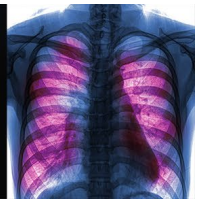
SYSTEMIC SCLEROSIS-ASSOCIATED INTERSTITIAL LUNG DISEASE
REAL CASES, REAL CONUNDRUMS, REAL CLINICAL SOLUTIONS



OVERVIEW

Interstitial lung disease (ILD) is a common sequela of systemic sclerosis (SSc) and is associated with significant morbidity and mortality. SSc-ILD is a heterogenous disorder without a lack of clear guidance on diagnosis, management, and follow-up. Pulmonary and extrapulmonary complications of SSc are common, with limited treatment options. Historically, mycophenolate and cyclophosphamide have served as the first-line treatments, while nintedanib and tocilizumab have recently emerged with new FDA approvals. Three cases are discussed in this activity by Flavia Castelino, MD, and Sonye Danoff, MD, PhD, that provide clinical insights into the risks of lung involvement, latest advances in guidelines and research, diagnostic testing, disease progression assessment, and shared decision-making. Join Drs. Castelino and Danoff for this active learning activity on the diagnosis and treatment of patients with SSc-ILD.

CONTENT AREAS

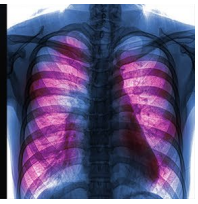
- Diagnosis
- Risk factors
- Shared decision-making
- First-line treatment
- Patient monitoring
- Treating progressive disease

FACULTY

Flavia Castelino, MD
Director, Scleroderma Program
Division of Rheumatology
Massachusetts General Hospital
Assistant Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Sonye K. Danoff, MD, PhD
Associate Professor of Medicine
Johns Hopkins Medicine
Baltimore, Maryland

ANNENBERG CENTER FOR HEALTH SCIENCES AT EISENHOWER
Imparting knowledge. Improving patient care.



CE INFORMATION

TARGET AUDIENCE

This activity was developed for a national audience of pulmonologists, radiologists, rheumatologists, dermatologists, and primary care physicians, and other clinicians who have a role in the diagnosis and treatment of patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD).

LEARNING OBJECTIVES

- Explain the risk for and symptoms suggestive of lung involvement in patients with scleroderma
- Discuss the latest advances in clinical guidelines and research related to systemic sclerosis-associated interstitial lung disease (SSc-ILD)
- Engage best practices in the diagnostic testing and disease-progression assessment of SSc-ILD
- Employ shared decision-making strategies to optimize health outcomes in patients with SSc-ILD, including in patients with associated comorbidities

Accreditation and Certification

The Annenberg Center for Health Sciences at Eisenhower is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The Annenberg Center for Health Sciences at Eisenhower designates this enduring material for a maximum of 1.5 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

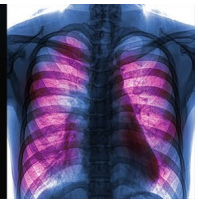
Disclosure Statement

It is the policy of the Annenberg Center for Health Sciences to ensure fair balance, independence, objectivity, and scientific rigor in all programming. All individuals with the potential to impact the content of an accredited education activity are expected to identify and reference off-label product use and disclose relationships with ACCME-defined ineligible companies.

The Annenberg Center for Health Sciences assesses relevant relationships with its instructors, planners, managers, and other individuals who are in a position to control the content of CE/CME activities. All relevant relationships that are identified are thoroughly vetted by the Annenberg Center for fair balance, scientific objectivity of studies utilized in this activity, and patient care recommendations. The Annenberg Center is committed to providing its learners with high-quality CE/CME activities and related materials that promote improvements or quality in healthcare and not a specific proprietary business interest of a commercial interest.

In accordance with the Accreditation Council for Continuing Medical Education Standards, parallel documents from other accrediting bodies, and Annenberg Center for Health Sciences policy, the following disclosures have been made:

Faculty
Flavia Castelino, MD



Consultant: Boehringer Ingelheim

Sonye K. Danoff, MD, PhD
Advisory Board: Boehringer Ingelheim, CSL Behring
Consultant: Boehringer Ingelheim, Galapagos, Galecto,
Research Support: Boehringer Ingelheim, Bristol Myers Squibb
Royalties: UpToDate

The faculty for this activity has disclosed that there will be discussion about the use of products for non-FDA approved applications.

Additional content planners
Michael Smith, PharmD (Medical Writer)
Consultant: Wolters-Kluwer

The following have no significant relationship to disclose:
Kam Newman, MD (Peer Reviewer)

Annenberg Center for Health Sciences
Staff at the Annenberg Center for Health Sciences at Eisenhower have no relevant commercial relationships to disclose.

The ideas and opinions presented in this educational activity are those of the faculty and do not necessarily reflect the views of the Annenberg Center and/or its agents. As in all educational activities, we encourage practitioners to use their own judgment in treating and addressing the needs of each individual patient, taking into account that patient's unique clinical situation. The Annenberg Center disclaims all liability and cannot be held responsible for any problems that may arise from participating in this activity or following treatment recommendations presented.

This activity is supported by an independent educational grant from Boehringer Ingelheim Pharmaceuticals, Inc.

This activity is an online enduring material. Successful completion is achieved by reading and/or viewing the materials, reflecting on its implications in your practice, and completing the assessment component.

The estimated time to complete the activity is 1.5 hours.

This activity was released on September 20, 2022 and is eligible for credit through September 20, 2023.

Our Policy on Privacy
Annenberg Center for Health Sciences respects your privacy. We don't share information you give us, or have the need to share this information in the normal course of providing the services and information you may request. If there should be a need or request to share this information, we will do so only with your explicit permission. See Privacy Statement and other information at https://annenberg.net/pages/privacyPolicy.php

Contact Information
For help or questions about this activity please contact Continuing Education:
ce@annenberg.net

Editor's Note: This is a transcript of a presentation on July 22, 2022. It has been edited and condensed for clarity.

Case 1 Question 1
Case background
35-year-old female with a history of Raynaud's presents to the clinic. Her Raynaud's was diagnosed 3 months prior to this visit. She presents for further evaluation of her disease.
Question 1
What proportion of patients with Raynaud's develop systemic sclerosis and what proportion of patients with systemic sclerosis have a diagnosis of Raynaud's? **a.** Approximately 95% and 25% **b.** Approximately 25% and 95% **c.** Approximately 10% and 60% **d.** Approximately 60% and 10%
Answer rationale
The correct answer is: **B** • Secondary Raynaud's phenomena has a wide differential, which includes systemic sclerosis. It is associated with systemic sclerosis in about one-quarter of patients.[1] When patient's carry a diagnosis of Raynaud's, it is important to include systemic sclerosis in the differential. • Nearly all patients (more than 95% has been reported) that have systemic sclerosis have a preceding diagnosis of Raynaud's.[2]
References
1. Temprano KK. A review of Raynaud's disease. *Mo Med*. 2016;113(2):123-126. 2. Adigun R, Goyal A, Hariz A. Systemic sclerosis. [Updated 2022 May 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430875/?report=classicLi Q, Wallace L,
Faculty Commentary ***Flavia Castelino, MD:*** Approximately 25% of patients with Raynaud's can go on to develop systemic sclerosis and it's important, when you're evaluating a patient with Raynaud's, to think about the broader differential. While, yes, some patients can have primary Raynaud's, which is not associated with a rheumatic disease, others can go on to develop other conditions such as lupus, systemic sclerosis for example. And when you are seeing a patient with systemic sclerosis, about 95% of them have Raynaud's, and Raynaud's is often 1 of the initial manifestations of systemic sclerosis. So, seeing a patient with Raynaud's should heighten your suspicion for an underlying rheumatic condition, and systemic sclerosis should be on that list. ***Sonye K. Danoff, MD, PhD:*** Dr. Castelino, how do you differentiate between somebody who just has cold fingers vs somebody who truly has Raynaud's?

Flavia Castelino, MD:
One thing that can be helpful, is that we often actually do nailfold capillary exams in our clinic visits, and typically a patient with primary Raynaud's would have normal nailfold capillaries. And then a patient who may have an underlying rheumatic disease may actually have some nailfold changes. So, that nailfold capillary exam can be quite informative. Sending to a rheumatologist early to get that exam is helpful as well.

Case 1 Question 2

Case background

During a further discussion with the patient, she also describes puffy hands, heartburn and mild dyspnea upon exertion. Given her constellation of symptoms, and what she has read on the internet, she is concerned for developing interstitial lung disease.

Question 2

For which of the following risk factors for early development of interstitial lung disease should this patient be screened, and what information about development of lung disease should be communicated to her?

- **a.** Extent of skin involvement (eg, limited, diffuse) is associated with high rates of lung disease
- **b.** mRSS alone is predictive of lung disease involvement
- **c.** Creatine phosphokinase levels are inversely associated with lung disease
- **d.** Age at onset is associated with worse lung disease

Answer rationale

The correct answer is: **A**

- Various factors have been associated with early development of interstitial lung disease, such as extent of skin involvement,[1-3] skin scoring, CPK levels, and hypothyroidism.[4,5] The prognosis of disease is much less clear, with 1 study reporting approximately one-third of patients have no decline in lung function when diagnosed with SSc-ILD. In these patients, male sex, higher skin scores, and dysphagia symptoms were the strongest predictors of decline.
- Skin scoring alone is not predictive of disease, but skin scoring in combination with extent of skin involvement provides a better understanding as skin scores often overlap in those that present with diffuse versus limited skin involvement.[2]
- Age alone is not a predictor of disease; however, patients with diffuse skin involvement tend to be younger, are diagnosed with Raynaud's younger, and have other associated comorbidities at younger ages than those with limited skin involvement.[2]

References

1. Gilson M, ZerkakD, Wipff J, et al. Prognostic factors for lung function in systemic sclerosis: prospective study of 105 cases. *Eur Respir J*. 2010;35:112-117. doi:10.1183/09031936.00060209
2. Walker UA, Tyndall A, Czirjak L, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR scleroderma trials and research group database. *Ann Rheum Dis*. 2007;66(6):754-763. doi:10.1136/ard.2006.062901
3. Wangkaew S, Euathrongchit J, Wattanawittasas P, et al. Incidence and predictors of interstitial lung disease (ILD) in Thai patients with early systemic sclerosis: inception cohort study. *Mod Rheumatol*. 2016;26:588-593. doi:10.3109/14397595.2015.1115455

4. McNearney TA, Reveille JD, Fischbach M, et al. Pulmonary involvement in systemic sclerosis: associations with genetic, serologic, sociodemographic, and behavioral risk factors. *Arthritis Rheum*. 2007;57:318-326. doi:10.1002/art.22532
5. Khanna D, Tashkin DP, Denton CP, et al. Etiology, risk factors, and biomarkers in systemic sclerosis with interstitial lung disease. *Am J Respir Crit Care Med*. 2020;201:650-660. doi:10.1164/rccm.201903-0563CI

Faculty Commentary

Sonye K. Danoff, MD, PhD:

There are a number of different risk factors for the development of interstitial lung disease (ILD) that have been identified in systemic sclerosis. We recognize that the extent of skin involvement is a very powerful predictor of the development of interstitial lung disease. There are certainly many other factors that can be associated with interstitial lung disease, and these can include issues like CPK levels and hypothyroidism, but for the average patient, the most important single predictor is the extent of skin involvement, and that is in addition to simply the presence of skin involvement and the modified Rodnan skin score**.**

Case 1 Question 3

Case background

Later during the visit, the patient describes new shortness of breath and fatigue in the last 3 months. Her shortness of breath is worse with exertion (1 flight of stairs).

Her past medical history is notable for hyperlipidemia (controlled with atorvastatin) and GERD (controlled with omeprazole). Her family and social history are unremarkable.

Physical exam findings:

- Vitals: BP 140/85 | Pulse 61 | Temp 36.4 °C (97.6 °F) | Ht 1.727 m (5' 8") | Wt 76.2 kg (168 lb) | SpO2 94% | BMI 25.54 kg/m2
- Gen: Pt is AAOx3, in NAD.
- HEENT: NC/AT, PERRL, nonicteric. EOMI. MMM, w/o exudates.
- Neck: Supple, NT, trachea midline
- Chest: bibasilar crackles, no wheezes
- CV: RRR; normal S1S2, no m/r/g appreciated
- Abd: soft, nontender, nondistended; NABS
- Extremities:
    - UE: no soft tissue swelling, warmth, effusion, erythema of DIPs, PIPs, MCPs, wrists, elbows b/l. Full range of motion of all joints.
    - LE: no soft tissue swelling, warmth, effusion, erythema of MTPs, ankles, knees b/l. Full range of motion of all joints.
- Skin: Evidence of sclerodactyly, evidence of scattered nailfold capillary dropout and giant capillaries, no digital ulcers
- mRSS 7

Lab Results:

- CBC unremarkable
- Chemistry unremarkable
- CK normal

Question 3

Which of the following diagnostic tests should be considered the highest priority at this time?

a. PM/Scl antibody
b. Antinuclear antibody
c. Anti-Th/To antibody
d. Pulmonary Function Tests
e. High Resolution Chest CT

Answer rationale

The correct answer is: **E**

- High resolution chest CT (HRCT) should be performed. It has also been correlated with pulmonary function tests and has been associated with mortality data.[1-4]
- Antibody testing may be helpful in the differential diagnosis of SSc and some are being explored for their associations with the development of SSc-ILD; however, their diagnostic capacity is limited without the context of other testing.[5,6]
- While pulmonary function tests are important to perform and monitor, they alone, are insufficient in diagnosing SSc-ILD based on a low sensitivity.[7]

References

1. Chung JH, Walker CM, Hobbs S. Imaging features of systemic sclerosis-associated interstitial lung disease. *J Vis Exp*. 2020;160. doi:10.3791/60300
2. Hoffman-Vold AM, Aalokken TM, Lund MB, et al. Predictive value of serial high-resolution computed tomography analyses and concurrent lung function tests in systemic sclerosis. *Arthritis Rheumatol*. 2015;67(8):2205-2212. doi:10.1002/art.39166
3. Goldin JG, Lynch DA, Strollo DC, et al. High-resolution CT scan findings in patients with symptomatic scleroderma-related interstitial lung disease. *Chest*. 2008;134(2):358-367. doi:10.1378/chest.07-2444
4. Goh NSL, Desai SR, Veeraraghavan S, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. *Am J Respir Crit Care Med*. 2008;177(11):1248-1254. doi:10.1164/rccm.200706-877OC
5. Kavanaugh A, Tomar R, Reveille J, et al. Guidelines for clinical use of the antinuclear antibody test and tests for specific autoantibodies to nuclear antigens. American College of Pathologists. *Arch Pathol Lab Med*. 2000;124(1):71-81. doi:10.5858/2000-124-0071-GFCUOT
6. Steen VD, Powell DL, Medsger TA. Clinical correlations and prognosis based on serum autoantibodies in patients with systemic sclerosis. *Arthritis Rheum*. 1988.31(2):196-203. doi:10.1002/art.1780310207
7. Bernstein EJ, Jaafar S, Assassi S, et al. Performance characteristics of pulmonary function tests for the detection of interstitial lung disease in adults with early diffuse cutaneous systemic sclerosis. *Arthritis Rheumatol*. 2020;72(11):1892-1896. doi:10.1002/art.41415

Faculty Commentary

Sonye K. Danoff, MD, PhD:
I think that, in considering testing in a patient for whom you have a concern for interstitial lung disease, the first question is, what drew you to think the patient might have interstitial lung disease? And obviously, in this case scenario, the things that would really draw your attention are firstly the fact that the patient's oxygen saturation on room air at rest is 94%. There is evidence of crackles on exam. You don't have mention of a suggestion of pulmonary hypertension, so there's no loud P2 or split S2 that's noted. You do have a really nice description for the extent of skin involvement and the presence of nailfold capillary dropout, so you have a really strong suggestion that this is a patient with systemic sclerosis, but you also have the very clear physical findings suggestive of the presence of interstitial lung disease. And when you have a patient for whom you're concerned about interstitial lung disease, while testing for autoantibodies, obviously, is a part of the workup, probably the highest priority is actually to get a high-resolution chest computed tomography (CT) scan. And the reason for this is that really when you look at the prognosis for patients who have interstitial lung disease, 1 of the strongest predictors is, in fact, the extent of lung involvement on the high-resolution CT scan. Clearly, pulmonary function testing (PFT) will be part of the workup, but probably the first priority would actually be to get the high-resolution CT scan.

Case 1 Question 4

Case background

Diagnostic tests revealed the following:

- ANA 1:1280, centromere pattern
- dsDNA, Ro, La, Scl-70, Sm/RNP negative

Pulmonary Function Tests:

- FEV1 and FVC are reduced, FEV1/FVC is within normal limits. TLC is decreased. FRC is decreased. RV is normal.
- RV/TLC ratio is normal. Single breath diffusion capacity is reduced. These data demonstrate a moderate restrictive ventilatory deficit with a moderate reduction in diffusion capacity.

High Resolution Chest CT Interpretation:

- Basilar dependent primarily posterior, peripheral ground-glass opacities which persist on prone imaging, with underlying reticulation, traction bronchiectasis and bronchiolectasis without evidence of honeycombing which would be consistent with a NSIP pattern, commonly seen in SSc-ILD
- Dilated fluid-filled esophagus also would be consistent with the patient's clinical history

Question 4

Based on the diagnostic tests, which results should be described to the patient to understand disease progression and mortality?

- **a.** Extent of disease on CT
- **b.** Reduced forced vital capacity
- **c.** None, her age and gender are predictive of mortality
- **d.** None, order a bronchoalveolar lavage for prognostication

Answer rationale

The correct answer is: **A**

- High resolution chest CT (HRCT) should be discussed with the patient as it has been correlated with pulmonary function tests and has been associated with mortality data.[1-4]
- FVC may also be beneficial to discuss with the patient, however, there is a large variation change in FVC. Approximately one-third of patients have no change, few (about 8%) have rapid decline, and most (nearly 60%) have a slow progressive decline. Serial monitoring of FVC would provide more beneficial information to the patient than a single reading.[5]

References

1. Chung JH, Walker CM, Hobbs S. Imaging features of systemic sclerosis-associated interstitial lung disease. *J Vis Exp*. 2020;160. doi:10.3791/60300
2. Hoffman-Vold AM, Aalokken TM, Lund MB, et al. Predictive value of serial high-resolution computed tomography analyses and concurrent lung function tests in systemic sclerosis. *Arthritis Rheumatol*. 2015;67(8):2205-2212. doi:10.1002/art.39166
3. Goldin JG, Lynch DA, Strollo DC, et al. High-resolution CT scan findings in patients with symptomatic scleroderma-related interstitial lung disease. *Chest*. 2008;134(2):358-367. doi:10.1378/chest.07-2444
4. Goh NSL, Desai SR, Veeraraghavan S, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. *Am J Respir Crit Care Med*. 2008;177(11):1248-1254. doi:10.1164/rccm.200706-877OC
5. Hoffman-Vold AM, Allanore Y, Alves M, et al. Progressive interstitial lung disease in patients with systemic sclerosis-associated interstitial lung disease in the EUSTAR database. ***Ann Rheum Dis***. 2021; 80 (2): 219-227. doi:10.1136/annrheumdis-2020-217455

Faculty Commentary

Sonye K. Danoff, MD, PhD:

One of the biggest concerns patients have when they are told that they have a diagnosis of interstitial lung disease is, what's going to happen next, what is my prognosis in this situation? And obviously, while it's difficult to prognosticate for the individual, there are certain features of disease that allow us to know that a disease is more likely to be progressive or perhaps less likely to be progressive. And, in this situation, the feature which is most associated with progression is actually the extent of involvement on the initial CT scan. In this case, you have a patient who has peripheral ground-glass opacities, you've got some traction bronchiectasis and bronchiolectasis. And so, it is suggestive of a nonspecific interstitial pneumonia (NSIP) pattern, but it also suggests that you might actually have the beginning of a fibrotic NSIP pattern and, again, the extent of disease on the CT scan is going to be the most predictive of the patient's subsequent course. Certainly, understanding what the patient's forced vital capacity (FVC) is, is critical, as pulmonary function testing is really 1 of the ways that we follow patients through their disease course. But there is some variability, and many patients who present with systemic sclerosis and ILD will actually have relatively preserved FVCs at the beginning of disease.

Her age and gender are obviously things that are fixed factors, and males generally have worse prognosis. Patients who are older have a worse prognosis. So, those are not necessarily things that you need to address with the patient. And, at present, we do not use bronchoalveolar lavage (BAL) for prognostication, largely because it hasn't been shown to be particularly predictive of response to therapy.

Case 1 Question 5

Case background

The patient states that she does not clearly understand the disease and what to expect from it, moving forward.

After a detailed discussion on risks of treatment, disease progression, and mortality, the patient decides she would like to proceed with treatment. However she would like to understand the benefit of treatment vs the risk of adverse effects.

Question 5

Which of the following statements best describes the likely benefit of treatment against the risks of treatment-related adverse effects?

a. Patients with significant lung function loss are most likely to benefit from treatment
b. Asymptomatic patients with stable disease are most likely to benefit from treatment
c. Patients with early-stage disease are most likely to benefit from treatment
d. Patients with late-stage disease are most likely to see improved FVC

Answer rationale

The correct answer is **C**.

- Patients have a hard time understanding the disease and its progression. They have high expectations of their providers and their communication about the disease and are often not provided time to ask questions.[1,2] Research has shown that both prognosis and mortality are often not discussed.[3]
- It is thought that patients with early disease are most likely to benefit, given the large uncertainty around disease progression. It should be communicated clearly to the patient that little data exist in predicting who progresses, but that with treatment, clinical outcomes have improved.[4-12]

References

1. Mouthon L, Alami S, Boisard AS, et al. Patients' views and needs about systemic sclerosis and its management: a qualitative interview study. *BMC Musculoskelet Disord*. 2017;230:18. doi.org/10.1186/s12891-017-1603-4
2. Denton CP, Laird B, Moros L, Flores JLL. Challenges in physician-patient communication for optimal management of systemic sclerosis-associated interstitial lung disease: a discourse analysis. *Clin Rheumatol*. 2020;39(10):2989-2998. doi:10.1007/s10067-020-05063-x
3. Denton CP, Laird B, Moros L, Flores JLL. Things left unsaid: important topics that are not discussed between patients with systemic sclerosis, their careers and their healthcare professionals – a discourse analysis. *Clin Rheumatol*. 2021;40(4):1399-1407. doi:10.1007/s10067-020-05371-2

4. Moore OA, Goh N, Corte T, et al. Extent of disease on high-resolution computed tomography lung is a predictor of decline and mortality in systemic sclerosis-related interstitial lung disease. *Rheumatol*. 2013;51(1):155-160. doi:10.1093/rheumatology/kes289
5. Hoffman-Vold AM, Maher TM, Philpot EE, et al. The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements. *Lancet Rheumatol*. 2020;2(2):E71-E83. doi:org/10.1016/S2665-9913(19)30144-4
6. Volkmann ER, Tashkin DP, LeClair H, et al. Treatment with mycophenolate and cyclophosphamide leads to clinically meaningful improvements in patient-reported outcomes in scleroderma lung disease: results of Scleroderma Lung Study II. *ACR Open Rheum*. 2020;2(6):362-370. doi:org/10.1002/acr2.11125
7. Volkmann ER, Tashkin DP. Treatment of systemic sclerosis-related interstitial lung disease: a review of existing and emerging therapies. *Ann Am Thorac Soc*. 2016;13(11):2045-2056. doi:10.1513/AnnalsATS.201606-426FR
8. Tashkin DP, Roth MD, Clements PJ, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease: Scleroderma Lung Study II (SLS-II), a double-blind, parallel group, randomized controlled trial. *Lancet Respir Med*. 2016;4(9):708-719. doi:10.1016/S2213-2600(16)30152-7
9. Tashkin DP, Elashoff R, Clements PJ, et al. Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. *Am J Respir Crit Care Med*. 2007;176:1026-1034. doi:10.1164/rccm.200702-326OC
10. Tashkin DP, Elashoff R, Clements PJ, et al. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med*. 2006;354(25):2655-2666. doi:10.1056/NEJMoa055120
11. McMahan ZH, Volkmann ER. An update on the pharmacotherapeutic options and treatment strategies for systemic sclerosis. *Expert Opin Pharmacother*. 2021;21(16):2014-2056. doi:10.1080/14656566.2020.1793960
12. Giacomelli R, Liakouli V, Berardicurti O, et al. Interstitial lung disease in systemic sclerosis: current and future treatment. *Rheumatol Int*. 2017;37(6):853-863. doi:10.1007/s00296-016-3636-7

Faculty Commentary

Flavia Castelino, MD:

Patients with early-stage disease are more likely to benefit from treatment. Now, the course of systemic sclerosis is quite varied between patients. Some may be caught earlier on when we can actually make differences in terms of their management of systemic sclerosis interstitial lung disease, and having that open discussion first, when you meet a patient, is really of utmost importance.

In terms of the other choices, well, yes, patients can benefit from treatment even later on. It's important to really think about the disease at the early stage and really start the screening and then also potential treatments early, at the diagnosis. In terms of benefit, there's still a lot of uncertainty in terms of disease progression and whether all these treatments will benefit an individual patient. However, really we need to stress to the patient that treating early can be beneficial, but the data itself is quite sparse, and there's a lot more research going on to understand the various predictors of progression of lung disease.

Dr. Danoff, if you also want to just weigh in on this, given your expertise in ILD, as well?

Sonye K. Danoff, MD, PhD:

Dr. Castelino, I really agree with what you said. I think that the point is that screening early is really critical because we can typically make the most impact in disease course. However, clearly, for patients who present later in disease, we would still treat with the goal of limiting the damage caused by the interstitial lung disease. I think that that's really important. It's a subtle point, but a very important point, that you've made.

Case 1 Question 6

Case background

The patient is grateful for the opportunity to ask questions and better understand her disease. After discussing the risks vs benefits of treatments, the patient has decided she wants to proceed with treatment.

Question 6

Based on the patient's current SSc-ILD status and past medical history, which of the following treatments is the most appropriate first-line choice?

a. Nintedanib
b. Cyclophosphamide
c. Mycophenolate mofetil
d. Tocilizumab
e. Azathioprine

Answer rationale

The correct answer is **C**.

- Both cyclophosphamide and mycophenolate mofetil (MMF) could be considered first-line. They are considered equally efficacious; however, MMF is better tolerated.[1-7]
- Nintedanib has shown a slower decline in FVC, but no clinically meaningful benefit for other outcomes. Nearly half of the patients in a study of nintedanib were already on MMF. Nintedanib is likely better reserved as a second- or third-line option.[8]
- Data for tocilizumab shows that it can also slow the rate of pulmonary decline, but has no impact on skin involvement of SSc. It would be a reasonable option for patients unable to take, or who have failed, MMF or cyclophosphamide.[9,10]
- The important distinction between nintedanib and tocilizumab use can be drawn from their study data. Nintedanib was primarily studied in patients with progressive ILD, regardless of diffuse or limited cutaneous involvement. On the other hand, tocilizumab was primarily studied in early diffuse cutaneous disease without significant pulmonary involvement.[11]
- Data supporting the use of azathioprine have shown that it does not reduce the decline in pulmonary function to the degree that other drugs, such as cyclophosphamide, do.[12]

References

1. Volkmann ER, Tashkin DP, LeClair H, et al. Treatment with mycophenolate and cyclophosphamide leads to clinically meaningful improvements in patient-reported outcomes in scleroderma lung disease: results of Scleroderma Lung Study II. *ACR Open Rheum*. 2020;2(6):362-370. doi.org/10.1002/acr2.11125

2. Volkmann ER, Tashkin DP. Treatment of systemic sclerosis-related interstitial lung disease: a review of existing and emerging therapies. *Ann Am Thorac Soc*. 2016;13(11):2045-2056. doi:10.1513/AnnalsATS.201606-426FR
3. Tashkin DP, Roth MD, Clements PJ, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease: Scleroderma Lung Study II (SLS-II), a double-blind, parallel group, randomized controlled trial. *Lancet Respir Med*. 2016;4(9):708-719. doi:10.1016/S2213-2600(16)30152-7
4. Tashkin DP, Elashoff R, Clements PJ, et al. Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. *Am J Respir Crit Care Med*. 2007;176:1026-1034. doi:10.1164/rccm.200702-326OC
5. Tashkin DP, Elashoff R, Clements PJ, et al. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med*. 2006;354(25):2655-2666. doi:10.1056/NEJMoa055120
6. McMahan ZH, Volkmann ER. An update on the pharmacotherapeutic options and treatment strategies for systemic sclerosis. *Expert Opin Pharmacother*. 2021;21(16):2014-2056. doi:10.1080/14656566.2020.1793960
7. Giacomelli R, Liakouli V, Berardicurti O, et al. Interstitial lung disease in systemic sclerosis: current and future treatment. *Rheumatol Int*. 2017;37(6):853-863. doi:10.1007/s00296-016-3636-7
8. Distler O, Highland KB, Gahlemann M, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. *N Engl J Med*. 2019; 380:2518-2528. doi:10.1056/NEJMoa1903076
9. Khanna D, Denton CP, Jahreis A, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomized, controlled trial. *Lancet*. 2016;387(10038):2630-2640. doi:10.1016/S0140-6736(16)00232-4
10. Khanna D, Lin CJF, Furst DE, et al. Tocilizumab in systemic sclerosis: a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2020;8(10):963-974. doi:10.1016/S2213-2600(20)30318-0
11. Khanna D, Lescoat A, Roofeh D, et al. Systemic sclerosis-associated interstitial lung disease: how to incorporate two Food and Drug Administration-approved therapies in clinical practice. *Arthritis Rheumatol*. 2022;74(1):13-27. doi:10.1002/art.41933
12. Nadashkevich O, Davis P, Fritzler M, Kovalenko W. A randomized unblinded trial of cyclophosphamide versus azathioprine in the treatment of systemic sclerosis. *Clin Rheumatol*. 2006;25(2):205-212. doi:10.1007/s10067-005-1157-y

Faculty Commentary

Sonye K. Danoff, MD, PhD:

For a patient who's presenting with systemic sclerosis with interstitial lung disease, we typically begin therapy with mycophenolate. The rationale for that is based on the Scleroderma Lung Studies which have shown that there's both efficacy of cyclophosphamide and mycophenolate for initial therapy, however mycophenolate is better tolerated, with less significant severe side effects. Therefore, mycophenolate would be the first drug that I would reach for.

Now, many people are thinking about nintedanib, which has had a recent positive clinical trial in the SENSCIS trial. However that is really a trial that was designed around patients who had progressive disease. In contrast, tocilizumab, which also has recently been in the news, was a study that was done on patients who actually had very, very early disease, and really was not focused on the treatment of interstitial lung disease, although there was a positive outcome. Those patients were not on other immunosuppressive agents, so it wasn't really a

head-to-head looking at tocilizumab vs mycophenolate.

And finally, azathioprine, which is a very common therapeutic agent used in other forms of connective tissue disease/ILD, has actually not been shown in systemic sclerosis to have the same level of efficacy as mycophenolate. Therefore, my initial choice would be mycophenolate for this patient.

Case 1 Question 7

Case background

The patient developed intolerable gastrointestinal side effects with the use of mycophenolate mofetil and self-discontinued after 3 days. After further discussion, the patient still wishes to pursue therapy.

Question 7

Which of the following options is the most appropriate to offer the patient at this time?

a. Nintedanib
b. Mycophenolic acid
c. Glucocorticoids
d. Tocilizumab

Answer rationale

The correct answer is **B**

- Given the skin involvement but intolerable GI side effects, it is reasonable to trial mycophenolic acid as it is enteric coated and has less GI side effects. There is data on its use in patients with SSc-ILD. Mycophenolic acid is enteric coated and generally has less GI side effects
- Nintedanib and tocilizumab can still be reserved given the availability of other treatments.[5-7]
- Monotherapy glucocorticoids are not likely beneficial but may be considered as adjuvant therapy to cyclophosphamide.[8]

References

1. Henes JC, Horger M, Amberger C, et al. Enteric-coated mycophenolate sodium for progressive systemic sclerosis—a prospective open-label study with CT histography for monitoring of pulmonary fibrosis. *Clin Rheumatol*. 2013;32(5):673-678. doi:10.1007/s10067-012-2155-5
2. Janardana R, Irodi A, Chebbi PP, et al. Mycophenolate in scleroderma-associated interstitial lung disease: Real-world data from rheumatology and pulmonology clinics in South Asia. *J Scleroderma Relat Disord*. 2021;6(3):271-276. doi:10.1177/23971983211024410
3. Simeon-Aznar CP, Fonollosa-Pla V, Tolosa-Vilella C, et al. Effect of mycophenolate sodium in scleroderma-related interstitial lung disease. *Clin Rheumatol*. 2011;30(11):1393-1398. doi:10.1007/s10067-011-1823-1
4. Manger B, Hiepe F, Schneider M, et al. Impact of switching from mycophenolate mofetil to enteric-coated mycophenolate sodium on gastrointestinal side effects in patients with autoimmune disease: a Phase III, open-label, single-arm, multicenter study. *Clin Exp Gastroenterol*. 2015;8:205-213. doi:10.2147/CEG.S81922

5. Distler O, Highland KB, Gahlemann M, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. ***N Engl J Med***. 2019;380:2518-2528. doi:10.1056/NEJMoa1903076
6. Khanna D, Denton CP, Jahreis A, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomized, controlled trial. *Lancet*. 2016;387(10038):2630-2640. doi:10.1016/S0140-6736(16)00232-4
7. Khanna D, Lin CJF, Furst DE, et al. Tocilizumab in systemic sclerosis: a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2020;8(10):963-974. doi:10.1016/S2213-2600(20)30318-0
8. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis Rheum*. 2006;54(12):3962-3970. doi:10.1002/art.22204

Faculty Commentary

***Flavia Castelino, MD**:*
This patient is having a hard time taking the mycophenolate mofetil and, in this case, answer B, mycophenolic acid or Myfortic could be indicated and typically the side effects seen with Myfortic, in terms of the gastrointestinal side effects, are often better tolerated. The medication itself is enteric-coated and often has less gastrointestinal side effects. In terms of these other medications, they can be considered if there is further disease progression, but currently the scenario here is that the patient is not tolerating their mycophenolate, therefore switching to a sister drug here in terms of mycophenolic acid can make sense.

Case 1 Question 8

Case background

Consider the scenario in which the patient chose an alternative initial management plan of intravenous cyclophosphamide and now presents to clinic 6 months later. Repeat pulmonary function tests have shown modest improvement since baseline.

Question 8

What is the best next step in treatment?

a. Continue treatment since maximal treatment response takes 6 to 12 months
b. Increase cyclophosphamide dose to achieve greater improvement in lung function
c. Add azathioprine to achieve greater improvement in lung function
d. Switch to oral cyclophosphamide as maintenance therapy

Answer rationale

The correct answer is **D**.

- A switch to oral cyclophosphamide is a reasonable option at this time given the equivalent efficacy data to the IV formulation, less serious adverse effects, and less adjuvant drug use.[1,2]
- Although the optimal duration is not known, most studies of cyclophosphamide show benefit to 24 months after 1 year of treatment.[3-6]

- In a study of patients that received IV cyclophosphamide, outcomes were worse in those treated with azathioprine vs oral cyclophosphamide.[8]
- There does not appear to be a dose-response curve for cyclophosphamide, as even low dose pulse regimens have shown to be effective, so increasing the dose is not likely to improve outcomes.[9,10]

References

1. Bruni C, Tashkin DP, Steen V, et al. Intravenous versus oral cyclophosphamide for lung and/or skin fibrosis in systemic scelerosis: an indirect comparison from EUSTAR and randomised controlled trials. *Clin Exp Rheumatol*. 2020;38(Suppl 125(3):161-168.
2. Bruni C, Tashkin DP, Steen V, et al. OPO144 Intravenous versus oral cyclophosphamide (CYC) for the treatment of interstitial lung involvement (ILD) and skin involvement in systemic sclerosis (SSC): safety and efficacy evaluation in a large multi-centre scleroderma cohort. *Ann Rheum Dis*. 2018;77:123.
3. Volkmann ER, Tashkin DP, LeClair H, et al. Treatment with mycophenolate and cyclophosphamide leads to clinically meaningful improvements in patient-reported outcomes in scleroderma lung disease: results of Scleroderma Lung Study II. *ACR Open Rheum*. 2020;2(6):362-370. doi:org/10.1002/acr2.11125
4. Volkmann ER, Tashkin DP. Treatment of systemic sclerosis-related interstitial lung disease: a review of existing and emerging therapies. *Ann Am Thorac Soc*. 2016;13(11):2045-2056. doi:10.1513/AnnalsATS.201606-426FR
5. Tashkin DP, Roth MD, Clements PJ, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease: Scleroderma Lung Study II (SLS-II), a double-blind, parallel group, randomized controlled trial. *Lancet Respir Med*. 2016;4(9):708-719. doi:10.1016/S2213-2600(16)30152-7
6. Tashkin DP, Elashoff R, Clements PJ, et al. Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. *Am J Respir Crit Care Med*. 2007;176:1026-1034. doi:10.1164/rccm.200702-326OC
7. Tashkin DP, Elashoff R, Clements PJ, et al. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med*. 2006;354(25):2655-2666. doi:10.1056/NEJMoa055120
8. Khanna D, Denton CP, Jahreis A, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomized, controlled trial. *Lancet*. 2016;387(10038):2630-2640. doi:10.1016/S0140-6736(16)00232-4
9. Khanna D, Lin CJF, Furst DE, et al. Tocilizumab in systemic sclerosis: a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2020;8(10):963-974. doi:10.1016/S2213-2600(20)30318-0
10. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis Rheum*. 2006;54(12):3962-3970. doi:10.1002/art.22204

Faculty Commentary

Sonye K. Danoff, MD, PhD:

In this situation, the patient has been given intravenous cyclophosphamide and has had improvement in their pulmonary function testing. And so, the question is really what's the next best steps. If you use IV cyclophosphamide, what do you follow on with? And just to back up, the reason why we think about switching from IV cyclophosphamide is because of the long-term risks associated with exposure to cyclophosphamide.

In general, after a patient has had 6 months of IV cyclophosphamide, the recommendation is to switch to oral cyclophosphamide for maintenance therapy.

Continuing it for 12 months, you're balancing the risk/benefit profile. The risks being the evolution of hemorrhagic cystitis and other, and cytopenias associated with cyclophosphamide. I would certainly not increase the dose. The point being that cyclophosphamide can have fairly significant toxicities at higher doses and azathioprine is really not indicated. One might argue that the other alternative would be to actually switch to oral mycophenolate which, again, would be a reasonable choice in this situation, and particularly if there was any concern about the potential for side effects related to the cyclophosphamide. And again, cyclophosphamide side effects tend to increase over time, so limiting the length of time the patient's on cyclophosphamide tends to be a favorable choice.

Would you have any comments on that, Dr. Castelino?

Flavia Castelino, MD:

In this case, while D is certainly a very valid answer in terms of switching the patient to oral cyclophosphamide, I think in practice what we tend to do is actually switch to oral mycophenolate as it is better tolerated. So, typically, after a 6-month course of IV cyclophosphamide, if the patient does get that now, we would move to oral mycophenolate. So, D is certainly a correct answer here, but there is another option in terms of using mycophenolate, as you mentioned.

Case 2 Question 1

Case background

A 30-year-old male presents to the clinic with progressive SSc-ILD. He was diagnosed with SSc at the age of 28, with diffuse skin involvement. Given his age and extent of skin involvement, he was deemed at high-risk for progressive disease and started on MMF. After a year of treatment, he presents to the clinic with progressive ILD. Upon presentation he has notable dyspnea upon minimal exertion and an HRCT reveals more extensive disease. His PFTs have shown a rapid decline in FVC from prior.

Question 1

Which of the following treatment options is most appropriate at this time?

- **a.** Continue MMF and add tocilizumab
- **b.** Continue MMF and add nintedanib
- **c.** Discontinue MMF and start tocilizumab
- **d.** Discontinue MMF and start nintedanib

Answer rationale

The correct answer is **B**.

- Patients' with rapidly progressive disease on a first-line therapy (MMF and cyclophosphamide) have few treatment options. They can be switched to a different drug or have combination therapy added.[1]
- Studies of nintedanib included patients on MMF, while studies of tocilizumab excluded them.[2-4]
- No studies exist to date comparing these methods. Given the patient's progression, background immunomodulation (continuing the MMF), while adding treatment is a reasonable approach.

References

1. Khanna D, Lescoat A, Roofeh D, et al. Systemic sclerosis-associated interstitial lung disease: how to incorporate two Food and Drug Administration-approved therapies in clinical practice. *Arthritis Rheumatol*. 2022;74(1):13-27. doi:10.1002/art.41933
2. Distler O, Highland KB, Gahlemann M, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. *N Engl J Med*. 2019; 380:2518-2528. doi:10.1056/NEJMoa1903076
3. Khanna D, Denton CP, Jahreis A, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomized, controlled trial. *Lancet*. 2016;387(10038):2630-2640. doi:10.1016/S0140-6736(16)00232-4
4. Khanna D, Lin CJF, Furst DE, et al. Tocilizumab in systemic sclerosis: a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2020;8(10):963-974. doi:10.1016/S2213-2600(20)30318-0

Faculty Commentary

Sonye K. Danoff, MD, PhD:

This question really focuses on what you would do in a patient who has progressive systemic sclerosis-associated ILD and I think that the decision is really somewhat challenging here. The correct answer is B, which is to add nintedanib. And the rationale for that is that there has been the INBUILD study which has shown that, for patients who are appropriately treated for their underlying interstitial lung disease who have progression based on CT, PFTs or symptoms, adding nintedanib slows the rate of decline of lung function.

In a patient who has extensive involvement of systemic targets, including skin, I think that it's pretty clear you would want to continue an immunosuppressive agent and whether you chose to continue mycophenolate or possibly either change to a different agent or add another agent, I think is something that I would really defer to my rheumatology colleagues on. And in terms of deciding between nintedanib and tocilizumab, again it just really goes back to the structure of the clinical trials where tocilizumab was tested in a population of patients who really were not selected for the presence of interstitial lung disease. A subset of the patients had interstitial lung disease, but it was primarily for early disease stage. It's just not well-shown in this population that there would be any benefit from tocilizumab. And again, the notion of discontinuing the underlying immunosuppressive agent is just a reminder that you would not discontinue it because the patient has a systemic disorder. And Dr. Castelino, do you want to just comment on sort of what you're thinking is around immunosuppressants in a patient who has progression?

Flavia Castelino, MD:

This patient also has diffuse skin involvement. So, that would be another reason to keep the patient on the mycophenolate, the immunosuppressant. The nintedanib studies focus more on fibrosis, but then understanding systemic sclerosis, we have to also think about the immune aspects. Keeping this patient on the mycophenolate makes sense as well. So, certainly option B, as you mentioned.

Case 2 Question 2

Case background

Based on discussion with the patient, he is interested in better understanding the expected benefits of treatment options that he has available to him.

Question 2

Which of the following drugs: benefits statements is true?

- **a.** Tocilizumab: tocilizumab is likely to preserve lung function and improve skin fibrosis
- **b.** Nintedanib: nintedanib is likely to preserve lung function but not skin fibrosis
- **c.** Rituximab: rituximab is more likely to improve lung function at 12 months
- **d.** Glucocorticoids: glucocorticoids in high doses are safe for patients on cyclophosphamide

Answer rationale

The correct answer is**: B**.

- Nintedanib and tocilizumab have not shown improvements in skin related outcomes, but have both shown preservation of lung function.[1-3]
- Rituximab is generally reserved as a third+ line option. When compared to standard treatments, outcomes are similar at 12 months.[4]
- Adjuvant glucocorticoids, if used, should be used at low doses. High dose glucocorticoids increase the risk of poor renal and infectious related outcomes when used in conjunction with cyclophosphamide.[5]

References

1. Distler O, Highland KB, Gahlemann M, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. *N Engl J Med*. 2019; 380:2518-2528. doi:10.1056/NEJMoa1903076
2. Khanna D, Denton CP, Jahreis A, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomized, controlled trial. *Lancet*. 2016;387(10038):2630-2640. doi:10.1016/S0140-6736(16)00232-4
3. Khanna D, Lin CJF, Furst DE, et al. Tocilizumab in systemic sclerosis: a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2020;8(10):963-974. doi:10.1016/S2213-2600(20)30318-0
4. Goswami RP, Ray A, Chatterjee M, et al. Rituximab in the treatment of systemic sclerosis-related interstitial lung disease: a systematic review and meta-analysis. *Rheum*. 2021;60(2):557-567. doi:10.1093/rheumatology/keaa550

5. Herrick AL. Controversies on the use of steroids in systemic sclerosis. *J Scleroderm Rel Dis*. 2017;2(2):84-91. doi:org/10.5301/jsrd.5000234

Faculty Commentary

Flavia Castelino, MD:

Nintedanib is likely to preserve lung function, but not skin fibrosis. And, as Dr. Danoff has mentioned previously, the studies using nintedanib and tocilizumab did not show any improvement in skin involvement and were done in 2 different patient populations. Typically, when we think about these drugs, tocilizumab and nintedanib and rituximab, in patients with scleroderma, nintedanib is often now the next line after the immunosuppressive agents.

In terms of the other options of rituximab, typically this is saved as a third-line option and there are studies ongoing in terms of looking at this is systemic sclerosis and other rheumatologic disease-associated ILD. In terms of adjuvant steroids, we tend to back away from this in the treatment of systemic sclerosis-ILD, particularly because of the risk of steroid-induced renal crisis in scleroderma and if steroids are ever used, we try to use just the very low dose, the lowest doses possible. Dr. Danoff, I don't know if you want to comment further on any of these treatments in your clinical practice.

Sonye K. Danoff, MD, PhD:

I just wanted to mention there's a very recently-reported trial comparing IV cyclophosphamide and rituximab in patients with a variety of connective tissue disorders (CTD)-ILDs and essentially the trial showed noninferiority of rituximab and cyclophosphamide, but it was not specifically in a systemic sclerosis patient population. But just so that our learners are aware that that study is also available at present.

Case 3 Question 1

Case background

40-year-old female with a history of anxiety presents for evaluation of a 4-month history of arthralgia, puffiness to hands and color changes in the cold, and dyspnea upon exertion (1 flight of stairs).

Past Medical History: Anxiety

Current medications: None

Social History: Married, 2 children, no tobacco, rare ETOH use

Physical Exam Findings:

- Vitals: BP 117/61 | Pulse 84 | Temp 37.1 °C (98.8 °F) | Ht 166.4 cm (5' 5.5") | Wt 79.4 kg (175 lb) | BMI 28.68 kg/m²
- Gen: Pt is AAOx3, in NAD.
- HEENT: NC/AT, PERRL, nonicteric. EOMI. MMM, w/o exudates.
- Neck: Supple, NT, trachea midline

- Chest: CTA b/l, no crackles, no wheezes
- CV: RRR; normal S1S2, no m/r/g appreciated
- Abd: soft, nontender, nondistended; NABS
- Extremities:
  - UE: no soft tissue swelling, warmth, effusion, erythema of DIPs, PIPs, MCPs, wrists, elbows b/l. Full range of motion of all joints.
  - LE: no soft tissue swelling, warmth, effusion, erythema of MTPs, ankles, knees b/l. Full range of motion of all joints.
- Skin: +sclerodactyly, no rashes, no ulcers appreciated. Nailfold capillary exam with evidence of dropout, dilated loops.
- MRSS: 12

Lab Results

- CBC, chemistry unremarkable
- CRP 4.2, ESR 18
- ANA 1:2560, speckled pattern
- dsDNA, SSA, SSB, Sm/RNP negative
- +Scl-70 (750)

Pulmonary Function Tests

- FEV1, FVC, and FEV1/FVC are within normal limits.
- TLC and subdivisions are normal.
- RV/TLC ratio is decreased. Single breath diffusion capacity is normal.
- Normal six-minute walk distance (580 meters, 94% predicted) without oxygen desaturation on room air.
- These test results indicate normal pulmonary function.

High Resolution Chest CT Interpretation

- Mild peribronchial fibrosis in the lung bases, likely nonspecific interstitial pneumonia

Question 1

What risk factors, that are present in the patient, have been associated with worsening of disease?

a. Diffuse skin involvement
b. Low skin thickness score
c. Current pulmonary function
d. Anxiety

Answer rationale

The correct answer is: **A**.

- The patient has a higher skin thickness score, which, along with diffuse skin involvement has been associated with a worse prognosis.[1,2]
- Current pulmonary function alone has not been associated with a worse prognosis, but should be monitored for disease progression. There are cohorts of patients that have evidence of ILD on radiography without a change in pulmonary function.[3]

- While many comorbidities have been researched, anxiety has not shown to be associated with worsened outcomes in patients, although it is fairly common in patients with pulmonary fibrosis.[4]

References

1. Fischer A, Swigris JJ, Groshong SD, et al. Clinically significant interstitial lung disease in limited scleroderma: histopathology, clinical features, and survival. *Chest*. 2008;134(3):601-605. doi:10.1378/chest.08-0053
2. Gilson M, ZerkakD, Wipff J, et al. Prognostic factors for lung function in systemic sclerosis: prospective study of 105 cases. *Eur Respir J*. 2010;35:112-117. doi:10.1183/09031936.00060209
3. Showalter K, Hoffmann A, Rouleau G, et al. Performance of forced vital capacity and lung diffusion cutpoints for associated radiographic interstitial lung disease in systemic sclerosis. *J Rheumatol*. 2018;45:1572-1576. doi:10.3899/jrheum.171362
4. Lee YJ, Choi SM, Lee YJ, et al. Clinical impact of depression and anxiety in patients with idiopathic pulmonary fibrosis. *PLoS One*. 2017;12(9):e0184300. doi:10.1371/journal.pone.0184300

Faculty Commentary

Flavia Castelino, MD:

Reviewing this patient's exam, she has evidence of sclerodactyly, so skin involvement of her hands, and she additionally has some nailfold capillary changes that are all indicative of systemic sclerosis. Her skin score is a 12. We don't have the breakdown of the skin score, but certainly that is a significant skin score in terms of alluding to diffuse skin involvement.

In terms of her other testing, she has pulmonary function tests that are primarily within normal pulmonary function. So, the fact that she has normal pulmonary function does not put her at increased risk. So, the answer here is A, that she has diffuse skin involvement and certainly a higher skin thickness score can be associated with a worse prognosis. As I mentioned, her pulmonary function is normal, so that certainly helps in terms of her prognosis as well. And then in terms of the other answer choices, low skin thickness score, her skin score is actually 12 which is significant and her anxiety also doesn't really have a role in terms of progression of her worsening of disease.

Case 3 Question 2

Case background

The patient has been diagnosed with early, diffuse scleroderma. Her pulmonary involvement is minimal.

Question 2

Which of the following systems are likely to be involved as her disease progresses?

a. Skin, GI, Pulmonary, Cardiac, Renal
b. Skin, GI, Neuro, Cardiac, Renal
c. Skin, GI, Lymphatic, Cardiac, Renal
d. Skin, GI, Reproductive, Cardiac, Renal

Answer rationale

The correct answer is **A**.

- There is a large heterogeneity in the disease course, which is why a systems-based approach to patient evaluation is important. Data from both Europe and the United States have shown that the most common symptoms were skin related in nearly three-quarters of patients, followed by gastrointestinal in more than two-thirds, pulmonary in about two-thirds, cardiac in about a third, and renal in less than 1 out of every 10 patients.[1,2]

References

1. Jaeger VK, Wirz EG, Allanore Y, et al. Incidences and risk factors of organ manifestations in the early course of systemic sclerosis: a longitudinal EUSTAR study. *PLoS ONE*. 2016;11(10):e0163894. doi:10.1371/journal.pone.0163894
2. Li Q, Wallace L, Patnaik P, et al. Disease frequency, patient characteristics, comorbidity outcomes and immunosuppressive therapy in systemic sclerosis and systemic sclerosis-associated interstitial lung disease: a US cohort study. *Rheumatology*. 2021;60(4):1915-1925. doi:org/10.1093/rheumatology/keaa547

Faculty Commentary

Flavia Castelino, MD:

Skin, gastrointestinal involvement, pulmonary involvement, cardiac and renal in terms of disease progression. But again, this can be quite varied based on individual patients and there is a lot of heterogeneity in systemic sclerosis. So, while this answer choice here is correct, it's important to really think about all these organ systems as you're evaluating a patient with systemic sclerosis.

In terms of skin, this is the primary manifestation, but many patients have significant GI involvement. Two-thirds of patients can have pulmonary involvement. We're learning a lot more about the cardiac involvement in scleroderma and a lot of the studies here have been done at autopsy, but certainly it's important to think about cardiac manifestations in systemic sclerosis. And, in terms of renal manifestations, we're seeing this less now since we're seeing less renal crisis because of the awareness of the use of steroids in systemic sclerosis.

Case 3 Question 3

Case background

The patient presents 1-year later with stable disease based on symptoms.

Question 3

Based on her current status, which is the most important routine surveillance test that should be considered?

a. Skin exams every 6 months
b. Pulmonary function tests every 6 months
c. High resolution chest CT every 6 months
d. Six-minute walk test every 3 months

Answer rationale

The correct answer is: **B**.

- While all of these should be done, the frequency of these monitoring parameters needs to be examined. Data has emerged that changes in PFTs have been associated with mortality and is an easy, noninvasive

test.[1] It is routine clinical practice to perform PFTs every 6 to 12 months, although this may vary by specialty.

- The exact frequency of any surveillance has not yet been established, but all of these should be considered. A rapid change in PFTs may prompt a repeat HRCT. The same may be said for a rapid change in symptoms (eg, dyspnea) prompting a repeat PFT. A true monitoring algorithm has yet to be developed.[2] Monitoring of progression of disease should be discussed with patients during each visit.

References

1. Goh NS, Hoyles RK, Denton CP, et al. Short-term pulmonary function trends are predictive of mortality in interstitial lung disease associated with systemic sclerosis. *Arthritis Rheumatol.* 2017;69:1670–1678. doi:10.1002/art.40130
2. Distler O, Assassi S, Cottin V, et al. Predictors of progression in systemic sclerosis patients with interstitial lung disease. *Eur Resp J*. 2020;55(5):1902026. doi:10.1183/13993003.02026-2019

Faculty Commentary

Sonye K. Danoff, MD, PhD:

The correct answer here is B, which is pulmonary function testing every 6 months. And the reason that this is so important is, as Dr. Castelino nicely pointed out, patients who present with just skin disease can still evolve into really a wide array of end-organ involvement. And obviously lung disease is probably the most serious in terms of the likelihood of increased morbidity and mortality. Maintaining a routine of following the pulmonary function tests is incredibly important. It can pick up small declines in lung function, even before patients may recognize them. It's important to continue to examine the patient's skin, as you would with any patient with a systemic disorder like systemic sclerosis. It's really not necessary to do high-resolution imaging on a regular basis. I think that that's something that we've come to appreciate, and it is that imaging is something that can be used when there's a clinical change for a patient, but probably doesn't need to be done on a routine basis. And whether or not to get a 6-minute walk test every 3 months, I think is also sort of an interesting question. It's not necessary as long as a patient has good control otherwise. At many of our scleroderma clinics, and Dr. Castelino can comment on this in a moment, we'll routinely do 6-minute walk tests every time a patient is seen in clinic and I think it provides valuable information and certainly it will help you understand what the functional consequence of disease is. But I do think that pulmonary function testing is something that should be done on a routine basis and one can consider doing 6-minute walk tests at 3-month follow-up for a stable patient, but is probably a little bit more than most clinics would do. But if the patient is coming in every 6 months for routine follow-up and it is feasible in the clinic to do a 6-minute walk test, I don't think it's an unreasonable thing to do, but certainly PFTs, I think, are fairly mandatory. Do you want to comment on the practice in your clinic with regard to 6-minute walk tests?

Flavia Castelino, MD:

Essentially what we do with the 6-minute walk test is we usually get that done at baseline. I do think 3 months is a bit aggressive in terms of monitoring the 6-minute walk test. One thing in scleroderma patients is other aspects of their disease can also impact the 6-minute walk test. So, if they have some muscle deconditioning, if they have just inability to really complete the walk itself just due to other factors from their skin, their muscle involvement and just deconditioning, I think it's important to keep that in mind when assessing the 6-minute walk test. But we certainly don't do it every three months, maybe even once a year. I think practices vary across the country.

Sonye K. Danoff, MD, PhD:
I think one of the other things that makes a 6-minute walk test a little bit problematic, again not to say that it shouldn't be done, but just to think about it is the very high rates of Raynaud's in these patients. And it really requires the set-up that you can actually be sure you can effectively monitor a pulse oximetry if that's part of what you're doing, which is pretty standard, and often requires something like a forehead probe or an ear probe to be used in order to be sure that you're accurately recording what the patient's oxygen saturation is.

Flavia Castelino, MD:
That's a very important point and I would encourage clinics to actually invest in those forehead probes, just because even just checking the pulse oximeter in a clinic for routine vitals is difficult at times in our scleroderma patients.

Case 4 Question 1

Case background

A 56-year-old Black male presents to the clinic for evaluation of his dyspnea. The dyspnea is most prominent during exertion and has worsened over the last year according to his reports. The year prior, he was regularly exercising but has since mostly stopped. He has intermittent, but worsened nonproductive cough. He has lost approximately 10 lb in the last year, but denies any other associated symptoms. His vaccinations are up-to-date; however, he has not received a COVID vaccine.

His vitals are stable at: BP 121/70 | Pulse 78 | Temp 36.5 °C (97.7 °F) | Ht 182.9 cm (6') | Wt 91.6 kg (202 lb) | BMI 27.4 kg/m²

His family history is negative for malignancy, cardiac or renal disease.
He denies the use of alcohol or tobacco products.

Upon physical examination he has notable, diffuse cutaneous involvement. His pulmonary function tests and chest CT have shown moderate interstitial lung disease. The patient has significant concerns about initiating immunosuppressive therapy.

Question 1

What nonimmunosuppressive preventive/treatment strategy is the most important to offer to this patient at this time?

a. Physical rehabilitation
b. Up-to-date vaccinations
c. Routine cancer screening
d. Angiotensin-converting enzyme inhibitor

Answer rationale

The correct answer is: **A**

- The patient would most clearly benefit from physical rehabilitation given his lack of exercise at the moment.[1]

- His vaccines are up-to-date, with the exception of a COVID vaccine, which should be discussed with him, particularly since has not started immunosuppressive therapy. Given his disease, he should receive the vaccine, but the series, including a booster, will take months to complete.[2]
- Although routine cancer screening should occur, this is less likely given his family history and the infrequency at which this is comorbid (relative to other diseases) to SSc-ILD.[3,4]
- Renal insufficiency in patients with SSc-ILD has significantly decreased since the addition of ACE inhibitors to the market; however, he is currently at low risk for this.[3,4]

References

1. Cottin V, Brown KK. Interstitial lung disease associated with systemic sclerosis (SSc-ILD). *Respir Res*. 2019;20:13. doi:org/10.1186/s12931-019-0980-7
2. Murdaca G, Noberasco G, Olobardi D, et al. Current take on systemic sclerosis patients' vaccination recommendations. *Vaccines (Basel)*. 2021;9(12):1426. doi:10.3390/vaccines9121426
3. Jaeger VK, Wirz EG, Allanore Y, et al. Incidences and risk factors of organ manifestations in the early course of systemic sclerosis: a longitudinal EUSTAR study. *PLoS ONE*. 2016;11(10):e0163894. doi:10.1371/journal.pone.0163894
4. Li Q, Wallace L, Patnaik P, et al. Disease frequency, patient characteristics, comorbidity outcomes and immunosuppressive therapy in systemic sclerosis and systemic sclerosis-associated interstitial lung disease: a US cohort study. *Rheumatology*. 2021;60(4):1915-1925. doi:org/10.1093/rheumatology/keaa547

Faculty Commentary

Flavia Castelino, MD:

This is often 1 of the under-discussed topics in scleroderma and care for scleroderma patients. Especially in a patient with scleroderma interstitial lung disease, getting them into a rehabilitation program early on, getting them into physical therapy as well, and occupational therapy is of utmost importance to just help with their muscle conditioning and their daily activities of living. In terms of answer B, up to date on vaccinations, it looks like this patient is up to date, however he has not received his COVID vaccine. So, certainly guiding the patient in terms of considering the COVID vaccination is also of importance, but it sounds like he's already up to date on these other vaccines.

In terms of routine cancer screening, so in all our scleroderma patients, we do encourage age-appropriate cancer screening. Scleroderma has been associated with an increased risk of malignancy, therefore it's just important to check in with the patient and make sure their primary care is additionally maintaining their cancer screening.

Case 4 Question 2

Case background

Despite appropriate treatment over the last 6 months, the patient has rapidly declined. He now has dyspnea at baseline. Based on his symptom progression, despite trials of several medications, you believe his disease has progressed and order a battery of tests.

Test results confirm that his SSc-ILD has progressed and he has also developed pulmonary arterial hypertension. He is negative for GERD and diabetes.

Question 2

Which of the following recommendations is most appropriate at this time?

- **a.** Refer patient for lung transplant evaluation
- **b.** Refer patient for pulmonary arterial hypertension management
- **c.** Refer patient for hematopoietic stem cell transplantation
- **d.** Refer patient to palliative care

Answer rationale

The correct answer is **A**.

- For the patient with rapidly progressive, multimorbid SSc-ILD, there are few options if treatment has failed. PAH management at this time, while important, is not going to change the trajectory of his underlying disease. HSCT is still fairly investigational, and the outcomes are not overwhelming.[1,2] Lung transplant may be his best option if he can tolerate it.[3,4] A referral to palliative care, if it aligns with the patient's goals of care, may also be appropriate.

References

1. Van Laar JM, Farge D, Sont JK, et al. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. *JAMA*. 2014;311(24):2490-2498. doi:10.1001/jama.2014.6368
2. Sullivan KM, Goldmuntz EA, Keyes-Elstein L, et al. Myeloablative autologous stem-cell transplantation for severe scleroderma. *N Engl J Med*. 2018;378(1):35-47. doi:10.1056/nejmoa1703327
3. Bernstein EJ, Peterson ER, Sell JL, et al. Survival of adults with systemic sclerosis following lung transplantation: a nationwide cohort study. *Arthritis Rheumatol*. 2015:67(5):1314-1322. doi:10.1002/art.39021
4. Launay D, Savale L, Berezne A, et al. Lung and heart-transplantation for systemic sclerosis patients. A monocentric experience of 13 patients, review of the literature and position paper of a multidisciplinary working group. *Presse Med*. 2014;43:e345-e363. doi:10.1016/j.lpm.2014.01.020

Faculty Commentary

Sonye K. Danoff, MD, PhD:

The patient has progressed and is declining rapidly. He has dyspnea at baseline, despite appropriate treatment. And he's also developed pulmonary hypertension. So, what would be the next step at this point in time? Obviously, the key with patients who have progressive disease is to actually think about where are they going and at the same time you're treating where they are right now, you have to really be focused on where you're headed. In this case, I would refer the patient for lung transplant evaluation which is answer A. I think that it is also appropriate to have the patient evaluated for management of pulmonary arterial hypertension. Clearly, in the patient with systemic sclerosis, there are well-done studies suggesting that there are benefits to treatment of pulmonary hypertension and part of what the goal is, is to control his symptom burden and this might be accomplished with the use of pulmonary hypertension therapy. Of course, it's not going to prevent progression of his interstitial lung disease, necessarily, but it would control symptom burden in the present moment.

In terms of referring for hematopoietic stem cell transplantation, I think that this is really still something that I would consider at an experimental level and, although there have been reports of successful hematopoietic stem cell transplants in some individual patients, this is a patient who comes with really multiple organ involvement with both interstitial lung disease and pulmonary hypertension. And generally, the presence of lung disease is considered to be a relative contraindication to stem cell transplantation. There really isn't any evidence at present that stem cell transplantation has benefit for interstitial lung disease.

And then the last question, the last potential answer, which is palliative care, is absolutely. I think that it is really important to recognize the symptom burden associated with interstitial lung disease in systemic sclerosis as well as other diseases and to engage supportive care that will improve patients' quality of life. Having palliative care engaged at this point or even earlier in the patient's course is quite appropriate with a focus on things like breathlessness management, strategies for coping with the stress associated with the diagnosis and progressing disease. I would consider these as kind of both/and responses rather than either/or responses.

Faculty Discussion: Pearls of Screening and Evaluation

Flavia Castelino, MD:
I would like to leave you with some pearls as you're evaluating a patient with systemic sclerosis. Typically, when a patient comes to us, they may have some Raynaud's or puffy hands and this can often be misunderstood as a rheumatoid arthritis or an arthritis manifestation. Teasing out some of these symptoms, including the onset of color changes to the fingers, development of any puffy hands or puffiness or swelling to the skin can be really informative. In terms of testing, when you're first seeing a patient, certainly the ANA antibody panel can be informative. If you do send off an ANA and it comes back with a nucleolar pattern, that should heighten your suspicion for systemic sclerosis and also to consider sending other systemic sclerosis antibodies, including an Scl70, anticentromere antibody and an RNA polymerase III antibody. These can be helpful in making the diagnosis of systemic sclerosis.

Sonye K. Danoff, MD, PhD:
When I see a patient who comes to me with interstitial lung disease, sometimes what I'm thinking about is does this patient have systemic sclerosis or another connective tissue disease. And just as Dr. Castelino mentioned, there are really 2 components to making the diagnosis, or maybe a few more components, but the first is just a really excellent physical exam and, as a pulmonologist, the lung exam, but truly the most important part when I'm making the diagnosis of a systemic disorder causing the ILD is everything else. So, really, a very careful skin exam, looking for rashes. With a patient who presents with puffy fingers or a very prominent history of Raynaud's, really looking at skin thickness and the extent of skin thickness. Looking for rashes. Does the patient have rashes on their hands, do they have them on their face, have they had a history of having rashes? I'm also really listening for a family history or personal history of autoimmune disease because many of our patients actually will have another family member who may not have the same autoimmune disease, but may have another autoimmune disease. And they themselves may have had a prior autoimmune disease, so maybe they had Grave's disease or something of that sort.

Those pieces of history are very helpful to me as an interstitial lung disease doctor. And then the physical exam,

obviously, and certainly listening for crackles, percussing out the lung field and making sure that the lung field is as full as you would expect for somebody. And the other thing that's important from my perspective is that not every patient who has interstitial lung disease is going to have crackles. We see patients who have—particularly with NSIP—who really don't have crackles on exam. So the absence of crackles doesn't dissuade me from a diagnosis of ILD. And then the other issue is, on exam, really listening for evidence of pulmonary hypertension or heart failure in general, because when a patient presents with ILD, often their presenting symptom is shortness of breath. And so really trying to tease out what is causing the shortness of breath.

Then, once a diagnosis is made, and obviously this is really something that I do hand-in-hand with my rheumatology colleagues, we'll then discuss what therapies are appropriate and, in my mind, pulmonary function testing is really critical in assessing where patients are when they present. Are they presenting early in the disease? Are they presenting sort of in a somewhat advanced state? Or are they presenting in a very advanced state? And I think that that's important in thinking about how you're going to interpret the response to therapy.

Imaging clearly is also very important and we try, if at all possible, to get noncontrast, high-resolution CT scans. And if there's a question of whether a patient's had a pulmonary embolus and a CT angiogram is necessary, then that's one thing. But if it is possible, if you're really thinking this is going to be an interstitial lung disease, then having a noncontrast, high-res CT scan is very, very helpful.

Then, as we do initial therapy, we've talked about some of the therapeutic agents and I think that both of us would reach for mycophenolate as our initial therapy, potentially, for our patients with newly-diagnosed systemic sclerosis-ILD. And then the question is really, is the patient getting better, staying the same or getting worse? And I think that that's often the point at which difficult decisions have to be made. What are your thoughts about initial therapy?

Flavia Castelino, MD:

Essentially, we start with mycophenolate. It has been helpful for both the skin as well as the lung and I think that's sort of our backbone of treatment now. Historically, methotrexate used to be used initially for skin involvement, but that has been a little bit tricky with using that in patients with potential lung involvement as well. So, I would say that mycophenolate mofetil has become the first-line therapy for systemic sclerosis, both for skin and for lung.

I do also want to make 1 more point about just differentiating the types of systemic sclerosis. So, limited vs diffuse. One of the things that can be helpful is that actually all these patients can develop interstitial lung disease. Limited systemic sclerosis used to be known by that acronym CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) which didn't include interstitial lung disease. But in screening all patients with scleroderma, it's important to think about interstitial lung disease as a potential component of their disease as well.

Sonye K. Danoff, MD, PhD:
And then when you have a patient who progresses, I think that this is often an issue where we get called, what should I do, a patient's been on mycophenolate, their lung function is declining. And obviously there are a

number of options and we've talked in this session about the use of a number of agents, including nintedanib, as well as rituximab and cyclophosphamide. How do you decide whether the patient is responding to treatment? What is your expectation when you treat a patient?

Flavia Castelino, MD:
We're looking for just even mild improvements in some of their pulmonary function parameters. Oftentimes, one thing that I've found with nintedanib, just in clinical practice, it's harder to use in our patients who have significant GI involvement just because of the diarrhea side effect. I think we're often trying different dosing with this medication, fine-tuning essentially the treatment plan to an individual patient. But it is a challenge in terms of managing these patients and trying to see how they respond, even sometimes the stability in symptoms where the patient may not be coughing as much or may just feel that, okay, they can get around the house breathing comfortably. That, in itself, is a positive in terms of showing stability.

Sonye K. Danoff, MD, PhD:
The other thing that I really focus on when we see a patient and maybe their pulmonary function tests are actually staying fairly stable, but they're still having a fair amount of symptom burden, I'll start to look for other comorbidities that might be contributing to it. And certainly, with our systemic sclerosis patients, reflux and esophageal dysmotility are very, very common. And so when we see patients who have a lot of cough, I'll often focus on trying to manage the esophageal dysmotility issues and minimize reflux in them. And when we have patients who have fairly stable FVCs or lung volumes, but their diffusing capacity is dropping and their oxygen requirement is going up, I very quickly think about the assessment of pulmonary hypertension. What's your practice in terms of assessing for pulmonary hypertension?

Flavia Castelino, MD:
Typically, in all our systemic sclerosis patients, we do annual echocardiograms. If they've been stable for some time, then we can spread it out to every 2 years, but at the start of their diagnosis, we do at least an annual echocardiogram. Is that what you do in your practice as well?

Sonye K. Danoff, MD, PhD:
Yes, it is, and I think it's actually very helpful because, particularly patients with interstitial lung disease, it can be difficult to pick up pulmonary hypertension since shortness of breath tends to be the same consequence of the interstitial lung disease as well as the pulmonary hypertension. So, we try to make sure we're screening once a year with an echocardiogram, particularly early in disease, but really for the patients with ILD, we actually continue for a fair number of years to screen them.

And then, as patients who do progress, and one of the things that we often think about is referral for lung transplantation. One of the concerns that will often come up with lung transplantation is actually the presence of esophageal dysmotility or reflux. The capacity to care for patients in a lung transplant program varies from program to program. Some are more open to taking care of patients who have reflux disease, and the concern around reflux is that it is associated with this bronchiolitis obliterans syndrome which is essentially rejection of the transplanted lung. However, it's important to determine whether an individual patient would be appropriate for transplant through referral to a center that might have a lot of expertise in that. What's your practice in terms of working with your pulmonologists for referral to transplant?

Flavia Castelino, MD:
One of the big things, as you mentioned, is the reflux, and a lot of our patients who we have been priming for lung transplant have often gotten rejected because of the reflux aspect. There are some centers that I've had patients go to, that have been successful with getting that lung transplant. I think certainly if a center is not willing to do the transplant, there are still options, but it definitely has been a challenge in terms of getting lung transplants for our patients because of the reflux component.

Sonye K. Danoff, MD, PhD:
And, the other thing that we talked about in this session was about palliative care and this is something that, as physicians, we really need to think about much earlier and we actually do it, we just don't name it. So, obviously when we have a patient who coughs, we try to control their cough. When we have a patient who is in pain, we try to deal with their pain. When we have a patient who is experiencing a lot of difficulties around their Raynaud's, we try to control their Raynaud's. And really, all of that is palliative care in the sense that it is targeted to symptoms. But I think that actually engaging palliative care as sort of a second layer of the care we provide to our patients is often very valuable. Obviously, at the most extreme point, we consider engaging hospice when we think patients are within 6 months of death, but I think that really early engagement of palliative care, and thoughtful engagement, is very valuable. I don't know what your experience is in terms of having rheumatologists who provide palliative care or do you tend to refer out to an external palliative care program?

Flavia Castelino, MD:
Unfortunately, we don't have rheumatology palliative care, but you certainly bring up a very important point. I think, as physicians in general, we don't discuss palliative care enough and maybe even early enough in the care of our patients with systemic sclerosis. In our hospital system, we refer just to the palliative care program which is part of the oncology program. That's our mode of referral at least in our hospital system.

Sonye K. Danoff, MD, PhD:
And the other piece of this is really the other parts of supportive care. For our patients who are hypoxemic with activity, obviously getting oxygen for our patients, making sure that they have an appropriate level of oxygen support for their needs, for their activity. Psychosocial support, either through support groups or through actually directed therapy for the patients or their family members, is quite helpful. And then we're very fortunate to have really good patient support groups in the community that are disease-specific support groups and referring patients to those disease-specific support groups that are very valuable. And then pulmonary rehab or physical rehab as yet another element of the sort of holistic care of our patients. Are there other things that you try to think about in that sort of wrap-around care for your patients?

Flavia Castelino, MD:
Right, when I think about caring for a scleroderma patient, it is multidisciplinary care, as you mentioned. I would also, in addition to just the pulmonary rehab component, I would include the occupational therapists. They can be really helpful in terms of helping with some of the sclerodactyly, building splints for our patients, giving exercises to help improve hand function. Physical therapy as well, and certainly a lot of these drugs, we need to go through different prior authorizations, etc, so liaising with both the pharmaceutical companies and also with the pharmacists just to get these approvals in process. And the primary care physician plays an important role in helping manage some of these other comorbid issues with the patients, making sure that they're screened appropriately for the various malignancies. It's a team approach and every different specialist can be

involved in the care of a patient with scleroderma.

Sonye K. Danoff, MD, PhD:
Absolutely. And one of the things that we really interface with our primary care physicians over is vaccination, making sure that our patients who are, by virtue of the fact they're going to be off and on immunosuppressive agents, will be at higher risk of more severe disease should they get common infections, like influenza. And now, obviously, the whole COVID pandemic has really focused a light on the potential for increased risk or perhaps decreased efficacy of vaccination in our patients who are on immunosuppression. How do you talk about those issues, particularly around COVID vaccination, with your patients?

Flavia Castelino, MD:
Typically, if our patients are on various immunosuppressive medications, we'll have them hold it for a couple of weeks. The American College of Rheumatology has specific guidelines in terms of the COVID vaccinations and the different immunosuppressive medications that we use. But oftentimes, patients are eager to get these vaccinations, given the extent of their disease. Certainly, juggling the immunosuppressive aspect with the vaccination schedule is important.

Sonye K. Danoff, MD, PhD:
There are also the alternative options that have evolved, particularly with COVID, for things like monoclonal antibody therapy for patients who don't form antibodies and so, while it is certainly not routine for all forms of vaccination, with COVID vaccination, we've sometimes used post-vaccination titers. I know that this remains controversial because we don't know for a fact that a patient who doesn't develop antibodies doesn't have some level of immunity, but certainly it appears that there are some patients who don't develop antibodies against COVID after vaccination and that might be a group where there'd be more focus on either repeat vaccination and, if that failed, then the provision of long-lasting monoclonal antibodies that are protective against COVID. These are topics that are really evolving incredibly rapidly now and I think that, even between now and when this is seen, there will probably be some new recommendations.

One of the things that often comes up with our patients is how do you, when a patient has difficulty with a medication and we talked about the difficulty with the mycophenolate causing upset stomach, how do you help a patient stay on therapy? Because we can have the most effective therapies in the world, which we don't, but if the patient doesn't take the therapy, then there is an increased risk of progression of their disease. What kind of counseling do you give to your patients in terms of being able to stay on therapy?

Flavia Castelino, MD:
We've found that a lot of our scleroderma patients are determined to try and [we want to] help them. Some of them are willing to go through some of these really horrible side effects just for taking the medication. I do say that sometimes patients are willing to reduce the dose and at least stay on the minimal possible dose to try and see if that will have effect. And some scleroderma patients, they may have difficulty swallowing. Then there's other options in terms of tablet size or changing the tablet size or even giving them a liquid formulation can sometimes be helpful as well.

Sonye K. Danoff, MD, PhD:
And that's really important is actually assessing with the patient, what is the barrier to staying on the therapy.

We mentioned briefly that one of the side effects of nintedanib can be diarrhea and this, obviously, can be a very limiting side effect. And also, talking with the patient about whether they are experiencing side effects and whether the side effects are really impairing quality of life because trying to balance the risk/benefit ratio for any individual patient is really important. And then I think that the second thing is really getting very granular with the patient about how are you taking it, what time of day, what do you take with it and trying to see if you can help them work with that to mitigate the side effects for therapies that we think will have benefit for them if they're able to take them. But also acknowledging that the side effects are sometimes the reason why patients decide not to take therapy or why we should encourage patients to stop a therapy.

The final thought I would like to leave people with is that we have made such an amazing amount of progress in the care of patients with systemic sclerosis. We really should say that the rheumatologists have made an amazing amount of progress in this. And I think that this is a time where there's going to be a lot more to be learned about how to optimize the management of our patients, but even right now we have the capacity to make a huge difference in the outcome of our patients and the key is really early recognition, referral to appropriate pulmonary, rheumatology colleagues to manage this if it's something that is outside of your wheelhouse. And then just really very consistent patient-focused care and joint decision-making with the patients about which therapies are beneficial and which ones have unacceptable side effects. Dr. Castelino, any last words?

Flavia Castelino, MD:

I would echo the sentiments and I would also say that if patients are not responding to any of these treatments, there's a lot of clinical trials available at different institutions across the country. Patients do have options now that weren't there about 10 years ago. Keep that in mind if your patients are still having a hard time with their condition, to consider also sending them to an institution that may have a clinical trial.