University Health Network
Toronto General Hospital Toronto Western Hospital Princess Margaret Hospital

SCLERODERMA INTERSTITIAL LUNG DISEASE (SSc-ILD)

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Financial Interest Disclosure
(over the past 24 months)

Company	Speaker / Honoraria	Advisory	Research
Astrozeneca	√		
Boehringer-Ingelheim	√	√	√
Gilead			√
Hoffman La-Roche	√	√	√
Medimmune			√
Prometic			√
Sanofi-Aventis			√

- There are very few approved therapies for CTD-ILD. As such, **MANY** pharmacologic treatments discussed in this talk involve “off-label” indications

At the end of this session, participants will be able to:

- Describe Scleroderma interstitial lung disease (SSc-ILD)
- Understand the risk factors for SSc-ILD development and its progression
- Discuss the evidence for and against anti-inflammatory and anti-fibrotic treatment of SSc-ILD

Background – What is ILD?

- What is it?
  - Chronic, progressive scarring of the scaffolding of the lung
  - Cause may be known (Scleroderma, asbestosis, farmer's lung, etc…)
  - Cause may be unknown (idiopathic Pulmonary Fibrosis - IPF)

- Why is it bad?
  - Stiff lungs → more work to breathe → breathless
  - Scarred lungs → poor gas exchange → low Oxygen levels
  - Progressive → lung function can get worse over time

Background – How do we assess ILD?

- As the lungs stiffen and shrink, the Vital Capacity (VC) gets smaller
- We measure the VC by asking patients to force the air out of their lungs
- We monitor the volume of this Forced Vital Capacity (FVC)
- A dropping forced vital capacity (FVC) means that the ILD is getting worse

Who gets SSc-ILD?

- SSc-ILD occurs in up to half of patients with SSc
- The clinical course of SSc-ILD is variable
  - Many patients have mild and stable ILD
  - Some can have severe and/or progressive disease
- How do we predict who will have mild disease and who will progress over time?

Wells AU, *et al, Semin Repir Crit Care Med 2014;35:213-221*

Risk Factors For Progressive ILD

- Recent diagnosis of SSc (within 4-5 years)
- Specific antibody profile (topoisomerase >> centromere)
- High volume of abnormal lung (> 20%)
- Low lung function at baseline (FVC < 70%)
- Dropping lung function (FVC drops ≥ 10%) over 6-12 months

Wells AU, *et al, Semin Repir Crit Care Med 2014;35:213-221*

Ms. S.C.

- 58 year old woman with Scleroderma
  - Lives in Thunder Bay and flies to Toronto for visits
- Referred to my clinic in 2008 for lung assessment
  - Fit and active with no lung symptoms
- Comes back 3 years later
  - Breathless for about 6 months
  - Dry hacking cough
  - Slowly getting worse
  - Not improving after antibiotics and puffers

Pulmonary Function Tests

Date	Dec 2008	Dec 2010	May 2011
FVC	2.3 L	2.0L	1.7 L

SSc-ILD Treatment: General Principles – Back To Basics

- Screen for and treat other causes of cough and breathlessness
  - Heart disease (pulmonary hypertension) and acid reflux
- Deconditioning is common
  - Refer to rehab if available
- Vaccinations should be strongly encouraged
  - Influenza vaccine annually
  - Pneumococcal vaccines every 5-10 years
  - COVID-19 vaccine (once available)

When to consider treating with drugs?

- Disease may not be active
  - Early disease may be found incidentally (ie. “subclinical”)
  - Late disease may be inactive (ie. “burned out”)
- Balance of risks and benefits must be weighed
  - Treatment recommendations are largely based on poor quality data
  - Once treatment is started, it is typically maintained for many years
- Treatment frequently started when patients have both:
  - Abnormal lung function
  - Worsening lung function (due to progressive ILD) over time
- Is this the right thing to do?

What treatments are available?

- Immunosuppresive therapy
  - Cyclophosphamide (Cytoxan)
  - Mycophenolate (Cellcept / Myfortic)
  - Rituximab (Rituxan)
- Anti-fibrotic therapy
  - Nintedanib (Ofev)

SSc-ILD Treatment: SLS-1 Scleroderma Lung Study 1

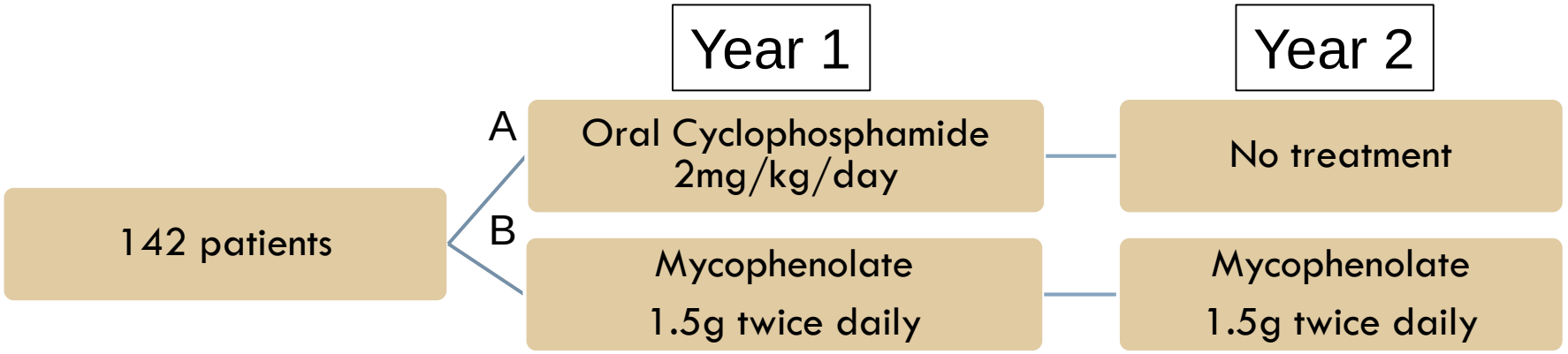
- Oral Cyclophosphamide vs. Placebo for 1 year in 158 patients
  - Modest improvement in FVC at 1 year
  - Further FVC increase at 18 months
  - Benefits lost after 1 year without treatment
  - Side effects were common
    - Low blood counts
    - Bladder problems
    - Increased risk of cancer

Tashkin DP *et al,* N Engl J Med 2006;354:2655-66.
Tashki DP *et al.* Am J Respir Crit Care Med 2007;176:1026–1034.

SLS-1: Take Home Messages

- Cyclophosphamide was the first drug to show that we can improve lung function in patients with SSc-ILD
- Benefits may fade over time if treatment is stopped
- Side effects are common and can be serious
- Are there other less toxic treatments that work?

SSc-ILD Treatment: SLS-2 Scleroderma Lung Study 2



- FVC improved similarly in both groups
- More side effects with Cyclophosphamide

Tashkin DP, *et al.* Lancet Respir Med. 2016 Jul 25. pii: S2213-2600(16)30152.7 [epub ahead of print]

SLS-II: Mycophenolate and Cyclophosphamide effect on SGRQ

- Mycophenolate and Cyclophosphamide both improve quality of life

Volkman ER, *et al. ARC Open Rheumatol.*. 2020 May 20. [epub ahead of print].

SLS-2: Take home messages

- Cyclophosphamide and Mycophenolate both likely improve FVC
- Cyclophosophamide has more side effects than Mycophenolate
- There are still a lot of unanswered questions…
  - Can we really make any conclulsions from a “negative” trial?
  - Are there some patients that benefit more than others?
  - When is the right time to start these drugs?
  - Is there a role for Cyclophosphamide first followed by Mycophenolate maintenance therapy?
  - Should Cyclophosphamide be used as “salvage” treatment for patients who are getting worse on Mycophenolate?

Ms. S. C.

- Ms. S. C. had a detailed discussion with her doctor
- She decided to take 6 months of Cyclophosphamide
- Followed by long term Mycophenolate for over 2 years

Date	Dec 2008	Dec 2010	May 2011	Nov 2011	Feb 2012	June 2012	Jan 2013	May 2014	Dec 2014
FVC	2.3 L	2.0L	1.7 L	1.9 L	2.1 L	2.2 L	2.2 L	2.2 L	2.4 L

Cyclophosphamide

Mycophenolate

Rituximab in SSc-ILD

- Prospective open label study of Rituximab vs. standard of care
  - All patients were offered Rituximab
- 51 patients were followed for a median of 4 years
  - 33 patients chose to be treated with Rituximab
  - 18 patients chose to stay on "standard of care"
- Rituximab associated with improved FVC over standard of care at 7 years
  - ΔFVC = +11.6% vs. – 16.6% (p=0.013)

Daoussis D, *et al.* Semin Arthritis Rheum. 2017 Apr;46(5):625-631.

Nintedanib in SSc-ILD

- Nintedanib is a different class of medications
  - In a class of drugs called "anti-fibrotics"
  - Stops the body from laying down scar tissue (fibrosis)
  - Initially developed for IPF (approved for IPF in 2015)

- Potential advantages of nintedanib
  - It does NOT suppress the immune system
  - Can be used in combination with other treatments

- Potential disadvantages of Nintedanib
  - Slows down progression – patients still get worse on treatment
  - Cannot get rid of the scar tissue that already exists
  - No effect on skin, joints and muscles (only affects the lungs)

Distler O, *et al.* N Engl J Med. 2019 Jun 27;380(26):2518-2528.

SENSCIS study: Nintedanib in SSc-ILD

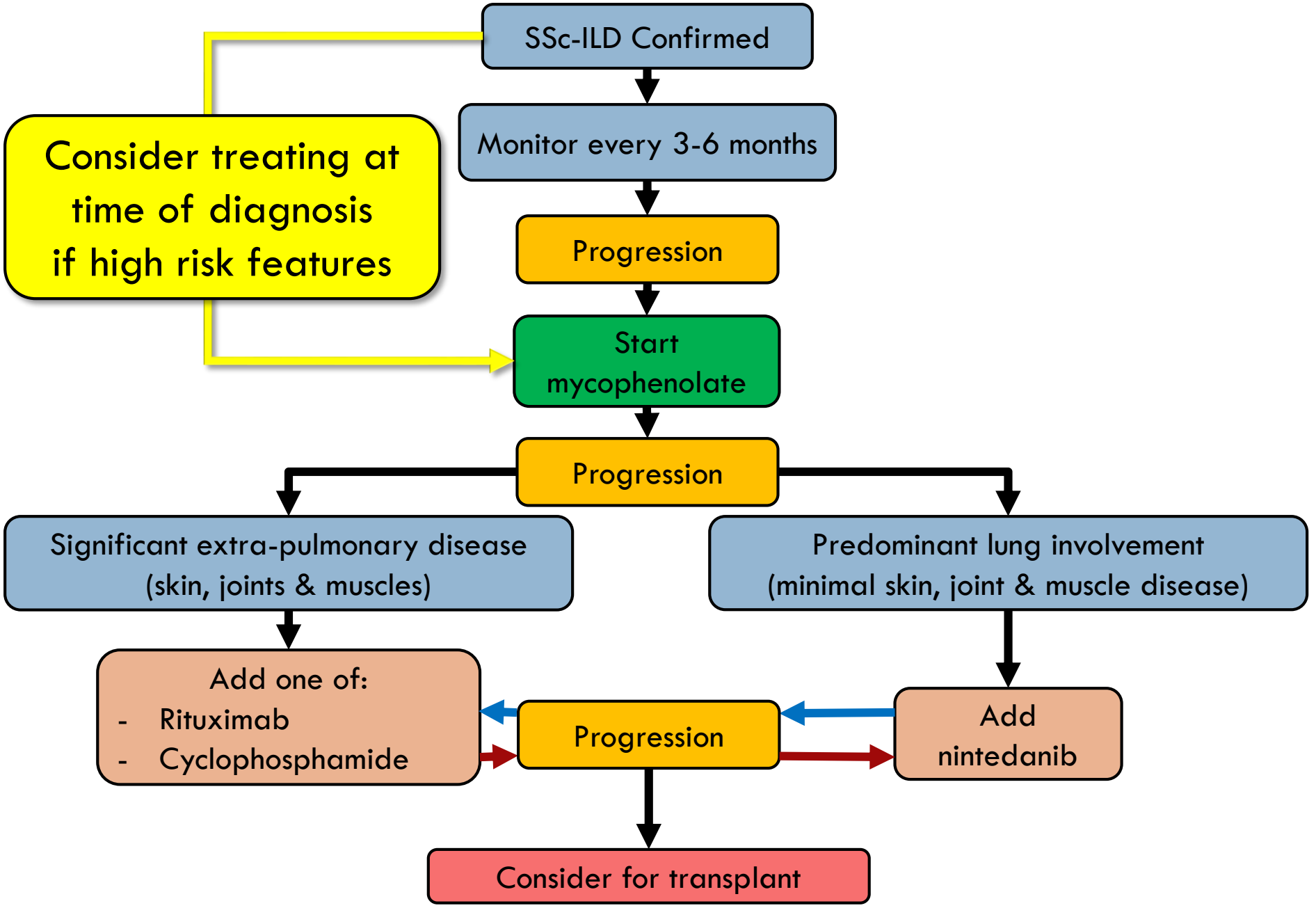
- Nintedanib vs. placebo x 1 year in 576 patients with SSc-ILD
  - SLS-1 (cyclophosphamide) = 158 patients
  - SLS-2 (mycophenolate) = 142 patients
  - Rituximab study = 51 patients

Distler O, *et al.* N Engl J Med. 2019 Jun 27;380(26):2518-2528.

Access in Canada

- Health Canada approval
  - Nintedanib approved for SSc-ILD on November 22, 2019
- Who is going to pay for it?
  - Nintedanib costs > $30,000 per year…
- Access
  - Private insurer coverage
    - Most private insurance policies cover nintedanib for SSc-ILD
  - Government coverage (exceptional access program)
    - Negotiations are ongoing
    - Coverage probably won't be available until 2022

Just tell me what to do…


SSc-ILD Confirmed
Monitor every 3-6 months
Consider treating at time of diagnosis if high risk features
Progression
Start mycophenolate
Progression
Significant extra-pulmonary disease (skin, joints & muscles)
Predominant lung involvement (minimal skin, joint & muscle disease)
Add one of:
- Rituximab
- Cyclophosphamide
Progression
Add nintedanib
Consider for transplant

Summary

- SSc-ILD occurs in half of patients with SSc
  - Risk factors for progression: early in disease course and progression over time
- Immunosuppressive therapy may improve lung function
  - Mycophenolate, Rituximab and Cyclophosphamide are all options
- Anti-fibrotic therapy is a new therapy for SSc-ILD
  - Nintedanib slows the rate of lung function decline
  - This is the first drug that is officially approved for use in SSc-ILD

Thank you to the UHN ILD clinic

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