ORIGINAL ARTICLE

OTOTOXICITY OF ANTIMYCOBACTERIAL THERAPY: MANIFESTATIONS, MECHANISMS OF MANAGEMENT AND CONTROL

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ABSTRACT

The aim: To study the nature and incidence of hearing loss related to tuberculosis (TB) or resulting from antimycobacterial therapy, and its impact on treatment outcomes in patients with multidrug-resistant TB (MDR-TB).

Materials and methods: An analysis of reports on adverse reactions, medical records and electronic database of the register of TB patients was made. The pathogen was microbiologically verified in all the patients. Patients underwent clinical and laboratory, instrumental, microbiological (BACTEC), molecular genetic (Xpert® MTB/RIF® Ultra, Xpert® MTB/XDR, GenoType® MTBDRplus/sl) examinations. To prevent the development of complications and to control adverse effects, alongside with the determination of the corrected QT interval, visual acuity, and color vision, brief peripheral neuropathy screen and audiometry were performed.

Results: During MDR-TB treatment with aminoglycosides, therapy was more commonly interrupted during the second episode of therapy (p=0,051), while treatment failure, longer treatment duration, and hearing impairment were almost equally observed in both groups (p=0,431, p=0,432, p=0,69). Treatment success was more commonly observed among patients receiving the first course of therapy. Some patients undergoing repeated antimycobacterial therapy were transferred to palliative care (p=0,13). The short-term treatment regimen effectively prevented ototoxicity.

Conclusions: Novel antimycobacterial agents and short-term TB treatment regimens increased patient compliance with treatment and reduced the incidence of certain adverse effects due to their monitoring and prevention. Due to the transition to mainly drug therapy, adverse effects such as ototoxicity were completely eliminated. This was due to personalized treatment selection, its monitoring, and assessing the outcomes.

KEY WORDS: multidrug-resistant tuberculosis, ototoxicity, treatment efficacy, adverse effect

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INTRODUCTION

A thousand-year history of tuberculosis (TB) is the history of mankind's struggle against the disease. This war for health continues today. Due to the discovery of antibiotics to which mycobacteria are sensitive, a strong arsenal against infection has been obtained. However, an extremely urgent concern which affects treatment efficacy and disrupts its possibilities - antibiotic resistance and adverse effects, has arisen [1,2]. The emergence of multidrug-resistant mycobacterial strains and the development of adverse effects result in treatment interruptions or therapy termination due to patient's refusal and the development of severe destructive TB forms. TB treatment regimens with injectable agents, specifically aminoglycosides, result in the development of ototoxic side effects which are irreversible [3-6]. The 8-month intensive phase of MDR-TB treatment with daily intramuscular administration of aminoglycosides, that was the standard chemotherapy for TB, did not change for a very long time [1-13], which often resulted in toxic damage to the ear – sensorineural hearing loss (SHL).

Factors that potentiate each other and contribute to the clinical presentation of the disease such as the toxic effect of mycobacterial by-products, the specific effect of aminoglycosides on the vestibulocochlear analyzer, the general toxic effect of antimycobacterial therapy, impaired blood rheology and microcirculation, allergic sensitization to antibiotics, are involved in the pathogenesis [3,5]. Other risk factors include concomitant ear diseases and disorders, head injuries, cerebrovascular accidents, myositis, etc. The mechanisms involved in ototoxicity are as follows: the competition between calcium and magnesium ions on the cell surface; an active energy-dependent transport of aminoglycosides into the cell; irreversible binding of antibiotics to phosphatidylinositol phosphate (PIP2), a physiologically important phospholipid of the cellular membrane which is involved in transferring second messenger signaling that causes long-term damage to recep-

tor cells. As a result, damaged ribosomes, altered protein synthesis, impaired oxygen metabolism in the inner ear are seen. The great challenge we face is the impossibility to eliminate the main causative agent of ototoxicity since aminoglycosides, as one of the first-line drugs for MDR-TB, should be used for a long time, that, in its turn, increases the risk of complications [1,5-7]. In addition, the approach to correcting adverse effects is complicated by the negative potentiation of antimycobacterial therapy ototoxicity by vascular agents included in the protocols for providing medical care 'Otolaryngology'.

A new era has set ambitious goals and built strategies of their implementation – less than 1 case per million population and no TB deaths by 2050. Novel roadmaps for TB elimination include the latest rapid diagnostic methods (Xpert® MTB/RIF® Ultra, Xpert® MTB/XDR, GenoType® MTBDRplus/sl, whole-genome sequencing), a wide range of modern antimycobacterial drugs (linezolid, bedaquiline, delamanid, pretomanid), relevant, short-term drug regimens, monitoring and prevention of adverse effects [4,8,10,11].

The new paradigm is the activation of the maximum efforts of the entire community, including medicine, for the control and elimination of TB. The principles of preventing and controlling infectious diseases should not be neglected. If one almost forgot about an infectious disease, it doesn't mean it was eliminated and disappeared. No, it persists, but constant surveillance, prevention, timely diagnosis, and high-quality treatment can protect us against TB, an insidious disease humanity has been battling for many centuries.

THE AIM

The paper analyzed the incidence of ototoxic responses to anti-TB drugs and treatment outcomes in patients with MDR-TB depending on the chosen treatment regimen. A case report of ineffective treatment with the transition from curative to palliative care in a patient who developed pronounced ototoxic changes is presented. The ability to completely eliminate ototoxic changes and minimize other side effects of antimycobacterial therapy, provided that short-term therapy regimens are used.

MATERIALS AND METHODS

An analysis of 374 reports on adverse reactions, medical records and electronic database of the register of patients treated at a communal non-profit enterprise "Ivano-Frankivsk Regional Phthisiopulmonology Center of Ivano-Frankivsk Regional Council" between 2017-2019 and 2020-2022 was made. The division into groups took place according to the frequency of episodes of treatment for tuberculosis. The first group is the primary treatment case, the second group is the repeated treatment case. TB was microbiologically verified in all the patients. According to the order of Ministry of Health of Ukraine (MoH) No. 420 dated September 14, 2014 "Unified Clinical Protocol of Primary, Secondary (Specialized), and Tertiary (Highly Specialized) Medical Care Tuberculosis" and the order of the MoH No. 530 dated February 25, 2020 and its edition No. 2161 dated October 6, 2021 "On Approval of Healthcare Standards in Tuberculosis", all the patients underwent mandatory laboratory, instrumental (X-ray, computed tomography, spirometry, fibrobronchoscopy, lung ultrasound, abdominal ultrasound, audiometry), molecular genetic (Xpert® MTB/RIF® Ultra, Xpert® MTB/XDR, GenoType® MTBDRplus/sl) examinations, sputum sample cytology, and phenotyping (BACTEC system, solid Lowenstein-Jensen medium) [11]. Adverse effects were monitored during treatment and according to the scheme developed on the basis of patient categories: peripheral neuropathy (PN) was graded using the scale for subjective PN assessment; audiometry was applied to identify impaired hearing; the corrected QT interval was determined; visual acuity and color vision were measured by the Ishihara color test; serum levels of bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) as indicators of hepatotoxicity and creatinine clearance levels as markers of nephrotoxicity were measured; complete blood count (CBC) was done to check for myelosuppression [8,10]. The data obtained were statistically processed using the Microsoft Excel package of statistical functions. The significance of the difference was determined by the Fisher's F-test for parametric data. A test statistic is about the ratio of sample variances.

RESULTS

An analysis of reports on adverse events during 2017-2019 showed that among 193 documented cases, 55 (28.5%) adverse effects followed treatment of drug-sensitive TB and 138 (71.5%) side effects developed in MDR-TB. The treatment regimen for MDR-TB included pyrazinamide (Z), levofloxacin (Lfx), aminoglycosides – kanamycin (Km) and capreomycin (Cp), ethionamide (Eto) or protionamide (Pt), cycloserine (CS), para-aminosalicylic acid (PAS) for 20 months, with the 8-month intensive phase involving once-daily intramuscular injections of aminoglycosides. During MDR-TB treatment, there were 29 (21.0%) cases of ototoxicity, including SHL, hearing loss, and its coexistence with vestibular disorders (dizziness, balance problems, unsteady gait). The rate of onset, the intensity of manifestations, and the effect on treatment outcomes depended on the number of treatment episodes (Table I).

Table I. Treatment efficacy in patients with ototoxic manifestations who received anti-tuberculosis drugs during 2017-2019, %

Treatment efficacy	Treatment episode I, n=10	Treatment episode II, n=19	Fisher's exact test, p
Treatment interruption	4 (40.0)	15 (78.9)	=0,051
Treatment failure	2 (20.0)	7 (36.8)	=0,431
Longer treatment duration	5 (50.0)	13 (68.4)	=0,432
Treatment success	8 (80.0)	7 (36.8)	=0,05
Hearing abnormality	5 (50.0)	12 (63.2)	=0,69
Palliative treatment	0 (0.0)	5 (13.7)	=0,13

Table II. Treatment efficacy in patients with ototoxic manifestations who received anti-tuberculosis drugs during 2020-2022, %

Treatment efficacy	Treatment episode I, n=2	Treatment episode II, n=2
Treatment interruption	0	0
Treatment failure	0	0
Longer treatment duration	1 (50,0)	2 (100)
Treatment success	2 (100)	2 (100)
Hearing abnormality	0	1(50,0)
Palliative treatment	0	0

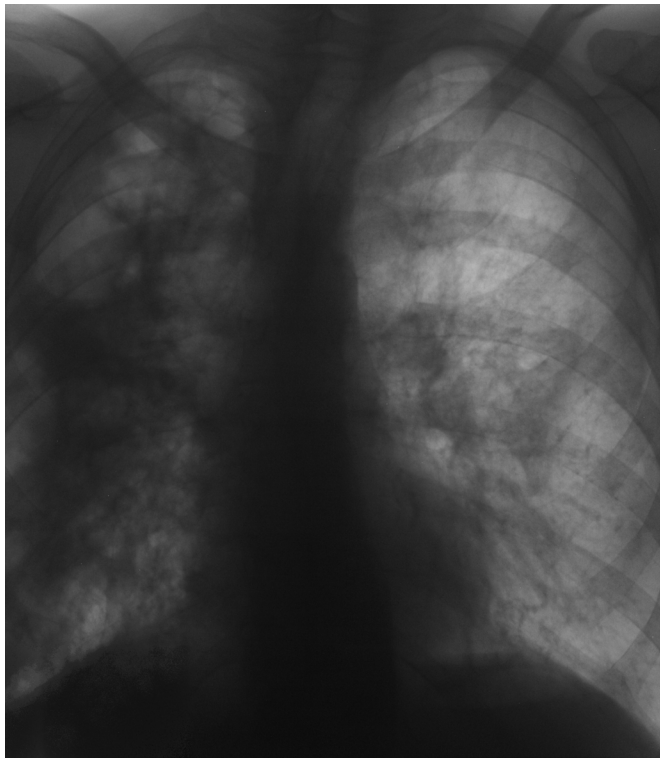

Fig. 1. Chest X-ray on hospital admission

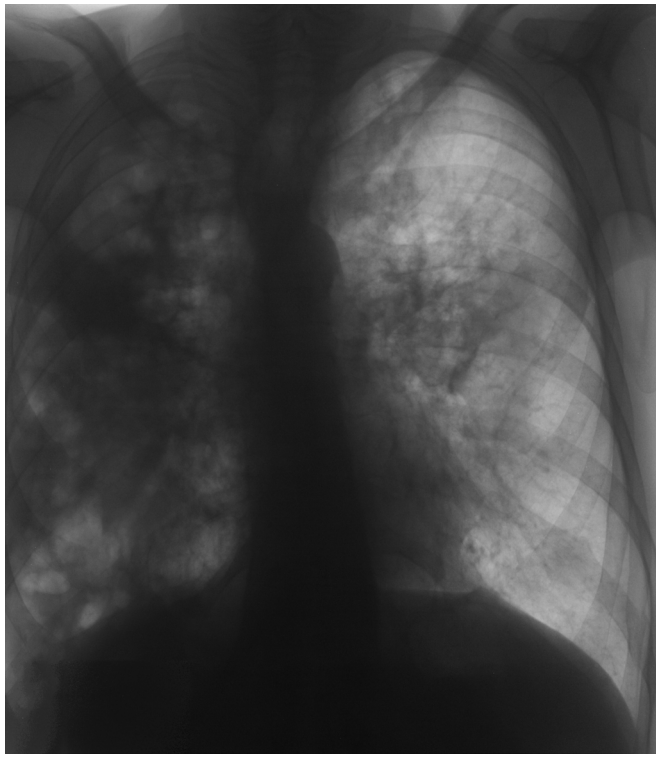

Fig. 2. Chest X-ray four months after starting TB treatment

With equal distributions of two samples according to Fisher's exact test, it can be seen that a statistically significant break in treatment is most often found in patients who had a repeated episode of treatment, which is confirmed by the reliability of the value p=0.051, more effective treatment according to the cured status was in patients with the first episode of treatment, shows reliability value p=0.05. According to other criteria of treatment effectiveness, such as failure, prolongation of treatment duration, hearing loss, palliative treatment, the same frequency of manifestation was observed both in the first and in the second episodes of treatment with the reliability of the value of the Fisher test, respectively p=0.431, p=0.432, p= 0.69, p=0.13. To correct

ototoxicity manifestation and prevent its progression, detoxification therapy, adenosine-triphosphoric acid (ATP), B vitamins, hepatoprotectors were administered. Vascular agents (cavinton, nootropil) were not used as they enhance the toxic effect of anti-TB drugs in the intensive phase of therapy. However, despite all the efforts made to control adverse effects, at the end of the first episode of MDR-TB treatment, 50% of convalescents reported hearing impairment, with the treatment success rate of 80.0%. No statistic reflects an individual case; hence we present a case report of pronounced toxicity when the patient refused TB treatment. A 35-year-old musician M. was admitted to inpatient treatment. The patient presented with coughing up white mucus, subfebrile temperature of 37.5 °C, general fatigue, weight loss, dyspnea on exertion. CBC: hemoglobin (Hbg) – 116 g/l, red blood cells (RBC) – 3.1×10^{12}/l, white blood cells (WBC) – 12.6×10^{9}/l; band neutrophils – 7%, segmented neutrophils – 65%, monocytes – 10%; lymphocytes – 12%; eosinophils – 6 %; erythrocyte sedimentation rate (ESR) – 28 mm/hr. Chest X-ray confirmed disseminated destructive TB (Fig 1). Recurrent MDR-TB was diagnosed: resistance I (isoniazid, rifampicin, ethambutol), resistance II (-). The following treatment regimen was created: 8 Z Lfx Km Eto Cs PAS /12 Z Lfx Eto Cs PAS.

During the first month of treatment, dizziness and hearing loss were observed. According to audiometry findings (mild SHL) and after ENT consultation, B vitamins, specifically B_1, B_6, B_{12}, at a dose of 2.0 ml every other day, 1 ml of 1% ATP solution intramuscularly for 10 days, and Heptral (1 capsule twice a day) were added to the treatment regimen. The treatment received did not normalize hearing loss. A one-week interruption of TB treatment and detoxification were suggested. Upon returning to the treatment regimen, hearing loss worsened – moderate SHL according to audiometry findings. The patient refused Km injections. The efficacy of further TB therapy reduced and three weeks after the termination of Km injections, intoxication symptoms, including fever up to 38.6 °C, general fatigue, dyspnea on exertion developed. CBC: Hbg – 115 g/l, RBC – 3.1×10^{12}/l, WBC – 13.6×10^{9}/l; band neutrophils – 7%, segmented neutrophils – 67%, monocytes – 10%; lymphocytes – 10%; eosinophils – 6%; ESR – 34 mm/hr; controlled chest X-ray was negative (Fig 2).

A decision on returning to the treatment regimen with Km was made. The patient agreed to change therapy. However, within the first month of returning to the standard TB treatment regimen, hearing loss worsened again. Despite the improvement of the general condition, the patient signed refusal of treatment form, was transferred to the category of palliate care, and left for another region.

The discovery of new antimycobacterial agents (linezolid, delamanid, bedaquiline, pretomanid) allowed for shortening treatment duration, modifying the regimens, and improving treatment efficacy up to 90.0%. Aminoglycosides are used only in cases when there is a need for an individualized treatment plan. Such approach significantly reduced the incidence of ototoxicity. Thus, during 2020-2022, 181 reports on adverse effects were documented: 139 (76.8%) adverse events were reported by patients receiving MDR-TB treatment and only four (2.9%) patients developed ototoxicity (individualized therapy with Km).

In patients with manifestations of ototoxicity, prolongation of the duration of treatment was noted during repeated treatment in 2 (100.0%) patients, a clinically significant decrease in hearing was observed in 1 (50.0%) patient during a repeated treatment episode.

These cases were successfully corrected by replacing the preparation by another agent from Group C. The 11-month modified short-term treatment regimen including bedaquiline (for 6 months), levofloxacin, clofazimine, ethionamide, ethambutol, isoniazid (high dose), pyrazinamide + levofloxacin, clofazimine, ethambutol, and pyrazinamide for 5 months produced no ototoxic effects.

DISCUSSION

TB is a very 'stubborn' disease which remains one of the most dangerous infectious killers worldwide. An understanding of mutual responsibility of the society and the need to make every effort possible to control the disease encourage constant progress in the development and improvement of both diagnostic methods and treatment regimens.

The main challenge is effective therapy which results in treatment success without any side effects being barriers in TB treatment and leading to unfavorable outcomes. Some adverse effects develop slowly, and the patient seems to adapt to changes, believing that they are the consequences of TB and that they will go away with recovery. Unfortunately, the outcomes are unfavorable as having a disability does not mean a person has good health. In some cases, however, serious adverse event develops, which progresses and results in patient's refusal of TB treatment [7,13].

Authors Ignat'eva V.I., Martsyniuk T.M. (2018) pay special attention to the negative effects of polychemotherapy on the central and peripheral nervous system. At the same time, special importance is attached to drugs of the group of aminoglycosides, which cause damage to the vestibule-cochlear nerve. It is noted that during the main course of chemotherapy in patients with MDR

TB of the lungs, medication complications occur, which are manifested by the «hearing loss» syndrome, namely: acute sensorineural deafness, bilateral eustachianitis, and drug-induced encephalopathy. Accordingly, there is a need to use additional methods of differential diagnosis: echoencephalography and audiometry. This makes the course of tuberculosis treatment more expensive and not always available on time [7]. Complaints related to hearing loss, as a rule, appear already at the stage of deep and irreversible damage to the cochlear nerve. This leads to deterioration of treatment results. The data obtained by us are comparable to the data of the above-mentioned authors. Moreover, among patients treated between 2017 and 2019, break in treatment is most often found in patients who had a repeated episode of treatment, which is confirmed by the reliability of the value p=0.051, more effective treatment according to the cured status was in patients with the first episode of treatment, shows reliability value p=0.05. Modern antimycobacterial agents and new, modified, short-term treatment regimens eliminate a lot of side effects leading to a deterioration in the patients' condition, treatment termination, and transfer to the category of palliative care [1,8,10]. The analysis of data on the efficacy of treatment and the incidence of ototoxicity as a side effect during the observed periods found that during 2017-2019, adverse events were significantly more common as compared to 2020-2022 – 21.0% and 2.9%, respectively. Among the cohort of patients with manifestations of ototoxicity in the period 2020-2022, only a prolongation of the treatment period was observed, which did not lead to palliative treatment. Also, in only one patient from the group of repeated episodes of therapy hearing loss was observed.

Among patients receiving the individualized treatment regimen, who periodically underwent detoxification and pathogenetic therapy due to adverse effect development, the high percentage of cases with longer treatment duration was noted.

CONCLUSIONS

1. Antimycobacterial therapy of multidrug-resistant pathogen strains with the addition of aminoglycosides increases the incidence of ototoxic adverse effects. This has the negative effect on the duration and efficacy of treatment.
2. A high frequency of ototoxic lesions was observed in patients with multidrug-resistant tuberculosis who were treated with aminoglycosides during the period 2017-2019 – 21,0%. The development and implementation of modified short-term treatment regimens for MDR-TB, in the period 2020-2022, minimizes the occurrence of further adverse events such as SHL - 2,9%, thereby allowing the patient to recover from TB without developing serious complications such as total hearing loss.
3. The development of ototoxic lesions led to the negative effect of treatment. Moreover, repeated cases of treatment were characterized by more significant changes. We noted that a statistically significant break in treatment is most often found in patients who had a repeated episode of treatment, which is confirmed by the reliability of the value p=0.051, more effective treatment was in patients with the first episode of treatment, shows reliability value p=0.05. Failure, prolongation of treatment duration, hearing loss, palliative treatment, was with the same frequency of manifestation was observed both in the first and in the second episodes of treatment with the reliability of the value of the Fisher test, respectively p=0.431, p=0.432, p= 0.69, p=0.13.
4. TB patients are recommended to be adapted to short-term drug regimens as much as possible by assessing the risks of adverse effects and their preventing to avoid treatment termination as the next step is the creation of the individualized treatment plan which may include aminoglycosides, if there is no other choice. Therapeutic drug monitoring, timely detection of adverse effects, their prevention and treatment are the keys to cure the patient.

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