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Methotrexate and Lung Disease in Rheumatoid Arthritis

A Meta-Analysis of Randomized Controlled Trials

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Objective. **Methotrexate has shown efficacy for the treatment of several diseases, especially rheumatoid arthritis (RA). Methotrexate has also been implicated as a causative agent in interstitial lung disease. Patients with RA may develop pulmonary manifestations of their disease and are at increased risk of respiratory infection. The aim of this study was to evaluate the relative risk (RR) of pulmonary disease among patients with RA treated with methotrexate.**

Methods. **We searched the PubMed and Cochrane databases (publication dates January 1, 1990 to February 1, 2013) for double-blind, randomized, controlled trials of methotrexate versus placebo or active comparator agents in adults with RA. Studies with <100 subjects or with a duration of <24 weeks were excluded. Two investigators independently searched both databases, and all of the investigators reviewed the selected studies. We compared differences in the RR using the Mantel-Haenszel random-effects method.**

Results. **A total of 22 studies with 8,584 participants met the inclusion criteria. Heterogeneity across studies was not significant (I^2 = 3%), allowing combination of the trial results. Methotrexate was associated with an increased risk of all adverse respiratory events (RR 1.10, 95% confidence interval [95% CI] 1.02−1.19) and respiratory infection (RR 1.11, 95% CI 1.02−1.21). Patients treated with methotrexate were not at increased risk of death due to lung disease (RR 1.53, 95% CI 0.46−5.01) or noninfectious respiratory events (RR 1.02, 95% CI 0.65−1.60). A subgroup analysis of studies in which pneumonitis was described revealed an increased risk associated with methotrexate (RR 7.81, 95% CI 1.76−34.72).**

Conclusion. **Our study demonstrated a small but significant increase in the risk of lung disease in patients with RA treated with methotrexate compared with other disease-modifying antirheumatic drugs and biologic agents.**

Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting ~1% of the population in the industrialized world (1). Patients with RA are at significant risk of disability and have increased mortality (1–6). Manifestations of RA include interstitial lung disease, and a higher rate of pulmonary infection in patients with RA contributes to overall and pulmonary-related fatalities (3,4,7).

Methotrexate (MTX) has shown efficacy in treating several diseases, including RA, psoriasis, psoriatic arthritis, inflammatory bowel disease, and small-vessel vasculitis (8). MTX is the most commonly recommended first-line disease-modifying treatment of RA (5,6). However, MTX is also implicated as a causative agent in lung disease (9–13). The incidence of MTX-related lung disease has been reported to be as high as 7.6% (9–11). Two forms of lung disease have been attributed to MTX. MTX-related interstitial lung disease presents most commonly during the first year of treatment, and reported pathologic findings in different studies include neutrophil infiltration, lymphocytic infiltration, alveolitis, and an increased CD4+:CD8+ ratio (14–16). Chronic pulmonary fibrosis due to MTX has been reported in case series (17,18); however, longitudinal

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studies have not demonstrated evidence of chronic deterioration of lung function in patients treated with MTX (19–21).

A variety of pulmonary manifestations may occur in patients with RA, including pleural effusions, interstitial lung disease, and pulmonary nodules (22). Interstitial lung disease is a common complication of RA (7,19,23). RA-related interstitial lung disease can also present with neutrophil or lymphocytic infiltration, alveolitis, and an increased CD4+:CD8+ ratio (24–26). MTX-related and RA-related interstitial lung disease share the predominant clinical features of dyspnea and nonproductive cough (27). MTX-related interstitial lung disease has been suggested to typically present more rapidly than RA-related lung disease; however, there is a significant overlap in time to onset. The clinical and histopathologic features of interstitial lung disease associated with RA may therefore be indistinguishable from those of MTX-related interstitial lung disease. A number of potential differences in the histologic findings between the 2 conditions have been proposed, but neither can be definitively diagnosed histologically. Type II pneumocyte hyperplasia and fibroblast proliferation have been reported as being suggestive, but not pathognomonic, of MTX toxicity (27).

Distinguishing MTX-induced lung toxicity from RA-associated lung disease is vital in the clinical setting, because MTX is an effective treatment of RA. The suspicion of MTX-induced lung injury frequently leads to cessation of MTX in patients who may otherwise be benefiting from the treatment (28). Although the criteria described by Searles and McKendry (29) or by Carson et al (9) are often used to diagnose MTX-induced pneumonitis, in practice it is difficult to definitively rule out infectious causes and RA-related interstitial lung disease.

In our experience, many cases of lung disease initially attributed to MTX are due to other causative factors, including, but not limited to, RA-associated interstitial lung disease and opportunistic infection, with some patients experiencing worsening lung disease following cessation of MTX. The aim of this study was to perform a meta-analysis of randomized controlled trials with a duration of at least 24 weeks, to evaluate whether MTX is associated with an increased risk of lung disease in adults with RA.

MATERIALS AND METHODS

Data sources and searches. A systematic search of the literature (publication dates from January 1, 1990 to February 1, 2013) was performed using the PubMed and Cochrane databases. We also searched for previously published meta-analyses and systematic literature reviews. The reference lists in the relevant articles were also reviewed.

The following keywords were used for the search: ((“methotrexate”[MeSH Term] OR “methotrexate”[All Fields]) AND (“arthritis, rheumatoid”[MeSH Term] OR (“arthritis”[All Fields] AND “rheumatoid”[All Fields]) OR “rheumatoid arthritis”[All Fields] OR (“rheumatoid”[All Fields] AND “arthritis”[All Fields]))) AND (“humans”[MeSH Term] AND Randomized Controlled Trial[ptyp] AND English [lang] AND “adult”[MeSH Term] AND (“1990/01/01”[PDAT]: “2013/02/01”[PDAT])).

Study selection. The literature search was performed independently by 2 of the authors (RC and CL), and discrepancies were resolved by consensus. The inclusion criteria for study selection were as follows: 1) double-blind, randomized, controlled trials; 2) human subjects with RA; 3) studies in English; 4) studies with a minimum of 2 arms, with patients in at least 1 arm receiving MTX and patients in at least 1 arm not receiving MTX; 5) studies including only adults (age >18 years); 6) trials with a duration of ≥ 24 weeks; 7) studies of ≥ 100 patients; and 8) studies in which respiratory side effects in the MTX and comparator groups were reported separately. In the case of multiple publications of a single randomized controlled trial, we included the publication most relevant to our inclusion criteria, in terms of detailed reporting of respiratory side effects. If the results of a study were reported at multiple time points, we included the study with the longest duration provided it remained a double-blind, randomized, controlled trial and respiratory adverse events were fully reported. If required, we reviewed previously published reports of the same trial in order to fully assess the trial protocol and risk of bias. This approach was taken to avoid including study subjects more than once in the meta-analysis.

Relevant articles were selected using a 2-step approach. First, titles and abstracts of the identified references were screened to exclude articles that did not deal with the topic of interest. Second, the full text of relevant articles was reviewed.

Data extraction and quality assessment. For each included study, data were extracted by 2 of the authors independently (RC and CL). Any discrepancies were resolved by discussion. The data were entered into a database by one of the authors (RC) and checked by the remaining authors.

The following variables were extracted: author(s), year of publication, population studied, number of patients, mean age and range, sex, duration of RA, percent rheumatoid factor positive, erosions at baseline, percent MTX naive, previous treatment with disease-modifying antirheumatic drugs (DMARDs), steroid treatment at baseline, folic acid/folinic acid treatment, study design and duration, comparator drug(s), and adverse events. Adverse events were extracted as both total respiratory adverse events and individual adverse events in each category reported in any individual trial. There was significant variation in the terminology used to describe respiratory adverse events in the included studies. In order to overcome this difficulty, adverse events were grouped into 2 subgroups: infectious adverse events and noninfectious ad-

verse events. Due to this heterogeneity in terminology, it was not possible to directly compare any specific adverse event, including "interstitial lung disease," that was not described in any of the trials.

Data synthesis and analysis. Meta-analysis was performed using RevMan version 5.1 software (30). Random-effects meta-analysis using the Mantel-Haenszel method was used throughout. Results are expressed as relative risks (RRs) with 95% confidence intervals (95% CIs). Random-effects meta-analysis was chosen, because although the I^2 statistic suggested little to no heterogeneity in the studies included, there were clear differences between studies in the type and number of respiratory adverse events reported, suggestive of the existence of more significant heterogeneity.

Assessment of bias. We used the criteria described in the Cochrane Handbook for Systematic Reviews 5.1.0 (31) to assess for trial-level risk of bias in the included studies. Two of the authors (RC and CL) independently assessed the studies for risk of bias. Any discrepancies were resolved by discussion and consensus. A risk-of-bias graph and summary were generated. Funnel plots were generated to assess for publication bias.

Sensitivity analysis. Sensitivity analysis was performed to assess the effect of trial size on meta-analysis outcome (trials with <500 participants versus trials with ≥500 participants), the effect of excluding studies in which safety data were reported by means other than intent-to-treat, and the effect of comparator drugs (biologic agents such as anti–tumor necrosis factor α [TNFα], rituximab, and tocilizumab versus other agents).

RESULTS

Literature search. The literature search produced 497 citations, 496 of which were obtained from the PubMed search. One additional citation was identified by manually searching the reference lists of included articles. Of the 497 initially produced citations, 475 were excluded after review of the abstract and/or full text of the article for the reasons shown in Figure 1. Twenty-two articles met the inclusion criteria and were included in the meta-analysis.

Study characteristics. The characteristics of the 22 included studies are shown in Table 1. The duration of the studies ranged from 24 weeks to 104 weeks, and the number of patients ranged from 102 to 999. The 22 articles described a total of 8,584 patients, 4,544 of whom received MTX and 4,040 of whom received comparator treatments. DMARDs were used as comparator agents in 9 studies (1 of which had a placebo group), biologic agents were used in 9 studies, chicken type II collagen was used in 2 studies, a small molecule immune modulator was used in 1 study, and a biologic agent plus cyclophosphamide was used in 1 study (32–53).



Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the studies included in the meta-analysis. * = In 184 studies, all groups received methotrexate (MTX); 70 studies were not double-blind randomized controlled trials; 22 studies involved <100 patients; 15 studies had a duration of <24 weeks; 6 studies did not involve rheumatoid arthritis disease; 3 studies involved no MTX and 2 studies involved no systemic MTX; 2 studies were not published in the English language; and 1 study was a duplicate. ** = In 59 studies, all groups received MTX; no safety data were provided in 57 studies; 21 studies were not double-blind randomized controlled trials; no specific respiratory data were provided in 20 studies; 6 studies involved no MTX; 2 studies involved <100 patients; in 2 studies, no specific safety data for MTX were provided; 1 study had a duration of <24 weeks; and 2 studies were duplicates.

Risk of lung disease. Methotrexate was associated with an increased risk of total adverse respiratory events relative to comparator agents (RR 1.10, 95% CI 1.02–1.19, $I^2 = 3\%$) (Figure 2). We further analyzed the included studies by categorizing respiratory adverse events as infectious or noninfectious. Methotrexate was associated with an increased risk of total infectious adverse respiratory events (RR 1.11, 95% CI 1.02–1.21, $I^2 = 0\%$) but was not associated with an increased risk of total noninfectious respiratory adverse events (RR 1.02, 95% CI 0.65–1.60, $I^2 = 42\%$) (additional information is available from the corresponding author). There was no difference in the risk of death due to lung disease

Table 1. Characteristics of the studies included in the meta-analysis*

Author, year (ref.)	No. of patients receiving MTX	No. of patients receiving comparator treatment	Study duration, weeks	Age, years†	Female sex, %	RF+, %	RA duration, years†	MTX naive, %	Comparator drug	Reported risk of lung disease
Ishaq et al, 2011 (32)	89	91	52	58	71	NA	4	NA	Leflunomide	+
Keystone et al, 2010 (33)	311	133	52	51	81	84	6	0	Golimumab	+/−
Jones et al, 2010 (34)	284	288	24	50	81	NA	6	67	Tocilizumab	+/−
Wei et al, 2009 (35)	158	296	24	47	81	NA	2	NA	CCII	−
Emery et al, 2009 (36)	478	159	24	49	83	NA	4	100	Golimumab	+/−
Lu et al, 2009 (37)	163	326	24	46	83	NA	4	NA	Iguratimod	−
Nishimoto et al, 2009 (38)	64	61	24	51	81	NA	9	0	Tocilizumab	+/−
Hu et al, 2009 (39)	118	120	24	49	85	89	8	NA	rhTNFR:Fc	−
Zhang et al, 2008 (40)	106	105	24	47	82	NA	2	NA	CCII	−
Nishimoto et al, 2007 (41)	145	157	52	53	81	NA	2	NA	Tocilizumab	+/−
Van der Heijde et al, 2006 (42)	459	223	104	53	77	74	7	57.4	Etanercept	+/−
Breedveld et al, 2006 (43)	525	274	104	52	74	NA	1	100	Adalimumab	+/−
Edwards et al, 2004 (44)	80	81	48	54	77	100	11	0	RTX ± CYC	+/−
Cohen et al, 2001 (45)	190	318	104	54	73	62	7	100	Leflunomide ± placebo	+/−
Bathon et al, 2000 (46)	217	415	52	50	75	88	1	100	Etanercept	+/−
Emery et al, 2000 (47)	498	501	104	58	71	NA	4	NA	Leflunomide	+
Haagsma et al, 1997 (48)	71	34	52	56	65	95	0	100	SSZ	+/−
Boers et al, 1997 (49)	76	79	56	49	59	75	0	100	SSZ	+/−
Rau et al, 1997 (50)	87	87	52	55	66	61	2	100	Gold	−
O'Dell et al, 1996 (51)	67	35	104	50	70	86	8	89	SSZ + HCQ	+/−
Williams et al, 1992 (52)	220	115	48	52	68	NA	5	100	Gold	+
Weinblatt et al, 1990 (53)	138	142	36	52	73	70	6	100	Gold	+

* MTX = methotrexate; RF = rheumatoid factor; RA = rheumatoid arthritis; NA = not available; + = yes; – = no; +/– = uncertain. CCII = chicken type II collagen; rhTNFR:Fc = recombinant human tumor necrosis factor receptor:Fc fusion protein; RTX = rituximab; CYC = cyclophosphamide; SSZ = sulfasalazine; HCQ = hydroxychloroquine.
† Mean or median, as reported in individual studies.

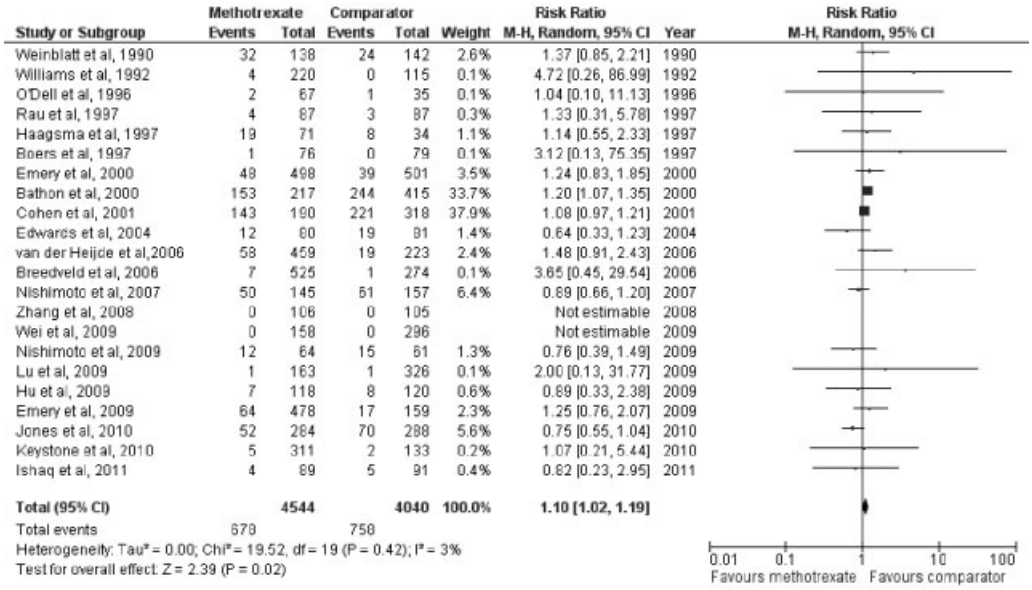


Figure 2. Forest plot of relative risk of total adverse respiratory events associated with methotrexate versus comparator agents. M-H = Mantel-Haenszel; 95% CI = 95% confidence interval.

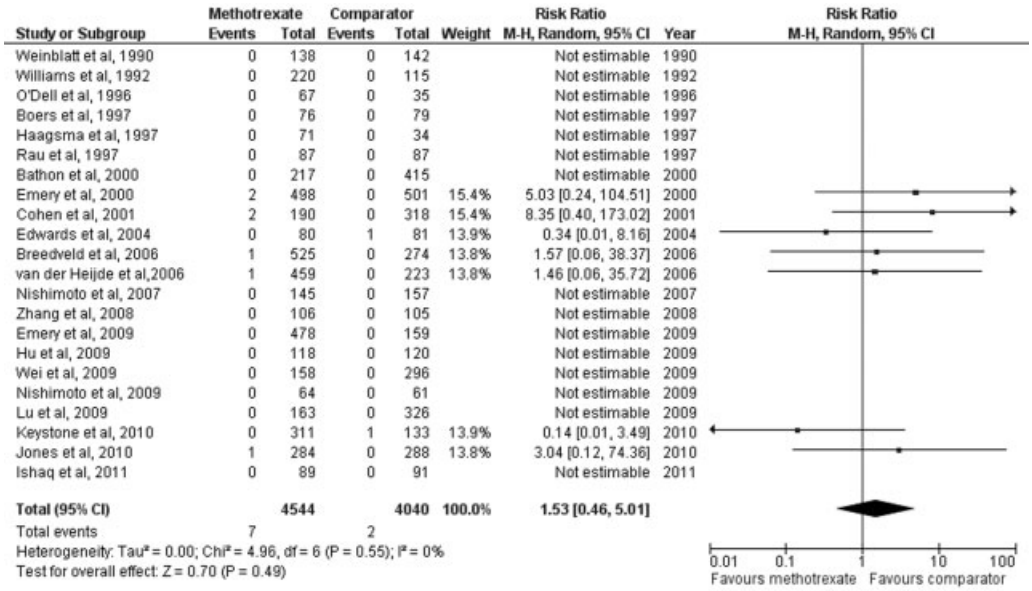


Figure 3. Forest plot of relative risk of death due to lung disease associated with methotrexate versus comparator agents. See Figure 2 for definitions.

between the 2 groups (RR 1.53, 95% CI 0.46–5.01, I^2 = 0%) (Figure 3). There was one reported death attributable to pneumonitis in a MTX-treated patient. A prespecified subgroup analysis of studies in which pneumonitis was specifically reported revealed an increased risk in the group treated with MTX (RR 7.81, 95% CI 1.76–34.72, I^2 = 0%) (Figure 4). All reported cases of pneumonitis were from studies published prior to 2002.

In general, the data suggested a low risk of bias in the included studies (additional information is available from the corresponding author). The most common potential risk identified was inadequate information to

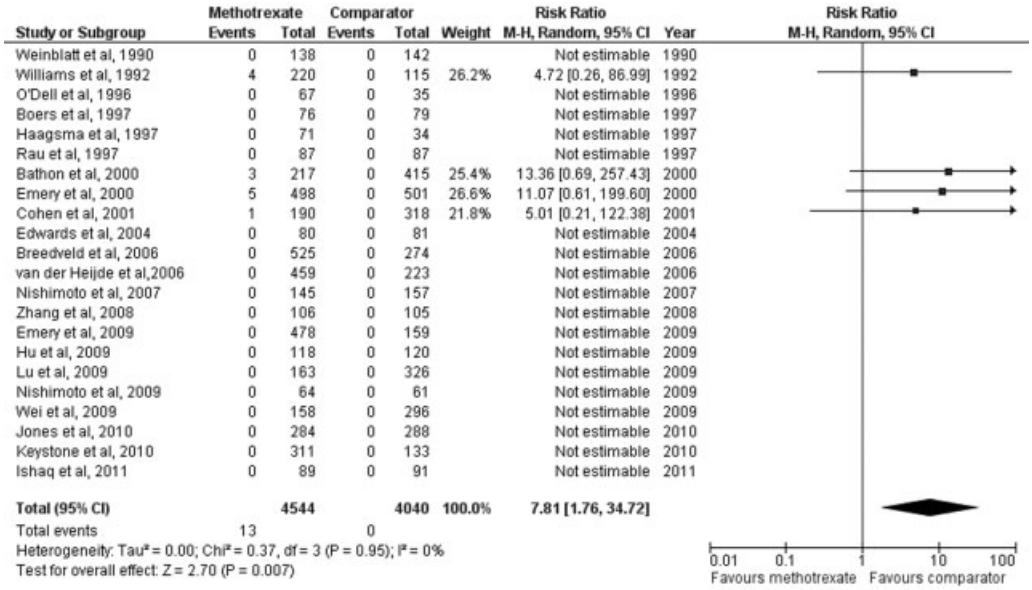


Figure 4. Forest plot of relative risk of pneumonitis associated with methotrexate versus comparator agents. See Figure 2 for definitions.

Table 2. Sensitivity analysis of total respiratory adverse events

Characteristic	No. of studies	No. of participants	Effect size (95% confidence interval)
Study size	22	8,584	1.10 (1.02−1.19)
<500 participants	15	3,755	0.96 (0.79−1.17)
≥500 participants	7	4,829	1.12 (0.98−1.28)
Safety population	22	8,584	1.10 (1.02−1.19)
Intent-to-treat	21	8,404	1.09 (1−1.19)
Other methodology	1	180	0.82 (0.23−2.95)
Comparator	22	8,584	1.10 (1.02−1.19)
Biologic agents	12	4,868	1.01 (0.84−1.21)
Other agents	10	3,716	1.11 (1−1.23)

allow assessment of the risk of selection bias. Eleven of the studies provided inadequate information to assess the risk of bias due to random sequence generation, and 16 of the studies provided inadequate information to assess the risk of bias due to allocation concealment. Twenty-one of the studies included safety data on the intent-to-treat population, and 1 study (32) presented safety data for study completers only. The funnel plot of total respiratory events showed no evidence of publication bias (additional information is available from the corresponding author).

Sensitivity analysis. Results of sensitivity and subgroup analyses are shown in Table 2. The interpretation of these results is limited by the numbers of participants in each subgroup. No effect of study size on overall results was observed. Exclusion of studies presenting safety outcomes for populations other than the intent-to-treat population had no effect on the overall results. Analysis of biologic agents versus other comparators showed a statistically significant difference for MTX compared with other synthetic DMARDs but not biologic agents, but this observation must be interpreted with caution due to the numbers involved.

DISCUSSION

In this study, MTX was associated with a small but significant increase in total respiratory adverse events and total infectious respiratory events compared with other DMARDs and biologic agents. Although there was no significant increase in the number of deaths due to lung disease in MTX-treated patients, one death due to pneumonitis in an MTX-treated patient was reported. A prespecified subgroup analysis demonstrated an increased risk of pneumonitis in patients receiving MTX, although none of the articles published since 2001 described cases of pneumonitis. There are several possible explanations for this observation. It is possible that the case mix in earlier trials conducted in RA was different from that in later trials, with the recruitment of patients at higher risk of pulmonary complications in earlier trials. There may have been a shift in the perception of MTX-induced lung complications around this time that led to differential reporting of adverse events, such that pulmonary complications were more likely to be attributed to MTX prior to 2002. An increased awareness of the clinical presentations of allergy may have led to decreased reporting of MTX-induced pneumonitis. The final possibility is that there was a true change in the incidence of these complications due to changes in environmental factors, infectious epidemiology, or the natural history of RA itself.

Subgroup analysis showed no significant difference between MTX and biologic agents but did show that respiratory complications were significantly more likely to develop in patients treated with MTX compared with other synthetic DMARDs, in particular sulfasalazine and gold. These differences may be true differences between the specific agents; however, they may also be a reflection of the relative potency of the agents, with more potent agents being more likely to cause respiratory complications. However, these subgroup analyses must be interpreted with caution due to the small number of patients in each group.

Several previous reports described the incidence of interstitial lung disease in patients treated with MTX. In retrospective studies, the incidence of MTX-induced lung disease has been estimated to be 3.5–7.6%, with a prevalence of 5% (9–11). Salliot and van der Heijde (12) estimated an incidence of 2.4% for MTX-related lung disease and an incidence of 0.43% for MTX-induced hypersensitivity pneumonitis, using pooled data from 21 prospective cohort studies with a duration of at least 2 years. Randomized controlled trials, including those in the current meta-analysis, were not included in that study (12). A recent prospective study estimated an incidence of 1 case of MTX-induced pneumonitis every 192 patient-years (13). The data set from the Rochester Epidemiology Project demonstrated that patients with RA have a 9-fold increased risk of interstitial lung disease (7). Risk factors for interstitial lung disease included older age, male sex, and more severe RA disease. The presence of interstitial lung disease significantly increases the risk of death in RA. Significantly, Bongartz et al (7) looked carefully at interstitial lung disease among MTX-treated patients, finding no cases

of alveolitis, and concluded that the association with MTX was likely due to channeling bias.

In light of these findings, we evaluated the pneumonitis data obtained in our study for possible confounders in the original studies. As outlined previously, the date of a trial was a significant confounder, with pneumonitis more likely to be reported in earlier studies. The weighted mean age of the patients was 54.3 years in studies describing pneumonitis compared with 50.7 years in studies in which pneumonitis was not reported. In studies in which pneumonitis was reported, 28% of the patients were male, whereas 22% of the patients were male in studies in which no cases of pneumonitis were reported. Patients with RA are at increased risk of premature mortality, with mortality rates among these patients being 1.5-fold higher than those in the general population (4). Respiratory events account for 9% of RA deaths, while medications account for <2% (4). An increasing body of evidence suggests that MTX reduces mortality in RA (54). It is therefore of vital importance not to implicate MTX as a causative agent in adverse events when insufficient evidence in available, because treatment with MTX may be lifesaving. Our study adds to previous publications as the first study to assess the risk of lung disease in patients with RA treated with MTX in clinical trials.

Our study has several strengths. The use of meta-analytic techniques enabled us to include a large number of patients (>8,000), more than half of whom were treated with MTX, who participated in studies with a mean study duration of 54 weeks. The inclusion of only double-blind, randomized, controlled trials helps eliminate potential treatment and ascertainment bias resulting from the existing perception that MTX can cause pneumonitis and chronic interstitial lung disease. It also provides a large number of subjects with similar demographic and disease characteristics as a control group. Individual clinical trials have limitations, which include a lack of sufficient power to robustly assess side effects, particularly those that are less common (55).

Our study also has some important limitations. Underreporting of unexpected outcomes or adverse events is possible when meta-analysis is used, and there were differences between studies in both the terminology and frequency of respiratory events reported. Detailed information on all respiratory events was not available in all articles, and we did not have access to the unpublished data. Folate supplementation may ameliorate MTX-induced adverse events including pneumonitis; unfortunately, we were unable to accurately assess the effect of folate supplementation due to unclear reporting of this in the majority of included studies. Limited analysis of the studies in which folate administration was definitively reported did not reveal any significant differences compared with the overall study results. The studies included in our meta-analysis were of relatively short duration, ranging from 24 weeks to 104 weeks; however, it has been suggested that MTX-induced interstitial lung disease may develop at any time during treatment and occurs in 48% of affected patients within 32 weeks of the initiation of MTX (27). Other investigators have previously reported the results of long-term MTX exposure in cohort studies with a duration of at least 2 years. Not all published data were included in our meta-analysis; we elected to focus on large-scale, high-quality studies that included full reporting of the relevant data, in order to minimize the impact of data collection errors on outcome.

A final limitation is that in nearly all cases the comparator drug was an active treatment, and some of these agents have also been reported to be associated with pulmonary adverse events. In addition, the temporal trends in the comparator drugs used in studies of MTX and the differing frequencies of adverse pulmonary events associated with these agents may have contributed to apparent changes in the relative frequency of adverse events associated with MTX. Historically, intramuscular gold and sulfasalazine, and more recently DMARDs such as leflunomide, have been linked to the development of interstitial lung disease (56–59). More recently, a possible link has emerged with the use of several biologic agents, initially anti-TNFα and more recently rituximab and tocilizumab (60–62). Interstitial lung disease is an uncommon side effect of drugs in general, and only a limited number of such agents have been described in the literature. Rather than each single drug causing interstitial lung disease as an agent-specific adverse event, it is perhaps more likely that if a link is present, it involves the modification of the underlying pulmonary disease process in RA by the implicated agents. In this context, the incidence of MTX-induced lung disease observed in patients who do not have RA is clearly of interest. The occurrence of interstitial lung disease in patients receiving MTX for the treatment of psoriasis has been reported in only a few case reports (17,63). However, because of the relatively small numbers of cases among patients with psoriasis, it is possible that these reports represent a chance co-occurrence and are not related to MTX treatment. The successful reintroduction of MTX in some patients

with MTX-induced interstitial lung disease, without recurrence of pulmonary disease, further calls into question the direct pathogenic role of MTX (64).

In conclusion, the results of our meta-analysis demonstrate a small increased risk of respiratory adverse events in patients with RA treated with MTX compared with other DMARDs and biologic agents but not an increased risk of death due to pulmonary disease. This observation has important implications for clinical decision-making in the treatment of RA, suggesting that the risk of MTX-induced lung disease may be lower than previously believed.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Conway had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Conway, Coughlan, O'Donnell, Carey.
Acquisition of data. Conway, Low.
Analysis and interpretation of data. Conway, Low, Coughlan, Carey.

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