Author's response to reviews

Title: Old drugs, old problems: Where do we stand in prediction of rheumatoid arthritis responsiveness to methotrexate and other synthetic DMARDs?

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Author's response to reviews: see over
Dear editor,

We are resubmitting our manuscript, reference 1038269087991507, entitled “Old drugs, old problems: Where do we stand in prediction of rheumatoid arthritis responsiveness to methotrexate and other synthetic DMARDs?”

We are grateful for the reviewers’ comments and have modified the manuscript taking into account their suggestions, which have been useful in improving the quality and rigor of the content.

Please see below the point-by-point response to the reviewers’ concerns and to the editor’s comments. The revised manuscript marked with track changes is also uploaded.

We hope that the reviewed version meets the expectations of the referees and the Editorial Board and is found suitable for publication in BMC Medicine.

Best regards,
Vasco C. Romão
Helena Canhão
João Eurico Fonseca
REVIEWER 1

1 – In the some of the articles analysed it is difficult to ascertain if the prognostic factors are related to MTX itself or may be related to other DMARDs or the combination of both. I think that this statement should be addressed in the introduction section.

We agree with the reviewer and we find this observation to be of the utmost importance. In fact, while there are a considerable number of articles that analyze methotrexate (MTX) in monotherapy, some consider associations with other DMARDs, making it difficult to ascertain which part of the effect seen is actually attributable to MTX. However, it is also true that in those articles – as in daily care – MTX is the mainstay-drug and other DMARDs are either accessory or complementary, and one might assume that the treatment outcome is the result mainly of MTX action, albeit influenced by other drugs. In summary, we agree with the reviewer that concomitant DMARDs might confound the results of response to MTX and, accordingly, we have introduced the following consideration in the “Discussion” section (page 36, 3rd paragraph):

“… third, several studies consider MTX in association with other DMARDs, making it difficult to ascertain whether the observed effect in those cases is the result of MTX itself, the associated DMARD or the combination of both; ...”

We are aware that the referee’s suggestion was to address this question in the “Introduction” but we consider that given the content and goal of that chapter, this sentence would fit better in this particular paragraph of the “Discussion”, where separate important comments are made on the results.
Taking into account that this review is addressed not only to rheumatologists, the impact and the recommendations of use of MTX in RA in the therapeutic strategy of RA may be of interest for the readers; therefore a small summary on this topic is appropriate.

Given the nature and target of this paper we agree that a summary of the current recommendations for the daily clinical practice use of MTX in RA is appropriate. In line with this, we have added a table adapted from the recommendations issued in the setting of the 3E Initiative by a multinational panel of experts, which included rheumatologists from our group.

The table – **Table 1** – has been inserted in the “Introduction” setting, with the following reference in the text (Page 4, paragraph 1):

“...Multinational recommendations have been issued for the use of MTX in RA management [10] and are summarized in Table 1. However, MTX is not effective or induces significative adverse events in a considerable proportion of patients [10] who are forced to discontinue it and switch to another DMARD regimen, generally with equally heterogeneous responses [5].”

The table has been placed in the manuscript in the “Tables” section, pages 59-60, and the numbers of the remaining tables have been updated both in this section and throughout the text. The table has been adapted with the permission of the journal (Annals of Rheumatic Diseases) [1].
The section of Genetic biomarkers of response seems to me to be too extensive and I suggest to shorten it of substantial form.

Taking the referee’s suggestion into account, we have eliminated and simplified several sentences and paragraphs of this chapter that we find to be redundant or less important. By doing this, we have managed to cut down two pages of the manuscript.

In addition, to overcome the length issue, and meet the reviewer’s concerns, we have substantially reduced the final part of the “Nongenetic biomarkers of response” section. The findings reported were mainly based on small studies and the implications for clinical practice and future research agenda were limited, and, in our opinion, less relevant than the following chapter. As such, we have still kept the references of the factors in question, but we have further reduced the text in approximately more one and a half pages.
REVIEWER 2

1 – The question regarding prediction of treatment response is not very new. Also in the context of current T2T treatment paradigms and wider dose adjustments used with MTX/DMARDs as opposed to biologicals and efficiency/cost-effectiveness reasons, a focus on biological treatment for this question might be more helpful (but not newer). This should be discussed. (…) A discussion on the distinction in studies on prediction of response to MTX/DMARD and biologicals is needed. Also in light of current treat to target treatment strategies and fast increase in treatment intensities to (biological) treatment.

We agree with the reviewer that the issue of predicting response to treatment is far from being a novel, groundbreaking one. Moreover, prediction of response to extensively used drugs such as MTX and other DMARDs has been thoroughly addressed in the literature for the past two decades. However, as we noted in the second and third paragraphs of the “Introduction” chapter (pages 4-5), despite all the research, to date there are no reliable factors that allow such prediction, making the aim of this review, while not innovative, still of critical relevance.

In fact, the concept of personalized therapy is becoming a central goal in the management of RA. Being able to predict which patient will respond to synthetic DMARDs would allow to individually select the most suited drug, avoiding exposure to non-effective therapies, exposure to potential adverse effects, waste of precious time to achieve disease control and use of costly biological drugs unnecessarily. All of this is exposed in the second paragraph of the “Introduction”.

We also share the vision of the referee that prediction of response to biologic therapies is of great importance and a current theme that needs to be addressed. However, this paper was commissioned to us by the editor of BMC Medicine, to focus on the theme of personalized therapy in rheumatoid arthritis and we, for the aforementioned reasons, decided to approach prediction of response to synthetic DMARDs, with MTX at the top.
2 – The review seems mainly narrative. The tables as present in the paper are not referenced throughout the text. Probably the tables could also be more informative, for example concerning other variables studied (multivariate analysis) in the (individual) papers. Some more quantitative summary might be helpful. Results seem an (subjective) opinion of the authors. (...) Due to the nature of the review there is (too) much text, although well written (some small ‘typos’) maybe referring more to tables and some more quantitative tables (see earlier comments) might improve the readability.

We have introduced in the beginning of each major chapter, references for the tables summarizing the findings reported in the text (pages 6, 17 and 24), as well as in the “Discussion” section, when debating the results for each class of response markers (pages 35, 36 and 37).

Given that this commissioned review did not have the purpose of being a systematic review (see comment made by the editor) and that there was a considerable amount of references and information, the purpose of the tables included in the manuscript was to summarize the body of data available for each factor. The tables translate what is said in the text, particularly in terms of whether it is possible or not to take conclusions on the predictability role of the markers considered. As such, they do indeed contain in part our opinion on interpretation of the reported results.
Abstract does not report on any results/conclusions from the review.

Results and conclusions were not previously included in the “Abstract” because as a global, non-systematic review on the theme, we decided to make a more general, introductive summary of the theme and of the article purpose. Nonetheless, and as suggested, we have added the following sentences in the end of the “Abstract”, which translate the main results and conclusions of the review:

“...Although it is still not possible to predict response to MTX, factors associated with increased effectiveness include male gender, non-smoking, early disease stage, absence of previous DMARD use, lower baseline disease activity measured by composite scores, concomitant corticosteroids and shared epitope negativity. Combination of distinct factors and replication of results in large studies will help to confirm these findings and allow prediction of individual response to MTX.”
We agree with Reviewer 2 that, indeed, the cellular cycle of MTX is not essential for daily clinical practice. However, when approaching the complex field of MTX pharmacogenetics, where several enzymes and transporters are enrolled, we find it helpful to include a schematic representation for readability purposes. It is easier for readers to refer to the figure while following through the text for clarification of the names and acronyms of the cellular elements in question.
Division of possible predictors in clinical, nongenetic biomarkers and genetic biomarkers might be counterintuitive. No single predictor is probably sufficient for response prediction in clinical practice. Therefore especially a combination of different predictors (irrespective of type of predictor) is of interest. The authors should at least discuss what/which combinations of predictors might have suitable predicting ability and how they can be used in clinical practice (i.e. when to make the decision not to start with MTX/DMARD treatment).

The division of predictors into three categories was adopted for two purposes: on one hand, it simplified the approach to a comprehensive subject and article such as this one; on the other hand, we find the division to be useful when translating the data into clinical practice, since it clearly separates immediate, easily accessible factors such as the clinical data (sex, disease duration, smoking status, etc) from others that can be more (RF, ACPA) or less (SNPs) attainable.

However, we agree with Referee 2 in that, most likely, accurate prediction of response is given by combinations of factors, rather than single predictors alone. This position is stated several times throughout the article, as the following examples demonstrate:

- (...) while some factors (female gender, established disease, previous DMARD use, smoking, high disease activity determined by composite scores, absence of concomitant corticosteroids, SE-positivity) seem to be individually associated with weaker response to MTX, drug effectiveness will ultimately be the result of multiple clinical and biological (genetic and nongenetic) variables that will interact to determine whether a patient respond or not to a particular drug. ("Discussion", page 35, paragraph 1)

- These findings clearly reinforce the notion that considering groups of potential predictive factors will be more efficient than simply analyzing them individually. Thus, including clinical, genetic and nongenetic biological factors is more effective than a parallel approach. ("Discussion", page 36, paragraph 1)
- *Combining distinct factors, adopting new approaches in emerging fields and applying them in larger standardized studies will help define prediction models and reach the longed-for goal of tailor-made therapy* ("Conclusions", page 40, paragraph 1)

We had not previously included a discussion on possible combinations of predictors usable in clinical practice, because the results present in the article are mostly based in the individual predictive value of each factor. We cited the few studies where combinations of different predictors were analyzed (page 35, paragraph 2), but highlighted that the results were not replicated.

In this line and as suggested by Referee 2, we have introduced the following paragraph in the "Discussion" section (page 37, paragraph 3):

"...As previously mentioned, combining different factors might be useful in determining whether a patient will respond to MTX. Although models such as the one developed by Wessels et al [22] might be more reliable for achieving this purpose, we can assume that starting and maintaining treatment with MTX will probably be more effective in male, non-smoking, DMARD-naïve, SE-negative patients with early, mild disease and that corticosteroids should be added as adjuvants. Other variables such as genetic determinants will be valuable in increasing the accuracy of the prediction model, but at the moment it is not possible to define them with certainty."
EDITORIAL REVISIONS

1 – Please include an authors’ information section at the end of your manuscript. You can include any relevant information about the author(s) that may aid the reader’s interpretation of the article, and understand the standpoint of the author(s). This may include details about the authors' qualifications, current positions they hold at institutions or societies, or any other relevant background information.

As suggested, we have included the following paragraph at the “Authors’ information” section (page 41):

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HC, MD, MMSc, PhD Principal Investigator at the Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa. She is Assistant Professor of Rheumatology and a Rheumatology Consultant at the Lisbon Academic Medical Centre. She is also the National Coordinator of Reuma.pt (Rheumatic Diseases Portuguese Register, Portuguese Society of Rheumatology).

JEF, MD, PhD is the Head of the Rheumatology Research Unit and of the Biobank at Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa. He is Assistant Professor of Rheumatology and a Rheumatology Consultant at the Lisbon Academic Medical Centre. He is also the President-Elect of the Portuguese Society of Rheumatology.
2 – Please confirm whether figure 1 was made exclusively for the manuscript, or if copyright permission was obtained to reproduce it from elsewhere.

We confirm that we made Figure 1 exclusively for the manuscript.
References