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Traditional and Short Course Treatment for Multidrug-Resistant Tuberculosis: A Comparative Study in National Referral Centers

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Background: Treatment of multidrug-resistant tuberculosis (MDR-TB) is difficult, expensive, and requires prolonged periods of time. Recent studies recommended short-course therapy (shorter regimen) for 9 months to one year. This study aimed to evaluate the response of the short-course therapy compared with traditional treatment in MDR-TB patients.

Materials and Methods: From all 94 referred MDR-TB cases, 48 patients were included in this study. Shorter regimen consisted of Moxifloxacin, Prothionamide, Amikacin, Clofazimine, Linezolid, Ethambutol, Pyrazinamide, and Cycloserine, and longer regimens consisted of the mentioned drugs, except Clofazimine and Linezolid, were prescribed randomly: in equal (24 in each group). The patients were monitored and evaluated for any complications and were followed for five years for relapse.

Results: The median age was 39 years. The median interval for smear conversion was 30 days (20- 58 days) and was shorter in the short-course group (36 vs. 49 days). Also, the mean interval of sputum culture conversion in the shorter group and standard was 32 and 56 days, respectively, which is not related to the outcome of treatment. Eight of twelve patients who developed severe adverse effects were in shorter regimen. There was no difference between the two groups for the outcome of TB treatment. There is no relation between the outcome and other factors. None of them relapsed after three years following the end of the treatment.

Conclusion: Shorter treatment can increase the cure rate and cooperation and adherence of the patients. It would be better to consider a shorter regimen in the national TB program for strengthening favorable treatment.

Keywords: Multidrug resistant; Shorter treatment; Adverse effects; Outcome

INTRODUCTION

Almost half a million individuals develop tuberculosis (TB) disease caused by rifampin- or multidrug-resistant (RR/MDR) strains of *Mycobacterium tuberculosis* (M.TB) every year (1). RR/MDR-TB treatment remains challenging and needs a standardized, individualized, and empirical combination regimen with lengthy durations. There is a substantial risk of unfavorable outcomes among these patients (1). The latest global treatment outcome data for people with RR/MDR TB show a global treatment success rate of 57% (1). However, individual outcomes can be improved by precision treatment guided by drug susceptibility testing (DST) (2).

In 2016, the World Health Organization (WHO) introduced guidelines that included the option of treating RR/MDR-TB with a standardized regimen of 9-12 months in duration (the "shorter regimen") as well as an option of an individualized regimen of 18-24 months (the "longer regimen") (3). Patients must meet the eligibility criteria for the shorter regimen, which consists of a high likelihood of susceptibility to fluoroquinolones (FQ) and second-line injectable agents, and no previous treatment with second-line drugs for more than 1 month (4). After reporting a treatment success rate (87.9%) of a shorter regimen in Bangladesh (5), confirmatory studies conducted in other countries (6, 7), all of which reported high treatment success rates over 89%. Subsequently, results of the first randomized controlled trial (RCT) study (STREAM study) with a shorter regimen were published, with a treatment success rate of 78.8% (8). Though these studies showed highly favorable outcomes with the shorter regimen, some issues remain uncertain.

First, it is unclear whether the shorter regimen is more effective than individualized longer regimens. Comparing the shorter regimen with longer regimens composed per 2016 WHO guidelines in some studies illustrated that relapse, death rates, and the time of culture conversion were high in the shorter regimen group, but not statistically significant; overall treatment success was noninferior in the shorter regimen (9, 10). Second, there should have been a wider debate on resistance to its constituent drugs (11-15). It should be too restrictive against the use of the shorter regimen in the presence of resistance to any of its component medications because of worse outcomes for people on this regimen (12, 16, 17). In 2018, WHO released an updated guideline, where injectable drugs were no longer recommended except for shorter regimen, and then the next guideline review by a Guideline Development Group (GDG) recommended fluoroquinolones [levofloxacin (Lfx) or moxifloxacin (Mxf)], bedaquiline (Bq), and linezolid (Lzd)] in a short regimen (18, 19). The combination of Bq, Lzd, and pretomanid for 26 weeks in patients with extensively drug-resistant (XDR) TB had a favorable outcome (88%) in the Nix TB study (20).

According to recommendation of the WHO guidelines 2016 and other studies for using the shorter regimen for RR/MDR TB treatment, we conducted a randomized study to assess the effectiveness of the shorter regimen. Other objectives were to identify the time of clearance of sputum smear and culture in a shorter regimen and compare it with a longer regimen. We monitored and determined the adverse effects (AEs) of anti-TB drugs in both groups and evaluated AEs in both regimens. Also, we counted occurrences of relapse and loss to follow-up in both groups.

MATERIALS AND METHODS

All confirmed RR/MDR-TB patients, who met the eligibility criteria for a short regimen (no previous treatment with second-line drugs for more than one month and not infected with *M.TB* resistant to fluoroquinolones or second-line injectable agents), were referred and admitted to Masih Daneshvari Hospital, and entered at this study. A randomized cohort study was conducted from May 2017 to May 2019, and the participants have been followed up for 3 years from TB-treatment completion. The study based on PICO question was done: Population will be RR/MDR- TB patients, Intervention: Shorter regimen, Control: longer regimen, and Outcome will be the outcome of RR/MDR- TB treatment, the time of clearance of sputum smear and culture, and relapse.

Study regimens

The shorter regimens were defined as standardized regimens with a duration of 12 months, consisting of moxifloxacin (Mfx), prothionamide (Pto), amikacin (Am), clofazimine (Cfz), linezolid (Lzd), ethambutol (EMB), pyrazinamide (PZA), and cycloserine (Cs) for 6 months, followed by 6 months of PZA, Mfx, Lzd, Cfz, and Cs. We substituted within-class drugs as the WHO had permitted:

amikacin or capreomycin instead of kanamycin (3).

According to the 2015 WHO guidelines, we defined longer regimens as individualized regimens that included levofloxacin (Lfx) or Mfx, Am, Cs, Pto, PZA, and EMB for at least 8 months, followed by 10-12 months of Lfx, Cs, and PZA or Pto if the sputum smear was converted to negative (21).

We composed longer regimens according to the 2015 guidelines, though guidelines changed in 2016/2018 (19, 21, 22). This new long regimen consisted of bedaquiline, Lzd, carbapenems, and delamanid (22). In addition, bedaquiline and delamanid were not available in our country until 2019.

Study design

We conducted a prospective randomized study from May 2017 to May 2019 to evaluate two shorter and longer regimens, assuming that the treatment success rate of the shorter regimen is noninferior to that of the longer regimens.

All peripheral health centers from 31 provinces in Iran cooperated in this project. Their cooperation was to refer the patients for confirmation of MDR diagnosis, initiation of treatment, direct observation of treatment after discharge from the hospital, and refer the patients who developed adverse effects of drugs.

All medications were provided by the principal investigator (PI). Written informed consent was obtained from the participants.

Patient selection

RR/MDR- TB patients were included in the study if they were confirmed by molecular DST methods or identified by the GeneXpert system and met WHO criteria for use of the shorter regimen: no previous treatment with second-line drugs for more than one month and not infected with *M.TB* resistant to fluoroquinolones or second-line injectable agents.

All adult patients over the age of 15 with RR/MDR TB were referred to Masih Daneshvari Hospital for this study and subsequently admitted. Patients remained in the hospital until they produced at least two negative sputum smears, with a one-week interval between tests. This included all pulmonary TB patients with a positive sputum smear for acid-fast bacilli (AFB) or a positive culture for *Mycobacterium tuberculosis*. HIV-positive patients were also included in this study, and there were no exclusion criteria for them.

All patients must have signed the informed consent and must have been willing to take the medication based on their regimen.

We did not exclude patients with missing outcome but we considered them as unfavorable outcomes. Also, the patients who were treated for less than the minimal recommended duration (8 and 17 months for shorter and longer regimens, respectively, as cut-offs for minimal duration) were not excluded.

Patients with non-tuberculous mycobacteria (these patients are resistant to H and R, but they are not classified as MDR) were excluded.

Bacteriological study

Sputum direct smear was performed using light-emitting diode fluorescence microscopy for AFB. Sputum culture was done with Ziehl-Neelsen staining.

Drug susceptibility testing is performed for first-line (consisting of isoniazid, rifampin, ethambutol, and pyrazinamide) and second-line anti-TB drugs using the proportion method on Löwenstein- Jensen medium (23). A molecular resistance test for isoniazid (INH) and rifampin (RIF) was performed on all TB patients at the hospital. The Swedish Institute for Infectious Disease Control (Solna, Sweden) and the Research Institute of Tuberculosis of the Japan Anti-Tuberculosis Association (Tokyo, Japan) regularly supervised our referral laboratory for quality control. The details have been thoroughly described elsewhere (24). Additionally, the Hain GenoType® MTBDRplus line-probe assay (Hain LifeScience GmbH,

Nehren, Germany) for INH and RIF was conducted on all patients with smear-positive sputum for rapid detection of resistance to these drugs.

Sputum smear and culture were examined monthly and every two months, respectively, to assess the treatment responses. For patients undergoing the GeneXpert assay, tests were conducted every three months. At the end of the treatment, sputum smear and culture tests were performed for all patients to report the outcomes.

Treatment outcome

The primary outcome included (1) the proportion of conversion of sputum smear and cultures at least within two and four months; (2) reporting and recording adverse events (AEs) during the treatment. The second outcome assessment was the proportion of the favorable outcome. Patients were considered as favorable outcome if sputum cultures had been converted and remained negative till the completion of treatment (after 12 months of initiation therapy), as a cure or complete definition. The unfavorable outcome was defined as follows: (1) death from any cause during the treatment, (2) failure, (3) loss to follow-up, or (4) not to evaluate. We considered the WHO definition for outcome (Table 1) (4).

Patient's sample

The present study was designed as a randomized controlled trial to compare the new shorter regimen with the longer regimens outlined in our National TB guideline (NTG). The hypothesis is that the treatment success rate of the shorter regimen is non-inferior to that of the longer regimen. Assuming that 85% of participants in the shorter arm and 60% in the longer arm (the non-inferiority margin) will achieve favorable outcomes, based on the WHO report of Iran in 2015, and accounting for a 20% loss to follow-up, we estimated that 26 participants would need to be recruited to achieve 80% power to demonstrate the non-inferiority of the shorter regimen compared to the longer regimen, with a two-sided significance level of 0.05.

Until this report, we reached 48 patients of all 94 referred MDR-TB patients, 24 patients in each arm. We were not able to continue the study for recruiting more patients because the new all-oral short-course regimen of RR/MDR- TB treatment was replaced with the old regimen, as the NTG, and we could not be against it.

Table 1. Summary table of outcome definitions for MDR-TB

Outcomes	Definitions
Cured	Patient initially bacteriologically confirmed (culture or molecular test), who completed treatment AND with at least 3 negative cultures in the last 8 months of treatment AND does not meet the definition of failure. If a single positive culture or smear is reported during that period, in the absence of concurrent clinical evidence of deterioration, the patient may still be considered cured, provided that the positive result is followed by at least three consecutive negative cultures obtained at intervals of no less than 30 days.
Completed	Patient who completed treatment AND has no signs of continued active disease AND does not meet the bacteriological criteria for cure.
Failure	Treatment terminated or need for permanent treatment change of at least 2 classes of anti-TB drugs because of one or more of the following: • Lack of monitoring cultures converting to negative by 6 months for MDR-TB (3 months for PDR-TB), and/or • Resistance amplification to rifampicin or isoniazid (PDR-TB) or to Group 2 or Group 3 drugs (MDR-TB), and/or • Bacteriological reversion (at least two positive smears or cultures at least 7 days apart after monitoring smears or cultures have become negative), or • A clinical decision has been made to terminate treatment early due to poor response or adverse events. These latter failures can be indicated separately in order to do a sub-analysis.
Interrupted	Patient who interrupted treatment for 2 months or more.
Death	Patient who died on TB treatment or while awaiting TB treatment, irrespective of the cause of death. The cause of death should be recorded.
Not evaluated	Patient whose treatment outcome is unknown (including patients "transferred out" to another treatment center, for whom the outcome is unknown).

MDR-TB: multidrug-resistant tuberculosis, PDR: polydrug-resistant

Management and monitoring of patients

Table 2 shows the doses and usage of each drug in the WHO shorter and longer regimens (3). Patients with

RR/MDR- TB were divided into two groups based on regimen; shorter regimen and a longer regimen in equal numbers. The shorter regimen consisted of moxifloxacin, prothionamide, amikacin, clofazimine, linezolid, ethambutol, pyrazinamide, and cycloserine for 12 months, while the longer regimen, which consisted of levofloxacin, prothionamide, cycloserine, amikacin, ethambutol, and pyrazinamide for 18- 24 months were prescribed to RR/MDR- TB patients.

Table 2. Drugs and doses used for RR/MDR- TB treatment

Drug	Dose and usage
Amikacin	15 mg/kg, daily, maximum 1g/day (intravenous or intramuscularly)
Cycloserine	500- 750 mg daily, once or divided in two, before or after a meal
Prothionamide	500- 750 mg daily, once, before or after a meal
Moxifloxacin	400- 600 mg daily, once, before or after a meal
Levofloxacin	500- 750 mg daily, once, before or after a meal
Ethambutol	15- 25 mg/kg, daily, once, before or after a meal
Pyrazinamide	20- 30 mg/kg, daily, once, before or after a meal
Linezolid	600 mg daily, once, before or after a meal
Clofazimine	100 mg daily, once, before or after a meal

RR/MDR- TB: Rifampin or multidrug-resistant tuberculosis, mg: Milligram, kg: kilogram

For all patients, baseline laboratory evaluation includes complete blood count (CBC), creatinine (Cr), potassium (K), and liver function test (LFT). HIV was checked for all patients using rapid diagnostic tests. All women of reproductive age were tested for pregnancy. Electrocardiography (ECG), audiometry, ophthalmologic examination, and psychological consulting were requested for all patients at the baseline of TB treatment. During the hospitalization, sputum smear was checked every two weeks. When two consecutive smears tested negative, the patient was discharged and referred to the peripheral health center (PHC) to continue treatment under the DOTS (Directly Observed Treatment, Short-course) program. In some cases, the patients preferred to be visited at our hospital by the PI.

Follow-up visits for all patients were conducted every four weeks during the first 24 weeks, followed by visits every 12 weeks until the end of treatment. After treatment, follow-up continued every 12 weeks for the first 26 weeks, then every 24 weeks until the conclusion of the study. We recorded occurrences of reinfection and relapse during the follow-up period, which extended for two years after the treatment ended.

During the follow-up, the clinical assessment included a physical examination, ophthalmologic evaluation, hearing tests, and an assessment for peripheral neuropathy. Laboratory tests, such as potassium (K), creatinine (Cr), liver function tests (LFT), and complete blood count (CBC) (if the patient was receiving Linezolid), were conducted. An electrocardiogram (ECG) was evaluated for patients receiving Clofazimine (Cfz) and Moxifloxacin (Mfx), if available and necessary. Additional examinations were performed as needed.

If there were abnormal results, the patient or health worker made a call to PI, and if it needed, the patient was referred to Masih Daneshvari hospital for admission or further evaluation.

Data collection and quality management

All data were collected and entered into SPSS v.16 (SPSS Inc., Chicago, IL) by the Principal Investigator (PI). Only the PI had access to the software's functionality and the dataset, as well as the ability to report the results. All records were thoroughly checked for completeness, reliability, and accuracy. The NIMAD regularly verified patient eligibility and the integrity of follow-up data. Participants' personal information was limited to what was necessary, in compliance with privacy protection laws to ensure confidentiality. Access to study documents was restricted to authorized personnel, specifically the PI.

Adverse events management

The patients were closely monitored and evaluated for any treatment complications both during their hospital stay and after discharge, conducted by qualified healthcare professionals (doctors in the hospital and health workers at the primary health center). It was essential for patients to

visit every month for the first six months, and then every three months thereafter, to assess their symptoms and laboratory tests. All patients received training and information regarding the symptoms of potential adverse effects from the medication. If any symptoms arose during TB treatment, the patient would return for evaluation and appropriate laboratory tests.

We did not exclude patients who experienced adverse effects. Instead, we managed these effects by temporarily discontinuing the responsible medications. For instance, in cases of drug-induced hepatitis where liver enzyme levels increased more than 3-5 times, we would suspend the use of pyrazinamide (PZA) and prothionamide (Pto) until liver function tests returned to normal levels. In cases of severe adverse events, such as thrombocytopenia, suicidal tendencies, severe hepatitis, and shock, clinicians would also discontinue the responsible medication.

Statistical analysis

All demographic and clinical information for TB patients was analyzed using SPSS v.16 (SPSS Inc., Chicago, IL). Categorical variables were compared using the χ^2or Fisher's exact test, and were reported with descriptive statistics (counts, percentages, and proportions). Continuous variables were described with a mean (standard deviation, SD) and medians (interquartile range, IQR), and were compared using the Student's t-test. The Mann–Whitney *U*-test was used to compare non-normally distributed continuous variables. A $p<0.05$ was considered significant.

Ethical considerations

The study protocol was reviewed and approved by the Elite Researcher Grant Committee under award number (962629), approval from the National Institute for Medical Research Development (NIMAD), and the NRITLD Scientific and Ethics Committee, Tehran, Iran.

RESULTS

A total of 48 participants were enrolled and analyzed from a pool of 94 patients referred to our hospital. Among these participants, 24 received a shorter treatment regimen, while the other 24 received a longer regimen. The median age of the participants was 39 years, with an interquartile range (IQR) of 30 to 51 years. Of the participants, 34 (70.8%) were Iranian, and 14 (28.2%) were female. Additionally, 46 (95.8%) had received prior treatment, with 17 (35.4%) having undergone anti-TB therapy (first-line drugs) more than once.

Chest X-rays revealed that 37 participants had cavities, with 11 (22.9%) showing bilateral cavities. Among all patients, 24 (50%) were confirmed to have multidrug-resistant tuberculosis (MDR-TB), and 24 (50%) were diagnosed with rifampicin-resistant tuberculosis (RR-TB).

37 (77.1%) patients completed the treatment with two sputum smears and culture results negative, of whom 20 (83.3%) received a shorter regimen.

Amikacin was administered based on the patients' conditions for a duration of 2 to 5 months. While there was no significant difference in the mean age between the two groups, the mean age in the longer treatment regimen group was higher than that in the shorter regimen group (45 years compared to 39 years). Additionally, the mean sputum smear grade in the longer regimen group was significantly higher than that in the shorter regimen group ($p=0.037$).

The overall median interval for both smear and culture conversion was 30 days, with a range of 20 to 58 days. The median time needed for smear conversion was 23 days for the shorter regimen and 37 days for the longer regimen. For culture conversion, the median times were 22 days for the shorter regimen and 30 days for the longer regimen.

In the shorter regimen group, the mean interval for sputum smear conversion was shorter but not statistically significant, showing 36 days compared to 49 days in the longer regimen ($p=0.22$). Similarly, the mean interval for sputum culture conversion was 32 days in the shorter group and 56 days in the longer group, which also did not correlate with treatment outcomes ($p=0.66$).

At the end of the second month of treatment, the shorter regimen group showed smear and culture conversion rates of 87.5% (21 out of 24) and 91.7% (22 out of 24), respectively. In contrast, the longer regimen group

had conversion rates of 75% (18 out of 24) for both smear and culture.

Although the smear and culture conversion rates after two months were comparable between the shorter and longer groups, the differences were not statistically significant (p=0.46 for smear conversion and p=0.24 for culture conversion) (Table 3).

In total, there were 29 adverse events (AEs) reported. Among these, 4 AEs led to the replacement or interruption of anti-tuberculosis agents, 8 AEs resulted in permanent discontinuation of treatment, and 17 AEs (due to increased skin pigmentation) required no action. In one case, amikacin was substituted with capreomycin because of elevated creatinine levels.

The drugs responsible for severe AEs were permanently discontinued: amikacin (associated with three cases of rising creatinine levels and one case of hearing loss), cycloserine (linked to one suicide and one case of psychosis), linezolid (causing two instances of anemia), pyrazinamide (related to one liver injury and one case of arthralgia with rising uric acid levels), and prothionamide (connected to one liver injury).

Clofazimine caused increased skin pigmentation in all patients undergoing the shorter regimen; however, we advised the use of appropriate sunscreen and moisturizers after showering. We did not discontinue clofazimine due to skin discoloration (Table 4).

Table 3. Characteristics of MDR-TB patients based on the type of treatment

Characteristics	Overall N=48	Type of treatment		p-value
		Shorter N=24	Longer N=24	
Age (Mean± SD)	42± 15	39.1±15.2	44.9± 14.5	0.18
Male gender	34 (70.8%)	17 (70.8%)	17 (70.8%)	1
Iranian	34 (70.8%)	16 (66.7%)	18 (75%)	0.52
History of smoking	23 (47.9%)	11 (45.8%)	12 (50%)	0.77
History of opium use	20 (41.7%)	9 (37.5%)	11 (45.8%)	0.56
HIV	5 (10.4%)	1 (4.2%)	4 (16.7%)	0.35
Diabetes mellitus	14 (29.2%)	4 (16.7%)	10 (41.7%)	0.11
Co-disease	22 (45.8%)	5 (20.8%)	17 (70.8%)	0.001
Duration of previous TB treatment (months)	6	7	8	0.58
Smear grade (median)	2	1	2	0.20
3+	20 (41.7%)	17 (45.9%)	3 (27.3%)	
2+	5 (10.4%)	3 (8.1%)	2 (18.2%)	
1+	12 (25%)	10 (27%)	2 (18.2%)	
Scanty	11 (22.9%)	7 (18.9%)	4 (36.4%)	
Cavitary image	37 (77.1%)	18 (75%)	19 (79.2%)	0.73
Adverse events¥	12 (25%)	8 (33.3%)	4 (16.7%)	0.32
Time to smear conversion (days)	42	36	49	0.22
Time to culture conversion (days)	44	33	56	0.13
Duration of Am. using (months)	3.61±2.04	3.66±1.33	3.55± 2.28	0.26
Treatment results				0.33
Cure	37 (77.1%)	20 (83.3%)	17 (70.8%)	
Failure	2 (4.2%)	0 (0%)	2 (8.3%)	
Interrupt	4 (8.3%)	1 (4.2%)	3 (12.5%)	
Death	5 (10.4%)	3 (12.5%)	2 (8.3%)	
Outcome				0.49
Good (cure)	37 (77.1%)	20 (83.3%)	17 (70.8%)	
Bad (failure+ death)	11 (22.9%)	4 (16.7%)	7 (29.2%)	

SD; standard deviation, HIV; human immunodeficiency virus, Am; amikacin

¥ Severe adverse events were considered.

Table 4. Relationship between adverse effects, outcome, and type of MDR-TB treatment

Outcome	Adverse effects	Type of treatment			p-value
		Shorter	Longer	Overall	
	No	13 (65%)	14 (82.4%)	27 (73%)	
	Psychosis (Cs)	1 (5%)	0 (0%)	1 (2.7%)	
	Hepatitis (PZA, Pto)	1 (5%)	1 (5.9%)	2 (5.4%)	
	Cr rising (Am)	0 (.0%)	1 (5.9%)	1 (2.7%)	
Good outcome	Hepatitis+ Cr rising	1 (5%)	1 (5.9%)	2 (5.4%)	0.67
	Anemia (Lzd)	1 (5%)	0 (0%)	1 (2.7%)	
	Anemia +Cr rising+ Suicide	1 (5%)	0 (0%)	1 (2.7%)	
	Arthralgia+ UA rising (PZA)	1 (5%)	0 (0%)	1 (2.7%)	
	Hearing loss (Am)	1 (5%)	0 (0%)	1 (2.7%)	
	No	3 (75%)	6 (85.7%)	9 (81.8%)	
Bad outcome	Rising urea+ Cr	0 (0%)	1 (14.3%)	1 (9.1%)	0.31
	Cr rising	1 (25%)	0 (0%)	1 (9.1%)	

Cs; cycloserine, PZA; pyrazinamide, Pto; prothionamide, Cr; creatinine, Am; amikacin, Lzd; linezolid, UA; uric acid

Table 5. Characteristics of RR/MDR-TB patients based on the treatment outcome

Characteristics	Overall	Outcome of treatment		p-value
	N= 48	Good	Bad	
		N=37	N= 11	
Age (Mean± SD)	42± 15	40.8±15.1	46.1± 14.5	0.30
Male gender	34 (70.8%)	24 (64.9%)	10 (90.9%)	0.14
Iranian	34 (70.8%)	25 (67.6%)	9 (81.8%)	0.47
History of smoking	23 (47.9%)	15 (40.5%)	8 (72.7%)	0.09
History of opium use	20 (41.7%)	13 (35.1%)	7 (63.6%)	0.16
HIV	5 (10.4%)	3 (8.1%)	2 (18.2%)	0.32
Diabetes mellitus	14 (29.2%)	11 (29.7%)	3 (27.3%)	1
Co-disease	22 (45.8%)	14 (37.8%)	8 (72.7%)	0.08
Duration of previous TB treatment (months)	6	8	6	0.48
Smear grade (median)	2	2	1	0.20
3+	20 (41.7%)	6 (25%)	14 (58.3%)	
2+	5 (10.4%)	4 (16.7%)	1 (4.2%)	
1+	12 (25%)	8 (33.3%)	4 (16.7%)	
Scanty	11 (22.9%)	6 (25%)	5 (20.9%)	
Cavitary image	37 (77.1%)	28 (75.7%)	9 (81.8%)	1
Type of MDR-TB treatment				0.49
Shorter	24 (50%)	20 (54.1%)	4 (36.4%)	
Longer	24 (50%)	17 (45.9%)	7 (63.6%)	
Duration of Am. using (months)	3.61±2.04	3.69±1.86	3.34± 2.65	0.63
Time to smear conversion (days)	42	46	27	0.15
Time to culture conversion (days)	44	41	50	0.66
Adverse events	12 (25%)	10 (27%)	2 (18.2%)	0.70

SD; standard deviation, HIV; human immunodeficiency virus, Am; amikacin

In total and regarding permanent discontinuation of drugs, the shorter regimen had more AEs than longer regimens (8 vs. 4), but there was no significant difference between the two groups (p=0.32)

There is no relationship between the outcome of treatment and developing adverse effects, but two patients (one of each group) died.

There was no significant relationship between treatment outcomes and other factors. The overall cure rate for tuberculosis (TB) treatment was 77%, which included 37 patients. The cure rates for the shorter regimen group and the longer regimen group were 83% and 71%, respectively (p=0.49) (Table 5).

Five patients died before completing six months of treatment, with three from the shorter regimen and two from the longer regimen. Additionally, six patients either interrupted treatment or experienced treatment failure, with five of these being in the longer regimen group. Of the four patients who experienced treatment interruptions, only one was evaluated using smear microscopy or culture; however, all were categorized as having interruptions. Importantly, no treatment failures were reported with the shorter regimen. In the longer regimen group, three patients (12.5%) experienced interruptions, compared to one patient (4.2%) in the shorter regimen group. The death rate was higher in the shorter regimen group at 12.5%, compared to 8.3% in the longer regimen group. Notably, none of the patients relapsed within three years following the end of treatment.

DISCUSSION

In this study involving 48 patients treated for relapsed/refractory and multidrug-resistant tuberculosis (RR/MDR-TB) with two different regimens—shorter and longer—we found that the short regimen was equally well tolerated. There was no significant difference in treatment success or culture conversion rates, and the shorter regimen had the advantage of being one year shorter than the longer one. Additionally, these findings indicated that the shorter regimen may reduce the rates of treatment failure and interruption, while increasing the cure rate (83% compared to 71%).

Several clinical trials have been conducted to determine the advantages and disadvantages of a shorter regimen for RR/MDR- TB treatment (2). The previous studies from 2010 to 2016 consisted of an injectable (like kanamycin) with more than four oral drugs (gatifloxacin, clofazimine, ethambutol, pyrazinamide supplemented with prothionamide and high-dose isoniazid) (5, 21, 25). The eligibility for this shorter treatment regimen was influenced by the sensitivity to all the drugs included in it, which resulted in limitations. In our study, we excluded 46 patients (49%) due to ineligibility. At our center, the rates of sensitivity and resistance to fluoroquinolones and aminoglycosides (AG) were 53% and 20%, respectively (Baghaei et al., 2021, unpublished data). The high rate of resistance to fluoroquinolones and AG, which is often associated with extensively drug-resistant tuberculosis (XDR-TB), necessitated changes and extensions to the regimen. Other studies have reported that the eligibility for the shorter regimen in various countries, including European MDR-TB cohorts, was only 7.8% (26), Pakistan, South Korea, Brazil, and Singapore ranged from 30 to 55% (15, 27-29).

In an individual patient-level data meta-analysis, they found that the success rate in shorter regimens was higher than in longer regimens without documented eligibility of patients (resistance to FQ and AG) (17). Additionally, the results of other meta-analyses of 12 non-randomized studies with linezolid-containing regimens and the results of several studies in Africa and Asia showed that the MDR-TB treatment success rate was 82% and 80%, respectively (16, 30). There are similarities to the findings of our current study and contrasts with the 2020 WHO report, with the 57% cure rate among the longer regimen (1).

The unfavorable bacteriological outcomes, such as failure or relapse, did not differ significantly with the shorter regimen but were significantly associated with resistance to pyrazinamide, prothionamide, and ethambutol (9, 17, 31); however, this association was not

observed in other studies (13, 32). Although the present study showed a higher rate of failure in longer regimens, none of our patients were resistant to pyrazinamide, ethambutol, and prothionamide.

The studies reported different results of the association of regimen and mortality rate. Some of them found a significant relationship, and others found no relation (17). Bedaquiline, delamanid, and linezolid, as new and repurposed drugs for RR/MDR-TB, have significantly improved the outcomes, particularly mortality (4, 31, 33). By contrast, in this study mortality rate in the shorter regimen was higher than in the longer regimen (12.5% vs. 8.3%), but this difference was not significant. Besides, we did not prescribe Bq or delamanid except Lzd.

The first line, most important primary outcome for evaluation of the efficacy of anti-TB treatment for RR/MDR- TB is the culture conversion at two months and six months (34, 35). However, that is a good surrogate marker, but the most important is the end-of-treatment outcome. Reports from South Africa, South Korea, and Latvia for culture conversion at two months were 52%, 57.4%, and 77%, respectively (34, 36, 37). Franke et al. conducted an observational study with regimens containing bedaquiline (63%), delamanid (27%), or both (10%), and reported 85% culture conversion within six months (38). In another nonrandomized controlled trial with a regimen containing linezolid, one of fluoroquinolones, clofazimine, cycloserine, and pyrazinamide, followed by a regimen with Bq instead of Cfz for 9-12 months, culture conversion at two and four months was 83.1% and 94.4% (39). Our results with the shorter regimen were similar to or better than those reported in other studies (91.7% at two months), and outcomes with the longer regimen were also comparable to or better than those previously reported (75%). Although culture conversion at two months can be appropriately used as a predictor factor of a favorable outcome, some reports support the 6-month culture conversion as a proper predictor (40, 41). Other studies declared the relationship with being culture positive at two months and recurrence (42). This contrasts with our study, with no recurrence. In the current study, all remaining patients (11 patients with death, interruption, and failure) in both shorter and longer regimens had culture conversion at six months (77%).

Many studies suggested some effective interventions to tolerate the AEs (26, 43, 44). The drugs, which caused the severe AEs, must be discontinued permanently, such as linezolid, because of anemia (39, 45). That was similar to our study of linezolid in two patients with anemia. We discontinued using amikacin because of creatinine rising and hearing loss, cycloserine because of suicide and psychos, pyrazinamide because of arthralgia/rising uric acid and liver injury, and prothionamide for liver injury. The adverse effects occurred more in the shorter regimen group, which was similar to other clinical trials (8, 46); nevertheless, there was no significant difference. Some results support the general tolerability of the shorter regimen; however, some AEs such as hearing loss (7.1%), prolongation of QT interval (8, 13, 46). None of these studies showed a significant difference between the two groups. Clofazimine is used in many studies as a noteworthy shortening medication (4, 7, 13, 47) and it is endurable with a low proportion of AEs, such as discomfort of gastrointestinal (10.5%), neurological disturbances (9-13%), and skin discoloration (28, 48, 49). Increasing pigmentation occurred in our study for all patients in the shorter regimen groups.

The strengths of the study were that consecutive patients were randomly enrolled; all patients had RR-TB or MDR-TB, were treated according to standardized shorter or longer regimens, and were monitored uniformly. Thus, the findings are likely representative of all patients admitted to the hospital. Despite the clinical relevance of this report, several limitations should be acknowledged. It was undertaken at a referral center; however, it should have been conducted in other TB centers in the country. We had some difficulties in this way:

1. We intended to conduct the study in another center after facing unknown problems through the project and obtaining the primary results in our center.

2. Through the carrying out of the project, the new all-oral drugs by the WHO and other studies aim to eradicate the need for injectable agents (50, 51). Many patients declined to sign the consent form after being informed of all available treatment options.
3. The coronavirus pandemic has also affected TB patients, as our center has been converted into a COVID-19 treatment facility.

Hence, continuing the study would be difficult not only in our center but also in other centers, if not impossible. We could not systematically collect the adverse effects except by phone call in all settings. Consequently, our sample size was too small.

CONCLUSION

In our center, we found that more than half of the patients with multidrug-resistant (MDR) and rifampicin-resistant (RR) tuberculosis (53%) were eligible for a short-course regimen. This regimen can improve patient adherence due to its shorter duration, which in turn could increase the success rate of treatment. We then initiated this new project in collaboration with NIMAD.

The present study showed that using a shorter regimen can improve patient adherence, which in turn leads to better outcomes. Although the shorter regimen showed higher rates of culture conversion and treatment success, these differences were not statistically significant. Adverse events (AEs) were more common with the shorter regimen, but they were tolerable and manageable.

Further studies and clinical trials are needed to clarify the new all-oral regimen and to evaluate other regimens with new drugs such as bedaquiline and delamanid. More intensive monitoring of patients is required to verify the efficacy of new drugs for the elimination of injectable drugs.

Recommendation

Active drug-safety monitoring and management for new drugs and regimens for RR/MDR- TB should be brought together with tuberculosis programs. Shortening regimen for RR/MDR- TB can be identified by new approaches, containing new drug administration such as bedaquiline and delamanid together.

It is necessary to evaluate the new WHO program with all oral anti-TB drugs and compare it with the present study. Although no use of injectable drugs in the new guideline seems to be recommended.

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