Reviewer's report

Title: Results from the 5-year, phase IV RENEW (Registry to Evaluate Novantrone Effects in Worsening Multiple Sclerosis) Study

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Reviewer: vittorio martinelli

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This paper presents the results of a large cohort of patients treated with Mitoxantrone in the USA and prospectively followed to evaluate long-term safety. The data collected show a detailed description of heart related SAE in the cohort of patients, occurring mainly during the MTX infusion period. Cardiotoxicity was found related to MTX cumulative dose, older age and previous or concomitant use of Methotrexate. Leukemia was reported in three patients, but unfortunately no clinical data are available for 1 patient (how long after MTX first and last doses did leukemia develop?)

The study is well written and literature data widely considered.

I have a few criticisms and recommendations:

In spite of the noteworthy advantages due to the prospective methodology of the study, more than half of the patients were lost to the 5 years planned follow up. More evidence and comments on this great limitation of the study should be described in the discussion, as well as the frequent SAEs reported by local PI as not related to MTX therapy. This could be the reason for the usual under-reports of adverse events and for an even higher risk for the patients in real world clinical practice.

The authors in table 6 present the clinical characteristics of the 12 patients who died, but no data on EDSS at MTX beginning, MTX cumulative dose and age. SAE presented during treatment or during Follow up should be described separately and the frequency as well. I would recommend to complete the table and to add a sentence in the discussion section, commenting the high incidence of infection-related deaths, highlighting the fact that MTX treatment relation was frequently not reported.

This is a relevant finding because, in clinical practice, neurologists must consider the high risk of severe infective disease, after MTX treatment, mainly in disable MS patients.

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

Quality of written English: Acceptable
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