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Intravenous cyclophosphamide improves functional outcomes in interstitial lung disease related to idiopathic inflammatory myopathies

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ABSTRACT

Objective: To compare the efficacy, toxicity and glucocorticoid (GC)-sparing effects of intravenous cyclophosphamide (iv CYC) with other immunosuppressive regimes as the induction treatment for Idiopathic Inflammatory Myopathy-Related Interstitial Lung Disease (IIM-ILD).
Methods: Observational comparative study of patients with IIM-ILD from the EPIMAR and Cruces cohorts. The main efficacy outcome was a 6 to 12-month improvement >10% in the forced vital capacity (FVC) from baseline.
Results: Overall, 47 patients were included: 22 (47%) in the CYC group and 25 (53%) in the non-CYC group (32% azathioprine, 28% GC alone, 20% mycophenolate, 16% calcineurin-inhibitors and methotrexate and 4% rituximab). 81% patients were female with a mean age of 50.4 years. FVC improvement was achieved by 64% patients in the CYC group vs. 32% in the non-CYC group ($p = 0.03$). In the logistic regression model, CYC was identified as the only independent predictor of FVC improvement (OR=3.97, 95% CI 1.07–14.75). Patients in the CYC group received more methyl-prednisolone pulses (MP) (59% vs. 28% in the non-CYC group, $p = 0.03$), less initial GCs doses >30 mg/d (19% vs. 77%, $p = 0.001$) and lower 6-month average doses of prednisone (11 mg/d vs. 31.1 mg/d, $p = 0.001$).
Conclusion: iv CYC showed better functional outcomes than other immunosuppressants in IIM-ILD. The additional use of MP is likely to potentiate the effects of CYC and allows lowering prednisone doses. Therefore, CYC in combination with MP could be considered as the first line induction therapy in IIM-ILD, without limiting its use to rapidly progressive, life-threatening or refractory disease.

Introduction

Idiopathic inflammatory myopathies (IIM) are a group of autoimmune diseases in which muscle injury is the main feature[1]. However, their manifestations may also include skin disease, arthritis, Raynaud's phenomenon or systemic symptoms, and they may even

Abbreviations: ANAs, Antinuclear antibodies.; AZA, Azathioprine.; CNI, Calcineurin inhibitors.; COPD, Chronic obstructive pulmonary disease.; CYC, Cyclophosphamide.; DLCO, Carbon monoxide diffusing capacity.; FVC, Forced vital capacity.; GCs, Glucocorticoids.; HF, Heart failure.; HRCT, High-resolution computed tomography; IIM, Idiopathic inflammatory myopathies.; ILD, Interstitial lung disease.; MMF, Mycophenolate.; MP, Methylprednisolone pulses.; OP, Organizing pneumonia.; PASP, Pulmonary artery systolic pressure.; PH, Pulmonary hypertension.; RTX, Rituximab.; SD, Standard deviation.; UIP, Usual interstitial pneumonia.

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present as amyopathic forms[2]. Interstitial lung disease (ILD) is the most frequent and most severe extramuscular complication of IIM, particularly in some subsets such as anti-synthetase[3–5]. The reported prevalence of pulmonary involvement in IIM ranges from 20–80%, with an overall mortality rate of 27%[6]. Despite these figures, treatment of IIM-related ILD (IIM-ILD) is not well defined. Recommendations are based on retrospective studies or case reports, and include first-line agents like glucocorticoids (GCs) alone or in combination with azathioprine (AZA), mycophenolate (MMF) or calcineurin inhibitors (CNI). Cyclophosphamide (CYC) and rituximab (RTX) are usually considered in the setting of life-threatening or refractory cases[7–9].

CYC is an alkylating agent widely used for severe manifestations of autoimmune diseases such as lupus nephritis or ANCA-associated vasculitis[10–12]. Despite its proven efficacy in this scenario of severe organic flares, studies supporting the use of CYC in systemic autoimmune diseases-related ILD are scarce. Only in patients with ILD due to scleroderma has CYC proved to improve lung function[13,14]. Given the lack of solid evidence supporting any specific immunosuppressive approach for IIM-ILD[15–21], CYC has been one of the agents used in patients from both cohorts. The aim of this study was to compare the efficacy, toxicity and GC-sparing effects of CYC with other immunosuppressive regimes as the induction treatment for IIM-ILD.

Materials and methods

Population and study protocol

This is an observational and multi-center cohort study analyzing patients with IIM-ILD during a follow-up period of 6 to 12 months from the beginning of induction treatment. The study involved centers from Argentina and Uruguay (EPIMAR cohort) and Spain (Cruces cohort). Patients were included between January 2015 and June 2019. In the EPIMAR cohort, patients over 18 years on active follow-up with ILD secondary to systemic sclerosis, Sjögren's syndrome, rheumatoid arthritis or IIM were recruited. ILD was defined as the presence of lung opacities suggestive of interstitial injury (irregular inter and/or intralobular septal thickening, traction bronchiectasis, cyst images, ground glass, honey combing) in a high-resolution computed tomography (HRCT) with slices no thicker than 2 mm[22]. For this study, we selected those patients in the EPIMAR cohort with a diagnosis of IIM. Patients with IIM and ILD fulfilling the same entry criteria were selected from the observational IIM cohort of the Autoimmune Diseases Research Unit, Hospital Universitario Cruces, Barakaldo, Spain.

Dermatomyositis and polymyositis were defined following the Bohan and Peter criteria; anti-synthetase syndrome was considered in the setting of ILD and the presence of the homonymous antibodies by line-blot assay (anti-Jo1, anti-PL7, anti-PL12 and/or EJ)[1,23]. All HRCT scans were evaluated by board-certified radiologists with a focus in thoracic imaging. The tomographic patterns were classified as nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP) or combined NSIP/OP pattern[22]. Patients with IIM and no respiratory symptoms in whom a HRCT scan disclosed an ILD during the diagnostic workout were included in the study and categorized as sub-clinical ILD.

All patients with IIM and ILD from both cohorts were included in the study, with the exception of those with anti-MDA5 dermatomyositis or those who presented with a usual interstitial pneumonia (UIP) pattern, given the different natural course and therapy of these conditions[1,2,6,19,24].

The EPIMAR protocol was approved by the Institutional review board for the Review of Research Studies of the Teaching and Research Department of the Hospital Privado de Comunidad and the Central Ethics Committee of the Province of Buenos Aires (File: 2919/1372/2016). Patients from Hospital Universitario Cruces were enrolled in the longitudinal IIM cohort study approved by the Ethics and Clinical Research Committee of the Basque Country (code PI2016107). All participants provided a signed informed consent.

Clinical and therapeutic variables

The following baseline variables were included: date of diagnosis of IIM; date of diagnosis and date of first therapy of ILD; demographic characteristics (gender, age at the beginning of symptoms of ILD); previous or active smoking; comorbidities, such as heart failure (HF) according to the Framingham criteria[25] or echocardiogram, asthma according to the GINA guidelines[26], chronic obstructive pulmonary disease (COPD) according to the GOLD guidelines[27]. In addition, a baseline 6-minute walk test was registered, where a desaturation of at least 5% was considered positive. For the purposes of this study, the following immunological data were extracted: antinuclear antibodies (ANAs), anti-Ro/SSa, anti-La/SSb, anti-U_1RNP and anti-synthetase antibodies. ANAs were considered positive according to the serological criteria proposed in the IPAF consensus 2015 ERS/ATS[22].

Induction treatment was initiated in the presence of symptoms, worsening lung function tests and/or active disease on HRCT scan and decided by the attending physicians according to the specific protocols of each participating site. Treatments received within the first six months after the diagnosis of ILD were recorded in a dichotomous (yes/no) fashion: GCs, CYC, AZA, MMF, MTX, CNI and RTX. All patients treated with CYC received a modified Eurolupus Nephritis regime, that is, they were given 6 fortnightly doses of 500 mg of iv CYC, which could be extended in case of insufficient response[11]. Regarding GC use, the initial dose of prednisone was classified in low-doses (<7.5 mg/d), medium-doses (7.5-30 mg/d) and high-doses (>30 mg/d)[28,29]. The average daily dose of prednisone within the first 6 months was calculated. Intravenous methylprednisolone pulses (MP), defined as >100 mg/d during 3–5 consecutive days, was considered a separated therapeutic option and the dose of MP was not added in the calculation of the cumulative prednisone dose, given the preferential activation of the non-genomic way by pulse therapy with a minimum impact on GC-related toxicity[28–30].

The variable "time to treatment" was defined as the number of months from the onset of symptoms of ILD (dyspnea, cough) to the initiation of immunosuppressive treatment. In case of sub-clinical disease, this variable was considered as the number of months from the diagnosis of ILD to treatment.

All patients had lung function tests, including forced vital capacity (FVC) +/- carbon monoxide diffusing capacity (DLCO), done at baseline (the time of starting treatment) and 6 to 12 months afterwards (after therapy). The study was carried out by qualified technicians or pneumologists and the best FVC value obtained was considered. FVC was expressed as a percentage of the theoretical value. NHANES III equation was used to calculate the predicted values[31]. DLCO was obtained with the single-breath technique. Differences between baseline and after therapy FVC and DLCO were calculated.

Outcomes

The main outcome was the improvement of FVC after therapy compared with baseline values, defined as an increase >10% using the American Thoracic Society criteria for idiopathic pulmonary fibrosis evaluation[22]. The secondary outcomes were FVC stability (all changes of FVC <10%), FVC worsening (decline of FVC >10% respect to baseline), DLCO improvement (increase of DLCO >15% respect to baseline), DLCO stability (all changes of DLCO <15%), DLCO worsening (decline of DLCO >15% respect to baseline). Severe infections were defined as those threatening life or requiring hospital admission. Death for any cause during the follow-up period was also included as a secondary outcome.

Statistical analysis

We compared the outcomes of patients divided in two groups: those receiving therapy with CYC (labeled as CYC group) and those receiving

other regimes not containing CYC (non-CYC group).

For the descriptive analysis, quantitative variables were summarized as mean and standard deviation (SD) or as median and range, as appropriate; qualitative variables were expressed as frequency and percentage. Differences between groups were tested using Chi-Square or Fisher's exact tests in the case of categorical variables and Student T test or Mann-Whitney U test in the case of continuous variables, as needed. In the univariate analysis, baseline characteristics, immunological profile, ILD clinical manifestations, characteristics and radiological pattern and treatments were compared between patients with and without FVC improvement.

A binary logistic regression analysis, including variables with marginal significance ($p<0.2$) in the univariate analysis, was performed to determine the factors independently related to FVC improvement. The final model included all predictors with a 95% confidence interval (95% CI) of the odds ratio (OR) not including 1. For all analyses, significance was defined as a P value of less than 0.05. Statistical analysis was performed using SPSS software.

Results

Study population

Among the 170 patients included in the EPIMAR and Cruces cohorts, the 47 patients with IIM-ILD fulfilled the study entry criteria: 22 (47%) in the CYC group and 25 (53%) in the non-CYC group. Among the latter, 32% received AZA, 28% GC alone, 20% MMF, 16% CNI or MTX and 4% RTX.

Table 1 summarizes the baseline clinical characteristics in the two study groups. Overall, 81% patients were female and the mean age at ILD diagnosis was 50.4 years. Regarding the immunological profiles, 53% of the patients presented ANA, 49% anti-Ro antibodies and 66% anti-synthetase antibodies. The mean time from IIM to ILD diagnosis was 14.6 months. NSIP was the most frequent radiological pattern (60%). The mean baseline FVC and DLCO were 66.6% and 57.9%, respectively. Desaturation ≥5% during a 6-minute walk test was identified in 21 patients (45%). No significant differences in the baseline variables, including gender, age, disease duration, comorbidities, immunological profiles, functional status and radiological patterns, were found between the CYC and non-CYC groups.

GC treatment

The differences in GC therapy between groups are shown on Table 2. GC were used in all patients, however, patients in the CYC group were treated more frequently with medium prednisone initial doses than patients in the non-CYC group (64% vs. 16%, respectively, $p<0.001$); on the contrary, high doses were used less frequently in the CYC group (18% vs. 80% in the non-CYC group, $p = 0.001$). Thus, the resulting 6-month average dose of prednisone was lower among patients in the CYC group (11 mg/d vs. 31.1 mg/d in the non-CYC group, $p = 0.001$). Patients in the CYC group received MP more frequently (59% vs. 28% in the non-CYC group, $p = 0.03$).

Outcomes

The main outcome (FVC improvement >10% from baseline) was achieved by 47% of the whole cohort, with significant differences between groups (64% in the CYC group vs. 32% in the non-CYC group, $p = 0.03$), (Table 3). If we further divide patients in the CYC group between those receiving and not receiving concomitant MP, a gradient in the response rates can be seen: 8/25 (32%) non-CYC patients vs. 5/9 (56%) CYC alone patients vs. 9/13 (69%) CYC-MP patients (p for trend=0.078). This possible synergistic effect of MP combined with CYC was not observed in patients receiving other immunosuppressive drugs after MP, with only 2/7 (29%) of such patients improving their FVC after therapy.

None of the patients in the CYC group experienced worsening in the FVC, vs. 24% patients in the non-CYC group ($p = 0.021$). No significant differences were found regarding changes in DLCO. Likewise, no differences were found in the occurrence of severe infections or death between both groups (Table 3).

The association of the main outcome with demographic, clinical, immunological and therapeutic variables was assessed in order to identify independent predictors of response and to evaluate the

Table 1
Patients characteristics according to treatment group.

	Global (n = 47)	CYC (n = 22)	Non-CYC (n = 25)	p-value
Baseline characteristics				
Female n	38 (81)	17 (77)	21 (84)	0.422
Age at ILD diagnosis (years) mean (SD)	50.4 (13.7)	52.5 (10.4)	48.7 (15.9)	0.321
Time from IIM to ILD diagnosis (months) mean (SD)	14.6 (36.1)	8.4(18)	19.5 (45.7)	0.299
Time from symptom onset to treatment (months) mean (SD)	10.6 (13.8)	10.7(14)	10.5 (13.8)	0.978
Present or past tobacco use n (%)	18 (38%)	9 (41%)	9 (36%)	0.391
COPD n (%)	0	0	0	–
Asthma n (%)	4 (9%)	2 (9%)	2 (8%)	0.610
Heart failure n (%)	5 (11%)	2 (9%)	3 (12%)	0.603
Immunological profile				
Antinuclear antibodies n (%)	25 (53%)	9 (41%)	16 (64%)	0.163
Anti-Ro n (%)	23 (49%)	11 (50%)	12 (48%)	0.448
Anti-synthetase antibodies n (%)	31 (66%)	14 (64%)	17 (68%)	0.422
Anti-RNP antibodies n (%)	1 (2%)	0	1 (4%)	0.553
ILD clinical manifestations and characteristics				
Subtle ILD n (%)	2 (4%)	1 (5%)	1 (4%)	0.699
Desaturation ≥5% during the 6-Minute Walk test n (%)	21 (45%)	9 (41%)	12 (48%)	0.528
Baseline FVC (%) mean (SD)	66.6 (16.4)	68 (17.5)	65.5 (15.8)	0.618
FVC <70% n (%)	26 (55%)	10 (45%)	16 (64%)	0.202
Baseline DLCO (%) mean (SD)	57.9 (21.3)	56.1 (23.1)	59.7 (19.7)	0.608
ILD Radiological pattern				
NSIP n (%)	28 (60%)	17 (77%)	11 (44%)	0.053
OP n (%)	8 (17%)	1 (5%)	7 (28%)	0.699
Others/Overlap n (%)	11 (23%)	3 (14%)	8 (33%)	0.138

CYC: Cyclophosphamide, ILD: Interstitial lung disease, SD: Standard deviation, IIM: Idiopathic inflammatory myopathy, COPD: Chronic obstructive pulmonary disease, FVC: Forced vital capacity, DLCO: Diffusion capacity of the lungs test, NSIP: Non-specific interstitial pneumonia, OP: Organizing pneumonia.

Table 2
Glucocorticoid treatment according to treatment group.

	Global (n = 47)	CYC (n = 22)	Other IS scheme (n = 25)	p-value
Initial prednisone dose				
<7.5 mg/d n (%)	5 (11%)	3 (14%)	2 (8%)	0.397
7.5-30 mg/d n (%)	18 (38%)	14 (64%)	4 (16%)	**<0.001**
>30 mg/d n (%)	24 (51%)	4 (18%)	20 (80%)	**<0.001**
6-month average dose of prednisone (mg/d) mean (SD)	22(22)	11(10)	31.1(25)	**0.001**
MP n (%)	20 (43%)	13 (59%)	7 (28%)	**0.03**

CYC: Cyclophosphamide IS: Immunosuppressant, SD: Standard deviation, MP: Methyl-prednisolone pulses.

Table 3
Outcomes according to treatment group.

	Global (n = 47)	CYC (n = 22)	Other IS scheme (n = 25)	p-value
FVC difference from baseline mean (SD)	8.4 (13.5)	11.9 (11.5)	5.6 (14.5)	0.120
FVC improvement/stability/worsening n (%)				
>10% FVC improvement	22 (47%)	14 (64%)	8 (32%)	**0.03**
FVC stability	18 (38%)	8 (36%)	11 (44%)	0.595
>10% FVC worsening	6 (13%)	0	6 (24%)	**0.021**
DLCO difference from baseline mean (SD)	3.2 (13.6)	3.5 (11.8)	3.1(15)	0.940
DLCO improvement/stability/worsening n (%)				
>15% DLCO improvement	8 (17%)	3 (14%)	5 (20%)	0.562
DLCO stability	16 (34%)	7 (32%)	9 (36%)	0.763
>15% DLCO worsening	6 (13%)	2 (9%)	4 (16%)	0.479
Major infections n (%)	4 (8.5%)	2 (9%)	2 (8%)	0.894
Deaths n (%)	0	0	0	–

CYC: Cyclophosphamide, IS: Immunosuppressant, FVC: Forced vital capacity, SD: Standard deviation, DLCO: Diffusion capacity of the lungs test.

independent role of CYC. In the univariate analysis, the main outcome had a positive association with CYC and a negative association with the average dose of prednisone (Table 4). These variables, as well as female gender and the positivity for anti-synthetase antibodies, were included as independent variables in the logistic regression model (Table 5). In the final model, CYC treatment was identified as the only independent predictor of FVC improvement (OR=3.97, 95% CI 1.07–14.75),

Discussion

This study shows that treatment with iv CYC of patients IIM-ILD results in a larger improvement of functional lung tests compared to other immunosuppressive regimes (including AZA, MMF, CNI and GCs monotherapy). In addition, our results confirm that high doses of GCs are no necessary to achieve such functional improvement, and also support that the addition of MP to the CYC regime further improves the response rates.

Most studies focused on the role of CYC in ILD secondary to systemic autoimmune diseases have been performed in patients with systemic sclerosis. Therefore, solid data on the effects of CYC in IIM-ILD are scarce [33]. Most authors have restricted the use of CYC to refractory, relapsing, severe or rapidly progressive forms of ILD, usually after the failure of GCs in monotherapy, AZA or MMF[15,16,18,20,21,32-34].

A systematic review published in 2015 showed that a significant improvement >10% in FVC and DLCO was seen in 57.6% and 64.3% of patients, respectively, after treatment with iv CYC[34]. A more recent meta-analysis by Barba *et Al.* showed that 56.4% patients with chronic IIM-ILD treated with CYC improved the FVC, vs. 89.2% patients receiving GCs monotherapy[35], however, the 3-month survival rate for rapidly-progressive-ILD was 72.4% in CYC-treated patients, compared with 51.7% treated with GCs alone. In addition, Mira-Avendano *et al.* did not find differences regarding clinical (severity of dyspnea) and functional outcomes (changes in FVC) after comparing oral CYC, AZA and MMF in GC-resistant patients[36].

In our study, iv CYC treatment resulted in an average 12% improvement of FVC from baseline. A clinically significant FVC improvement >10% was accomplished in 63.6% of patients, vs 32% of patients treated with other immunosuppressive regimes. Indeed, the multivariate analysis identified CYC as the only independent factor related to the main outcome of our study, a FVC improvement >10%.

A number of circumstances may explain the apparent disparity between our results and those previously discussed. We did not include patients with anti-MDA5-positive myositis, which is typically a life-threating disease in which CYC use is encouraged[1,19]. Likewise, we excluded patients with UIP pattern, with a natural course less likely to be influenced by immunosuppressive therapy[1,2,6]. In previous studies, most patients given CYC had severe disease refractory to other treatment

Table 4
Differences between patients with FVC improvement and those without.

	FVC improvement Yes (n = 22)	No (n = 25)	p-value
Baseline variables			
Gender (female) n	16 (73)	22 (88)	0.170
Age at ILD diagnosis (years) mean (SD)	51.8 (12.4)	49.2 (14.9)	0.521
Time from IIM to ILD diagnosis (years) mean (SD)	17.5 (45.3)	12 (26.3)	0.611
Present or past tobacco consumption n (%)	10 (45%)	8 (32%)	0.259
COPD n (%)	0	0	–
Asthma n (%)	2 (9%)	2 (8%)	0.645
Heart failure n (%)	3 (14%)	2 (8%)	0.438
Immunological profile			
Antinuclear antibodies n (%)	11 (50%)	14 (56%)	0.453
Anti-Ro n (%)	10 (45%)	13 (52%)	0.438
Anti-synthetase antibodies n (%)	12 (55%)	19 (76%)	0.064
Anti-RNP antibodies n (%)	0	1 (4%)	0.532
Anti-centromere antibodies n (%)	0	1 (4%)	0.532
Anti-ScL-70 antibodies n (%)	1 (5%)	0	0.478
ILD clinical manifestations and characteristics			
Subtle ILD n (%)	1 (5%)	1 (4%)	0.722
Desaturation ≥5% during the 6-Minute Walk test n (%)	11 (50%)	10 (40%)	0.347
Baseline FVC mean (SD)	64.9 (14.7)	68.1 (18%)	0.514
FVC <70% n (%)	13 (59%)	13 (52%)	0.485
Baseline DLCO mean (SD)	58.6 (24.5)	57.1 (18.1)	0.830
ILD Radiological pattern			
NSIP n (%)	14 (64%)	14 (56%)	0.283
OP n (%)	4 (18%)	4 (16%)	0.843
Others/Overlap n (%)	4 (18%)	7 (28%)	0.428
Treatment			
Time from symptom onset to treatment (months) mean (SD)	9.8 (15.4)	11.3 (12.4)	0.727
Initial prednisone dose			
<7.5 mg/d n (%)	2 (9%)	3 (12%)	0.562
7.5-30 mg/d n (%)	12 (55%)	6 (24%)	0.06
>30 mg/d n (%)	8 (36%)	16 (64%)	0.06
6-months average dose of prednisone (mg/d) mean (SD)	14.5 (14.7)	29.4 (25.5)	**0.023**
MP n (%)	11 (50%)	9 (36%)	0.386
CYC n (%)	14 (64%)	8 (32%)	**0.03**

ILD: Interstitial lung disease, SD: Standard deviation, IIM: Idiopathic Inflammatory myopathy, COPD: Chronic obstructive pulmonary disease, FVC: Forced vital capacity, DLCO: Diffusion capacity of the lungs test, NSIP: Non-specific interstitial pneumonia, OP: Organizing pneumonia. MP: Methylprednisolone pulses. CYC: Cyclophosphamide.

Table 5
Logistic regression analysis of factors related to FVC improvement.

	Initial model OR	95% CI	Final model OR	95% CI
Female	1.56	0.29–8.45		
Anti-synthetase antibodies	2.63	0.59–11.61		
6-month average dose of prednisone	0.98	0.94–1.03		
CYC	2.06	0.47–9.01	3.97	1.07–14.75

CYC: Cyclophosphamide, OR: Odds ratio, CI: Confidence interval.

schemes[15,16,18-21,33,36]. By contrast, GCs in monotherapy were usually given to patients with OP and/or mild forms of disease[7,9,33]. Therefore, there may be a bias towards worse outcomes in patients treated with CYC. Thus, our study offers a real-life view of patients with non-UIP and non-MDA5-positive IIM-ILD treated with a variety of first-line immunosuppressive therapies. In this scenario, iv CYC was associated with clearly superior outcomes. In line with our results, Yamasaki et al. identified that prompt CYC treatment was a predictor of treatment response in naive patients[20]. Therefore, the earlier the better for starting therapy with CYC, which should be best used as a first line agent.

Another important point of our study refers to the use of prednisone and MP. Unlike the results from Barba *et al.*, most authors have shown that up to 87% of ILD-IIM are refractory to GC monotherapy[2,7,9,33,36]. In any scenario, the mean dose of prednisone usually exceeds 30 mg/d during the initial 6 months of therapy, both in schemes with and without steroid-sparing agents. At these doses and duration of therapy, GCs secondary effects are of major concern[37,38]. Our results point to a significant reduction of prednisone doses among patients treated with CYC, most of whom also received MP. Moreover, our data strongly suggest that MP potentiates the effects of CYC on IIM-ILD.

Indeed, the combination CYC-MP has been extensively used in patients from the Lupus-Cruces cohort[39,40]. The rationale for this is the activation of the non-genomic pathway with the repeated administration of MP, enhancing the anti-inflammatory GC activity during induction treatment and, at the same time, allowing a rapid reduction of oral prednisone doses[39]. In patients with lupus nephritis, a modified Eurolupus Nephritis regime with repeated bi-weekly MP combined with CYC after the three initial MP pulses have resulted in high complete response rates over 80% with reduced oral prednisone doses and, hence, almost null GC toxicity[39,41]. The results of this study support the efficacy of such a regime also in patients with IIM-ILD.

Some limitations have to be considered. This is a relatively small, observational, non-randomized study. However, the two groups compared did not present any baseline, clinical, immunological or radiological difference, allowing a more robust comparison of CYC efficacy on the main outcome. On the other hand, the small numbers of patients who received GCs alone, AZA, MMF, ICN or rituximab made it impossible to compare each of these treatment groups with CYC. Also, prior use of immunosuppressants for reasons other than ILD (i.e. myositis) was not registered and considered, presumably creating certain bias. Similarly, more detailed information regarding adverse effects, other than severe infection or death, was lacking. The follow up of this study was only one year and maintenance treatments after the 6-month induction period were not assessed. We were not able to evaluate serial DLCO in all patients. Therefore, conclusions about long-term outcomes and the best approach after CYC treatment could not be made. Lastly, the exact scheme of MP was not available for all patients, thus this variable was simplified to a dichotomous (y/n) one. However, we were able to compare two treatment groups in a multicenter study to test our main hypothesis, and although our results cannot be considered definitive, they support a therapeutic approach that could be further investigated in future works.

In summary, this study provides new evidence about the better functional outcomes of iv CYC over other immunosuppressive regimes in patients with IIM-ILD. The additional use of MP is likely to potentiate the effects of CYC and allows lowering prednisone doses, thus potentially minimizing GC-related toxicity. Therefore, CYC in combination with MP should be considered as the first line induction therapy in this setting, not being limited to rapidly progressive, life-threatening or refractory disease.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

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