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Original article

Efficacy of rituximab in slowing down progression of rheumatoid arthritis–related interstitial lung disease: data from the NEREA Registry

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Abstract

Objectives. To asses the clinical course in RA-related interstitial lung disease (RA-ILD) patients with and without rituximab (RTX). The influence of other variables was also evaluated.

Methods. A longitudinal multicentre study was conducted in RA diagnosed with ILD from 2007 until 2018 in Madrid. Patients were included in a registry [pNEumology RhEumatology Autoinmune diseases (NEREA)] from the time of ILD diagnosis. The main endpoint was functional respiratory impairment (FI), when there was a decline ≥5% in the predicted forced vital capacity compared with the previous one. Pulmonary function was measured at baseline and in follow-up visits every 6–12 months. The independent variable was therapy with RTX. Covariables included sociodemographic, clinical, radiological and other therapies. Survival techniques were used to estimate the incidence rate (IR) and 95% CI of functional impairment, expressed per 100 patient-semesters. Cox multivariate regression models were run to examine the influence of RTX and other covariates on FI. Results were expressed as the hazard ratio (HR) and CI.

Results. A total of 68 patients were included. FI occurred in 42 patients [IR 23.5 (95% CI 19, 29.1)] and 50% of them had FI within 1.75 years of an ILD diagnosis. A multivariate analysis showed that RTX exposure resulted in a lower risk of FI compared with non-exposure [HR 0.51 (95% CI 0.31, 0.85)]. Interstitial pneumonia, glucocorticoids, disease activity and duration also influenced FI.

Conclusion. RA-ILD patients deteriorate over time, with the median time free of impairment being <2 years. Patients exposed to RTX had a higher probability of remaining free of FI compared with other therapies. Other factors have also been identified.

Key words: rheumatoid arthritis, interstitial lung disease, observational study, rituximab and prognosis

Rheumatology key messages

- Long-term cohort studies are warranted to characterize the course of early ILD in RA.
- Our results support a beneficial effect of RTX in the management of RA-ILD patients.
- Knowledge of potential factors associated to lung progression are crucial for RA-ILD patient management.

Introduction

RA is a chronic systemic autoimmune disease affecting 1% of the population worldwide [1]. RA is associated with severe morbidity and impaired functional capacity, leading to a decreased quality of life and increased mortality [2, 3].

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CLINICAL SCIENCE

Besides joint inflammation, RA patients can suffer additional manifestations, including lung involvement, a relatively common extra-articular manifestation of the disease [4, 5], particularly interstitial lung disease (ILD), accounting for the most severe and prevalent pulmonary manifestation in RA patients [6]. RA-related ILD (RA-ILD) may appear as a consequence of chronic immune activation promoting aberrant fibroproliferation, although it can also be precipitated by drugs or infectious agents [6]. ILD in RA contributes significantly to decreased quality of life, progressive chronic disability, high utilization of healthcare resources and higher mortality [7–9].

RA-ILD usually leads to progressive pulmonary function deterioration and represents a challenge to the treatment of RA. A standard of care is currently lacking for RA-ILD and evidence drawn from ILD associated with other CTDs is largely taken as a guideline. In spite of little available data recommending their use and dosage, glucocorticoids and immunosuppressants are usually prescribed by clinicians in daily practice [4, 10–12]. Immunosuppressive drugs, including MMF, have been suggested to improve or stabilize the disease in RA-ILD patients [13], but no large randomized controlled trials have yet been undertaken.

While treatment of RA has been greatly improved in recent years with the introduction of biologic therapies, the use of anti-TNF therapies is limited in the care of patients with RA-ILD because of safety concerns [14]. This fact, along with the demonstration of follicular B cell and plasma cell infiltrates in lung specimens from patients, has led to a preferential use of rituximab (RTX). Despite the potential rationale for B cell–targeted therapies in RA-ILD, clinical evidence for the efficacy and safety of RTX in the context of ILD is scarce. Furthermore, patients with RA-ILD are normally excluded from formal clinical trials due to comorbidity. Recently some observational studies of RTX in RA-ILD have been published [15–17] that show patients remained stable or improved after treatment. Notably, those patients who deteriorated or died already had severe ILD prior to RTX initiation. According to these findings, RTX appears to be an acceptable therapeutic choice for patients with RA-ILD, although large comparative studies should be conducted.

To better understand the clinical course of patients with RA-ILD, we recently launched an observational multicentre registry (NEREA). The objective of our study was to describe the characteristics of RA-ILD patients from the registry, assess the incidence rate (IR) of functional respiratory impairment and evaluate the possible influence of RTX compared with other therapeutic alternatives on the prognosis of these patients. The influence of other variables was also analysed.

Methods

Setting

Two tertiary hospitals of the National Health System of the Community of Madrid, Spain—Hospital Clínico San Carlos (HCSC) and Hospital Fundación Jiménez Díaz (FJD)—were the setting for our study, covering catchment areas of ∼400 000 people each. The rheumatology and pneumology services of each hospital provide care to this entire population.

Study design

This is a multicentre prospective observational study. Patients were included from February 2007 through February 2018 and followed up until lost to follow-up or the end of the study (October 2018).

Patients

All patients were included from the time of ILD diagnosis and were enrolled, included and followed up at special multidisciplinary Rheumatology–Autoimmune Disease–Interstitial Lung Disease (RAD-ILD) units by a pneumologist and a rheumatologist.

Patient data were recorded in the Spanish NEREA Registry. Briefly, the NEREA contains RAD-ILD data integrated in local databases from patients with any of the following disorders according to EULAR and ACR classification criteria: RA, systemic sclerosis, Sjögren's syndrome, idiopathic inflammatory myopathy, systemic lupus erythematosus and mixed CTD. A diagnosis of ILD according to the guidelines of the European Respiratory Society/American Thoracic Society (ERS/ATS) was mandatory [18]. Patients with interstitial pneumonitis with autoimmune features were also included according to the 2015 preliminary criteria from the ERS/ATS task force.

The study included patients in the NEREA registry with a diagnosis of RA [19]. Patient data for this project were obtained during routine clinical practice and patients provided signed informed consent in order to participate. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices and was approved by the local institutional review boards.

Variables

The primary outcome was the presence of pulmonary functional impairment, defined as a decline of $\geq$5% in the predicted forced vital capacity (FVC) per visit compared with the previous one. Pulmonary function tests were performed at baseline and every 6–12 months.

Independent variable

The independent variable was therapy with RTX, used according to clinical practice in RA management.

The following covariates were included: sociodemographic baseline characteristics; clinical characteristics, including baseline comorbidity, duration of RA disease, BMI, smoking habit; disease-related variables, including RF, ACPA and ESR at baseline; pulmonary function tests (PFTs) at baseline and during every follow-up visit [FVC, predicted diffusing capacity of the lungs for carbon monoxide (DLCO)]; RA-ILD patterns at baseline, based on high-resolution CT as follows: usual

interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP) and others [cryptogenic organizing pneumonia (COP) and other types of idiopathic interstitial pneumonia (IIP)]; and treatments prescribed prior to ILD diagnosis and during follow-up, including glucocorticoids (yes/no) up to 2 months before ILD diagnosis and their use during follow-up (from the time of diagnosis until 2 months later), prior use of DMARDs, defined as any DMARD administered in the 6 months prior to ILD diagnosis and oxygen therapy. Concurrent DMARDs were recorded as start and end dates. The list of DMARDs included AZA, MMF, CYC, MTX, LEF, antimalarials (AMs), tacrolimus, TNF inhibitors, abatacept (ABA), tocilizumab (TZL) and the antifibrotic agent pirfenidone (PIRF).

Statistical analysis

Descriptive statistics of patients' characteristics are expressed as mean (S.D.) or median [interquartile range (IQR)] for continuous variables, while proportions are shown in the case of categorical variables.

Survival techniques (multiple failures) were used to estimate the IR and 95% CI of functional impairment, expressed per 100 patient-semesters. Kaplan–Meier curves were set to account for functional impairment over time. Time of observation was the period from the ILD diagnosis to the occurrence of any of the following points: lost to follow-up, main outcome or end of the study. It is important to note that the drug prescription method, i.e. real-life conditions, hampered the categorization of therapeutic patterns. Thus, patients were included in different groups and contributed with patient-semester at risk to both, exposed and not exposed to RTX treatment

Cox bivariate analyses were done to asses the differences between functional impairment and covariates. Cox multivariate regression models (adjusted by age, sex, disease severity and all variables with a *P*-value <0.15 in the bivariate analysis) were run to examine the possible influence of RTX and other covariates in the development of functional impairment. RTX was used in a time-dependent manner. FVC, concomitant glucocorticoids and other DMARDs were also used in a time-dependent manner. Results were expressed as the hazard ratio (HR) and CI. Proportional hazards assumption was tested using Schoenfeld residuals and scaled Schoenfeld residuals. All analyses were performed using Stata version 13 statistical software (StataCorp, College Station, TX, USA). A two-tailed *P*-value <0.05 was considered statistically significant.

Results

Sixty-eight RA ILD patients, 46 from HCSC and 22 from FJD, were included, with a total follow-up of 361.2 patient-semesters and a maximum follow-up of 11 years. Table 1 includes a detailed description of the patients. Many of them were women (65%) in their late 60s. In most patients (91%), the RA diagnosis preceded ILD. The mean lag time was 12.2 years (S.D. 13.2), with slight differences between hospitals, being longer for FJD patients.

Along with being overweight, which was observed in 75% of patients, the most frequent comorbidities at baseline were hypertension and hypercholesterolemia, with small differences between hospitals. The average age, the percentage of women, the disease activity (ERS criteria) and the duration of RA disease were similar between patients with and without RTX.

The mean baseline FVC was 95.7 (S.D. 19), the values being higher in patients from HCSC. For DLCO, baseline levels were normal (>80%) in 30% of the patients, 40% had a mild DLCO deterioration (60–80%), 20% had a moderate reduction (40–60%) and the remaining 10% showed severe DLCO (<40%) [20]. Approximately 60% of the patients had functional deterioration at the end of the study in terms of FVC and DLCO. Crude differences between initial/final FVC and initial/final DLCO showed a median of 4 points worsening (95% CI −13, +11) and 3.4 points worsening (95% CI −12, +6.8), respectively.

Regarding ILD patterns, at baseline, UIP was the most frequently found (16 patients were defined as possible UIP), followed by NSIP. CT scans were performed in 58% of the patients during the follow-up, showing deterioration in 33%, while 65% remained stable and 2% showed improvement. Interestingly, on only two occasions—both corresponding to patients on RTX—the radiological pattern shifted from NSIP towards possible UIP.

Concerning laboratory parameters, RF was positive in 88% of the patients and the mean ESR at baseline was 40.2 (S.D. 26). ACPA was positive in 81% of the patients, with higher titres in patients from FJD.

The number of patients taking glucocorticoids increased from 70% ($n=48$) before ILD diagnosis to 87% during follow-up. At study entry, the mean dosage of corticoids was 9 mg. As for supplemental oxygen, 3 of the patients were already using it at study entry, whereas 20% ($n=14$) needed supplemental oxygen during follow-up. None of them was on RTX.

Regarding ongoing DMARDs at study entry (Fig. 1), 75% of the patients ($n=51$) were on MTX, 30% ($n=21$) on LEF, 29% ($n=20$) on AM and 18% ($n=12$) on AZA. With respect to biologic agents, 25% ($n=17$) were taking anti-TNF (90% of them in combination with MTX) and 5.8% ($n=4$) were being treated with RTX. From the time of ILD diagnosis and during the follow-up (Table 1 and Fig. 1), the use of these drugs was modified. There was an increase mainly in the use of RTX, AZA and ABA. In contrast, there was a decrease in the use of MTX, LEF and anti-TNF. Interestingly, 80% of the patients discontinued MTX within the first year of the study.

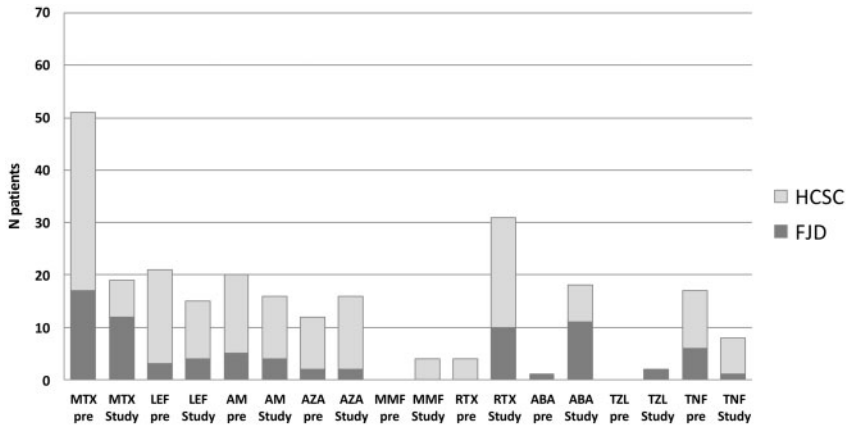
A total of 31 patients received RTX during the follow-up, with a mean exposure of 20.6 months, a median exposure of 15.6 months (95% CI 4, 32.7) and a maximum of 8.8 years. Regarding discontinuations, it was due to a

Table 1 Sociodemographic and clinical characteristics of the patients

Characteristics	All ($n = 68$)	FJD ($n = 22$)	HCSC($n = 46$)	*P*-value
Women, *n* (%)	44 (64.7)	15 (68)	29 (63)	0.4
Age at ILD diagnosis, mean (S.D.), years	70.3 (9.1)	70.9 (11.3)	69.9 (9.4)	0.4
BMI, median (IQR)	27.4 (24.8–31.1)	27.7 (25.1–30.7)	25.9 (22.8–32)	0.6
Lag time to ILD diagnosis, median (IQR),[a] years	8.4 (1.9–18.7)	14.6 (3.1–26.8)	8.1 (1.5–13.9)	0.1
Work status ($N = 56$), *n* (%)				
Active	12 (22)	4 (33.4)	8 (18.2)	0.2
Housewife	15 (27)	1 (8.3)	14 (31.8)	
Retired	29 (51)	7 (58.3)	22 (50)	
Smokers (active and formers), *n* (%)	38 (57.5)	11 (50)	27 (61.3)	0.2
RF positive ($N = 66$), *n* (%)	58 (87.8)	19 (90.4)	39 (86.6)	0.5
RF, median (IQR)[a]	199.5 (61–312)	208 (110–304)	150 (56–312)	0.5
Anti-CCP positive ($N = 54$), *n* (%)	44 (81.5)	18 (94.7)	26 (74.3)	0.08
Anti-CCP, median (IQR)[a]	301 (42–513)	340 (78–400)	270 (20–795)	0.5
ESR, median (IQR)[a]	39 (18–53)	41 (27–59.5)	36 (16–52)	0.2
Comorbidity, *n* (%)				
Hypertension	34 (50)	10 (45)	24 (52)	0.7
Cholesterol	28 (41.2)	6 (27)	22 (47)	0.1
Ischaemic heart disease	5 (7.3)	3 (13.6)	2 (4.4)	0.3
Cerebrovascular disease	5 (7.3)	0	5 (10.8)	–
Peripheral vascular disease	9 (13.2)	0	9 (19.6)	–
Cancer	6 (8.8)	0	6 (13)	–
Diabetes mellitus	9 (13.2)	4 (18.2)	5 (10.8)	0.4
Congestive heart failure	5 (7.3)	3 (13.6)	2 (4.4)	0.3
Sleep apnoea syndrome	4 (5.8)	2 (9)	2 (4.4)	0.5
Depression	8 (11.7)	1 (13.6)	5 (10.8)	0.7
Renal failure (dialysis)	2 (2.9)	0	2 (4.4)	–
Liver disease	5 (7.3)	1 (4.5)	4 (8.7)	0.4
Ulcus disease	4 (5.8)	0	4 (8.7)	–
Hypothyroidism	7 (10.3)	3 (13.6)	4 (8.7)	0.6
Gastro-oesophageal reflux	3 (4.4)	2 (9)	1 (2.2)	0.2
Emphysema	14 (20.5)	2 (9)	10 (21)	0.4
PTF parameters				
FVC, median (IQR)[a]	94 (78–111)	81 (72–100)	103 (84–111)	0.02
DLCO ($N = 60$), median (IQR)[a]	67.9 (52.3–82.8)	66.2 (54–88.7)	69.2 (52.3–80.7)	0.8
Radiographic ILD pattern, *n* (%)				
UIP	39 (57.4)	11 (50)	28 (60.8)	0.8
NSIP	22 (32.4)	6 (27.3)	16 (34.8)	
Other	7 (10.2)	5 (22.7)	2 (4.4)	
Therapy during the follow-up, *n* (%)				
Corticoids	59 (87)	19 (86)	40 (87)	0.9
Oxygen	14 (20.6)	6 (27.3)	8 (17.4)	0.3
AZA	16 (23.5)	2 (9.1)	14 (30.4)	0.07
MMF	4 (5.9)	0	4 (8.7)	–
MTX	15 (22)	8 (36)	7 (15)	0.01
LEF	15 (22)	4 (18)	11 (23)	0.7
AM	16 (23.5)	4 (18)	12 (26)	0.5
Anti-TNF-ADA	7 (10.3)	2 (2.9)	5 (10.8)	0.7
Anti-TNF-ETN	3 (4.4)	0	4 (5.8)	0.6
Anti-TNF-IFX	0	0	0	–
Anti-TNF-CERTO	1 (1.5)	0	1 (2.2)	0.5
RTX	31 (45.6)	10 (45.6)	21 (45.6)	0.9
ABA	12 (26.5)	7 (32)	5 (10.8)	0.004
TZL	2 (2.9)	2 (9.1)	0	–
CYC	2 (2.9)	0	1 (4.3)	–
Tacro	1 (1.5)	1 (4.5)	0	–
PIRF	2 (2.9)	0	2 (4.3)	–

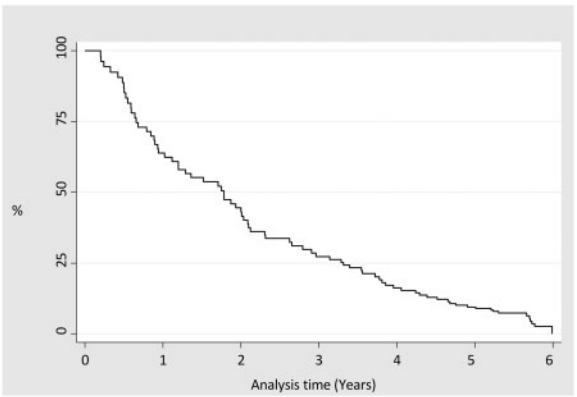
[a]25th–75th percentile. Tacro: tacrolimus; anti-TNF: TNF inhibitors including ADA (adalimumab), ETN (etanercept), IFX (infliximab), CERTO (certolizumab). Analyses were performed by Student's *t*-test, Mann–Whitney *U*-test, Pearson's χ^2 and Fisher's exact test.

FIG. 1 Number of patients by different therapies until the time of ILD diagnosis and during the follow-up



Centres: HCSC and FJD; pre: previous ILD diagnosis; study: during the follow-up; TNF: TNF inhibitors including ADA (adalimumab), ETN (etanercept), IFX (infliximab), CERTO (certolizumab).

FIG. 2 Kaplan–Meier survival estimate curve



Pulmonary functional impairment.

lack of effect in three patients (9.7%), an adverse event in two patients (one sepsis and one pancytopenia) and in six patients the drug was stopped due to articular improvement (19.3%), of which two patients remained in joint remission at the end of the study and four others restarted RTX because of disease flare at an average of 1.6 years after the last infusion. All patients started on an RA treatment schedule, but dosing and repetitions during follow-up were not constant. Depletion of B cells was confirmed in all patients undergoing optimization regimes of RTX, with a mean number of RTX cycles per patient of 3.4 (range 1–18).

Pulmonary functional impairment occurred in 42 patients (63%) with 85 events and an estimated IR of 23.5 per 100 patient-semesters (95% CI 19, 29.1). As shown in the Kaplan–Meier survival curve (Fig. 2), 50% of the patients reached functional deterioration at 1.75 years from ILD diagnosis. Table 2 shows the IR of deterioration. The IR in patients taking glucocorticoids prior to ILD diagnosis was lower than in those not taking glucocorticoids. Once the ILD diagnosis was established, the limited exposure to MTX, ABA or anti-TNF hindered evaluation of their respective IRs. Interestingly, patients taking RTX or AZA during the study had a lower IR. Concerning ILD patterns, IR was higher in UIP than in NSIP or any other pattern.

Bivariate analyses are detailed in Table 3. To examine the possible efficacy of RTX in slowing pulmonary impairment, independent of additional factors, a final model was developed (Table 4). Exposure to RTX had less risk of deterioration compared with non-exposure. Exposure to AZA, which was initially included, was dropped from the model [HR 1.04 (95% CI 0.4, 2.5), $P = 0.8$]. Similarly, DLCO (defined as >45% *vs* <45%) was dropped from the model [HR 0.69 (95% CI 0.25, 1.3), $P = 0.25$]. Other variables independently associated with lower risk of impairment were lower RA disease duration until ILD diagnosis, higher disease activity at baseline, use of glucocorticoids at ILD diagnosis and emphysema. As expected, a UIP pattern was associated with a higher risk of deterioration as compared with an NSIP pattern. The proportionality of these regression models was tested with a *P*-value of 0.8.

Discussion

To our knowledge, this is the first observational study that assessed and compared the effect of RTX on RA-ILD in terms of functional impairment and in the long term. In our study, patients exposed to RTX remained stable compared with those without the drug. Moreover, we confirm previously identified risk factors of progression in RA-ILD and propose new ones.

As a whole, the population with RA-ILD can be considered complex patients. The NEREA RA-ILD patients were comparable to others. Our patients were in their late 60s and most had positive RF and/or ACPA [9, 17, 21–24]. In addition, several had associated comorbidities, with hypertension and dyslipidaemia being most common [25]. The UIP morphological pattern was seen

Table 2 Incidence rate of functional deterioration by different variables

Variable	Patient-semester	Events	IR	95% CI
Gender				
Female	257.75	60	23.3	18.1, 29.9
Male	103.47	25	24.2	16.3, 35.7
Centre				
FJD	92.7	23	24.8	16.5, 37.2
HCSC	268.5	63	23.1	18, 29.6
RF				
<200	183.3	39	21.3.8	15.5, 29.1
>200	177.9	46	25.8	19.3, 34.5
Anti-CCP				
<300	159.9	46	28.7	21.5, 38.4
>300	116.2	21	18.7	11.7, 27.7
Radiographic ILD pattern				
UIP	196.3	52	26.5	20.2, 34.7
NSIP	114.9	22	19.1	12.6, 29.1
Other	49.9	11	22.0	12.2, 39.7
Glucocorticoids during follow-up				
Yes	294.5	70	23.7	18.8, 30
No	66.6	15	22.5	13.5, 37.3
Glucocorticoids until time of ILD diagnosis				
Yes	254.03	55	21.6	16.6, 28.2
No	107.3	30	28.0	19.6, 40.1
RTX during follow-up				
Yes	252.4	20	18.3	11.8, 28.8
No	108.8	65	25.7	20.2, 32.8
AZA during follow-up				
Yes	52.7	9	17.0	8.8, 32.7
No	308.4	76	24.6	19.6, 30.8
ABA during follow-up				
Yes	16.2	7	43	20.5, 90.3
No	344.9	78	22.6	18.1, 28.2
MTX until time of ILD diagnosis				
Yes	130.2	31	23.8	16.7, 33.8
No	230.99	54	23.4	17.9, 30.5
MTX during follow-up				
Yes	25.1	10	39.6	21.3, 73.7
No	336.0	75	22.3	17.7, 27.9
Anti-TNF until time of ILD diagnosis				
Yes	261.9	66	25.2	19.0, 32.1
No	99.3	19	19.1	12.2, 29.9
Anti-TNF during follow-up				
Yes	34.3	10	29.1	15.6, 54.1
No	326.8	75	22.9	18.2, 28.7

Anti-TNF: TNF inhibitors including ADA (adalimumab), ETN (etanercept), IFX (infliximab), CERTO (certolizumab).

most often, followed by NSIP, as in other settings [26, 27].

Many studies have suggested that ILD can occur before and throughout the course of RA [22, 23]. In our study, ILD preceded joint involvement in 10% of the patients, while the usual was the opposite, with a mean lag time of 12 years between conditions. Despite this, NEREA RA-ILD patients had an acceptable FVC at baseline, being slightly worse in those from FJD, probably in relation to a longer lag time until ILD diagnosis. Lack of screening in clinical practice results in a high variability in the estimation of subclinical ILD, which ranges from 19 to 57% [28]. Current data support that radiographic findings have the tendency to progress in 50% of subclinical cases [29]. Considering that ILD may be asymptomatic in the early stages [30], a systematic screening should be encouraged in order to reduce the existing diagnostic delay. In this sense, the detection of bibasilar crackles during routine pulmonary auscultation of every RA patient could be an easy and inexpensive way to suspect lung disease and conduct a directed workup.

Regarding therapies, 70% of our patients were on glucocorticoids prior to ILD diagnosis and the proportion increased to 90% during the follow-up. As expected, most of the patients were on MTX, anti-TNF, LEF or AM

Table 3 Bivariate analysis

Variable	HR	95% CI	*P*-value
Centre (HCSC *vs* FJD)	0.95	0.6, 1.4	0.8
Gender (female *vs* male)	1.1	0.68, 1.7	0.7
Age at ILD diagnosis	1.004	0.97, 1.03	0.7
BMI	1.002	0.9, 1.04	0.9
Lag time to ILD diagnosis	1.01	0.99, 1.02	0.07
Work status ($N = 56$), *n* (%)			
Active	1	–	–
Housewives	0.7	0.36, 1.6	0.5
Retired	0.8	0.4, 1.5	0.5
Smoker			
Never	1	–	–
Active	0.8	0.5, 1.2	0.3
Former	0.9	0.6, 1.5	0.7
RF >200	1.2	0.8, 1.8	0.3
Anti-CCP >300	0.2	0.3, 1.2	0.2
ESR (>40 *vs* lower)	0.7	0.4, 1.1	0.14
Comorbidity			
Hypertension	0.86	0.5, 1.3	0.5
Cholesterol	0.97	0.6, 1.5	0.9
Ischaemic heart disease	0.6	0.17, 2.5	0.5
Cerebrovascular disease	1.02	0.6, 1.6	0.9
Peripheral vascular disease	0.7	0.4, 1.37	0.4
Cancer	1.67	0.74, 3.7	0.2
Diabetes mellitus	1.2	0.47, 3.2	0.6
Congestive heart failure	1.05	0.5, 2.2	0.8
Sleep apnoea syndrome	2.04	0.9, 4.5	0.07
Depression	1.1	0.6, 2.0	0.6
Renal failure (dialysis)	1.6	1.2, 2.2	0.004
Emphysema	0.55	0.3, 0.95	0.03
Liver disease	0.9	0.4, 1.8	0.8
Ulcus disease	0.7	0.33, 1.6	0.5
Hypothyroidism	1.1	0.6, 1.9	0.7
Gastro-oesophageal reflux	1.4	1.01, 1.9	0.03
PTF parameters			
FVC	0.99	0.98, 1.005	0.3
Baseline DLCO	0.99	0.99, 1.008	0.9
Radiographic ILD pattern, *n* (%)			
UIP	1	–	–
NSIP	0.7	0.4, 1.2	0.2
Other	0.7	0.3, 1.6	0.4
Therapy until time of ILD diagnosis			
Corticosteroids	0.7	0.5, 1.1	0.1
MTX	1.04	0.7, 1.6	0.8
Anti-TNF	0.7	0.3, 1.4	0.3
Therapy during the follow-up, *n* (%)			
Corticosteroids	0.9	0.5, 1.6	0.8
AZA	0.6	0.25, 1.6	0.3
RTX	0.7	0.5, 1.1	0.1
Oxygen	1.1	0.6, 1.7	0.7

Anti-TNF: TNF inhibitors including ADA (adalimumab), ETN (etanercept), IFX (infliximab), CERTO (certolizumab).

before ILD diagnosis [31, 32]. Since the ILD diagnosis, and in agreement with many publications [14, 33–35], MTX and TNF inhibitors were frequently withdrawn, possibly as a result of the potential poor risk–benefit balance. During the follow-up, almost half of the patients started on RTX, while the other half received AZA, ABA or MMF, in descending order of frequency.

The clinical course of RA-ILD can range from asymptomatic to rapidly progressive. However, in case of clinical disease, symptoms usually progress and a decline in pulmonary function is expected [7, 21]. Whereas DLCO is highly sensitive for predicting the presence of ILD, lung volume might be more useful for assessing disease extent [10]. A decrease in FVC of ≥10% over a

Table 4 Multivariate analysis

Variables	HR	95% CI	*P*-value
Centre (HCSC *vs* FJD)	1.6	0.76, 3.37	0.2
Gender (female *vs* male)	1.33	0.7, 2.5	0.3
Age at ILD diagnosis, years	0.98	0.96, 1.005	0.1
Lag time to ILD diagnosis, years	1.03	1.01, 1.04	0.000
Anti-CCP (>300 *vs* lower)	0.63	0.33, 1.19	0.16
ESR (>40 *vs* lower)	0.48	0.3, 0.76	0.002
Comorbidity			
Emphysema	0.37	0.19, 0.70	0.002
Gastro-oesophageal reflux	2.6	1.12, 6.22	0.026
PTF parameters: FVC	1.008	0.99, 1.02	0.120
Radiographic ILD pattern			
UIP	1	–	–
NSIP	0.35	0.19, 0.64	0.001
Other	0.68	0.28, 1.6	0.4
Therapy until time of ILD diagnosis			
Glucocorticoids	0.57	0.34, 0.97	0.039
Therapy during the follow-up			
RTX *vs* other	0.51	0.31, 0.85	0.01

12 month period is considered clinically relevant in the assessment of deterioration [8, 10]. However, recent publications suggest that a 5% difference in FVC is clinically meaningful in the short term [36]. Thus the current study assessed the IR of functional impairment as a decrease in FVC $\geq$5% over a 6 month period.

Our patients progressed over time. In our study, 63% of patients suffered functional impairment over time, the IR being 23.5 per 100 patient-semesters (95% CI 19, 29.1). Moreover, 50% of the patients had functional deterioration at 1.75 years from the diagnosis of ILD. The good news was that we were able to show the positive effect of RTX on functional pulmonary stabilization compared with other therapies. There are few publications addressing this issue. A case report from Hartung *et al*. [37] suggested RTX as an alternative treatment for RA-ILD. More recently, 3 large observational studies of RA-ILD patients on RTX, showed that most patients either remained stable or improved after treatment over time [15, 16, 24]. Nevertheless, none of them compared RTX to other therapies. In the study by Druce *et al.* [38], RA-ILD patients treated with RTX appeared to have lower mortality rates than those on anti-TNF agents, although the difference did not achieve statistical significance.

Regarding the potential role of other therapies in functional progression, MMF has been suggested to be a good option [13]. Nonetheless, we could not draw conclusions from our patients on MMF due to the low use of this drug. Similarly, our data did not allow us to extract firm conclusions about the possible role of ABA, TNF inhibitors or MTX. We could not demonstrate the efficacy of glucocorticoids throughout follow-up, but it has been recorded as a dichotomous variable, and almost 90% of our patients were taking them, thus reducing the possibility of finding differences in our sample.

In this study we were able to replicate previous findings about the role of different sociodemographic and clinical factors on the decline of pulmonary function in RA-ILD. Briefly, we corroborated that UIP had a poorer prognosis in terms of functional deterioration [7, 21, 39]. In addition, we observed that brief disease duration from RA to ILD, higher disease activity at baseline, treatment with glucocorticoids prior to ILD diagnosis and emphysema were associated with a lower risk of functional lung deterioration over time. However, data regarding emphysema should be taken with caution since this factor appears to act as a confounder rendering FVC values higher in ILD patients [40]. It was also interesting to find the adverse impact of gastro-oesophageal reflux on disease prognosis. Positively, this effect could be expected, considering the role of microaspirations in the promotion of lung inflammation.

In different RA-ILD cohort studies using mortality as the primary endpoint, several factors predicting poor survival have been identified. In brief, older age, male gender, ILD severity, RA disease activity, the extent of fibrosis on high-resolution CT, a UIP pattern and acute exacerbations have been identified as predictors of poor prognosis [41–47]. Regarding biomarkers, positivity of RF or ACPA, high lactate dehydrogenase levels [48], KL-6 and IL-6 also seem to confer a poorer prognosis [49].

As major limitations of our study, we need to acknowledge the retrospective nature of the design and also the small sample size, as the prevalence of clinically significant RA-ILD could rise to 10% of RA patients [50]. In contrast, the inclusion of non-selected patients from two tertiary hospitals with non-standardized immunosuppressive therapy and a long-term follow-up provides an overall vision of real-world evidence in this field. Since the patients that attended special RA-ILD units were subject to standardized evaluations, homogeneous,

objective and every 6 months outcomes were available for analysis, as adjusted for confounders to prevent possible bias.

In conclusion, we underline the progressive decline in pulmonary function in patients with RA-ILD. Our results support the beneficial effect of RTX in the management of RA-ILD from both an articular and respiratory perspective. Notably, it appears that early detection and treatment might be a major goal in order to improve patient outcomes. The impact of other potential associated factors on progression in RA-ILD patients, such as types of radiological patterns, baseline comorbidities and lower ESR at the time of ILD diagnosis, may help clinicians in daily practice. This notwithstanding, our data need to be replicated in additional cohort studies in order to gain further insights into the management and prognosis of RA-ILD patients.

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