Rituximab and mycophenolate mofetil combination in patients with interstitial lung disease (EVER-ILD): a double-blind, randomised, placebo-controlled trial

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Summary

Background

Standard of care for interstitial lung disease (ILD) with a nonspecific interstitial pneumonia (NSIP) pattern proposes mycophenolate mofetil (MMF) as one of the first step therapies while rituximab is used as rescue therapy.

Methods

In a randomised, double blind, two-parallel group, placebo-controlled trial (NCT02990286), patients with connective tissue disease-associated ILD or idiopathic interstitial pneumonia (with or without autoimmune feature) and a NSIP pattern (defined on NSIP pathological pattern or on integration of clinico-biological data and a NSIP-like HRCT pattern) were randomly assigned in a 1:1 ratio to receive rituximab (1000 mg) or placebo on day 1 and day 15 in addition to MMF (2 g daily) for six months. The primary endpoint was the change in percent of predicted forced vital capacity (FVC) from baseline to 6 months analysed by a linear mixed model for repeated measures analysis. Secondary endpoints included progression-free survival (PFS) up to 6 months and safety.

Findings

Between January 2017 and January 2019, 122 randomised patients received at least one dose of rituximab (n=63) or placebo (n=59). The least-squares mean change from baseline to 6 months in FVC (% predicted) was +1.60 (SE 1.13) in the rituximab+MMF group and -2.01 (SE 1.17) in the placebo+MMF group (between-group difference, 3.60 [95% CI 0.41 to 6.80]; p=0.0273). PFS was better in the rituximab+MMF group (crude HR 0.47 [95%CI 0.23 to 0.96]; p=0.03). Serious adverse events occurred in 26 patients of the rituximab+MMF group (41%) and in 23 of the placebo+MMF group (39%). Nine infections were reported in the

rituximab+MMF group (five bacterial infections, 3 viral infections, 1 other) and four bacterial infections in the placebo+MMF group.

Interpretation

Combination of rituximab and MMF was superior to MMF alone in patients with ILD and a NSIP pattern. The use of this combination must consider the risk of viral infection.

Introduction

Non-specific interstitial pneumonia (NSIP) is a pathological pattern of ILD with a temporally uniform interstitial process with varying proportions of interstitial inflammation and fibrosis[1, 2]. Although lung biopsy is required to formally diagnose ILD with a NSIP pattern, most often the risks of lung biopsy outweigh the benefits of establishing a secure diagnosis, and the diagnosis relies on the integration of clinical, biological and HRCT data in a multidisciplinary discussion (MDD) meeting. In the absence of pathological information, the integration of available data into a presumptive diagnosis of ILD with a NSIP-like HRCT pattern (defined as basal predominant reticular abnormalities with peri-bronchovascular extension and subpleural sparing, associated with ground-glass attenuation[2, 3]) can facilitate management decisions for the use of immunomodulatory therapy.

A NSIP pathological pattern is a common feature of ILD associated with connective tissue diseases (CTD-ILD)[1], idiopathic interstitial pneumonia with autoimmune features (IPAF)[4] and some idiopathic ILD (iILD)[5]. In the absence of specific clinical trials, current knowledge on the treatment of ILD with a NSIP pattern was obtained in multicentre clinical trials in scleroderma-related ILD (SSc-ILD)[6, 7], where NSIP is the most common ILD pattern. Immunosuppression with mycophenolate mofetil (MMF) is presently the most common first-step therapy[8] in progressive CTD-ILD, and by extension in interstitial pneumonia with autoimmune features (IPAF) and some patients with idiopathic ILD with a NSIP pattern. Mycophenolic acid induces apoptosis of T- and B-lymphocytes and inhibits vascular smooth muscle proliferation, myofibroblast differentiation, and adhesion of circulating inflammatory cells to endothelial cells[9]. In patients with some CTDs who do not respond to first-line treatment, rituximab can be used as a rescue therapy [10, 11]. Rituximab is a chimeric monoclonal antibody that targets the CD20 protein and induces cell death of pre-B and

mature B-lymphocytes. There is a rationale for rituximab use in ILD with a NSIP pattern, since immunoglobulin deposits and lymphocytes CD20+ infiltrates are observed in patients with a NSIP pathological pattern [12]. We hypothesized that the association of MMF and rituximab could have an additive efficacy in patients with ILD with a NSIP pattern.

Therefore, we conducted the EVER-ILD phase 3, randomised controlled trial to assess the efficacy and safety of rituximab plus MMF versus MMF alone in patients with ILD and a NSIP pathological pattern or NSIP-like HRCT pattern.

Methods

Trial design

This was a multicentre, randomised, double blind, two-parallel group, placebo-controlled, superiority trial. The methods of this study have been previously described[13] (appendix pp23-89). The trial was conducted at 17 academic French centres specialised in rare pulmonary diseases including ILDs, all being part of the OrphaLung and RespiFIL (Filière Santé Maladies Respiratoires Rares) networks.

All trial aspects were conducted in accordance with the ethical principles of the Good Clinical Practice guidelines and the Declaration of Helsinki, in compliance with French laws. This trial is registered with ClinicalTrials.gov (NCT02990286).

Participants

Eligible patients were aged ≥18 and had a diagnosis of CTD-associated ILD or idiopathic interstitial pneumonia. Two idiopathic interstitial pneumonia groups were individualized : 1/interstitial pneumonia with autoimmune features (IPAF) categorized as a patient group that exhibit evidence of autoimmunity without meeting criteria for a defined connective tissue disease and 2/interstitial pneumonia without an identified cause or autoimmunity

(iILD). The consensus diagnosis of ILD with a NSIP pattern was defined by the local MDD based on a NSIP pathological pattern (ILD with a NSIP pathological pattern) when available or on integration of available clinico-biological data and a NSIP-like HRCT pattern (ILD with a NSIP-like HRCT pattern). NSIP-like HRCT pattern was defined as basal predominant reticular abnormalities with peri-bronchovascular extension and subpleural sparing, associated with ground-glass attenuation[2, 3].

Patients were eligible if they did not respond to, or relapsed after, a first line of glucocorticoids and/or immunosuppressive treatment (appendix pp 5).

Main reasons for exclusion were significant respiratory disorders other than CTD-ILD, IPAF or iILD, other severe or unstable medical condition (as per investigator's judgement), and a pattern of typical or possible[14]/probable[15] usual interstitial pneumonia (UIP). The presence of significant pulmonary hypertension proven by right heart catheterization was an exclusion criterion. However, patients with a possible elevated pulmonary arterial pressure (systolic pulmonary arterial pressure >=45 on echocardiography) not confirmed by right heart catheterization could be included. When lung biopsy was available, patients with a histological pattern other than NSIP were excluded. Full inclusion and exclusion criteria are described in appendix pp 42-44.

After a screening period of up to 30 days, eligible patients were randomly assigned by the investigator via a centralised web-based interactive response system (CSOnline) to receive rituximab (1000 mg) or placebo on day 1 and day 15 in addition to MMF (2 g daily) for six months. The 2 g daily dose of MMF was selected to limit the risk of infection with combined immunosuppression. Allocation sequences were generated in a 1:1 ratio using a computer-generated randomisation schedule by an independent statistician, not involved in patient recruitment or follow-up. Randomisation was stratified on type of ILD groups (differentiated

CTD-ILD or IPAF vs. iILD) and on FVC% predicted at inclusion (<50% vs ≥50%). Randomisation was done through permuted blocks. Blinding and dosing administration can be found in the supplementary material (appendix pp 6, 47 and 63).

Outcomes

The primary efficacy endpoint was change in FVC (percent of predicted, absolute FVC %) from baseline to 6 months. FVC was measured within each study centre in a standardized manner according to ATS/ERS recommendations[16] and ECCS reference equations by technicians blinded to study treatment group[17].

Secondary efficacy endpoints included progression free survival (PFS) measured over the 6 month follow-up, changes from baseline to 6 months in the SF-36 v1.3 quality of life questionnaire, cumulative doses of glucocorticoids over the 6 month treatment period, changes from baseline to 6 months in FVC (ml), and changes from baseline to 6 months in visual analogic scales (VAS, 0-10 cm) for dyspnea and cough, DLCO in % of predicted, 6-minute-walk test, autoantibodies, blood CD19 lymphocytes count, and serum gammaglobulins. PFS was defined as the time to a first acute exacerbation or FVC absolute decline ≥ 10 predicted percentage points, MMF withdrawal or registration on a pulmonary transplantation list or death, whichever occurred first. An acute exacerbation was defined by (1) progressive dyspnea over 1 month or less; (2) new pulmonary infiltrates on chest radiography or computed tomography, and (3) the absence of an overt underlying cause of rapid deterioration. Changes from baseline to 6 months in HRCT chest images were assessed by two thoracic radiologists with expertise in ILDs, who scored the extent of ILD and the severity of traction bronchiectasis (appendix pp6). Rituximab pharmacokinetics were secondary outcomes but will be reported separately. Safety was assessed by clinical and

laboratory parameters and the recording of adverse events, as coded with the use of the Medical Dictionary for Regulatory Activities, version 23. The pharmacovigilance experts adjudicated the adverse events and determined whether or not they were related to the study treatment. They were blinded to treatment arm assignment except for potentially related unexpected serious events where they requested the unblinding (i.e. for 2 SUSARs). There were no exploratory endpoints in this trial.

Statistical analysis

Assuming a power of 90%, a 5% two-sided type I error rate and anticipating an extreme 10% drop-out rate, 122 patients (61 per group) were needed to show a 5% between-group difference in the change of FVC percent of predicted value at 6 months, based on a common standard deviation for FVC change between baseline and 6 months of 8%[18]. In case a randomised patient did not receive any dose of the allocated treatment, we planned to randomise additional patients until we reached our target sample size of 122 patients. Efficacy and safety analyses included all randomly assigned participants who received at last one dose of rituximab or placebo on day 1 of the treatment period. Patients who withdrew consent to study participation were not included in the analysis as required by French law. We used two-sided significance tests with a type I error of 5%.

For the primary analysis, we used a linear mixed model for repeated measures to compare differences between study groups in the slope of FVC measurements over the 6 months study period (time points at baseline, 3 and 6 months). The model included treatment group, visit and treatment-by-visit interaction as fixed-effects. We used a model with random individual intercepts and slopes over time. The treatment effect was assessed using the treatment-by-visit interaction. This model assumes data are missing at random, and missing

data were not imputed for the primary analysis. For patients who did not attend all the study visits, we used all available FVC measurements in the primary analysis. We performed different imputation sensitivity analyses to assess the impact of missing data and the robustness of the treatment effect under different assumptions for missing data (appendix Table S8 Fig. S2 pp 19 and 22).

A priori subgroups were defined by stratification variables for randomisation: ILD groups (CTD-ILD or IPAF vs. iILD) and FVC in % predicted value at inclusion (< 50% vs. ≥ 50%). We also performed post hoc exploratory subgroup analyses (appendix pp 7)

For secondary efficacy endpoints, all data from baseline to 6 months were used without imputation of values for patients who discontinued early. We reported p values with no adjustment for multiplicity and for descriptive purposes only. The predicted change in FVC in ml between baseline and 6 months was analysed using the same method as for the primary endpoint. Progression-free survival was described by Kaplan-Meier curves and compared between study groups using a log-rank test and unadjusted Cox proportional hazards model. A Cox proportional hazards model with *post-hoc* adjustment on stratification variables was also fitted. Between-group comparisons for absolute changes between baseline and 6 months in continuous outcomes were performed with Student's *t*-tests.

Analyses were performed using SAS software version 9.4 (SAS Institute) and R software version 4.0.3 was used for creating some of the figures[19].

Results

Between January 26, 2017 and January 25, 2019, 126 patients with ILD and a NSIP pathological pattern or a NSIP-like HRCT pattern were randomised (Figure 1). Three patients did not receive the intervention and 1 patient withdrew consent. Among the 122 patients who received at least one dose of the assigned treatment, 63 were in the rituximab group and 59 were in the placebo group. 60 (95%) and 59 (94%) of 63 patients in the rituximab group and 58 (98%) and 55 (93%) of 59 in the placebo group completed the 3-month and 6 month-visit, respectively.

The baseline characteristics and previous treatments of the patients were similar in the two treatment groups (Table 1 and appendix table S1 p 8). In the overall population, mean age was 66.1 (SD 12.0) years. At baseline, mean FVC % predicted was 66.7 (SD 21.5) in the rituximab + MMF group and 70.2 (SD 22.5) in the placebo + MMF group, and % predicted DLCO was 40.1 (SD 13.5) and 38.6 (SD 14.8), respectively.

The patients were divided by MDD in investigator centres into the CTD group (n=43, 35%), the IPAF group (n=36, 30%) and the iILD group (n=43, 35%). Within the CTD-ILD group, 23 patients (53%) were diagnosed with systemic sclerosis, 8 (19%) with inflammatory myositis, 7 (16%) with Sjögren syndrome, 3 (7%) with rheumatoid arthritis and 2 (5%) with mixed connective tissue disease (appendix table S2, p 9). Surgical lung biopsies confirming definite NSIP were available for 10 patients (16%) in the rituximab + MMF group and 5 patients (8%) in the placebo group. One patient in the IPAF group had a pathological diagnosis of desquamative interstitial pneumonia and was wrongly included. For one patient, biopsy was non-contributory. In this patient grouped with patients without lung biopsies (n=106), the concordance in the determination of the NSIP-like HRCT pattern was 86% between the local MDD and a posteriori centralized review by 2 thoracic radiologists (appendix table S3 p 10).

Three patients did not receive the second infusion of rituximab (2 for anaphylactoid reactions and one because of a cardiac procedure) and one patient did not receive the second infusion of placebo (ILD progression and death). Mycophenolate mofetil discontinuation before 6 months was more frequent in the rituximab + MMF group (14 patients, 22%) than in the placebo + MMF group (9 patients, 15%) (appendix table S4, p 11).

Linear mixed model analysis showed a significant difference in absolute change from baseline in FVC % predicted between groups at 6 months. The least-squares mean (LSM) change from baseline to 6 months in FVC % predicted was +1.60 (SE 1.13) in the rituximab + MMF group compared with -2.01 (SE 1.17) in the placebo + MMF group (between-group difference, 3.60 [95% CI 0.41 to 6.80]; p=0.0273; figure 2, table 2). Results were replicated when adjusted for stratification variables (FVC % predicted at baseline and type of disease) (table 2).

Variation of FVC in ml up to 6 months was consistent with the result of the primary outcome (appendix figure S1, p 18). LSM change from baseline to M6 was +41 ml (SE 30) in the rituximab + MMF group and −59 ml (SE 31) in the placebo + MMF group (between-group difference, 100 ml [95% CI 15 to 185], p=0.0207).

Progression-free survival (PFS) was greater in the rituximab + MMF group than in the placebo + MMF group (crude hazard ratio [HR] 0.47 [95% CI 0.23 to 0.96]; p=0.03; Figure 3). A greater number of patients presented investigator-reported exacerbation as first event of PFS in the placebo + MMF group than in the rituximab group + MMF (respectively 8 patients vs 2) (appendix table S5, p 12). Results for the *post-hoc* adjusted Cox proportional hazards are provided in appendix table S6, p 13).

No between-group differences in change from baseline to 6 months were noted for the physical composite score and the mental composite score of the SF36 questionnaire

(appendix, table S7, p 14-15). The mean cumulated glucocorticoid dose over the 6 months of the study was 1862 mg (SD 1756) in rituximab + MMF group and 2314 mg (SD 2082) in placebo + MMF group (p=0.20). No significant between group difference was observed in change from baseline to 6 months in 6-minute walk distance, DLCO, dyspnea and cough, in HRCT ILD extent nor bronchiectasis scores. Decrease in CD19 counts from baseline to 6 months was significantly greater in the rituximab + MMF group than in the placebo + MMF group. Change in gammaglobulin serum levels from baseline to 6 months did not differ between groups. Change in autoantibody status between baseline and 6 months did not differ between groups (appendix, table S7 and S8, p14-16).

Post hoc sensitivity analyses of the primary outcome with different methods for handling missing data yielded P values ranging from 0.02 to 0.11 and were consistent with the results of the primary analysis (appendix, table S9, figure S2, pp 17, 20). These findings showed that the primary results were robust and were not influenced by alternative assumptions about missing data.

Results of the prespecified and post hoc subgroup analyses for the percentage predicted FVC are presented in figure 4. Rituximab and MMF combination demonstrated a consistent treatment effect on the percentage predicted FVC across the majority of subgroups. The benefit of combination could be less in the subgroups of patients who have walked less than 150m, with a systolic pulmonary arterial pressure > 45 mmHg, with oxygen therapy > 10H/d or with UIP or indeterminate HRCT pattern after posteriori centralized review.

Overall, 54 patients in the rituximab + MMF group (86%) and 57 in the placebo + MMF group (97%) experienced at least one adverse event (table 3). A total of 36 serious adverse events in the rituximab + MMF group and 33 in the placebo + MMF group were reported, with 26 patients (41%) and 23 patients (39%) experiencing at least one serious adverse event. More

patients experienced serious adverse events considered to be related to study treatment in the rituximab + MMF group compared to placebo + MMF (15 patients vs 6). Non-infectious respiratory tract disorders (3 patients in the rituximab + MMF group vs 12 in the placebo + MMF group), and cardiac disorders (5 patients vs 2) were reported as the most frequent serious adverse events. Nine infections were reported in the rituximab + MMF group (2 urinary tract infections, 3 pneumonia, 2 influenzae virus infections, 1 varicella, 1 other without microbiological documentation) and four infections in the placebo + MMF group (3 pneumonia, 1 sepsis). Infusion-related reactions were uncommon in both groups (3 patients in the rituximab + MMF group and 1 in the placebo + MMF group). During the 6-month follow-up period 3 deaths were reported in the rituximab + MMF group (all due to end-stage respiratory failure) and 4 in the placebo + MMF group (1 infectious pneumonia with acute exacerbation of fibrosis and 3 acute respiratory failure). No fatal SAEs were assessed as possibly related to rituximab and MMF combination.

Discussion

In the EVER-ILD trial, we investigated the efficacy and safety of a combination of rituximab and MMF in comparison with a combination of placebo and MMF, in patients with ILD with a NSIP pathological pattern or NSIP-like HRCT pattern who were previously treated with either glucocorticoids or an immunosuppressive agent. Rituximab + MMF led to a significant improvement in change from baseline to 6 months in FVC % predicted in comparison with placebo and MMF. Progression-free survival over the 6-month study period was higher in the rituximab plus MMF group. Combination of MMF and rituximab was not associated with more frequent adverse events.

The EVER-ILD study is the first randomised, double-blind, placebo-controlled trial showing that combined immunosuppressive treatment with rituximab and MMF combination is beneficial in ILD with a NSIP pattern. The benefit in FVC was approximately 3.6% of the predicted value and 100 mL over the 6-month study period in patients treated with the combination of rituximab plus MMF. Besides improving respiratory function, rituximab and MMF combination improved progression-free survival. The latter appeared to result mainly from a reduced first exacerbation frequency.

Although the evidence was restricted to uncontrolled retrospective studies[20–23], previous data suggested that combination of rituximab and MMF may be beneficial relative to MMF in ILD. Narvaez et al. reported that rituximab rescue therapy used as an add-on treatment to MMF improves FVC in SSc-ILD patients with non-UIP HRCT patterns[23]. While considerable research effort has been devoted to idiopathic pulmonary fibrosis (IPF) and other ILDs with the progressive fibrotic phenotype[24], to our knowledge the present randomised placebo-controlled trial is the first to focus on ILD with a NSIP pattern.

Low FVC and DLCO are significant risk factors for acute exacerbation of ILD. In the present study, many patients had severe disease as 23/122 (19%) had FVC less than to 50% and 47/115 (41%) had DLCO less than 30% or could not perform the DLCO test. It is likely that patient severity explains the high rate of patients with at least one investigator-reported exacerbation and death in comparison to previous studies. In the INBUILD trial, where patients with FVC <50% or with DLCO <30% or who could not perform the DLCO test were excluded, the exacerbation or death rate at 1 year was 9.7%[24]. In the absence of an independent committee on the clinical evaluation criteria to adjudicate on acute exacerbations in EVER-ILD study, investigators may have over-reported acute respiratory events as acute exacerbation.

The natural history of some ILDs includes gradual deterioration of respiratory function. In the placebo groups of prospective studies in SSc-ILD[25], FVC decreased over the course of the trial (-4.6% and -2.6% of predicted FVC at week 48 in FOCUSScED and SLS-I studies respectively), and FVC decline was barely reduced in the group with immunosuppressive monotherapy (-0.4% and -1% in FOCUSScED and SLS-I studies respectively)[6, 26]. Apart from the EVER-ILD trial, there are few prospective studies in ILD that showed an improvement in FVC. In the SLS-II study, MMF and cyclophosphamide increased FVC at 12 months compared to baseline with a plateau at 24 months of +2.19% predicted value (95% CI 0.53-3.84) in the MMF group[7]. In the RECITAL study which assessed rituximab compared with cyclophosphamide, patients in both treatment groups had increased FVC at 24 weeks (cyclophosphamide group (+99 mL [SD 329]) and the rituximab group (+97 mL [SD 234]) [27].

The safety profile of rituximab was similar to that described in previous trials[20, 23, 28]. The rituximab and MMF combination was well tolerated. Patients in the rituximab plus MMF

group had more frequent infections (9 patients vs 4), cardiac disorders (5 patients vs 2) and infusion-related reactions (3 patients vs 1). The infections observed with the rituximab and MMF combination were mainly non-serious viral infections, as previously reported with rituximab[29]. An important point is that patients were enrolled in EVER-ILD prior to the COVID-19 pandemic. We have no formal explanation for the tendency to greater frequency of intolerance to MMF in the MMF+rituximab group compared to the MMF+placebo group. Additional research may be needed to assess a potential effect of rituximab on MMF pharmacokinetics.

The main limitation of the study concerns the diagnosis of ILD with a NSIP pattern. NSIP has a pathological definition thus a formal diagnosis of NSIP requires lung biopsy. The majority of our patients did not have lung biopsy after evaluation in MDD of the benefit/risk balance because of the presence of a CTD or autoimmune features, because of ILD severity or the presence of comorbidities, and/or because of the patient's refusal (appendix S3 pp 10). In the absence of a lung biopsy, the presence of an NSIP-like HRCT pattern could be a determining factor in the decision of the choice of treatment during an MDD because an NSIP pathological pattern is present in 65-90% of patients with NSIP-like HRCT pattern[30]. The quality of the HRCT analysis becomes essential. In EVER-ILD, the concordance in the determination of the NSIP-like HRCT pattern was 86% between the local MDD and a posteriori centralized review by 2 thoracic radiologists. Despite this imperfect concordance, sensitivity analyses for the primary endpoint with exclusion of 15 patients with UIP and indeterminate HRCT pattern after the centralized review, were consistent with the results of the primary analysis (Appendix table S10 pp 18). Even if the absence of lung biopsy is a weakness of the pragmatic EVER-ILD study, its results can help in decision-making in patients with presumptive diagnosis of ILD with a NSIP-like HRCT pattern.

In summary, we show that treatment of ILD with a NSIP pattern with the rituximab and MMF combination results in improved lung function from baseline to 6 months as measured by FVC, in comparison with MMF alone. Rituximab and MMF combination might be a reasonable strategy for patients with a diagnosis of ILD with a NSIP pattern in MDD. Further studies are needed to evaluate the potential impact of rituximab use beyond 6 months as a maintenance therapy. The rituximab and MMF combination was associated with an increase in non-serious viral infections. The use of rituximab must be evaluated according to the benefit/risk balance, in particular during a viral pandemic.

Contributors

The research concept of the study was developed by SMA and TA. All authors undertook the study. AC conceptualised the statistical analyses, calculated the sample size. AC and JL did the statistical analysis. SMA, TA, AC and JL accessed and verified the data. All authors participated in the development and finalisation of the manuscript and vouch for the trial's fidelity to the protocol. All authors had full access to all the data in the study. SMA, AC, JM and TA had final responsibility for the decision to submit for publication.

Declaration of interests

Stephane Jouneau has received fees, funding or reimbursement for national and international conferences, boards, expert or opinion groups, research projects over the past 3 years from AIRB, Bellorophon Therapeutics, Biogen, Boehringer, Chiesi, Fibrogen, Galecto Biotech, Gilead, LVL, Novartis, Olam Pharm, Pfizer, Pliant Therapeutics, Roche, Sanofi-Genzyme, Savara.

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Data sharing

We will make anonymised individual participant data available to the scientific community with as few restrictions as feasible, while retaining exclusive use until the publication of major outcomes. Data requests from qualified researchers should be submitted to SMA (s.marchandadam@univ-tours.fr) for consideration.

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Table 1: Demographic and baseline characteristics of study participants

	Rituximab + MMF $n_R=63$	Placebo +MMF $n_P=59$
Sex – Female	35 (55.6)	38 (64.4)
Age (years)	64.7 (12.1)	67.5 (11.9)
BMI (kg/m²)	29.0 (5.4)	28.4 (5.2)
Years since ILD diagnosis	3.8 (4.9)	2.9 (2.7)
FVC (% predicted value)	66.7 (21.5)	70.2 (22.5)
FVC (ml), $n_R=63$, $n_P=58$	2046 (767)	1971 (724)
FEV1/FVC (%), $n_R=63$, $n_P=57$	85.7 (11.0)	86.9 (14.0)
DLCO, $n_R=60$, $n_P=55$		
Unfeasible	9 (15.0)	12 (21.8)
% of predicted value, $n_R=51$, $n_P=43$	40.1 (13.5)	38.6 (14.8)
6 MWD (m), $n_R=61$, $n_P=55$	364 (148)	325 (179)
O2 > 10h/day at baseline	13 (20.6)	17 (28.8)
Histopathologic NSIP	10 (15.8)	5 (8.5)
ILD groups		
CTD-ILD	25 (39.7)	18 (30.5)
IPAF	17 (27.0)	19 (32.2)
Idiopathic ILD	21 (33.3)	22 (37.3)
Glucocorticoids at baseline	46 (73.0)	50 (84.7)
Glucocorticoids dose at baseline (mg/d)	15 [10;20]	17.5 [10;25]
Previous treatment received for ILD*		
None**	2 (3.2)	0
Glucocorticoids alone	36 (57.1)	33 (55.9)
Immunosuppressive agent alone	2 (3.2)	0
Glucocorticoids + Immunosuppressive agent	23 (36.5)	26 (44.1)

Data are n (%) or mean (SD) or median [Q1;Q3]. 6MWD=6-minute walk distance. BMI=body mass index. CTD=connective tissue disease. DLCO=carbon monoxide diffusing capacity. FEV_1=forced expiratory volume in 1 second. FVC=forced vital capacity. HRCT= High-resolution computed tomography. ILD=interstitial lung disease. IPAF=interstitial pneumonia with autoimmune features. MMF=mycophenolate mofetil. NSIP=non-specific interstitial pneumonia.

*Any previous treatments were considered and were specified in appendix table S1

**Patients with a contraindication to glucocorticoids

Table 2: Primary efficacy endpoint

LSM change in FVC % predicted value from baseline to M6	Rituximab + MMF n_R=63	Placebo + MMF n_P=59	Between-group difference- (95% CI)	p-value
Primary analysis	1.60 (-0.63 to 3.82)	-2.01 (-4.31 ; 0.29)	3.60 (0.41 to 6.80)	0.0273
Adjusted model on stratification variables*	1.53 (-0.69 to 3.76)	-2.04 (-4.35 to 0.26)	3.58 (0.38 to 6.79)	0.0288

Data are least squares means with 95% CIs estimated by a mixed-effects model for repeated measures. CI=Confidence interval. FVC=forced vital capacity. ILD=interstitial lung disease. MMF=mycophenolate mofetil. *Stratification variables: FVC % predicted at baseline (<50% vs ≥50%) and type of ILDs (differentiated CTD-ILD or IPAF vs idiopathic ILD).

Table 3: Summary of all AEs

	Rituximab + MMF (n_R=63)	Placebo + MMF (n_P=59)
Any adverse event	54 (86)	57 (97)
Related to study treatment	36 (57)	27 (46)
Any serious adverse event	26 (41)	23 (39)
Most common serious adverse event		
Respiratory tract disorders	3 (5)	12 (20)
Infection	9 (14)	4 (7)
Cardiac disorders	5 (8)	2 (3)
Leading to discontinuation of study treatment	3 (5)	1 (2)
Fatal adverse event	3 (5)	4 (7)
Related to study treatment	15 (24)	6 (10)
Infection	9 (14)	4 (7)
Infusion related reaction	3 (5)	1 (2)

Data are n (%) of patient with adverse event. MMF=mycophenolate mofetil

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Figure 1: Enrolment and randomisation in the overall population.

PFTs=pulmonary function tests

Figure 2: Variation from Baseline in Forced Vital Capacity (FVC). Shown is the least squares mean (LSM) change from baseline in FVC (in percent of predicted) over the 6 months trial period in the rituximab + MMF group and the placebo + MMF group. The I bars indicate the confidence interval (CI).

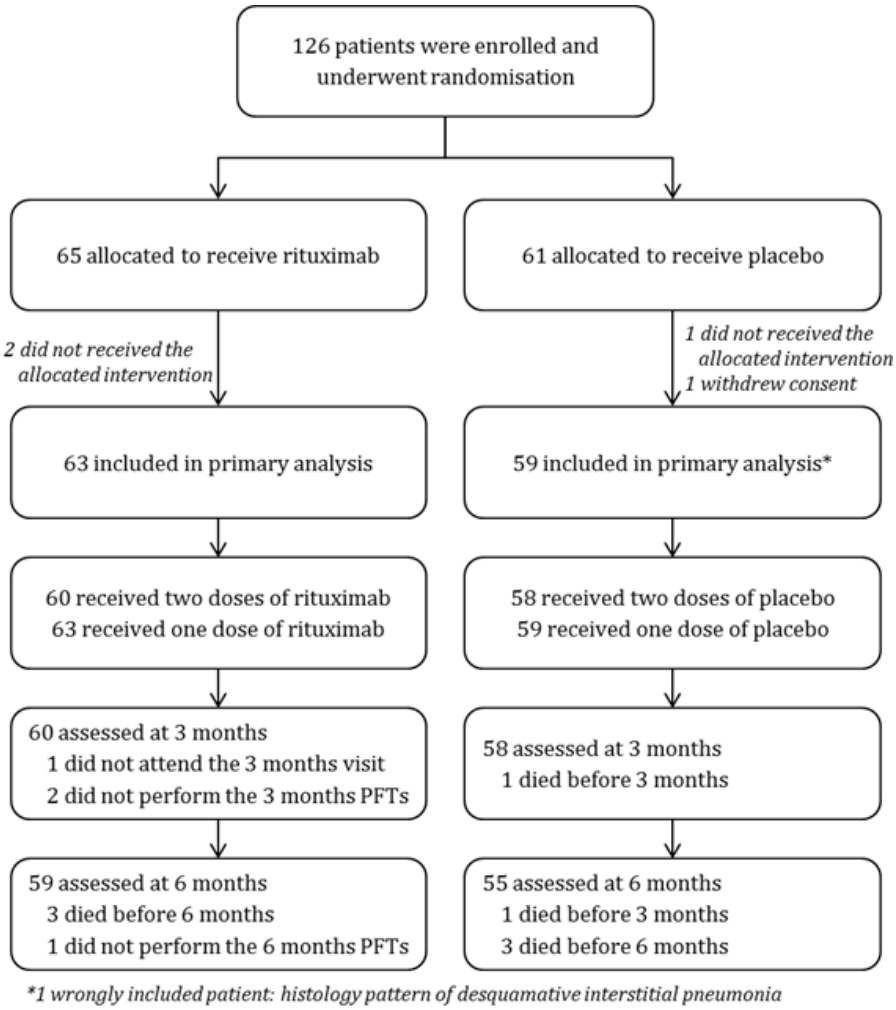
MMF = mycophenolate mofetil.

Figure 3: Time-to-event analyses, from baseline, for patients who PFS defined as >10% absolute decline in percent predicted FVC, first acute exacerbation, MMF discontinuation for disease degradation, registration on lung transplant list or death.

CI=confidence interval. FVC = forced vital capacity. MMF = mycophenolate mofetil. PFS = progression free survival.

Figure 4: Subgroup analyses of mean change in forced vital capacity from baseline to M6.

BMI=body mass index. CI=confidence interval. CTD=connective tissue disease. DLCO=carbon monoxide diffusing capacity. FVC=forced vital capacity. HRCT= high-resolution computed tomography. ILD=interstitial lung disease. IPAF=interstitial pneumonia with autoimmune features. NSIP=non-specific interstitial pneumonia. PASP= estimate pulmonary artery systolic pressure using echocardiography. VAS= visual analogic scales.



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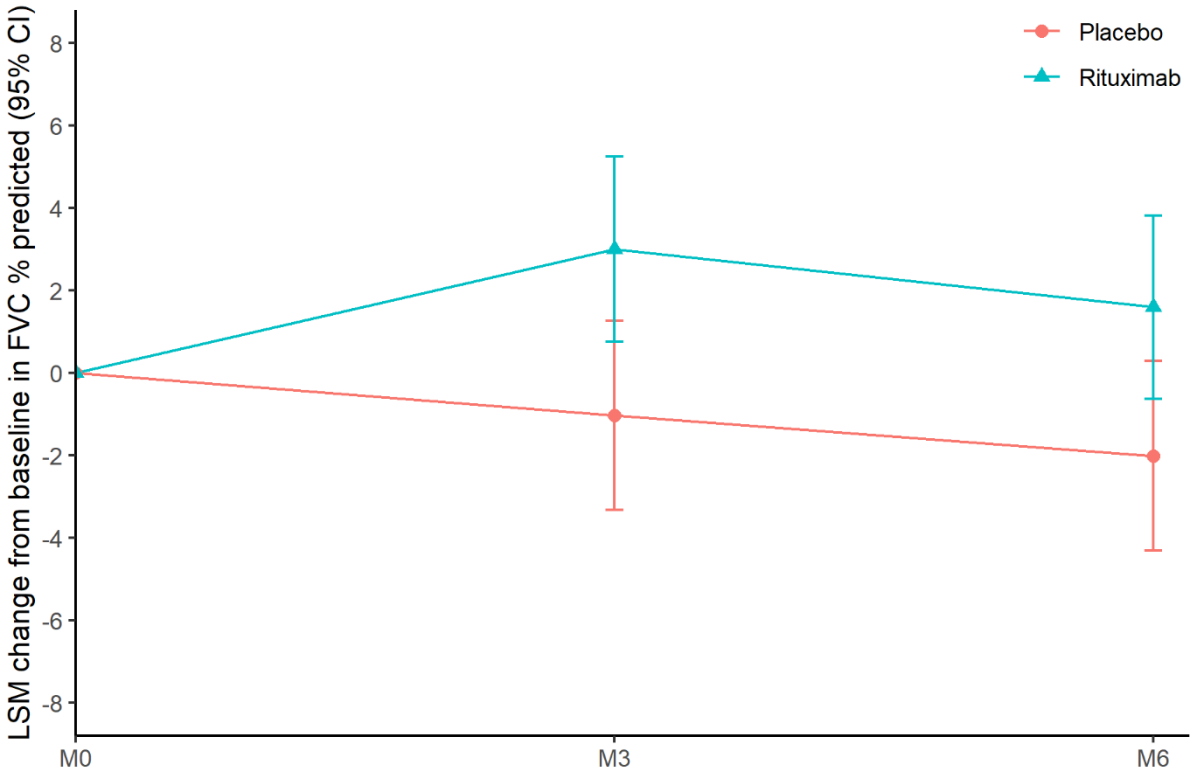

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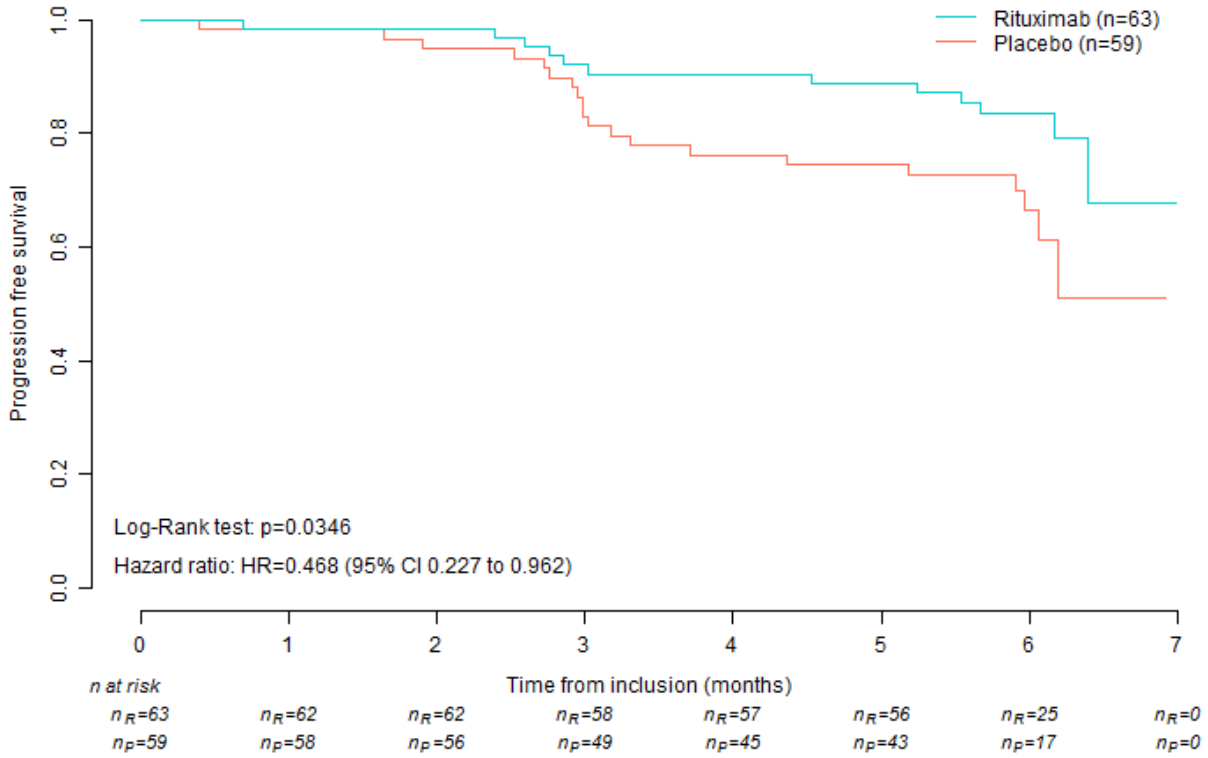

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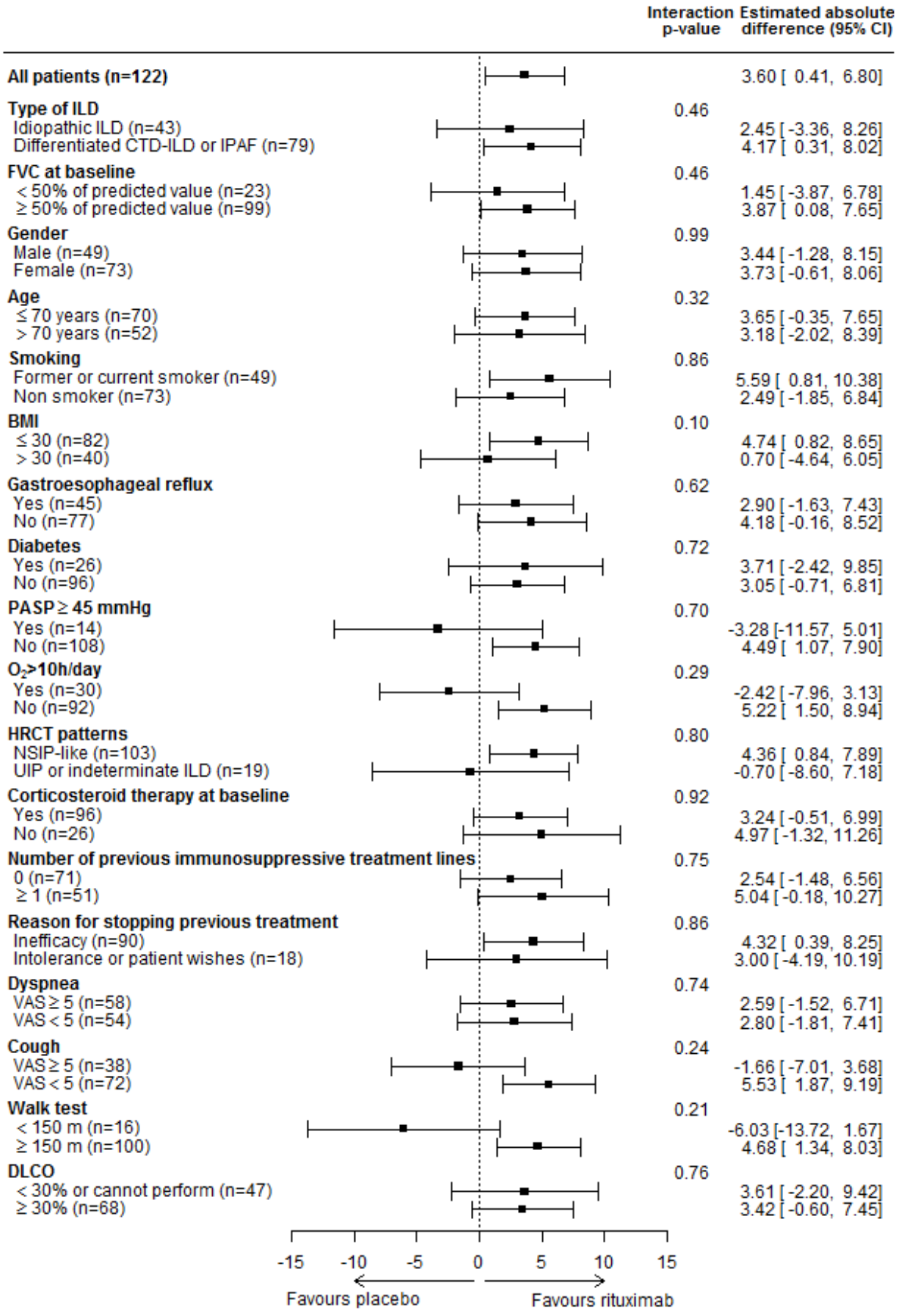

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