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Comparison of different treatments for isoniazid-resistant tuberculosis: an individual patient data meta-analysis

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Summary

Background—Isoniazid-resistant, rifampicin-susceptible (INH-R) tuberculosis is the most common form of drug resistance, and is associated with failure, relapse, and acquired rifampicin resistance if treated with first-line anti-tuberculosis drugs. The aim of the study was to compare success, mortality, and acquired rifampicin resistance in patients with INH-R pulmonary tuberculosis given different durations of rifampicin, ethambutol, and pyrazinamide (REZ); a fluoroquinolone plus 6 months or more of REZ; and streptomycin plus a core regimen of REZ.

Methods—Studies with regimens and outcomes known for individual patients with INH-R tuberculosis were eligible, irrespective of the number of patients if randomised trials, or with at least 20 participants if a cohort study. Studies were identified from two relevant systematic reviews, an updated search of one of the systematic reviews (for papers published between April 1, 2015, and Feb 10, 2016), and personal communications. Individual patient data were obtained from authors of eligible studies. The individual patient data meta-analysis was performed with propensity score matched logistic regression to estimate adjusted odds ratios (aOR) and risk differences of treatment success (cure or treatment completion), death during treatment, and acquired rifampicin resistance. Outcomes were measured across different treatment regimens to assess the effects of: different durations of REZ (≤6 months *vs* >6 months); addition of a fluoroquinolone to REZ (fluoroquinolone plus 6 months or more of REZ *vs* 6 months or more of REZ); and addition of streptomycin to REZ (streptomycin plus 6 months of rifampicin and ethambutol and 1–3 months of pyrazinamide *vs* 6 months or more of REZ). The overall quality of the evidence was assessed using GRADE methodology.

Findings—Individual patient data were requested for 57 cohort studies and 17 randomised trials including 8089 patients with INH-R tuberculosis. We received 33 datasets with 6424 patients, of which 3923 patients in 23 studies received regimens related to the study objectives. Compared with a daily regimen of 6 months of (H)REZ (REZ with or without isoniazid), extending the duration to 8–9 months had similar outcomes; as such, 6 months or more of (H)REZ was used for subsequent comparisons. Addition of a fluoroquinolone to 6 months or more of (H)REZ

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Contributors

DM, FF, and DF designed the study and protocol. All authors (except DM, PZL, AB, FF, ZYL, and DF) contributed individual patient data. FF, DM, PZL, AB, and ZYL analysed the data. DM and FF wrote the initial draft of the manuscript. All authors provided critical input and revisions to drafts of the manuscripts, and approved the final manuscript.

See **Online** for appendix

Declaration of interests

We declare no competing interests.

was associated with significantly greater treatment success (aOR 2·8, 95% CI 1·1–7·3), but no significant effect on mortality (aOR 0·7, 0·4–1·1) or acquired rifampicin resistance (aOR 0·1, 0·0–1·2). Compared with 6 months or more of (H)REZ, the standardised retreatment regimen (2 months of streptomycin, 3 months of pyrazinamide, and 8 months of isoniazid, rifampicin, and ethambutol) was associated with significantly worse treatment success (aOR 0·4, 0·2–0·7). The quality of the evidence was very low for all outcomes and treatment regimens assessed, owing to the observational nature of most of the data, the diverse settings, and the imprecision of estimates.

Interpretation—In patients with INH-R tuberculosis, compared with treatment with at least 6 months of daily REZ, addition of a fluoroquinolone was associated with better treatment success, whereas addition of streptomycin was associated with less treatment success; however, the quality of the evidence was very low. These results support the conduct of randomised trials to identify the optimum regimen for this important and common form of drug-resistant tuberculosis.

Introduction

One of several major challenges impeding global tuberculosis control is the steady increase in the prevalence and severity of drug resistance.[1] WHO has estimated that 17% of isolates from patients newly diagnosed with tuberculosis have some form of drug resistance.[2] Globally, the most common form of drug-resistant tuberculosis is isoniazid-resistant, rifampicin-susceptible (INH-R) tuberculosis, which is estimated to account for 8% of all new cases.[3] In most low-income and middle-income countries, access to drug susceptibility testing is very limited, so both new and previously treated patients receive standardised regimens with first-line tuberculosis drugs. The expanded access to the Xpert MTB/Rif assay means that INH-R tuberculosis will continue to be missed because this test does not identify the mutations (in KatG and INHa)[4] associated with INH-R tuberculosis. A 2016 systematic review[5] estimated that treatment of patients with unrecognised INH-R tuberculosis with the standard regimen recommended for new cases[6] would result in combined failure and relapse occurrence of 16%, and an 8% incidence of acquired rifampicin resistance.

Despite INH-R tuberculosis' frequent occurrence and major effect on outcomes, the disease has received remarkably little therapeutic research. The last randomised trial[7] specifically investigating treatments for INH-R tuberculosis was published more than 20 years ago; in that trial, the best regimen, of three tested, resulted in failure or relapse in more than 11% of patients. The previously recommended retreatment regimen, designed to manage INH-R tuberculosis, was never tested in a randomised trial.[8] As such, the optimum regimen composition, particularly regarding the use of fluoroquinolones, and duration of treatment remain controversial.[3,6,9–11]

We conducted a systematic review and meta-analysis of individual patient data of the treatment of patients with INH-R tuberculosis to address three main questions: (1) what is the optimum duration of a daily regimen of REZ (rifampicin, ethambutol, and pyrazinamide); (2) would the addition of a fluoroquinolone to 6 months or more of REZ be beneficial (and as a subquestion, would the addition of a fluoroquinolone to a regimen of 6 months or more of rifampicin plus ethambutol but only 1–3 months of pyrazinamide

be beneficial); and (3) would the addition of streptomycin to a core regimen of 6 or more months of rifampicin plus ethambutol but only 1–3 months of pyrazinamide be beneficial (essentially the regimen formerly recommended by WHO for retreatment)? The benefit of including isoniazid in each of these regimens was also addressed. We assessed treatment success (cure or completion), death (from any cause) during treatment, failure or recurrence of disease after success, and acquired rifampicin resistance.

Methods

Search strategy and selection criteria

Randomised controlled trials and observational trials were eligible for inclusion in this systematic review. Only studies that were published after Jan 1, 1990, were eligible, reasoning that studies published before this date would be unlikely to have used fluoroquinolones, the effect of which was one of our main objectives. Other specific criteria for inclusion were that the study authors agreed to share their data; that the regimens and outcomes were known for individual patients; and at least 20 participants were treated for INH-R tuberculosis if a cohort study. Randomised trials that included patients with INH-R tuberculosis were eligible irrespective of the number of patients.

We defined INH-R tuberculosis as tuberculosis with isolates with phenotypic resistance to isoniazid, and susceptibility to rifampicin, with or without additional resistance to pyrazinamide, ethambutol, or streptomycin.

Regimens of interest for this analysis were REZ, REZ plus a fluoroquinolone, and REZ plus streptomycin (all with or without isoniazid). We excluded patients who did not receive any of the regimens specified.

The outcomes included in this analysis were: (1) treatment success (cure or treatment completion[12]) compared with treatment failure or relapse combined; (2) acquired rifampicin resistance in patients with failure or relapse; and (3) death from any cause during tuberculosis treatment compared with success, failure, and relapse combined.

Studies were identified from the following sources: the search of a published systematic review on pulmonary INH-R tuberculosis (completed on March 31, 2015, and published online in 2016);[5] an updated search up to Feb 10, 2016, using the same search terms and databases as the systematic review published in 2017;[5] a review on INH-R tuberculosis in children;[13] personal communications from authors of studies identified through the searches and earlier reviews, and personal communications from authors responding to an invitation at a WHO European regional resistant tuberculosis surveillance meeting. Two authors (DM and FF) screened the sources for inclusion; consensus was reached in all cases. We wrote to authors of potentially eligible studies to request individual participant data. Authors that agreed to share data signed formal data-sharing agreements.

Data analysis

De-identified patient-level information was obtained from an online data-sharing platform (Platform for Aggregations of Clinical TB Studies initiative[14]) or directly from the

authors. This information included demographic data, clinical characteristics (comorbidities including HIV, site and extent of tuberculosis disease, results of chest radiography, and smear microscopy), and pretreatment drug susceptibility testing. Treatment information included drugs given, duration, end of treatment outcomes, and adverse events. Individualised regimens were tailored to individual patients' characteristics, and drug susceptibility testing results. Centre-level information included diagnostic laboratory methods, usual treatment doses and supervision, and treatment outcome definitions. Relapse was defined as any recurrence of disease within 2 years after successful treatment. In studies that distinguished re-infection from relapse using molecular methods, re-infections were excluded.[12]

Variables from each dataset were mapped to a common set of variables for all patients. These variables were verified by comparing the clinical characteristics of each study population with description of these characteristics in the published papers.

The outcome of adverse events from anti-tuberculosis drugs was intended to be assessed, but could not be analysed because these outcomes were either not reported or reported with very different definitions.

Because the studies included in the individual patient data meta-analysis were mainly observational, we assessed bias and quality using eight criteria. These were two critical criteria (sampling method and outcome definition) and six important criteria (participation rate, attrition rate, completeness of information for age, HIV status, cavity at chest-x ray, and smear). We regarded studies as being high quality if they met both critical criteria and at least four important criteria (appendix pp 12–13); as being moderate quality if they met one critical criterion and at least four important criteria, or two critical criteria and at least three important criteria; and as low quality if they did not meet the requirements for being high or moderate quality. We assessed overall quality of the evidence from this individual patient data meta-analysis following the GRADE criteria.[15]

All analyses excluded patients who did not complete treatment because of patient decision, or whose outcomes were unknown (lost contact with patient, transfer out, or other). For individualised regimens, we estimated the actual duration from dates when drugs were started and stopped. For standardised regimens or randomised trials, if actual treatment duration was not available, we used the planned duration. We could not analyse the treatment duration if the outcome was death, which could occur at any time during treatment, because the duration of therapy was determined by the outcome. However, the analysis of mortality was restricted to the same datasets used for the analysis of treatment success (ie, studies in which the regimens used and durations of regimens corresponded to the study questions).

We used propensity score matching[16] (caliper method with a difference of 0·02 allowed, 1:1 matching with replacement) based on age, sex, HIV co-infection, acid fast bacilli smear, past history of tuberculosis treatment, and resistance to other first-line drugs, if the drug was used.

We used a random-effects (random intercept and random slope for matched pairs) model (using Proc GLIMMIX in SAS) to estimate adjusted odds ratios (aOR) and 95% CI of the three outcomes. We calculated risk differences using fixed-effects generalised linear models with identity link, adjusted for the propensity score. To test for heterogeneity of effect across studies, we used a generalised linear mixed model with a simulation-based approach specifically for the individual patient data meta-analysis, to calculate the I^2 statistic.[17]

For all outcomes and all questions, we performed sensitivity analyses that were restricted to the subgroup of patients who had not received isoniazid; restricted to the subgroup with cavitation on chest radiography; stratified by country income level (high-income countries *vs* low-income or middle-income countries); and, for the fluoroquinolone questions, restricted to patients who received levofloxacin or moxifloxacin. All analysis was performed using SAS, version 9.4 (SAS Institute, Carey, NC, USA).

This project was approved by an ethics committee of the McGill University Health Center Research Institute (14274BMB) and by local ethical review boards when necessary. The study protocol is available upon request.

Role of the funding sources

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We considered all studies on INH-R tuberculosis that were included in a systematic review[5] to be eligible for inclusion (33 trials and 19 cohort studies). We re-reviewed the 49 excluded studies from this systematic review, and identified 20 that had been excluded because regimens were individualised, multiple regimens had been used without stratifying results by regimen, some extra-pulmonary tuberculosis cases were included, or outcomes for INH-R tuberculosis were mixed with other resistance patterns. We thought these studies might have suitable individual data, and so wrote to these authors. 95 studies included in the review[13] on INH-R tuberculosis in children were considered eligible. We identified seven additional studies published after March 31, 2015, through the updated search.[5] Five of the contacted authors provided additional unpublished datasets; three have since been published.[18–20] Three regional or national surveillance datasets were provided by those responding to an invitation to all participants at a WHO European regional resistant tuberculosis surveillance meeting (Viiklepp P, unpublished; Skrahina A, unpublished; Erkens C, Akkermann OW, unpublished). De-identified patient-level information was obtained from an online data-sharing platform (Platform for Aggregations of Clinical TB Studies initiative[14]) for two studies, and directly from the authors for the remainder.

74 studies (57 observational studies and 17 randomised controlled trials) were identified as potentially eligible (figure), with an expected population of 8089 patients with INH-R tuberculosis. We received 33 datasets (27 from observational studies and six from randomised controlled trials) with adequate treatment and outcome information for 5502

patients with pulmonary INH-R tuberculosis. In ten datasets, with 762 patients, no patients received any of the regimens of interest (Cegielski P, Griffith D, unpublished);[18,21–28] in the remaining 23 datasets (Ahuja SD, Trieu L, unpublished; three other unpublished [CE, OWA; AS; PV]),[19,20,29–46] 3923 patients received one of the regimens of the study questions and 817 patients received other regimens. The characteristics of the patients from the 23 centres are summarised in the appendix (pp 1–3). 15 studies (four unpublished [CE, OWA; AS; PV; SDA, LT])[19,29–31,33,35,37–39,41,44] contributed data for the question of duration of (H)REZ (REZ with or without isoniazid), 15 studies for the question of addition of a fluoroquinolone to (H)REZ (three unpublished [CE, OWA; SDA, LT; AS]),[19,29–31,33,35,37–39,41,44,46] 15 studies to the related question of a fluoroquinolone plus only 1–3 months of pyrazinamide (three unpublished [CE, OWA; AS; SDA, LT]),[19,29–31,33,35,37–39,41,44,46] and all 23 studies for the question of addition of streptomycin (three unpublished [CE, OWA; AS; PV]).[19,20,29–39,40–46] The characteristics of the populations compared in each of the main analyses are summarised in the appendix (pp 16–19). The regimens received by the 817 excluded patients from these centres are listed in the appendix (p 4). This included 139 patients who received high-dose isoniazid (450 mg per day or more) who could not be analysed because they received several accompanying regimens. The characteristics of the 762 patients in the ten studies in which all patients were excluded are summarised in the appendix (pp 14–15).

Isoniazid resistance was defined as a critical concentration of 0·1 μg/mL or 0·2 μg/mL in 21 centres, 0·25 μg/mL in one study, and 0·2 μg/mL or 1·0 μg/mL in one study. The outcome definitions and drug doses given were in accordance with WHO guidelines (appendix pp 5–11). Daily regimens were used in all but one study.[44] Therapy was directly supervised throughout treatment for 2018 patients in 14 centres. Actual duration of therapy was known in 16 studies (2422 participants, of whom duration was not known in 15), and planned duration in the remaining seven studies (1501 participants). Overall, 345 (9%) of all 3923 patients were either lost to follow-up, transferred out of the respective study without known outcome, or decided to stop therapy (patient decision). In 19 of 23 studies, recurrence or relapse was measured during follow-up, which exceeded 1 year in about two-thirds of patients; only two of these centres[29,34] used molecular methods to identify re-infection. Quality assessments are summarised in the appendix (pp 12–13); on the basis of the criteria selected, quality was deemed to be low in one study, moderate in four, and high in the remainder.

The analysed population included only 37 children, 119 patients with diabetes, and 249 patients with HIV infection with or without antiretroviral treatment; these small numbers precluded separate analyses, for any study questions, within these subgroups.

Our first question concerned the optimum duration of (H)REZ. Patients receiving 6 months of (H)REZ were older, more likely to be treated in high-income countries, and less likely to have positive acid-fast bacilli smears than patients receiving more than 6 months (H)REZ (appendix p 16).

The effect of treatment duration on mortality could not be assessed because duration of therapy was truncated by death. No significant difference was found between the 6 month

(H)REZ regimen and the more than 6 months (H)REZ regimen for the outcomes of success or acquired rifampicin resistance (table 1). When patients taking isoniazid (at usual doses) for at least 1 month were excluded, outcomes were similar (table 1). As such, we combined all individuals who received 6 months or more of REZ, with or without isoniazid (usual doses), as the comparator group for all analyses.

Our second question concerned the optimum use of a fluoroquinolone. In total, 251 patients received a fluoroquinolone for at least 1 month in addition to at least 6 months of REZ, of whom 165 received a later generation fluoroquinolone. Clinical characteristics were very similar between patients who received 6 months or more of (H)REZ plus a fluoroquinolone and patients who received 6 months or more of (H)REZ without a fluoroquinolone, except that 513 (98%) of 524 patients given a fluoroquinolone were treated in high-income countries (appendix p 17).

The 251 patients who received a fluoroquinolone had significantly higher odds of treatment success than patients who did not, but no significant difference was found between groups for acquired resistance to rifampicin or mortality (table 2). Estimates of effect were similar, and non-significant, when restricting the analysis to the subgroup of patients who did not receive isoniazid or patients who received only later generation fluoroquinolone.

Only 118 patients received a fluoroquinolone plus 6 or more months of rifampicin and ethambutol plus 1–3 months of pyrazinamide; of these patients, 105 received a later generation fluoroquinolone. This population was substantially older and less likely to have cavitation or positive acid-fast bacilli smears than the comparison group (appendix p 18). In these patients, there was no significant difference in success when a fluoroquinolone was added, with similar results in the analysis that was restricted to patients given a later generation fluoroquinolone (table 3). The estimates of effect in this population were very imprecise because of the small number of patients who received this regimen.

Our third question concerned the optimum use of streptomycin. The 325 individuals who received the standardised retreatment regimen were more likely to have cavitary disease, poly-drug resistance, or previous tuberculosis treatment (reflecting the usual indication for this regimen), compared with the 1350 who received 6 months or more of (H)REZ (appendix p 19).

The streptomycin-containing regimens were associated with significantly lower odds of success when all patients were considered; however, in the analysis that was restricted to patients who did not receive isoniazid, no significant difference between groups was found for success (table 4). Mortality was virtually identical in patients who did or did not receive streptomycin in analyses with and without patients receiving isoniazid. An insufficient number of patients was available to analyse acquired rifampicin resistance.

Stratified analyses by country income level were limited by the fact that some treatments (ie, 6 months of REZ plus fluoroquinolones) were predominantly used in centres in high-income countries, whereas streptomycin was used almost exclusively in low-income and middle-income countries. In analyses restricted to studies in high-income countries, 6 months of REZ was associated with very similar outcomes compared with the longer duration of REZ,

and the addition of a fluoroquinolone had no significant effect on success (appendix p 20). When analyses were restricted to low-income and middle-income countries, streptomycin-containing regimens had no significant effect on success and mortality (appendix p 21).

The analyses restricted to patients with cavitation on chest radiography found the addition of a fluoroquinolone or streptomycin to be no more or less beneficial than in the primary analyses (appendix p 22–23). Finally, the duration of the fluoroquinolone did not seem to be a determinant of success (appendix p 24). Even though most studies were deemed high quality, we considered the risk of bias to be high because all but two studies were observational, and most provided individualised treatment. Estimates of effect were generally imprecise with wide confidence intervals because of the small number of patients receiving the regimens of interest. We also have concerns over the directness of the findings regarding the fluoroquinolones to low-income and middle-income settings, and regarding the streptomycin analyses to high-income settings. Hence, overall the evidence from this individual patient data meta-analysis should be considered of very low quality.

In general, in analyses of heterogeneity (ie, estimated I^2 from a generalised linear mixed model adjusted for the same confounding factors used in the propensity score matching) in which I^2 was estimable, heterogeneity was low (<50%; tables 1–4).

Discussion

We assembled a large set of individual data of patients with INH-R tuberculosis, mostly from observational studies. This study fills an important knowledge gap on the relative efficacy of different regimens to treat INH-R-tuberculosis. Compared with a core regimen containing REZ, addition of a fluoroquinolone was associated with significantly higher odds of success, whereas a treatment regimen with streptomycin added in the first months of treatment and a shorter pyrazinamide treatment period (the retreatment regimen) was associated with worse results.

This study had a number of important strengths. Individual data for a large number of patients with mono-resistance or poly-resistance to isoniazid were assembled. Treatment outcomes were defined according to published recommendations.[12] Data were contributed from 23 centres in 18 countries from a wide range of resource levels, enhancing generalisability of results. Having individual patient data meant we could adjust for measured confounding patient characteristics such as age, previous treatment, HIV, sputum smear, and additional resistance.

Nevertheless, the study also had important limitations. Despite extensive efforts to assemble the largest possible number of patients treated for INH-R tuberculosis, the numbers of patients who received certain regimens of interest, such as the fluoroquinolone with only 1–3 months of pyrazinamide treatment, were very small, providing limited power, or, as was the case with high-dose isoniazid, simply too few participants to perform any analyses. Laboratory methods were not standardised across centres, and although most centres used the same critical concentration, other differences in laboratory methods might have contributed to between-centre differences in outcomes, resulting in reduced precision.

All studies used phenotypic methods to perform drug susceptibility testing, which might underestimate rifampicin resistance and could have affected results.[47] Relapse might have been overestimated because it was distinguished from re-infection using molecular methods in only two of the 19 studies that reported recurrence. We did not include patients lost to follow-up (during treatment) in any analysis because of their uncertain outcomes; fortunately, this accounted for 10% of all patients in the 23 studies (appendix p 3).

All but two[44,45] of the 23 studies included in the analyses were observational. Ten studies used individualised regimens, which might lead to confounding by indication because sicker patients might have been more or less likely to receive certain drugs or durations. The most important limitation is that the regimens used, particularly use of streptomycin or a fluoroquinolone, might have been confounded with differences in patient or centre characteristics, such as country income level. Despite adjustment for individual-level characteristics, residual confounding might have occurred due to unmeasured differences in patient characteristics such as nutritional status. Additionally, treatment given at different centres might have been confounded with differences between centres, such as resources available for patient support. To account for these differences, we did sensitivity analyses restricted to studies from high-income or low-income and middle-income countries only. For most of these analyses, estimates of effect were similar, but less precise, due to fewer studies and patients included.

Additional limitations were the small number of children, patients with HIV, and patients with diabetes, limiting generalisability to these important groups of patients. Less than half the studies reported acquired rifampicin resistance during treatment; the resulting smaller numbers limit our inferences for this outcome. The effect of treatment duration on mortality could not be assessed because duration of therapy was truncated by death. A final limitation was that adverse drug reactions could not be analysed, as planned, because these were not reported or were reported using widely varying definitions, methods of investigation, and management. Non-standardised reporting of adverse events in the treatment of drug-resistant tuberculosis has been noted in other reviews of drug-resistant tuberculosis treatment.[48,49] Overall, the quality of evidence was rated as very low for all regimens using GRADE methodology.

The study has several important implications for treatment of INH-R tuberculosis or of patients in whom isoniazid cannot be used. First, these findings emphasise the importance of detecting this form of drug resistance. Second, the regimen of 6 months of REZ provides good results in patients with INH-R tuberculosis; more than 6 months of this regimen was not associated with improved outcomes. This study provides evidence of benefit from adding a fluoroquinolone to a core regimen that includes REZ, although the optimum duration and specific type of fluoroquinolone have not been clarified. Given that pyrazinamide is the most toxic of the present first-line drugs,[50] the major advantage of adding a fluoroquinolone would be if pyrazinamide could be reduced to the initial 2 months. Because of the small number of patients who received this regimen, the imprecision of results precludes firm conclusions, but the promising results motivate further evaluation. An additional implication of this study is that the standardised retreatment regimen[8] seems to be of limited benefit in patients with confirmed INH-R tuberculosis. A final treatment

implication is that isoniazid at normal doses is of minimal benefit in patients with INH-R tuberculosis, even with the use of the low critical concentration of 0·1–0·25 μg/mL to define resistance with drug susceptibility testing. Response to treatment might vary according to genotypic forms of isoniazid resistance;[51] as such, complete genotypic information would be informative in future studies.

We conclude that, for the treatment of INH-R tuberculosis, addition of a fluoroquinolone to a core regimen of 6 months of daily REZ seems to provide optimum outcomes, although we could not define the best fluoroquinolone, the optimum duration of fluoroquinolone, or the optimum duration of pyrazinamide. Addition of isoniazid and prolongation of daily REZ beyond 6 months seem to provide no benefits. Addition of streptomycin, particularly the streptomycin-containing retreatment regimen previously recommended, was associated with significantly worse treatment success. These results, based on observational data, must be considered very low-quality evidence, and so are insufficient to support strong treatment recommendations. However, the results do strongly support the conduct of randomised trials to identify the optimum regimen for this important and common form of drug-resistant tuberculosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in context

Evidence before this study

Drug-resistant tuberculosis is one of the major challenges impeding global tuberculosis control. Isoniazid-resistant, rifampicin-susceptible (INH-R) tuberculosis is the most common form of drug-resistant tuberculosis. In settings where drug susceptibility testing is not accessible or there is access only to Xpert MTB/RIF assay, INH-R tuberculosis will be missed and treated with standard regimens. Despite the frequent occurrence of INH-R tuberculosis and its major effect on outcomes, remarkably little research on therapy for INH-R tuberculosis has been done. As such, the optimum regimen for INH-R tuberculosis, including use of fluoroquinolones and duration of treatment, remains controversial. We built this individual patient data meta-analysis upon a 2017 systematic review and aggregate data meta-analysis, in which four electronic databases (Cochrane Database of Systematic Reviews and randomised trials, PubMed, Embase, and HealthStar) were searched with the terms “tuberculosis” AND “treatment” OR “therapy” AND “INH” OR “isoniazid resistance” for prospective or retrospective cohorts or randomised clinical trials published in English, French, or Spanish between Jan 1, 1948, and March 31, 2015. The systematic review found that treatment of patients with unrecognised INH-R tuberculosis with the standard regimen recommended for newly diagnosed patients would result in combined failure and relapse rates of 16%, and 8% of patients would acquire rifampicin resistance. All studies included in this review were deemed eligible for the individual patient data meta-analysis. We added previously excluded studies that might have been suitable for individual data analysis, plus studies included in a review on INH-R tuberculosis in children, and seven additional studies published after May 31, 2015, identified from an updated search finalised on Feb 10, 2016, using the same search terms and databases and eligibility criteria as the original review. Additionally, five of the authors contacted for papers identified during the systematic review provided other unpublished datasets (three now published), and three regional or national surveillance datasets were provided by authors responding to an invitation to all participants at a WHO European regional resistant tuberculosis surveillance meeting.

Added value of this study

To our knowledge, this is the first individual patient data meta-analysis on treatment outcome for INH-R tuberculosis. Individual-level data were compiled from 33 studies, and among 23 of these studies (21 cohorts and two randomised clinical trials), a total of 3923 patients received one of the regimens of interest. We assessed bias using an eight-item scale: two critical criteria (sampling method and outcome definition) and six important criteria (participation rate, attrition rate, completeness of information for age, HIV status, cavity at chest-x ray, and smear). On the basis of these criteria, the quality was judged low in one study, moderate in four, and high in the remainder.

Compared with 6 months of REZ (rifampicin, ethambutol, and pyrazinamide), longer duration of REZ did not result in significantly improved treatment success or less acquired drug resistance. Addition of a fluoroquinolone to a core regimen of at least 6

months of REZ was associated with improved success and less acquired drug resistance, but no difference in mortality. Addition of a fluoroquinolone to a regimen with 2–3 months of pyrazinamide plus 6 or more months of rifampicin and ethambutol had no significant effect on success. The retreatment regimen (streptomycin added to 6 months of rifampicin and ethambutol plus 1–3 months of pyrazinamide) was associated with significantly worse success compared with at least 6 months of REZ.

Implications of all the available evidence

The findings of this study emphasise the importance of detecting INH-R tuberculosis and support the use of a fluoroquinolone in addition to a core regimen of 6 months of REZ. The addition of isoniazid, and prolongation of REZ beyond 6 months, seem to provide no benefits for this condition. Our results support a move away from the use of the streptomycin-containing retreatment regimens previously recommended. Because of the observational nature of the data, these results are graded very low quality evidence; as such, these results are insufficient to support strong treatment recommendations. However, the results do support the conduct of randomised trials to define the optimum treatment of this common and overlooked condition, particularly to assess the optimum type and duration of fluoroquinolone treatment and the optimum duration of pyrazinamide treatment.

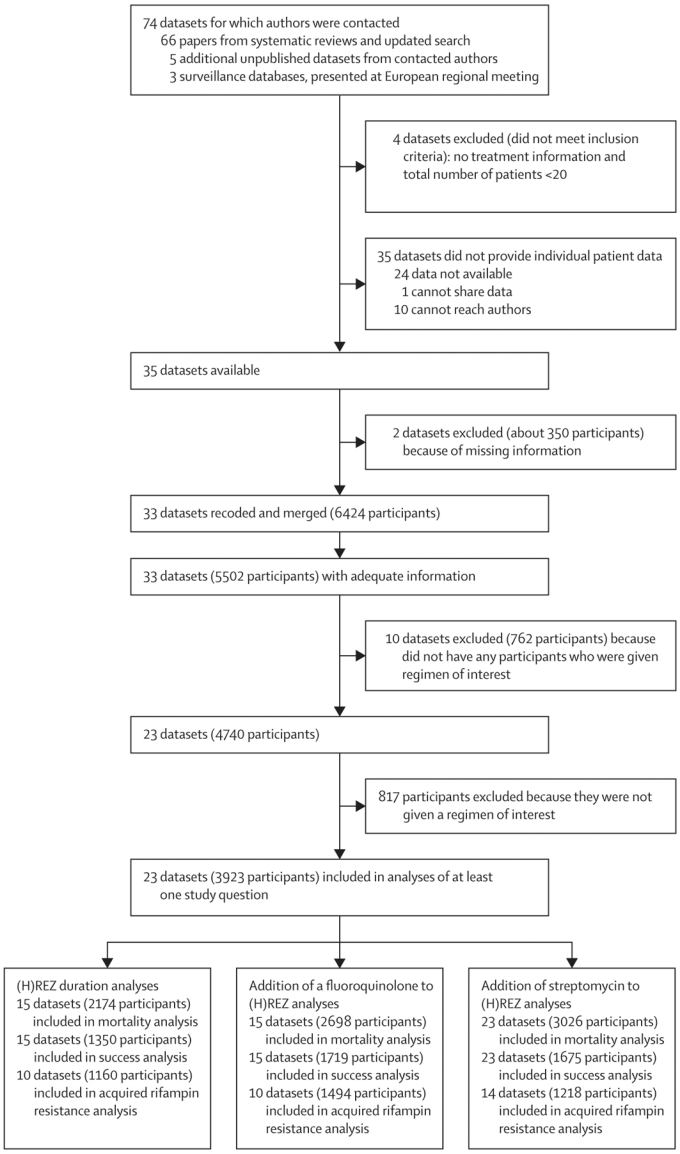

Figure: Study selection

(H)REZ=rifampicin, ethambutol, and pyrazinamide, with or without isoniazid.

Table 1:

Treatment success and acquired rifampicin resistance of different durations of daily regimen of rifampicin, ethambutol, and pyrazinamide, with or without isoniazid

	Regimen	Number of datasets included	Number of events/number of patients on treatment	I^2 *	Number of pairs used†	Propensity score matched analysis‡	
						aOR (95% CI)	Risk difference per 1000 patients treated (95% CI)
Analyses in all patients (with or without isoniazid)							
Success	6(H)REZ	15	254/262	NE§	262	2·4 (1·0 to 5·5)	40 (0 to 80)
Success	>6(H)REZ	NA	999/1088	NA	NA	1 (ref)	0 (ref)
Acquired rifampicin resistance	6(H)REZ	10	1/168¶	NE§	168	0·2 (0·0 to 1·7)	−10 (−60 to 40)
Acquired rifampicin resistance	>6(H)REZ	NA	43/992¶	NA	NA	1 (ref)	0 (ref)
Patients who received isoniazid excluded							
Success	6REZ	13	136/142	36%	140	2·5 (0·9 to 7·5)	50 (−10 to 100)
Success	>6REZ	NA	701/785	NA	NA	1 (ref)	0 (ref)
Acquired rifampicin resistance	6REZ	8	0/84	NE§	84	NE	NE
Acquired rifampicin resistance	>6REZ	NA	43/729	NA	NA	1 (ref)	0 (ref)

aOR=adjusted odds ratio. (H)REZ=daily regimen of rifampicin, ethambutol, and pyrazinamide, with or without isoniazid. 6(H)REZ=6 months of (H)REZ. >6(H)REZ=more than 6 months of (H)REZ. REZ=daily regimen of rifampicin, ethambutol, and pyrazinamide. 6REZ=6 months of REZ. >6REZ=more than 6 months of REZ. NE=not estimable. NA=not applicable.

*I^2 estimated for the aOR using a generalised linear mixed model with a simulation-based approach specifically for the individual patient data meta-analysis.[21]

†Number of pairs used in propensity score matched analysis; for example, 262 patients who received 6(H)REZ and an equal number who received the comparator were analysed for the outcome of success.

‡Estimates based on pairs matched for age, sex, HIV status, past tuberculosis treatment, sputum acid-fast bacilli smear (positive *vs* negative), and resistance to other drugs besides isoniazid, if used. Some patients were missing information for these variables: past tuberculosis treatment (n=111 [8%]); acid-fast bacilli smear (n=27 [2%]); HIV (n=114 [8%]); polyresistance, age, and sex (n=0 [0%]). HIV status was missing, but assumed to be negative, in three studies (720 patients) in settings in which the prevalence of HIV co-infection in patients with active tuberculosis was less than 5% based on WHO surveillance data.

§The I^2 could not be calculated because the τ^2 (on which the I^2 is based) was not estimated in SAS.

¶Number of patients treated is less than that used in the success analysis because patients who did not respond to treatment or relapsed but who did not have acquired drug resistance or non-rifampicin-acquired resistances were excluded from this analysis.

Table 2:

Association of use of fluoroquinolones with treatment success, mortality, and acquired rifampicin resistance

	Regimen	Number of datasets included	Number of events/ number of patients on treatment	I^2 *	Number of pairs used†	Propensity score matched analysis‡	
						aOR (95% CI)	Risk difference per 1000 patients treated (95% CI)
Analyses in all patients (with or without isoniazid)							
Mortality (all durations)	(H)REZ +FQ	15	25/524	12%	522	0·7 (0·4 to 1·1)	−20 (−50 to 0)
Mortality (all durations)	(H)REZ	NA	97/2174	NA	NA	1 (ref)	0 (ref)
Success	≥6(H)REZ + FQ	15	245/251	36%	248	2·8 (1·1 to 7·3)	50 (0 to 90)
Success	≥6(H)REZ	NA	1253/1350	NA	NA	1 (ref)	0 (ref)
Success (restricted to later generation FQ: Moxi/Levo/ Gati)	≥6(H)REZ + FQ	15	161/165§	44%	164	2·9 (0·9 to 9·3)	60 (−20 to 140)
Success (restricted to later generation FQ: Moxi/Levo/ Gati)	≥6(H)REZ	NA	1253/1350	NA	NA	1 (ref)	0 (ref)
Acquired rifampicin resistance	≥6(H)REZ + FQ	10	1/221¶	2%//	220	0·1 (0·0 to 1·2)	−30 (−60 to 0)
Acquired rifampicin resistance	≥6(H)REZ	NA	44/1160¶	NA	NA	1 (ref)	0 (ref)
Patients who received isoniazid excluded							
Mortality	REZ + FQ	14	8/219	0	205	0·4 (0·2 to 1·1)	−20 (−60 to 20)
Mortality	REZ	NA	41/1054	NA	NA	1 (ref)	0 (ref)
Success	≥6REZ + FQ	14	131/135	33%	127	5·4 (1·8 to 16·6)	130 (−40 to 230)
Success	≥6REZ	NA	837/927	NA	NA	1 (ref)	0 (ref)
Acquired rifampicin resistance	≥6REZ + FQ	9	1/111	NE**	107	0·1 (0·0 to 1·0)	−70 (−140 to 0)
Acquired rifampicin resistance	≥6REZ	NA	43/813	NA	NA	1 (ref)	0 (ref)

aOR=adjusted odds ratio. (H)REZ=daily regimen of rifampicin, ethambutol, and pyrazinamide, with or without isoniazid. FQ=fluoroquinolone. ≥6(H)REZ=6 months or more of (H)REZ. REZ=daily regimen of rifampicin, ethambutol, and pyrazinamide. ≥6REZ=6 months or more of REZ. NE=not estimable. NA=not applicable.

*I^2 estimated for the aORs using a generalised linear mixed model with a simulation-based approach specifically for the individual patients data meta-analysis.[21]

†Number of pairs used in propensity score matched analysis; for example, 248 people who received (H)REZ + FQ and an equal number who received the comparator were analysed for the outcome of success.

‡Estimates based on pairs matched for age, sex, HIV status, past tuberculosis treatment, sputum acid-fast bacilli smear (positive *vs* negative), and resistance to other drugs besides isoniazid, if used. Some patients were missing information for these variables: past tuberculosis treatment (n=213 [8%]); acid-fast bacilli smear (n=219 [8%]); HIV (n=222 [8%]); polyresistance, age, and sex (n=0 [0%]). HIV was

missing, but assumed to be negative in three studies (1164 patients) in settings in which the prevalence of HIV co-infection in patients with active tuberculosis was less than 5%, based on WHO surveillance data.

[§] Of 165 patients treated, 67 received isoniazid for 1 month or longer and 98 did not receive any isoniazid.

[¶] Number of patients treated is less than in the success analysis because patients who did not respond to treatment or relapsed but who did not have acquired drug resistance or non-rifampicin-acquired resistances were excluded from this analysis.

[//] This is an unadjusted I^2 value; an adjusted value could not be calculated.

[**] I^2 could not be calculated because the τ^2 (on which the I^2 is based) was not estimated in SAS.

Table 3:

Association of use of a fluoroquinolone plus 1–3 months of pyrazinamide with treatment success and acquired rifampicin resistance

	Regimen	Number of datasets included	Number of events/ number of patients on treatment	I^2 *	Number of pairs used in matching†	aOR (95% CI) from propensity score matched analysis‡	Risk difference per 1000 patients treated (95% CI)
Success (all FQ)	≥6(H)RE(1–3)Z + FQ	15	117/118§	NE¶	108	5·2 (0·6 to 46·7)	40 (−20 to 90)
Success (all FQ)	≥6(H)REZ	NA	1253/1350‖	NA	NA	1 (ref)	0 (ref)
Success (restricted to later generation FQ: Moxi/Levo/Gati)	≥6(H)RE(1–3)Z + FQ	15	104/105	NE¶	97	5·2 (0·6 to 47·2)	50 (−30 to 120)
Success (restricted to later generation FQ: Moxi/Levo/Gati)	≥6(H)REZ	NA	1253/1350	NA	NA	1 (ref)	0 (ref)
Acquired rifampicin resistance	≥6(H)RE(1–3)Z + FQ	10	0/113**	NE¶	..	NE	NE
Acquired rifampicin resistance	≥6(H)REZ	NA	44/1160**	NA	NA	1 (ref)	0 (ref)

Comparisons are between patients given ≥6(H)RE(1–3)Z + FQ compared with patients given ≥6(H)REZ (analyses were not done in patients who did not receive isoniazid because there were too few of these patients). aOR=adjusted odds ratio. FQ=fluoroquinolone. ≥6(H)RE(1–3)Z + FQ=6 months or more of a daily regimen of rifampicin plus ethambutol plus 1–3 months of pyrazinamide plus a fluoroquinolone, with or without isoniazid. ≥6(H)REZ=6 months or more of daily regimen of rifampicin, ethambutol, and pyrazinamide, with or without isoniazid. NE=not estimable. NA=not applicable.

*I^2 estimated for the aOR using a generalised linear mixed model with a simulation-based approach specifically for the individual patient data meta-analysis.[21]

†Number of pairs used in propensity score matched analysis; for example, 108 people who received ≥(H)6RE(1–3)Z + FQ and an equal number who received the comparator were analysed for the outcome of success.

‡Estimates based on pairs matched for age, sex, HIV status, past tuberculosis treatment, sputum acid-fast bacilli smear (positive *vs* negative), and resistance to other drugs besides isoniazid, if used. Some patients were missing information for these variables: past tuberculosis treatment (n=124 [7%]); acid-fast bacilli smear (n=55 [3%]); HIV (n=165 [10%]); polyresistance, age, and sex (n=0 [0%]). HIV was missing, but assumed to be negative in three studies (738 patients) in settings in which the prevalence of HIV co-infection in patients with active tuberculosis was less than 5% based on WHO surveillance data.

§Of 118 patients treated, 82 received isoniazid for 1 month or more and 36 did not receive isoniazid.

¶I^2 could not be calculated because the τ^2 (on which the I^2 is based) was not estimated in SAS.

‖Of 1350 patients treated, 423 had isoniazid for 1 month or more and 927 did not.

**Number of patients treated is less than in the success analysis because patients who did not respond to treatment or relapsed but who did not have acquired drug resistance or non-rifampicin-acquired resistances were excluded from this analysis.

Table 4:

Association of use of streptomycin with treatment success, mortality, and acquired rifampicin resistance

	Regimen	Number of datasets included	Number of events/number of patients on treatment	I^2 *	Number of pairs used†	Propensity score matched analysis‡	
						aOR (95% CI)	Risk difference per 1000 patients treated (95% CI)
Analyses done in all patients (with or without isoniazid)							
Mortality (all durations)	(H)REZ + SM	23	40/763	14%	756	0·9 (0·6 to 1·3)	−10 (−30 to 20)
Mortality (all durations)	(H)REZ	NA	103/2263	NA	NA	1 (ref)	0 (ref)
Success	≥6(H)RE(1–3)Z + 2SM	23	271/325	0	296	0·4 (0·2 to 0·7)	−120 (−190 to −60)
Success	≥6(H)REZ	NA	1253/1350	NA	NA	1 (ref)	0 (ref)
Acquired rifampicin resistance	≥6(H)RE(1–3)Z + 2SM	14	6/58§	NE¶	..	NE‖	
Acquired rifampicin resistance	≥6(H)REZ	NA	44/1160§	NA	NA	1 (ref)	0 (ref)
Patients who received isoniazid excluded							
Mortality	REZ + SM	14	6/136	NE¶	133	1·2 (0·4 to 4·1)	0 (−50 to 60)
Mortality	REZ	NA	41/1054	NA	NA	1 (ref)	NA
Success	≥6RE(1–3)Z + 2SM	14	89/107	NE¶	105	0·5 (0·2 to 1·2)	−80 (−170 to 10)
Success	≥6REZ	NA	837/927	NA	NA	1 (ref)	0 (ref)

The analysis of acquired rifampicin resistance was not performed in patients who did not receive isoniazid because there were too few of these patients. aOR=adjusted odds ratio. (H)REZ=daily regimen of rifampicin, ethambutol, and pyrazinamide, with or without isoniazid. SM=streptomycin. ≥6(H)RE(1–3)Z=6 months or more of a daily regimen of rifampicin plus ethambutol plus 1–3 months of pyrazinamide, with or without isoniazid. 2SM=2 months of streptomycin. ≥6(H)REZ=6 months or more of daily regimen of rifampicin, ethambutol, and pyrazinamide, with or without isoniazid. REZ=daily regimen of rifampicin, ethambutol, and pyrazinamide. NA=not applicable. NE=not estimable.

*I^2 estimated for the aORs using a generalised linear mixed model with a simulation-based approach specifically for the individual patient data meta-analysis.[21]

†Number of pairs used in propensity score matched analysis; for example, 296 people who received 6(H)REZ + SM and an equal number who received the comparator were analysed for the outcome of success.

‡Estimates based on pairs matched for age, sex, HIV, past tuberculosis treatment, sputum acid-fast bacilli smear (positive *vs* negative), and resistance to other drugs besides isoniazid, if used. Some patients were missing information for these variables: past tuberculosis treatment (n=366 [12%]); acid-fast bacilli smear (n=206 [7%]); HIV (n=199 [7%]); polyresistance (n=64 [2%]); age (n=33 [1%]); and sex (n=33 [1%]). HIV was missing, but assumed to be negative in six studies (1389 patients) in settings in which the prevalence of HIV co-infection in patients with active tuberculosis was less than 5% based on WHO surveillance data.

§Number of patients treated is less than in success analysis because patients who did not respond to treatment or relapsed but who did not have acquired drug resistance or non-rifampicin-acquired resistances were excluded from this analysis.

¶I^2 could not be calculated because the τ^2 (on which the I^2 is based) was not estimated in SAS.

//Propensity score matching models did not converge.