Systemic Sclerosis Clinical Trials

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Disclosures

• Investigator- Abbott, **Actelion**, Amgen, Bristol-Myers Squibb, Centocor, **Genentech**, Genmab, Isis, Medimmune, Mediqest, Otsuka, Regeneron, United Therapeutics, **NIH** (GAIT, SLS, SCOT, ASC01, ASSET)
• Consultant- **Genentech**, UCB, **Actelion**, Crescendo Biosciences
• Some drugs I discuss may be “off label”.
Risk vs. Benefit in SSc

• NO FDA-approved treatments for SSc per se
• Drugs approved for other diseases available, not always equally effective:
  – Pulm Htn therapies
  – Methotrexate for joint/tendon disease
  – PPI for GERD
• Make recommendations based on small case series, retrospective analyses, personal experience
• For one trained in the scientific method, and aware of the often guarded prognosis of those with SSc, this is frustrating
Types of Clinical Research

• Retrospective Chart reviews
• Registries, Repositories, and Databases
• Prospective +/- Randomized Open-label trials
• Prospective Comparator trials
• Prospective Double-blind controlled Trials.
• Open-label extension trials
• Translational Research
• “Big-data” retrospective analyses
Randomized Prospective Trials

- **Pro’s**
  - Background influences on outcome minimized
  - Data carefully collected at specified intervals
  - Usually have careful FDA or NIH oversight

- **Con’s**
  - Minimal flexibility to alter regimen to fit the individual
  - Study visit schedule can be difficult to adhere to
  - Individual may not benefit directly
Patient Selection Criteria

• Is *Always* a compromise between:
  – Most scientifically rigorous design
  – Ethical considerations
  – Practical considerations (enrollability)
  – Safety considerations (effect of new drugs on sickest patients always uncertain)
  – Regulatory considerations (adequate but not disproportionate gender/ethnic representation)
Why is SSc research so challenging?

- Disease is rare
- Clinically heterogeneous (LcSSc vs DcSSc; variable heart, lung, kidney disease)
- Pathophysiology includes altered immunology, vascular biology, and fibrosis
- Poor animal models to develop drug candidates
- The disease complexity and variability narrows the eligible research participant pool for studies
- Variable disease progression is difficult to assess
- Many outcome measures insensitive to change
- All of above compromise feasibility and generalizability

So how do we move the dial on treatment options?
Perform trials of *Focused* therapies

- **Rituximab for SSc-PAH; ACES trial ASC01**
- **ILD trials**
  - SLS-II (completed)
  - Nintendanib (starting),
  - SLS-III (MMF +/- pirfenadone) (proposed)
- **Riocuguat for Digital Ulcers (proposed)**
- **Topical NTG for CTD-associated RP (proposed)**
- **Abatacept for DcSSc skin; ACES trial ASSET (starting)**
- **Tocilizumab for DcSSc skin (underway elsewhere)**
- **Autologous abdominal fat pad mesenchymal stem cells for SSc hand contractures (possible)**
Translational Research

- Translating basic research advances into improved patient care through:
  - Improved diagnostic precision and accuracy
  - Improved prognostic accuracy
  - More rational selection of therapy
  - Prognostication of therapeutic efficacy
  - Novel approaches to therapy informed by basic science discovery
Overview of ACES-type trials with “translational” components

- Tests of Disease markers (serum, DNA, tissue)
- Analysis of combined data
- Disease Mechanisms
- Development of Diagnostic Tools
- Therapy
- Improved understanding of clinical outcomes
SSc Trial design improvements

• Measurement of Non-primary endpoint Major Clinical manifestations of SSc as secondary endpoints
  – Eg. skin, joint/tendon, lung, heart, GI
• Frequent inclusion of biomarker studies (including skin biopsies)
• Better fundamental research guiding trial treatment selection to mechanistically promising candidates
Pulmonary Hypertension (PH)

- RBC Absorption of Oxygen within the lungs requires a low blood pressure circuit
- Normal Mean (average) pulmonary artery pressure 14-18 mm Hg, increases to 20-25 mm with exercise
- PH defined as Mean PAP > 25 mm Hg @ rest.
- %DLCO lower than %FVC on PFTs raises suspicion
- Can be estimated with Echo, requires Right heart catheterization for precise and accurate determination
PH screening tools

- History of worsening dyspnea (shortness of breath), cough, poor exercise tolerance, heart palpitations, lower extremity edema
- Blood tests (BNP, NT-proBNP)
- Pulmonary function tests including DLCO
- 6 minute walk test (for distance and/or oxygen desaturation)
- 12-lead Electrocardiogram (EKG)
- Echocardiogram (Echo)
- Right heart catheterization (sometimes combined with Left heart catheterization); Gold standard
Pulmonary Hypertension Therapies by Class

- Prostaglandin analogues
  - Epoprostanol
  - Iloprost
  - Treprostinil

- Endothelin Receptor antagonists (ERA)
  - Bosentan
  - Ambrisentan
  - Macitentan

- Phosphodiesterase type-5 (PDE-5) inhibitors
  - Sildenafil
  - Tadalafil
  - Vardenafil

- Soluble guanylate cyclase stimulation
  - Riociguat (Adempas)
PH observational studies

- **PHAROS**
  - Registry to follow subjects at high risk of, or with early PAH
  - Annual evaluations and blood draws
  - Multiple analyses of this dataset now published; additional analyses underway

PHAROS supported by Scleroderma Foundation, Actelion and Gilead Sciences
Is SSc-PH driven by immunologic mechanisms?

- Animal models suggest this may be the case.
- SSc-PH responds more poorly than other forms of PH to existing PH therapy.
- Lung transplant and the required immunosuppression may arrest progression of PH.
- Experience with some individual patients suggests that immunosuppression may help.
Rituximab-SScPAH Study

Key Inclusion Criteria:
- ✔ 18 – 75 years old
- ✔ Systemic sclerosis diagnosis
- ✔ SSc-PAH diagnosis within 5 years
- ✔ On PAH treatment for 12 weeks, with stable doses for 4 weeks (subjects will remain on these treatments throughout the trial)

Key Exclusion Criteria:
- ✗ Persistent hypotension
- ✗ Coronary artery disease
- ✗ Significant renal insufficiency
- ✗ Infection
- ✗ Recent immunosuppressive treatment, any exposure to a lymphocyte depleting agent
- ✗ Significant interstitial lung disease
- ✗ Concurrent treatment in a trial using non-FDA approved agent
Endpoints

- **Primary**: Change in pulmonary vascular resistance measured by right heart catheterization from baseline to 24 weeks after treatment initiation.

- **Secondary**: 6MWD, Time to clinical worsening, % of subjects changing meds, QOL, digital ulcers, Raynaud phenomenon, DLCO and O2 saturation
ASC01 (Rituximab for SSc-PAH) – Study Sites

Central / Mountain

2. University of Colorado at Denver
   ~ Drs. David Badesch, Aryeh Fischer
9. University of Michigan (Ann Arbor)
   ~ Drs. Dinesh Khanna, Valerie McLaughlin
10. University of Minnesota
    (Minneapolis) – Dr. Jerry Molitor,
    Mark Pritzker
12. University of Texas Houston
    ~ Drs. Maureen Mayes, Bela Patel
13. University of Texas
    Southwestern (Dallas) ~ Drs.
    Fernando Torres, Andreas Reimold
14. Utah University (Salt Lake City) ~
    Drs. Boaz Markewitz, Tracy Frech
Abatacept for DcSSc

- Will randomize volunteers with DcSSc to Abatacept weekly sc vs. placebo
- Drug approved for use in RA
- Small prior trial suggests possible efficacy
- Requires skin biopsies during trial
- 52 week trial with 24 week OLE
- Planned escape @ 24 weeks for clinical worsening
The Value of Clinical Research

Society benefits when research participation improves overall care and the public health
You benefit if you are an individual with a newly treatable condition
You may or may not benefit directly however from participation in the trial
REMEMBER- It’s a trial because we don’t know the intervention works
The Therapeutic Misconception

- Participant impression that the Study Intervention is likely to help them personally
  - “My Doctor wouldn’t put me on this, if he didn’t think it would help”
- Remember: It is a trial of the Intervention precisely because we don’t know if it will help.
IOM Responsible Research:
A Systems Approach to Protecting Research Participants

Since the beginning of modern history, we have sought cures for disease and injury and searched for ways to improve our lives through scientific investigation. Often, these goals can only be met by studying humans and the human condition. By volunteering to participate in research, many individuals have provided scientists with capabilities that they would otherwise lack, and in so doing, deserve society’s deepest gratitude and respect.
Making a Difference

• What can you do to move the needle?
  – Educate the public-don’t hide
  – Participate( when appropriate) in clinical and translational research
  – Join foundations supporting rare diseases with research, education and lobbying efforts
  – Lobby legislators for laws to assist those with inadequate treatment options
  – Find an “Ice Bucket Challenge”
Never doubt that a small group of thoughtful, committed citizens can change the world. Indeed, it is the only thing that ever has.

Margaret Mead
Name Painting (1935-1963) #1
Jim Dine
UMN  SSc current and pending Trials

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NO guinea pigs!
University of Minnesota
Scleroderma Research

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Questions?