Figures and figure supplements

A randomised double blind placebo controlled phase 2 trial of adjunctive aspirin for tuberculous meningitis in HIV-uninfected adults

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192 patients assessed for eligibility

72 patients excluded†
- 30 did not meet inclusion criteria
- 10 declined to participate
- 33 had diagnosis other than TBM

120 participants randomised

41 allocated to placebo
- 0 withdrew
- 2 lost to follow-up

41 included in the intention-to-treat analysis
- 5 excluded:
  - 1 confirmed other diagnosis
  - 4 <30 days of study drug

36 included in the per-protocol analysis

39 allocated to aspirin 81mg
- 0 withdrew
- 0 lost to follow-up

39 included in the intention-to-treat analysis
- 8 excluded:
  - 1 confirmed other diagnosis
  - 1 MDR TB
  - 6 <30 days of study drug

31 included in the per-protocol analysis

40 allocated to aspirin 1000mg
- 0 withdrew
- 0 lost to follow-up

40 included in the intention-to-treat analysis
- 9 excluded:
  - 9 <30 days of study drug

31 included in the per-protocol analysis

† Further details of reasons for exclusion given in supplementary file 2 (table S2). One participant could have more than one reason for exclusion.
Figure 2. Forest plots of ITT, per-protocol and planned sub-group analysis of aspirin 81 mg versus placebo (A) and aspirin 1000 mg versus placebo (B) for the primary efficacy outcome. Estimates for subgroups without events were obtained via Firth’s penalized likelihood. Panels show 8 month survival plots for the ITT (C) and per-protocol (D) populations.

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Figure 2—figure supplement 1. C (panel within Figure 2). ITT population survival in each group over 8 months.

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Figure 2—figure supplement 2. D (panel within Figure 2). Per-protocol population survival in each group over 8 months.

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Aspirin 81mg: HR = 1.42 (0.37 - 5.16), P = 0.592
Aspirin 1000 mg: HR = 0.36 (0.04 - 1.81), P = 0.230
Figure 3. LCMS lipid mediator profiles in the CSF of adults with TBM according to treatment with aspirin or placebo. CSF was collected from participants at baseline and 30 days after 81 mg, 1000 mg or placebo administration. (A) Partial least squares discriminant analysis 2-dimensional score Figure 3 continued on next page
plot of the distinct LM-SPM profiles identified in day 30 CSF at the indicated intervals (top panel) and corresponding 2-dimensional loading plot. Grey ellipse in the score plots denotes estimated 95% probability regions (bottom panel). Grey circles in the loading plot represent LM with a variable in importance score $\geq 1$. (B) Relative regulation of Thromboxane B$_2$ (the stable TXA$_2$ further metabolite), Prostaglandins (PGD$_2$, PGE$_2$, PGF$_2$) and Protectins (PD1, 17R-PD1, 22-OH-PD1, 10S, 17S-diHDDA, PCTR1, PCTR2 and PCTR3) by day 30 compared to baseline values (absolute values given in supplementary file 6). Results for B are mean $\pm$ s.e.m, $n = 30$ for placebo, $n = 26$ for 81 mg and $n = 26$ for 1000 mg group. Comparisons between treatment groups assessed using one-way ANOVA followed by multiple comparisons test. Only p-values $< 0.05$ given in the figure (all other comparisons non-significant).

DOI: https://doi.org/10.7554/eLife.33478.013
Figure 3—figure supplement 1. Lipid mediator profiles of CSF from participants with TBM. Lipid mediators (LM) were extracted, identified and quantified using LM profiling. (A,B) Multiple reaction monitoring chromatograms for identified mediators. (C) tandem mass fragmentation spectra employed in the identification of PD1 and 15-epi-LXA₄. Results are representative of 82 patients.

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