Original Research Article

A rational pharmacotherapeutic study of the prevalent prescription patterns of delamanid, ofloxacin, levofloxacin, and bedaquiline among the multi-drug resistant tuberculosis patients in global multi-centre tertiary care hospitals

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ABSTRACT

Background: Delamanid, a nitro-dihydro-imidazooxazole, is a bactericidal cell wall methoxy-mycolic and keto-mycolic acids biosynthesis inhibitor in actively replicating, dormant, and intracellular tuberculosis, and both drug-susceptible and drug-resistant strains of *M. tuberculosis* and *M. kansasii*, decreasing hydrophobicity and facilitating better bacterial drug penetration. Delamanid promotes intracellular generation of microbiocidal nitrogen oxidative intermediaries including nitric oxide, toxic even to dormant *M. tuberculosis*. Ofloxacin, the racemic mixture and levofloxacin, the S-or levorotatory isomer of ofloxacin, are bactericidal to *M. tuberculosis*, MAC, *M. fortuitum*, and other atypical mycobacteria, with inhibitory effect on DNA gyrase, DNA topoisomerase IV and IL-1α, IL-6, IL-8. Bedaquiline, a novel diarylquinoline, inhibits mycobacterial adenosine triphosphate synthase of *M. tuberculosis*, disrupting mycobacterial energy metabolism and replication. Bedaquiline's initial bacteriostatic action is followed by a bactericidal effect after 5-7 days. The objective was to perform a rational pharmacotherapeutic study of the prevalent prescription patterns of delamanid, ofloxacin, levofloxacin, and bedaquiline, among the multi-drug resistant tuberculosis patients, in global multi-centre tertiary care hospitals.
Methods: A multi-centre, retrospective, observational and analytical study of clinical prescriptions of 100 multi-drug resistant tuberculosis patients in hospitals, were performed. For 24-48 weeks, these patients had been prescribed anti-tubercular drugs, like delamanid 100 mg and ofloxacin 400 mg twice daily, levofloxacin 750 mg and bedaquiline 400 mg once daily followed by 200 mg thrice weekly, as part of MDR-TB treatment regimens. The no. of prescriptions for each drug were recorded, and the corresponding prescription rates were statistically derived in percentages.
Results: Delamanid was most commonly prescribed (32 prescriptions, 32%), followed by ofloxacin (29 prescriptions, 29%), levofloxacin (24 prescriptions, 24%), and bedaquiline (15 prescriptions, 15%). The completeness of the prescription contents, the dose of drug, the duration of treatment, the instructions of medication, the frequency of drug intake, the name of the drug and the dosage form of the drug were observed in 100% of prescriptions.
Conclusions: Prescription frequency of delamanid was followed by ofloxacin, levofloxacin and bedaquiline. Prescription content analyses showed 100% completeness.

Keywords: Prescription patterns, Delamanid, Ofloxacin, Levofloxacin, Bedaquiline, Multi drug-resistant tuberculosis

INTRODUCTION

World Health Organisation estimated that over 480,000 cases of multidrug-resistant (MDR) tuberculosis occur every year globally, 9% of them being affected by extensively drug-resistant (XDR) strains of *Mycobacterium tuberculosis*. MDR, to at least rifampicin and isoniazid, is mainly acquired by alteration of the bacilli or by alteration of drug target through mutation or bacilli titration of the drug through overproduction of target. The treatment of MDR/XDR-TB is unfortunately long, expensive, producing further resistance, with increased occurrence of adverse events, and the success rate largely unsatisfactory (<20% among cases with resistance patterns beyond XDR), mostly due to the insufficient number of active drugs during both intensive and continuation phases.[1-4] Delamanid, a nitro-dihydro-imidazo-oxazole, is a bactericidal cell wall methoxy-mycolic and keto-mycolic acids biosynthesis inhibitor in actively replicating, dormant, and intracellular tuberculosis, and both drug-susceptible and drug-resistant strains of *M. tuberculosis* and *M. kansasii*, decreasing hydrophobicity and facilitating better bacterial drug penetration. Delamanid promotes intracellular generation of microbiocidal nitrogen oxidative intermediaries including nitric oxide, toxic even to dormant *M. tuberculosis*.[5] Ofloxacin, the racemic mixture, and levofloxacin, the S-or levorotatory isomer of ofloxacin, are bactericidal to *M. tuberculosis*, MAC, *M. fortuitum*, and other atypical mycobacteria, with their inhibitory effect on DNA gyrase, DNA topoisomerase IV and pro-inflammatory cytokines interleukins: IL-1α, IL-6, IL-8 and tumour necrosis factor α, and with their superinducing effect on IL-2. Bedaquiline, a novel diarylquinoline, inhibits mycobacterial adenosine triphosphate synthase of *M. tuberculosis*, disrupting mycobacterial energy metabolism and replication. The initial bacteriostatic action is followed by a bactericidal effect after 5-7 days.[6-11]

According to the structure activity relationship studies of quinolones as antitubercular agents, the β-keto carboxylic acid moiety is required for hydrogen bonding interactions with DNA bases, and therefore it is essential for their anti-tubercular activity. The substituent at N-1 and C-8 positions should be relatively small and lipophilic to enhance the activity. Fluorine at C-6 is the best substituent, and it improves cell penetration and gyrase affinity. Substituents at the C-7 position are very essential and attribute to the physicochemical properties, bioavailability, lipophilicity and safety. Mycobacteria have lipid rich cell wall, and lipophilicity is an important consideration in the design and activity of newer antitubercular agents. Several research studies revealed that increasing the lipophilicity of the side chain at C-7, improves the anti-TB activity. The methoxy group at C-8 was found to enhance the lipophilicity and decrease the possibility of the development of resistance to quinolones as in moxifloxacin. Based on this concept, several fluoroquinolone derivatives had been synthesized and evaluated for their anti-tubercular activities against different TB strains. A series of N-4-piperazinyl ciprofloxacin-cephalosporin conjugates was synthesized, and these conjugates were evaluated for their *in vitro* antitubercular activity. A group of 1-aryl fluoroquinolones was synthesized, and these compounds were tested for their *in vitro* antitubercular activity against *M. tuberculosis*, which exhibited 98% growth inhibition. A new fluoroquinolone bearing an aromatic moiety at C-7 and an alkyl group at N-1 was synthesized and the compound was tested *in vitro* against *M. tuberculosis* H37Rv, which was subsequently found to be effective against *M. tuberculosis* H37Rv. Similarly, novel fluoroquinolone derivative containing an oxime functional moiety was synthesized and the compound was evaluated against *M. tuberculosis* H37Rv. The results revealed that this compound has considerable anti-tubercular activity. Moreover, a series of N-4-piperazinyl derivatives of ciprofloxacin was synthesized, and these compounds were screened for their *in vitro* anti-tubercular activity, which exhibited activity against *M. tuberculosis* H37Rv strain. Independently, a novel dihydro artemisinin-fluoroquinolone conjugate experienced remarkable *in vitro* activity against *M. tuberculosis* H37Rv strain. A novel C-7 fluoroquinolone derivative containing a 3-alkoxyimino-4-(cyclopropylanimo) methyl pyrrolidine moiety was designed, synthesized and tested against *M. tuberculosis* H37Rv ATCC 27294 strain and MDR *M. tuberculosis* 6133 clinical isolates. Results revealed that this compound has shown remarkable activity against MTB H37Rv ATCC 27294 and MDRMTB 6133 clinical isolate. A new ciprofloxacin-pallidum complex was synthesized, and its antitubercular activity was evaluated. It exhibited good antitubercular activity. A novel ciprofloxacin derivative demonstrated remarkable improvement in lipophilicity, when a substituted benzyl moiety was introduced to the N-4-piperazine ring. The antimycobacterial results revealed that the compound has good *in vitro* activity against *Mycobacterium tuberculosis* H37Rv ATCC 27294. A novel ciprofloxacin derivative was synthesized and evaluated for its antimycobacterial *in vitro* and *in vivo* activity against *Mycobacterium tuberculosis* H37Rv, multi-drug resistant *Mycobacterium tuberculosis* and *Mycobacterium smegmatis,* and this compound was found to be effective *in vitro* against *M. tuberculosis* H37Rv and multi-drug-resistant *Mycobacterium tuberculosis*. A new C-7 fluoroquinolone derivative with enhanced lipophilicity was synthesized by the introduction of N-alkyl-1,3-propanediamine at C-7, and this compound displayed activity against *Mycobacterium tuberculosis*.[12]

Objective

This rational pharmacotherapeutic study was performed with an objective to assess the prevalent prescription patterns of different anti-tubercular drugs, like, delamanid, ofloxacin, levofloxacin, and bedaquiline, in treating the multi-drug resistant tuberculosis patients, in global multi-centre tertiary care hospitals.

METHODS

Ethical approval

At first, the Institutional Ethics Committee clearance and approval was taken. The study was conducted in accordance with the ethical principles of declaration of Helsinki and Good Clinical Practices contained within the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH-E6), and in compliance with the global regulatory requirements. Written permissions to access the relevant medical records were obtained from the hospitals, outlining the aims of the study. The study involved almost negligible risk, of any type, to the patients. The design provided an equal opportunity to all the eligible patients to be included in the study. The patients who were included in the study were assured confidentiality, and a written informed consent was obtained from each patient.

Study design

A global, multi-centre, retrospective, observational and analytical study of the clinical prescriptions was performed.

Study population

The study population consisted of 100 treated multi drug-resistant tuberculosis patients.

Selection criteria of the study population

The inclusion criteria were as follows: (i) patients of any gender, (ii) patients within 18 and 55 years, (iii) patients presenting with multi drug-resistant tuberculosis with a baseline drug susceptibility testing result confirming MDR-TB (sample collected either before starting MDR-TB treatment or ≤1 month after commencement), (iv) WHO definitions, criteria and categorisations for tuberculosis, (v) co-operative and conscious patients, (vi) patients willing to undergo all pre and post- treatment investigations and willing to complete the entire course of treatment, (vii) patients who have given consent and are willing to go for a follow-up, (viii) patients not taking any previous anti-tubercular drug, (ix) patients not taking any concomitant medication.

The exclusion criteria were as follows: (i) uncooperative or unconscious patients, (ii) patients below 18 and above 55 years, (iii) patients presenting with any category other than multi drug-resistant tuberculosis, (iv) patients with a history of hypersensitivity to any of the study drugs, (v) patients with high risk diseases or co-morbidities, (vi) cardiac, renal or any other associated complications or co-morbidities, (vii) any chronic disease intervening with the study data, (viii) immunocompromised patients, (ix) patients suffering from gastrointestinal diseases like peptic ulcer, regional enteritis and ulcerative colitis, (x) pregnant or lactating women (women of child bearing potential are required to have a negative urine pregnancy test result and to agree to use an effective form of contraception for the duration of study), (xi) children or very old patients, (xii) other associated medical illness or disorders having impact on study results, (xiii) female patients using hormonal contraceptives.

Study period

The study period, comprising of the periods for the research study and the compilation of the study literature, was 1 year 2 months, from December, 2006 to January, 2007; June, 2015 to September, 2015; August, 2016 to September, 2016; and October, 2020 to March, 2021.

Place of study

The research study and the compilation of the study literature was done in the Departments of Pharmacology, Clinical Pharmacology, Molecular Pharmacology, Rational Pharmacotherapeutics, Pharmacovigilance, Pathology, Clinical Pathology, Internal Medicine, Paediatrics, Neonatology, Tuberculosis, Chest Diseases and Respiratory Medicine, Cardiology, Clinical Research in global multi-centre tertiary care hospitals: Dr. Moumita Hazra's Polyclinic And Diagnostic Centre, Hazra Nursing Home, Rama Medical College Hospital and Research Centre, All India Institute of Medical Sciences, J. J. M. Medical College, Bapuji Hospital, Chigateri General Hospital, GIOSTAR Institute of Regenerative Medicine Institutes, Hospitals and Laboratories.

Study procedure

A study of the clinical prescriptions of 100 multi-drug resistant tuberculosis patients in the hospitals, were made. From the clinical prescriptions of 100 multi drug-resistant patients, thorough patients' history with complete examination details and the prescription patterns were obtained with the study proforma, and the following data were observed, thoroughly analysed and recorded: the patients' participation assessment and adherence to treatment (including patients who completed the study thoroughly), patients who were dropout patients due to adverse effects, lost to follow-up patients, and patients who withdrew voluntarily; the demographic characteristics, including age, gender, race, body mass index, duration of symptoms of tuberculosis, severity of tuberculosis symptoms, present controller medications, the patients' present and past history, smoking history, respiratory history including respiratory infection and immunological history, chronic obstructive pulmonary disease, history of MDR-TB contacts, past TB treatment history, defined as new cases (≤1 month of antituberculosis treatment), previously treated cases (first and second line anti-tuberculosis drugs), presence of cavities on chest radiograph, sputum smear microscopy results (negative, low [scanty or 1+] and high bacillary load [2+ or 3+]), and drug susceptibility testing results, cardiac history, history of co-morbidities, family history, personal history, socio-

economic history, reproductive history, concomitant medication history, surgical history, the symptomatic effect of treatment on tuberculosis. Details of complete general physical examination, and systemic examination, including oto-rhino-laryngo-tracheal, respiratory and cardio-pulmonary examinations, were recorded. The WHO definitions of treatment outcomes requiring at least five consecutive negative culture results during the final 12 months of treatment were to be classified as cured, and either 2 positive results among the five cultures recorded in the final 12 months, one positive in any one of the final 3 cultures, or a clinical decision, was to be considered, to continue or discontinue treatment depending on the treatment success or failure respectively. Favourable outcome was defined as a combination of cured and treatment completed, and unfavourable outcome as a combination of death and failure. Multi drug-resistance was defined as resistance to at least rifampicin and isoniazid, that had been detected at baseline. For 24-48 weeks, these patients had been prescribed anti-tubercular drugs, like oral delamanid 100 mg twice daily, oral ofloxacin 400 mg twice daily, oral levofloxacin 750 mg once daily, and oral bedaquiline 400 mg once daily followed for 2 weeks followed by 200 mg thrice weekly for 22 weeks, as part of MDR-TB treatment regimens, recommended by WHO, the American thoracic society, U. S. centers for disease control and prevention, European respiratory society, infectious diseases society of America and similar associations, ratified by grading of recommendations, assessment, development, and evaluation (GRADE) methodology.[13,14] The prescription patterns of all 4 drugs were analysed. The number of prescriptions of 100 patients treated with each drug: delamanid, ofloxacin, levofloxacin, and bedaquiline was recorded, and the percentage of prescriptions for each drug was calculated. The prescription content analysis, of all the 100 prescriptions, was done. The different aspects of the prescription contents, like (i) the completeness of the prescription contents, (ii) the dose of drug, (iii) the duration of treatment, (iv) the instructions of medication, (v) the frequency of drug intake, (vi) the name of the drug and (vii) the dosage form of the drug was thoroughly analysed and recorded, and the various observations were statistically recorded as the prescription content analysis percentages.

Statistical analysis

The study data were statistically analysed with different percentages.

RESULTS

Hundred patients were treated for multi-drug resistant tuberculosis. All the patients completed the treatment thoroughly. There were no dropout patients due to adverse effects, none was lost to follow-up and none of the patients withdrew voluntarily. The patients' adherence to treatment was very high. The demographic characteristics for delamanid, ofloxacin, levofloxacin, or bedaquiline, were comparable.

Delamanid was most commonly prescribed significantly (32 prescriptions, 32%), followed by ofloxacin (29 prescriptions, 29%), levofloxacin (24 prescriptions, 24%), and bedaquiline (15 prescriptions, 15%), as depicted in Figure 1.

The prescription rates of anti-tubercular drugs were as follows: delamanid>ofloxacin>levofloxacin>bedaquiline.

Adverse effects were negligible in either group. Tolerability was good for both the drugs.
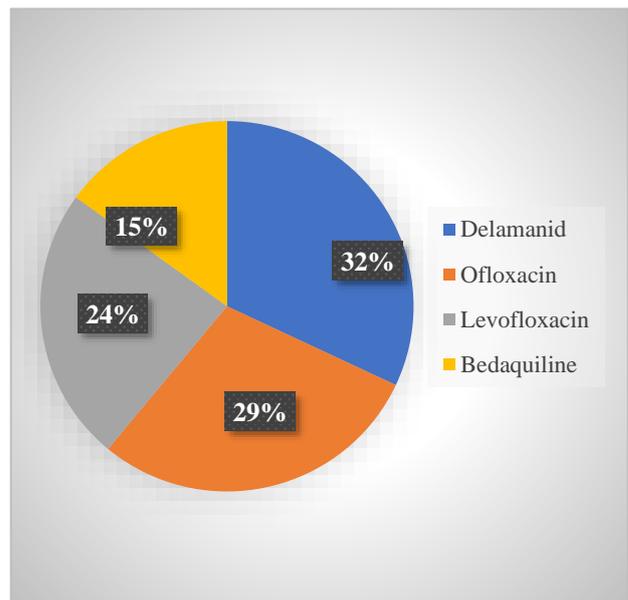
Figure 1: The prescription rates of different anti-tubercular drugs in percentages.

Table 1: Prescription content analysis for different anti-tubercular drugs.

Prescription contents	Result (%)
Completeness of prescription Contents	100 (100)
Dose of drug	100 (100)
Duration of treatment	100 (100)
Instructions of medication	100 (100)
Frequency of drug intake	100 (100)
Name of the drug	100 (100)
Dosage form of the drug	100 (100)

Table 1 depicts the prescription content analysis in percentages for different anti-tubercular drugs.

The completeness of the prescription contents, the dose of drug, the duration of treatment, the instructions of medication, the frequency of drug intake, the name of the drug and the dosage form of the drug were observed in 100% of prescriptions, as depicted in Table 1.

DISCUSSION

Delamanid, an "orphan drug", is approved for the treatment of adult pulmonary multi-drug resistant (MDR)-TB, when an effective treatment regimen cannot otherwise be composed, the reasons happening to be resistance or tolerability. It is a pro-drug which gets activated by the enzyme deazaflavin dependent nitroreductase (Rv3547). A reactive intermediate metabolite is formed between delamanid and desnitro-imidazooxazole derivative.[15-17] Delamanid is prescribed to be administered along with food, because the absorption gets better with food. After oral administration, the maximum concentration is observed at 4-5 hours. After drug discontinuation, the half-life is 38 hours. Steady state concentration is reached after 10-14 days. In early trials, delamanid exposure was not found to be proportional to the dosage and it plateaued at 300 mg. This might be due to the poor water solubility of the drug and the limited absorption at higher doses.[16] Delamanid has minimal effects on cytochrome P450 enzymes (CYP) in concentrations up to $100\,\mu M$, since it is not metabolized by the CYP. Therefore, interactions with other drugs should not be a problem. In patients coinfected with HIV, the lack of interaction with ART is a major advantage. Delamanid can be administered with rifampicin without either drug affecting the metabolism of the other. This is an important advantage over bedaquiline which is metabolized by CYP.[5] Delamanid is largely metabolized by albumin in serum, and to a much less extent by cytochrome P450 enzymes. The natural resistance rate to delamanid is very low (1.3%). The inhibitory concentrations of delamanid (IC50) for methoxy and keto mycolic acid biosynthesis, 0.036 mcg/mL and 0.021 mcg/mL respectively, are very less.[5] The primary safety concern with delamanid is QTcF interval prolongation, although this observation has yet not been associated with any clinical cardiac events.[18] Hypoalbuminemia has been associated with an increased risk of QTc prolongation. Therefore, delamanid is contraindicated in patients with albumin level of 2.8 g/dL. QTc prolongation may also be produced due to co-administration with strong CYP3A inhibitors (e.g., lopinavir/ritonavir) and fluoroquinolones. Thus, frequent monitoring of electrocardiograms throughout the treatment period is recommended, if delamanid is required to be co-administered with these drug classes. The other adverse effects are nausea, vomiting, dizziness, low serum potassium levels, paraesthesia, anxiety and tremor.[19]

In the clinical trials on the early bactericidal activity of delamanid, it was observed that there was increased reduction in CFU, observed with 200 mg/day and 300 mg/day doses. Delamanid showed monophasic bactericidal activity, in contrast to rifampicin and isoniazid, which showed biphasic activity. In the short-term clinical trial of delamanid, high sputum culture conversion rates were observed in the treatment group compared to patients on placebo and background regimen. In the long-term clinical trials, there was significant reduction in mortality in the long-term delamanid treated group. In terms of efficacy, delamanid demonstrated activity in an early bactericidal activity trial in drug susceptible pulmonary TB patients and increased 2-month sputum culture conversion rates when added to an optimized background regimen in MDR-TB patients in a phase 2b global clinical trial. In addition, recent results outside clinical studies show favourable responses in highly resistant TB patients including extensively drug resistant (XDR)-TB when treated with delamanid-containing regimens in routine programmatic settings. Overall, delamanid appears to be a well-tolerated and safe anti-TB drug when compared to other drugs used to treat MDR-TB.[18] Pre-clinical and clinical studies have shown that delamanid has high potency, least risk for drug-drug interactions and better tolerability, and post-antibiotic effect against intracellular bacilli, and these advantages of delamanid will be helpful in reducing the treatment time and risk of toxicity in MDR-TB.[19] A phase IIb randomised controlled trial in adults with pulmonary MDR-TB, showed improved rates of sputum culture conversion at 2 months when an OBR was augmented with delamanid, as compared to placebo. An open label extension of this trial found that patients who consumed delamanid for 2-6 months had more positive outcomes (cured or completed treatment) and lower mortality than those who took delamanid for ≤2 months.[20] It has been included in the world health organization (WHO) model list of essential medicine by the WHO expert committee on selection and use of essential medicines.[21] Researchers who are investigating the properties of the nitro-dihydro-imidazooxazoles, found that delamanid had superior activity against MTB than other closely related compounds.[5] It is hoped that these new drugs will improve the treatment of drug-resistant forms of TB, in terms of both better outcomes and quality of life for patients.[22]

An important advantage over other medications is that it is not metabolized by CYP enzymes and can be given in combination with ART, rifampicin, or with other drugs metabolized by CYP enzymes. Delamanid has an affordable cost and easy availability for the patients.[19]

Patients likely to benefit from delamanid treatment are XDR-TB, pre-XDR-TB and MDR-TB patients.[18]

With the advent of quinolones, and later the fluorinated 4-quinolones, the fluoroquinolones, the medical world has certainly taken long strides in treating enormous number of maladies.[23]

Fluoroquinolones are chemical derivatives of quinoline, the prodrome of chloroquine. Fluoroquinolones, a family of 6-fluoro-7-piperazinyl-4-quinolones, are broad spectrum synthetic antimicrobial agents derived from quinolones with the addition of a fluorine atom attached to the central ring.[24]

Substitution at C-7 or its N-4-piperazinyl moiety was found to affect potency, bioavailability, and physicochemical properties. Also, it can increase the

affinity towards mammalian topoisomerases that may shift quinolones from antibacterial to anticancer candidates. Moreover, the presence of DNA topoisomerases in both eukaryotic and prokaryotic cells makes them excellent targets for chemotherapeutic intervention in antibacterial and anticancer therapies.[12]

Fluoroquinolones are quite significantly efficacious for their bactericidal inhibitory effect on: (i) DNA gyrase, caused by the binding of fluoroquinolones to the A subunits (gyr A), thus inhibiting the replication and transcription of bacterial DNA, responsible for the proper functioning of the cell, and the subsequent change of conformity of DNA gyrase molecule caused by the binding of fluoroquinolones to the DNA binding groove between A (gyr A) and B (gyr B) subunits; (ii) Par C subunits (par C) and Par E subunits (par E) of DNA topoisomerase IV, thus inhibiting decatenation and relaxation of DNA and segregation of replicating chromosomes or plasmids in bacteria; (iii) Pro-inflammatory cytokines, like interleukins : IL-1α, IL-6, IL-8, and tumour necrosis factor α, leading to attenuation of inflammatory response and exhibiting multiple immunomodulatory actions.[23,25]

Fluoroquinolones also have superinducing effect on interleukin IL-2.[23]

First-generation quinolones (e.g., nalidixic acid) achieve minimal serum levels. Second-generation quinolones (e.g., ciprofloxacin) have increased gram-negative and systemic activity. Third-generation quinolones (e.g., levofloxacin) have expanded activity against gram-positive bacteria and atypical pathogens. Fourth-generation quinolones (e.g., trovafloxacin) have significant activity against anaerobes. Fifth-generation quinolones (e.g., aravofloxacin) have activity against multi-resistant pathogens.[23]

They are characterized by advantageous pharmacokinetic properties; higher concentrations in the lungs; and an excellent safety profile comparable to other antibiotics used to treat respiratory infections, such as macrolides and β-lactams.

The newer fluoroquinolones have broad-spectrum bactericidal activity, excellent oral bioavailability, good tissue penetration and favourable safety and tolerability profiles.[23]

Fluoroquinolones possess an ever-expanding spectrum of clinical indications like multiple, multi-resistant, concurrent and recurrent infections, including drug-resistant tuberculosis, drug-resistant leprosy, *coronaviridae*- 19, Ebola virus, dengue virus, vaccinia virus, Papovavirus, human cytomegalovirus, varicella-zoster virus, herpes simplex virus types 1 and 2, hepatitis C virus and HIV; refractory inflammations; malignancies; immune disorders and complicated and refractory diseases and disorders, due to their profound bactericidal, anti-viral, anti-fungal, anti-protozoal, comedolytic and anti-comedogenic, anti-inflammatory, immunomodulatory (transcription factors - like NFB/NFAT/AP1-mediated, and on regulation of cyclic AMP or phosphodiesterases), anti-neoplastic, pro-apoptotic, p53 mediated S phase arrest/TGFβ1 targeted G2 phase cell cycle arrest, anti-proliferative (by suppression of OncomiR expression, impairment of telomerase activity, DNA synthesis inhibition, and inhibition of cell colony formation), anti-metastatic (migration, invasion and metastasis-MET inhibitor), and cancer stemness regulator potential.

Fluoroquinolones are active against *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma species*, *Chlamydia species*, *Chlamydophila species*, *Legionella species*, *Enterobacteriaceae*, *Pseudomonas aeruginosa* (particularly ciprofloxacin), *Mycobacterium tuberculosis*, some atypical mycobacteria, some methicillin-sensitive staphylococci, *Campylobacter species*, *salmonellae*, *Shigella*, *Vibrio*, *Yersinia enterocolitica*, *Chlamydia trachomatis*, *Legionella*, and are also indicated in anthrax prophylaxis and meningococcal prophylaxis.

The dual inhibitory activity of fluoroquinolones against the bacterial replication enzymes, DNA gyrase and topoisomerase IV, protects them from the development of resistance. A mutant prevention concentration (MPC) of an antibiotic for a particular organism can be defined, at which the selection of resistant mutants during treatment is suppressed. For MTB, the MPC90 (MPC for 90% of strains) for fluoroquinolones have been found to be ciprofloxacin>levofloxacin>gatifloxacin>moxifloxacin respectively. So, gatifloxacin and moxifloxacin are less likely to provoke the development of resistance. Several studies have recommended that levofloxacin is the first-choice fluoroquinolone for MDR-TB. Ofloxacin is also effective for MDR-TB, being the racemic mixture of the S-or levorotatory isomer of ofloxacin: levofloxacin. The complementary list of the model essential medicines list currently lists three fluoroquinolones for the treatment of MDR-TB: ciprofloxacin, ofloxacin and levofloxacin.[26]

Fluoroquinolones, like ofloxacin, levofloxacin, ciprofloxacin and moxifloxacin, are relatively new potent oral bactericidal drugs for TB, that have gained prominence as well tolerated alternatives to first line anti-tubercular drugs. They are active against *Mycobacterium avium* complex, *M. fortuitum* and some other atypical mycobacteria as well. Moxifloxacin is the most active fluoroquinolone against *M. tuberculosis*, while levofloxacin is more active than ofloxacin and ciprofloxacin. On the other hand, ciprofloxacin is more active than levofloxacin against atypical mycobacteria. The fluoroquinolones penetrate cells and kill mycobacteria lodged inside macrophages as well. Though ciprofloxacin was initially used in tuberculosis, it is not favoured now because of its extensive use in other bacterial infections and chances of resistance. The primary indication of fluoroquinolones is for the treatment of drug resistant tuberculosis. They have also been tried in first line regimens for new cases. Substitution of ethambutol with moxifloxacin to accompany rifampicin, isoniazid and

pyrazinamide in the 4-drug regimen has been found to enhance the rate of bacillary killing and cause faster sputum conversion. In contrast, ciprofloxacin, ofloxacin and levofloxacin did not enhance the sterilizing ability of rifampicin and isoniazid, and were no better than ethambutol. Thus, addition of moxifloxacin to rifampicin, isoniazid and pyrazinamide regimen holds the possibility of reducing the duration of treatments of tuberculosis from 6 months with rifampicin, isoniazid, pyrazinamide and ethambutol used currently. However, experience with moxifloxacin in the treatment of tuberculosis is still limited, and it is not routinely used. Fluoroquinolones are a key component of all regimens for multi drug-resistant tuberculosis, except when the bacilli are found to be resistant to them. The revised national tuberculosis control programme of India has included ofloxacin or levofloxacin in the standardized regimen for multi drug-resistant tuberculosis. If used alone, mycobacterial resistance to ofloxacin, levofloxacin and ciprofloxacin develops rapidly by the mutation of DNA gyrase gene. Experimental data indicates that the resistance against moxifloxacin is slow to develop.[27]

Fluoroquinolones have early bactericidal activity (EBA), which is the decline in colony-forming units in sputum over the first two days of treatment, reflecting rapid killing of metabolically active organisms, an important factor in interrupting transmission, over days 2-7.

Experimental studies have demonstrated that levofloxacin exerts antioxidative and NO regulatory effects in an animal model of H1N1 influenza virus induced lung injury, and significantly improves survival. In particular, levofloxacin exhibited scavenging actions against neutrophil-derived hydroxyl radicals and suppressed NO production, leading to decreased markers of oxidative stress and NO metabolites in the lungs of H1N1 influenza virus infected animals. A recent in silico study demonstrated that the fluoroquinolones, ciprofloxacin and moxifloxacin, exert strong capacity for binding to SARS-CoV-2 main protease (Mpro), indicating that fluoroquinolones may inhibit SARS-CoV-2 replication. Furthermore, fluoroquinolones may bind to the Mpro active site more strongly than chloroquine and nelfinavir, a protease inhibitor antiretroviral drug used in the treatment of the AIDS.[24]

Ofloxacin has more potent gram-positive activity; separation of the more active S-or levo rotatory isomer yields levofloxacin, which has even better anti-microbial activity. Bioavailability of both of these drugs is excellent, such that intravenous and oral doses are the same; levofloxacin is dosed once daily as opposed to twice daily dosing for ofloxacin.[28]

Drugs such as ofloxacin have been second-line anti-TB agents for many years, but they are limited by the rapid development of resistance. Adding C8 halogen and C8 methoxy groups markedly reduces the propensity for drug resistance. Of the C8 methoxy quinolones, moxifloxacin is being studied to replace either isoniazid or ethambutol.

Fluoroquinolone microbial kill is best explained by AUC0-24/MIC ratio. This time for the emergence of resistance harmonizes well with the speed of resistance emergence in patients.[28]

In documented drug resistance, therapy should be based on the evidence of susceptibility, and should include: (1) At least three drugs to which the pathogen is susceptible, (2) with at least one of the injectable anti-TB agents, (3) In the case of MDR-TB, (4) Use of four to six medications for better outcome, (5) At least 18 months of therapy.

The addition to the regimen of a fluoroquinolone and the surgical resection of the main lesions have been associated with improved outcome.

In the patients of disseminated *M. avium* complex, a potential fourth drug includes levofloxacin, for definitive and suppressive therapy. Patients should be treated on suppressive therapy until all three of the following criteria are met: (1) Therapy duration of at least 12 months, (2) CD4 count >100/mm³ for at least 6 months and (3) Asymptomatic for MAC infection

In *M. kansasii*, *M. fortuitum* complex, *M. malmoense*, fluoroquinolones have been prescribed as alternative anti-tubercular agents and in *M. haemophilum*, quinolones have been prescribed as a first-line therapy.[28]

Fluoroquinolones are active against gram-negative and gram-positive bacteria, anaerobes, mycobacteria and atypical pathogens. Respiratory fluoroquinolones, levofloxacin and moxifloxacin, constitute fist line therapeutic agents for the management of severe community-acquired pneumonia, according to the treatment guidelines.

Hybridization of different pharmacophores from various bioactive substances into a single molecule is the potential weapon to prevent the drug resistance since this strategy can provide new leads with complementary activities and/or multiple pharmacological targets. Fluoroquinolone and isatin are common pharmacophores, and their derivatives possess various biological activities. Obviously, hybridization of these two pharmacophores into one molecule may result in novel candidates with broader spectrum, higher efficiency, lower toxicity as well as multiple mechanisms of action. Therefore, fluoroquinolone-isatin hybrids have the potential for clinical deployment in the control and eradication of various diseases. Fluoroquinolone-isatin hybrids are potential anti-bacterial, anti-tubercular, anti-viral and anti-cancer agents. Their structure-activity relationship paves the way for the further rational development of this kind of hybrids.[29]

WHO recommendations state that the shorter regimen for MDR-TB would improve the adherence, and its "relatively" low cost would ensure sustainability; which

are extremely important in resource-limited settings and in resourceful countries.[30]

This retrospective, observational, and analytical study involves almost negligible risk, of any type, to the patients, which is in complete consideration of the ailing patient ethics towards these patients, who had been suffering from a life-threatening disease of multi-drug resistant tuberculosis and had been treated from the disease; and also, this study would certainly facilitate a wider, better and thorough analysis of the complete cycle of their multi-dimensional disease of multi-drug resistant tuberculosis and their treatment patterns.[15]

In this rational pharmacotherapeutic study, conducted to assess the prevalent prescription patterns of different anti-tubercular drugs, like, delamanid, ofloxacin, levofloxacin, and bedaquiline, in treating the multi-drug resistant tuberculosis patients, in global multi-centre tertiary care hospitals, it was observed that delamanid was most commonly prescribed significantly (32 prescriptions, 32%), followed by ofloxacin (29 prescriptions, 29%), levofloxacin (24 prescriptions, 24%), and bedaquiline (15 prescriptions, 15%). The prescription rates of anti-tubercular drugs were as follows: delamanid>ofloxacin>levofloxacin>bedaquiline. The completeness of the prescription contents, the dose of drug, the duration of treatment, the instructions of medication, the frequency of drug intake, the name of the drug and the dosage form of the drug were observed in 100% of prescriptions.

This pharmaco-epidemiological study would remain a milestone in the development of newer anti-tubercular, respiratory, smooth muscular, and anti-inflammatory diagnostics and therapeutics; in the development of faster, better, safer, more precise and cost-effective therapeutics; in the cure of patients suffering from drug-resistant tuberculosis; and, finally in the enhancement of respiratory health, healthy life, quality of life, and life span, among the future generations.

CONCLUSION

The prescription frequency of delamanid was followed by ofloxacin, levofloxacin and bedaquiline. The prescription content analyses showed 100% completeness.

ACKNOWLEDGEMENTS

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