








## ORIGINAL RESEARCH

Real-life efficacy and safety of  
nintedanib in systemic sclerosis-  
interstitial lung disease: data from an  
Italian multicentre study

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**ABSTRACT**

**Introduction** Nintedanib (NTD) has been shown to be effective in systemic sclerosis (SSc)-interstitial lung disease (ILD). Here we describe the efficacy and safety of NTD in a real-life setting.

**Methods** Patients with SSc-ILD treated with NTD were retrospectively evaluated at 12 months prior to NTD introduction; at baseline and at 12 months after NTD introduction. The following parameters were recorded: SSc clinical features, NTD tolerability, pulmonary function tests and modified Rodnan skin score (mRSS).

**Results** 90 patients with SSc-ILD (65% female, mean age 57.6±13.4 years, mean disease duration 8.8±7.6 years) were identified. The majority were positive for anti-topoisomerase I (75%) and 77 (85%) patients were on immunosuppressants. A significant decline in %predicted forced vital capacity (%pFVC) in the 12 months prior to NTD introduction was observed in 60%. At 12 months after NTD introduction, follow-up data were available for 40 (44%) patients and they showed a stabilisation in %pFVC (64±14 to 62±19, p=0.416). The percentage of patients with significant lung progression at 12 months was significantly lower compared with the previous 12 months (60% vs 17.5%, p=0.007). No significant mRSS change was observed. Gastrointestinal (GI) side effects were recorded in 35 (39%) patients. After a mean time of 3.6±3.1 months, NTD was maintained after dose adjustment in 23 (25%) patients. In nine (10%) patients, NTD was stopped after a median time of 4.5 (1–6) months. During the follow-up, four patients died.

**Conclusions** In a real-life clinical scenario, NTD, in combination with immunosuppressants, may stabilise lung function. GI side effects are frequent and NTD dose adjustment may be necessary to retain the drug in patients with SSc-ILD.

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

⇒ Nintedanib has been approved for the treatment of patients with systemic sclerosis (SSc)-interstitial lung disease (ILD) but no real-life data are available.

**WHAT THIS STUDY ADDS**

⇒ This study provides the first real-life evidence on nintedanib's effectiveness and safety on patients with SSc-ILD.  
⇒ Combination therapies including rituximab or tocilizumab with nintedanib are reported for the first time in our study.

**HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY**

⇒ Our study would help practising physicians on how to manage nintedanib's side effects when treating patients with SSc-ILD and would offer a first insight on how this new drug has been included in the armamentarium of SSc-ILD treatments.

**INTRODUCTION**

Systemic sclerosis (SSc) is a rare connective tissue disease characterised by vasculopathy, immune dysfunction leading to skin and internal organs fibrosis.<sup>1</sup> In SSc, interstitial lung disease (ILD) is one of the most frequent causes of morbidity and a major determinant of SSc prognosis.<sup>2</sup> The prevalence of SSc-ILD is extremely variable ranging from 35% to 75% of patients,<sup>3,4</sup> and the course of SSc-ILD may be unpredictable due to a high interindividual variability. Recently, a EUSTAR Study found that while 30% of patients with SSc-ILD experience progression in a 12-month period, only a minority of patients had a

continuous rapid decline in lung function.<sup>5</sup> Therefore, the expected rate of severe decline over time is expected to be between 20% and 30%. Baseline %predicted forced vital capacity (%pFVC), diffuse cutaneous subset (dcSSc), male sex and positivity for anti-topoisomerase I are known risk factors for severe progression.<sup>6</sup> Recently, two drugs (tocilizumab (TCZ) and nintedanib (NTD)) have been approved for the treatment of SSc-ILD after two phase III randomised clinical trials.<sup>7</sup> In 2019, NTD, a multi-tyrosine kinase inhibitor blocking the receptor for FGF, VEGF and PDGF,<sup>8</sup> has been the first drug approved for progressive SSc-ILD. The approval study, SENSICIS trial,<sup>9</sup> was performed in patients with early disease (<7 years), regardless of their disease subset, but with a high-resolution CT (HRCT) showing  $\geq 10\%$  lung fibrosis. In contrast with the TCZ trial,<sup>10</sup> patients treated with NTD were allowed to be on stable background immunosuppression and 48% of patients were on mycophenolate mofetil (MMF) background therapy, while TCZ and rituximab (RTX),<sup>11 12</sup> which are also used for the treatment of SSc-ILD, were not allowed. The primary endpoint of the study was the annual rate of decline in FVC: over the study period, the adjusted annual rate of change in FVC was significantly lower in the NTD group compared with the placebo group ( $-52\text{ mL/year}$  vs  $-93\text{ mL/year}$ ,  $p=0.04$ ). No significant modification was observed in the modified Rodnan skin score (mRSS) between the two groups. Moreover, while no subgroup was identified as better responder, the combination of stable MMF plus NTD provided the best scenario for prevention of decline. The most common adverse event reported, experienced by 76% of NTD patients was diarrhoea, but it was usually mild and easily manageable with transient reduction of NTD and/or anti-diarrhoea drugs. Up today, only the results of the SENSICIS trials are available for assessing the efficacy and safety of NTD in patients with SSc-ILD.

The aim of our study was to provide the first real-life data on the effectiveness and safety of NTD in a multi-centre retrospective study.

## METHODS

Patients classified as SSc, according to the 2013 American College of Rheumatology/European Alliance of Associations for Rheumatology criteria,<sup>13</sup> were identified in 10 Italian scleroderma referral centres and were retrospectively reviewed. Patients treated with NTD were identified. At NTD introduction, the following disease characteristics were collected: age, disease duration, disease subset (limited cutaneous SSc (lcSSc), dcSSc or sine scleroderma), mRSS, antibody profile, presence of SSc-related major organ involvement, concomitant and previous immunosuppressive therapies, reason for NTD initiation, HRCT pattern. Moreover, lung function tests (LFTs) including %pFVC, %predicted total lung capacity (%pTLC) and %predicted diffusing capacity for carbon monoxide (%pDLCO) at 12 months prior to NTD introduction and at 6 and 12 months since NTD introduction

were collected. Lung disease progression was calculated in the year preceding NTD introduction and in the year following NTD introduction. Lung progression was defined as decrease  $\geq 10\%$  in FVC and/or decrease of FVC  $\geq 5\%$  with a reduction of DLCO  $\geq 15\%$  (OMERACT progression).<sup>14</sup> All adverse events were recorded. Data were analysed using SPSS V.21.0 (IBM). Categorical variables were expressed as numbers or percentages and quantitative variables as mean (SD). The Mann-Whitney test or Wilcoxon rank-sum test, as appropriate, was used to compare continuous variables. P values of  $<0.05$  were considered statistically significant.

## RESULTS

### Baseline characteristics

Among 10 centres, 90 patients with SSc-ILD were included in our study: 65 (72%) women, mean age of  $57.6 \pm 13.4$  years, mean disease duration of  $8.8 \pm 7.6$  years. The vast majority of patients had a positivity for anti-topoisomerase I (67 patients, 74%) confirmed in immunoblotting, while only five patients (6%) had a positivity for anti-centromere antibody. As about disease features, the vast majority of patients had gastro-oesophageal reflux disease (84 patients, 93%), 9 patients (10%) myositis, 10 patients (11%) myocardial involvement, 11 patients (12%) a history of digital ulcers and 1 patient had concomitant pulmonary arterial hypertension. Moreover, 18 patients (20%) were active or former smokers, 7% were diagnosed with chronic obstructive pulmonary disease and 6 patients (7%) were also diagnosed with cancer (only one with squamous cell lung cancer). The vast majority of patients had already been treated with immunosuppressants prior to NTD introduction (84 patients, 93%) (see [table 1](#)). In six (7%) patients, NTD was the first-line treatment for SSc-ILD. At baseline, 71 (79%) patients were on corticosteroids (mean daily prednisone dose  $6.0 \pm 3.0\text{ mg}$ ) and 77 (85%) on immunosuppressants (see [table 1](#)). More specifically, 63 (70%) patients were on MMF with a mean dose of  $2.0 \pm 0.6\text{ g}$  daily, 19 (21%) on RTX all with a regimen of 2 g repeated every 6 months, 5 (5%) on TCZ with a dose of 162 mg weekly, 2 on methotrexate (dose 7.5 and 10 mg weekly) and 2 on azathioprine (both with a dose of 100 mg daily). When comparing baseline characteristics, no clinical or physiological feature was statistically significantly associated with the combination of RTX+NTD or TCZ+NTD (data not shown).

Baseline HRCTs were available for all but one patient. The HRCT extent was  $>10\%$  in all patients and the scans were in keeping with usual interstitial pneumonia (UIP) pattern in 28 (31%) and non-specific interstitial pneumonia (NSIP) pattern in 61 (69%) patients. At 12 months prior to NTD introduction, LFTs were available for 68 out of 84 patients (81%) who had started NTD due to ILD progression. They showed a significant drop in %pFVC from  $63 \pm 19\%$  at 12 months prior to NTD introduction to  $59 \pm 18\%$  ( $p=0.007$ ) at NTD introduction. LFT lung progression was observed in 41 (60%) patients,

**Table 1** Clinical and demographic characteristics of our multicentre cohort of patients with SSc-ILD

Clinical and demographic characteristics	90 patients
Female, n (%)	65 (72)
Age (years), mean±SD	57.6±13.4
Disease duration (years), mean±SD	8.8±7.6
Smokers, n (%) (active or former)	18 (20)
Cutaneous subset	
Diffuse, n (%)	40 (44.0)
Limited, n (%)	41 (45)
Sine scleroderma, n (%)	9 (10)
Autoantibodies	
Anti-topoisomerase I Ab, n (%)	67 (74)
Anti-RNA polymerase III Ab, n (%)	2 (2)
Anti-centromere Ab, n (%)	5 (5)
Anti-U1-RNP Ab, n (%)	6 (7)
Anti-Th/T0, n (%)	2 (2)
Organ involvement	
GI involvement	83 (92)
Myositis	9 (10)
Myocarditis	10 (11)
Scleroderma renal crisis	0 (0)
Digital ulcer	11 (12)
Pulmonary arterial hypertension	1 (1)
Previous therapies	84 patients
Mycophenolate mofetil, n (%)	65 (77)
Methotrexate, n (%)	8 (9)
Cyclophosphamide, n (%)	31 (37)
Azathioprine, n (%)	14 (17)
Tocilizumab, n (%)	6 (7)
Rituximab, n (%)	26 (31)
Concurrent therapies	77 patients
Corticosteroids, n (%)	71 (92)
Mycophenolate mofetil, n (%)	63 (81)
Methotrexate, n (%)	2 (3)
Cyclophosphamide, n (%)	0 (0)
Azathioprine, n (%)	2 (3)
Tocilizumab, n (%)	5 (6)
Rituximab, n (%)	18 (23)
Baseline HRCT	89 patients
NSIP, n (%)	61 (69)
UIP, n (%)	28 (31)

Ab, antibodies; GI, gastrointestinal; HRCT, high-resolution CT; ILD, interstitial lung disease; n, number; NSIP, non-specific interstitial pneumonia; SSc, systemic sclerosis; UIP, usual interstitial pneumonia.

according to OMERACT. All patients were started on NTD dose of 150 mg two times per day.

### Follow-up data

Six-month follow-up data were available for 49 (54%) patients. Six patients (7%) had suspended NTD treatment within the first 6 months of treatment (see the Safety section). Considering the entire cohort, compared with baseline, at 6 months, a stabilisation of LFT parameters was observed: %pFVC from 65±16 to 67±17,  $p=0.141$ ; %pTLC from 65±15 to 62±15,  $p=0.118$  and %pDLCO from 42±18 to 43±18,  $p=0.961$ ; (table 2). This effect was more pronounced in the 15 patients with UIP pattern which showed a statistically significant increase in %pFVC (from 55±15 to 59±16,  $p=0.035$ ) but not in other pulmonary function test parameters compared with patients with NSIP pattern which showed an overall stabilisation (%pFVC from 69±15 to 70±17,  $p=0.895$ ).

In the whole cohort, a statistically significant reduction in the mRSS was also observed from 6±5 to 5±5 ( $p=0.003$ ). Even in the subanalysis performed only in patients with dcSSc, a significant reduction in the mRSS from 10±5 to 9±5 at 6 months ( $p=0.010$ ) was observed. No significant difference was found when comparing patients concomitantly treated with background immunosuppression and patients treated with NTD monotherapy (data not shown).

For 40 (44%) patients, 12-month follow-up data were available. The characteristics of patients with and without 12-month follow-up were comparable but for a lower percentage of patients with sine scleroderma (2.5% vs 16%,  $p=0.040$ ) in the cohort followed up at 12 months (see online supplemental table 1). Nine patients (10%) suspended NTD treatment and four patients died within the 12 months since NTD introduction (see the Safety section). Considering the whole cohort, compared with baseline, a stabilisation of LFT parameters was observed at 12 months for all parameters but %pDLCO: %pFVC from 64±18 to 62±19,  $p=0.416$ ; %pTLC from 64±17 to 61±17,  $p=0.096$  and %pDLCO from 37±16 to 34±15,  $p=0.019$  (see table 2). When comparing patients with UIP and NSIP pattern, a statistically significant reduction in the %pDLCO was observed only in patients with UIP (from 34±14 to 29±13,  $p=0.050$ ). A stabilisation in all remaining parameters was observed in both subgroups of patients. Seven (17.5%) patients showed lung progression at 12 months. Nonetheless, the percentage of patients who showed lung progression was statistically significantly lower at 12 months since NTD introduction compared with the 12 months prior to NTD introduction (60% vs 17.5%,  $p=0.007$ ). These data were also confirmed when analysing only the subgroup of patients with 12-month follow-up (42.5% vs 12.5%,  $p=0.003$ ). Of note, all but one patient of those who significantly progressed at 12 months had a UIP pattern.

At 12 months, no significant change in mRSS was observed, and this was also confirmed in the subanalysis performed in patients with dcSSc (mRSS from



**Table 2** Modifications of LFTs over time in patients with SSc-ILD treated with nintedanib

	Baseline	6 months	P value	Baseline	12 months	P value
%predicted FVC	65±16	67±17 (49 patients)	0.141	64±18	62±19 (40 patients)	0.416
%predicted TLC	65±15	62±15 (49 patients)	0.118	64±17	61±17 (40 patients)	0.096
% predicted DLCO	42±18	43±18 (49 patients)	0.961	37±16	34±15 (40 patients)	0.019

DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; ILD, interstitial lung disease; LFTs, lung function tests; SSc, systemic sclerosis; TLC, total lung capacity.

11±6 to 11±7 at 12 months;  $p=0.623$ ). No significant difference was found when comparing patients concomitantly treated with background immunosuppression and patients treated with NTD monotherapy (data not shown).

A subanalysis was also performed in patients treated with the combination of RTX plus NTD and TCZ plus NTD. In the first group (RTX plus NTD) which included a total of 18 patients, the efficacy of the treatment was comparable with the whole cohort as no significant change was observed in the LFT parameters at 6 nor at 12 months (see [table 3](#)), whereas only a mildly statistically significant improvement in the mRSS was found only at 6 months ( $7\pm5$  vs  $5\pm5$ ,  $p=0.032$ ). Of note, in this group, the vast majority (14 patients, 78%) was treated with a combination of MMF plus RTX plus NTD. The second group (TCZ plus NTD) included a total of five patients, of which three treated also with MMF. Only three patients reached the 12-month follow-up and no significant changes in LFTs nor in the mRSS were observed (data not shown).

### Safety

Gastrointestinal (GI) side effects were recorded in 35 (39%) patients: diarrhoea was the most common complaint (29%), followed by nausea/vomiting (21%) and weight loss (13%). In seven patients, liver toxicity was also observed. As about patients with digital ulcers, in three patients, a worsening of a previous digital ulcer was observed throughout the study period, whereas in one patient with no history of digital ulcer, a new-onset digital ulcer was observed.

In 25 patients (28%), NTD dose adjustment to 100 mg two times per day was required. In the vast majority of cases, the reasons were GI side effects (91%), whereas in three (3%) cases, NTD dose was reduced due to liver toxicity. Only four cases (4%) of respiratory infections were observed in the entire cohort over the observation

period. The mean time to NTD dose adjustment was  $3.6\pm3.1$  months. Only in two (8%) patients the adverse events did not improve after NTD dose reduction and therefore NTD therapy was stopped. In nine (10%) patients, including the two in which NTD dose reduction was initially attempted, NTD was stopped after a median time of 4.5 (1–6) months. The reasons for NTD withdrawal were persistent diarrhoea in five patients, subocclusion, untreatable nausea and vomiting, worsening of digital ulcer and gangrene and liver toxicity in one patient each. During the follow-up, after a median time of 10 (6–14) months, four patients died.

The toxicity profile was also analysed in the subgroup of patients treated concomitantly with RTX or TCZ. In the first group (RTX plus NTD), the percentage of patients who experienced GI side effects was 44%, whereas the proportion of patients requiring NTD dose reduction was 33% and the rate of NTD discontinuation was 17% ( $p$  not significant for all comparisons). In the second group (TCZ plus NTD), only one patient (20%) experienced GI adverse events, whereas the rate of patients requiring NTD reduction was 40% and no patients required NTD suspension. No patient treated with combination therapy with either RTX or TCZ died during the follow-up.

### DISCUSSION

This is the first real-life study evaluating the role of NTD for the treatment of patients with SSc-ILD. Our multi-centre study confirms the effectiveness of NTD in stabilising lung function in patients with SSc-ILD as well as the lack of a significant effect on skin fibrosis. Moreover, for the first time, we reported the use of NTD in combination with other immunosuppressive drugs that were not included in the SENSICIS Study such as the combination with TCZ or RTX.

**Table 3** Modifications of LFTs over time in patients with SSc-ILD treated with nintedanib in combination with RTX

	Baseline	6 months	P value	Baseline	12 months	P value
%predicted FVC	64±16	66±15 (13 patients)	0.278	68±16	66±10 (7 patients)	0.581
%predicted TLC	60±14	58±9 (13 patients)	0.636	62±13	56±8 (7 patients)	0.129
% predicted DLCO	48±20	46±14 (13 patients)	0.489	45±13	39±12 (7 patients)	0.155

DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; ILD, interstitial lung disease; LFTs, lung function tests; RTX, rituximab; SSc, systemic sclerosis; TLC, total lung capacity.

It is well known that patients with SSc-ILD have a variable course, but a significant percentage of patients can have a progressive phenotype associated with a rapid decline in FVC and eventually death.<sup>15</sup> Differently to the SENSICIS trial, in which about half of the patients were on NTD monotherapy, in our real-life study, NTD was associated with a concomitant immunosuppressive treatment in 86% of patients. This is a novel result which might reflect how NTD has been rapidly introduced in clinical practice by Italian SSc referral centres. The combination of NTD with other immunosuppressive drugs is not a novelty. In fact, a recent EUSTAR survey showed how the majority of physicians (88%) expert in treating patients with SSc-ILD consider that NTD should be combined with other immunosuppressive treatments instead of using it as monotherapy.<sup>16</sup> Moreover, it should also be noticed that besides the efficacy in preserving lung function, our study showed that the progressive phenotype (defined according to OMERACT definitions) observed in 60% of our patients could be effectively counteracted in the majority of patients with NTD therapy. This result is particularly important as patients with progressive ILD phenotype, being a significant percentage of the whole population with SSc,<sup>5</sup> are the most difficult to treat. As previously stated, in our study, we evaluated the combination of NTD with other immunosuppressive drugs and, among them, also with targeted therapies which were not allowed in SENSICIS trial. In our cohort, 18 patients (20% of the entire study population) were treated concomitantly with RTX, while the vast majority was actually treated with a triple combination therapy including also MMF. The combination of RTX plus MMF has already been reported in some retrospective case series,<sup>17–19</sup> while the addition of NTD to this treatment scheme is reported in our patients for the first time. Obviously, the major concern about this combination treatment is safety. However, in our cohort, no major adverse event was detected in terms of increased risk of infection nor a significant increase in other adverse events, in particular of the GI system, was observed. Recently, the use of TCZ in combination with NTD has been suggested by SSc-ILD experts as a possible upfront combination therapy potentially stabilising or even improving patients' lung function, similarly to haematopoietic stem cell transplantation but with fewer side effects.<sup>20,21</sup> In our five patients treated with this combination, an overall satisfactory efficacy with no major adverse event was observed. Unfortunately, likely due to the limited number of patients included and the relatively longer disease duration of treated patients, we could not clearly highlight whether the use of combination therapy with either RTX or TCZ could be used and appropriate for more severe patients as baseline features did not differ from the overall population.

However, it should be highlighted that in the patients evaluated in this retrospective real-life study, the disease duration ( $8.8 \pm 7.6$  years) was significantly higher than those studied in the SENSICIS trial, where disease duration had to be  $<7$  years. Clearly, this aspect reflects the real-life

nature of our study where the addition of NTD was made in patients already on treatment with other immunosuppressive drugs for SSc-ILD. A recent EUSTAR Study<sup>22</sup> showed that higher disease duration does not immediately translate into a lower rate of SSc-ILD progression. In fact, it is known that SSc-ILD can frequently progress also in late disease stages, and for this reason, the addition of NTD in a long-lasting disease should not be discouraged. Besides the longer disease duration, the characteristics of our study population are comparable with the approval study even when considering the percentage of patients with a limited cutaneous or a diffuse cutaneous phenotype. Moreover, the high prevalence of positivity for anti-topoisomerase I patients (confirmed by immunoblotting), both in patients with lcSSc and dcSSc, confirms the central role of this autoantibody in identifying patients with ILD-SSc with progressive lung disease regardless of their cutaneous phenotype.

The possibility of including also patients with lcSSc has indeed been one of the greatest achievements of the SENSICIS trial, compared with the focuSSc trial, where only patients with dcSSc phenotype could be recruited. In fact, patients with lcSSc, who have long been neglected in other SSc trials,<sup>23</sup> represent the majority of population with SSc and it is known that the progression of SSc-ILD can be significant even in this subset of patients.<sup>24</sup>

The reduction of the mRSS observed in our patients after 6 months, both in the entire population and in patients with dcSSc, may be considered for the moment only marginal as it is below the minimal clinically important differences of 5 points.<sup>25</sup> Moreover, this trend was not confirmed after 12 months.

An important contribution of our study is also the safety assessment of NTD in a large cohort of patients with SSc-ILD. In the SENSICIS Study, GI side effects emerged as the major issue for NTD. In particular, it was reported that 76% of patients experienced diarrhoea (49% of cases classified as mild/moderate), whereas the overall discontinuation rate was 16%. In our study, in agreement with the SENSICIS data and the more recently published SENSICIS ON publication,<sup>26</sup> the use of NTD was associated with GI side effects in population with SSc-ILD, though the percentage of patients who experienced significant diarrhoea was lower than in the SENSICIS trial and the SENSICIS ON Study (29%), and the discontinuation rate was also lower (10%). We found that 28% of patients required NTD dose reduction to 100mg two times per day due to the appearance of side effects over the study period, and this adjustment was made after a mean time of 3 months since NTD introduction. This strategy, which was also included in the original SENSICIS protocol, where it was applied in 48% of patients over the 52 weeks,<sup>27</sup> seemed highly effective in our population as only two patients abandoned the treatment after dose reduction. This suggests that dose reduction should be promptly attempted in patients complaining of side effects after NTD introduction as this strategy can be effective in the majority of cases.

It should also be commented that compared with the SENSICIS trial where severe vasculopathy was an exclusion criterion, in our real-life study, we also included 11 patients with digital ulcers and we observed a worsening in 27% of these patients. More interestingly, in one patient with no history of digital ulcer, a new digital ulcer was also recorded. Given the limited number of patients included in our study, we could not clearly assess a role for NTD in these patients. Nonetheless, our observation might suggest that NTD introduction should be carefully weighed in patients with severe vasculopathy and that larger cohorts of patients should be studied to investigate whether the use of NTD could be associated with a worse digital ulcer outcome in specific populations of patients.

The major limitation of our study is clearly the retrospective nature; nonetheless, the number of patients included and the possibility of evaluating the real-life effectiveness of NTD, especially in combination with other drugs that were excluded in the SENSICIS trials, offer a new perspective on the modality of use of NTD in scleroderma referral centres in Italy. We could not evaluate whether the stabilisation in lung function was associated with a better quality of life due to the absence of a systematic evaluation of this parameter.

## CONCLUSIONS

Our real-life data confirm that NTD is useful in the management of SSc-ILD. In this scenario, our data indicate that NTD may be efficiently used also in combination with other immunosuppressants in a long-standing disease, thus further contributing to the stabilisation of pulmonary function. GI side effects were frequently observed; however, the overall safety of the drug was clearly confirmed. In fact, the GI side effects could be easily managed, and the NTD dose adjustment was very helpful to retain the drug.

While NTD was efficient on lung involvement, its efficacy on skin involvement remains unclear and needs to be thoroughly evaluated in the future on a larger population with SSc.

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