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Editorial

The current pharmacological landscape of tuberculous meningitis: where to next?

Nguyen Thi Hoang Mai ^{1,2}

Guy E Thwaites ^{2,3} *

1. Hospital for Tropical Diseases, Ho Chi Minh City, Viet Nam
2. Oxford University Clinical Research Unit, Ho Chi Minh City, Viet Nam
3. Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom

* Corresponding author

Professor Guy Thwaites

Director, Oxford University Clinical Research Unit, 764 Vo Van Kiet, Quan 5, Ho Chi Minh City, Viet Nam

Tel: +84 8 39237954

Fax: +84 8 39238904

gthwaites@oucru.org

Mycobacterium tuberculosis causes around 9 million new cases of tuberculosis and 1.5 million deaths annually ¹. Effective anti-tuberculosis chemotherapy has been available for more than 50 years, yet tuberculosis kills more people than any other bacterial infection. Whilst pulmonary tuberculosis is the commonest form of the disease, and is also responsible for the on-going transmission of the bacteria, *M. tuberculosis* can affect almost any organ. Indeed, the diverse clinical manifestations and consequences of extra-pulmonary tuberculosis present physicians with some of the most difficult diagnostic and therapeutic challenges in the practice of clinical medicine.

Tuberculous meningitis (TBM) is the most challenging and dangerous of all forms of tuberculosis and has been the major focus of our research for the last 15 years. TBM kills or disables almost half of all sufferers. It is characterized by a slowly progressive meningo-encephalitis with necrotising granulomatous inflammation predominantly affecting the basal meninges. Inflammatory exudates can obstruct the passage of cerebrospinal fluid (CSF) leading to hydrocephalus; small and medium sized intracerebral arteries can become inflamed and occluded leading to infarcts and stroke syndromes; and granulomas may enlarge to form tuberculomas which can cause mass-effects, seizures, and coma ². Current pharmacological strategies to prevent and treat these complications can be divided broadly into those that directly target the bacteria and those that target the host inflammatory response.

It is easy to get lost in TBM's pharmacological landscape for there are few fixed points of reference. Targeted bacterial killing by combination short-course (6-month) anti-tuberculosis chemotherapy, defined by high-quality clinical trials, has made an enormous contribution to the treatment and control of pulmonary tuberculosis since its introduction in 1970s. Yet how the same anti-tuberculosis drugs, so effective in the treatment of pulmonary tuberculosis, should be best employed in the treatment of TBM, remain very uncertain. Devoid of clinical trial data, most authorities have simply recommended using standard first-line pulmonary tuberculosis regimens for TBM, albeit for 3-6 months longer (although

supporting evidence for longer treatment is also lacking). The potential problem with this approach is that the blood-brain barrier reduces the concentrations of anti-tuberculosis drugs in the brain which may attenuate both bacterial killing and clinical response. This has been of particular concern in very young children, who require higher doses than adults for the treatment of all forms of tuberculosis, and for rifampicin, a highly effective anti-tuberculosis drug which only achieves CSF concentrations of around 10-20% of blood ^{3,4,5}.

The suggestion that TBM may require higher doses of anti-tuberculosis drugs than pulmonary tuberculosis is not new. Peter Donald and Johan Schoeman have been strong proponents of this approach for more than 20 years in South Africa. They first published their experience of the use of a 6-month, four-drug regimen of isoniazid, rifampicin, ethionamide (all at 20mg/kg/day) and pyrazinamide (40mg/kg/day) in 1998 ⁶ and have subsequently reported excellent outcomes in many children treated with this regimen ⁷. The regimen has never, however, been subject to a randomised controlled trial.

In the treatment of pulmonary tuberculosis, there is growing interest in much higher rifampicin doses (up to 35mg/kg/day are being studied) because bacterial killing increases proportionally with dose ⁸. For TBM, rifampicin's limited passage across the blood-brain barrier further supports the hypothesis that higher doses will lead to enhanced bacterial killing and improved survival. A recent randomized comparison of higher dose intravenous rifampicin (around 13mg/kg/day) with standard oral dose (10mg/kg/day) in 60 Indonesian adults with TBM, found that the higher intravenous dose was associated with a more than 50 percent reduction in mortality ⁹. This remarkable result added weight to the argument that recommended TBM regimens based on pulmonary tuberculosis treatment were inadequate and needed modification.

In this context, there has been gathering anticipation surrounding the results of a trial we have been conducting in Vietnam comparing a hyper-intensive versus standard anti-tuberculosis regimen for adults

with TBM ¹⁰. The study promised to provide some badly needed definitive clinical trial evidence. 817 adults with TBM were randomly allocated treatment with either a standard anti-tuberculosis regimen consisting of isoniazid (5mg/kg/day), rifampicin (10mg/kg/day), pyrazinamide (25mg/kg/day) and ethambutol (20mg/kg/day) for 3 months, followed by rifampicin and isoniazid at the same doses for a further 6 months, or the same regimen with higher dose rifampicin (15mg/kg/day) and levofloxacin (20 mg/kg/day) for the first 8 weeks of treatment. The results, published in the *New England Journal of Medicine* in January 2016, were disappointing ¹¹. The intensified treatment regimen was not associated with improved survival or any other measure of treatment response. Only those with TBM caused by isoniazid resistant bacteria showed any suggestion of benefit from the intensified regimen.

Why didn't the intensified regimen improve outcomes in our trial? When we designed the study in 2009 there was concern that even modest increases in rifampicin doses might cause unacceptable increases in drug-induced hepatitis. The choice of 15mg/Kg/day of rifampicin seemed reasonable at the time, although we now know that much higher doses are probably well-tolerated. It is possible that the dose chosen may not have been high enough to induce a significant clinical effect. Pharmacokinetic sub-studies are awaited, but the rifampicin CSF concentrations may not have been as high as those achieved in the Indonesian study when the drug was given intravenously and increased survival. If this is the case, the need to explore intensified anti-tuberculosis treatment is unlikely to end with this trial's results, and higher doses of rifampicin, possibly administered intravenously for the first few weeks, will require further investigation in large pragmatic clinical trials. In addition, the role of the new anti-tuberculosis drugs in the treatment of TBM – bedaquiline and delamanid – needs investigation.

Where to next? With these disheartening trial results our attention has returned to the second therapeutic strategy: controlling the inflammatory response. We are close to completing a phase IIb randomized double blind comparison of aspirin 81mg/day or 1000mg/day, or placebo, for the adjunctive

treatment of 120 Vietnamese adults with TBM. Based on the results of previous small studies from India and South Africa ^{12, 13}, we hypothesise that aspirin will reduce the incidence of cerebral infarction, a common complication of TBM. We anticipate the results of our study will be available in early 2017.

Twelve years ago we completed a trial of adjunctive dexamethasone in 545 Vietnamese adults with TBM and found dexamethasone was associated with a 30% reduction in mortality ¹⁴. The benefit was predominantly seen in HIV-uninfected individuals, with uncertain effect in the 98 HIV-infected patients randomised. Furthermore, despite the careful study of all patients enrolled into the trial, an anti-inflammatory effect linked to outcome was not found ¹⁵. An explanation for this puzzling finding was only forthcoming upon our subsequent discovery that a common functional promoter variant (C/T transition) in the gene encoding leukotriene A4 hydrolase (*LTA4H*), which determines the balance of pro- and anti-inflammatory eicosanoids, appeared to predict response to dexamethasone in HIV-uninfected participants ¹⁶. We therefore hypothesise that *LTA4H* genotype determines the host inflammatory response to *M. tuberculosis* infection, influences corticosteroid treatment response, and provides a basis for personalising TBM corticosteroid treatment. To address this hypothesis we are preparing to perform an *LTA4H* genotype stratified randomised controlled trial of dexamethasone in HIV-uninfected adults with TBM. In addition, we will also perform a parallel randomised controlled trial in HIV-infected individuals with TBM to determine definitively whether adjunctive dexamethasone improves outcome in this important population. TBM is especially common in HIV-infected individuals, yet the current evidence base from which to determine whether or not to give corticosteroids to these patients is limited to the 98 patients recruited to our earlier controlled trial ¹⁴.

We believe these new trials will answer important clinical questions and provide a powerful infrastructure to investigate pathophysiology and other novel genetic determinants of treatment response. Assuming meningeal and pulmonary tuberculosis have common pathophysiological pathways,

we will investigate whether TBM treatment response determinants influence pulmonary tuberculosis severity and outcome. We believe TBM is a powerful model for understanding and optimising both antimicrobial and anti-inflammatory therapies and will open new windows on the pharmacological landscape of tuberculosis treatment.

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