BMJ Open Respiratory Research

Mycophenolate and azathioprine efficacy in interstitial lung disease: a systematic review and meta-analysis

Francesco Lombardi ,[1] Iain Stewart ,[2] Laura Fabbri ,[2] Wendy Adams,[3] Leticia Kawano-Dourado ,[4,5] Christopher J Ryerson,[6] Gisli Jenkins ,[7] REMAP-ILD Consortium

To cite: Lombardi F, Stewart I, Fabbri L, *et al*. Mycophenolate and azathioprine efficacy in interstitial lung disease: a systematic review and meta-analysis. *BMJ Open Respir Res* 2024;**11**:e002163. doi:10.1136/bmjresp-2023-002163

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjresp-2023-002163).

FL and IS contributed equally.

Received 1 November 2023
Accepted 7 February 2024

For numbered affiliations see end of article.

Correspondence to
Dr Francesco Lombardi; lombardi.f89@gmail.com

ABSTRACT

Objectives Mycophenolate mofetil (MMF) and azathioprine (AZA) are immunomodulatory treatments in interstitial lung disease (ILD). This systematic review aimed to evaluate the efficacy of MMF or AZA on pulmonary function in ILD.

Design Population included any ILD diagnosis, intervention included MMF or AZA treatment, outcome was delta change from baseline in per cent predicted forced vital capacity (%FVC) and gas transfer (diffusion lung capacity of carbon monoxide, %DLco). The primary endpoint compared outcomes relative to placebo comparator, the secondary endpoint assessed outcomes in treated groups only.

Eligibility criteria Randomised controlled trials (RCTs) and prospective observational studies were included. No language restrictions were applied. Retrospective studies and studies with high-dose concomitant steroids were excluded.

Data synthesis The systematic search was performed on 9 May. Meta-analyses according to drug and outcome were specified with random effects, I^2 evaluated heterogeneity and Grading of Recommendations, Assessment, Development and Evaluation evaluated certainty of evidence. Primary endpoint analysis was restricted to RCT design, secondary endpoint included subgroup analysis according to prospective observational or RCT design.

Results A total of 2831 publications were screened, 12 were suitable for quantitative synthesis. Three MMF RCTs were included with no significant effect on the primary endpoints (%FVC 2.94, 95% CI −4.00 to 9.88, I^2=79.3%; %DLco −2.03, 95% CI −4.38 to 0.32, I^2=0.0%). An overall 2.03% change from baseline in %FVC (95% CI 0.65 to 3.42, I^2=0.0%) was observed in MMF, and RCT subgroup summary estimated a 4.42% change from baseline in $\%DL_{CO}$ (95% CI 2.05 to 6.79, I^2=0.0%). AZA studies were limited. All estimates were considered very low certainty evidence.

Conclusions There were limited RCTs of MMF or AZA and their benefit in ILD was of very low certainty. MMF may support preservation of pulmonary function, yet confidence in the effect was weak. To support high certainty evidence, RCTs should be designed to directly assess MMF efficacy in ILD.

PROSPERO registration number CRD42023423223.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Mycophenolate mofetil (MMF) and azathioprine (AZA) are two immunomodulatory drugs used in the treatment of connective tissue disease with both drugs having mechanisms that target lymphocytes. While increasingly used in treatment of interstitial lung disease (ILD), there is limited evidence for the efficacy of MMF or AZA in improving outcomes.

WHAT THIS STUDY ADDS

⇒ We undertook a systematic review and meta-analysis to assess whether administration MMF or AZA in ILD was associated with changes in pulmonary function and gas transfer. There was an unclear benefit of MMF on ILD. There was no significant difference in outcome when compared with placebo or standard of care. A minor increase in per cent predicted forced vital capacity and diffusion lung capacity of carbon monoxide from baseline was observed in MMF. Studies on AZA were limited.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Findings may provide indication of an attenuation on lung function decline, however, all estimates should be considered weak evidence with a high likelihood that additional trials may change effect estimates in a manner sufficient to influence decision-making. The limited number of controlled studies in MMF and AZA highlight an important need for additional well-designed randomised controlled trials to directly test their efficacy in ILD.

INTRODUCTION

Interstitial lung disease (ILD) is a diverse group of conditions that affect the interstitial structure of the lungs. These diseases can be characterised by progressive lung damage, resulting in symptoms such as dyspnoea, decreased exercise tolerance and a diminished quality of life.[1] Forced vital capacity (FVC) and the diffusion lung capacity of carbon monoxide (DL_{CO}) are widely used to assess the severity of disease and predict prognosis of people with ILD.[2]

Mycophenolate mofetil (MMF) and azathioprine (AZA) are two immunomodulatory drugs commonly used in the treatment of connective tissue disease (CTD) and associated ILD (CTD-ILD). MMF works by blocking the de novo synthesis of DNA, thereby inhibiting the proliferation of lymphocytes. AZA is a purine analogue that hinders purine synthesis and becomes incorporated into DNA during the anabolic process. Similar to MMF, this mechanism of action makes both drugs more specific for targeting lymphocytes, as lymphocytes do not have a salvage pathway in DNA synthesis.[3]

There is limited evidence for the safety or efficacy of MMF or AZA in improving outcomes for people with ILD.[4] This systematic review and meta-analysis aims to assess whether the administration of MMF or AZA in ILD is associated with changes in pulmonary function and gas transfer, and to synthesise evidence of safety profiles.

METHODS

Search strategy

The prespecified protocol was submitted to PROSPERO on 3 May 2023 and registered on 16 May 2023 (CRD42023423223). The search strategy was last performed on 9 May 2023.

The population was defined as people with ILD (Idiopathic pulmonary fibrosis (IPF), chronic hypersensitivity pneumonia and all CTD-ILD, including systemic scleroderma) the intervention was MMF or AZA; the comparator was placebo or standard of care; the primary outcomes were per cent predicted FVC (%FVC) and DL_{CO} (%DL_{CO}). Adverse events, respiratory symptoms, quality of life and mortality were investigated as secondary outcomes. Relevant studies were searched in Medline and Embase using comprehensive search terms (online supplemental documents 1 and 2). Relevant ongoing trials were searched on clinicaltrials.gov (online supplemental document 3).

Inclusion criteria

Eligible studies included interventional randomised controlled trials (RCTs) and observational prospective studies of adults (>18 years old) diagnosed with any ILD, where at least one arm was treated with MMF or AZA. Low doses of steroids concomitant with or prior to MMF or AZA treatment were allowed, while we excluded studies with concomitant high-dose therapies (≥20 mg/day of prednisone or equivalent). Finally, we excluded studies that did not report %FVC or %DL_{CO}. No language restrictions were applied.

Study selection and data extraction

Two authors (FL and LF) independently assessed the titles and abstracts of the identified studies according to the eligibility criteria. Subsequently, two authors (FL and LF) evaluated the full text of the selected articles to determine their inclusion. Any disagreements were resolved through discussion and consensus with a third author (IS) resolving any remaining disagreements.

Data were independently extracted using a proforma and confirmed by two authors (FL and LF). Extracted data included study design, authors, year of publication; patient data namely age, reported sex or gender, duration of disease at the time of evaluation, aetiology of the disease and intervention characteristics, including MMF or AZA treatment, dose and duration of treatments. Primary outcomes of interest, %FVC and %DL_{CO}, were extracted, along with any secondary outcomes reported, at baseline and follow-up time point closest to 12 months.

Continuous primary outcomes were collected as mean and SD at baseline and follow-up time points. When studies reported other summary values, these were converted to mean and SD.[5] Secondary outcomes reported as dichotomous and categorical variables were extracted as ratio and/or per cent.

Risk of bias

Two authors (FL and LF) independently used the Cochrane 'Risk of Bias' assessment tool 2.0 to evaluate the included RCTs prior to quantitative synthesis.[6] Risk of bias in the observational prospective studies was assessed using the Newcastle-Ottawa Quality Assessment Scale.[7] To assess the risk of bias in single-arm observational cohorts, specifically for evaluation of 'selection bias' and 'comparative bias' on the Newcastle-Ottawa Quality Assessment Scale, baseline time points were considered as the 'not exposed cohort' and the follow-up time point as the 'exposed cohort'. Studies that were determined to have a high risk of bias were excluded from quantitative synthesis.

Statistical analysis

When two or more studies were available for a specific treatment, a random effects meta-analysis with inverse-variance was performed to evaluate the effect of the treatment on %FVC and %DL_{CO} values. Estimates were expressed as weighted mean difference (WMD) with 95% CI.

Where there were sufficient RCT data, the primary endpoint analysis assessed the delta difference in %FVC and %DL_{CO} at follow-up from baseline in respiratory function for MMF or AZA relative to the comparator. In a secondary endpoint analysis, the difference in %FVC and %DL_{CO} between follow-up and baseline in people receiving of MMF or AZA was compared. Analyses were performed according to drug, prespecified subgroup analyses were performed according to study design (RCT or prospective observation study) and follow-up time (6 months or 12 months and over).

Heterogeneity was evaluated using I^2 statistic to interpret the proportion of the total variability that was due to between-study heterogeneity, as well as inspection of forest plots. All analyses were performed by using Stata SE V.17.0.

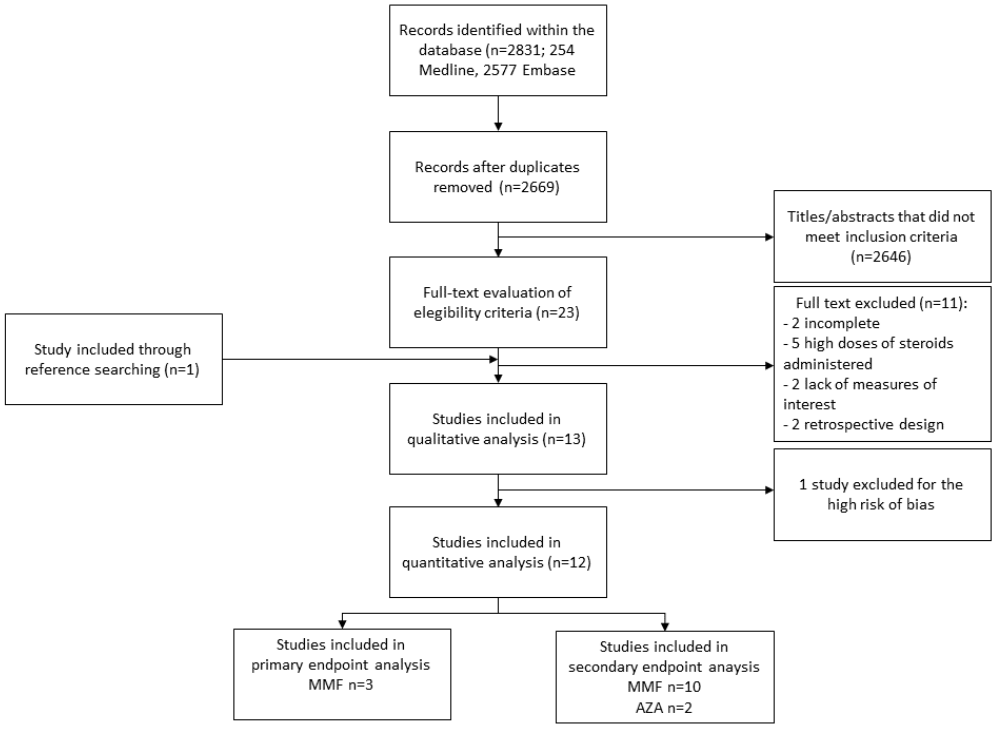

Figure 1 Preferred reporting items for systematic review and meta-analysis (PRISMA) flow of study search and inclusion. AZA, azathioprine; MMF, mycophenolate mofetil.

Assessment of certainty of evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of evidence in effect estimates from RCT data exclusively. The level of certainty was evaluated as high, moderate, low or very low, considering factors of risk of bias, inconsistency, indirectness, imprecision and publication bias.[8] Publication bias was inspected with asymmetry in funnel plots and Egger's test.

Patient and public involvement

Representatives from the Action for Pulmonary Fibrosis charity were involved in the design and dissemination of this systematic review. Members of the REMAP-ILD Consortium include charity representatives.

RESULTS

Search of relevant studies

A total of 2831 publications from Embase and Medline were identified. After removal of duplicates and evaluating the titles and abstracts, 23 studies were assessed for eligibility. Among these, 11 studies were excluded due to retrospective design (n=2), incompleteness (n=2), lack of the outcome of interest (n=2) or the presence of concomitant treatment with high doses of steroids (n=5) (figure 1, online supplemental table 1). A total of 13 studies were eligible for qualitative synthesis (table 1).[9–21] Separately, four ongoing MMF studies were identified, including one phase II RCT, two open-label trials and one prospective cohort study; two studies address pulmonary involvement of systemic sclerosis, one study recruits participants with fibrotic hypersensitivity pneumonitis and one study focuses on idiopathic inflammatory myopathy ILD (online supplemental document 3).

Risk of bias

A moderate risk of bias was observed for the blinding of outcome assessment in all the included RCTs,[12 14 15 19–21] as there were no mentioned strategies to blind the pulmonary function test evaluations (figure 2A). Roig *et al*[21] and Zhang *et al*[20] were considered at high risk of bias in terms of blinding of participants and personnel, as they compared intravenous and oral (per os) treatments without implementing a double dummy strategy. Due to the high risks of bias across a number of domains and insufficient data reporting, the study by Roig *et al*[21] was excluded from quantitative synthesis. In the assessment of prospective observational studies, six studies[10 11 13 16–18] had selection bias in the ascertainment of exposure, but all studies were considered adequate (figure 2B, online supplemental table 2).

MMF and AZA efficacy in primary endpoint relative to comparator

MMF or AZA were tested in a total of four trials, with three trials using MMF[15 19 20] and one trial using AZA.[14] Only MMF trials were included in primary analysis with a total of 249 participants, of which 119 were in the intervention

Table 1 Reported study characteristics of included cohorts

Author	Year	Country and involved centres	Type of study	Treatment (higher dose)	Comparator	Participants in treatment arm	Participants in comparator arm	Type of disease	Duration of disease (months)	Duration of FU (months)	Baseline %FVC	Baseline $\%DL_{co}$
Mankikian *et al*[12]*	2023	France Multicentre	Randomised controlled trial	MMF (2000 mg/die)	N/A*	59	N/A*	ILD with NSIP pattern	34.8	12	70.2	38.6
Nadashkeviech *et al*[14]	2006	Ukraine and Canada Multicentre	Randomised unblinded trial	AZA (2.5 mg/kg/die)	CYC (2.0 mg/kg/die)	30	30	SSc	6.6	18	91.7	84.8
Naidu *et al*[15]	2020	India Monocentric	Randomised controlled trial	MMF (2000 mg/die)	Placebo	20	21	SSc	72	6	75.6	43
Roig *et al*[21]	2010	Spain Monocentric	Not randomised unblinded trial	AZA (2 mg/kg/die	CYC (750 mg/m^2 pulsed intravenous)	25	21	IPF	NA	24	76	68
Volkmann *et al*[19]	2017	USA Multicentric	Post hoc analysis from two RCTs	MMF (3000 mg/die)	Placebo	69	79	SSc	25.2	24	66.5	54
Zhang *et al*[20]	2015	China Monocentric	Randomised unblinded trial	MMF (1500 mg/die)	Placebo	30	30	CTD-ILD	NA	12	72.3	58
Derk *et al*[9]	2009	USA Monocentric	Prospective open label	MMF (1500 mg ×2/die)	N/A	15	N/A	SSc	11	12	99.2	71.2
Henes *et al*[10]	2012	Germany Monocentric	Prospective open label	Enteric-coated mycophenolate sodium (540 mg/die)	N/A	11	N/A	SSc	26	12	78.0	75.1
Liossis *et al*[11]	2006	Greece Monocentric	Prospective open label	MMF (2000 mg/die)	N/A	6	N/A	SSc	NA	8	65.6	64.2
Mendoza *et al*[13]	2012	USA Monocentric	Prospective open label	MMF (average dose 2.02 g/die)	N/A	25	N/A	SSc	<24	N/A	N/A	69
Paone *et al*[16]	2007	Italy Monocentric	Prospective open label	AZA (2 mg/kg/die)	N/A	13	N/A	SSc	16	12	89.5	73.6
Simeón-Aznar *et al*[17]	2011	Spain Monocentric	Prospective open label	Mycophenolate sodium (720 mg ×2/die)	N/A	14	N/A	SSc	78	12	64	40
Vaiarello *et al*[18]	2020	Italy Monocentric	Prospective open label	MMF (1500 mg ×2/die)	N/A	10	N/A	SSc	60	24	73	68

*Participants of the interventional arm (MMF+rituximab) of this study have not been included in the systematic review.
AZA, azathioprine; CTD, connective tissue disease; $\%DL_{co}$, per cent predicted diffusion lung capacity of carbon monoxide; FU, follow-up; %FVC, per cent predicted forced vital capacity; ILD, interstitial lung disease; IPF, Idiopathic Pulmonary Fibrosis; MMF, mycophenolate mofetil; N/A, not available; RCT, randomised controlled trial.

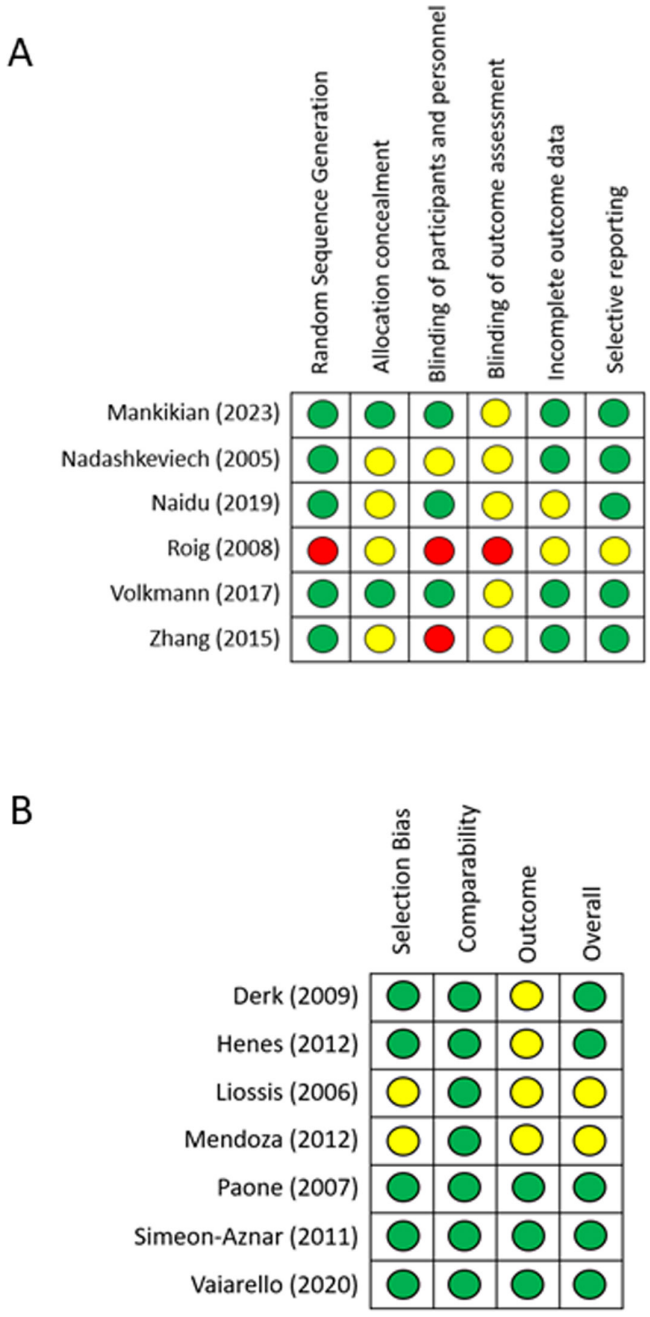

Figure 2 Qualitative synthesis: risk of bias. (A) Risk of bias in RCTs assessed using Cochrane ROB2.0 tool. (B) Risk of bias assessed using Newcastle-Ottawa Quality assessment scale for cohort studies. Green has been assessed as: three or four stars in selection bias; two stars in comparability, three stars in outcome. Yellow has been assessed as: two stars in selection bias; one star in comparability, two stars in outcome. RCTs, randomised controlled trial; ROB2.0, Risk of Bias 2.0.

arm and 130 were in the comparator arm (figure 3A). In primary analysis, the overall delta change in %FVC values from baseline to follow-up was not significantly different between the intervention and comparator arms (WMD 2.94, 95% CI −4.00 to 9.88, I^2=79.3%). Significant heterogeneity was observed and the estimate was interpreted to have very low certainty (table 2, online supplemental figure 1A).

The overall delta change in $\%DL_{CO}$ from baseline to follow-up was not significantly different in the interventional arm compared with the comparator arm (WMD %DLco −2.03, 95% CI −4.38 to 0.32, I^2=0.0% (figure 3B). Heterogeneity was not observed and the estimate was interpreted to have very low certainty (table 2, online supplemental figure 2B).

MMF or AZA efficacy in secondary endpoints

A total of 6 prospective observational studies[9–11 16–18] and 5 RCTs[12 14 15 19 20] were included in secondary analysis of the difference between follow-up and baseline in %FVC, including a combined sample of 267 evaluated at baseline and 244 at follow-up, representing 7.5% loss to follow up. In prespecified subgroup analysis by drug (online supplemental figure 3A), treatment with AZA suggested a decline in %FVC with treatment, although this was not statistically significant (two studies; WMD −6.14, 95% CI −12.88 to 0.61, I^2=48.3%). Treatment with MMF was observed to have a small and significant increase in %FVC value at follow-up (nine studies; WMD 2.03, 95% CI 0.65 to 3.42, I^2=0.0%). Additional subgroup analyses performed on MMF treatment observed similar effect sizes according to study design and very low certainty of evidence (figure 4A, table 2), while a greater effect of MMF was observed at follow-up of 12 months or over with no significant heterogeneity between time points (online supplemental figure 4A).

Data from a total of 7 observational studies[9–11 13 16–18] and 5 RCTs[12 14 15 19 20] were available for analysis of $\%DL_{CO}$, including 262 and 234 patients, respectively, at baseline and follow-up representing a 10.7% loss to follow up. In subgroup analysis by drug (online supplemental figure 3B), treatment with AZA suggested a decline (two studies; −5.72, 95% CI −13.79 to 2.34, I^2=49.8%), while treatment with MMF suggested an increase (10 studies; 1.62, 95% CI −1.70 to 4.94, I^2=60.5%), although effect estimates did not reach significance and substantial heterogeneity was observed. Additional subgroup analyses performed on MMF treatment observed a significant decline in $\%DL_{CO}$ in prospective observation studies (WMD −1.36, 95% CI −2.37 to −0.36, I^2=0.0%) and a significant improvement in RCTs (WMD 4.42, 95% CI 2.05 to 6.79; I^2=0.0%), with substantial heterogeneity between subgroups and very low certainty in evidence (figure 4B, table 2). Subgroup analysis on follow-up time did not observe a significant effect in $\%DL_{CO}$ with no significant heterogeneity observed between groups (figure 4B).

Qualitative synthesis of adverse events

All the studies reported adverse events. The most frequent adverse events in the treated arms were diarrhoea and pneumonia, followed by lympho/leucopenia, anaemia and skin infection (online supplemental table 3).

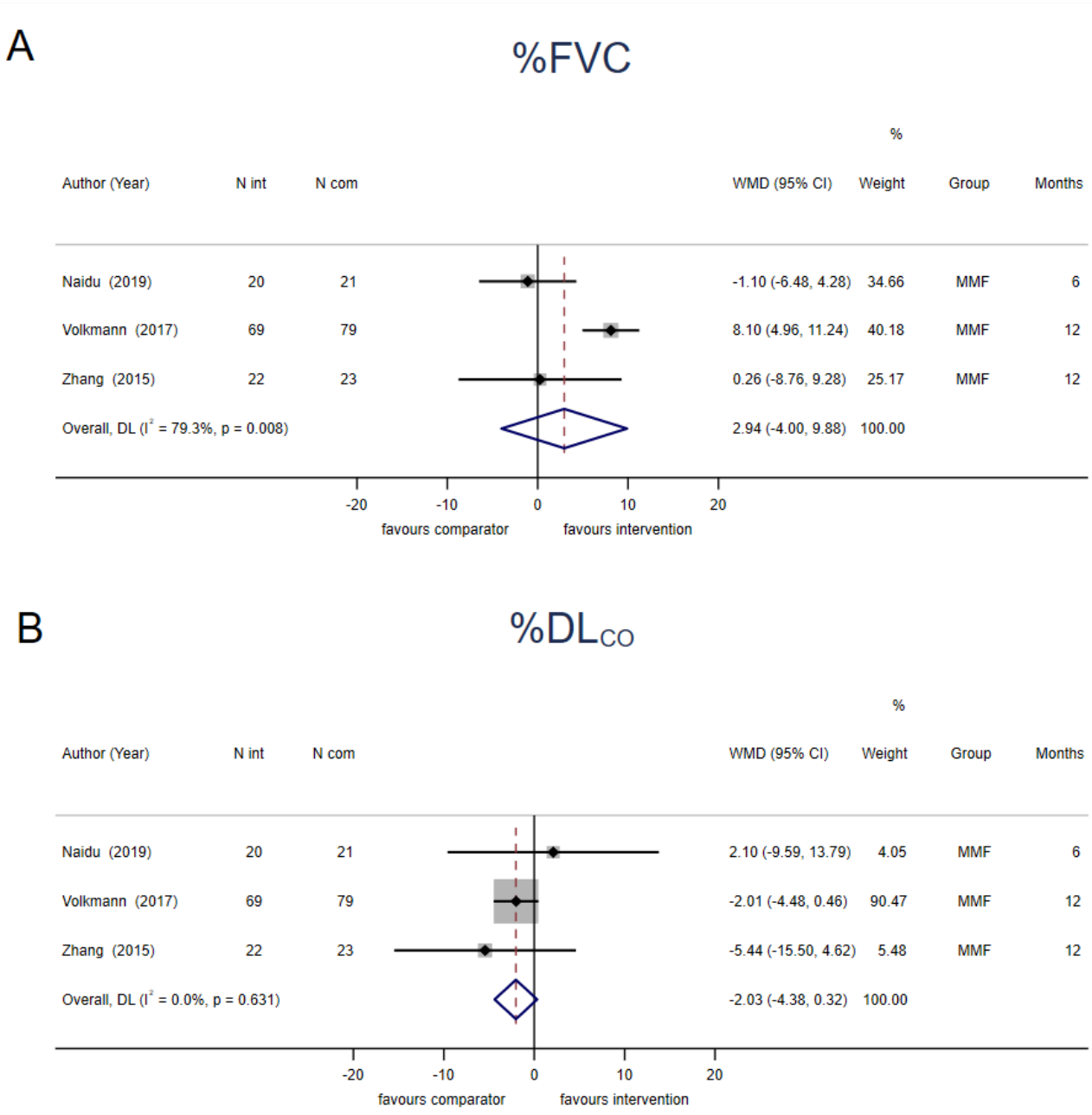

Figure 3 Primary endpoint analysis of efficacy on pulmonary function relative to comparator. (A) Forest plot of difference in %FVC in treatment of MMF versus comparators at follow-up. (B) Forest plot of difference in %DLco in treatment of MMF versus comparators at follow-up. Positive values indicate improvement relative to comparator, negative values indicate decline relative to comparator. Presented with cohort size (N) for intervention and comparator, weighted mean difference (WMD) and 95% CI. Follow-up time reported in months. %DLco, per cent predicted diffusion lung capacity of carbon monoxide; %FVC, per cent predicted forced vital capacity; MMF, mycophenolate mofetil.

Four studies reported on respiratory symptoms.[11 12 15 18] In the study by Mankikian *et al*, no significant difference was observed in the change from baseline in dyspnoea and cough between the treated patients and the placebo group. Naidu *et al* reported an improvement in respiratory symptoms in both arms of the study, with no significant difference between the treatment and control groups. Liossis *et al* reported an improvement in respiratory symptoms compared with baseline after administration of MMF. Vaiarello *et al* evaluated symptoms during a cardiopulmonary exercise test before and after MMF treatment, observing no significant difference in dyspnoea measured by the Borg scale.

Two studies reported change in quality of life.[12 15] Mankikian *et al* and Naidu *et al* evaluated the change of quality of life between the interventional and the control arm using respectively the SF-36 V.1.3 questionnaire and the Medical Outcome Survey SF-36 V.2. Both these

Table 2 GRADE approach to rate certainty of effect estimates

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty (overall score)*
(a) Primary outcome: MMF effect in %FVC delta difference at follow-up relative to comparators							
3	RCTs	Moderate	High inconsistency	Moderate indirectness	High imprecision	Low	⊕○○○ **Very Low**
(b) Primary outcome: MMF effect in $\%DL_{CO}$ delta difference at follow-up relative to comparators							
3	RCTs	Moderate	Moderate inconsistency	Moderate indirectness	High imprecision	Low	⊕○○○ **Very Low**
(c) Secondary outcome: MMF effect in %FVC change from baseline							
4	RCTs	Moderate	Moderate inconsistency	Moderate indirectness	High imprecision	Low	⊕○○○ **Very Low**
(d) Secondary outcome: MMF effect in $\%DL_{CO}$ change from baseline							
3	RCTs	Moderate	Low inconsistency	Moderate indirectness	High imprecision	Low	⊕○○○ **Very Low**

*4 ⊕⊕⊕⊕ **High**=This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low. 3 ⊕⊕⊕○ **Moderate**=This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate. 2 ⊕⊕○○ **Low**=This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high. 1 ⊕○○○ **Very low**=This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.
†Substantially different=a large enough difference that it might affect a decision.
$\%DL_{CO}$, per cent predicted diffusion lung capacity of carbon monoxide; FVC, forced vital capacity; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; MMF, mycophenolate mofetil; RCT, randomised controlled trial.

studies reported no difference in the QoL in MMF arm compared with control. None of the included studies reported on mortality.

DISCUSSION

This systematic review and meta-analysis suggested an unclear benefit of MMF or AZA on FVC or DL_{CO} in people with ILD. Secondary endpoint analysis of change over time stratified by treatment suggested a minor increase in %FVC or $\%DL_{CO}$ compared with baseline in MMF treated groups. The review highlighted a limited number of trials and prospective observational studies that directly tested the effect of MMF or AZA on lung function in the current literature, particularly precluding interpretations on the efficacy of AZA.

All estimates based on MMF RCT data were of very low GRADE certainty of evidence. Risk of bias was deemed moderate as one trial included unblinded participants, one study was post hoc analysis of trial data, and all trials had potential issues in blinding of outcome assessment. Heterogeneity and differences in the direction of effect across RCTs contributed to inconsistency. Imprecision was considered high due to limited RCTs, small samples and small effect sizes with wide CIs. Indirectness was deemed moderate as studies included different diagnoses. There was no strong evidence of publication bias. While these findings provide some indication of the effect, all estimates should be considered weak evidence with a high likelihood that additional studies may change effect estimates in a manner sufficient to influence decision-making.

Primary endpoint analysis in MMF observed no significant effect of treatment vs comparator groups for %FVC or $\%DL_{CO}$, although a non-significant effect in $\%DL_{CO}$ favoured comparator. In contrast, secondary endpoint analysis suggested that MMF treatments could improve on baseline pulmonary function, although this may be insufficient relative to placebo. In further subanalyses restricted to MMF, greater improvement in %FVC was observed at longer follow-up, with no difference according to study design. Conversely, greater improvement in $\%DL_{CO}$ was observed in trial designs, with no difference according to follow-up timing. While heterogeneity was minimised in subgroup analyses, effect sizes were small.

In the narrative review of adverse events, we found that both treatments were well tolerated, however, studies on real-world data suggest difficulties in tolerability.[4] The most frequent adverse events observed with MMF and AZA treatment included respiratory infections and haematological disorders. It is noteworthy that these adverse events were often mild and did not typically require specific treatment nor differ to events encountered in standard treatments. MMF or AZA interruption due to adverse events led to treatment discontinuation only in a few cases. Symptoms appeared to slightly improve after treatment commenced, but stricter interventional vs placebo studies are needed to assess the real effect on patient-reported outcomes.

The first meta-analysis examining the safety and efficacy of MMF in ILD associated with systemic sclerosis, conducted by Tzouvelekis *et al* included both retrospective

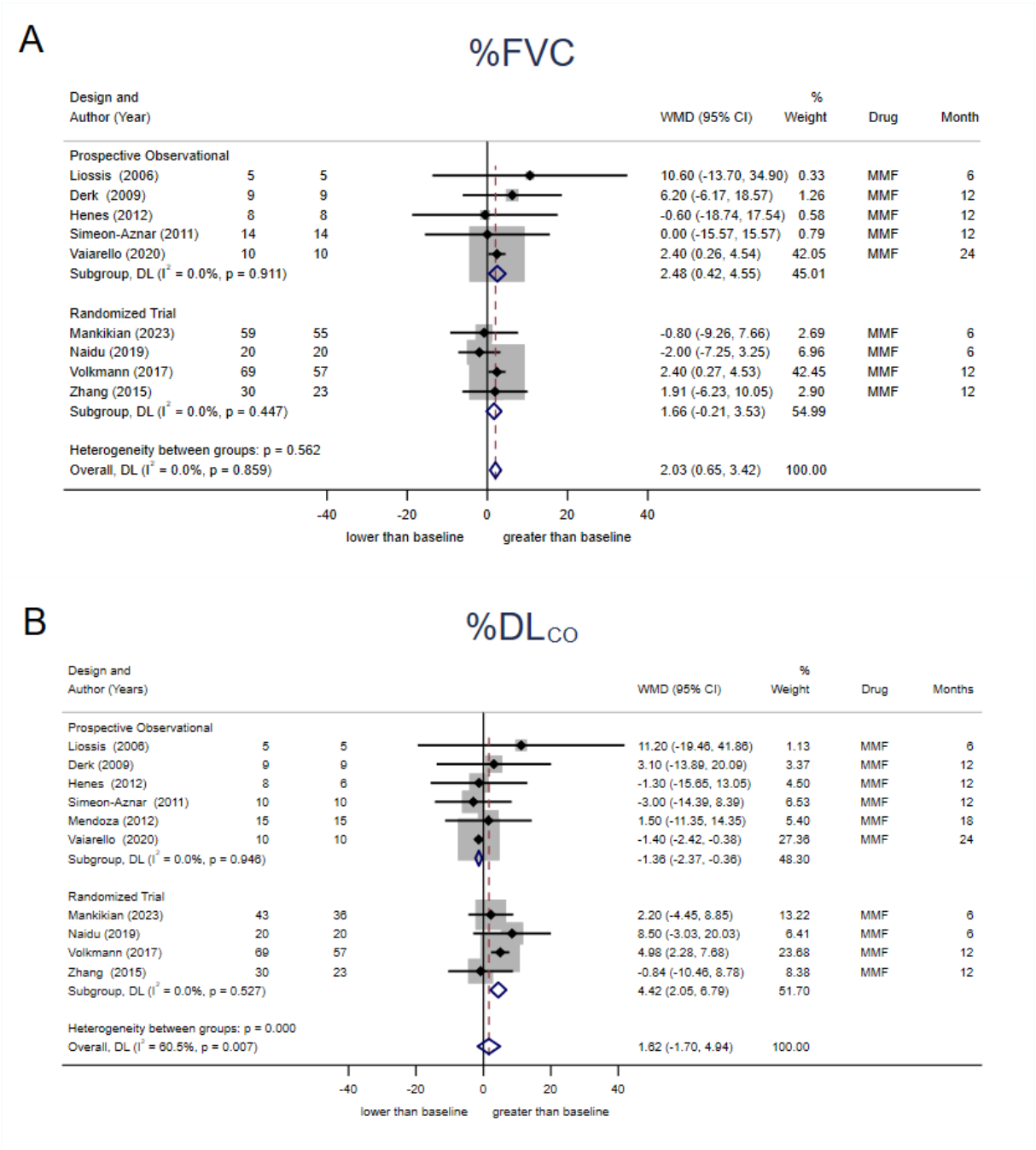

Figure 4 Secondary endpoint analysis of efficacy on pulmonary function compared with baseline. Subgroup analysis of MMF overall and summary estimates presented by study design of trial or prospective observational study.[4] (A) Forest plot of change in %FVC at follow-up versus baseline. (B) Forest plot of change in %DLco versus baseline. Positive values indicate improvement relative to baseline, negative values indicate decline relative to baseline. Presented with cohort size (N) for intervention and comparator, weighted mean difference (WMD) and 95% CIs. Follow-up time reported in months. %DLco, per cent predicted diffusion lung capacity of carbon monoxide; %FVC, per cent predicted forced vital capacity; MMF, mycophenolate mofetil.

and one prospective study. The outcomes of their study align with our findings, indicating an acceptable safety profile for MMF without clear evidence regarding its effectiveness on pulmonary function.[22] Similarly, network meta-analysis in systemic sclerosis associated ILD did not identify significant treatment efficacy of MMF, nor AZA in combination with cyclosporin-A.[23] Further studies are necessary across ILD diagnoses to ascertain potential efficacy in disease subtypes.

This study employed a comprehensive search strategy and strict inclusion criteria, which focused on prospective designs and trials. To support quality, estimates were specifically provided for trial designs along with GRADE assessment. We did not include restrictions on study

language or cohort size. MMF and AZA were evaluated in prespecified subgroup analysis based on drug. Where study designs included other treatments, data were collected to support interpretation of MMF or AZA with omission of the drug in comparator arms. Effects regarding AZA should be interpreted with great caution due to limited studies and insufficient studies for primary analysis. Those involving AZA included an active intervention of Cyclosporin-A in the comparator, with addition of AZA in the treatment group, precluded specific interpretation of AZA alone. The limited representation of AZA in the recent literature may be partially attributed to the results of the PANTHER trial, where AZA in combination with n-acetylcysteine and prednisone led to worse outcomes in patients with IPF.[24] Mankikian *et al* designed an RCT randomising rituximab+MMF versus MMF, we extracted data only from the MMF arm for secondary endpoints.[12] Furthermore, studies were not consistent in ILD diagnosis inclusion, with the majority of prospective observational studies including systemic sclerosis-associated ILD; trials included IPF, non-specific interstitial pneumonia and CTD-ILD, which may contribute to heterogeneity in effect estimates. While ongoing studies were identified, MMF studies did not included blinded phase III RCTs and no AZA studies were identified.

In conclusion, the beneficial impact of MMF and AZA on pulmonary function in patients with ILD is uncertain with some weak evidence that suggests a need to further investigate the effect of MMF in preserving function. While MMF and AZA were generally well tolerated in patients with ILD, it is important to note that the certainty of effects on pulmonary function was very low. Further well-designed RCTs across diagnoses of fibrotic and inflammatory ILD are necessary to support high certainty evidence.

Author affiliations
[1]Pulmonary Medicine, Policlinico Universitario Agostino Gemelli, Roma, Italy
[2]National Heart & Lung Institute, Imperial College London, London, UK
[3]Action for Pulmonary Fibrosis, London, UK
[4]HCOR Research Institute, Hospital do Coracao, Sao Paulo, Brazil
[5]Pulmonary Division, University of Sao Paulo, Sao Paulo, Brazil
[6]Medicine, The University of British Columbia, Vancouver, British Columbia, Canada
[7]Imperial College London, London, UK

Twitter Laura Fabbri @istamina and Gisli Jenkins @IPFdoc

Acknowledgements We express our gratitude to librarian Jacqueline Kemp, Imperial College London, for her valuable assistance in the development of the search strategy. Additionally, we would like to extend our thanks to Dr Liu Bin, Imperial College London, for providing the translation of Chinese manuscripts.

Collaborators REMAP-ILD Consortium: Alexandre Biasi Cavalcanti (Hospital of Coracao), Ali Mojibian (Black Tusk Research Group), Amanda Bravery (Imperial College Clinical Trials Unit), Amanda Goodwin (University of Nottingham), Ana Etges (Federal University of Rio Grande do Sul), Ana Sousa Marcelino Boshoff (Imperial College Clinical Trials Unit), Andreas Guenther (Justus-Liebig-University of Giessen), Andrew Briggs (London School of Hygiene and Tropical Medicine), Andrew Palmer (University of Tasmania), Andrew Wilson (University of East Anglia), Anjali Crawshaw (University Hospitals Birmingham), Anna-MariaHoffmann-Vold (Oslo University Hospital), Anne Bergeron (University Hospitals Geneva), Anne Holland (Monash University), Anthony Gordon (Imperial College London), Antje Prasse (Hannover Medical School), Argyrios Tzouvelekis (Yale University), Athina Trachalaki (Imperial College London), Athol Wells (Royal Brompton Hospital), Avinash Anil Nair (Christian Medical College Vellore), Barbara Wendelberger (Berry Consultants), Ben Hope-Gill (Cardiff and Vale University Hospital), Bhavika Kaul (U.S. Department of Veterans Affairs Center for Innovation in Quality, Effectiveness, and Safety; Baylor College of Medicine and University of California San Francisco), Bibek Gooptu (University of Leicester), Bruno Baldi (Pulmonary Division, Heart Institute (InCor), University of Sao Paulo Medical School, Sao Paulo, Brazil), Bruno Crestani (Public Assistance Hospital of Paris), Carisi Anne Polanczyk (Federal University of Rio Grande do Sul), Carlo Vancheri (University of Catania), Carlos Robalo (European Respiratory Society), Charlotte Summers (University of Cambridge), Chris Grainge (University of Newcastle), Chris Ryerson (Department of Medicine and Centre of Heart Lung Innovations, University of British Columbia), Christophe von Garnier (Centre Hospitalier Universitaire Vaudois), Christopher Huntley (University Hospitals Birmingham), Claudia Ravaglia (University of Bologna), Claudia Valenzuela (Hospital Universitario de La Princesa), Conal Hayton (Manchester University Hospital), Cormac McCarthy (University College Dublin), Daniel Chambers (Queensland Health), Dapeng Wang (National Heart and Lung Institute, Imperial College London), Daphne Bablis (Imperial College Clinical Trials Unit), David Thicket (University of Birmingham), David Turner (University of East Anglia), Deepak Talwar (Metro Respiratory Centre Pulmonology & Sleep Medicine), Deji Adegunsoye (University of Chicago), Devaraj Anand (Royal Brompton Hospital), Devesh Dhasmana (University of St. Andrews), Dhruv Parek (Brimingham University), Diane Griffiths (University Hospitals Birmingham), Duncan Richards (Oxford University), Eliana Santucci (Hospital of Coracao), Elisabeth Bendstrup (Aarhus University), Elisabetta Balestro (University of Padua), Eliza Tsitoura (University of Crete), Emanuela Falaschetti (Imperial College London), Emma Karlsen (Black Tusk Research Group), Ena Gupta (University of Vermont Health Network), Erica Farrand (University of California, San Fransisco), Fasihul Khan (University of Nottingham), Felix Chua (Royal Brompton Hospital), Fernando J Martinez (Weill Cornell Medicine), Francesco Bonella (Essen University Hospital), Francesco Lombardi (Division of Pulmonary Medicine, Fondazione Policlinico Universitario Agostino Gemelli IRCCS), Gary M Hunninghake (Brigham and Women's Hospital), Gauri Saini (Nottingham University Hospital), George Chalmers (Glasgow Royal Infirmary), Gisli Jenkins (Imperial College London), Gunnar Gudmundsson (University of Iceland), Harold Collard (University of California, San Francisco), Helen Parfrey (Royal Papworth Hospital NHS Foundation Trust), Helmut Prosch (Medical University of Vienna), Hernan Fainberg (Imperial College London), Huzaifa Adamali (North Bristol NHS Trust), Iain Stewart (National Heart and Lung Institute, Imperial College London), Ian Forrest (Newcastle Hospitals NHS Foundation Trust), Ian Glaspole (Alfred Hospital), Iazsmin Bauer-Ventura (The University of Chicago), Imre Noth (University of Virginia), Ingrid Cox (University of Tasmania), Irina Strambu (University of Medicine and Pharmacy), Jacobo Sellares (Hospital Clínic de Barcelona), James Eaden (Sheffield University Hospitals), Janet Johnston (Manchester Royal Infirmary NHS Foundation Trust), Jeff Swigris (National Jewish Health), John Blaikley (Manchester University), John S Kim (University of Virginia), Jonathan Chung (The University of Chicago), Joseph A Lasky (Tulane & Pulmonary Fibrosis Foundation), Joseph Jacob (University College London), Joyce Lee (University of Colorado), Juergen Behr (Ludwig Maximilian University of Munich), Karin Storrer (Federal University of Sao Paulo), Karina Negrelli (Hospital of Curacao), Katarzyna Lewandowska (Institute of Tuberculosis and Lung Diseases), Kate Johnson (The University of British Colombia), Katerina Antoniou (University of Crete), Katrin Hostettler (University Hospital Basel), Kerri Johannson (University of Calgary), Killian Hurley (Royal College of Surgeons, Ireland), Kirsty Hett (Cardiff and Vale University Health Board), Larissa Schwarzkopf (The Institute for Therapy Research), Laura Fabbri (National Heart and Lung Institute, Imperial College London), Laura Price (Royal Brompton Hospital), Laurence Pearmain (Manchester University), Leticia Kawano-Dourado (Hcor Research Institute, Hospital do Coracao, Sao Paulo, Brazil. 2. Pulmonary Division, University of Sao Paulo, Sao Paulo, Brazil. 3. MAGIC Evidence Ecosystem Foundation, Oslo, Norway), Liam Galvin (European Pulmonary Fibrosis Federation), Lisa G. Spencer (Liverpool University Hospitals NHS Foundation Trust), Lisa Watson (Sheffield University Hospitals), Louise Crowley (Queen Elizabeth Hospital, University Hospitals Birmingham), Luca Richeldi (Agostino Gemelli IRCCS University Hospital Foundation), Lucilla Piccari (Department of Pulmonary Medicine, Hospital del Mar, Barcelona (Spain)), Manuela Funke Chambour (University of Bern), Maria Molina-Molina (IDIBELL Bellvitge Biomedical Research Institute), Mark Jones (Southampton University), Mark Spears (University of Dundee Scotland), Mark Toshner (University of Cambridge), Marlies Wijsenbeek-Lourens (Erasmus University Medical Hospital), Martin Brutsche (Kantonsspital St.Gallen), Martina Vasakova (Faculty Thomayer Hospital), Melanie Quintana (Berry Consultants), Michael Gibbons (University of Exeter), Michael Henry (Cork University Hospital), Michael Keane (University College Dublin), Michael Kreuter (Heidelberg University Hospital), Milena Man Iuliu Hatieganu (University of Medicine and Pharmacy), Mohsen Sadatsafavi (The University of British Colombia), Naftali Kaminski (Yale University), Nazia Chaudhuri (Ulster University), Nick Weatherley (Sheffield University Hospitals), Nik Hirani (The University of Edinburgh), Ovidiu Fira Mladinescu Victor Babes (University of Medicine and Pharmacy), Paolo Spagnolo (University of Padua), Paul Beirne (Leeds Teaching Hospitals NHS Foundation Trust), Peter Bryce (Pulmonary Fibrosis Trust), Peter George (Royal Brompton Hospital), Philip L Molyneaux (Imperial College London), Pilar Rivera

Ortega (Interstitial Lung Disease Unit, Department of Respiratory Medicine, Wythenshawe Hospital. Manchester University NHS Foundation Trust. United Kingdom.), Radu Crisan-Dabija (University of Medicine and Pharmacy "Grigore T. Popa" Iasi), Rahul Maida (University of Birmingham), Raphael Borie (Public Assistance Hospital of Paris), Roger Lewis (Berry Consultants), Rui Rolo (Braga Hospital), Sabina Guler (University Hospital of Bern), Sabrina Paganoni (Massachusetts General Hospital), Sally Singh (University of Leicester.), Sara Freitas (University Hospital Coimbra), Sara Piciucchi (Department of Radiology, GB Morgagni Hospital; Azienda USL Romagna), Shama Malik (Action for Pulmonary Fibrosis), Shaney Barratt (North Bristol NHS Trust), Simon Hart (University of Hull), Simone Dal Corso (Monash University), Sophie Fletcher (Southampton University), Stefan Stanel (Manchester University NHS Foundation Trust), Stephen Bianchi (Thornbury Hospital), Steve Jones (Action for Pulmonary Fibrosis), Wendy Adams (Action for Pulmonary Fibrosis).

Contributors FL: protocol development, formal analysis, data curation, writing–original draft. IS: protocol development, formal analysis, methodology, supervision, writing–original draft, guarantor. LF: protocol development, data curation, writing–review and editing. WA: protocol development, writing–review and editing. LK-D: protocol development, writing–review and editing. CJR: protocol development, writing–review and editing. GJ: conceptualisation, protocol development, supervision, writing–review and editing.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests GJ is supported by a National Institute for Health Research (NIHR) Research Professorship (NIHR reference RP-2017-08-ST2-014). GJ is a trustee of Action for Pulmonary Fibrosis and reports personal fees from Astra Zeneca, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Chiesi, Daewoong, Galapagos, Galecto, GlaxoSmithKline, Heptares, NuMedii, PatientMPower, Pliant, Promedior, Redx, Resolution Therapeutics, Roche, Veracyte and Vicore. CJR reports grants from Boehringer Ingelheim, and honoraria or consulting fees from Boehringer Ingelheim, Pliant Therapeutics, Astra Zeneca, Trevi Therapeutics, Veracyte, Hoffmann-La Roche, Cipla. FL, IS, LF, WA and LK-D report no competing interests.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval No ethical approval was sought as the study uses summary information from published literature.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. We cited published study.

ORCID iDs
Francesco Lombardi http://orcid.org/0000-0003-2254-5119
Iain Stewart http://orcid.org/0000-0002-1340-2688
Laura Fabbri http://orcid.org/0000-0002-8250-6464
Leticia Kawano-Dourado http://orcid.org/0000-0003-0784-1331
Gisli Jenkins http://orcid.org/0000-0002-7929-2119

REFERENCES

1 Cottin V, Wollin L, Fischer A, *et al*. Fibrosing interstitial lung diseases: knowns and unknowns. *Eur Respir Rev* 2019;28:180100.
2 Nasser M, Larrieu S, Si-Mohamed S, *et al*. Progressive fibrosing interstitial lung disease: a clinical cohort (the PROGRESS study). *Eur Respir J* 2021;57:2002718.
3 Broen JCA, van Laar JM. Mycophenolate mofetil, azathioprine and tacrolimus: mechanisms in rheumatology. *Nat Rev Rheumatol* 2020;16:167–78.
4 Wong AW, Khor YH, Donohoe K, *et al*. Prescribing patterns and tolerability of mycophenolate and azathioprine in patients with nonidiopathic pulmonary fibrosis fibrotic interstitial lung disease. *Ann Am Thorac Soc* 2022;19:863–7.
5 McGrath S, Zhao X, Steele R, *et al*. Estimating the sample mean and standard deviation from commonly reported quantiles in meta-analysis. *Stat Methods Med Res* 2020;29:2520–37.
6 Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
7 Wells GA, Shea B, O'Connell D, *et al*. *The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses*. 2009.
8 Santesso N, Glenton C, Dahm P, *et al*. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. *J Clin Epidemiol* 2020;119:126–35.
9 Derk CT, Grace E, Shenin M, *et al*. A prospective open-label study of mycophenolate mofetil for the treatment of diffuse systemic sclerosis. *Rheumatology (Oxford)* 2009;48:1595–9.
10 Henes JC, Horger M, Amberger C, *et al*. Enteric-coated mycophenolate sodium for progressive systemic sclerosis - a prospective open-label study with CT histography for monitoring of pulmonary fibrosis. *Clin Rheumatol* 2013;32:673–8.
11 Liossis SNC, Bounas A, Andonopoulos AP. Mycophenolate mofetil as first-line treatment improves clinically evident early scleroderma lung disease. *Rheumatology (Oxford)* 2006;45:1005–8.
12 Mankikian J, Caille A, Reynaud-Gaubert M, *et al*. Rituximab and mycophenolate mofetil combination in patients with interstitial lung disease (EVER-ILD): a double-blind, randomised, placebo-controlled trial. *Eur Respir J* 2023;61:2202071.
13 Mendoza FA, Nagle SJ, Lee JB, *et al*. A prospective observational study of mycophenolate mofetil treatment in progressive diffuse cutaneous systemic sclerosis of recent onset. *J Rheumatol* 2012;39:1241–7.
14 Nadashkevich O, Davis P, Fritzler M, *et al*. A randomized Unblinded trial of cyclophosphamide versus azathioprine in the treatment of systemic sclerosis. *Clin Rheumatol* 2006;25:205–12.
15 Naidu GSRSNK, Sharma SK, Adarsh MB, *et al*. Effect of mycophenolate mofetil (MMF) on systemic sclerosis-related interstitial lung disease with mildly impaired lung function: a double-blind, placebo-controlled, randomized trial. *Rheumatol Int* 2020;40:207–16.
16 Paone C, Chiarolanza I, Cuomo G, *et al*. Twelve-month azathioprine as maintenance therapy in early diffuse systemic sclerosis patients treated for 1-year with low dose cyclophosphamide pulse therapy. *Clin Exp Rheumatol* 2007;25:613–6.
17 Simeón-Aznar CP, Fonollosa-Plá V, Tolosa-Vilella C, *et al*. Effect of mycophenolate sodium in scleroderma-related interstitial lung disease. *Clin Rheumatol* 2011;30:1393–8.
18 Vaiarello V, Schiavetto S, Foti F, *et al*. Mycophenolate mofetil improves exercise tolerance in systemic sclerosis patients with interstitial lung disease: a pilot study. *Rheumatol Ther* 2020;7:1037–44.
19 Volkmann ER, Tashkin DP, Li N, *et al*. Mycophenolate mofetil versus placebo for systemic sclerosis–related interstitial lung disease: an analysis of scleroderma lung studies I and II. *Arthritis Rheumatol* 2017;69:1451–60.
20 Zhang G, Xu T, Zhang H, *et al*. Randomized control multi-center clinical study of mycophenolate mofetil and cyclophosphamide in the treatment of connective tissue disease related interstitial lung disease. *Zhonghua Yi Xue Za Zhi* 2015;95:3641–5.
21 Roig V, Herrero A, Arroyo-Cózar M, *et al*. Comparative study of oral azathioprine and intravenous cyclophosphamide pulses in the treatment of idiopathic pulmonary fibrosis. *Arch Bronconeumol* 2010;46:15–9.
22 Tzouvelekis A, Galanopoulos N, Bouros E, *et al*. Effect and safety of mycophenolate mofetil or sodium in systemic sclerosis-associated interstitial lung disease: a meta-analysis. *Pulm Med* 2012;2012:143637.
23 Erre GL, Sebastiani M, Fenu MA, *et al*. Efficacy, safety, and tolerability of treatments for systemic sclerosis-related interstitial lung disease: a systematic review and network meta-analysis. *J Clin Med* 2020;9:1–18.
24 Idiopathic Pulmonary Fibrosis Clinical Research Network, Raghu G, Anstrom KJ, *et al*. Prednisone, azathioprine, and N-Acetylcysteine for pulmonary fibrosis. *N Engl J Med* 2012;366:1968–77.