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Fluoroquinolone-resistant tuberculosis: implications in settings with weak healthcare systems

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SUMMARY

Fluoroquinolones (FQ) play an essential role in the treatment and control of multidrug-resistant tuberculosis (MDR-TB). They are also being evaluated as part of newer regimens under development for drug-sensitive TB. As newer FQ-based regimens are explored, knowledge of FQ resistance data from high TB burden countries becomes essential. We examine available FQ resistance data from high TB burden countries and demonstrate the need for comprehensive surveys to evaluate FQ resistance in these countries. The factors driving FQ resistance in such conditions and the cost of such resistance to weak healthcare systems are discussed. The need for a comprehensive policy for addressing the issue of FQ resistance is highlighted.

1. Introduction

The latest Global Tuberculosis Report estimates that 3.5% of new and 20.5% of previously treated tuberculosis (TB) cases diagnosed in 2013 were multidrug-resistant (MDR).[1] There has been considerable recent progress in the treatment of TB, and the TB drug pipeline now holds the promise of a number of new TB drugs, as well as novel regimens,[2] including for the treatment of MDR-TB. Despite such progress, the success rate for MDR-TB treatment globally is reported to be only 48%, with weak healthcare systems recognized as contributing to low cure rates.[1] Weaknesses in healthcare systems are recognized to be drivers of antimicrobial resistance in low- and low–middle-income countries (LIC and LMIC).[3]

Fluoroquinolones (FQ) are broad-spectrum antibiotics that were shown to be useful in the treatment of TB in 1984,[4] and have since become essential components of TB regimens, particularly for drug-resistant disease (Table 1).

The emergence of FQ-resistant *Mycobacterium tuberculosis* (MTB) is thus a cause for significant concern. FQ act by inhibiting DNA gyrase, an enzyme required for bacterial DNA synthesis. MTB resistance to FQ is associated primarily with mutations in DNA gyrase, a tetramer composed of two A and two B subunits, encoded by *gyr*A and *gyr*B, respectively.[13] Mutations in the *gyr*A gene are associated with high-level FQ resistance, while mutations in *gyr*B are associated with low-level resistance. A second mechanism conferring FQ resistance in MTB is through efflux pumps that act by removing the drug from bacterial cells.[5,14]

This review explores the relationship between FQ resistance in TB and healthcare system constraints, and considers options for addressing this concern.

2. FQ resistance in high TB burden countries

The 2014 Global Tuberculosis Report indicates a FQ resistance rate of 17% in MDR-TB strains tested.[1] Amongst the 22 high TB burden countries, however, data on FQ-resistant MTB are limited, with reports in some cases based on a small sample size (Table 2). While much of the available FQ resistance data is for MDR-TB, FQ resistance in non MDR-TB is reported from China, India, and Pakistan (Table 2). The prevalence of FQ resistance in MTB has led to discussions related to the use of FQ agents for infections other than TB (in particular community-acquired pneumonia (CAP)) in driving such resistance.[40]

3. Prior FQ exposure as a risk factor for FQ-resistant TB

FQ exposure is a recognized risk factor for the development of FQ resistance in many nosocomial as well as community-acquired pathogens.[41–44] Higher FQ-resistant MTB in patients with a history of respiratory infections has been attributed to widespread FQ

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Table 1
Fluoroquinolone agents used in the treatment of tuberculosis

Agent	Activity against MTB (MIC ranges, μg/ml)[5]	Use in TB treatment regimens[a]	Programmatic recommendations (WHO)[6,7]
Second-generation			
Ofloxacin	1.0–2.0	Has been used as first- and second-line agent[8,9]	Recommended for inclusion in MDR-TB regimens Not currently recommended as first-line agent
Ciprofloxacin	0.5–4.0	In vitro activity, but may lack in vivo efficacy. Trials as first-line agent for drug-sensitive TB resulted in higher relapse rates[10,11]	Not recommended
Levofloxacin	1.0	More efficacious than ofloxacin for second-line treatment, but ofloxacin resistance may lead to treatment failure[8,12]	Recommended for inclusion in MDR-TB regimens Not currently recommended as first-line agent
Third-generation			
Gatifloxacin	0.2–0.25	Has been used in standard first- and second-line regimens. New data on shortened regimens available[8]	Not included in WHO guidelines. Lower preference due to side effects
Fourth-generation			
Moxifloxacin	0.12–0.5	Has been used in standard first- and second-line regimens. New data on shortened regimens available[8]	Recommended for inclusion in MDR-TB regimens Not currently recommended as first-line agent

MTB, *Mycobacterium tuberculosis*; MIC, minimum inhibitory concentration; TB, tuberculosis; WHO, World Health Organization; MDR, multidrug-resistant.
[a] First- and second-line, where mentioned, refer to standard regimens. First-line treatment for drug-sensitive TB: 2 months of HRZE + 4 months of HR (where H = isoniazid, R = rifampicin, Z = pyrazinamide, and E = ethambutol); 4 months of HRE is used in settings with high isoniazid resistance. Second-line treatment regimens are used for MDR-TB; it is recommended that these include at least a fluoroquinolone in addition to pyrazinamide, an injectable anti-TB drug, ethionamide (or prothionamide), and either cycloserine or para-aminosalicylic acid.[7]

usage in these individuals.[18] The impact of FQ on the development of resistance in MTB has mostly been discussed in the context of CAP.[45–48] A recent meta-analysis evaluating the association of prior FQ usage and the development of resistance in MTB reports a three-fold higher risk of FQ-resistant MTB in patients prescribed FQ before TB diagnosis.[40] Prolonged FQ exposure (defined as more than 10 days of treatment), or multiple FQ prescriptions have been highlighted as significant risk factors for the development of FQ resistance in MTB.[45,49,50] Evidence such as this has led to strong recommendations for avoiding FQ in national CAP guidelines.[51] Despite these recommendations, the majority of national CAP treatment guidelines in TB-endemic countries continue to include FQ as first-line treatment due to the fact that high global resistance rates amongst respiratory pathogens to alternative agents, including macrolides, limit options.[48]

A recent review of global FQ resistance rates reports a much higher odds ratio for FQ resistance in MDR-TB as compared to non-MDR-TB.[52] Such resistance is associated with the use of a second-line therapy including FQ in the management of MDR-TB[31,52,53] and is attributed to inadequate treatment protocols.[54,55] Hence strict supervision of second-line therapy is recommended.[56] These recommendations are supported by a recent study from Taiwan, where for both primary FQ resistance and acquired FQ resistance, rates decreased significantly following the implementation of a successful directly observed therapy DOT-Plus programme.[57]

4. Impact of FQ resistance on MTB treatment

Considerable data are available reporting delayed sputum culture conversion and treatment failure in TB patients with FQ resistance.[51,58–60] Resistance to ofloxacin has been linked with delayed culture conversion in a recent study from Pakistan.[61] An earlier systematic review of 36 trials reporting end-of-treatment or follow-up outcomes for MDR-TB patients had reported FQ resistance as being associated with poor outcomes (including any of death, default, transfer out, or treatment failure).[62] While the results of this review may have been biased due to trial and outcome heterogeneity, the findings are nevertheless a cause for concern given the significant role of FQ in MDR-TB treatment. These findings are consistent with another more recent study that analysed individual patient data from 31 published cohorts of patients with MDR-TB and extensively drug-resistant TB (XDR-TB).[63] Using data on drug sensitivity, treatment, and outcome (cure/treatment completion, failure/relapse/death), this study reports in vitro susceptibility to second-line drugs including FQ as being consistently and significantly associated with higher odds of treatment success.[63] More worrisome is the emergence of XDR-TB strains in patients on second-line treatment. A study performed in nine countries reported an XDR acquisition rate of 17% in patients with baseline FQ resistance.[53]

Attempts to shorten the duration of first-line TB therapy have led to the inclusion of FQ in shorter, 4-month regimens.[64] Recent phase 3 trials of three such regimens, two containing moxifloxacin and the third gatifloxacin, do not show non-inferiority of the shorter regimens, indicating that shortening treatment to 4 months was not effective.[65–67] Moreover, these regimens have raised concern about the efficacy in areas with high FQ resistance, wherein treatment failure and the emergence of MDR-TB strains is likely.

In contrast, excellent outcomes for a 9-month gatifloxacin-based regimen have increased optimism for improved and shorter MDR-TB management.[68–71] However, given that FQ resistance was the strongest risk factor for a bacteriologically unfavourable outcome, the protocol needs to be evaluated in high FQ-resistant TB settings.[71] Whether a higher dose of newer FQ may still be successful in such settings requires investigation.

5. Cross-resistance to newer FQ and other second-line TB drugs

The use of newer FQ for the management of ofloxacin-resistant MDR- and XDR-TB is recommended.[72] Nevertheless, a significant proportion of ofloxacin-resistant strains are also resistant to the newer FQ.[36,73,74] Newer FQ should thus not be used indiscriminately for drug-resistant TB in high FQ resistance settings without prior susceptibility testing.[59,75] Additionally FQ resistance has