Dosing of RIFAMPIN in TB Meningitis

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Situation – Formal CDC and CDPH Guidelines do not include High-Dose rifampin dosing in TB meningitis (TBM)

Background – When licensed decades ago, Rifampin supplies were scarce such that the minimum effective dose of 10 mg/kg/day became the standard. Studies of high dosage have since shown less selection of resistance and shorter time to sputum conversion but shortening of treatment duration has been inconsistent and 10 mg/kg/day remains the published guideline for all TB. Still, overall mortality of TBM remains up to ~20%, with neurologic residua in ~25+% of survivors.

However, during the past decade, the poor penetration of rifampin into CSF and CNS has finally received clinical attention. CSF PK/PD shows that even with inflamed meninges, 10 mg/kg/day produces a ratio of CSF rifampin to the MIC of Mtbc that barely exceeds the MIC in only ~10% of TB meningitis patients. This is in stark contrast with clinical data for most antibiotics and pathogens in which a "target attainment" of at least 2x the MIC (preferably 4x) is required for clinical cure (and TB is more resistant to killing than most bacterial pathogens). Thus, rifampin dosage in TB meningitis has been the focus of various studies addressing the microbiology, pharmacology, safety, and clinical efficacy. In 2018 when dose-ranging studies of safety showed similar rates of intolerance regardless of dosages, UCI initiated recommendation of high dose rifampin in TB meningitis and selected other patients with very serious disease on a case-by-case basis.

Assessment –

- **Randomized Controlled Trial** – Robust RCTs with numbers adequate for definitive assessment of clinical efficacy are needed in addition to the publishes RCT in 817 Vietnamese adults which not surprisingly showed no benefit of 15-vs-10 mg/kg/day mostly PO (Heemskerk et al), likely because the target attainment in CSF of 15mg/kg/day even IV is marginal (see below and Dian et al).
- **Pharmacology** – Studies of basic PK/PD parameters have defined vastly improved PK/PD attainment of 2, 4, or even 8x the drug/bug MIC ratios in CSF, comparing 10 mg/kg/day against 15-20 mg/kg/day IV, and against 30-35mg/kg/day PO (e.g., Cresswell et al). Furthermore, 35 mg/kg/day PO achieves similar ratios compared to 20 IV (Wasserman et al) and represents ideal care for PO therapy. Attainment of optimal target ratios is most important at the start of therapy when the organism load is the highest.
- **Safety** – Regarding the critical importance of safety for high dosage, the conclusion from several RCTs vs 10 mg/kg/day confirms prior retrospective and observational studies, that adverse drug events are no different in dosage up to 35 mg/kg/day PO (e.g., Dian et al). Another study, though observational and non-randomized, analyzed 10 years of experience (88 cases) with prospective higher dose (up to 32 mg/kg/day) treatment of designated severe TB cases, including 26 with TBM &/or CNS disease; adverse reactions were no different between 15-20 mg/kg/day and 30-32 mg/kg/day (Seijger et al).
- **Outcomes** – Assessment of clinical outcomes, mortality, and neurological residua from meningitis is problematic due to small numbers in most trials. However, a number of such studies, including RTC (Dian et al) and pharmacokinetic data in relation to mortality (Svensson et al) showed at least strong trends toward lower mortality (30 mg/kg/day in the Dian study).

Recommendation –

That current guidance for therapy of TB Meningitis should include high-dose rifampin (at least 20 mg/kg/day IV or 30-35 mg/kg/day PO).

References –

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Seijger C, et al. High-dose rifampicin in tuberculosis: Experiences from a Dutch tuberculosis centre. PLoS One. 2019;14(3):e0213718. Published 2019 Mar 14. doi:10.1371/journal.pone.0213718

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The California TB Controllers Association responds with the following:

High dosage of Rifampin for TB meningitis is a current reasonable practice strategy to optimize outcomes. Clinicians should consider an individual's comorbidities (e.g., pre-existing liver disease, risk for toxicity) and drug-drug interactions when starting and modifying TB treatment. Additional adjunctive treatment to optimize TB meningitis therapy should be considered given the significant morbidity and mortality associated with this disease.