PATIENT-LEVEL POOLED ANALYSIS OF STUDY 31/A5349, A STRATIFIED MEDICINE APPROACH



Vincent Chang
PhD Candidate
vincent.chang@ucsf.edu

OTHER AUTHORS: Marjorie Imperial, Patrick Phillips, Wendy Carr, Ekaterina Kurbatova, Andrew Vernon, Marc Weiner, Kelly E. Dooley, Susan Dorman, John L. Johnson, Susan Swindells, Richard E. Chaisson, Payam Nahid, Rada M Savic, and the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium

INTRODUCTION

Study 31/A5349 (NCT02410772) was a phase 3 randomized controlled trial assessing 4-month regimens of once-daily isoniazid, rifapentine, and pyrazinamide plus moxifloxacin (HPZM) or ethambutol (HPZE) compared to the 6-month isoniazid, pyrazinamide, ethambutol, and rifampicin standard treatment for drug-sensitive tuberculosis (TB). While HPZM arm successfully demonstrated noninferiority, HPZE arm did not. Nonetheless, 82% of participants receiving HPZE were cured. Through a pooled analysis of patient-level data, we defined phenotypes that are hard to treat and populations who may be treated with the 4-month HPZE regimen.

METHODS

We included 2343 patients in the microbiologically eligible population from all arms in the analysis. Parametric time-to-event analysis identified significant predictors for TB-related unfavorable outcomes, which were used to define low, moderate, and high-risk groups. Post hoc noninferiority analyses were performed on HPZE and HPZM regimens stratified by risk group.

RESULTS

Major risk factors for TB-related unfavorable outcomes in both experimental arms were rifapentine exposure and baseline disease burden, as measured by GeneXpert cycle threshold and disease extent on chest x-ray. Low risk was defined as GeneXpert ≥ 18 ct and disease extent < 50%, with 5% and 3% unfavorable outcomes when treated with HPZE and HPZM regimens respectively (Fig 3). The moderate risk group in HPZM is defined as (GeneXpert ≥ 18 ct and disease extent ≥ 50%) or (GeneXpert < 18 ct and disease extent < 50%) with 4.5% unfavorable outcomes. For HPZE, patients with HIV or diabetes were at higher risk of unfavorable outcomes compared to HIV-negative or non-diabetic patients (HIV: 16.1% unfavorable outcomes vs 8.9%, HR = 1.95 (95% CI: 1.03, 3.7); Diabetes: 43% vs 8.9%, HR = 6.53 (CI: 2.8, 15)). Therefore for HPZE, patients living with HIV or diabetes presenting with moderate-risk baseline disease characteristics were defined as high-risk. The high-risk group for HPZM was defined as GeneXpert < 18 ct and disease extent ≥ 50% with 11.6% unfavorable outcomes. For HPZE, the high-risk group had 19.1% unfavorable outcomes which consisted of these patients along with the aforementioned patients living with HIV or diabetes. Post hoc noninferiority analyses of HPZM and HPZE regimens stratified by risk group demonstrated noninferiority in their respective low and moderate risk groups, while neither experimental regimen demonstrated noninferiority in the high-risk groups (Fig 1) .

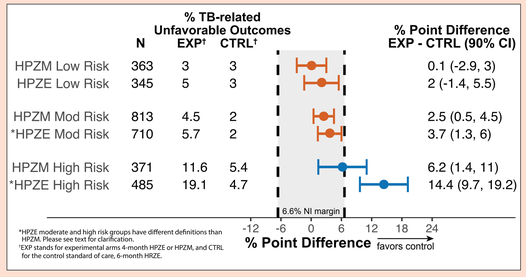

Figure 1. Post-hoc noninferiority analysis of HPZE and HPZM risk groups. Low and moderate risk patients can be treated successfully with 4M HPZE.

THE VAST MAJORITY (70%) OF STUDY 31 DRUG-SENSITIVE TUBERCULOSIS PATIENTS MAY BE TREATED WITH 4-MONTH RIFAPENTINE BASED (HPZE) REGIMEN.

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LONGER HPZM TREATMENT DURATIONS AND/OR HIGHER DOSES SHOULD BE FURTHER INVESTIGATED FOR PATIENTS WITH HIGH DISEASE BURDEN.

University of California San Francisco

Savic Lab

TBTC Tuberculosis Trials Consortium

RISK GROUPS DEFINITIONS

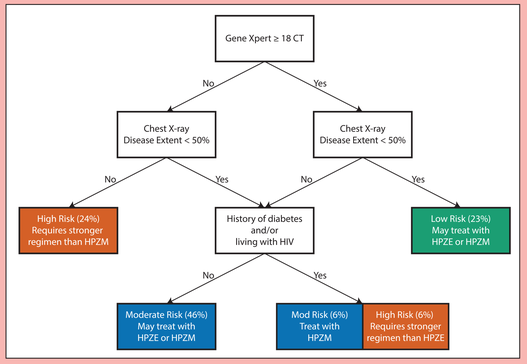

Figure 2. Treatment selection decision tree. Low, moderate, and high-risk groups were defined using most significant baseline predictors for treatment outcome: GeneXpert, chest x-ray disease extent, history of diabetes, and HIV status. Percentage of S31 patients in each risk group are in parantheses in each colored risk group box. Low-risk group and moderate-risk group population were noninferior to equivalent HRZE population (Fig 1). High-risk group did not achieve noninferiority when compared to high-risk HRZE population and therefore higher doses and/or longer treatment durations should be further investigated for these patients. Kaplan Meier curves of stratified by risk group and regimen can be found below in

*Moderate-risk patients living with HIV or diabetes are considered high-risk for HPZE and therefore should not be treated with HPZE. However, treated with HPZM these patients have noninferior outcomes when compared to HRZE standard of care.

KAPLAN MEIER ESTIMATES

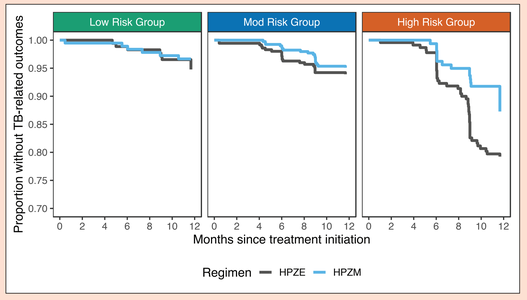

Figure 3. Moxifloxacin is crucial in high-risk group population. Risk group Kaplan-Meir estimates stratified by regimen. The substitution of ethambutol for moxifloxacin is increasingly important going from low to moderate to high-risk group population. In the high-risk group, 11.6% of HPZM patients experienced TB-related unfavorable outcomes compared to 19.1% of HPZE patients at 12 months.

Our post-hoc analysis demonstrates that the HPZE regimen can also be used for the vast majority of patients that present with low or moderate risk characteristics. However, patients living with HIV and/or diabetes should be treated with HPZM.

Although high-risk patients have marked improvement in outcomes with moxifloxacin, further interventions should be investiaged as these patients did not achieve noninferiority compared with equivalent HRZE patients.