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Original Article

Clinical science

Lung ultrasound and high-resolution computed tomography quantitative variations during nintedanib treatment for systemic sclerosis-associated interstitial lung disease

Marco Di Battista [1,2,*], Andrea Delle Sedie[1], Chiara Romei[3], Laura Tavanti[4], Mattia Da Rio[1], Riccardo Morganti [5], Alessandra Della Rossa[1], Marta Mosca[1]

[1]Rheumatology Unit, University of Pisa, Pisa, Italy
[2]Department of Medical Biotechnologies, University of Siena, Siena, Italy
[3]Radiology Unit, University of Pisa, Pisa, Italy
[4]Cardiovascular Thoracic Department, University of Pisa, Pisa, Italy
[5]Section of Statistics, University of Pisa, Pisa, Italy

*Correspondence to: Marco Di Battista, Rheumatology Unit, University of Pisa, via Roma 67, Pisa 56123, Italy. E-mail: dibattista.marco91@gmail.com

Abstract

Objectives: Lung ultrasound (LUS) and high-resolution CT (HRCT) are commonly used for the evaluation of interstitial lung disease (ILD). Nintedanib (NIN) is an antifibrotic therapy approved for systemic sclerosis-associated ILD (SSc-ILD). We assessed LUS and quantitative HRCT changes in SSc-ILD patients treated with NIN during a 1 year follow-up, evaluating relationships between imaging variations and functional or quality-of-life outcomes.

Methods: SSc-ILD patients who started NIN were enrolled and followed for 12 months. Pulmonary function tests and patient-reported outcome measures (PROMs) were assessed half-yearly and quarterly, respectively. LUS was performed quarterly evaluating the presence of B-lines (BL) and pleural line irregularities (PLI). HRCT was repeated after 1 year and quantitatively analysed with CALIPER software.

Results: Ten patients (70% female, mean age 62 years) were enrolled. The mean total number of both BL and PLI was constantly decreased during NIN treatment, being significantly reduced after 12 months (from 175.1 [66.7] to 120.8 [70.3] for BL, $P = 0.005$; and from 50.6 [32.5] to 37.2 [22.4] for PLI, $P = 0.05$). Male gender, smoking habit and baseline forced vital capacity <70% predicted were associated with worse LUS outcomes. A greater reduction in both BL and PLI was observed in those who improved in PROMs, especially modified Medical Research Council dyspnoea scale ($P = 0.016$ and $P = 0.04$, respectively) and Saint George's Respiratory Questionnaire ($P = 0.006$ and $P = 0.026$, respectively). No significant changes in the CALIPER percentages of normal parenchyma or ILD elements were observed after 12 months of NIN, thus paralleling the stabilization obtained at pulmonary function tests.

Conclusion: We present preliminary results on NIN effects on SSc-ILD as assessed by LUS, a useful method for frequently repeated monitoring, and CALIPER, a valid implementation whenever a HRCT is performed.

Keywords: systemic sclerosis, nintedanib, interstitial lung disease, lung ultrasound, quantitative HRCT

Rheumatology key messages

- B-lines and pleural line irregularities show an improvement during nintedanib treatment for SSc-ILD.
- CALIPER parameters tend to remain stable during antifibrotic treatment, paralleling pulmonary function tests.
- Lung ultrasound and quantitative HRCT are useful to monitor SSc-ILD patients treated with nintedanib.

Introduction

Systemic sclerosis (SSc) is a complex autoimmune connective tissue disease characterized by a multifaceted pathogenesis and a heterogeneous clinical profile. Despite progress in early diagnosis, interstitial lung disease (ILD) represents a major complication and is one of the leading causes of morbidity and mortality in SSc, heavily burdening patients' quality of life [1, 2]. Pulmonary function tests and high-resolution CT (HRCT) are necessary investigations for an adequate assessment of ILD at baseline and during follow-up [3]. More recently, HRCT has been implemented with quantitative post-processing software, namely Computer-Aided Lung Informatics for Pathology Evaluation and Ratings (CALIPER), yielding promising results [4]. Among ILD

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imaging techniques, lung ultrasound (LUS) has emerged as a non-invasive, practical and cost-effective tool, demonstrating important utility not only for the established form of the disease, but also for the early diagnosis of SSc-ILD [5–10]. Few data are available about the prognostic value of B-lines (BL) [11, 12], whereas evidence regarding the possible role of LUS in monitoring is still lacking.

Nintedanib (NIN) is an antifibrotic drug first approved in 2014 for the treatment of idiopathic pulmonary fibrosis (IPF) and then in 2019 for SSc-ILD. NIN has proved to slow the progression of the disease, reducing the decline in forced vital capacity (FVC) [13]. So far, there is very little evidence on HRCT changes during NIN therapy in SSc-ILD and nothing regarding LUS. The primary aim of this study was to assess LUS and HRCT quantitative changes in SSc-ILD patients treated with NIN during a 1-year follow-up. Secondly, we sought to evaluate any relationship between imaging changes and NIN efficacy as derived from functional and quality-of-life outcomes.

Methods

Adult patients fulfilling 2013 EULAR/ACR criteria for SSc [14] who required the initiation of NIN for progressive fibrosing ILD were enrolled in this study. The evaluation of the progressive features of ILD as well as the decision to initiate NIN were discussed in a multidisciplinary group composed of rheumatologists, pulmonologists and radiologists. Ethical approval was obtained from the local ethical committee (CEAVNO, approval no. 15914). Each patient voluntarily agreed to participate and gave written informed consent to publish the material.

Epidemiological and SSc-specific data were collected. Patients were regularly followed up every 3 months for 1 year, during which imaging, spirometric and quality-of-life assessments were repeated. Safety data were also recorded at each visit. NIN was started at the dosage of 150 mg bid and was administered alone or in combination with immunosuppressants; in such cases the immunosuppressive therapy was stable for at least 6 months. No new pulmonary drugs were added during the 1-year follow-up.

Pulmonary function tests were performed at baseline and every 6 months, collecting the outcomes of FVC, diffusing capacity of the lungs for carbon monoxide (DLCO) and DLCO corrected for alveolar volume (KCO). A decline in FVC of $\geq$10%, or a decline in FVC of 5–10% along with a decline in DLCO of 15% was considered a clinically meaningful index of worsening for progressive ILD [15]. To assess SSc-ILD-related quality of life, the following patient-reported outcomes measures (PROMs) were administered quarterly. (i) The modified Medical Research Council (mMRC) dyspnoea scale: this measures the degree of disability that dyspnoea imposes on day-to-day activities on a scale from 0 to 4 [16]; improvement or worsening were considered based on a decrease or increase of at least one point in mMRC, respectively. (ii) The Leicester cough questionnaire (LCQ): a 19-items tool that evaluates the impact of chronic cough across physical, psychological and social domains [17]; a $\geq$1.3 points increase in LCQ total score was considered as a clinically meaningful improvement [18]. (iii) The Saint George's Respiratory Questionnaire (SGRQ): a 50-items tool that broadly assesses health-related quality of life in respiratory diseases on a scale ranging from 0 to 100; a $\geq$8 points decrease in SGRQ total score was considered as a clinically meaningful improvement [19].

Lung ultrasound

LUS was performed at baseline and quarterly for 1 year by a 5-years' experienced single operator blinded to the results of pulmonary function tests, HRCT and PROMs. Intraclass correlation coefficient >0.9 was achieved on 10 SSc-ILD patients examined twice in one week and not included in the present study. A 4–13 MHz linear probe (MyLab Class C, Esaote, Genoa, Italy) was used to assess 55 intercostal spaces on each patient. On the anterior side of the chest, with the patient in the supine position, the parasternal, mid-clavicular and anterior axillary spaces were scanned, from II to V on the right and from II to IV on the left. On the posterior side of the chest, with the patient in the sitting position, the paravertebral spaces from I to IX and the mid-scapular and posterior axillary spaces from VI to IX were scanned bilaterally. Each space was assessed on a longitudinal scan (with respect to the long axis of the ribs) for the presence of B-lines (BL—quantitative score) and pleural irregularities (PLI—semiquantitative score, 0–1–2) [20], then added to obtain a total BL score and a total PLI score. BL (a vertical hyperechoic reverberation artifact that arises from the pleural line, extends to the bottom of the screen without fading, and moves synchronously with lung sliding) and PLI (a loss of regularity that may be associated with an increase in thickness, which may be focal, diffuse, linear or nodular) were defined according to Delle Sedie *et al.* [21]. LUS images were scored during live scanning and evaluated only in areas where the ultrasound beam was perpendicular to the pleura, to minimize position artifacts.

High-resolution CT

Patients underwent HRCT at baseline and after 12 months. All HRCT examinations were performed with a 64-detector CT system (Somatom Sensation, Siemens Medical Systems, Erlangen, Germany) and images were obtained from the entire lung parenchyma. The imaging protocol consisted of a non-contrast-enhanced scan in supine position with a field of view between 290 and 340 mm, 100–120 kV peak, 250 mA, 512 × 512 matrix. The scans were reconstructed with a sharp kernel for lung (B60f), slice thickness of 1.5 mm and increment of 1 mm. All HRCT examinations were performed during a full inspiration breath-hold. An expert thoracic radiologist first reviewed the images to determine the HRCT pattern, distinguishing between usual interstitial pneumonia (UIP) and non-specific interstitial pneumonia (NSIP). The HRCT scans were subsequently processed by the texture analysis software CALIPER (Biomedical Imaging Resource, Mayo Clinic, Rochester, MN, USA), which analyse the entire lung volume, thus obtaining quantitative data about the principal signs of ILD such as honeycombing (HC), ground glass (GG) and reticulation (RET), as well as on pulmonary vascular-related structures (VRS) and normal parenchyma (Fig. 1). The software output is represented by percentage values, compared with the entire lung volume.

Statistical analysis

Categorical data were described with absolute and relative frequency, continuous data by mean and standard deviation. A paired sample Student's *t*-test was conducted to assess changes in LUS and HRCT parameters. Pearson's correlation coefficient was computed to assess relationship between

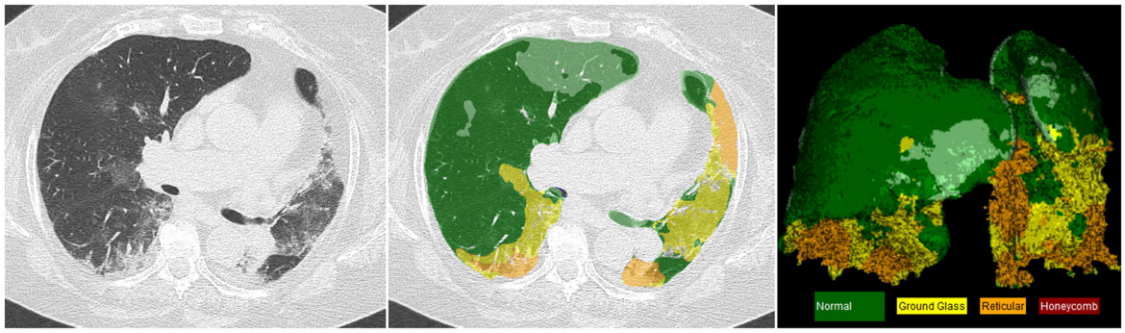

Figure 1. Axial and 3D lung texture analysis by CALIPER software

continuous variables. Significance was set at 0.05 and all analyses were carried out with SPSS Statistics v.28 (IBM Corp., Armonk, NY, USA) and R software (R Core Team 2023; R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

Ten SSc patients (70% female, mean age 62 [10.9] years) starting NIN for progressive fibrosing ILD were enrolled. Table 1 summarizes epidemiological and SSc-specific characteristics of the cohort. Notably, all of them had previously been treated with immunosuppressants but only four patients continued immunosuppressive therapy in combination with NIN. Two patients were on oxygen therapy at enrolment, and only one patient was receiving low dose (<5 mg/die prednisone) steroids for non-pulmonary reasons.

One patient had to prematurely discontinue NIN 3 weeks after the enrolment due to unbearable gastrointestinal adverse effects and was therefore excluded from the study. Diarrhoea was the most frequent adverse effect in the remaining nine patients (66.6%) and led to the reduction of NIN dosage to 100 mg bid in those six patients after a mean period of 3.5 months. One patient had a myocardial infarction during a sepsis 7 months after drug initiation, and NIN was discontinued on cardiological indication: after this event the patient only repeated HRCT at 12 months.

Efficacy outcomes are reported in Fig. 2. All nine patients treated with NIN achieved stabilization of spirometric parameters; none progressed. Regarding PROMs after 1 year of therapy, mMRC improved in 66.6% of cases and was stable in the rest. Three patients (33.3%) showed an improvement in chronic cough as measured by LCQ, whereas the rest remained stable. Finally, SGRQ was improved in 77.7% of patients, stable in one case and slightly worsened in another.

Lung ultrasound variations

As showed in Fig. 3, during the treatment with NIN a mean BL total number constant decrease was observed, and thus there was a significant reduction from 175.1 (66.7) at the baseline to 120.8 (70.3) after 1 year ($P = 0.005$). The same was observed for mean PLI total number, which was 50.6 (32.5) at the baseline and then constantly decreased reaching statistical significance after 1 year at 37.2 (22.4) ($P = 0.05$). A strong direct correlation was found between mean total number of BL and PLI at any time point ($r > 0.85$ and $P < 0.01$ at any time point).

Table 1. Epidemiological and clinical characteristics of the SSc-ILD cohort ($n = 10$)

Characteristic	Value
Female, *n* (%)	7 (70)
Age, mean (S.D.), years	62 (10.9)
Former smokers, *n* (%)	3 (30)
Disease duration, mean (S.D.), years	12.6 (9.9)
Skin subset	
Diffuse cutaneous, *n* (%)	9 (90)
Limited cutaneous, *n* (%)	1 (10)
Autoantibodies	
Anti-topoisomerase I, *n* (%)	8 (80)
Anti-RNA polymerase III, *n* (%)	2 (20)
Concomitant immunosuppressant	
Mycophenolate mofetil, *n* (%)	3 (30)
Tocilizumab, *n* (%)	1 (10)

Female patients showed a significant decrease of both BL and PLI over time ($P = 0.022$ and $P = 0.003$, respectively), as opposed to male patients who did not. Patients who never smoked had a greater reduction of mean BL total number ($P = 0.017$), whereas the concomitant intake of immunosuppressants was associated with a greater decrease of mean PLI total number ($P = 0.03$). No correlations emerged between age or disease duration and LUS changes during NIN treatment, or between spirometric parameters at any time point and BL or PLI mean total number. When considering patients ($n = 3$) with a baseline FVC < 70% predicted, no significant changes occurred to either LUS parameter over time. When considering PROMs results, a greater reduction of both BL and PLI was observed in those who improved in the mMRC scale ($P = 0.016$ and $P = 0.04$, respectively). An improvement in LCQ was significantly associated with a PLI total number reduction ($P = 0.04$). Finally, a greater reduction of both BL and PLI was observed in patients with an improved SGRQ ($P = 0.006$ and $P = 0.026$, respectively).

HRCT variations

At baseline HRCT, a UIP pattern was present in 60% of patients and a NSIP pattern in the rest. Analysing CALIPER after 12 months of NIN treatment, no significant changes in GG, HC, RET, VRS or normal parenchyma percentages were observed (Fig. 4). There were no meaningful associations between the variation of CALIPER parameters and epidemiological data, SSc-specific features, baseline FVC < 70% predicted and PROMs

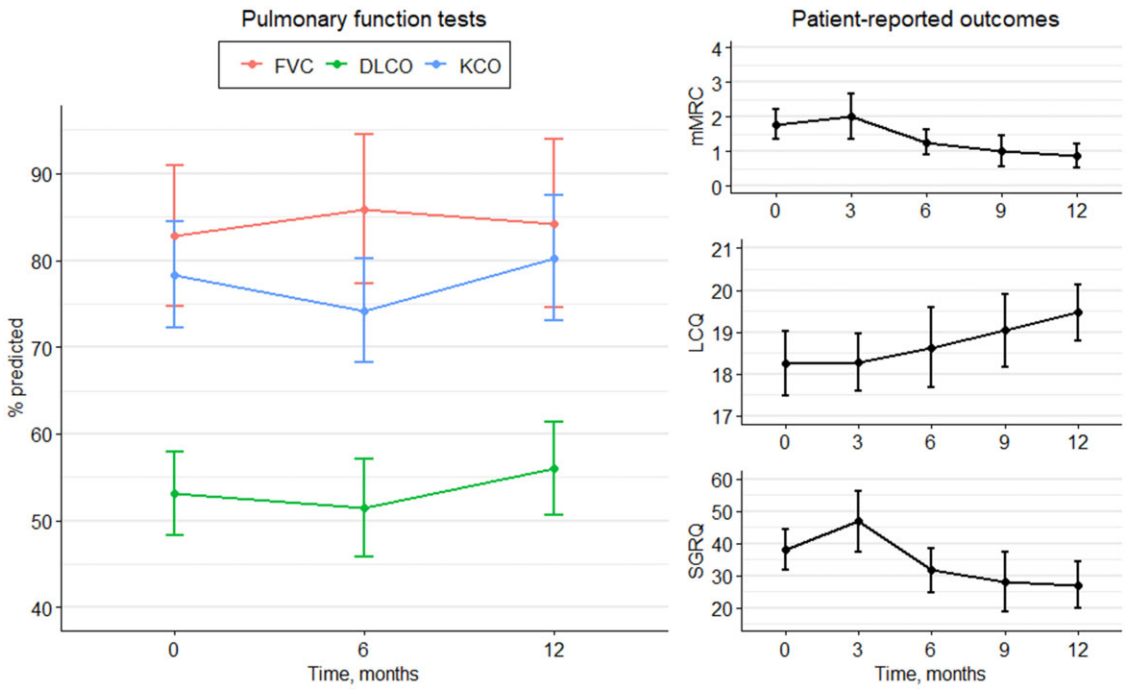

Figure 2. Efficacy outcomes as evaluated by spirometric values and PROMs. DLCO: diffusing capacity of the lungs for carbon monoxide; FVC: forced vital capacity; KCO: DLCO corrected for alveolar volume; LCQ: Leicester cough questionnaire; mMRC: modified Medical Research Council; PROM: patient-reported outcome measure; SGRQ: Saint George's Respiratory Questionnaire

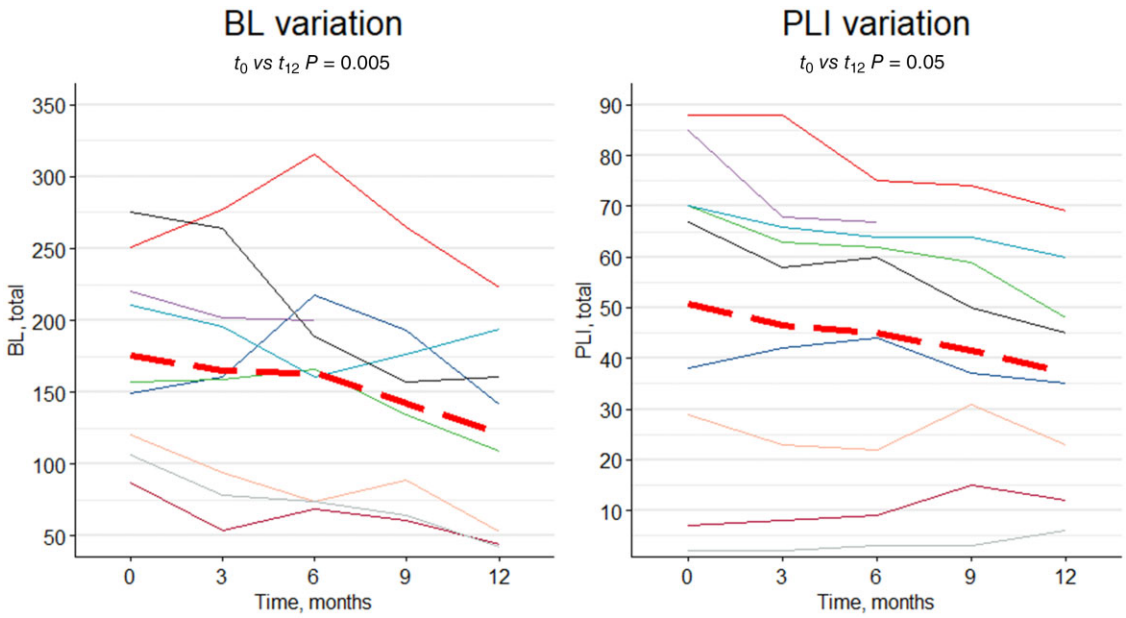

Figure 3. Lung ultrasound individual and mean variations during NIN treatment. BL: B-line; NIN: nintedanib; PLI: pleural line irregularities

results. Notably, no differences emerged between CALIPER parameters when considering HRCT patterns. On the other hand, several significant strong correlations were observed between CALIPER elements and pulmonary function tests both at baseline and after 12 months (Fig. 5). In particular, DLCO and KCO were negatively correlated with GG and VRS extent and directly correlated with normal parenchyma extent at both time points.

Discussion

Given its proven efficacy in slowing the decline of FVC, NIN is currently a pivotal drug in the management of SSc-ILD. However, little is known about imaging changes during NIN treatment. We therefore conducted this study to evaluate whether a 1-year antifibrotic therapy is associated with any variation in the two most important and promising imaging

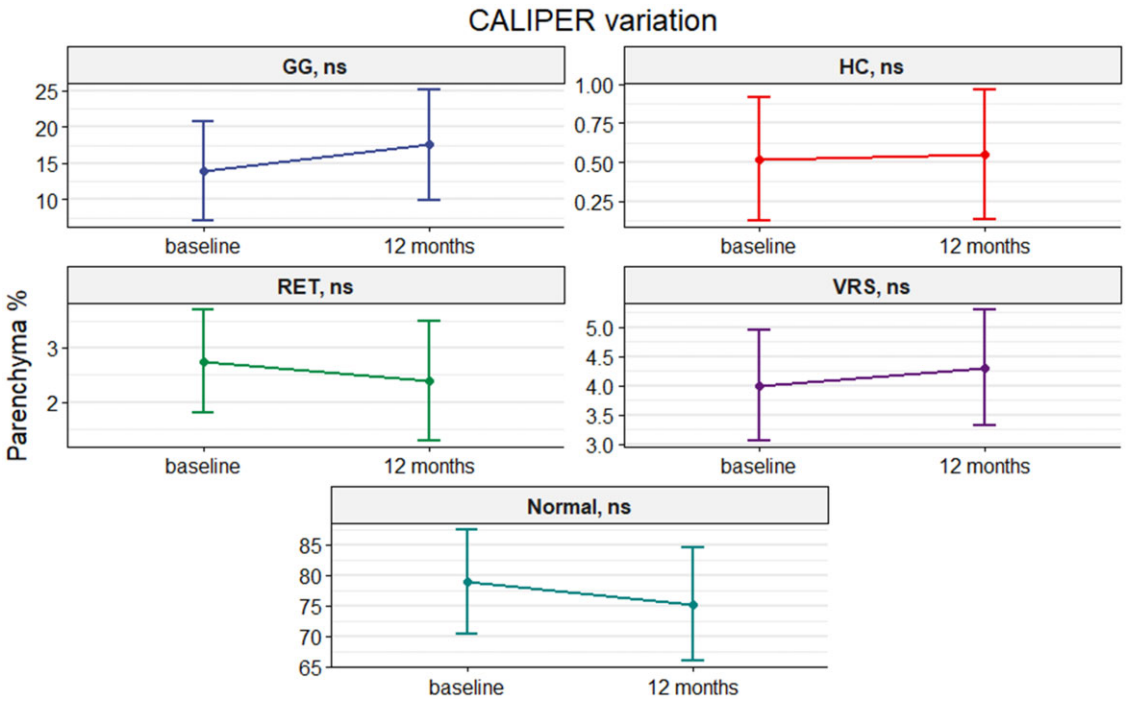

Figure 4. CALIPER parameters mean variation during NIN treatment. All *P*-values are not significant (ns). GG: ground glass; HC: honeycombing; RET: reticulation; VRS: vascular-related structures

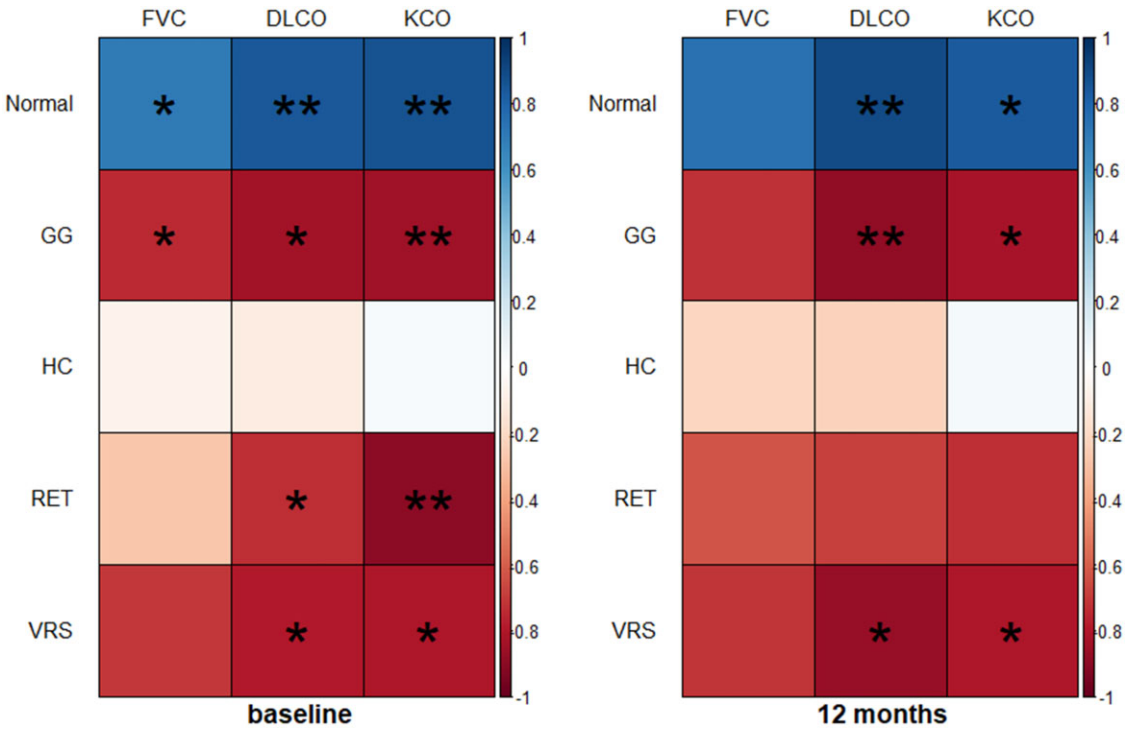

Figure 5. Correlations between CALIPER parameters and pulmonary function tests before and after NIN treatment. *P*-values: **P*<0.05, ***P*<0.01. DLCO: diffusing capacity of the lungs for carbon monoxide; FVC: forced vital capacity; GG: ground glass; HC: honeycombing; KCO: DLCO corrected for alveolar volume; NIN: nintedanib; RET: reticulation; VRS: vascular-related structures

techniques for ILD, namely CALIPER quantitative HRCT and LUS.

Although this was not the primary end-point of the study, in our cohort NIN confirmed its efficacy leading to a stabilization of spirometric parameters. Moreover, it was generally associated with an improvement or stabilization of PROMs. In particular, we observed an improvement in SGRQ in three-quarters of the cohort, an interest finding considering that in the SENSCIS trial this end-point was not met even with a lower meaningful cut-off [13]. The safety profile was consistent with what is reported in a recent meta-analysis of five NIN trials [22].

Given its advantages of feasibility, cost and absence of radiations, LUS is nowadays an increasingly used imaging technique both in research and in clinical practice. An increasing amount of evidence has been collected on the diagnostic and prognostic role of BL and PLI, but almost nothing is known about the role of LUS in monitoring SSc-ILD [11, 20, 23]. We evaluated BL and PLI quarterly and observed a constant reduction of both these LUS parameters during NIN treatment, reaching statistical significance after 12 months. The outcome of LUS appears to be influenced by some classic negative prognostic factors for SSc-ILD such as male gender, smoking habit or baseline FVC < 70% predicted. Although no correlations emerged between LUS and spirometric trends, we interestingly observed a significant association of BL and PLI with quality of life as assessed by three different PROMs. On this basis, LUS could be considered as an easy method to effectively monitor SSc-ILD patients treated with NIN.

Shortly after its development, several studies applied CALIPER to obtain a quantitative characterization of ILD in SSc [24, 25]. Baqir *et al.* used this software to monitor SSc-ILD patients treated with mycophenolate mofetil and described a stabilization over time of the different CALIPER percentages [26]. More recently, the effects of antifibrotic treatments on HRCT have been investigated with semi-quantitative and quantitative analyses in IPF patients [27, 28]. In particular, Lancaster *et al.* applied another quantitative analysis, namely the Quantitative Lung Fibrosis score, on 113 IPF patients and observed after 6 months that the cases treated with NIN had fewer fibrotic changes than those treated with placebo [28]. We used CALIPER to investigate changes in HRCT during NIN treatment for SSc-ILD, and after 12 months we did not observe significant reductions in normal parenchyma or increases in ILD elements (GG, HC and RET). Overall, it seems that NIN brings a 1-year stabilization of the various elements that characterize lung involvement on HRCT. These findings also agree with the stabilization observed on pulmonary function tests. Moreover, the strong correlations observed between some CALIPER elements and DLCO and KCO strengthen the relationship between this quantitative analysis and efficacy outcomes.

To the best of our knowledge, this is the first study to investigate NIN effects on SSc-ILD with LUS and CALIPER. However, some limitations burden our work. First of all, we lack a placebo control group, and this is due to the exploratory nature of the study, which only involved patients already candidates to start NIN. Furthermore, the small population size limits any generalization that could be achieved with a larger multicentric cohort. Regarding LUS, it has to be said that there is still no common consensus on the number of intercostal spaces to be assessed, thus limiting any comparison with other work. In this study we opted for a more comprehensive scanning protocol, which, however, certainly turns out to be more time-consuming. Moreover, clinical cut-offs for improvement, stability or worsening during patient monitoring have not yet been defined for either BL or PLI. Finally, two patients had a HRCT without technically adequate CALIPER segmentations and were therefore removed from the quantitative analysis, thereby further reducing the small cohort number.

Our preliminary data show an improvement in LUS score and a stabilization of CALIPER results in SSc-ILD patients after NIN therapy. The apparently different outcome could be related to the different physical principles that underlie the two imaging techniques, but further studies and more data are needed to clarify this issue.

Conclusion

Although our results are certainly preliminary and need to be confirmed in larger cohorts, LUS and quantitative analysis of HRCT are tools with interesting potential to assess the efficacy of NIN antifibrotic therapy in patients with SSc-ILD. Finally, we propose LUS as a useful method for the monitoring of therapy efficacy, while the use of CALIPER could help to substantiate HRCT.

Data availability

All data relevant to the study are included in the article. Further data are available from the corresponding author upon reasonable request.

Author contributions

Marco Di Battista (Conceptualization, Investigation, Statistical analysis, Data curation, Writing—original draft, Visualization), Andrea Delle Sedie (Conceptualization, Writing—review and editing, Visualization), Alessandra Della Rossa (Conceptualization, Writing—review and editing, Visualization), Chiara Romei (Investigation, Data curation, Writing—review and editing, Visualization), Mattia Da Rio (Investigation), Riccardo Morganti (Statistical analysis), Laura Tavanti (Writing—review and editing) and Marta Mosca (Supervision).

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