Original Article

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Side Effects Encountered in Treatment of Multidrug-resistant Tuberculosis: A 3-Year Experience at First Dots Plus Site of Chhattisgarh

Puneet Bhardwaj[1], Atul Manoharrao Deshkar[2], Rahul Verma[3]

[1]Associate Professor, Department of Chest and Tuberculosis, Government Chhattisgarh Institute of Medical Sciences, Bilaspur, Chhattisgarh, India, [2]Associate Professor and Head, Department of Physiology and Coordinator Medical Education Unit, Government Chhattisgarh Institute of Medical Sciences, Bilaspur and Secretary IMA College of General Practitioners, Chhattisgarh, India, [3]Associate Professor, Department of Ophthalmology, Government Chhattisgarh Institute of Medical Sciences, Bilaspur, Chhattisgarh, India

Abstract

Background: The emergence of strains of *Mycobacterium tuberculosis* that are resistant to anti-mycobacterial agents is a worldwide problem.

Materials and Methods: We included patients who are admitted to the Institute between 2011 and 2015 with an intention to report frequency of side effects in cases of multi-drug resistant tuberculosis (MDR-TB), as a part of pharmacovigilance program. A questionnaire-based study of 150 patients who received MDR-TB treatment under directly observed treatment, short-course plus program.

Results: One or more side effects developed in 125/150 (83.33%) of patients. Gastrointestinal side effects (76%); psychiatric (44.7%); arthralgia and hyperuricemia (31.3%); central nervous system (22.7%); ototoxicity (22%); peripheral neuropathy (18.7%); menstrual disturbances (4.7%); hepatitis, visual disturbances, nephrotoxicity (4% each); and hypothyroidism (0.6%).

Conclusion: Timely management of side effects helps in retaining patients that lead to the success of treatment, despite the high occurrence of side effects.

Key words: Chhattisgarh, Directly observed treatment short-course, Multidrug-resistant tuberculosis, Side effect

INTRODUCTION

The emergence of strains of *Mycobacterium tuberculosis* that is resistant to antimycobacterial agents is a worldwide problem.[1] Multidrug-resistant tuberculosis (MDR-TB) has been an area of growing concern and is posing a threat to the control of TB. A project by the international union against TB and lung diseases started in 1994-1997 for global drug resistance surveillance with the help of World Health Organization (WHO). The global TB report 2014 estimated that a 3.1% of newly diagnosed and 20.5% of previously treated cases had MDR-TB. It has been estimated that 480,000 cases emerged, and 210,000 deaths occurred due to MDR-TB globally in 2013. In India, estimates showed that the prevalence of MDR-TB among new and previously treated patients was 2.2% and 15%, respectively. It is estimated that 99000 cases of MDR-TB emerge every year out of which 62000 were among notified cases of TB in 2013. MDR-TB is usually a man-made problem and results mainly due to mismanagement of the disease. Serious side effects have been observed in many studies.[2]

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The most cost-effective public health measure for the control of TB is the identification and cure of infectious TB cases, i.e., patients with smear-positive pulmonary TB. Nevertheless, National TB Programs provide for the identification and cure of all patients with TB. These guidelines cover the treatment of patients, both adults and children, with smear-positive pulmonary TB, smear-negative

Corresponding Author: Dr. Atul Manoharraao Deshkar, Department of Physiology, Chhattisgarh Institute of Medical Sciences, Bilaspur, Chhattisgarh, India. Phone: +91-9893008889. E-mail: dratuldeshkar@gmail.com

pulmonary TB, and extrapulmonary TB.[3] Adequate timely early diagnosis, optimal treatment, and proper compliance are needed to curb the epidemic. The last part compliance is very important because the lack of compliance in previous treatment is usually a cause of MDR-TB. The long 2-year course of MDR-TB treatment with reserve antitubercular drugs is full of side effects, which many times add to the agony of patients, and they leave treatment. These reserve drugs are having a lot of side effects. To know the frequency of side effects, the present study was done.

Definition of MDR-TB

MDR-TB is defined as disease due to *M. tuberculosis* that is resistant to isoniazid and Rifampicin with or without resistance to other drugs (the culture and drug susceptibility test results being done from an accredited laboratory).[4] MDR-TB, is an important obstacle to TB control. In 2013, MDR-TB represented 480,000 incident TB cases worldwide and, as denoted by global experts including the WHO.[5]

Studies claim that medications used in the treatment of MDR-TB are less potent and associated with a greater number of side effects.[6] Rapid and early diagnosis of MDR-TB improve survival and are of a public health benefit.[7]

MATERIALS AND METHODS

This study was done at first directly observed treatment, short-course (DOTS) plus the site of Chhattisgarh state established in the department of Chest and TB Chhattisgarh institute of medical sciences, Bilaspur (Chhattisgarh). We included patients who are admitted to the Institute between 2011 and 2015. First, MDR suspects were identified here and all linked districts. These suspects were screened by gene expert and confirmed by intermediate reference laboratory (i.e., reference lab) Raipur under DOTS-plus program. All patients who were resistant to rifampicin (R) and isoniazid (H) were diagnosed as MDR-TB. All rifampicin resistant (monoresistance) patients were also treated for MDR-TB. After diagnosis patients were admitted and screened as per DOTS-plus framework. All HIV-positive patients were excluded from the study. All patients having other preexisting diseases were also excluded from the study. We did not include transferred outpatients. Side effects observed during the course of 18-24 months of treatment were included. Doses of drugs given were according to weight band as per revised national TB control program. Dosages and weight (in kg) band recommendations are as shown in Table 1. All patients had tab pyridoxine 100 mg. All patients were hospitalized for an initial period of 7 days. After discharge monitoring was done monthly by recalling the patients or by the help of DOTS-plus supervisors. All patients who completed at least 6 months of treatment were included. All new side effects which occurred after initiation of MDR-TB treatment were listed and evaluated. Their side effects which appeared at any time during treatment were recorded (i.e., intensive/continuation phase). Monthly meetings of senior treatment supervisors also contributed to data collection. Among the 200 plus patients registered in our DOTS-plus site, 150 patients met the above criteria and included in the study. An investigation done were as per DOTS-plus program. Additional investigations such as audiometry were done when needed. The DOTS-plus regime employed was kanamycin, ethambutol, pyrazinamide, cycloserine, ethionamide, levofloxacin, and pyridoxine; sometimes para-aminosalicylic acid (PAS) was used. If patient's weight changes, his doses were also changed according to weight band with his next supply of drugs.

OBSERVATION AND RESULTS

We registered 150 patients for this study. Among them, 108 were male (72%) and 42 (28%) were females with the overall mean age of 34.8 years. Injection kanamycin was administered in IP, i.e., first 6 months, on all weekdays except Sundays.

The side effects are summarized in Table 2. The side effects of varying degree were observed in 125/150 patients (82.33%), although most of the side effects were mild in nature and subsided with pharmacotherapy and counseling. Gastrointestinal (GI) side effects were the most common 114/150 (i.e., 76% of total patients) nausea, vomiting, loss of appetite were the most common. These symptoms were responded to counseling, food and drug intake advice. In severe cases, we had to treat with pantoprazole 40 mg + domperidone 30 mg. None of the patients left treatment due to these side effects. Most of these side effects occurred during first 6 months of treatment.

Ototoxicity was also a common side effect with the hearing loss of varying degree. We did audiometry in all patients complaining of hearing loss. This ototoxicity appeared in 33/150 patients (22%). The majority of patients treated were with increased hydration, ginko biloba, and counseling. This side effect mostly occurred during first 6 months. Our three patients went almost deaf during treatment and in five patients' kanamycin were stopped. Central nervous system symptoms were observed in 34 patients (22.7%). The most common was dizziness tremors and insomnia. They responded to symptomatic treatment, one patient of convulsions also responded to symptomatic treatment. No patient left treatment due to complications.

Arthralgia and hyperuricemia occurred in 47 cases (31.3%), and most cases occurred during first 6 months. Symptoms of

most patients were very trivial and did not need any treatment, while although etoricoxib 120 mg was used in some patients. Hyperuricemia was treated with febuxostat 40 mg BID or 80 mg BID, and all patients responded. Although morbidity was there, but it did not cause any disruption in treatment.

Slight nephrotoxicity observed in 6 patients (4%), i.e., elevation of 0.5 mg serum creatinine from base level but did not cause any problem in management, visual disturbances occurred in six patients (4%) who were treated symptomatically, and counseling, five patients had refractory error which was corrected.

Hepatitis occurred in six patients (4%), and we have to stop hepatotoxic drugs for 10-14 days. The patients responded to symptomatic management.

Most patients with dermatological complications complained of itching (21/150, i.e. 14%) which responded to symptomatic treatment with cetirizine 10 mg. Two patient developed rashes which were managed by a dermatologist. No patient left the treatment.

One patient developed hypothyroidism (although he was not taking PAS), which responded to oral thyroxine, gynecomastia was developed in two cases counseling was done for that. Menstrual irregularity occurred in 7 patients (4.7%), which did not cause any change is treatment. All female patients were counseled for family planning.

Psychiatric disturbances occurred in 67 patients (44.7%); most patients suffered from anxiety and mild depression who responded to counseling and in some cases treated with drugs such as clonazepam and escitalopram. More severe cases were treated by a psychiatrist with olanzapine 10 mg, suicidal tendencies developed in 2 patients and 5 patients suffered from severe psychosis. Two patients continued treatment by stopping cycloserine, but 5 patients left the treatment in the continuation phase.

Peripheral neuropathy developed in 28 patients (18.7%). This side effect increased with the duration of treatment. Most patients responded by increasing the dose of pyridoxine and by adding methylcobalamin and sometimes pregabalin. One patient developed severe neuropathy and cycloserine was replaced by PAS, and dose of ethionamide was reduced; however, she continued treatment under cover of other medicines.

DISCUSSION

Chan *et al*. (2004) stated improvement was statistically significant for surgery and among older patients for fluoroquinolone therapy.[8] The side effects of varying degree occurred in 125/150 patients (83.33%) but the majority of these are very trivial and responded to symptomatic treatment and counseling, GI side effects were the most common but responded to treatment. Most important side effects we observed were ototoxicity (22%) and psychiatric (44.7%). These side effects were more disturbing and caused the threat of losing our patients. We should keep track of these two side effects. Gatell *et al*. 1987 analyzed risk factors predisposing to auditory toxicity of aminoglycosides from records of 187 patients enrolled in three prospective randomized trials comparing the toxicity of netilmicin, tobramycin, and amikacin.[9] Ototoxicity is more important in initial 6 months and psychiatric disorders increase with length of treatment. In these two disorders, high familial support is required so patient and his family members to be counseled properly. There two are the most common reason of default in our study. Timely intervention, treatment, and counseling are the key to success. The

Table 1: Dosage and weight band recommendations

Drug	16-25 Kg	26-45 Kg	>45 Kg
Kanamycin (mg)	500	500	750
Levofloxacin (mg)	250	750	1000
Ethambutol (mg)	400	800	1200
Pyrazinamide (mg)	500	1250	1500
Cycloserine (mg)	250	500	750
Ethionamide (mg)	375	500	750
PAS (mg)	5	10	12
Pyridoxine 50 (mg)	50	100	100

PAS: Para-aminosalicylic acid

Table 2: Distribution of side effects

Side effects	First 6 month	After 6 month	Total
GI: Diarrhea, vomiting, abdominal pain, loss of appetite, metallic taste, sulfurous belching, and excessive salivation	93	21	114
Ototoxicity	31	2	33
CNS symptoms: Dizziness, vertigo, convulsions, slurred speech, tremors, and insomnia	21	13	34
Arthralgia and hyperuricemia	35	12	47
Nephrotoxicity	5	1	6
Visual disturbances	4	2	6
Hepatitis	3	3	6
Skin rash and pruritus	15	6	21
Psychiatric	31	36	67
Hypothyroidism and goiter	1	-	1
Gynecomastia and menstrual disturbances	4	3	7
Peripheral neuropathy	8	20	28

CNS: Central nervous system, GI: Gastrointestinal

frequency and early occurrence of ototoxicity may be due to the extended exposure to aminoglycosides during or prior to MDR-TB treatment. It is worth noting that 38.3% of patients had previous exposure to streptomycin. This is consistent with the finding from Moore *et al*., who showed an association between ototoxicity and cumulative duration of aminoglycosides. We did not find nephrotoxicity due to aminoglycosides that much high as ototoxicity and was similar to observation of other workers. Psychiatric disorders were also very frequent in our study. Many patients under treatment suffered from some of depression, and this was partly attributable to a loss of confidence due to long-suffering, previous treatment failures and long treatment need. Hence, there is need of good counseling by doctors and other staff to win the trust and confidence of the patient. The main culprit of psychiatric disorders was cycloserine, and we have to stop or replace drug in some patients because we were not able to manage patient with counseling and pharmacotherapy. A headache was attributed to quinolones in some patients and responded to pharmacotherapy and counseling. Hypothyroidism was very few because very few patients were on PAS. In one female patient severe disturbing peripheral neuropathy occurred, and we had to stop cycloserine and ethionamide dose were reduced. Hence, ototoxicity, psychiatric, and neurological complications are more important and of concern. Prasad *et al*. opined that the primary objective in the control of MDR-TB is to prevent its development in the first place. This can be done by DOTS, which is the most cost-effective method of treatment and prevention of MDR-TB.[10]

CONCLUSION

There was a high rate of side effects in the treatment of MDR-TB. However, a high rate of side effects does not prevent care of these patients. We conclude by saying that effect should be made to continue treatment in the face of side effects as long as they fall short of being life-threatening. The timely and aggressive management of side effects and good counseling is, therefore, important in keeping patients in treatment.

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