Author's response to reviews

Title: Mesalazine in the initial management of severely acutely malnourished children with environmental enteric dysfunction: a pilot randomised controlled trial

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Author's response to reviews: see over
Mesalazine in the initial management of severely acutely malnourished children with environmental enteric dysfunction: a pilot randomised controlled trial

Response to reviewers’ comments (version 1)

14th July 2014

We are very grateful for the encouraging feedback from both reviewers. Specific points raised in the reviews are addressed below, new material is highlighted in red type.

Reviewer 1: Mark Manary

Thank-you for your comments and review.

Minor Essential Revisions

1. The term malnutrition is used in the manuscript, and I think it is not meaningful. I would suggest using the terms SAM, MAM and stunting. Additionally growth faltering can be used to describe reduced rate of linear growth.

   Thank-you for this comment. It is important to note that the children enrolled in this study needed to be severely acutely malnourished (SAM) and stunted, and in fact the degree of stunting was severe (median HAZ -3.13 and -3.73 in the mesalazine and placebo arms, respectively). We have clarified the terminology used throughout along the lines suggested, including in the title (spelling out ‘acute malnutrition’ if we are referring to SAM and MAM together).

2. Tuberculosis does not need to be capitalized and should be spelled out in the text.

   Thank-you, we have changed this.

3. Is treatment with mesalazine contraindicated in any common infections with SAM, such as tuberculosis or gram negative sepsis, if so make that clear.

   We have provided clarification on the grounds on which exclusion criteria were decided in the Study Methods, page 7:

   “The exclusion criteria were decided on the basis of contraindications listed in the Summary of Product Characteristics, pre-existing conditions that the investigator group felt increased the risk to participants (e.g. HIV infection, bloody diarrhoea, other overt infection requiring hospital admission), or likely futility in the presence of other major medical problems (e.g. tuberculosis, cerebral palsy). We did not consider concurrent or recent viral infection or administration of a live viral vaccine to be a contraindication to administration. Although Reye’s syndrome has
historically been associated with salicylate (mainly aspirin) use in these circumstances, we were unable to find even a single report of Reye’s associated with mesalazine, and such cautions are not advised when it is used in the context of IBD.”

While we are unaware of any robust evidence on the efficacy or safety of mesalazine in the presence of the conditions mentioned (tuberculosis of Gram –ve sepsis), we considered that a common-sense approach would be to ensure treatment of any major overt infections prior to initiating therapy. Furthermore, we asked parents to withhold the study drug during acute diarrhoeal episodes, as clarified in the Study Methods, page 10:

“Carers were asked to withhold the study drug if the child developed diarrhoea, blood in stools or unexplained bruising, and to bring the child for assessment as soon as possible. Study drug was suspended until diarrhoeal episodes had resolved.”

4. A limitation of the trial is that damage to the gut mucosa in kwashiorkor, the condition of most of the subjects, might well be different than environmental enteropathy associated with stunting. During the vulnerable period with SAM it might be better to have a gut with the maximum capacity to mount an inflammatory response, while in a state of chronic malnutrition it might be better to reduce the inflammatory response. This should be noted in the discussion, the trial is not generalizable to less severe populations.

Thank-you for this valuable comment. We have incorporated these points in the Study Discussion on page 19:

“The enrolment of children who were severely acutely malnourished as well as stunted was ethically appropriate because children with SAM are at the highest risk of continued growth disturbance, illness and death, meaning that they have the most to gain from any potential new intervention. However, even though these results suggest a maladaptive inflammatory enteropathy, it may be that ensuring optimal capacity to respond to a new pathogen challenge takes precedence over optimising growth in the context of SAM, where vulnerability to major infection is intense. Targeting those with moderate acute malnutrition or non-acutely malnourished children would be likely to increase the chances of detecting any nascent IGF-1-mediated linear growth benefit and presents the most plausible scenario under which such interventions could be used in the field. In this regard, a limitation of the study is that the inflammatory enteropathy found in kwashiorkor (which was present in 73% of those enrolled) may be qualitatively different to that present in the context of other forms of acute malnutrition, and to the form of EED that appears to be prevalent with stunting. Results of the current trial should not be considered generalisable either to children with stunting but without acute malnutrition or to populations of moderately or severely malnourished children without high prevalence of kwashiorkor, and future studies in such groups will need to take a similarly cautious and thorough approach as we
have here. That said, such studies should consider the use of more intensive treatment schedules because although mesalazine is a good agent for maintenance of remission in IBD, it is less effective in induction. Difficulty in diagnosing tuberculosis in acutely malnourished children may preclude the use of systemic immunosuppressants, but longer courses or higher doses of mesalazine could reasonably be trialled.”

Reviewer 2: William Petri

Thank-you for your comments and review.