

NINTEDANIB: A NEW HOPE FOR PATIENTS WITH SYSTEMIC
SCLEROSIS-ASSOCIATED INTERSTITIAL LUNG DISEASE

by

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Scleroderma, or systemic sclerosis, is a rare autoimmune disease group that causes hardening and tightening of the skin. Systemic diffuse scleroderma is a subtype that can also damage internal organs. Systemic sclerosis-associated interstitial lung disease (SSc-ILD) is a condition in which the interstitial lung tissue becomes inflamed and undergoes irreversible fibrosis and is the leading cause of death for patients with diffuse scleroderma. Its progression is generally measured by the decline in forced vital capacity. Nintedanib (NIN) is a promising antifibrotic treatment that is FDA approved to treat SSc-ILD. This is a literature review in which three studies were selected to investigate the effectiveness and safety of NIN in comparison to an impactful precursor study. The selected studies indicate that NIN is associated with diminished lung progression and potentially reduces lung attenuation. NIN is an effective and safe treatment that can improve a SSc-ILD patient's quality of life and extend their lifespan.

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Introduction

Scleroderma

Scleroderma, also known as systemic sclerosis, is a group of rare autoimmune diseases that share a common symptom: hardening and tightening of the skin. Within the United States, there are around 276-300 cases per million and the most common demographic are adults assigned female at birth.¹ The severity of this disease increases among African and Native Americans, with a worsening prognosis if they are over the age of 45.¹ In 2013, Gelber et al.² reported African American patients had a higher (43%) cumulative incidence of mortality compared to white patients (35%) after 10 years. Although there are no clear genetic predispositions, investigators have seen higher prevalence of scleroderma within first degree relatives; with the majority of genetic factors falling into genes controlling inflammation and autoimmunity.^{3,4} This disease unfolds as an “excessive deposition of collagen” causing issues such as microvascular damage.⁵ Scleroderma is a chronic illness and difficult to diagnose due to the variety of symptoms. As a result of the various manifestations of the disease, there are two clear divisions: localized and systemic.

Localized scleroderma is a category in which the disease only affects the skin and the relatively superficial layers of fat, muscle, and fascia.⁶ Patients will present with discolored patches of skin. Within this category there are various manifestations associated with the descriptive term morphea. Circumscribed morphea is associated with only a few patches of discoloration.⁶ Generalized morphea involves various patches that affect multiple anatomical regions.⁶ Linear scleroderma is more common in children and presents as bands of discoloration on extremities or other regions.⁶ Patients with localized scleroderma are less often associated with increased mortality rates due to the advancement of treatments.⁷ These symptoms can go away

on their own, however, a small percentage of these patients will progress from localized to systemic scleroderma.

Systemic scleroderma (SS) is a more severe development of the disease not only affecting the skin but also damaging internal organs and blood vessels. There are three main types of SS: limited, sine, and diffuse. Limited scleroderma is the most common type and characterized with hardening of the skin around the distal extremities and the face.¹ If it becomes more internalized, limited SS will affect the gastrointestinal (GI) tract, cause musculoskeletal pain, and the patient will present with severe Raynaud's phenomenon (RP). This phenomenon entails the constriction of blood vessels within the fingers, which will become pale, when the patient is exposed to a cold temperature.⁸ It is recommended to monitor the disease's progression to determine if it is becoming more aggressive. Those with sine sclerosis have systemic organ disease and RP yet do not experience any skin thickening. Out of all the types of SS, diffuse scleroderma is the most dangerous subtype due to the significant organ damage it can cause throughout the body. Diffuse scleroderma will also harden the skin of proximal extremities and the trunk. There are individuals that will not develop systemic organ disease, however, it will most likely begin affecting organs within three years of its onset.¹ Diagnosing a patient with diffuse scleroderma can be challenging since there are many symptoms and a variety of scleroderma subtypes; even so, early detection is essential to manage the internal organ involvement.⁷ At this stage of the disease progression, the only path to follow is to alleviate the numerous symptoms and to frequently monitor various internal organs to prevent any detrimental progression.

Symptoms of diffuse scleroderma

Raynaud's phenomenon (RP) is often the first symptom that presents in patients with systemic scleroderma, even before any visible skin thickening. When the patient is exposed to the cold or is distressed, their fingers will become pale due to the constriction of peripheral blood vessels.⁸ However, those with diffuse scleroderma will experience RP either at the same time or shortly after their skin begins to thicken.⁷ If this symptom worsens, it can cause ulcers at the fingertips and overall loss of tissue.⁷ Additionally, disability within diffuse scleroderma is caused by the progression of musculoskeletal disease. This process will "entrap joints and tendons", causing a multitude of issues such as pain and weakness.¹ For many of these patients GI disease, such as esophageal dysfunction, causes poor quality of life (QOL) due to GI reflux disease and further damage the esophagus.¹

Scleroderma patients are susceptible to heart disease, which is fatal if not noticed in its beginning stages. The poor prognosis is related to various silent clinical signs such as pericardial effusion, the accumulation of fluid in the pericardium, and valvular disease.⁹ If scleroderma manifests within the kidneys, there is a possibility that it will develop into scleroderma renal crisis (SRC). This medical emergency is caused by "malignant hypertension and progressive renal failure" and is developed in about 10% of patients.¹⁰ Pulmonary diseases, comprised of pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD), have become the main cause of death within diffuse scleroderma, now surpassing SRC.¹¹ Between both of these diseases, systemic sclerosis-associated ILD (SSc-ILD) has the higher mortality rate of 33% and requires further investigation.¹²

Interstitial lung disease

Approximately 50% of patients with diffuse scleroderma will develop ILD at the five year mark from diagnosis.¹² The longer a patient with SSc-ILD goes undiagnosed, the worse their prognosis becomes. In order to diagnose a patient noninvasively with SSc-ILD, high-resolution computed tomography (HRCT) imaging is necessary.¹³ If this imaging demonstrates a pattern of nonspecific interstitial pneumonitis (NSIP) or the less common usual interstitial pneumonitis (UIP) pattern, SSc-ILD is diagnosed.^{13,14} NSIP is an autoimmune-associated disorder causing inflammation of the alveolar (air sacs) walls that will eventually lead to permanent scars.¹⁵ UIP also causes progressive scarring within the pulmonary interstitium and is a defining characteristic of idiopathic pulmonary fibrosis but can be seen in ILD.¹⁶ Both present patterns of chronic fibrosis in HRCT imaging.

To create the most effective intervention and prevention of SSc-ILD progression, it is essential to have patients undergo frequent testing.¹² There are two preferred methods to measure their pulmonary function; the first being forced vital capacity (FVC).¹² This measurement is based on the maximum amount of air the patient can expel after inhaling deeply.¹⁷ Once there is a decline of $\geq 10\%$ from the patient's baseline, it is considered as progression of ILD.¹³ The second test is diffusion lung capacity for carbon monoxide (DLCO), which is the measurement of the capacity that patient's lungs have to transfer inspired CO into the bloodstream.^{12,18} A 5-9% decline in FVC and a $\geq 15\%$ decline in DLCO is indicative of progression.¹³ This disease has complicated mechanisms that result in the progression of inflammation and the irreversible fibrosis of lung tissue.¹² Treatments for SSc-ILD center around the disease's advancement and its various theoretical mechanisms; yet they can only slow its progression.

Invasive treatments of ILD

Currently investigators consider two invasive treatments for SSc-ILD: autologous hematopoietic stem cell transplantation (AHSCT) and lung transplantation (LTx).¹⁹ Both treatments are limited and have multiple requirements, therefore are considered as a last resort. The first treatment involves a three step process that begins with the collection of mobilized stem cells, continues with the administration of immunoablative or myeloablative regimens, and ends with the infusion of the proper autologous stem cells.²⁰ Immunoablation is the overall destruction a patient's immune resistance.²⁰ AHSCT trials have been reported to not only stabilize internal organ function but also improve skin thickening.²⁰ While it is more effective than other immunosuppressive therapies in terms of long-term survival, there is risk for fatal infections due to the aggressiveness of the treatment.²⁰ The selection and monitoring of patients needs to be conducted very carefully to ensure the success of AHSCT.¹⁹

If patients are unresponsive to various medical therapies, they would be considered a potential candidate for LTx.¹¹ However, if other organs are involved, this possibility is limited. This option is often a last resort if the disease has progressed too far. There are a few overlapping phases and various screenings required in order for the patient to prepare for LTx.²¹ The first step requires transplant referral, then the transplant center will follow up with an evaluation period.²¹ As soon as the patient is accepted, the transplant team will actively list the patient; throughout this process their disease progression consistently managed by ILD specialists.²¹ Common risk factors post-surgery include advanced age, weight status, and the use of immunosuppressants.²¹ Recently, researchers found a 70% survival rate for patients with SSc-ILD 5 years post-surgery.²² After a successful LTx, patients will have a significantly improved QOL, however, they will need to have recurrent check-ups to identify any comorbidities.²¹

Immunomodulatory agent treatments

The most common conservative treatment route for advanced SSc-ILD includes the following immunomodulatory medications: cyclophosphamide (CYC) and mycophenolate mofetil (MMF).¹⁹ They are both cytotoxic (toxic to cells) and are considered to be disease modifying anti-rheumatic drugs (DMARD).¹⁹ DMARDs are a class of suppressive immunomodulatory drugs designed to treat various inflammatory arthritides such as rheumatoid arthritis.^{19,23} Immunomodulators are drugs that change a patient's immune system to combat a certain illness; either stimulating or suppressing the immune system.²⁴ These drugs are more commonly used to treat cancer patients to aid other treatments.²⁴

Historically, CYC is commonly used to treat SSc-ILD and has demonstrated preservation of pulmonary function.²⁵ It has been administered as either intravenous (IV) pulses or orally.²⁵ However, it can be too toxic for patients and cause a multitude of side effects, such as bone marrow suppression, thus limiting the duration of treatment.^{25,26} Recently, there has been a shift towards the administration of MMF because it is safer than CYC in terms of its toxicity.¹⁴ MMF is an immunosuppressant most often used in combination with other medications for patients receiving organ transplants.²⁷ Various clinical trials have shown improved FVC and dyspnea measures.¹⁴ In recent trials, clinicians prescribed MMF, resulting in similar outcomes to CYC without producing significant toxicity levels or fertility concerns commonly associated with CYC.¹⁹

Biologic drug treatments

Another class of drugs recently used to treat SSc-ILD are biologic DMARDs. Biologic drugs are laboratory produced proteins that target pathways of the immune response, specifically for inflammation.²⁸ Drugs such as rituximab (RTX) and tocilizumab (TCZ) have been used as

part of an earlier start in the treatment of SSc-ILD. If the ILD is just beginning to develop, it might be better to use this alternative rather than the harsher cytotoxic therapies.¹⁴ Various studies of these treatments have demonstrated a decrease in lung function decline.¹⁴

RTX is a type of chimeric monoclonal antibody, which is a singular antibody produced from a non-human organism. It targets a specific type of CD20, a class of transmembrane protein located on B cells.¹⁹ Recently, researchers report improved outcomes regarding FVC and DLCO.¹⁹ TCZ is an anti-IL6 receptor monoclonal antibody that helps reduce inflammation and thus improve the symptoms of SSc-ILD.¹⁹ Interleukin-6 (IL6) is a cytokine that induces the expression of proteins responsible for acute inflammation.²⁹ Due to the numerous outcomes associated with significant improvement, TCZ has been approved by the Food and Drug Administration (FDA) as a form of treatment for SSc-ILD.¹⁹ TCZ is being used earlier to manage SSc-ILD at its beginning stages rather than waiting for enough progression to begin DMARDs.¹⁹

Anti-fibrotic treatments

Lung fibrosis is the irreversible build-up of scar tissue within the lungs and thus anti-fibrotics are designed to attenuate fibrosis. Progressive fibrosis of the lung's interstitial tissue leads to mechanical stiffness which will negatively impact lung function.¹² Drug treatments cannot reverse the effects of fibrosis nor completely halt the process, however they may reduce the rate of decline in lung function.¹² The main anti-fibrotics currently being studied and administered to patients with SSc-ILD are pirfenidone (PFD) and nintedanib (NIN).¹⁹ Both drugs have been used to treat idiopathic pulmonary fibrosis (IPF) which has clinical and pathological overlap with SSc-ILD.³⁰ PFD is prescribed as an oral medication but in recent randomized control trials (RCTs) there wasn't a significant reduction in DLCO decline in comparison to the control group.³⁰ There are more studies underway to combine MMF and PFD to examine the

efficacy on the primary endpoint difference rate in FVC.¹⁹ On the other hand, NIN has more promising evidence to support its efficacy as a treatment for SSc-ILD.

Nintedanib

NIN is a tyrosine kinase inhibitor that competitively binds to adenosine triphosphate (ATP)-binding pockets of certain receptors in order to prevent the release of specific growth factors that contribute to lung fibrosis.¹⁹ Tyrosine kinase is an enzyme whose role is to transfer a phosphate group from ATP to tyrosine residues of certain proteins within a cell.³¹ It was first approved by the FDA to treat IPF in 2014, and was recently been approved in 2019 for SSc-ILD.¹⁹ Within IPF, the tyrosine kinases will activate cell-signaling pathways that cause the pathogenesis of IPF. After a large, randomized, double-blind, and placebo-controlled study in patients with IPF, researchers found NIN “significantly reduced the rate of decline in FVC” over the span of 52 weeks.³² Even though IPF and SSc-ILD have distinct triggers, their pathophysiological processes both result in the build-up of scar tissue.³³

Another reason for the use of NIN to treat SSc-ILD is because various animal models with aspects of SSc-ILD in which NIN was used, demonstrated antifibrotic effects.³³ Recently, in a large-scale, randomized, double-blinded trial, which was placebo-controlled, researchers investigated the effectiveness and safety profile of NIN in human patients with SSc-ILD.¹² Investigators administered 150 mg of NIN or a placebo orally twice daily.³³ The most common adverse effects were diarrhea (75.7% from NIN group), nausea (31.6%), and vomiting (24.7%).³³ As previously mentioned, the best method to determine the disease’s progression and indications of reduced life expectancy is the decline in FVC.³² At the primary end-point of the trial (52 weeks) patients taking NIN (52.4 ml) had a smaller annual rate of decline of FVC than those receiving the placebo (93.3 ml) within a 95% confidence interval and a p-value of 0.04.³³ NIN’s

effectiveness is still being studied and more trials are underway to evaluate prognosis in SSc-ILD patients.

Research question and methods

This paper is a literature review about scleroderma, SSc-ILD, and the recently approved drug treatment nintedanib. The question I answered throughout my research was: how effective is NIN as a treatment for patients with SSc-ILD? I was inspired to write about this disease from personal experience regarding how complicated and confusing diffuse scleroderma can be even with limited medical knowledge. My goal is to help highlight and inform others about scleroderma, a complicated and not well-known disease, and explain why nintedanib is important to improving the prognosis of ILD. Additionally, it is critical to condense the available literature to potentially help guide researchers and health care professionals recommending treatments to patients with SSc-ILD.

I conducted six steps for my literature review based on the handbook of eHealth Evaluation: 1) forming the research question (using the PICO method), 2) searching the existing literature, 3) screening papers for inclusion and exclusion, 4) determining the qualities of the main studies, 5) extracting data from those papers, and 6) analysis of the data.³⁴ Each letter in PICO stands for a different part of the research question: patient or problem (P), intervention (I), comparison (C), and outcome (O).³⁵ The existing literature was hand-searched using the search terms: “nintedanib” and “interstitial lung disease” and “scleroderma” within the database PubMed. To define various terms, reputable sources such as Cleveland Clinic were hand-searched as well.

The inclusion criteria for the selected studies included articles on PubMed that are trial based on NIN. The terms “nintedanib” and “lung disease” and “scleroderma” were used to find

NIN trials. Many of the remaining studies were subset analyses from the findings of Distler et al.³³ and thus my exclusion criteria included the following keyword: SENSISCIS. This was the previously mentioned large randomized double-blind trial which included patients with ILD associated with systemic sclerosis.³³ From those articles, I excluded papers of patients with sine scleroderma and limited scleroderma, as well as investigations focusing a drug-to-drug interaction or antibodies.

Results

Study Selection

In total, three studies met inclusion criteria: a global RCT³⁷, a retrospective cohort study³⁸, and a case report³⁹ and were published after the global success of the Efficacy and Safety of Nintedanib in Systemic Sclerosis (SENSISCIS) trial by Distler et al.³³. These authors' research facilitated the previously mentioned FDA approval in 2019 and inspired further research regarding NIN's efficacy and safety in a clinical setting. This is the first formative study with substantial results and associated with the largest sample in comparison to the selected studies. Therefore, it will be used as a baseline to compare the selected studies.

A subgroup analysis of Flaherty et al.'s³⁶ larger INBUILD trial, the same type of global study as the SENSISCIS trial, was published by Matteson et al.³⁷ in 2022 and focused on using NIN with patients that had ILD due to an autoimmune disease such as scleroderma. Approximately 23% of these patients had SSc-ILD, were diagnosed with diffuse scleroderma for an average of 4 years and were mostly older females in both the NIN and placebo groups. In an Italian multicenter cohort study published by Campochiaro et al.³⁸ in 2023, researchers prescribed each patient NIN and retrospectively analyzed their results while maintaining any previous immunosuppressive treatments. Their patients held an older female majority; however,

their average diffuse scleroderma duration was 8.8 years. Each of these studies were associated with significant findings as well as accompanying adverse effects. The final selected article was a case report by Nishino et al.³⁹ in 2021 regarding a 73-year-old woman with systemic scleroderma and pulmonary fibrosis, one of the key symptoms of ILD. This patient was given NIN for 8 months and her improvement analyzed from chest computed tomography (CT) scans.³⁹

Forced vital capacity

In each of the cohort studies investigators measured forced vital capacity (FVC) to determine NIN's effectiveness in slowing down fibrosis within patients with SSc-ILD. The yearly rate of decline in FVC (ml/year) was measured for the NIN and placebo groups in both the SENSICIS trial and Matteson et al. studies. The latter study group found the data significantly favored NIN when compared to the placebo.³⁷ Additionally, autoimmune disease-related ILD patients had a reduced yearly rate of decline for NIN (-75.9 ml/year) in comparison to the placebo (-178.6 ml/year).³⁷ Campochiaro et al.³⁸ measured the percent predicted FVC (%pFVC) 12 months before NIN introduction (baseline), as well as 6 months and 12 months after NIN introduction. Approximately 17% of patients with a UIP pattern in their HRCT scans had a significant increase in %pFVC from 55% to 59% at six months.³⁸ At baseline 60% of patients had a significant decline in %pFVC whereas 44% of patients had a stabilized %pFVC from 64% to 62% 12 months after NIN introduction.³⁸ While these results are promising, there were other important variables reported for the majority of these studies.

Secondary factors

The SENSICIS researchers and Campochiaro et al. evaluated skin thickness using the modified Rodnan skin score (mRSS), which gives a score ranging from 0-3 (0 is no skin

thickening and 3 is severe skin thickening), and reported no significant mRSS change compared to baseline.^{7,33,38} Within the SENSICIS trial, researchers analyzed various secondary endpoints associated with the St. George's Respiratory Questionnaire (SGRQ), a self-completed questionnaire about the patient's perceived QOL that specializes in respiratory diseases, and found a minimal difference from baseline.^{33,40} Campochiaro et al. additionally identified the percentage of patients with lung progression, percent predicted total lung capacity (%pTLC), and percent predicted DLCO (%pDLCO).³⁸ They reported 60% of patients had significant lung progression 12 months prior to using NIN but it lowered to 17.5% 12 months after NIN introduction.³⁸ At six months, both %pTLC (65% to 62%) and %pDLCO (42% to 43%) stabilized from baseline.³⁸ At 12 months, there was a stabilization of %pTLC (64% to 61%) but not of %pDLCO, which significantly declined from 37% to 34%.³⁸ Campochiaro et al. also analyzed the results of patients using NIN in combination with other immunosuppressants (RTX, TCZ, or MMF with either RTX/TCZ) however, none of these patients had significant changes in their lung function tests at either follow up.³⁸ Overall, the data across the studies highlights NIN's effectiveness in diminishing lung progression for SSc-ILD.

There is preliminary evidence pointing to NIN being an important factor in the lung's attenuation from the earlier stages of ILD. Nishino et al.³⁹ reported their patient had come into the clinic with SSc-interstitial pneumonia with signs of dyspnea. Their initial CT scan included ground-glass opacities, areas within the lung that are attenuated based on bronchial and vascular markings, within the lower lobes of her lungs. Therefore, they initially treated her with prednisolone (corticosteroid) and tacrolimus (immunosuppressant).^{39,41} After a follow-up CT scan, they noticed an expansion of ground-glass opacities and changed the treatment to NIN for 8 months.³⁹ Within the final CT scan, these researchers reported the ground-glass opacities had

regressed and the patient had decreased dyspnea.³⁹ The results are promising, however further research is needed to determine NIN's effectiveness against interstitial pneumonia and aid in ground-glass opacity regressions.

Adverse effects

Although NIN has produced promising results, it is also important to evaluate its safety by investigating associated adverse effects (AE). Across all three studies, the key adverse effects were related to the digestive system, specifically along the GI tract. Matteson et al.³⁷ reported that 63.4% of the NIN group and 27.3% of the placebo group experienced diarrhea. This was the most frequent AE, causing discontinuation of the trial for 17.1% of patients in the NIN group and 10.2% of patients in the placebo group.³⁷ The most common adverse effect for the SENSICIS trial was diarrhea as well.³³ This combination of adverse effects led to the discontinuation of 16% of patients in the NIN group and 8.7% of the placebo group.³³ Campochiaro et al.³⁸ reported 29% of patients experienced diarrhea and seven patients had an observable liver toxicity. Twenty-eight percent of patients required a 33% dosage reduction of NIN and 10% of patients discontinued treatment.³⁸

In advanced stages of diffuse scleroderma, mortality can occur despite rigorous treatment. Over the course of Matteson et al.'s study, death occurred in 9.8% of participants in the NIN group and 12.5% of participants in the placebo group.³⁷ Within the SENSICIS trial death occurred in 3.5% of NIN group and 3.1% of the placebo group; both groups experiencing a mixture of cardiovascular and respiratory related causes.³³ During Campochiaro et al.'s study, four patients pass away within 4-14 months with a median time of 10 months.³⁸ It is important to reiterate the overall negative impact of diffuse scleroderma throughout the body; their heart, kidneys, and GI tract could be affected along with their lungs. Due to the severity of SSc-ILD, it

is highly recommended to start their treatment as soon as possible once they are diagnosed with ILD.

Discussion

Throughout all these studies there is significant evidence that NIN helps reduce the progression of SSc-ILD. The scope of the SENSICIS study produced enough data for further subset analyzes regarding the effectiveness of NIN by other researchers. All the selected studies illustrated how lung progression is significantly diminished after using NIN for one year in comparison to the placebo. For patients with SSc-ILD, diminishing lung progression is equivalent to extending their life span and the improvement of their QOL as it becomes easier to breathe. Producing drastic changes within patients that have had the disease for years, one can wonder how much NIN could help them at the earlier stages of SSc-ILD. There is preliminary evidence that NIN can aid in the regression of ground-glass opacities that are caused by a symptom of ILD, interstitial pneumonia.³⁹ Although these results are clinically promising, there are still gaps in knowledge related to effective treatments for SSc-ILD that need to be answered with further research.

Currently, there is a lack of US studies available with respect to NIN being an effective treatment for SSc-ILD. Only Distler et al.³³ and Matteson et al.³⁷ included US subjects within their global investigations. Additionally, diversity throughout all the studies is essential to better understand how SSc-ILD can be effectively managed across different persons. Notably, there should be data to compare different population demographics to each other. As previously mentioned, African Americans and Native Americans are at greater risk than other populations for more severe forms of scleroderma.¹ Yet Matteson et al. only had 5 participants from either demographic group in their study which inhibits further analysis.³⁷ Future researchers should

consider studies within the US that include more at-risk populations at the forefront of their analysis to determine how beneficial NIN is for them.

There are many routes future researchers could take to further investigate NIN. A point of interest is the effectiveness of NIN when used along with other immunosuppressants.

Campochiaro et al.³⁸ dedicated a portion of their study to this matter but were without significant findings. Creating more trials that compare NIN alone to NIN with another immunosuppressant such as RTX will help inform clinicians of NIN's compatibility with other treatments. On the other hand, researchers could also compare the effectiveness of NIN to TCZ which is the other FDA approved treatment for SSc-ILD.¹⁹ If NIN is an antifibrotic and TCZ is a biologic immunosuppressant, could there be a better mechanism that should be treated for patients with SSc-ILD?

One of the main reasons that patients discontinue treatments in general including and the use of NIN are associated adverse effects. Patients with SSc-ILD already undergo multiple treatments for symptoms outside of ILD and can be more susceptible to adverse effects.¹ The most common adverse effects were related to the GI tract and involved nausea and diarrhea. Keeping this in mind, it is important to listen to a patient's discomfort and change the dosage when possible. Determination of a minimal effective dose could inform clinicians and potentially reduce AEs in patients. If patients discontinue treatment, ILD will most likely progress at a faster rate and decrease their lifespan. Campochiaro et al.³⁸ explained they would lower the dosage if the patient's adverse effects persisted and only 10% of patients completely discontinue treatment in comparison both Distler et al.'s³³ (16%) and Matteson et al.'s³⁷ (17.1%) NIN groups. In general, medical professionals should keep the wellbeing of their patients in mind which includes having consistent conversations with them to limit adverse effects.

This literature review is associated with several limitations. These include available published data, time, and person-power. While initially inspired by the promising results associated with the use of NIN through the SENSICIS study, I anticipated there would be more follow-up studies which would further explain the effect of treatments for SSc-ILD globally and in the US. However, to-date, the available findings are limited to 3 cohort studies with limited US and demographic representation. It is possible the available data will increase in the near future, due to approval of NIN within the US by the FDA. Additionally, based upon the potential scope of this project and associated timelines, there was a limited amount of time to collect and analyze potential articles for this review. As a literature review by a primary investigator, this project addresses a realistic approach in addressing NIN as a viable treatment for SSc-ILD, even though the exclusion criteria were increased to create a reasonable effort associated with this question. However, a more robust approach for synthesizing the literature could be more complete if conducted through a systematic review or meta-analysis and accompanied with a larger number of personnel to meet demands of the effort required for analyzing the highest level of evidence. Importantly, additional databases such as Web of Science or Medline could have been used to increase the scope of available studies, but PubMed was the only database utilized for this literature review. Lastly, the only chosen studies were either published or translated in English which may have limited the number of articles included in this review.

Conclusion

Scleroderma, or systemic sclerosis, is an autoimmune disease group that shares skin hardening as a common symptom. Systemic diffuse scleroderma is a subtype in which the disease begins affecting internal organs such as the heart and kidneys. Once the lungs are affected the patient will develop interstitial lung disease, a life-threatening condition that results

in the progression of inflammation and the irreversible fibrosis of interstitial lung tissue. There are several treatments for SSc-ILD depending on the associated mechanism of progressive decline in lung function, but the more recently approved treatment antifibrotic NIN has shown promising results. While future investigations should increase the diversity of the demographics of patients to further our understanding of population specific outcomes, NIN is associated with diminished lung progression which can extend the lifespan and improve quality of life of patients with systemic sclerosis and interstitial lung disease.

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