Reviewer’s report

Title: Methotrexate therapy impacts on red cell distribution width and its predictive value for cardiovascular events in patients with rheumatoid arthritis

Version: 1 Date: 09 Dec 2017

Reviewer: Miguel Ángel González-Gay

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This study indicates that red cell distribution width (RDW) may be a marker of future cardiovascular events in patients with rheumatoid arthritis (RA) not taking methotrexate (MTX). It is already known that MTX, Methotrexate inhibits dihydrofolate reductase, which leads to accumulation of polyglutamated folates. Consequently RDW may be increased in patients taking this synthetic DMARD. Nevertheless, several studies indicate that MTX use is associated with reduction in the mortality of patients with RA, mainly due to a reduction in the cardiovascular mortality. Therefore, it is possible that the anti-inflammatory effect mediated by MTX may compensate the potential negative effect derived from its anti-folic action.

The authors confirmed the expected association of cardiovascular events and age/disease duration.

This study is of potential interest. I do not have major points of criticism. Potential limitations have been elegantly discussed by the authors. Methods are sound. Results are presented clearly. However, I have a few comments/suggestions that from my point of view may improve the Discussion:

1) Page 11: Lines 19-21: Highlight the potential relevance of "the genetic component" in the risk of cardiovascular disease associated to RA as follows:

Therapy and CV events with other important variables including classic cardiovascular risk factors, "the genetic component" or iron homeostasis. [3, 31, and a new Ref. 32]


2) Page 11-Line 21: Also, add the following paragraph along with the corresponding references:
"In this regard, patients with RA who carried the methylene tetrahydrofolate reductase (MTHFR) 1298 allele C frequency were found to have an increased frequency of cardiovascular events after 5 years and 10 years of follow-up. Moreover, patients carrying the MTHFR 1298 AC and CC genotypes had a significantly decreased flow-mediated endothelium-dependent vasodilatation (a marker of endothelial dysfunction that is an early step in the atherogenesis process) when compared with those carrying the MTHFR 1298 AA genotype [new Ref. 33]. More recent results also indicate that MTHFR expression is significantly reduced in patients with RA compared to controls [new Ref. 34]. It was found especially true for RA patients with ischemic heart disease [new Ref. 34]. Taken these considerations together, these results indicate that MTHFR gene may influence the risk of subclinical atherosclerosis and cardiovascular disease in patients with RA."


Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

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