



Commentary

Aspirin in tuberculous meningitis

Angharad G Davis^{a,b,c}, Robert J Wilkinson^{a,b,c,d}^a The Francis Crick Institute, Midland Road, London NW1 1AT, United Kingdom^b Faculty of Life Sciences, University College London, WC1E 6BT, United Kingdom^c Wellcome Centre for Infectious Diseases Research in Africa, University of Cape Town, Observatory 7925, South Africa^d Department of Infectious Diseases, Imperial College London, W12 0NN, United Kingdom

ARTICLE INFO

Article History:

Received 29 March 2021

Accepted 12 April 2021

Available online 7 May 2021

Neurological sequelae in tuberculous meningitis (TBM) lead to significant morbidity and mortality. Stroke is common, occurring in 15–57% of cases and associated with poor outcome [1]. As yet, there are few adjunctive therapies which can prevent often life-threatening complications. Aspirin, a widely available and inexpensive drug, has been considered as adjunctive therapy for some time with the first clinical trial of aspirin in TBM taking place over a decade ago. In this issue of EClinicalMedicine, Rohilla and colleagues present results from a meta-analysis of the three randomised controlled trials (RCT) including 365 patients receiving aspirin as adjunctive therapy in TBM. They conclude that although there is no mortality benefit, aspirin reduces stroke, which may have implications for clinical management of TBM. However, as exemplified by this meta-analysis by differing dosing regimens and choice of clinical endpoints, there is a lack of consensus what dose and duration of aspirin may be optimal.

Aspirin inhibits the cyclooxygenase pathway of arachidonic acid metabolism, and thus reduces downstream production of prostanooids [2]. At low doses (75–150 mg/day) aspirin also prevents ischaemic infarction via inhibition of thromboxane A2 and platelet aggregation [3]. The latter accounts for its widespread use as secondary prevention in cardiovascular disease, and may help to prevent stroke in TBM where there is a prothrombotic state [4]. At higher doses (>600 mg/day) aspirin has additional anti-inflammatory properties via inhibition of proinflammatory eicosanoids, tumor necrosis factor (TNF)- α and promotion of molecules that contribute to resolution of inflammation [5]. These mechanisms likely account for its efficacy in inflammatory conditions such as rheumatic fever at 4000 mg/day [6]. In TBM, aspirin's anti-inflammatory and pro-resolving properties were explored in the zebrafish in which the hyperinflammatory LTA4H phenotype treated with aspirin showed reduced expression of pro-inflammatory eicosanoids and TNF- α , with

subsequent modulation of the inflammatory response [7]. These findings provided rationale for the use of high dose aspirin (1000 mg/day) in the Mai et al. RCT included within this analysis, where downstream CSF analysis demonstrated dose-dependant inhibition of thromboxane A2 and upregulation of pro-resolving CSF protectins [8]. In this study there was no significant increase in adverse events due to high dose aspirin; a concern given concomitant dexamethasone and platelet dysfunction in TBM. Given that a hypercoagulable [4] and hyper-inflammatory state contribute to pathogenesis, this dual mechanism of action and therefore potential dose-dependent effects are important considerations for future use of aspirin in TBM.

Similarly to optimal dose, optimal duration of treatment with aspirin in TBM is poorly understood, demonstrated here by the differing treatment duration in the three RCTs (1 month, 60 days, 3 months). Mortality in TBM occurs predominantly in the two weeks after diagnosis [9] however neuroinflammatory sequelae that lead to morbidity can develop beyond this time. In a recent study of patients with TBM, acute infarcts were predominantly observed on baseline scans (26/60,43%) with only 1/33 undergoing follow-up imaging demonstrating new evidence of infarction 60 days later. Here, 89% of patients showed worsening MRI findings despite treatment including 82% (27/33) with new or enlarged tuberculomas and 76% (25/33) with worsening meningeal enhancement [10]. The discussion around optimal duration therefore must consider the mechanism for which aspirin is used, which in turn reverts to discussion on optimal dose and mechanisms of action; optimal duration may differ depending on whether low (anti-platelet) or high (anti-inflammatory) doses are being used, and whether use is to prevent stroke, or whether there is potential to prevent other neuroinflammatory sequelae.

Consideration of means to assess outcome is also required; the authors concluded that aspirin may have a role in stroke prevention, which was a secondary outcome in this meta-analysis, however there were substantial differences in the type and timing of brain imaging conducted by each study. Pre- and post-contrast MRI is the modality of choice in TBM, but access to this is limited, particularly in settings where TBM is common. CT imaging is limited in its ability to detect new infarcts in particular those that are acute, small (e.g. lacunar), or located in the posterior fossa, which must be considered within the analyses. The finding that radiological changes occurred in the absence of clinical deterioration in the aforementioned study, also supports the need for pre-specified imaging timepoints despite clinical course [10].

DOI of original article: <http://dx.doi.org/10.1016/j.eclinm.2021.100819>.E-mail address: r.j.wilkinson@imperial.ac.uk (A.G. Davis).<https://doi.org/10.1016/j.eclinm.2021.100871>2589-5370/© 2021 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

This meta-analysis provides welcome stimulus for discussion on the potential benefit of aspirin in TBM, however also highlights the lack of consensus on its use. Results from RCT underway (NCT03927313, NCT04145258) will shed light on this, in particular optimal dosing, and may in turn increase what is currently a weak armoury of host directed therapies for patients with TBM.

Declaration of Competing Interest

The authors are funded in part by Wellcome [104803, 211159, 230135]. For the purpose of Open Access, the authors have applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission. The authors are also supported by the Francis Crick Institute which receives its core funding from Cancer Research UK (FC0010218), the UK Medical Research Council (FC00101218), and Wellcome (FC00101218). The authors also receive support from EDCTP (RIA2017T-2019 109237), NIH (R01AI145436) and Meningitis Now. The authors declare no conflict of interests.

References

- [1] Selvaraj JU, et al. Identification of predictors of cerebrovascular infarcts in patients with tuberculous meningitis. *Int J Mycobacteriol* 2020;9(3):303–8.
- [2] Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nat New Biol* 1971;231(25):232–5.
- [3] Richman IB, Owens DK. Aspirin for primary prevention. *Med Clin North Am* 2017;101(4):713–24.
- [4] Schoeman J, et al. Coagulant and fibrinolytic status in tuberculous meningitis. *Pediatr Infect Dis J* 2007;26(5):428–31.
- [5] Botting RM. Vane's discovery of the mechanism of action of aspirin changed our understanding of its clinical pharmacology. *Pharmacol Rep* 2010;62(3):518–25.
- [6] Cilliers A, Adler AJ, Saloojee H. Anti-inflammatory treatment for carditis in acute rheumatic fever. *Cochrane Database Syst Rev* 2015(5):CD003176.
- [7] Tobin DM, et al. Host genotype-specific therapies can optimize the inflammatory response to mycobacterial infections. *Cell* 2012;148(3):434–46.
- [8] Mai NT, et al. A randomised double blind placebo controlled phase 2 trial of adjunctive aspirin for tuberculous meningitis in HIV-uninfected adults. *Elife* 2018;7.
- [9] Marais S, et al. Presentation and outcome of tuberculous meningitis in a high HIV prevalence setting. *PLoS ONE* 2011;6(5):e20077.
- [10] Dian S, et al. Brain MRI findings in relation to clinical characteristics and outcome of tuberculous meningitis. *PLoS ONE* 2020;15(11):e0241974.