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

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Abstract

Objectives

To assess predictive factors for rheumatoid arthritis interstitial lung disease (RA-ILD) in two large early RA inception cohorts with a particular focus on methotrexate (MTX) exposure.

Design

Multicenter prospective early RA inception cohort studies; the early RA study (ERAS) and the early RA network (ERAN)

Setting

Secondary care, ERAS 9 centers, ERAN 23 centers in England, Wales and the Republic of Ireland

Participants

Patients with new diagnosis of RA, n=2701.Standardised data including demographics, drug therapies and clinical outcomes including the presence of RA-ILD were collected at baseline, within 3- 6 months, at 12 months and annually thereafter.

Primary and secondary outcome measures

Primary outcome was the association of MTX exposure on RA-ILD diagnosis. Secondary outcomes were the association of demographic, comorbid and RA specific factors on RA-ILD diagnosis and the effects of MTX exposure on time to RA-ILD diagnosis.

Results

Of 92 eligible ILD cases, 39 occurred in 1578 (2.5%) MTX exposed and 53 in 1114 (4.8%) non-MTX exposed cases. MTX exposure was associated with a significantly reduced risk of developing RA-ILD (O.R. 0.48, CI 0.3, 0.79 p=0.004) and longer time to ILD diagnosis (O.R. 0.41, CI 0.23, 0.75 p=0.004) versus non-MTX exposed cases. Sub analysis of RA-ILD cases only developing after any csDMARD treatment showed MTX exposure not to be associated with RA-ILD diagnosis (O.R. 0.85 CI 0.49, 1.49 p=0.578) and a non-significant trend for delayed ILD diagnosis (O.R. 0.54 CI 0.28, 1.06 p=0.072). Other independent baseline predictors of RA-ILD

diagnosis on multivariate logistic analysis were higher age of RA onset, ever smoking, male gender, rheumatoid nodules and longer time from first RA symptom to first out-patient visit.

Conclusions

MTX treatment was not associated with an increased risk of RA-ILD diagnosis. On the contrary evidence suggested that MTX may delay the onset of ILD.

Article Summary

Strengths and Limitations

- Multicenter prospective early RA inception cohort study recruiting 2701 patients
- Standardised data collection with up to 25 years follow-up
- Diagnosis of RA-ILD made by participating rheumatology centers, or from death certification, without independent verification
- Univariate, multivariate logistic, time varying logistic and time to event Cox proprtional hazards analyses assessed MTX-exposure, demographic and RA specific factors predictive of RA-ILD diagnosis
- High proportion of missing smoker status data from ERAS patients recruited 1986 - 2001

Introduction

Methotrexate (MTX) is now firmly established globally as the anchor drug for the management of rheumatoid arthritis (RA), recommended for first line use, to which other conventional synthetic, targeted synthetic and biologic disease modifying anti rheumatic drugs (cs/ts/b DMARDs) are generally added (1,2). In addition to an excellent ability to suppress synovitis and restore physical function, there is compelling data demonstrating a beneficial effect on long term cardiovascular disease (3) and hence restoration of life expectancy to that of the normal population.

A hypersensitivity pneumonitis is a rare adverse effect of MTX described in 0.43% (4), generally subacute in presentation, with progression of characteristic symptoms over a period of days to weeks (5). This usually occurs early, within the first year of treatment, but has been reported up to 3 years after starting MTX (4,5). This organ specific hypersensitivity reaction has led to a creeping concern in routine practice that MTX may also be associated with an increased incidence or exacerbation of the interstitial lung disease (ILD) that is associated with RA, and may be a reason to withhold MTX from RA patients with any lung disease. RA-ILD is an uncommon but significant life threatening extra-articular manifestation, clinically significant in up to 5% of RA patients, with subclinical HRCT evidence in 33% or more, a median survival from diagnosis of approximately 3 years, contributing to the overall excess mortality of RA (2, 6-12). MTX is contraindicated if a patient has insufficient respiratory reserve to survive hypersensitivity pneumonitis. However, evidence is lacking that would deter initiation of MTX treatment in people with mild respiratory disease on grounds of an adverse effect on any other form of lung injury such as ILD. Indeed, the considerable benefits of MTX are such that a decision to withhold it as a treatment option for RA should be reluctantly made, and only for sound reasons.

Evidence that MTX may cause or have an adverse impact on RA-ILD is sparse. Meta-analysis of randomised controlled trials (RCT) of MTX in RA has reported an increased risk of all adverse respiratory events and respiratory infections, but not of death due to lung disease or non-infectious respiratory events, with follow up duration of 24-104 weeks (13). Due to inherent difficulties separating RA-ILD from putative MTX related ILD, a meta-analysis of MTX versus placebo or active comparator agents in RCTs from non-malignant inflammatory

disorders not themselves associated with ILD is of interest (14). This has shown no MTX associated risk of lung disease in studies ranging from 16 – 52 weeks follow up. These relatively short duration analyses, in patients pre-selected for RCTs, are reassuring but require substantiation from RA inception cohorts or patient registries with all-comers included and longer follow up. Sequential lung function tests in cohorts of MTX treated RA patients followed prospectively for up to 5 years have shown a sequential decline, with inconsistent interpretation that this is in keeping with (15), or in excess of (16), expected age related changes. Interpretation of these studies is limited by a lack of inclusion of non-MTX treated control RA patients. In another cohort comparing 55 MTX treated with 73 non-MTX treated patients with established RA, there was no adverse influence of MTX on pulmonary function tests over 2 years, including a sub analysis of those found to have largely sub clinical pulmonary fibrosis on HRCT (17).

We report the diagnosis of RA-ILD, its predictive factors and relation to MTX treatment, in two large multi-centre RA inception cohorts, the early rheumatoid arthritis study (ERAS) and the early rheumatoid arthritis network (ERAN), recruiting from 1986 – 2012 with review up to 25 years.

METHODS

Patient Databases

The study used data from ERAS (1986-2001) and ERAN (2002-2012), two multi-center early RA inception cohorts. ERAS recruited 1465 patients (<2 years disease duration, no prior csDMARD therapy) from nine district general hospitals in England, followed yearly for up to 25 years (median follow up 10 years). ERAN recruited 1236 patients (<3 years disease duration) from 23 centres in England, Wales and Ireland, followed yearly for up to 10 years (median follow up 6 years). Ethical approval was obtained from East Hertfordshire local research ethics committee (ERAS) and the Trent research ethics committee (ERAN). All participants gave informed consent. STROBE reporting cohort guidelines have been followed (von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies).

Recruitment into ERAS and ERAN was based on clinician diagnosis with 70% of patients fulfilling the minimum ARA criteria (18) for RA at baseline and 96% by last visit. Patients subsequently reclassified as non-RA were excluded from the study.

Clinical and laboratory measures

Information on demographic, clinical, treatment, laboratory and functional features was recorded in both cohorts at baseline, between 3 and 6 months, at 12 months and then once yearly on standardized case report forms (CRF), as previously described (19-21). Disease activity (DAS) was calculated according to the original three variable method (22) in ERAS and the four variable DAS28 method (23) in ERAN. A transformation formula was used to make DAS and DAS28 comparable (24). Source data verification was undertaken by an experienced nurse practitioner at visits to each center. Combined analysis of ERAS and ERAN is possible since they are consecutive inception cohorts with similar design, including the variables captured, timing of assessments and patient recruitment.

Treatment profiles

Patients were treated according to usual care in each of the ERAS and ERAN centres, without specific protocols, strategies or other external influences. Treatment details were entered onto the CRF at each ERAS/ERAN data collection visit. At baseline all patients in ERAS were csDMARD naïve and in ERAN 13.5% had commenced a csDMARD within a few weeks of first secondary care visit. In ERAS, csDMARD use was mainly sequential monotherapy with/without steroids, generally favouring initial sulphasalazine (SSZ) monotherapy, with a gradual switch to MTX monotherapy such that SSZ and MTX were used in equal proportions as first csDMARD by 2002, and then in ERAN MTX became the most likely initial choice thereafter (20), this reflecting contemporary best practice. Combination csDMARDS were generally used for more severe RA and were introduced at earlier time-points in the later years of ERAS and in 25% of those who received any csDMARDs in ERAN (20,21). Only a small proportion of patients received bDMARDs, which were available from 2002 onwards (<2% by 1 year and <10% by 3 years).

Median time from RA symptom onset to first rheumatology outpatient visit (baseline assessment) was 6 months in both cohorts, and to first csDMARD initiation 8 months in ERAS and 7 months in ERAN.

ILD identification

Co-morbidities including respiratory disease were entered on the CRF at each visit. Death certification was received from the NHS medical research information service (MRIS) and subsequently the NHS health and social care information center (HSCIC) for all recruited patients. The diagnosis of ILD at each center was according to standard practice, with confirmatory evidence from standard investigations including pulmonary function tests, chest radiographs and HRCT scans. ILD was deemed to be present if the terms pulmonary fibrosis or interstitial lung disease were listed on the CRF or the death certificate.

MTX exposed ILD group

Patients were included in the analysis as MTX exposed ILD if they were recorded on the CRF as starting MTX at any time prior to the first record of ILD, either on the CRF or the death certificate.

Non-MTX exposed ILD group

Patients were included in the analysis as non-MTX exposed ILD if they were recorded as having ILD on the CRF without record of prior MTX treatment. As the analysis was concerned with the onset of ILD, patients who started MTX at any time point after ILD was first recorded on the CRF remained in the non-exposed group, as ILD was first diagnosed before MTX treatment. Patients who were recorded as having ILD on the death certificate but not on the last CRF were included in the non-MTX exposed group if the time interval between last CRF and death was less than 2 years, and no MTX treatment had been recorded on the CRFs throughout ERAS/ERAN data collection. It was considered that this was too short a time for any potential but unknown MTX use after the last CRF to have had an effect, had it been introduced. If this time interval was 2 years or longer patients were excluded from the analysis as they could have been exposed to MTX for the first time after last CRF and before the first record of ILD on the death certificate, and as such any potential MTX exposure during this time could have had an effect. Patients where the first record of ILD and MTX use was on the same CRF were considered non-MTX exposed as the maximum time MTX could have been used since the preceding CRF was 1 year and this was considered too short to have had an effect on ILD within the same period.

Statistical analysis

All analysis used statistical software Stata/IC 15.1. Analyses were performed on the entire cohort and on a subgroup excluding patients where ILD was recorded at the baseline visit. The excluded patients had developed ILD either preceding or synchronously with RA and prior to any csDMARD use for RA. First univariate analyses were performed for associations of baseline covariates with RA-ILD development. Next multivariate binary logistic models were fitted to the data to determine independent baseline predictors of RA-ILD. As there were multiple data collection points across the ERAS and ERAN follow up period, multivariate time-varying analysis using cox proportional hazards models were created to include multiple data entries for covariates with repeated measures. Finally Cox regression time to event analysis was used to assess the relation between time of ILD diagnosis and first RA symptoms in MTX exposed and non-MTX exposed ILD cases.

A detailed description of the univariate and multivariate model analyses is given in supplementary material

RESULTS

A flow chart of patient selection in shown in Fig 1. From 2,701 patients a total of 101 cases of ILD were recorded (3.7%) of which 25 were present at baseline (25%). None of the baseline ILD cases had been treated with csDMARDs prior to first CRF. Nine ILD cases were excluded from analysis because the only record of ILD was on the death certificate and over 2 years had elapsed between this and the last CRF, during which time csDMARD treatment was unknown. There were 1,578 MTX exposed cases of whom 1,539 (97.5%) were not and 39 (2.5%) were diagnosed with ILD, and 1,114 non-MTX exposed cases of whom 1,061 (95.2%) were not and 53 (4.8%) were diagnosed with ILD. Of the 53 non-MTX exposed ILD cases, 19 (35%) were treated with MTX after ILD was diagnosed.

Demographic features of the ERAS and ERAN cohorts are shown in Table 1. These were generally similar across both cohorts, however there were significant differences in age of RA onset (older in ERAN), baseline smoking status (more current and ex smokers in ERAN) and MTX use (79% ERAN vs. 41% ERAS). The prevalence of ILD was 3.2% in ERAN and 4.2% in ERAS (n.s.). The median dose of MTX across both cohorts was 12.5mg but following contemporary practice this increased with time; ERAS 10mg, ERAN 20mg per week. Table 2 shows demographic features of MTX exposed and non-MTX exposed cases, where MTX exposed

patients were significantly more likely to have developed RA at a younger age, be in a higher DAS category, be male, current or ex-smokers, RF positive and nodular. In the MTX exposed cases the median time of exposure to MTX before the first record of ILD was 45 months (ERAS 47 and ERAN 26 months).

In 5 patients drug induced pulmonary pneumonitis was recorded, of whom 3 were thought to be due to MTX (one was also on a TNF inhibitor), 1 sulphasalazine and 1 leflunomide. In the 3 MTX associated cases, MTX was withdrawn, all survived and none subsequently developed RA-ILD.

Univariate analyses of the relation between new diagnosis of RA-ILD and a range of binary and continuous variates are shown in Supplementary Tables 1a and 1b. This indicated that MTX exposure was associated with a significantly reduced odds ratio of developing ILD (O.R. 0.51, CI 0.32, 0.79 p=0.001). Male gender, baseline positive RF, ever smoking, presence of nodules, age of RA onset and baseline ESR significantly increased the odds of ILD diagnosis. Patients who developed ILD were at RA onset a mean 7 years older (p<0.0001) and had a mean baseline ESR score of 10 mm/hr higher (p=0.014) than patients who did not develop ILD. Mean DAS28 score at first record of ILD in MTX exposed cases was 3.77 and in non-MTX exposed cases 4.27 (T test p=0.30).

Table 3 shows the covariates independently associated with ILD diagnosis in the best fit multivariate model. This confirms non-MTX exposure, male gender, higher age of RA onset, baseline nodules, ever smoking and higher baseline ESR to be independently predictive of ILD. Unlike univariate analysis in this model longer time from first RA symptom to first OPD visit was associated with ILD and baseline major co morbidities (excluding respiratory) were protective. This group of conditions included cardiac disease, other cardiovascular conditions (e.g. hypertension, cerebrovascular disease), diabetes, thyroid disease, osteoarthritis, spinal disorders, malignancies and gastrointestinal conditions as defined by ICD10 criteria.

As we were specifically interested in the relation of ILD onset to MTX exposure a supplementary analysis was performed excluding 25 cases with ILD recorded at baseline, therefore restricting analysis to cases where ILD was only diagnosed after any csDMARD exposure. The univariate analyses showed similar findings (Supplementary Table 2a and 2b)

with male gender, RF positivity, ever smoking, nodules, age of RA onset and baseline ESR all remaining significantly associated with onset of ILD. The OR of MTX exposure and RA-ILD was 0.96 (CI 0.57, 1.63 p=0.872), indicating no association. Longer time between first RA symptoms and the first outpatient appointment was borderline significant (p=0.053). In the multivariate model (Table 3) higher age of RA onset, RF positivity, ever smoking and longer time from first RA symptom to first OPD visit were independently associated with ILD and there remained no evidence that MTX exposure was associated with ILD (OR=0.85, CI=0.48, 1.49 p=0.578). As seen in the main analysis baseline major comorbidities were independently protective.

As there was a large number of patients in ERAS with missing smoking status at baseline (n=549), a sensitivity analysis was performed by running the multivariate analysis in smokers, non smokers and those with missing smoking status data (see supplementary Table 3). This continued to show no association between methotrexate use and ILD in smokers (OR=1.56, CI= 0.74, 3.29, p=0.240) and in those with missing smoking data (OR=1.35, CI=0.33, 5.52, p=0.681), but MTX use was associated with a reduction in ILD diagnosis in non-smokers (OR=0.24, CI=0.08, 0.70, p=0.009).

The multivariate time varying analysis, incorporating multiple data entries for covariates measured at each follow up visit (e.g. DAS, individual DAS components, HAQ, full details in supplementary materials) resulted in no additional significant co-variate associations with RA-ILD onset. The best fit model with the lowest Akaike information criterion (AIC) score showed significant associations with age of RA onset and current smoking status and continued to show no association with MTX exposure (H.R. 0.98 CI 0.87, 1.11 p=0.763).

The relation between time to ILD diagnosis after first RA symptoms in the MTX exposed and non-MTX exposed groups is shown in Fig 2a (entire cohort) and 2b (excluding 25 cases with ILD diagnosed prior to any csDMARD use). The MTX exposed ILD group includes 39 patients, for 29 of whom the time of diagnosis of ILD was recorded on the CRF. In the remaining 10 cases ILD was only recorded on the death certificate and a mean 6.6 (range 3-11) years had elapsed between this and last CRF. For these cases the time of ILD diagnosis was unknown and pragmatically was recorded as last CRF + 2 years. This will therefore be a potentially earlier record of time of ILD diagnosis in 10 MTX exposed cases. The non-MTX exposed ILD

group includes 53 patients, for 23 of whom the time of ILD diagnosis was recorded on the CRF. In 5 cases ILD was only recorded on the death certificate and not on the last CRF, with an interval of less than 2 years, and for these the time of ILD diagnosis was recorded as last CRF + 1 year. For the 25 cases where ILD was recorded on the baseline CRF (Fig 2a only) the time of diagnosis was taken as synchronous with RA onset. The entire cohort analysis shows a significant delay in time to diagnosis of ILD in MTX exposed compared to non-MTX exposed cases (OR 0.41 CI 0.23, 0.75 p=0.004) and a weak effect of higher age of RA onset (OR 1.03 CI 1.0, 1.06 p=0.028), but no influence of any of the other co-variates independently associated with ILD onset in the multivariate model. The analysis excluding 25 cases with ILD diagnosed at baseline, pre csDMARD treatment, showed the same effect of higher age of RA onset (OR 1.03 CI 1.0, 1.06 p=0.048), and a non-significant trend for delayed ILD diagnosis in MTX exposed cases (O.R. 0.54 CI 0.28, 1.06 p=0.072).

Discussion

We report an overall prevalence of RA-ILD of 3.7% in ERAS and ERAN, two large RA inception cohorts, recruiting between 1986 and 2012 with maximum follow up 25 years. These findings extend the earlier report of RA-ILD from the ERAS cohort alone (8), and are in keeping with previous studies, including the UK BRILL network which reported 2 -3 % prevalence across its recruiting centers (10-12). ILD was already present at baseline assessment in 25 patients, representing 24.7% of the entire ILD group, these cases developing ILD either before or synchronously with first joint symptoms. This is similar to the UK BRILL cohort where 10% developed ILD before joint disease and 7% synchronously (10), and consistent with our earlier report from ERAS alone where ILD was present at baseline in 12/52 (23%) cases (8). Discrepancies may reflect the method of detection as demonstrated by Gabbay et al who studied 36 patients with early RA and found abnormalities consistent with RA-ILD using a range of clinical, physiological and imaging modalities in 58%, but this was clinically significant in only 14% (9).

The results of the multvariate analysis concurred with other studies (8-11) in finding an association of RA-ILD diagnosis with male gender, increasing age of RA onset, baseline nodules, ever smoking and baseline ESR. As was found with our earlier report from ERAS alone (8), there was no association between MTX exposure and ILD, either on univariate or multivariate analyses. On the contrary MTX exposure was protective in the entire cohort

and not predictive in the supplementary analysis excluding cases with ILD at baseline prior to any csDMARD use. This concurs with the meta analyses of RCTs by Conway et al who found no association of MTX use and ILD in RA and non-RA inflammatory diseases (13,14), with the prospective 2 year study reported by Dawson et al of 128 RA patients with established disease (17), and a recent report from the same group in 106 RA patients commencing MTX and followed for 10 years (25). The implication for rheumatologists is to be especially vigilent for the development of RA-ILD in male patients who are RF positive, have nodules, a history of ever smoking and older age of RA diagnosis. MTX should only be witheld from RA patients with insufficient respiratory reserve to make it unlikely that they would survive hypersensitivity pneumonitis. Our findings refute concerns amongst clinicians that there is an association with MTX exposure and RA-ILD, and provide no justification to delay or deny patients MTX for fear of inducing RA-ILD while seeking specialist opinions or further investigations of potential respiratory disease or other comorbid features. Such delays are likely to worsen RA outcomes by unnecessarily denying patients the anchor csDMARD for this disease.

Of interest is the finding of a significant association between ILD diagnosis and increased time from RA symptom onset to first outpatient visit on multivariate analysis in both the entire cohort and the analysis excluding cases with ILD at baseline prior to any csDMARD. Both of the other two measures of time to secondary care intervention, first RA symptom to first csDMARD and first outpatient appointment to first csDMARD, were consistent with this association, with the interval being a mean 3.42 and 2.56 months longer respectively in patients who subsequently developed ILD (excluding those with ILD already diagnosed at baseline). This is perhaps supportive of the so called 'window of opportunity' whereby a delay in treatment leads to worse outcomes. The explanation for the protective effect of baseline co-morbidities (excluding respiratory) on RA-ILD is not immediately apparent, and we speculate that this might be explained by treatment differences, for example as malignancy was one of the more common major comorbidities, previous cancer therapies may have afforded immuno-suppressive effects.

Interestingly there was a trend for ILD to be less prevalent in the later 2002-2012 ERAN cohort (3.2%) than the 1986-2001 ERAS cohort (4.2%) based on a sample size of 101 cases. This is in contrast to a report of increasing prevalence over time among US veterans from

1985-2006, assumed due to increased awareness and investigation of respiratory symptoms coupled with increased survival (26,27). The reason for an apparent decreasing ILD prevalence in ERAN is unclear, however it is noteworthy that this was seen despite a significant increase in two exacerbating factors, age of RA onset and current smoking, in ERAN compared to ERAS. Intriguingly MTX use was higher in ERAN, raising the question whether MTX may have had a protective effect on ILD development despite the higher risk factors in ERAN. This is supported by the multivariate analysis where MTX use was associated with a significantly lower OR of ILD in the entire cohort and in the time to onset analysis where ILD was diagnosed significantly later in MTX exposed versus non-MTX exposed cases. These effects remained numerically suggestive in the secondary analysis excluding cases where ILD was diagnosed prior to any csDMARD exposure. A protective effect of MTX could have been due to better overall RA disease control than in the non-MTX exposed group, where the majority received SSZ and a minority hydroxychloroquine or leflunomide (20,21). This is supported by the higher DAS28 score at first record of ILD in non-MTX exposed compared to MTX exposed cases, although the difference was not significant. Further evidence for an association between RA-ILD and worse disease control comes from the USA Rochester cohort followed up to 2006, where parameters indicative of more severe RA, such as ESR, nodules and destructive joint changes were associated with ILD (11). Similarly, in the UK BRILL cohort anti-CCP antibodies showed the strongest association with ILD (10), this being a recognised marker of disease severity. Unfortunately there were insufficient numbers of ERAS/ERAN patients with baseline anti-CCP to assess the impact of this on ILD. However, we found higher baseline ESR to have a significnnt association with RA-ILD on univariate and multivariate analysis, this being mean 8.64 mmHg higher in patients who developed ILD. Although the ERAS/ERAN cohorts were not designed to compare treatment effects, the conclusion from our findings is that MTX has no association with the development of RA-ILD and may lead to a delayed onset and lower incidence of RA-ILD perhaps as a consequence of better overall RA disease control, or specific lung mediated immune suppression

Strengths and Limitations of this study

The strength of this study is inherent in the nature of ERAS and ERAN, two real world large inception early RA cohorts, recruiting all-comers, treated according to contemporary best

practice, with the rigour of regular standardised assessments and data collection allowing data to be pooled and analysed collectively. In contrast to RCTs the data from ERAS and ERAN are not restricted to defined RA populations with strict inclusion and exclusion criteria, nor to treatment strategies confined by protocol. ERAS and ERAN are also unique in size recruiting 2701 patients compared for example to 582 in the Rochester cohort (11), and in the long duration of follow up, adding to the strength of these analyses. A limitation of the data is the lack of external confirmation of ILD case verification, this being dependent on the reporting of ILD by each center on the CRF, or the doctor completing the death certificate. Whilst the diagnosis of ILD is strongly influenced by investigations, with incrementally increasing detection from clinical signs to pulmonary function tests and HRCT images, and much sub clinical disease being present (5,9), we believe that the specific diagnostic features of ILD and thoroughness of clinical work up by recruiting centers were sufficient to have confidence in the accuracy of ILD reporting. Furthermore, credibility of ILD reporting in ERAS/ERAN is gained from the prevalence being in keeping with other cohorts where it was possible to independently verify the diagnosis for each case (9-12). We have assumed that all cases of ILD occurring at baseline were RA related. This would seem the most likely aetiology, especially in those where the onset was synchronous with joint disease, but potentially other causes might have explained ILD in some cases where ILD predated RA. Given this uncertainty the analyses were repeated with the exclusion of these baseline cases, with no change in our conclusions with respect to predictors of ILD and the relation to MTX treatment. A further limitation is that smoking status was missing in a large proportion of ERAS patients, because its importance was not appreciated at the time data was collected in the 1980s. However, the sensitivity analysis, running the multivariate model stratified by smoking status at baseline, did not change the lack of association between MTX and RA-ILD onset.

In conclusion we report a prevalence of RA-ILD in the ERAS/ERAN cohorts of 3.7% with significant predictive factors in line with other studies, namely male gender, older age of RA onset, high ESR, nodules, ever smoking and RF positivity. We also show a significant association of ILD with a longer time from first RA symptoms to secondary care intervention supporting the 'window of opportunity'. We have found no association between MTX treatment and RA-ILD diagnosis, and on the contrary provide evidence suggestive that MTX

exposed RA patients may have a delayed onset of ILD. There seems no reason to confuse the association of MTX and hypersensitivity pneumonitis with the onset of RA-ILD. Assuming baseline lung function is sufficient to withstand an episode of hypersensitivity pneumonitis, there are no other respiratory contraindications to the use of this very effective 'anchor' csDMARD in patients with RA.

Key messages

- In ERAS/ERAN, RA-ILD is significantly associated with male gender, older age of RA onset, ESR, nodules, ever smoking, RF positivity and a longer time from first RA symptoms to first secondary care visit.
- There is no association between onset of RA-ILD and MTX treatment
- MTX may have a protective role in delaying the onset of RA-ILD

Conflicts of Interest

The authors have no conflicts of interest to declare

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Author Contributions Statement

PK: Conception of work, data interpretation, manuscript drafting

AB, KS Statistical analysis, data interpretation, manuscript revision

EN, AY Statistical support, data interpretation, manuscript revision

DA, PC, JD data interpretation, manuscript revision

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Data Statement

Dataset available from Prof A. Young, Center for Health Services and Clinical Research and Post Graduate Medicine, University of Hertfordshire, Hatfield, UK

Table 1. Demographic features of the ERAS and ERAN cohorts

		Total		ERAS		ERAN		Chi-squared p-value
Number		2701		1465		1236		
Gender	Male	893	33.1%	492	33.6%	401	32.4%	0.530
	Female	1808	66.9%	973	66.4%	835	67.6%	
Age of RA onset	<55	1146	42.4%	659	45.0%	487	39.4%	0.013
	56-64	728	27.0%	380	25.9%	348	28.2%	
	65+	827	30.6%	426	29.1%	401	32.4%	
Baseline Smoker Status	Never	995	36.8%	528	36.0%	467	37.8%	<0.001
	Current	594	22.0%	179	12.2%	415	33.6%	
	Ex-Smoker	518	19.2%	209	14.3%	309	25.0%	
	Other	26	1.0%			26	2.1%	
	Missing	568	21.0%	549	37.5%	19	1.5%	
MTX Exposure	No	1114	41.2%	857	58.5%	257	20.8%	<0.001
	Yes	1578	58.4%	602	41.1%	976	79.0%	
	Missing	9	0.3%	6	0.4%	3	0.2%	
ILD Diagnosis	No	2600	96.3%	1404	95.8%	1196	96.8%	0.206
	Yes	101	3.7%	61	4.2%	40	3.2%	

Key

RA: rheumatoid arthritis, MTX: methotrexate, ILD: Interstitial Lung disease

Table 2. Demographic features of MTX exposed and non-MTX exposed cases

		Total		Non-MTX exposed		MTX exposed		Chi-squared p-value
Total		2692		1114		1578		
Gender	Male	1804	67.0%	721	64.7%	1083	68.6%	0.034
	Female	888	33.0%	393	35.3%	495	31.4%	
Age of RA onset	<55	1144	42.5%	436	39.1%	708	44.9%	<0.001
	55-64	723	26.9%	277	24.9%	446	28.3%	
	65+	825	30.6%	401	36.0%	424	26.9%	
Baseline Smoking Status	Never	991	36.8%	346	31.1%	645	40.9%	0.058
	Current	594	22.1%	179	16.1%	415	26.3%	
	Ex-smoker	518	19.2%	172	15.4%	346	21.9%	
	Other	25	0.9%	2	0.2%	23	1.5%	
	Missing	564	21.0%	415	37.3%	149	9.4%	
Baseline Erosions	No erosions	1883	69.9%	808	72.5%	1075	68.1%	0.117
	Erosions	699	26.0%	276	24.8%	423	26.8%	
	Missing	110	4.1%	30	2.7%	80	5.1%	
Baseline RF	-ve	977	36.3%	462	41.5%	515	32.6%	<0.001
	+ve	1633	60.7%	628	56.4%	1005	63.7%	
	Missing	82	3.0%	24	2.2%	58	3.7%	
Baseline Nodules	None	2515	93.4%	1057	94.9%	1458	92.4%	0.010
	Nodules	177	6.6%	57	5.1%	120	7.6%	
Baseline DAS	<1.6	31	1.2%	5	0.4%	26	1.6%	<0.001
	1.6-2.59	298	11.1%	163	14.6%	135	8.6%	
	2.6-3.2	345	12.8%	180	16.2%	165	10.5%	
	>3.2-4.19	543	20.2%	243	21.8%	300	19.0%	
	4.2-5.1	-	-	-	-	-	-	
	>5.1	1415	52.6%	503	45.2%	912	57.8%	
	Missing	60	2.2%	20	1.8%	40	2.5%	

Table 3 Multivariate logistic analysis showing co-variates independently associated with RA-ILD development

	Entire cohort, including RA-ILD onset pre any csDMARD	Wald test	Sub group of RA-ILD onset after any csDMARD exposure	Wald test
	O.R.	p value	O.R. (95% C.I.)	p value
Methotrexate exposure	0.48 (0.3, 0.79)	0.004	0.85 (0.49, 1.49)	0.578
Age RA onset	1.04 (1.02, 1.06)	<0.001	1.04 (1.02, 1.06)	<0.001
Smoking, ever, baseline	1.91 (1.13, 3.25)	0.016	2.21 (1.21, 4.03)	0.01
Male gender	1.74 (1.05, 2.86)	0.03	1.44 (0.83, 2.48)	0.193
RF positive, baseline			2.02 (1.07, 3.82)	0.029
RA nodules, baseline	2.19 (1.08, 4.41)	0.029		
Onset - OPD	1.03 (1.0, 1.07)	0.04	1.04 (1.00, 1.07)	0.027
Baseline major co-morbidities*	0.67 (0.46, 0.98)	0.037	0.62 (0.40, 0.95)	0.027
Baseline ESR	1.01 (1.0, 1.02)	0.047		

Key

RF: rheumatoid factor,

Onset - OPD: time from first RA symptoms to first hospital out patient appointment

*excluding respiratory

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Figure 1

Diagram showing patient selection and allocation to MTX exposed and non MTX exposed groups

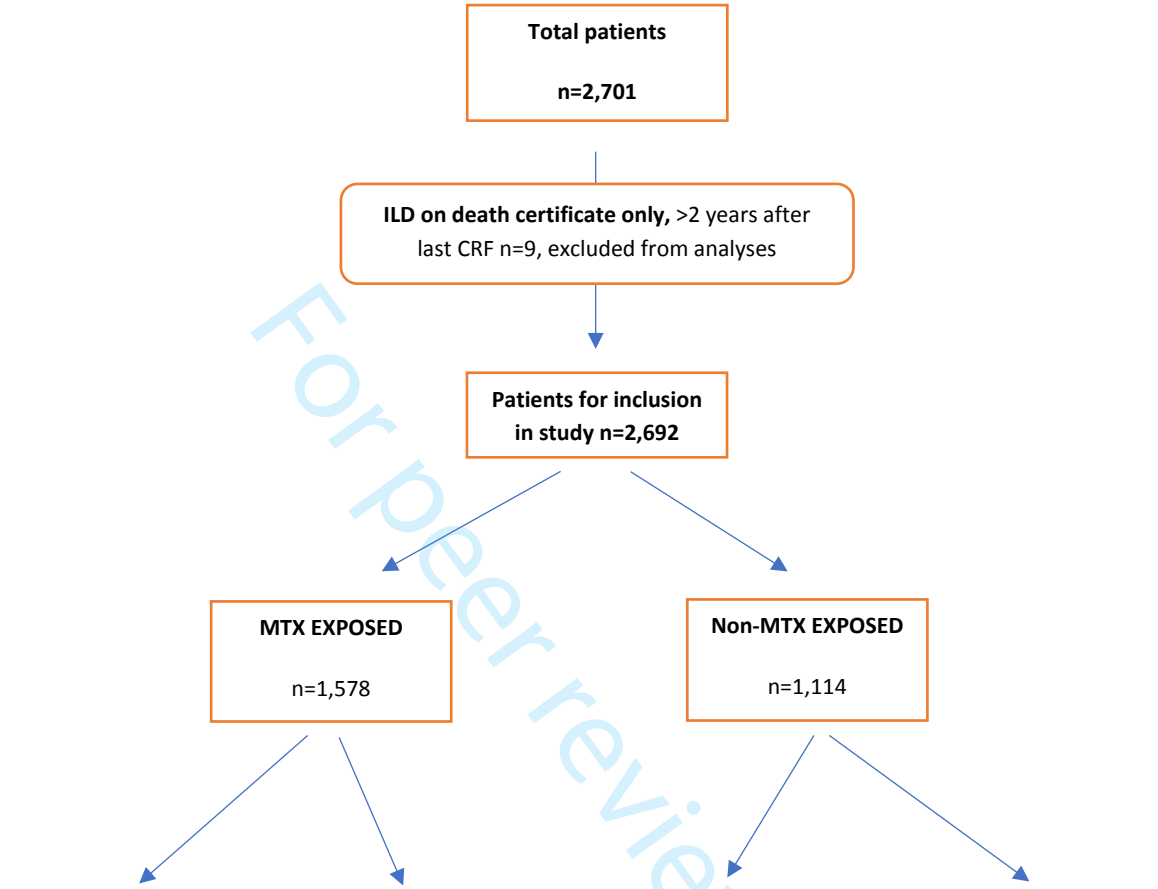
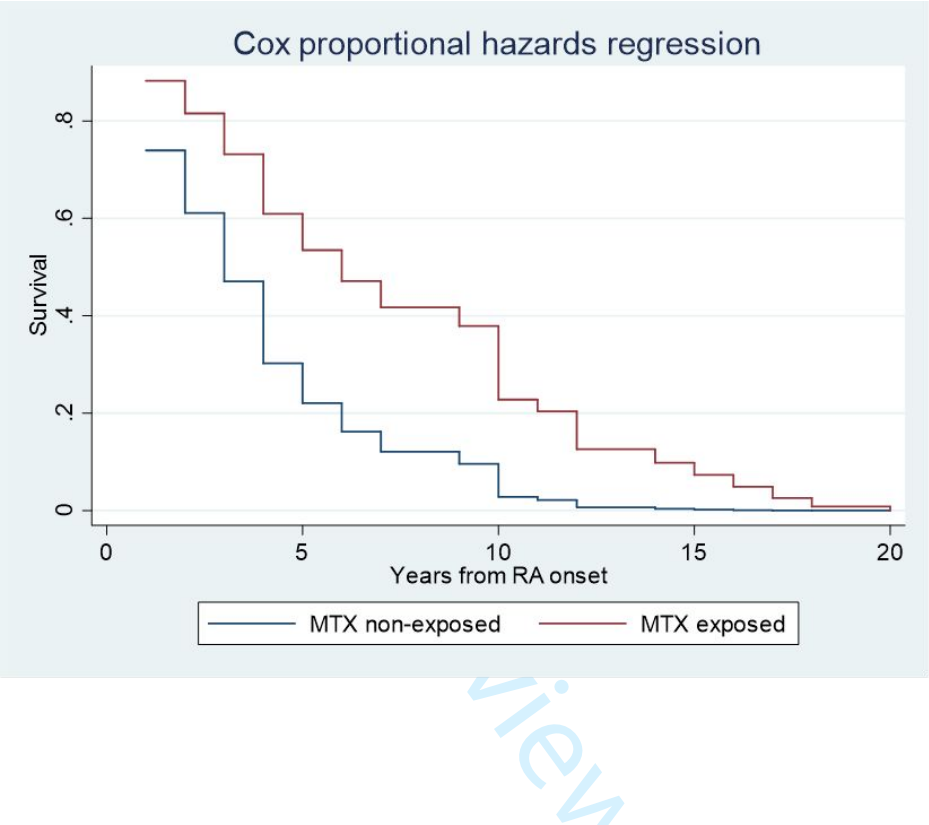


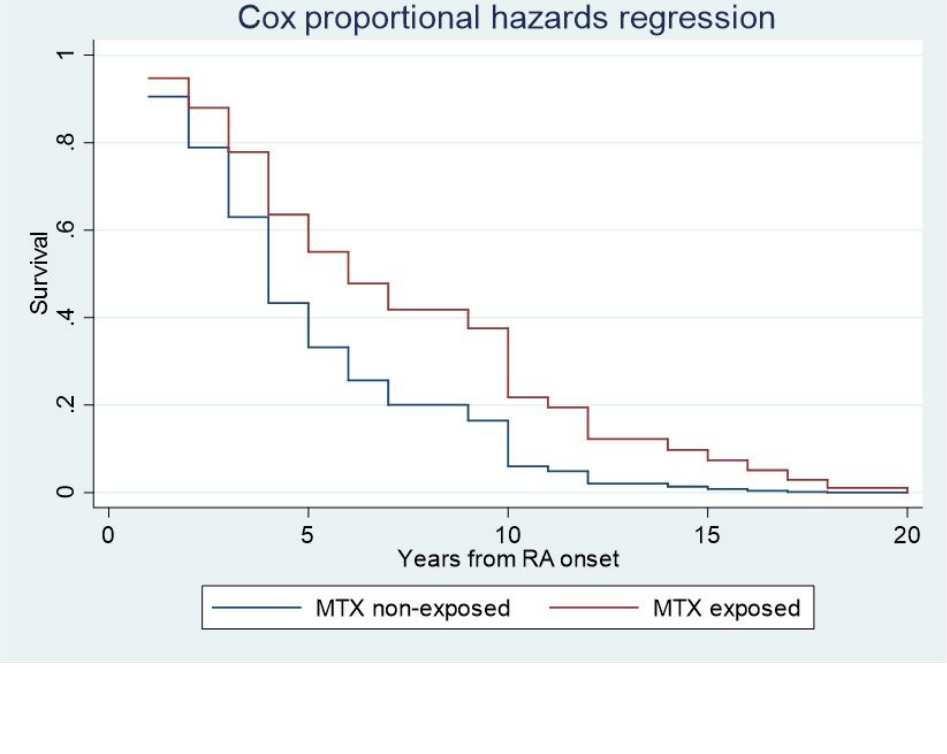
Figure 2a and 2b

Cox proportional time to event analysis showing time of onset of ILD from first joint symptoms of RA in MTX exposed and non MTX exposed groups 2a Entire cohort and 2b excluding cases with ILD at baseline prior to any csDMARD use.

2a



2b



Supplementary Material

Statistical analyses

Univariate analysis

The relation between onset of ILD and binary covariates [MTX exposure, gender, baseline: rheumatoid factor (RF, positive/negative), smoking status (ever/never), presence of nodules, extra articular RA major, minor and combined, respiratory major, minor and combined, presence of erosions] was analysed by Chi Squared test, and continuous covariates [age of RA onset, baseline: DAS, ESR, tender joint count (TJC), swollen joint count (SJC), patient global assessment (PGA), Hb, BMI, health assessment questionnaire score (HAQ), number of comorbidities major, minor and combined (including respiratory), number of major comorbidities (excluding respiratory), time from RA symptom onset to first outpatient appointment (months), time from first outpatient appointment to first DMARD (months), time from RA symptom onset to first DMARD (months)] was analysed by t test.

Multivariate analysis model

Binary logistic models were fitted to the data, using the diagnosis of ILD as the outcome variable. The initial covariates included were: MTX exposure (Y/N), gender (M/F), age at onset of RA (years) and presence of rheumatoid factor at baseline (+ve/-ve). Additional covariates were added to the model in turn, to assess whether they improved the model fit. It was not possible to use log likelihood ratio tests (LRTs) to compare models because of varying levels of missing data. Instead, the p-value from each covariate's Wald test was considered, to determine whether there was evidence to include them in the model, as well as assessing whether the odds ratios for other covariates had changed. All covariates significant ($p<0.05$) and borderline significant ($p<0.1$ and >0.05) in the univariate analysis were tested and also some non significant covariates in the univariate analysis were included because they might be of clinical interest (DAS, Hb, TJC, SJC and PGA, all at baseline). Anti-cyclic citrullinated peptide (anti CCP) antibody data was only collected at a few centres and was insufficient to include in any model.

Multivariate time-varying analysis

Cox proportional hazards models were applied to the data, with the diagnosis of ILD as the binary outcome variable at each year (measured from baseline) that a patient participated in the study. 54 (53.5%) patients of the 101 with ILD had known diagnosis dates or could be approximated to the nearest year. This was up to a maximum of 15 years, to match the time-varying data available for analysis. Of the 54, 48 were diagnosed during the study and so were included within the fitted models. The fixed covariates considered were: gender (M/F), age at onset of RA (years), maximum follow-up (years) and smoking status at baseline (ever/never). Time varying co-variates were DAS, patient global assessment, tender joint count, swollen joint count, ESR, health assessment questionnaire, haemoglobin, BMI, erosions, rheumatoid nodules, major comorbidities. Age at onset of RA, baseline smoking status and maximum follow-up were found to be statistically significant in combination, with all three hazard ratios >1 and all corresponding p-values <0.03. However, maximum follow-up was discounted from the model since adding any time-varying covariates removed its significance. Sex was selected a priori to be in the model to improve precision.

Next, time-varying covariates were considered: MTX exposure (Y/N), DAS (and individually PGA, TJC, SJC and ESR), HAQ, haemoglobin (g/L), presence of rheumatoid factor (RF, +ve/-ve), presence of erosions (Y/N), presence of nodules (Y/N), BMI and number of major comorbidities (excluding respiratory). The model was built by individually adding each covariate, then examining its hazard ratio and corresponding p-value to assess for statistical significance. The components of DAS were assessed both individually and in combination. Covariates were retained if $p<0.1$. Akaike information criterion (AIC) was used to compare the fit of each interim model to those previously fitted, with the final model having the lowest AIC value.

Cox regression time to event analysis

The relation between time of ILD diagnosis after first RA symptoms was explored in the MTX exposed ILD and non-MTX exposed ILD groups using Cox regression time to event analysis, adjusting for the same confounders as in the multivariate model. The time of onset of ILD in relation to first symptoms of RA was taken as the first record of this on the ERAS/ERAN CRF.

Where ILD was recorded on the death certificate but not on the last CRF this time was recorded as last CRF + 1 year if the interval was less than 2 years, and as last CRF + 2 years if this interval was 2 years or longer. In patients with ILD at baseline the time of ILD onset was taken to be synchronous with first RA symptoms.

Supplementary Table 1a.

Univariate analysis showing association of RA-ILD with baseline binary covariates

		n	ILD		No ILD		Odds Ratio	CI	Chi-squared test p-value
			n	%	n	%			
MTX	Yes	2692	39	2.5%	1539	97.5%	0.51	(0.32, 0.79)	0.001
	No		53	4.8%	1061	95.2%			
Gender	M	2692	44	5.0%	844	95.0%	1.91	(1.23, 2.96)	0.002
	F		48	2.7%	1756	97.3%			
Rheumatoid Factor	Positive	2610	65	4.0%	1568	96.0%	1.65	(1.01, 2.77)	0.038
	Negative		24	2.5%	953	97.5%			
Anti-CCP (ever)	Positive	333	9	3.8%	225	96.2%	1.94	(0.39, 18.74)	0.394
	Negative		2	2.0%	97	98.0%			
Smoker Status	Ever	2692	56	4.9%	1081	95.1%	2.18	(1.31, 3.74)	0.002
	Never		23	2.3%	968	97.7%			
Rheumatoid Nodules	None	2692	79	3.1%	2436	96.9%	2.44	(1.22, 4.54)	0.003
	Nodules		13	7.3%	164	92.7%			

Extra-Articular RA features	Yes	2692	11	3.7%	286	96.3%	1.10	(0.54-2.10)	0.774
	No		81	3.4%	2314	96.6%			
Respiratory co-morbidities	Yes	2692	7	5.0%	134	95.0%	1.52	(0.58-3.35)	0.299
	No		85	3.3%	2466	96.7%			
Erosions at baseline	Yes	2582	26	3.7%	673	96.3%	1.12	(0.67-1.81)	0.644
	No		63	3.3%	1820	96.7%			

Key

MTX: methotrexate, CCP: anti-cyclic citrullinated peptide antibody

Extra-Articular RA features: Tendon sheath disease, Sjogren's syndrome, ocular rheumatoid disease, Raynaud's

Respiratory comorbidities: History of chronic obstructive pulmonary disease, asthma, pneumonia, tuberculosis, pleural disease

Supplementary Table 1b.

Univariate analysis showing association of RA-ILD with baseline continuous covariates

	N	ILD			No ILD			Difference	t-test
		n	Mean	CI	N	Mean	CI		p-value
Age RA onset (years)	2692	92	62.8	(60.68, 64.95)	2600	55.87	(55.32, 56.42)	6.93	<0.0001
DAS28	2495	91	4.51	(4.17, 4.85)	2541	4.38	(4.32, 4.45)	0.13	0.445
ESR	2495	85	47.38	(41.33, 53.42)	2410	36.87	(35.77, 37.96)	10.51	0.001
TJC	2681	91	10.92	(8.55, 13.30)	2590	10.14	(9.77, 10.52)	0.78	0.455
SJC	2684	92	12.32	(9.64, 14.99)	2592	12.21	(11.76, 12.67)	0.11	0.935
PGA	2632	90	46.66	(41.35, 51.96)	2542	43.63	(42.62, 44.64)	3.03	0.2786
Hb	2652	92	12.8	(12.48, 13.13)	2560	12.85	(12.79, 12.91)	-0.05	0.798
Onset-OPD (months)	2666	91	9.16	(7.69, 10.64)	2575	8.22	(7.98, 8.47)	0.94	0.174
OPD-csDMARD (months)	2379	83	7.14	(2.93, 11.36)	2296	5.57	(4.95, 6.19)	1.57	0.356
Onset-csDMARD (months)	2383	84	16.49	(12.13, 20.85)	2299	14.34	(13.58, 15.09)	2.15	0.294
Comorbidities major	2692	92	0.48	(0.35, 0.60)	2600	0.49	(0.46, 0.52)	-0.01	0.863
Comorbidities minor	2692	92	0.4	(0.28, 0.52)	2600	0.33	(0.31, 0.35)	0.07	0.212
Comorbidities combined	2692	92	0.8	(0.63, 0.98)	2600	0.82	(0.87, 0.86)	-0.02	0.949

Comorbidities major excluding respiratory	2692	92	0.4	(0.28, 0.52)	2600	0.47	(0.44, 0.50)	-0.07	0.394
BMI baseline	2377	77	25.9	(24.82, 26.98)	2300	26.56	(26.35, 26.76)	-0.66	0.256
HAQ at baseline	2650	92	1.22	(1.07, 1.37)	2558	1.11	(1.08, 1.14)	0.11	0.2024

Key

DAS28: 28 joint disease activity score, ESR: erythrocyte sedimentation rate, TJC: tender joint count, SJC: swollen joint count, PGA: patient global assessment, Hb: haemoglobin, BMI: body mass index, HAQ: health assessment questionnaire, Onset-OPD: time from first RA symptoms to first secondary care outpatient visit, OPD-csDMARD: time from first secondary care outpatient visit to start of conventional synthetic disease modifying anti-rheumatic drug therapy, Onset-csDMARD: time from first RA symptoms to start of conventional synthetic disease modifying anti-rheumatic drug therapy, Co-morbidities major and minor: as per ICD 10 definitions.

Supplementary Table 2a.

Univariate analysis showing association of RA-ILD with baseline binary covariates, excluding cases with ILD at baseline prior to any csDMARD use.

		n	ILD		No ILD		Odds Ratio	CI	Chi-squared test p-value
			n	%	n	%			
Total			67		2600				
MTX	Yes	2667	39	58.2%	1539	59.2%	0.96	(0.57, 1.63)	0.872
	No		28	41.8%	1061	40.8%			
Gender	M	2667	30	44.8%	844	32.5%	1.69	(1.00, 2.83)	0.034
	F		37	55.2%	1756	67.5%			
Rheumatoid Factor	Positive	2588	52	77.6%	1568	60.3%	2.11	(1.16, 4.03)	0.010
	Negative		15	22.4%	953	36.7%			
Anti CCP (ever)	Positive	330	6	9.0%	225	8.7%	1.29	(0.23, 13.31)	0.755
	Negative		2	3.0%	97	3.7%			
Smoker Status	Ever	2106	41	61.2%	1081	41.6%	2.29	(1.25, 4.41)	0.004
	Never		16	23.9%	968	37.2%			
Rheumatoid Nodules	None	2667	57	85.1%	2436	93.7%	2.61	(1.16, 5.27)	0.005
	Nodules		10	14.9%	164	6.3%			
Extra-Articular RA features	Yes	2667	11	16.4%	286	11.0%	1.59	(0.74, 3.11)	0.164
	No		56	83.6%	2314	89.0%			
Respiratory comorbidities	Yes	2667	7	10.4%	134	5.2%	2.15	(0.81, 4.82)	0.056
	No		60	89.6%	2466	94.8%			
Erosions at baseline	Yes	2560	18	26.9%	673	25.9%	0.99	(0.54, 1.74)	0.981
	No		49	73.1%	1820	70.0%			

Key

csDMARD: conventional synthetic disease modifying anti-rheumatic drug, MTX: methotrexate, CCP: anti-cyclic citrullinated peptide antibody

Extra-Articular RA features: Tendon sheath disease, Sjogren's syndrome, ocular rheumatoid disease, Raynaud's

Respiratory comorbidities: History of chronic obstructive pulmonary disease, asthma, pneumonia, tuberculosis, pleural disease

Supplementary Table 2b.

Univariate analysis showing association of RA ILD with baseline continuous covariates, excluding cases with ILD at baseline prior to any DMARD use.

	n	ILD			No ILD			Difference	t-test
		N	Mean	CI	N	Mean	CI		p-value
Age of RA onset (years)	2667	67	61.01	(58.45, 63.58)	2600	55.87	(55.32, 56.42)	5.14	0.004
DAS28	2607	66	4.43	(4.04, 4.82)	2541	4.38	(4.32, 4.45)	0.05	0.821
ESR	2473	63	45.51	(38.76, 52.26)	2410	36.87	(35.77, 37.96)	8.64	0.014
TJC	2656	66	10.74	(7.89, 13.60)	2590	10.14	(9.77, 10.52)	0.6	0.623
SJC	2659	67	11.46	(8.70, 14.22)	2592	12.21	(11.76, 12.67)	-0.75	0.608
Baseline PGA	2608	66	48.35	(42.08, 54.62)	2542	43.63	(42.62, 44.64)	4.72	0.146
Hb	2627	67	12.93	(12.55, 13.31)	2560	12.85	(12.79, 12.91)	0.08	0.659
Onset-OPD (months)	2642	67	9.78	(7.96, 11.59)	2575	8.22	(7.98, 8.47)	1.56	0.053
OPD-csDMARD (months)	2357	61	8.13	(2.66, 13.60)	2296	5.57	(4.95, 6.19)	2.56	0.197
Onset-csDMARD (months)	2361	62	17.76	(12.27, 23.25)	2299	14.34	(13.58, 15.09)	3.42	0.151
Comorbidities (major)	2667	67	0.43	(0.30, 0.57)	2600	0.49	(0.46, 0.52)	-0.06	0.532
Comorbidities (minor)	2667	67	0.46	(0.31, 0.61)	2600	0.33	(0.31, 0.35)	0.13	0.053
Comorbidities (combined)	2667	67	0.9	(0.69, 1.10)	2600	0.82	(0.87, 0.86)	0.08	0.542

Comorbidities major excluding respiratory	2667	67	0.33	(0.21, 0.45)	2600	0.47	(0.44, 0.50)	-0.14	0.127
BMI	2356	56	25.98	(24.70, 27.25)	2300	26.56	(26.35, 26.76)	-0.58	0.390
HAQ	2625	67	1.28	(1.10, 1.45)	2558	1.11	(1.08, 1.14)	0.17	0.090

Key

DAS28: 28 joint disease activity score, ESR: erythrocyte sedimentation rate, TJC: tender joint count, SJC: swollen joint count, PGA: patient global assessment, Hb: haemoglobin, BMI: body mass index, HAQ: health assessment questionnaire, Onset-OPD: time from first RA symptoms to first secondary care outpatient visit, OPD-csDMARD: time from first secondary care outpatient visit to start of conventional synthetic disease modifying anti-rheumatic drug therapy, Onset-csDMARD: time from first RA symptoms to start of conventional synthetic disease modifying anti-rheumatic drug therapy, Co-morbidities major and minor: as per ICD 10 definitions.

Supplementary Table 3

Multivariate analysis stratified by smoking; showing effects of baseline co-variates on RA-ILD diagnosis in smokers, non-smokers and those with missing smoker status at baseline.

	Overall		Non-smokers		Smokers		Missing	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
n	2015		949		1066		552	
Methotrexate exposed	0.85 (0.49, 1.49)	0.578	0.24 (0.08, 0.70)	0.009	1.56 (0.74, 3.29)	0.240	1.35 (0.33, 5.52)	0.681
Male gender	1.44 (0.83, 2.48)	0.193	0.70 (0.20, 2.52)	0.587	1.8 (0.95, 3.41)	0.073	1.38 (0.38, 5.02)	0.629
Age of RA onset	1.04 (1.02, 1.06)	<0.001	1.03 (0.99, 1.07)	0.097	1.05 (1.02, 1.08)	0.001	1.03 (0.99, 1.08)	0.172
Baseline RF	2.02 (1.07, 3.82)	0.029	1.88 (0.64, 5.57)	0.254	2.20 (1.00, 4.86)	0.051	2.83 (0.58, 13.85)	0.199
Onset-OPD (months)	1.04 (1.00, 1.07)	0.027	1.005 (0.93, 1.08)	0.902	1.05 (1.01, 1.09)	0.012	0.98 (0.87, 1.10)	0.699
Baseline Major Comorbidities (Excl Resp)	0.62 (0.40, 0.95)	0.027	0.43 (0.15, 1.24)	0.119	0.64 (0.4, 1.04)	0.070	0.30 (0.04, 2.39)	0.254

Baseline Smoker Status	2.21 (1.21, 4.03)	0.010					
Constant	0.0009 (0.0002, 0.005)	<0.001	0.005 (0.0004, 0.07)	<0.001	0.0006 (0.00008, 0.005)	<0.001	0.002 (0.00006, 0.05)	0.001

Key

RA: Rheumatoid arthritis, RF: rheumatoid factor

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2,3

Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4.5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	5, 6
	#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a not a matched study
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6, 7, 8
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	6, 7, 8

Bias	#9	Describe any efforts to address potential sources of bias	8 and Supplementary materials
Study size	#10	Explain how the study size was arrived at	n/a not an intervention study
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	8 and Supplementary materials
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8 and Supplementary materials
	#12b	Describe any methods used to examine subgroups and interactions	8 and Supplementary materials
	#12c	Explain how missing data were addressed	8 and Supplementary materials
	#12d	If applicable, explain how loss to follow-up was addressed	8 and Supplementary materials
	#12e	Describe any sensitivity analyses	8 and Supplementary materials

Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	8, Figure 1
	#13b	Give reasons for non-participation at each stage	8
	#13c	Consider use of a flow diagram	Figure 1
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	7, 8, 9 Table 1 Table 2
	#14b	Indicate number of participants with missing data for each variable of interest	Table 2
	#14c	Summarise follow-up time (eg, average and total amount)	5
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	8 - 11
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which	Supplementary Tables 1a, 1b, 2a, 2b

		confounders were adjusted for and why they were included	
	#16b	Report category boundaries when continuous variables were categorized	Table 3, Tables 1a, 1b, 2a, 2b, 3
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	na
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	9, 10 Table 3, Supplementary Table 3
Key results	#18	Summarise key results with reference to study objectives	11, 12, 13, 14, 15
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	13, 14
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	14, 15
Generalisability	#21	Discuss the generalisability (external validity) of the study results	12, 15
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for	15

the original study on which the present article is based

BMJ Open

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

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

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Rheumatoid arthritis, interstitial lung disease, methotrexate

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Abstract

Objectives

To assess predictive factors for rheumatoid arthritis interstitial lung disease (RA-ILD) in two early RA inception cohorts with a focus on methotrexate (MTX) exposure.

Design

Multicenter prospective early RA inception cohort studies; the early RA study (ERAS) and the early RA network (ERAN)

Setting

Secondary care, ERAS 9 centers, ERAN 23 centers in England, Wales and the Republic of Ireland

Participants

Patients with new diagnosis of RA, n=2701.Standardised data including demographics, drug therapies and clinical outcomes including the presence of RA-ILD were collected at baseline, within 3- 6 months, at 12 months and annually thereafter.

Primary and secondary outcome measures

Primary outcome was the association of MTX exposure on RA-ILD diagnosis. Secondary outcomes were the association of demographic, comorbid and RA specific factors on RA-ILD diagnosis and the association of MTX exposure on time to RA-ILD diagnosis.

Results

Of 92 eligible ILD cases, 39 occurred in 1578 (2.5%) MTX exposed and 53 in 1114 (4.8%) non-MTX exposed cases. The primary analysis of RA-ILD cases only developing after any csDMARD treatment (n=67) showed MTX exposure not to be associated with incident RA-ILD (O.R. 0.85 CI 0.49, 1.49 p=0.578) and a non-significant trend for delayed ILD diagnosis (O.R. 0.54 CI 0.28, 1.06 p=0.072). In an extended analysis including RA-ILD cases present at RA diagnosis (n=92), MTX exposure was associated with a significantly reduced risk of incident RA-ILD (O.R. 0.48, CI 0.3, 0.79 p=0.004) and longer time to ILD diagnosis (O.R. 0.41, CI 0.23, 0.75 p=0.004). Other

independent baseline associations with incident RA-ILD were higher age of RA onset, ever smoking, male gender, rheumatoid nodules and longer time from first RA symptom to first out-patient visit.

Conclusions

MTX treatment was not associated with an increased risk of RA-ILD diagnosis. On the contrary evidence suggested that MTX may delay the onset of ILD.

Article Summary

Strengths and Limitations

- Multicenter prospective early RA inception cohort study recruiting 2701 patients
- Standardised data collection with up to 25 years follow-up
- Diagnosis of RA-ILD made by participating rheumatology centers, or from death certification, without independent verification
- Univariate, multivariate, time varying and time to event Cox proportional hazards analyses assessed MTX-exposure, demographic and RA specific factors associated with RA-ILD diagnosis
- High proportion of missing smoker status data from ERAS patients recruited 1986 - 2001

Introduction

Methotrexate (MTX) is now firmly established globally as the anchor drug for the management of rheumatoid arthritis (RA), recommended for first line use, to which other conventional synthetic, targeted synthetic and biologic disease modifying anti rheumatic drugs (cs/ts/b DMARDs) are generally added (1,2). In addition to an excellent ability to suppress synovitis and restore physical function, there is compelling data demonstrating a beneficial effect on long term cardiovascular disease (3) and hence restoration of life expectancy to that of the normal population.

A hypersensitivity pneumonitis is a rare adverse effect of MTX described in 0.43% (4), generally subacute in presentation, with progression of characteristic symptoms over a period of days to weeks (5). This usually occurs early, within the first year of treatment, but has been reported up to 3 years after starting MTX (4,5). This organ specific hypersensitivity reaction has led to a creeping concern in routine practice that MTX may also be associated with an increased incidence or exacerbation of the interstitial lung disease (ILD) that is associated with RA, and may be a reason to withhold MTX from RA patients with any lung disease. RA-ILD is an uncommon but significant life threatening extra-articular manifestation, clinically significant in up to 5% of RA patients, with subclinical HRCT evidence in 33% or more, a median survival from diagnosis of approximately 3 years, contributing to the overall excess mortality of RA (2, 6-12). MTX is contraindicated if a patient has insufficient respiratory reserve to survive hypersensitivity pneumonitis. However, evidence is lacking that would deter initiation of MTX treatment in people with mild respiratory disease on grounds of an adverse effect on any other form of lung injury such as ILD. Indeed, the considerable benefits of MTX are such that a decision to withhold it as a treatment option for RA should be reluctantly made, and only for sound reasons.

Evidence that MTX may cause or have an adverse impact on RA-ILD is sparse. Meta-analysis of randomised controlled trials (RCT) of MTX in RA has reported an increased risk of all adverse respiratory events and respiratory infections, but not of death due to lung disease or non-infectious respiratory events, with follow up duration of 24-104 weeks (13). Due to inherent difficulties separating RA-ILD from putative MTX related ILD, a meta-analysis of MTX versus placebo or active comparator agents in RCTs from non-malignant inflammatory

disorders not themselves associated with ILD is of interest (14). This has shown no MTX associated risk of lung disease in studies ranging from 16 – 52 weeks follow up. These relatively short duration analyses, in patients pre-selected for RCTs, are reassuring but require substantiation from RA inception cohorts or patient registries with all-comers included and longer follow up. Sequential lung function tests in cohorts of MTX treated RA patients followed prospectively for up to 5 years have shown a sequential decline, with inconsistent interpretation that this is in keeping with (15), or in excess of (16), expected age related changes. Interpretation of these studies is limited by a lack of inclusion of non-MTX treated control RA patients. In another cohort comparing 55 MTX treated with 73 non-MTX treated patients with established RA, there was no adverse influence of MTX on pulmonary function tests over 2 years, including a sub analysis of those found to have largely sub clinical pulmonary fibrosis on HRCT (17).

We report the association of MTX-exposure, and other demographic and RA specific factors with incident cases of RA-ILD in two large multi-centre RA inception cohorts, the early rheumatoid arthritis study (ERAS) and the early rheumatoid arthritis network (ERAN), recruiting from 1986 – 2012 with review up to 25 years.

METHODS

Patient Databases

The study used data from ERAS (1986-2001) and ERAN (2002-2012), two multi-center early RA inception cohorts. ERAS recruited 1465 patients (<2 years disease duration, no prior csDMARD therapy) from nine district general hospitals in England, followed yearly for up to 25 years (median follow up 10 years). ERAN recruited 1236 patients (<3 years disease duration) from 23 centres in England, Wales and Ireland, followed yearly for up to 10 years (median follow up 6 years). Ethical approval was obtained from East Hertfordshire local research ethics committee (ERAS) and the Trent research ethics committee (ERAN). All participants gave informed consent. STROBE reporting cohort guidelines have been followed (von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies).

Recruitment into ERAS and ERAN was based on clinician diagnosis with 70% of patients fulfilling the minimum ARA criteria (18) for RA at baseline and 96% by last visit. Patients subsequently reclassified as non-RA were excluded from the study.

Patient and Public involvement

A patient representative from the National Rheumatoid Arthritis Society (NRAS) was involved in the design and conduct of ERAN, including decisions concerning which RA outcomes should be collected. By consenting to recruitment patients were aware that the purposes of the study included examining the consequences of a range of RA outcomes. As patients were recruited at the time of, or very soon after, the diagnosis of RA they had limited experience of the disease to determine their priorities for ERAS/ERAN analyses. ILD was one of many outcomes that patients knew were to be studied. As ILD is established as one of the most severe complications of RA, and one of the leading causes of premature death, patients were interested in any findings that might add to our knowledge of this complication.

Patients were not involved in the recruitment process to ERAS/ERAN. Patients were not specifically involved in the statistical design of the analysis of ERAS/ERAN data on associations of factors with RA-ILD.

At recruitment patients were informed that "the results of this study would be made available to participating clinicians and will be the subject of international presentations and articles in peer-reviewed scientific journals". Participants will not be notified of the results individually, but we will request that a summary of the findings be made available to all patients with RA via the patient newsletter of NRAS.

Clinical and laboratory measures

Information on demographic, clinical, treatment, laboratory and functional features was recorded in both cohorts at baseline, between 3 and 6 months, at 12 months and then once yearly on standardized case report forms (CRF), as previously described (19-21). Disease activity (DAS) was calculated according to the original three variable method (22) in ERAS and the four variable DAS28 method (23) in ERAN. A transformation formula was used to make

DAS and DAS28 comparable (24). Source data verification was undertaken by an experienced nurse practitioner at visits to each center. Combined analysis of ERAS and ERAN is possible since they are consecutive inception cohorts with similar design, including the variables captured, timing of assessments and patient recruitment. Follow up across ERAS and ERAN was relatively high given the long term of both prospective studies, and of those not followed to death or closure, cases lost to follow up for no known reason were only 13.7% overall (12.5% ERAS, 15% ERAN).

Treatment profiles

Patients were treated according to usual care in each of the ERAS and ERAN centres, without specific protocols, strategies or other external influences. All centers followed the 1992 good practice guidance outlined by the British Society for Rheumatology and Royal College of Physicians (25). Treatment details were entered onto the CRF at each ERAS/ERAN data collection visit. At baseline all patients in ERAS were csDMARD naïve and in ERAN 13.5% had commenced a csDMARD within a few weeks of first secondary care visit. In ERAS and ERAN, initial csDMARD use was as monotherapy with/without steroids in >90%, favouring sulphasalazine (SSZ) from 1986-2001, with a switch to MTX monotherapy such that SSZ and MTX were used in equal proportions as first csDMARD in 2002, and thereafter in ERAN MTX became the most likely initial choice (20, 21), this reflecting contemporary best practice. Combination csDMARDS were generally used for more severe RA and were introduced at earlier time-points in the later years of ERAS and in 25% of those who received any csDMARDs in ERAN (20,21). In ERAN the most frequently used combinations of csDMARDs were MTX/SSZ, MTX/SSZ + hydroxychloroquine (HCQ) and MTX/HCQ (21). Only a small proportion of patients received bDMARDs, which were available from 2002 onwards (<2% by 1 year and <10% by 3 years).

Median time from RA symptom onset to first rheumatology outpatient visit (baseline assessment) was 6 months in both cohorts, and to first csDMARD initiation 8 months in ERAS and 7 months in ERAN.

ILD identification

Co-morbidities including respiratory disease were entered on the CRF at each visit. Death certification was received from the NHS medical research information service (MRIS) and

subsequently the NHS Health and Social Care Information center (HSCIC) for all recruited patients four monthly with last data inclusion for this analysis June 2018. The diagnosis of ILD at each center was according to standard practice, with confirmatory evidence from standard investigations including pulmonary function tests, chest radiographs and HRCT scans. ILD was deemed to be present if the terms pulmonary fibrosis or interstitial lung disease were listed on the CRF or the death certificate using ICD-10 criteria.

As the development of RA-ILD is insidious, setting a time of onset had to be pragmatic. In cases where ILD was recorded on the baseline CRF the time of diagnosis was taken as synchronous with RA onset (n=25). In cases where the first record of ILD was on a CRF the date of onset was taken as then (n=52). Where the only record of ILD was on the death certificate, and not on the last CRF, the date taken as onset of ILD was recorded as last CRF + 1 year if the time from last CRF to death was 2 years or less (n=5), and recorded as last CRF + 2 years if this interval was more than 2 years (n=10).

MTX exposed ILD group

Patients were included in the analysis as MTX exposed ILD if they were recorded on the CRF as starting MTX at any time prior to the first record of ILD, either on the CRF or the death certificate.

Non-MTX exposed ILD group

Patients were included in the analysis as non-MTX exposed ILD if they were recorded as having ILD on the CRF without record of prior MTX treatment. As the analysis was concerned with the onset of ILD, patients who started MTX at any time point after ILD was first recorded on the CRF remained in the non-exposed group, as ILD was first diagnosed before MTX treatment. Patients who were recorded as having ILD on the death certificate but not on the last CRF were included in the non-MTX exposed group if the time interval between last CRF and death was less than 2 years, and no MTX treatment had been recorded on the CRFs throughout ERAS/ERAN data collection. As the development of RA-ILD is slow it was considered that this was too short a time for any potential but unknown MTX use after the last CRF to have had an effect, had it been introduced. If this time interval was 2 years or longer patients were excluded from the analysis as they could have been exposed to MTX for the first time after last CRF and before the first record of ILD on the death certificate, and as

such any potential MTX exposure during this time could have had an effect. Patients where the first record of ILD and MTX use was on the same CRF were considered non-MTX exposed as the maximum time MTX could have been used since the preceding CRF was 1 year and this was considered too short to have had an effect on the development of ILD within the same period.

Statistical analysis

All analysis used statistical software Stata/IC 15.1. The primary analyses included all cases of incident RA-ILD reported after any csDMARD exposure. An extended analysis was performed on the entire cohort of incident RA-ILD including patients where ILD was recorded at the baseline visit. These additional cases had developed ILD either preceding or synchronously with RA and prior to any csDMARD use for RA. First univariate analyses were performed for associations of baseline covariates with RA-ILD development. Next multivariate binary logistic models were fitted to the data to determine independent baseline predictors of RA-ILD. As there were multiple data collection points across the ERAS and ERAN follow up period, multivariate time-varying analysis using cox proportional hazards models were created to include multiple data entries for covariates with repeated measures. Finally Cox regression time to event analysis was used to assess the relation between first RA symptoms and time of ILD diagnosis in MTX exposed and non-MTX exposed ILD cases, and with respect to other baseline co-variates.

A detailed description of the univariate and multivariate model analyses is given in supplementary material

RESULTS

A flow chart of patient selection in shown in Fig 1. From 2,701 patients a total of 101 cases of ILD were recorded (3.7%) of which 25 were present at baseline (25%). None of the baseline ILD cases had been treated with csDMARDs prior to first CRF. Nine ILD cases were excluded from analysis because the only record of ILD was on the death certificate and over 2 years had elapsed between this and the last CRF, during which time csDMARD treatment was unknown. There were 1,578 MTX exposed cases of whom 1,539 (97.5%) were not and 39 (2.5%) were diagnosed with ILD, and 1,114 non-MTX exposed cases of whom 1,061 (95.2%)

were not and 53 (4.8%) were diagnosed with ILD. Of the 53 non-MTX exposed ILD cases, 19 (35%) were treated with MTX after ILD was diagnosed.

Demographic features of the ERAS and ERAN cohorts are shown in Table 1. These were generally similar across both cohorts, however there were significant differences in age of RA onset (older in ERAN), baseline smoking status (more current and ex smokers in ERAN) and MTX use (79% ERAN vs. 41% ERAS). The prevalence of ILD was 3.2% in ERAN and 4.2% in ERAS (n.s.). The median dose of MTX across both cohorts was 12.5mg but following contemporary practice this increased with time; ERAS 10mg, ERAN 20mg per week. Table 2 shows demographic features of MTX exposed and non-MTX exposed cases, where MTX exposed patients were significantly more likely to have developed RA at a younger age, be in a higher DAS category, RF positive, nodular, male, and borderline more likely to be current or ex-smokers. 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). The mean DAS28 score at first record of RA-ILD in MTX exposed cases was 3.77 and in non-MTX exposed cases 4.27 (T test p=0.30).

As we were specifically interested in the relation of ILD onset to MTX exposure the primary analysis was restricted to cases where ILD was only diagnosed after any csDMARD exposure (n=67), excluding 25 cases with ILD recorded at baseline. Univariate analyses of the relation between new diagnosis of RA-ILD and a range of binary and continuous variates are shown in Supplementary Tables 1a and 1b. This shows no association of MTX exposure and incident RA-ILD; O.R. 0.96, CI 0.57, 1.63 p=0.872. Male gender (p=0.034), RF positivity (p=0.01), ever smoking (p=0.004), rheumatoid nodules (p=0.005), age of RA onset (p=0.004) and baseline ESR (p=0.014) were all significantly associated with incident RA-ILD. Longer time between first RA symptoms and the first outpatient appointment (p=0.053), respiratory co-morbidities (p=0.056) and minor comorbidities (p=0.053) were borderline significant. Patients who developed ILD were at RA onset a mean 5.14 years older and had a mean baseline ESR score of 8.64 mm/hr higher than patients who did not develop ILD.

Table 3 shows the covariates independently associated with ILD diagnosis in the best fit multivariate model. This confirms higher age of RA onset, ever smoking, RF positivity, and longer time from first RA symptom to first OPD visit were independently associated with

incident RA-ILD and there remained no evidence that MTX exposure was associated with RA-ILD onset (OR=0.85, CI 0.48, 1.49 p=0.578). Unlike univariate analysis in this model baseline major co morbidities (excluding respiratory) were protective. This group of conditions included malignancies, cardiac disease, other non-cardiac cardiovascular conditions (e.g. hypertension, cerebrovascular disease), diabetes, thyroid disease, osteoarthritis, spinal disorders and gastrointestinal conditions as defined by ICD-10 criteria.

Extending the analysis to all 92 RA-ILD cases, including 25 recorded at baseline prior to any csDMARD use, produced similar results on univariate analysis (see Supplementary Tables 2a, 2b) with male gender (p=0.002), baseline positive RF (p=0.038), ever smoking (p=0.002), presence of rheumatoid nodules (p=0.003), age of RA onset (p<0.0001) and baseline ESR (p=0.001) all associated with incident RA-ILD. MTX exposure was associated with a significantly reduced odds ratio of developing ILD (O.R. 0.51, CI 0.32, 0.79 p=0.001). Patients who developed ILD were at RA onset a mean 6.93 years older and had a mean baseline ESR score of 10.51 mm/hr higher than patients who did not develop ILD. In the multivariate model (Table 3) higher age of RA onset, ever smoking, male gender, baseline rheumatoid nodules, higher baseline ESR and longer time from first RA symptom to first OPD visit were independently associated with incident RA-ILD. MTX exposure (O.R. 0.48, CI 0.3, 0.79) and baseline major comorbidities (excluding respiratory) were associated with significantly reduced odds of RA-ILD onset.

As there was a large number of patients in ERAS with missing smoking status at baseline (n=549), a sensitivity analysis of the primary cohort was performed by running the multivariate analysis in smokers, non smokers and those with missing smoking status data (see supplementary Table 3). This continued to show no association between methotrexate use and incident RA-ILD in smokers (OR=1.56, CI= 0.74, 3.29, p=0.240) and in those with missing smoking data (OR=1.35, CI=0.33, 5.52, p=0.681), but MTX use was associated with a reduction in incident RA-ILD in non-smokers (OR=0.24, CI=0.08, 0.70, p=0.009).

The multivariate time varying analysis, incorporating multiple data entries for covariates measured at each follow up visit (e.g. DAS, individual DAS components, HAQ, full details in supplementary materials) resulted in similar co-variate associations with incident RA-ILD. The best fit model (see Supplementary Table 4) with the lowest Akaike information criterion (AIC)

score showed significant associations with age of RA onset (p=0.002), HAQ (p=0.007) and ESR (p=0.01) and continued to show no association with MTX exposure (H.R. 0.96 CI 0.82, 1.12 p=0.629).

The relation between time to RA-ILD diagnosis after first RA symptoms in the MTX exposed and non-MTX exposed groups is shown in Fig 2 (primary analysis) and Fig 3 (extended cohort). The MTX exposed ILD group included 10 cases where RA-ILD was only recorded on the death certificate and a mean 6.6 (range 3-11) years had elapsed between this and last CRF. For these cases the time of ILD diagnosis was unknown and pragmatically was recorded as last CRF + 2 years, introducing a bias to earlier record of time of RA-ILD diagnosis. The primary analysis, excluding 25 cases with RA-ILD diagnosed at baseline pre csDMARD treatment, showed higher age of RA onset associated with earlier RA-ILD diagnosis (HR 1.03 CI 1.0, 1.06 p=0.048) and a non-significant trend for longer time to RA-ILD diagnosis in MTX exposed cases (HR 0.54 CI 0.28, 1.06 p=0.072). The extended cohort analysis showed a significantly longer time to diagnosis of RA-ILD in MTX exposed compared to non-MTX exposed cases (HR 0.41 CI 0.23, 0.75 p=0.004) and the same effect of higher age of RA onset and earlier diagnosis (HR 1.03 CI 1.0, 1.06 p=0.028), but no influence of any of the other covariates independently associated with RA-ILD onset in the multivariate model, see Table 4.

Discussion

We report an overall prevalence of RA-ILD of 3.7% in ERAS and ERAN, two large RA inception cohorts, recruiting between 1986 and 2012 with maximum follow up 25 years. These findings extend the earlier report of RA-ILD from the ERAS cohort alone (8), and are in keeping with previous studies, including the UK BRILL network which reported 2 -3 % prevalence across its recruiting centers (10-12). ILD was already present at baseline assessment in 25 patients, representing 24.7% of the entire ILD group, these cases developing ILD either before or synchronously with first joint symptoms. This is similar to the UK BRILL cohort where 10% developed ILD before joint disease and 7% synchronously (10), and consistent with our earlier report from ERAS alone where ILD was present at baseline in 12/52 (23%) cases (8). Discrepancies may reflect the method of detection as demonstrated by Gabbay et al who studied 36 patients with early RA and found

abnormalities consistent with RA-ILD using a range of clinical, physiological and imaging modalities in 58%, but this was clinically significant in only 14% (9).

The results of the multvariate analysis concurred with other studies (8-11) in finding an association of incident RA-ILD with increasing age of RA onset, ever smoking and positive rheumatoid factor in the primary analysis and also male gender, baseline rheumatoid nodules and ESR on the extended analysis. As was found with our earlier report from ERAS alone (8), there was no association in the primary analysis between MTX exposure and incident RA-ILD, either on univariate or multivariate analyses. On the contrary MTX exposure was associated with significantly less RA-ILD in the extended analysis. This concurs with the meta analyses of RCTs by Conway et al who found no association of MTX use and ILD in RA and non-RA inflammatory diseases (13,14), with the prospective 2 year study reported by Dawson et al of 128 RA patients with established disease (17), and a recent report from the same group in 106 RA patients commencing MTX and followed for 10 years (26). The implication is to be especially vigilent for the development of RA-ILD in male patients who are RF positive, have nodules, a history of ever smoking and older age of RA diagnosis. MTX should only be witheld from RA patients with insufficient respiratory reserve to make it unlikely that they would survive hypersensitivity pneumonitis. Our findings refute concerns amongst clinicians that there is an association with MTX exposure and RA-ILD onset, and provide no justification to delay or deny patients MTX for fear of inducing RA-ILD while seeking specialist opinions or further investigations of potential respiratory disease or other comorbid features. Such delays are likely to worsen RA outcomes by unnecessarily denying patients the anchor csDMARD for this disease. Reassurance of the benign effect of MTX on established RA-ILD comes from no association found between MTX and hospitalised severe ILD episodes in USA National Databank for Rheumatic Diseases (27) and mortality from ILD in the USA Veterans Affairs Rheumatoid Arthritis Registry (28). Furthermore, a retrospective analysis of prognostic factors in 78 cases of RA-ILD, where MTX was specifically used as a therapeutic agent in 67%, found this to be strongly associated with survival (29).

Of interest is the finding of a significant association between incident RA-ILD and increased time from RA symptom onset to first outpatient visit on multivariate analysis in both the primary analysis and extended cohort. Both of the other two measures of time to secondary

care intervention, first RA symptom to first csDMARD and first outpatient appointment to first csDMARD, were consistent with this association, with the interval being a mean 3.42 and 2.56 months longer respectively in patients who subsequently developed ILD in the primary analysis. This is perhaps supportive of the so called 'window of opportunity' whereby a delay in treatment leads to worse outcomes. The explanation for the protective effect of baseline major co-morbidities (excluding respiratory) on incident RA-ILD in both the primary analysis and the extended cohort is not immediately apparent. We speculate that this might be explained by treatment differences, for example as malignancy was one of the more common major comorbidities, previous cancer therapies may have afforded immuno-suppressive effects.

Interestingly there was a trend for ILD to be less prevalent in the later 2002-2012 ERAN cohort (3.2%) than the 1986-2001 ERAS cohort (4.2%) based on a sample size of 101 cases. This is in contrast to a report of increasing prevalence over time among US veterans from 1985-2006, assumed due to increased awareness and investigation of respiratory symptoms coupled with increased survival (30,31). The reason for an apparent decrease in incident RA-ILD in ERAN is unclear, however it is noteworthy that this was seen despite a significant increase in two exacerbating factors, age of RA onset and current smoking, in ERAN compared to ERAS. MTX use was higher in ERAN, raising the intriguing question whether MTX may have had a protective effect on ILD development despite the higher risk factors in ERAN. This is supported by the time to event analysis where MTX exposure was associated with a significantly longer time to RA-ILD onset in the extended analysis and a trend supporting this in the primary analysis with fewer cases. A protective effect of MTX could have been due to better overall RA disease control than in the non-MTX exposed group, where the majority received SSZ and a minority hydroxychloroquine or leflunomide (20,21). This is supported by the lower DAS28 score at first record of ILD in MTX exposed compared to non-MTX exposed cases, although the difference was not significant. A positive influence of MTX is also supported by Rojas-Serrano et al who found a strong survival effect of MTX on established RA-ILD (29). Further evidence for an association between RA-ILD and worse disease control comes from the USA Rochester cohort followed up to 2006, where parameters indicative of more severe RA, such as ESR, nodules and destructive joint changes were associated with ILD (11). Similarly, in the UK BRILL cohort anti-CCP antibodies showed

the strongest association with ILD (10), this being a recognised marker of disease severity. Unfortunately there were insufficient numbers of ERAS/ERAN patients with baseline anti-CCP to assess the impact of this on ILD. However, we found higher baseline ESR to have a significant association with incident RA-ILD on univariate and multivariate analysis, this being mean 8.64 mmHg higher in patients who developed ILD in the primary analysis. Although the ERAS/ERAN cohorts were not designed to compare treatment effects, the conclusion from our findings is that MTX has no association with the development of RA-ILD and may lead to a delayed onset and lower incidence of RA-ILD perhaps as a consequence of better overall RA disease control, or specific lung mediated immune suppression

Strengths and Limitations of this study

The strength of this study is inherent in the nature of ERAS and ERAN, two real world large inception early RA cohorts, recruiting all-comers, treated according to contemporary best practice, with the rigour of regular standardised assessments and data collection allowing data to be pooled and analysed collectively. In contrast to RCTs the data from ERAS and ERAN are not restricted to defined RA populations with strict inclusion and exclusion criteria, nor to treatment strategies confined by protocol. ERAS and ERAN are also unique in size recruiting 2701 patients compared for example to 582 in the Rochester cohort (11), and in the long duration of follow up, adding to the strength of these analyses. The primary analysis of 67 incident RA-ILD cases allowed us to focus on the association with MTX by excluding cases with ILD occurring before any csDMARD use.

It is possible that treatment decisions, being at the discretion of each center, were influenced by channelling bias, whereby patients perceived to be at higher risk of RA-ILD, such as those with lung disease, might have been excluded from MTX exposure. However, there was no difference in MTX exposure between those with and without baseline respiratory co-morbidities, and MTX exposed patients were more likely to be current and ex smokers (Table 2), so this seems unlikely. We have assumed that all cases of ILD occurring at baseline were RA related. This would seem the most likely aetiology, especially in those where the onset was synchronous with joint disease, but potentially other causes might have explained ILD. As ERAS closed to follow up in 2011 and ERAN in 2013 it is possible that new cases of RA-ILD were missed after last CRF and pre death. However, we have reported

RA-ILD survival to be a median of 3 years (5 year survival 38.8%) in ERAS (8) and with last CRF 2011-2013 and latest death certification reports included up to June 2018 it is not likely that many new cases in this period have been missed. Nonetheless we have had to exclude 9 RA-ILD cases from analysis, as we could not confirm that they remained non-MTX exposed, given lack of follow up data between last CRF + 2 years and death when RA-ILD was first notified. Our incident RA-ILD cases available for analysis are therefore lower than reality. A further limitation of the data is the lack of external confirmation of ILD case verification, this being dependent on the reporting of ILD by each center on the CRF, or the doctor completing the death certificate. Whilst the diagnosis of ILD is strongly influenced by investigations, with incrementally increasing detection from clinical signs to pulmonary function tests and HRCT images, and much sub clinical disease being present (5,9), we believe that the specific diagnostic features of ILD and thoroughness of clinical work up by recruiting centers were sufficient to have confidence in the accuracy of ILD reporting. Furthermore, credibility of ILD reporting in ERAS/ERAN is gained from the prevalence being in keeping with other cohorts where it was possible to independently verify the diagnosis for each case (9-12). Another limitation is that smoking status was missing in a large proportion of ERAS patients, because its importance was not appreciated at the time data was collected in the 1980s. However, the sensitivity analysis, running the multivariate model stratified by smoking status at baseline, did not change the lack of association between MTX and RA-ILD onset.

In conclusion we report a prevalence of RA-ILD in the ERAS/ERAN cohorts of 3.7% with independent significant incident associations in line with other studies, namely older age of RA onset, ever smoking, nodules, RF positivity, male gender, and high ESR. We also show a significant association of incident RA-ILD with a longer time from first RA symptoms to secondary care intervention supporting the 'window of opportunity'. We have found no association between MTX treatment and incident RA-ILD, and on the contrary provide evidence suggestive that MTX exposed RA patients may have a delayed onset of ILD. There seems no reason to confuse the association of MTX and hypersensitivity pneumonitis with the onset of RA-ILD. Assuming baseline lung function is sufficient to withstand an episode of hypersensitivity pneumonitis, there are no other respiratory contraindications to the use of this very effective 'anchor' csDMARD in patients with RA.

Key messages

- In ERAS/ERAN, incident RA-ILD is significantly associated with older age of RA onset, ever smoking, nodules, RF positivity, male gender, ESR, and a longer time from first RA symptoms to first secondary care visit.
- There is no association between incident RA-ILD and MTX treatment
- MTX may have a protective role in delaying the onset of RA-ILD

Conflicts of Interest

The authors have no conflicts of interest to declare

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Author Contributions Statement

PK: Conception of work, data interpretation, manuscript drafting

AB, KS Statistical analysis, data interpretation, manuscript revision

EN, AY Statistical support, data interpretation, manuscript revision

DW, PC, JD data interpretation, manuscript revision

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Data Statement

Dataset available from Prof A. Young, Center for Health Services and Clinical Research and Post Graduate Medicine, University of Hertfordshire, Hatfield, UK

Figure Legends

Figure 1

Diagram showing patient selection and allocation to MTX exposed and non-MTX exposed groups

Figure 2

Cox proportional time to event analysis showing time of onset of RA-ILD from first joint symptoms of RA in MTX exposed and non-MTX exposed groups. Primary analysis: cases with RA-ILD first recorded after any csDMARD exposure, n=67

Figure 3

Cox proportional time to event analysis showing time of onset of RA-ILD from first joint symptoms of RA in MTX exposed and non-MTX exposed groups. Extended cohort; all cases with RA-ILD including those diagnosed at baseline before any csDMARD exposure, n=92

Table 1. Demographic features of the ERAS and ERAN cohorts

		Total		ERAS		ERAN		Chi-squared p-value
Number		2701		1465		1236		
Gender	Male	893	33.1%	492	33.6%	401	32.4%	0.530
	Female	1808	66.9%	973	66.4%	835	67.6%	
Age of RA onset	<55	1146	42.4%	659	45.0%	487	39.4%	0.013
	56-64	728	27.0%	380	25.9%	348	28.2%	
	65+	827	30.6%	426	29.1%	401	32.4%	
Baseline Smoker Status	Never	995	36.8%	528	36.0%	467	37.8%	<0.001
	Current	594	22.0%	179	12.2%	415	33.6%	
	Ex-Smoker	518	19.2%	209	14.3%	309	25.0%	
	Other	26	1.0%			26	2.1%	
	Missing	568	21.0%	549	37.5%	19	1.5%	
MTX Exposure	No	1114	41.2%	857	58.5%	257	20.8%	<0.001
	Yes	1578	58.4%	602	41.1%	976	79.0%	
	Missing	9	0.3%	6	0.4%	3	0.2%	
ILD Diagnosis	No	2600	96.3%	1404	95.8%	1196	96.8%	0.206
	Yes	101	3.7%	61	4.2%	40	3.2%	

Key

RA: rheumatoid arthritis, MTX: methotrexate, ILD: Interstitial Lung disease

Table 2. Demographic features of MTX exposed and non-MTX exposed cases

		Total		Non-MTX exposed		MTX exposed		Chi-squared p-value
Total		2692		1114		1578		
Gender	Male	1804	67.0%	721	64.7%	1083	68.6%	0.034
	Female	888	33.0%	393	35.3%	495	31.4%	
Age of RA onset	<55	1144	42.5%	436	39.1%	708	44.9%	<0.001
	55-64	723	26.9%	277	24.9%	446	28.3%	
	65+	825	30.6%	401	36.0%	424	26.9%	
Baseline Smoking Status	Never	991	36.8%	346	31.1%	645	40.9%	0.058
	Current	594	22.1%	179	16.1%	415	26.3%	
	Ex-smoker	518	19.2%	172	15.4%	346	21.9%	
	Other	25	0.9%	2	0.2%	23	1.5%	
	Missing	564	21.0%	415	37.3%	149	9.4%	
Baseline Erosions	No erosions	1883	69.9%	808	72.5%	1075	68.1%	0.117
	Erosions	699	26.0%	276	24.8%	423	26.8%	
	Missing	110	4.1%	30	2.7%	80	5.1%	
Baseline RF	-ve	977	36.3%	462	41.5%	515	32.6%	<0.001
	+ve	1633	60.7%	628	56.4%	1005	63.7%	
	Missing	82	3.0%	24	2.2%	58	3.7%	
Baseline Nodules	None	2515	93.4%	1057	94.9%	1458	92.4%	0.010
	Nodules	177	6.6%	57	5.1%	120	7.6%	
Baseline DAS	<1.6	31	1.2%	5	0.4%	26	1.6%	<0.001
	1.6-2.59	298	11.1%	163	14.6%	135	8.6%	
	2.6-3.2	345	12.8%	180	16.2%	165	10.5%	
	>3.2-4.19	543	20.2%	243	21.8%	300	19.0%	
	4.2-5.1	-	-	-	-	-	-	
	>5.1	1415	52.6%	503	45.2%	912	57.8%	
	Missing	60	2.2%	20	1.8%	40	2.5%	

Table 3 Multivariate logistic analysis showing co-variates independently associated with RA-ILD development

	Primary analysis, RA-ILD onset after any csDMARD exposure, n=67	Wald test	Extended cohort, including RA-ILD onset pre any csDMARD, n=92	Wald test
	O.R. (95% C.I.)	p value	O.R. (95% C.I.)	p value
Methotrexate exposure	0.85 (0.49, 1.49)	0.578	0.48 (0.3, 0.79)	0.004
Age RA onset	1.04 (1.02, 1.06)	<0.001	1.04 (1.02, 1.06)	<0.001
Smoking, ever, baseline	2.21 (1.21, 4.03)	0.01	1.91 (1.13, 3.25)	0.016
Male gender	1.44 (0.83, 2.48)	0.193	1.74 (1.05, 2.86)	0.03
RF positive, baseline	2.02 (1.07, 3.82)	0.029		n.s.
RA nodules, baseline		n.s.	2.19 (1.08, 4.41)	0.029
Onset - OPD	1.04 (1.00, 1.07)	0.027	1.03 (1.0, 1.07)	0.04
Baseline major co-morbidities*	0.62 (0.40, 0.95)	0.027	0.67 (0.46, 0.98)	0.037
Baseline ESR	-	n.s.	1.01 (1.0, 1.02)	0.047

Note: Variables not reported did not reach statistical significance in the respective models.

Key

RF: rheumatoid factor,

Onset - OPD: time from first RA symptoms to first hospital out patient appointment

*excluding respiratory

Table 4 Cox regression time to event analysis showing associations of methotrexate exposure and baseline co-variates with time from RA first symptoms to RA-ILD onset

	Primary analysis, RA-ILD onset after any csDMARD exposure, n=67		Extended cohort, including RA-ILD onset pre any csDMARD, n=92	
	H.R. (95% C.I.)	p value	H.R. (95% C.I.)	p value
Methotrexate exposure	0.54 (0.28, 1.06)	0.072	0.41 (0.23, 0.75)	0.004
Age RA onset	1.03 (1, 1.06)	0.048	1.03 (1, 1.06)	0.028
Smoking, ever, baseline	1.09 (0.52, 2.26)	0.817	1.16 (0.61, 2.22)	0.654
Male gender	1.02 (0.51, 2.03)	0.966	0.85 (0.47, 1.54)	0.587
RF positive, baseline	0.96 (0.69, 1.32)	0.799	1.08 (0.85, 1.38)	0.512
Onset - OPD	0.98 (0.94, 1.03)	0.424	0.98 (0.94, 1.02)	0.276
Baseline major co-morbidities*	1.26 (0.69, 2.28)	0.452	1.09 (0.63, 1.9)	0.762

Key

RF: rheumatoid factor,

Onset - OPD: time from first RA symptoms to first hospital out patient appointment

*excluding respiratory

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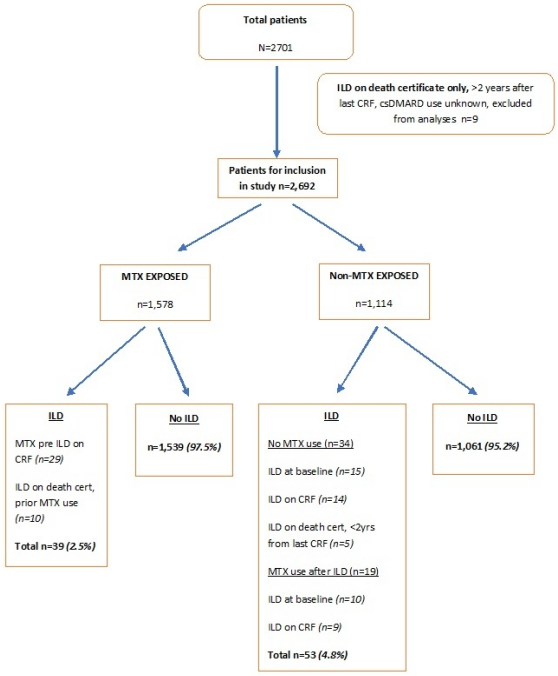

Figure 1

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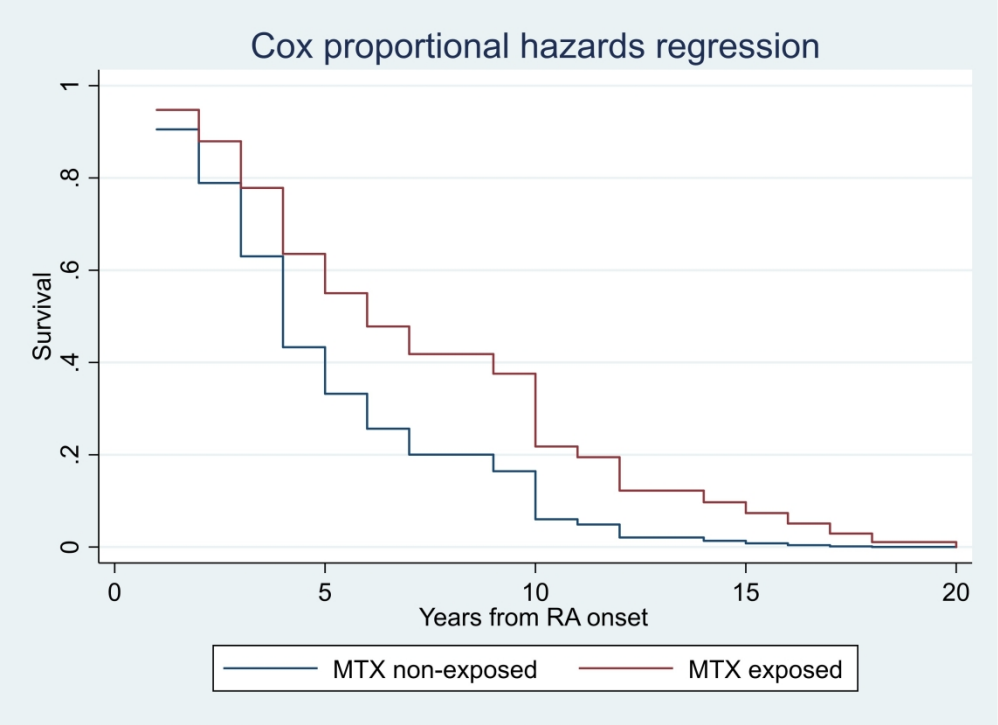

Figure 2

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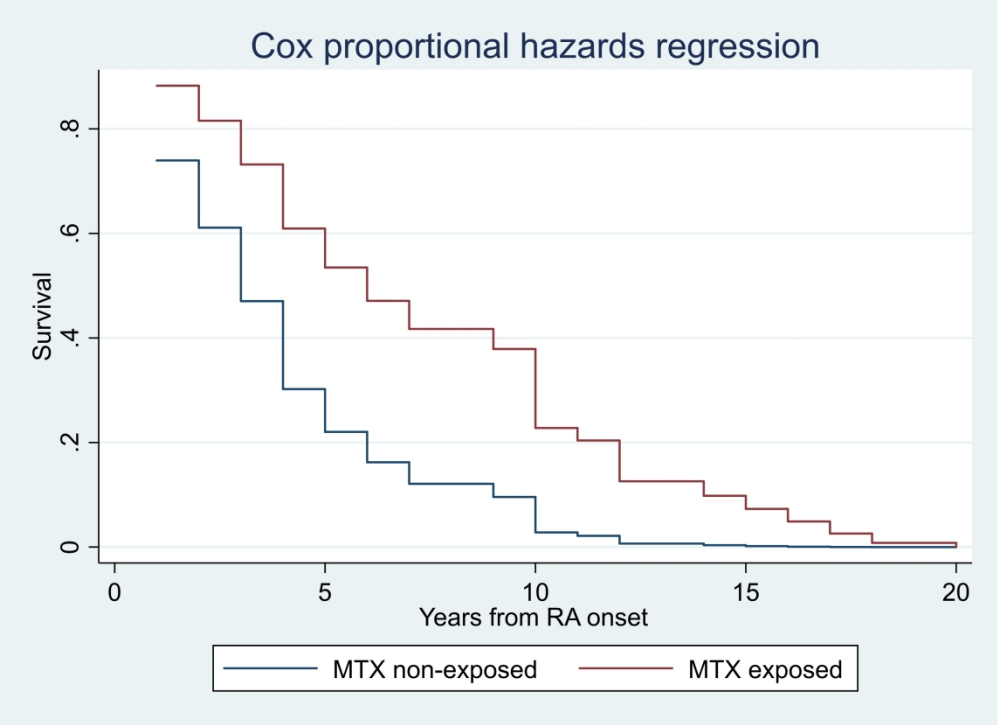

Figure 3

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Supplementary Material

Statistical analyses

Univariate analysis

The relation between onset of RA-ILD and binary covariates [MTX exposure, gender, baseline: rheumatoid factor (RF, positive/negative), smoking status (ever/never), presence of nodules, extra articular RA major, minor and combined, respiratory major, minor and combined, presence of erosions] was analysed by Chi Squared test, and continuous covariates [age of RA onset, baseline: disease activity score (DAS), ESR, tender joint count (TJC), swollen joint count (SJC), patient global assessment (PGA), Hb, BMI, health assessment questionnaire score (HAQ), number of comorbidities major, minor and combined (including respiratory), number of major comorbidities (excluding respiratory), time from RA symptom onset to first outpatient appointment (months), time from first outpatient appointment to first DMARD (months), time from RA symptom onset to first DMARD (months)] was analysed by t test.

Multivariate analysis model

Binary logistic models were fitted to the data, using the diagnosis of ILD as the outcome variable to examine possible differences within the variables The initial covariates included were: MTX exposure (Y/N), gender (M/F), age at onset of RA (years), and presence of rheumatoid factor at baseline (+ve/-ve). Additional covariates were added to the model in turn, to assess whether they improved the model fit. It was not possible to use log likelihood ratio tests (LRTs) to compare models because of varying levels of missing data. Instead, the p-value from each covariate's Wald test was considered, to determine whether there was evidence to include them in the model, as well as assessing whether the odds ratios for other covariates had changed. All covariates significant ($p<0.05$) and borderline significant ($p<0.1$ and >0.05) in the univariate analysis were tested and also some non significant covariates in the univariate analysis were included because they might be of clinical interest (DAS, Hb, TJC,

SJC and PGA, all at baseline). Anti-cyclic citrullinated peptide (anti CCP) antibody data was only collected at a few centres and was insufficient to include in any model.

Multivariate time-varying analysis

Cox proportional hazards models were applied to the data, with the diagnosis of ILD as the binary outcome variable at each year (measured from baseline) that a patient participated in the study. 54 (53.5%) patients of the 101 with ILD had known diagnosis dates or could be approximated to the nearest year. This was up to a maximum of 15 years, to match the time-varying data available for analysis. Of the 54, 48 were diagnosed during the study and so were included within the fitted models. The fixed covariates considered were: gender (M/F), age at onset of RA (years), maximum follow-up (years) and smoking status at baseline (ever/never). Time varying co-variates were DAS, patient global assessment, tender joint count, swollen joint count, ESR, health assessment questionnaire, haemoglobin, BMI, erosions, rheumatoid nodules, major comorbidities. Age at onset of RA, baseline smoking status and maximum follow-up were found to be statistically significant in combination, with all three hazard ratios >1 and all corresponding p-values <0.03. However, maximum follow-up was discounted from the model since adding any time-varying covariates removed its significance. Sex was selected a priori to be in the model to improve precision.

Next, time-varying covariates were considered: MTX exposure (Y/N), DAS (and individually PGA, TJC, SJC and ESR), HAQ, haemoglobin (g/L), presence of rheumatoid factor (RF, +ve/-ve), presence of erosions (Y/N), presence of nodules (Y/N), BMI and number of major comorbidities (excluding respiratory). The model was built by individually adding each covariate, then examining its hazard ratio and corresponding p-value to assess for statistical significance. The components of DAS were assessed both individually and in combination. Covariates were retained if $p<0.1$. Akaike information criterion (AIC) was used to compare the fit of each interim model to those previously fitted, with the final model having the lowest AIC value.

Cox regression time to event analysis

The relation between time of ILD diagnosis after first RA symptoms was explored in the MTX exposed ILD and non-MTX exposed ILD groups using Cox regression time to event analysis, adjusting for the same confounders as in the multivariate model. The time of onset of ILD in relation to first symptoms of RA was taken as the first record of this on the ERAS/ERAN CRF.

Where ILD was recorded on the death certificate but not on the last CRF this time was recorded as last CRF + 1 year if the interval was less than 2 years, and as last CRF + 2 years if this interval was 2 years or longer. In patients with ILD at baseline the time of ILD onset was taken to be synchronous with first RA symptoms.

Supplementary Table 1a.

Primary univariate analysis showing association of incident RA-ILD with MTX exposure and baseline binary covariates, excluding cases with ILD at baseline prior to any csDMARD use.

		n	ILD		No ILD		Odds Ratio	CI	Chi-squared test p-value
			n	%	n	%			
Total			67		2600				
MTX	Yes	2667	39	58.2%	1539	59.2%	0.96	(0.57, 1.63)	0.872
	No		28	41.8%	1061	40.8%			
Gender	M	2667	30	44.8%	844	32.5%	1.69	(1.00, 2.83)	0.034
	F		37	55.2%	1756	67.5%			
Rheumatoid Factor	Positive	2588	52	77.6%	1568	60.3%	2.11	(1.16, 4.06)	0.010
	Negative		15	22.4%	953	36.7%			
Anti CCP (ever)	Positive	330	6	9.0%	225	8.7%	1.29	(0.23, 13.51)	0.755
	Negative		2	3.0%	97	3.7%			
Smoker Status	Ever	2106	41	61.2%	1081	41.6%	2.29	(1.25, 4.41)	0.004
	Never		16	23.9%	968	37.2%			
Rheumatoid Nodules	None	2667	57	85.1%	2436	93.7%	2.61	(1.16, 5.27)	0.005
	Nodules		10	14.9%	164	6.3%			
Extra-Articular RA features	Yes	2667	11	16.4%	286	11.0%	1.59	(0.74, 3.14)	0.164
	No		56	83.6%	2314	89.0%			
Respiratory comorbidities	Yes	2667	7	10.4%	134	5.2%	2.15	(0.81, 4.83)	0.056
	No		60	89.6%	2466	94.8%			
Erosions at baseline	Yes	2560	18	26.9%	673	25.9%	0.99	(0.54, 1.75)	0.981
	No		49	73.1%	1820	70.0%			

Key

csDMARD: conventional synthetic disease modifying anti-rheumatic drug, MTX: methotrexate, CCP: anti-cyclic citrullinated peptide antibody

Extra-Articular RA features: Tendon sheath disease, Sjogren's syndrome, ocular rheumatoid disease, Raynaud's

Respiratory comorbidities: History of chronic obstructive pulmonary disease, asthma, pneumonia, tuberculosis, pleural disease

Supplementary Table 1b.

Primary univariate analysis showing association of incident RA-LD with baseline continuous covariates, excluding cases with ILD at baseline prior to any DMARD use.

	n	ILD			No ILD			Difference	t-test p-value
		N	Mean	CI	N	Mean	CI		
Age of RA onset (years)	2667	67	61.01	(58.45, 63.58)	2600	55.87	(55.32, 56.42)	5.14	0.004
DAS28	2607	66	4.43	(4.04, 4.82)	2541	4.38	(4.32, 4.45)	0.05	0.821
ESR	2473	63	45.51	(38.76, 52.26)	2410	36.87	(35.77, 37.96)	8.64	0.014
TJC	2656	66	10.74	(7.89, 13.60)	2590	10.14	(9.77, 10.52)	0.6	0.623
SJC	2659	67	11.46	(8.70, 14.22)	2592	12.21	(11.76, 12.67)	-0.75	0.608
PGA	2608	66	48.35	(42.08, 54.62)	2542	43.63	(42.62, 44.64)	4.72	0.146
Hb	2627	67	12.93	(12.55, 13.31)	2560	12.85	(12.79, 12.91)	0.08	0.659
Onset-OPD (months)	2642	67	9.78	(7.96, 11.59)	2575	8.22	(7.98, 8.47)	1.56	0.053
OPD-csDMARD (months)	2357	61	8.13	(2.66, 13.60)	2296	5.57	(4.95, 6.19)	2.56	0.197
Onset-csDMARD (months)	2361	62	17.76	(12.27, 23.25)	2299	14.34	(13.58, 15.09)	3.42	0.151
Comorbidities (major)	2667	67	0.43	(0.30, 0.57)	2600	0.49	(0.46, 0.52)	-0.06	0.532
Comorbidities (minor)	2667	67	0.46	(0.31, 0.61)	2600	0.33	(0.31, 0.35)	0.13	0.053
Comorbidities (combined)	2667	67	0.9	(0.69, 1.10)	2600	0.82	(0.87, 0.86)	0.08	0.542

Comorbidities major excluding respiratory	2667	67	0.33	(0.21, 0.45)	2600	0.47	(0.44, 0.50)	-0.14	0.127
BMI	2356	56	25.98	(24.70, 27.25)	2300	26.56	(26.35, 26.76)	-0.58	0.390
HAQ	2625	67	1.28	(1.10, 1.45)	2558	1.11	(1.08, 1.14)	0.17	0.090

Key

DAS28: 28 joint disease activity score, ESR: erythrocyte sedimentation rate, TJC: tender joint count, SJC: swollen joint count, PGA: patient global assessment, Hb: haemoglobin, BMI: body mass index, HAQ: health assessment questionnaire, Onset-OPD: time from first RA symptoms to first secondary care outpatient visit, OPD-csDMARD: time from first secondary care outpatient visit to start of conventional synthetic disease modifying anti-rheumatic drug therapy, Onset-csDMARD: time from first RA symptoms to start of conventional synthetic disease modifying anti-rheumatic drug therapy, Co-morbidities major and minor: as per ICD 10 definitions.

Supplementary Table 2a.

Univariate analysis showing association of incident RA-ILD with MTX exposure and baseline binary covariates, extended data set including RA-ILD cases recorded at baseline

		n	ILD		No ILD		Odds Ratio	CI	Chi-squared test p-value
			n	%	n	%			
MTX	Yes	2692	39	2.5%	1539	97.5%	0.51	(0.32, 0.79)	0.001
	No		53	4.8%	1061	95.2%			
Gender	M	2692	44	5.0%	844	95.0%	1.91	(1.23, 2.96)	0.002
	F		48	2.7%	1756	97.3%			
Rheumatoid Factor	Positive	2610	65	4.0%	1568	96.0%	1.65	(1.01, 2.77)	0.038
	Negative		24	2.5%	953	97.5%			
Anti-CCP (ever)	Positive	333	9	3.8%	225	96.2%	1.94	(0.39, 18.74)	0.394
	Negative		2	2.0%	97	98.0%			
Smoker Status	Ever	2692	56	4.9%	1081	95.1%	2.18	(1.31, 3.74)	0.002
	Never		23	2.3%	968	97.7%			
Rheumatoid Nodules	None	2692	79	3.1%	2436	96.9%	2.44	(1.22, 4.54)	0.003
	Nodules		13	7.3%	164	92.7%			

Extra-Articular RA features	Yes	2692	11	3.7%	286	96.3%	1.10	(0.54-2.10)	0.774
	No		81	3.4%	2314	96.6%			
Respiratory co-morbidities	Yes	2692	7	5.0%	134	95.0%	1.52	(0.58-3.35)	0.299
	No		85	3.3%	2466	96.7%			
Erosions at baseline	Yes	2582	26	3.7%	673	96.3%	1.12	(0.67-1.81)	0.644
	No		63	3.3%	1820	96.7%			

Key

MTX: methotrexate, CCP: anti-cyclic citrullinated peptide antibody

Extra-Articular RA features: Tendon sheath disease, Sjogren's syndrome, ocular rheumatoid disease, Raynaud's

Respiratory comorbidities: History of chronic obstructive pulmonary disease, asthma, pneumonia, tuberculosis, pleural disease

Supplementary Table 2b.

Univariate analysis showing association of incident RA-ILD with baseline continuous covariates, extended data set including RA-ILD cases recorded at baseline

	N	ILD			No ILD			Difference	t-test
		n	Mean	CI	N	Mean	CI		p-value
Age RA onset (years)	2692	92	62.8	(60.68, 64.95)	2600	55.87	(55.32, 56.42)	6.93	<0.0001
DAS28	2495	91	4.51	(4.17, 4.85)	2541	4.38	(4.32, 4.45)	0.13	0.445
ESR	2495	85	47.38	(41.33, 53.42)	2410	36.87	(35.77, 37.96)	10.51	0.001
TJC	2681	91	10.92	(8.55, 13.30)	2590	10.14	(9.77, 10.52)	0.78	0.455
SJC	2684	92	12.32	(9.64, 14.99)	2592	12.21	(11.76, 12.67)	0.11	0.935
PGA	2632	90	46.66	(41.35, 51.96)	2542	43.63	(42.62, 44.64)	3.03	0.2786
Hb	2652	92	12.8	(12.48, 13.13)	2560	12.85	(12.79, 12.91)	-0.05	0.798
Onset-OPD (months)	2666	91	9.16	(7.69, 10.64)	2575	8.22	(7.98, 8.47)	0.94	0.174
OPD-csDMARD (months)	2379	83	7.14	(2.93, 11.36)	2296	5.57	(4.95, 6.19)	1.57	0.356
Onset-csDMARD (months)	2383	84	16.49	(12.13, 20.85)	2299	14.34	(13.58, 15.09)	2.15	0.294
Comorbidities major	2692	92	0.48	(0.35, 0.60)	2600	0.49	(0.46, 0.52)	-0.01	0.863
Comorbidities minor	2692	92	0.4	(0.28, 0.52)	2600	0.33	(0.31, 0.35)	0.07	0.212
Comorbidities combined	2692	92	0.8	(0.63, 0.98)	2600	0.82	(0.87, 0.86)	-0.02	0.949

Comorbidities major excluding respiratory	2692	92	0.4	(0.28, 0.52)	2600	0.47	(0.44, 0.50)	-0.07	0.394
BMI baseline	2377	77	25.9	(24.82, 26.98)	2300	26.56	(26.35, 26.76)	-0.66	0.256
HAQ at baseline	2650	92	1.22	(1.07, 1.37)	2558	1.11	(1.08, 1.14)	0.11	0.2024

Key

DAS28: 28 joint disease activity score, ESR: erythrocyte sedimentation rate, TJC: tender joint count, SJC: swollen joint count, PGA: patient global assessment, Hb: haemoglobin, BMI: body mass index, HAQ: health assessment questionnaire, Onset-OPD: time from first RA symptoms to first secondary care outpatient visit, OPD-csDMARD: time from first secondary care outpatient visit to start of conventional synthetic disease modifying anti-rheumatic drug therapy, Onset-csDMARD: time from first RA symptoms to start of conventional synthetic disease modifying anti-rheumatic drug therapy, Co-morbidities major and minor: as per ICD-10 definitions.

Supplementary Table 3

Multivariate analysis stratified by smoking; showing effects of baseline co-variates on incident RA-ILD in smokers, non-smokers and those with missing smoker status at baseline.

	Overall		Non-smokers		Smokers		Missing	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
N	2015		949		1066		552	
Methotrexate exposed	0.85 (0.49, 1.49)	0.578	0.24 (0.08, 0.70)	0.009	1.56 (0.74, 3.29)	0.240	1.35 (0.33, 5.52)	0.681
Male gender	1.44 (0.83, 2.48)	0.193	0.70 (0.20, 2.52)	0.587	1.8 (0.95, 3.41)	0.073	1.38 (0.38, 5.02)	0.629
Age of RA onset	1.04 (1.02, 1.06)	<0.001	1.03 (0.99, 1.07)	0.097	1.05 (1.02, 1.08)	0.001	1.03 (0.99, 1.08)	0.172
Baseline RF	2.02 (1.07, 3.82)	0.029	1.88 (0.64, 5.57)	0.254	2.20 (1.00, 4.86)	0.051	2.83 (0.58, 13.85)	0.199
Onset-OPD (months)	1.04 (1.00, 1.07)	0.027	1.005 (0.93, 1.08)	0.902	1.05 (1.01, 1.09)	0.012	0.98 (0.87, 1.10)	0.699
Baseline Major Comorbidities (Excl Resp)	0.62 (0.40, 0.95)	0.027	0.43 (0.15, 1.24)	0.119	0.64 (0.4, 1.04)	0.070	0.30 (0.04, 2.39)	0.254
Baseline Smoker Status	2.21 (1.21, 4.03)	0.010						
Constant	0.0009 (0.0002, 0.005)	<0.001	0.005 (0.0004, 0.07)	<0.001	0.0006 (0.00008, 0.005)	<0.001	0.002 (0.00006, 0.05)	<0.001

Key

RA: Rheumatoid arthritis, RF: rheumatoid factor

Supplementary Table 4

Multivariate time varying analysis best fit model showing the association of fixed and time-varying co-variates on incident RA-ILD.

		Hazard Ratio (95% CI)	p
Fixed	Age of RA onset	1.07 (1.02, 1.11)	0.002
	Baseline Smoker Status	1.52 (0.61, 3.79)	0.365
	Gender (male)	1.19 (0.47, 2.99)	0.712
Time-varying	Methotrexate	0.96 (0.82, 1.12)	0.629
	Rheumatoid Factor	1.05 (0.96, 1.15)	0.279
	HAQ	1.15 (1.04, 1.26)	0.007
	ESR	1 (1, 1.01)	0.01
	SJC	0.99 (0.98, 1)	0.058

Legend

HAQ Health Assessment Questionnaire; ESR erythrocyte sedimentation rate; SJC swollen joint count

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

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Abstract

Objectives

To assess predictive factors for rheumatoid arthritis interstitial lung disease (RA-ILD) in two early RA inception cohorts with a focus on methotrexate (MTX) exposure.

Design

Multicenter prospective early RA inception cohort studies; the early RA study (ERAS) and the early RA network (ERAN)

Setting

Secondary care, ERAS 9 centers, ERAN 23 centers in England, Wales and the Republic of Ireland

Participants

Patients with new diagnosis of RA, n=2701.Standardised data including demographics, drug therapies and clinical outcomes including the presence of RA-ILD were collected at baseline, within 3- 6 months, at 12 months and annually thereafter.

Primary and secondary outcome measures

Primary outcome was the association of MTX exposure on RA-ILD diagnosis. Secondary outcomes were the association of demographic, comorbid and RA specific factors on RA-ILD diagnosis and the association of MTX exposure on time to RA-ILD diagnosis.

Results

Of 92 eligible ILD cases, 39 occurred in 1578 (2.5%) MTX exposed and 53 in 1114 (4.8%) non-MTX exposed cases. The primary analysis of RA-ILD cases only developing after any csDMARD treatment (n=67) showed MTX exposure not to be associated with incident RA-ILD (O.R. 0.85 CI 0.49, 1.49 p=0.578) and a non-significant trend for delayed ILD diagnosis (O.R. 0.54 CI 0.28, 1.06 p=0.072). In an extended analysis including RA-ILD cases present at RA diagnosis (n=92), MTX exposure was associated with a significantly reduced risk of incident RA-ILD (O.R. 0.48, CI 0.3, 0.79 p=0.004) and longer time to ILD diagnosis (O.R. 0.41, CI 0.23, 0.75 p=0.004). Other

independent baseline associations with incident RA-ILD were higher age of RA onset, ever smoking, male gender, rheumatoid nodules and longer time from first RA symptom to first out-patient visit.

Conclusions

MTX treatment was not associated with an increased risk of RA-ILD diagnosis. On the contrary evidence suggested that MTX may delay the onset of ILD.

Article Summary

Strengths and Limitations

- Multicenter prospective early RA inception cohort study recruiting 2701 patients
- Standardised data collection with up to 25 years follow-up
- Diagnosis of RA-ILD made by participating rheumatology centers, or from death certification, without independent verification
- Univariate, multivariate, time varying and time to event Cox proportional hazards analyses assessed MTX-exposure, demographic and RA specific factors associated with RA-ILD diagnosis
- High proportion of missing smoker status data from ERAS patients recruited 1986 - 2001

Introduction

Methotrexate (MTX) is now firmly established globally as the anchor drug for the management of rheumatoid arthritis (RA), recommended for first line use, to which other conventional synthetic, targeted synthetic and biologic disease modifying anti rheumatic drugs (cs/ts/b DMARDs) are generally added (1,2). In addition to an excellent ability to suppress synovitis and restore physical function, there is compelling data demonstrating a beneficial effect on long term cardiovascular disease (3) and hence restoration of life expectancy to that of the normal population.

A hypersensitivity pneumonitis is a rare adverse effect of MTX described in 0.43% (4), generally subacute in presentation, with progression of characteristic symptoms over a period of days to weeks (5). This usually occurs early, within the first year of treatment, but has been reported up to 3 years after starting MTX (4,5). This organ specific hypersensitivity reaction has led to a creeping concern in routine practice that MTX may also be associated with an increased incidence or exacerbation of the interstitial lung disease (ILD) that is associated with RA, and may be a reason to withhold MTX from RA patients with any lung disease. RA-ILD is an uncommon but significant life threatening extra-articular manifestation, clinically significant in up to 5% of RA patients, with subclinical HRCT evidence in 33% or more, a median survival from diagnosis of approximately 3 years, contributing to the overall excess mortality of RA (2, 6-12). MTX is contraindicated if a patient has insufficient respiratory reserve to survive hypersensitivity pneumonitis. However, evidence is lacking that would deter initiation of MTX treatment in people with mild respiratory disease on grounds of an adverse effect on any other form of lung injury such as ILD. Indeed, the considerable benefits of MTX are such that a decision to withhold it as a treatment option for RA should be reluctantly made, and only for sound reasons.

Evidence that MTX may cause or have an adverse impact on RA-ILD is sparse. Meta-analysis of randomised controlled trials (RCT) of MTX in RA has reported an increased risk of all adverse respiratory events and respiratory infections, but not of death due to lung disease or non-infectious respiratory events, with follow up duration of 24-104 weeks (13). Due to inherent difficulties separating RA-ILD from putative MTX related ILD, a meta-analysis of MTX versus placebo or active comparator agents in RCTs from non-malignant inflammatory

disorders not themselves associated with ILD is of interest (14). This has shown no MTX associated risk of lung disease in studies ranging from 16 – 52 weeks follow up. These relatively short duration analyses, in patients pre-selected for RCTs, are reassuring but require substantiation from RA inception cohorts or patient registries with all-comers included and longer follow up. Sequential lung function tests in cohorts of MTX treated RA patients followed prospectively for up to 5 years have shown a sequential decline, with inconsistent interpretation that this is in keeping with (15), or in excess of (16), expected age related changes. Interpretation of these studies is limited by a lack of inclusion of non-MTX treated control RA patients. In another cohort comparing 55 MTX treated with 73 non-MTX treated patients with established RA, there was no adverse influence of MTX on pulmonary function tests over 2 years, including a sub analysis of those found to have largely sub clinical pulmonary fibrosis on HRCT (17).

We report the association of MTX-exposure, and other demographic and RA specific factors with incident cases of RA-ILD in two large multi-centre RA inception cohorts, the early rheumatoid arthritis study (ERAS) and the early rheumatoid arthritis network (ERAN), recruiting from 1986 – 2012 with review up to 25 years.

METHODS

Patient Databases

The study used data from ERAS (1986-2001) and ERAN (2002-2012), two multi-center early RA inception cohorts. ERAS recruited 1465 patients (<2 years disease duration, no prior csDMARD therapy) from nine district general hospitals in England, followed yearly for up to 25 years (median follow up 10 years). ERAN recruited 1236 patients (<3 years disease duration) from 23 centres in England, Wales and Ireland, followed yearly for up to 10 years (median follow up 6 years). Ethical approval was obtained from East Hertfordshire local research ethics committee (ERAS) and the Trent research ethics committee (ERAN). All participants gave informed consent. STROBE reporting cohort guidelines have been followed (von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies).

Recruitment into ERAS and ERAN was based on clinician diagnosis with 70% of patients fulfilling the minimum ARA criteria (18) for RA at baseline and 96% by last visit. Patients subsequently reclassified as non-RA were excluded from the study.

Patient and Public involvement

A patient representative from the National Rheumatoid Arthritis Society (NRAS) was involved in the design and conduct of ERAN, including decisions concerning which RA outcomes should be collected. By consenting to recruitment patients were aware that the purposes of the study included examining the consequences of a range of RA outcomes. As patients were recruited at the time of, or very soon after, the diagnosis of RA they had limited experience of the disease to determine their priorities for ERAS/ERAN analyses. ILD was one of many outcomes that patients knew were to be studied. As ILD is established as one of the most severe complications of RA, and one of the leading causes of premature death, patients were interested in any findings that might add to our knowledge of this complication.

Patients were not involved in the recruitment process to ERAS/ERAN. Patients were not specifically involved in the statistical design of the analysis of ERAS/ERAN data on associations of factors with RA-ILD.

At recruitment patients were informed that "the results of this study would be made available to participating clinicians and will be the subject of international presentations and articles in peer-reviewed scientific journals". Participants will not be notified of the results individually, but we will request that a summary of the findings be made available to all patients with RA via the patient newsletter of NRAS.

Clinical and laboratory measures

Information on demographic, clinical, treatment, laboratory and functional features was recorded in both cohorts at baseline, between 3 and 6 months, at 12 months and then once yearly on standardized case report forms (CRF), as previously described (19-21). Disease activity (DAS) was calculated according to the original three variable method (22) in ERAS and the four variable DAS28 method (23) in ERAN. A transformation formula was used to make

DAS and DAS28 comparable (24). Source data verification was undertaken by an experienced nurse practitioner at visits to each center. Combined analysis of ERAS and ERAN is possible since they are consecutive inception cohorts with similar design, including the variables captured, timing of assessments and patient recruitment. Follow up across ERAS and ERAN was relatively high given the long term of both prospective studies, and of those not followed to death or closure, cases lost to follow up for no known reason were only 13.7% overall (12.5% ERAS, 15% ERAN). Full details of reasons for discontinuation in ERAS and ERAN are shown in Supplementary Table 1.

Treatment profiles

Patients were treated according to usual care in each of the ERAS and ERAN centres, without specific protocols, strategies or other external influences. All centers followed the 1992 good practice guidance outlined by the British Society for Rheumatology and Royal College of Physicians (25). Treatment details were entered onto the CRF at each ERAS/ERAN data collection visit. At baseline all patients in ERAS were csDMARD naïve and in ERAN 13.5% had commenced a csDMARD within a few weeks of first secondary care visit. In ERAS and ERAN, initial csDMARD use was as monotherapy with/without steroids in >90%, favouring sulphasalazine (SSZ) from 1986-2001, with a switch to MTX monotherapy such that SSZ and MTX were used in equal proportions as first csDMARD in 2002, and thereafter in ERAN MTX became the most likely initial choice (20, 21), this reflecting contemporary best practice. Combination csDMARDS were generally used for more severe RA and were introduced at earlier time-points in the later years of ERAS and in 25% of those who received any csDMARDs in ERAN (20,21). In ERAN the most frequently used combinations of csDMARDs were MTX/SSZ, MTX/SSZ + hydroxychloroquine (HCQ) and MTX/HCQ (21). Only a small proportion of patients received bDMARDs, which were available from 2002 onwards (<2% by 1 year and <10% by 3 years).

Median time from RA symptom onset to first rheumatology outpatient visit (baseline assessment) was 6 months in both cohorts, and to first csDMARD initiation 8 months in ERAS and 7 months in ERAN.

ILD identification

Co-morbidities including respiratory disease were entered on the CRF at each visit. Death certification was received from the NHS medical research information service (MRIS) and subsequently the NHS Health and Social Care Information center (HSCIC) for all recruited patients four monthly with last data inclusion for this analysis June 2018. The diagnosis of ILD at each center was according to standard practice, with confirmatory evidence from standard investigations including pulmonary function tests, chest radiographs and HRCT scans. ILD was deemed to be present if the terms pulmonary fibrosis or interstitial lung disease were listed on the CRF or the death certificate using ICD-10 criteria.

As the development of RA-ILD is insidious, setting a time of onset had to be pragmatic. In cases where ILD was recorded on the baseline CRF the time of diagnosis was taken as synchronous with RA onset (n=25). In cases where the first record of ILD was on a CRF the date of onset was taken as then (n=52). Where the only record of ILD was on the death certificate, and not on the last CRF, the date taken as onset of ILD was recorded as last CRF + 1 year if the time from last CRF to death was 2 years or less (n=5), and recorded as last CRF + 2 years if this interval was more than 2 years (n=10).

MTX exposed ILD group

Patients were included in the analysis as MTX exposed ILD if they were recorded on the CRF as starting MTX at any time prior to the first record of ILD, either on the CRF or the death certificate.

Non-MTX exposed ILD group

Patients were included in the analysis as non-MTX exposed ILD if they were recorded as having ILD on the CRF without record of prior MTX treatment. As the analysis was concerned with the onset of ILD, patients who started MTX at any time point after ILD was first recorded on the CRF remained in the non-exposed group, as ILD was first diagnosed before MTX treatment. Patients who were recorded as having ILD on the death certificate but not on the last CRF were included in the non-MTX exposed group if the time interval between last CRF and death was less than 2 years, and no MTX treatment had been recorded on the CRFs throughout ERAS/ERAN data collection. As the development of RA-ILD is slow it was considered that this was too short a time for any potential but unknown MTX use after the last CRF to have had an effect, had it been introduced. If this time interval was 2 years or

longer patients were excluded from the analysis as they could have been exposed to MTX for the first time after last CRF and before the first record of ILD on the death certificate, and as such any potential MTX exposure during this time could have had an effect. Patients where the first record of ILD and MTX use was on the same CRF were considered non-MTX exposed as the maximum time MTX could have been used since the preceding CRF was 1 year and this was considered too short to have had an effect on the development of ILD within the same period.

Statistical analysis

All analysis used statistical software Stata/IC 15.1. The primary analyses included all cases of incident RA-ILD reported after any csDMARD exposure. An extended analysis was performed on the entire cohort of incident RA-ILD including patients where ILD was recorded at the baseline visit. These additional cases had developed ILD either preceding or synchronously with RA and prior to any csDMARD use for RA. First univariate analyses were performed for associations of baseline covariates with RA-ILD development. Next multivariate binary logistic models were fitted to the data to determine independent baseline predictors of RA-ILD. As there were multiple data collection points across the ERAS and ERAN follow up period, multivariate time-varying analysis using cox proportional hazards models were created to include multiple data entries for covariates with repeated measures. Finally Cox regression time to event analysis was used to assess the relation between first RA symptoms and time of ILD diagnosis in MTX exposed and non-MTX exposed ILD cases, and with respect to other baseline co-variates.

A detailed description of the univariate and multivariate model analyses is given in supplementary material

RESULTS

A flow chart of patient selection in shown in Fig 1. From 2,701 patients a total of 101 cases of ILD were recorded (3.7%) of which 25 were present at baseline (25%). None of the baseline ILD cases had been treated with csDMARDs prior to first CRF. Nine ILD cases were excluded from analysis because the only record of ILD was on the death certificate and over 2 years had elapsed between this and the last CRF, during which time csDMARD treatment was unknown. There were 1,578 MTX exposed cases of whom 1,539 (97.5%) were not and 39

(2.5%) were diagnosed with ILD, and 1,114 non-MTX exposed cases of whom 1,061 (95.2%) were not and 53 (4.8%) were diagnosed with ILD. Of the 53 non-MTX exposed ILD cases, 19 (35%) were treated with MTX after ILD was diagnosed.

Demographic features of the ERAS and ERAN cohorts are shown in Table 1. These were generally similar across both cohorts, however there were significant differences in age of RA onset (older in ERAN), baseline smoking status (more current and ex smokers in ERAN) and MTX use (79% ERAN vs. 41% ERAS). The prevalence of ILD was 3.2% in ERAN and 4.2% in ERAS (n.s.). The median dose of MTX across both cohorts was 12.5mg but following contemporary practice this increased with time; ERAS 10mg, ERAN 20mg per week. Table 2 shows demographic features of MTX exposed and non-MTX exposed cases, where MTX exposed patients were significantly more likely to have developed RA at a younger age, be in a higher DAS category, RF positive, nodular, male, and borderline more likely to be current or ex-smokers. 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). The mean DAS28 score at first record of RA-ILD in MTX exposed cases was 3.77 and in non-MTX exposed cases 4.27 (T test p=0.30).

As we were specifically interested in the relation of ILD onset to MTX exposure the primary analysis was restricted to cases where ILD was only diagnosed after any csDMARD exposure (n=67), excluding 25 cases with ILD recorded at baseline. Univariate analyses of the relation between new diagnosis of RA-ILD and a range of binary and continuous variates are shown in Supplementary Tables 2a and 2b. This shows no association of MTX exposure and incident RA-ILD; O.R. 0.96, CI 0.57, 1.63 p=0.872. Male gender (p=0.034), RF positivity (p=0.01), ever smoking (p=0.004), rheumatoid nodules (p=0.005), age of RA onset (p=0.004) and baseline ESR (p=0.014) were all significantly associated with incident RA-ILD. Longer time between first RA symptoms and the first outpatient appointment (p=0.053), respiratory co-morbidities (p=0.056) and minor comorbidities (p=0.053) were borderline significant. Patients who developed ILD were at RA onset a mean 5.14 years older and had a mean baseline ESR score of 8.64 mm/hr higher than patients who did not develop ILD.

Table 3 shows the covariates independently associated with ILD diagnosis in the best fit multivariate model. This confirms higher age of RA onset, ever smoking, RF positivity, and

longer time from first RA symptom to first OPD visit were independently associated with incident RA-ILD and there remained no evidence that MTX exposure was associated with RA-ILD onset (OR=0.85, CI 0.48, 1.49 p=0.578). Unlike univariate analysis in this model baseline major co morbidities (excluding respiratory) were protective. This group of conditions included malignancies, cardiac disease, other non-cardiac cardiovascular conditions (e.g. hypertension, cerebrovascular disease), diabetes, thyroid disease, osteoarthritis, spinal disorders and gastrointestinal conditions as defined by ICD-10 criteria.

Extending the analysis to all 92 RA-ILD cases, including 25 recorded at baseline prior to any csDMARD use, produced similar results on univariate analysis (see Supplementary Tables 3a, 3b) with male gender (p=0.002), baseline positive RF (p=0.038), ever smoking (p=0.002), presence of rheumatoid nodules (p=0.003), age of RA onset (p<0.0001) and baseline ESR (p=0.001) all associated with incident RA-ILD. MTX exposure was associated with a significantly reduced odds ratio of developing ILD (O.R. 0.51, CI 0.32, 0.79 p=0.001). Patients who developed ILD were at RA onset a mean 6.93 years older and had a mean baseline ESR score of 10.51 mm/hr higher than patients who did not develop ILD. In the multivariate model (Table 3) higher age of RA onset, ever smoking, male gender, baseline rheumatoid nodules, higher baseline ESR and longer time from first RA symptom to first OPD visit were independently associated with incident RA-ILD. MTX exposure (O.R. 0.48, CI 0.3, 0.79) and baseline major comorbidities (excluding respiratory) were associated with significantly reduced odds of RA-ILD onset.

As there was a large number of patients in ERAS with missing smoking status at baseline (n=549), a sensitivity analysis of the primary cohort was performed by running the multivariate analysis in smokers, non smokers and those with missing smoking status data (see supplementary Table 4). This continued to show no association between methotrexate use and incident RA-ILD in smokers (OR=1.56, CI= 0.74, 3.29, p=0.240) and in those with missing smoking data (OR=1.35, CI=0.33, 5.52, p=0.681), but MTX use was associated with a reduction in incident RA-ILD in non-smokers (OR=0.24, CI=0.08, 0.70, p=0.009).

The multivariate time varying analysis, incorporating multiple data entries for covariates measured at each follow up visit (e.g. DAS, individual DAS components, HAQ, full details in supplementary materials) resulted in similar co-variate associations with incident RA-ILD. The

best fit model (see Supplementary Table 5) with the lowest Akaike information criterion (AIC) score showed significant associations with age of RA onset (p=0.002), HAQ (p=0.007) and ESR (p=0.01) and continued to show no association with MTX exposure (H.R. 0.96 CI 0.82, 1.12 p=0.629).

The relation between time to RA-ILD diagnosis after first RA symptoms in the MTX exposed and non-MTX exposed groups is shown in Fig 2 (primary analysis) and Fig 3 (extended cohort). The MTX exposed ILD group included 10 cases where RA-ILD was only recorded on the death certificate and a mean 6.6 (range 3-11) years had elapsed between this and last CRF. For these cases the time of ILD diagnosis was unknown and pragmatically was recorded as last CRF + 2 years, introducing a bias to earlier record of time of RA-ILD diagnosis. The primary analysis, excluding 25 cases with RA-ILD diagnosed at baseline pre csDMARD treatment, showed higher age of RA onset associated with earlier RA-ILD diagnosis (HR 1.03 CI 1.0, 1.06 p=0.048) and a non-significant trend for longer time to RA-ILD diagnosis in MTX exposed cases (HR 0.54 CI 0.28, 1.06 p=0.072). The extended cohort analysis showed a significantly longer time to diagnosis of RA-ILD in MTX exposed compared to non-MTX exposed cases (HR 0.41 CI 0.23, 0.75 p=0.004) and the same effect of higher age of RA onset and earlier diagnosis (HR 1.03 CI 1.0, 1.06 p=0.028), but no influence of any of the other covariates independently associated with RA-ILD onset in the multivariate model, see Table 4.

Discussion

We report an overall prevalence of RA-ILD of 3.7% in ERAS and ERAN, two large RA inception cohorts, recruiting between 1986 and 2012 with maximum follow up 25 years. These findings extend the earlier report of RA-ILD from the ERAS cohort alone (8), and are in keeping with previous studies, including the UK BRILL network which reported 2 -3 % prevalence across its recruiting centers (10-12). ILD was already present at baseline assessment in 25 patients, representing 24.7% of the entire ILD group, these cases developing ILD either before or synchronously with first joint symptoms. This is similar to the UK BRILL cohort where 10% developed ILD before joint disease and 7% synchronously (10), and consistent with our earlier report from ERAS alone where ILD was present at baseline in 12/52 (23%) cases (8). Discrepancies may reflect the method of detection as

demonstrated by Gabbay et al who studied 36 patients with early RA and found abnormalities consistent with RA-ILD using a range of clinical, physiological and imaging modalities in 58%, but this was clinically significant in only 14% (9).

The results of the multvariate analysis concurred with other studies (8-11) in finding an association of incident RA-ILD with increasing age of RA onset, ever smoking and positive rheumatoid factor in the primary analysis and also male gender, baseline rheumatoid nodules and ESR on the extended analysis. As was found with our earlier report from ERAS alone (8), there was no association in the primary analysis between MTX exposure and incident RA-ILD, either on univariate or multivariate analyses. On the contrary MTX exposure was associated with significantly less RA-ILD in the extended analysis. This concurs with the meta analyses of RCTs by Conway et al who found no association of MTX use and ILD in RA and non-RA inflammatory diseases (13,14), with the prospective 2 year study reported by Dawson et al of 128 RA patients with established disease (17), and a recent report from the same group in 106 RA patients commencing MTX and followed for 10 years (26). The implication is to be especially vigilent for the development of RA-ILD in male patients who are RF positive, have nodules, a history of ever smoking and older age of RA diagnosis. MTX should only be witheld from RA patients with insufficient respiratory reserve to make it unlikely that they would survive hypersensitivity pneumonitis. Our findings refute concerns amongst clinicians that there is an association with MTX exposure and RA-ILD onset, and provide no justification to delay or deny patients MTX for fear of inducing RA-ILD while seeking specialist opinions or further investigations of potential respiratory disease or other comorbid features. Such delays are likely to worsen RA outcomes by unnecessarily denying patients the anchor csDMARD for this disease. Reassurance of the benign effect of MTX on established RA-ILD comes from no association found between MTX and hospitalised severe ILD episodes in USA National Databank for Rheumatic Diseases (27) and mortality from ILD in the USA Veterans Affairs Rheumatoid Arthritis Registry (28). Furthermore, a retrospective analysis of prognostic factors in 78 cases of RA-ILD, where MTX was specifically used as a therapeutic agent in 67%, found this to be strongly associated with survival (29).

Of interest is the finding of a significant association between incident RA-ILD and increased time from RA symptom onset to first outpatient visit on multivariate analysis in both the

primary analysis and extended cohort. Both of the other two measures of time to secondary care intervention, first RA symptom to first csDMARD and first outpatient appointment to first csDMARD, were consistent with this association, with the interval being a mean 3.42 and 2.56 months longer respectively in patients who subsequently developed ILD in the primary analysis. This is perhaps supportive of the so called 'window of opportunity' whereby a delay in treatment leads to worse outcomes. The explanation for the protective effect of baseline major co-morbidities (excluding respiratory) on incident RA-ILD in both the primary analysis and the extended cohort is not immediately apparent. We speculate that this might be explained by treatment differences, for example as malignancy was one of the more common major comorbidities, previous cancer therapies may have afforded immuno-suppressive effects.

Interestingly there was a trend for ILD to be less prevalent in the later 2002-2012 ERAN cohort (3.2%) than the 1986-2001 ERAS cohort (4.2%) based on a sample size of 101 cases. This is in contrast to a report of increasing prevalence over time among US veterans from 1985-2006, assumed due to increased awareness and investigation of respiratory symptoms coupled with increased survival (30,31). The reason for an apparent decrease in incident RA-ILD in ERAN is unclear, however it is noteworthy that this was seen despite a significant increase in two exacerbating factors, age of RA onset and current smoking, in ERAN compared to ERAS. MTX use was higher in ERAN, raising the intriguing question whether MTX may have had a protective effect on ILD development despite the higher risk factors in ERAN. This is supported by the time to event analysis where MTX exposure was associated with a significantly longer time to RA-ILD onset in the extended analysis and a trend supporting this in the primary analysis with fewer cases. A protective effect of MTX could have been due to better overall RA disease control than in the non-MTX exposed group, where the majority received SSZ and a minority hydroxychloroquine or leflunomide (20,21). This is supported by the lower DAS28 score at first record of ILD in MTX exposed compared to non-MTX exposed cases, although the difference was not significant. A positive influence of MTX is also supported by Rojas-Serrano et al who found a strong survival effect of MTX on established RA-ILD (29). Further evidence for an association between RA-ILD and worse disease control comes from the USA Rochester cohort followed up to 2006, where parameters indicative of more severe RA, such as ESR, nodules and destructive joint changes

were associated with ILD (11). Similarly, in the UK BRILL cohort anti-CCP antibodies showed the strongest association with ILD (10), this being a recognised marker of disease severity. Unfortunately there were insufficient numbers of ERAS/ERAN patients with baseline anti-CCP to assess the impact of this on ILD. However, we found higher baseline ESR to have a significant association with incident RA-ILD on univariate and multivariate analysis, this being mean 8.64 mmHg higher in patients who developed ILD in the primary analysis. Although the ERAS/ERAN cohorts were not designed to compare treatment effects, the conclusion from our findings is that MTX has no association with the development of RA-ILD and may lead to a delayed onset and lower incidence of RA-ILD perhaps as a consequence of better overall RA disease control, or specific lung mediated immune suppression

Strengths and Limitations of this study

The strength of this study is inherent in the nature of ERAS and ERAN, two real world large inception early RA cohorts, recruiting all-comers, treated according to contemporary best practice, with the rigour of regular standardised assessments and data collection allowing data to be pooled and analysed collectively. In contrast to RCTs the data from ERAS and ERAN are not restricted to defined RA populations with strict inclusion and exclusion criteria, nor to treatment strategies confined by protocol. ERAS and ERAN are also unique in size recruiting 2701 patients compared for example to 582 in the Rochester cohort (11), and in the long duration of follow up, adding to the strength of these analyses. The primary analysis of 67 incident RA-ILD cases allowed us to focus on the association with MTX by excluding cases with ILD occurring before any csDMARD use.

It is possible that treatment decisions, being at the discretion of each center, were influenced by channelling bias, whereby patients perceived to be at higher risk of RA-ILD, such as those with lung disease, might have been excluded from MTX exposure. However, there was no difference in MTX exposure between those with and without baseline respiratory co-morbidities, and MTX exposed patients were more likely to be current and ex smokers (Table 2), so this seems unlikely. We have assumed that all cases of ILD occurring at baseline were RA related. This would seem the most likely aetiology, especially in those where the onset was synchronous with joint disease, but potentially other causes might have explained ILD. As ERAS closed to follow up in 2011 and ERAN in 2013 it is possible that

new cases of RA-ILD were missed after last CRF and pre death. However, we have reported RA-ILD survival to be a median of 3 years (5 year survival 38.8%) in ERAS (8) and with last CRF 2011-2013 and latest death certification reports included up to June 2018 it is not likely that many new cases in this period have been missed. Nonetheless we have had to exclude 9 RA-ILD cases from analysis, as we could not confirm that they remained non-MTX exposed, given lack of follow up data between last CRF + 2 years and death when RA-ILD was first notified. Our incident RA-ILD cases available for analysis are therefore lower than reality. A further limitation of the data is the lack of external confirmation of ILD case verification, this being dependent on the reporting of ILD by each center on the CRF, or the doctor completing the death certificate. Whilst the diagnosis of ILD is strongly influenced by investigations, with incrementally increasing detection from clinical signs to pulmonary function tests and HRCT images, and much sub clinical disease being present (5,9), we believe that the specific diagnostic features of ILD and thoroughness of clinical work up by recruiting centers were sufficient to have confidence in the accuracy of ILD reporting. Furthermore, credibility of ILD reporting in ERAS/ERAN is gained from the prevalence being in keeping with other cohorts where it was possible to independently verify the diagnosis for each case (9-12). Another limitation is that smoking status was missing in a large proportion of ERAS patients, because its importance was not appreciated at the time data was collected in the 1980s. However, the sensitivity analysis, running the multivariate model stratified by smoking status at baseline, did not change the lack of association between MTX and RA-ILD onset.

In conclusion we report a prevalence of RA-ILD in the ERAS/ERAN cohorts of 3.7% with independent significant incident associations in line with other studies, namely older age of RA onset, ever smoking, nodules, RF positivity, male gender, and high ESR. We also show a significant association of incident RA-ILD with a longer time from first RA symptoms to secondary care intervention supporting the 'window of opportunity'. We have found no association between MTX treatment and incident RA-ILD, and on the contrary provide evidence suggestive that MTX exposed RA patients may have a delayed onset of ILD. There seems no reason to confuse the association of MTX and hypersensitivity pneumonitis with the onset of RA-ILD. Assuming baseline lung function is sufficient to withstand an episode of

hypersensitivity pneumonitis, there are no other respiratory contraindications to the use of this very effective 'anchor' csDMARD in patients with RA.

Key messages

- In ERAS/ERAN, incident RA-ILD is significantly associated with older age of RA onset, ever smoking, nodules, RF positivity, male gender, ESR, and a longer time from first RA symptoms to first secondary care visit.
- There is no association between incident RA-ILD and MTX treatment
- MTX may have a protective role in delaying the onset of RA-ILD

Conflicts of Interest

The authors have no conflicts of interest to declare

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Author Contributions Statement

PK: Conception of work, data interpretation, manuscript drafting

AB, KS Statistical analysis, data interpretation, manuscript revision

EN, AY Statistical support, data interpretation, manuscript revision

DW, PC, JD data interpretation, manuscript revision

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Data Statement

Dataset available from Prof A. Young, Center for Health Services and Clinical Research and Post Graduate Medicine, University of Hertfordshire, Hatfield, UK

Figure Legends

Figure 1

Diagram showing patient selection and allocation to MTX exposed and non-MTX exposed groups

Figure 2

Cox proportional time to event analysis showing time of onset of RA-ILD from first joint symptoms of RA in MTX exposed and non-MTX exposed groups. Primary analysis: cases with RA-ILD first recorded after any csDMARD exposure, n=67

Figure 3

Cox proportional time to event analysis showing time of onset of RA-ILD from first joint symptoms of RA in MTX exposed and non-MTX exposed groups. Extended cohort; all cases with RA-ILD including those diagnosed at baseline before any csDMARD exposure, n=92

Table 1. Demographic features of the ERAS and ERAN cohorts

		Total		ERAS		ERAN		Chi-squared p-value
Number		2701		1465		1236		
Gender	Male	893	33.1%	492	33.6%	401	32.4%	0.530
	Female	1808	66.9%	973	66.4%	835	67.6%	
Age of RA onset	<55	1146	42.4%	659	45.0%	487	39.4%	0.013
	56-64	728	27.0%	380	25.9%	348	28.2%	
	65+	827	30.6%	426	29.1%	401	32.4%	
Baseline Smoker Status	Never	995	36.8%	528	36.0%	467	37.8%	<0.001
	Current	594	22.0%	179	12.2%	415	33.6%	
	Ex-Smoker	518	19.2%	209	14.3%	309	25.0%	
	Other	26	1.0%			26	2.1%	
	Missing	568	21.0%	549	37.5%	19	1.5%	
MTX Exposure	No	1114	41.2%	857	58.5%	257	20.8%	<0.001
	Yes	1578	58.4%	602	41.1%	976	79.0%	
	Missing	9	0.3%	6	0.4%	3	0.2%	
ILD Diagnosis	No	2600	96.3%	1404	95.8%	1196	96.8%	0.206
	Yes	101	3.7%	61	4.2%	40	3.2%	

Key

RA: rheumatoid arthritis, MTX: methotrexate, ILD: Interstitial Lung disease

Table 2. Demographic features of MTX exposed and non-MTX exposed cases

		Total		Non-MTX exposed		MTX exposed		Chi-squared p-value
Total		2692		1114		1578		
Gender	Male	1804	67.0%	721	64.7%	1083	68.6%	0.034
	Female	888	33.0%	393	35.3%	495	31.4%	
Age of RA onset	<55	1144	42.5%	436	39.1%	708	44.9%	<0.001
	55-64	723	26.9%	277	24.9%	446	28.3%	
	65+	825	30.6%	401	36.0%	424	26.9%	
Baseline Smoking Status	Never	991	36.8%	346	31.1%	645	40.9%	0.058
	Current	594	22.1%	179	16.1%	415	26.3%	
	Ex-smoker	518	19.2%	172	15.4%	346	21.9%	
	Other	25	0.9%	2	0.2%	23	1.5%	
	Missing	564	21.0%	415	37.3%	149	9.4%	
Baseline Erosions	No erosions	1883	69.9%	808	72.5%	1075	68.1%	0.117
	Erosions	699	26.0%	276	24.8%	423	26.8%	
	Missing	110	4.1%	30	2.7%	80	5.1%	
Baseline RF	-ve	977	36.3%	462	41.5%	515	32.6%	<0.001
	+ve	1633	60.7%	628	56.4%	1005	63.7%	
	Missing	82	3.0%	24	2.2%	58	3.7%	
Baseline Nodules	None	2515	93.4%	1057	94.9%	1458	92.4%	0.010
	Nodules	177	6.6%	57	5.1%	120	7.6%	
Baseline DAS	<1.6	31	1.2%	5	0.4%	26	1.6%	<0.001
	1.6-2.59	298	11.1%	163	14.6%	135	8.6%	
	2.6-3.2	345	12.8%	180	16.2%	165	10.5%	
	>3.2-4.19	543	20.2%	243	21.8%	300	19.0%	
	4.2-5.1	-	-	-	-	-	-	
	>5.1	1415	52.6%	503	45.2%	912	57.8%	
	Missing	60	2.2%	20	1.8%	40	2.5%	

Table 3 Multivariate logistic analysis showing co-variates independently associated with RA-ILD development

	Primary analysis, RA-ILD onset after any csDMARD exposure, n=67	Wald test	Extended cohort, including RA-ILD onset pre any csDMARD, n=92	Wald test
	O.R. (95% C.I.)	p value	O.R. (95% C.I.)	p value
Methotrexate exposure	0.85 (0.49, 1.49)	0.578	0.48 (0.3, 0.79)	0.004
Age RA onset	1.04 (1.02, 1.06)	<0.001	1.04 (1.02, 1.06)	<0.001
Smoking, ever, baseline	2.21 (1.21, 4.03)	0.01	1.91 (1.13, 3.25)	0.016
Male gender	1.44 (0.83, 2.48)	0.193	1.74 (1.05, 2.86)	0.03
RF positive, baseline	2.02 (1.07, 3.82)	0.029		n.s.
RA nodules, baseline		n.s.	2.19 (1.08, 4.41)	0.029
Onset - OPD	1.04 (1.00, 1.07)	0.027	1.03 (1.0, 1.07)	0.04
Baseline major co-morbidities*	0.62 (0.40, 0.95)	0.027	0.67 (0.46, 0.98)	0.037
Baseline ESR	-	n.s.	1.01 (1.0, 1.02)	0.047

Note: Variables not reported did not reach statistical significance in the respective models.

Key

RF: rheumatoid factor,

Onset - OPD: time from first RA symptoms to first hospital out patient appointment

*excluding respiratory

Table 4 Cox regression time to event analysis showing associations of methotrexate exposure and baseline co-variates with time from RA first symptoms to RA-ILD onset

	Primary analysis, RA-ILD onset after any csDMARD exposure, n=67		Extended cohort, including RA-ILD onset pre any csDMARD, n=92	
	H.R. (95% C.I.)	p value	H.R. (95% C.I.)	p value
Methotrexate exposure	0.54 (0.28, 1.06)	0.072	0.41 (0.23, 0.75)	0.004
Age RA onset	1.03 (1, 1.06)	0.048	1.03 (1, 1.06)	0.028
Smoking, ever, baseline	1.09 (0.52, 2.26)	0.817	1.16 (0.61, 2.22)	0.654
Male gender	1.02 (0.51, 2.03)	0.966	0.85 (0.47, 1.54)	0.587
RF positive, baseline	0.96 (0.69, 1.32)	0.799	1.08 (0.85, 1.38)	0.512
Onset - OPD	0.98 (0.94, 1.03)	0.424	0.98 (0.94, 1.02)	0.276
Baseline major co-morbidities*	1.26 (0.69, 2.28)	0.452	1.09 (0.63, 1.9)	0.762

Key

RF: rheumatoid factor,

Onset - OPD: time from first RA symptoms to first hospital out patient appointment

*excluding respiratory

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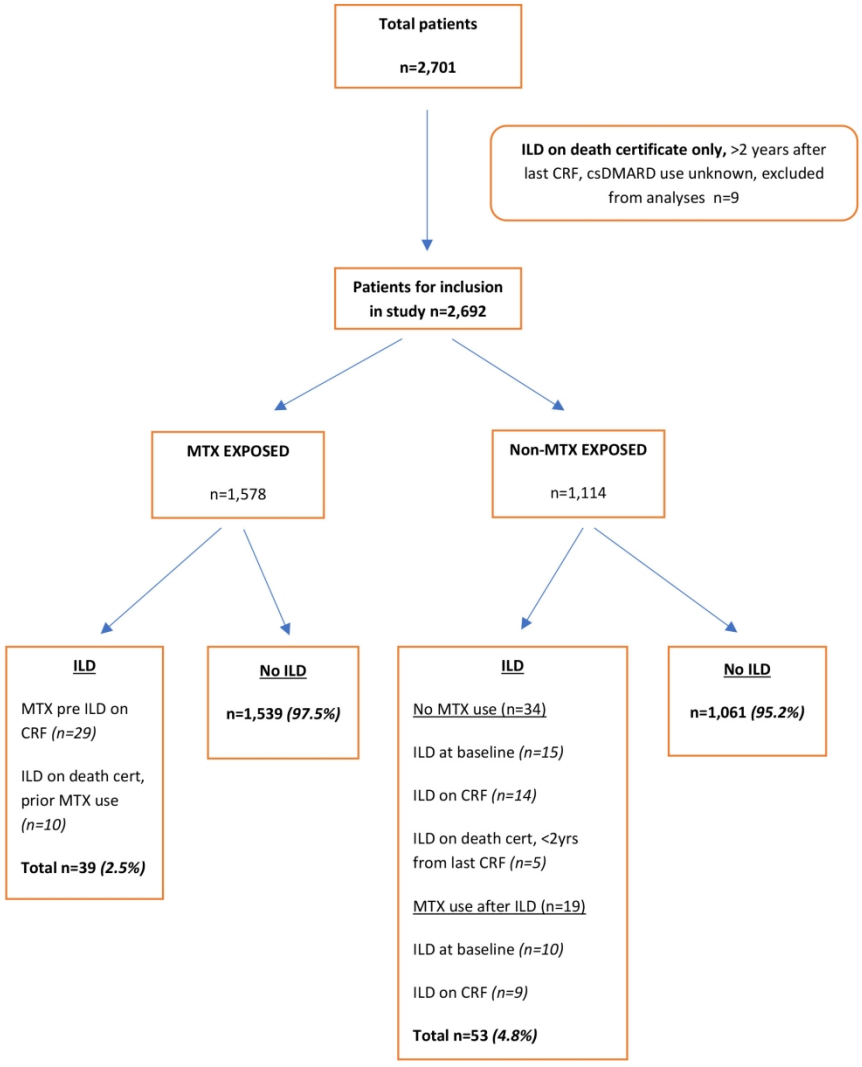

Figure 1

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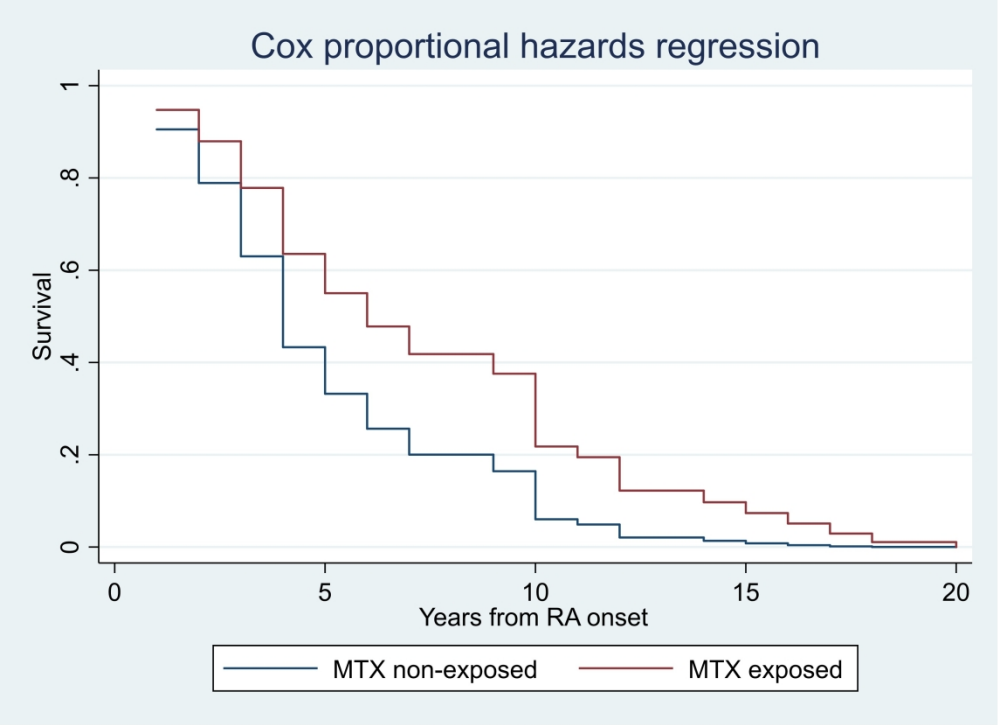

Figure 2

875x636mm (96 x 96 DPI)

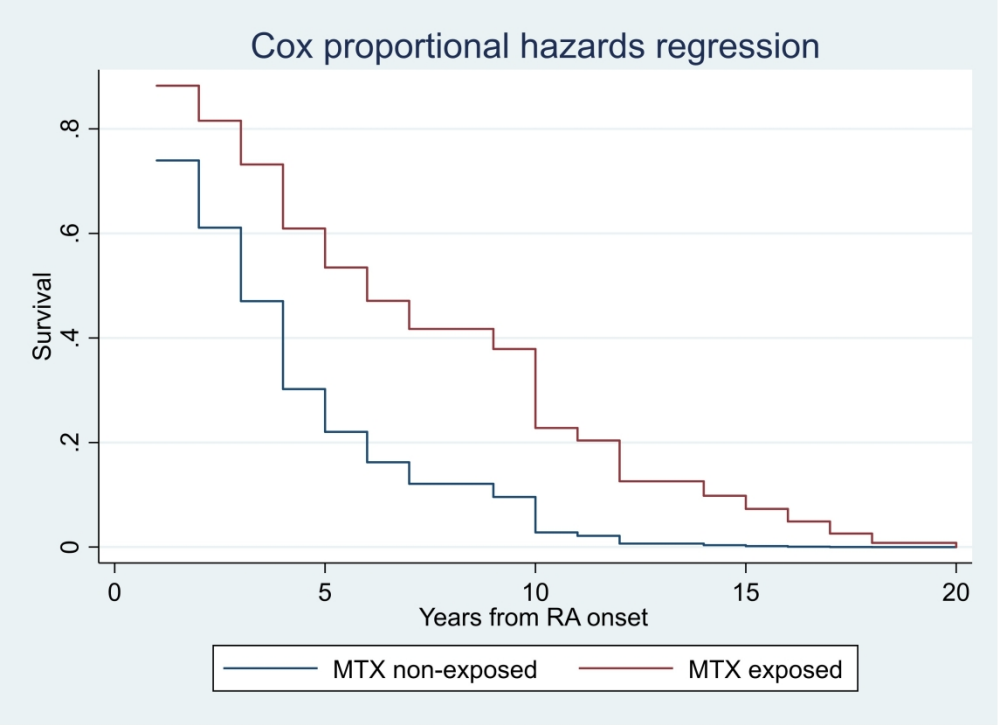

Figure 3

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Supplementary Material

Statistical analyses

Univariate analysis

The relation between onset of RA-ILD and binary covariates [MTX exposure, gender, baseline: rheumatoid factor (RF, positive/negative), smoking status (ever/never), presence of nodules, extra articular RA major, minor and combined, respiratory major, minor and combined, presence of erosions] was analysed by Chi Squared test, and continuous covariates [age of RA onset, baseline: disease activity score (DAS), ESR, tender joint count (TJC), swollen joint count (SJC), patient global assessment (PGA), Hb, BMI, health assessment questionnaire score (HAQ), number of comorbidities major, minor and combined (including respiratory), number of major comorbidities (excluding respiratory), time from RA symptom onset to first outpatient appointment (months), time from first outpatient appointment to first DMARD (months), time from RA symptom onset to first DMARD (months)] was analysed by t test.

Multivariate analysis model

Binary logistic models were fitted to the data, using the diagnosis of ILD as the outcome variable to examine possible differences within the variables The initial covariates included were: MTX exposure (Y/N), gender (M/F), age at onset of RA (years), and presence of rheumatoid factor at baseline (+ve/-ve). Additional covariates were added to the model in turn, to assess whether they improved the model fit. It was not possible to use log likelihood ratio tests (LRTs) to compare models because of varying levels of missing data. Instead, the p-value from each covariate's Wald test was considered, to determine whether there was evidence to include them in the model, as well as assessing whether the odds ratios for other covariates had changed. All covariates significant ($p<0.05$) and borderline significant ($p<0.1$ and >0.05) in the univariate analysis were tested and also some non significant covariates in the univariate analysis were included because they might be of clinical interest (DAS, Hb, TJC,

SJC and PGA, all at baseline). Anti-cyclic citrullinated peptide (anti CCP) antibody data was only collected at a few centres and was insufficient to include in any model.

Multivariate time-varying analysis

Cox proportional hazards models were applied to the data, with the diagnosis of ILD as the binary outcome variable at each year (measured from baseline) that a patient participated in the study. 54 (53.5%) patients of the 101 with ILD had known diagnosis dates or could be approximated to the nearest year. This was up to a maximum of 15 years, to match the time-varying data available for analysis. Of the 54, 48 were diagnosed during the study and so were included within the fitted models. The fixed covariates considered were: gender (M/F), age at onset of RA (years), maximum follow-up (years) and smoking status at baseline (ever/never). Time varying co-variates were DAS, patient global assessment, tender joint count, swollen joint count, ESR, health assessment questionnaire, haemoglobin, BMI, erosions, rheumatoid nodules, major comorbidities. Age at onset of RA, baseline smoking status and maximum follow-up were found to be statistically significant in combination, with all three hazard ratios >1 and all corresponding p-values <0.03. However, maximum follow-up was discounted from the model since adding any time-varying covariates removed its significance. Sex was selected a priori to be in the model to improve precision.

Next, time-varying covariates were considered: MTX exposure (Y/N), DAS (and individually PGA, TJC, SJC and ESR), HAQ, haemoglobin (g/L), presence of rheumatoid factor (RF, +ve/-ve), presence of erosions (Y/N), presence of nodules (Y/N), BMI and number of major comorbidities (excluding respiratory). The model was built by individually adding each covariate, then examining its hazard ratio and corresponding p-value to assess for statistical significance. The components of DAS were assessed both individually and in combination. Covariates were retained if $p<0.1$. Akaike information criterion (AIC) was used to compare the fit of each interim model to those previously fitted, with the final model having the lowest AIC value.

Cox regression time to event analysis

The relation between time of ILD diagnosis after first RA symptoms was explored in the MTX exposed ILD and non-MTX exposed ILD groups using Cox regression time to event analysis, adjusting for the same confounders as in the multivariate model. The time of onset of ILD in relation to first symptoms of RA was taken as the first record of this on the ERAS/ERAN CRF.

Where ILD was recorded on the death certificate but not on the last CRF this time was recorded as last CRF + 1 year if the interval was less than 2 years, and as last CRF + 2 years if this interval was 2 years or longer. In patients with ILD at baseline the time of ILD onset was taken to be synchronous with first RA symptoms.

Supplementary Table 1

ERAS ERAN reasons for discontinuation from follow up

	All ERAS + ERAN		Cohort			
			ERAS		ERAN	
	n	%	n	%	n	%
Reason for discontinuation	2701	100%	1465	100%	1236	100%
Died	491	18%	360	25%	131	11%
Lost to follow up	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%

Supplementary Table 2a.

Primary univariate analysis showing association of incident RA-ILD with MTX exposure and baseline binary covariates, excluding cases with ILD at baseline prior to any csDMARD use.

		n	ILD		No ILD		Odds Ratio	CI	Chi-squared test p-value
			n	%	n	%			
Total			67		2600				
MTX	Yes	2667	39	58.2%	1539	59.2%	0.96	(0.57, 1.63)	0.872
	No		28	41.8%	1061	40.8%			
Gender	M	2667	30	44.8%	844	32.5%	1.69	(1.00, 2.83)	0.034
	F		37	55.2%	1756	67.5%			
Rheumatoid Factor	Positive	2588	52	77.6%	1568	60.3%	2.11	(1.16, 4.06)	0.010
	Negative		15	22.4%	953	36.7%			
Anti CCP (ever)	Positive	330	6	9.0%	225	8.7%	1.29	(0.23, 13.51)	0.755
	Negative		2	3.0%	97	3.7%			
Smoker Status	Ever	2106	41	61.2%	1081	41.6%	2.29	(1.25, 4.41)	0.004
	Never		16	23.9%	968	37.2%			
Rheumatoid Nodules	None	2667	57	85.1%	2436	93.7%	2.61	(1.16, 5.27)	0.005
	Nodules		10	14.9%	164	6.3%			
Extra-Articular RA features	Yes	2667	11	16.4%	286	11.0%	1.59	(0.74, 3.14)	0.164
	No		56	83.6%	2314	89.0%			
Respiratory comorbidities	Yes	2667	7	10.4%	134	5.2%	2.15	(0.81, 4.83)	0.056
	No		60	89.6%	2466	94.8%			
Erosions at baseline	Yes	2560	18	26.9%	673	25.9%	0.99	(0.54, 1.75)	0.981
	No		49	73.1%	1820	70.0%			

Key

csDMARD: conventional synthetic disease modifying anti-rheumatic drug, MTX: methotrexate, CCP: anti-cyclic citrullinated peptide antibody

Extra-Articular RA features: Tendon sheath disease, Sjogren's syndrome, ocular rheumatoid disease, Raynaud's

Respiratory comorbidities: History of chronic obstructive pulmonary disease, asthma, pneumonia, tuberculosis, pleural disease

Supplementary Table 2b.

Primary univariate analysis showing association of incident RA-LD with baseline continuous covariates, excluding cases with ILD at baseline prior to any DMARD use.

	n	ILD			No ILD			Difference	t-test p-value
		N	Mean	CI	N	Mean	CI		
Age of RA onset (years)	2667	67	61.01	(58.45, 63.58)	2600	55.87	(55.32, 56.42)	5.14	0.004
DAS28	2607	66	4.43	(4.04, 4.82)	2541	4.38	(4.32, 4.45)	0.05	0.821
ESR	2473	63	45.51	(38.76, 52.26)	2410	36.87	(35.77, 37.96)	8.64	0.014
TJC	2656	66	10.74	(7.89, 13.60)	2590	10.14	(9.77, 10.52)	0.6	0.623
SJC	2659	67	11.46	(8.70, 14.22)	2592	12.21	(11.76, 12.67)	-0.75	0.608
PGA	2608	66	48.35	(42.08, 54.62)	2542	43.63	(42.62, 44.64)	4.72	0.146
Hb	2627	67	12.93	(12.55, 13.31)	2560	12.85	(12.79, 12.91)	0.08	0.659
Onset-OPD (months)	2642	67	9.78	(7.96, 11.59)	2575	8.22	(7.98, 8.47)	1.56	0.053
OPD-csDMARD (months)	2357	61	8.13	(2.66, 13.60)	2296	5.57	(4.95, 6.19)	2.56	0.197
Onset-csDMARD (months)	2361	62	17.76	(12.27, 23.25)	2299	14.34	(13.58, 15.09)	3.42	0.151
Comorbidities (major)	2667	67	0.43	(0.30, 0.57)	2600	0.49	(0.46, 0.52)	-0.06	0.532
Comorbidities (minor)	2667	67	0.46	(0.31, 0.61)	2600	0.33	(0.31, 0.35)	0.13	0.053
Comorbidities (combined)	2667	67	0.9	(0.69, 1.10)	2600	0.82	(0.87, 0.86)	0.08	0.542

Comorbidities major excluding respiratory	2667	67	0.33	(0.21, 0.45)	2600	0.47	(0.44, 0.50)	-0.14	0.127
BMI	2356	56	25.98	(24.70, 27.25)	2300	26.56	(26.35, 26.76)	-0.58	0.390
HAQ	2625	67	1.28	(1.10, 1.45)	2558	1.11	(1.08, 1.14)	0.17	0.090

Key

DAS28: 28 joint disease activity score, ESR: erythrocyte sedimentation rate, TJC: tender joint count, SJC: swollen joint count, PGA: patient global assessment, Hb: haemoglobin, BMI: body mass index, HAQ: health assessment questionnaire, Onset-OPD: time from first RA symptoms to first secondary care outpatient visit, OPD-csDMARD: time from first secondary care outpatient visit to start of conventional synthetic disease modifying anti-rheumatic drug therapy, Onset-csDMARD: time from first RA symptoms to start of conventional synthetic disease modifying anti-rheumatic drug therapy, Co-morbidities major and minor: as per ICD 10 definitions.

Supplementary Table 3a.

Univariate analysis showing association of incident RA-ILD with MTX exposure and baseline binary covariates, extended data set including RA-ILD cases recorded at baseline

		n	ILD		No ILD		Odds Ratio	CI	Chi-squared test p-value
			n	%	n	%			
MTX	Yes	2692	39	2.5%	1539	97.5%	0.51	(0.32, 0.79)	0.001
	No		53	4.8%	1061	95.2%			
Gender	M	2692	44	5.0%	844	95.0%	1.91	(1.23, 2.96)	0.002
	F		48	2.7%	1756	97.3%			
Rheumatoid Factor	Positive	2610	65	4.0%	1568	96.0%	1.65	(1.01, 2.77)	0.038
	Negative		24	2.5%	953	97.5%			
Anti-CCP (ever)	Positive	333	9	3.8%	225	96.2%	1.94	(0.39, 18.74)	0.394
	Negative		2	2.0%	97	98.0%			
Smoker Status	Ever	2692	56	4.9%	1081	95.1%	2.18	(1.31, 3.74)	0.002
	Never		23	2.3%	968	97.7%			
Rheumatoid Nodules	None	2692	79	3.1%	2436	96.9%	2.44	(1.22, 4.54)	0.003
	Nodules		13	7.3%	164	92.7%			

Extra-Articular RA features	Yes	2692	11	3.7%	286	96.3%	1.10	(0.54-2.10)	0.774
	No		81	3.4%	2314	96.6%			
Respiratory co-morbidities	Yes	2692	7	5.0%	134	95.0%	1.52	(0.58-3.35)	0.299
	No		85	3.3%	2466	96.7%			
Erosions at baseline	Yes	2582	26	3.7%	673	96.3%	1.12	(0.67-1.81)	0.644
	No		63	3.3%	1820	96.7%			

Key

MTX: methotrexate, CCP: anti-cyclic citrullinated peptide antibody

Extra-Articular RA features: Tendon sheath disease, Sjogren's syndrome, ocular rheumatoid disease, Raynaud's

Respiratory comorbidities: History of chronic obstructive pulmonary disease, asthma, pneumonia, tuberculosis, pleural disease

Supplementary Table 3b.

Univariate analysis showing association of incident RA-ILD with baseline continuous covariates, extended data set including RA-ILD cases recorded at baseline

	N	ILD			No ILD			Difference	t-test
		n	Mean	CI	N	Mean	CI		p-value
Age RA onset (years)	2692	92	62.8	(60.68, 64.95)	2600	55.87	(55.32, 56.42)	6.93	<0.0001
DAS28	2495	91	4.51	(4.17, 4.85)	2541	4.38	(4.32, 4.45)	0.13	0.445
ESR	2495	85	47.38	(41.33, 53.42)	2410	36.87	(35.77, 37.96)	10.51	0.001
TJC	2681	91	10.92	(8.55, 13.30)	2590	10.14	(9.77, 10.52)	0.78	0.455
SJC	2684	92	12.32	(9.64, 14.99)	2592	12.21	(11.76, 12.67)	0.11	0.935
PGA	2632	90	46.66	(41.35, 51.96)	2542	43.63	(42.62, 44.64)	3.03	0.2786
Hb	2652	92	12.8	(12.48, 13.13)	2560	12.85	(12.79, 12.91)	-0.05	0.798
Onset-OPD (months)	2666	91	9.16	(7.69, 10.64)	2575	8.22	(7.98, 8.47)	0.94	0.174
OPD-csDMARD (months)	2379	83	7.14	(2.93, 11.36)	2296	5.57	(4.95, 6.19)	1.57	0.356
Onset-csDMARD (months)	2383	84	16.49	(12.13, 20.85)	2299	14.34	(13.58, 15.09)	2.15	0.294
Comorbidities major	2692	92	0.48	(0.35, 0.60)	2600	0.49	(0.46, 0.52)	-0.01	0.863
Comorbidities minor	2692	92	0.4	(0.28, 0.52)	2600	0.33	(0.31, 0.35)	0.07	0.212
Comorbidities combined	2692	92	0.8	(0.63, 0.98)	2600	0.82	(0.87, 0.86)	-0.02	0.949

Comorbidities major excluding respiratory	2692	92	0.4	(0.28, 0.52)	2600	0.47	(0.44, 0.50)	-0.07	0.394
BMI baseline	2377	77	25.9	(24.82, 26.98)	2300	26.56	(26.35, 26.76)	-0.66	0.256
HAQ at baseline	2650	92	1.22	(1.07, 1.37)	2558	1.11	(1.08, 1.14)	0.11	0.2024

Key

DAS28: 28 joint disease activity score, ESR: erythrocyte sedimentation rate, TJC: tender joint count, SJC: swollen joint count, PGA: patient global assessment, Hb: haemoglobin, BMI: body mass index, HAQ: health assessment questionnaire, Onset-OPD: time from first RA symptoms to first secondary care outpatient visit, OPD-csDMARD: time from first secondary care outpatient visit to start of conventional synthetic disease modifying anti-rheumatic drug therapy, Onset-csDMARD: time from first RA symptoms to start of conventional synthetic disease modifying anti-rheumatic drug therapy, Co-morbidities major and minor: as per ICD-10 definitions.

Supplementary Table 4

Multivariate analysis stratified by smoking; showing effects of baseline co-variates on incident RA-ILD in smokers, non-smokers and those with missing smoker status at baseline.

	Overall		Non-smokers		Smokers		Missing	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
N	2015		949		1066		552	
Methotrexate exposed	0.85 (0.49, 1.49)	0.578	0.24 (0.08, 0.70)	0.009	1.56 (0.74, 3.29)	0.240	1.35 (0.33, 5.52)	0.681
Male gender	1.44 (0.83, 2.48)	0.193	0.70 (0.20, 2.52)	0.587	1.8 (0.95, 3.41)	0.073	1.38 (0.38, 5.02)	0.629
Age of RA onset	1.04 (1.02, 1.06)	<0.001	1.03 (0.99, 1.07)	0.097	1.05 (1.02, 1.08)	0.001	1.03 (0.99, 1.08)	0.172
Baseline RF	2.02 (1.07, 3.82)	0.029	1.88 (0.64, 5.57)	0.254	2.20 (1.00, 4.86)	0.051	2.83 (0.58, 13.85)	0.199
Onset-OPD (months)	1.04 (1.00, 1.07)	0.027	1.005 (0.93, 1.08)	0.902	1.05 (1.01, 1.09)	0.012	0.98 (0.87, 1.10)	0.699
Baseline Major Comorbidities (Excl Resp)	0.62 (0.40, 0.95)	0.027	0.43 (0.15, 1.24)	0.119	0.64 (0.4, 1.04)	0.070	0.30 (0.04, 2.39)	0.254
Baseline Smoker Status	2.21 (1.21, 4.03)	0.010						
Constant	0.0009 (0.0002, 0.005)	<0.001	0.005 (0.0004, 0.07)	<0.001	0.0006 (0.00008, 0.005)	<0.001	0.002 (0.00006, 0.05)	<0.001

Key

RA: Rheumatoid arthritis, RF: rheumatoid factor

Supplementary Table 5

Multivariate time varying analysis best fit model showing the association of fixed and time-varying co-variates on incident RA-ILD.

		Hazard Ratio (95% CI)	p
Fixed	Age of RA onset	1.07 (1.02, 1.11)	0.002
	Baseline Smoker Status	1.52 (0.61, 3.79)	0.365
	Gender (male)	1.19 (0.47, 2.99)	0.712
Time-varying	Methotrexate	0.96 (0.82, 1.12)	0.629
	Rheumatoid Factor	1.05 (0.96, 1.15)	0.279
	HAQ	1.15 (1.04, 1.26)	0.007
	ESR	1 (1, 1.01)	0.01
	SJC	0.99 (0.98, 1)	0.058

Legend

HAQ Health Assessment Questionnaire; ESR erythrocyte sedimentation rate; SJC swollen joint count