Prevention and management of gastrointestinal side effects in patients with systemic sclerosis-interstitial lung disease receiving anti-fibrotic therapy: a modified Delphi consensus study

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Abstract

Objective

Interstitial lung disease (ILD) is one of the most common manifestations of systemic sclerosis (SSc), with most patients requiring treatment with immunosuppressive or anti-fibrotic agents to control ILD progression. Since gastrointestinal (GI) tract complications are widespread in this patient setting, we focused on their prevention and management.

Methods

We conducted a modified Delphi study following best practices for consensus studies. We involved 20 expert rheumatologists from 8 Italian regions in two online rounds conducted between April and September 2024.

Results

An agreement of at least two-thirds of panellists was achieved on most topics explored, including the need for a preliminary evaluation of GI status in patients with SSc-ILD undergoing anti-fibrotic therapy (100% agreement), taking into account the presence of pre-existing diarrhoea (100%), weight loss (95%) and nausea/loss of appetite (100%), the definition of specific tests and exams for these conditions, the need of informing patients on potential GI complications (100%) and nutritional preventive advice (85%), and the monitoring of GI status during anti-fibrotic therapy (100%), at 3-month intervals (75%). Further, dose-reduction of anti-fibrotic therapy and, if needed, temporary discontinuation, was agreed in presence of side effects including diarrhoea (95%) or weight loss (85%). In the presence of nausea or loss of appetite, dose-reduction was also agreed, with no immediate need for drug discontinuation (90%).

Conclusion

This study provided a detailed list of expert-based recommendations to guide everyday clinical practice of SSc-ILD, though prospective validation is needed to confirm their effectiveness in preventing and managing GI side effects.

Key words

anti-fibrotic therapy, Delphi consensus, gastrointestinal side effects, interstitial lung disease, systemic sclerosis

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Introduction

Systemic sclerosis (SSc) is a rare autoimmune connective tissue disease, characterised by widespread organ involvement and significant clinical heterogeneity (1). The disease is associated with substantial morbidity and mortality, primarily due to complications affecting the lungs, gastrointestinal tract, kidneys and cardiovascular system. Gastrointestinal manifestations occur in nearly all SSc patients and include gastroesophageal reflux disease, gastroparesis, small intestinal bacterial overgrowth and malabsorption, significantly impacting nutritional status and quality of life. Interstitial lung disease (ILD) represents one of the most common and life-threatening manifestations of SSc, affecting up to 50% of patients and serving as a leading cause of mortality (2, 3). The progression of SSc-associated ILD is highly variable, driven by the SSc clinical phenotype (4), but most patients require treatment with immunosuppressive or anti-fibrotic agents to prevent or delay disease progression. Nintedanib, the only therapy approved in Europe for the treatment of SSc-ILD, is a small molecule tyrosine kinase inhibitor that showed efficacy in reducing the decline in lung functions in the pivotal SENSCIS trial (5-7). However, this therapeutic benefit comes with significant challenges in managing gastrointestinal side effects. Notably, the SENSCIS trial revealed higher rates of gastrointestinal adverse events in SSc-ILD patients compared to those observed in previous nintedanib trials in idiopathic pulmonary fibrosis (8, 9), likely reflecting the pre-existing GI involvement characteristic of SSc (5, 8, 9). The combination of pre-existing SSc-related gastrointestinal dysfunction and nintedanib-induced adverse events creates a complex clinical scenario requiring careful management (10-13). Real-world studies have confirmed that gastrointestinal complications can significantly impact treatment adherence and patient quality of life, potentially compromising the therapeutic benefits of anti-fibrotic therapy (14). Therefore, developing comprehensive strategies for prevention and management of gastrointestinal complications in SSc-ILD patients receiving nintedanib is essential for optimising treatment outcomes.

Few guidelines focus on managing gastrointestinal symptoms in SSc (15, 16), and recommendations for patients with associated ILD and treated with nintedanib are even more limited. In the Summary of Medicine Product Characteristics, it is recommended to handle gastrointestinal adverse reactions through symptomatic treatment (*e.g.* anti-diarrheal and anti-emetic therapy) and, possibly, dose-reduction and nintedanib discontinuation (17). However, information is still scant. In this context, consensus studies involving physicians who manage SSc-ILD may be valuable for addressing this knowledge gap (3, 18). Therefore, we conducted an online Delphi study of Italian disease experts, focusing on prevention and management of potential gastrointestinal complications in SSc-ILD patients, before and during anti-fibrotic therapy. Our aim was to develop good clinical practice indications to assist and improve patient management by rheumatologists.

Methods

This modified e-Delphi study was conducted following established guidelines for defining consensus in Delphi studies (19), and adhered to best practices, including anonymity, iteration, controlled feedback, and statistical stability of consensus (20). Reporting followed the recent ACCORD guidelines for consensus methods in biomedicine (21). The study protocol was not prospectively registered. The whole project was conducted between October 2023 and November 2024. As nintedanib is currently the only approved agent for SSc-ILD in Europe, the terms "anti-fibrotic therapy" and "nintedanib" are generally used interchangeably in the manuscript, and the consensus recommendations primarily pertain to nintedanib.

Literature review

A non-systematic literature review was conducted between October and November 2023 to identify knowledge gaps regarding gastrointestinal

complications of SSc-ILD patients in relation to anti-fibrotic therapy use, and to inform the Delphi method. We searched PubMed/MEDLINE and Google Scholar for papers published since 2019 (*i.e.* year of FDA approval of nintedanib for SSc-ILD and publication SENSCIS trial findings (5)), using the following terms combined through Boolean operators: "systemic sclerosis", "interstitial lung disease", or "SSc-ILD" (for the disease), "anti-fibrotic" or "nintedanib" (for the therapy), "gastrointestinal", "side effects", "adverse events", or "complications" (for outcomes). We included original articles, consensus documents, reviews and commentaries on the topic, in English or Italian. The main findings of these studies were synthesised and discussed with the Executive Committee (EC).

Executive committee/kick-off meeting

The EC included two clinicians with expertise in SSc-ILD management, *i.e.* one rheumatologist (N.D.P.) and one gastroenterologist (C. O.), and two Delphi methodology experts (P.M., C.G.). During the kick-off meeting of the EC (October 31, 2023), project methods and timeline were presented and literature review findings were discussed. Further, participation criteria and the main sections and items of the questionnaire (in Italian) for the first Delphi iteration were defined.

Questionnaires for the Delphi iterations

The first questionnaire included two screening questions, agreed within the EC, to examine the eligibility of the panellists. Invited participants were required to be eligible and proceed with the study, to 1) have managed at least 5 SSc-ILD patients during the 5 years before the survey, and 2) have ever prescribed anti-fibrotic therapy to at least one SSc-ILD patient. Three separate sections of investigation were determined for the Delphi questionnaires: 1) patient management before starting anti-fibrotic therapy; 2) overall patient management during anti-fibrotic therapy; 3) management of side effects during anti-fibrotic therapy. Each section included a number of items, mainly dichotomous or multiple-choice questions. For a few items and at the end of each section, an open-ended field allowed the panellists to provide specific comments. Questions were designed to achieve a high level of consensus among the expert panellists (22).

Questionnaire validation was conducted through assessment of face and content validity (23). Face validity was evaluated through examination of the questionnaire elements, to determine whether the tool would be applicable to nonexperts. Content validity was assessed through expert analysis of the questionnaire elements, to determine whether the tool was adequately comprehensive for each domain of investigation. The questionnaire was iteratively revised and improved by all EC members between December 2023 and March 2024, until the final version was defined. Pilot testing of the questionnaire was performed by a member of the EC (C.G.).

Expert panel and Delphi iterations

The Delphi consensus was addressed to Italian rheumatologists with expertise in SSc-ILD management. Panellists were identified primarily by the EC clinicians, with no specific rationale for the total number of invitations but ensuring inclusion of experts from various Regions of Italy. EC members were not included in the panellist list and thus did not participate in the voting rounds.

An initial contact email was sent to all potential Delphi panellists on April 15, 2024, introducing the project and inviting them to participate. On April 18, 2024, the first iteration of the study was started: an e-mail containing a link to the e-Delphi questionnaire, conducted through the SurveyMonkey® platform (24), was sent to all the panellists. The link was active until May 3, 2024. The aim of each iteration was to reach an agreement between experts on the items proposed. Out of 28 panellists invited in the first Delphi round, 20 (71%) met the predefined participation criteria and entirely completed the first iteration questionnaire. Following response analysis, a second iteration was deemed necessary (based on predefined criteria described below) for some of the topics considered. Using the same methods and criteria of the first round, a short questionnaire for a subsequent Delphi iteration was prepared, reviewed and finally approved by the EC. The second iteration was conducted from July 23, 2024, to September 8, 2024. Before each question/statement proposed in the second round, quantitative responses of the first iteration for the corresponding item were provided, generally presented through synthetic graphs. A total of 20 rheumatologists completed the second round. Consistency of responses between the two iterations was generally high, thus indicating satisfactory accuracy in the definition of the statements. After the second round, iterations were discontinued and the Delphi process was concluded.

Pre-defined classification of consensus

Consensus in the Delphi iterations was defined by the percentage level of agreement among panellists. Responses were examined in aggregate to ensure anonymity of experts. The convergence criterion for consensus was pre-specified and defined according to the stability of results, to a threshold, equal to two-thirds of the response frequency. For each questionnaire item, the evidence was classified through the following Focus Levels (25, 26): "A": substantial agreement among the respondents (*i.e.* ≥67%), in the subsequent Delphi round there is no need to reconsider the item; "B": moderate-to-high variability in responses, in the subsequent Delphi round it is required to reconsider the item; "C": frequent (*i.e.* >33%) "I do not know" answers, in the subsequent Delphi round it is required to reconsider the item.

For Focus Level "A", agreement of 67% to 99% of panellists was defined as "majority consensus" and an agreement of 100% of panellists was defined as "full consensus".

Ethics

This study was based on a survey of clinicians who contributed with their expertise and professional opinions. No patients were involved in the Del-

Table I. Consensus results on SSc-ILD patient management before starting anti-fibrotic therapy (Italy, 2024).

Question/topic	Most frequent reply	n. (%) of panellists	Type of agreement	Round of agreement
1. Before starting anti-fibrotic therapy, do you usually evaluate personally the patient with progressive fibrosing SSc-ILD with regards to gastroenterological status?	Yes	20/20 (100%)	Full consensus	1
Evaluation of pre-existing diarrhoea				
2. At the moment of deciding to prescribe an anti-fibrotic therapy, do you usually consider the potential presence of pre-existing diarrhoea lasting for at least 4 weeks?	Yes	20/20 (100%)	Full consensus	1
3. If so, is the assessment of pre-existing diarrhoea lasting for at least 4 weeks usually based on patient self-report?	Yes	19/20 (95%)	Majority	1
4. And does the evaluation of pre-existing diarrhoea lasting for at least 4 weeks also include laboratory or clinical analyses?	Yes	16/20 (80%)	aMajority	1
5. In case of pre-existing diarrhoea lasting for at least 4 weeks before starting anti-fibrotic therapy, additional analyses to be requested include coproculture, faecal calprotectin and colonoscopy. Do you agree with this statement?	Yes	17/20 (85%)	Majority	2
Evaluation of weight loss				
6. At the moment of deciding to prescribe an anti-fibrotic therapy, do you usually consider any potential patients' weight loss?	Yes	19/20 (95%)	Majority	1
7. If so, is the assessment of weight loss usually based on patient self-report?	Yes	17/19 (89%)	Majority	1
8. And is the evaluation of weight loss also based on laboratory or clinical analyses, or on the use of scores or questionnaires?	Yes	17/19 (89%)	Majority	1
9. In case of weight loss before starting anti-fibrotic therapy, additional analyses to be requested include laboratory analyses, a visit and evaluation from a specialist, and nutritional tests. Do you agree with this statement?	Yes	20/20 (100%)	Full consensus	2
Evaluation of presence of nausea/loss of appetite				
10. At the moment of deciding to prescribe an anti-fibrotic therapy, do you usually consider the potential presence of nausea/loss of appetite?	Yes	20/20 (100%)	Full consensus	1
11. If so, is the assessment of presence of nausea/loss of appetite usually based on patient self-report?	Yes	20/20 (100%)	Full consensus	1
12. And does the evaluation of presence of nausea/loss of appetite also include laboratory or clinical analyses?	Yes	16/20 (80%)	Majority	1
13. In case of presence of nausea/loss of appetite before starting anti-fibrotic therapy, additional analyses to be requested include mainly EGD/gastroscopy. Do you agree with this statement?	Yes	16/20 (80%)	Majority	2
Other aspects				
14. Before prescribing an anti-fibrotic therapy, in addition to your gastroenterological evaluation, do you usually also ask for an in-depth evaluation from a specialist in gastroenterology?	No	14/20 (70%)	Majority	1

EGD: esophagogastroduodenoscopy; SSc-ILD: systemic sclerosis-interstitial lung disease.

phi rounds, and the study does not fall within the scope of those requiring ethical approval in Italy (Determine AIFA: 8th August 2024, https://www.gazzettaufficiale.it/eli/id/2024/08/20/24A04320/sg; 20th March 2008, https://www.gazzettaufficiale.it/eli/id/2008/03/31/08A02109/sg). All panellists were informed electronically of the aims and funding of the research before survey initiation, both in the contact e-mail and on a preliminary page of the survey, and provided consent to participate in the same page.

Results

A total of 20 rheumatologists from 8 Regions of Italy fulfilled the predefined expert criteria and completed the two Delphi rounds. Eight (40%) of them worked in a Scientific Institute/Hospital of Medical Research (Istituto di Ricovero e Cura a Carattere Scientifico, IRCCS), 5 (25%) in a major teaching hospital (Policlinico), and 7 (35%) in a general hospital. Most of the participants' institutions (17 out of 20, 85%) were affiliated with a Scleroderma Unit.

Patient management before starting anti-fibrotic therapy

Table I describes the consensus findings regarding the management of SSc-ILD patients before starting anti-fibrotic therapy. There was unanimous expert consensus (100% agreement) on the necessity of preliminary gastroenterological evaluation of SSc-ILD patients. All panellists considered that pre-existing diarrhoea (≥4 weeks duration) should be assessed for optimal patient management when prescribing an anti-fibrotic therapy. The majority agreed that, in addition to collecting self-reported patient information (95% agreement), comprehensive laboratory and clinical analyses should also be performed (80% agreement), including stool culture, faecal calprotectin and colonoscopy (85% agreement). Regarding weight loss, 19 out of 20 experts (95%) agreed this condition should be evaluated when prescribing anti-fibrotic therapy. This assessment should include both patient-reported information and comprehensive in-

Table II. Consensus results on SSc-ILD patient management during anti-fibrotic therapy (Italy, 2024).

Question/topic	Most frequent reply/ies	n. (%) of panellists	Type of agreement	Round of agreement
1. Do you usually provide the patient starting anti-fibrotic therapy with any useful information on the potential occurrence of gastrointestinal side effects?	Yes	20/20 (100%)	Full consensus	1
2. During follow-up visits after starting anti-fibrotic therapy, which gastrointestinal side effects do you usually monitor? [a]	Diarrhoea	20/20 (100%)	Full consensus	1
	Abdominal pain	19/20 (95%)	Majority	1
	Nausea	19/20 (95%)	Majority	1
	Weight loss	18/20 (90%)	Majority	1
	Loss of appetite	18/20 (90%)	Majority	1
3. During follow-up visits after starting anti-fibrotic therapy, is monitoring of weight loss, diarrhoea, loss of appetite and nausea usually based on patient self-report?	Yes	20/20 (100%)	Full consensus	1
4. During follow-up visits after starting anti-fibrotic therapy, to monitor aspects such as weight loss, diarrhoea, loss of appetite and nausea, it is suggested to conduct laboratory analyses including CBC, serum GOT/GPT, CRP, TSH and creatinine, and/or use questionnaires/scores including MUST score, BMI and UCLA GIT score. Do you agree with this statement?	Yes	19/20 (95%)	Majority	2
5. Do you usually plan regular follow-up visits to specifically monitor anti-fibrotic therapy?	Yes	20/20 (100%)	Full consensus	1
6. If so, how often do you usually reassess the patient?	Every 3 months	15/20 (75%)	Majority	1
7. During anti-fibrotic therapy, in order to prevent/avoid the onset of gastrointestinal side effects (such as diarrhoea, weight loss, nausea/loss of appetite), do you usually provide nutritional advice to the patient?	Yes	17/20 (85%)	Majority	1

BMI: body mass index; CBC: complete blood count; CRP: C-reactive protein; GIT: gastrointestinal tract; GOT: glutamic oxaloacetic transaminase; GPT: glutamate-pyruvate transaminase; MUST: Malnutrition Universal Screening Tool; SSc-ILD: systemic sclerosis-interstitial lung disease; TSH: thyroid-stimulating hormone.
[a] multiple answers were allowed.

vestigative workup (89% agreement), encompassing laboratory tests, nutritional analyses and specialistic evaluation (100% agreement). Unanimous consensus was achieved (100% agreement) that nausea and loss of appetite should be considered when prescribing anti-fibrotic therapy. Beyond patient-reported symptoms (100% agreement), most panellists agreed that evaluation may include additional investigations (80% agreement), primarily esophagogastroduodenoscopy (80% agreement). Most rheumatologists agreed that routine referral to a gastroenterology specialist is not generally required before prescribing anti-fibrotic therapy (70% agreement).

Patient management during anti-fibrotic therapy

Table II shows the consensus results regarding the management of SSc-ILD patients during anti-fibrotic treatment. Unanimous consensus was achieved regarding patient education about potential gastrointestinal side effects that may occur during therapy, and on scheduling regular follow-up visits to monitor the patient (every 3 months according to 75% of panellists). Gastrointestinal side effects that should be monitored included diarrhoea (100% agreement), abdominal pain (95%), nausea (95%), weight loss (90%) and loss of appetite (90%), through both patient-reported information (100%) and comprehensive clinical assessments (95%). These assessments included laboratory tests (*i.e.* complete blood count, liver enzymes, C-reactive protein, TSH and creatinine) and validated assessment tools (*i.e.* Malnutrition Universal Screening Tool [MUST] score, body mass index [BMI] and gastrointestinal tract [UCLA GIT] score). Most experts agreed on providing nutritional advice to the patient during anti-fibrotic therapy to prevent potential gastrointestinal side effects (85%). However, no consensus was reached across two Delphi rounds regarding the necessity of referring the patient to a nutrition specialist to minimise the occurrence of gastrointestinal side effects.

Management of side effects during anti-fibrotic therapy in SSc-ILD patients

Table III reports the consensus findings on the management of side effects during anti-fibrotic therapy in SSc-ILD patients. For diarrhoea management, the majority of panellists (95%) agreed on temporary dose-reduction and on considering temporary discontinuation if dose-reduction proves insufficient. Most panellists also agreed on symptomatic diarrhoea treatment alongside dose-reduction/treatment discontinuation (84% agreement) and endorsed probiotic supplementation (90% agreement) administered at repeated cycles (75% agreement). No consensus emerged regarding loperamide use for diarrhoea treatment across two Delphi rounds. For weight loss management, 85% of experts agreed on temporary dose-reduction and on considering temporary discontinuation of treatment. The use of dietary supplements was suggested in patients experiencing weight loss during anti-fibrotic therapy (75% agreement). Regarding the presence of nau-

Table III. Consensus results on the management of side effects during anti-fibrotic therapy in SSc-ILD patients (Italy, 2024).

Question/topic	Most frequent reply/ies	n. (%) of panellists	Type of agreement	Round of agreement
Management of diarrhoea				
1. During anti-fibrotic therapy in a patient with SSc-ILD, in the case of diarrhoea, it is generally suggested to reduce the drug dose, evaluating a temporary discontinuation of treatment and subsequent restart. Do you agree with this statement?	Yes	19/20 (95%)	Majority	2
2. In your clinical practice, do you usually accompany dose-reduction of the drug (with possible temporary discontinuation of treatment and subsequent restart) with a therapy for diarrhoea?	Yes	16/19 (84%)	Majority	2
3. During anti-fibrotic therapy in a patient with SSc-ILD, in the case of diarrhoea, which supplements – if any – do you usually suggest? [a]	Probiotics	18/20 (90%)	Majority	1
4. During anti-fibrotic therapy in a patient with SSc-ILD, in the case of diarrhoea, would you recommend the use of probiotics at point of need or at repeated cycles?	At repeated cycles	15/20 (75%)	Majority	2
Management of weight loss				
5. During anti-fibrotic therapy in a patient with SSc-ILD, if weight loss occurs, it is generally suggested to reduce the drug dose, evaluating a temporary discontinuation of treatment and subsequent restart. Do you agree with this statement?	Yes	17/20 (85%)	Majority	2
6. During anti-fibrotic therapy in a patient with SSc-ILD, if weight loss occurs, which supplements – if any – do you usually suggest? [a]	Dietary supplements	15/20 (75%)	Majority	1
Management of nausea/loss of appetite				
7. During anti-fibrotic therapy in a patient with SSc-ILD, if nausea or loss of appetite is present, it is generally suggested to continue the treatment, evaluating a potential dose-reduction and keeping the patient monitored. Do you agree with this statement?	Yes	18/20 (90%)	Majority	2
8. During anti-fibrotic therapy in a patient with SSc-ILD, in the case of nausea or loss of appetite, it is generally suggested to use dietary supplements and prokinetic drugs. Do you agree with this statement?	Yes	15/20 (75%)	Majority	2
Nutritional advice				
9. During anti-fibrotic therapy, in presence of gastrointestinal side effects (such as diarrhoea, weight loss, nausea/loss of appetite), do you usually provide nutritional advice to the patient?	Yes	17/20 (85%)	Majority	1
10. During anti-fibrotic therapy, in presence of gastrointestinal side effects (such as diarrhoea, weight loss, nausea/loss of appetite), do you usually refer the patient to a specialist in nutrition?	Yes	14/20 (70%)	Majority	1

SSc-ILD: systemic sclerosis-interstitial lung disease.
[a] multiple answers were allowed.

sea or loss of appetite, the majority of panellists (90%) agreed to manage the issue by keeping the patient monitored, without discontinuing anti-fibrotic therapy, and by evaluating a potential dose-reduction. Dietary supplements and prokinetic drugs were recommended for patients experiencing nausea or loss of appetite (75% agreement), although no consensus was reached on their use on an as-needed *versus* continuous basis.

Both direct provision of nutritional counselling (85% agreement) and referral to nutrition specialists (70% agreement) were endorsed for managing gastrointestinal side effects during anti-fibrotic therapy.

Discussion

The clinical relevance of gastrointestinal adverse events in SSc-ILD patients treated with anti-fibrotic therapy is underscored by data from the pivotal SENSCIS trial, which demonstrated substantially higher rates of gastrointestinal complications compared to those observed in nintedanib trials for idiopathic pulmonary fibrosis (INPULSIS studies). Specifically, diarrhoea occurred in 75.7% of SSc-ILD patients *versus* a range of 61.5% to 63.2% in idiopathic pulmonary fibrosis patients, and nausea was more frequent in SSc-ILD, too (31.6% *vs*. 22.7% to 26.1% in idiopathic pulmonary fibrosis patients) (5, 8, 9). This increased susceptibility likely reflects the pre-existing gastrointestinal dysfunction characteristic of SSc, in which nearly all patients experience GI manifestations that significantly impact nutritional status and quality of life (1). A recent study identified a few independent factors, including body mass index, cardiomyopathy and selected laboratory biomarkers, that were associated with severe lower GI involvement in SSc patients (27). Sex may also play a role in the occurrence of selected gastrointestinal adverse events, as in a pooled-analysis of four randomised controlled trials nausea and vomiting occurred more frequently

in female than in male ILD patients treated with nintedanib (28). The importance of avoiding gastrointestinal adverse events has been further highlighted in a previous study (29) as a key determinant in patient decision-making when considering therapeutic options for SSc-ILD. Preventing adverse effects during anti-fibrotic treatment is therefore a critical unmet clinical need.

The higher susceptibility of SSc patients to nintedanib-induced gastrointestinal adverse events may be explained by several converging pathogenic mechanisms. Nintedanib's inhibition of VEGF, PDGF, and FGF signalling pathways, essential for epithelial integrity and intestinal repair (30), may exacerbate the pre-existing gastrointestinal dysfunction characteristic of SSc. Furthermore, nintedanib or its metabolites may directly compromise intestinal epithelial integrity through inflammatory processes (31) and adversely affect intestinal smooth muscle function and motility (32). Given that gastrointestinal involvement in SSc is nearly universal and encompasses altered motility, malabsorption, and epithelial dysfunction (33, 34), these mechanisms synergistically contribute to enhanced susceptibility to drug-induced gastrointestinal complications. This biological rationale strongly supports the importance of comprehensive pre-treatment assessment and preventive strategies identified in our consensus.

This expert consensus identified several key strategies to enhance prevention of gastrointestinal complications before initiating anti-fibrotic therapy. Pre-treatment assessment strategies achieved unanimous expert agreement and include three core components: i) comprehensive gastroenterological status assessment when deciding to initiate anti-fibrotic treatment; ii) thorough evaluation of diarrhoea, weight loss, and nausea (while avoiding delays in anti-fibrotic therapy initiation, given the importance of early treatment in progressive SSc-ILD (14)), with specific examinations and tests endorsed for each condition; and iii) provision of comprehensive patient education regarding potential gastrointestinal side effects combined with preventive nutritional counselling to reduce adverse event risk.

Following anti-fibrotic therapy initiation, ongoing surveillance of gastrointestinal status was recommended through quarterly follow-up visits, incorporating selected laboratory analyses and validated assessment tools such as BMI, MUST (35), and UCLA GIT score (36). While these recommendations are based on expert consensus rather than high-level evidence, they provide practical guidance that may help control the occurrence and severity of gastrointestinal complications in clinical practice. It is important to note that these recommendations should be adapted to individual patient characteristics, local healthcare resources, and clinical judgment. The frequency and intensity of monitoring may need to be adjusted based on the patient's baseline gastrointestinal status, severity of SSc involvement, and tolerance to therapy.

Notwithstanding recent advances in the study of SSc (37), limited quantitative data exist regarding real-world management of gastrointestinal side effects in SSc-ILD patients treated with nintedanib (the only anti-fibrotic therapy currently available for SSc-ILD in Europe) once these complications develop. Recent real-world studies in SSc-ILD and idiopathic pulmonary fibrosis demonstrated that temporary nintedanib dose adjustment represents an effective strategy for maintaining anti-fibrotic treatment benefits against functional FVC decline in patients experiencing gastrointestinal adverse events (11, 38). Our consensus findings align closely with these real-world data, as Italian experts unanimously agreed that drug dose-reduction, with temporary discontinuation if needed, represents the recommended approach for patients with diarrhoea or weight loss. For patients experiencing nausea or loss of appetite, dose adjustment should be considered, but drug discontinuation was not recommended. Additionally, the expert panel endorsed adjunctive probiotic therapy for diarrheal side effects, dietary supplementation for weight loss, appetite loss, and/or nausea, and prokinetic drugs for nausea or appetite loss as complementary management strategies. These consensus-based strategies provide practical guidance for clinicians managing this complex clinical scenario. Notably, consensus was not achieved on several clinically relevant topics despite two Delphi rounds, highlighting areas of ongoing uncertainty in clinical practice. These included the use of loperamide for symptomatic diarrhoea treatment, the routine referral to nutrition specialists before initiating therapy to prevent gastrointestinal complications, and the optimal timing of dietary supplement and prokinetic drug administration (as-needed *vs*. continuous use). The lack of consensus on loperamide use may reflect concerns about its potential to mask underlying complications or exacerbate constipation in patients with complex gastrointestinal involvement. Similarly, the divergence in opinions regarding nutrition specialist referral likely reflects variability in local healthcare resources and individual practice patterns across Italian centres. The uncertainty about continuous *versus* as-needed supplementation reflects the absence of specific evidence guiding optimal dosing strategies in this population.

These areas of non-consensus emphasise the need for individualised clinical decision-making. In the absence of strong expert agreement, clinicians should tailor their approach based on patient-specific factors, including the severity of gastrointestinal symptoms, nutritional status, comorbidities and local availability of specialist support. Future research should prioritise these controversial areas to provide evidence-based guidance where expert-opinion currently diverges.

While this study focused on clinical management strategies, it is important to acknowledge that gastrointestinal side effects significantly impact patient quality of life and treatment satisfaction. The comprehensive monitoring and evaluation protocols recommended here must be balanced against the potential burden on patients, including frequent clinic visits, multiple laboratory assessments, and invasive procedures such as endoscopy. Shared decision-making approaches that incorporate patient empowerment and pref-

erences regarding the balance between intensive monitoring and quality of life should be encouraged, as in other rheumatologic diseases (39). Future studies incorporating patient-reported outcomes and quality of life measures will be valuable to assess whether these recommendations achieve their ultimate goal of improving not only clinical outcomes but also patient wellbeing and treatment adherence.

Study limitations include those inherent to expert consensus methods (40), specifically the absence of original quantitative data and consequently lower evidence level. The protocol of this Delphi study was not prospectively registered in any online platform. Additionally, the lack of prospective validation of these recommendations represents a key limitation that should be addressed in future research. Although our results may offer limited scientific novelty, they provide significant clinical utility. A significant limitation is that this Delphi study involved exclusively Italian experts and was conducted entirely within the Italian healthcare context. This geographical restriction may limit the generalisability of our recommendations to other countries with different healthcare systems, clinical practice patterns, resource availability, and regulatory frameworks. Practice patterns in SSc-ILD management, access to specialist care (gastroenterologists, nutritionists), and the organisation of follow-up visits may vary substantially across different countries and healthcare settings. Therefore, while the core principles of preventing and managing gastrointestinal complications during anti-fibrotic therapy are universally relevant (*i.e.* the evaluation on the presence of diarrhoea, weight loss and nausea/loss of appetite before starting and during anti-fibrotic therapy; the indications on dose-reduction and potential temporary discontinuation of treatment in patient experiencing diarrhoea or weight loss; the indications on the management of side effects, including the use of probiotics in case of diarrhoea, of dietary supplementation for weight loss, appetite loss, and/or nausea, and of prokinetic drugs for nausea or appetite loss), the specific operational recommendations (such as frequency of visits, types of investigations, and referral pathways) should be adapted to local contexts. International multicentre Delphi studies would be valuable to validate these findings across diverse healthcare systems and to identify which recommendations are universally applicable versus those requiring regional adaptation. However, it is important to note that the underlying clinical issues addressed, specifically the universal nature of SSc-related gastrointestinal dysfunction and nintedanib-associated adverse events, are broadly applicable across different healthcare settings.

In conclusion, expert consensus was achieved on multiple examined topics, providing practical, evidence-informed guidance for physicians managing SSc-ILD patients receiving anti-fibrotic therapy. Beyond its primary objective of reducing gastrointestinal side effects in this patient population, this study may improve recognition and proactive management of gastrointestinal complications among rheumatologists caring for SSc-ILD patients and stimulate future research on preventing complications related to anti-fibrotic use. Specifically, future studies should focus on prospective validation of these recommendations, development of predictive biomarkers for gastrointestinal susceptibility, and evaluation of preventive interventions in randomised controlled trials. These efforts will be essential for translating expert consensus into evidence-based clinical practice guidelines and ultimately improving outcomes for SSc-ILD patients receiving life-saving anti-fibrotic therapy.

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