ICAP Journal Club

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Article

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Study Summary

The Tuberculosis Trials Consortium Study 31/AIDS Clinical Trials Group A5349 (Study 31/A5349) was a multicenter, randomized, open-label, phase 3, non-inferiority trial that compared the efficacy and safety of tuberculosis (TB) treatment regimens that included rifapentine, with or without moxifloxacin for 4 months, to the standard 6-month regimen in participants with drug-susceptible pulmonary TB.

Study Setting

- Thirty-four sites in Brazil, China (Hong Kong), Haiti, India, Kenya, Malawi, Peru, South Africa, Thailand, Uganda, the United States, Vietnam, and Zimbabwe.

Methods

- Participants were ≥12 years of age and had newly diagnosed smear- or Xpert MTB/RIF-positive pulmonary TB that was susceptible to isoniazid, rifampin, and fluoroquinolones.
- Persons with HIV infection were required to have a CD4 count of ≥100 cells/cubic millimeter.
- Participants were randomly assigned (1:1:1) to one of three regimens:
    - 8 weeks of once-daily rifampin, isoniazid, pyrazinamide, and ethambutol followed by 18 weeks of once-daily rifampin and isoniazid (control group);
    - 8 weeks of once-daily rifapentine, isoniazid, pyrazinamide, and ethambutol followed by 9 weeks of once-daily rifapentine and isoniazid (rifapentine group);
    - 8 weeks of once-daily rifapentine, isoniazid, pyrazinamide, and moxifloxacin followed by 9 weeks of once-daily rifapentine, isoniazid, and moxifloxacin (rifapentine-moxifloxacin group).
- Rifapentine was administered at a dose of 1200 mg/day and moxifloxacin at 400 mg/day. Other drugs were administered at standard doses adjusted for body weight. The medications in each regimen were administered seven days per week, including at least five days of in-person directly observed therapy per week.

- Randomization was stratified according to trial site, presence of cavitation on chest radiography and HIV status.
- Participants were evaluated at week 2, 4, 8, 12, 17, 22, 26 and then every three months from month 9 to 18. Sputum specimens were collected for mycobacterial cultures at all scheduled visits at or after week 17.
- Phenotypic testing of drug susceptibility to at least isoniazid, rifampin, and fluoroquinolones was performed on the *M. tuberculosis* isolates obtained at baseline and on the first of any isolates obtained at or after week 17.
- The primary efficacy outcome was survival free of TB at 12 months after randomization.
- The primary outcome status was determined for each participant as follows:
    - Favorable status was assigned if a participant was alive and free of TB at 12 months, had either an *M. tuberculosis*–negative result on sputum culture at month 12 or was unable to produce sputum, or produced sputum that was contaminated but without evidence of *M. tuberculosis*.
    - Unfavorable status was assigned if a participant had *M. tuberculosis*–positive cultures from two sputum specimens at or after week 17 without an intervening negative culture; died, withdrew, or was lost to follow-up during the treatment period with a positive culture when last seen; died from TB during post-treatment follow-up; or received additional treatment for TB.
    - Status was not assessable if a participant did not have an unfavorable outcome and met any of the following criteria: did not attend the month 12 visit but had a negative culture when last seen; had a change in treatment because of pregnancy; died from a cause unrelated to TB during the follow-up period; received additional treatment for TB after exogenous reinfection was identified; or died from an accident or violent cause during the treatment period.
- Other efficacy outcomes included time to stable conversion of sputum cultures to negative, defined as two negative cultures without an intervening positive culture.
- The primary safety outcome was an adverse event of grade 3 or higher with an onset during the on-treatment period, defined as the period during which the trial medications were administered and up to 14 days after the last dose.
- The primary efficacy analysis was performed in the microbiologically eligible and the assessable analysis populations.
    - The microbiologically eligible population included all the participants except those who had no evidence of *M. tuberculosis*–positive cultures, had TB that was resistant to isoniazid, rifampin, or fluoroquinolones, or who were enrolled in violation of the eligibility criteria.
    - The assessable population included participants in the microbiologically eligible population who met the criteria for favorable or unfavorable status with respect to the primary outcome.
- The non-inferiority margin was set at 6.6 percentage points.

Study Population and Follow-up

- Between January 2016 and October 2018, 5,124 people underwent screening and 2,516 were assigned to a treatment group.
- Of these, 173 participants were excluded from the microbiologically eligible population, which comprised 2,343 participants (768 in the control group, 791 in the rifapentine–moxifloxacin group and 784 in the rifapentine group).
- The assessable population comprised 2,234 participants (726 in the control group, 756 in the rifapentine–moxifloxacin group and 752 in the rifapentine group).
- The baseline demographic and clinical characteristics of the participants were similar in the three treatment groups. The median age of participants was 31 years (range 13 to 81), 71% were male, 72% were Black, 8% were HIV-positive, 77% had cavitation on chest radiography and 11% had a prior course of TB treatment.
- Among the microbiologically eligible population, 94.8% in the control group, 96.0% in the rifapentine–moxifloxacin group, and 96.2% in the rifapentine group were retained in the trial through the end of the 12-month follow-up or were known to have died during this period.

Efficacy Outcomes

- The rifapentine–moxifloxacin regimen was found to be non-inferior to the control regimen for both analysis populations.
    - In the microbiologically eligible population, an unfavorable outcome occurred in 15.5% of participants in the rifapentine–moxifloxacin group and in 14.6% of those in the control group (adjusted absolute difference 1.0%; 95% confidence interval [CI] −2.6 to 4.5).
    - In the assessable population, an unfavorable outcome occurred in 11.6% of the rifapentine–moxifloxacin group and in 9.6% of the control group (adjusted absolute difference 2.0%; 95% CI −1.1 to 5.1).
- The rifapentine regimen was not shown to be non-inferior to the control regimen in either analysis population, with an adjusted absolute difference of 3.0% (95% CI −0.6 to 6.6) in the microbiologically eligible population and 4.4% (95% CI 1.2 to 7.7) in the assessable population.
- Sensitivity analyses, including in the per-protocol and intention-to-treat populations, were consistent with the findings in the primary analyses.
- The time to stable conversion of sputum cultures to negative was shorter in the 4-month regimen groups, with hazard ratios for liquid media of 1.4 (95% CI 1.2 to 1.5) in the rifapentine–moxifloxacin group and 1.3 (95% CI 1.2 to 1.4) in the rifapentine group, compared to the control group.
- Among the participants in the microbiologically eligible population, culture conversion in liquid media occurred by 8 weeks in 63.4% of those in the control group, 78.5% of those in the rifapentine–moxifloxacin group, and 74.2% of those in the rifapentine group.

Safety Outcomes

- There was no difference found in the occurrence of grade 3 or higher adverse events during the on-treatment period between the rifapentine–moxifloxacin group and the control group (18.8% vs. 19.3%; adjusted difference −0.6%; 95% CI −4.3 to 3.2).
- The percentage of participants who had a grade 3 or higher adverse event during the on-treatment period was lower in the rifapentine group (14.3%) than in the control group (adjusted difference −5.1%; 95% CI −8.7 to −1.5).
- All-cause mortality during the on-treatment period was similar across the treatment regimens (0.8% in the control group, 0.4% in the rifapentine–moxifloxacin group, and 0.5% in the rifapentine group).
- In looking at adverse events known to be associated with a medication, the percentage of participants with grade 3 or higher transaminase levels was similar across the treatment regimens. A higher percentage of participants in the rifapentine-based regimen groups had a grade 3 or higher serum total bilirubin level compared to the control group (1.0% in the control group, 3.3% in the rifapentine–moxifloxacin group, and 2.4% in the rifapentine group).
- Cardiac disorders of grade 3 or higher were reported in 3 participants (0.4%) in the rifapentine–moxifloxacin group during the on-treatment period, and of these only one event was considered to be related to the trial regimen (palpitations with QT prolongation).
- No difference was found in premature discontinuation between the rifapentine–moxifloxacin group and the control group (risk difference −1.0%; 95% CI −3.6 to 1.6). However, premature discontinuation occurred less frequently with the rifapentine regimen than with the control regimen (risk difference −3.3%; 95% CI −5.7 to −0.9).

Critical Analysis

This multicenter, randomized, open-label, phase 3 trial demonstrated that a 4-month regimen containing rifapentine and moxifloxacin was non-inferior to the standard 6-month regimen for treatment of drug-susceptible pulmonary TB. However, a 4-month regimen containing rifapentine without moxifloxacin did not meet the criteria for non-inferiority compared to the standard regimen. The incidence of grade 3 or higher adverse events was similar in the rifapentine-moxifloxacin group and the control group, and was slightly lower in the rifapentine group.

The following points should be considered when interpreting the study findings:

- The trial design did not allow for blinding of the participants or staff at the trial sites to group assignment. However, the microbiologists who handled the sputum specimens and the team at the data coordinating center were unaware of group assignment.

- In total, 8% of the trial participants were co-infected with HIV and only 3% were under the age of 18, which limits the ability to compare regimens in these populations.
- Participants with liver disease, known prolonged QT syndrome and pregnant or breastfeeding women were excluded from study enrollment, therefore the safety of the trial regimens in these groups is unknown.
- Despite a higher incidence of hyperbilirubinemia in the rifapentine-based regimen groups, there was no difference in the proportion of participants meeting the criteria for drug-induced liver injury.
- There was no clinical evidence of increased risk of cardiotoxicity, although electrocardiographic monitoring, that could detect subclinical QT prolongation associated with moxifloxacin, was not a required component of the study.
- Only participants with demonstrated drug susceptibility to isoniazid, rifampin, and fluoroquinolones were included. However, rapid drug-susceptibility testing, especially for moxifloxacin and isoniazid, is not readily available in many real-world settings.
- Food improves absorption of rifapentine in the gut, especially high-fat foods. In this study, participants were counseled to take rifapentine within one hour after ingesting food, regardless of fat content, as this was considered more feasible in diverse settings.

Implications

This multicenter, randomized, open-label, phase 3 trial found that a shorter 4-month regimen containing rifapentine and moxifloxacin was non-inferior to the standard 6-month regimen for treatment of drug-susceptible pulmonary TB, and had a similar safety profile. These results suggest that programs should consider including the 4-month trial regimen as an option for the treatment of TB. A shorter course of treatment has the potential to reduce costs and conserve TB program resources, while also greatly improving the experience of people receiving treatment for TB disease.

This article synopsis was written by Cassia Wells. Share your thoughts on this article or suggest an article for Journal Club by emailing her at caw2208@columbia.edu.