Study of risk factors and clinical management of patients with clinical non-response due to low plasma levels of anti-tubercular drugs

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Abstract

This study was carried out to assess the role of therapeutic drug monitoring of crucial first-line anti-tubercular drugs [rifampicin (R) and isoniazid (H)] among 75 non-responding proven drug-sensitive tuberculosis (TB) patients on treatment followed by intervention in field conditions. The intervention was done in the form of either an increase in the dosage of R and H in patients with minimally low drug levels or a modification of the regimen in a certain group of patients with significantly low drug levels by augmenting it with three or four second-line drugs in addition to standard first-line drugs. This study also aimed to determine the relationship between the measured plasma concentration of anti-tubercular drugs and various demographic, microbiological, radiological, and malabsorption factors, and the presence of comorbidities affecting them. The study also focused on the clinical impact of the intervention for low plasma levels of anti-tubercular drugs on TB treatment outcomes. In our study, overall, 85.5% of patients had low levels of any drug. In 85.3% of patients, R levels were low, and in 39.1%, H levels were low. On univariate analysis, low body mass index (BMI), hypoalbuminemia, bilateral disease on chest X-rays, and the presence of cavities were found to be significantly associated with low drug levels, while none of the factors were independently significantly associated. Low BMI, pulmonary TB, and disseminated TB, far-advanced disease, and bilateral disease on chest X-ray, presence of cavities, and only low R levels were associated with unfavorable outcomes, with none of the factors found to be significant on multivariate analysis. In our study, it was seen that the treatment outcome was favorable in 59.6% of patients in whom this intervention was done by augmenting the treatment regimen with three/four second-line drugs along with increasing the dose of R and H.

To conclude, various factors may be associated with low plasma levels of anti-tubercular drugs. If such patients show clinical non-response after ≥6 months of treatment and have significantly low drug levels, with an absence of drug resistance, their treatment regimen may need augmentation with three/four second-line drugs along with an increase in the dose of R and H, which may lead to a favorable outcome.

Introduction

Globally, tuberculosis (TB) is one of the top 10 causes of death and the leading cause of death from a single infectious agent. Despite the availability of standardized treatment regimens for the

management of drug-sensitive TB (DST) and drug-resistant TB (DR-TB) in India, many patients are suffering from it, and the national program of India has geared up for a DST-based regimen for DR-TB. As per the Global TB report 2023, globally, 10.6 million people developed TB disease, and about a quarter of the world's TB cases were reported from India in 2022 [1].

Sometimes, despite compliance with treatment, a slower response or no response to treatment is observed. The reasons for slow response are diverse and include extensive disease, comorbidities like diabetes, human immunodeficiency virus (HIV), late initiation of treatment, poor compliance with treatment, inadequate regimen, and low plasma levels of anti-TB drugs [2-5]. Low plasma drug levels can be a consequence of malabsorption, inaccurate dosing, altered metabolism, or drug-drug interactions. Therapeutic drug monitoring (TDM) of anti-tubercular drugs (ATD) could improve patient outcomes in patients who are not responding to anti-tubercular treatment (ATT) despite demonstrated susceptibility of mycobacteria to these drugs. TDM, especially for ATD, although not yet popular in India, is well known in clinical pharmacology [2,3,6]. This study was done with an aim to assess the role of TDM among non-responding TB patients where drug resistance had been ruled out, followed by intervention in field conditions. This study also aimed to determine the relationship between plasma concentration of ATD and the factors affecting it, such as demographics, microbiological and radiological profile, nutritional status, malabsorption due to gastrointestinal (GI) disease, and comorbidities. We also studied the clinical impact of the intervention for low plasma levels of anti-TB drugs on TB treatment outcomes.

Materials and Methods

A retrospective study was conducted to evaluate the occurrence and possible factors associated with low plasma levels of ATD in patients of DST who were not responding to treatment despite appropriate anti-TB treatment/regimen. Among patients with low plasma levels, the dosage of ATDs was increased, or the regimen was modified, and the patients were followed up to assess their response to treatment.

Setting and patients

The study was carried out at a tertiary referral TB hospital in northern India. A total of 75 DST patients (both pulmonary and extrapulmonary), who were not responding to treatment despite an appropriate regimen, and still showing absence of drug resistance, were enrolled. Common causes of non-response, such as inadequate dosage of drugs, inaccurate regimen, other causes of immune suppression, resistance to anti-TB drugs, poor drug compliance, *etc*., were first ruled out. For ruling out malabsorption, D-xylose, plasma immunoglobulin G, and plasma immunoglobulin A tests were done in all cases, and duodenal biopsy was done in selected cases, wherever it was possible. Subsequently, drug levels of standard anti-TB drugs like rifampicin (R) and isoniazid (H), in the plasma of patients, were measured.

Study design

Patients were referred by their treating physician to this center with a concern of a slow clinical response or no response to therapy after more than 3 months, despite patients being compliant and on adequate dosage as per their weight bands. Also, drug resistance was ruled out by subjecting the most appropriate sample, if available, with genotypic and phenotypic laboratory methods at a national referral laboratory. Research and ethical approval were obtained from the Institutional Research and Ethical Committee (office letter no. NITRD/RC/2024/2521, letter no. NITRD/EC/2024/7497, respectively).

All enrolled patients underwent a comprehensive clinical examination and a detailed medical history. All the findings were entered into a clinical data-collection form, including patient demographics, duration of signs and symptoms, laboratory parameters, and findings of the chest X-ray [7].

Measurement of drug concentration

Patients were given a minimum of 6 doses of ATT for 6 consecutive days on the same time in the morning. On the 7th day morning, patients ingested their usual doses of all medications under direct observation. 3 mL of venous blood was drawn, 2 hours post-dosing of the ATT drugs. Blood was collected in a green top heparinized vacutainer. The sample was centrifuged to separate the plasma. 10 µL of 5% ascorbic acid was added to 1 mL of plasma. The separated plasma samples were transported in dry ice to the National Institute for Research in Tuberculosis, Chennai, to measure the plasma peak concentrations of R and H. Drug levels were measured using high-performance liquid chromatography [8]. The normal range of therapeutic levels of the drugs was defined as 3 to 6 µg/mL for H and 8 to 24 µg/mL for R [3,9]. Drug concentrations were compared with published reference ranges from studies in human volunteers.

If drug levels were minimally low, we adjusted the doses upward. After a minimum of 2 weeks of treatment with the new TB drug dosages, plasma drug levels were reassessed to ascertain whether the drug levels had improved and come within the normal therapeutic range.

Treatment augmentation

In a certain set of patients who had received treatment with first-line drugs for 6 months or more and had not responded favorably to treatment, though drug sensitive (by genotypic and phenotypic methods) and had significantly low plasma drug levels of standard first-line drugs, they were declared as treatment failures. Their regimen was augmented with three or four second-line drugs, which are used to treat DR-TB. Given the unique mechanisms of action of these medications, when compared to standard first-line therapy, it was assumed that their use could improve the outcomes when used as adjuvant therapy, in addition to increasing the dose of first-line drugs.

Tuberculosis treatment outcome

All patients were followed up clinically, radiologically, and bacteriologically. TB treatment outcomes (cured/treatment completed, failure, death, or default) were noted at the end of ATT. Cured and treatment completed were considered favorable outcomes; while default, death, and failure were considered unfavorable outcomes.

Data analysis

Statistical analyses were performed using SPSS 22.0 (IBM, Chicago, IL, USA). Plasma drug levels were dichotomized into normal if they were within or above the expected range or low if they were below the expected range. Variables were compared between patients with low and normal drug levels using the student *t*-test for continuous variables and a chi-square (χ^2) test or Fisher's exact test

for categorical variables. A p-value of <0.05 was considered statistically significant.

Both univariate and multivariate logistic regression models were used to assess the risk factors independently associated with low drug levels. The influence of various factors on treatment outcome among such patients was also evaluated. Role of interventions, such as only dose increase of first-line drugs or dose increase with augmentation with three or four second-line drugs, on TB treatment outcome was also studied.

Results

A total of 75 patients, with 44 (58.7%) having pulmonary TB, were enrolled. Out of the total, 35 (46.7%) patients were males. The demographic, clinical, and radiological profile of patients is given in Table 1. Out of 75 patients, 64 (85.3%) had low levels of any drug on first TDM, and the remaining 11 (14.7%) had normal levels. The prevalence of a low plasma concentration of R and H was 59/75 (78.7%) and 30/75 (40%), respectively. The number of patients who received pyrazinamide (PZA) was the lowest since the majority of the patients stopped PZA after 2 months of initiating treatment. In 6 patients, the outcome could not be determined because they did not report back after the first TDM was done. Out of 59 patients having any low levels of drugs, in which dosage was increased, only 28 (47.5%) patients reported for repeat TDM. In all these 28 patients, repeat levels of R and H were within therapeutic range as per reference values.

On univariate analysis, low body mass index (BMI), hypoalbuminemia, bilateral disease on chest X-ray and presence of cavity were found to be significantly associated with low drug levels, while none of the factors was independently associated with low drug levels on multiple logistic regression analysis (Table 2).

Low R levels were associated with male sex, low BMI, anemia, hypoalbuminemia, bilateral disease on chest X-ray, and the presence of cavity on univariate analysis. Multiple logistic regression analysis showed male sex and low BMI were independently associated with low R levels (Table 3).

When we compared patients with a favorable outcome and an unfavorable outcome at the end of augmented/revised treatment, low BMI, pulmonary TB, and disseminated TB, far-advanced disease on chest X-ray, bilateral disease on chest X-ray, presence of cavity on chest X-ray, and only low R levels were associated with an unfavorable outcome. However, none of the factors was found to be significant on multivariate analysis (Table 4).

Table 1. Demographic, clinical and radiological profile of 75 tuberculosis patients enrolled for therapeutic drug monitoring.

Variable	Numbers
Age (years), mean±SD	29.5±12
Age (years), median (IQR)	28 (21-35)
Male sex, n (%)	35 (46.66)
History of previous ATT, n (%)	75 (100)
Duration of ATT (months), median (IQR)	12 (7.7-19.7)
HIV infected, n (%)	1 (1.33)
Weight, (mean±SD) kg	49.96±13.39
Body mass index, (mean±SD) kg/m2	19.28±3.78
Patients with PTB with or without EPTB, n (%)	44 (58.66)
Patients with EPTB, n (%)	31 (41.34)
Cavity lesions on chest X-ray, n (%)	
Yes	32/44 (72.72)
No	12/44 (27.28)
Cavity lesions, n (%)	
Single	5/32 (15.62)
Multiple	27/32 (84.37)
Chest X-ray severity, n (%)	
Mild	14/44 (31.82)
Moderate	14/44 (31.82)
Far advanced	16/44 (36.36)
Extent of disease on chest X-ray, n (%)	
Unilateral	18/44 (40.91)
Bilateral	26/44 (59.09)
Serum albumin (mean±SD), g/dL	18/44 (40.91)
Hypoalbuminnemia, n (%)	3.65±0.6132 (42.67)
Hemoglobin (mean±SD), g/dL	11.71±1.72
Anaemia, n (%)	40 (53.3)
Leucocyte count, $\times 10^9$/L (median, IQR)	6570 (8950-5350)

ATT, anti-tubercular treatment; EPTB, extrapulmonary tuberculosis; HIV, human immunodeficiency virus; IQR, interquartile range; PTB, pulmonary tuberculosis; SD, standard deviation; anaemia <13 gm/dL in males, <12 gm/dL in females; hypoalbuminemia <3.5 gm/dL.

Discussion

Slow or no response to therapy can result in prolonged infectiousness, extended treatment duration, acquired drug resistance, or recurrence of TB after treatment [10-12]. Cost-effectiveness and cost-utility, lack of population (ethnicity) specific therapeutic ranges of plasma drug levels, requirement of infrastructure, and trained manpower are some of the challenges for TDM in India. In the current study, 75 patients were enrolled who were not responding clinically and microbiologically, despite showing sensitivity to standard first-line drugs by both genotypic and phenotypic methods. TDM was done with an aim to assess the role of TDM followed by intervention in such patients in field conditions. This study also aimed to determine the relationship between measured plasma concentration of ATD and the factors affecting it, such as demographics, microbiological and radiological profile, nutritional status, malabsorption due to GI disease, and comorbidities.

Overall, 85.5% patients had low levels of any drug, with R (85.3%) followed by H (39.1%) having low levels. The findings were similar to the other studies done on TDM. In Botswana, 30-37% had low levels of H, 78-84% had low levels of R, but only 1-5% had low levels of PZA [12,13]. In Australia, 48% of H levels and 46% of R levels were below the normal range [14]. In Indonesia, 70% of 62 TB patients had low R concentrations [15].

In the current study, low BMI, hypoalbuminemia, bilateral disease on chest X-ray, and the presence of cavity were the factors found to be significantly associated with overall low drug levels on univariate analysis, but none had a significant independent association. Similarly, in some other studies, anemia, hypoproteinemia, chronic malnutrition, and malabsorption were the most common causes for low drug levels [16-20].

In our study, low levels of R were associated with malesex, low BMI, anemia, hypoalbuminemia, bilateral disease on chest X-ray, and the presence of cavity. Among these factors, male sex and low BMI were found to be independent factors associated with low levels of R. Low levels of R were also associated with unfavorable treatment outcomes. Many studies have suggested that current dosing of R may be suboptimal, resulting in lower dose/kg, which may or may not affect the treatment outcome [6,21].

Table 2. Characteristics of tuberculosis patients with low and normal drug levels (univariate analysis).

Variable	Patients with low levels (n=64)	Patients with normal levels (n=11)	p
Age	29.5±11.89	26.09±11.77	0.30
Sex, n (%)			
Males	33 (51.56)	3 (27.27)	0.136
Females	31 (48.43)	8 (72.72)	
Duration of ATT in months (range)	12 (8-21.2)	11 (6.5-18.2)	0.26
Type of TB, n (%)			
PTB with/without EPTB	38 (59.38)	6 (54.54)	0.5
Only EPTB, n (%)	27 (42.18)	5 (45.46)	
Low BMI, n (%)			
Yes	29 (45.31)	1 (18.18)	0.04
No	35(54.68)	10 (81.81)	
Pulmonary-CXR, n (%)			
Unilateral	13/38 (34.2)	5 /6 (83.3)	0.034
Bilateral	25/38 (65.8)	1/6 (16.7)	
Pulmonary-CXR cavity, n (%)			
Yes	30/38 (78.9)	2/6 (33.3)	0.038
No	8/38 (21.1)	4/6 (66.7)	
Pulmonary-CXR cavity, n (%)			
Single	4/30 (13.33)	1/2 (50)	1.667
Multiple	26/30 (86.66)	1/2 (50)	
Pulmonary-CXR severity, n (%)			
Mild	11/38 (28.9)	3/6 (50)	0.662
Moderate	12/38 (31.6)	2/6 (33.3)	
Far advanced	15/38 (39.5)	1/6 (16.7)	
Anemia, n (%)			
Yes	36/64 (56.25)	4/11 (36.36)	0.221
No	28/64 (43.75)	7/11 (63.63)	
Hypoalbuminemia, n (%)			
Yes	31/64 (48.43)	1/11 (9.09)	0.0147
No	33/ 64 (51.5)	10/11 (90.90)	

ATT, anti-tubercular treatment; BMI, body mass index; CXR, chest X-ray; EPTB, extrapulmonary tuberculosis; PTB, pulmonary tuberculosis; TB, tuberculosis; anemia <13 gm/dL in males, <12 gm/dL in females; hypoalbuminemia <3.5gm/dL; low BMI <18.5kg/m^2.

Table 3. Factors associated with initially low serum levels of rifampicin (with or without isoniazid) among patients who had their levels measured. (n=75) (univariate analysis).

Variable	Patients with low levels (n=59)	Patients with normal levels (n=16)	p
Age	30.42±12.2	26.3±12.1	0.11
Sex, n (%)			
Males	32 (54.23)	3	0.02
Females	27 (45.77)	13	
Duration of ATT (months)	12.5 (8-22)	10.5 (7.2-16.7)	0.36
Type of TB, n (%)			
PTB with/without EPTB	38 (64.40)	6 (37.5)	0.08
EPTB	21 (35.60)	10 (62.5)	
Low BMI, n (%)			
Yes	29 (49.15)	2 (12.5)	0.009
No	30 (50.85)	14 (87.5)	
Pulmonary-CXR, n (%)			
Unilateral	13 (29.54)	5 (11.36)	0.034
Bilateral	25 (56.81)	1 (2.27)	
Pulmonary-CXR cavity, n (%)			
Yes	30 (68.2)	2 (4.5)	0.038
No	8 (18.2)	4 (9.09)	
Pulmonary-CXR cavity, n (%)			
Single	4 (12.5)	1 (3.12)	0.28
Multiple	26 (81.2)	1 (3.12)	
Pulmonary-CXR severity, n (%)			
Mild	11 (25)	3 (6.8)	-
Moderate	12 (27.3)	2 (4.5)	
Far advanced	15 (34.09)	1 (2.27)	
Anemia			
Yes	36 (61.02)	4 (25)	0.01
No	23 (38.98)	12 (75)	
Hypoalbuminemia, n (%)			
Yes	31 (52.5)	2 (12.5)	0.0042
No	28 (47.5)	14 (87.5)	

ATT, anti-tubercular treatment; TB, tuberculosis; PTB, pulmonary tuberculosis; EPTB, extrapulmonary tuberculosis; BMI, body mass index; CXR, chest X-ray; anaemia, <13 gm/dL in males, <12 gm/dL in females; hypoalbuminemia, <3.5 gm/dL.

Additionally, patients having low BMI usually have low albumin levels, resulting in poor drug absorption with more drug being available for hepatic clearance [16,22]. The findings of this study suggest that R is a main medication to prioritize for early TDM for patients for whom TB therapy is failing. The Government of India has considered malnutrition among TB patients as a serious concern and framed a national policy to provide financial aid to all TB patients by transferring a cash incentive every month to their accounts till the completion of treatment as an initiative to improve their nutritional status [23].

Patients with TB and HIV co-infection are at an increased risk of significant drug-drug interactions due to the intake of a large number of drugs, and these patients may have reduced drug absorption [13]. Patients with diabetes mellitus (DM) may have gastroparesis, which may lead to delayed and/or reduced drug absorption [6]. Several studies have reported both HIV and DM to be associated with decreased plasma levels of R and H [4,5,6,13,23-28]. However, in our study, there were only two patients with diabetes, and only one patient was HIV positive; hence, their effect could not be studied on drug levels.

The relationship between plasma drug concentrations and TB treatment outcome is difficult to predict. Multiple factors, such as the bacillary load, type of strain, virulence, minimum inhibitory concentration in relation to drug concentrations, drug concentra-

Table 4. Factors associated with favorable and unfavorable outcomes among 69 patients who were initiated on the revised regimen after the blood levels (univariate analysis).

Risk factor	Subgroup	Favorable outcome (n=48), n (%)	Unfavorable outcome (n=21), n (%)	p
Gender	Male	19 (39.6)	13 (61.9)	0.087
	Female	29 (60.4)	8 (38.1)	
HIV	No	48 (100)	20 (95.2)	0.304
	Yes	0	1 (4.8)	
Smoker	No	47 (97.9)	19 (90.5)	0.218
	Yes	1 (2.1)	2 (9.5)	
DM	No	47 (97.9)	20 (95.2)	0.519
	Yes	1 (2.1)	1 (4.8)	
Duration of ATT	<12 months	27 (56.2)	7 (33.3)	0.080
	>12 months	21 (43.7)	14 (66.7)	
BMI	18.5-22.9	18 (37.6)	6 (28.5)	0.010
	>23	15 (31.2)	1 (4.8)	
	<18.5	15 (31.2)	14 (66.7)	
Type of patient	PTB with/without EPTB	21 (43.8)	18 (85.7)	0.001
	EPTB	27 (56.2)	3 (14.3)	
Pulmonary-CXR	Normal	27 (56.2)	3 (14.3)	0.000
	Unilateral	12 (25)	4 (19)	
	Bilateral	9 (18.8)	14 (66.7)	
Pulmonary-CXR	Normal	27 (56.25)	3 (14.3)	0.003
	Cavity yes	15 (31.25)	15 (71.42)	
	Cavity no	6 (12.5)	3 (14.28)	
No. of cavity in CXR	No cavity	33 (68.75)	6 (28.6)	0.000
	Single	5 (10.4)	0 (0)	
	Multiple	10 (20.8)	15 (71.4)	
Pulmonary-CXR	Normal	27 (56.25)	3 (14.28)	0.003
	Mild	8 (16.66)	4 (19.04)	
	Moderate	8 (16.66)	5 (23.8)	
	Severe	5 (10.42)	9 (42.85)	
Anemia	No	26 (54.16)	5 (23.8)	0.020
	Yes	22 (45.84)	16 (76.2)	
Hypoalbuminemia	No	31 (64.6)	7 (33.3)	0.016
	Yes	17 (35.4)	14 (66.7)	
Any blood drug level	Normal	9 (18.8)	1 (4.8)	0.263
	Reduced	39 (81.2)	20 (95.2)	
Isoniazid level	Normal	27 (56.25)	10 (47.62)	0.769
	Low	18 (37.5)	9 (42.85)	
	High	3 (6.25)	2 (9.53)	
Rifampicin level	Normal	14 (29.16)	1 (4.8)	0.027
	Low	34 (70.84)	20 (95.2)	
Intervention done	No action	9	1	0.031
	Dose increased	11	1	
	Dose increased + augmentation of regimen	28	19	

ATT, anti-tubercular treatment; BMI, body mass index; CXR, chest X-ray; DM, diabetes mellitus; HIV, human immunodeficiency virus; anemia <13 gm/dL in males, <12 gm/dL in females; hypoalbuminemia <3.5 gm/dL; low BMI <18.5kg/m^2.

Table 5. Comparison of the blood levels of the anti-tubercular drugs at the baseline and after the next therapeutic drug monitoring (TDM), where TDM could be repeated (n=28).

Drug	1st TDM	2nd TDM	p
Isoniazid (mean±SD) (Median, IQR)	3.67±2.44 3.49 (1.41-5.46)	6.43±6.0 4.89 (3.2-8.18)	0.049
Rifampicin (mean±SD) (Median, IQR)	4.83±3.23 5.06 (2.2-6.7)	10.7±5.1 10.02 (8.66-13.05)	0.00001

IQR, interquartile range; SD, standard deviation; TDM, therapeutic drug monitoring.

tions at the site of lesion, duration of infection, extent of disease, and the immune status and nutritional status of the subject, play a role in treatment outcome in addition to drug concentrations [29]. Few studies have examined whether low drug concentrations of anti-TB drugs affect patient response to TB treatment [6,11,30-32]. Low BMI, PTB, and disseminated TB, far-advanced disease on chest X-ray, bilateral disease on chest X-ray, presence of cavity on chest X-ray, and low levels of R were associated with unfavorable outcome in our study on univariate analysis, but none had a significant independent association.

In our study, low plasma levels of only H were not related to TB treatment response. This finding differs from those of previous studies that showed that H and PZA levels were associated with poorer treatment outcomes [33-35]. Our study observed that only low R levels were associated with poorer treatment outcome, similar to one study from India and another systematic meta-analysis [33,34]. However, it has also been observed that not all patients with low plasma levels have poor outcomes [27,35,36]. The one reason may be that sufficient follow-up was not done in such patients after TB treatment completion to rule out early relapse.

In 59 patients having any low levels of drugs, the dosage was increased. However, only 28 (47.5%) patients among them reported for repeat TDM. In all these patients, repeat levels of R and H were within therapeutic range as per reference values (Table 5). The studies which had been done repeat TDM after adjusting the dosages to achieve therapeutic target levels are very few [21,35]. Financial issues, logistical issues, and poor patient compliance for follow-up were the main reasons for not performing repeat TDM in these studies, including ours.

In 68.1% (47/69) of cases, who had taken drugs for at least 6 months of treatment with first-line drugs and demonstrated drug sensitivity and had significantly low drug levels on first TDM, another intervention was done. This included augmentation of the standard drug regimen with three or more drugs from the second-line class of anti-TB drugs in addition to increasing the dose of first-line drugs.

In our study, it was seen that the treatment outcome was favorable in 28/47 (59.6%) patients in whom this intervention was done.

The strength of this study is that this is the first study from a high TB prevalence country, wherein the intervention following the demonstration of low blood levels of anti-TB drugs in non-responding TB patients has been discussed. Despite various logistical challenges, the plasma levels of ATT could be repeated in many patients to guide the intervention. Globally, such studies are limited.

The study had some limitations. The effect of comorbidities like diabetes and HIV on low drug levels could not be assessed due to the small number of such patients in this study. Also, repeat measurements could not be performed in all in whose dosages were adjusted. Hence, the estimation of the dose adjustment necessary to achieve therapeutic drug levels was incomplete. Being a time-consuming and expensive operation, correlating the clinical response to treatment in TB patients with drug exposure [the area under the concentration-time curve from 0 to 24 hours] for crucial anti-TB medications could not be done. Also, genotypic tests like cytochrome polymorphism and N-acetyltransferase 2 gene mutation tests could not be done as a cause for low drug levels in our study population.

Conclusions

To summarize, the low drug levels, particularly of R, are an important cause for non-response to treatment despite demonstrated drug sensitivity. Various risk factors associated with low drug levels are low BMI, hypoalbuminemia, bilateral disease on chest X-ray, and the presence of cavity. Patients with such risk factors may require a higher dose of standard anti-TB drugs from the beginning for a favorable treatment response. Demonstration of low drug levels, although difficult to predict, is clinically important in determining the success of a treatment regimen. It is recommended that the facilities for TDM should be available in the country for non-responders, as it provides objective/key information for the treating physician to make informed dosing decisions. If the patient presents before completion of 6 months and/or has minimally low drug levels, the levels of R and H may need to be increased to achieve adequate drug levels. However, if the patient presents after receiving 6 months of treatment and/or has significantly low drug levels, the regimen needs to be augmented with 3 or 4 second-line drugs in addition to increasing the dose of R and H.

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