PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Is incident rheumatoid arthritis interstitial lung disease associated with methotrexate treatment? Results from a multivariate analysis in the ERAS and ERAN inception cohorts.
AUTHORS	Kiely, Patrick; Busby, Amanda; Nikiphorou, Elena; Sullivan, Keith; Walsh, David; Creamer, Paul; Dixey, Josh; Young, Adam

VERSION 1 - REVIEW

REVIEWER	Suzan Verstappen University of Manchester
REVIEW RETURNED	01-Jan-2019

GENERAL COMMENTS	This study aims to address the research question whether rheumatoid arthritis interstitial lung disease is related to methotrexate treatment. To answer the question data from two well-known observational studies, ERAS and ERAN, are used. Although clinically a very important question, there are a number of methodological issues that should be addressed and the focus of the primary analysis should be on the development of incident ILD. Comments: - The authors aim to address the research question whether RA-ILD is related to MTX treatment. However, the primary analysis is conducted in the whole patient population including patients with ILD at baseline before any of the patients had been treated with csDMARDs. To address their question, the primary analysis should focus on the development of incident ILD and exclude those patients with ILD at baseline. - A number of assumptions are made with respect to exposure and outcome. However, it is important to provide more detailed information about loss to follow-up, time between last CRF and death certificates, until when death certificates were obtained etc. Patients having ILD on their death certificate, but not on the last CRF, were included in the non-MTX exposed group if the time between last CRF and death was <2 years. Maximum follow-up duration is 25 years, meaning that those patients recruited to ERAS were followed until 2011 if they had not left the study before this date. Depending on the year until which death certificates were obtained, this may mean that this could have led to bias since these patients may have been excluded from the study since time since last CRF was>2 years. Furthermore, is it possible that patients develop ILD and will recover without ILD being recorded

	on the death certificate or for those still alive at end of study not being known of having ILD since patients are no longer participating in the study? Clearly describe date of ILD used in analysis in method section and not in result section. - There is no mention about those patients who were lost to follow-up and reasons and the possible impact this may have had on the final results. - It is not clear why logistic regression analysis is performed since Cox regression analysis is the correct analysis to addresses the research question. - A total of 2692 were included in the study, but only 2015 patients were included in the multivariable study due to missing data for any of the variables in the multivariable regression analysis. Although sub-group analysis are performed in those with and without smoking data, the events in these sub groups may become too small and the analysis may be underpowered to draw any conclusions. Did the authors consider imputing the data? - The result section should be restructured based on the suggestions about primary research question above. In addition, it is not always why certain information is provided. For example, “In 5 patients drug induced pulmonary ….. “ - What were the csDMARDs mainly used in the non-MTX group? - Smoking status is defined as ever/never. Was no data on current smoking status available? - As described in the introduction and discussion section, clinicians may not prescribe MTX in in which they fear development of ILD. Could this have introduced some channeling bias in this study? - Table 3, data on ESR is missing

REVIEWER	Jorge Rojas-Serrano Interstitial Lung Disease and Rheumatology Unit, Instituto Nacional de Enfermedades Respiratorias, Ismael Cosio Villegas. México City, México
REVIEW RETURNED	02-Jan-2019

GENERAL COMMENTS	Is rheumatoid arthritis interstitial lung disease related to methotrexate treatment? Results from a multivariate analysis in the ERAS and ERAN inception cohorts. bmjopen-2018-028466 This is a study that contributes to the knowledge of the association between ILD and methotrexate in RA. After Conway´s et al metanalysis, a cohort study like this, is in perfect time to add pertinent information about the association of methotrexate and ILD. I have a few comments This is an association study, indeed, no predictive model is presented in the article. So, before anyone asks about the ROC curve of the predictive model, I recommend the authors to change predictive factors to risk factors associated to ILD in RA. I think that the discussion about the contraindication of using methotrexate in patients with lung disease is outdated. Authors are missing two recent studies that may be included in the manuscript: England BR et al Clin Rheumatol 2018 https://doi.org/10.1007/s10067-018-4314-9) , and Rojas Serrano j Clin Rheumatol 2017 doi: 10.1007/s10067-017-3707-5 . In this studies, further information about the effect on survival of methotrexate on RA patients with lung disease is provided. Also,

	Wolfe et al. https://doi.org/10.1080/03009740601153774 published in 2007 a study analyzing the association of ILD with DMARDs. Please, verify the results of time to diagnosis of ILD after methotrexate exposure. Authors are using OR instead of HR. Also, figure 2a is very hard to understand, because it includes (I assume) patients that had a ILD diagnosis at baseline evaluation, please provide a short explanation of this fact so readers may have a better understanding of the graph. Hypersitivity pneumonitis secondary to methotrexate does really exists? The proposed diagnostic criteria (modified Searles and McKeadry criteria) are specific? One of the most difficult parts of reviewing this manuscript is that to much space of the article is dedicated to a diagnosis that is hard to sustain.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Suzan Verstappen

Institution and Country: University of Manchester

Please leave your comments for the authors below

This study aims to address the research question whether rheumatoid arthritis interstitial lung disease is related to methotrexate treatment. To answer the question data from two well-known observational studies, ERAS and ERAN, are used. Although clinically a very important question, there are a number of methodological issues that should be addressed and the focus of the primary analysis should be on the development of incident ILD.

Thank you for your supportive comments that this is clinically a very important question. We have emphasised through out the manuscript that the analysis concerns co-variates associated with incident RA-ILD, and consistently used this term throughout and added it to the title so as not to confuse our work with the course or outcome of established RA-ILD.

Comments:

- The authors aim to address the research question whether RA-ILD is related to MTX treatment. However, the primary analysis is conducted in the whole patient population including patients with ILD at baseline before any of the patients had been treated with csDMARDs. To address their question, the primary analysis should focus on the development of incident ILD and exclude those patients with ILD at baseline.

Thank you for this helpful comment with which we agree. We had previously considered this emphasis of presentation of the data in the first submission of the manuscript, as we are principally interested in the effect of MTX exposure (as opposed to other demographic and RA specific factors such as RF factor and nodules), and so have changed the results section and associated Tables and Figures appropriately. We now report a primary analysis focusing on incident RA-ILD in cases where this only developed after any csDMARD use, and an extended analysis including the additional 25 cases of RA-ILD recorded at baseline which provide greater power to assess the association of other demographic and RA specific baseline factors.

- A number of assumptions are made with respect to exposure and outcome. However, it is important to provide more detailed information about loss to follow-up, time between last CRF and

death certificates, until when death certificates were obtained etc. Patients having ILD on their death certificate, but not on the last CRF, were included in the non-MTX exposed group if the time between last CRF and death was <2 years

Thank you for this comment and request for more information which we have provided in the manuscript.

Lost to follow up for no reason was relatively low for long duration prospective cohort data at 13.7% and this has been added to the methods section. Here are the full reasons for discontinuation in ERAS ERAN. We haven't added all of this data, but could do so if you feel necessary

ERAS ERAN 2018 Follow up status, reasons for discontinuation

		total		Cohort ERAS		ERAN	
		n	%	n	%	n	%
total		2701	100%	1465	100%	1236	100%
Reasons For Discontinuation	Died	491	18%	360	25%	131	11%
	Lost to FUp	370	14%	187	13%	183	15%
	Pt Choice	119	4%	70	5%	49	4%
	Moved discharged	154	6%	114	8%	40	3%
	Comorbidity	28	1%	21	1%	7	1%
	Remission	30	1%	28	2%	2	0%
	Closure	1509	56%	685	47%	824	67%

Death certificate information is provided 4 monthly and we included information supplied by HSCIC up to June 2018 when the statistical analyses were performed. This has been added to the methods section. Information regarding time from last CRF to death certificate is given, and a fuller explanation of our pragmatic decisions regarding inclusion and exclusion of some cases, and the time taken as onset of ILD, in the context of this being an insidious slow onset process, have been added to the methods. In the strengths and limitations section of the discussion we have clarified how cases may have been missed.

Maximum follow-up duration is 25 years, meaning that those patients recruited to ERAS were followed until 2011 if they had not left the study before this date. Depending on the year until which death certificates were obtained this may mean that this could have led to bias since these patients may have been excluded from the study since time since last CRF was>2 years.

Death certificate information was obtained up to June 2018, this has been added to methods and this point covered in the strengths and limitations section of the discussion.

Furthermore, is it possible that patients develop ILD and will recover without ILD being recorded on the death certificate or for those still alive at end of study not being known of having ILD since patients are no longer participating in the study?

We agree that there may be patients still alive who may have developed RA-ILD since last CRF and not reported to us as they have not yet died. We have reported RA-ILD survival to be 3 years in ERAS and so think it unlikely that we would have missed many cases. We have acknowledged this possibility in the limitations section of the discussion. We doubt there would be many cases of RA-ILD recovering, and so escaping mention on the death certificate, given the poor prognosis.

Clearly describe date of ILD used in analysis in method section and not in result section.

This has been done and we agree is better in this section.

- There is no mention about those patients who were lost to follow-up and reasons and the possible impact this may have had on the final results.

This was a low % for long duration cohort studies, overall 13.7%. Sensitivity analysis shows no difference in baseline characteristics of these cases compared to the rest of the cohort. Data not included.

- It is not clear why logistic regression analysis is performed since Cox regression analysis is the correct analysis to addresses the research question.

Thank you for your comments; we agree that Cox regression analysis is appropriate for our research question and that is why we have included this analysis. However, in our manuscript we chose to present both the Cox regression analysis as well as the logistic regression analysis, the latter to examine in greater depth possible differences within the variables. The multivariable logistic regression analysis also allowed us to take into account cases of ILD which occurred beyond the maximum follow up time of each patient (i.e. on death certificates). We have left both of these analyses in our manuscript as we think both are valuable. We have included more data from the time to event Cox proportional analysis (association of MTX exposure/baseline co-variates with time from first RA symptoms to RA-ILD onset) and included this as a new Table 4. We have also included more data from the multivariate time varying Cox proportional hazards models (incorporating data from co variates with multiple data points collected through follow up) in Supplementary Table 4.

- A total of 2692 were included in the study, but only 2015 patients were included in the multivariable study due to missing data for any of the variables in the multivariable regression analysis. Although sub-group analysis are performed in those with and without smoking data, the events in these sub groups may become too small and the analysis may be underpowered to draw any conclusions. Did the authors consider imputing the data?

We considered imputing the data but did not think that it was appropriate since we could not be certain that the data was missing at random. The initial CRF for ERAS did not include a question on smoking status, so this data was collected retrospectively. This meant that it was unavailable for those patients who had died/were lost to follow up.

- The result section should be restructured based on the suggestions about primary research question above.

As above, this has been done

In addition, it is not always certain why information is provided. For example, “In 5 patients drug induced pulmonary ….. “

This section refers to the incidence of hypersensitivity pneumonitis in ERAS/ERAN. The other reviewer raised comment about this, and we have decided to remove this from the manuscript, in case it causes confusion.

- What were the csDMARDs mainly used in the non-MTX group?

More information about this has been added to the ‘treatment profiles’ section of the methods, and the references give more details.

- Smoking status is defined as ever/never. Was no data on current smoking status available?

Data on current smoking as a category is shown in Table 1 and 2. Analyses combined current and ex-smoker into the category ‘ever smoker’.

- As described in the introduction and discussion section, clinicians may not prescribe MTX in in which they fear development of ILD. Could this have introduced some channeling bias in this study?

Yes this is a possibility. We have looked at MTX exposure in patients with and without baseline respiratory co-morbidities (to see if fewer patients with respiratory co morbidities were exposed to MTX) and found no difference. Furthermore Table 2 shows that there were borderline significantly more current and ex smokers in the MTX exposed patients than the non-MTX exposed (p=0.058). Acknowledgement of this important possible bias has been added to the limitations section of the discussion, but for these 2 reasons we think this an unlikely confounder.

- Table 3, data on ESR is missing

We had only included the data in this table that reached statistical significance, as it is derived from logistic modelling, explaining missing sections. This has been clarified in the Table.

Reviewer: 2

Reviewer Name: Jorge Rojas-Serrano

Institution and Country: Interstitial Lung Disease and Rheumatology Unit, Instituto Nacional de Enfermedades Respiratorias, Ismael Cosio Villegas. México City, México

Please state any competing interests or state ‘None declared’: None Declared

Please leave your comments for the authors below

Is rheumatoid arthritis interstitial lung disease related to methotrexate treatment? Results from a multivariate analysis in the ERAS and ERAN inception cohorts.

bmjopen-2018-028466

This is a study that contributes to the knowledge of the association between ILD and methotrexate in RA. After Conway´s et al metanalysis, a cohort study like this, is in perfect time to add pertinent information about the association of methotrexate and ILD.

Thank you for your very helpful comments and appreciating the importance of this work to current clinical practice

I have a few comments

This is an association study, indeed, no predictive model is presented in the article. So, before anyone asks about the ROC curve of the predictive model, I recommend the authors to change predictive factors to risk factors associated to ILD in RA.

Thank you for making this important point, with which we agree. We have not developed a predictive model, and so have changed the text, removed ‘predictive’ as a term and consistently used ‘associated’

I think that the discussion about the contraindication of using methotrexate in patients with lung disease is outdated. Authors are missing two recent studies that may be included in the manuscript: England BR et al Clin Rheumatol 2018 https://doi.org/10.1007/s10067-018-4314-9) , and Rojas Serrano j Clin Rheumatol 2017 doi: 10.1007/s10067-017-3707-5 . In this studies, further information about the effect on survival of methotrexate on RA patients with lung disease is provided. Also, Wolfe et al. https://doi.org/10.1080/03009740601153774 published in 2007 a study analyzing the association of ILD with DMARDs.

Thank you very much for drawing these 3 important publications to our attention. They are all concerned with survival and outcome in established cases of RA-ILD (rather than onset of RA-ILD), and all add important reassurance of the effect of MTX in this disease. Indeed, your own work makes the opposite point that MTX is strongly associated with survival. They have been added to the discussion. Thank you for this.

Please, verify the results of time to diagnosis of ILD after methotrexate exposure.

We have reported this in the results 'In the MTX exposed cases the median time from exposure to MTX to the first record of ILD was 45 months (ERAS 47 and ERAN 26 months).'

Authors are using OR instead of HR.

We present ORs for logistic regression and HRs for the Cox regression analyses. We have been through the text and Tables to make sure we've used the correct ones where appropriate.

Also, figure 2a is very hard to understand, because it includes (I assume) patients that had a ILD diagnosis at baseline evaluation, please provide a short explanation of this fact so readers may have a better understanding of the graph.

We have expanded the legend to Figure 2a and 2b, which has now been changed in order of presentation of the data, following the advice of Reviewer 1. We hope this is now easier to follow.

Hypersitivity pneumonitis secondary to methotrexate does really exists? The proposed diagnostic criteria (modified Searles and McKeadry criteria) are specific? One of the most difficult parts of reviewing this manuscript is that to much space of the article is dedicated to a diagnosis that is hard to sustain.

We are uncertain whether you are referring to our report of 5 cases of hypersensitivity pneumonitis in the ERAS/ERAN cohort, and whether the diagnostic criteria for this were fulfilled, and indeed whether you think they are specific. Reviewer 1 also raised a question about why we had included this information and so we have removed this from the manuscript.

If you are referring to the diagnosis of RA-ILD in the ERAS/ERAN cohort, we have carefully explained our criteria for case selection in the methods, included discussion of this in the limitations section of the discussion, and highlighted the reassurance that our prevalence is similar to other cohorts. We have also added information concerning our pragmatic approach to recording the time of onset of ILD, in the methods. We are trying to be as transparent as possible regarding the assumptions required when analysing large cohort studies spanning 25 years.

VERSION 2 – REVIEW

REVIEWER	Suzan Verstappen University of Manchester
REVIEW RETURNED	20-Feb-2019

GENERAL COMMENTS	Many thanks for addressing all queries. It would be best to include the table with information on loss to follow-up in the Supplementary file.

REVIEWER	Jorge Rojas Serrano Unidad de Enfermedades del Intersticio Pulmonar y Reumatologia. Instituto Nacional de Enfermedades Respiratorias, Ismael Cosio Villegas Méwxico
REVIEW RETURNED	18-Feb-2019

GENERAL COMMENTS	I have no further comments. I think the articule should be accepted for publication.

VERSION 2 – AUTHOR RESPONSE

As requested a new Supplementary Table (Supplementary Table 1) has been added to show the detailed reasons for discontinuation from follow up in the entire ERAS and ERAN cohorts, and in each separately. This has been indicated to the reader within the Clinical and Laboratory measures subsection of the Methods section of the main manuscript.