Reviewer's report

Title: Efficacy and safety of pamidronate in Modic type 1 changes: study protocol for a prospective, randomized, controlled clinical trial.

Version: 1 Date: 23 October 2013

Reviewer: Marissa Lassere

Reviewer's report:

It is good to see RCTs of interventions that show promise in pilot studies. The protocol is generally internally sound and well articulated with a number of strengths. However, I have a number of comments/questions/requests.

Major compulsory revisions

1. State clearly that the trial is a phase 2 trial (as is noted in its information on ClinicalTrials.gov) and that there are no published controlled trials of pamidronate in erosive degenerative disease. I can find only one open study, the authors’ pilot study (ref 25). Also please provide the hypothesis.

2. Describe the findings of Modic type 1 change and summarize the history that this is a validated clinical finding, especially in light of reference 1 which seems to pretty clearly show that Modic type 1 patients do not satisfy standard ankylosing spondylitis criteria. I presume the Modic 1 change marker is meant to confer a different prognosis compared to those without it. The typical reader (including many rheumatologists) will probably not be familiar with this information. I understand that Modic type 1 changes also occur in the normal population. Can this also be mentioned. The issue of course is that back pain is very common and Modic type 1 change is common therefore the two can coincide in the single subject. Are there published classification criteria? This is important regarding the generalisability of the trial results.

3. Discuss the dosage regimen used, 90mg/day x 2 days as this exceeds all regimens identified in the US pamidronate label. For example, in the treatment of osteolytic bone lesions of multiple myeloma, the dose is 90mg monthly.

4. (i) Discuss the known toxicity profile of pamidronate including renal toxicity and why no exclusion/inclusion criteria address this.

(ii) Furthermore, regarding the inclusion criteria, that the pain is inflammatory in nature is not indicated. Inflammatory back pain has certain characteristics that is not captured with the inclusion criteria as specified in the manuscript. Can the authors please confirm that subjects have symptoms of inflammatory back pain and specify how this is determined?

5. The sample size calculation is accurate only if one assumes the SD of the difference (test vs. control) of the change scores (initial vs. final) is the same as the historical SD of the change score found for treated patients in the open pilot study (ref 25). This is unlikely given that this is a blinded study. Generally in blinded studies the difference scores are smaller but the SD may be larger. If so
this will translate into a needed larger trial size. Furthermore the open label results were those seen at 6 months and not 3 months.

6. There are an enormous number of statistical analyses planned. Can the authors confirm that the primary analysis is VAS pain difference at 3 months using a Student t test if normally distributed and Mann Whitney if not, without adjustment as any adjustments are discretionary. There are only 4 subjects per block on pamidronate and 4 on placebo. How are you going to use this in the analysis. Any differences may occur by chance and adjustments may threaten the randomised nature of the study?

7. Can you clarify that failures at three months are provided a brace? How does efficacy of a brace at 6 months relevant to this trial of pamidronate efficacy? It is not at all clear from the protocol. It there a crossover component to this trial.

8. How are you adjusting for analgesic use and other co interventions during the study. What if the pamidronate group use more analgesia or require more physiotherapy visits?

9. How will dropouts be analysed?

10. Some of the text should be rewritten to improve readability and for accuracy.

"The primary outcome measure will be the variation between D0 and D90 (11, 14, 17) of spinal pain assessed by VAS (25) between the treatment group and the placebo group (with a standard deviation of the pain variation assessed by VAS fixed to 30 [8, 25])."

(i) Do you mean:

The primary outcome measure will be the difference between D0 and D90 (11, 14, 17) of spinal pain assessed by VAS (25) between the treatment group and the placebo group"

"with a standard deviation of the pain variation assessed by VAS fixed to 30 [8, 25])."

(ii) How do you fix the SD? I don't understand?

"all statistical tests will be considered for a type I error # of 5%"

(iii) there are a great many secondary outcomes both as measures and the statistical tests that will be used. If all of them are assessed at 5% some will be significant by chance. Please comment.

"The number of patients included and the inclusions curve, the number of visits corresponding to the number of patients included, the real number of visits conducted, and the ratio between the two will be presented by group."
"As a first pilot study conducted a few years ago in our department showed good efficacy (25), we decided to objectivize more clearly the efficacy of pamidronate on this cause of disabling, chronic low back pain in this prospective study. The inclusions started in January 2013 and will continue until the end of December 2014, with results becoming available from spring 2015."

The results from our pilot study, an open-label study of 10 subjects were encouraging (25), but clearly the efficacy of pamidronate in this condition required further investigation in a prospective blinded randomised controlled trial. Subject recruitment began in January 2013 and will continue until the end of December 2014, with results becoming available from March 2015."

11. Could the manuscript be written so that it conforms to CONSORT guidelines.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests