doi • 10.5578/tt.64054
Tuberk Toraks 2018;66(1):16-25
Geliş Tarihi/Received: 14.11.2017 • Kabul Ediliş Tarihi/Accepted: 29.01.2018

KLİNİK ÇALIŞMA
RESEARCH ARTICLE

Occurrence of adverse events in patient receiving community-based therapy for multidrug-resistant tuberculosis in Pakistan

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SUMMARY

Occurrence of adverse events in patient receiving community-based therapy for multidrug-resistant tuberculosis in Pakistan

Introduction: *Pakistan ranks 4th among 22 multidrug resistant tuberculosis (MDR-TB) high burden countries. The increasing rate of MDR-TB in Pakistan underscores the importance of effective treatment programs of drug-resistant TB. Clinical management of MDR-TB requires prolonged multidrug regimens that often cause adverse events (AEs).*

Materials and Methods: *This retrospective case series study include all patients who were enrolled for MDR-TB treatment during January 2014 till April 2015 at Programmatic Management of Drug Resistant TB (PMDT) unit at tertiary care hospital, Lady Reading Hospital (LRH) Peshawar Pakistan. In this study we sought to ascertain the occurrence of treatment related adverse events and factors associated with these events. Here we also examined the frequency of and reasons for changing drug regimens. We further sought to determine whether the occurrence of adverse events negatively impacts the treatment outcome and management of adverse effects without requiring the discontinuation of MDR-TB therapy.*

Results: *At the time of analysis final outcomes of all 200 enrolled patients exist. Among these 52.5% were females and (81.5%) were aged ≤ 44 years. Among study cases 155 (77.2%) experienced at least one adverse event during treatment. The most commonly reported events were psychiatric issues (70%) whereas the less common was skin rashes (7.5%). A change in drug dose due to adverse events occurred in 16.5% cases, while 13.5% cases had at least one drug discontinued temporarily. Younger age and lung cavities at baseline were positive association with occurrence of adverse events. Association was also found between adverse events and treatment outcomes (OR 0.480, 0.236-0.978, p= 0.041).*

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Conclusion: *Adverse events were prevalent among MDR-TB patients treated at PMDT-LRH Peshawar. All patients who were younger aged and cavitory lungs should be closely monitored for occurrence of adverse events.*

Key words: *Multidurg resistant TB, adverse events, Peshawar, Pakistan*

ÖZET

Pakistan'da çok ilaca dirençli tüberküloz için toplum temelli tedavi alan hastalarda advers etki gelişimi

Giriş: *Çok ilaca dirençli tüberkülozun (ÇİD-TB) yüksek oranda görüldüğü 22 ülke arasında Pakistan dördüncü sıradadır. ÇİD-TB'nin Pakistan'da artan oranı ilaca dirençli tüberkülozda etkin tedavi programlarının önemini vurgulamaktadır. ÇİD-TB'nin klinik tedavisi sıklıkla advers etkilere sebep olan uzun çok ilaçlı rejimler gerektirir.*

Materyal ve Metod: *Bu retrospektif olgu serisi araştırmasına Ocak 2014-Nisan 2015 tarihleri arasında üçüncü basamak hastanesi olan Lady Reading Hospital (LRH) Peshawar Pakistan'da bulunan Programmatic Management of Drug Resistant TB (PMDT) ünitesine başvuran tüm hastalar dahil edildi. Bu araştırmada tedavi ilişkili advers etki ve bu etkilerle ilişkili faktörler değerlendirildi. Ayrıca ilaç rejimlerinin değiştirilme sıklığı ve sebepleri incelendi. Ayrıca advers olayların tedavi üzerine olumsuz etkileri ve advers etkiler ile ÇİD-TB tedavisi kesilmesi ilişkisi değerlendirildi.*

Bulgular: *Analizde 200 hastanın son verileri kullanıldı. Hastaların %52.5'i kadın, %81.5'i ≤ 44 yaşındaydı. Yüz elli beş (%77.2) hasta tedavi süresince en az bir kez advers olay ile karşılaştı. En sık görülen %70 olguda psikiyatrik olaylar, en az görülen %7.5 olguda deri döküntüsüydü. %16.5 olguda advers etkiler nedeniyle ilaç dozunda değişiklik görülürken %13.5 olguda en az bir ilaca geçici olarak ara verildi. Genç yaş ve başlangıçta akciğer kavitesi olması advers etki gelişimiyle ilişkili bulundu. Ayrıca advers etki ve tedavi başarısı arasında da ilişki saptandı (OR= 0.480, 0.236-0.978, p= 0.041).*

Sonuç: *PMDT-LRH Peshawar'da tedavi edilen ÇİD-TB olgularında advers etkiler sıktır. Genç ve akciğerinde kavite olan olgular advers etki gelişimi açısından yakın takip edilmelidir.*

Anahtar kelimeler: *Çok ilaca dirençli tüberküloz, advers etkiler, Peshawar, Pakistan*

INTRODUCTION

Multidrug resistant tuberculosis (MDR-TB) defined as TB with isolates showing resistance to at least isoniazid and rifampicin is a growing hazard to human health world- wide and threat to control of tuberculosis (1,2). It significantly contributes to TB morbidity and mortality on global level (3).

Treatment of MDR-TB is difficult, complicated, very expensive, challenging and needs extensive experience and skills as compared to delayed with drug susceptible TB. Reserve drugs for DR-TB, known as second line drugs (SLDs) are less effective, poorly tolerated and associated with wide range of adverse events (AEs) or adverse drug events (ADRs) as compared to first line anti tuberculosis drugs (FLDs), thus causing frequent interruption, change and close monitoring of regimen (4). Despite the toxicity and lesser efficacy of second-line drugs compared with first-line treatment (5), MDR-TB treatment programs have achieved cure rates of even greater than 80% in some settings (6-8).

One of the major concerns about SLDs is their potential to cause serious adverse effects. These adverse effects range from minor (e.g., changes in color of skin or bodily fluids, headache) to life threatening (e.g., hepatitis and renal failure) (9-11). Some ADRs are nearly ubiquitous in patients receiving multidrug anti-tuberculosis treatment (e.g., mild gastritis) and rarely require the discontinuation of therapy. Other, more severe effects (e.g., hepatitis, renal failure, severe gastritis) have been reported infrequently but may require more dramatic interventions (12).

Sticking close to treatment is a critical factor in the management of MDR-TB and adverse events that comes with SLDs could have a major impact on this adherence (13). The experience of MDR-TB treatment pilot projects has contributed to greater knowledge about these adverse reactions in various populations (4,14,15). However, there is a great need of more data and work on the characteristics and management of adverse reactions to equip the clinicians, program managers, and health care professionals with more knowledge so that MDR-TB treatment strategies could be reshaped. In addition, little is known about whether the occurrence of adverse reactions negatively impact treatment outcome.

Pakistan ranks 4th among top 22 MDR-TB countries. Based on 3.7% primary resistance and 18% resistance in re-treatment cases, WHO has estimated an annual incidence of about > 13.000 MDR-TB cases in

Pakistan (16). The increasing rate of MDR and XDR-TB in Pakistan underscores the importance of effective treatment programs of drug-resistant TB. Expanding access to MDR-TB therapy is urgently needed, yet poor implementation of such therapy can worsen the problem of XDR-TB. We sought to ascertain the occurrence of adverse effects associated with MDR-TB therapy in a tertiary care hospital at Peshawar Pakistan, where the therapy was individualized according to patients' infecting strains and was delivered through a community-based treatment program. We further sought to determine whether the occurrence of adverse reactions negatively impacts the treatment outcome and the management of adverse effects without requiring the discontinuation of MDR-TB therapy.

MATERIALS and METHODS

a. Study Design and Setting

In Pakistan DR-TB patients are treated under programmatic management of drug resistant TB (PMDT) for which different PMDT centres are in operation through out the country. The study centre (PMDT site at Lady Reading Hospital Peshawar, Pakistan) is one of the oldest centres in the country. Here DR-TB patients are provided with ambulatory care, and medicines are taken under the supervision of a treatment supporter who is an educated family member. Patients undergo clinical evaluation and investigation on monthly basis according to WHO guidelines.

b. Treatment

Under PMDT, patients are treated with a standardized treatment regimen (STR) consisting of amikacin (15 mg/kg, max 1000 mg daily), levofloxacin (750 mg daily), cycloserine (10-20 mg/kg, max 1000 mg daily, divided twice a day), ethionamide (10-20 mg/kg, max 1000 mg daily, divided twice a day), and pyrazinamide (20-30 mg/kg, max 2000 mg daily). After reporting and conformation of DST results, regimen is individualized for each patient. Aminoglycosides were administered for the minimum period of 8 months, and other drugs for minimum 20 months. Treatment regimens varied, as the treatment is tailored according to drug susceptibility patterns.

c. AE or ADEs Monitoring and Management

Initially patients are screened at baseline for any pre-existing symptoms, after which they are examined and evaluated on monthly basis by the clinician. On each visit, patients are screened for ADEs using a standardized screening module, which includes common complaints, such as peripheral neuropathy (numbness, burning, or pain), nausea, and rashes. The clinician and Psychologist evaluate positive findings and grade them in accordance with severity.

Adverse events were assessed for second-line drugs included in the WHO Model List of Essential Drugs: Injecables (Am, Cm), cycloserine (Cs), ethionamide (ETH), levofloxacin (Lfx), and para-aminosalicylic acid (PAS).

d. Data Collection and Analysis

Initially all data was entered into an Electronic Medical Record (ENRS; Electronic Nominal Reporting/ Recording System). Analysis was conducted using SPSS (SPSS version 16, SPSS Inc., Chicago, IL) after exporting the data from ENRS. Qualitative data were compared using Chi-Squared test or Fisher Exact test. Quantitative data were compared using Student's t-test. Univariate and multiple logistic regression models were used to generate effect estimates of the association between the occurrence of adverse reactions and poor treatment outcome. The statistical significance level was set at $p< 0.05$.

Ethical Approval

The study was approved by Research and Ethics Committee of the Postgraduate Medical Institute, Lady Reading Hospital Peshawar Pakistan.

RESULTS

This was a retrospective case series study performed among all 200 MDR-TB patients consecutively enrolled into the PMDT centre at LRH, between January 2014 to April 2015. All patients had final treatment outcomes at the time of analysis.

The median age of these patients was 26 (range 10-79) years and most of the patients 132 (66.0%) belonged to rural area. Of these patients, 105 (52.5%) were female. The median initial weight for these patients was 44 kg (range 16-78) (Table 1).

The median treatment duration was 24.0 months (range 1.0-34.0) with median duration of injectable drug use was 8.6 months (range 0-27.5). MDR-TB cases in this cohort received a mean of six anti-tubercular drugs over the course of treatment, ranging from three to eight drugs. Isolates of the cases were found to be resistant to a median of six drugs (range 2-12) at the start of treatment (Table 1).

Table 1. Clinical and treatment characteristics of patient cohort (n= 200)

Characteristics	No adverse reaction (n= 45) n (%)	Adverse reaction (n= 155) n (%)
Gender		
Male	25 (21.4)	70 (73.6)
Female	20 (19.0)	85 (81.0)
Age (years)		**26.0 (10-79)**
≥ 14	0	8 (100.0)
15-44	22 (14.2)	133 (85.8)
45-64	20 (58.8)	14 (41.2)
≥ 65	0	3 (100.0)
Weight (kg)		**44.0 (16-78)**
< 40	50 (83.3)	10 (16.7)
40-60	91 (74.0)	32 (26.0)
> 60	9 (81.8)	2 (18.2)
Residence		
Urban	12 (17.6)	56 (82.4)
Rural	33 (25.0)	99 (75.0)
Marital status		
Married	30 (22.7)	102 (77.3)
Unmarried	15 (22.4)	52 (77.6)
Widow	0 (0.0)	1 (100.0)
Previous TB treatment episodes		
Less than or equal to 1 year	26 (20.5) 101 (79.5)	101 (79.5)
Greater than 1 year	19 (26.0) 54 (74.0)	54 (74.0)
Previous use of second-line drug		
Yes	5 (29.4)	12 (70.6)
No	40 (21.9)	143 (78.1)
Registration group		
New	8 (72.8)	3 (27.3)
Relapse	8 (25.9)	23 (74.1)
Category I Failure	16 (19.3)	67 (80.7)
Category II Failure	10 (17.3)	62 (82.7)
Lung cavitations at baseline chest X-ray		
No cavitations	22 (17.9)	101 (82.1)
Unilateral cavitations	10 (40.0)	15 (60.0)
Bilateral cavitations	13 (25.0)	39 (75.0)

One hundred and fifty five (77.2%) patients' experienced at least one drug(s) related adverse event during the treatment. Frequency of different types of adverse events reported during treatment is shown in Table 2. Psychiatric problems (depression and psychosis) and Nausea were the most common events, reported in70.0% and 52.2% respectively followed by joint pains (47.5%) and body aches (42.5%) at least once during the treatment. Other significant serious adverse drug reactions observed were hearing loss, gastritis, insomnia, vomiting, tinitis, anorexia, vertigo and skin rashes in 22%, 18%, 17%, 11.5%, 10.5%, 9.0%, 8.5% and 7.5% of these cases respectively. Most (78.5%) of the adverse reactions occurred during the first 12 months of treatment. The frequency of reporting at least one adverse event decreased with the passage of time, from 78.5% (during the first 6 months of therapy), to 66.3% (during the next 7-12 months), 39.7% (during months 13-18) and 22.7% after 18 months of the treatment. During the entire course of

Table 2. Frequency of MDR-TB cases with specific adverse event and definitions of adverse events (n= 155)

Adverse events	Frequency of event (%)	Definition
Psychiatric issues		
Depression	70.0	Presence of depression, as diagnosed by clinical psychologist
Gastro-intestinal tract (GIT) disorders		
Nausea	52.5	Persistent nausea, causing anorexia or loss of appetite as reported by patient
Gastritis	18	Reported by any patient
Vomiting	11.5	Vomiting, ranging from mild (treated with anti-emetic) to moderate (treatable by adjusting treatment or with anti-emetic and/or proton pump inhibitors) to severe (uncontrolled vomiting with dehydration, requiring stopping treatment)
Anorexia	9.0	Reported by any patient
Neurological disorders		
Hearing loss	22	Hearing loss confirmed by audiometry Reported by patient
Decrease in sleep (insomnia)	17	Reported by any patient
Tinnitus	10.5	Persistent ringing in the ears based on patient report
Vertigo	8.5	Reported by any patient
Dermatological disorder		
Skin rash	7.5	Signs of rash or dermatological reaction related to medication
Arthralgia (joint pain)	47.5	
Body aches	42.5	

therapy, a median of three (range 0-12) different types of adverse events were reported per case. A total of 45 (22.5%) cases experienced zero adverse events, while more than half of the patients (59%) had one to three and 33.5% had experienced four or more adverse events during this cohort.

ADRs were monitored closely and it was ascertained to avoid permanent discontinuation of any drug(s) which may pose the patient to a life threatening situation or any permanent harm. Five patients (3.2%) required discontinuation of full course of an offending agents due to life threatening ADRs, while in 21 (13.5%) patients' the causative drug(s) were temporarily discontinued. Decrease in drug dose due to any ADR during the therapy was reported in 26 (16.5%) cases. Among temporarily discontinued drugs, frequency of cycloserine was the highest and was discontinued in12 patients for until the problem was resolved. Injectables and PZA were temporarily stopped in 5 and 4 patients respectively. All the offending drugs stopped temporarily during the course of treatment were resumed after the ADRs were subsided. No ADR led to permanent termination of the entire MDR-TB treatment.

In general, ADRs were managed symptomatically. Dose of the culprit drugs was reduced or it was temporarily stopped. Re-introduction of the agent was generally attempted after symptoms improved. Treatment of MDR-TB in the entire cases was streamlined by confirming the drug susceptibility testing (DST), and patients received all the drugs to which *Mycobacterium tuberculosis* was susceptible. For this reason, adding an alternate drug to replace the culprit drug was not an option.

In this study we also assessed whether the occurrence of an adverse reaction was associated with unfavorable treatment outcome (death, default, or treatment failure). On univariate analysis, the occurrence of an adverse reaction was negatively associated with favorable outcome (p= 0.04) with an odd ratio (OR) of 0.46 [95% confidence interval (CI) 0.236-0.978]. Table 3 shows the results of the nominal logistic regression analysis predicting the factors associated with adverse events. Multivariate analysis predicted that, being younger age and lung cavities were associated with adverse events (age OR 10.529, 95% CI 4.721-23.481; lung cavitation 1.955, 95% CI 0.999-3.827) (Table 4).

Table 3. Univariate analysis of factors potentially contributing to the occurrence of adverse events (n=200)

Patients characteristics	Adverse Reactions: Presence of adverse reactions	Adverse Reactions: Absence of adverse reactions	95% CI	Odd ratio	p
Gender					
Male	70 (73.7)	25 (26.3)	0.338-1.285	0.659	0.219
Female	85 (81.0)	20 (19.0)			
Age (years)					
≤ 44	141 (86.5)	22 (13.5)	4.721-23.48	10.529	**< 0.001**
> 44	14 (37.8)	23 (62.2)			
Weight (kg)					
< 40	65 (83.3)	13 (16.7)	0.884-3.760	1.824	0.101
≥ 40	85 (73.3)	31 (26.7)			
Residence					
Urban	56 (82.4)	12 (17.6)	0.744-3.252	1.556	0.238
Rural	99 (75.0)	33 (25.0)			
Duration of sickness					
≤ 1 year	101 (79.5)	26 (20.5)	0.694-2.691	1.367	0.365
> 1 year	54 (74.0)	19 (26.0)			
Previous use of second-line drug					
Yes	12 (70.6)	5 (29.4)	0.223-2.018	0.671	0.476
No	143 (78.1)	40 (21.9)			
Lung cavitations at baseline chest X-ray					
Cavitations	101 (82.1)	22 (17.9)	0.999-3.827	1.955	**0.04**
No cavitations	54 (70.1)	23 (29.9)			

Table 4. Multivariate analysis showing factors associated with the occurrence of adverse reactions (n= 200)

	B	SE	Wald	Df	Sig	Exp (B)	95% CI: Lower	95% CI: Upper
Age ≥ 44	2.142	0.764	7.860	1	0.005	0.117	0.026	0.525
Lung cavitation	4.108	0.729	31.741	1	0.000	0.016	0.004	0.069

Note: Only those predictors given in Table which are significant in analysis.
B: Bet, SE: Standard error, Df: Degree of freedom, Exp (B): OR, CI: Confidence interval.

DISCUSSION

Treatment of MDR-TB is difficult as it requires longer duration and drugs used are associated with wide range of adverse drug events (ADRs). Many studies reported the occurrence of ADRs with MDR-TB treatment. Adverse events like ototoxicity with aminoglycoside use, are well recognized (17). Less common adverse effects, e.g. severe psychiatric manifestations with the use of cycloserine, have also been reported (18). Also few other documented international studies investigating the adverse effects of MDR-TB treatment have been conducted in Europe, the Middle East and South America (4,15,19,20). A study conducted in Istanbul, Turkey, from 1992-2004 on 263 patients with multidrug-resistant tuberculosis revealed ototoxicity (42%), psychiatric disorders (21%), gastrointestinal disturbances (14%), arthralgia (11%), epileptic seizures (10%), hepatitis (5%), and dermatological effects (4.5%) (15). In comparison, a study conducted in Lima, Peru, from 1996-1998 on MDR-TB patients reported mild gastritis (100%), dermatological effects

Table 5. Comparison of adverse events occurs in the present study with some other studies (n= 155)

Adverse events	Present study	Bloss et al. (26)	Shin et al. (19)	Furin et al. (4)	Nathanson et al. (25)	Jacob et al. (34)	Sagwa et al. (35)	Torun et al. (15)
Depression	70.0	13	8.6	18.3	6.2	8.3	8	21.3
Nausea	52.5	58	75.4		32.8		64	14.0
Arthralgia joint pain)	47.5	13.4	47.1	6.7	16.4	15.9	28	11.4
Body aches	42.5							
Hearing loss	22	19	14.6	6.7	12.0	28.7	25	41.8
Gastritis	18			100	8.6			14.1
Decrease in sleep	17				11.6			
Vomiting	11.5	39				20.5		
Tinnitus	10.5	12.1			5.1		45	
Anorexia	9.0		75.4					
Vertigue	8.5				14.3			
Skin rash	7.5	8.6	16.0	43.3	4.6	14.0	13	4.5

(43%), peripheral neuropathy (17%), depression (18%), and anxiety (11%) (4).

Present study suggests that ADRs during MDR-TB treatment were very common in this cohort (2014-15 cohort) at PMDT-LRH Peshawar, Pakistan. This study showed that 77.2% of the cases experienced at least one treatment-related ADR which is consistent with the findings of other studies conducted at Istanbul and Tomsk, where 69% and 73% of MDR-TB patients experienced at least one side effect respectively (19,21). Table 5 showed finding of the present study compared with some other studies. Other important finding of this study was that maximum number of ADRs occurred at early stage of therapy, particularly during the first 6 months of treatment which is similar to the studies India and the United States (22,23). Possible explanation for this could be the use of Injectables, which are often associated with ADRs, and given during the first 6-9 months of treatment. Closed monitoring and prompt intervention during the early months of treatment should be a fundamental part of MDR-TB management (15).

Other studies have found a high baseline incidence of anxiety and depression in MDR-TB patients, often related to disease-associated stress [4,18]. Second-line anti-TB drugs cycloserine, fluoroquinolones and thioamides have been associated with psychiatric symptoms during MDR-TB treatment (24). In our study, 70.0% of studied patients' experienced psychiatric adverse events during the treatment, including depression, anxiety, and psychosis. At our PMDT site MDR-TB physicians and clinical psychologist work closely to ensure successful management of patients with MDR-TB. There is well established referral and treatment system for psychiatric emergencies in the psychiatry unit of the same hospital. Patients with any psychatirc symptoms are counseled by the clinical psychologist on monthly basis and are referred to psychiatry unit if necessary. In case of psychosis or depression, patients are treated with ant-psychotic or anti-depressants. Any other serious issues like suicidal or homicidal tendencies are handled through hospitalization. When ancillary medication fails to give the desired response, the culprit drug(s) was temporarily stopped.

Another significant ADRs associated with MDR-TB therapy is GIT disturbances which is reported by various studies with range of 10.8%-100% (4,8,15,25,26). It was also observed in our study that 52.5% of the patients experienced nausea, 18.0% had gastritis, 11.5% patients were complaining of vomiting and 9.0% of the study cases reported anorexia.

Arthralgia (joint pain) and generalized body aches, which badly affected patients' daily routine is another common ADRs. In a study conducted by Datta et al., (2010) in Kashmir, 13.4% patients developed arthralgia attributed to pyrazinamide, which was relieved by non-steroidal anti-inflammatory drugs in most of the

cases (27). Our study showed that 47.5% of the study cases experienced joint pain and 42.5% of the patients had generalized body aches during their course of treatment.

Neurological disorders are predominantly associated with the use of parenteral anti-tubercular agents (aminoglycosides and aminopeptides) (17,28-32). The drug-specific rate of patient-reported tinnitus in the current study is 10.5%, decrease in sleep (insomnia), vertigo and hearing loss were reported by 17%, 8.5% and 22% of the study cases respectively. These findings are comparable to 15.4%-33% reported in studies conducted elsewhere (15,17,28). When any of the patient observed symptomatic or patient reported by him/her, then the subject case were referred for audiometric tests and if validated by audiometric tests, was treated accordingly. Ototoxicity occurs more frequent during early stages of treatment due to the extended exposure to aminoglycosides. Present study showed that ototoxicity was decreased with the passage of time and during the continuation phase, no further problem was found.

SLD's are also associated with dermatological reaction/skin rashes. The present study found that 7.5% of the study cases had skin rashes during the course of treatment.

Approximately 17% of the cases required either temporary or permanent discontinuation of at least one SLD. It was found that 4.4% of the cases, the culprit drug was permanently discontinued, which is comparably lower than finding of other studies (30-56%) (15,22). Most commonly discontinued drugs were cycloserin (in 7.6% cases), injectables (in 3.1%) and PZA (in 2.5% cases). In 16.5% ADRs were eliminated by minimizing the dose of offending drugs. Possible reason for minimal discontinuation of the culprit drug(s) is that at the present study centre (PMDT-LRH), national guidelines for the treatment of MDR-TB are strictly followed to ensure the best expected treatment outcome.

Another important finding of the present study pointed out that younger, and patients' with high baseline intensity of MDR-TB (baseline cavitary disease) were more likely to experience ADRs during the treatment. While it has been shown by previous studies that females and aged MDR-TB patients reported the ADRs more frequently (19). This is the first study in this region to analyse the factors related to number of different adverse events reported during MDR-TB treatment. A better understanding of who may be at increased likelihood of developing more adverse events during the treatment may help with identifying and monitoring high-risk patients prior to starting the therapy.

Present study was extended to find any correlation between ADRs and treatment outcome. It was observed that the occurrence of an adverse reaction was negatively associated with favorable outcome, a very important issue. It is the most important point of this study because major concerned of everyone is with outcome of MDR-TB treatment and it is due to the fact that due to ADRs, culprit drug(s) became discontinue in some cases and their also a possibility that patient(s) by themselves discounted the culprit drug(s) without informing their supporters, family members and treatment site people.

One limitation of this study is that laboratory conformation was not present for all of the adverse events, which may resulted in reporting bias as over- or under-reporting. In addition, it is often difficult to ascribe an adverse event to the administration of one particular drug; therefore, the associations are not necessarily causal. Details about common adverse events and suspected agents are published else where (24,33).

This study high lights the intricacies associated with MDR-TB treatment and emphasizes the importance of careful clinical monitoring and timely management of adverse events. The frequency of adverse events requiring alterations in treatment suggests important limitations of current anti-TB therapy and emphasizes the need for urgent efforts to develop new, less toxic anti-TB drugs with shorter regimens to treat MDR-TB patients.

There was a high rate of ADRs in the treatment of MDR-TB. However, it does not prevent cure of such cases. Our study suggests that efforts should be made to continue treatment in the face of side effects as long as they fall short of being life threatening. Timely and aggressive management of ADRs is therefore important for patients' compliance and desired therapeutic outcome. Careful clinical monitoring, laboratory analysis and a multidisciplinary approach are essential in the follow-up of MDR-TB cases.

Conclusion

Although the management of MDR-TB is a complex health intervention requiring multidrug therapy for

18-24 months, this study demonstrates that adverse reactions do not appear to be a major obstacle to the implementation of PMDT projects. This study suggests that there is a need for counselling before initiation of treatment, which is again reinforced during treatment. These initiatives can lead to better compliance and minimizing default rate.

The data used in this study reflect real-life MDR-TB treatment practices and patient experiences. From this study we were able to generate a tentative hypothesis that some adverse events occur more in MDR-TB patients with younger age and more serious patients, which is clinically important when treating this sub-group of patients.

ACKNOWLEDGEMENTS

We acknowledge the outstanding contributions from the PMDT staff, National TB control Programme Pakistan (NTP), Provincial TB Control Programme Khyber Pakhtunkhwa (PTP KPK), Association for Community Development (ACD) and Lady Reading Hospital Peshawar (LRH) in this programme.

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