Author's response to reviews

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

Authors:

Stella Cecchetti (stellacecchetti@hotmail.fr)
Bruno Pereira (bpereira@chu-clermontferrand.fr)
Antoine Roche (aroche@chu-clermontferrand.fr)
Christophe Deschaumes (cdeschaumes@chu-clermontferrand.fr)
Dihya Abdi (dabdi@chu-clermontferrand.fr)
Emmanuel Coudeyre (ecoudeyre@chu-clermontferrand.fr)
Jean-Jacques Dubost (jjdubost@chu-clermontferrand.fr)
Sylvain Mathieu (smathieu@chu-clermontferrand.fr)
Sandrine Malochet-Guinamand (smalochet@chu-clermontferrand.fr)
Anne Tournadre (atournadre@chu-clermontferrand.fr)
Marion Couderc (mcouderc@chu-clermontferrand.fr)
Marielle Vayssade (mvayssade@chu-clermontferrand.fr)
Coline Daron (cdaron@chu-clermontferrand.fr)
Martin Soubrier (msoubrier@chu-clermontferrand.fr)

Version: 3
Date: 15 January 2014

Author's response to reviews: see over
Efficacy and safety of pamidronate in Modic type 1 changes: study protocol for a prospective, randomized, controlled clinical trial

Please find below a point-by-point response to the concerns raised following the review of the original manuscript.

Editorial’s request: As requested, we added Marion Couderc in the Authors’ Contributions section.

Reviewer’s report:

1: We have stated that this is a phase 2 trial in the abstract too. The hypothesis indicating the clinical population, the intervention and the outcome has been provided in the Background/Introduction section; we did not, of course, overly detail it, for the Methods section right below did.

2: Erosive Degenerative Disk Disease (EDDD) is mostly a french denomination for a type of non-infectious erosive disease of the spine, among others, such as crystal deposition disease, erosive discopathy in patients under chronic haemodialysis, rheumatic diseases with inflammatory discopathy…EDDD is the degenerative, or osteoarthritic, subcategory of non-infectious erosive disk diseases. Erosions are, we admit, not an essential feature of Modic type 1 changes, but the two have often been associated, since studies have described a constant presence of Modic type 1 changes in EDDD (1). Moreover, usually superficial erosions have been described as one of the elementary bone lesions in degenerative disk disease associated with Modic type 1 changes (2). Since “Modic type 1 changes” is supposedly a radiological definition and doesn’t encompass the clinical aspect, it has been accepted for a long time, in France at least, that we speak of EDDD, recently changed to “Active Discopathy”. Since our pilot study had kept the EDDD appellation, we chose not to change it to “Active Discopathy” or “Degenerative Disk Disease with Modic type 1 Changes”, which, we recognize, would have probably been more accurate.

As for the correlation between Modic type 1 changes and back pain, it is indeed still a matter of debate. There is however, to this date, far more evidence in favor of a real relationship between the two than otherwise. A 2008 systematic review (3) thus found “a positive association between VESC (Vertebral endplate signal changes (Modic change)) and LBP in the majority of studies reporting on this subject”, with ORs for the studies that reported a statistically significant positive association ranged from 2.0 to 19.9. Moreover, “a positive association between VESC and LBP has not only been found in the majority of studies of patients with LBP from different countries, but also in the general and working populations. In other words, there is a considerable consistency in this association.”

Another 2008 review (4) confirmed the possibility of asymptomatic individuals with Modic changes but emphasized on its infrequency (5-7), and concluded that type 1 changes are “likely to be inflammatory in origin and seem to be strongly associated with active low back symptoms and segmental instability, thus reflecting a state of active degeneration and biomechanical instability of the lumbar spine”.

In the light of this, we chose not to reflect this controversy in the manuscript, for this study’s purpose was not to re-open this debate, but propose a treatment to patients with both low back pain and Modic type 1 changes, which reduced the chance of them merely being imaging biomarkers with no clinical significance.


Finally, we removed the “mixed pattern” from the manuscript, since Modic type 1 changes are indeed usually associated with a rather inflammatory pattern (8).

5: We have added the sample size considerations in the Discussion section.

6: We have included our response in the Discussion section.

7: We are sorry if we have not been clear enough concerning the rigid back brace. We have proposed it in case of failure at three months, not as part of the evaluated treatment, but merely as a rescue treatment whose efficacy is still not entirely clear (9), but is far less invasive than surgery. It was never part of our hypothesis, which only concerns pamidronate, and we will only include it in our analysis as an ancillary treatment, such as medications and physiotherapy.


9: We agree with the reviewer. The part concerning missing data was completed in the Statistical Considerations section.

10 (iii): We agree and thank the reviewer for the additional comment. As we indicated in the previous response, it seems that adjustment for multiplicity can be discussed according to published opinions, which vary tremendously. But it is clear that the risk of a type I error is high and multiplicity is an issue in regards of the three timepoints evaluations. We might think that using random-effects model will decrease this risk. However, as suggested by the reviewer, due to multiple comparisons envisaged at these three timepoints evaluations, the inflation of type I error was taken into account for each additional endpoint (Bonferroni adjustment should not be too conservative with only three timepoints).

11: We have once again reviewed our manuscript according to the CONSORT 2010 checklist, and have not found it lacking, apart from the Results section, which we cannot, since our study is currently ongoing and we have no result so far, write in this manuscript yet. Can the reviewer tell us precisely in what aspects the manuscripts does not follow the CONSORT Guidelines?

The authors declare that they have no conflicts of interest and have given their written permission to publish this work.

The contents of the manuscript have not been published elsewhere. Correspondence should be addressed to:

Dr Martin SOUBRIER, Service de Rhumatologie
CHU Gabriel Montpied
58 rue Montalembert
63003 CLERMONT FERRAND CEDEX 1
FRANCE

We hope that this manuscript will meet your requirements.

Sincerely

S Cecchetti, B Pereira, A Roche, C Deschaumes, D Abdi, E Coudeyre, JJ Dubost, S Mathieu, S Malochet-Guinamand, A Tournadre, M Couderc, M Vayssade, C Daron, M Soubrier