IJPSR (2021), Volume 12, Issue 11 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 27 December 2020; received in revised form, 19 May 2021; accepted, 26 May 2021; published 01 November 2021

EFFICACY OF DRUGS IN DRUG-RESISTANT TUBERCULOSIS: A RETROSPECTIVE OBSERVATIONAL STUDY

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Keywords:

Tuberculosis, Efficacy, Resistance, DR-TB, MDR-TB

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ABSTRACT: Introduction: Drug-resistant tuberculosis (DR-TB) emerged from the time anti-tuberculosis drugs were discovered and used. It has become a formidable obstacle in the eradication of tuberculosis. India is in second position after China with tuberculosis, where about 20% of patients with DR-TB were not treated due to inappropriate coordination and diagnostic facilities. **Method and Materials:** A retrospective observational study aimed to assess various resistance patterns, distribution among genders, and efficacy of DR-TB regimen (2016-2019). Institutional ethical clearance with approval from the state and district TB center were obtained, and a structured data collection form was created to collect patient details registered under Ernakulam district TB unit, Kerala, India. Data obtained were statistically analyzed with Mantel-Cox test using SPSS version 25. **Results and Discussion:** Study shows that rifampicin resistant tuberculosis (RR-TB) is most common form of DR-TB in newly diagnosed patients. In previously treated patients, both Multidrug Resistance and RR-TB were recorded as 38%. Rifampicin and isoniazid were drugs with high resistance and on comparing the efficacy, shorter regimen had higher efficacy than conventional regimen. High failure and death rates were observed with conventional regimen. Survival analysis showed a higher survival rate with shorter regimen. **Conclusion:** Resistance emergence was a very frequent obstacle to overcome with the existing established sensitive drug therapy against tuberculosis. The causes and factors remain unclear, but solution lies in innovative diagnostic approaches and individualized selection of drug regimens. Resistance, if continued to be unnoticed, could lead to a shortage of effective existing drugs, prompting the development of newer drugs.

INTRODUCTION: Drug resistance tuberculosis (DR-TB) has become an unavoidable obstacle in tuberculosis (TB) control and has emerged from the time anti-tuberculosis drugs were discovered and used [1]. Increased number of resistances in patients and changing treatment regimens is a challenge in TB treatment.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(11).5968-73

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(11).5968-73

Multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) are the main forms of DR-TB. Others type of resistance includes Rifampicin resistant tuberculosis (RR-TB) and Isoniazid mono or poly resistant tuberculosis.

When the Mycobacterium tuberculosis strain is resistant to at least rifampicin (R) and Isoniazid (INH, H) it becomes MDR-TB, along with INH and R; when resistance occurs to fluoroquinolones and second-line injectable drugs, it becomes XDR-TB [2]. Rifampicin resistance tuberculosis and INH mono resistance tuberculosis occur when the TB

strains are resistant to the most powerful anti –TB drugs Rifampicin and Isoniazid.

Social habits like alcohol and tobacco smoking increase the existing risk of tuberculosis by a factor of 3.3 and 1.6 [3]. Due to the use of multiple drugs in TB treatment, patient adherence and corporation become a necessity. Along with these factors, the occurrence of side effects and adverse drug effects increase the burden of TB control.

Management and treatment of TB are strictly based on the drug susceptibility test (DST) and culture reports to provide appropriate treatment at the earliest. DR-TB is commonly seen in person with previous TB treatment history or treatment failure history, so a treatment regimen should be selected based on an appropriate diagnostic procedure. Inappropriate and irregular treatment facilities, cross-resistance, and bacterial mutations are the main reason for the spread of resistant strains in DR-TB patients [4].

Under the guidance of the revised national tuberculosis control program (RNTCP), a DOTS-plus strategy has been adopted to provide a customized treatment regimen for DR-TB patients based on DST reports. Depending on the duration of the initial phase, the treatment of DR-TB varies. It takes about 9-11 months for a shorter regimen and 24-27 months for a conventional regimen. Treatment of DR-TB becomes more challenging in special cases of pregnancy, children, HIV co-infection, renal and liver impairment, and other serious medical conditions [5].

There is an increased prevalence of MDR-TB cases in India, indicating the need for strict surveillance and treatment to provide a better clinical outcome [6]. According to the Indian TB report 2019, there was a high risk of tuberculosis among working-age groups, which affects the development of the country. In the year 2018, an estimate of 58347 patients with MDR/RR-TB and 8809 patients with H mono/poly TB cases were diagnosed in India. Out of this, about 20% were not put on treatment due to inappropriate coordination and diagnostic facilities [7].

Following this, a study to assess various resistance patterns, efficacy, and safety of the DR-TB regimen was designed, which adds up a piece of new knowledge to society. Thus, the aim of the study was constructed to assess the variation in resistance pattern which had occurred in DR-TB cases, with special emphasis to identify which anti-TB regimen is more effective and safer in the treatment of drug-resistant tuberculosis.

METHODOLOGY:

Study Design and Study Settings: A retrospective observational study was conducted in the Ernakulam district of Kerala in India, under the district tuberculosis center (DTC), Ernakulam, which includes 8 TB units with 113 subunits.

Ethics, Privacy, and Confidentiality: The study protocol was approved by the Institutional Human Ethics Committee (IHEC), and the proposed plan of the study was approved by the State TB cell, District TB center (DTC), Operational Research (OR) committee, Directorate of health service, Kerala, India. Data was procured from medical records of registered patients and did not involve any kind of patient interaction; thus, the informed consent form was not applicable. Throughout the study, the privacy and confidentiality of patients and medical records were ensured under DTC.

Subject Recruitment and Study Participants: The study enrolled all patients registered under the Ernakulam district TB center under the norms of RNTCP during 2016-2019. The study excluded patients with HIV co-infection and those aged below 12 years due to privacy concerns. A total of 146 patients were included in the study after exclusion criteria.

Data Collection: The study recorded data using a collection form formulated based on RNTCP [8,] and the data collection form included demographics details (age, sex), previous history, drug sensitivity pattern before and after treatment, the efficacy of treatment based on outcomes, *etc***.** Each data was later cross-checked using district and concerned TB unit records.

Data Analysis: The recorded data were entered into excel 2016, and statistical analysis was performed using SPSS version 25 and G Power version 3.1.9.2. All data were expressed in frequency and percentage; the log-rank test was done to analyze the survival rate.

RESULTS: A total of 146 patients above 12 years of age were enrolled in the study. Many registered patients were not included as they were transferred to some other TB center or where sudden death occurred, even before the initiation of treatment. Out of the registered individuals, 78.76% of the patients were males, and 21.23% were females **Table 1**.

TABLE 1: DISTRIBUTION OF AGE CONCERNING GENDER

Age	Sex		Total
	Male	Female	
12-15 years	0	1(3.22%)	1 (0.67%)
16-25 years	9(7.8%)	6(19.35%)	15 (10.13%)
26-45 years	30(26.08%)	15(48.38%)	45 (30.82%)
46-65 years	62(53.9%)	8(25.8%)	70 (47.94%)
≥66 years	14(12.17%)	1(3.22%)	15 (10.13%)
Total	115 (78.76%)	31 (21.23%)	146 (100%)

Among the registered 146 patients, 98 (67.12%) patients had a previous history of PTB, and 10 (6.84%) had a previous history of MDR-TB with male predominance **Table 2**. The same strain of mycobacterium tuberculosis due to regrowth leads to recurrence of TB, knowns as reinfection or relapse with strain mutation and which was recorded as 18.49% of cases.

TABLE 2: DETAILS OF THE PREVIOUS HISTORY

Particulars	Male	Female	Total
PTB history	78 (79.59%)	20 (20.40%)	98 (67.12%)
Recurrence among PTB patients	22 (81.48%)	5 (18.51%)	27 (18.49%)
Previous DR history	8 (80%)	2 (20%)	10 (6.84%)

PTB- Pulmonary tuberculosis, DR-Drug resistant

On observing and comparing the type of resistance in patients with TB and comparing the sex with the type of TB in both males and females **Fig. 1**. It was found that the greatest number of cases were diagnosed with RR-TB (41.09%) and MDR-TB (40.4%). The middle line represents standard error. It was also estimated that the majority of patients who were newly diagnosed emerged with RRTB, whereas previously treated patients emerged mostly with MDR -TB **Fig. 2**. As previously treated patients are at high risk of developing resistance compared to others, a strict diagnosis and long-term treatment with more toxic anti-TB drugs have become essential.

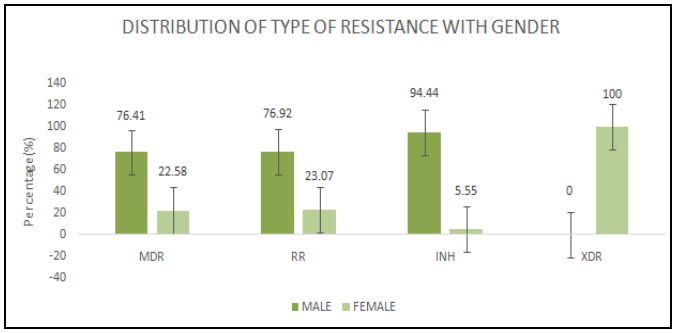

FIG. 1: DISTRIBUTION OF TYPE OF RESISTANCE WITH GENDER. MDR-Multidrug resistance, RR-Rifampin resistance, INH- Isoniazid resistance, XDR-Extensively drug-resistant

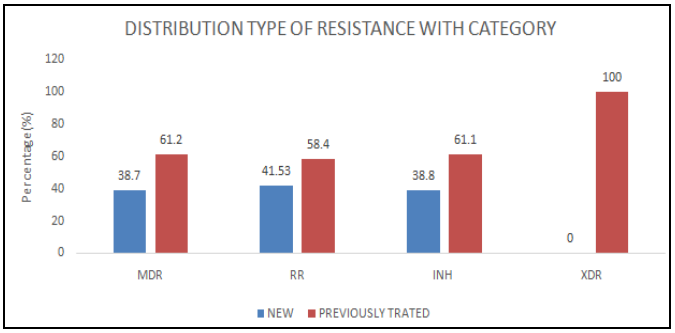

FIG. 2: DISTRIBUTION TYPE OF RESISTANCE WITH CATEGORY. MDR-Multidrug resistance, RR-Rifampin resistance, INH- Isoniazid resistance, XDR-Extensively drug-resistant

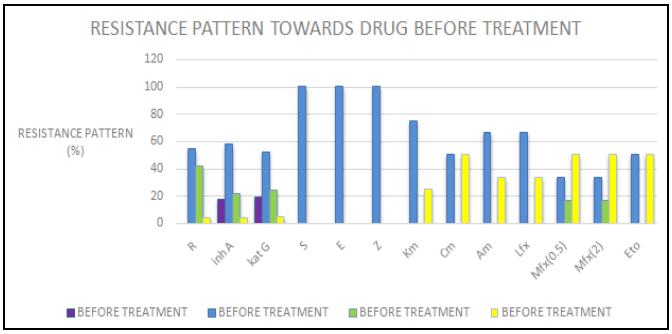

FIG. 3: RESISTANCE PATTERN TOWARDS DRUG BEFORE TREATMENT. R-Rifampicin, inh A-Inhibin alpha gene, kat G- Mycobacterium tuberculosis catalase-peroxidase-, S-Streptomycin, E-Ethambutol, Z- Pyrazinamide, Km-Kanamycin, Cm- Capreomycin, Am- Amikacin, Lfx- Levofloxacin, Mfx-Moxifloxacin, Eto- Ethionamide

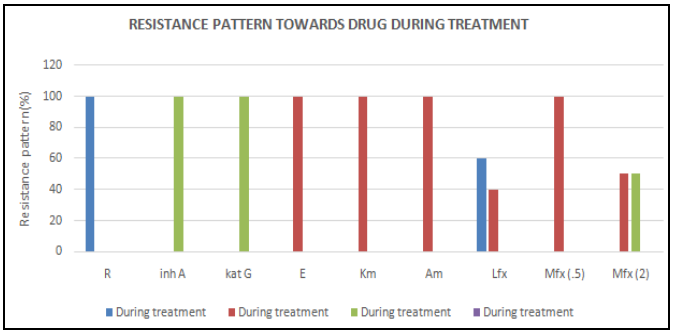

FIG. 4: RESISTANCE PATTERN TOWARDS DRUG DURING TREATMENT. R-Rifampicin, inh A-Inhibin alpha gene, kat G- Mycobacterium tuberculosis catalase-peroxidase, E-Ethambutol, Km-Kanamycin, Am- Amikacin, Lfx- Levofloxacin, Mfx-Moxifloxacin

The data on the resistance pattern of tuberculosis towards each drug before the treatment and additional resistance that occurred during the treatment **Fig. 3, 4** indicated that (excluding INH mono poly resistance), all patients are resistant to rifampicin (127). About 73.28% had isoniazid resistance because of Kat G or INH A.11.25% of the population have only resistance to the isoniazid. In total 26.02% had only rifampicin resistance. Resistance to other anti-TB drugs is quite low compared with Isoniazid and Rifampicin. One patient was identified with XDR TB. After R and INH, the drugs levofloxacin and ethambutol were observed with 6.84% & 5.47% of resistance, respectively. During treatment, many of them had additional resistance due to noncompliance and other individual factors.

On scrutinizing the efficacy of the treatment regimen based on the outcome **Table 3**. It was noted that the positive outcome of the conventional regimen is 52.04% and the shorter regimen is 53.18%. The study cannot comment on the newer drug regimen as the subjects were fewer. The percentage of failure in the conventional regimen (10.95%) is higher when compared with a shorter regimen (2.12%). Also, those who died in the conventional regimen are 15.1%, which is much higher than the shorter regimens (10.63%). The study recorded 12 newer drug regimens of which 6 are ongoing. In the remaining 6 cases, 4 (66.66%) patients passed away, and two were cured of the disease. The number of patients who were lost to follow-up in both conventional as well as shorter regimens was the same. Patients following conventional regimen undertake a long duration of therapy and face related stigma problems, whereas, in a shorter regimen, the major obstacle is ADR caused by the drugs. The severity of ADR with a shorter regimen can be hazardous due to the high dose administered and while considering the effectiveness of the different regimens, shorter and conventional were equally effective. Though safety was more reliable with the conventional regimen, and status of the newer regimen is still doubtful because of the high rate of death, mainly by QT prolongation.

Out of 19 patients with ongoing treatment, 3 were from INH-MONO, 10 shorter, 2 newer, and 4 conventional regimens. Most of the patients in shorter and conventional regimens were culture-negative from the 4th month onwards, showing high chances for cure rate, but in newer and INH-MONO regimens, most of them were culture positive.

TABLE 3: EFFICACY OF REGIMEN

	Positive			Negative				Treatment	N
	Cured	T.C	T.O	Failure	Died	LTFU	ADR	Ongoing	
INH	4 (26.7)	5 (33.3)	-	1 (6.66)	3 (20)	2 (13.3)	-	3	18
Conv.	23 (31.5)	15 (20.5)	2 (2.7)	8 (10.95)	11 (15.1)	14 (19.2)	-	4	77
Shorter	7 (14.9)	18 (38.23)	-	1 (2.12)	5 (10.6)	9 (19.1)	7 (12.8)	6	53
Bdq	1(25)	1(25)	-	-	2(50)	-	-	5	9
Dlm	-	-	-	-	2 (100)	-	-	1	3

T.C- Treatment completed, T.O- Transferred out, LTFU- Lost to follow up, ADR- Adverse drug reaction, Conv. - Conventional

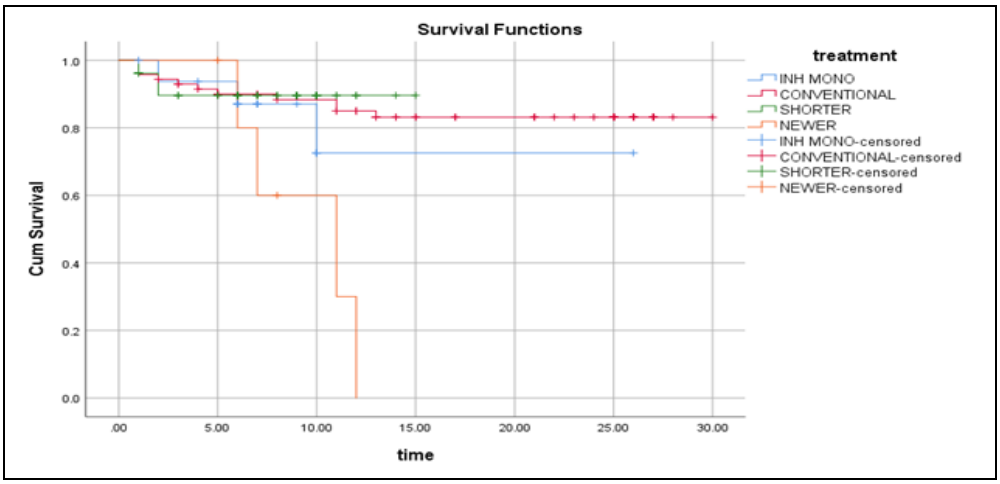

FIG. 5: LOG-RANK SURVIVAL ANALYSIS

Survival Distributions for the Different Levels of Treatment with Log-Rank: From Log-rank (Mantel-Cox) survival analysis **Fig. 5** it was observed that all treatment regimens were significantly different in survival rate (P=0.005) when compared with one another. Survival with shorter regimen at 15th month was 90% (95% confidence interval [CI], 12.4 to 14.7), conventional regimen was 82% (95% CI, 23.7 to 28.1), INH mono was 75% (95% CI, 15.5 to 26.1) and newer at 12th month was 0% (95% CI,6.92 to 12) respectively.

DISCUSSION: The development of drug resistance is a major threat globally. Exposure to anti-TB drugs led to the emergence of drug resistance in previously treated MDR-TB patients. Even newly diagnosed patients are expressing strains of resistance to tubercular drugs. This study involved patients from both these domains where resistance was evaluated for its factors and additional reasons for the contribution of the occurrence of resistance due to exposure to tubercular drugs.

In this study, the drugs with high resistance were INH and R, because being the main drugs in the standard regimen of TB treatment, their suboptimal administration may lead to high resistance.

Globally *via* bacteriologically confirmed TB, tested for RR resistance were 41% in 2017 which progressed to 51% in 2018 [9]. As per the global TB report 2016, there was 3.9 % of newly diagnosed and 21% of PTB cases with Multi-Drug Resistant – Tuberculosis [10]. In our study also the rate of previously treated patients was high with 61.2% in MDR-TB, 58.4% in RR-TB, 61.1% in INH MONO, and 1.14 in XDR-TB.

According to Chien JY *et al.,* 2015 and Basel K *et al.*, 2019, the efficacy or positive outcome of INH monotherapy is 74% in Europe and 84% in China, but in this study, it was recorded as 60%. The probable reason was the chances of conversion to MDR are high, with low compliance to therapy and other confounding factors [11, 12].

Khan A.F *et al.,* 2017 & Du Y 2019 found that the shorter regimen has high efficacy when compared with the standard regimen [13, 14.] Du Cros P *et al.,* 2017 say that both regimens have the same efficacy in case of outcomes [14]. In our study, we obtained only a slight variation for conventional (52.04%) and shorter regimens (53.18%) in terms of positive outcome and efficacy. Due to the less duration of the therapy, a shorter regimen increases patient compliance, thus increase the cure rate. In the case of a conventional regimen with an increase in the duration of treatment, patient compliance decreases. According to WHO 2016, the use of a shorter regimen for DR-TB aimed to have a positive impact on treatment cost, patient compliance, and cure rates [15].

Till now, only a few studies have executed a survival analysis of treatment regimens in DR-TB patients. In our study, the outcome of interest was to compare the survival analysis using Log-rank survival analysis of the four anti-TB regimens i.e., a shorter, conventional, INH mono and newer regimens. From the data obtained, the shorter regimen had a high survival rate and least with that of a newer regimen. Newer drugs such as Bedaquiline and Delamanid have reported serious adverse drug effects like QTcF prolongation which reduces the patient survival rate. More studies on the safety and efficacy of newer drugs are of great concern and require further analysis to establish safety.

These studies' main limitation was, being a retrospective study and thus did not obtain an opportunity for direct patient interaction and accurate patient follow up because of the longer duration of treatment in DR-TB patients and as many patients were still on treatment.

Only a Few studies till now have evaluated the resistance pattern, efficacy and survival analysis of the DR-TB regimen, which adds more strength to these findings.

CONCLUSION: The aim to wipe out TB is still a challenging task due to the emergence of resistance. So accurate diagnostic criteria and appropriate treatment regimen are the need of time. Resistance patterns should be studied carefully, and treatment modification to be promptly done with high effectiveness.

Our study concludes that while comparing to other regimens, a shorter regimen has high Efficacy and survival rate. RR-TB and MDR-TB being the most

common form of DR-TB, INH and rifampin were the drugs with high resistance. The safety of newer drugs is under concern, and the exact efficacy of newer drugs in patients is not exactly found. More studies are required to conclude newer regimens such as Delamanid and Bedaquiline safety and effectiveness.

"Treatment without a cure is still a failure, so we must unite together to end tuberculosis."

AUTHORSHIP: All authors contributed equally.

ACKNOWLEDGEMENT: We thank state and district Tuberculosis coordinators for their permission, support, and assistance given during the project period.

CONFLICT OF INTEREST: The authors declare that there is no conflict of interest.

FUNDING: No funds were received by the authors.

ETHICS APPROVAL NO: Institutional ethical clearance was obtained (No:012/IHEC/10/2019/ NCP) along with permission from Kerala State TB cell No: 281/STC/DHS/2019

REFERENCES:

1. Kim CK, Shin SY, Kim HJ and Lee K: Drug resistance patterns of multidrug- and extensively drug-resistant tuberculosis in Korea: amplification of resistance to oral second-line drugs. Ann Lab Med. 2017; 37(4): 323-26.
2. Saldanha N, Runwal K, Ghanekar C, Gaikwad S, Sane S and Pujari S: High prevalence of multi drug resistant tuberculosis in people living with HIV in Western India. BMC Infectious Diseases 2019; 19(1): 1-6.
3. Silva DR, Muñoz-Torrico M, Duarte R, Galvão T, Bonini EH, Arbex FF, Arbex MA, Augusto VM, Rabahi MF and Mello FCQ: Risk factors for tuberculosis: diabetes, smoking, alcohol use, and the use of other drugs. J Bras Pneumol 2018; 44(2): 145-52.
4. Kurz SG, Furin JJ and Bark CM: Drug-Resistant Tuberculosis: Challenges and Progress. Infect Dis Clin North Am 2016; 30(2): 509-22.
5. Singh A, Prasad R and Kushwaha RAS: Treatment outcome of multidrug-resistant tuberculosis with modified DOTS-plus strategy: A 2 years' experience. Lung India 2019; 36(5): 384-92.
6. Goyal V, Kadam V, Narang P and Singh V: Prevalence of drug-resistant pulmonary tuberculosis in India: systematic review and meta-analysis. BMC Public Health 2017; 17(1): 817.
7. India TB report 2019, New Delhi, health Ministry (244).https://tbcindia.gov.in/WriteReadData/India%20TB%20Report%202019.pdf
8. PMDRT, Guidelines on programmatic management of Drug-Resistant Tuberculosis in India, New Delhi, Revised National Tuberculosis Control Programme, 2017, Annexure 15M: RNTCP PMDT Treatment Book, 251-63.
9. Global tuberculosis report 2019. Geneva: World Health Organization; August 2019. [Online]Available from: https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf
10. Prasad R, Gupta N and Banka A: Shorter & cheaper regimen to treat multidrug-resistant tuberculosis: A new hope. Indian J Med Res 2017; 146(3): 301-03.
11. Chien JY, Chen YT, Wu SG, Lee JJ, Wang JY and Yu CJ: Treatment outcome of patients with isoniazid mono-resistant tuberculosis. Clin Microbiol Infect 2015; 21(1): 59-68.
12. Basel K, Anke K, Vahur H, Raquel D, Lena F, Sarah J, Cathriona K, Csaba K, Maria KK, Dimitrios P, Ivan S, Dick VS and van der Werf Marieke J: Isoniazid (INH) mono-resistance and tuberculosis (TB) treatment success: analysis of European surveillance data, 2002 to 2014. Euro Surveill. 2019; 24(12): 1800392
13. Khan AH, Sulaiman SAS and Laghari M: Treatment outcomes and risk factors of extra-pulmonary tuberculosis in patients with co-morbidities. BMC Infect Dis 2019; 19(1): 691.
14. Du Y, Qiu C and Chen X: Treatment outcome of a shorter regimen containing clofazimine for multidrug-resistant tuberculosis: a randomized control trial in China. Clin Infect Dis 2020; 71(4): 1047-54.
15. Geneva: WHO; 2016. World Health Organization. The Use of Molecular Line Probe Assays for the Detection of Resistance to Second-Line Anti-Tuberculosis Drugs. WHO/HTM/TB/2016.07.

How to cite this article:
Jose J, Babu LP, Robin N, Babu JV and George S: Efficacy of drugs in drug resistant tuberculosis: a retrospective observational study. Int J Pharm Sci & Res 2021; 12(11): 5968-73. doi: 10.13040/IJPSR.0975-8232.12(11).5968-73.