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Should we use nintedanib as early therapy in patients with SSc-ILD?

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ABSTRACT

Systemic sclerosis (SSc) is a heterogeneous autoimmune disease, where a significant proportion of patients develop interstitial lung disease (ILD), which is the major cause of mortality. In recent years, the diagnosis of SSc-ILD has improved a lot, and caring rheumatologists, together with pulmonologists, regularly screen and follow the development and course of ILD. Considerable progress has also been made in the treatment of SSc-ILD based on several clinical trials. The recommendations for immunosuppressive treatment have been modified and supplemented with targeted agents (tocilizumab, rituximab), and antifibrotic drugs such as nintedanib registered as a new treatment for SSc-ILD. However, there are no clear recommendations regarding the start and timing of nintedanib treatment. A debate on the early introduction of nintenadib or not took place on the 7th edition of the International Congress on Controversies in Rheumatology and Autoimmunity (CORA) in March/2023, and this review summarizes the main arguments that were discussed in this session.

1. Introduction

Systemic sclerosis (SSc) is a heterogeneous connective tissue disease characterized by different organ manifestations. Interstitial lung disease (ILD) is one of the most important clinical manifestations, which is the leading cause of mortality in the disease, responsible for up to 17% of SSc-related deaths [1]. The prevalence of SSc-ILD varies between 35 and 70% [2]. Risk factors associated with the development of SSc-ILD include male sex, diffuse cutaneous form (dcSSc), presence of anti-topoisomerase I antibodies (ATA), African-American race. Risk factors for ILD progression include shorter disease duration, ATA positivity, extent of fibrosis on high-resolution computed tomography (HRCT) >20%, decreased baseline forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO), gastroesophageal reflux disease and arthritis [3,4]. Early and accurate diagnosis of SSc-ILD is important to enable appropriate management and to start early treatment. It is also a crucial question which patient to start treating and when. It is well known that SSc is also heterogeneous in terms of ILD. Many patients experience clinically significant progression, especially in the first 3–5 years after the onset of the disease, and mortality rate is higher in patients with more extensive disease. Around 30% of SSc-ILD patients from the European Scleroderma Trials and Research (EUSTAR) group database showed progression within one year and 67% of all ILD patients progressed at any time over the mean 5-year follow up. In addition, there are patients who remain stable for years, others decline first and then become stable again [5]. The Scleroderma Lung Study (SLS) I and II showed that SSc-ILD participants who had an increase in the total quantitative radiographic extent of ILD scores ≥2% at 12 months (SLS I) or 24 months (SLS II) experienced significantly worse long-term survival than those with change scores <2% [6]. Our goal is to improve the survival and it can be said that in this heterogeneous group of patients it is often a challenge to start the appropriate treatment and its timing. Following SSc patients, ILD with a progressive phenotype should be selected for optimal patient management. In addition to traditional immunosuppressive drugs (mycophenolate mofetil [MMF], cyclophosphamide [CYC] etc), more patients receive targeted therapy (tocilizumab [TCZ], rituximab [RTX]) and/or antifibrotic therapy (nintedanib). In the clinical trials completed so far, patients received mono- and combination treatment, and more and more data are available from the real world about the clinical results of combination treatments that have not been used in studies so far (e.g. rituximab + nintedanib, tocilizumab + nintedanib, etc.) [7]. On the other hand, we do not have a precise recommendation whether to use these drugs in an early combination or to build them up gradually, or when to start the

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antifibrotic treatment. Taking into account the fact that even a small progression of fibrosis detected on HRCT results in a significant deterioration of survival, we must definitely push for anti-fibrosis treatment. At the same time, we know that due to the high rate of unpleasant side effects, we cannot expose our patients to those who do not necessarily benefit from the treatment. There are arguments in favor of early initiation of nintedanib and there are also arguments against the need for early treatment. A debate on the early introduction of nintenadib or not took place on the 7th edition of the International Congress on Controversies in Rheumatology and Autoimmunity (CORA), that was organized in Turin, Italy, in 2023, and this review summarizes the main arguments that were discussed in this session.

2. Should we use nintedanib as early therapy in patients with SSc-ILD? PROS

ILD is detectable in more than half of patients with SSc, with remarkably high morbidity and mortality [1,8]. While the extent of ILD does vary on baseline HRCT, an analysis of the Norwegian SSc (Nor-SSc) cohort has revealed that it is the mere diagnosis of SSc-ILD that significantly affects the outcome [2]. The main pathogenetic mechanism of SSc-ILD is self-sustaining progressive lung fibrosis secondary to excessive extracellular matrix deposition by activated fibroblasts and myofibroblasts, in response to chronic epithelial and endothelial injury as well as inflammation [9]. Until a few years ago, targeting the inflammatory component with immunosuppressants (IS) was the only available treatment. More recently, the SENSCIS trial has clearly demonstrated the efficacy of nintedanib in stabilizing lung function in patients with SSc-ILD [10]. Indeed, the drug was associated with a statistically significantly lower annual rate of change in FVC compared to placebo (delta 41 mL/y and 44% of preservation). Nintedanib is primarily a tyrosine-kinase inhibitor with antifibrotic properties, but it exerts also anti-inflammatory, anti-proliferative and anti-angiogenic activities [11]. Therefore, there is a strong mechanistic rationale for its early use in patients with SSc-ILD, independently of ILD extent [2]. Furthermore, follow-up studies in the SENSCIS cohort [12,13] shown the prolonged benefit of nintedanib over time, with annual FVC decline rates similar to those observed in SENSCIS, lending further support to long-term treatment.

Nintedanib has proven efficacious in a wide range of SSc-ILD patients; indeed, the inclusion criteria for the SENSCIS trial were purposely not stringent, with a disease duration of up to 7 years and an extent of fibrosis >10%, thus allowing the enrollment of a diversified and comprehensive cohort of SSc patients that mirrors the heterogeneity of the disease [14]. The baseline features of the study population (i.e. prevalence of Leroy subsets [15], and SSc-specific autoantibodies) were also in line with the epidemiology of the disease. Almost half of patients (48%) had the limited cutaneous form of SSc (lcSSc), whereas most trials conducted so far mainly enrolled patients with dcSSc, making it difficult to generalize the results to the entire SSc population. In fact, lcSSc is the most frequent disease subset and may be associated with a relevant frequency of ILD and a significant risk of ILD progression [16].

A subgroup analysis of the SENSCIS study population stratified by baseline characteristics [17] showed no influence of age, sex, Leroy subset or ATA positivity on the response to nintedanib. This reinforces the benefit of its early use in all patients with SSc-ILD, irrespective of their individual disease-specific features. Moreover, the drug has shown similar efficacy in both patients with the Non Specific Interstitial Pneumonia (NSIP)– the most common in SSc – and Usual Interstitial Pneumonia (UIP) – the most severe – pattern of ILD [18].

Until recently, IS was the only therapy available for SSc-ILD. In 2022 the Food and Drug Administration has approved TCZ, an IL-6 receptor inhibitor, for the treatment of SSc-ILD. Unlike the SENSCIS trial, the FocuSSced trial [19] showed the efficacy of TCZ vs. placebo in stabilizing FVC values over 48 weeks only in patients with early (disease duration <5 years) inflammatory dcSSc, a highly selected SSc population, which accounts for around 1% of all scleroderma patients. Moreover, a subsequent observational study, showed that the effect of TCZ in preserving lung function is lower in ATA negative than in ATA positive patients [20]. Based on this data, a recent American expert panel achieved very limited consensus on the therapeutic use of this drug in SSc-ILD and exclusively in this small subgroup of patients; furthermore, the consensus agreement was lower among pulmonologists than among rheumatologists [21]. A subgroup analysis of patients randomized to placebo in the SENSCIS cohort [22] has shown a significantly higher rate of FVC decline in those with shorter disease duration, elevated inflammation markers and higher mRSS vs. patients without these features. Notably, nintedanib reduced the rate of FVC decline across SSc subgroups, with a numerically greater effect in patients with risk factors for rapid FVC decline, suggesting that not only TCZ but also nintedanib may be efficacious in stabilizing FVC in this patient subset.

Regarding combination therapy, nearly half of the patients in the SENSCIS trial were on MMF at enrollment. A similar reduction in the rate of annual FVC decline was demonstrated in patients who were receiving MMF at baseline and in those who were not, suggesting a possible additive effect of the two drugs [23]. The efficacy of nintedanib monotherapy in SSc-ILD is equally important, as some patients with SSc-ILD do not have organ involvement other than the lung that requires immunosuppression. The same subgroup analysis found a similar frequency of adverse events, in particular gastrointestinal (GI), irrespective of whether patients were taking MMF at baseline, thus reassuring on the safety and tolerability of this combination therapy. Given the strong rationale for combining IS and nintedanib, further research is warranted on the combination between nintedanib and drugs other than MMF.

A recent clinical practice guideline on progressive pulmonary fibrosis suggests adding nintedanib in patients with fibrotic ILD other than idiopathic pulmonary fibrosis (IPF) who progress despite appropriate treatment [24]. However, ILD progression in SSc occurs in phases rather than gradually over time, and a 1-year period of FVC decline is often followed by a period of stability, with further decline thereafter [5]. Therefore, by waiting for ILD progression to occur before initiating maximal therapy, we may miss the opportunity to prevent pulmonary damage and impact on the natural history of this life-threatening disease. The data on ILD behavior, the strong pathogenetic rationale and the evidence on the efficacy of nintedanib across the spectrum of SSc-ILD patients, support its use since the early stages of the disease.

3. Should we use nintedanib as early therapy in patients with SSc-ILD? CONS

Despite widespread enthusiasm within the SSc community for the introduction of nintedanib in the therapeutic armamentarium of SSc-ILD, a number of factors are likely to restrict its use to a minority of patients. Unlike SSc-associated pulmonary arterial hypertension — in which all patients experience progressive disease and a remarkably poor prognosis [25] — the spectrum of SSc-ILD is highly heterogeneous, ranging from mild and stable to progressive forms [26]. Data from the EUSTAR database show that 73% to 77% of patients did not experience disease progression in each 12-month period over a mean follow-up of 5 years, although only a minority of them (89/826, 11%) were on IS [5]. Accordingly, a recent European expert consensus statement pointed out that, once the diagnosis of SSc-ILD has been established, the first step is to assess whether treatment is required, as “some patients might not need pharmacological therapy” [27]. Therefore, by introducing upfront nintedanib in SSc-ILD cases we may overtreat our patients, thus exposing them to unnecessary side effects.

According to a consensus statement on progressive pulmonary fibrosis, traditional therapies (i.e., IS in connective tissue disease-associated ILD) meet the needs of most patients with fibrotic ILD other than IPF [28]. Unlike IPF, wherein antifibrotics are the only drugs able to reduce functional decline and disease progression, the SSc community has four valid options for the treatment of SSc-ILD: CYC, MMF, TCZ and

RTX. To date, the efficacy of these drugs in SSc-ILD has been demonstrated in the setting of the following randomized controlled trials: the SLS I [29], II [30] and III [31] for CYC and/or MMF; the FaSScinate [32] and FocuSSced [19] trials for tocilizumab; the DESIRES [33] and RECITAL [34] trials for RTX. It is also worth noticing that, unlike the INBUILD and SENSCIS trials, in which nintedanib proved efficacious in *reducing* the annual rate of FVC decline vs. placebo, the SLS II showed that CYC and MMF were both able to *improve* the adjusted FVC % from baseline to 24 months by 2.86 (95% CI 1.19–4.58) and 2.17 (95% CI 0.53–3.84), respectively. Owing to its safer and more tolerable profile compared to CYC, MMF is the drug of choice in SSc-ILD, as highlighted by both the American and European expert consensus [21,27].

In the SENSCIS trial, nintedanib did not exert any beneficial effect on manifestations of SSc other than ILD, including the mRSS, which is considered a surrogate marker of disease severity in SSc [35]. Accordingly, recent algorithms for the treatment of SSc-ILD [36,37] have proposed nintedanib as first-line monotherapy only in patients without evidence of active skin or joint disease, who do not require immunosuppression. Since skin involvement and arthritis are two of the major risk factors for the development of progressive ILD in SSc [35,4,16] it follows that patients with SSc-ILD requiring nintedanib monotherapy represent a small subgroup.

A major concern with the use of nintedanib in SSc is the frequent occurrence of gastrointestinal side effects, as the disease affects the GI tract in over 90% of patients [38]. In the SENSCIS trial, diarrhoea was reported in 75.7% of patients treated with nintedanib (vs. 31.6% in the placebo arm), leading to permanent drug discontinuation in 6.9% (vs. 0.3% in the placebo arm), and $\geq$ 1 dose reduction and/or treatment interruption in 48.3% (vs. 12.2% in the placebo arm) [39]. A post-hoc analysis of data from the INPULSIS I and II (IPF), SENSCIS (SSc-ILD), and INBUILD (progressive fibrosing-ILD) trials revealed that nausea, vomiting, elevated liver enzymes, dose reductions, and treatment interruptions were more frequent in female patients [40]. This data should be strongly considered in SSc, given that over 75% of SSc-ILD patients in the SENSIC trial were female, in line with the remarkably higher frequency of the disease among females. In the SENSCIS trial, the type and frequency of adverse events did not differ significantly between patients on combination nintedanib-MMF and patients on nintedanib monotherapy [23], although the safety profile of the two drugs is very similar; however, the GI side effects are likely to be more common with combination therapy vs. MMF alone outside the setting of a clinical trial. Side effects ought to be counterbalanced by the benefit perceived by the patients. Yet, in the SENSIC trial, no differences in respiratory symptoms or health-related quality of life were observed between placebo and nintedanib-treated patients.

As mentioned earlier, the use of nintedanib in SSc is limited almost exclusively to combination therapy with IS. Yet, despite the strong rationale for targeting both the inflammatory and fibrotic component of SSc-ILD [41], the additive effect of nintedanib on top of MMF in preserving lung function is rather weak. In the SENSCIS trial, compared to MMF alone, the combination of MMF and nintedanib provided an additional benefit of only 20 mL in terms of preserved FVC over one year [23].

Preliminary data from the SLS III [31]— designed specifically to assess the efficacy of upfront combination of pirfenidone + MMF vs. MMF alone — showed that combination therapy led to a more rapid improvement in FVC % at 6 months compared to MMF alone, but the effect was lost after 18 months, wherein a similar improvement in both groups was observed. This data argues against a durable additive benefit of early combination of antifibrotic therapy + MMF vs. MMF alone.

Overall, the available evidence suggests that the risk-benefit ratio of early treating with nintedanib patients with SSc-ILD is favorable only in a minority of them. Therefore, early introduction of a drug that is likely to be continued for many years (if not lifelong) should be considered on a case-by-case basis, for instance as add-on therapy in patients with progressive SSc-ILD despite IS, in those intolerant to IS, or in patients at high risk of severe progressive ILD [21]. These patients, we believe, are likely to benefit the most from early treatment with nintedanib.

4. Conclusions

In recent years, significant progress has been made in the diagnostic and therapeutic possibilities of SSc, as a result of which the quality of life and survival of patients have improved. The use of immunosuppressive treatments for SSc-ILD has changed, new targeted medications have been approved, one of them being the antifibrotic nintedanib. However, the data from clinical trials do not fully cover daily practice, so there are still questions about the optimal initiation of immunosuppressive and antifibrotic treatment. At the beginning of the CORA debate session, early nintedanib supporters were in the majority, and at the end of the discussion, the number of those choosing early treatment increased. Overall, it can be said that in progressive forms of SSc-ILD patients, the introduction of early antifibrotic treatment seems to be justified, but at the same time, possible side effects and the risk-benefit ratio must be considered. In order to reduce side effects, it is essential to provide the patient with appropriate education and consult with diet and lifestyle advice. Further extensive investigations and observations are required to refine the treatment recommendations.

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Data availability

Data will be made available on request.

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