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CASE SERIES

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One-year clinical experience on the use of Nintedanib in systemic sclerosis

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Abstract

We reviewed 11 patients with systemic sclerosis-related ILD who were referred to our Scleroderma Unit from January 2020 to January 2021 and started Nintedanib. Non-specific interstitial pneumonia (NSIP) was prevalent (45%), usual interstitial pneumonia (UIP) and UIP/NSIP pattern were both 27%. Only one patient had a history of smoking. Eight patients were on mycophenolate mofetil (MMF), eight were treated with corticosteroids (mean dose 5 mg/day of Prednisone or equivalent), and three were on Rituximab. The mean modified British Council Medical Questionnaire (mmRC) decreased from 3 to 2.5. Two patients had to reduce their daily dose to 200 mg/day for severe diarrhoea. Nintedanib was generally well tolerated.

KEYWORDS
autoimmunity, fibrosis, interstitial lung disease, rare disease, systemic sclerosis

INTRODUCTION

Systemic sclerosis (SSc) is a complex autoimmune disease, and [1,2] one of the most common and severe SSc manifestations is interstitial lung disease (ILD) [3]. In 2019 Nintedanib (NTB) was approved for the treatment of SSc-related ILD, following the results of two randomized clinical trials (RCTs) [4,5] which demonstrated a significant reduction in the annual rate of decline in forced vital capacity (FVC).

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Patients and methods

We studied 11 patients (six females, five males, and mean age 62.7 ± 8 standard deviation (SD)) with disease duration (from the first non-Raynaud's symptom) 8 years (±7SD), who were referred to Reggio Emilia and Modena Scleroderma Units from January 2020 to January 2021. Patients fulfilled the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria [6] for SSc and consented to the study. The patients had been previously treated with conventional immunosuppressive drugs (see Table 1 for further details). Patients had clinical evaluation (at baseline and every 3 months, if not otherwise needed), underwent a high-resolution lung computed tomography (HRCT) (before starting NTB, 6 months after and then according to clinical need), respiratory function tests (before starting NTB and then every 6 months), complete laboratory blood work-up, echocardiogram (before starting NTB and then according to clinical need). Every 3 months, during clinical evaluation, patients completed two questionnaires: the BORG dyspnea scale and the Modified British Medical Research Council Questionnaire (mMRC).

TABLE 1 Scleroderma patients' characteristics and response to Nintedanib treatment

Sex *N* (%)	
F	6 (45.5%)
M	5 (54.5%)
Age (mean ± SD)	62.7 ± 8
Smoke *N* (%)	1 (9.1%)
Comorbidities *N* (%)	
Gastroesophageal reflux disease	9 (81.8%)
Dyslipidemia	4 (36.4%)
Arterial hypertension	3 (27.3%)
Hiatal hernia with esophagitis	2 (18.2%)
Chronic obstructive pulmonary disease	2 (18.2%)
Diabetes	2 (18.2%)
Coronary heart disease	2 (18.2%)
Latent turberculosis	1 (9.1%)
Disease duration years (mean ± SD)	8 ± 7
SSc subset *N* (%)	
Diffuse cutaneous	6 (54.5%)
Limited cutaneous	5 (45.5%)
mRSS T0 (mean ± SD)	9.23 ± 10
mRSS T1 (mean ± SD)	10 ± 10
Antibodies *N* (%)	
Antitopoisomerase I	8 (72.7%)
Pm-Scl 75	2 (18.2%)
CENP B	1 (9.1%)
HRCT fibrosis extension *N* (%)	
>20%	9 (81.8%)
<20%	2 (18.2%)
ILD pattern *N* (%)	
NSIP	5 (45.5%)
UIP	3 (27.3%)
UIP/NSIP	3 (27.3%)
mMRC T0	3
mMRC T1	2,5
Borg T0	7.27
Borg T1	6
FVC ml T0 (mean ± SD)	2233.6 ± 1066
FVC ml T1 (mean ± SD)	2223 ± 1080
DLCO % T0 (mean ± SD)	34.5 ± 13.6
DLCO % T1 (mean ± SD)	39.1 ± 16.3
O2 3L/min T0 *N* (%)	5 (45.5%)
O2 3L/min T1 *N* (%)	5 (45.5%)
Ongoing therapies N (%)	
MMF	8 (72.7%)
MMF + Steroid	7 (63.6%)
Steroid	8 (72.7%)
RTX	3 (27.3%)
Nintedanib dosage 150 mgx2 *N* (%)	11 (100%)
Side effects *N* (%)	
Diarrhoea	3 (27.3%)
Weight loss	3 (27.3%)
Partial intestinal obstruction	1 (9.1%)
Nausea	1 (9.1%)
Worsening pulmonary arterial hypertension	1 (9.1%)
Irritability	1 (9.1%)
Abdominal pain	1 (9.1%)
Liver enzyme alteration	0 (0%)
Other blood sample alterations	0 (0%)
Drug withdraw *N* (%)	2 (18.2%)
Death for other cause	1 (9.1%)

Abbreviations: Borg: Borg dyspnea scale; DLCO: diffusing capacity of the lungs for carbon monoxide; FVC: forced vital capacity; HRCT: high resolution computed tomography; ILD: interstitial lung disease; mMRC: modified British Council Medical Questionnaire; mRSS: modified Rodnan skin score; O_2: oxygen therapy; SSc: systemic sclerosis.

RESULTS

Anti-topoisomerase antibodies were prevalent (eight patients, 72.7%), followed by anti Pm-scl75 (two patients, 18%) and anti-centromere (one patient, 9%). Six patients had diffuse cutaneous systemic sclerosis and five had limited cutaneous systemic sclerosis.

Non-Specific Interstitial Pneumonia (NSIP) was the most frequent HRCT pattern (five patients, 45%), followed by Usual Interstitial Pneumonia (UIP) and UIP/NSIP pattern (respectively three patients (27%) each). Only one patient was a former smoker. The median Modified Rodnan Skin Score (mRSS) at baseline was 12 points without any significant improvement during follow-up. Patients continued their immunosuppressive therapy for lung involvement: eight were on Mycophenolate Mofetil (MMF) (seven of them in association with glucocorticoids ≤5 mg/day of Prednisone or equivalent), eight were on corticosteroids alone (mean dose 5 mg/day of Prednisone or equivalent), and three were on Rituximab (two infusions every 6 months) (RTX). Mean FVC was 2233.6 mL [±1066 mL] (59% predicted) at beginning of NTB therapy and remained stable during the 12-month follow-up period. Unfortunately, we do not have FVC data for all patients (Figure 1).

The mmRC decreased from a median value of 3 at baseline to 2.5 at and the Borg scale of dyspnea from 7 to 6. Neither differences were significant. Five patients were on oxygen therapy (mean O_2 flow 3 L/min) without any significant airflow adjustment during the follow-up. One patient had nausea, one general malaise and three lost weight (less than 2 kg). Five patients had diarrhoea: two required a definitive dose reduction (200 mg/day) with a decrease of MMF to 1 gm/day for a limited period of time (approximately 2 months); one had to discontinue NTB. Patients with diarrhoea were treated with

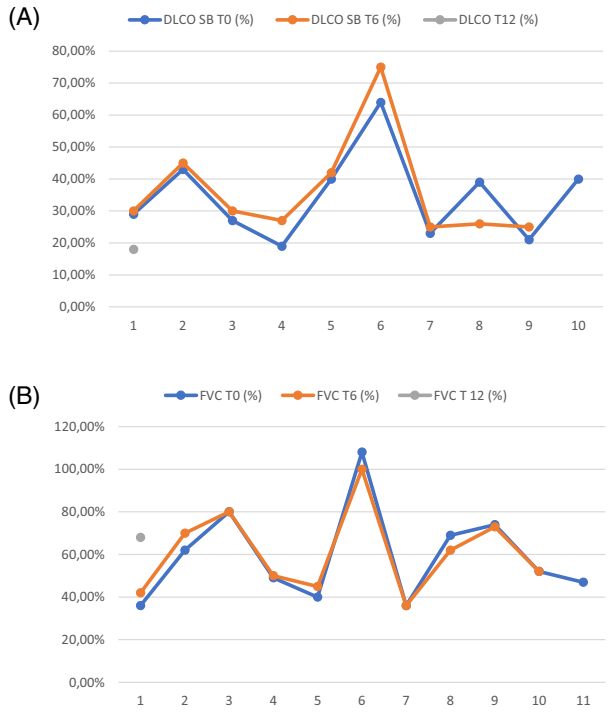

FIGURE 1 (A) Diffusing capacity for carbon monoxide (DLCO) at baseline (T0), after 6 months (T6), and after 12 months (T12). Baseline data are available for 10 patients. (B) Forced vital capacity (FVC) at baseline (T0), after 6 months (T6), and after 12 months (T12). Baseline data are available for 11 patients

antidiarrehal and probiotics. One patient had a partial intestinal obstruction (not caused by NTB). We did not find any liver enzyme elevation, nor other significant blood sample abnormalities. One patient died from an acute cardiovascular event, not related to NTB (Table 1).

DISCUSSION

We report real-life experience on the use of NTB in SSc-related patients over 12-month, focusing on its tolerability and safety profile. NTB showed a low rate of discontinuation due to severe adverse events (SAEs). Diarrhoea was the most frequent adverse event: only two patients had to reduce their daily dose. Severe diarrhoea was ameliorated by reducing the concomitant use of MMF to 1 gm/day (from the starting dose of 2 mg/day), for a limited period (approximately for a couple of months). The use of anti-diarrheal medications and probiotics might mitigate symptoms. No patient had previous history of non-infectious diarrhoea. Minor weight loss could be related to the drug itself or to the disease but did not lead to discontinuation of NTB. We did not experience any laboratory test abnormality or thrombotic events.

AUTHOR CONTRIBUTIONS

Luca Magnani conception or design of the work, the acquisition, analysis or interpretation of data for the work. Amelia Spinella conception or design of the work, the acquisition, analysis or interpretation of data for the work. Sofia Testoni drafting the work or revising it critically for important intellectual content. Federica Lumetti drafting the work or revising it critically for important intellectual content. Chiara Scelfo drafting the work or revising it critically for important intellectual content. Lucia Dardani drafting the work or revising it critically for important intellectual content. Gianluigi Bajocchi final approval of the version to be published. Enrico Clini final approval of the version to be published. Carlo Salvarani final approval of the version to be published. Dilia Giuggioli conception or design of the work, the acquisition, analysis or interpretation of data for the work.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

ETHICS STATEMENT

This study was approved by Institutional review board or ethics committee. Name of the institution: Comitato Etico dell'Area Vasta Emilia Nord. Approval number: Delibera del Direttore Generale n. 0242.

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