spleen. The primary TK parameters were calculated by non-compartmental method. The maximum concentration of FS-1 in the blood (C_{max}) and the time it was reached (t_{max}) were found visually on the graph. The TK parameters for oral doses of FS-1 are given in **Table 2**.

FS-1 is absorbed quite rapidly from the gastrointestinal tract; the maximum values of its concentrations in the blood were reached within 1–1.5 hours after its administration. During the first 10–30 minutes, the concentration of FS-1 in the blood increased and reached a maximum after 2 hours. The level of the drug was further reduced, and at the end of 96 hours, the detection limit was reached. High values of the volume of distribution, according to the generally accepted point of view, can be interpreted as a sign of a wide distribution of the drug in the body. At the same time, the rate of distribution of FS-1 in the organs was lower than in the blood, therefore, accumulation does not take place. The nature of the relationship between the dose of FS-1 and the area under the pharmacokinetic curve (AUC) in the blood, as well as the constancy of the invariant TK parameters, indicate that the dynamics of drug absorption, distribution, and elimination obey the basic principles of linear kinetics. The primary metabolites of FS-1 include iodides, which are excreted in the urine [48].

In addition, chronic toxicity was examined during 180-day oral administration in rabbits. The characteristic symptoms of iodine toxicity in rabbits were not detected at a dose of 30 mg/kg [47–51].

Despite the fact that iodine does not have mutagenic properties, there is evidence of the effect of high iodide doses on the development of mice. Although the mechanisms of toxic effect of

TK parameter	Dose, mg/kg		
	30	**116**	**233**
AUC(mg·h/L)	138.2 ± 19.5	382.4 ± 49.6	669.5 ± 103.1
Cl (L·h/kg)	0.22 ± 0.03	0.30 ± 0.04	0.35 ± 0.05
MRT (h)	24.6 ± 3.5	20.2 ± 2.7	23.1 ± 3.6
β (h^{-1})	0.026 ± 0.003	0.025 ± 0.004	0.026 ± 0.004
$V_β$ (L/kg)	8.2 ± 1.2	12.0 ± 1.6	13.5 ± 2.1
C_{max} (mg/L)	9.0 ± 0.2	34.1 ± 5.0	45.1 ± 9.6
t_{max} (h)	2	1	1
$t_{1/2(β)}$ (h)	26.6 ± 3.7	26.6 ± 3.6	26.6 ± 3.7

Table 2. Toxicokinetic parameters of FS-1 after single oral administration of three doses to rats by non-compartmental method, n = 6.

high iodide doses on pregnant females and embryos have not been revealed, it is assumed that this is due to impaired thyroid function in pregnant females. Thyroid hormones in turn affect sex glands of animals [52]. An evaluation of the embryotoxic properties of FS-1 was performed on a bird model using *Gallus gallus* chicken embryos at different developmental stages [53]. Embryotoxicity was assessed by the effect of FS-1 on survival and developmental pathology. At a concentration of 3 mg/mL, the mortality rate of 10-day embryos was 100%, whereas for 12- and 18-day-old embryos, it was 80 and 50%, respectively. At the same time, developmental abnormalities were not detected. The toxicity of FS-1 toward chicken embryos depends on the concentration and developmental stage [54]. The Spearman's correlation coefficient was greater than 0.976 at $p < 0.001$, which indicates a high dependence. It is known that iodides can exhibit toxicity to the reproductive function in two ways: through oxidative stress in the testis of rats and thyroid dysfunction in pregnant females [52, 55].

One of the problems encountered in the clinical trials of new drugs is that there could be various unforeseen immunotoxic reactions [56, 57]. As already noted, iodine complexes have immunotropic properties [15, 58]. Therefore, the immunotoxicity and allergenicity of FS-1 were studied in various tests:

a. Intradermal and conjunctival test

b. Active and passive (ovary) cutaneous anaphylaxis

c. mast cell degranulation

d. Anaphylactogenicity

e. Induction of delayed-type hypersensitivity reaction

f. Analysis of changes in mass and cellularity of the popliteal lymph node

g. Assessment of specific lysis of human peripheral blood leukocytes

h. Analysis of the relative count of basophils and eosinophils in human peripheral blood

i. Determination of mass and cellularity of immune organs and antibody response in guinea pigs

The study found that FS-1 does not possess anaphylactogenicity, does not cause type I allergic reaction and does not influence the formation of a delayed-type hypersensitivity reaction, does not have immunopathological and immunotoxic effects, and does not cause disorders and/or dysfunctions in the processes involved in normal maintenance of immune status in the tested doses, even against the background of antigenic stimulus [59, 60].

The preparation of a tablet dosage form of FS-1 is the most important stage in the pharmaceutical development of novel drug [34, 61, 62].

After the oral administration of FS-1 tablets to rats (Wistar), LD_{50} was found to exceed 2000 mg/kg [43]. The observed clinical and pathomorphological signs of damage to the body of animals with FS-1 are similar to the symptoms of poisoning with iodine solutions [50].

Toxicology of iodides and iodates was well studied in numerous animal species, as well as in humans, whereas the data on iodine complexes including Lugol's solution and PVP-iodine are very scarce [51, 63].

The toxicity of FS-1 tablets associated with repeated administration was examined in rats (Wistar) after 28-day oral administration. It was found that the organs for the damaging action of FS-1 included the thyroid gland, liver, and kidneys. There were changes in the blood parameters: the levels of leukocytes and lymphocytes and alanine aminotransferase and aspartate aminotransferase increased. But these changes were reversible, and after 28 days of recovery period, all parameters were normalized [43].

It is known that prolonged exposure to or intake of high doses of the iodine-containing drugs is accompanied by thyrotoxic reactions in the form of iodine-induced hypothyroidism [64]. Due to excessive intake of iodine, the Wolff-Chaikoff effect occurs, which develops within a few days [65]. This is accompanied by a temporary reduction of the thyroid hormone level due to a decrease in the Na+/I-symporter activity (NIS) [66]. The Wolff-Chaikoff effect is transient, and the level of hormones with the withdrawal of the iodine-containing drugs is restored in a few days. It was noted that the chronic effect of iodine doses (in Japan, for example, up to several milligrams per day are consumed with food, exceeding the WHO recommended standards (90–200 μg)) frequently does not cause any hypothyroid or thyrotoxic conditions [67]. Therefore, rats were also analyzed for the level of thyroid-stimulating hormone (TSH), thyroxine (T4), and triiodothyronine (T3). The findings of the studies have shown that the levels of TSH, T3, and T4 in the blood serum of rats did not change. It has been established that the T3/T4 ratio in all studied groups was in the range of 0.20–0.50. The absence of significant changes in the T3/T4 ratio in animals of all groups indicates a normal rate of deiodization. As a result, the highest nontoxic dose (NOAEL) of FS-1 was established, which was of 100 mg/kg [43]. Summarizing the results obtained, it can be noted that high doses of FS-1 lead to the development of thyrotoxicosis in rats and not hypothyroidism, as with excessive intake of iodides into the animal organism [51].

5. Conclusion

FS-1 is highly effective against various Gram-positive and Gram-negative bacteria, including those resistant to antibiotics. MIC varied over a wide range from 0.02 to 0.3 mg/mL. At that, FS-1 has a synergistic effect with some antimicrobial agents. The main mechanism of action of FS-1 consists in membrane lytic activity. In addition, the investigational drug affects the gene expression in bacteria. The effectiveness of FS-1 in combination with ATBD of the first- and second-line was examined in the guinea pig models of tuberculosis. FS-1 has pronounced anti-inflammatory and antitoxic effects. The CC_{50} value in MDCK cells is more than 5 mg/mL. This is 16 times higher than the MIC. FS-1 does not have mutagenic and genotoxic properties. The acute oral toxicity of FS-1 in rats is LD_{50} of more than 2000 mg/kg. The extent of FS-1 distribution in the organs is not greater than in the blood. Its kinetics is linear. The primary metabolites include iodides. At the same time, FS-1 possesses embryonic toxicity in

chicken embryos but does not lead to developmental abnormalities. FS-1 does not cause allergic reactions and does not possess immunotoxic properties. The liver, kidney, and thyroid gland are the target organs for toxic injuries induced by repeated administration of FS-1. At the same time, thyrotoxicosis develops but not hypothyroidism. NOAEL value is 100 mg/kg of rats after 28-day oral administration and 30 mg/kg in rabbits after 180-day administration.

Conflict of interest

Authors report grants from Ministry of Investments and Development of the Republic of Kazakhstan, during the conduct of the studies.

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