

October 05, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 12218-review.doc).

Title: How to choose the best biological treatment for rheumatoid arthritis? A systematic review of effectiveness

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The manuscript has been improved according to the suggestions of reviewers:

Dear Reviewers,

Thank you for your comments concerning our manuscript.

Your comments are all very valuable and helpful in the revision and improvements of our paper and they also have very important guiding significances to our research, as well.

We have studied your comments carefully and have made corrections that we hope will meet your expectations.

Revised portions are marked in yellow in the paper.

The main corrections in the paper and the responses to your comments are as follows:

Reviewers' comments

Original text	Reviewer 1	Answer
Title		
How to choose the best biological treatment for rheumatoid arthritis? A systematic review of effectiveness	The review fails to deliver the title.	Suggestion accepted. The title was modified to: <i>“What is the best biological treatment for rheumatoid arthritis? A systematic review of effectiveness.”</i>
Abstract		
“Biological disease-modifying antirheumatic drugs (bDMARD) are indicated for individuals in whom disease activity remains in spite of treatment with synthetic disease-modifying antirheumatic drugs (sDMARD)”.	The use of Biological disease-modifying antirheumatic drugs (bDMARD) verses synthetic disease-modifying antirheumatic drugs (sDMARD). Does this mean BDMARD are not acting systemically?	To better explain the indication of sDMARD and bDMARD we changed the text: <i>According to the American College Rheumatology (ACR) and European League Against Rheumatism (EULAR), sDMARD is the first choice treatment for RA patients. Biological disease-modifying antirheumatic drugs (bDMARD) are indicated when disease</i>

Original text	Reviewer 1	Answer
		<p><i>activity remains in spite of treatment with sDMARD.</i></p> <p>Text modified in abstract page 3, line 2.</p>
<p>“In cases of therapeutic failure with tumor necrosis factor inhibitors (anti-TNF), the best results were achieved using rituximab, etanercept (as second anti-TNF) or abatacept”.</p>	<p>In cases of therapeutic failure with tumor necrosis factor inhibitors (anti-TNF), the best results were achieved using rituximab, etanercept (as second anti-TNF) or abatacept.</p> <p>From the review it is not clear that rituximab and etanercept also anti-TNF or not.</p> <p>Did they fail or got the best result?? The other anti-TNF biological therapies are lacking in the study.</p>	<p>In the section introduction we had described the types of bDMARD: the anti-TNFs and the non anti-TNF:</p> <p>“The aim of the present study was to assess the effectiveness of the anti-TNFs adalimumab, etanercept, infliximab, golimumab and certolizumab pegol and of the non anti-TNF rituximab, tocilizumab and abatacept”.</p> <p>Text presented in introduction page 4, line 11.</p> <p>For therapeutic failure, we found only studies that evaluated three bDMARD drugs, rituximab, etanercept, and abatacept.</p>
<p>The present systematic review with meta-analysis found that relative to treatment-naïve patients, adalimumab and etanercept were more effective when combined with methotrexate than when used alone and that in the case of therapeutic failure with anti-TNF</p>	<p>Long confusing sentences need to be revised, example:</p> <p>The present systematic review with meta-analysis found that relative to treatment-naïve patients, adalimumab and etanercept were</p>	<p>Suggestion accepted. We changed the sentence to clarify the text:</p> <p><i>“The present systematic review with meta-analysis found that relative to anti-TNF treatment-naïve patients, adalimumab and</i></p>

Original text	Reviewer 1	Answer
<p>agents, rituximab, abatacept and etanercept were more effective; however, more evidence exists for the use of rituximab.</p>	<p>more effective when combined with methotrexate than when used alone and that in the case of therapeutic failure with anti-TNF agents, rituximab, abatacept and etanercept were more effective; however, more evidence exists for the use of rituximab.</p>	<p><i>etanercept were more effective when combined with methotrexate than when used alone. Furthermore, in case of therapeutic failure with anti-TNF agents; rituximab and abatacept (non anti-TNF) and etanercept (as second anti-TNF) were more effective. However, more studies of effectiveness were found for the rituximab”.</i></p> <p>Text modified in in abstract page 3, line 16.</p>
<p>“In cases of therapeutic failure with tumor necrosis factor inhibitors (anti-TNF), the best results were achieved using rituximab, etanercept (as second anti-TNF) or abatacept”.</p>	<p>If rituximab, abatacept and etanercept are not anti-TNF then what are they in the abstract explained as second anti-TNF therapies.</p> <p>The generics and the mechanism of action of these biological drugs would have been useful to understand the differences.</p> <p>Rituximab, etanercept and abatacept are not anti-TNF... they are given as second anti-TNF in the abstract. A sentence to explain the generic and the mechanism of the action will be appropriate.</p>	<p>Suggestion accepted. We changed the sentence to clarify the text:</p> <p><i>“Furthermore, in case of therapeutic failure with anti-TNF agents; rituximab and abatacept (non anti-TNF) and etanercept (anti-TNF) were more effective. However, more studies of effectiveness were found for the rituximab.”</i></p> <p>Text modified in page 3, line 16.</p> <p>With respect to generics and the mechanism of action, we changed the sentence including generics and the mechanism of action:</p>

Original text	Reviewer 1	Answer
		<p><i>“Tumor necrosis factor inhibitors (anti-TNF) are inhibitors of tumor necrosis factor alpha, rituximab is depleting B lymphocyte, abatacept is blocking of costimulation of T lymphocyte and tocilizumab is a blocking interleukin-6 receptor.”</i></p> <p>Text modified in page 3, line 37.</p>
Core tip		
<p>“The present systematic review of the effectiveness of biological disease-modifying antirheumatic drugs included cohort observational studies that reported treatment results applied in real-life conditions; thus, these studies are able to fill in gaps in knowledge left by clinical trials”.</p> <p>In the section introduction we explained more with this subject: “Appropriate knowledge of the effectiveness profiles of all of these strategies is relevant for choosing the best option for each patient. In this regard, observational studies are particularly interesting, as they seek to understand treatments in the actual practice setting. Thus,</p>	<p>Also sentence: that reported treatment results applied in real-life conditions;</p> <p>Does this mean not computer animation studies? Are there any trials not applied in real life conditions not explained</p>	<p>We changed the sentence in introduction to clarify the text:</p> <p><i>“Appropriate knowledge of the effectiveness profiles of all of these strategies is relevant for choosing the best option for each patient. In this regard, observational studies are particularly interesting, as they seek to understand treatments in the actual practice setting. Thus, this type of study could contribute to decide the choice of treatments, the elaboration of clinical protocols, and the formulation of health policies. The present systematic review selected cohort observational studies. These types of studies more accurately represent real-life conditions</i></p>

Original text	Reviewer 1	Answer
this type of study could contribute to decide the choice of treatments, the elaboration of clinical protocols, and the formulation of health policies. The present systematic review selected cohort observational studies to complement the information provided by reviews of randomized clinical trials”		<p><i>(actual practice setting) and are able to provide complementary data to the results of randomized clinical studies conducted in controlled conditions.”</i></p> <p>Text modified in introduction page 4, line 5.</p>
Introduction		
Introduction: was to assess the effectiveness of the anti-TNFs adalimumab, etanercept, infliximab, golimumab and certolizumab pegol and of the non anti-TNF bDMARD rituximab, tocilizumab and abatacept, in the treatment of active RA by means of a systematic review with meta-analysis”.	<p>The aim is not clear. Did authors review different commercial brands of anti TNF antibodies or evaluated all different biological therapies.</p> <p>It is not clear whether the review is about different anti-TNF antibodies since only their commercial names used or all biological drugs.</p>	<p>It was used, in the search strategy, several combinations of terms corresponding to the disease, interventions and type of study. The drugs’ brand names were also included in the search strategy.</p> <p>The text that explain the search strategy was described in the section methods page 4, line 22.</p> <p>Our search strategy is available in: Supplementary table 1 - Search strategies</p>
“Among the bDMARD, tumor necrosis factor inhibitors (anti-TNF) represent the first choice after failure of regimens that included sDMARD, as there is evidence of the post-	<p>Introduction: second paragraph does not make sense.</p> <p>...in addition to a greater amount of</p>	<p>Suggestion accepted. We changed the sentence to clarify the text:</p> <p><i>“Among the bDMARD, anti-TNF represent the</i></p>

Original text	Reviewer 1	Answer
marketing efficacy of such agents, in addition to a greater amount of information security”.	information security (4,5). What this means not clear.	<i>first choice after failure of regimens that included sDMARD, and there is more evidence of the post-marketing efficacy and safety for anti-TNF agents.”</i> Text modified in introduction page 3, line 39.
Materials and methods		
“Values of $I^2 > 40\%$ and $p < 0.10$ on the chi-square test were considered as indicative of significant heterogeneity”.	Statistical analysis: $p < 0.10$ on the chi-square test were considered as indicative of significant heterogeneity. Is this correct?	In an attempt to establish whether studies are consistent, reports of meta-analyses commonly present a statistical test of heterogeneity. The test seeks to determine whether there are genuine differences underlying the results of the studies (heterogeneity), or whether the variation in findings is compatible with chance alone (homogeneity). Although the most common cut off point of significance is $p < 0.05$, to evaluate the heterogeneity in metanalysis the Cochrane Collaboration Handbook suggest the value of $p < 0.10$ on the chi-square test. As a statistically significant result may indicate a problem with heterogeneity, and lots of meta-analysis includes small sample sizes or few in number studies, resulting in low power of the analysis, to be more conservative, a p value of 0.10, rather than the

Original text	Reviewer 1	Answer
		<p>conventional level of 0.05 is adopted. In such cases, when $p > 0.10$ there will be a larger chance that studies are not heterogeneous.</p> <p>In according to the Cochrane Collaboration Handbook values of $I^2 > 40\%$ and $p < 0.10$ on the chi-square test were considered as indicative of significant heterogeneity.</p>
Discussion		
<p>“Some studies reported that the participants in randomized clinical trials exhibited greater disease activity and fewer associated comorbidities compared to those patients treated in the clinical practice setting; additionally, that the practice of prescribing became less rigorous over time”</p>	<p>Some sentences are not clear like:.. additionally, that the practice of prescribing became less rigorous over time. The point is not clear.</p>	<p>Suggestion accepted. We changed the sentence to clarify the text</p> <p><i>“Some studies reported that the participants in randomized controlled clinical trials exhibited greater disease activity and fewer associated comorbidities compared to those patients treated in the actual practice setting. The practice of prescribing has been modified over time in real-life. bDMARDs (specially in clinical trials) were prescribed only when patients presented high activity of disease and, now, the medicines are prescribed when the activity is moderate or high.”</i></p> <p>Text modified in page 10, line 25.</p>

Original text	Reviewer 1	Answer
<p>“This study found that the participants who used adalimumab or etanercept exhibited better results compared to the participants who used infliximab, and adalimumab and etanercept exhibited similar results”.</p>	<p>Discussion: 1st sentence I could not understand the difference.</p>	<p>We changed the sentence to clarify the text.</p> <p><i>“Patients who used adalimumab and etanercept presented similar results among them and better outcomes compared to patients under infliximab therapy.”</i></p> <p>Text modified in page 9, line 25.</p>
<p>“An analysis of subgroup treatment-naïve participants did not find any differences in the results, probably because most of the participants under treatment were anti-TNF naïve”.</p>	<p>Again second sentence: there was no difference between treated patients because they were anti TNF-naïve?</p> <p>Why that made difference.</p>	<p>Among the 35 observational studies included, nine studies assessed anti-TNF-naïve participants, and 11 studies analyzed cases of therapeutic failure with at least one anti-TNF agent; the remainder of the studies did not inform whether therapeutic failure had occurred or did not separate patients into subgroups.</p> <p>Suggestion accepted. We changed the sentence to clarify the text.</p> <p><i>The analysis of subgroup of anti-TNF naïve participants showed better results for adalimumab and etanercept compared to infliximab. The results were similar to the group with all patients (anti-TNF-naïve and/or therapeutic failure), probably because most of the participants under treatment were anti-</i></p>

Original text	Reviewer 1	Answer
		<p><i>TNF naïve</i>".</p> <p>Text modified in page 9, line 24.</p>
Conclusion		
<p>"The results of the observational studies included in this review, which reflect the "real-life" use of bDMARD, revealed that adalimumab or etanercept in combination with methotrexate might represent the best choices for treatment-naïve individuals. Rituximab, abatacept or etanercept might be used in cases of therapeutic failure with anti-TNF agents; however, there is more evidence for the use of rituximab".</p>	<p>Final sentence assuming the Conclusion is very long and does not make sense</p>	<p>Suggestion accepted.</p> <p>We changed the sentence to clarify the text.</p> <p><i>"The results of the observational studies included in this review, which reflect the "real-life" use of bDMARD. The best choices for bDMARD treatment-naïve individuals are adalimumab or etanercept in combination with methotrexate. In cases of therapeutic failure with anti-TNF agents rituximab or abatacept (non anti-TNF) or etanercept (as second anti-TNF) might be used; however, more studies of effectiveness were found for rituximab".</i></p> <p>Text modified in page 10, line 36.</p>
Other questions		
<p>"Table 4 - Meta-analysis of the outcomes for patients with treatment-naïve"</p>	<p>Table 4 what are the patients with treatment-naïve. (these patients never treated with anti-TNF or any kind treatments at all?</p>	<p>These patients had never taken anti-TNFs drugs before the study.</p> <p>Change was made in title of table 4.</p>

Original text	Reviewer 1	Answer
		<i>“Table 4 - Meta-analysis of the outcomes for anti-TNF naïve patients”</i>
---	The study does not include more recent data after Nov 2013, while over 130 new related articles have been published since 2014.	<p>This systematic review has been updated to August 31, 2014.</p> <p><i>“We searched for studies in the PubMed, EMBASE, Cochrane Controlled Trials Register and LILACS databases (until August 2014), in the grey literature and conducted a manual search”.</i></p> <p>Text modified in page 3, line 7.</p>
---	Attention is given on the abstract form 4 local Brazilian journals for 2012-2013. Not clear.	We conducted a manual search in the 2012 and 2013 editions of four rheumatology journals (Journal Rheumatology, Rheumatology, Rheumatology International and the Brazilian Journal of Rheumatology). However, only the last one is Brazilian. Therefore, we did not give Brazilian Journals preference.
---	What was difference between these anti-TNF antibodies that made such a difference is not given? What makes these biological therapies distinct not stated.	In the section discussion we explained that some studies reported the patients using infliximab required dose escalation more often compared to those who used etanercept and

Original text	Reviewer 1	Answer
		adalimumab. Additionally, in cases of therapeutic failure the mechanisms of action may be responsible for the differences in study, the anti-TNF are inhibitors of tumor necrosis factor alpha, rituximab is depleting B lymphocyte, abatacept is blocking of costimulation of T lymphocyte.
---	Did all trails use the same dose same duration of the study, same severity of disease...?	The doses used are in accordance with clinical trials for each drug in the treatment of rheumatoid arthritis. Then the same doses were used biological except for infliximab (3 to 5 mg/kg). The duration of study was described in table 1. Furthermore, the results of the severity of the disease (DAS 28) was described in supplementary table 2.
---	Redundancies, exhaustive long sentences which keep repeating need to be eliminated.	These sentences were revised.
---	Overall, the review needs to be updated; revised and generic names and a short mechanism of action of each drug would be helpful to understand the difference between biological and trials, outcome.	The review has been updated to August 31, 2014. One observational cohort study was included. Flouri et al, 2004. Comparative effectiveness and survival of infliximab, adalimumab, and etanercept for rheumatoid arthritis patients in

Original text	Reviewer 1	Answer
		<p>the Hellenic Registry of Biologics: Low rates of remission and 5-year drug survival. <i>Semin Arthritis Rheum</i> 2014; 43: 447-57</p> <p>With respect to generics and the mechanism of action, we changed the sentence including generics and the mechanism of action:</p> <p><i>“Tumor necrosis factor inhibitors (anti-TNF) are inhibitors of tumor necrosis factor alpha, rituximab is depleting B lymphocyte, abatacept is blocking of costimulation of T lymphocyte and tocilizumab is a blocking interleukin-6 receptor.”</i></p> <p>Text modified in page 3, line 37.</p>
---	While the review fail to explain difference between biological drugs and the reason behind that caused these changes (efficacy of the drug or the way the study was done) affected the outcomes.	In according to the data reported in the supplementary table 2, the patients have similar characteristics so the results are due to the effectiveness of the drugs.
---	English language being optimized.	English language was optimized. The study have been submitted for a English language editing companies. The certificate is attached.
---	References are not always in accordance.	References have been revised.

Original text	Reviewer 1	Answer
---	Quality of first 3 tables should be optimized.	Tables were optimized.
---	In manuscript I read use of EULAR 2010 guidelines, is it wrong or right?	The text was modified in page 4 line, 20: <i>“...whose diagnoses were confirmed based on the ACR 1987 and the more recent ACR/EULAR 2010 criteria”.</i> ACR 1987 and ACR/EULAR 2010 refer to diagnoses criteria.

Original text	Reviewer 2	Answer
---	The authors present an extensive revision about the effectiveness of the biological treatment for rheumatoid arthritis. The paper is well written. It explores the best treatment options for patients with DMARDs failure and provides useful and practical information for clinicians involved in the care of patients with this disease.	Thank you for the comment

Original text	Reviewer 3	Answer
Abstract: “The present systematic review with meta-analysis found that relative to treatment-naïve patients, adalimumab and etanercept were more effective when combined with	The review/metanalyses is well done. However, I would like to draw attention of authors on following sentence reported in abstract and conclusion that may not be clear	The text was modified: <i>Abstract: “The present systematic review with meta-analysis found that relative to anti-TNF</i>

Original text	Reviewer 3	Answer
<p>methotrexate than when used alone and that in the case of therapeutic failure with anti-TNF agents, rituximab, abatacept and etanercept were more effective; however, more evidence exists for the use of rituximab”.</p> <p>Conclusion: “The results of the observational studies included in this review, which reflect the “real-life” use of bDMARD, revealed that adalimumab or etanercept in combination with methotrexate might represent the best choices for treatment-naïve individuals. Rituximab, abatacept or etanercept might be used in cases of therapeutic failure with anti-TNF agents; however, there is more evidence for the use of rituximab</p>	<p>to the reader: “ Rituximab, abatacept or etanercept might be used in cases of therapeutic failure with anti-TNF agents;...” Because etanercept is an anti-TNF.</p>	<p><i>treatment-naïve patients, adalimumab and etanercept were more effective when combined with methotrexate than when used alone. Furthermore, in case of therapeutic failure with anti-TNF agents; rituximab and abatacept (non anti-TNF) and etanercept (as second anti-TNF) were more effective. However, more studies of effectiveness were found for the rituximab”.</i> Page 3, line 16.</p> <p>Conclusion: “<i>The results of the observational studies included in this review, which reflect the “real-life” use of bDMARD. The best choices for bDMARD treatment-naïve individuals are adalimumab or etanercept in combination with methotrexate. In cases of therapeutic failure with anti-TNF agents rituximab or abatacept (non anti-TNF) or etanercept (as second anti-TNF) might be used; however, more studies of effectiveness were found for rituximab”.</i> Page 10, line 36.</p>

Original text	Reviewer 4	Answer
---	It is of interest. Since prospective studies carry more weight than retrospective studies, it would have been better if the authors included	We prefer to keep the retrospective studies since their exclusion could preclude some important analyses in the therapeutic failure

Original text	Reviewer 4	Answer
	only prospective studies	subgroup, comparisons with etanercept versus control (DAS28 and EULAR good response). Moreover, removing the retrospective studies did not affect the results.
---	There was no study on golimumab or certolizumab pegol. Therefore, the statement that adalimumab and etanercept should be used as first line agents is not supported by their data.	Golimumabe and certolizumab pegol were included in the search, but no study of effectiveness was found. More evidence of the effectiveness for anti-TNF agents (adalimumab and etanercept) were observed in this systematic review, so both represent the first choice after failure of regimens that included sDMARD.
---	English language also needs a bit polishing	English language was optimized. The study have been submitted for a English language editing companies. The certificate is attached.

We greatly appreciate your warm work and hope that the corrections can meet expectations.
Once again, thank you very much for your comments and suggestions.

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