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Effectiveness and safety of a modified short-term regimen of antimycobacterial therapy to treat rifampicin-resistant tuberculosis in elderly patients with concomitant diabetes (a clinical case)

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Key words: modified short course regimen, antimycobacterial therapy, rifampicin-resistant tuberculosis, elderly, diabetes mellitus.

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Aim. To analyze the effectiveness and safety of a modified short-term regimen (mSTR) of antimycobacterial therapy (AMBT) for rifampicin-resistant tuberculosis (RR-TB) in a 71-year-old patient with type 2 diabetes mellitus (T2DM) on the clinical case example of own observation.

Materials and methods. A clinical case from own observation of the patient who was treated at the clinical base of the Department of Phthisiology and Pulmonology of Zaporizhzhia State Medical University – Pulmonary Tuberculosis Department No. 2 of the Communal Non-profit Organization "Zaporizhzhia Regional Phthisio-Pulmonology Clinical Treatment and Diagnostic Center" is presented.

Results. The presented case demonstrates the high safety and efficacy of all oral mSTR, including Lfx-Bdq-Lzd-Cfz-Cs, in the elderly person with RR-TB and concomitant decompensated T2DM who was smear-negative after 4 months as a result of treatment with 9-month mSTR AMBT (Lfx, Bdq, Lzd, Cfz, Cs). Positive radiological dynamics were observed all the time and residual changes in the lungs after tuberculosis were diagnosed at the end of the treatment course. These results complement indications for the use of mSTR, including Lfx-Bdq-Lzd-Cfz-Cs, in RR-TB patients.

Conclusions. mSTR AMBT (Lfx, Bdq, Lzd, Cfz, Cs) is effective and safe in elderly patients with RR-TB and concomitant decompensated type 2 diabetes mellitus when adequate treatment of diabetes and timely correction of antimycobacterial drug side effects are undertaken.

Ключові слова: модифікований короткостроковий режим, антимікобактеріальна терапія, рифампіцин-стійкий туберкульоз, похилий вік, цукровий діабет.

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Ефективність і безпека модифікованого короткострокового режиму антимікобактеріальної терапії рифампіцин-стійкого туберкульозу в осіб похилого віку з супутнім цукровим діабетом (клінічний випадок)

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Мета роботи – на прикладі клінічного випадку власного спостереження проаналізувати ефективність і безпеку модифікованого короткострокового режиму (мКРЛ) антимікобактеріальної терапії (АМБТ) рифампіцин-стійкого туберкульозу (RR-TB) у 71-річного пацієнта з цукровим діабетом 2 типу.

Матеріали та методи. Наведено клінічний випадок власного спостереження за пацієнтом, який перебував на лікуванні в відділенні легеневого туберкульозу № 2 Комунального некомерційного підприємства «Запорізький регіональний фтизіопульмонологічний клінічний лікувально-діагностичний центр» Запорізької обласної ради – клінічній базі кафедри фтизіатрії і пульмонології Запорізького державного медичного університету.

Результати. Наведений випадок демонструє високу безпеку й ефективність повністю перорального мКРЛ, що включає Lfx, Bdq, Lzd, Cfz і Cs, у пацієнта похилого віку з одночасним перебігом RR-TB і декомпенсованого цукрового діабету 2 типу. На тлі 9-місячного мКРЛ АМБТ (Lfx, Bdq, Lzd, Cfz, Cs) у хворого похилого віку з супутнім декомпенсованим цукровим діабетом 2 типу бактерієвиділення припинилося через 4 місяці. Протягом усього періоду спостереження визначали позитивну рентгенологічну динаміку, а наприкінці курсу лікування в легенях діагностували залишкові зміни після перенесеного туберкульозу. Результати, що одержали, доповнюють показання щодо застосування в пацієнтів із RR-TB мКРЛ, що включає Lfx, Bdq, Lzd, Cfz і Cs.

Висновки. В осіб похилого віку, які хворі на RR-TB із супутнім декомпенсованим цукровим діабетом 2 типу, ефективним і безпечним є мКРЛ АМБТ (Lfx, Bdq, Lzd, Cfz, Cs) при адекватному лікуванні діабету та своєчасній корекції побічних дій антимікобактеріальних препаратів.

Standardized and modified short-term treatment regimens (sSTR and mSTR, duration of 9–12 months) for multidrug-resistant tuberculosis (MDR-TB) and rifampicin-resistant tuberculosis (RR-TB) treatment are currently being widely introduced and studied in many countries, including Ukraine.

So, P. N. Mahardani et al. [5] conducted a study on the efficacy and safety of sSTR for MDR-TB: the intensive phase lasted 4 months and included kanamycin (Km), isoniazid (INH), clofazimine (Cfz), ethambutol (E), prothionamide (Pto), pyrazinamide (Z), gatifloxacin (Gfx) and the continuation phase lasted 8 months and included Cfz-E-Z-Gfx-Pto. Km was used in high doses in that case. The authors have found that 12-month sSTR provided good MDR-TB treatment efficacy in terms of treatment success and shorter therapy duration compared to the 20–24-month traditional regimen.

The high effectiveness of such sSTR in patients with MDR-TB/RR-TB is evidenced by the data of a prospective observational study by Q. Nie et al. [8]. High-dose Gfx-based sSTR was used in comparison with previous studies. The authors also emphasize that severe adverse reactions, above all, hepatotoxicity and QT interval prolongation, should not be ignored when using this regimen.

Significantly higher efficacy of STR (9–12 months) was indicated in patients with MDR-TB compared to the standard treatment (20–24 months) as results of study by E. Zhdanova et al. [1].

Adverse factors influencing outcome of sSTR MDR-TB/RR-TB treatment were studied in a retrospective cohort study by A. Y. Soeroto et al. [6]. So, the researchers have found that significant independent factors that reduced the chances of successful treatment completion were a history of previous TB treatment, culture conversion for more than 2 months, and malnutrition in patients. At the same time, D. M. Kokebu et al. [7] have found that the predictors for Standardized Treatment Regimens of Anti-tuberculosis drugs for Multidrug-Resistant Tuberculosis (STREAM) sSTR failure in MDR-TB patients were: male sex, a significantly positive baseline smear degree, MDR-TB/HIV co-infection, and the presence of costo-diaphragmatic obliteration.

Souleymane M. B. et al. [13] investigated the use of all-oral mSTR, including bedaquiline and linezolid (Bdq/Lzd), in patients with RR-TB. The authors have found high safety, efficacy, and adherence to this regimen, confirming its continuity in the practice of the treatment for RR-TB patients. The effectiveness and safety of-all oral mSTR in patients with MDR-TB was also studied by T. Avaliani et al. [4]. The authors have determined that good treatment outcomes were achievable in people with fluoroquinolone-sensitive TB. Schwbel V. et al. [11] also have noted that RR-TB patients with initial resistance to fluoroquinolones had a lower efficacy of mSTR and an increased risk of any adverse treatment outcome.

Kendall E. A. et al. [9] examining the effects of a 9-month MDR-TB regimen have concluded that this approach to antimycobacterial therapy (AMBT) would double access to treatment (by saving resources or capacity) and ensure long-term effectiveness.

Bada F. O. et al. [3] compared the cost of 9-month sSTR (including the second-line injectable drugs) with 20-month standard MDR-TB/RR-TB treatment in Nigeria. They have concluded that sSTR models such as the 9–12-month outpatient model and the model when patients were hospitalized during the first 4 months of treatment reduced the cost of MDR-TB/RR-TB treatment by approximately 5470 US dollars.

Kohler S. et al. [12] studying the costs of purchasing and importing drugs for 20-month, 9-month and 4–6-month AMBT regimens have concluded that the introduction of shorter AMBT regimens could reduce the cost of high-drug resistance TB control programs.

Trauer J. M. et al. [10] have found in their study that shorter MDR-TB treatment regimens could reduce the transmission of Mycobacterium tuberculosis (MBT) resistant strains. Han W. M. et al. [2] also indicated that STR helped to reduce the number of new cases of MDR-TB and the percentage of resistance among new infections.

Thus, the use of sSTR and mSTR in patients with MDR-TB/RR-TB has high safety, efficacy, and adherence. At the same time, such regimens are cost-effective (reduce the cost of MDR-TB/RR-TB control programs), provide long-term effectiveness and lower the transmission of resistant MBT strains. But there is no evidence in the literature about the safety and efficacy of sSTR and mSTR in older RR-TB patients with concomitant type 2 diabetes mellitus (T2DM), which served as the basis for writing this article.

Aim

To analyze the effectiveness and safety of mSTR AMBT for RR-TB in a 71-year-old patient with T2DM on the clinical case example of own observation.

Materials and methods

A clinical case from own observation of the patient who was treated at the clinical base of the Department of Phthisiology and Pulmonology of Zaporizhzhia State Medical University – Pulmonary Tuberculosis Department No. 2 of the Communal Non-profit Organization "Zaporizhzhia Regional Phthisio-Pulmonology Clinical Treatment and Diagnostic Center" of Zaporizhzhia Regional Council (CNO ZRPPCTDC ZRC) is presented.

Case report

Patient M., male, 71 years old.

From anamnesis. He did not have a history of prior tuberculosis. He was diagnosed with hypertension in 1995 and took antihypertensive drugs from 2003; T2DM was diagnosed in 2006, and he was prescribed constant use of Glymepiride, insulin therapy was administered in February 2022. Worsening of the condition was noted after hypothermia in November 2021. The patient repeatedly consulted a family doctor and received non-specific antibacterial therapy for left-sided pneumonia treatment. The therapy was not effective, as negative dynamics were determined on a control chest X-ray examination dated 03.03.2022 (*Fig. 1*).

A sputum analysis by using GeneXpertUltra molecular genetic (MG) method was done due to radiological changes.

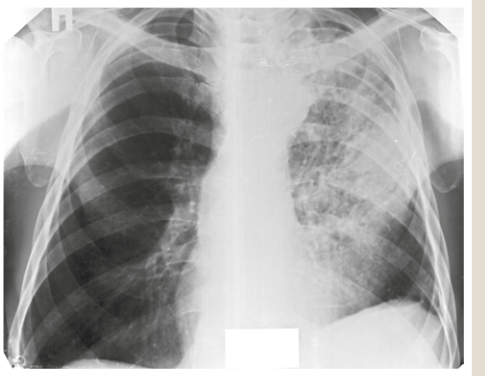


Fig. 1. Chest X-ray from 03.03.2022. There are focal and infiltrative shadows, consolidated in some areas, with destructions from 0.5 up to 2.0 cm in diameter. The left lung hilum is infiltrated, there are no changes in the right lung.

Table 1. Blood tests of the clinical case in dynamics

Blood indicators, units	10.03.2022	07.04.2022	04.05.2022	13.06.2022	11.07.2022	12.08.2022	08.09.2022
Hb, g/l (RV = 110–160)	99	107	100	98	111	108	115
Er, ×1012/l (RV = 3.9–5.3)	3.25	3.48	3.26	3.16	3.5	3.44	3.75
WBC, ×109/l (RV = 4–9)	9.6	9.3	7.9	7.7	9.1	7.3	5.0
pl, ×109/l (RV = 150–390)	347	257	226	217	301	288	221
Ef, % (RV = 2–4)	0	0	1	0	3	4	3
b/n, % (RV = 1–4)	27	22	19	17	2	5	4
s/n, % (RV = 52–72)	60	62	66	70	76	74	67
Lf, % (RV = 19–37)	3	10	7	18	17	14	23
m, % (RV = 3–10)	10	5	7	5	2	3	4
ESR, mm/h (RV = 1–10)	57	64	43	45	16	48	12

RV: reference values; **Hb:** hemoglobin; **Er:** erythrocytes; **WBC:** leukocytes; **pl:** platelets; **Ef:** eosinophils; **b/n:** band neutrophils; **s/n:** segmented neutrophils; **Lf:** lymphocytes; **m:** monocytes; **ESR:** erythrocyte sedimentation rate.

Table 2. Biochemical blood analyses of the clinical case in dynamics

Biochemical blood indicators, units	10.03.2022	07.04.2022	10.05.2022	13.06.2022	11.07.2022	12.08.2022	08.09.2022
Bilirubin, mmol/l (RV = up to 21)	12.48	8.6	9.75	8,9	9.7	8.8	9.9
ThT, units (RV = up to 4)	4.09	4.6	5.11	4.55	4.7	4.12	4.55
AlAt, mmol/l/h (RV = 0.16–0.44)	0.56	0.48	0.35	0.85	2.11	1.56	1.55
AsAt, mmol/l/h (RV = 0.91–1.75)	0.39	0.26	0.27	0.67	1.65	0.86	0.89
TP, g/l (RV = 64–85)	82.9	69.6	80.4	68.8	76.4	71.5	72.5
Creatinine, μmol/l (RV = 62–115)	103.2	73.6	108.5	124.2	146.3	127.6	96.1
Urea, mmol/l (RV = 2.5–8.3)	8.81	8.4	8.7	8.13	7.22	7.45	8.65
RUN, mmol/l (RV = 12.5–25.0)	4.11	3.9	4.0	3.8	3.37	3.4	4.04
α-amylase, g/l × h (RV = 2–4)	8.47	2.06	11.0	2.55	3.49	8.26	2.35
Potassium, mmol/l (RV = 2–4)	5.21	5.08	5.52	4.03	4.32	5.15	4.0
Sodium, mmol/l (RV = 2–4)	133.1	132.5	130.7	140.3	139.7	141.4	138.7
Calcium, mmol/l (RV = 2–4)	1.58	1.48	1.51	1.35	1.41	1.36	1.41
Chlorine, mmol/l (RV = 2–4)	92	96.4	95.0	101.9	103.0	104.5	104.2
Magnesium, mmol/l (RV = 2–4)	0.93	1.07	1.02	0.96	0.91	0.89	0.88

RV: reference values; **ThT:** thymol test; **AlAt:** alanine aminotransferase; **AsAt:** aspartate aminotransferase; **TP:** total protein; **RUN:** residual urea nitrogen.

Table 3. Urine analyses of the clinical case in dynamics

Urine analysis indicators, units	10.03.2022	24.03.2022	07.04.2022	06.05.2022	13.06.2022	11.07.2022	12.08.2022	08.09.2022
Protein, g/l	0.33	0.132	0.033	traces	traces	traces	traces	traces
Glucose, %	1.5	1.5	1.0	0.5	not detected	not detected	not detected	0.1
Ketone bodies	not detected	not detected	not detected	not detected	not detected	not detected	not detected	not detected

Mycobacteria tuberculosis (MBT+) resistant to rifampicin (Rif+) were detected.

Based on such results, the age (71 years) of the patient and concomitant T2DM, the patient was referred to CNO ZRPPCTDC ZRC, where an additional examination was performed.

Sputum analysis: genotypic drug sensitivity test (gDST) (XpertMBT/XDR) MG-, Cultural test (C) + (BACTEC), phenotypic (phDST) (-).

Blood tests of the clinical case in dynamics are demonstrated in *Table 1*, biochemical blood analyses – *Table 2*, blood glucose – *Fig. 2*, urine analysis – *Table 3*.

Blood test for HIV (rapid test): negative.

Blood test for HCV (rapid test): negative.

Electrocardiogram (ECG): voltage is sufficient, sinus rhythm, heart rate – 90/min, heart electrical axis (HEA) is not deviated, incomplete blockade of the right branch of the bundle of His. Signs of left ventricular myocardial hypertrophy. Diffuse changes in the myocardium of the ventricles, QTcF = 404 msec.

Conclusion of an endocrinologist: Type 2 diabetes mellitus of moderate severity, stage of decompensation.

Conclusion of a therapist: Diabetic nephropathy. Arterial hypertension, stage II, degree I. I degree heart failure (HF), functional class (FC) II. Anemia of chronic disease, moderate degree.

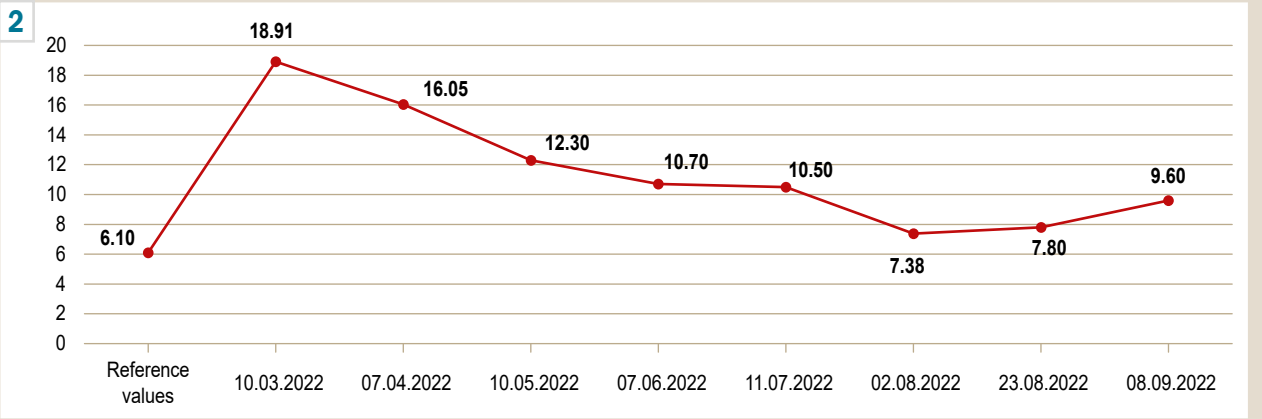
Conclusion of an ophthalmologist: Initial cataract, retinal angiosclerosis OD, 1st degree myopia OS.

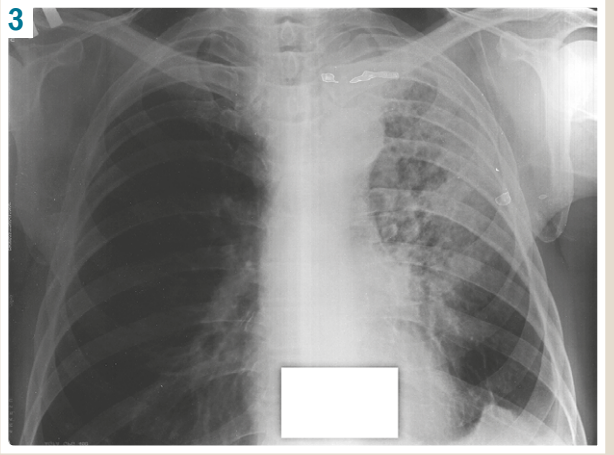
A diagnosis was made: Rifampicin-resistant TB (RR-TB) infiltrative of the left lung. Destruction +, MBT+ microscopy (Acid fast bacilli (AFB)) + MG+ Rif+ gDST (-) C + phDST (-). Histology (Hist) 0 (Newly diagnosed tuberculosis (ndTB)). Cohort 1 (2022). Type 2 diabetes mellitus, mild severity, stage of decompensation. Diabetic nephropathy. Arterial hypertension, stage II, degree I. I degree HF, FC II. Anemia of chronic disease, mild degree.

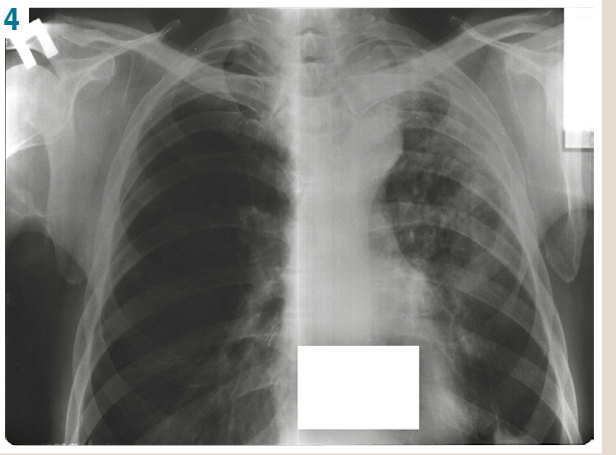
From March 11, 2022, the following treatment was prescribed:

– course of mSTR AMBT according to the scheme: levofloxacin (Lfx), bedaquiline (Bdq), linezolid (Lzd), clofazimine (Cfz), cycloserine (Cs);

– treatment of T2DM according to the scheme: Glymepiride + Humodar C25 100R, in the evening – Humodar C25 100R;







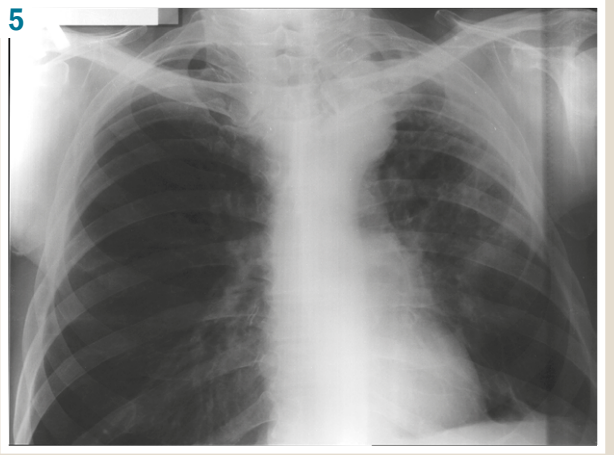


Fig. 2. Blood glucose of the clinical case in dynamics, mmol/l.

Fig. 3. Chest X-ray from 10.06.2022: slight resorption of infiltration and foci is determined over the entire left pulmonary field, cavitation persists. The left lung hilum is infiltrated. There are no changes in the right lung. The left dome of the diaphragm is deformed due to pleurodiaphragmatic fusion.

Fig. 4. Chest X-ray from 07.09.2022. The upper lobe of the left lung is reduced in volume due to pneumofibrosis; partial resorption of foci and infiltration is determined in the upper lobe and S6, cavity lesions are reduced to 1.0–0.5 cm in diameter. The left lung hilum is fibrously changed, pulled up. The left dome of the diaphragm is deformed due to pleuro-diaphragmatic fusion. There are no changes in the right lung. The right edge of the spine is naked.

Fig. 5. Chest X-ray from 09.12.2022. The left lung is reduced in volume due to fibrous changes. There are numerous, mostly intense, focal shadows in the left upper lung field. The costal pleura is thickened up to the 5th rib level. The left lung hilum is deformed. The left costo-diaphragmatic sinus is obliterated. There are no changes in the right lung. Mediastinal organs are shifted to the left.

– pathogenetic and symptomatic therapy.

Sputum analysis from 08.04.2022: AFB- C+.

ECG from 11.04.2022: voltage is sufficient, sinus rhythm, heart rate – 90/min, HEA is not deviated, less expressed changes in the myocardium, QTcF = 427 msec.

Sputum analysis from 06.05.2022: AFB+ C-.

ECG from 10.05.2022: voltage is sufficient, sinus rhythm, heart rate – 77/min, HEA is not deviated, less expressed changes in the myocardium, QTcF = 428 msec.

After 3 months of the complex treatment with mSTR AMBT (Lfx, Bdq, Lzd, Cfz, Cs), the patient had positive radiological dynamics (*Fig. 3*).

ECG from 10.06.2022: voltage is sufficient. Atrial fibrillation, tachysystolic form, heart rate – 138/min, HEA is not deviated, QTcF = 403 msec.

Sputum analysis from 13.06.2022: AFB+ C-.

Conclusion of the therapist from 13.06.2022: Heart rhythm disturbance (atrial fibrillation). Anemia of chronic disease, mild degree. Symptomatic therapy was prescribed.

ECG from 21.06.2022: voltage is sufficient, sinus rhythm, supraventricular extrasystole, heart rate – 71/min, HEA is not deviated, QTcF = 435 msec.

Conclusion of a neurologist from 23.06.2022: Diabetic polyneuropathy of the lower extremities.

Sputum analysis from 11.07.2022: AFB- C (a growth of other flora).

ECG from 11.07.2022: voltage is sufficient, sinus rhythm, heart rate – 69/min, HEA is not deviated, incomplete blockade of the right branch of the bundle of His. QTcF = 428 msec.

Abdominal ultrasound (US) examination from 05.08.2022: There are signs of hepatomegaly, diffuse changes in the liver and pancreas. I degree calicoectasia. Bilateral renal microlithiasis.

ECG from 10.08.2022: voltage is sufficient, sinus rhythm, heart rate – 68/min, HEA is not deviated, incomplete blockade of the right branch of the bundle of His. QTcF = 436 msec.

Sputum analysis from 12.08.2022: AFB-.

After 6 months of the complex treatment with mSTR AMBT (Lfx, Bdq, Lzd, Cfz, Cs), the patient continued to present positive radiological dynamics (*Fig. 4*).

ECG from 07.09.2022: voltage is sufficient, sinus rhythm, heart rate – 64/min, HEA is not deviated, unchanged ECG pattern. QTcF = 420 msec.

Sputum analysis from 08.09.2022: AFB- C (a growth of other flora).

Abdominal US from 08.09.2022: There are signs of hepatomegaly, diffuse changes in the liver, pancreas and renal parenchyma (diabetic nephropathy). I degree calicoectasia. Bilateral renal microlithiasis.

Sputum analysis from 12.10.2022: AFB- C-.

Sputum analysis from 14.11.2022: AFB-.

Sputum analysis from 07.12.2022: AFB-.

9 months after completing the mSTR AMBT (Lfx, Bdq, Lzd, Cfz, Cs) course, the patient had positive X-ray dynamics with the formation of residual changes after tuberculosis (*Fig. 5*).

Thus, the 71-year-old patient suffering from both RR-TB and decompensated T2DM received 9-month course of mSTR AMBT (Lfx, Bdq, Lzd, Cfz, Cs) (39 weeks – 273 doses). Alongside that, he also was treated for diabetes according to the scheme: in the morning – Glymepiride + Humodar C25 100R, in the evening – Humodar C25 100R. Side effects of antimycobacterial drugs were timely corrected during the treatment (anemia caused by Lzd – with Heferol; increased AlAt and AsAt caused by Cfz Bdq Lfx – with Carsil; QTcF interval prolongation and arrhythmia caused by Cfz Bdq – with Bisoprolol and Triductane). Prevention of diabetic angioneuropathy progression caused by Lzd Cs was carried out by the following way: Vitaxon (vitamin B6 100 mg/day) and Dialipon 600 mg/day.

The elderly person with RR-TB and concomitant decompensated T2DM was smear-negative after 4 months as a result of treatment with 9-month mSTR AMBT (Lfx, Bdq, Lzd, Cfz, Cs). Positive radiological dynamics were observed during all that time, and residual changes in the lungs after tuberculosis were diagnosed at the end of the treatment course.

Discussion

The presented case demonstrates the high safety and efficacy of all oral mSTR, including Lfx-Bdq-Lzd-Cfz-Cs, in the elderly person with RR-TB and concomitant decompensated T2DM. These results are in agreement with those of M. B. Souleymane et al. [13], T. Avaliani et al. [4] and V. Schwbel et al. [11].

However, the novelty is that the results of such study are presented for the first time in the elderly person with RR-TB and concomitant decompensated T2DM. There is no information in the literature about possible side effects of antimycobacterial drugs in such comorbid patients and methods for their correction. According to our study results, the patient with RR-TB and concomitant decompensated T2DM had the following adverse reactions to antimycobacterial drugs during treatment: anemia caused by Lzd (corrected with Heferol), increased AlAt and AsAt caused by Cfz Bdq Lfx – (corrected with hepatoprotectors), QTcF interval prolongation and arrhythmia caused by Cfz Bdq (corrected with Bisoprolol and Triductane), diabetic angioneuropathy progression caused by Lzd and Cs (corrected with vitamin B6 and Dialipon).

These results complement indications for the use of mSTR, including Lfx-Bdq-Lzd-Cfz-Cs, in RR-TB patients.

Conclusions

mSTR AMBT (Lfx, Bdq, Lzd, Cfz, Cs) is effective and safe in elderly patients with RR-TB and concomitant decompensated type 2 diabetes mellitus when adequate treatment of diabetes and timely correction of antimycobacterial drug side effects are undertaken.

Prospects for further research is studying the impact of new AMBT regimens for the treatment of MDR-TB/RR-TB patients with comorbidities.

Conflicts of interest: authors have no conflict of interest to declare.
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