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Efficacy and safety of a step-down regimen of low dosage of glucocorticoids combined with early administration of synthetic or biologic immunosuppressants in anti-synthetase syndrome: A pilot study

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ABSTRACT

Introduction: Anti-synthetase syndrome (ASS) is a rare autoimmune disease characterized by the presence of anti-aminoacyl-transfer-RNA synthetase antibodies (ARS) and the involvement of muscles, skin, joints, and lungs. Despite increasing interest and evidence, optimal clinical management remains unclear due to a lack of randomized control trials. This study aims to evaluate the efficacy and safety of a treatment regimen involving early co-administration of glucocorticoids and immunosuppressants, with rapid prednisone tapering.

Materials and methods: We prospectively enrolled patients referred to our multidisciplinary "Myositis Clinic" with a diagnosis of ASS. Clinical, serological, instrumental and medications data were collected at baseline and at 6 and 12 months follow-up. According to treatment protocol, patients were treated with traditional synthetic immunosuppressants or rituximab (RTX) depending on clinical manifestations. Prednisone (PDN) was gradually tapered and eventually discontinued within 6 or 12 months.

Results: A total of twenty-seven subjects were enrolled: arthritis, myositis and ILD were assessed in 9, 16 and 18 patients, respectively, and all of them had an active disease. RTX was administered after methotrexate (MTX) in 4 cases of refractory joint involvement and co-administration of a second immunosuppressant was necessary in 2 patients. When muscle involvement was present, first-line therapy was MTX, followed by mycophenolate mofetil (MMF) or RTX, which allowed to achieve low disease activity or remission, respectively. Eight ILD-patients were treated with MMF and switched to RTX in 5 cases of inefficacy, but all patients were in clinical remission at the end of follow-up. At 12 months, 12 patients discontinued PDN.

Conclusions: This study is the first to prospectively report on the efficacy and safety of a stepwise, steroid-sparing treatment ASS encompassing various domains. MTX, as well as other synthetic immunosuppressants, showed limited efficacy in ASS-related arthritis, while RTX emerged as a promising option. This study recommends early RTX use in case of arthritis, suggesting it as a pivotal treatment for ILD too, and raises questions regarding maintenance therapy and treatment-free remission.

Introduction

Once considered a subtype of myositis, anti-synthetase syndrome (ASS) is a protean autoimmune disease characterized by the positivity of anti-aminoacyl-transfer-RNA synthetase antibodies (ARS) and the involvement of striate muscle, skin, joints and lungs with different degrees of severity.

The classical triad [1] includes arthritis, myositis and interstitial lung disease (ILD), which may present separately or in combination. Many other accompanying symptoms may occur, too: a systemic involvement

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may lead to fever, malaise, weight loss and anorexia, while skin may be variously affected through Gottron's papules, heliotrope rash, V-sign and mechanic's hands (MH) or hiker's feet, being the latter probably the most specific features of ASS. Lung involvement is quite heterogeneous: however, the onset of an ASS-associated interstitial lung disease (ILD) is surely detrimental in prognostic terms, standing the high probability of progressive clinical course leading to chronic respiratory failure and death in a relevant percentage of cases [2,3].

Despite a growing interest in this condition and the increasing number of published evidence, particularly in the comprehension of the pathogenetic role of the antibodies [4–7], no clear-cut evidence exist about the optimal clinical and therapeutic management of this condition. Due to the lack of randomized control trials (RCTs) and meta-analysis, the choice of the treatment *de facto* relies on the experience of the clinicians primarily facing the disease and scanty data exist about the long-term prognosis of these patients, including the onset of adverse events related to the treatment.

Thus, aim of this study was to evaluate the efficacy and safety of a regimen characterized by the early co-administration of glucocorticoids (GCs) and biologic or synthetic immunosuppressants, according to disease extent and activity, and by the rapid tapering of prednisone (PDN) within 6 or 12 months from diagnosis.

Materials and methods

Study design

We prospectively collected clinical and serological findings, coupled with imaging features, of all patients referred for the first time to our multidisciplinary "Myositis clinic" and "Myositis with lung involvement clinic" from September 2019 to January 2023 and followed-up for at least one year. Patients with a previous diagnosis of ASS and referred to our Clinic for a second opinion were included, too. According to our Centre protocol, all medical examinations of patients referred to the aforementioned clinics were conducted together by a rheumatologist and a pulmonologist with a relevant expertise in the management of myositis, myositis-associated ILD and idiopathic ILDs. Exclusion criteria were inactive disease and the lack of a definite subset of clinical and serological findings.

Study population

The diagnosis of ASS was made in patients fulfilling Connors [8], Solomon [9] or Lega [10] criteria.

All patients underwent myositis specific (MSA) and associated (MAA) antibodies assessment in our hospital laboratory, employing a line blot analysis (Euroimmune Autoimmune Inflammatory Myopathies 18 Ag, Lubeck, Germany) which was analyzed by a single biologist with 30 years of experience in the field of autoimmunity.

At baseline and then every 3 months during the first year and then every 6 months in those achieving remission, all patients underwent a complete rheumatologic assessment. The presence of active disease was evaluated considering clinical (symptoms and signs such as fever, muscle weakness, dyspnea and/or cough, mechanic's hands and/or other suggestive cutaneous lesions), laboratory (increase in myonecrosis and inflammatory markers) and instrumental findings (abnormal pulmonary function tests; interstitial lung involvement on HRCT; active synovitis and/or erosions on joint ultrasound; edema and/or PD on muscle MRI/ultrasound); muscle strength was assessed through Manual Muscle Test sore (MMT-8), while overall damage and disease activity through Myositis Damage Index (MDI) and Myositis Disease Activity Assessment Tool (MDAAT); physician's global disease activity was assessed on a 10 cm VAS as part of the MDAAT, ranging from 0 (no evidence of disease activity) to 10 (extremely active or severe disease activity). The following exams were requested at every evaluation: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete blood count (CBC), transaminase, creatin-kinase (CK), myoglobin, aldolase, ferritin, lactate dehydrogenase (LDH), creatinine. Accompanying features [11] such as fever, mechanic's hands (MH), Raynaud findings, as well as skin involvement other than MH, were reported at every visit. Improvement was assessed evaluating the variation of MDAAT and of serological, imaging and PFTs parameters, while remission was defined as normality of enzymes and no clinical sign and symptom of disease. Adverse events attributable to current and previous treatments were recorded, too, at every timepoint. Serious adverse events were considered those leading to hospitalization or risk of death.

In case of suspected muscle involvement, patients underwent thighs magnetic resonance imaging (MRI) and/or Power Doppler Ultrasound (PDUS) and/or muscle biopsy. Similarly, in case of suspected arthritis, PDUS of affected joints was performed by three rheumatologists experienced in musculoskeletal ultrasonography.

At baseline, all patients also underwent an extended respiratory functional assessment with pulmonary function tests (PFTs), including static lung volumes measurements through plethysmography and diffusion capacity assessment, and a complete clinical pulmonological evaluation: if clinically requested, high resolution computed tomography (HRCT) of the chest was performed at our Radiology department by two radiologists experienced in the field of ILD. In case of HRCT performed elsewhere, images were acquired and collectively discussed in a multidisciplinary setting. In case of clinical suspect of systemic involvement of disease, specific diagnostic assessments were conducted by specialists (e.g. dermatologists, cardiologists, nephrologist) with a specific expertise on the management of patients with ASS and/or ILD: results and therapeutic advices were discussed in a multidisciplinary discussion, as well.

In patients with a definite ILD, a concomitant pneumological and rheumatological evaluation, including PFTs, was performed at every time-point.

Treatment protocol

After the diagnosis of ASS, patients were allocated to two different subgroups according to the presence or not of a disease-specific lung involvement.

In case of ILD, patients were treated with 50 mg of oral PDN in association with mycophenolate mofetil (MMF) or rituximab (RTX) as second-line treatment in case of lack of efficacy of MMF.

PDN was tapered according to the following scheme: full dosage for one month, or at least until a stabilization was achieved, and gradually tapered to 5 mg at 6 months, according to our protocol for giant cell arteritis [12]; PDN was eventually discontinued at 12 months.

Antifibrotic therapy with nintedanib 150 mg bid was started in association with steroid or immunosuppressive treatment if ILD shows a progressive pattern in absence of symptoms or signs suspect for ASS activity. Progression of ILD was assessed according to the criteria endorsed by the recent international guidelines for the diagnosis of progressive pulmonary fibrosis [13].

Non-ILD patients were further subdivided according to the presence of a definite myositis. In this case, PDN was prescribed at the dosage of 50 mg, in association with subcutaneous methotrexate (MTX) at the dosage of 0,2–0,3 mg/kg/week. In recalcitrant cases, MMF was employed as second-line treatment, followed by RTX and calcineurin inhibitors (CNI) as third and fourth choice, respectively. Azathioprine (AZA) was limited to those patients with stable disease and desire of pregnancy.

In those patients in which musculoskeletal involvement was prevalent, hydroxychloroquine was prescribed in case of arthralgias, while MTX, at the dosage of 0,2 mg/kg/week and in association with 25 mg of PDN, was preferred when ultrasound (US) assessment evidenced a definite arthritis. In case of lack of response, RTX and baricitinib (BAR) were employed as second- and third-line treatments, respectively. In both cases, if remission was achieved, PDN was gradually tapered and

discontinued at 6–12 months (Fig. 1).

Finally, for those with limited, recalcitrant skin involvement despite the treatment, topical tacrolimus 0,1 % was employed.

Patients without a previous diagnosis of osteoporosis were treated according to American College of Rheumatology guidelines for glucocorticoids-induced osteoporosis [14], while the vaccination against SARS-CoV-2, influenza, S. pneumoniae and Herpes Zoster (recombinant vaccine, when available) suggested in all of them. Prophylaxis against P. Jirovecii was prescribed in all patients treated with RTX during the whole course of the treatment.

Study end points and assessment

Participants were assessed at baseline and then at 6 and 12 months.

The main end point of our study was the proportion of patients achieving full remission at 12 months with our treatment scheme.

Other end points were the reduction of MDAAT, the stabilization of MDI, the overall survival and the variation of serological, imaging and PFTs parameters.

Sustainability of the therapy was assessed analyzing the cumulative number of AEs and correlating them to severity of disease and immunosuppressive treatments.

Statistical analysis

Patients' characteristics were reported using median and interquartile range (IQR) for the quantitative variables, and absolute/relative frequency values for qualitative variables. The Clinical outcomes, safety and treatments differences were examined by Chi-square, Kruskal-Wallis, Fisher or Mann-Whitney U test, when appropriate. Kaplan-Meier and Log-rank test were used to estimate survival and evaluate differences between subgroups. A p-value <0.05 was considered significant. Analysis was carried out using SPSS/GraphPad/STATA.

Ethics

The study was carried out in accordance with the Declaration of Helsinki and its amendments and was approved by local ethical committee (Rhelabus 22271).

Results

Patients

Our cohort included 27 patients, whose demographic, clinical and laboratory data, including previous treatments before the referral to our center are summarized in Table 1.

At the time of the first visit, all patients had active disease, while at 12 months most of them achieved clinical remission (Table 2).

Arthritis

A definite, US proven, arthritis, was assessed in 9 patients. Erosive features were evidenced in 3 of them, all anti-JO-1 and SSA positive; one was also positive for RF and ACPA and another one for RF. All these patients, according to our protocol, were initially treated with MTX at a dosage of 10-20 mg/week, which nevertheless was effective only in 4. All subjects suffering from refractory arthritis, plus another one whose course was complicated by the onset of myositis despite the remission of arthritis, were subsequently switched to RTX. Anti-CD20 was nevertheless ineffective in the two patients with concomitant positivity of RF and ACPA, who respectively required the co-administration of MTX and BAR for achieving remission.

Myositis

Striate muscle involvement was evidenced in 16 patients, with mean CK value at baseline of 489,45 UI/ml. Seven of them were naïve to any treatment, while the remaining 8 were referred to our center after failing at least one conventional immunosuppressant (MTX in 5 of them, MMF in 4, cyclosporine, cyclophosphamide (CYC) and intravenous immunoglobulins (IVIG) in one, each); in the last one, myositis occurred months after the arthritis, when the patient was already in treatment with MTX.

Five naïve patients were treated with MTX, while the other ones

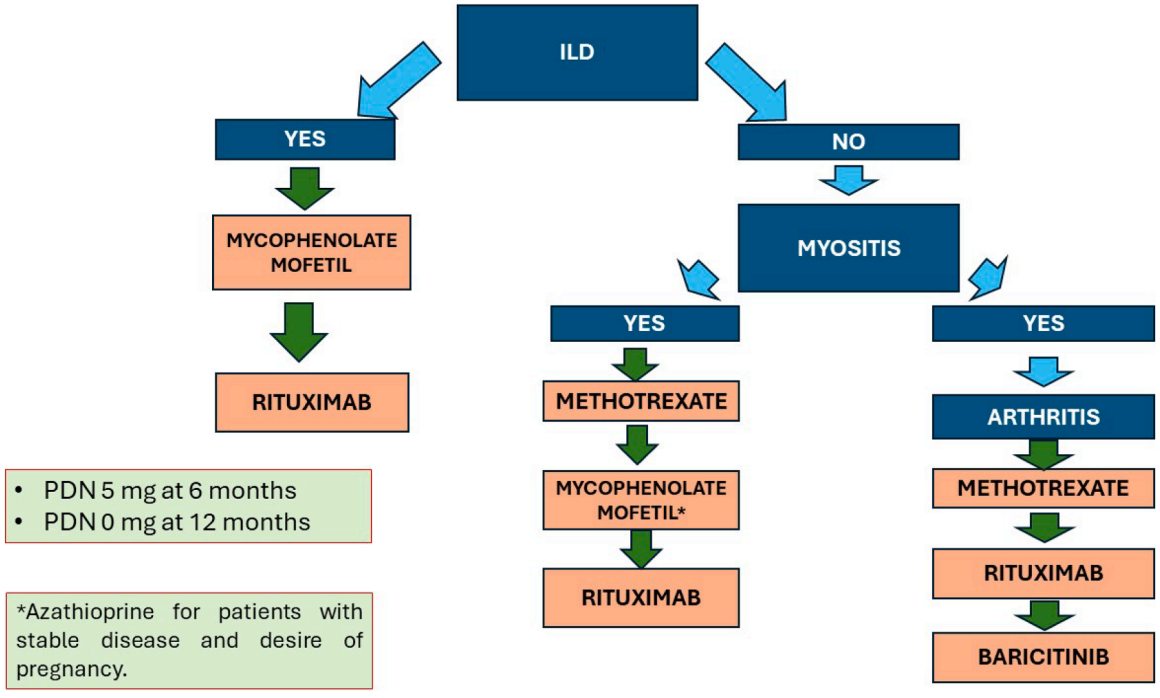

Fig. 1. Induction scheme for the treatment of ASS.
Legend: ILD: interstitial lung disease; PDN: prednisone.

Table 1
Demographic, clinical and laboratory data of patients.

VARIABLE	N (%)	MEAN VALUE ± SD
Age at onset		49,81 ± 16,87
Age at diagnosis		54,19 ± 16,39
Sex		
Male	6 (22,2)	
Female	21 (77,7)	
MSA		
JO-1	15 (55,5)	
PL-7	5 (18,5)	
PL-12	2 (7,4)	
EJ	2 (7,4)	
OJ	1 (3,7)	
Other antibodies		
ACPA	1 (3,7)	
Pm-Scl	2 (7,4)	
RF	2 (7,4)	
SSA	18 (66,6)	
SSB	2 (7,4)	
Clinical features		
Myositis	16 (59,2)	
Arthritis/arthralgia	17 (62,9)	
ILD	18 (66,6)	
CT pattern:		
- *NSIP*	14	
- *UIP*	3	
- *OP*	1	
Weight loss	6 (22,2)	
Fever	11 (40,7)	
Dysphagia	2 (7,4)	
Dysphonia	3 (11,1)	
Mechanic's hands	15 (55,5)	
Raynaud phenomenon	4 (14,8)	
Other cutaneous involvement	12 (44,4)	
Patients referred from other centers	17 (62,9)	
Duration of disease before first assessment at our center (months)		63,22 ± 65.96
Previous GC treatment	11 (40,7)	
Previous non biological treatments		
HCQ	5 (18,5)	
MTX	8 (29,6)	
MMF	4 (14,8)	
CsA	1 (3,7)	
AZA	1 (3,7)	
LEF	1 (3,7)	
IVIG	1 (3,7)	
Nintedanib	3 (11,1)	

Legend: ACPA: anti-cyclic citrullinated protein antibodies; AZA: azathioprine; CsA: cyclosporine; F females; GC glucocorticoids; HCQ: hydroxychloroquine; ILD: interstitial lung disease; IVIG: intravenous immunoglobulins; LEF: leflunomide; M males; MSA: myositis specific antibodies; MTX: methotrexate; MMF: mycophenolate mofetil; NSIP: non specific interstitial pneumonia; OP: organizing pneumonia; RF: rheumatoid factor; SD: standard deviation; UIP: usual interstitial pneumonia .

respectively with MMF, due to a concomitant ILD, and AZA, in light of the desire of pregnancy, and all but the latter had an excellent response to treatment. In one case, MTX was withdrawn due to the onset of AE.

Among the relapsing patients, 4 were treated with MMF and all but one achieved low disease activity, while a full remission was assessed in those who underwent RTX. Notably, all these patients were taking a third-line treatment and had previously failed at least two conventional immunosuppressants.

ILD

ILD was evidenced in 18 patients, in whom non-specific interstitial pneumonia (NSIP) was the most common radiological HRCT pattern (14 patients), while usual interstitial pneumonia and organizing pneumonia pattern were reported in 3 and 1 patient, respectively. Mean diffusing capacity for carbon monoxide (DLCO), forced expiration (FEV1) and FVC (forced vital capacity) at baseline were 60,18 %, 91,45 % and 90,72 %, respectively and three were already in treatment with nintedanib. MMF was prescribed in first line in 8 patients but within 12 months 5 of them were switched to RTX due to primary inefficacy (defined as the persistence or worsening of clinical and/or functional pulmonary symptoms and signs, demonstrated by radiological progression or stability of parenchymal lesions or deterioration of pulmonary function parameters). RTX was immediately prescribed in the remaining patients, generally due to a previous lack of response to other immunosuppressants and, in one case, due to a concomitant, severe, arthritis. At the end of the observational period, all patients were in clinical remission and PFTs assessment displayed a substantial stability throughout the observation period (Table 3).

Notably, no patients showed clinical, respiratory functional or radiological progression of ILD during the follow-up and, therefore, didn't required the administration of antifibrotic drugs after the start of RTX.

Glucocorticoids

A statistically significant reduction in GCs dosage was assessed as early as 6 months, while at 12 months 12 patients, all in full remission, were able to permanently discontinue steroids (Table 4).

Adverse events

Adverse events (AE) likely related to the immunosuppressive treatment were reported in 7 patients, leading in one case to hospitalization due to a severe pneumonia.

Discussion

Our study is the first one prospectively reporting the efficacy and safety of a definite stepwise, steroid-sparing treatment scheme encompassing almost all domains of ASS.

Consistently with previously reported, most patients displayed anti-JO-1 positivity, while the other MSA accounted all together for less than 50 %. Anti-SSA were positive in 66,6 % of patients, while rheumatoid factor (RF) and anti-cyclic citrullinated protein antibodies (ACPA) in 7,4 % and 3,7 %, respectively. The latter were associated to a severe, recalcitrant, erosive arthritis, as already reported in previous cohorts [15].

Clinical presentation was heterogeneous, but lung, joints and striate muscle resulted affected, even though in different percentage, in the majority of subjects and up to 25,9 % suffered from the triad composed by myositis, arthritis and ILD.

Even though almost the totality patients suffered from arthralgias, only 9 had a definite arthritis, which is a ratio comparable to some cohorts [16] but way lower than reported in other, more recent, studies [17–19]. The discrepancy of our findings with some other previously reported may be presumably explained by the strict inclusion criteria of our study, in which we carefully distinguished arthralgias from arthritis performing US in all patients complaining from such symptoms.

In our cohort, which is the first one prospectively evaluating the effectiveness of MTX, disappointing evidence was reported, as this drug was effective in less than half of patients and wasn't able to prevent the onset of myositis in one of the few who achieved remission of arthritis.

Table 2
Disease activity and damage indices at baseline and during follow-up.

		Baseline (mean value ± SD)	6 months (mean value ± SD)	12 months (mean value ± SD)	*p*
MDAAT					
	Constitutional	2,84 ± 2,57	1,39 ± 1,6	0,56 ± 0,9	<,001
	Cutaneous	1,76 ± 1,6	1 ± 1,4	0,31 ± 0,6	0,001
	Skeletal	3,36 ± 2,9	1,39 ± 2,2	0,75 ± 1,4	0,002
	Gastrointestinal	0,12 ± 0,6	0,11 ± 0,5	0,13 ± 0,5	0,333
	Pulmonary	3,2 ± 2,8	2,22 ± 2,1	1,06 ± 1,5	<,001
	Cardiovascular	0	0	0	
	Other	0	0	0	
	Extramuscular	4,4 ± 1,7	2,61 ± 1,7	1,31 ± 1,3	<,001
	Muscle	2,32 ± 2,1	1,22 ± 2,1	0,5 ± 1,1	<,001
	Global	4,56 ± 1,6	2,83 ± 1,7	1,38 ± 1,4	<,001
MDI		1,08 ± 1,6	1,56 ± 1,6	1,93 ± 1,6	0,028
MMT8		146,4 ± 5,1	148,1 ± 3,1	148,47 ± 3,6	0,019
CDASI activity		1,08 ± 1	0,61 ± 1,24	0,07 ± 0,26	<,001
CDASI damage		0	0	0	

Legend: CDASI: Cutaneous Dermatomyositis Disease Area and Severity Index; MDAAT: myositis disease activity assessment tool; MDI: muscle damage index; MMT-8: manual muscle test; SD standard deviation.

Table 3
Lung function tests at baseline and during follow-up.

	Baseline (mean value ± SD)	6 months (mean value ± SD)	12 months (mean value ± SD)	*p*
DLCO	75,47 ± 24,8	58,92 ± 12,4	63,23 ± 14,3	0,664
FEV1	96,69 ± 18,5	90,90 ± 20,6	89,64 ± 20,3	1
FVC	95,19 ± 20	92,2 ± 20	92,17 ± 23,7	0,498

Legend: DLCO: diffusing capacity for carbon monoxide; FEV1: forced expiration; FVC: forced vital capacity; SD standard deviation.

Moreover, data on MTX in this condition is currently scarce and its use in ASS-related arthritis *de facto* relies only on the long-standing evidence coming from rheumatoid arthritis [20]; the lack of robust data and our experience seem to not advice to prescribe MTX in this subset of patients. Curiously, one of the few patients who brilliantly responded to MTX was the only one suffering from arthritis mutilans, which is a very rare and severe feature of ASS.

RTX is well known for having a paramount role in the whole management of all features of ASS, but studies specifically designed for musculoskeletal domain are lacking: in a review [21] including 100 ASS treated with anti-CD20 agents, only 2 suffered from arthritis.

Therefore, our cohort, although limited to 6 patients, is the largest evaluating the efficacy of RTX in ASS-arthritis through serial US assessment. Surprisingly, RTX was poorly effective in the 2 patients with erosive arthritis and concomitant positivity of RF and ACPA. In these subjects, only the administration of MTX or BAR in addition to anti-CD20 allowed to achieve remission.

Even though sometimes overlooked, arthritis remains a troublesome feature of ASS and a complete remission is usually achieved in less than half of patients [18]. In light of the notorious inefficacy of synthetic immunosuppressants (CYC, MMF, AZA) in this domain [18], patients should be immediately addressed to drugs with a demonstrated efficacy for arthritis; nevertheless, our study seems not to support the use of MTX either, therefore RTX should be employed as early as possible, keeping in mind that patients with concomitant positivity of ACPA and/or RF probably belong to a more severe subset of disease and deserve a more aggressive treatment.

A similar approach was attempted for myositis, too, in which patients were treated with MTX, MMF and RTX. It could be surprising that in our cohort, according to our protocol, we did not routinely employ AZA as induction treatment, even though it is reported to be one of the preferred agents for myositis in ASS [18]. Such a choice was taken in light of its long latency of action, which makes this drug not suitable for an induction scheme, and to its non-superiority versus MTX [22], which moreover was supposed to be effective in arthritis, in which AZA has never proved a substantial efficacy. The immediate administration of immunosuppressants in association to oral GCs was associated to a good clinical response in our cohort, but only a minority of patients achieved remission after the first-line treatment: at last follow-up, almost all patients in remission had been switched to RTX.

Same findings were reported for ILD, which represented the most common finding in our cohort, accounting for the highest morbidity. Following our stepwise protocol, naïve patients were treated with MMF, which nevertheless proved a poor efficacy, being halted and replaced with RTX in more than half of them at 6 months. RTX itself was immediately prescribed at baseline in those who had already failed at least one conventional immunosuppressant and/or suffered from arthritis. At last follow-up visit, all but 3 ILD-ASS were in treatment with RTX and a substantial stabilization of HRCT and PFTs findings was evidenced in all of them.

In our study, MMF displayed a limited efficacy in the overall management of ASS. Despite the lack of prospective, well designed, studies, MMF is one of the most employed drugs in ASS, accounting for 16 % of the prescription in the AENEAS collaborative cohort [20] and has been suggested to be employed for mild ILD [23]. Nevertheless, data are generally extrapolated from other connective tissue diseases and the largest study retrospectively assessing the efficacy of MMF in idiopathic inflammatory myopathies (IIM) [24], evidenced a significant lower response ratio in ASS patients, particularly those with ILD and displaying anti-JO-1 positivity, both associated to an unfavorable outcome. Such findings are confirmed in our cohort, in which more than half of patients, most of whom with anti-JO-1 and ILD, were treated with MMF, which nevertheless was discontinued for primary inefficacy in almost all of them.

RTX is well known to be effective in IIM and the positivity of ARS antibodies is strongly associated to a better response to treatment [21, 25]. Ours, to the best of our knowledge, is the first prospective study and

Table 4
Mean glucocorticoids dosage at baseline and during follow-up.

	Baseline (mean value ± SD)	6 months (mean value ± SD)	12 months (mean value ± SD)	*p*
PDN equivalent	21,35 ± 19,1	6,54 ± 11,4	1,5 ± 2,3	0,001

Legend: PDN: prednisone; SD standard deviation.

one the largest in this setting; according to our experience, we found an efficacy comparable to previously reported [21], particularly for the stabilization of ILD, but a way higher safety. In most cases [26–29], a high ratio of infections was reported, accounting for up to a 21 % mortality rate [28]; nevertheless, all these patients were in treatment with moderate to high (>10 mg) of GCs, while in our cohort low dosage of prednisone were achieved at 6 months. Moreover, none of our patients required the administration of antifibrotic drugs after the start of the treatment: this represents a major achievement, given the fact that the progression of lung fibrosis despite the immunosuppressive treatment represents a poor prognostic factor in this subset.

Finally, and contrary to previously reported, none of our patients died during follow-up, despite a mean observational period comparable to previously reported [18].

Some other drugs were not employed in our protocol: hydroxychloroquine is not supported by any data, except for limited skin domain [30], while the superiority of CYC over RTX in ASS-ILD has never been demonstrated [31] and cannot be employed for maintenance due to its narrow therapeutic window. Similarly, due to the poor availability of intravenous immunoglobulin, in our clinical setting we limit their use to recalcitrant dermatomyositis, in which an unequivocal efficacy has been demonstrated in PRODERM trial [32]. Finally, we were not able to report any data about CNI, which, in our protocol, were supposed to be employed after the failure of RTX. Among the other biological DMARDs, which could theoretically be useful in the management of arthritis in course of ASS and displaying a better safety profile than RTX, evidence are still lacking: tocilizumab, although potentially effective in rapidly progressive ILD and recalcitrant arthritis, has been employed in 16 patients and only 2 of them were affected by ASS [33]; similarly, abatacept, investigated in phase III trial NCT02971683, did not meet primary or secondary endpoints.

Some other limitations should be disclosed: first, the numerosity of the sample which, although comparable to other studies [18,34–36], remains too little to draw any firm conclusions; secondly, the lack of control group may flaw our findings, but is justified by the absence of any previous guidelines on the treatment of ASS; third, none of our patients suffered from rapidly progressive ILD, therefore we were not able to provide any data about this subset of disease, which accounts for the highest mortality; fourth, as most of our patients displayed anti-Ro/SSA positivity, we could not stratify the cohort to assess whether these MAA were associated with a poorer response to treatment; fifth, we did not employ confirmatory tests other than LIA; finally, most patients were not treatment-naïve, therefore it is arguable that the previous therapies have blurred the results of this study.

In conclusion, our findings seem to support that a precocious administration of RTX may cover most aspects of ASS [26]; in particular, the use of synthetic immunosuppressants does not seem effective nor able to prevent the onset of further complications, rather delaying the achievement of remission. Moreover, the achievement of low dosage of glucocorticoids and even their precocious discontinuation is not associated to a worse outcome, but seems to reduce the onset of AE, which in our cohort were limited to a minority of patients and only in one case led to hospitalization.

Several other questions remain nevertheless unanswered: in particular, further studies should be addressed in order to assess how long and at which dosage RTX should be administered for maintenance and whether a treatment-free remission can be achieved.

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Consent to participate

Patient's informed consent to use personal data was obtained.

CRediT authorship contribution statement

Edoardo Conticini: Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Paolo Cameli:** Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Silvia Grazzini:** Writing – original draft, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Miriana d'Alessandro:** Supervision, Project administration, Investigation, Formal analysis, Data curation. **Laura Bergantini:** Supervision, Project administration, Investigation, Formal analysis, Data curation. **Brunetta Porcelli:** Supervision, Investigation, Formal analysis, Data curation. **Maria Antonietta Mazzei:** Investigation, Formal analysis, Data curation. **Luca Cantarini:** Supervision, Resources, Investigation, Formal analysis, Data curation. **Elena Bargagli:** Validation, Supervision, Resources, Investigation, Formal analysis, Data curation, Conceptualization. **Bruno Frediani:** Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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