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Research Article

THE ADVERSE DRUG REACTIONS OF INTERMITTENT AND DAILY REGIMENS IN THE TREATMENT OF THE INTENSIVE PHASE OF TUBERCULOSIS

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ABSTRACT

Objective: To study the adverse drug reactions (ADRs) of intermittent and daily anti-tubercular therapy in intensive phase (IP), in patients attending the RNTCP unit, Government Medical College (GMC), Thrissur.

Methods: A prospective observational study was done at the RNTCP unit, GMC, Thrissur, during October 2016-2017. Two hundred and thirty-five patients satisfying inclusion criteria, receiving anti-tubercular therapy as intermittent and daily regimens were selected. Demographic data, risk factors, comorbidities, and investigations were recorded and patients were followed up for IP. Results of investigations, treatment outcome, and ADRs recorded after IP. ADRs were monitored and its causality and severity were assessed. Data were entered in MS Excel and analyzed using SPSS. Qualitative variables are represented as proportions and quantitative as mean and standard deviation. Associations were analyzed using appropriate statistical tests. Analysis was performed using paired t-test $p<0.05$ taken as significant.

Results: Orange-red urine and secretions were the most common ADR, followed by nausea, fatigue, heartburn, etc. Significant increase in random blood sugar, renal function tests (RFTs), and liver function tests (LFT) after treatment, then before noticed. 84.4% of patients from the daily group and 78% of patients from the intermittent group experienced ADRs. Causality was assessed using Naranjo's algorithm and severity using a modified Hartwig and Siegel scale.

Conclusion: The majority of patients developed ADRs, which were mild and managed symptomatically. Some reactions required alteration of therapy, reduction of drug dose, or change of suspected drug. To conclude, meticulous monitoring of ADRs in patients on anti-tubercular drugs is mandatory.

Keywords: Tuberculosis, RNTCP, Intensive phase, Intermittent regimen, Daily regimen, Adverse drug reactions, Naranjo algorithm, Modified Hartwig Siegel scale.

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INTRODUCTION

This study aimed to determine the occurrence and pattern of various adverse drug reactions (ADRs) associated with the use of anti-tubercular drugs, and the treatment outcome in daily and intermittent regimens. Tuberculosis (TB) treatment can be given daily or intermittently, which are equally effective in matters of case detection rate, sputum conversion rate, and treatment completion. The national treatment regimens for TB recommend the use of four first-line anti-TB drugs; isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) [1]. TB treatment has two phases: An initial intensive phase (IP) and a continuation phase (CP). The recommended regimen is 2HRZE/4HRE.

Ever since the introduction of directly observed treatment, short (DOTS), intermittent therapy either throughout the entire 6-month course or only during the CP in the last 4 months has been widely adopted to facilitate treatment supervision on an outpatient basis. Treatment was given 3 times a week. Lower cost, lesser ADRs, and the feasibility of the supervised dosing under the directly observed therapy, which ensures compliance were the factors favoring it. However, with increasing concern of drug resistance and relapses, WHO, in 2010, advised daily treatment as the preferred drug regimen for treatment of all patients with TB.

In 2017, RNTCP introduced a daily regimen in various states in India. Under a daily regimen, fixed-dose combinations (FDCs) of drugs, based on body weight are given, which reduces pill burden and increases patient compliance.

There is confusion about whether the daily regimen or the intermittent regimen is superior to combat the global TB emergency and prevent the development of multidrug resistance [2]. With the rather unusual biological characteristics of *Mycobacterium TB*, the disease shows a distinctive natural history and a very slow response to existing chemotherapy.

A multidrug regimen for a prolonged period of time is necessary to achieve a complete cure in TB patients. However, it has been associated with an increased incidence of side effects, which vary from mild skin rash to fatal anaphylactic shock or mild gastrointestinal upset to hepatic toxicity. A severe side effect to one of the primary anti-TB drugs can lead to discontinuation of that drug, thus resulting in several complications, including increased morbidity and mortality. Whereas the use of alternative agents can cause problems such as toxicity and incompliance and can lead to treatment failure and relapses [3]. Therefore, it is necessary to be vigilant about any ADRs that can occur with the use of anti-tubercular drugs [4]. ADRs aggravate patient suffering and incur substantial additional costs because of added outpatient visits, tests, and in more serious instances, hospitalizations [5,6].

METHODS

Study design

A prospective observational study.

Study setting

RNTCP unit of the Department of Pulmonary Medicine, Government Medical College (GMC), Thrissur, Kerala, India.

Study participants
Patients diagnosed with TB and receiving intermittent and daily anti-tubercular regimens during the study period.

Inclusion criteria
1. Adults diagnosed with TB
2. HIV seronegative patients
3. Willing to participate in the study and to give informed consent.

Exclusion criteria
1. Pregnant and lactating mothers
2. Patients with chronic liver disease or chronic renal disease
3. Multidrug-resistant TB, extremely drug-resistant TB.

Study period
One year from the date of Ethical Committee clearance (October 2016-2017).

Sample size
Two hundred and thirty-five patients.

It was calculated using the formula, n = 4pq/d [2]

p=proportion of ADRs in each group
q=100-p
d=allowable error = 20% of p
p_1=proportion of ADRs in daily group – 35% [2].
sample size of daily group=185
p_2=proportion of ADRs in intermittent regimen – 25.58% [2].
sample size of intermittent group = 284

$$n = \frac{p1 + p2}{2}$$

$$= \frac{185 + 284}{2}$$

=235.

The power of the study was 80%.

Study procedure
The study was initiated after approval from the Institutional Ethics Committee, GMC, Thrissur. The eligible TB patients, attending the RNTCP unit, GMC, Thrissur, were enrolled in the study after considering the inclusion and exclusion criteria. Patients were categorized into two groups based on the treatment regimen received.

Patients who were prescribed ATT daily formed one group and the ones who were prescribed ATT thrice in a week formed the other group. After enrolling the patients, written informed consent was taken from these patients. The relevant data were collected using a questionnaire, which included the epidemiological data of the patient such as age, gender, marital status, contact details, education, occupation, risk factors, comorbidities, history of ATT if any, and family history of TB. A history of alcohol consumption or smoking was also noted. The height, weight, and BMI were recorded at the baseline before initiation of treatment and at the end of the IP of therapy.

The type of TB of the patient was noted. The results of baseline investigations such as sputum AFB, random blood sugar (RBS), liver function tests (LFT), and renal function tests (RFT) were recorded before the initiation of treatment. The doses of the drugs given were noted. The ADRs that can occur due to anti-tubercular drugs were well explained to the patients and they were advised to report, whenever it occurs, to the RNTCP unit.

The patients were regularly followed up for the period of IP of therapy, which was usually 2–3 months. At the end of IP, the results of sputum AFB, RBS, LFT, and RFT, which were routinely done, were recorded again. Any ADRs observed during this period were also recorded. A positive response to treatment was indicated by sputum conversion, in the case of sputum-positive pulmonary TB and an improvement in symptoms, in the case of sputum-negative pulmonary TB and extra pulmonary TB. At the end of IP, the treatment outcome was noted.

The data obtained at the time of initiation of therapy, and after the IP were collected, assessed, and analyzed. The types of adverse reactions were assessed. The causality of individual adverse reactions was assessed using "Naranjo algorithm," which evaluated the degree of association of ADR with suspected drugs and involved a set of questionnaires ascribed with a certain score (−1–+2) based on three types of responses –yes, no, or do not know. A total score was calculated and the association was termed as definite, probable, possible, or doubtful. The severity of individual adverse reactions was assessed using modified Hartwig and Siegel ADR severity assessment scale and was classified as mild, moderate, and severe.

Data analysis
Data were collected, coded, and entered in Microsoft Excel and were analyzed using SPSS version 18 software. Qualitative variables were represented as proportions and quantitative variables as mean and standard deviation. Associations were analyzed using appropriate statistical tests. Analysis was performed using a paired t-test $p<0.05$ was taken as significant.

Budget for the study (Author's funding)
All the expenses were met by the first author.

Specification of drugs used in the study
- Isoniazid – Macleods Pharmaceuticals Ltd, Andheri East, Mumbai, India
- Rifampicin – Lupin Ltd., Aurangabad, Maharashtra, India
- Pyrazinamide – Micron Pharmaceuticals, Vapi, Gujarat, India
- Ethambutol – Lupin Ltd., Aurangabad, Maharashtra, India.

FDC containing 75 mg isoniazid, 150 mg rifampicin, 400 mg ethambutol, 275 mg pyrazinamide-akuriT-4 – Lupin Ltd., Aurangabad, Maharashtra, India.

Limitations of the study
I considered only the initial IP of therapy. Some adverse reactions can appear late in the course of the therapy. The efficacy of a regimen is judged not only by sputum conversion rate but also by relapse rate. Hence, I may not have estimated the overall default rate and ADRs throughout the chemotherapy.

Whether any ethical issues are expected in this study
Ethical clearance was obtained from the Institutional Ethics Committee and informed consent from patients.

RESULTS

Risk factors
The most common risk factor reported in the study population was smoking (51.1%), followed by alcohol intake (47.7%). 20.9% of patients were suffering from diabetes mellitus. 11.9% of the study population had a family history of TB, whereas 9.4% had a history of TB, as depicted in Figure 1.

Comorbidities
Eighty-seven patients (37%) were suffering from some comorbidities, as denoted by Table 1.

Type of TB
The maximum number of patients had extra pulmonary TB (51.5%), followed by sputum-positive pulmonary TB (41.3%), as depicted in Figure 2.

Treatment
One hundred patients were treated with intermittent regimens. Hundred and thirty-five were treated with a daily regimen, as depicted in Figure 3.

Treatment outcome
The majority of the patients had an improvement with treatment; Two hundred and fifteen patients (91.5%), as depicted in Figure 4.

Treatment outcome in intermittent and daily regimen
Ninety-six percent of patients in intermittent regimen and 88.1% of patients in daily regimen showed an improvement after treatment, as denoted by Table 2.

Sputum conversion
In total, 88 patients (90.7% of sputum-positive pulmonary TB) had sputum conversion, of which 41 patients (95.3%) were from the intermittent group and 47 patients (87%) from the daily group, as denoted by Table 3.

Adverse effects

Alterations in laboratory parameters

RBS, LFT, and RFT have shown a statistically significant increase after treatment, compared to their baseline values before treatment ($p<0.001$) as shown in Tables 4 and 5.

ADRs

The most common adverse effect reported was orange-red urine and secretions and it was seen in all the patients taking ATT. Excluding that, 81.7% of the total number of patients experienced some sort of adverse effects. Seventy-eight patients from intermittent group (78%) and 114 patients from daily group (84.4%) experienced adverse effects. The distribution of adverse effects in total patients is given in Table 6 and the distribution of adverse effects in patients on both intermittent and daily regimens is given in Table 7.

Causality assessment of adverse reactions by Naranjo's algorithm

The causality of individual ADR was assessed by Naranjo's algorithm and is shown in Table 8. Most of the ADRs were "Possible" (60.1%), whereas none of the ADRs were "definite" due to anti-tubercular drugs.

Assessment of severity of ADR using modified Hartwig and Siegel scale

The severity of ADRs is assessed using modified Hartwig and Siegel scale and is shown in Table 9. Most of the ADRs were mild (88.4%).

DISCUSSION

TB is the most rampant communicable disease in developing countries and it imposes a major burden on the health-care system [4]. TB can be

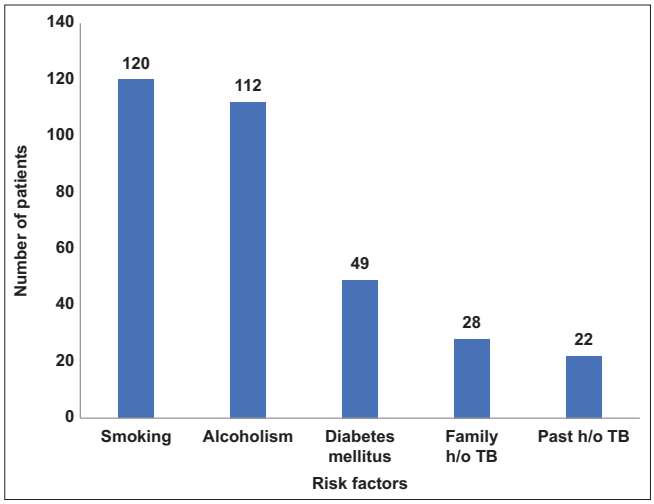

Fig. 1: Risk factors of the study population

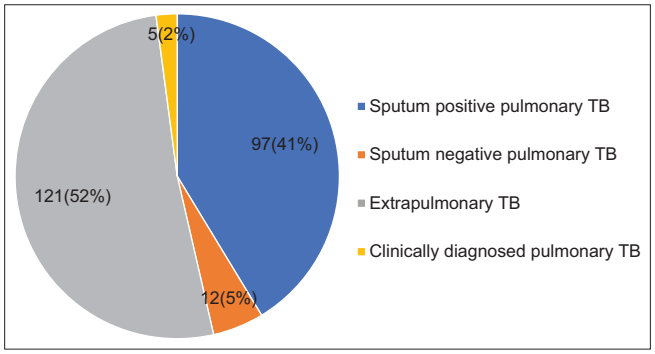

Fig. 2: Distribution of study population based on the type of TB

Table 1: Distribution of comorbidities in the study population

Comorbidity	Number of patients	Percentage
Diabetes mellitus	49	20.9
Visual disturbances	26	11.1
Hypertension	22	9.4
COPD	12	5.1
Dyslipidemia	8	3.4
Others	7	3
Heart diseases	6	2.6
Psychiatric illness	6	2.6
Hearing problems	4	1.7
Drug allergies	3	1.3

Table 2: Distribution of patients in both intermittent and daily regimen groups based on their treatment outcome

Treatment outcome	Intermittent regimen		Daily regimen	
	Number of patients	Percentage	Number of patients	Percentage
Improvement	96	96	119	88.1
Worsening	1	1	4	3
Death	3	3	12	8.9

Table 3: Regimen-wise distribution of patients with sputum-positive pulmonary TB, before and after treatment

Sputum positivity	Before treatment			After treatment		
	Total	Intermittent	Daily	Total	Intermittent	Daily
1+	39	23	16	2	1	1
2+	23	6	17	3	1	2
3+	35	14	21	4	0	4
Total patients	97	43	54	9	2	7
Percentage (%)	41.3	18.3	23	3.8	0.8	3

Table 4: Alterations in laboratory parameters after anti-tubercular therapy and results of paired samples t-test

Laboratory parameter	Mean	Standard deviation	t	Mean difference	Significance (95% CI)
RBS before Rx	129.84	67.41	6.98	25.92	0.001 (33.29, 18.6)
RBS after Rx	155.76	99.32			
Total Bilirubin before Rx	0.73	0.23	4.87	0.30	0.001 (0.42, 0.18)
Total Bilirubin after Rx	1.03	0.98			
DB before Rx	0.31	0.13	4.77	0.22	0.001 (0.31, 0.13)
DB after Rx	0.53	0.69			
OT before Rx	36.16	18.35	3.63	33.55	0.001 (51.78, 15.32)
OT after Rx	69.71	142.07			
PT before Rx	28.88	18.94	4.07	25.95	0.001 (38.52, 13.39)
PT after Rx	54.83	100.7			
BU before Rx	26.7	9.04	7.31	2.12	0.001 (2.69, 1.54)
BU after Rx	28.82	9.28			
S. Cr before Rx	0.86	0.23	3.30	0.09	0.001 (0.15, 0.04)
S. Cr after Rx	0.95	0.44			

RBS: Random blood sugar, Rx: Treatment, DB: Direct bilirubin, OT: SGOT, PT: SGPT, BU: Blood urea, S. Cr: Serum Creatinine, CI: Confidence interval

Table 5: Derangement in laboratory parameters in patients

Adverse effect	Total patients	Number of patients in intermittent group	Number of patients in daily group	Percentage in intermittent regimen	Percentage in daily regimen
Deranged diabetic control	45	15	30	15	22.2
Altered LFT	21	9	12	9	8.9
Altered RFT	3	1	2	1	1.5

LFT: Liver function test, RFT: Renal function test

Table 6: Distribution of adverse effects in total study population

Adverse effect	Total number of patients	Percentage of total patients
Nausea	137	58.3
Heartburn	66	28.1
Vomiting	47	20
Abdominal pain	18	7.7
Diarrhea	7	3
Constipation	6	2.6
Pruritus	25	10.6
Rashes	15	6.4
Peripheral neuropathy	12	5.1
Mucosal lesions	3	1.3
Deranged diabetic control	45	19.11
Jaundice/Raised liver enzymes	21	8.9
Renal function impairment	3	1.3
Visual disturbances	9	3.8
Hearing problems	2	0.9
Fatigue	72	30.6
Arthralgia/myalgia	32	13.6
Somnolence	22	9.4
Insomnia	12	5.1
Vertigo	8	3.4
Orange-red urine, secretions	235	100

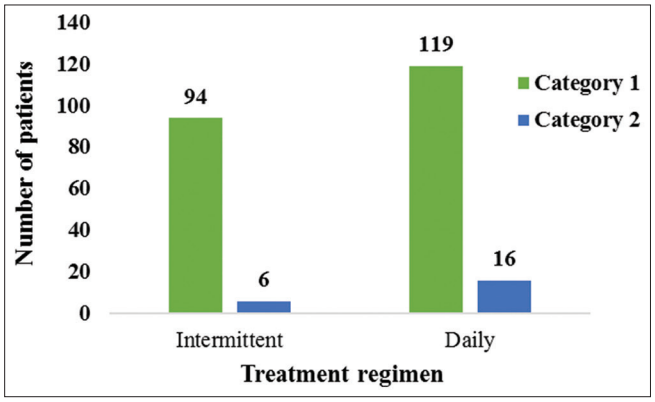

Fig. 3: Distribution of study population based on treatment regimen and category

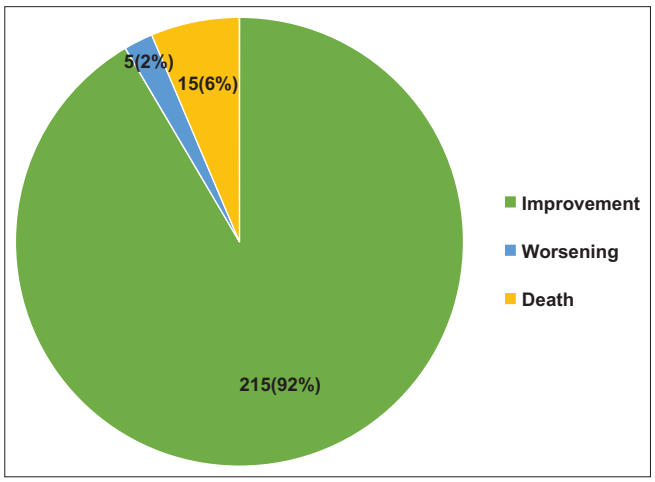

Fig. 4: Distribution of patients based on their treatment outcome

treated with intermittent or daily anti-tubercular therapy. This prospective observational study recorded ADRs of antitubercular drugs of both regimens. Causality assessment was done using the Naranjo algorithm; ADR severity assessment using modified Hartwig and Siegel scale.

The sample size of the present study was 235. It comprises 100 patients taking intermittent regimens and 135 patients taking daily regimens. It was large when compared to a study done in Kolkata by Mandal *et al.*, where the number of patients was 83, with 43 in intermittent group and 40 in daily group [2]. In a study done in Manipur by Sinha *et al.*, on the ADRs to anti-TB drugs in DOTS therapy, 122 patients were considered [5].

The most common risk factor reported in this study was smoking (51.1%), followed by alcohol intake (47.7%). 20.9% of patients were suffering from diabetes mellitus. 11.9% of the study population had a family history of TB, whereas 9.4% had a history of TB. In the study by

Table 7: Distribution of adverse effects in patients on both intermittent and daily regimens

Adverse effect	Number of patients in intermittent regimen group	Number of patients in daily regimen group	Percentage of patients in intermittent regimen (%)	Percentage of patients in daily regimen (%)
Nausea	63	74	63	54.8
Heartburn	22	44	22	32.6
Vomiting	18	29	18	21.5
Abdominal pain	6	12	6	8.9
Diarrhea	2	5	2	3.7
Constipation	5	1	5	0.7
Pruritus	6	19	6	14
Rashes	6	9	6	6.7
Peripheral neuropathy	0	12	0	8.9
Mucosal lesions	1	2	1	1.5
Deranged diabetic control	15	30	15	22.2
Jaundice/raised liver enzymes	9	12	9	8.9
Renal function impairment	1	2	1	1.5
Visual disturbances	0	9	0	6.7
Hearing problems	0	2	0	1.5
Fatigue	33	39	33	28.9
Arthralgia/myalgia	9	23	9	17
Somnolence	10	12	10	8.9
Insomnia	4	8	4	5.9
Vertigo	2	6	2	4.4
Orange-red urine, secretion	100	135	100	100

Table 8: Causality assessment of individual ADRs by Naranjo's algorithm

Adverse effects	Number of patients	Possible	Probable	Definite
Nausea	137	130	7	0
Heartburn	66	59	7	0
Vomiting	47	40	7	0
Abdominal pain	18	15	3	0
Diarrhea	7	6	1	0
Constipation	6	6	0	0
Pruritus	25	10	15	0
Rashes	15	0	15	0
Peripheral neuropathy	12	11	1	0
Mucosal lesions	3	3	0	0
Deranged diabetic control	45	45	0	0
Altered liver function test	21	0	21	0
Altered renal function test	3	0	3	0
Visual disturbances	9	7	2	0
Hearing problems	2	1	1	0
Fatigue	72	72	0	0
Arthralgia/myalgia	32	32	0	0
Somnolence	22	22	0	0
Insomnia	12	12	0	0
Vertigo	8	8	0	0
Orange-red urine, secretions	235	0	235	0
Total	797	479	318	0
Percentage (%)	100	60.1	39.9	0

Table 9: Severity assessment of individual ADRs by modified Hartwig and Siegel scale

Adverse effect	Number of patients	Mild	Moderate	Severe
Nausea	137	130	7	0
Heartburn	66	59	7	0
Vomiting	47	40	7	0
Abdominal pain	18	15	3	0
Diarrhea	7	6	1	0
Constipation	6	6	0	0
Pruritus	25	10	15	0
Rashes	15	0	15	0
Peripheral neuropathy	12	11	1	0
Mucosal lesions	3	2	1	0
Deranged diabetic control	45	45	0	0
Altered liver function test	21	0	21	0
Altered renal function test	3	0	3	0
Visual disturbances	9	0	9	0
Hearing problems	2	0	2	0
Fatigue	72	72	0	0
Arthralgia/myalgia	32	32	0	0
Somnolence	22	22	0	0
Insomnia	12	12	0	0
Vertigo	8	8	0	0
Orange-red urine, secretion	235	235	0	0
Total	797	705	92	0
Percentage (%)	100	88.4	11.6	0

Hochberg *et al*., 48.6% were smokers, all of them were taking alcohol and 35.2% had diabetes [7].

In this study, 37% were suffering from some comorbidities. Diabetes mellitus was the most common, followed by visual disturbance, hypertension, COPD, etc.

In the present study, the maximum number of patients had extra pulmonary TB (51.5%), out of which the majority had tubercular pleural effusion, which was followed by sputum-positive pulmonary TB (41.3%).

In a study by Prakasha *et al*., 58.7% had pulmonary TB including 37.81% who had sputum-positive pulmonary TB and 41.3% had extrapulmonary TB including pleural involvement being the most common [8].

In this study, the majority of the patients had an improvement with treatment (91.5%). ninety-six percent of patients in intermittent regimen and 88.1% of patients in daily regimen showed an improvement after treatment. This was a statistically significant association between treatment regimen and treatment outcome.

In the present study, 90.7% of patients had sputum smear conversion. 95.3% from intermittent group and 87% from daily group constitute that. In the study by Mandal *et al*, at the end of the IP, sputum smear conversion was shown by 94.87% in intermittent regimen and 94.74% in daily regimen [2].

In this study, RBS, LFT, and RFT have shown a statistically significant increase after treatment, compared to their baseline values before treatment ($p<0.001$).

In the present study, 81.7% of the total number of patients had some adverse effects, excluding orange-red urine and secretions, which were reported by all the patients. In the study by Sinha *et al*, 69.01% showed one or more ADRs [5]. In a study by Sharma *et al*., 64.6% experienced some ADRs [9]. In a study by Chhetri *et al*., 54.74% reported the occurrence of ADRs [6]. In the study by Mandal *et al*., 30.12% of patients experienced some ADRs [2].

In this study, 78% of patients from intermittent group and 84.4% of patients from daily group experienced adverse effects. In the study by Mandal *et al*., in intermittent group, ADRs were noted in 25.58%, and in daily group, ADRs were reported more (in 35%) [2].

In the present study, the most common ADR was orange-red urine and secretions, which was reported in all patients, and it was followed by nausea in 58.3%, fatigue in 30.6%, and heartburn in 28.1%.

In the study by Mandal *et al*., the most common ADR in intermittent group was gastrointestinal disturbance (9.30%), followed by raised serum transaminase levels (6.98%); whereas the most common ADR in daily group was GI intolerance, mainly, epigastric pain and fullness in 15% cases [2].

In this study, using the Naranjo Algorithm causality assessment scale, 60.1% of ADRs were possible, 39.9% were probable, and none was definite in nature. In the study by Sharma *et al*, using WHO causality assessment scale, all the ADRs were possible in nature [9]. In the study by Chhetri *et al*., 70.67% of the ADRs were classified as ADRs "possibly" due to suspected drugs [6].

In the present study, using modified Hartwig and Siegel ADR severity assessment scale, 88.4% experienced mild ADRs, 11.6% had moderate ADRs, and none had severe ADRs. In the study by Chhetri *et al*., 93.33% were classified as "mild (level 1)" [6]. In the study by Sharma *et al*., 16.2% of patients experienced mild ADRs, 43.1% of patients had moderate and only 5.4% of patients had severe ADRs [9]. In the study by Sinha *et al*., Most of the ADRs (73.24%) were mild, and only 15.49% were severe reactions (hepatic dysfunction) [5].

Prevention is always better than cure. Hence, through various health education programs, a proper awareness toward the preventive measures and risk factors of TB must be taught to the public. It can also be incorporated into educational curriculums. Furthermore, attention must be given to the development of effective prophylactic strategies and agents, along with newer treatment modalities for TB. Further studies and research in this field are warranted.

CONCLUSION

The present study was a prospective observational study done with the primary objective to evaluate the ADRs of intermittent and daily anti-tubercular therapy in the IP, in 235 patients attending the RNTCP unit of the Department of Pulmonary Medicine, GMC, Thrissur. The study period was for 1 year, from October 2016 to October 2017. The following conclusions were derived from the study:

- The most common risk factor reported in the study population was smoking, followed by alcohol intake and diabetes mellitus
- More than a quarter of patients were suffering from some comorbidities, with diabetes mellitus as the most common. It was followed by visual disturbances and hypertension
- More than half of the patients had extrapulmonary TB, followed by sputum-positive pulmonary TB
- The majority of the patients from both regimens had an improvement with treatment, but few had shown worsening with treatment, and few patients died
- Most of the sputum-positive pulmonary TB from both regimens had sputum conversion
- There was a statistically significant increase in RBS, RFT, and LFT after treatment in both regimens, compared to that before treatment
- The majority of the patients had some ADRs to anti-tubercular drugs
- More ADRs were seen in daily group
- All patients reported orange-red urine and secretions; other common adverse effects were nausea, fatigue, heartburn, vomiting, deranged diabetic control, and arthralgia/myalgia. It was mostly managed symptomatically and it neither needed a discontinuation of the drug nor a change of the drug
- Less than a quarter of patients reported adverse effects such as severe gastric intolerance, altered liver function, and renal function, pruritus and rashes, and visual and hearing disturbances, which were managed by either reducing the dose of the drug or by changing the suspected drug
- The causality assessment of the adverse reactions by the Naranjo algorithm showed that most of them were "possible" and the rest were "probable" due to anti-tubercular drugs
- The severity of ADRs assessed using modified Hartwig and Siegel scale showed that most of them were "mild" and the rest were "moderate"
- To conclude, both intermittent and daily treatment regimens for TB yielded great outcomes and were highly efficacious. However, anti-tubercular drugs were associated with a lot of ADRs. Most of the reactions were mild, and neither needed a discontinuation of the drug nor a change of the drug. However, some reactions required alteration of therapy, either reduction of the dose of the drug or change of the suspected drug
- Therefore, all the above-mentioned findings emphasize the necessity for the meticulous monitoring of ADRs in patients administered with anti-tubercular drugs, throughout the course of the treatment, irrespective of their treatment regimen.

CONFLICT OF INTERESTS

Nil.

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