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**Evaluation of efficacy and safety of rituximab in combination with mycophenolate mofetil
in patients with nonspecific interstitial pneumonia non-responding to a first-line
immunosuppressive treatment (EVER-ILD): a double-blind placebo-controlled randomized
trial**

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Competing Interest

TBA, JMN, JC, MF and SMA have no conflict of interest to declare regarding this study.

RB have no conflict of interest to declare regarding this study.

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Protocol number: V2 18 November 2016

Strengths and limitations of this study

- ➔ This is the first trial to evaluate the efficacy and safety of rituximab versus placebo, in association with mycophenolate mofetil in a broad range of patients with nonspecific interstitial pneumonia that did not respond to a first-line therapy.
- ➔ EvER-ILD is a national multicentric phase III randomized placebo-controlled study, covering all French territory; therefore, its results will be more generalizable and will help make clearer recommendations for treatment of ILD patients, non-responders to a first-line treatment.
- ➔ This trial will also allow to address rituximab pharmacokinetics and pharmacodynamics in ILD patients, and also help evaluate other biomarkers for predicting clinical outcomes.

ABSTRACT

Introduction

Nonspecific interstitial pneumonia (NSIP) are rare but severe diseases, with high mortality and morbidity, with no effective pharmacological treatment allowing for long-term remission, and therefore no clear therapeutic recommendations. Classic immunosuppressants are used as first-line treatment, with only one third of patients being responders and no clear recommendations exist for the choice of the second-line therapy. The EvER-ILD study is the first one to prospectively evaluate the efficacy and safety of rituximab and mycophenolate mofetil (MMF) versus placebo and MMF in a broad range of NSIP patients that did not respond to a first-line therapy. A pharmacokinetic-pharmacodynamic analysis based on rituximab serum concentrations will allow identification of potential factors associated with therapeutic response and/or adverse effects.

Methods

EvER-ILD study is a French multicenter, prospective, randomized, double blind, placebo-controlled, superiority trial. Patients with severe and progressive NSIP non-responding to a first line immunosuppressive treatment will be randomized in 2 groups of treatment: one course of rituximab plus 6 months MMF (RTX-MMF group) and one course of placebo plus 6 months MMF (Placebo-MMF group). The primary outcome is the change in Forced Vital Capacity (FVC, % of predicted) from baseline to 6 months. Several clinical, biological, and quality of life secondary outcomes will be measured at 3, 6 and 12 months. A sample size of 122 patients (61 patients per group) would allow to show a point difference between groups in the change of FVC at 6 months, based on a common standard deviation for FVC change of 8% with a power of 90%, alpha 5% two-sided, and anticipating an extreme 10% drop-out rate.

Ethics and dissemination

The protocol was approved by the French Research Ethics Committee (CPP Tours Ouest 1 2016-R28) on November 10, 2016, and by the French competent authority (ANSM, reference 160771A-22) on December 1st, 2016. This article refers to protocol V2, dated November 18, 2016. An independent data safety monitoring board will review safety and tolerability data for the duration of the trial. Results will be disseminated via peer reviewed publication and presentation at international conferences.

Trial registration number: NCT02990286 (clinicaltrials.gov), EudraCT 2016-003026-16

(European Medicines agency).

INTRODUCTION

Interstitial lung diseases (ILDs) form a heterogeneous group of 150 rare diseases with various causes [1]. ILDs with nonspecific interstitial pneumonia (NSIP) are characterized by common clinical presentation including shortness of breath, chronic cough and inspiratory crackles on auscultation, common histopathological anomalies of the pulmonary interstitium, and similar radiographic anomalies showing bilateral ground-glass opacities [2]. NSIP may be observed in a wide variety of clinical settings, including connective tissue diseases (CTD-NSIP), interstitial pneumonia with autoimmune features (IPAF) and idiopathic non-specific interstitial pneumonitis (iNSIP). NSIP have a severe prognosis, since the 5-years survival probability varies from 42% to 77% depending on the underlying cause [3]. Standard of care for severe, progressive CTD-NSIP, and by extension for severe iNSIP and IPAF-NSIP, include corticosteroids or immunosuppression with intravenous (IV) cyclophosphamide as first-step therapy, with a low 34% response rate and, for non-responders, a median survival of 50 months [3, 4, 5, 6]. In non-responders a second line immunosuppressant is usually necessary, but no recommendation [7, 8, 9] exists on the drug to be used, since very few clinical trials evaluated the efficacy of immunosuppressive drugs in ILD patients. The recent creation of the IPAF entity identifies a subgroup of specific CTD-ILD (mostly in the form of NSIP) with auto-immune features who do not have the diagnostic criteria of differentiated CTD. The IPAF prognosis is mainly related to pulmonary involvement [10]. The therapeutic management of IPAF is unknown since no prospective therapeutic studies have been conducted in these new entities. Nineteen percent of the patients in the INBUID trial had an iNSIP but subgroup data are not available [11].

Mycophenolate mofetil (MMF) is a prodrug of mycophenolic acid which inhibits inosine monophosphate dehydrogenase, the rate-limiting enzyme in the de novo synthesis of guanosine nucleotides. Mycophenolic acid induces the apoptosis of active T- and B-lymphocytes, since their proliferation is critically dependent of the de novo synthesis of purines, and inhibits the vascular smooth muscle proliferation, the myo-fibroblast differentiation and the adhesion of circulating inflammatory cells to endothelial cells. MMF is an accepted alternative as second-line treatment in refractory CTD-NSIP [12]. Rituximab (RTX) is a chimeric monoclonal antibody targeting the CD20 protein, which is primarily found on the cell membrane of pre-B and mature B-lymphocytes, leading to their destruction.

There is a rationale for RTX use in patients with CTD-NSIP, since immunoglobulins and complement depots in the pulmonary capillaries [13, 14] and lymphocytes CD20+ infiltrates were observed in patients with NSIP [15]. Several case reports, retrospective case-series [16, 17] and one prospective proof of concept randomized trial [18] have shown that RTX could be beneficial on pulmonary function in subgroups of ILDs. The association of MMF, acting predominantly on T-cells, and RTX, acting predominantly on B-cells, could theoretically have an additive efficacy in NSIP, even if efficacy data [16, 17] are sparse. Furthermore, treatment intensification seems necessary for non-responder NSIP patients whose prognosis is poor (median survival, 50 months) [3]. We therefore hypothesized that RTX would have a beneficial effect in association with MMF in patients with a radiologic and/or pathological pattern of NSIP, in various etiologic settings (iNSIP, CTD-NSIP, IPAF-NSIP), who did not respond to a first-line immunosuppressive treatment and will be superior to treatment with MMF alone.

Objectives

The main objective of the EvER-ILD study is to evaluate the efficacy on lung function at 6 months after one course of RTX versus one course of placebo added-on a 6-month MMF treatment in a NSIP patients, non-responding to a first line immunosuppressive treatment. The secondary objectives of the study are 1) to evaluate the efficacy of one course of RTX versus placebo on top of 6 months MMF treatment on progression free survival, quality of life of patients, corticosteroid-sparing, and other functional, radiographic parameters or biological parameters; 2) to evaluate the safety of one course of RTX on top of 6 months MMF treatment all throughout the study period; 3) to describe the pharmacokinetics (PK) of RTX and the pharmacokinetic-pharmacodynamic (PK-PD) relations in these diseases; 4) to identify variables associated with clinical response and, if possible, with the adverse effects of RTX on top of 6 months MMF treatment; 5) to describe the evolution of patients at 12 months in terms of efficacy; 6) to establish genetic and serum sample collections for the study of potential biomarkers of response to treatment in ILD patients.

METHODS AND ANALYSIS

This trial protocol is reported following the SPIRIT guidelines (<https://www.equator-network.org/>).

Study Design

EvER-ILD study (Figure) is an interventional, multicenter, prospective, randomized, double blind, two-parallel group, placebo-controlled, superiority trial, comparing one course of RTX to one course of placebo on top of 6 months MMF treatment in patients with severe and progressive CTD-NSIP, IPAF-NSIP and iNSIP non-responders to a first line immunosuppressant.

The study is planned for a 4-year duration with a recruitment period of 36 months (planned at the beginning of 2016) and a maximum 12-months follow-up period for each patient. Duration of treatment will be 15 days for RTX /placebo (day 1 and 15) and 6 months for MMF (from day 1 to 6 months).

Study setting

Patients will be selected for recruitment by trained lung specialists in 18 academic centers specialized in rare pulmonary diseases including ILDs, the OrphaLung network, within RespiFIL (Filière Santé Maladies Respiratoires Rares). The rare pulmonary disease reference center (Lyon) and the corresponding competence centers are homogeneously distributed all over the French territory. These centers form a network that includes the majority of hospital-based or liberal lung specialists, and meet twice annually. The objective of this network is to improve clinical care, education and research in the field of rare pulmonary diseases.

Patients recruitment

Inclusion criteria

- Adult patients aged 18 years and older,
- A diagnosis of ILD: ILD associated with differentiated CTD or IPAF (based on internationally accepted criteria), or, idiopathic ILD,
- A diagnosis of NSIP based on: i) a histological pattern of NSIP, or, ii) High Resolution Computer Tomography (HRCT) findings suggestive of NSIP defined as basal predominant reticular abnormalities with traction bronchiectasis, peri-bronchovascular extension and subpleural sparing, frequently associated with ground-glass attenuation [2],
- Patients who did not respond or relapsed or were not able to continue at least one first-

line immunosuppressive treatment of ILD: corticosteroids, azathioprine, cyclophosphamide or other immunosuppressants. For the assessment of clinical response, the absence of response was defined as: either a decrease in CVF or an insufficient increase in CVF (defined by a variation in CVF <10% in % predicted FVC),

- Patients having rights to French social security,
- Written informed consent obtained from subject, with a specific check box on the Consent form of the study, understanding the risk for men and women treated with MMF. And additional written consent from subject on the care and contraception agreement form for women of childbearing potential treated with MMF,
- Ability for subject to comply with the requirements of the study.

Exclusion criteria

- Known diagnosis of significant respiratory disorders (asthma, tuberculosis, sarcoidosis, aspergillosis, or cystic fibrosis) other than CTD-NSIP, IPAF-NSIP and iNSIP
- Evidence of any clinically significant, severe or unstable, acute or chronically progressive cardiac (severe heart failure New York Heart Association Class IV or severe uncontrolled cardiac disease), other medical disease (other than NSIP) or surgical disorder, or any condition that may affect patient safety in the judgment of the investigator.
- HRCT pattern of typical usual interstitial pneumonia (UIP)
- For patients with idiopathic ILD, HRCT pattern of possible UIP (no evocative of NSIP)
- Histological pattern other than pattern of NSIP
- A first line treatment with MMF or RTX
- Known hypersensitivity to MMF or RTX or sulfonamide antibiotics
- Past or current treatment with immunosuppressive treatments other than corticosteroids:
 - a) azathioprine, cyclophosphamide, methotrexate, cyclosporine, tacrolimus, leflunomide, within 2 weeks prior to inclusion,
 - b) intravenous immunoglobulins, hydroxychloroquine or other monoclonal antibody therapies (such as but not limited to etanercept, adalimumab, efalizumab, infliximab, golimumab, certolizumab) within 6 months prior to inclusion
- Patients registered on a pulmonary transplantation list
- Patients with known hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) hereditary deficiency (such as Lesch-Nyhan and Kelley-Seegmiller syndrome)

- Pregnant or breastfeeding women, or women of child-bearing potential not using two reliable contraceptive methods (including for female partners of sexually active men treated with MMF) and men not using a contraceptive method (condom), or women and men having a pregnancy project during the year following randomization.
 - Patients at significant risk for infectious complications: HIV positive, other known immunodeficiency syndromes, untreated tuberculosis, hepatitis B and C or other known viral infection, infection requiring anti-infectious treatment in the preceding 4 weeks
 - Current history of substance and/or alcohol abuse
 - Deprivation of liberty, under judicial protection
 - Participation in another biomedical research with experimental drug or medical device
- This study does not accept healthy volunteers.

Interventions

Patients will be randomized to experimental (RTX-MMF) or control (placebo-MMF) groups. The experimental group will receive: i) one course of RTX, consisting of one RTX infusion of 1000 mg IV / 500 ml solution on day 1, and a second RTX infusion of 1000 mg IV / 500 ml solution on day 15; ii) 1 gram twice daily on oral route of MMF (2 grams daily) for 6 months. The control group will receive: i) one course of placebo of RTX, administered identically and consisting of two IV infusions of 500 ml of saline (0.9% sodium chloride) on day 1 and on day 15; ii) 1 gram twice daily on oral route of MMF (2 grams daily) for 6 months.

The choice of the dose of MMF proposed in our study (2 g/day) is that authorized for graft rejection [19] and which off-label use is accepted for severe auto-immune diseases [20]. The choice of the dose and schedule of RTX proposed (one course of two 1000 mg IV infusions) is approved in rheumatoid arthritis [21] and was used in the majority of previous observational study, with a total cumulative dose being lower than that used for hematologic cancers or vasculitis.

Modifications of MMF doses or temporary or definitive interruptions of MMF will be allowed depending on the clinical status of the patient and on the judgement of the investigator. Use of any cytotoxic or immunosuppressive treatments other than corticosteroids (prednisone) and study treatments, any biologic agent and live vaccines are prohibited during the study duration.

Outcomes

The primary endpoint is the change in FVC (in % of predicted) from baseline to 6 months, since decline in FVC correlates with increased risk of subsequent mortality in ILD patients [22] and FVC is one of the core set of outcomes defined in ILD. Data obtained from the two groups of patients (RTX-MMF and placebo-MMF) will be compared to each other. FVC will be measured within each study center in a standardized manner according to the ATS/ERS recommendations [23] and ECCS reference equations [24].

The secondary endpoints are:

- 1) Progression free survival (PFS) measured at 3, 6 and 12 months; PFS is defined as the time i) to the first acute exacerbation, or ii) to an absolute decline of 10 % points in the percentage of the predicted FVC, or iii) to the necessity to withdraw MMF with/without a new immunosuppressive treatment (except corticoids), or iv) to death or v) registration to a lung transplantation list.
- 2) Changes from baseline to 6 months in the quality of life score as measured by the SF-36 v1.3 questionnaire [25], and changes from baseline to 6 months in the visual analogic scales (VAS) of dyspnoea and cough.
- 3) Cumulative doses of corticoids for the 2 groups at 6 months.
- 4) Change from baseline to 3 months in the FVC (% of predicted).
- 5) Changes from baseline to 6 months in diffusing capacity for carbon monoxide (DLCO).
- 6) Changes from baseline to 6 months in the 6-minutes-walking test.
- 7) Changes from baseline to 6 months in autoantibodies concentration.
- 8) Changes from baseline to 6 months in biological markers related to lymphocyte B depletion: CD19 lymphocytes count and gammaglobulins level.
- 9) Changes from baseline to 6 months in HRCT of the chest images.
- 10) All adverse events and in particular serious infectious adverse events and biological blood disorders during the 6 months of treatment period will be collected.
- 11) RTX Pharmacokinetics parameters: distribution volume, RTX clearance and half-life.

Safety outcomes

All serious adverse events and in particular infectious adverse events during the study period, beginning after randomization and until visit 4 at 6 months, will be collected.

Study procedures

Patients will be included in the study after informed signed consent and if all inclusion criteria are fulfilled without any exclusion criteria (Table). The duration of the study for each patient will be of 6 months, with an additional observational follow-up until 12 months. Randomization will be performed at the inclusion visit (V0). Study treatment will be started within one month since randomization (V1). Study visits will take place at each RTX or placebo infusion (day 1, V1, and day 15, V2), then at months 3 (V3) and 6 (V4). HRCT and forced vital capacity will be performed at inclusion visit unless already done within 4 months prior inclusion. During each visit a physical examination including body weight, height and SpO2 at every visit will be performed. Biological assessments including blood count, renal and hepatic functions, lymphocytes and gammaglobulins will be regularly performed at clinical visits and between visits as required to monitor treatment safety. Autoantibodies including anti-nuclear, anti-CCP, anti-dsDNA, anti-Ro (SS-A), anti-La (SS-B), anti-ribonucleoprotein, anti-Smith, anti-topoisomerase (Scl-70), anti-tRNA synthetase, anti-PM-Scl, anti-MDA-5 autoantibodies and rheumatoid factor will be performed at day 1, 6 months and 1 year. MMF treatment will be supplied for 3 months on day 1 and at month 3. Urine pregnancy test will be performed for women of childbearing age at inclusion and at 3 months. A final routine medical consultation will take place at one year (routine clinical data collection). If a patient is prematurely discontinued from treatment, all assessments planned in the study will be performed. In case of an early definitive MMF discontinuation, a supplementary study visit will be performed at discontinuation of MMF.

Pharmacokinetics and DNA collection

Blood samples will be collected before (trough) and 2 hours after (peak) the end of the two RTX /placebo infusions, and at 3 and 6 months after the first RTX infusion (6 timepoints per patient). Each blood sample will be shipped to the Touraine Biological Resource Center of Tours (BRC-T) for storage at -80°C. At the end of the study sera of patients treated with RTX will be transferred and analyzed by the Pilot centre for Therapeutic Antibodies Monitoring (PiTAM/ CePiBac) of University Hospital Center of Tours. Serum concentrations of RTX will be measured using a validated ELISA technique [26]. The PK of RTX will be assessed using population compartmental PK modeling and the relationship between biopharmaceutical PK and clinical and/or biological markers of efficacy will be assessed using direct Emax and

indirect PK-PD models. For the DNA/serum collection, a 7 ml and 5 ml blood samples will be collected at day 1 and shipped to BRC-T.

Randomization and blinding

After informed consent signature and once screening procedures have been done, participants will be randomly assigned via a web-based interactive response system (COnline) to receive either RTX or placebo in addition to MMF with a 1:1 ratio allocation. We will use a computer-generated randomization schedule performed by an independent statistician not otherwise involved in patient recruitment or follow up. Randomization will be stratified on subgroups of ILDs defined as follows: differentiated CTD-NSIP or IPAF-NSIP vs. iNSIP, and on Forced Vital Capacity (FVC) in % predicted at inclusion defined as follows: $\leq 50\%$ vs $> 50\%$.

In this trial, the patients, investigators and caregivers including technicians in charge of respiratory tests, biologists and radiologists will be blinded from the treatment allocation. Indistinguishable saline infusions (same volume, same rate infusion algorithm) and same premedication will be administered. Opaque bags will be used for RTX or saline preparations in order to maintain blinding. All PK analyses and blood lymphocytes phenotyping will be centrally performed at the end of the study, without risk of unblinding. FVC will be measured in a standardized manner according to the ATS/ERS recommendations [23] and ECCS reference equations [24], by a technician unaware of the allocation status of the patient. The treating physician or the sponsor may unblind a patient's treatment assignment only when this knowledge is essential for the appropriate clinical management of the patient.

Sample size calculation

Assuming a power of 90%, a type I error rate of 5% two-sided and anticipating an extreme 10% drop-out rate, 122 patients (61 per group) would be sufficient 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% [27].

Statistical analysis

The statistical preliminary evaluation and analysis of the study was performed by a biostatistics expert (AC).

Statistical analysis will be conducted using the intention-to-treat principle. Participants who would withdraw consent to study participation will be discarded, as required by the French legislation. We will use two-sided significance tests with a type I error of 5%. For the primary analysis, we will use a mixed-model repeated measures analysis (PROC MIXED in SAS software) to evaluate difference in mean change between the study groups for FVC measurements over the 6-months study period, with planned measurements at baseline and at 3 and 6 months. The regression model will include treatment group, visit, treatment-by-visit interaction as fixed-effects. We will use a model with Random individual intercepts and slopes over time. The treatment effect will be assessed using the treatment by visit interaction. This model will assume that data are missing at random, and missing data will not be imputed for the primary analysis. All available FVC will be used in the primary analysis including measurements from patients who will prematurely discontinue the study medication. Analysis of secondary outcomes corresponding to repeated measures such as quality of life, DLCO, 6-minutes walk test will also use linear mixed models as for the analysis of the primary outcome. Progression free survival will be compared between study groups using a log-rank test. Other comparisons will use chi-square or Fisher test for categorical outcomes and Student or Wilcoxon rank sum tests for continuous outcomes. Baseline characteristics will be reported per group as numbers and percentages for categorical variables and as means (SD) or medians (IQR) for respectively normally and non-normally distributed quantitative variables. A priori defined sub-groups are defined as: 1) type of disease: CTD-NSIP or IPAF-NSIP vs iNSIP (stratification variable); 2) FVC% \leq 50% vs $>$ 50% at inclusion (stratification variable). Other sub-groups might be defined a priori depending on evolution of knowledge before data unblinding. Sensitivity analyses will be performed under different assumption regarding missing data.

Data management and quality control

Data from source documents will be captured into the protocol-specific electronic Case Report Form (eCRF) by the site study personnel. A data review will be done prior to locking the database. A clinical research associate appointed by the sponsor will regularly perform on-site visits, according to the monitoring plan. An audit may be performed at any time by people appointed by the sponsor who are independent of those responsible for the study.

Adverse events reporting

Patient safety will be ensured through the regular visits and blood samples (blood count, gammaglobulins level, renal and hepatic functions). Serious adverse event (SAE) will have to be reported by the investigator to the sponsor immediately and within a maximum of 24 hours after learning of the occurrence. Non-serious adverse events will be reported in the e-CRF. Safety evaluation parameters are infusion related reactions, infections, bone marrow depression, hypogammaglobulinemia, renal or hepatic impairment. A significant risk of teratogenicity with MMF led the European and French authorities to establish strict recommendations for the prescription and dispensation of MMF to women of childbearing potential or female partners of sexually active men. If a woman (either a participant of female partner of a male participant) becomes pregnant during the clinical trial, the pregnancy must be reported to the sponsor as SAE.

Ethics, approval and dissemination

The protocol was approved by an independent French ethic committee (Comité de Protection des Personnes Tours Ouest 1) on Sept 27, 2016. The protocol was authorized by the French health authority (ANSM – Agence Nationale de Sécurité du Médicament et des produits de santé) on Dec 1st, 2016. The collection of serum and DNA samples was declared to ANSM at the same time. The study protocol is registered on ClinicalTrials.gov: NCT02990286.

An independent Data and Safety Monitoring Board (DSMB) with at least 3 members with expertise in lung diseases, biostatistics and clinical pharmacology, independent from the sponsor, will meet regularly and whenever necessary to review safety data and make recommendations about the continuation, amendments or termination of the clinical trial.

Any written or oral communication of the results of the study will be previously agreed by the principal investigator and, if necessary, by the scientific committee constituted for the study. Publication of the main results will mention the sponsor and the funding source. We will follow the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2014) from the International Committee of Medical Journal Editors (ICMJE).

Participant confidentiality and data protection

In accordance with French laws and regulations, research staff with direct access to source data will take all necessary precautions to ensure the confidentiality of information. All information regarding participants forwarded to the sponsor will be made anonymous. All data transferred between sites will be encrypted, and no individual will be identifiable from the stored data. Identifiable patient information will be stored in a locked cabinet, accessible only to research members at the site of the data collection. All original records will be archived at trial sites for 15 years. The clean database file will be anonymized and kept for 15 years.

Patients and public involvement

Patients and/or public were not involved in the study design, recruitment or conduct of the study.

DISCUSSION

ILD NSIP is a severe disease with severe prognosis. This trial should better define the optimal management of patients with ILD NSIP.

~~Regarding the risks of RTX + MMF association, the few available studies did not report an increased risk of adverse effects [28, 29]. However, an increased risk of adverse effects is foreseeable, that is why one of the objectives of our study is to evaluate the safety of rituximab in association with MMF as compared to placebo + MMF all throughout the study period.~~

The EVER-ILD trial has several strengths. First, EVER-ILD trial is the first to evaluate the efficacy and safety of an intensive strategy based on rituximab and MMF compared to placebo and MMF in a broad range of patients with NSIP pattern that did not respond to a first-line therapy, whatever the etiologic context (CTD-NSIP, IPAF-NSIP, or idiopathic-NSIP). We are aware of only one ongoing double-blind randomized trial, comparing RTX to cyclophosphamide as first line treatment, in some patients with CTD- NSIP, the RECITAL study (NCT01862926) [30]. However, only patients with NSIP related to scleroderma, inflammatory myositis and mixed connective tissue diseases are considered in this randomized controlled trial. ~~EVER-ILD trial is the first to evaluate the efficacy and safety of an intensive strategy based on rituximab and MMF compared to placebo and MMF in a broad range of patients with NSIP pattern that did not respond to a first-line therapy,~~

~~whatever the etiologic context (CTD-NSIP, IPAF-NSIP, or idiopathic-NSIP).~~ Second, it is a randomized, double blind, controlled trial following a methodology that will allow to establish the efficacy of an intensive strategy based on RTX and MMF to MF alone. Third, if the intensive strategy will be shown to be effective in preserving or improving lung function, ~~this~~ EVER-ILD trial could lead to practical recommendations for the treatment of these severe diseases and improve the quality of life of patients. Fourth, EVER-ILD trial will also allow to address rituximab PK and PK-PD relations in ILD patients, and also help to evaluate other biomarkers for predicting clinical outcomes. If such a relation exists, drug monitoring could be further proposed in clinical practice allowing to maximize the benefit-risk balance for patients.

One concern may be related to the safety of such intensive strategy. However, current therapy such as corticosteroids or IV cyclophosphamide is quite limited by adverse effects and the risk of infections due to significant immunosuppression. Regarding the risks of RTX - MMF association, the few available studies did not report an increased risk of adverse effects [28, 29]. However, an increased risk of adverse effects is foreseeable, that is why one of the objectives of our study is to evaluate the safety of rituximab in association with MMF as compared to placebo + MMF all throughout the study period.

Rituximab has a higher cost per patient, but necessitates fewer visits and could be more convenient for patients, and eventually less expensive overall [30]. Even if EVER-ILD trial was not designed to study the cost effectiveness of this strategy, the trial data should contribute to further health economic analyses.

Conclusions and perspectives

The EVER-ILD trial is the first trial to evaluate the efficacy and safety of an intensive strategy based on rituximab and MMF compared to MMF alone in a broad range of patients with NSIP pattern that did not respond to a first-line therapy. Further clinical trials will be necessary to confirm our findings and to evaluate the cost effectiveness of such intensive strategies.

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Author's contribution

Prof Sylvain Marchand-Adam is the principal investigator of the EVER-ILD trial. TBA and SMA conceived the research and wrote the first draft of the protocol. AC made substantial contributions to the conception and design of the study. JMN, RB, HN, MF, JC, BC, VC made significant revisions to the manuscript. All authors read and approved the final version of the manuscript.

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Scientific committee

Professors Sylvain Marchand-Adam, Theodora Bejan-Angoulvant, Vincent Cottin.

Patients consent for publication

Not required for this trial protocol

Data Availability Statement

Medical researchers can obtain individual deidentified participant data collected during the trial, study protocol, statistical analysis plan and analytical code immediately following

publication for any purpose by contacting the principal investigator. The original protocol is available upon request to the principal investigator.

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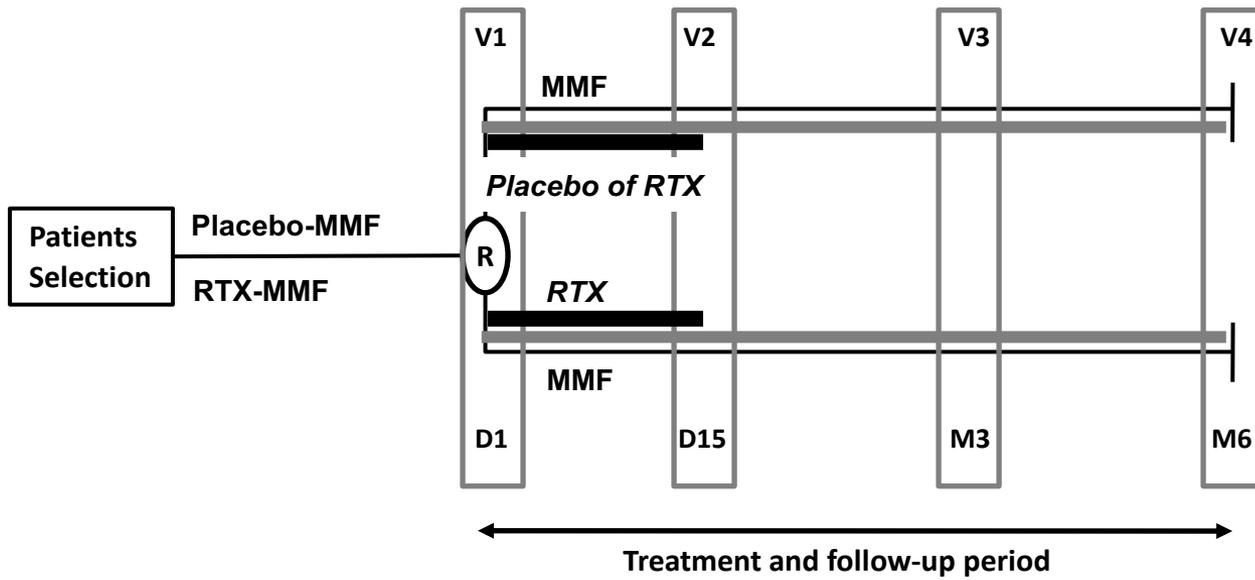


Table: Study visits, interventions and assessments.

VISITS	Inclusion	V1 (D1)	V2 (D15)	V3 (M3)	V4 (M6)	V5 (M12)
<i>DAYS</i>	<i>-28 to -7 days</i>	Day 1	Day 15 <i>+/-3 days</i>	Month 3 <i>+/-10 days</i>	Month 6 <i>+/-15 days</i>	Months 12 <i>+/-3 months</i>
PATIENT INFORMATION						
Eligibility Criteria	X					
Informed signed consent (+ care and contraception specific form for women)	X					
Randomization	X					
Vaccine status check (pneumococcus, HBV)	X					
HBV, HCV, HIV serologies	X					
Demographic characteristics		X				
ILD and medical/surgical history		X				
Prior/concomitant medications		X	X	X	X	
Physical examination	X	X	X	X	X	
Arterial oxygen saturation		X	X	X	X	
Urine pregnancy test	X	X		X		
INTERVENTION						
MMF treatment & delivery		X		X		
MMF compliance				X	X	
RTX or Placebo administration		X	X			
BIOLOGICAL WORK-UP						
Renal function		X		X	X	
Liver function		X	X	X	X	
Blood count		X	X	X	X	

C-reactive protein		X		X	X	
Autoantibodies		X			X	X
Lymphocyte phenotype, gammaglobulins		X			X	X
EFFICACY						
Blood sample DNA collection		X				
Blood samples serum collection		X	X	X	X	
Forced Vital Capacity	X	X		X	X	X
DLCO		X			X	
HRCT	X				X	X
6-minute walking test		X			X	X
QoL (SF-36)		X			X	
VAS of dyspnoea and cough		X			X	
PHARMACOKINETICS (PK)						
Blood samples for rituximab concentration		X	X	X	X	
SAFETY EVALUATION						
Adverse events (severe or not)		X	X	X	X	