

Differences Among Fluoroquinolones in the Treatment of MDR-TB

Proposal

The Complementary List of the Model Essential Medicines List currently lists three fluoroquinolones for treatment of MDR-TB: ciprofloxacin, ofloxacin and levofloxacin.

It is proposed to delete ciprofloxacin and ofloxacin and list levofloxacin only. A square box listing is not proposed because there is insufficient clinical experience with newer fluoroquinolones in MDR-TB.

Introduction

The standard treatment of *Mycobacterium tuberculosis* (MTB) is a treatment program of isoniazid, rifampicin, ethambutol and pyrazinamide given for two months, followed by isoniazid and rifampicin given for a further four months. These four drugs are referred to as "first-line" drugs. Multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB) is defined as a strain that is resistant *in vitro* to at least isoniazid and rifampicin, although many strains are resistant to other drugs as well. Treatment must then proceed with "second-line" drugs, which are in some cases older agents formerly regarded as first-line but now displaced (eg, streptomycin) and in other cases drugs of lower efficacy or greater toxicity.

In 2000 the WHO/IUATLD program of drug resistance surveillance reported that across a range of countries the median prevalence of MDR-TB in new cases was 1% (range 0-14%) and in previously-treated patients 9% (range 0-48%).

Treatment of MDR-TB is not, in principle, different from that of drug-sensitive tuberculosis: at least three drugs must be used to which the organism is sensitive and (preferably) which the patient has not previously received. The difficulty is that in strains resistant to multiple drugs it can be hard to identify three drugs to which the strain is sensitive, that without isoniazid and rifampicin treatment must be prolonged (18 months according to WHO recommendations), and that the drugs which can be used are often of marginal efficacy and/or more toxic, so that rates of cure are much lower than with first-line treatment.

Fluoroquinolones are active against *Mycobacterium tuberculosis* (MTB). They have been trialed as replacements for some current first-line drugs, and used also in MDR-TB. The fluoroquinolones that have been used in the treatment of tuberculosis are ciprofloxacin, ofloxacin, levofloxacin (the S- isomer – the active isomer - of the racemic mixture ofloxacin), sparfloxacin, gatifloxacin, and moxifloxacin.

Data will be presented for these drugs on two primary outcomes:

- differences among the drugs in successful treatment of MDR-TB;
- differences among the drugs in adverse effects;

and three secondary outcomes:

- differences in *in vitro* sensitivity of *Mycobacterium tuberculosis* to fluoroquinolones in relation to usual serum levels of the drugs;
- differences among the drugs in rapid early killing;
- differences in liability to provoke resistance.

There is a very large volume of data available for review on this topic, but much is of poor quality or poorly reported. There is a paucity of randomised controlled trials of individual fluoroquinolones in the treatment of MDR-TB and a total absence of large, well-designed comparative randomised controlled trials.

Information for this review was identified by:

- searching the Cochrane Central database of randomised controlled trials and the PubMed database, using the strategy of the Cochrane Handbook (www.cochrane.dk/cochrane/handbook/hbook.htm, Appendix 5b.3 accessed December 1, 2006) to identify randomised controlled trials;
- searching PubMed using the MeSH terms "Mycobacterium tuberculosis, drug effects" *and* "fluoroquinolone", and using "multi-drug resistant tuberculosis [tw] *and* treatment [tw]", "tuberculosis [tw] *and* ciprofloxacin [tw]" (and then each target drug in turn);
- searching reference lists in the Cochrane systematic review and other recent publications.

1. Results of Treatment with Fluoroquinolones in Patients with MDR-TB

There are no well-designed randomised controlled trials comparing the various fluoroquinolones in MDR-TB. A systematic review, published in the Cochrane Library in 2005,¹ found three trials using fluoroquinolones in patients with known MDR-TB, and one in patients who may have had MDR-TB, but most were of rather low methodological quality.

Choice of comparator for trials in MDR-TB is a problem. WHO has suggested that optimal practice for treating MDR-TB is to develop an individualised regimen for each patient, based on *in vitro* sensitivities and the patient's treatment history,² although in some medium-resource settings standardised regimens have been employed with good results.³ However, the practice of individualising treatment makes it more difficult to plan randomised controlled trials, and there would be doubt over the applicability of trials in which standardised regimens were used.

No published reports of trials have been found of the use of fluoroquinolones in treatment of MDR-TB since the Cochrane review was released. One trial of moxifloxacin substituted for ethambutol in patients with drug-sensitive organisms that was in progress when the Cochrane review was published has now reported, and found no difference between the moxifloxacin and ethambutol groups.⁴

The available trials are summarised in Table 1, with data taken from the Cochrane review (except for Jadad scores, which were calculated on the basis of the descriptions of trial methods in the review). All of these trials were published in Chinese and only one is indexed in PubMed, where no abstract is available, and the original versions have not been reviewed.

Three outcomes from the Cochrane review are reported here: sputum culture conversion to negative after 8 weeks treatment (important as an index of rapid control of infectivity), treatment failure at 12 months (the definition of this outcome in the trials is unclear, however), and total adverse events. Interpretation of the results is hampered by the use of unusual doses of fluoroquinolones and/or regimens not meeting accepted standards for treatment of MDR-TB.

Table 1: Results of randomised controlled trials of fluoroquinolones in patients with (or possibly having) MDR-TB. Trial references in reference 1. Jadad scores calculated according to Jadad A. *Randomised Controlled Trials*. London, BMJ, 1998, p51. **Abbreviations:** SF = sparfloxacin, OF = ofloxacin, LF = levofloxacin, INH = isoniazid, RIF = rifampicin, EMB = ethambutol, PZA = pyrazinamide, SM = streptomycin; SCN = sputum culture negative after 8wk treatment, TF = treatment failure at 1 year, AE = total adverse events.

| Author, Year | Jadad Score | Patients | Comparison | ... added to | Results |
|--------------|-------------|---|--------------------------|--|---|
| Huang, 2000 | 1 | MDR-TB, re-treatment, n = 104 | SF 200 bd vs OF 300 bd | INH 300 + RIF 450 + EMB 750 + PZA 1500 + SM 750 | SCN: SF 28/52 vs OF 8/52; TF: n/a; AE: SF 16/52 vs OF 10/52 |
| Ji, 2001 | 1 | MDR-TB, re-treatment, n = 69 | SF 200 vs OF 200 | INH 300 + PZA 1500 | SCN: n/a; TF: SF 1/31 vs OF 4/38; AE: SF 2/31 vs OF 3/38 |
| Sun, 2000 | 1 | MDR-TB, re-treatment, n = 80 | SF 100 qds vs OF 200 tds | INH 200 + RIF 150 + prothionamide 200 tds | SCN: SF 14/40 vs OF 11/40; TF: SF 6/40 vs 8/40; AE: SF 5/40 vs OF 11/40 |
| Lu, 2000 | 3 | Untreated or treatment failure after <6mo, not known MDR-TB n = 144 | LF 300 od vs OF 600 od | INH 300 + EMB 750-1000 + PZA 1500 +thioacetazone 600 | SCN: LF 59/75 vs OF 56/69; TF: LF 3/75 vs 2/69; AE LF 11/75 vs OF 13/69 |

In drug-sensitive tuberculosis there have been randomised controlled trials of ciprofloxacin substituted for either ethambutol (EMB) + pyrazinamide (PZA) (two trials) or rifampicin (RIF) (one trial) and ofloxacin substituted for EMB (one trial). Ciprofloxacin compared to EMB + PZA was associated with a higher rate of treatment failure at 12

months (8/163 vs 4/165) and of relapse (7/82 vs 0/86), and compared to RIF may have been associated with higher rates of treatment failure (1/30 vs 0/30) and relapse (3/30 vs 1/30). Ofloxacin compared to EMB did not appear to be associated with increased relapse rates (0/79 vs 0/77).

On the basis of these results the Cochrane reviewers did not find any reason to conclude that there were any differences among sparfloxacin, levofloxacin and ofloxacin in either drug-sensitive or MDR-TB. However, the shortcomings of the trials make this conclusion provisional. Particularly having regard to the rather marked differences between levofloxacin and ofloxacin found in one case series (see below) it is unfortunate that the dose of levofloxacin used in the trial comparing it to ofloxacin was very low.

The Cochrane reviewers did conclude that ciprofloxacin cannot be recommended in the treatment of tuberculosis. However, the clearly higher rate of relapse and treatment failure with ciprofloxacin was seen in only one trial, and is accounted for by only a small number of patients.

Some useful information can be gathered from case series. The results are shown in Table 2.

The case series selected for presentation here are those that are large, carefully studied, and offer information about the efficacy of fluoroquinolones as a class or one fluoroquinolone compared to another. Case series with follow-up too short to provide data on cure as an outcome (eg, reference 8) have been excluded.

It should be noted that all of these reports concern previously treated patients, rather than those with newly acquired MDR-TB, and that (probably) all the patients were HIV negative. In two series^{3,5} patients were given a month's supply of treatment at a time and not supervised at all, and in another⁶ they were supervised only while they were in hospital (usually as long as they were receiving parenteral aminoglycosides), and this compromises the applicability of the results to standard treatment conditions.

The study of Yew and others has been widely quoted as demonstrating the superiority of levofloxacin over ofloxacin, and in its choice of drug doses, systematic use of DOT, and careful follow-up it is certainly the most relevant of the case series to optimal practice. However, the data covered many years, and there was a secular trend to increasing use of levofloxacin in later years, so that other factors may have been the cause of the apparent advantage associated with levofloxacin therapy.

Table 2: Selected case series of treatment of MDR-TB with fluoroquinolones. **Abbreviations:** DOT = directly observed therapy; OF = ofloxacin, CS = cycloserine, PT = prothionamide, AG = aminoglycoside, PZA = pyrazinamide, PAS = para-amino salicylic acid, OF = ofloxacin, LF = levofloxacin; R = resistant, S = sensitive.

| Author and Year | Patients | Treatment Regimen | Outcomes |
|-----------------------------|--|--|---|
| Park, 2004 ⁹ | Seoul; n =142; all re-treatment; not DOT; HIV status not reported | OF 200-300 bd + CS + PT + AG + PZA or PAS | 63/142 (44%) cured, 22/142 failed or died: 10/22 (45%) baseline R to OF failed vs 12/63 (19%) baseline S to OF failed |
| Yew, 2003 ⁶ | Hong Kong; n =106, data for 99 (7 "absconded"); all re-treatment; DOT; all HIV -ve | LF 600-800 od (40/99) or OF 600-800 od (59/99) + 4 others; 25/99 R to OF at baseline, LF 14/25, OF 11/25 | S to OF: LF cured 25/26 (96%), OF cured 42/48 (88%); R to OF: LF cured 11/14(79%), OF cured 5/11 (45%) |
| Chiang, 2006 ⁷ | Taipei; n = 299; all re-treatment; not DOT; HIV tested in 35/299, all -ve | 125/299 OF 300-400 bd + other 2 nd line, 113/299 2 nd line without OF, 61/299 re-treated with 1 st line drugs | OF: 74/125 (59%) cured, 17/125 failed or died (34/125 "defaulted"), 2/74 (3%) "cured" relapsed No OF: 44/113 (39%) cured, 35/113 failed or died (34/113 "defaulted"), 3/44 (7%) "cured" relapsed |
| Tahaoglu, 2001 ⁸ | Istanbul; n = 158; all re-treatment; ?DOT; HIV status not reported | 126/158 OF 400-800 od + AG + other 2 nd line, 32/158 AG + other 2 nd line | OF: 102/126 (81%) cured No OF: 19/32 cured (59%) |

2. Adverse Effects

The expected adverse effects of fluoroquinolones, notably mental disturbance, have been observed during treatment of tuberculosis.³ The exact frequency of adverse effects attributable to fluoroquinolones is hard to determine because all MDR-TB patients receive numerous drugs together, some of which cause similar adverse effects (eg, cycloserine is recognised to cause mental effects similar to those of fluoroquinolones). Stopping one drug at a time is often unacceptable because of the risk of leaving a patient receiving only one effective anti-tuberculous agent, and so promoting the acquisition of resistance by the infecting strain.

The rates of adverse effects attributed to fluoroquinolones in reported series have been low, and in one careful study levofloxacin-containing regimens were associated with lower overall adverse event rates than regimens containing first-line drugs.⁹ In a large North American study of treatment of MDR-TB ofloxacin was associated with the lowest rate of cessation (3/124 patients) because of adverse events of all drugs used (including first-line drugs).¹⁰ These differences are mainly due to the absence of liver injury with fluoroquinolones, which is a common problem with first-line agents.

There are no trial data to suggest that one fluoroquinolone causes fewer adverse events than others in the treatment of tuberculosis. Sparfloxacin has been regarded as an unattractive option for treatment of MDR-TB because of photo-toxicity and cardiotoxicity,¹¹ but the data from the randomised controlled trials in China did not reveal this to be a serious problem (although the doses used were low).

3. *In Vitro* Sensitivity of *Mycobacterium tuberculosis* to fluoroquinolones.

Representative values for minimum inhibitory concentration (MIC) of fluoroquinolones for MTB in communities with a low prevalence of primary fluoroquinolone resistance are shown in Table 3. The threshold MIC for declaring ofloxacin-resistance is normally taken to be 2µg/mL. Of greater importance than MIC is the relation of peak serum concentration with usual doses (C_{max}) to MIC, also shown. For comparison, usual values for isoniazid MIC (for isoniazid-sensitive strains) are also given.

Reported C_{max} values are problematic, values in formal pharmacokinetic studies being generally lower and much less variable than those reported in clinical studies. For consistency values from the US Approved Product Information for the highest repeated doses are presented here. Because fluoroquinolones are not licensed for the treatment of tuberculosis in the USA the available data are, in some cases, for relatively low doses. In general, C_{max} for fluoroquinolones is linearly related to dose, and is higher with repeated dosing than with single doses.

There is evidence in relation to fluoroquinolone action against non-mycobacterial pathogens that the ratio of overall 24 hour drug exposure (area under the curve = AUC) to MIC is correlated with clinical effect. C_{max}/MIC ratios are given in preference here because emerging practice in the treatment of tuberculosis is to use large once daily doses of fluoroquinolones in order to maximise C_{max} .

Table 3: MIC₉₀ (the MIC for 90% of strains) and C_{max} data for fluoroquinolones and isoniazid. MIC₉₀ for fluoroquinolones from Ginsburg et al,¹² and UptoDate.¹³ C_{max} for fluoroquinolones from US Approved Product Information for each drug. MIC₉₀ and C_{max} for isoniazid from Davies PO, *Clinical Tuberculosis*, ed 3, London, Arnold, 2003, pp172-3.

| | MIC ₉₀ , µg/mL | C_{max} , µg/mL | C_{max}/MIC |
|---------------------|---------------------------|-------------------|---------------|
| Ciprofloxacin 500mg | 0.5-1.0 | 3.0 | 3-6 |
| Ofloxacin 400mg | 0.5-1.3 | 4.6 | 3-9 |
| Levofloxacin 750mg | 0.5-1.0 | 8.6 | 8-15 |
| Sparfloxacin 400mg | 0.25-0.5 | 1.3 | 3-6 |
| Gatifloxacin 400mg | 0.25-0.5 | 4.2 | 8-15 |
| Moxifloxacin 400mg | 0.25-0.5 | 3.2 | 6 |
| Isoniazid 300mg | 0.01-0.06 | 3-5 | 20-50 |

It appears from these data that the fluoroquinolones most closely approximating the values seen with isoniazid, at the doses currently used, are levofloxacin and gatifloxacin. It should be noted, however, that the dose of ofloxacin represented in this data is, in effect, much lower than that of levofloxacin.

4. Early Bactericidal Activity

Early bactericidal activity (EBA) is conventionally (but arbitrarily) defined as the decline in colony-forming units in sputum over the first two days of treatment.¹⁴ It is thought that this reflects rapid killing of metabolically active organisms, and that this is an important factor in interrupting transmission. There are many uncertainties about the interpretation of EBA (pyrazinamide, for example, has very low EBA but is essential in short-course regimens) but it is probably true that when comparing drugs *within a class* (such as the fluoroquinolones) higher EBA *suggests* a greater likelihood of clinical effect.¹¹

EBA over the period 2-5 days ("extended EBA") has been proposed as an index of a drug's ability to kill more slowly metabolising organisms (confusingly, this is also referred to as "sterilising ability"). Rifampicin, which is known from randomised controlled trials to be essential for cure in short-course regimens and is therefore the paradigm drug in this context, has high EBA in this period.

Table 4 shows EBA (days 0-2) for fluoroquinolones and, for comparison, isoniazid (against susceptible strains). Table 5 shows extended EBA (days 2-7) for fluoroquinolones and, for comparison, rifampicin (against rifampicin-sensitive strains).

It appears that ciprofloxacin has lower EBA than the other fluoroquinolones, but that the rest cannot be distinguished, given the patchiness of the data. Data for extended EBA are very sparse, but it does not appear likely that there are any important differences among the fluoroquinolones tested.

5. Development of Resistance During Treatment

Acquisition of fluoroquinolone resistance during treatment has been observed frequently.^{12,15,16,17} This is of concern because it results in early relapse and because resistance to one fluoroquinolone often involves resistance to others.⁹ However, at least some cases of the development of resistance during treatment have involved either inadequate doses (eg, ofloxacin 300mg od) or monotherapy.^{9,12} Nevertheless, although *in vitro* resistance to fluoroquinolones does not exclude effective treatment,⁴ previous use of fluoroquinolones in a patient's treatment halves the chance of successful treatment of MDR-TB.⁶

Fluoroquinolone-resistant strains of MTB in patients with MDR-TB is related, in most communities, to previous tuberculosis treatment of those patients with fluoroquinolones. Fluoroquinolone-resistant MDR-TB in patients not previously treated for MTB with fluoroquinolones is increasing, however, and has become common in many areas.^{3,17} This has been attributed to use of fluoroquinolones in patients who have unsuspected tuberculosis; there are reports of the acquisition of fluoroquinolone resistance by MTB after as little as 23 and 13 days of fluoroquinolone treatment.^{12,18}

It has been suggested that 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 reported to be 2, 1.8, 1.0 and 1.2 µg/mL for ciprofloxacin,

levofloxacin, gatifloxacin and moxifloxacin respectively.¹⁹ The C_{max}/MPC ratios for these drugs, using the C_{max} data from Table 3, would then be 1.5, 4.8, 4.2 and 2.7, respectively, and all except ciprofloxacin would seem likely to be roughly equivalent. It has been suggested on grounds such as these that gatifloxacin and moxifloxacin are less likely to provoke the development of resistance,^{12,20} but there are no clinical data supporting this suggestion. Further, it is not clear that the MPC₉₀ (ie, 10% of strains *will* be able to select for resistant clones) is the appropriate cut-off in the context of MDR-TB treatment, where the other drugs a patient is receiving may be of low efficacy.

Summary and Recommendations

Fluoroquinolones are almost certainly effective in the treatment of MDR-TB, and outcomes are uniformly worse in patients in whom they cannot be used. Of the available drugs, ciprofloxacin is probably inferior, based on trial outcomes supported by pharmacodynamic and pharmacokinetic considerations.

One retrospective case-series suggests that levofloxacin is (rather markedly) superior to ofloxacin in the treatment of MDR-TB, and this is consistent with levofloxacin's higher C_{max}/MIC. This may, however, simply reflect the doses used. The available randomised controlled trials do not provide useful information on this point.

On the basis of this very scanty evidence it is recommended that levofloxacin be the first-choice fluoroquinolone for MDR-TB. A square box is not recommended because, although ofloxacin is effective for MDR-TB, there is no reason to list both the racemic mixture and the S- isomer. Sparfloxacin, gatifloxacin and moxifloxacin are possible alternatives on *in vitro* evidence, but published experience with these drugs in MDR-TB is very limited. Ciprofloxacin is not an appropriate alternative for routine use.

Table 4: EBA (days 0-2) for fluoroquinolones and isoniazid. Note the higher dose of levofloxacin used in the study reported in this table.

| EBA (days 0-2) (logCFU/mL/d) | Ciprofloxacin varying doses | Ofloxacin 800mg | Levofloxacin 1000mg | Sparfloxacin 400mg | Gatifloxacin 400mg | Moxifloxacin 400mg | Isoniazid 300mg |
|-----------------------------------|---------------------------------------|--------------------|------------------------|-----------------------|-----------------------|-----------------------|--------------------|
| Johnson et al, 2006 ²⁰ | - | - | 0.45 | - | 0.35 | 0.33 | 0.67 |
| Gosling et al, 2003 ²¹ | - | - | - | - | - | 0.53 | 0.77 |
| Sirgel et al, 1997 ²² | 0.09 (500mg), 0.205 (1500mg) | - | - | - | - | - | 0.66 |
| Sirgel et al, 2000 ²³ | - | 0.17 | - | - | - | - | 0.48 |
| Ginsburg et al, 2003 | 0.09 (500mg) | 0.39 | - | - | - | - | 0.58 |
| Jindani et al, 2003 ²⁴ | - | - | - | - | - | - | 0.59 |
| | | | | | | | - |

Table 5: Extended EBA (days 2-7) for fluoroquinolones and rifampicin.

| Extended EBA (days 2-5 or 7), (logCFU/mL/d) | Ciprofloxacin 750mg | Ofloxacin 800mg | Levofloxacin 1000mg | Sparfloxacin 400mg | Gatifloxacin 400mg | Moxifloxacin 400mg | Rifampicin 600mg |
|--|------------------------|--------------------|------------------------|-----------------------|-----------------------|-----------------------|---------------------|
| Johnson et al, 2006 | - | - | 0.18 | - | 0.17 | 0.17 | - |
| *Pletz et al, 2004 ²⁵ | - | - | - | - | - | 0.27 | - |
| Sirgel et al, 2000 | - | 0.20 | - | - | - | - | 0.24 |
| Kennedy et al, 1995 ⁴⁶ | 0.20 | - | - | - | - | - | - |

* This value is a mean for days 0-5. Some reviews have counted it as an estimate of early EBA.

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