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REVIEW

Rituximab for rheumatoid arthritis-related interstitial lung disease: A systematic review and meta-analysis

Tarun Krishna Boppana, Saurabh Mittal, Karan Madan, Anant Mohan, Vijay Hadda, Randeep Guleria

All India Institute of Medical Sciences, Pulmonary, Critical Care and Sleep Medicine, Delhi, India

Correspondence: Saurabh Mittal, MD.
E-mail: saurabh_kgmu@yahoo.co.in

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ABSTRACT

Objectives: This systematic review and meta-analysis aimed at summarizing the evidence of efficacy and safety of rituximab in rheumatoid arthritis-related interstitial lung disease (RA-ILD).

Materials and methods: PubMed and Embase databases were searched until June 22, 2022, to identify studies on RA-ILD treated with rituximab, confined to predefined inclusion and exclusion criteria. A systematic review and meta-analysis were performed on the included studies to assess the overall stabilization or improvement in ILD, changes in percent-predicted (%-predicted) forced vital capacity (FVC), and %-predicted diffusion capacity of lungs for carbon monoxide (DLCO) following rituximab therapy.

Results: A total of 15 studies (4 prospective and 11 retrospective studies) were included, with a total of 314 patients. There were 105 (60.7%) females out of 173 subjects for whom sex details were available from seven studies. The overall pooled proportion of patients with stabilization or improvement in ILD was 0.88 [95% confidence interval (CI): 0.76-0.96, p=0.02]. Rituximab improved FVC from baseline by 7.50% (95% CI: 1.35-13.65; p=0.02, fixed effect). Similarly, rituximab improved DLCO by 6.39% (95% CI: 1.366-14.43; p=0.12, random-effect). Two retrospective studies reported reduced mortality with rituximab therapy compared to tumor necrosis factor-alpha inhibitors.

Conclusion: Treatment with rituximab in RA-ILD was associated with a significant improvement in %-predicted FVC, as well as stabilization or improvement in ILD after one year of treatment.

Keywords: Anti-CD20, meta-analysis, rheumatoid arthritis-related interstitial lung disease, rituximab.

Rheumatoid arthritis (RA) is a rheumatological disorder involving multiple body systems; however, joint involvement remains the primary clinical manifestation. It is also associated with various pulmonary manifestations, including pleural effusion, bronchiolitis, rheumatoid nodules, bronchiectasis, and interstitial lung disease (ILD).[1] RA-related ILD (RA-ILD) is usually due to aberrant immune system activation leading to fibroproliferation. ILD in RA patients contributes to significant morbidity leading to poor quality of life, disability, and increased mortality.[2] The common radiological and histological patterns include usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), organizing pneumonia, desquamative interstitial pneumonia, and unclassifiable ILD. The treatment of ILD in patients with RA continues to remain a challenge. Several medications have been used by clinicians and are suggested in the literature, but no large randomized controlled trials are available to guide the treatment of RA-ILD. Recent years have witnessed several immunosuppressive and antifibrotic therapeutic strategies in RA-ILD. The therapeutic options range from cyclophosphamide, azathioprine, and mycophenolate mofetil (MMF) to rituximab. Disease-modifying antirheumatic drugs and anti-tumor necrosis factor-alpha (TNF-α) agents, which are used to treat joint symptoms, are also used to treat RA-ILD.[3] Among specific therapies, cyclophosphamide is associated with several adverse effects, including cytopenias, infection, and gonadal toxicity. MMF, an alternative agent, is better tolerated but has gastrointestinal as well as hematological side effects.[4] Rituximab is one agent that has shown promise in treating systemic sclerosis-associated ILD (SSc-ILD).[5] Rituximab is

a chimeric anti-cluster of differentiation (CD)20 monoclonal antibody molecule that has been used for the off-label treatment of RA-ILD. There are multiple studies and case reports available that have described the use of rituximab in RA-ILD.[6,7] However, no randomized trial has been done to assess the efficacy of the same, and its efficacy in RA-ILD remains unclear. Hence, we conducted this systematic review and meta-analysis to analyze the current evidence for the efficacy and safety of rituximab therapy in the treatment of RA-ILD.

MATERIALS AND METHODS

Literature search

The existing literature was searched for any previous systematic review on the efficacy of rituximab in RA-ILD, and no reviews were retrieved. The search was conducted in the PubMed and Embase databases using the following keywords: (rheumatoid arthritis) AND (interstitial lungdisease OR ILD OR diffuse parenchymal lung disease OR DPLD) AND (Rituximab OR anti-CD 20). No language filters were applied, and a search was conducted until June 22, 2022. The retrieved articles were managed on a data referencing software, and duplicates were removed. All the abstracts were screened, and full texts were retrieved for the articles where information from the abstract was unclear. Articles providing no original data were excluded.

Eligibility criteria

Studies describing the use of rituximab in patients with RA-ILD were included if they provided information on patient outcomes (in terms of lung function changes, radiological change, clinical change or overall change). However, we excluded articles describing single case reports and conference abstracts.

Study selection

Two reviewers independently conducted the search, study selection, and data collection. All the disagreements were resolved by mutual discussion, along with a third reviewer's involvement. All the relevant references were screened and included as per inclusion criteria. The full texts of all potentially relevant articles were retrieved for a detailed review. The primary outcome was the improvement or stabilization of lung function and ILD (radiological or overall). Improvement in lung function was defined as a ≥10% increase in forced vital capacity (FVC) or a ≥15% increase in diffusion capacity of lungs for carbon monoxide (DLCO). Where lung function outcomes were not available, an overall improvement reported by authors or an improvement in high-resolution computed tomography of the chest was recorded as an improvement. Stabilization of lung function was defined as a <10% improvement or <10% decline in FVC.[7] The time-point for repeat assessment was at 6-and 12 months.

Other secondary outcomes included change in percent-predicted (%-predicted) FVC, change in %-predicted DLCO, and impact on survival and adverse events associated with therapy.

Data abstraction

A predesigned data extraction format was used to extract data by both reviewers independently. The following information was extracted on the form: authors; year of publication; study design (prospective, retrospective, randomized controlled trial); baseline characteristics of patients, including the number of patients that met the inclusion criteria, age, sex, duration of RA-ILD, treatments before and concurrent with rituximab; total dose and regimen of rituximab; baseline FVC and DLCO; FVC and DLCO at follow-up; adverse events associated with rituximab.

Quality assessment

Quality assessment was based on the Newcastle-Ottawa Scale for the cohort studies.[8] Two reviewers independently assessed the quality of the studies, and any disagreements were resolved after discussion with the third reviewer. The quality assessment results are shown in Supplementary Table 1.

Statistical analysis

The STATA statistical analysis software version 15.0 (StataCorp., College Station, TX, USA) was used for statistical analysis. The proportional meta-analysis was performed using the random-effects model for the primary outcome (i.e., the proportion of patients having stability or improvement in disease). The effects of rituximab on FVC and DLCO were recorded, and the pooled effect of change in %-predicted FVC

and DLCO was presented as a weighted mean difference with corresponding 95% confidence intervals (CIs) using a random-effects model. The analyses for these outcomes were conducted using the means and standard deviations provided in the articles. Wherein median and range of FVC and DLCO were provided, the mean and standard deviation values were calculated using Luo et al.[9] and Wan et al.'s[10] methods, respectively. RevMan 5.4 software (Revman International, Inc., New York, USA) was used to generate forest plots.

Heterogeneity was calculated using the I-squared (I^2) statistic representing the percentage of total variation across studies.[11] A sensitivity analysis was also carried out. We repeated all results after excluding the studies where the efficacy of rituximab in RA-ILD was not the primary focus of the study. Begg and Mazumdar's[12] tests and contoured funnel plots were used to estimate publication bias. A p-value ≤0.05 was taken as significant publication bias.

RESULTS

The search results are shown in Figure 1 as a flow diagram. A total of 595 articles were identified. After removing duplicates and noneligible studies, 15 studies were included in the final analysis.

Characteristics of included studies

The basic details of the included studies are summarized in Table 1. Among these, only five studies were the ones with a primary focus on the efficacy of rituximab in RA-ILD.[6,7,13-15] One focused on the safety of rituximab in RA-ILD,[16] and one compared the mortality of TNF-α inhibitors and rituximab for RA-ILD.[17] Four studies focused on rituximab in connective tissue disease-associated ILD (CTD-ILD),[18-21] and data only on RA-ILD was extracted. Four studies had their primary focus on RA-ILD, and rituximab use was also described in the outcomes.[22-25] Four studies were prospectively conducted,[6,15,24,25] while 11 were retrospective analyses. All studies included patients who were naïve for rituximab therapy.

A total of 314 patients from 15 studies were included in this review. ILD patterns were available from 10 studies including 212 patients.[7,13-16,18,20,22-24] Amongst these, 100 (47.1%) had UIP pattern, while 76 (35.8%) had NSIP pattern. There were 105 (60.7%) females out of 173 subjects for whom sex details were available from seven studies.[7,14-18,21] The dose of rituximab used was mentioned in nine studies. In eight studies, 1000 mg was given in two doses two weeks apart, while it was variable in one study. The dose was usually repeated after six months in three studies,[14,15,23] while one study mentioned that it was repeated at relapse.[7]

Efficacy measures

The outcome measures for the included studies are summarized in Table 2. Nine studies

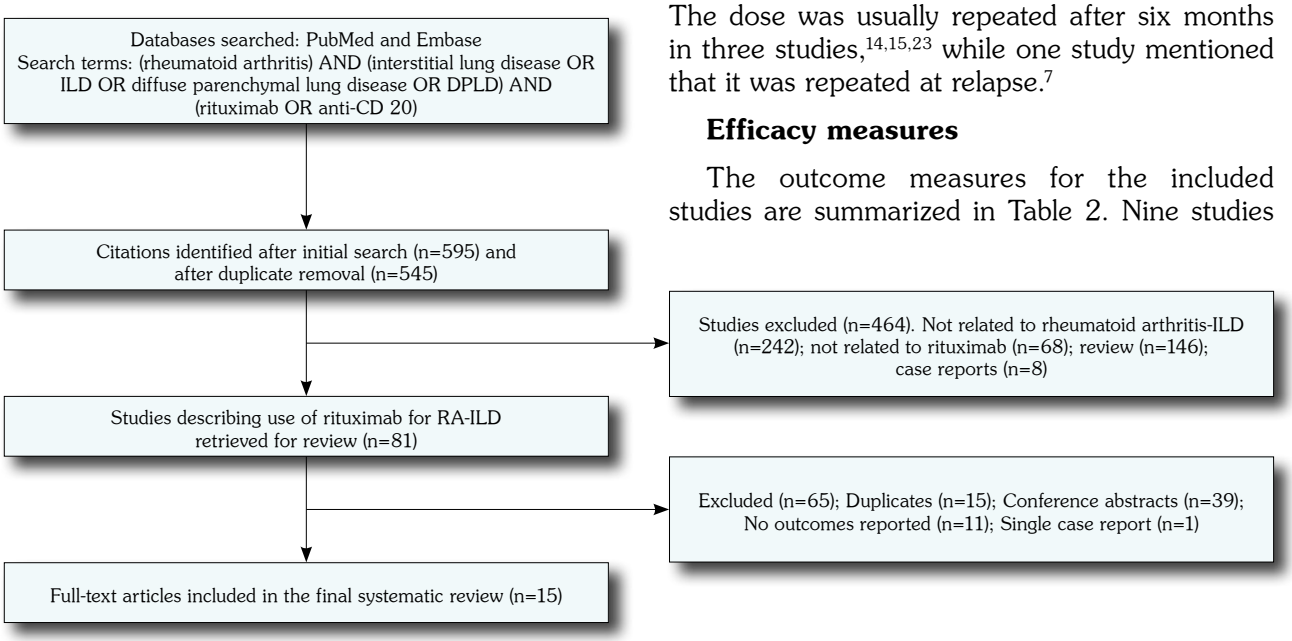

Figure 1. Flow diagram of the study selection process for this systematic review and meta-analysis.
ILD: Interstitial lung disease; RA: Rheumatoid arthritis.

Table 1. The basic details of the studies describing the use of rituximab in RA-ILD included in the systematic review

Author and year	Primary focus of the study	Number of RA-ILD cases treated with rituximab	Study design	Dose of rituximab	ILD duration (years)	Radiological ILD pattern	Age (year)	Females		Concomitant or previous medications (wherever available)			
								n	%		n	%	Mean±SD
Vadillo et al.[6] 2020	Rituximab in RA-ILD	31	Prospective 10 years	NA	NA	NA	NA	NA		NA			
Yusof et al.[7] 2017	Rituximab in RA-ILD	56	Retrospective	1000 mg two doses, repeated on relapse	Median 5 years (IQR 3-7)	NSIP 33 UIP 20	Median 64 (IQR 59-72)	36	64	Methotrexate Azathioprine Leflunomide Mycophenolate mofetil	28 5 2 1	78 14 5 3	
Fui et al.[13] 2020	Rituximab in RA-ILD	14	Retrospective	1000 mg two doses	NA	UIP 9 NSIP 3 Nodular ILD 2	62.64±3.227	NA		NA			
Matteson et al.[15] 2012	Rituximab in RA-ILD	10	Prospective	1000 mg two doses, repeat at 6 months	3.2 years; range 0.0 to 7.5	UIP 4 NSIP 6	64.7 years (range 43 to 80)	6	60	NA			
Narváez et al.[14] 2020	Rituximab in progressive RA-ILD	31	Retrospective	1000 mg two doses, repeat at 6 months	Median 21 (9-38) months	UIP 13 NSIP 10 Others 8	61±12	18	58	Leflunomide Mycophenolate mofetil Azathioprine	21 7 2		
Chartrand et al.[18] 2015	Rituximab in CTD-ILD	15; 9 received multiple cycles	Retrospective	1000 mg two doses	2.5±2.1	NSIP 7 UIP 4	62.9±10.3	10	66.7	Mycophenolate mofetil Methotrexate Leflunomide Azathioprine	3 4 1 1		
Cronin et al.[16] 2021	JAK inhibitors and rituximab safety in RA-ILD	14 (13 ILD, 1 ILD with bronchiectasis); 5 only bronchiectasis	Retrospective	1000 mg two doses	Median 3 years	UIP 2 Probable UIP 5 Fibrotic NSIP 1	Median 70 (IQR 59-76)	14	73.7	Prednisolone Methotrexate Leflunomide Azathioprine Hydroxychrloroquine Sulfasalazine	6 2 2 2 6 4		
Mena-Vázquez et al.[25] 2021	Assess the effect of DMARDs on RA-ILD	10	Prospective	NA	NA	NA	NA	NA		NA			
Atienza-Mateo et al.[19] 2020	Rituximab in CTD-ILD	5	Retrospective	Variable	NA	NA	NA	NA		Previously patients had received biologicals	3		
Mena-Vázquez et al.[24] 2021	Predictors of progression and mortality in RA-ILD	13	Prospective 5 years	NA	NA	UIP 9 NSIP 4	NA	NA		NA			
Druce et al.[17] 2017	Mortality comparison between TNF inhibitors and rituximab for RA-ILD	43	Retrospective	NA	Median 5 (IQR 3-13)	NA	64.7 (11.4)	19	44.2	Previously number of conventional synthetic DMARDs use was			3.2±1.2
Duarte et al.[23] 2019	RA-ILD description	26	Retrospective	NA (mean 4 cycles)	NA	NSIP 10 UIP 4 OP 2 Unclassifiable 1	NA	NA		NA			
Fitzgerald et al.[21] 2015	Rituximab for CTD-ILD	4 (2 ILD, 2 Rheumatoid nodules)	Retrospective	1000 mg two doses	NA	NA	Median 56.5 (IQR 52-58.3)	2	50	Previously Etanercept Methotrexate Azathioprine Cyclophosphamide Adalimumab	 2 2 1 1 1		
Robles-Perez et al.[20] 2020	Rituximab in severe CTD-ILD	5	Retrospective	1000 mg two doses	NA	NSIP 2 LIP 1 UIP emphysema 1 Unclassifiable 1	NA	NA		NA			
Kelly et al.[22] 2021	RA-ILD outcomes	37	Retrospective	NA	Median 4 years	77% UIP	Median age 7	NA		NA			

RA: Rheumatoid arthritis; ILD: Interstitial lung disease; SD: Standard deviation; NA: Not available; IQR: Interquartile range; NSIP: Nonspecific interstitial pneumonia; UIP: Usual interstitial pneumonia; OP: Organizing pneumonia; JAK: Janus-like kinase; DMARD: Disease-modifying antirheumatic drugs.

Table 2. The reported efficacy and safety of rituximab in RA-ILD in the studies included in this systematic review

Author and year	Number of cases	Follow-up duration	Main results	Complications
Vadillo et al.[6] 2020	31	Mean exposure of 20.6 months	Associated with reduced risk of functional impairment (5% worsening in FVC) on multivariate analysis [HR: 0.51 (0.31-0.85)]	Discontinuation: 3 due to no effect, 2 due to adverse events, 6 due to joint disease worsening
Md Yusof et al.[7] 2017	56	195 patient-years (37 PFT and 44 overall response was available)	7/37 (19%) had improvement in PFTs, 25/37 (68%) were stable and 5/37 (13%) had worsening of their PFTs On overall lung assessment, 7/44 (16%) had improved, 23/44 (52%) were stable and in 14/44 (32%) ILD had progressed	78 adverse events in 33 patients; 15 infections, 12 deaths, 3 malignancy and 48 hospitalizations
Fui et al.[13] 2020	14	12 months	FVC (% predicted): Pre-rituximab 87.11±6.136; post-rituximab 93.014±23.01 DLCO (% predicted): Pre- and post-rituximab 53.76±5.372 and 54.9±15.2 respectively	Two: one infection, one hypogammaglobulinemia
Matteson et al.[15] 2012	10	48 weeks	FVC change 2.4% (-12 to 17%); DLCO change 11.6% (-22 to 47%) [presented as mean (range)] The DLco had worsened by at least 15% (at least ≥3 mL/min/mm Hg) in 1 patient, was stable in 4 patients, and increased by >15% of baseline in 2 patients The FVC declined by at least 10% (and at least ≥200 mL) in 1 patient, was stable in 4 patients, and increased by at least 10% in 2 patients	One withdrew medication; one unrelated death, one death due to pneumonia
Narváez et al.[14] 2020	31	1 and 2 years	Change in FVC at 1 year + 8.06% (10.9 to 5.2); p<0.001 Change in DLCO at 1 year + 12.7% (16.3 to 9.1); p<0.001 Change in FVC at 2 year + 11.2% (15.6 to 6.8); p<0.001 Change in DLCO at 2 year + 14.8% (19.3 to 10.3); p<0.001 Data is presented as mean (95% confidence interval)	Serious adverse events in five cases (3 withdrawl due to recurrent respiratory infections, 2 deaths)
Chartrand et al.[18] 2015	15; 9 received multiple cycles	26 weeks	>10% improve in FVC in 4 patients; <10% improvement in FVC in 3; >10% decline in FVC in 2 patients	NA
Cronin et al.[16] 2021	14 (13 ILD, 1 ILD with bronchiectasis); 5 only bronchiectasis	2.14 years (SD=1)	No data available	4 hospitalization (1 died)
Mena-Vázquez et al.[25] 2021	10	2 years	9 improved 1 worsened (died)	NA
Atienza-Mateo et al.[19] 2020	5	6 months	FVC (% predicted): Pre-rituximab 84.60±25.08; post-rituximab 93.43±24.54 (mean of differences + 8.83%, p=0.022) DLCO also improved	NA
Mena-Vázquez et al.[24] 2021	13	NA	Associated with reduced risk of progression	2 deaths: 1 progression of ILD 1 progression and lung infection
Druce et al.[17] 2017	43	150.7 patient-years	All cause mortality in patient-years: rituximab= 53.0 (22.9-104.6) per 1000 patient-years TNF-inhibitors= 94.8 (74.7-118.7) per 1000 patient-years	7 deaths (1 reported to be due to RA-ILD)

Table 2. Continued

Author and year	Number of cases	Follow-up duration	Main results	Complications
Duarte et al.[23] 2019	26	6.7±4.1 years	Only 17/26 follow-ups available. 12 stable, 3 improvement, 2 progression (radiological and lung function)	7 stopped; 6 due to non-response and 1 due to carcinoma prostate
Fitzgerald et al.[21] 2015	4 (2 ILD, 2 Rheumatoid nodules)	4.5 months	FVC 37.4 to 47.1 in 1 and 98.6 to 109.5 in another; both improved; DLCO also improved Both patients with nodules had reduction	NA
Robles-Perez et al.[20] 2020	5	2 years	4 improved [FVC 0.2 (3.6)% and DLCO 11 (9.9)% at 1 year]; 2 maintained improvement at 2 years	NA
Kelly et al.[22] 2021	37		All-cause mortality: Anti-TNF therapies *vs.* rituximab (31% *vs.* 8%, p=0.03) Respiratory mortality: Anti-TNF therapy *vs.* rituximab (15% *vs.* 4%, p=0.04) Survival: rituximab *vs.* Anti-TNF therapy at three (92% *vs.* 82%), five (82% *vs.* 76%) and seven years (80% *vs.* 64%; p=0.037) Cox modeling demonstrated rituximab was associated with a 48% reduction in mortality compared with anti-TNF therapies (HR: 0.519; 95% CI: 0.262, 1.03)	NA

RA: Rheumatoid arthritis; ILD: Interstitial lung disease; FVC: Forced vital capacity; HR: Hazard ratio; NA: Not available; PFT: Pulmonary function tests; SD: Standard deviation; CI: Confidence interval.

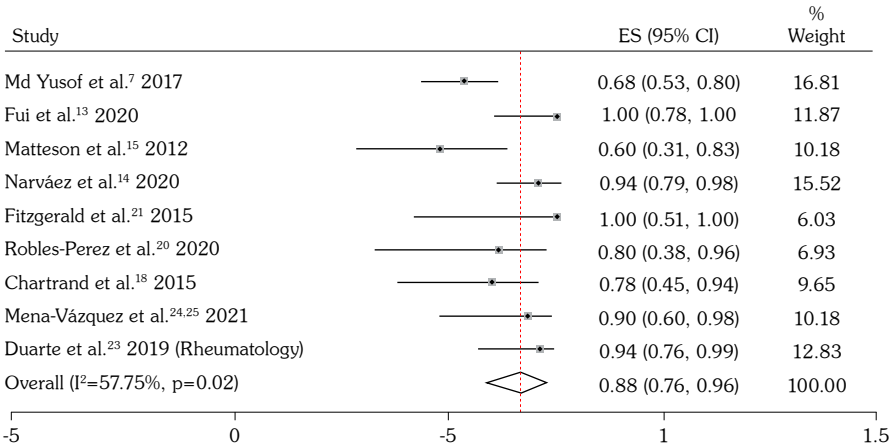

Figure 2. The forest plot depicting the pooled proportion of patients who had stabilization or improvement in RA-ILD following rituximab therapy.

RA: Rheumatoid arthritis; ILD: Interstitial lung disease; CI: Confidence interval; ES: Effect size.

reported the proportion of patients who had an improvement or stabilization of ILD following initiation of rituximab.[7,13-15,18,20,21,23,25] Out of the 144 patients for whom the outcome was available, 119 had improvement or stabilization of ILD (70 patients had improvement, while 49 patients had stabilization). The overall pooled proportion of patients was 0.88 (95% CI: 0.76-0.96, p=0.02, Figure 2). There was significant heterogeneity among studies (I^2=57.75%), and there was no publication bias as assessed by the funnel plot as well as Begg and Majumdar test (p=0.91, Supplementary Figure 1).

The mean pre-and post-rituximab %-predicted FVC values were available from five studies.[13-15,19,21] The duration of follow-up was 12 months in two,[13,14] 48 weeks in one,[15] six months in one,[19] and 4.5 months in one study.[21] Cumulatively, the mean difference in %-predicted FVC after and before rituximab was 7.50% (95% CI: 1.35-13.65; p=0.02, fixed effect; Figure 3). There was no significant heterogeneity among the studies reporting a change in %-predicted FVC (I^2=0%).

The mean pre- and post-rituximab %-predicted DLCO values were available from three studies.[13-15] Cumulatively, the mean difference in %-predicted DLCO after and before rituximab was 6.39% (95% CI: 1.366-14.43; p=0.12, random-effect; Figure 4). There was some heterogeneity among the studies reporting a change in %-predicted DLCO (I^2=58%, p=0.09).

One study reported that rituximab was associated with a reduced risk of worsening of lung function (5% worsening in FVC) on

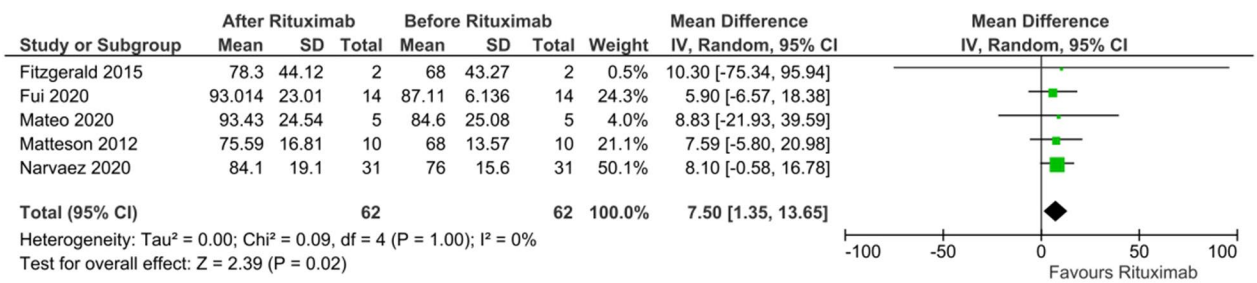

Figure 3. The pooled analysis for the change in %-predicted FVC following rituximab therapy in RA-ILD.

SD: Standard deviation; CI: Confidence interval; FVC: Forced vital capacity; RA: Rheumatoid arthritis; ILD: Interstitial lung disease.

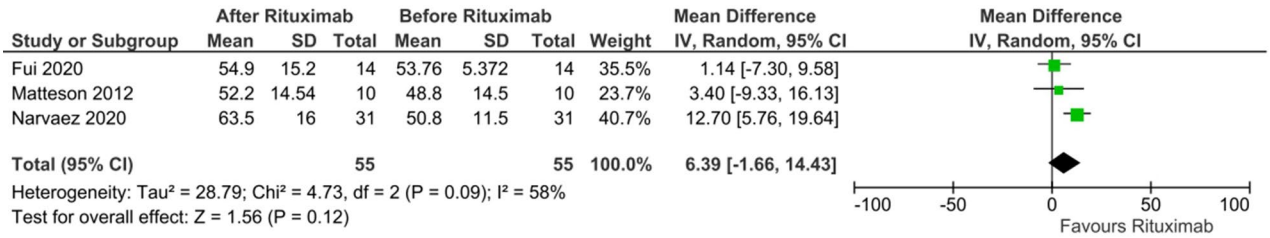

Figure 4. The pooled analysis for the change in %-predicted DLCO following rituximab therapy in RA-ILD.
SD: Standard deviation; CI: Confidence interval; DLCO: Diffusion capacity of lungs for carbon monoxide; RA: Rheumatoid arthritis; ILD: Interstitial lung disease.

multivariate analysis (hazard ratio [HR]: 0.51 [0.31-0.85]).[6]

Comparison to TNF-α inhibitors and impact on mortality

In one study, all-cause mortality was 53.0 (22.9-104.6) per 1,000 patient-years in the rituximab group, while it was 94.8 (74.7-118.7) per 1,000 patient-years in the TNF-α inhibitor group.[17] In another study, Cox modeling demonstrated that rituximab was associated with a 48% reduction in mortality compared to anti-TNF drugs (HR: 0.519; 95% CI: 0.262-1.03).[22]

Sensitivity analysis

We performed a sensitivity analysis of the rituximab effects by including only the studies exclusively reporting data on RA-ILD patients. The cumulative proportion of patients having improvement or stabilization of lung function was 0.85 (0.62-0.99) from four studies.[7,13-15] Additionally, the mean change in %-predicted FVC described in those three studies was 7.43% (1.14-13.72%).[13-15] These results are shown in Supplementary Figures 2 and 3.

Publication bias

Publication bias was estimated with funnel plots and Begg and Mazumdar test. All p-values were >0.05, suggesting an absence of significant publication bias.

Adverse events

The adverse events of using rituximab in RA-ILD were described in nine articles.[6,7,13-17,23,24] The common severe adverse events included hypogammaglobulinemia and infections, such as pneumonia. However, the exact incidence of drug-related side effects could not be calculated.

DISCUSSION

To date, there is no specific treatment for RA-ILD, and due to the lack of robust evidence to make any recommendations, no definite consensus statements are available to guide the therapy for RA-ILD. Traditionally, RA-ILD patients who have NSIP or organizing pneumonia patterns are treated with steroids, according to data usually extrapolated from idiopathic interstitial pneumonia experience rather than any evidence for the same. Additional immunosuppressive drugs, such as azathioprine, are also added with the same extrapolation. The use of cyclophosphamide and MMF is usually guided by their efficacy in SSc-ILD.[26,27] The treatment practices for patients with UIP-pattern ILD vary significantly and include observation to aggressive immunosuppression.[28] The beneficial effect of rituximab in RA-ILD has a biological plausibility supported by the pathophysiology of the disease. B lymphocytes play a critical role in the pathogenesis of RA and ILD.[29] The anti-cyclic citrullinated peptide antibody (formed by B cells) is found in almost 60 to 70% of RA patients and is associated with a higher risk of ILD.[30] The anti-CD20 molecule rituximab leads to the depletion of B cells and has been utilized in many diseases associated with autoantibody formation. The off-label use of rituximab for RA-ILD has been done for many years, given the pathogenic role of B cells in the initiation and progression of RA-ILD. This drug has been shown to stabilize lung function in SSc-ILD.[5] However, its use in RA-ILD is not extensively described. Even the recently completed large RECITAL (rituximab versus intravenous cyclophosphamide in patients with CTD-ILD in the UK) trial on the efficacy of

rituximab in CTD-ILD did not include patients with RA-ILD.[31] This systematic review attempts to fill this void by summarizing the evidence for the anti-CD20 biological agent rituximab in treating RA-ILD.

The meta-analysis demonstrated stabilization or improvement in RA-ILD in a significant proportion of patients (mean: 88%, 95% CI: 76-96%), which is the key parameter to assess the efficacy of any therapy in ILDs. Furthermore, the lung function, as assessed by %-predicted FVC, demonstrated stabilization or improvement. Similar results were found in the sensitivity analysis as well. However, no significant improvement was noted in the %-predicted DLCO values following rituximab. The minimal clinically important difference (MCID) for FVC at 12 months in studies on SSc-ILD has been described as 3.0 to 5.3%, while no such MCID values exist for lung function change in RA-ILD.[32] The mean improvement found in this meta-analysis is 7.5%, suggesting a significant change, even if SSc-ILD MCID values are used.

The use of rituximab for various CTD-ILDs has significantly increased over the last few years. However, the strongest evidence for the same remains for SSc-ILD. Another group of ILD patients using rituximab are the ones associated with inflammatory muscle diseases.[33] A large randomized controlled trial in patients with CTD-ILD (systemic sclerosis, mixed connective tissue disorder, or inflammatory muscle disease) has shown that rituximab improves lung function and quality of life with lesser side effects than cyclophosphamide.[31] Since autoantibodies remain at the center of all these disorders, including RA, rituximab continues to be used for joint symptoms in RA. However, its role in RA-ILD is unclear, and it prompted us to conduct this systematic review. The newly emerging data regarding the use of antifibrotic therapies in progressive fibrosis ILD, including RA-ILD, and the potential combination between immunosuppressive therapies, including rituximab, with antifibrotic drugs needs further research to rationalize their use.

This meta-analysis had several limitations. The studies included were mainly retrospective, and most had no control group. Only two retrospective studies compared mortality outcomes between rituximab and other biologic agents. The number of patients included was small, and lung function assessment was done within one year, most often suggesting the need for longer follow-up to identify the long-term effects of rituximab therapy. As there was a wide variation in prior and concomitant immunosuppressive therapy, its effect could not be considered. We could not perform a subgroup analysis based upon the radiological patterns to identify if any specific patterns may respond better. In addition, most studies did not define the exact inclusion criteria and whether only patients with progressive disease were included. The disease duration prior to enrollment and prior progression is also one crucial parameter in defining future outcomes. Similarly, the disease duration effect before rituximab was not accounted for. Therefore, we could not conclude if early initiation of rituximab in the course of the disease affects the lung function outcomes. The key issue highlighted in this meta-analysis is the paucity of literature on this important clinical question. No randomized studies were found addressing this issue.

In conclusion, in this systematic review and meta-analysis, rituximab therapy was associated with the stabilization of ILD. Furthermore, there was a significant improvement in FVC, but not DLCO, after one year of therapy. However, there is only low-quality evidence to support this conclusion. Due to limited evidence, there is an urgent need for further studies, including randomized controlled trials comparing the effectiveness of the different regimens of rituximab and combination therapy of rituximab with other immunosuppressive agents.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept: S.M.; Design, analysis: S.M., T.K.B.; Control/supervision: S.M., R.G.; Data collection, literature review: S.M., T.K.B., K.M.; Writing the article: T.K.N., S.M., A.M., V.H.; Critical review: S.M., K.M., R.G.

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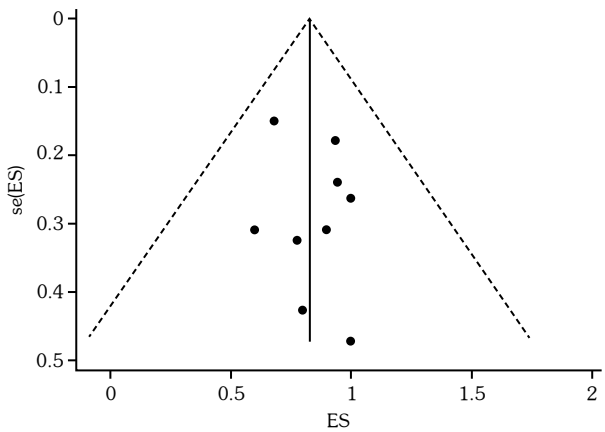
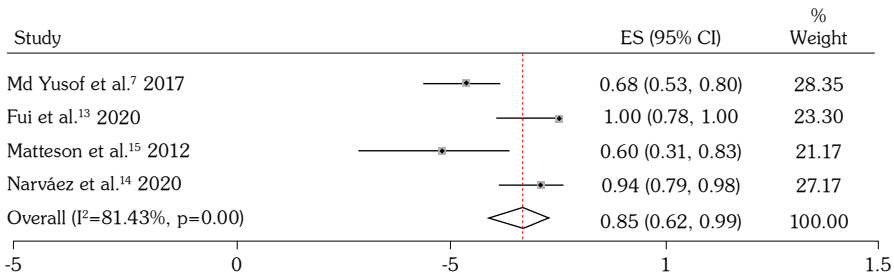
Supplementary Table 1. Quality assessment of the fifteen studies that were included in this systematic review (Newcastle Ottawa Scale)

	Selection				Comparability	Outcome			
	1	2	3	4	5\6	7	8	9	Total score
Chartrand et al.[18] 2015	*		*	*		*	*	*	6
Cronin et al.[16] 2021	*		*	*		*	*	*	6
Druce et al.[17] 2017	*	*	*	*	*/*	*	*	*	9
Duarte et al.[23] 2019	*		*	*		*	*	*	6
Fitzgerald et al.[21] 2015	*		*	*		*	*	*	6
Fui et al.[13] 2020	*		*	*		*	*	*	6
Kelly et al.[22] 2021	*		*	*		-	-	-	3
Atienza-Mateo et al.[19] 2020	*		*	*		*	*	*	6
Matteson et al.[15] 2012	*		*	*		*	*	*	6
Mena-Vázquez et al.[24] 2021	*		*	*		-	-	-	3
Mena-Vázquez et al.[25] 2021	*		*	*		*	*	*	6
Narváez et al.[14] 2020	*		*	*		*	*	*	6
Robles-Perez et al.[20] 2020	*		*	*		*	*	*	6
Vadillo et al.[6] 2020	*		*	*		-	-	-	3
Md Yusof et al.[7] 2017	*		*	*		*	*	*	6



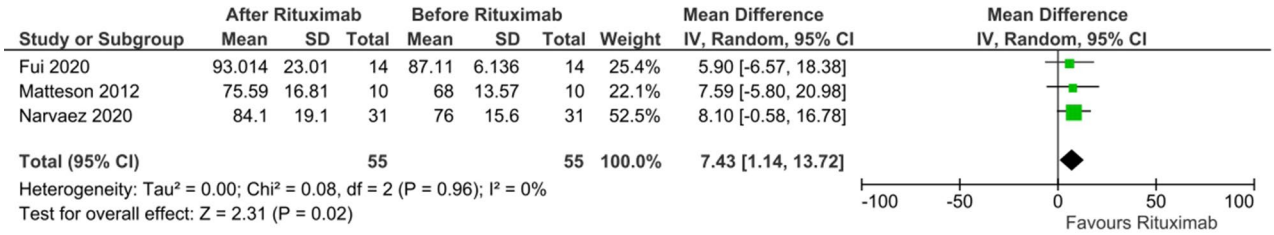
Supplementary Figure 1. The funnel plot for the included studies for the outcome "stabilization or improvement in RA-ILD." It shows the effect size of each study on the X-axis and the standard error on the y-axis. The symmetric distribution of studies on each side of the central line suggests a lack of publication bias.

RA: Rheumatoid arthritis; ILD: Interstitial lung disease; ES: Effect size.



Supplementary Figure 2. The forest plot depicting the pooled proportion of patients who had stabilization or improvement in RA-ILD in the sensitivity analysis.

RA: Rheumatoid arthritis; ILD: Interstitial lung disease; CI: Confidence interval; ES: Effect size.



Supplementary Figure 3. The pooled analysis for the change in %-predicted FVC following rituximab therapy in the sensitivity analysis.

SD: Standard deviation; CI: Confidence interval; FVC: Forced vital capacity.