Efficacy and safety of World Health Organization group 5 drugs for multidrug-resistant tuberculosis treatment

Nicholas Winters\textsuperscript{1,2}, Guillaume Butler-Laporte\textsuperscript{1} and Dick Menzies\textsuperscript{1,2}

**Affiliations:**
\textsuperscript{1}Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, McGill University, Montreal, QC, Canada.
\textsuperscript{2}Dept of Epidemiology and Biostatistics, McGill University, Montreal, QC, Canada.

**Correspondence:**
Dick Menzies, Montreal Chest Institute, Room K1.24, 3650 St Urbain, Montreal, QC, Canada, H2X 2P4.
E-mail: Dick.Menzies@mcgill.ca

**ABSTRACT**

The efficacy and toxicity of several drugs now used to treat multidrug-resistant tuberculosis (MDR-TB) have not been fully evaluated.

We searched three databases for studies assessing efficacy in MDR-TB or safety during prolonged treatment of any mycobacterial infections, of drugs classified by the World Health Organization as having uncertain efficacy for MDR-TB (group 5).

We included 83 out of 4002 studies identified. Evidence was inadequate for meropenem, imipenem and terizidone. For MDR-TB treatment, clarithromycin had no efficacy in two studies (risk difference (RD) $-0.13$, 95% CI $-0.40$--$-0.14$) and amoxicillin–clavulanate had no efficacy in two other studies (RD $0.07$, 95% CI $-0.21$--$-0.35$). The largest number of studies described prolonged use for treatment of non-tuberculous mycobacteria. Azithromycin was not associated with excess serious adverse events (SAEs). Clarithromycin was not associated with excess SAEs in eight controlled trials in HIV-infected patients (RD $0.00$, 95% CI $-0.02$--$-0.02$), nor in six uncontrolled studies in HIV-uninfected patients, whereas six uncontrolled studies in HIV-infected patients clarithromycin caused substantial SAEs (proportion $0.20$, 95% CI $0.12$--$0.27$).

For most group 5 drugs we found inadequate evidence of safety for prolonged use or for efficacy for MDR-TB, although macrolides appeared to be safe in prolonged use.

@ERSpublications

Weak evidence for the efficacy and safety of group 5 drugs for MDR-TB suggests they should be evaluated using RCTs http://ow.ly/P8I3t

This article has supplementary material available from erj.ersjournals.com

Received: April 24 2015 | Accepted after revision: June 22 2015 | First published online: Sept 17 2015

Support statement: This study was supported by funding provided by the World Health Organization. Funding information for this article has been deposited with FundRef.

Conflict of interest: Disclosures can be found alongside the online version of this article at erj.ersjournals.com

The content of this work is copyright of the authors or their employers. Design and branding are copyright ©ERS 2015.
Introduction

Tuberculosis (TB) is one of the most deadly communicable diseases in the world, causing an estimated 9 million new cases and 1.9 million deaths in 2013 [1]. Of these, an estimated 480,000 patients had multidrug-resistant TB (MDR-TB) [1], defined as resistance to at least rifampicin and isoniazid [2], and ∼43,000 patients had extensively drug-resistant TB (XDR-TB) [1], defined as MDR-TB with additional resistance to any fluoroquinolone and any second-line injectable [3]. Treatment of MDR-TB is challenging as it is very expensive (the cost to treat each MDR-TB and XDR-TB patient is approximately US$134,000 and US$430,000, respectively [4]), requires lengthy use of more toxic second-line anti-TB drugs [5, 6], yet is associated with higher failure and death rates than drug-susceptible TB.

Drugs used in the treatment of MDR- and XDR-TB include amoxicillin–clavulanate (AMX–CLV), meropenem, imipenem–cilastatin, thioridazine, terizidone and the macrolides: clarithromycin and azithromycin [7]. The efficacy and toxicity of these agents are unclear, as there are few published data regarding their use in TB treatment; hence these are considered group 5 drugs by the World Health Organization. Systematic reviews have been published assessing the efficacy and toxicity of linezolid [8–10] and clofazimine [9, 11], as well of the safety (only) of terizidone [12] and the efficacy (only) of macrolides [10], but there have been no reviews of the other second-line drugs used for the treatment of MDR-TB.

We have conducted a systematic review and meta-analysis to assess the efficacy and toxicity of AMX–CLV, meropenem, imipenem–cilastatin, thioridazine, terizidone and the macrolides when used for the treatment of microbiologically confirmed Mycobacterium tuberculosis. We also included reports describing toxicity of the same drugs used to treat any mycobacterial disease for ≥6 months. We included original research articles describing results of randomised controlled trials (RCTs), cohort or case–control studies published in the peer-reviewed literature between 1946 and October 20, 2014. We also identified relevant articles from the references cited in the retrieved articles and previously published reviews.

Methods

Search strategy

We performed two separate searches, using the MEDLINE, Embase and Cochrane library databases, for studies reporting efficacy or toxicity of AMX–CLV, meropenem, imipenem/cilastatin, thioridazine, terizidone and the macrolides clarithromycin and azithromycin when used for the treatment of microbiologically confirmed Mycobacterium tuberculosis. We also included reports describing toxicity of the same drugs used to treat any mycobacterial disease for ≥6 months. We included original research articles describing results of randomised controlled trials (RCTs), cohort or case–control studies published in the peer-reviewed literature between 1946 and October 20, 2014. We also identified relevant articles from the references cited in the retrieved articles and previously published reviews.

We developed comprehensive search strategies separately for efficacy and toxicity using a combination of keywords and search terms. We included all search terms related to tuberculosis and our drugs of interest as exploded medical subject headings (MeSH) and free-text keywords in titles or abstracts. The full search terms for each database and search can be found in the online supplementary material.

Study selection

We included original articles published in the peer-reviewed literature, written in any language, that described efficacy and toxicity of at least one of the drugs of interest used for the treatment of ≥20 human subjects with MDR-TB, or that described toxicity of these drugs during use for ≥6 months to prevent or treat NTM infections. The studies of NTM were included as these are mycobacterial infections that require prolonged treatment in both HIV-infected and -uninfected patients. Hence we believed the information regarding toxicity would be potentially applicable to patients treated for MDR- or XDR-TB. Studies of patients who had strictly extrapulmonary MDR-TB were excluded from the analysis of efficacy as treatment outcomes are rarely confirmed bacteriologically, introducing greater uncertainty in estimates of efficacy. Articles were excluded if they were reviews, in vitro, pharmacokinetic or laboratory studies, studies of animals or reported results that overlapped with a previous report. The search results (titles and abstracts, and then full text) were screened for inclusion independently by two authors (N. Winters and G. Butler-Laporte). Differences at each stage were resolved by consensus.

Data abstraction

Data abstraction was performed by two authors for included studies, using a standardised data abstraction form. We judged quality on two criteria: 1) if treatment outcomes were defined according to Laserson criteria (cured: MDR-TB patients completed treatment as planned and had at least five consecutive negative sputum cultures during the final 12 months of treatment; treatment completed: completed treatment as planned but did not meet the definition for cure due to lack of bacteriological results; failed: if two or more cultures out of the five in the final 12 months were positive, or if one out of the final three...
cultures were positive) [2]; and 2) whether adverse events were classified based on *a priori* published definitions such as the Common Terminology Criteria for Adverse Events guidelines [13]. All studies were included regardless of whether they met these quality criteria. For each study we recorded data on the average age of the patients, HIV prevalence, the companion drugs and mean number of drugs in the regimen, duration of drug use, dosage, whether the drug treatment was standardised or individualised, duration of follow-up and description of the study design.

**Data synthesis**

We estimated efficacy by comparing the proportion with treatment success (cured or completed) among patients with MDR-TB who received one of the drugs of interest with those who did not receive that drug. For toxicity in both MDR-TB and NTM, we abstracted the occurrence of serious adverse events (SAEs), defined as grade 3 or 4 adverse events if reported, or whether the drug of interest was stopped due to adverse events. Risk differences (RD), *i.e.* the absolute difference in observed risk of SAE between those receiving a treatment and those not receiving it were estimated in controlled studies, meaning data studies reporting the occurrence of SAEs in patients who received and did not receive the drug of interest. In uncontrolled studies we calculated the proportion of patients in whom SAEs occurred that were attributed to the drug of interest. Random effects models were used to generate pooled effect estimates (RD or proportions) and their 95% confidence intervals for treatment success and toxicity using R (version 3.1.0; http://cran.r-project.org/)

---

**FIGURE 1** Flow diagram of the search strategy and selection of studies, as well as a guide as to in which figure and table the information in each box can be found (meta-analyses were performed on all studies marked controlled or uncontrolled). SAEs: serious adverse events; AMX–CLV: amoxicillin–clavulanate; TZD: terizidone; mac: macrolide; mero: meropenem; MDR-TB: multidrug-resistant tuberculosis; CLR: clarithromycin; NTM: non-tuberculous mycobacteria; AZI: azithromycin. #: no meta-analysis was performed.

DOI: 10.1183/13993003.00649-2015
with the package meta version 4.0–2 (http://CRAN.R-project.org/package=meta). We stratified analyses based on whether outcomes were reported in patients who received or did not receive the drug of interest (RCTs or controlled cohorts) or were reported without comparison groups (case series). Additionally, we stratified analyses by the HIV status of the subjects and by MDR-TB versus NTM for toxicity. We assessed heterogeneity of studies by using the coefficient of inconsistency (I²) and its 95% confidence interval [14].

Results
As seen in figure 1, 4002 potentially relevant titles were identified: 657 from MEDLINE, 3613 from Embase and 17 from the Cochrane Library. Eight citations were included from the references of a previously published systematic review by HWANG et al. [15]. After removing duplicates we screened 3437 studies, 3214 of which were excluded during title and abstract review. A further 140 of the 223 full texts reviewed were excluded, for reasons listed in figure 1, leaving a total of 83 studies included in this review.

We grouped the studies based on whether authors had reported efficacy or toxicity of our drugs of interest, whether the patients had HIV co-infection or not and whether patients were treated for MDR-TB or NTM infection. We further stratified studies by whether they included a control or comparison group. The numbers of studies included in each of these subgroups are summarised in figure 1. The design and treatment characteristics of all studies included in this review are summarised in online supplementary tables S1–S7 [15–97]. Of the 25 included studies of MDR-TB, 20 were retrospective cohort studies (three of which compared one or more of our drugs of interest to a group not receiving the drug), three were prospective cohort studies (one of which compared one of our drugs of interest to a group not receiving the drug), and one was a randomised trial. Sample sizes ranged from 38 to 1027 and the average ages of the patients ranged from 28 to 45 years.

We found only one study reporting the efficacy of MDR-TB treatment with meropenem and only one study reporting toxicity of this drug used for MDR-TB. Therefore we could not perform a meta-analysis for meropenem (online supplementary material). No studies were found that reported efficacy or SAEs of imipenem–cilastatin or thioridazine. Hence, no further results are presented for meropenem, imipenem–cilastatin and thioridazine.

Efficacy
We found only two controlled studies [85, 96] that examined the impact of AMX–CLV on treatment success in MDR-TB; as seen in table 1, the pooled RD was 0.07 (95% CI −0.21–0.35). Results were similar in the two controlled studies [85, 96] that assessed the impact of clarithromycin: the pooled RD for

<table>
<thead>
<tr>
<th>Type of design</th>
<th>Effect measure</th>
<th>Studies</th>
<th>Patients</th>
<th>Range of outcomes</th>
<th>Heterogeneity (I²) %</th>
<th>Pooled estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTM SAEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-infected</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Controlled</td>
<td>Risk difference</td>
<td>8</td>
<td>1088/1111</td>
<td>0.00–0.02</td>
<td>0</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Uncontrolled</td>
<td>Proportion</td>
<td>6</td>
<td>584</td>
<td>0.06–0.27</td>
<td>82.1</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Controlled</td>
<td>Risk difference</td>
<td>7</td>
<td>1215/1196</td>
<td>0.00–0.09</td>
<td>94.9</td>
</tr>
<tr>
<td>HIV-uninfected</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Controlled</td>
<td>Risk difference</td>
<td>3</td>
<td>174/175</td>
<td>−0.01–0.11</td>
<td>0</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Uncontrolled</td>
<td>Proportion</td>
<td>15</td>
<td>615</td>
<td>0.00–0.22</td>
<td>64.5</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Uncontrolled</td>
<td>Proportion</td>
<td>5</td>
<td>197</td>
<td>0.00–0.09</td>
<td>45.2</td>
</tr>
<tr>
<td>MDR-TB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-uninfected</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMX–CLV</td>
<td>Controlled</td>
<td>Risk difference</td>
<td>2</td>
<td>73/272</td>
<td>−0.02–0.31</td>
<td>43.6</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Controlled</td>
<td>Risk difference</td>
<td>2</td>
<td>86/257</td>
<td>−0.29 to −0.02</td>
<td>65.9</td>
</tr>
<tr>
<td>SAEs</td>
<td>AMX–CLV</td>
<td>Uncontrolled</td>
<td>Proportion</td>
<td>3</td>
<td>77</td>
<td>0.04–0.60</td>
</tr>
</tbody>
</table>

Data are presented as n, unless otherwise stated. SAEs: serious adverse events; AMX–CLV: amoxicillin–clavulanate. #: number of patients receiving/not receiving the drug of interest in controlled studies, or number of patients receiving the drug in uncontrolled studies; ¶: minimum outcome and maximum outcome (risk difference or proportions) found in studies in a given category.
among patients with MDR-TB, SAEs that were attributed to one of the drugs of interest were only controlled studies (fig. 4a) was 0.01 (95% CI [0.00–0.12–0.07]) in the pooled RD for patients experiencing a SAE in the three controlled studies of toxicity of use of azithromycin (fig. 2b [21, 41, 47–49]), there was significant heterogeneity between the controlled studies of toxicity of use of azithromycin for NTM in HIV-infected subjects, although only moderate heterogeneity between studies of SAEs attributed to azithromycin (fig. 2b [21, 41, 47–49]) in the uncontrolled studies of NTM treatment in HIV-uninfected patients. The estimated risk of SAEs was low in the controlled studies (pooled RD 0.04, 95% CI [0.00–0.08]) and in the uncontrolled studies of azithromycin (proportion 0.03, 95% CI [0.00–0.08]).

In HIV-infected patients treated with clarithromycin for NTM, the pooled RD for toxicity was 0.00 (95% CI [0.02–0.02]) in the controlled studies (fig. 3a [17, 22, 38, 42, 69, 79, 87, 95]) compared to a pooled proportion of 0.20 (95% CI 0.12–0.27) in the uncontrolled studies (fig. 3b [18, 23, 26, 29, 31, 36]). In HIV-uninfected patients treated with clarithromycin for NTM (fig. 4a [44, 55, 72] and 4b [30, 32, 41, 46, 49, 51, 56, 59, 62, 68, 74, 82, 86, 92, 94]), the pooled RD for patients experiencing a SAE in the three controlled studies (fig. 4a) was 0.01 (95% CI [0.00–0.06–0.07]), compared to a pooled SAE proportion of 0.04 (95% CI [0.02–0.07]) in the 15 uncontrolled studies (fig. 4b).

Among patients with MDR-TB, SAEs that were attributed to one of the drugs of interest were only reported for AMX–CLV in three uncontrolled studies. As seen in table 1, in these studies the pooled proportion of patients who experienced an SAE from AMX–CLV was 0.12 (95% CI 0.00–0.28).

### Serious adverse events

The pooled estimates for all the studies included in these meta-analyses are summarised in table 1. There were no controlled studies of the use of azithromycin for treatment of NTM in HIV-negative patients or uncontrolled studies of azithromycin used in HIV-positive patients. As seen in figure 2a [28, 38, 39, 52, 53, 64, 77], there was significant heterogeneity between the controlled studies of toxicity of use of azithromycin for NTM in HIV-infected subjects, although only moderate heterogeneity between studies of SAEs attributed to azithromycin (fig. 2b [21, 41, 47–49]) in the uncontrolled studies of NTM treatment in HIV-uninfected patients. The estimated risk of SAEs was low in the controlled studies (pooled RD 0.04, 95% CI [0.00–0.08]) and in the uncontrolled studies of azithromycin (proportion 0.03, 95% CI [0.00–0.08]).

In HIV-infected patients treated with clarithromycin for NTM, the pooled RD for toxicity was 0.00 (95% CI [0.02–0.02]) in the controlled studies (fig. 3a [17, 22, 38, 42, 69, 79, 87, 95]) compared to a pooled proportion of 0.20 (95% CI 0.12–0.27) in the uncontrolled studies (fig. 3b [18, 23, 26, 29, 31, 36]). In HIV-uninfected patients treated with clarithromycin for NTM (fig. 4a [44, 55, 72] and 4b [30, 32, 41, 46, 49, 51, 56, 59, 62, 68, 74, 82, 86, 92, 94]), the pooled RD for patients experiencing a SAE in the three controlled studies (fig. 4a) was 0.01 (95% CI [0.00–0.06–0.07]), compared to a pooled SAE proportion of 0.04 (95% CI [0.02–0.07]) in the 15 uncontrolled studies (fig. 4b).

Among patients with MDR-TB, SAEs that were attributed to one of the drugs of interest were only reported for AMX–CLV in three uncontrolled studies. As seen in table 1, in these studies the pooled proportion of patients who experienced an SAE from AMX–CLV was 0.12 (95% CI 0.00–0.28).

---

**FIGURE 2** Forest plots of serious adverse events with azithromycin for treatment of non-tuberculous mycobacteria infections in a) HIV-positive patients [controlled studies]; b) HIV-negative patients [uncontrolled studies]. #: serious adverse events defined as grade 3–4 adverse events, or drug stopped because of adverse events.
In controlled studies, HIV-infected and HIV-uninfected patients receiving macrolides for NTM infection or disease did not have a higher risk of SAEs. In uncontrolled studies the use of clarithromycin was associated with higher risk of SAE in HIV-infected patients. In three controlled studies AMX–CLV was associated with excess SAEs in MDR-TB treatment, but we found no evidence of toxicity in three studies of patients treated for NTM with AMX–CLV. Four controlled studies found no evidence of efficacy of clarithromycin or AMX–CLV for treatment of MDR-TB.

Our study had several limitations. The most important limitation was the very small number of controlled studies, and with small numbers of patients, that assessed efficacy and toxicity of only a few of the drugs of interest used for the treatment of MDR-TB. Hence we were only able to perform meta-analysis for a few of the drugs we studied. Furthermore, only one randomised trial of MDR-TB treatment was identified; the remainder were cohort studies in which patients were not allocated randomly to the regimens. Hence it is likely that the results are affected by selection bias in that more seriously ill patients, with more extensive resistance patterns may have been more likely to receive these second-line drugs.

For studies of patients treated with these drugs for NTM, the quality of studies was generally higher, particularly among HIV-infected patients as the majority of these studies were randomised trials. However, the evidence from studies of NTM treatment among HIV-uninfected patients was limited as the studies were not randomised, patients were on several drugs at once, and dosage used or length of therapy was often not reported. For the 13 RCTs included (six clarithromycin, six azithromycin and one with both drugs), the quality of the studies were moderate and most had too few patients to have adequate power to detect differences in SAEs.

Despite these limitations, our study had several strengths. We constructed a comprehensive search strategy that included RCTs and cohort studies; the latter often are conducted under conditions more...
representative of clinical practice. The sensitive search strategy also resulted in a large number of articles, decreasing the likelihood that studies were missed. Additionally, we were able to stratify studies based on HIV status, allowing the interpretation of outcomes separately for each group of patients. With this stratification we were able to show that HIV-positive patients did not have any greater risk of SAEs than HIV-uninfected persons, at least in studies with stronger designs (randomised trials).

As treatment of MDR-TB is costly and requires lengthy use of many drugs, administration of safe and effective drugs is crucial. This is especially important given the potential costs of several of the drugs reviewed. We found no evidence of efficacy of any of the drugs reviewed in the few controlled studies, while in the uncontrolled cohorts, the cure rate of patients was inversely proportional to the number of patients receiving these drugs. However, this finding may be biased by the selection of sicker patients with more extensive disease and resistance to receive these second-line drugs. Although azithromycin and clarithromycin had low rates of adverse events, the lack of evidence for the efficacy of these drugs does not support their use for treatment of MDR-TB.

**Conclusion**

We found no evidence for efficacy of AMX–CLV, terizidone or macrolides in the treatment of MDR-TB. Although we found a low risk of toxicity with prolonged use of these drugs, the lack of evidence of their efficacy suggests a need to re-evaluate their inclusion in treatment regimens for MDR-TB. However, RCTs are required to properly assess the efficacy and safety of these drugs in the treatment of MDR-TB.


DOI: 10.1183/13993003.00649-2015