PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Potential risk of TNF inhibitors on the progression of interstitial lung disease in patients with rheumatoid arthritis
AUTHORS	Nakashita, Tamao; Ando, Katsutoshi; Kaneko, Norihiro; Takahashi, Kazuhisa; Motojima, Shinji

VERSION 1 - REVIEW

REVIEWER	Joshua Solomon National Jewish Health USA
REVIEW RETURNED	16-Jun-2014

GENERAL COMMENTS	Thank you for allowing me to review your manuscript entitled "Potential risk of TNF-alpha inhibitors on the exacerbation of interstitial lung disease in patients with rheumatoid arthritis". Below are my comments. 1. There are numerous grammatical errors and confusing sentence structure. For example, page 5, page 36, starting with “Since most pulmonary events…”. Also in that sentence, the statement “…reported to be occurred…” is incorrect. Page 7, line 43 states “…proportion of patients was treated…” I would carefully proofread the spelling and grammar. 2. The authors interchange the terms “exacerbation” and “ILD events” and “progression”. As we have a specific definition for exacerbations of ILD, I would make sure you aren’t using this term to refer to a gradual worsening in ILD (as it seems you are doing in sentences such as the first line of the conclusion in the abstract). 3. Did all patient entering your center with RA get CT scans routinely before biologic therapy? If not, using those with only CTs would be a limitation as I assume they had symptoms or signs that were concerning for lung disease. Also your exclusion criteria may have excluded sicker patients as you excluded those without a year followup or healthier patients (those without imaging data). 4. The grading of CTs can miss those with progression. It would not account for those with progressive fibrosis that didn’t extend lesions in a cranial-caudal distribution. For example, a patient with basilar ground glass that progressed to more reticulation and honeycombing but didn’t extent to involve a higher percentage of the lung parenchyma 5. The implication that 10% of patients with RA treated with TNF agents have new ILD or significant radiographic progression within a year is a bit unbelievable, especially given very large population based studies in the past showing a significantly smaller effect. I would recommend that the authors treat this shocking result with a healthy degree of skepticism and really call on more robust data

	before making the strong conclusions that exist in this paper. There are other cofounders that aren't mentioned (i.e was reflux/aspiration looked at? Could this be bucillamine or bucillamine +TNF? What was the pattern of disease? UIP vs NSIP? Did we rule out infection in all those with progression?) 6. As KL-6 levels were only increased at the time of the ILD event (and not at baseline per the paper), its incorrect to say that KL-6 provides "early" detection of these events.

REVIEWER	Shin-ya Kawashiri Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences Japan
REVIEW RETURNED	10-Jul-2014

GENERAL COMMENTS	I cannot accurately evaluate this manuscript because essential Tables is not attached.

REVIEWER	Kentaro Watanabe Department of Respiratory Medicine, Fukuoka University School of Medicine, JAPAN
REVIEW RETURNED	12-Jul-2014

GENERAL COMMENTS	1) "ILD events" should be strictly defined. According to the description in page 5, "ILD events" could include not only emergence and exacerbation of ILD but also pulmonary infection. How did authors differentiate true emergence and exacerbation of ILD from non-ILD events? Imaging data and the discontinuation of ILD therapy may not be sufficient for the diagnosis of emergence or exacerbation of ILD. 2) In Figure 2A for 14 patients with "ILD events", ILD grade after "ILD events" was the same as the in 10 patients. Such a mild change of images may not be sufficient for the diagnosis of drug-induced emergence and exacerbation of ILD or exacerbation of preexisting ILD. 3) There was no description of the follow-up information for patients with "ILD events", Did they receive steroids and/or antibiotics? What were the treatment results? 4) No tables uploaded.

VERSION 1 – AUTHOR RESPONSE

General comments from Reviewer #1:
Thank you for allowing me to review your manuscript entitled "Potential risk of TNF-alpha inhibitors on the exacerbation of interstitial lung disease in patients with rheumatoid arthritis". Below are my comments.
Responses to the general comments from the reviewer #1:
We appreciate that reviewer #1 raised several weakness as well as strengths. According to the reviewers' comment, we re-checked the whole manuscript and revised points which reviwer #1

pointed out. We believe that our revision and point-by-point responses fully meet the expectations of reviewer #1.

Specific comment #1
There are numerous grammatical errors and confusing sentence structure. For example, page 5, page 36, starting with “Since most pulmonary events…”. Also in that sentence, the statement “…reported to be occurred…” is incorrect. Page 7, line 43 states “…proportion of patients was treated…” I would carefully proofread the spelling and grammar.
Response to specific comment #1
Thank you for your comment. According to the reviewers’ comment, we re-checked the whole manuscript with the adviser (native speaker) and revised these points.
In addition, in page 5 of the original manuscript which reviewer #1 pointed out, we previously represented “most pulmonary events, including pulmonary infection and emergence and exacerbations of ILD, here referred to as ILD events“. However, in actually, pulmonary infection is not included in “ILD events” in this study. This mention makes the reader difficult to understand our methods correctly. Then, in our revised manuscript, we corrected this sentence as follows. We apologize for our careless mistake.

Page 5: Since the majority of pulmonary events have been reported to be occurred within one year after initiation of biological therapy [17,18], we established one year as a reasonable follow-up period for this study.
Page 7: Patients with pre-existing ILD were older (66.1 vs. 57.8 years, $p<0.001$), higher class of RA (2.3 vs. 2.0, $p<0.001$) and had a greater proportion of male (45% vs. 18%, $p<0.001$) and patients who were treated with TNF-alpha inhibitors (79% vs. 53%, $p<0.01$) than those without pre-existing ILD.

Specific comment #2
The authors interchange the terms “exacerbation” and “ILD events” and “progression”. As we have a specific definition for exacerbations of ILD, I would make sure you aren’t using this term to refer to a gradual worsening in ILD (as it seems you are doing in sentences such as the first line of the conclusion in the abstract).
Response to specific comment #2
Thank you for your comment. We rechecked the whole manuscript and confirmed that the emergence of ILD or its progression referred to as “ILD events”. In the revised manuscript, we standarized its representation as follows and also changed the title to“Potential risk of TNF-alpha inhibitors on the progression of interstitial lung disease in patients with rheumatoid arthritis”.
We assessed chest computed tomography (CT) before initiation of biologic therapy and grouped 163 patients according to the presence of ILD (with [n = 58] and without pre-existing ILD [n = 105]). Next, we evaluated serial changes of chest CT after its treatment and visually assessed the emergence of ILD or its progression, which referred to as “ILD event”.

Specific comment #3
Did all patient entering your center with RA get CT scans routinely before biologic therapy? If not, using those with only CTs would be a limitation as I assume they had symptoms or signs that were concerning for lung disease. Also your exclusion criteria may have excluded sicker patients as you excluded those without a year followup or healthier patients (those without imaging data).
Response to specific comment #3
In our institution, we routinely performed chest CT for detecting latent infection and interstitaial lung disease before initiation of biologic therapy. (Needless to say, if patients have the data within a short period, we substitute it as the basis for our decision.) To make this point clear, we added this mention in the revised manuscript (page 6) as follows.
Since many forms of toxicity and infection are induced in the lungs of patients given agents to treat RA, we routinely perform chest CT for detecting latent infection and ILD before initiation of biologic

therapy and take chest X-rays (CXR) every 3-6 months after its treatment. We re-assess chest CT if a new lesion is detected on CXR or a patient complains of respiratory symptoms for more than two weeks.

Specific comment #4
The grading of CTs can miss those with progression. It would not account for those with progressive fibrosis that didn't extend lesions in a cranial-caudal distribution. For example, a patient with basilar ground glass that progressed to more reticulation and honeycombing but didn't extent to involve a higher percentage of the lung parenchyma.
Response to specific comment #4
We agree with the reviewer's comment. We understand that the analysis of cranial-caudal distribution in CT is not perfect to evaluate the interstitial lung leisons. However, at present, the definition of ILD progression is not clearly prescribed. Furthermore, since it have been reported that the pattern of abnormality included honeycombing does not influence prognosis (Am J Respir Crti Care Med 2008; 177, 433-9), the assessment of basilar lesions is controversial as evaluationg ILD progression. Then, we used the previous established method. In acutually, most patients whose basilar lesions (included honeycombing) were progressed also had the progression of vertical reticular lesions. Then, we consider that this method is not perfect, but it's possible to assess ILD progression in our clinical situation. Accordingly, we believe that we do not need to add these points furthermore.

Specific comment #5
The implication that 10% of patients with RA treated with TNF agents have new ILD or significant radiographic progression within a year is a bit unbelievable, especially given very large population based studies in the past showing a significantly smaller effect. I would recommend that the authors treat this shocking result with a healthy degree of skepticism and really call on more robust data before making the strong conclusions that exist in this paper. There are other cofounders that aren't mentioned (i.e was reflux/aspiration looked at? Could this be bucillamine or bucillamine +TNF? What was the pattern of disease? UIP vs NSIP? Did we rule out infection in all those with progression?)
Response to specific comment #5
Thank you for your comment, and we agree this point is very important. Our result is shocking and we consider that TNF-alpha inhibitors have the potential risk of ILD progression in patients with pre-existing ILD. However, since there are possibilities that other confounders exist as the reviewer #1 mentioned, we could not call on the strong conclusion.
Since this is a retrospective study, pathologic features of ILD (UIP vs NSIP) were not verified and more of our patients with ILD events had been treated with bucillamine than those without ILD events. Then, we should prospectively evaluate these points and already mentioned these weaknesses of our study as the limitation (page 13). Accordingly, we believe that we do not need to add these points furthermore. Thank you for your recommendation.

Specific comment #6
As KL-6 levels were only increased at the time of the ILD event (and not at baseline per the paper), its incorrect to say that KL-6 provides "early" detection of these events.
Response to specific comment #6
We agree with the reviewer's comment that it's incorrect to say that KL-6 provides "early" detection of these events. We excluded the mention of "early" in the whole manuscript (abstract, page 11 and 13).

Point-by-point responses to the reviewer #2
General comments from Reviewer #2:
I cannot accurately evaluate this manuscript because essential Tables is not attached.
Responses to the general comments from the reviewer #2:
We aporogize that essential Tables were not uploaded for any reasons. In this revision, we attached

Tables in the last of our manuscript.

Point-by-point responses to the reviewer #3

Specific comment #1

“ILD events” should be strictly defined. According to the description in page 5, “ILD events” could include not only emergence and exacerbation of ILD but also pulmonary infection. How did authors differentiate true emergence and exacerbation of ILD from non-ILD events? Imaging data and the discontinuation of ILD therapy may not be sufficient for the diagnosis of emergence or exacerbation of ILD.

Response to specific comment #1

Thank you for your comment and we apologize for our careless mistake. In actually, pulmonary infection is not included in “ILD events” in this study. This sentence makes the reader difficult to understand our methods correctly. Then, we delete this representation and corrected this sentence in our revised manuscript as follows.

Since the majority of pulmonary events have been reported to be occurred within one year after initiation of biological therapy [17,18], we established one year as a reasonable follow-up period for this study.

Specific comment #2

In Figure 2A for 14 patients with “ILD events”, ILD grade after “ILD events” was the same as the in 10 patients. Such a mild change of images may not be sufficient for the diagnosis of drug-induced emergence and exacerbation of ILD or exacerbation of preexisting ILD.

Response to specific comment #2

Thank you for your comment. As the reviewer #3 pointed out, we understand that a mild change of images is not sufficient for the diagnosis of ILD progression. However, at present, the definition of ILD progression is not clearly prescribed. Furthermore, since it have been reported that the pattern of abnormality (included honeycombing) does not influence prognosis (Am J Respir Crti Care Med 2008; 177, 433-9), the assessment of basilar lesions is also controversial as evaluationg ILD progression. Then, we used the previous established method and the diagnosis of ILD progression was confirmed by two pulmonologists and one radiologist. To make it clear, we added this representation in Page 6 as follows.

We believe that this method is not perfect, but it’s possible to assess ILD progression in our clinical situation. To assess our retrospective data, we consider that we should prospectively re-evaluate our condlusion and we mentioned this point in the limitation of our study.

Serial changes of these scores were also evaluated by two pulmonologists and one radiologist.

Specific comment #3

There was no description of the follow-up information for patients with “ILD events”, Did they receive steroids and/or antibiotics? What were the treatment results?

Response to specific comment #3

We agree with the reviewer’s comment and added their follow-up information in the Result section as follow.

Total nine patients discontinued TNF-alpha inhibitors and/or ILD treatment including prednisolone was started, but two of these patients died from ILD events (Figure 2A). Meanwhile, we had carefully observed other five patients which had mild progression with its treatment, but further progression of ILD was not detected.

Specific comment #4

No tables uploaded.

Response to specific comment #4

We aporogize that essential Tables were not uploaded for any reasons. In this revision, we attached Tables in the last of our manuscript.

VERSION 2 – REVIEW

REVIEWER	Shin-ya Kawashiri Nagasaki University, Japan
REVIEW RETURNED	23-Jul-2014

GENERAL COMMENTS	This report showed the risk of ILD events in RA patients treated with biologic DMARDs. Although this result is important and interesting, the authors should significantly modify this manuscript or mention some points. Major points 1. The authors described this study is direct comparison of TNF inhibitors and non-TNF inhibitors. However, a background of patients treated with TNF inhibitors is significantly different from that of patients treated with non-TNF inhibitors. Thus, this study is not direct comparison. The authors conclude TNF inhibitors have the potential risk of ILD events. However, the proportion of patients treated with TNF inhibitors is greater and that treated with non-TNF inhibitors is smaller in patients with pre-existing ILD. This point seriously affects the results. The authors should deliver accurate results by multivariate logistic analysis. Minor points 1. TNF-alpha inhibitors should be changed to TNF inhibitors because etanercept is not TNF-alpha inhibitor. 2. The information of concomitant DMARDs and steroid, and KL-6 should be shown in Table 1. 3. The stage and class of RA are not usually described by the average value. 4. As one of the limitation of this study, the authors described that they could not evaluate pathologic features of ILD. Is infection excluded?

VERSION 2 – AUTHOR RESPONSE

General comments from Reviewer:
This report showed the risk of ILD events in RA patients treated with biologic DMARDs. Although this result is important and interesting, the authors should significantly modify this manuscript or mention some points.

Responses to the general comments from reviewer:
We appreciate that reviewer raised several weakness as well as strengths. According to the reviewers' comment, we re-checked our manuscript and revised points which reviwer pointed out. We believe that our revision and point-by-point responses fully meet the expectations of the reviewer.

Major comment from reviewer
The authors described this study is direct comparison of TNF inhibitors and non-TNF inhibitors. However, a background of patients treated with TNF inhibitors is significantly different from that of patients treated with non-TNF inhibitors. Thus, this study is not direct comparison. The authors conclude TNF inhibitors have the potential risk of ILD events. However, the proportion of patients

treated with TNF inhibitors is greater and that treated with non-TNF inhibitors is smaller in patients with pre-existing ILD. This point seriously affects the results. The authors should deliver accurate results by multivariate logistic analysis.

Response to major comment
Thank you for your comment. As the reviewer pointed out, in our study, a background of patients treated with TNF inhibitors is different from that of patients treated with non-TNF inhibitors.
We have undestood that we should deliver accurate results by multivariate analysis, and consulted the specialist of statistics about these points before submitted. However, only four in ILD event group and one patient in non-ILD event group were treated with bucillamine, and these are very small population. According to the reviewer's comment, we re-consulted the other specialist of statistics about this point. But his advice is the same and finally concluded that the multivariate analysis could not evaluate our results correctly.
Importantly, in our clinical experience and this study, 1) ILD event was caused within one year after initiation of biological therapy, which was the similar result of previously reported. 2) The treatment of bucillamine didn't cause ILD event in our experience regardless of its long use. 3) Its population is very small. 4) Two pulmonary specialists judged that the participation of TNF inhibitor was exceedingly suspected in each patient. Accordingly, we consider that the biological treatment is important for ILD events.
However, we also understand that our results indicate the possibility that other confounders exist. Then, we mentioned this point correctly (especially for the treatment of bucillaine) and suggested its possibility as the limitation of our study.
As the reviewer pointed out, on the other hand, we agreed the point that this was not direct comparison. Then, we excluded the term of "direct" in our Discussion section.

Specific minor comment #1
TNF-alpha inhibitors should be changed to TNF inhibitors because etanercept is not TNF-alpha inhibitor.
Response to specific minor comment #1
We agreed this point. We rechecked the whole manuscript and changed to TNF inhibitors from TNF-alpha inhibotors.

Specific minor comment #2
The information of concomitant DMARDs and steroid, and KL-6 should be shown in Table 1.
Response to specific comment #2
We understand that this point is important. However, we have the data of KL-6 in limited patients without pre-existing ILD (although we have the data in all patients with pre-exising ILD). Additionally, we could find the data of detail informations for concomitant DMARDs and steroid in patients with ILD events, but could not pick up it in some patients without ILD events by retrospective review. Then, it's difficult to add these data of all patients in this study and we should prospectively evaluate these points.

Specific minor comment #3
The stage and class of RA are not usually described by the average value.
Response to specific comment #3
We understand that the stage and class of RA are not usually described by the average value. However, in this study, we foused lesions in lung and would like to indicate that these scores were not different in each group. Then, we simply indicated this point and we believe that we do not need to add detail informations furthermore.

Specific minor comment #4
As one of the limitation of this study, the authors described that they could not evaluate pathologic

features of ILD. Is infection excluded?
Response to specific minor comment #4
As mentioned in the method section, we excluded patients that we could not eliminate the possibility of the infection. Meanwhile, since this is the retrospective study, we could not evaluate pathologic features of ILD. We consider that this point is our limitation in our study and mentioned in Discussion section (limitation and conlusion).