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ORIGINAL RESEARCH

Increased mortality in patients with RA-associated interstitial lung disease: data from a French administrative healthcare database

Pierre-Antoine Juge ,[1,2] Lidwine Wémeau-Stervinou,[3] Sebastien Ottaviani,[1] Guillaume Desjeux,[4] Joe Zhuo,[5] Virginie Vannier-Moreau,[6] René-Marc Flipo ,[7] Bruno Crestani,[8] Philippe Dieudé [1,2]

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For numbered affiliations see end of article.

Correspondence to
Dr Pierre-Antoine Juge; pierreantoine.juge@aphp.fr

ABSTRACT

Objectives Interstitial lung disease (ILD) is a severe extra-articular manifestation of rheumatoid arthritis (RA). The objectives of this study were to estimate mortality rate in patients with RA-ILD and identify factors affecting mortality.

Methods Data from a French national claims database (Système National des Données de Santé) from 2013 to 2018 were analysed. Adults with an RA diagnosis (International Classification of Diseases (ICD)-10 codes M05, M06.0, M06.8 and M06.9) were included. ILD diagnosis was defined with ICD-10 code J84. Mortality rates were compared between patients with RA with and without ILD, using Cox proportional hazards regression, after matching 1:1 for age, sex, age at RA-ILD onset and RA duration.

Results Among 173 132 patients with RA, 4330 (3%) also had ILD (RA-ILD). After matching, RA-ILD was associated with an increased mortality rate (HR 3.4, 95% CI 3.1 to 3.9). The HR for mortality was greater for: patients aged <75 years (HR 4.8, 95% CI 3.9 to 5.9) versus ≥75 years (HR 3.0, 95% CI 2.6 to 3.5); patients with ILD onset occurring before RA onset (HR 8.4, 95% CI 5.5 to 13.0) versus ILD onset occurring after RA onset (HR 2.9, 95% CI 2.6 to 3.3); and men (HR 5.2, 95% CI 4.4 to 6.2) versus women (HR 3.6, 95% CI 3.0 to 4.2).

Conclusion In this nationwide cohort study, RA-ILD was associated with increased mortality rate (vs in patients with RA without ILD), notably for those aged <75 years, those whose ILD preceded RA onset and men.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Rheumatoid arthritis (RA) associated with interstitial lung disease (ILD; RA-ILD) is an extra-articular manifestation with poor prognosis.

WHAT THIS STUDY ADDS

⇒ The current data highlight an increased mortality associated with RA-ILD compared with RA alone, for patients aged <75 years, in patients whose ILD preceded RA onset and in male patients.

⇒ RA treatment strategies are largely discordant by ILD status.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Such observations warrant the development of international treatment guidelines for patients with RA-ILD.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disease with an estimated global prevalence of 0.5% among adults.[1] Extra-articular manifestations are observed in about 50% of patients with RA, with interstitial lung disease (ILD) being one of the most frequent.[2 3] Frequency estimates of ILD among patients with RA (RA-ILD) vary considerably in the literature, from 2% to 50%.[4–9] This variability is due to several factors, such as the lack of consensus regarding the definition of RA-ILD (ie, clinical vs subclinical ILD), heterogeneity of the tools used to assess ILD (eg, chest X-ray, high-resolution CT (HRCT), pulmonary function tests), heterogeneity of the RA population and different methodological approaches (ie, small cohort studies vs national healthcare database).

RA-ILD is a severe condition. ILD has been associated with a 2-fold to 10-fold increase in mortality in patients with RA; the median survival time for patients with RA-ILD ranges from 3 to 10 years.[10–14] RA-ILD is a heterogeneous disease with various progression profiles. Progression of RA-ILD is observed in about half of all patients over a 4-year period, meaning that the other half maintains stable lung disease.[15 16] Factors associated with mortality in patients with RA-ILD have been poorly investigated. Older age, higher RA

disease activity, lower baseline diffusing capacity of carbon monoxide and lower forced vital capacity and some chest HRCT scan features (usual interstitial pneumonia pattern, presence of fibrotic features and extension of abnormalities) have been associated with an increased mortality in patients with RA-ILD.[13–15 17 18] However, most of the studies dedicated to the evaluation of mortality in RA-ILD are small, retrospective case–control studies, thereby limiting interpretation of results.

Existing healthcare databases provide accessible, real-world observations that can be used to advance our current knowledge of RA-ILD. The objectives of this study were to estimate the prevalence, incidence and mortality rate for patients with RA-ILD, and to identify independent risk factors affecting mortality in patients with RA-ILD, using data from a French national healthcare claims database.

METHODS

Study design and data source

This retrospective analysis used the Système National des Données de Santé (SNDS), a French national healthcare claims database containing data from approximately 97% of the French population.[19] The SNDS database includes: (1) data regarding diseases, discharges, diagnoses and disability status allowing full expenditure reimbursement, coded using the International Classification of Diseases, 10th revision, Clinical Modification (ICD-10-CM) codes, (2) mortality date and (3) medical treatment information made available from drug reimbursement. Investigators had access to patient records as defined by the patient population below. Data from 1 January 2013 to 31 December 2018 were included in the current analysis. No data cleaning methods were required.

Patient population

Validated ICD-10-CM codes were used to identify patients in the SNDS database.[20] Adults with an RA diagnosis (ICD-10-CM codes M05 (RA with rheumatoid factor), M06.0 (RA without rheumatoid factor), M06.8 (other specified RA) and M06.9 (RA unspecified)) and ≥2 distinct delivery dates of disease-modifying antirheumatic drugs (DMARDs) were included. DMARDs included were abatacept, adalimumab, anakinra, azathioprine, baricitinib, certolizumab pegol, cyclophosphamide, ciclosporin, etanercept, golimumab, hydroxychloroquine, infliximab, leflunomide, methotrexate (MTX), rituximab, sulfasalazine, tocilizumab and tofacitinib. Onset of RA was defined as the first date of occurrence between RA diagnosis and the first known DMARD reimbursement. For patients with RA-ILD, ILD diagnosis was defined using the ICD-10-CM code J84 (other interstitial pulmonary diseases) and as having ≥1 CT scan during the observation period. RA-ILD was defined as ILD before RA: when the first code of J84 occurred prior to RA; ILD after RA: when the first date of RA was prior to the first occurrence date of J84 code; and ILD concurrent with RA: when the difference between the occurrence dates was 1 year or less. To be included, the patient had to receive reimbursements ≥6 months after the onset of RA-ILD, except if the patient died. Patients with adult-onset Still's diseases (M06.1), rheumatoid bursitis (M06.2) or inflammatory polyarthropathy (M06.4) were excluded.

Endpoints and assessments

For the overall study population, demographic characteristics, prevalence of RA-ILD (2013–2018), incidence of RA-ILD (2014–2018) and mortality (2013–2018) were examined. Timing of ILD onset relative to RA diagnosis was assessed for patients with RA-ILD.

Statistical analysis

Descriptive statistics (mean (SD)) and proportions were used to describe the cohort. The prevalence and incidence of RA-ILD were estimated per 100 000 inhabitants and 100 000 person-years, respectively. Characteristics of patients with RA-ILD and patients with RA but without ILD (RA-noILD) were compared in a univariate analysis using a χ^2 test. Cox proportional hazards regression was used to estimate HRs and corresponding 95% CIs for mortality rate in the matched population. Mortality was evaluated according to age, sex and temporality of ILD onset, compared with RA onset. Sensitivity analyses were performed by estimating HRs after matching for diabetes, arterial disease, dyslipidaemia and cardiac disease, with p values determined by log rank test. To control for potential confounding, a subgroup of patients was matched 1:1 for age, sex, year of birth and duration of RA. If no match was possible between the two populations (RA-ILD and RA-noILD), the observation was deleted.

All statistical analyses were conducted using SAS-Guide V.9.4 software (Statistical Analysis System, Cary, North Carolina, USA).

Patient and public involvement

Given the retrospective nature of the current study, there was no patient or public involvement.

RESULTS

Prevalence and incidence

Of the 173 132 patients with RA included in the overall study population, 4330 (3%) met the criteria for RA-ILD. Overall, the prevalence of RA-ILD was 6.5 per 100 000 inhabitants and the incidence of RA-ILD was 1.0 per 100 000 person-years. Both the prevalence and incidence of RA-ILD were higher in women versus men and increased with age (online supplemental table 1).

Baseline characteristics of patients with RA-ILD and RA-noILD

Baseline population characteristics are stated in table 1. Compared with those with RA-noILD, the RA-ILD cohort had a higher proportion of men (40% vs 27%, respectively) and were older at RA diagnosis (mean (SD) age: 63.3 (14) vs 56.9 (15) years, respectively). Mean (SD) RA

Table 1 Patient characteristics before matching

	RA-noILD (n=168 182)	RA-ILD (n=4330)	P value*
Age at RA diagnosis, mean (SD), years	56.9 (15)	63.3 (14)	<0.001†
Age at index date, ‡years			
Mean (SD)	56.9 (15)	63.3 (14)	<0.001†
<65, n (%)	113 657 (68)	2244 (52)	
65–74, n (%)	31 473 (19)	1157 (27)	<0.001
≥75, n (%)	23 052 (14)	929 (21)	
Male sex, n (%)	45 468 (27)	1725 (40)	<0.001
RA disease duration, mean (SD), years	7.9 (7)	7.6 (7)	NS
Comorbidities, n (%)			
Cardiac disease	106 165 (63)	3678 (85)	<0.001
Arterial disease	32 495 (19)	1644 (38)	<0.001
Diabetes	21 084 (13)	926 (21)	<0.001
Dyslipidaemia	55 267 (33)	1935 (45)	<0.001

*Bivariate analysis using χ^2 test.
†Bivariate analysis using Student's t-test.
‡For patients with RA-ILD, this is the date when both RA and ILD diagnoses were assigned; for the matched RA cohort, this is the matching date.
ILD, interstitial lung disease; NS, not significant; RA, rheumatoid arthritis; RA-ILD, RA with ILD; RA-noILD, RA without ILD.

Table 2 Patient characteristics after matching

	RA-noILD (n=4293)	RA-ILD (n=4293)
Age at RA diagnosis, mean (SD), years	62.8 (13)	62.7 (14)
Age at index date, *years		
Mean (SD)	68.3 (12)	68.3 (12)
<65, n (%)	1473 (34)	1473 (34)
65–74, n (%)	1331 (31)	1331 (31)
≥75, n (%)	1489 (35)	1489 (35)
Male sex, n (%)	1707 (40)	1707 (40)
RA disease duration, mean (SD), years	4.8 (5)	4.8 (5)
Comorbidities, n (%)†		
Cardiac disease	3131 (73)	3643 (85)
Arterial disease	1116 (26)	1630 (38)
Diabetes	655 (15)	914 (21)
Dyslipidaemia	1761 (41)	1912 (45)

*For patients with RA-ILD, this is the date when both RA and ILD diagnoses were assigned; for the matched RA cohort, this is the matching date.
†There was a significantly higher proportion of patients with RA-ILD with cardiac disease, arterial disease, diabetes and dyslipidaemia compared with RA-noILD.
ILD, interstitial lung disease; NS, not significant; RA, rheumatoid arthritis; RA-ILD, RA with ILD; RA-noILD, RA without ILD.

disease duration was similar between patients with RA-ILD (7.6 (7) years) compared with patients with RA-noILD (7.9 (7) years). Compared with those with RA-noILD, a higher proportion of patients with RA-ILD had cardiac disease (85% vs 63%, respectively), arterial disease (38% vs 19%, respectively), diabetes (21% vs 13%, respectively) and dyslipidaemia (45% vs 33%, respectively).

For the matched subgroup comparison, 8586 patients were included. No match was possible for 37 patients with RA-ILD. After matching, the subgroups displayed similar demographic and disease characteristics; however, the proportions of patients with cardiac disease, arterial disease, diabetes and dyslipidaemia were significantly higher (p<0.001) in patients with RA-ILD compared with RA-noILD (table 2).

Mortality rate in patients with RA-ILD

The mortality rate in patients with RA-ILD was 1.71 per 100 000 inhabitants. Over the study period, mortality rate increased with each ascending age group: 0.28 per 100 000 inhabitants for patients aged <65 years, 4.60 per 100 000 inhabitants for patients aged 65–74 years and 11.4 per 100 000 inhabitants for patients aged ≥75 years. Before matching, between-group HR risk of mortality was higher in patients with RA-ILD than in those with RA-noILD (HR 3.4, 95% CI 3.2 to 3.6).

Within the matched subset, the adjusted HR for mortality (HR 3.4, 95% CI 3.1 to 3.9) was threefold greater in patients with RA-ILD than in patients with RA-noILD (figure 1). Sensitivity analyses also illustrated a higher risk of mortality for patients with RA-ILD compared with RA-noILD when matching for arterial disease (HR 2.6, 95% CI 2.3 to 3.0), cardiac disease (HR 3.3, 95% CI 2.9 to 3.7), diabetes (HR 3.1, 95% CI 2.5 to 3.9) and dyslipidaemia (HR 3.0, 95% CI 2.6 to 3.5) (all p<0.001; online supplemental figure 1).

When comparing patients with RA-ILD versus patients with RA-noILD, the mortality rate was higher for patients aged <75 years (HR 4.8, 95% CI 3.9 to 5.9) than for patients aged ≥75 years (HR 3.0, 95% CI 2.6 to 3.5) (figure 2). Further, mortality rates were higher when the onset of ILD preceded RA onset (HR 8.4, 95% CI 5.5 to 13.0) compared with RA onset preceding ILD onset (HR 2.9, 95% CI 2.6 to 3.3) (figure 2). Higher rates for mortality were seen in both male and female patients with RA-ILD when compared with RA-noILD (male: HR 5.2, 95% CI 4.4 to 6.2; female: HR 3.6, 95% CI 3.0 to 4.2) (figure 2).

Treatment patterns and hospitalisations for matched patients with RA-ILD and RA-noILD

Annual treatment patterns and hospitalisations in patients with RA-ILD and RA-noILD are given in table 3. Overall, a lower proportion of patients with RA-ILD received MTX (33–35% vs 61–65% for RA-noILD), while a greater proportion received non-tumour necrosis factor

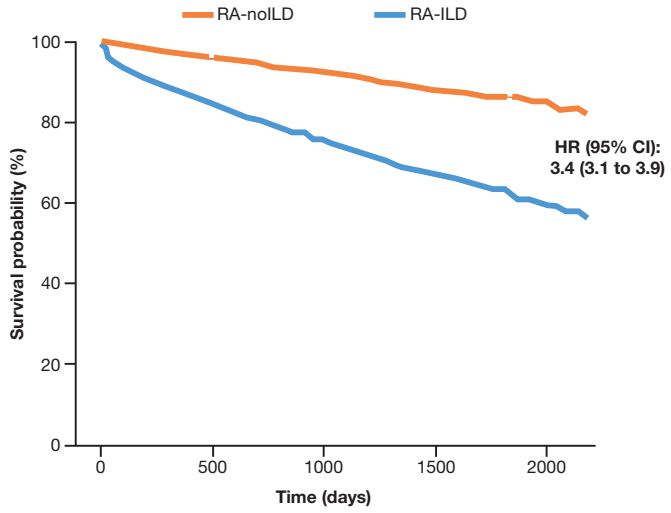

Figure 1 Survival in patients with RA-ILD versus RA-noILD in the matched population. ILD, interstitial lung disease; RA, rheumatoid arthritis; RA-ILD, RA with ILD; RA-noILD, RA without ILD.

inhibitor (TNFi) biological DMARDs (23–28% vs 6–11% for RA-noILD) and corticosteroids (77–82% vs 61–65% for RA-noILD). Lastly, a larger proportion of patients with RA-ILD were hospitalised compared with patients with RA-noILD (79–98% vs 33–43%, respectively).

DISCUSSION

In this large French population-based epidemiological study, RA-ILD was diagnosed in 3% of patients with RA, had a prevalence of 6.5 per 100 000 inhabitants and was associated with a threefold greater HR for mortality than patients with RA-noILD. Increased mortality was more pronounced in patients aged <75 years, patients who developed ILD prior to RA onset and in male patients.

Previous estimates for the prevalence of clinical RA-ILD vary considerably.[5–9] Such variation is notably due to methodological differences between studies. The estimate of clinical RA-ILD from the present study (3%; n=4330/173 132) was toward the lower end of previous estimates,

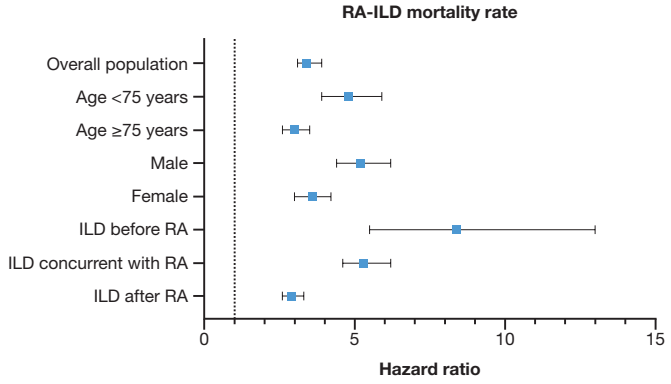

Figure 2 Forest plot showing HR for mortality in patients with RA-ILD compared with patients with RA-noILD. ILD, interstitial lung disease; RA, rheumatoid arthritis; RA-ILD, RA with ILD; RA-noILD, RA without ILD.

Table 3 Comparison of annual treatment patterns and hospitalisations between patients with RA-noILD and patients with RA-ILD in the matched population

Year	2013		2014		2015		2016		2017		2018	
	RA-noILD	RA-ILD	RA-noILD	RA-ILD	RA-noILD	RA-ILD	RA-noILD	RA-ILD	RA-noILD	RA-ILD	RA-noILD	RA-ILD
Treated patients, n	817	817	1524	1492	2162	2040	2854	2599	3478	3062	4030	3445
Type of treatment												
Non-MTX csDMARD	19	35	19	33	19	34	18	32	16	29	15	26
MTX	65	33	65	35	65	34	63	34	61	34	61	34
TNFi	16	12	16	12	15	11	16	11	15	11	14	10
Other bDMARD	6	24	8	23	9	24	9	26	10	27	11	28
tsDMARD*									0	0	2	3
All DMARDs	88	77	88	78	87	78	85	77	82	76	82	75
Corticosteroids	61	79	65	82	65	82	64	81	62	78	61	77
Hospitalisations	33	98	40	88	42	83	43	82	42	80	43	79

Data are presented as percentages unless noted otherwise. Percentages do not add up to 100 because patients could be in more than one category.
*In line with approvals, tsDMARD use was not available prior to 2017.
bDMARD, biological DMARD; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; ILD, interstitial lung disease; MTX, methotrexate; RA, rheumatoid arthritis; RA-ILD, RA with ILD; RA-noILD, RA without ILD; TNFi, tumour necrosis factor inhibitor; tsDMARD, targeted synthetic DMARD.

which is similar to what was found in a recent Danish national healthcare database study and other American health insurance registry studies.[10 21 22] Variation among previous estimates using administrative claims to identify patients with RA-ILD is by definition limited to the population of patients meeting the criteria for clinically significant ILD, and concomitantly excludes patients with subclinical RA-ILD. Nonetheless, this approach may be relevant to evaluate the disease burden of RA-ILD, as it considers the most significant cases of ILD.

In previous decades, progress in RA treatment led to a decrease in mortality due to comorbidities, such as cardiovascular events, in patients with RA.[18] However, in a recent American epidemiological study, while RA-related overall mortality rates decreased from 2005 to 2018, RA-ILD-related mortality rates remained stable over the same period, suggesting that improvement of overall outcomes in RA had limited effect in patients with RA-ILD.[23] The increased mortality rate observed in our study is supported by other healthcare claims database analyses showing significantly increased mortality rates in these patients.[10 21 24 25] However, we did have some novel findings. In the current study, the difference in mortality rate between patients with RA-ILD and those with RA-noILD was greatest in patients aged <75 years, in patients who developed ILD prior to RA onset, in male patients and in patients with cardiometabolic risk factors. The excess mortality observed in patients with ILD prior to RA may correspond to a more advanced, and therefore more severe, lung disease. Regarding the finding of a greater difference in mortality rate in patients aged <75 years, the burden of RA-ILD appears to be higher in young patients free from other comorbidities. We have also previously reported that a higher number of rare variants of telomere-related genes contributed to younger patients being more susceptible to RA-ILD.[26] Additionally, shorter telomere lengths have been associated with worse survival in idiopathic pulmonary fibrosis (IPF).[27] Considering the similarities between IPF and RA-ILD,[28] the excess mortality in younger patients in the present study may be partially explained by an excess of rare telomere-regulated genes variants in this population. Further investigation of mortality among patients according to age should be conducted in dedicated studies. The lower survival rates, when assessed by cardiometabolic risk factors, suggest that RA-ILD-associated health deterioration is not simply a function of pulmonary failure and fibrosis, but that there may be a systemic worsening of health status among patients with RA-ILD. This may also be reflective of the higher proportion of hospitalisations observed for patients with RA-ILD compared with RA-noILD in the current study. Nevertheless, these results underscore the greater burden of ILD in those patients. Such observations contain clinical relevance, whereby these patients may be considered to potentially have severe RA-ILD and as such may benefit from careful follow-up procedures and specific management.

To date, an important unmet need in RA-ILD management is the lack of international guidelines regarding how patients with RA-ILD should be treated. Our study revealed differences in RA treatments according to ILD status. Indeed, patients with RA-ILD were less likely to be prescribed MTX and more likely to receive non-TNFi biological DMARDs than those with RA-noILD. These findings align with the perception that some DMARDs, notably MTX, may exert a potentially harmful impact on patients with RA-ILD.[29] Regarding MTX, this perception contradicts recent evidence demonstrating the lack of contribution of MTX to RA-ILD occurrence and progression.[30–34] Besides, recent studies have identified an association between high RA disease activity and mortality in patients with RA-ILD, meaning that inappropriate cessation of the recommended first-line DMARD could strongly impact prognosis in such patients.[18 33] Nevertheless, future studies identifying how specific treatments may affect mortality rates among patients with RA-ILD will better inform clinical decision-making for these patients.

This current study has limitations. First, a healthcare claims database is not adequate to assess preclinical RA-ILD, leading to a potential misclassification bias. Second, the absence of information about HRCT pattern data did not allow for detailed analyses identifying potential characteristics specific to a given RA-ILD pattern. Third, the limited period of analysis (January 2013 to December 2018) did not enable comparative analyses over time. Additionally, data not collected by the SNDS database, such as smoking status, limited the ability to examine alternative variables that may impact mortality rates among patients with RA-ILD. Last, the treatment modalities reported herein reflect everyday clinical practice in France and may not be generalisable to other countries. However, the current study contained notable strengths, such as the size of the overall cohort, which comprised nearly all of the French population. Additionally, congruent with previous work, we used validated diagnostic codes for both RA and ILD stratification, reinforcing the reliability of our findings.

In conclusion, this is the largest European epidemiological study of RA-ILD, highlighting the burden of RA-ILD. Patients with RA-ILD had a threefold increase in mortality rate compared with those with RA-noILD. Higher mortality rates were more evident in patients aged <75 years, patients who developed ILD prior to RA diagnosis and in male patients. The presence of ILD influenced the choice of RA treatment, highlighting the need for international guidelines for management of RA in patients with RA-ILD.

Author affiliations
[1]INSERM UMR 1152, Université Paris Cité, Paris, Île-de-France, France
[2]Service de Rhumatologie, Hôpital Bichat - Claude-Bernard, AP-HP, Paris, Île-de-France, France
[3]Service de Pneumologie et Immuno-Allergologie, CHRU de Lille, Lille, Hauts-de-France, France
[4]Real World Digital Contract Research Company, Sanoïa, Gémenos, France

[5]Worldwide Health Economics and Outcomes Research, Bristol Myers Squibb, Princeton, New Jersey, USA
[6]Medical ImmunoScience/Rhumatologie, Bristol Myers Squibb, Rueil-Malmaison, France
[7]Service de Rhumatologie, CHRU de Lille, Lille, Hauts-de-France, France
[8]Service de pneumologie A, Hôpital Bichat - Claude Bernard, AP-HP, Paris, Ile de France, France

Correction notice This article has been corrected since it was first published online. Lidwine Wémeau-Stervinou was incorrectly listed as Lidwine Wemeau. In addition to this, some of the data in the *Baseline characteristics of patients with RA-ILD and RAnoILD* section was incorrectly listed as a citation when it should have been a data point. The section now reads '…(mean (SD) age: 63.3 (14) vs 56.9 (15) years, respectively). Mean (SD) RA disease duration was similar between patients with RA-ILD (7.6 (7) years) compared with patients with RA-noILD (7.9 (7) years'.

Twitter Pierre-Antoine Juge @Juge_P_A

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Contributors Study conception and design: P-AJ, GD, JZ, VV-M, BC, R-MF, PD. Acquisition of data: GD, PD. Data analysis: GD, PD. Data interpretation: P-AJ, LW, SO, GD, JZ, VV-M, R-MF, BC, PD. All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. PD is the guarantor for this manuscript.

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Competing interests PA-J has received grant/research support from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Medac, Novartis, Roche Chugai and Societe Francaise de Rhumatologie; and consultancy fees from Bristol Myers Squibb. LW has received consultancy fees from Boehringer Ingelheim, Bristol Myers Squibb, Roche and Sanofi. SO has received consultancy fees from AbbVie, Bristol Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novartis, Roche-Chugai, SOBI and UCB. GD has received consultancy fees from Bristol Myers Squibb. JZ and VV-M are employees of and shareholders in Bristol Myers Squibb. R-MF has received speakers bureau fees from AbbVie, Bristol Myers Squibb, Eli Lilly, Janssen, Medac, Merck Sharp & Dohme, Novartis, Pfizer and Roche-Chugai; and grant/research support from Amgen, Janssen, Novartis and Pfizer. BC has received consultancy fees from Apellis, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Novartis, Roche and Sanofi; and grant/research support from Boehringer Ingelheim, Bristol Myers Squibb and Roche. PD has received consultancy fees from Boehringer Ingelheim, Bristol Myers Squibb, Chugai, Eli Lilly, Medac, Novartis, Pfizer and Sanofi; and grant/research support from Bristol Myers Squibb, GlaxoSmithKline and Pfizer.

Patient consent for publication Not applicable.

Ethics approval This study was conducted in accordance with the International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices, and applicable regulatory requirements.[35] The current study was approved by the Creation of an Expert Committee for Research, Studies and Evaluations in the Field of Health (CEREES), and by the National Commission on Informatics and Liberty (CNIL), reference DR 2019-200.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data that support the findings of this study are available from Bristol Myers Squibb but restrictions apply to the availability of these data, which were used under license for the current study. Data are available from the authors upon reasonable request and with permission of Bristol Myers Squibb. Data requests are sent through an independent review committee to evaluate who provide the final decision on requests. Bristol Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html.

ORCID iDs
Pierre-Antoine Juge http://orcid.org/0000-0002-3766-9600
René-Marc Flipo http://orcid.org/0000-0001-5528-8070
Philippe Dieudé http://orcid.org/0000-0002-4814-0307

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