

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk of tuberculosis in patients treated with TNF- α antagonists: A systematic review and meta-analysis of randomized controlled trials
AUTHORS	Zhang, Zheng; Fan, Wei; Yang, Gui; Xu, Zhigao; Wang, June; Cheng, Qingyuan; Yu, Mingxia

VERSION 1 - REVIEW

REVIEWER	Giuseppe Murdaca University of Genova, Genova, Italy
REVIEW RETURNED	05-Jul-2016

GENERAL COMMENTS	The authors discuss the risk of TB in patients receiving anti-TNF-alpha agents. The article is interesting. I suggest to describe the pre-treatment examinations which are needed (I.E. mantoux test etc) and prophylaxis in patients with manotux and/or quantiferon before administration of anti-TNF-alpha agents (see and add as references Murdaca et al. concerning the topic).
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REVIEWER	Dr Susanna Dodd University of Liverpool UK
REVIEW RETURNED	14-Jul-2016

GENERAL COMMENTS	<p>English could be improved.</p> <p>For example,</p> <p>Results Tuberculosis risk and TNF-α antagonists</p> <p>1) "Given the limited number of studies of single drug, Subgroup analysis were only performed when at least three studies were included" should be reworded as "Given the limited number of single drug studies, subgroup analysis was performed only when at least three studies were available for a particular drug".</p> <p>2) "Compared with control group, there were all no statistically significant difference in the risk of tuberculosis" should be reworded as "None of these subgroup analyses indicated statistically significant differences in the risk of tuberculosis between patients treated with TNF-α antagonists versus control."</p> <p>Discussion</p> <p>1) "Except for some common diseases TNF-α antagonists are often</p>
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	<p>used for, like RA, UC, AS, and PsA, the disease types also containe Asthma, Sarcoidosis and GvH. The pooled results indicated that the use of TNF-α antagonists would increase the risk of TB in patients about 2 times." should be reworded as "In addition to the diseases most commonly treated by TNF-α antagonists (RA, UC, AS and PsA), this meta-analysis included studies treating patients with Asthma, Sarcoidosis and GvH. The pooled results indicate that treatment with TNF-α antagonists approximately doubles the risk of TB."</p> <p>2) "Secondly, we didn't evaluate the difference among the patients with different drugs exposure caused by inconsistent endpoints, which might lead to a possible bias." should be reworded as "Secondly, we were not able to evaluate differences attributable to particular drug exposure because of inconsistent endpoints." (if I have understood the sentence correctly).</p> <p>3) "We also assessed the level of evidence using the GRADE approach, which was suggested to preferably be used for grading evidence by the British Medical Journal since 2006." should be reworded as "We also assessed the level of evidence using the GRADE approach, which has been recommended for grading evidence by the British Medical Journal since 2006."</p> <p>4) "So it should be paid more attention and more strict clinical trials are needed, for the safety of biological treatment in clinical use." should be reworded as "We recommend that this elevated risk of tuberculosis is brought to the attention of prescribing clinicians, and that further high quality research is conducted to assess the safety of biological treatment in clinical use."</p>
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REVIEWER	Betul Sozeri Umraniye Education and Research hospital, Istanbul, Turkey
REVIEW RETURNED	05-Aug-2016

GENERAL COMMENTS	Accept.
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REVIEWER	Dr. Eva Salgado COMPLEXO HOSPITALARIO UNIVERSITARIO DE OURENSE SPAIN
REVIEW RETURNED	02-Dec-2016

GENERAL COMMENTS	<p>THIS IS A SISTEMATIC REVIEW AND META-ANALYSIS THAT TRY TO AESS THE RISK OF TUBERCULOSIS IN PATIENTS TREATED WITH TNF ANTAGONISTS.</p> <p>MAJOR COMMENTS</p> <p>-Authors must provide an explicit statement of questions being addressed with reference to PICOS as PRISMA stament #4 recommends</p> <p>-Eligibility criteria of selected studies as PICO would be specified as</p>
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	<p>PRISMA stament #6 recommends</p> <p>-Authors must have to provide as supplementary material the full electronic search strategy for at least one database, as PRISMA stament #8 recommends</p> <p>-Stratified analysis (meta-regression) by disease (indication of the TNF) is mandatory. As for example Rheumatoid Arthritis disease has been described as an independent risk factor for tuberculosis disease.</p> <p>-Stratified analysis (meta-regression) by tuberculosis rate of background population is mandatory.</p> <p>-If a previous latent TB screening and how this was performed must be appear in the descriptive table.</p> <p>-If authors include so different diseases, only a random-effect approach would be allowed. Afterwards a sensitivity analysis by disease is preferred.</p> <p>-When authors say that "This is the first metaanalysis, to our knowledge, to evaluate the TB risk in all patients treated with TNF<math>\alpha</math> antagonists", this is not completely true. They indeed take into account other similar meta-analysis in reference (reference 10-12)</p> <p>-Please re-write the sentence "Our previous studies showed that TNF<math>\alpha</math> played a critical role in the occurrence and development of inflammation and tumor, meanwhile we confirmed that the TNF<math>\alpha</math> monoclonal antibody we prepared, as a TNF<math>\alpha</math> antagonist, significantly suppressed the growth of breast cancer". These are only data in animal models and in vitro models. The sentence is confusing and seems that antiTNF have proven efficacy in clinical models for breast cancer.</p> <p>MINOR COMMENTS In abstract please delet that you use RevMan, this is a secondary information.</p> <p>The pooled estimated IR of active TB, taking into account the exposure time would be nicer than only OR</p>
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VERSION 1 – AUTHOR RESPONSE

Replies to Reviewer 1

(1) The authors discuss the risk of TB in patients receiving anti-TNF-alpha agents. The article is interesting. I suggest to describe the pre-treatment examinations which are needed (I.E. mantoux test etc) and prophylaxis in patients with manotux and/or quantiferon before administration of anti-TNF-alpha agents (see and add as references Murdaca et al. concerning the topic).

Answer: Thanks for the kind advice. We have referred to Murdaca's studies concerning the topic and cited as reference 54. For the first advice, we have evaluated whether a previous latent TB screening was performed in each included studies and this information is appeared in supplementary appendix 2. For the second advice, we also evaluated whether prophylaxis in patients with manotux and/or

quantiferon before administration of anti-TNF-alpha agents was conducted. However, for each included studies, patients were excluded when they are positive at TB screening and no preventative treatment for TB was administrated. So we did not describe the information in our article.

Replies to Reviewer 2

(1) English could be improved.

Answers: We are very sorry for our poor English in the manuscript, and we have thoroughly edited the paper according to your advices. Revised portion is marked in red in the revised paper. Special thanks to you for your kindly comments.

Replies to Reviewer 4

MAJOR COMMENTS

(1) Authors must provide an explicit statement of questions being addressed with reference to PICOS as PRISMA statement #4 recommends.

Answers: Thanks for the suggestion. We have referred to the PRISMA statement and cited as reference 14. According to the PRISMA stament #4 recommends: provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS), we re-wrote the statement of questions in the 'Introduction' section. Revised portion is marked in red in the revised paper.

(2) Eligibility criteria of selected studies as PICO would be specified as PRISMA statement #6 recommends.

Answers: Thanks for the suggestion. We have referred the PRISMA statement and cited as reference 14. According to the PRISMA stament #6 recommends: specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale, we re-wrote the eligibility criteria in the 'Inclusion and exclusion criteria' section. Revised portion is marked in red in the revised paper. In addition, we re-designed flow diagram of study selection according to PRISMA statement (Figure 1).

(3) Authors must have to provide as supplementary material the full electronic search strategy for at least one database, as PRISMA stament #8 recommends.

Answers: Thanks for the suggestion. We have referred to the PRISMA statement and cited as reference 14. According to the PRISMA stament #8 recommends: present full electronic search strategy for at least one database, including any limits used, such that it could be repeated, we have provided as supplementary appendix 1 the full electronic search strategy for Medline.

(4) Stratified analysis (meta-regression) by disease (indication of the TNF) is mandatory. As for example Rheumatoid Arthritis disease has been described as an independent risk factor for tuberculosis disease.

Answers: Thank you a lot for the comment. The subgroup analyses by disease under treatment were added to the text (Figure 3). Significantly increased TB risk associated with anti-TNF- α drugs in RA patients (OR 2.29 [1.09-4.78], P = 0.03) was found.

(5) Stratified analysis (meta-regression) by tuberculosis rate of background population is mandatory.

Answers: Thank you a lot for the comment. The subgroup analyses by TB rate of the geographic location were added to the text (Figure 4). Geographic location of the study classified according to the rate of TB (World Health Organization, incidence TB estimation, 2014). Countries with an incidence rate (IR) $\geq 40/100\ 000$ are considered as high-incidence TB areas. The ORs for studies that in or out of high TB rate areas were 2.39 (95% CI 0.97, 5.90, P=0.06) and 1.64 (95% CI 0.70, 3.88, P=0.26) respectively.

(6) If a previous latent TB screening and how this was performed must be appear in the descriptive table.

Answers: Thanks for the suggestion. We have evaluated whether a previous latent TB screening was performed in each included studies and this information is appeared in supplementary appendix 2.

(7) If authors include so different diseases, only a random-effect approach would be allowed. Afterwards a sensitivity analysis by disease is preferred.

Answers: Thank you a lot for the comment, this comment is a good question. Random-effect model has been applied in our meta-analysis. Sensitivity analysis using random-effects model has also been conducted, which suggested that pooled results did not change substantially by any one of included studies (supplementary appendix 5).

(8) When authors say that "This is the first metaanalysis, to our knowledge, to evaluate the TB risk in all patients treated with TNF α antagonists", this is not completely true. They indeed take into account other similar meta-analysis in reference (reference 10-12).

Answers: Thanks for the suggestion. This sentence has been corrected as "This meta-analysis evaluated the TB risk of these drugs across a variety of condition in RCTs with low heterogeneity."

(9) Please re-write the sentence "Our previous studies showed that TNF α played a critical role in the occurrence and development of inflammation and tumor, meanwhile we confirmed that the TNF α monoclonal antibody we prepared, as a TNF α antagonist, significantly suppressed the growth of breast cancer". These are only data in animal models and in vitro models. The sentence is confusing and seems that antiTNF have proven efficacy in clinical models for breast cancer.

Answers: Thanks for the suggestion. This sentence has been corrected as "Our previous study has showed that TNF α played a critical role in the occurrence and development of inflammation and tumor, and that the TNF α monoclonal antibody we prepared, as a TNF α antagonist, significantly suppressed the growth of breast cancer in animal model"

MINOR COMMENTS

(1) In abstract please delete that you use RevMan, this is a secondary information.

Answers: Thanks for the suggestion. We have deleted that we use RevMan in abstract.

(2) The pooled estimated IR of active TB, taking into account the exposure time would be nicer than only OR.

Answers: Thank you a lot for the comment, this comment is a good question and innovative. The incidence rate (IR) is defined as being relative to the dimension of the population and the time; this value is expressed by relation to a number of individuals and to a duration. Because of the relatively short follow-up period in the RCTs, we did not apply IR in our meta-analysis. Moreover, previous

meta-analyses, including Ai et al. (Ai JW, Zhang S, Ruan QL, et al. The Risk of Tuberculosis in Patients with Rheumatoid Arthritis Treated with Tumor Necrosis Factor-alpha Antagonist: A Metaanalysis of Both Randomized Controlled Trials and Registry/Cohort Studies. J Rheumatol 2015;42(12):2229-37), Souto et al. (Souto A, Maneiro JR, Salgado E, et al. Risk of tuberculosis in patients with chronic immune-mediated inflammatory diseases treated with biologics and tofacitinib: a systematic review and meta-analysis of randomized controlled trials and long-term extension studies. Rheumatology (Oxford) 2014;53(10):1872-85) and Singh et al. (Singh JA, Wells GA, Christensen R, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev 2011(2):Cd008794), applied pooled estimated OR/RR to evaluate the risk of TB after receiving anti-TNF-alpha agents in RCTs. IR was only used in longitudinal cohort studies or long-term extension studies (Ai et al. and Souto et al.).

In all, we found the comments and suggestions above are quite helpful, and we revised my manuscript point by point. Some changes we didn't list here, but marked in red in the revised manuscript.

Once again, thank you very much for your comments and suggestions. We look forward to hearing from you soon.

VERSION 2 – REVIEW

REVIEWER	EVA SALGADO COMPLEXO HOSPITALARIO UNIVERSITARIO DE OURENSE
REVIEW RETURNED	16-Jan-2017

GENERAL COMMENTS	I think that with these new corrections, this article could be published
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