ORIGINAL RESEARCH

Efficacy of non-conventional synthetic DMARDs for patients with rheumatoid arthritis-associated interstitial lung disease: a systematic review and meta-analysis

Haoming Yuan,1,9 Shaoxin Cui,1 Lin Yang,1 Jiehan Cui,1 Xiaoqing Wang,1 Meng Ding,1 Lu Jin,1 Yanru Wang,1 Fei Chang,1 Hongtao Jin,1 Jun Ma,2,3 Min Shi,4,5 Aijing Liu1,2,5

ABSTRACT

Objectives We conducted a systematic review and meta-analysis to determine the efficacy of non-conventional synthetic disease-modifying antirheumatic drug (ncs-DMARD) strategies on patients with rheumatoid arthritis (RA)-associated interstitial lung disease (ILD).

Methods PubMed, EMBASE, the Cochrane Library and Web of Science were searched for relevant articles from inception to 1 June 2022. The results obtained from the analysis were expressed as mean difference (MD), effect size and 95% CI.

Results A total of 17 studies, including 1315 patients with RA-ILD, were eligible. The ncs-DMARDs included abatacept, rituximab, tocilizumab, tumour necrosis factor inhibitors and Janus kinase inhibitors. Compared with the baseline, there were no significant changes in forced vital capacity (FVC), forced expiratory volume in the first second (FEV1) and diffusion lung capacity for carbon monoxide (DLCO). Of note, FVC was obviously increased in rituximab subgroup (MD=−4.62, 95% CI −8.90 to −0.33, p=0.03). Also, high-resolution CT non-progression rate and mortality rate due to ILD progression in patients with RA-ILD were 0.065 (95% CI 0.746 to 0.834, p=0.015) and 0.049 (95% CI 0.035 to 0.065, p=0.000), respectively.

Conclusion ncs-DMARDs alone or combined with conventional therapy might be an optimal and promising treatment for stabilising or improving ILD in patients with RA-ILD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Interstitial lung disease (ILD) is the most common extra-articular manifestation of rheumatoid arthritis (RA). For the past of years, non-conventional synthetic disease-modifying antirheumatic drugs (ncs-DMARDs) have been widely used in patients with RA. However, therapeutic impacts of ncs-DMARDs on patients with RA-ILD were controversial in the previous literature.

WHAT THIS STUDY ADDS

In this study, almost all ncs-DMARDs used in RA were comprehensively analysed to explore their effects on the pulmonary changes of patients with RA-ILD. The pooled results showed that the pulmonary conditions of patients after ncs-DMARD treatment were stable, relatively.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

Our results indicated ncs-DMARD therapy favours stable or improved lung disease in patients with RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterised by destructive joint disease and extra-articular manifestation.1 Interstitial lung disease (ILD) is the most common extra-articular manifestation, affecting 2–17% of patients with RA based on clinical symptoms and high-resolution CT (HRCT) chest scan findings.2–4 The severe ILD caused by RA negatively affects people’s health worldwide.5 It has been reported that the death hazard rate in patients with RA-ILD is 2–10 times that of patients with RA without ILD,6 making it the second leading cause of premature death in patients with RA after cardiovascular disease. At present, the exact pathogenesis of RA-ILD remains unclear. It was found that the MUC5B promoter variant, elevated interleukin-17A receptor and citrullination in the lung tissue may contribute to the onset and progression of RA-ILD.7–9 It is
also worth noting that apart from the natural course of RA and infection, disease-modifying antirheumatic drugs (DMARDs) may induce or worsen ILD. In this situation, making the decision with patients in therapeutic regimens is more complicated.

In recent years, non-conventional synthetic DMARDs (ncs-DMARDs), including biological DMARDs (bDMARDs) and target DMARDs (tDMARDs), have been used for patients with RA with poor response or intolerance to conventional synthetic DMARDs (cs-DMARDs). bDMARDs generally include interleukin-6 receptor inhibitors, anti-CD20 monoclonal antibody, tumour necrosis factor inhibitors (TNFis) and costimulatory molecular receptor such as CTLA-4Ig, while tDMARDs encompass Janus kinase inhibitors (JAKis), including tofacitinib (JAK 1 and 3 inhibitors) and baratinib (JAK 1 and 2 inhibitors).

Growing evidence highlights that ncs-DMARDs for RA have a good curative effect; however, their therapeutic impact on the progression and outcomes of ILD in patients with RA is controversial. Antoniou et al found that patients with RA-ILD had significantly improved exercise tolerance and stabilised lung function after 1 year of therapy with infliximab. On the contrary, Lindsay et al showed that a patient with RA-ILD presented with progressive dyspnoea and severe ground-glass changes in HRCT after 6 weeks of etanercept. Here, we conducted a systematic literature review and meta-analysis to evaluate the impact of ncs-DMARDs on the ILD outcomes in patients with RA to provide therapeutic decisions for ncs-DMARDs in patients with RA-ILD.

METHODS
The present study was registered on PROSPERO (CRD42022356816) and performed based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.

Search strategy
PubMed, the Cochrane Library, EMBASE and Web of Science Databases were searched for relevant literature published from inception to 1 June 2022, using the following search terms: rheumatoid arthritis, interstitial lung disease and ncs-DMARDs approved for treatment of RA (online supplemental appendix 1).

Study selection
Two investigators (HY/SC) independently scanned the titles and abstracts of all retrieved articles to select matched studies. Any researcher disagreements were resolved through discussion, and a third person (LY) determined the final result. The inclusion criteria were as follows: (1) the study population included patients diagnosed with adult RA-ILD, without consideration of gender, race and pattern of ILD of patients; (2) the therapeutic regimen of patients included the application of ncs-DMARDs alone (at least one dose) or in combination with others; (3) clinical trials as well as cohort and case–control studies. Exclusion criteria were as follows: (1) non-English literature; (2) repeatedly published data; (3) literature with incomplete data or lacking target indicators; (4) review articles, letters, conference proceedings, editorials and case reports.

Data extraction and outcome measures
Two reviewers (HY/SC) independently extracted the following information by using a data extraction form: first author, published year, country, research type, sample size (female/male), mean age, duration of RA-ILD, follow-up time, pattern of ILD, other airway diseases, types of ncs-DMARDs, adverse events (AEs) and indicators. In the case of unavailability of detailed information, the data were obtained by contacting the original author through email. The Cochrane risk of bias assessment tool and Newcastle–Ottawa Scale (NOS) were used to evaluate the bias risk of randomised controlled trials (RCTs) and non-RCT studies. The certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework classified with high, moderate, low or very low grade. The primary outcomes were forced vital capacity (FVC) and diffusion lung capacity for carbon monoxide (DLCO). The second outcomes were forced expiratory volume in the first second (FEV1), non-progression rate of HRCT and fatality rate. The non-progression rate of HRCT was defined as the percentage of stable or improved images in patients with RA-ILD who underwent HRCT. The fatality rate was calculated as the percentage of patients with RA-ILD who died due to ILD progression.

Statistical analysis
The extracted data, including FVC, FEV1 and DLCO, were analysed using Revman V.5.4 software (Cochrane Collaboration). Single-group results (eg, non-progression rate of HRCT and fatality rate) were pooled and analysed by using STATA V.16.0. For continuous outcomes, pooled outcomes were presented as a mean difference (MD) and 95% CI for analysis, while for single-group rates, effect size and 95% CI were used for analysis. The I² value was used to evaluate heterogeneity. Generally, we used the fixed-effects model to analyse substantial homogeneous trials (I²≤50%, p>0.1). When statistical heterogeneity existed (I²50%, p<0.1), we used a random-effects model followed by sensitivity analyses and subgroup analyses, which were carried out by gradually removing studies and performed according to types of drugs. STATA V.16.0 software and Egger's test were used to evaluate publication bias for studies involving FVC and DLCO.

RESULTS
Study selection
According to the above search strategy, 2601 articles were initially retrieved from five databases, and 2208 were acquired after the removal of duplicates. Next, the titles and abstracts of articles were screened for potential eligibility, and 33 were considered for full-text review, which
met the inclusion criteria. Finally, 17 studies, including 16 quantitative studies, were identified. All the included patients met the 1987 American College of Rheumatology (ACR) or the 2010 ACR/European Alliance of Associations for Rheumatology classification criteria of RA. Details of the study screening are shown in figure 1.

Study characteristics
A total of 17 clinical studies with 1315 adult patients with RA-ILD were included, all of which were self-controlled studies. The studies were conducted in seven different countries, more precisely four in Spain,19–22 five in Italy,23–27 one in Greece,28 four in Britain,29–32 one in South Korea,33 one in Japan34 and one in the USA.35 The age range of patients was 49–83 years, and the follow-up time was approximately 6–70 months. There were three studies with abatacept (ABA) treatment,20 23 27 eight with rituximab (RTX),19 21 22 25 30–32 35 one with tocilizumab (TCZ),26 four with TNFis,28–30 33 two with JAKis,24 27 and one without detailed information of bDMARDs.34 The concomitant cs-DMARDs involved methotrexate (MTX), azathioprine (AZA), mycophenolate mofetil (MMF), leflunomide (LEF), tacrolimus (TAC), immunoglobulins, sulfasalazine (SSZ) and hydroxychloroquine (HCQ). Of all the 1315 patients, 231 were classified as usual interstitial pneumonia (UIP) by HRCT, 200 non-specific interstitial pneumonia (NSIP), 102 as others, including organising pneumonia, cryptogenic organising pneumonia, mixed patterns, etc. Also, the ILD radiological patterns of the remaining 782 were unknown. Detailed information is shown in table 1.

Quality evaluation of the included studies
A total of 17 articles were evaluated using the NOS,17 3 of which were of moderate quality and 14 were of high quality, as shown in online supplemental table 1. The evidence quality of outcomes judged by GRADE18 is depicted in online supplemental table 2. Concerning FVC and DLCO, evidence ranged from moderate to very low, and for HRCT non-progression and fatality rates, evidence ranged from moderate to low. We observed FEV1 with moderate quality of evidence.

FVC and FEV1
FVC, one of the crucial components of the pulmonary function test (PFT), is a significant indicator for detecting
<table>
<thead>
<tr>
<th>References</th>
<th>Year</th>
<th>Country</th>
<th>Sample size (female/male)</th>
<th>Age (mean±SD or median, IQR) (years)</th>
<th>Duration of RA disease (mean±SD or median, IQR)</th>
<th>Duration of ILD disease (mean±SD or median, IQR)</th>
<th>Follow-up times (mean±SD or median, IQR)</th>
<th>ILD radiological patterns (n)</th>
<th>Other airway disease* (n, %)</th>
<th>Adverse events (n)</th>
<th>Types of ncs-DMARD treatment</th>
<th>Literature quality evaluation</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atienza-Mateo et al²³</td>
<td>2020</td>
<td>Spain</td>
<td>5 (NA)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>6.0 (6.0) months</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>RTX</td>
<td>①③④ NOS 5</td>
<td></td>
</tr>
<tr>
<td>Cassone et al²³</td>
<td>2020</td>
<td>Italy</td>
<td>44 (32/12)</td>
<td>65.0 (11)</td>
<td>89.0 (142.0) months</td>
<td>20.0 (58.0) months</td>
<td>26.5 (38.0) months</td>
<td>UIP (19); NSIP (22); other (3)</td>
<td>10 (22.7) Non-respiratory infection (1)</td>
<td>ABA</td>
<td>①③④ NOS 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d’Alessandro et al²³</td>
<td>2020</td>
<td>Italy</td>
<td>4 (NA)</td>
<td>NA</td>
<td>NA</td>
<td>6.0 (6.0) months</td>
<td>NA</td>
<td>UIP (1); NSIP (2); other (1)</td>
<td>NA</td>
<td>None</td>
<td>JAKis FEV/PVC NOS 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detoaxis et al²⁶</td>
<td>2016</td>
<td>Greece</td>
<td>42 (27/15)</td>
<td>60.1±7.9</td>
<td>NA</td>
<td>12.0 (12.0) months</td>
<td>NA</td>
<td>Respiratory infections (3)</td>
<td>NA</td>
<td>NA</td>
<td>NOS 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dixon et al²⁷</td>
<td>2010</td>
<td>Britain</td>
<td>299 (57/242)</td>
<td>63.0±10.0</td>
<td>12.0 (7.0–20.0) years</td>
<td>20.0 (58.0) months</td>
<td>26.5 (38.0) months</td>
<td>UIP (1); NSIP (2); other (8)</td>
<td>NA</td>
<td>TNFs</td>
<td>NOS 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Druce et al²⁸</td>
<td>2017</td>
<td>Britain</td>
<td>352 (198/154)</td>
<td>62.8±10.5</td>
<td>11.1±9.7 years</td>
<td>NA</td>
<td>801.3 (NA) person-years</td>
<td>UIP (22); NSIP (12); other (8)</td>
<td>NA</td>
<td>Respiratory infections (1); hypogammaglobulinaemia (1)</td>
<td>NOS 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durante et al²⁰</td>
<td>2019</td>
<td>Britain</td>
<td>26 (NA)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>23.3 (6.0–36.0) months</td>
<td>UIP (4); NSIP (10); other (3)</td>
<td>NA</td>
<td>NA</td>
<td>RTX</td>
<td>①③④ NOS 7</td>
<td></td>
</tr>
<tr>
<td>Fernández-Diaz et al²⁰</td>
<td>2020</td>
<td>Spain</td>
<td>263 (150/113)</td>
<td>64.6±10.0</td>
<td>9.7±8.7 years</td>
<td>12.0 (6.0–36.0) months</td>
<td>NA</td>
<td>Respiratory infections (29); other infections (3); infusion reaction (1)</td>
<td>ABA</td>
<td>①③④⑤ NOS 8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fui et al²⁵</td>
<td>2019</td>
<td>Italy</td>
<td>14 (NA)</td>
<td>62±3.2</td>
<td>NA</td>
<td>12.0 (12.0) months</td>
<td>NA</td>
<td>Non-respiratory infection (1); hypogammaglobulinaemia (1)</td>
<td>RTX</td>
<td>①③④ NOS 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koo et al²⁹</td>
<td>2015</td>
<td>Korea</td>
<td>24 (21/3)</td>
<td>68.5±14.8</td>
<td>107.8±51.1 months</td>
<td>NA</td>
<td>20.0 (2.0–58.0) months</td>
<td>UIP (5); NSIP (1); other (NA)</td>
<td>1 (4.2)</td>
<td>TNFs</td>
<td>NOS 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kurata et al²⁰</td>
<td>2019</td>
<td>Japan</td>
<td>23 (NA)</td>
<td>NA</td>
<td>NA</td>
<td>70.9±73.4 weeks</td>
<td>NA</td>
<td>62 (26.1)</td>
<td>NA</td>
<td>NA</td>
<td>JAKis bDMARDs NOS 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manfredi et al²⁶</td>
<td>2019</td>
<td>Italy</td>
<td>28 (18/10)</td>
<td>64.0 (15.0)</td>
<td>11.5 (13.0) years</td>
<td>12.0 (34.0) months</td>
<td>32.0 (44.0) months</td>
<td>UIP (1); NSIP (13); other (1)</td>
<td>NA</td>
<td>NA</td>
<td>NOS 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matteson et al²⁶</td>
<td>2012</td>
<td>USA</td>
<td>10 (6/4)</td>
<td>64.7±9.3</td>
<td>13.8±10.9 years</td>
<td>3.2±1.9 years</td>
<td>48.0 (48.0) weeks</td>
<td>UIP (4); NSIP (6)</td>
<td>NA</td>
<td>NA</td>
<td>NOS 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menéndez-Vázquez et al²¹</td>
<td>2022</td>
<td>Spain</td>
<td>19 (13/6)</td>
<td>67.7±9.7</td>
<td>151.0 (8.3–204.4) months</td>
<td>82.2 (37.4–120.1) months</td>
<td>45.3 (22.7–79.9) months</td>
<td>UIP (14); NSIP (5)</td>
<td>NA</td>
<td>Respiratory infections (13); other infections (5)</td>
<td>NOS 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Narvaez et al²²</td>
<td>2020</td>
<td>Spain</td>
<td>31 (18/13)</td>
<td>61.0±12.0</td>
<td>48.0 (19.0–16.0) months</td>
<td>21.0 (9.0–38.0) months</td>
<td>24.0 (24.0) months</td>
<td>UIP (13); NSIP (10); other (8)</td>
<td>NA</td>
<td>Respiratory and other infections (10); hypogammaglobulinaemia (9)</td>
<td>NOS 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tardella et al²⁰</td>
<td>2022</td>
<td>Italy</td>
<td>75 (52/23)</td>
<td>59.5±7.7</td>
<td>7.5±3.2 years</td>
<td>NA</td>
<td>18.0 (18.0) months</td>
<td>NA</td>
<td>NA</td>
<td>ABA, JAKis</td>
<td>NOS 7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
the resistance of the respiratory tract. In the current study, some patients with RA-ILD presented with abnormalities in FVC. Meta-analysis of 12 studies, including 465 patients with RA-ILD, showed that FVC did not significantly change after being treated with ncs-DMARDs, including ABA, RTX, TNFis, TCZ and JAKis (MD=−0.93, 95% CI −2.91 to 1.05, p=0.36), as shown in figure 2A. A fixed-effects model was used for low heterogeneity for either the pooled or each subgroup (I²=0%, p=0.55; figure 2A). The subgroup analysis was performed according to ncs-DMARD types, detecting no significant change in patients with RA-ILD in FVC after receiving ABA but evident amelioration after RTX treatment (MD=0.37, 95% CI −2.29 to 3.03, p=0.79 for ABA; MD=−4.62, 95% CI −8.90 to −0.33, p=0.03 for RTX; figure 2A). Additionally, four patients with RA-ILD who received baricitinib showed a nearly 10% increase in \( \text{FEV}_1/\text{FVC} \) after 6 months of follow-up in the research by d’Alessandro et al.\(^{24} \)

\( \text{FEV}_1 \) is closely related to FVC, which refers to the volume of exhaled air in the first second of maximum exhalation after maximum deep inspiration. As shown in figure 2B, \( \text{FEV}_1 \) changes in three studies, including 75 patients with RA-ILD, were compared before and after ncs-DMARD treatment. The analysis of the fixed-effects model proved that the \( \text{FEV}_1 \) remained unchanged in patients with RA-ILD who received ncs-DMARDs (I²=39%, p=0.20; MD=0.16, 95% CI −0.85 to 6.17, p=0.96; figure 2B).

### Diffusion lung capacity for carbon monoxide

DLCO reflects the diffusion function of the lung. Here, a meta-analysis of nine studies with 313 patients with RA-ILD showed that the result of the pooled DLCO changes was not significant after ncs-DMARDs involving ABA, RTX, TCZ and JAKis (MD=−2.16, 95% CI −5.41 to 1.10, p=0.19), as shown in figure 3A. A random-effects model was used for analysis because of the high heterogeneity (I²=54%, p=0.02; figure 3A). Furthermore, we performed sensitivity analysis by sequentially removing studies. As shown in figure 3B, after eliminating Narváez et al.\(^{25} \) in the RTX group with the wide 95% CI, there were no apparent changes in the left of merging results, indicating the outcomes were stable and reliable (MD=−0.81, 95% CI −2.95 to 1.32, p=0.46; figure 3B). The results of subgroup analysis according to the different ncs-DMARDs showed no apparent changes in DLCO in patients with RA-ILD treated with ABA or RTX (I²=0%, MD=−0.65, 95% CI −3.58 to 2.28, p=0.66 for ABA; I²=0%, MD=0.01, 95% CI −4.16 to 4.17, p=1.00 for RTX; figure 3B). Our results revealed stable lung diffusion function in patients with RA-ILD after ABA or RTX treatment.

### Non-progression rate of HRCT

In our meta-analysis, all the HRCT images of patients with RA-ILD were assessed at the baseline and the end of the follow-up time (12–45 months). The assessment
was done by an experienced radiologist with a blind approach and identified by another senior radiologist if there were suspicious cases. Our results demonstrated that the HRCT non-progression rate in patients with RA-ILD treated with ncs-DMARDs (ABA, RTX, TCZ, JAKis) was 0.792 (95% CI 0.746 to 0.834, p=0.000 by STATA V.16.0 software; figure 4) in 399 patients from 10 studies, which means the pulmonary radiographical images of majority of the patients with RA-ILD were steady or improved. Next, we used a homogeneous fixed-effects model to analyse the subgroup data based on ncs-DMARD types ($I^2=12.399\%$; figure 4), finding that the non-progression rate of HRCT in patients treated with ABA was 0.804 (95% CI 0.747 to 0.856, p=0.000), and the rate of RTX was 0.661 (95% CI 0.542 to 0.773, p=0.000; 80.4% vs 66.1%; figure 4).

Figure 2. (A) Meta-analysis of self-control studies to assess FVC changes in patients with RA-ILD treated with different types of ncs-DMARDs; (B) meta-analysis of self-control studies to assess FEV1 changes in patients with RA-ILD treated with different types of ncs-DMARDs. ABA, abatacept; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; ILD, interstitial lung disease; JAKis, Janus kinase inhibitors; ncs-DMARDs, non-conventional synthetic disease-modifying antirheumatic drugs; RA, rheumatoid arthritis; RTX, rituximab; TCZ, tocilizumab; TNFis, tumour necrosis factor inhibitors.
**Figure 3**

(A) Meta-analysis of self-control studies to assess DLCO changes in patients with RA-ILD treated with different types of ncs-DMARDs; (B) meta-analysis of self-control studies to assess DLCO changes in patients with RA-ILD treated with different types of ncs-DMARDs after sensitivity analysis. ABA, abatacept; DLCO, diffusion lung capacity for carbon monoxide; ILD, interstitial lung disease; JAKis, Janus kinase inhibitors; ncs-DMARDs, non-conventional synthetic disease-modifying antirheumatic drugs; RA, rheumatoid arthritis; RTX, rituximab; TCZ, tocilizumab.
Yuan H, et al. RMD Open 2023;9:e003487. doi:10.1136/rmdopen-2023-003487

Fatality rate
Our meta-analysis of single-group rate in five studies involving 749 patients with RA-ILD treated with ncs-DMARDs. ABA, abatacept; ES, effect size; HRCT, high-resolution CT; ILD, interstitial lung disease; JAKis, Janus kinase inhibitors; NA, not applicable; ncs-DMARDs, non-conventional synthetic disease-modifying antirheumatic drugs; RA, rheumatoid arthritis; RTX, rituximab; TCZ, tocilizumab.

Publication bias
Regarding FVC and DLCO in patients with RA-ILD, the p values of Egger’s test were all >0.05 (FVC, p=0.160; DLCO, p=0.852; figure 6), indicating no publication bias.

DISCUSSION
After repeated screening and checking, 17 self-controlled studies encompassing 1315 patients with RA-ILD were included. Despite different types of ncs-DMARDs, our data showed that ncs-DMARD therapeutic regimen might effectively stabilise PFT or HRCT and decrease the fatality rate of patients with RA-ILD owing to progressive ILD.

To explore the impact of ncs-DMARDs on ILD in patients with RA, we also focused on indicators including FVC, FEV1, DLCO and HRCT changes. Our results showed that the overall FVC data indicated the stable pulmonary situation of patients after treatment, achieving higher statistical significance after 6–70 months of follow-up in the RTX group, suggesting improving lung function in patients with RA-ILD. In particular, Fernandez-Diaz et al showed that FVC of patients with RA-ILD with ABA treatment steadily rose (86.2% to 87.6%) after 12 months of follow-up, which was followed by a slightly downward trend (86.2% to 85.1%) at the end of 22 months.30 This was probably due to the progression of the primary disease, which suggests that more aggressive therapeutic drugs should be considered. Regarding FEV1, our results detected no statistical significance in patients with RA-ILD while indicating that ncs-DMARD therapy could stabilise patients’ lung function. Unsurprisingly, the FEV1, which is closely related to FVC, was not significantly improved in the RTX group because of insufficient data.

In addition, regardless of whether Narváez et al’s study was excluded from the sensitivity analysis or not,22 DLCO of patients with RA-ILD treated with ABA and RTX was relatively stable, suggesting that patients did not have an apparent deterioration of lung diffuse function. Meanwhile, Tardella et al31 showed that JAKis combined with steroids might slightly improve the DLCO of the patients (59.7% to 62.8%). Consistent with the above observations, in some case reports, JAKis regimen improved DLCO without pulmonary deterioration or infection in patients with RA-ILD after 8–12 months of follow-up.36 37

As shown in figure 4, 11 of 19 studies calculated the non-progression rate of HRCT after treatment with ncs-DMARDs. Additionally, the HRCT pattern of ILD made a difference in the prognosis of RA. One identified UIP as the predominant pattern; however, in our population, the percentages of patients with a UIP pattern versus an NSIP pattern were similar (18% vs 15%, respectively). Nonetheless, with 782 patients with unknown patterns, it is challenging to truly know the predominant radiological pattern of ILD in our pooled population. Of the five studies in this report,22 23 31 32 35 radiographical worsening data were recorded in 15 of the 38 patients with UIP patterns. In contrast, only 9 of the 53 patients with NSIP pattern had deterioration of HRCT, indicating the NSIP type may better respond to ncs-DMARDs. Of note, HRCT after RTX treatment was not routinely performed in all patients (if stable), which might decrease the real non-progression rate in the RTX group.

It was reported that the median survival of patients with RA after diagnosis of ILD was 2.6–8.5 years in different US cohort studies, which was significantly shorter than the expected years of patients with RA of the same age and sex, about 16% of whom died from ILD deterioration.39 40 For the death of patients with RA-ILD treated with ncs-DMARDs, the fatality rate due to ILD deterioration was 0.049 years, the fatality rate of patients with RA-ILD treated with ncs-DMARDs might effectively stabilise PFT or HRCT and decrease the fatality rate of patients with RA-ILD owing to progressive ILD.
with ncs-DMARDs, our meta-analysis revealed that with 3.8-year follow-up, the fatality rate due to ILD deterioration (ILD as the main cause of death) was 6.4% and 16.5%, respectively in TNFis and RTX subgroup. Notably, the pulmonary comorbidities (such as chronic obstructive pulmonary disease or asthma) in patients from the...
RTX group were more severe (41.9%). On the contrary, Kelly et al found that RTX therapy was more effective than our results suggested (4% vs 16.5%), although it was based on respiratory mortality, including that caused by infection or pulmonary embolism. These differences were explained by inconsistency in the evaluation criteria of death cause, ILD severity, HRCT patterns and pulmonary comorbidities, all of which might contribute to the relatively high case fatality rate in the RTX group observed in the present study. At the same time, the other differences in sample sizes should not be ignored. In our data, the other AEs including infections (respiratory, n=62; others, n=14), hospitalisation owing to non-infections (n=48), local infusion reaction (n=1) and hypogammaglobulinaemia (n=10) were reported during ncs-DMARD treatment. However, there was no exact link between infection and the combined use of ncs-DMARD strategies.

As far as drug details are concerned, RTX and TNFis were entirely applied with either cs-DMARDs (MTX, AZA, MMF, LEF, TAC, SSZ, HCQ) or glucocorticoids, while ABA, TCZ and JAKis were recorded as monotherapy or combined regimen. The overall risk of lung exacerbation attributed to MTX is controversial. Some research reported that MTX treatment led to RA-ILD progression in patients with RA. Nevertheless, in our literature, the majority of studies indicated that MTX did not cause the progression of ILD. Similarly, growing studies suggested that MTX in monotherapy or combined with bDMARDs was not associated with an increased risk of RA-ILD in patients, actually it might be equally effective and safe. Importantly, the 2021 ACR guidelines for RA treatment conditionally favour MTX for patients with mild and stable airway or parenchymal lung disease, because of the anchor status as a DMARD and lack of alternatives with efficacy and long-term safety. As glucocorticoids with stable low doses (eg, prednisolone and methylprednisolone) were found to be used in most patients with RA throughout the follow-up, we confirmed that steroid use had no impact on ILD outcomes in our data. It is worth mentioning that antifibrotic drugs (eg, nintedanib and pirfenidone) were not applied in the patients enrolled in our research, providing little therapeutic influence on our final results.

Undoubtedly, increased evidence indicates rheumatoid factor (RF) and/or anti-cyclic citrullinated protein (CCP) seropositivity has been the risk factors for ILD susceptibility. Of the 11 studies in our data, the RF and anti-CCP seropositivity were recorded in 727 of 891 (81%) and 295 of 339 (87%) patients, respectively. Regarding the relationship between the RF or anti-CCP seropositivity and the effect of the biological treatments on the progression of ILD, four of our included studies indicated that the RF seropositivity was irrelevant to RA-ILD deterioration after ncs-DMARD treatment (ABA, JAKi, TNFis); inversely, Detorakis et al found that serum levels of anti-CCP considerably decreased in the RA-ILD group following TNFi treatment. More studies with stratified seropositive or seronegative group are needed to provide detailed information.

Nevertheless, the present study has some limitations. First, the included literature was mainly self-controlled studies, where the natural course of the disease might interfere with clinical outcomes. Simultaneously, we should consider the impact of combining regimens on disease progression. Future well-designed RCTs with different ncs-DMARD therapy groups (monotherapy, combination and cs-DMARDs alone) on RA-ILD are needed to further confirm reported findings. Second, the outcomes of certain ncs-DMARDs such as TCZ and JAKis were insufficient due to few eligible studies, and data from relevant clinical trials with large sample sizes are essential. Finally, due to confounding factors, it is necessary to conduct stratified analysis, for example, comorbidities, radiographical patterns and the severity of ILD. A new concept, progressive pulmonary fibrosis (PPF), was proposed in 2022. It was defined by meeting at least two of three criteria (worsening symptoms, radiological progression and physiological progression) occurring in the past year without an alternative explanation other than idiopathic pulmonary fibrosis in patients with ILD. Hence, it is critical to recognise early PPF state in patients with RA-ILD and timely adjust treatment regimen in order to improve patients’ prognosis.

CONCLUSION

Our data suggest that ncs-DMARD therapy might stabilise FVC, FEV₁ and DLCO values in the pooled data. Of note, there was a significant improvement in FVC changes in the RTX subgroup. In addition, patients’ HRCT non-progression and fatality rates after ncs-DMARD treatment were 79.2% and 4.9%, respectively. Generally speaking, ncs-DMARDs alone or combined with conventional therapy might be an optimal and promising treatment that could stabilise lung function and arrest the progression of ILD in patients with RA-ILD.

Author affiliations

1Department of Rheumatology and Immunology, The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei, China
2Hebei Research Center for Stem Cell Medical Translational Engineering, Shijiazhuang, Hebei, China
3Department of Anatomy, Hebei Medical University, Shijiazhuang City, Hebei, China
4Department of Clinical Laboratory, The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei, China
5Hebei Key Laboratory of Laboratory Medicine, The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei, China

Contributors HY, SC, LY, JC, FC and AL designed the review protocol. HY, SC and LY developed the search strategy and selected studies. HY, XW and YW extracted data. HY, LJ, MD and HJ analysed the data. HY drafted the manuscript, while SC and LY contributed to the drafting of the review. AL, JM and MS revised the manuscript critically for important intellectual content. AL was responsible for the overall content as the guarantor. All authors approved the final version of the article. All authors had access to all the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding This work was supported by Clinical Medicine Excellent Talent Project of Hebei Government Foundation (303-2021-58-18).

Competing interests None declared.
Rheumatoid arthritis

Patient consent for publication Not required.
Ethics approval Not applicable.
Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. All data relevant to the study are included in the article or uploaded as supplemental information.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: https://creativecommons.org/licenses/by/4.0/.

ORCID iDs
Haoming Yuan http://orcid.org/0000-0003-4099-0515
Aijing Liu http://orcid.org/0000-0002-5762-5592

REFERENCES


