

Disease-modifying antirheumatic drugs and risk of incident interstitial lung disease among patients with rheumatoid arthritis: A systematic review and meta-analysis

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ABSTRACT

Objective: To investigate the association of disease-modifying antirheumatic drugs (DMARDs) and risk of incident interstitial lung disease (ILD) among patients with rheumatoid arthritis (RA) using a systematic literature review and meta-analysis.

Methods: We performed a systematic literature review and meta-analysis of studies examining the association of DMARDs with incident RA-ILD. PubMed, Embase, Web of Science, and Cochrane Library were searched from inception to November 2023 for randomized controlled trials (RCTs), observational studies, and post-marketing surveillance studies that investigated adults with RA and compared DMARDs of interest with placebo, no DMARDs, or other DMARDs. The outcome was incident ILD. We summarized the literature on DMARDs and incident RA-ILD risk. Among studies with sufficient quality, we performed meta-analyses to obtain odds ratios (OR) and 95 % confidence intervals (95 %CI) using the Mantel-Haenszel method.

Results: Among 3,612 studies, we identified a total of 40 papers that encompassed 486,465 patients with RA and 3,928 incident ILD outcomes that were included in the final systematic review and meta-analysis. Among the studies, 24 were RCTs, 4 were prospective cohort studies, 9 were retrospective cohort studies, 2 were case-control studies, and 1 was a post-marketing surveillance study. The pooled analysis from RCTs revealed no statistically significant difference in the odds of ILD development for any specific DMARD across all comparisons examined. The largest identified RCT (Oral Surveillance trial) of tofacitinib ($n = 2,911$) vs. tumor necrosis factor inhibitor (TNFi, $n = 1,451$) found no relationship with incident ILD (OR 0.94, 95 %CI 0.52 to 1.69, $p = 0.828$). In 7 observational studies, the use of methotrexate (MTX) yielded a pooled OR for ILD of 0.49 (95 %CI 0.32 to 0.76, $p < 0.001$) compared to those not using MTX. In a single observational study, tofacitinib users had an OR for ILD of 0.36 (95 %CI 0.15 to 0.87, $p = 0.024$) compared to TNFi users.

Conclusion: Observational data suggest no increased risk for any DMARD for incident RA-ILD risk, and perhaps a potential protective role of MTX and tofacitinib. However, these studies may be susceptible to bias, and no specific DMARD showed associations with incident RA-ILD in RCTs. Further well-designed prospective studies are warranted for definitive conclusions on the potential relationship between DMARDs and RA-ILD risk.

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that requires long-term treatment with disease-modifying antirheumatic drugs (DMARDs). Interstitial lung disease (ILD) is a prominent extra-articular manifestation of RA, affecting 7–12 % of RA patients and contributing to a three-fold increased risk of mortality compared to RA without ILD [1, 2]. Clinicians grapple with the challenge of effectively managing joint disease in RA patients while minimizing potential pulmonary toxic effects [3].

The association between the use of DMARDs and the development of ILD in RA patients remains unclear. Methotrexate (MTX) is the cornerstone treatment of RA and has been implicated in drug-induced pneumonitis [4,5], however, findings from recent studies [6,7] indicate MTX is not associated with an increased risk of RA-ILD, and may even have a protective role in RA-ILD risk. Fewer studies have investigated the risk of incident ILD in RA patients treated with biologic or targeted synthetic DMARDs (b/tsDMARDs). A recent large retrospective cohort study [3] demonstrated that patients with RA treated with tofacitinib had a reduced risk of ILD compared with patients treated with adalimumab. However, in that study, relatively fewer patients were taking tofacitinib and the findings could be confounded by factors such as line of therapy [8]. Most previous systematic literature review and meta-analysis focused on DMARDs and their association with any lung disease [9–11] in RA patients, rather than specifically investigating the risk of RA-ILD. One systematic literature review [12] investigated the cases of induced or exacerbated interstitial lung disease (ILD) in RA associated with DMARDs. However, it did not conduct a meta-analysis; instead, it solely concentrated on case reports or case series, without incorporating randomized controlled trials.

This systematic literature review and meta-analysis aimed to address these knowledge gaps by systematically synthesizing available evidence. We sought to provide a more comprehensive understanding of the risk of ILD associated with different DMARD among RA patients, offering insights to guide clinicians in making informed treatment decisions.

Methods

Protocol and registration

This study was registered on PROSPERO (CRD42023485052) and conducted in accordance with the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [13].

Search strategy

PubMed, Embase, Web of Science, and the Cochrane Library were searched for relevant literature published from inception to November 7, 2023, using Medical Subject Heading (MeSH) terms and free text. The strategy included synonyms for “rheumatoid arthritis”, “interstitial lung disease”, “disease-modifying antirheumatic drugs”, and the specific DMARDs of interest which included conventional synthetic DMARDs (csDMARDs), biological DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs) (Supplementary Table S1). We also manually searched for relevant additional references from papers that passed full text screen.

Inclusion criteria

We included studies that involved adult patients diagnosed with RA without known ILD, receiving treatment with specific DMARDs of interest and with assessment for the outcome of incident ILD. The DMARDs of interest encompassed csDMARDs such as MTX, leflunomide (LEF), hydroxychloroquine (HCQ), sulfasalazine (SSZ), and iguratimod (IGU); bDMARDs including tumor necrosis factor inhibitors (TNFi) such

as infliximab (IFX), etanercept (ETN), adalimumab (ADA), certolizumab (CTZ), and golimumab (GOL); the CTLA-4 agonist abatacept (ABA); interleukin-6 receptor inhibitors (IL6i) such as tocilizumab (TCZ) and sarilumab (SAR); CD20 inhibitor rituximab (RTX); and interleukin-1 inhibitors (IL1i) including anakinra (ANA). Additionally, tsDMARDs comprising Janus kinase inhibitors (JAKi) such as tofacitinib, upadacitinib, baricitinib, filgotinib and peficitinib were also included. The comparison group consisted of individuals who underwent placebo administration, DMARDs within the same class, DMARDs across different classes, or no DMARD usage and assessed for the outcome of incident ILD. The studies of interest included randomized controlled trials (RCTs), retrospective or prospective cohort studies, case-control studies, and post-marketing surveillance studies. There were no restrictions to patient language, sex, or ethnicity.

Exclusion criteria

We excluded papers or abstracts that were not human studies, irrelevant to adult patients with RA or lacked sufficient data on DMARDs of interest and ILD outcomes. Additionally, case reports, case series, cross-sectional studies, review articles, or other non-original articles were also excluded.

Data extraction

Two authors independently screened all available studies for inclusion. For discrepancies, a third author (JAS) adjudicated to determine the final result. Data from each study were extracted using a predefined data collection form, which included basic information (first author, year of publication, geographical region, and study design) and patient characteristics (number of RA patients, number of ILD outcomes, drug dosage and usage, age, sex, disease duration, RA disease activity, and follow-up time in the treatment and comparator groups).

Risk of bias assessment

For RCTs, we used the Cochrane risk of bias tool 2.0 to assess the risk of bias. The main domains assessed were randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Regarding the classification, the risk of bias was assessed as low, high or unclear [14].

For observational studies, we used the Newcastle-Ottawa scales [15]. For case-control studies, three domains were evaluated: selection of the studies (adequacy of the case definition, representativeness of the cases, selection of the controls, definition of the controls), comparability (comparability of cases and controls on the basis of the design or analysis), and exposure (ascertainment of exposure, same method of ascertainment for cases and controls, non-response rate). The domains evaluated for cohort studies included the selection of the studies (representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at the start of the study), comparability (comparability of cohorts), and outcome (assessment of outcome, adequate length of follow-up, adequacy of follow-up cohorts).

Papers or abstracts with 3 or 4 stars in selection domain, and 1 or 2 stars in comparability domain, and 2 or 3 stars in outcome/exposure domain were considered to have acceptable quality. Conversely, those with fewer than 1 star in the selection domain or outcome/exposure domain, or no stars in the comparability domain, were classified as having poor quality, and were excluded from further analysis. Studies falling outside these criteria would be considered to have fair quality [16].

Data synthesis and analysis

STATA 18.0 software was employed for data analysis when at least

two studies had the same outcome data. For studies with zero events, if zero events occurred in both groups, we described them without including in the meta-analysis. If zero events occurred in only one group, we applied a continuity correction [17]. Results were presented as odds ratio (OR) with corresponding 95 % confidence intervals (CI). Pooled estimates were calculated using random-effects or fixed-effects models, depending on the heterogeneity observed among the included studies. If significant heterogeneity was observed ($I^2 > 50\%$), the random-effects model was applied for pooled estimation; otherwise, the fixed-effects model was utilized. The assumption of homogeneity was deemed invalid for $p < 0.1$. To investigate potential reasons for significant heterogeneity, sensitivity analysis was conducted excluding one study at a time to examine study outliers. We performed pre-specified subgroup analyses based on different comparisons across study designs.

Results

Literature search

Following the search strategy, a total of 4196 references were initially identified from four databases, along with 1353 from related references. After removing 1937 duplicates and 3358 irrelevant abstracts, 254 citations underwent full text eligibility review. We excluded 207 ineligible studies and 7 studies [18–24] had high risk of bias (Supplementary Table S2). Ultimately, a total of 40 citations [3,6,25–62] encompassing 486,465 patients with RA and 3928 incident ILD outcomes, were included in the final review (Fig. 1 and Table 1).

Table 1

Summary of included studies.

	Number of studies (n = 40)	Total number of patients with RA (n = 486,465)	Total number of patients with incident ILD (n = 3928)
Publication year			
Before 2000	4	2515	5
2001 to 2010	5	2549	6
2011 to 2020	25	446,272	3096
2021 or later	6	35,129	821
Study design			
Randomized controlled trial	24	17,815	83
Post-marketing surveillance study	1	13,013	77
Cohort study	13	454,237	3274
Case-control study	2	1400	494
Geographic region			
USA/Canada	10	450,850	3258
Europe	7	7301	97
Asia and Pacific	12	16,129	103
Multiple regions	11	12,185	470

Abbreviations: ILD, interstitial lung disease; RA, rheumatoid arthritis.

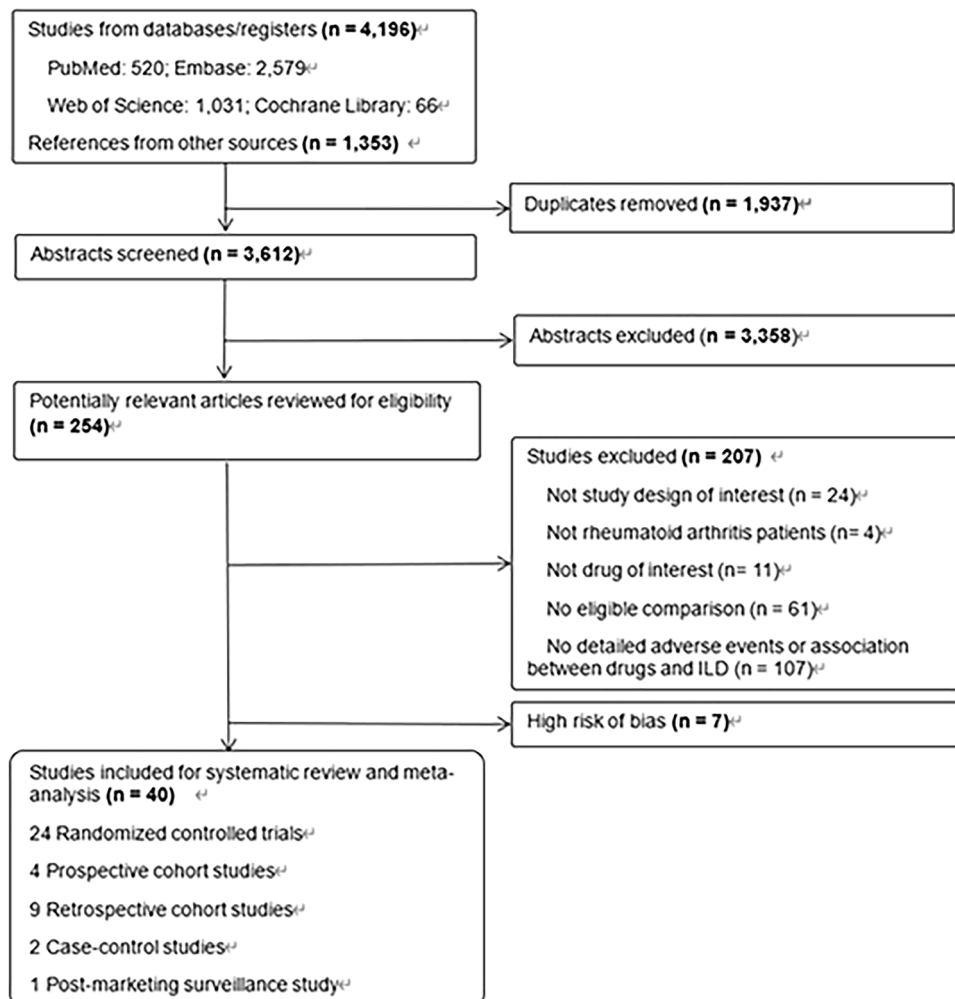


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the studies included in the meta-analysis.

Study characteristics

Among the eligible citations were 24 randomized controlled trials [25-30,38-47,50,54,55,57-60,62], 4 prospective cohort studies [31,32,49,51], 9 retrospective cohort studies [3,33,34,48,50,52,53,56,61], 2 case-control studies [6,35], and 1 post-marketing surveillance study [36]. The studies encompassed different geographic regions, with 10 conducted in the USA and/or Canada, 7 in Europe, 12 in Asia, and 11 spanning multiple regions. More than half of the studies ($n = 24$) were published within the last decade (2011–2020). There were 15 studies focused on csDMARD [6,25-38], 21 on bDMARDs [3,39-58], and 9 on tsDMARDs [3,27,30,41,47,59-62]. Among each broad DMARD class, MTX (among csDMARDs) [6,25-36], TNFi (among bDMARDs) [39-53] and tofacitinib (among tsDMARDs) [3,30,41,59-61] accounted for the majority of studies (Fig. 2). Other csDMARDs (LEF [25,26,37], SSZ [38], and IGU [38]), bDMARDs (TCZ [3,54-56], ABA [3,50,56], RTX [3,56,57], and ANA [58]), and tsDMARDs (baricitinib [27,47,62]) were relatively less reported. There were no studies eligible for HCQ, SAR, upadacitinib, filgotinib, and peficitinib.

Systematic review and meta-analysis results

MTX

Pooled analysis of five RCTs [25-29] indicated no statistically significant difference in the odds of developing ILD when comparing MTX with alternative agents (Supplementary Figure S1, OR 1.37, 95 %CI 0.41 to 4.59, $p = 0.614$; $I^2 = 0.0\%$, $p = 0.849$). Considered separately, there was also no statistical difference in the occurrence of ILD when comparing MTX with placebo [25,26] (OR 2.00, 95 %CI 0.21 to 19.30, $p = 0.550$; $I^2 = 0.0\%$, $p = 0.987$), no MTX [27,28] (OR 0.28, 95 %CI 0.03 to 2.74, $p = 0.277$; $I^2 = 0.0\%$, $p = 0.898$), or LEF [25,26,29] (OR 3.02, 95 %CI 0.47 to 19.21, $p = 0.242$; $I^2 = 0.0\%$, $p = 1.000$) (Fig. 3). An additional RCT [30], with a sample size of 760 participants followed

over 12 months, revealed no incident ILD events in the MTX vs. no MTX comparison (Supplementary Table S3). However, 7 observational studies [6,31-36] demonstrated MTX to be associated with lower odds of developing incident ILD comparing with alternative agents (Supplementary Figure S1, OR 0.43, 95 %CI 0.28 to 0.67, $p < 0.001$; $I^2 = 54.5\%$, $p = 0.031$). In comparison to no MTX [6,31-36], MTX indicated a 51 % lower odds of ILD development (Fig. 3, OR 0.49, 95 %CI 0.32 to 0.76, $p = 0.001$; $I^2 = 41.8\%$, $p = 0.113$).

LEF, SSZ, and IGU

Three RCTs [25,26,37] (Supplementary Table S4) encompassing a total of 1020 participants, with a mean follow-up duration of 14 months, compared LEF with placebo and no ILD events occurred in either group. A similar result was observed in a single RCT [38] (Supplementary Table S5) comparing SSZ with placebo involving 229 participants with a follow-up duration of 28 weeks. This RCT also compared IGU with either placebo or SSZ with a total of 376 participants and found no statistical difference in the odds of ILD (Supplementary Figure S2 and Table S6, OR = 1.51, 95 %CI 0.06 to 37.40, $p = 0.803$; OR = 3.20, 95 %CI 0.13 to 79.29, $p = 0.477$).

TNFi

Pooled analysis of eight RCT [39-46] showed no statistically significant difference in the odds of incident ILD development when comparing TNFi with alternative agents (Supplementary Figure S3, OR 0.98, 95 %CI 0.37 to 2.56, $p = 0.959$; $I^2 = 11.1\%$, $p = 0.344$). When analyzed separately, no statistical difference was observed in the occurrence of ILD when comparing TNFi with placebo [39-42] (OR 1.50, 95 %CI 0.38 to 5.58, $p = 0.560$; $I^2 = 1.5\%$, $p = 0.385$), no TNFi [43] (OR 4.93, 95 %CI 0.24 to 103.10, $p = 0.304$), inter-class comparisons [44,45] (OR 0.81, 95 %CI 0.19 to 3.41, $p = 0.771$; $I^2 = 0.0\%$, $p = 0.543$), and MTX [46] (OR 0.07, 95 %CI 0.00 to 1.43, $p = 0.085$) (Fig. 4 and Supplementary Table S7). One additional RCT [47] comparing TNFi with

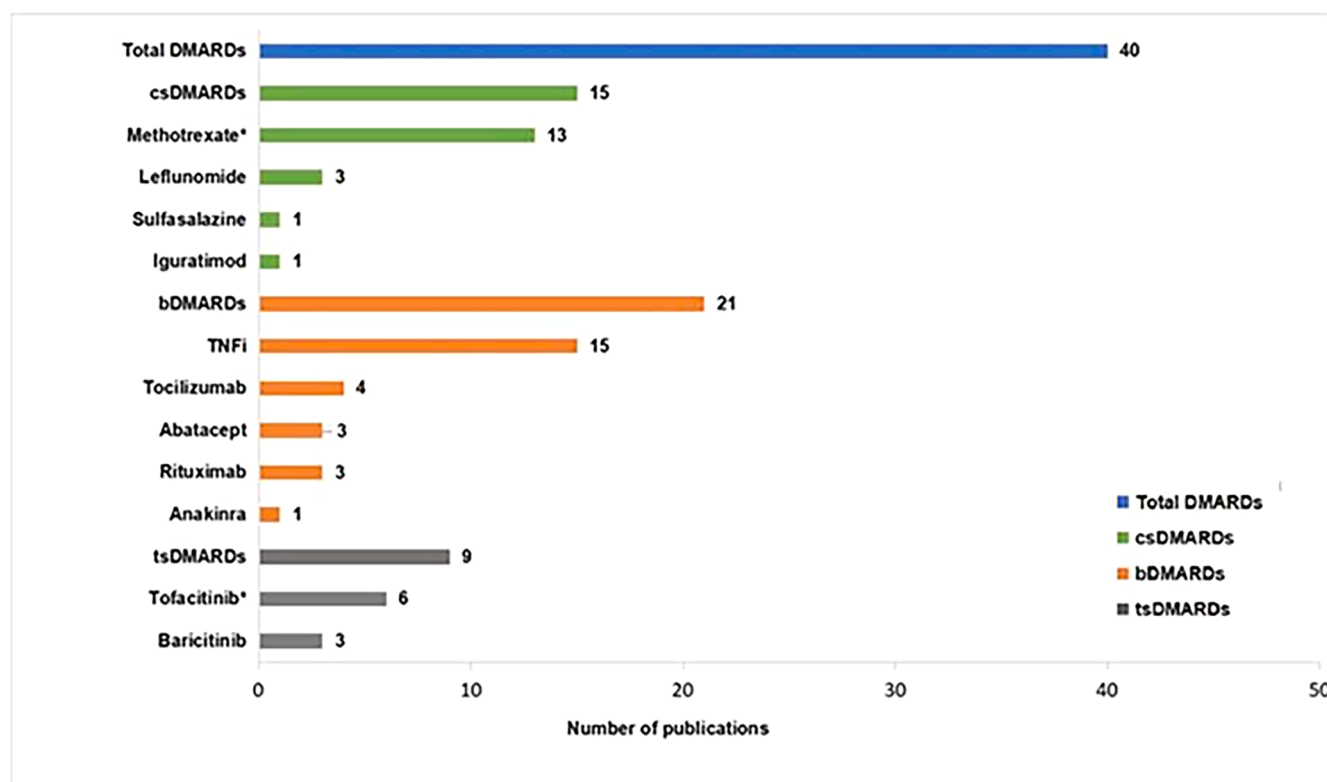


Fig. 2. Number of studies by class of DMARDs and specific DMARDs. TNFi included adalimumab (6 studies), etanercept (5 studies) and its biosimilar (LBEC0101, 1 study), infliximab (2 studies) and its biosimilar (GB242, 1 study), certolizumab (3 studies) and golimumab (1 study). DMARDs, disease-modifying antirheumatic drugs; TNFi, tumor necrosis factor inhibitors; ILD, interstitial lung disease.

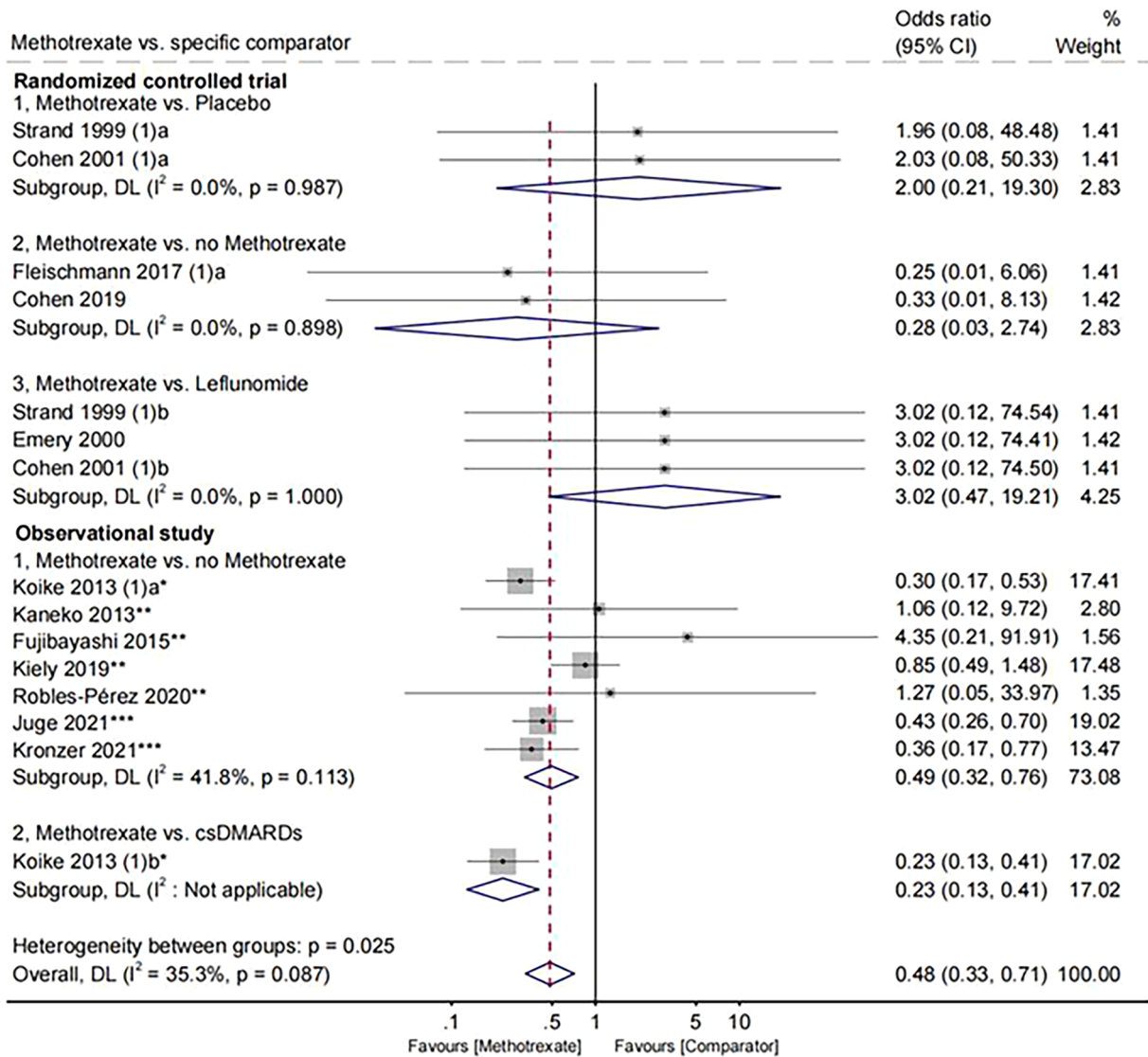


Fig. 3. Odds ratios for incident interstitial lung disease in patients with rheumatoid arthritis treated with methotrexate compared with specific agents in eligible studies. *Post-marketing surveillance studies, **Cohort studies, ***Case control studies.

placebo, encompassing 818 participants with a follow-up duration of 12 months, revealed no occurrence of incident ILD events in either group. All of the 6 eligible observational studies were cohort studies [48–53] and there was no significant difference in the odds of developing ILD when comparing with no TNFi [48–52] (OR 0.97, 95 %CI 0.37 to 2.51, $p = 0.947$; $I^2 = 55.5\%$, $p = 0.061$), inter-class comparisons [53] (OR 0.89, 95 %CI 0.46 to 1.74, $p = 0.735$; $I^2 = 0.0\%$, $p = 0.547$) and MTX [53] (OR 1.21, 95 %CI 0.62 to 2.37, $p = 0.579$) (Fig. 4 and Supplementary Table S7).

TCZ, RTX, ABA, and ANA

In the two RCTs [54,55] comparing with placebo (OR 1.49, 95 %CI 0.15 to 14.36, $p = 0.731$; $I^2 = 0.0\%$, $p = 0.991$), and in the two cohort studies [3,56] comparing with TNFi (OR 1.19, 95 %CI 0.82 to 1.72, $p = 0.363$; $I^2 = 42.9\%$, $p = 0.186$), participants treated with TCZ exhibited a tendency towards higher odds of ILD events, however, the difference did not reach statistical significance (Supplementary Figure S4 and Table S8). Similar findings were observed in these two cohort studies [3, 56] comparing RTX with TNFi (Supplementary Figure S5 and Table S9), yielding an overall pooled OR of 1.30 (95 %CI 0.98 to 1.73, $p = 0.072$; $I^2 = 0.0\%$, $p = 0.775$). However, in the single RCT [57] comparing RTX with TNFi, it demonstrated lower odds of ILD development

(Supplementary Figure S5 and Table S9, OR 0.21, 95 %CI 0.01 to 4.38, $p = 0.314$).

For the two eligible cohort studies [3,56] comparing ABA with TNFi, the overall pooled OR was 0.87 (95 %CI 0.40 to 1.87), which indicated a tendency towards lower odds of ILD events with no statistical difference (Supplementary Figure S6 and Table S10). Although, there was high heterogeneity detected among these two studies ($I^2 = 69.9\%$), this heterogeneity did not reach statistically significant ($p = 0.068$). When compared with no ABA group [50], participants treated with ABA showed a lower odds of ILD development with significant difference in a single cohort study (OR 0.07, 95 %CI 0.01 to 0.70, $p = 0.023$).

One single RCT [58] (Supplementary Figure S7 and Table S11) with a total of 501 participants and a follow-up duration of 24 weeks compared ANA with placebo found no statistical difference in the odds of ILD occurrence (OR 3.02, 95 %CI 0.12 to 74.59, $p = 0.499$).

Tofacitinib

Pooled analysis of four RCTs [30,41,59,60] indicated no significant difference in the odds of developing ILD when comparing tofacitinib with alternative agents (Supplementary Figure S8 and Table S12, OR 0.84, 95 %CI 0.48 to 1.47, $p = 0.542$; $I^2 = 0.0\%$, $p = 0.506$). For specific

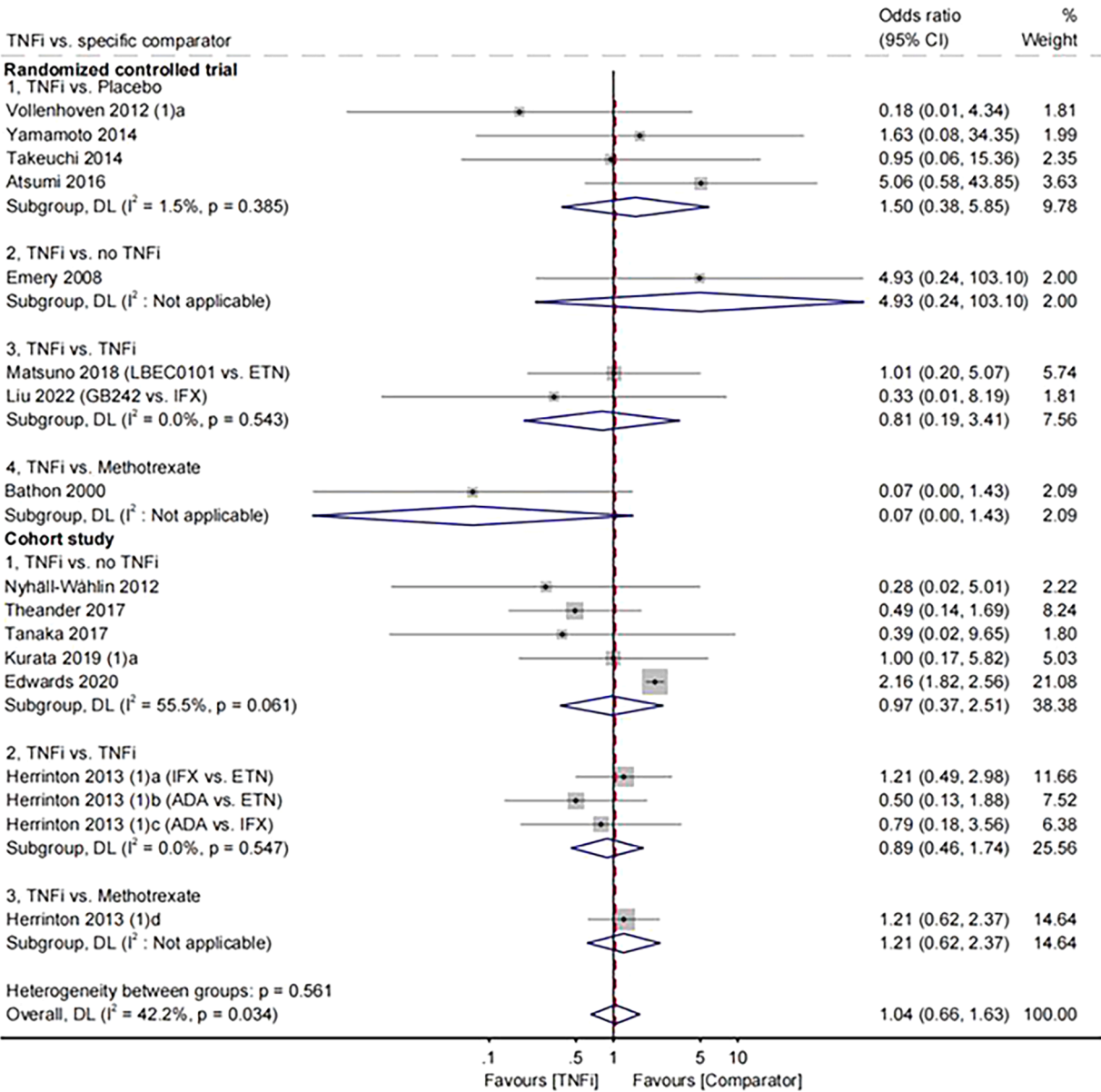


Fig. 4. Odds ratios for incident interstitial lung disease in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors compared with specific agents in eligible studies. TNFi, tumor necrosis factor inhibitors, included adalimumab (ADA), etanercept (ETN) and its biosimilar (LBEC0101), infliximab (IFX) and its biosimilar (GB242), certolizumab (CTZ) and golimumab (GOL).

comparisons, when compared with TNFi [30,60], tofacitinib showed a trend towards reducing the likelihood of ILD development. Although this difference did not reach statistical significance (Fig. 5, OR = 0.91, 95 % CI 0.51 to 1.62, $p = 0.742$; $I^2 = 0.0\%$, $p = 0.543$) in the two RCTs [30,60] which included ORAL Surveillance trial, it did reach significance in a single eligible US-wide cohort study using pharmacy claims data [3] (OR = 0.36, 95 % CI 0.15 to 0.87, $p = 0.024$).

Baricitinib

For baricitinib, all three eligible studies were RCTs [27,47,62]. Whether compared with alternative agents, or compared with specific comparator such as placebo [47,62], no baricitinib [27], MTX [27], or TNFi [47], there were no significant differences in the risk of ILD occurrence (Supplementary Figure S9 and Table S13, OR 1.32, 95 % CI 0.33 to 5.29, $p = 0.698$; $I^2 = 0.0\%$, $p = 0.899$).

Discussion

This meta-analysis, encompassing 40 studies, provides a comprehensive summary of the existing literature on the risk of incident ILD among RA patients associated with specific DMARDs. According to the findings from RCTs, MTX, IGU, TNFi, TCZ, ANA, tofacitinib, and baricitinib did not show an increased risk of ILD compared to placebo. However, in observational studies, the overall pooled analysis found 51 % lower odds (95 %CI 0.32 to 0.76, $p < 0.001$) of ILD development for MTX-treated patients comparing with those who did not receive MTX. When compared to TNFi, tofacitinib demonstrated a significant 64 % decrease in the odds of developing ILD. However, there were no significant differences observed with ABA, RTX, and TCZ. Overall, there were no associations of any DMARD with incident ILD in any RCT, including the Oral Surveillance trial that had a large sample size and long follow-up with active comparator. However, there were associations in observational studies regarding lower odds of ILD for both methotrexate and tofacitinib, though these could be explained by bias

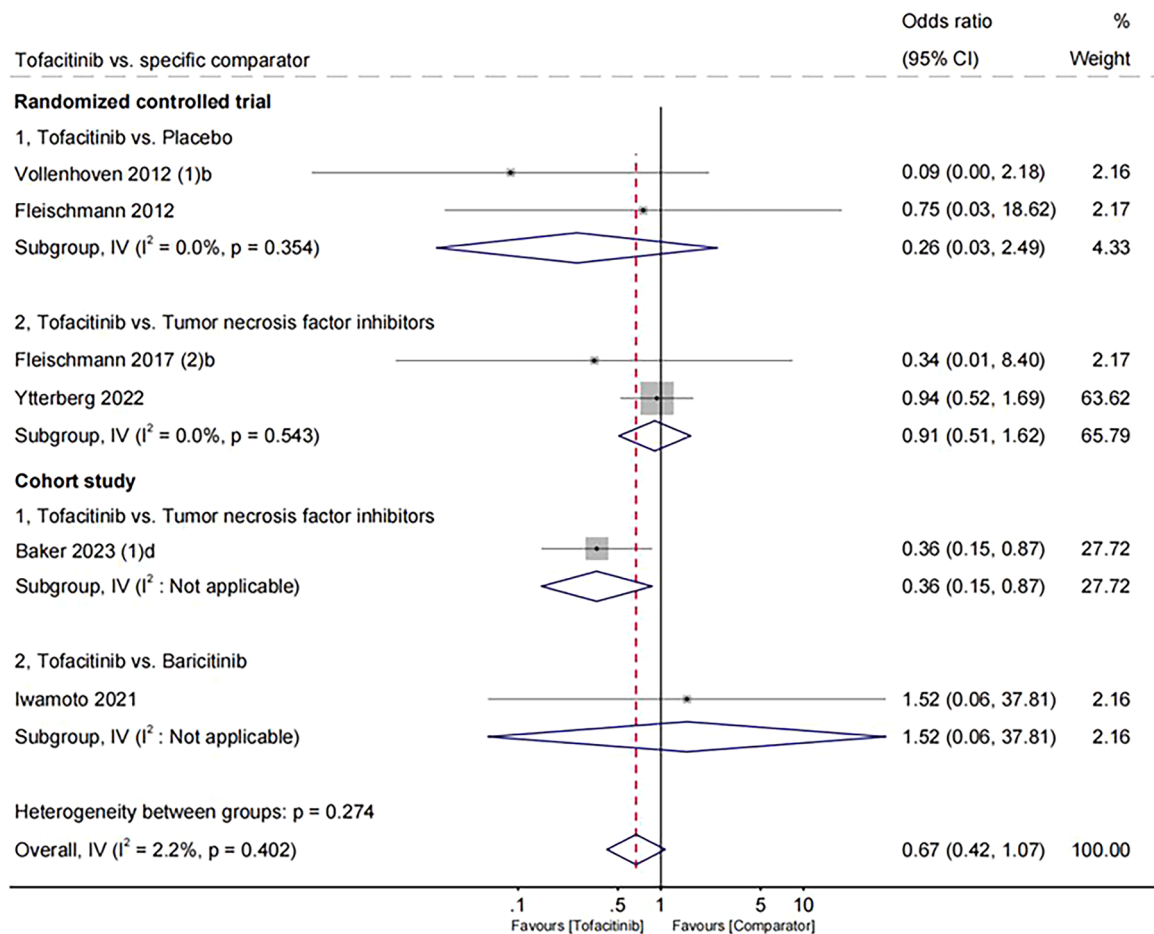


Fig. 5. Odds ratios for incident interstitial lung disease in patients with rheumatoid arthritis treated with tofacitinib compared with specific agents in eligible studies.

given their study design. The lack of increased ILD risk for any DMARD may be reassuring. This systematic review and meta-analysis summarizes the current state of evidence related to evidence of DMARDs for ILD risk and highlights research gaps that will ultimately require dedicated RCTs to definitively establish a link between specific DMARDs and ILD risk.

MTX, although firmly established as the first-line treatment for RA, has been known to be associated with acute pneumonitis and concerns have been raised about its potential to cause ILD. However, findings from our meta-analysis suggested MTX had no increased risk in RA-ILD in pooled placebo-controlled studies and actually demonstrated a protective effect against ILD development in meta-analysis of observational studies. This aligns with previous meta-analysis of RCTs by Conway et al., indicating MTX was not associated with an increased risk of noninfectious respiratory adverse events among patients with RA [9] (relative risk: 1.02, 95 % CI 0.65 to 1.60, $I^2 = 42\%$) or patients with psoriasis, psoriatic arthritis, and inflammatory bowel disease [63] (relative risk 1.07, 95 %CI 0.58 to 1.96, $I^2 = 0.0\%$). Additionally, in a retrospective analysis [64] of prognostic factors in 78 cases of RA-ILD, where MTX was specifically employed as a therapeutic agent in 67 % of cases, a strong association with survival was observed. Possible mechanisms have been proposed to explain the potential protective effect of MTX against ILD. MTX has potent anti-inflammatory properties [65], which may help to reduce the levels of pro-inflammatory cytokines, such as TNF and interleukin-1, that are implicated in the pathogenesis of RA-ILD. By suppressing these cytokines, MTX may attenuate the inflammatory processes that contribute to the development and progression of ILD. Previous research [66] indicated MTX can induce apoptosis on rheumatoid arthritis synovial fibroblasts through

upregulating circadian transcriptional factors PAR bZIP, it may also have potential effect on the lung fibroblasts by inhibiting producing excessive amounts of collagen and other extracellular matrix components. A previous study [67] indicated that patients with remission or low disease activity have lower risk of incident ILD as a potential mechanism for a protective effect of DMARDs such as MTX.

RCTs would have the strongest design protecting against potential bias and we found no relationship of MTX with incident ILD. The largest placebo-controlled trial of methotrexate was the CIRT study [68,69], and showed increased risk of pulmonary adverse events and pneumonitis (not ILD), but was not included in this meta-analysis since it did not study patients with RA. Dedicated trials are needed to firmly establish a potential protective effect of MTX on incident ILD. It is also important to consider that physicians may refrain from prescribing MTX to patients with known or suspected respiratory conditions, even in the absence of a formal ILD diagnosis, due to concerns about its potential pulmonary toxicity. This selective prescribing practice may introduce confounding by indication in observational studies, as patients who do not receive MTX may already have an elevated risk of developing ILD. As a result, the lower incidence of ILD observed among MTX users in some studies may be reflective of this pre-existing selection bias rather than a true protective effect of the drug. We note that the meta-analysis restricting to RCTs of methotrexate had no statistical association with incident ILD.

Fewer studies have investigated ILD risk in patients with RA treated with non-csDMARDs. In a recent large retrospective cohort study, Baker et al. compared 1559 tofacitinib-treated patients over a total 3381 person-years with 4677 adalimumab-treated patients over a total 10,000 person-years and found 64 % lower odds (95 %CI 0.15 to 0.87, $p = 0.024$) of ILD development that was statistically significant. However,

the pooled analysis of the two RCTs, which included Oral Surveillance (2911 tofacitinib-treated patients and 1451 TNFi-treated patients with a median follow-up duration of 4.0 years), demonstrated no significant difference in the odds of ILD development (OR 0.94, 95 %CI 0.52 to 1.69, $p = 0.828$). This may align with findings indicating that tofacitinib could be efficacious in managing ILD associated with dermatomyositis, as well as with reports indicating its beneficial effects in RA-ILD, attributed to its anti-inflammatory and antifibrotic properties [70-72]. The potential protective effect of tofacitinib against ILD may be attributed to its ability to inhibit JAK-STAT signaling, which has been implicated in the pathogenesis of ILD [73,74]. By suppressing the production of pro-inflammatory cytokines and the activation of fibroblasts, tofacitinib may help to attenuate the inflammatory and fibrotic processes that contribute to ILD. However, the trials included in this meta-analysis showed no statistical difference despite very large sample size, long follow-up, and adjudicated incident ILD in the Oral Surveillance trial. This suggests that the observational study findings may have been confounded due to factors such as channeling bias rather than a true biologic effect on incident ILD. Abatacept, which targets T cell co-stimulation, may modulate the immune response in the lungs and potentially lower the risk of ILD [75]. Several studies [76-79] have reported neutral or even positive effects of abatacept on the progression of ILD in patients with RA. Furthermore, a recent study [79] provides additional support for the potential benefit of early abatacept administration in preventing the progression of RA-ILD, regardless of the specific radiological pattern. While our current study focuses on future risk of incident RA-ILD, these previous studies suggest that abatacept might also have a protective effect that could extend to reducing the incidence of new ILD cases among patients with RA.

Pooled analysis of two cohorts demonstrated RTX and TCZ showed no difference in the risk of RA-ILD development when comparing with TNFi. This is despite RTX being often used to treat RA-ILD and TCZ having an FDA indication to treat systemic sclerosis-related ILD. In real-world settings, there were notable variations in baseline characteristics between patients who received alternate modes of action (MOA) compared to those treated with anti-TNFs. Typically, patients undergo cycles of TNFi treatment before considering therapeutic options like TCZ, RTX, or ABA. Consequently, individuals exposed to alternate MOA may exhibit more severe and prolonged disease manifestations. Additionally, physicians' perceptions could influence the selection or avoidance of these newer therapies for patients with ILD risk factors, concomitant lung diseases such as asthma/COPD, or subtle manifestations of ILD. Thus, there may be channeling bias as patients were more likely to have received RTX if they had pre-existing ILD than if they did not (19.8 % vs. 8.5 %; $p < 0.0001$), unlike with TNFi therapy [56].

To our knowledge, this is the first meta-analysis comprehensively investigating the association of various contemporary DMARDs encompassing csDMARDs, bDMARDs, and tsDMARDs, and the risk of incident ILD among patients with RA. Of note, we found no evidence that TNFi were associated with incident ILD, suggesting that these medications may be safe to use related to ILD risk. This study presents a comprehensive systematic literature review and meta-analysis involving a large number of studies and providing robust insights into the association between DMARDs and incident ILD among RA patients. By including various types of studies such as RCTs, prospective and retrospective cohort studies, case-control studies, and post-marketing surveillance studies, the analysis captures a wide range of data sources, enhancing the generalizability of the findings. We used recommended tools to assess for risk of bias for all identified studies and excluded studies from the meta-analysis deemed to have high risk of bias to ensure the robustness and reliability of our findings. Furthermore, heterogeneity does not exceed 10 % in all comparisons of randomized controlled trials (RCTs). In observational studies, except for two comparisons (TNFi vs. no TNFi, ABA vs. TNFi), heterogeneity did not exceed 50 % for any other comparison. This enhances confidence in the consistency of the results across different studies and strengthens the reliability of the

findings.

Our study has several limitations that warrant consideration. First, it is important to note that some of the included studies, particularly the RCTs, were not specifically designed to assess the risk of ILD as a primary outcome. Thus, there may have been unrecognized incident ILD cases that could bias findings toward the null in RCTs. Also, many RCTs had very short follow-up that may not allow for the clinical diagnosis of an insidious disease such as ILD and could have included some patients with pre-existing ILD. Thus, we included observational studies that could have longer follow-up, many of which were dedicated to incident ILD ascertainment. Second, the lack of standardized definitions and criteria for diagnosing and reporting ILD across studies may contribute to variability in outcome ascertainment and misclassification bias. For example, many observational studies use administrative data such as billing codes to identify ILD that may not be accurate [80]. Lastly, the observational nature of many included studies precludes establishing causality, and the potential for unmeasured confounding cannot be entirely ruled out. Publication bias could also affect observational studies, where researchers were more motivated to publish statistically significant findings. Despite the comprehensive nature of the systematic review, many of the results of specific DMARDs had wide confidence intervals, so we were unable to detect modest differences. However, we were able to detect statistically significant results for methotrexate and tofacitinib. Our study offers valuable insights for the rheumatology community by highlighting significant gaps in the current literature and underscoring the need for more rigorous and long-term studies. The results may also help plan definitive RCTs for RA-ILD risk to choose specific DMARDs to investigate and their expected effect sizes. Although the statistical power may be limited due to the combination of small studies with few events, our analysis synthesizes the available evidence to provide a comprehensive overview of the existing research on DMARDs and the risk of incident RA-ILD.

In conclusion, the results of our systematic literature review and meta-analysis demonstrate no increased RA-ILD risk for any DMARD and that MTX may have a protective effect on RA-ILD risk, while tofacitinib could lower the likelihood of ILD development compared to TNFi. However, those conclusions are drawn from observational studies, and there were no associations of any specific DMARD with incident ILD in RCTs, underscoring the necessity for additional well-designed prospective studies to substantiate these findings.

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Declaration of competing interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.semarthrit.2024.152561](https://doi.org/10.1016/j.semarthrit.2024.152561).

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