MESA: TESIS DOCTORALES PREMIADAS

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Optimization strategies for the first line treatment of tuberculosis

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Background

In tuberculosis (TB), the standard dose of rifampicin established 40 years ago leads to underexposure in a significant subgroup of people with TB[1]. In this thesis the main objectives were 1) reviewing the evidence regarding the use of optimized doses of rifampicin and 2) evaluate this optimisation in difficult-to-treat people with TB.

Methods

We conducted systematic review and a Meta-Analysis to summarize the available evidence regarding rifampicin doses (objective 1). Using the demographic, safety, and efficacy data from the systematic review, we designed and implemented a phase 2 clinical trial exploring the safety of optimized doses of rifampicin in people with difficult-to-treat TB. Most of the research included in this thesis was performed within the EU-funded projects EUSAT-RCS and EU-PEARL[2,3].

Results

With the results of several clinical trials in the last two decades, what the optimal dose of rifampicin might be remains uncertain[4]. Previous trials were characterized by large heterogeneity in background regimens besides rifampicin dose, and in trial design. Thus, we conducted a Bayesian Network Meta-Analysis (NMA)[5]. The review included data from 3654 participants that were young males with a low comorbidity burden. The NMA showed an increased risk of overall and hepatic adverse events for 40 mg/kg/day but no other doses (including 50 mg/kg/day). Increasing doses improved sputum culture conversion at week 8 (RR 1.3, 95% CrI: 1.1, 1.7 for SCC with 35 mg/kg/day) but did not show a benefit in mortality for TB meningitis or relapse for pulmonary TB. In contrast, recent trials showed that in some populations the best balance could be 25mg/kg/day, and that doses of 35mg/kg could increase early mortality in people with HIV and TB meningitis[6,7].

RIAlta is a phase 2b/c non-randomized clinical trial comparing the standard dosing of rifampicin in historical controls with 35mg/kg/day in the prospective cohort (R35 group)[8]. We included people underrepresented in previous trials (e.g., age >60, diabetes, malnutrition, extrapulmonary TB). The primary outcome is safety, with early sputum culture conversion as co-primary endpoint. At the time of writing this report, there were 32 participants enrolled in the R35 group, and we had data from 117 historical controls. In the central monitoring analysis, the rate of adverse events leading to treatment modifications, was similar in both groups.

The continuation of the trial is at risk due to high staff turnover and lack of funding, common challenges in TB trials. Novel biomarkers could make trial implementation more straightforward. However, treatment-monitoring biomarker development in TB is characterised by a high attrition rate with only sputum culture validated as a (poor) surrogate for clinical efficacy[9]. Including the

perspective of people affected by TB from the design stage could also mitigate some risks[10].

Conclusion

Optimal doses of rifampicin may be between 25 and 35 mg/kg/day, depending on individual characteristics. If safety is similar in difficult to treat cases, the benefits in terms of early sputum clearance and, possibly, relapse reduction, may be larger. In contrast, rifampicin optimisation may not improve mortality in TB meningitis.

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Prevalencia de aislamiento y enfermedad por micobacterias no tuberculosas en pacientes con EPOC de alto riesgo

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En los últimos años se ha detectado un aumento de aislamientos respiratorios de micobacterias no tuberculosas (MNT), siendo el principal factor de riesgo la presencia de daño pulmonar previo. Una de las enfermedades respiratorias crónicas más frecuentes es la EPOC, sin embargo hay muy pocos datos de la prevalencia real de aislamiento de MNT en pacientes con EPOC. Además, se ha sugerido que tratamientos habituales en la EPOC, como los corticoides inhalados, podrían incrementar el riesgo de desarrollar enfermedad pulmonar por MNT (EP-MNT). El aislamiento de MNT en pacientes con EPOC tiene trascendencia terapéutica, especialmente en el uso de macrólidos frecuentemente usados a dosis bajas y de forma prolongada para prevenir agudizaciones.

El objetivo principal de esta tesis doctoral fue determinar la prevalencia de aislamiento de MNT y de EP-MNT según criterios