An Overview on Fluoroquinolone Drugs for the Treatment of Tubercular Infection

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ABSTRACT

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The fluoroquinolones-levofloxacin, moxifloxacin and gatifloxacin have potent bactericidal activities against *Mycobacterium tuberculosis*. They have the potential activity in managing both drug-susceptible and drug-resistant tuberculosis as well as the possibility of shortening the period of therapy. The emergence of drug-resistance, fluoroquinolone-resistant, multidrug-resistant and extensively drug-resistant tuberculosis created a challenge to control the tuberculosis globally. The newer fluoroquinolones have clinical efficacy in some of the patients. So, the utility of new fluoroquinolone drugs for the treatment of tuberculosis is needed.

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ABSTRACT

1. Introduction

Quinolones are synthetic drugs synthesized by structural modification of the 4-oxo-1, 4 dihydroquinolone nucleus or the 1, 8 naphthyridone nucleus. Fluorination of these basic molecules, usually at position 6, resulted in the fluoroquinolones (FQs). Levofloxacin is the S(-) enantiomer of the parent racemic compound ofloxacin, whereas moxifloxacin and gatifloxacin are regarded as later generation C-8-methoxy FQs. The levofloxacin, moxifloxacin and gatifloxacin are newer FQs that have potent antituberculosis (anti-TB) activity, much of which is due to the C-8-methoxy moiety. An comprehensive review addressed the efficacy of FQs in TB, together with patient tolerability/safety, for the following indications-(i) first-line treatment of drug-susceptible (DS) pulmonary TB, (ii) first-line treatment of multidrug-resistant (MDR) TB and (iii) treatment of patients with intolerance to standard first-line anti-TB drugs. The data were insufficient to support the use of older FQs, especially ciprofloxacin, as substitute agents for DS or DR-TB. This view was also shared FQs used for treating TB. The role of FQs in treating TB is largely restricted to levofloxacin, moxifloxacin and gatifloxacin.

FQs for the treatment of MDR-TB

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The MDR-TB has confirmed the dose-dependent efficacy of ofloxacin in the treatment of TB and the 800 mg once-daily dose was found to be superior to the 300 mg once-daily dose, achieving a more rapid and higher proportion of culture negativity. The use of FQs (ofloxacin and ciprofloxacin) for the treatment of MDR-TB have emerged\textsuperscript{11}, with success rates usually around 70%. A study on MDR-TB has shown that the use of FQs was independently linked to the improved initial microbiological outcome, as well as survival from all causes of death.\textsuperscript{10} The pivotal role of the FQs in the chemotherapy of MDR-TB.

The six standardized treatment regimens for MDR-TB\textsuperscript{11}, the most effective treatment regimen required a minimum duration of nine months with gatifloxacin, clofazimine, ethambutol, and pyrazinamide supplemented by prothionamide, kanamycin and high-dose isoniazid during an intensive phase of a minimum of four months, giving a relapse-free success rate of 87.9%. The treatment success rate for the earlier ofloxacin-containing regimen was only 69.0%.\textsuperscript{12} The combination of amikacin, ethionamide, moxifloxacin and pyrazinamide has shown good efficacy.\textsuperscript{13} In the use of moxifloxacin for MDR-TB, the treatment success rate was only 51.7%.\textsuperscript{14} There was no clear report of the chemotherapy response rate for several patients with MDR-TB.\textsuperscript{15} The optimal duration of treatment for MDR-TB using a FQs-containing regimen is currently unknown. It was successfully improved when the length of treatment was at least 18 months, and if patients received directly observed therapy throughout.\textsuperscript{16} However, some patients could be adequately treated with newer FQs for shorter periods to achieve a relapse-free cure.

The FQ resistance in Mycobacterium tuberculosis (Mtb) can emerge following the injudicious use of this class of drugs, especially in the setting of MDR-TB, alongside the suboptimal use of accompanying drugs too few in numbers and/or too low a dosage.\textsuperscript{17, 18} Poor drug quality can also be an issue. Overzealous use of FQs in the treatment of infections of the lower respiratory tract and other origins might also contribute to the development of FQR-TB.\textsuperscript{19} As aminoglycosides/capreomycin also have potent anti-TB activity, the “loss” of these second-line injectable preparations together with FQs, through their suboptimal use in the treatment of MDR-TB, would result in the development of extensively drug-resistant (XDR) TB.\textsuperscript{20} This latter disease poses an even more “complicated” scenario of drug resistance than FQR, MDR-TB, and is generally linked with a treatment success rate of 50% or less.\textsuperscript{21} A analysis of the treatment outcomes and survival based on drug resistance patterns in MDR-TB strongly underscores the appropriateness of the definition XDR-TB and its association with a dismal prognosis.\textsuperscript{22}

The potential usefulness of levofloxacin in treating DR-TB\textsuperscript{23}, a comparison between ofloxacin and levofloxacin\textsuperscript{24} has also revealed that the latter FQ, when substituting for the former, in regimens with similar accompanying drugs, resulted in higher success rates for both ofloxacin-susceptible (96.2% vs. 87.5%) and ofloxacin-resistant (78.6% vs. 45.5%) MDR-TB treatment. Thus, levofloxacin is quite likely to be more efficacious than ofloxacin when included in multidrug regimens for treating MDR-TB, including the “difficult” forms.

The C-8-methoxy FQs-moxifloxacin and gatifloxacin might also have activity against ofloxacin-resistant Mtb isolates, including those that are MDR, notwithstanding the phenomenon of partial cross-resistance among members of the FQ class.\textsuperscript{25, 26} Indeed, these two newer FQs have lower mutant prevention concentrations for Mtb and should have a greater potential to restrict the development of bacillary resistance.\textsuperscript{27} However, it appears that for efficient suppression of development of DR-TB, high-dose moxifloxacin is preferable, but could well be limited by intolerability.\textsuperscript{28} In a meta-analysis on the treatment outcomes of patients with XDR-TB\textsuperscript{29}, 43.7% exhibited a cure or treatment completion.

**Newer FQs for the treatment of DS-TB**

The most commonly encountered indication for the use of FQs in the current practice is intolerance to standard first-line anti-TB drugs, especially due to hepatic dysfunction.\textsuperscript{4} Although some patients can be satisfactorily returned to the originally scheduled first-line drug regimen, most affected patients require the use of a relatively non-hepatotoxic regimen, on an in-terim or definitive basis.\textsuperscript{30} Earlier reports on this subject largely involved ofloxacin, used in conjunction with streptomycin, and ethambutol.\textsuperscript{31} In case of definitive treatment of TB, ofloxacin/levofloxacin can be used together with isoniazid/ rifampicin, plus perhaps even low-dose pyrazinamide, depending on the liver reserve.\textsuperscript{32} A retrospective study of a cohort of tuberculosis patients with liver injury prescribed an alternative therapeutic regimen
Safety/tolerance of newer FQs

The beneficial use of moxifloxacin in treating TB in human immunodeficiency virus (HIV)-infected patients when conventional arthroplasty was found to be modest after controlling for sex, age, other antibiotic use, serum albumin, duration of hospital stay and nasogastric feeding. Although the risk for potential cardiotoxicity is perhaps higher for moxifloxacin, as compared to levofloxacin (55), a randomized trial involving the cardiac rhythm safety of moxifloxacin versus levofloxacin in elderly patients with community-acquired pneumonia has shown them to have a comparable risk and safety. However, it is important to remember that this may not be the case when considering long-term use of these FQs in the treatment of TB. Extreme caution must thus be exercised in patients with underlying cardiac diseases or QTc prolongation, especially for those with risk factors for torsades de pointes. Gatifloxacin use is associated with GI and neurological adverse reactions like moxifloxacin. It also has potential cardiotoxicity. However, most importantly, it is associated with dysglycaemia, especially in older patients.

Despite the promise of the newer FQs in the future treatment of TB, such optimism is somewhat tempered by the escalating rates of FQ resistance in *M. tuberculosis*. Many parts of the
Conclusions

Preliminary evidences clarified that levofloxacin might have immunomodulating potential in addition to anti-TB activity. Thus, further exploration and evaluation are still needed in order to develop optimum regimens.

References

55. C. Carbon, Chemotherapy, 2001, 47: 9

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