Infect Dis Ther
https://doi.org/10.1007/s40121-024-01102-1

REVIEW

Optimizing Pyrazinamide Use: A Low-Hanging Fruit in Improving Outcomes with Tuberculous Meningitis? Narrative Review

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Received: October 4, 2024 / Accepted: December 16, 2024

ABSTRACT

Tuberculous meningitis (TBM) disables more than a third of its sufferers. Recent research has focused on optimizing the antitubercular regimen, mainly by increasing the dosage of rifampicin. However, pyrazinamide, with higher penetration into the central nervous system, is generally overlooked. We discuss the potential clinical impact of using pyrazinamide throughout antitubercular therapy in TBM, in contrast to only the intensive phase. This approach may improve the treatment outcomes and reduce disability in TBM. We summarize the available data regarding this approach from in vitro studies, clinical cohorts, toxicity data, and baseline resistance rates. Additionally, we discuss the two ongoing clinical trials evaluating this approach.

PLAIN LANGUAGE SUMMARY

Tuberculosis (TB) is a disease caused by the organism *Mycobacterium tuberculosis*. TB meningitis (TBM) is a medical condition in which the layers covering the brain are infected with TB bacteria. TBM is one of the worst forms of TB as it kills a lot of people who suffer with the disease and leaves many permanently disabled. Currently, the World Health Organization recommends 12 months of treatment for TBM. The drugs used in the treatment are rifampicin, isoniazid, ethambutol, and pyrazinamide. Usually, pyrazinamide is given only for the first 2 months of TB treatment. Many studies have shown that pyrazinamide penetrates the brain better than other drugs and kills TB bacteria more effectively. In addition, ethambutol does not get into the brain well compared to other drugs. In this narrative review, we present evidence to reconsider the duration of pyrazinamide usage beyond 2 months for improving the results of TBM treatment. We also report the challenges of this approach, such as side effects and pyrazinamide resistance.

Keywords: Pyrazinamide; Tuberculous meningitis; Treatment; Duration

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Published online: 03 January 2025

Key Summary Points

Tuberculous meningitis (TBM) is associated with poor treatment outcomes despite longer duration of treatment.

In the current regimen, both pyrazinamide and isoniazid achieve optimal therapeutic levels in the brain. However, pyrazinamide is used only during the first 2 months of treatment.

There is an urgent need to reconsider the inclusion of medications which could achieve optimal therapeutic levels at the site of infection in the treatment regimen of TBM for the whole duration of treatment.

The role of extended use of pyrazinamide in the intensified regimens for improving the treatment outcomes in TBM needs further evaluation in clinical trials.

INTRODUCTION

Tuberculous meningitis (TBM) has high morbidity and mortality rates. Almost one-fourth of adults with TBM are at risk of death despite treatment for a longer duration with standard antituberculosis therapy (ATT) and steroids, making it one of the most severe and debilitating forms of tuberculosis (TB). Around half of them recover with significant residual neurological disability [1]. The causes of poor outcomes in TBM are multifactorial, complicated by delayed diagnosis and imprecise diagnostics. Another crucial factor is the lack of clear evidence for the drug regimen used in the management of TBM in adults and children. The drugs used in the management of drug-sensitive tuberculous meningitis (DS TBM) are similar to those used in pulmonary tuberculosis, except for a longer duration [2]. However, it is largely known that these drugs have varying penetration across the blood brain barrier (BBB) into the cerebrospinal fluid (CSF) and their treatment outcomes tend to be poor [3]. Of the four drugs used in DS TBM management, isoniazid and pyrazinamide have very good CSF penetration, often comparable to that of plasma concentrations [4, 5]. Isoniazid is used throughout the treatment regimen; however, the role of pyrazinamide ends with the intensive phase of treatment in the current treatment guidelines for TBM. There is a scarcity of controlled clinical trials for optimal drugs and duration of treatment in TBM. The guidelines for treatment are still derived from observational studies and clinical practice rather than randomized controlled trials (RCTs). Here, we review the role of pyrazinamide, a potent sterilizing drug with good CSF penetration in the management of TBM, with a particular focus on the duration of its use.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

SEARCH METHODOLOGY

We searched MEDLINE via PubMed, Google Scholar, and Cochrane Library for all the literature in the English language without any geographical or time restrictions. We used Medical Subject Headings (MeSH) and free text words. The search included terms or combinations of words such as "tuberculous meningitis epidemiology," "Central nervous system (CNS)-TB epidemiology," "pyrazinamide," "tuberculous meningitis," "pyrazinamide resistance," "pyrazinamide toxicity," "pyrazinamide pharmacokinetics," "pyrazinamide in clinical trials," and "pyrazinamide in continuation phase."

EPIDEMIOLOGY OF TBM

The burden of TBM and the mortality due to this disease are largely unknown. Assuming a similar case detection rate as all forms of TB for TBM, Dodd et al. estimated that 164,000 adults (95% UI 129,000–199,000) developed TBM globally in 2019. The prevalence of TBM among people living with HIV (PLHIV) was 23% [6]. Dodd et al. also estimated that 5.6% of TB deaths were caused by TBM and the mortality was close to

50% in adults [6]. Navarro-Flores et al. included 53 studies representing 12,621 participants from 28 countries in a systematic review and estimated the prevalence of CNS TB to be 2 per 100,000 inhabitants. The prevalence of TBM among persons hospitalized for general conditions was 7.4%, among those with meningitis it was 14.63%, and among those with TB it was 3.67% [7]. Stadelman et al. included 39 primary research articles with 5752 adults with TBM in their systematic review and estimated a pooled 6-month mortality of 24% (95% CI 19–29%). Mortality rates ranged from 2% to 67% in Asia and 23% to 80% in sub-Saharan Africa. Mortality was significantly higher among PLHIV (57%; 95% CI 48–67%) than among HIV-negative individuals (16%; 95% CI 10–24%). The physical disability rate was 32% (95% CI 22–43%) among survivors [8]. Our estimation of CNS TB prevalence including TBM in India was 2%, and the case fatality rate was 35%, with a relative risk of 5.6 compared to other forms of TB [9].

CURRENT TBM DRUG REGIMEN: IS THIS ADEQUATE?

Currently, the World Health Organization (WHO) recommends 2 months of isoniazid (INH), rifampicin, ethambutol, and pyrazinamide followed by 7–10 months of rifampicin and isoniazid for TBM [2]. Concepts of pulmonary TB have been applied without considering the distinct development, intensity, and penetration potential of anti-TB medications. These drugs have variable ability to cross the BBB and achieve wide-ranging concentrations in the CSF and brain.

Rifampicin

The recommended dose of rifampicin was 10 mg/kg. Though there is a higher cellular penetration and sustained efficacy against intracellular pathogens, the drug's CSF concentrations are less than 30% of plasma levels [10, 11]. Rifampicin concentrations in the CSF were below the level of detection in approximately 67% of patients with TBM receiving standard oral adult dose (8–10 mg/kg) in Indonesia [12]. Recent evidence suggests the need for higher doses of rifampicin to achieve optimal therapeutic levels in CSF. CSF levels exceeding the minimum inhibitory concentration (MIC) were obtained with high-dose intravenously administered (20 mg/kg/day) and orally administered (35 mg/kg/day) rifampicin without causing any additional harm [13].

Isoniazid

Isoniazid has favorable CSF pharmacokinetics (PK), achieving peak concentrations (Cmax) that are marginally lower than in blood [14]. Isoniazid metabolism is influenced by the *NAT2* genotype. Isoniazid acetylator status could affect plasma and CSF concentrations, and the need for higher doses in fast acetylators is another gray area and a matter of concern [14]. Yunivita et al. showed that slow acetylators had higher drug concentrations of isoniazid in the plasma and CSF compared to fast acetylators [15]. Fast acetylators may require dosages as high as 600mg to reach optimal therapeutic CSF levels. Personalized dosing based on *NAT2* status can minimize toxicity risks, including hepatotoxicity, and maximize therapy efficacy [14]. Resistance to isoniazid increases the risk of developing resistance to other first-line medications, such as rifampicin, and decreases the probability of successful treatment. This raises the possibility of multidrug-resistant tuberculosis [16].

Ethambutol

Ethambutol has very poor penetration through the BBB and the therapeutic levels achieved are minimal in the CSF. The action of ethambutol at the site of disease is negligible; hence, its contribution to TBM treatment is questionable [14]. Ethambutol initially showed promise with an effective minimum inhibitory concentration (MIC) when used at doses of 50 mg/kg or more. Retrobulbar neuritis brought on by this dose led to a decrease in the dosage and decreased its efficacy. Early studies found no ethambutol in the CSF after administration of a dose of 50 mg/kg in healthy volunteers, while later studies

detected low concentrations (0–1.98 µg/ml) in patients with TBM 3–4 h after dosing. In some patients with TBM, ethambutol may reach concentrations near the lower MIC for *Mycobacterium tuberculosis*, but this decreases the healing progresses [16, 17]. Overall, ethambutol's contribution to TBM treatment is likely minimal as a result of its limited CSF penetration. Ethambutol, in addition to rifampicin and isoniazid, is recommended in the continuation phase of drug-sensitive pulmonary TB and TBM in India. The use of a drug that achieves low therapeutic levels in the brain with known cumulative mitochondrial toxicity, especially when administered for a longer duration, needs to be reconsidered.

Pyrazinamide

Pyrazinamide is bactericidal and kills intracellular bacilli. Pyrazinamide has several advantages because of its unique mechanism of action in inhibiting multiple targets, activity against persisters, and synergism with isoniazid and rifampicin [18]. Replacement of ethambutol with pyrazinamide or omission of pyrazinamide in the regimen was shown to reduce relapse rates in pulmonary TB during earlier trials [18]. During the early years of ATT, extending pyrazinamide beyond the continuation phase was associated with reduced relapse rates in a pulmonary TB trial [19]. The current strategy of discontinuing pyrazinamide in the continuation phase emerged after a clinical trial in Hong Kong [20]. The trial studied four regimens given thrice weekly for 6 months: three regimens contained rifampicin and isoniazid for 6 months, streptomycin for 4 months, and pyrazinamide, which was given for 2, 4, or 6 months; one regimen contained rifampicin and isoniazid, no streptomycin, and pyrazinamide was given for a period of 6 months. The relapse rates during the 30-month follow-up period were 3%, 5%, and 3% in the pyrazinamide 2, 4 and 6 months groups respectively given along with rifampicin, isoniazid and streptomycin [20].

Drugs with low molecular weight, moderate lipophilicity, and lower binding to plasma proteins readily enter the CSF and pyrazinamide has similar properties [21]. The levels of pyrazinamide achieved in the CSF are not affected by patient age, gender, disease stage, presence of active disease, use of steroids, duration of treatment, and co-administration with ethambutol or streptomycin [22]. Hence, pyrazinamide may be pivotal for use in the continuation phase of TBM, especially for reducing relapse when used along with isoniazid and rifampicin in the continuation phase. It could also be considered for shortening the duration of TBM treatment, given its sterilizing effect on metabolically dormant *M. tuberculosis* [23].

Two (rifampicin and ethambutol) of the four medications in the intensive phase of treatment penetrated the BBB poorly and only one achieved an optimal therapeutic level in the continuation phase of treatment for this severe form of TB. With the above evidence, the current recommended treatment regimen in the continuation phase could be weak, as patients might be on effective monotherapy with isoniazid, given the low rifampicin levels in the CSF. This problem is accentuated when there is accompanying isoniazid monoresistance, which affects around 7–11% of patients with tuberculosis globally [24]. Diagnosing this problem is difficult, as TBM is a paucibacillary disease, and mycobacterial cultures are seldom positive in the CSF.

PHARMACOKINETICS (PK)/ PHARMACODYNAMICS (PD) OF PYRAZINAMIDE IN TBM

Phuapradit et al. performed serial measurements of plasma and CSF levels of pyrazinamide 1500 mg administered along with isoniazid, rifampicin, and streptomycin from initiation to 6 months of treatment. They demonstrated that good therapeutic levels were achieved even at 6 months of treatment in patients with TBM. There was a good correlation between CSF and plasma levels [25]. Stemkens et al. showed that pyrazinamide dose is associated with plasma and CSF levels, and plasma levels could predict CSF values. They showed that higher exposure to pyrazinamide was achieved during the first few days of treatment compared to the levels

at 10 days, probably because of the interaction with rifampicin [5]. PK/PD modeling based on three clinical trials for pulmonary TB showed that there was no association between high doses of pyrazinamide (>4500 mg) with or without rifampicin and hepatotoxicity [26].

Therapeutic drug monitoring (TDM) uses the PK/PD knowledge of a particular drug to optimize the drug treatment at an individual level. Understanding the drug concentrations in the plasma as well as the site of infection could guide in personalizing the drug treatment in order to maintain the concentrations within the optimal therapeutic range [27]. TDM can assist in directing pyrazinamide dose modifications in complex TBM cases, particularly where resistance or potential adverse reactions are a concern. The role of TDM in optimizing the treatment for TBM at a personalized level, its feasibility, impact on treatment outcome, and implementation challenges in high-burden countries need to be explored further.

PYRAZINAMIDE RESISTANCE

The final considerations included the global resistance rates, toxicity, and relapse. The global pyrazinamide resistance rate was 16.2% (95% CI 11.2–21.2) and varied according to the geographic region [28]. A systematic review including 66 reports based on single nucleotide polymorphism distribution reported that the pooled pyrazinamide resistance was 16.2% (95% CI 11.2–21.2) among all patients with TB. The resistance rate was almost threefold [41.3% (29.0–53.7)] and fourfold [60.5% (52.3–68.6)] higher in patients at higher risk for multidrug resistant (MDR)-TB and diagnosed with MDR-TB, respectively. The review also estimated that 1.4 million persons with newly diagnosed TB could have pyrazinamide resistance annually [28]. In India, pyrazinamide resistance was reported to be approximately 7% and 9% among new and previously treated patients, respectively. This is higher when compared to ethambutol resistance rate (2.8%) [29]. Pyrazinamide resistance is known to influence the treatment outcomes in patients with drug-sensitive and drug-resistant pulmonary TB [29]. The impact of pyrazinamide resistance on TBM treatment outcome is largely unknown and needs to be studied.

PYRAZINAMIDE SIDE EFFECTS

Optimizing pyrazinamide doses may yield a favorable outcome in the treatment of TBM provided higher doses are tolerated well [5]. Chen et al. showed that higher pyrazinamide exposure is associated with positive treatment outcomes, but the side effects of pyrazinamide must be taken into consideration [30]. Transient elevations of liver enzymes which did not necessitate treatment discontinuation were observed when pyrazinamide (1500 mg) was used for a period up to 12 months during earlier days of TBM management [31]. Hepatotoxicity, arthralgia, hyperuricemia, and resultant gout are the most common side effects of pyrazinamide. A nested case–control study with a cohort of 3007 participants evaluated the hepatotoxicity of pyrazinamide- and isoniazid-containing regimens, with or without rifampicin in the continuation phase. Chang et al. concluded that the risk of hepatotoxicity was 2.6% after 12 weeks of treatment with an adjusted odds of 2.5 to 2.8 times compared to the standard regimens containing rifampicin and isoniazid [32]. Hyperuricemia and gouty arthritis are known complications of pyrazinamide when used alone or in combination with rifampicin, isoniazid, and ethambutol [33]. The arthralgia due to pyrazinamide toxicity is often non-deformative, non-erosive, and reversible after completion of treatment [34].

The mechanism of pyrazinamide-induced hepatotoxicity is not well established but is attributed to the formation of pyrazinoic acid, an active metabolite formed by the action of amidase on pyrazinamide. However, it was hypothesized that the co-administration of an amidase inhibitor (bis-*p*-nitrophenyl phosphate) could prevent pyrazinamide-induced liver injury [35]. The PK parameters (Cmax) of pyrazinamide were evaluated against liver enzyme levels, and no concrete relationship was established between high-dose pyrazinamide and

hepatotoxicity [26]. Pyrazinamide increases uric acid levels by retaining uric acid in the form of urate crystals, resulting in hyperuricemia, which is characterized by joint pain (arthralgia) and gouty arthritis. A short course of aspirin may be considered in the intensive phase of treatment to prevent pyrazinamide-induced arthralgia [36]. These systemic exposures and toxicities could be reduced by formulating novel drug delivery systems such as nanoparticles, enhancing its targeted delivery [37].

INTENSIFIED SHORTER REGIMENS

Van Toorn et al. shortened TBM therapy to 6 months (HRZEth) by continuing pyrazinamide (40 mg/kg) into the continuation phase, replacing ethambutol with ethionamide (Eth) and increasing isoniazid and rifampicin doses to 20 mg/kg. They showed excellent clinical outcomes in children and adolescents with this regimen [38]. This strategy, often called Cape Town regimen, has been incorporated into the South African National guidelines for TBM. A systematic review evaluating the outcomes of a 6-month intensive regimen with a 12-month regimen for TBM among children and adolescents showed that outcomes such as death (5.5% vs. 23.9%) and survival with or without sequelae (94.6% vs. 75.4%) were better in the intensive regimen group. Neurological sequelae among survivors (66% vs. 36.3%) were higher in the shorter regimen compared to the 12-month regimen [39]. Following these data and others, WHO guidelines now recommend a 6-month intensified regimen with isoniazid, rifampicin, pyrazinamide, and ethionamide (6HRZEto) as an alternative option to the 12-month regimen (2HRZE/10HR) for children and adolescents [40]. More evidence is needed to translate these guidelines to adults. First, the PK data for pyrazinamide should be favorable. The mean CSF-to-plasma concentration ratio just a day after administration of pyrazinamide was 90% (range 55–115%) among Indonesian adults with TBM [5]. Pyrazinamide achieves excellent CSF concentrations with a positive correlation between the administered oral dose, plasma, and the CSF concentrations [5]. Such correlations strengthen the argument for increasing the duration of pyrazinamide use during the continuation phase. A systematic review by Ryan et al. comparing 6-month regimens with a longer one for TBM showed that relapses are uncommon and are similar in both the groups [41].

ONGOING TRIALS FOR TBM WITH LONGER DURATION OF PYRAZINAMIDE

The current INSHORT TBM (NCT05917340) trial aims to look at a more prolonged duration of pyrazinamide (6 months) along with an intensified regimen in the initial phase of treatment to reduce mortality and disability in adults with TB [42]. The SURE trial (ISRCTN40829906) evaluates the safety and efficacy of a monthly daily regimen of rifampicin, isoniazid, pyrazinamide, and levofloxacin with or without aspirin in children with TBM. IMAGINE TBM (NCT05383742) is another trial comparing 6 months of high-dose rifampicin, high-dose isoniazid, linezolid, and pyrazinamide with the standard 9-month regimen. In addition to the clinical outcomes of pyrazinamide-containing regimens in the continuation phase, these trials may also shed light on the drug–drug interactions between pyrazinamide and drugs such as high-dose rifampicin and fluoroquinolones. As we await evidence from these clinical trials, it is time to reconsider the duration of pyrazinamide use in TBM. Single-center, small retrospective or prospective observational studies examining the duration of pyrazinamide administration and clinical outcomes will also shed some light on this crucial clinical decision. We believe that there is an urgent need for an optimal regimen for the management of TBM with appropriate drugs and duration to improve treatment outcomes, and pyrazinamide is definitely a low-hanging fruit that is worth considering.

PROGRAMMATIC IMPLICATIONS

Currently, fixed-dose combinations, are recommended for the management of TB including TBM. Intensified regimens for shortening the

treatment duration require individual formulations to optimize the regimen. Continuation of pyrazinamide in the continuation phase, if proven effective and safe, requires individual formulations, and its availability in the market is limited.

WAY FORWARD

Scaling up this strategy to routine care requires several steps. The ongoing RCTs will provide evidence whether continuing pyrazinamide will improve disability-free survival in TBM, with a good safety profile. The relative, proportional improvement in the primary outcome in these trials should be compared with other ongoing trials, specifically involving agents with good CNS penetration like linezolid. Large observational studies, though important for safety data, are unlikely to report on the efficacy of the approach, as the effect size is likely to be mild to moderate. The pharmacokinetic data linked to patient outcomes from the trials can be important in influencing policy. Joint modeling exercises from the clinical trial data will inform target exposures and the doses needed to attain them. Pyrazinamide resistance rates across diverse regions need to be studied. This will require strengthening of laboratory capacity as pyrazinamide susceptibility testing is challenging with high false positive rates. In summary, prolonging the duration of pyrazinamide in the current or augmented doses appears to be a promising approach and needs further study in the management of TBM.

Author Contributions. Bella Devaleenal Daniel, Abi Manesh, Balaji Ramraj, Leeberk Raja Inbaraj: Idea, conceptualization and design, writing the original draft, reviewing it critically and editing. Shanmugapriya Kumaravadivelu, Kathirvel Subramanian: design, writing the original draft and review. All authors approve the submitted version and are accountable for all the aspects of the work.

Funding. No funding or sponsorship was received for this manuscript.

Data availability. This is based on the review of the available literature and does not contain any new studies with human participants or animals.

Declarations

Conflict of Interest. The authors (Bella Devaleenal Daniel, Leeberk Raja Inbaraj, Shanmugapriya Kumaravadivelu, Kathirvel Subramanian, Balaji Ramraj, Abi Manesh) declare that they do not have any conflicts of interest.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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