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ORIGINAL ARTICLE:

Efficacy and safety of rituximab in patients with chronic hypersensitivity pneumonitis (cHP): a retrospective, multicentric, observational study

Marion Ferreira^{1,2}, Raphaël Borie³, Bruno Crestani³, Pierre Rigaud⁴, Lidwine Wemeau⁵, Dominique Israel-Biet⁶, Sylvie Leroy⁷, Sébastien Quétant⁸, Laurent Plantier^{1,2}, Jean-Charles Dalphin⁹, Vincent Cottin¹⁰, Sylvain Marchand-Adam^{1,2}, on behalf of the OrphaLung network

¹ Department of Pneumology and Respiratory Functional Exploration, University Hospital of Tours, Tours, France

² INSERM U-1100, Faculty of Medicine of Tours, Tours, France

³ Department of Pneumology, Bichat Hospital, APHP, Paris, France

⁴ Department of Pneumology, Tenon Hospital, Paris, France

⁵ Department of Pneumology, University Hospital of Lille, Lille, France

⁶ Department of Pulmonology, European Hospital Georges Pompidou, Paris, France.

⁷ Department of Pulmonary Medicine and Allergology, CHU de Nice, CNRS UMR 7275 – Institut de Pharmacologie Moléculaire et Cellulaire, Nice, Université Côte d'Azur, France.

⁸ Department of Pneumology and Physiology, Besançon Hospital, Besançon, France

⁹ Department of Pneumology, Grenoble Alpes Hospital, Grenoble, France

¹⁰ Reference coordinating for rare pulmonary disease, department of Pneumology, Louis Pradel Hospital, MUR 754, Claude Bernard University, Lyon, France

Corresponding author full contact details:

Name: FERREIRA Marion

Address: 2 Boulevard Tonnellé

Post code: 37520

City: LA RICHE

Country: FRANCE

Email: marion-ferreira@hotmail.fr

Twitter account name (optional): @FerreiraMarion2

ABSTRACT: *(maximum 250 words structured as follow)*

Background: There are chronic forms of hypersensitivity pneumonitis (cHP) that can progress to pulmonary fibrosis. There is no recommended treatment for patients whose respiratory condition continues to deteriorate in spite of antigen avoidance. Whether rituximab may be beneficial to patients with cHP is unknown. The aim of this study was to describe the course of 20 patients with cHP under rituximab therapy.

Methods: This retrospective study was conducted from November 2018 to July 2019 in 7 French university hospitals. Forced Vital Capacity (FVC) was measured 6 months before rituximab therapy onset (M-6), at rituximab onset (M0), and 6 months later (M+6).

Results: FVC decreased significantly in the 6 months preceding the introduction of rituximab (65% [44; 112%] at M-6 versus 59% [39; 102%] at M0; $p=0.0001$), but it did not differ significantly from that at 6 months after the introduction of rituximab (61% [38; 99%]). The decline in FVC between M0 and M+6 (-3% [-15; + 19%]) was significantly less than between M-6 and M0 (-8% [-21; 0%]) ($p=0.0002$). Between M0 (37% [16; 73%]) and M + 6 (45% [15; 70%]), the median DLCO remained stable ($p = 0.12$). DLCO improved at M+6 in 5 of the 8 patients (63%) for whom a DLCO value was available at M+6 improved their DLCO.

Conclusion: Rituximab seems well tolerated, and may lead to stabilization or improvement of lung function in some patients.

Short title: Rituximab, hypersensitivity pneumonitis

Keywords: hypersensitivity pneumonitis, rituximab, forced vital capacity

INTRODUCTION:

Hypersensitivity pneumonitis (HP) results from repeated exposure to a variety of inhaled particles. In previously sensitized individuals, these antigens elicit an exaggerated immunological response within the small airways and pulmonary parenchyma [1].

In contrast to idiopathic pulmonary fibrosis (IPF), there are no defined criteria for chronic HP (cHP) diagnosis, which is established by bringing together clinical, radiological and pathological information at multidisciplinary team meetings. To determine probability of cHP, Morisset et al proposed an algorithm based on compatible symptomatology, exposure to antigens known to be pathogenic or presence of serum precipitins, typical computerized tomography (HRCT) features, and histopathological characteristics [2].

Vasakova et al distinguished between acute forms with symptoms lasting less than 6 months, and chronic forms. These chronic forms can be associated with fibrosis shown on the HRCT as well as by histological analysis. Chronic forms can progress to an imaging pattern of pulmonary fibrosis and show histological features similar to those of non-specific interstitial pneumonitis (NSIP) or usual interstitial pneumonitis (UIP) [3]. Chronic HP has a poor prognosis; in a longitudinal study of 160 cHP cases, the survival rate at 5 years was 31% [4].

Pathophysiology is not fully understood, although type III and type IV hypersensitivity to inhaled antigen are suspected. The coexistence of genetic and environmental susceptibility factors can cause an exaggerated immune response, causing inflammation in the lungs [1]. Inflammatory mediators secreted by activated lymphocytes and macrophages play a role in the local inflammatory state. In addition, B cells secrete immunoglobulins G (IgG) specific to the antigens underlying HP. Fibrocytes and interleukin-17 are involved in the fibrotic appearance of chronic HP [5].

Management of HP is primarily based on antigen avoidance [6], even if, fibrosing forms of the disease can continue to progress. There is no pharmacological treatment for cHP and only lung transplantation can improve the survival rate of patients with impaired respiratory function [7]. Although the mechanisms of pulmonary inflammation and fibrosis in cHP are complex, T and B lymphocytes probably play a central role [5]. This indicates the use of anti-inflammatory or immunosuppressive drugs such as systemic corticosteroids, but with no influence on long-term survival [8][9]. Several retrospective studies evaluating two main lines of therapeutic options: on the one hand immunoregulatory molecules (corticosteroids, azathioprine and mycophenolate mofetil) and in the other hand anti-fibrotic

molecules have been published. The first reported the use of pirfenidone [10] which was not shown to have a significant effect on forced vital capacity (FVC) decline. Introduction of mycophenolate mofetil and azathioprine was associated with improved gas exchange and in reduction of dose in those who were in treatment with prednisone [11]. Two other retrospective studies found less treatment related-adverse events compared to those treated with prednisone alone without a significant effect on disease progression [12] or an improvement in carbon monoxide diffusing capacity (DLCO) and reduction in dose of corticosteroids with mycophenolate mofetil or azathioprine [13]. More recently, a prospective, randomized, double-blind, INBUILD study found that the annual decline in FVC is reduced in patients with active fibrotic interstitial lung disease (ILD) treated with nintedanib; a quarter of these patients had cHP [14].

Another treatment option for patients with cHP is rituximab [15], an anti-CD20 monoclonal antibody depleting B lymphocytes which has been shown to be beneficial in ILD associated with connective tissue disease [16]. A patient with histologically proven HP, who did not respond to corticosteroids, showed improved FVC after taking rituximab [17]. Two other clinical case reports published in 2019 showed similar results [15][18]. A retrospective study of 6 patients with cHP found that lung function stabilized or improved in 3 and continued to deteriorate in the other 3, after treatment with rituximab [19]. To date, there is no recommended treatment for patients whose respiratory function continues to deteriorate in spite of antigen avoidance.

We hypothesized that rituximab could benefit patients with cHP who have not responded to standard treatment including antigen avoidance and corticosteroid therapy. Our aim was to study changes in FVC in 20 cHP cases after 6 months of treatment.

METHODS:

This retrospective and observational study was conducted in the pulmonology departments of seven French University Hospitals. All patients treated with rituximab between January 2014 and June 2019 and with a diagnosis of cHP validated during a multidisciplinary team meetings with criteria adapted from Morisset et al. [3] (**Table 1**) were screened for our analysis. We included patients with no improvement in lung function (deterioration in their FVC) after a minimum of 3 months treatment including antigen avoidance and who had received at least one injection of rituximab. There were no exclusion criteria.

Primary endpoint was change in FVC (% of the predicted value) 6 months after initiation of rituximab. Secondary endpoints included change in percentage of the predicted value of FVC at 12 months and change in the percentage of the predicted value of DLCO at 6 months. We also studied changes in corticosteroids dose at 6 months and any side effects, in particular infection, in the 12 months following onset of treatment with rituximab.

Local research ethics committee approval was in place for retrospective review of cHP patients.

Statistical analysis

Characteristics of the participants were identified with quantitative (median; [minimum-maximum]) and qualitative (frequency) variables. For analysis of the primary endpoint, given the small size of the study population, non-parametric tests were used. The Wilcoxon test was used to analyze changes in FVC and DLCO before and after treatment with rituximab.

To compare characteristics of responders and non-responders to rituximab (positive or strictly negative change), and to identify predictors of response to treatment, a Mann Whitney test was used for the unpaired quantitative variables and Chi2 test for qualitative variables. The sample was too small to perform multivariate statistical analyses.

Statistical analyzes and graphs were performed using Excel software and GraphPadPrism 6 software. For all analyzes, a $p < 0.05$ was considered significant.

RESULTS:

Patients

The sample comprised 20 patients who had been treated with rituximab between January 8, 2014 and June 14, 2019. Median duration of follow-up after the first administration was 18 months [6; 50 months]. Forty percent (10/20) of patients had a history smoking; all were former smokers, with a median cumulative smoking rate of 30 pack-years [5; 60 pack-years]. One of the 20 patients (5%) had no history of antigen exposure. For the others, exposure was domestic in 85% (17/20) of cases and occupational in 10% (2/20). The most frequently found precipitins were avian (50%) or household molds (10%). Sixty-five percent (13/20) of patients had had a surgical lung biopsy and histological analysis supporting the diagnosis of cHP. All chest CT were suggestive of cHP; majority of patients had HRCT signs of fibrosis : 90% with traction bronchiectasis, 75% with intra-lobular reticulations, 65% with lobular distortions and 45% with honeycombing. Thus, the probability of diagnosis, according to criteria adapted from Morisset et al. [3], was definite

for 55% of patients (11/20) and very likely for the remaining 45% (9/20) (Table 1). The median number of infusions received was 3 [2; 10] with a dosage of 500 or 1000 mg and an interval of 6 months between doses (**Table S2**). Characteristics of the study population are presented in **Table 2**.

Six months before the introduction of rituximab (M-6), 20 patients had impaired respiratory function with median FVC of 65% [44; 112%] and median DLCO of 47% [21; 68%] in the 8 patients whom DLCO was available at the initiation of rituximab (M0) and M+6 too. All patients received rituximab because their respiratory function had deteriorated significantly, with a median FVC of 59% [39; 102%] ($p = 0.0001$) at M0. One patient who presented 112% of FVC at M-6 and 102% at M0 was treated with rituximab because the dissociation of the DLCO value which appeared low to begin with, because he had received none clinical benefit from the corticosteroid therapy and because he had major fibrosis lesions on his HRCT scan. All patients had previously received systemic corticosteroids, with a median dose of 18 mg [10; 60 mg] at M0 (**Table 2**).

Evolution of lung function and corticosteroids

We analyzed changes in FVC 6 months after the start of treatment (M+6). Between M0 and M+6, FVC remained stable (59% [39; 102%] versus 61% [38; 99%]; $p=0.28$). All patients showed a decrease in FVC between M-6 and M0, and in seven cases (35%), FVC improved or remained stable at M+6 (**Figure 1**). Although FVC continued to decline after administration of rituximab, the rate of decline was significantly less between M0 and M+6 (-3% [-15; + 19%]) than between M-6 and M0 (-8% [-21; 0%]); $p=0.0002$). At M+12, FVC data were available for 13 of the 20 patients, who showed a significant decrease between M-6 (62% [51; 80%]) and M0 (55% [39; 74%]; $p=0.03$), with no significant change between M0 and M+12 (52% ([31; 74%]; $p=0.10$). Twelve of the 20 patients (60%) had a rituximab administration between M+6 and M+12. The decline over the 12-month period between M0 and M+12 (-7% [-15; + 10%]), was significantly less than over the 6-month period between M-6 and M0 (-8% [-21; 0%]; $p=0.0017$).

Data for DLCO at initiation of rituximab were only available for 8 of the 20 patients; median DLCO was 47% [21; 68%] 6 months before the first administration of rituximab, and 37% [16; 73%] at onset. Between M-6 and M0, DLCO showed a downward trend. At M+6, the median DLCO remained stable (41% [15; 70%]; $p = 0.29$) (**Figure 2**), and improved in five of the 8 patients (63%).

Median daily dose of corticosteroid between M-6 and M0 remained stable (15mg/d of prednisone [0; 40mg] and 18mg/d [10; 60mg] respectively; $p=0.55$), while it decreased significantly between M0 and M+6 (12mg/d [0; 30mg]; $p=0.013$) (**Figure 3**). The corticosteroid dose of 11 patients was reduced between M0 and M+6, remained the same for 8 patients and was increased by 10mg to the M-6 dose for one patient.

Safety and tolerability of rituximab

Seven patients (35%) had developed an infection within 12 months of the first injection of rituximab; 6 had respiratory infections with no microbiological identification, and no *Pneumocystis* infection and one had a urinary tract infection caused by *Escherichia coli*. Of the 6 patients with viral or bacterial respiratory infection, only one had no co-trimoxazole prophylaxis. One patient (5%) died from his respiratory infection.

Responder analysis

We compared 2 groups of patients: “responders” ($n=7$), whose FVC at M+6 showed a positive change; and “non-responders” ($n=13$), whose FVC showed a strictly negative change compared to M0.

Monovariate analysis revealed that no parameter was significantly associated with improvement in FVC at M+6, only the absence of a UIP or NSIP pattern on histology analysis tended to be approach statistical significance ($p=0.06$) (**Table S1**).

DISCUSSION:

To our knowledge, this is the largest study suggesting a possible beneficial effect of rituximab in a cohort of patients with cHP whose condition has not improved despite antigen avoidance and corticosteroid therapy. The data support the hypothesis that rituximab could limit FVC decline. For seven (30%) of the 23 patients in this study, FVC improved or remained stable 6 months after the introduction of rituximab. When a histological analysis was available, the absence of UIP or NSIP could be associated with improved FVC.

Our study population was generally comparable to that of other cohorts of cHP [12][11][20][4][21][22]. In those studies, 32 to 57% of the patients were male (47% in our study), ages ranged between 61 and 65 years (63 years for our sample), and 34 to 56% had never smoked (52% of our patients). Antigen exposure was avian in 41 to 59% of cases (48% in our study). At the radiological level, honeycombing was found on 37 to 60% of scans (48% in our study) and air trapping was observed in 54 to 82% of cases (61% in our study).

However, some differences between our patients and those cohorts should be noted: FVC was more severely impaired at M-6 and M0 in our patients than in the other cohorts (63% and 56% vs 73 and 65% at M-6 and M0 respectively). Antigen exposure was not found in 9% of our cases, compared to 11 to 41% in the other cohorts. Finally, the median value of broncho-alveolar lavage (BAL) lymphocytosis was higher in our patients (32% vs 14 to 20%).

Rituximab is a monoclonal antibody that depletes B cells [17]. After binding of the Fab fragment of rituximab and the CD20 antigen of B lymphocytes, the Fc fragment activates immune effectors responsible for lysis of B lymphocytes [23]. It was therefore initially used in lymphoproliferative syndromes and is now used in many autoimmune pathologies and its efficacy has been observed in diffuse interstitial pathologies associated with anti-synthetase syndrome or scleroderma [24][25]. Despite the lack of randomized trials evaluating rituximab in cHP, many centers have used it in patients who have not responded to antigen avoidance and/or corticosteroid therapy, based on its efficacy in the treatment of severe ILD associated with connective tissue disease [16]. The rationale for using this molecule is that it allows a systemic deactivation of the immune system in order to prevent the progression of fibrosis, stabilizing and possibly improving the condition of patients with pulmonary disease from a clinical, functional and radiological point of view [26].

There are many hypotheses regarding the mechanisms whereby rituximab stabilizes or improves the lung function of patients with ILD with autoimmune features. Rituximab induces rapid depletion of CD20 + B lymphocytes present in peripheral circulation; although the role of these lymphocytes in the production of autoantibodies is well documented, the action of rituximab in ILD is probably only partially explained by the inhibition of this function. Clinical observations of patients with idiopathic thrombocytopenic purpura or graft-versus-host reaction have suggested that rituximab may "normalize" self-reactive T cells [27]. B cell repopulation following introduction of rituximab comprises antigenically undetermined B cells, suggesting a resetting of the immune system, which may contribute to therapeutic effect [19].

Finally, use of rituximab seems to be relatively safe: we documented 30% of infections (7/23 patients), most of them respiratory with only one reported death, attributable to a pulmonary infection. In the only retrospective study that tested rituximab in 50 patients with ILD, the respiratory infection rate was 22% without death directly related to rituximab toxicity or an infection secondary to its use [16]. If we plan to treat cHP patients with long-term rituximab, we must consider potential risks associated with the treatment, and in particular in comparison with prolonged corticosteroid therapy or other possible treatments

such as mycophenolate mofetil or azathioprine. In the supplementary data, Adegunsoye et al detail the side effects of these molecules: in the 24 patients treated with azathioprine, 4 patients presented grade II upper respiratory infections, 2 patients recurrent grade III urinary tract infections; for the 28 patients under mycophenolate mofetil, there were 4 grade IV respiratory toxicities without specifying whether they were infections and 3 recurrent urinary tract infections [12]. With rituximab, there is a risk of hepatitis B reactive and there are reported cases of hepatitis C reactive, CMV infection, VZV infection, tuberculosis and fungi infections [28]. In addition, long term hypogammaglobulinemia has been observed after repeated rituximab courses [29]. Thus, there are recommendations for hepatitis B vaccination in patients treated with rituximab and hepatitis B and C screening should be done before rituximab onset; other vaccinations are recommended: Streptococcus pneumonia, Haemophilus influenza and Neisseria meningitidis [28]. The other treatments that can be used in cHP are not without risk: corticosteroids expose the risk of bacterial (tuberculosis), viral (herpes viruses), fungal (Pneumocystis jirovecii) and parasitic infections; Aza and MMF can be complicated by viral (CMV, VZV) and fungal (Pneumocystis jirovecii) infections. Vaccine recommendations also exist for measures associated with these molecules [28].

This retrospective study, without a control group has certain limitations. First, missing data did not allow to calculate monthly declines in FVC or DLCO. In addition, the apparent change in the decline in FVC can be due to the effect of treatment but alternatively could in part be explained in part by the natural course of FVC, which is not linear. We have also to criticize that even if the change in FVC decline appears statistically significant, absolute values are little different and are not necessarily associated with clinical benefit. There is a large inter-individual variability in FVC variation at M+6, reflecting a variety of possible responses to treatment. Subgroup analysis by presence of serum precipitins or of the level of immunoglobulins G could not be performed. Finally, heterogeneity in the number of rituximab infusions received by our patients limits the comparison. Bellan et al. stressed the importance of repeating courses of treatment with rituximab in order to be able to observe its benefits [30]. A larger study population could have better identified some predictors of response.

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DECLARATION OF INTEREST

We have no conflicts of interest to disclose.

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TABLES and FIGURES:

*Table 1: diagnostic criteria for chronic hypersensitivity pneumonitis (adapted from Morisset [3]). The diagnosis is "very likely" when the probability is greater than 70%; the diagnosis is "likely" when the probability is greater than 50%. * Images compatible with thoracic CT scan: diffuse centrilobular micronodulation, diffuse ground glass, preserved lobules (mosaic) and expiratory trapping, presence of thin-walled cysts, traction bronchiectasis, intralobular reticulations, honeycombing, emphysema. ** Suggestive histology: peribronchiolar lymphocytic infiltration, malformed granulomas, giant cells, peribronchiolar fibrosis*

| Probability of diagnosis | Definite | Definite | Very likely | Very likely | Likely | Likely | Not selected |
|---------------------------------------|------------|------------|-------------|-------------|------------|-----------|--------------|
| Antigenic exposure and/or precipitins | Yes | Yes | No | Yes | No | Yes | No |
| Chest CT* | No | Compatible | Compatible | Compatible | Compatible | No | Compatible |
| Lymphocytes > 40% at BAL cell count | No | Yes | No | No | Yes | Yes | No |
| Biopsy** | Suggestive | No biopsy | Suggestive | No biopsy | No biopsy | No biopsy | No biopsy |
| Alternative diagnosis considered | No | No | No | No | No | No | No |

Table 2: Epidemiological characteristics of study patients (total number n = 20). Data presented as median [minimum-maximum] or n (%)

| | |
|---|-------------|
| Age at diagnosis (year) | 64 [54;83] |
| BMI (kg/m ²) | 29 [20;41] |
| Sex men/women | 9/11 |
| Tobacco: n (%) | |
| Current smoker | 0 (0) |
| Former smoker | 10 (50) |
| Never-smoker | 10 (50) |
| Cumulative smoking (pack-years) | 30 [5;60] |
| Gastroesophageal reflux : n (%) | 8 (40) |
| Antigenic exposure (interrogation/enviromental investigation) : n (%) | 2 (10) |
| Occupantional | 17 (85) |
| Domestic | 1 (5) |
| Not found | |
| Serum precipitins: n (%) | |
| Avian | 10 (50) |
| Farmer's lungs | 1 (5) |
| Household mold | 2 (10) |
| mineral | 1 (5) |
| Antigenic exposure without precipitins | 6 (30) |
| No antigenic exposure, no precipitins found | 0 (0) |
| Video-assisted lung biopsy: n (%) | 13 (65) |
| Dosage of corticosteroids at the initiation of rituximab (mg/day of prednisone) | 18 [10;60] |
| Crackles: n (%) | 17 (85) |
| FVC at initiation of rituximab (n=20) | 59 [39;102] |
| DLCO at initiation rituximab (n=9) | 35 [16;73] |
| CT abnormalities: n (%) | |
| Diffuse centrilobular micronodulation | 3 (15) |
| Diffuse ground glass opacity | 29 (90) |
| Preserved lobules (mosaic) and expiratory trapping | 13 (65) |
| Presence of thin-walled cysts | 3 (15) |
| Traction bronchiectasis | 18 (90) |
| Intra-lobular reticulations | 15 (75) |
| Scissure and lobular distortions | 13 (65) |
| Honeycombing | 9 (45) |
| Emphysema | 3 (15) |
| Histological abnormalities (n = 13/20): n (%) | |
| Peribronchiolar lymphocytic infiltration | 13 (100) |
| Granulomas | 7 (54) |
| Giant cells | 11 (85) |
| Peribronchiolar fibrosis | 13 (100) |
| UIP like pattern | 3 (23) |
| NSIP like pattern | 8 (62) |
| Other pattern | 2 (15) |
| BAL lymphocytosis (n=16/20) | |
| Lymphocytosis n (%) | 12 (75) |
| Median | 32 [10;50] |
| HP diagnostic probability: n (%) | |
| Likely | 0 (0) |
| Very Likely | 9 (45) |
| Definite | 11 (55) |

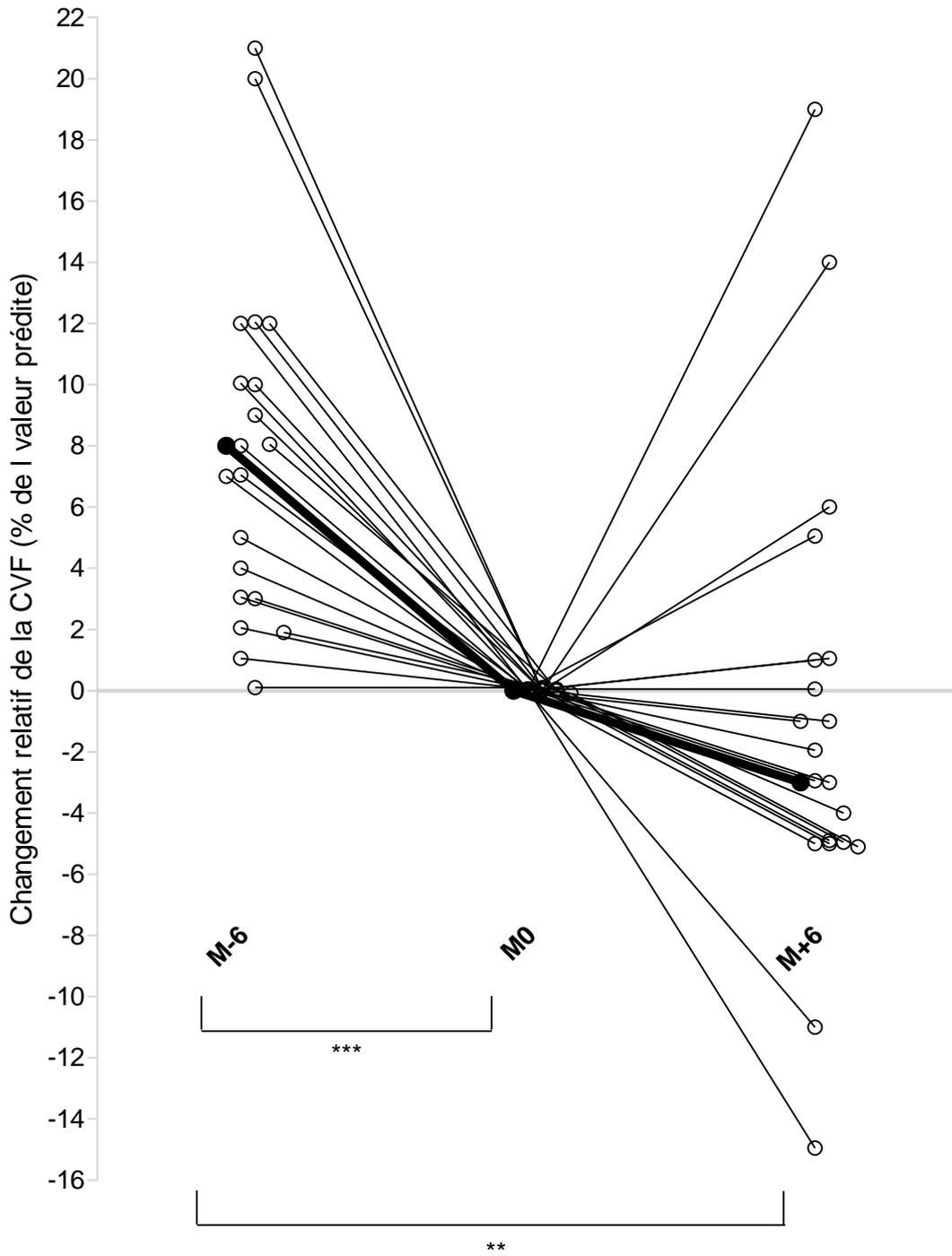


Figure 1: relative change in FVC (% of predicted value), 6 months before and after the introduction of rituximab (n = 20). The median value is represented by the bold line. ** and ***: p < 0.01 and < 0.001, respectively.

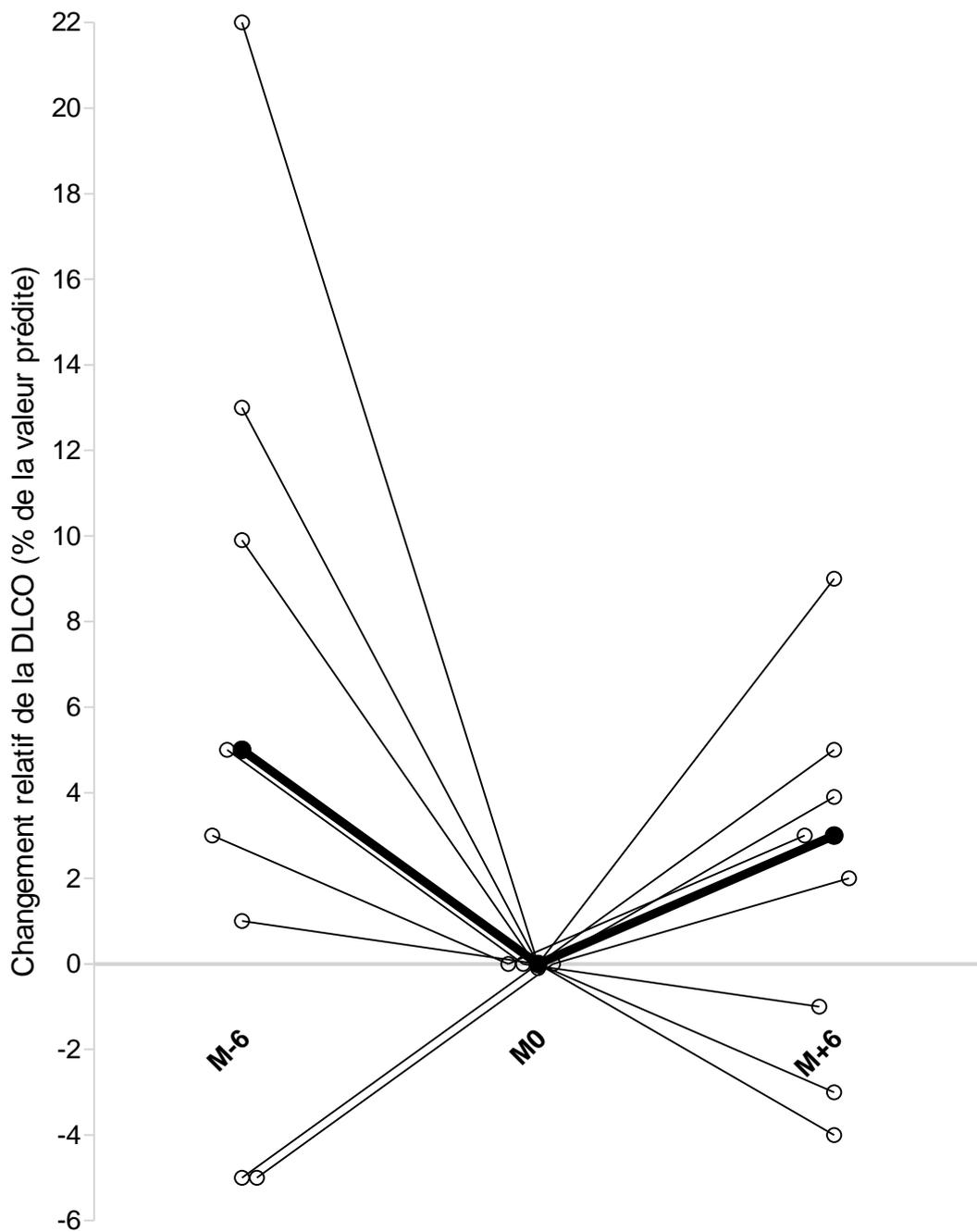


Figure 2: relative change in DLCO (% of predicted value) in 8 patients (for whom a DLCO value was available at the initiation of rituximab), 6 months before and after the introduction of rituximab. The median value is represented by the bold line.

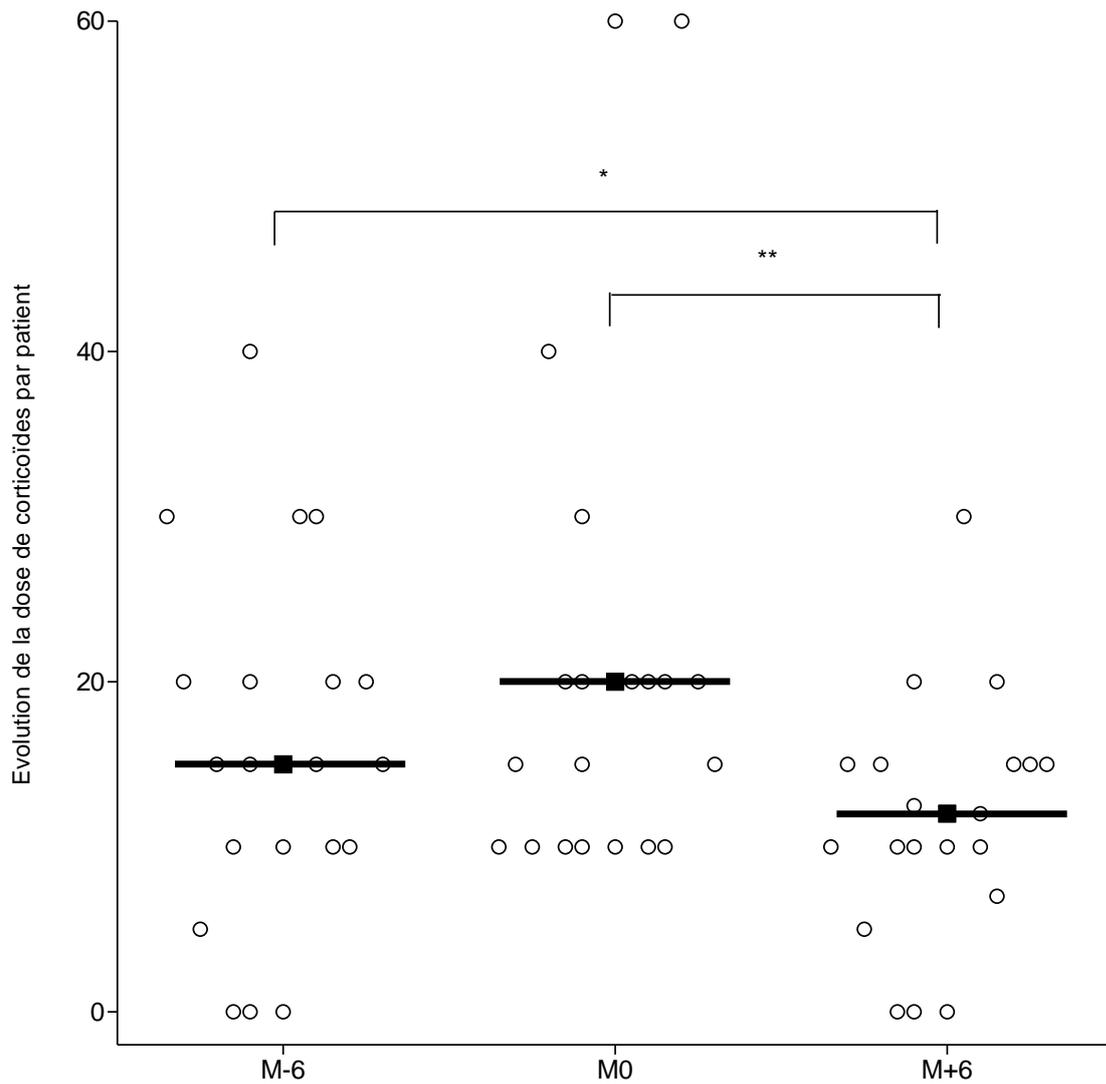


Figure 3: Difference in the dose of corticosteroids 6 months before and after the introduction of rituximab ($n = 20$). The median values are represented by the bold lines. * and **: $p < 0.05$ and < 0.01 respectively.

SUPPLEMENTARY INFORMATION

Table S1- Determinants of variation in FVC (monivariate analysis). n = 20 in responders (variation in FVC at M + 6 greater than or equal to 0%) vs non-responders (variation in FVC at M+6 less than 0%)

| | | Responders n=7 | Non-responders n=13 | p |
|---|--|----------------|---------------------|-------------|
| Age at diagnosis (year) | | 68 [56;83] | 61 [54;74] | 0.14 |
| Men (%) | | 3 (43) | 5 (38) | 0.85 |
| Surgical biopsy Responders (n=4/7) No responders (n=9/13) | Peribronchiolar lymphocytic infiltration (%) | 4 (100) | 9 (100) | 1 |
| | Malformed granulomas (%) | 2 (50) | 5 (56) | 0.85 |
| | Giant cells (%) | 3 (75) | 8 (89) | 0.49 |
| | Peribronchiolar fibrosis (%) | 4 (100) | 9 (100) | 1 |
| | UIP like (%) | 0 (0) | 3 (33) | 0.06 |
| | NSIP like (%) | 2 (50) | 6 (67) | |
| Aspect not suggestive of UIP or NSIP | 2 (50) | 0 (0) | | |
| Compatible chest CT pattern (%) | | 7 (100) | 13 (100) | 1 |
| Exposure to a known HP antigen (%) | | 6 (86) | 12 (92) | 0.64 |
| BAL lymphocytosis (LBA available: responders n = 6/7, non responders n = 8/13) | | 5 (71) | 8 (88) | 0.13 |
| Lymphocytosis | | 32 [18;43] | 38 [18;50] | 0.77 |
| Diagnostic probability | Certain (%) | 2 (29) | 8 (62) | 0.16 |
| | Very likely (%) | 5 (71) | 5 (38) | |
| | Likely (%) | 0 (0) | 0 (0) | |
| Clinical symptoms | Dyspnea (%) | 7 (100) | 13 (100) | 1 |
| | Cough (%) | 5 (71) | 9 (69) | 0.92 |
| | Deterioration in general condition(%) | 2 (29) | 5 (39) | 0.66 |
| | Crackles (%) | 6 (86) | 11 (85) | 0.95 |
| DLCO alteration (%) | | 6 (86) | 13 (100) | 0.16 |
| Hypoxemia (%) | | 6 (86) | 12 (92) | 0.64 |
| Chest CT at diagnosis | Diffuse centrilobular micronodulation (%) | 2 (29) | 1 (8) | 0.21 |
| | Diffused ground glass (%) | 7 (100) | 11 (85) | 0.27 |
| | Preserved lobules (mosaic) and expiratory trapping (%) | 3 (43) | 10 (77) | 0.13 |
| | Presence of thin-walled cysts (%) | 1 (14) | 2 (15) | 0.95 |
| | Traction bronchiectasis (%) | 6 (86) | 12 (92) | 0.64 |
| | Intra-lobular reticulations (%) | 6 (86) | 9 (69) | 0.42 |
| | Scissorial and lobular distortions (%) | 6 (86) | 7 (54) | 0.15 |
| | Honeycombing (%) | 4 (57) | 5 (39) | 0.42 |
| Emphysema (%) | | 2 (29) | 1 (8) | 0.21 |
| BMI at diagnosis | | 28 [20;41] | 32 [24;37] | 0.91 |
| Cardiovascular comorbidities | High blood pressure (%) | 3 (43) | 7 (54) | 0.64 |
| | Ischemic heart disease (%) | 1 (14) | 2 (15) | 0.95 |
| | Type 2 diabetes (%) | 2 (29) | 2 (15) | 0.48 |
| | Dyslipidemia (%) | 0 (0) | 1 (8) | 0.45 |
| | Obesity (%) | 2 (29) | 6 (46) | 0.44 |
| | Tight aortic stricture (%) | 1 (14) | 0 (0) | 0.16 |
| Respiratory comorbidities | Sleep apnea syndrome (%) | 2 (29) | 2 (15) | 0.48 |
| | Pulmonary hypertension(%) | 1 (14) | 1 (8) | 0.64 |
| Tobacco | History of smoking (%) | 3 (43) | 7 (54) | 0.64 |
| | Former or non-smoker at diagnosis (%) | 7 (100) | 13 (100) | 1 |
| | Pack-Years | 30 [5;35] | 30 [5;60] | 1 |
| Gastroesophageal reflux (%) | | 2 (29) | 6 (46) | 0.44 |
| Occupational exposure (%) | | 1 (14) | 1 (6) | 0.60 |
| Domestic exposure (%) | | 6 (86) | 11 (85) | 0.95 |
| Exposure not found (%) | | 0 (0) | 1 (8) | 0.45 |
| Rituximab | Number of infusions | 4 [3;6] | 3 [2;10] | 0.29 |
| Corticosteroids | Posology M-6 | 15 [10;30] | 15 [0;40] | 0.57 |
| | Rituximab initiation dosage | 15 [10;20] | 20 [10;60] | 0.41 |
| | Posology M+6 | 13 [10;20] | 10 [0;30] | 0.33 |
| FVC | M-6 | 62 [51;96] | 71 [44;112] | 0.55 |
| | M0 | 54 [39;93] | 64 [41;102] | 0.22 |
| | M+6 | 61 [40;99] | 60 [38;95] | 0.70 |
| DLCO | M-6 | 31 [14;68] | 37 [21;57] | 0.95 |
| | M0 | 50 [30;73] | 32 [16;41] | 0.13 |
| | M+6 | 52 [26;70] | 41 [15;49] | 0.30 |
| Infection | Respiratory infection with rituximab (%) | 1 (14) | 6 (46) | 0.15 |

Table S2 : regimen of rituximab administration in 20 patients. The injections on day 0 and day 15 are considered as a single infusion.

| Patient | Dosage at first administration: Day 0 (mg) | Dosage at second administration: Day 15 (mg) | Dosage for maintenance (mg) | Number of rituximab infusions |
|---------|---|---|-----------------------------|-------------------------------|
| 1 | 1000 | 1000 | 500 | 4 |
| 2 | 500 | 500 | 500 | 3 |
| 3 | 500 | 500 | 500 | 5 |
| 4 | 500 | 500 | 500 | 3 |
| 5 | 500 | 500 | 500 | 10 |
| 6 | 500 | 500 | 500 | 6 |
| 7 | 1000 | 1000 | 1000 | 3 |
| 8 | 500 | 500 | 500 | 2 |
| 9 | 1000 | 1000 | 500 | 4 |
| 10 | 1000 | 1000 | 500 | 3 |
| 11 | 1000 | 1000 | 500 | 6 |
| 12 | 1000 | 1000 | 500 | 2 |
| 13 | 1000 | 1000 | 500 | 3 |
| 14 | 1000 | 1000 | 500 | 3 |
| 15 | 1000 | 1000 | NA | 3 |
| 16 | 1000 | 1000 | NA | NA |
| 17 | 1000 | 1000 | NA | NA |
| 18 | 660 | 660 | 660 | 4 |
| 19 | 1000 | 1000 | 500 | 2 |
| 20 | 1000 | 1000 | 500 | 2 |