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Rituximab and Cyclophosphamide in Antisynthetase Syndrome–related Interstitial Lung Disease: An Observational Retrospective Study

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ABSTRACT. ***Objective.*** Antisynthetase syndrome (AS)-related interstitial lung disease (ILD) has a poor prognosis. Intravenous cyclophosphamide (IV CYC) and rituximab (RTX) are the main treatments currently used for moderate to severe ILD. Here, we compare the efficacy of CYC followed by standard immunosuppressive treatment (IST) versus RTX in AS-related ILD.

Methods. This observational retrospective study was conducted between 2003 and 2016 in 3 tertiary care centers. All patients with AS-related ILD and treated with CYC or RTX with at least 6 months of follow-up were included. Pulmonary progression-free survival (PFS), defined according to the American Thoracic Society guidelines, was assessed at 6 months and 2 years. All severe adverse events (AE) were recorded.

Results. Sixty-two patients were included. Thirty-four patients received 2–12 monthly IV CYC pulses, followed by standard IST in 30 cases (88%). The RTX group included 28 patients. Following the initial Day 1 to Day 15 infusions, RTX was repeated every 6 months in 26 cases (93%) and 15 patients (54%) concomitantly received another IST. The median steroid dose was similar between both groups. Although RTX and CYC demonstrated similar PFS at 6 months (92% vs 85%, respectively), RTX was superior at 2 years (HR 0.263, 95% CI 0.094–0.732, $P = 0.011$). Interestingly, lower diffusing lung capacity for carbon monoxide (DLCO) at baseline was independently predictive of poor 2-year PFS [0.965 (0.936–0.995), $P = 0.023$]. Forced vital capacity and DLCO improved in both groups without significant differences. Serious AE were similar in both groups.

Conclusion. Despite similar PFS at 6 months, RTX was associated with a better 2-year PFS compared to CYC in patients with AS-related ILD.

Key Indexing Terms: antisynthetase syndrome, cyclophosphamide, interstitial lung disease, rituximab

Antisynthetase syndrome (AS) is a heterogeneous autoimmune disease[1] characterized by the presence of inflammatory myopathy, interstitial lung disease (ILD), Raynaud phenomenon, fever, arthritis, mechanic's hands[2,3,4,5], and serum autoantibodies to anti-aminoacyl-tRNA synthetases (anti-ARS). More recent studies have reported a characteristic myopathological pattern and AS is now considered a distinct subset of inflammatory myopathy[6,7,8].

ILD has been reported in over 70% of patients with AS[1] and is the key prognostic factor in terms of morbidity and mortality[1,9,10,11,12]. Nonetheless, assessment of ILD severity at diagnosis is currently difficult[13]. Appropriate immunosuppressive therapy choice is challenging and based on the results of small retrospective studies[14,15,16,17,18,19]. To date, no prospective trial has validated any immunosuppressive treatment (IST)[20]. In Europe, intravenous (IV) cyclophosphamide (CYC) has been preferred for the treatment of severe and/or acute-onset AS-related ILD. This therapeutic strategy has been largely extrapolated from systemic sclerosis–related ILD treatment[21] and a small number of retrospective studies[14,16]. Previously, a retrospective work has reported the efficacy of anti-CD20 therapy using rituximab (RTX) both on muscle[22] and pulmonary involvement[23,24,25,26]. CYC and RTX therapy have

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never been compared with one another, either retrospectively or prospectively, to our knowledge.

We therefore performed a multicenter retrospective study comparing CYC and RTX efficacy and tolerance in AS-related ILD.

MATERIALS AND METHODS

Patients. This retrospective study was conducted in 3 university hospitals between 2003 and 2016. Recruitment of the patients was done from the database of the hospital pharmacy; in these centers registration of CYC and RTX are mandatory. Patients over 18 years were included if they presented with (1) at least 2 consecutive positive tests for anti-ARS [ELISA or multiplex immunoassay (Luminex) for Jo1 and/or line-blot assay (Euroimmun) testing for Jo1-PL7-PL12-EJ-OJ]; 2) AS-related ILD with or without other clinical manifestations of AS; (3) absence of previous treatment with CYC or RTX; and (4) 6 months of follow-up.

Patients were excluded if they (1) received both CYC and RTX at the same time (0–6 months); (2) received CYC or RTX for extrapulmonary manifestations; (3) received 6 months of follow-up after first administration of RTX or CYC; or (4) presented any confounding situations at enrollment, such as pulmonary infection or heart failure.

Treatment. We compared 2 therapeutics strategies: CYC induction followed by standard IST versus RTX induction followed by RTX every 6 months.

Ethical considerations. This study was approved by the local ethical committee and supervised by the reference center (CPP IDV VI, June 26, 2012) According to French law, patients were reported anonymously. Consent was necessary to be recorded in the center database.

Data collection. Medical records were retrospectively reviewed to collect clinical, immunological, and histological data as well as detailed medical treatments. Clinical outcomes and adverse events (AE) occurring in the 2 years following either CYC or RTX treatment were collected. Imaging data was collected at inclusion, 6 months (± 2 months), 1 year, and 2 years (± 2 months). Corticosteroids were regularly evaluated by a physician after 1 month, 3 months, and 6 months, and then every 6 months thereafter depending on the disease evolution.

Definitions. Onset of the disease was defined as the occurrence of any AS manifestation[1,2,3,4,5]. Anti-ARS–related ILD was defined as follows: (1) ILD according to international consensus[27,28,29,30,31,32] on computed tomography (CT) scan features [reviewed by an experienced radiologist at the time the CT were performed (standard of care), then blindly and retrospectively by our experienced radiologist (MLC)], and abnormal pulmonary function tests (PFT) with forced vital capacity (FVC) < 70% and/or corrected diffusing lung capacity for carbon monoxide (cDLCO) < 70%; (2) its association with 2 positive anti-ARS test; and (3) the absence of an alternative diagnosis (including infectious pneumonia or heart failure). The New York Heart Association (NYHA) Functional Classification[33] was used to categorize patient-reported function.

American Thoracic Society/European Respiratory Society classification[27,32,34] was used to identify ILD patterns, including nonspecific interstitial pneumonia (NSIP), organized pneumonia (OP), usual interstitial pneumonia (UIP), or combination of both NSIP and OP.

Similar to some prospective pulmonary trials[35], we used a composite evaluation to determine ILD course. Improvement of ILD was defined as the improvement of at least 2 of the following features: (1) clinical features (i.e., improvement in NHYA class); (2) PFT evaluation (i.e., relative FVC improvement of ≥ 10% and/or cDLCO improvement of ≥ 15%)[30,31,32]; and (3) improvement of ILD extension in the lung parenchyma on CT scan[36]. Conversely, ILD worsening was defined as worsening of at least 1 of the following features: (1) clinical features (i.e., worsening in NHYA class); (2) PFT evaluation (i.e., relative FVC decrease of ≥ 10% and/or cDLCO decrease of ≥ 15%; or (3) CT scan worsening of ILD extension score. Patients not meeting definitions of improvement or worsening were considered to be stable.

Treatment-related severe AE (SAE) was defined as all treatment-related complications leading to the patient's hospitalization or treatment discontinuation.

Endpoints. Our primary endpoint was pulmonary progression-free survival (PFS), which was defined by the absence of worsening of pulmonary involvement during the follow-up period and the absence of treatment-related SAE.

Statistical analysis. Each group was analyzed using descriptive statistics based on median, minimum, and maximum. CYC and RTX groups were compared using bivariate statistical analyses (nonparametric Mann-Whitney and paired Wilcoxon tests for continuous variables and Fisher exact tests for categorical variables). Kaplan-Meier curves were used to describe PFS in CYC and RTX groups. Bivariate and multivariate Cox models were used to compare CYC to RTX PFS. Only a 2-sided P value < 0.05 was considered significant. Analyses were performed using R statistical software (v3.3.1, R-Foundation for Statistical Computing).

The choice of adjustments was done *a priori*, from the variables that were most probably confounders (i.e., those associated with the prescription of either treatment and associated with the outcome).

RESULTS

Patient selection. Among more than 1200 inflammatory myopathies in the database, we identified 214 patients with AS. Eighty-five of these patients (40%) had been treated with CYC or RTX previously. Twenty patients were excluded because CYC or RTX had been given for extrapulmonary manifestations. Three others were also excluded due to simultaneous CYC and RTX treatment. We thus included 62 patients, 34 in the CYC group and 28 in the RTX group. Patients characteristics are described in Table 1. Year of enrollment was comparable in both groups ($P = 0.3$).

CYC group. At baseline, the median Manual Muscle Testing of Eight Muscles (MMT8) score was 77 (range 53–80; Table 1). PFT showed a median cDLCO of 32% (range 15–65) and FVC of 53% (range 29–121; Table 2). CT scan patterns were consistent with NSIP (n = 19, 56%), UIP (n = 5, 14%), OP (n = 2, 6%), and NSIP/OP (n = 8, 24%).

CYC was administered in all patients at 750 mg/m^2/month intravenously, in combination with high-dose steroids. The median number of monthly CYC infusions was 6 (range 2–12). Following this "induction" therapy period, CYC was switched to another IST in 30 (88%) patients [azathioprine (AZA; n = 14), mycophenolate mofetil (MMF; n = 12), methotrexate (n = 2), and cyclosporine/tacrolimus (n = 2)], while steroids were progressively tapered. Monthly IV immunoglobulins (IVIG) were also initially administered in 7 patients due to severe muscle involvement (Table 3).

At 6 months, PFT showed a significantly increased median FVC and median cDLCO of 53% to 62% ($P = 0.01$) and of 31.5% to 35% ($P = 0.01$), respectively. Over this period, the median MMT8 score improved to 80 (range 72–80, $P = 0.006$), and the median creatine kinase (CK) level decreased dramatically to 100 IU/L (range 24–1860, $P < 0.0001$).

After 6 months of treatment, besides this global PFT

Table 1. Patients characteristics at baseline.

	Total Cohort, N = 62	RTX, n = 28	CYC, n = 34	*P*
Demographics				
Age	54 (45–63)	54 (44–63)	54 (45–60)	0.85
Sex (M/F)	14/48	7/21	7/27	0.77
Disease duration before RTX or CYC, mos	38.5 (10.7–71.3)	46.7 (13.7–80.1)	30.2 (2–53.3)	0.12
Previous lines of treatment	2 (1–3)	2 (1–3)	1 (0–2)	0.004
Previous treatments, %		CS (96); AZA (57); IVIG (36); MTX (39); MMF (46); CSA (7); anti–TNF-α (7); CYC (43)	CTC (100); AZA (32); IVIG (9); MTX (24); MMF (24); SSZ (6); anti–TNF-α (3); RTX (3)	
Clinical features, %				
Myalgia	82	86	79	0.68
Muscle weakness	71	75	68	0.63
Arthralgia/arthritis	76	86	68	0.23
Cutaneous involvement	55	57	53	0.78
Heart involvement	10	7	12	0.76
Fever	61	64	59	0.72
Cough	87	82	91	0.55
MMT8	78 (71–80)	78 (59–80)	77 (53–80)	0.43
Immunological features, %				
Jo1	69	82	59	0.12
PL7	18	14	21	0.59
PL12	8	4	12	0.68
Ro52	53	54	53	0.97
Laboratory features				
Hb	12.4 (11.2–13.3)	12 (11–12.8)	12.6 (11.6–13.3)	0.45
CK	722 (188–1683)	735 (210–1491)	766 (340–2032)	0.85
Albumin (n = 31)	34 (31–38)	35 (33–38)	33 (31–36)	0.49
CRP	13 (3–35)	11 (0–30)	13 (8–36)	0.19

Values are median (IQR) unless otherwise specified. AZA: azathioprine; CK: creatine kinase; CRP: C-reactive protein; CS: corticosteroids; CYC: cyclophosphamide; CSA: cyclosporine; Hb: hemoglobin; IVIG: intravenous immunoglobulin; MMF: mycophenolate mofetil; MMT8: Manual Muscle Testing of Eight Muscles; MTX: methotrexate; PH: pulmonary hypertension; RTX: rituximab; SSZ: sulfasalazine; TNF-α: anti–tumor necrosis factor- α.

Table 2. Baseline ILD features.

	Total Cohort, n = 62	Rituximab, n = 28	Cyclophosphamide, n = 34	*P*
PFT				
FVC (% predicted value)	63 (45–75)	64 (54–91)	53 (43–64)	0.036
FEV1 (% predicted value)	62 (46–69)	63 (51–72)	56 (44–64)	0.18
TLC (% predicted value)	63 (47–78)	68 (52–82)	55 (44–68)	0.23
cDLCO (% predicted value)	39 (24–52)	45 (31–57)	32 (24–39)	0.01
Dyspnea (NYHA)	3	3	3	0.1
CT scan patterns, % (n)				
NSIP	66	78 (22)	56 (19)	0.13
OP	5	4 (1)	6 (2)	0.88
UIP	8	0	14 (5)	0.33
NSIP/OP	21	18 (5)	24 (8)	0.71

Values are median (Q1–Q3) unless otherwise specified. cDLCO: corrected diffusing lung capacity for carbon monoxide; CT: computed tomography; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; ILD: interstitial lung disease; NSIP: nonspecific interstitial pneumonia; NYHA: New York Heart Association; OP: organized pneumonia; PFT: pulmonary function test; TLC: total lung capacity; UIP: usual interstitial pneumonia.

improvement, 29 out of 34 patients (85%) achieved the primary endpoint of pulmonary PFS (Table 3). Four patients needed to discontinue CYC before 6 months of treatment had been completed due to ILD worsening according to our criteria: 2 patients worsened on PFT, 2 on CT scan, and 2 on NYHA dyspnea class. One additional patient developed a SAE attributed to CYC (thrombotic microangiopathy).

When considering PFT at 2 years (Figure 1), FVC and

Table 3. Patient features at follow-up.

	Rituximab	Cyclophosphamide	*P*
PFT			
FVC evolution at 6 mos (% of baseline)	+4.5 (−14, 34), n = 22	+4 (−35, 65), n = 33	0.46
cDLCO evolution at 6 mos (% of baseline)	+2 (-12, 19), n = 21	+3 (−14, 28), n = 32	0.86
FVC evolution at 1 yr (% of baseline)	+7 (−9, 30), n = 24	+4 (−19, 37), n = 19	0.18
cDLCO evolution at 1 yr (% of baseline)	+1 (−10, 21), n = 24	+4 (−12, 34), n = 17	0.61
FVC evolution at 2 yrs (% of baseline)	+7 (−12, 34), n = 16	+5 (−13, 27), n = 8	0.73
cDLCO evolution at 2 yrs (% of baseline)	+5 (−10, 57), n = 16	+3 (−4, 20), n = 9	0.78
CT scan, n			
Improvement of ILD extension	11/24	8/30	0.16
Worsening of ILD extension	1/24	8/30	0.03
Additional treatments, n			
AZA	6	14	
MTX	3	2	
MMF	5	12	
CalciNI	1	2	
IVIG	2	7	
None	13	0	
Adverse events, % (n)			
All infections	36 (10)	38 (13)	1.0
Severe infections	4 (1)	12 (4)	0.37
Death	4 (1)	3 (1)	1.0

Values are median (Q1–Q3) unless otherwise specified. AZA: azathioprine; CalciNI: calcineurin inhibitor (cyclosporine or tacrolimus); cDLCO: corrected diffusing lung capacity for carbon monoxide; CT: computed tomography; FVC: forced vital capacity; ILD: interstitial lung disease; IVIG: intravenous immunoglobulin; MTX: methotrexate; MMF: mycophenolate mofetil; PFT: pulmonary function tests.

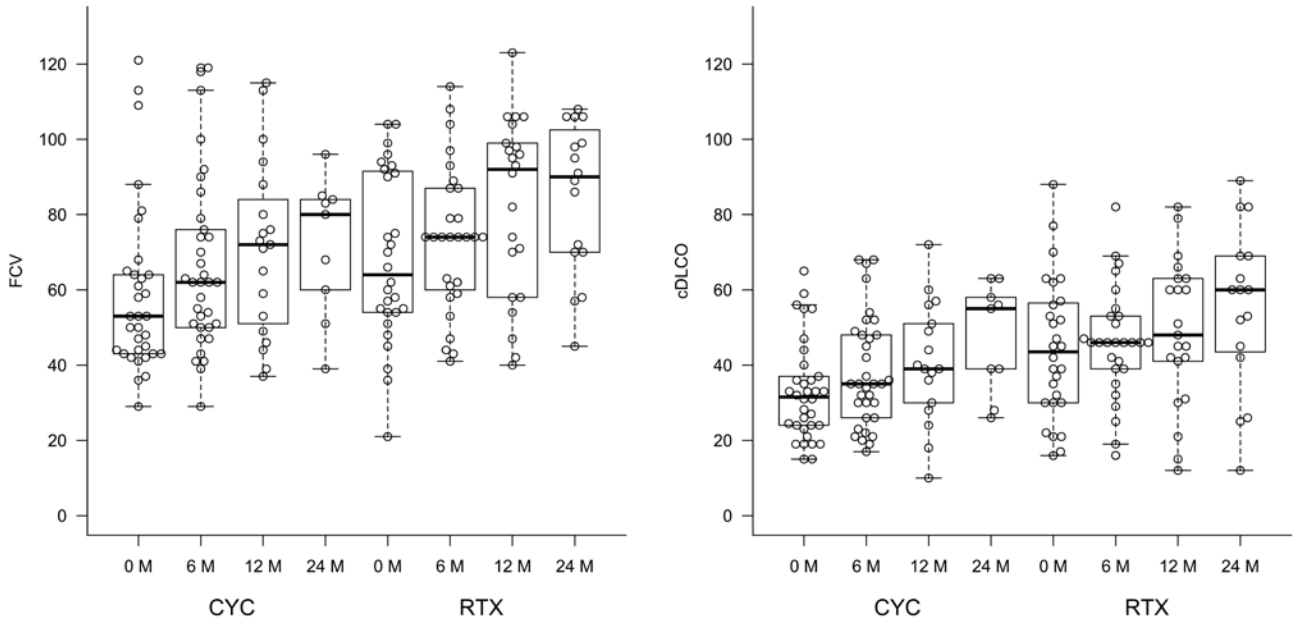

Figure 1. Similar FVC and cDLCO evolution over time in CYC and RTX groups. cDLCO: corrected diffusing lung capacity for carbon monoxide; CYC: cyclophosphamide; FVC: forced vital capacity; RTX: rituximab.

cDLCO gradually improved during the follow-up. Median FVC increased from 53% at baseline to 80%, corresponding to a nonsignificant increase of 5% (range −13% to 27%, P = 0.15). Similarly, median cDLCO nonsignificantly increased from 32% at baseline to 55% after 2 years, corresponding to a median increase of 3% after 2 years (range −4% to 20%, P = 0.31). When considering all follow-up data, 8 patients had CT scan improvement, 14 were stable, and 8 had worsened (mean follow-up = 18.4 months). Of note, 4 patients did not have a CT scan at follow-up or had a SAE that made CT scans

uninterpretable. NYHA class decreased from a median of 3 at baseline to 2 at 12 months ($P = 0.1$) and at 2 years ($P = 0.03$).

According to our definitions, 8 patients (24%) remained event-free at 2 years. Indeed, 16 patients had ILD worsening (47%): 6 according to %FVC and/or %DCLO, 8 on the basis of ILD extension on CT scan, and 3 according to NYHA class. In addition, 4 patients were censored (1 lost to follow-up and 3 patients reached the end of study in 2017) and 6 patients presented with a CYC-related SAE (18%), including 1 early thrombotic microangiopathy, infectious pneumonia (leading to death in 1 case), and 1 aseptic meningitis.

Of note, 2 extrapulmonary relapses (muscle and joints) occurred during the 2-year follow-up period.

RTX group. At baseline, median MMT8 score was 78 (range 59–80; Table 1). PFT disclosed a median cDLCO of 45% (range 17–88%) and FVC of 64% (range 21–104%; Table 2). CT scan patterns were consistent with NSIP (n = 22, 78%), OP (n = 1, 4%), and NSIP/OP (n = 5, 18%).

Two infusions of 1 g of RTX on Day 1 to Day 15 or a dose of 375 mg/m^2 once weekly for 4 weeks were administered. High-dose steroids were administered in 27 of 28 patients (96%). All patients had maintenance RTX infusions of 1 g every 6 months. The median number of maintenance RTX infusions was 3 (range 2–10). Fifteen patients (54%) also received another IST concomitantly: AZA (n = 6), MMF (n = 5), methotrexate (n = 3, and cyclosporine/tacrolimus (n = 1). Monthly IVIG was also administered initially in 2 patients (8%); 13 patients (46%) were treated with RTX and steroids only (Table 2).

The median FVC but not median cDLCO increased significantly at 6 months from 64% to 74% ($P = 0.002$) and from 45% to 46% ($P = 0.1$), respectively. Over this period, the median MMT8 score improved to 80 (range 65–80, $P = 0.015$) and the median CK level decreased to 128 IU/L (range 33–5686, $P = 0.01$). After 6 months of treatment, 25 of 28 patients (89%) achieved a primary endpoint (Table 3). ILD worsening was observed in 2 patients on CT scan only. One patient developed a SAE (acute respiratory distress syndrome).

At 2 years, FVC and cDLCO had improved during follow-up period (Figure 1). Median FVC increased significantly from 64% at baseline to 92% at 12 months and 90% after 2 years of follow-up, corresponding to a median increase of 7% at 12 months ($P = 0.0005$) and 7% after 2 years ($P = 0.008$). Although nonsignificant, median cDLCO increased from 45% at baseline to 48% at 12 months and 60% after 2 years of follow-up [(median increase of 1% at 12 months ($P = 0.4$) and 5% after 2 years ($P = 0.1$)]. Eleven patients had CT scan improvement, 12 were stable, and 1 had worsening (mean of follow-up = 17.5 mos). Four patients could not be analyzed owing to the lack of CT scan control or SAE that made CT scans uninterpretable. When considering dyspnea, NYHA decreased from a median of 3 at baseline to 1.5 at 12 months ($P = 0.001$) and 1 after 2 years of follow-up ($P = 0.003$).

Thus, at 2 years, 15 patients achieved the primary endpoint (event-free survival = 54%), whereas 3 patients had ILD worsening (11%). According to our definitions, %FVC and/or %cDCLO worsened in 1 case and chest CT scan in 2 cases, but no patients improved their NYHA class. In addition, 8 were censored (2 lost to follow-up and 6 reaching the end of study) and 2 presented with a SAE (7%) attributed to RTX, including 1 acute respiratory distress syndrome and 1 infectious pneumonia leading to patient death.

Of note, 4 extrapulmonary relapses occurred during the follow-up period [muscle (n = 2, joints (n = 2)].

Comparison of RTX versus CYC. To further compare CYC and RTX efficacy and tolerance, we performed bivariate analyses demonstrating some differences between both groups at baseline (Table 1 and Table 2). First, the CYC group seemed to display worse PFT than the RTX group at inclusion. Indeed, median FVC and cDLCO were significantly lower in the CYC group compared to the RTX group (53% vs 64%, $P = 0.04$) and 32% vs 45% ($P = 0.01$), respectively (Figure 1). Second, the RTX group seemed to have more refractory disease compared to the CYC group as reflected by the number of previous lines of immunosuppressive treatment: 2.32 ± 1.45 versus 1.35 ± 1.39 ($P = 0.004$), respectively. Of note, there were no other significant differences among the groups, including clinical, biological, and radiological features (Table 1 and Table 2).

Maintenance therapy was strictly different between groups. In the CYC group, the maintenance therapy was mainly MMF and AZA, while in the RTX group all patients had RTX as maintenance therapy. Therefore, groups were not comparable for the maintenance therapy and no adjustment could be made. The comparison is mainly about RTX as attack treatment followed by RTX as maintenance therapy, versus CYC as attack treatment followed by MMF or AZA as maintenance therapy. The unadjusted difference of PFS between CYC + MMF versus CYC + AZA adjusted on the treatment line was not significant (HR 0.89, 95% CI 0.31–2.59, $P = 0.84$), but the actual statistical precision was very low, with only 8 events in the CYC + AZA group and 6 events in the MMF group.

Steroid tapering did not differ between groups as doses were similar between groups at 6 months [RTX 10 mg (range 8–17.5) vs CYC 10 mg (range 8–15), $P = 0.59$] and 1 year [RTX 5 mg (range 0–6) vs CYC 5 mg (0–8), $P = 0.79$]. Bivariate Cox analyses demonstrated a better pulmonary PFS in the RTX group compared to the CYC group after 2 years of follow-up (unadjusted HR 0.223, 95% CI 0.084–0.59, $P = 0.003$). A multivariate Cox model adjusted for cDLCO and the previous lines of treatment was subsequently performed to overcome baseline differences observed between both groups. At 2 years of follow-up, the RTX strategy appears to be a protective factor (adjusted HR 0.263, 95% CI 0.094–0.732, $P = 0.011$). After additional adjustment for the date of treatment initiation, the HR was estimated at 0.248 (95% CI 0.089–0.691, $P = 0.008$). Further, baseline cDLCO was significantly associated with pulmonary PFS at 2 years (adjusted HR 0.964, 95% CI 0.935–0.994, $P = 0.019$). Previous immunosuppressive lines had a nonsignificant

association with pulmonary PFS at 2 years (adjusted HR 1.226, 95% CI 0.553–2.718, $P = 0.62$; Table 4).

In order to take into account the effect of losses to follow-up, we performed a maximum bias analysis, assuming that losses to follow-up in the CYC group are all event-free at 2 years, while losses to follow-up in the RTX group have an event at the date of loss to follow-up. In the model adjusted for DLCO and treatment line, the effect of RTX is still significant (HR 0.369, 95% CI 0.148–0.917, $P = 0.032$).

Proportional hazards assumption might not be met according to a proportional hazards chi-square test on Schoenfield residuals ($P = 0.09$). Yet, as there was no obvious inversion of hazards, Cox models were kept. Kaplan-Meier survival analyses confirmed these results (Figure 2).

DISCUSSION

ILD is the key prognostic factor in AS[1,9,11,12,37]. In this study, we describe the largest cohort of patients with AS-related ILD treated with CYC or RTX. Our cohort shares similar characteristics than other reported cohorts[7,9]. However, due to the retrospective nature of our work, recruitment and evaluation bias may have occurred. Of note, the medication dosages were unusually and fairly uniform — this is usually a bias in cohort treatment studies — and a strong quality indicator of this study despite being observational. Although patients displayed similar clinical and immunological features in both groups at baseline, we acknowledge that patients in the CYC group presented with more severe ILD, with lower cDLCO and FVC compared to the RTX group. This could reflect the physician's preference to use CYC in severe and/or rapidly progressive ILD. Moreover, RTX therapy has shown its efficacy only recently in AS, and is mostly given as second-line treatment. The lack of standardized treatment algorithms also could affect therapeutic efficacy, yet patients in the RTX group presented a more refractory disease course than patients from the CYC group. Nonetheless, despite these slight differences, we observed a similar evolution of PFT in both groups after 2 years, when considering FVC and cDLCO as quantitative variables.

Moreover, PFT that are crucial criteria in idiopathic pulmonary fibrosis[32] could be influenced by respiratory muscle involvement; improvement of muscle involvement could lead to increased FVC, while ILD may worsen. Similarly, analyzing CT scans could be distorted in the case of AE, such as pneumonia or heart failure, regarding both the fibrosing and the extension scores of ILD. Evaluation based solely on PFT or CT scan features may thus lead to misinterpretation. Finally, NYHA class is a categorical classification score that is not sensitive enough to change over time to be the sole variable for describing patients' outcomes, and does not only evaluate dyspnea but also relates to symptoms including fatigue, muscle weakness, or other cofounding variables. One of our limitations was the absence of a validated dyspnea scale. They were not performed routinely and were not available for our patients; a control prospective study should include it.

cDLCO, which is the PFT variable less likely to influenced by muscle involvement, was a good predictive factor in our multivariate analyses: the higher the cDLCO is at inclusion, the better the 2-year pulmonary PFS. However, we did not show any significant variation between the 2 groups on the basis of PFT variables. Thus, combining different variables in a global and composite index such as pulmonary PFS seemed to be the more relevant choice.

Few studies have specifically evaluated the efficacy of CYC in patients with inflammatory myopathy–related ILD. In these small series[14,15,16,17,18,19], population and assessment criteria were often heterogeneous. Marie, *et al*[16] showed an improvement of ILD in 16 of 25 patients (64%), and Yamasaki, *et al*[14] reported an improvement in 13 of 17 patients (75%). Herein, we observed similar results with a 6-month pulmonary PFS of 82% in the CYC group, persisting in only 24% after 2 years (including censored patients). Six SAE occurred in this group over the study period, most of them (5 of 6) occurring in the CYC therapy period (during the first 6 months) rather than during later use of another IST. These results suggested that the strategy of administering CYC followed by standard IST allows good short-term results despite low early tolerance.

As a whole, RTX has shown its efficacy in inflammatory myopathies, with over 78% of responses[38]. Until now, RTX use in anti-ARS–related ILD is still rather rare. Two recent retrospective studies suggested, however, the efficacy of RTX in anti-ARS–related ILD in terms of both PFT and CT scan improvement[24,39]. Nevertheless, a 25% mortality rate was reported[24]. With mortality being mainly due to severe infections, this suggests caution in patients sometimes treated with previous immunosuppressive drugs. In a prospective study from our group[23], we reported an improvement of the FVC value in 50% of patients with refractory AS-related ILD. In the current study, we confirmed the efficacy of RTX as an induction therapy with a 92% pulmonary PFS at 6 months. Moreover, at 2 years, 15 patients (54%) were still free of pulmonary progression

Table 4. Bivariate and multivariate analyses at 2 years.

	Bivariate HR (95% CI)	*P*	Multivariate HR (95% CI)	*P*
Rituximab	0.223 (0.084–0.59)	0.003	0.263 (0.094–0.732)	0.011
cDLCO baseline, %	0.958 (0.93–0.986)	0.004	0.964 (0.935–0.994)	0.019
Previous no. IST at baseline ≥ 2	0.814 (0.381–1.74)	0.60	1.226 (0.553–2.718)	0.62

cDLCO: corrected diffusing lung capacity for carbon monoxide; IST: immunosuppressive treatment.

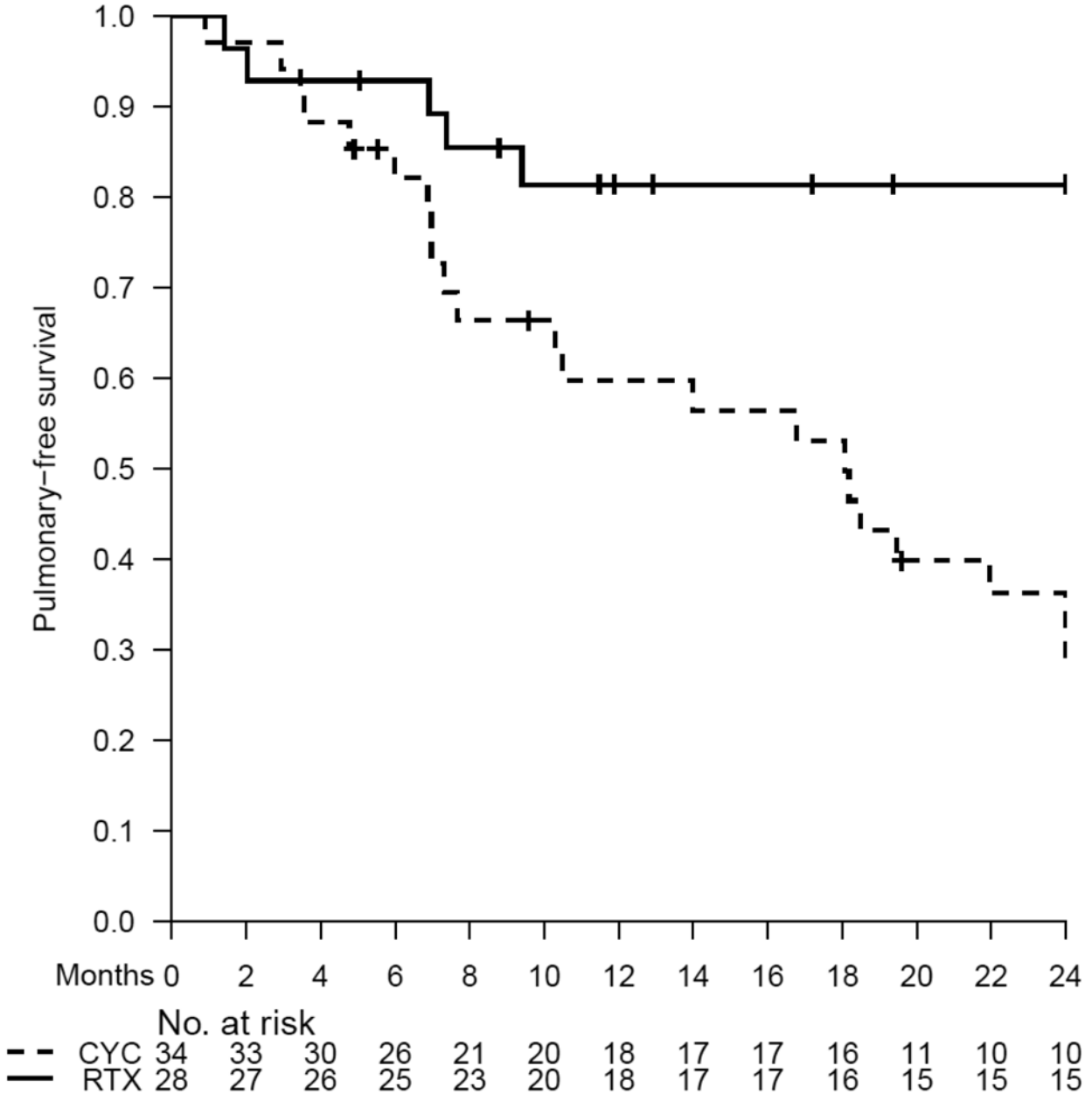

Figure 2. Pulmonary progression-free survival curves after 2 years of follow-up. CYC: cyclophosphamide; RTX: rituximab.

(including the patients lost to follow-up). Only 2 patients experienced a SAE in this group, which is fewer than reported in other cohorts[23]. Our result demonstrated that RTX has a good efficacy profile and is well tolerated, despite being used in a subset of refractory patients.

To the best of our knowledge, no study has compared the efficacy and tolerance of long-term RTX and CYC strategies in anti-ARS–related ILD. Both PFS (93% and 82%, respectively) were comparable during the first 6 months of treatment. Importantly, and despite similar improvement of PFT, the CYC and RTX survival curves dramatically and significantly separated after 6 months of treatment. In light of the multivariate analyses, RTX treatment appears to be a clear protective factor regarding ILD progression. When comparing pulmonary PFS using bivariate and multivariate Cox models, we were able to show a better 2-year pulmonary PFS in the RTX group as compared to the CYC group. We noticed that this difference was observed from the time of IST introduction, following the CYC. Our data thus confirmed the interest of RTX in AS-related ILD and identified 2 distinct phases in the treatment of patients with anti-ARS–related ILD. First, the induction phase was comparable between RTX and CYC treatment. Second, the maintenance phase (after 6 months of follow-up) was clearly in favour of RTX compared to CYC followed by IST. Of note, there was no difference between patients with low doses of steroids plus RTX alone (13 of 28 patients) versus RTX combined with

another IST (15 of 28 patients). This difference was persistent in 15 patients for which follow-up was greater than 2 years (data not shown). Possible explanations might be a lower efficacy of IST compared to repeated RTX infusions, which has not been shown for any standard IST to date,[16,17,18] or a lower compliance to standard IST as compared to RTX infusions, which are given intravenously[40].

Considering 2 distinct phases, our data clearly support both the use of CYC or RTX as induction therapy, and clearly showed the superiority of RTX as maintenance therapy. Prospective trials are needed to confirm these results and to find the best in new treatment strategies.

RTX and CYC demonstrated similar efficacy as induction therapy at 6 months in refractory AS-related ILD. Promisingly, RTX appeared to be more effective than the other IST as maintenance therapy (after 6 months).

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