The Importance of Understanding the Natural History of Sarcoidosis

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Conflicts

• Funded by FDA: R01-FD005993
• PI for industry-sponsored studies, but not relevant to this talk.
Objectives

• Purpose of studying natural history
• Background of natural history
• The importance for clinical trials and treatment
• Development of a retrospective cohort
• Results
• Where we go from here.
Purpose

• Long term objective is to decrease health burden of sarcoidosis by development of evidence-based treatment and management guidelines.

• The objective of this project is to define the natural history of sarcoidosis to inform design of clinical trials for drug development and use.
  – Patient selection
  – Understand outcomes and how they change over time
  – Avoid unnecessary treatment
Natural History of Sarcoidosis in the Literature

   Zych D, Krychniak W, Pawlicka L, Zielinski J.
   PMID: 3589194
   Similar articles

87. Evidence that steroids alter the natural history of previously untreated progressive pulmonary sarcoidosis.
   Odium CM, FitzGerald Mx.
   PMID: 3575916
   Similar articles

88. The natural history and management of sarcoidosis.
   Bascom R, Johns CJ.
   PMID: 3511618
   Similar articles
Natural History

“The progression of a disease process in an individual over time in the absence of treatment.”

Natural History

 Median time 5.3 months

Latency Period

Natural History

“The progression of a disease process in an individual over time in the absence of treatment.”

Clinical Presentation of Sarcoidosis

![Diagram showing the time course of sarcoidosis with possible outcomes]

- **T0**: Initial assessment
- **T1**: Time point for evaluation
- **T2**: Follow-up time point

- **A**: Worsening
- **B**: Chronic
- **C**: Improving

Severity of Disease vs. Time

Questions: What could be the causes of worsening and improving states in sarcoidosis?
Where is the patient in the natural history of disease?

Central Hypothesis is that patients can be segregated into one of these three cohorts.
...And how often do I assess?

T0: Inception
T1: Diagnosis
T2: Post-Diagnosis

Will differ by organ involvement.....
The Importance of Understanding Natural History

Defining natural history will allow us to identify patients who are in earlier stages in order to alleviate the severity of disease as it progresses over time.

T1a: Targeted earlier time of diagnosis
T1b: Standard time of diagnosis
Treat those who need it earlier.....avoid in those who don’t.

There is opportunity to intervene earlier in the natural history of disease if these patients can be identified earlier in their course.

Treatment of Sarcoidosis

Conclusions from the Cochrane Reviews of Immunosuppressive Therapy for Pulmonary Sarcoidosis (1, 2)

- **Corticosteroids**: “Oral steroids improved the chest X-ray and a global score of CXR, symptoms and spirometry over 6-24 months, but there is little evidence of an improvement in lung function. There are no data beyond two years to indicate whether oral steroids have any modifying effect on long-term disease progression.”

- **Immunosuppressive and cytotoxic therapy**: “The current body of evidence supporting the use of immunosuppressive agents and cytotoxic therapies is limited. Side-effects associated with some of the therapies were severe.”

Expert Opinions:
1. “Watch and Wait”
2. Treat if vital organ function is threatened.
3. Only treat if symptomatic*
4. How long and how much and what with is variable

*definition of “symptomatic” is up to you!
Limitations of Drug Development in Sarcoidosis

• Valid Primary Outcome?
• Rare Disease
  – Maximize effect with smallest sample size
• Heterogeneity of Disease (Patient Selection)
  – Who is getting worse?
• Slope of Change/Endpoints
  – How frequent should we be evaluating endpoints
Anti-TNF Therapy in Sarcoidosis

Figure 3: Primary end-point of FVC for golimumab, ustekinumab versus placebo in patients with chronic pulmonary sarcoidosis. Note: the placebo group had the greatest improvement in lung function of the three groups.

Treat?

ALL HAVE NORMAL FVCs
There is currently no effective strategy to predict likelihood of disease progression at the time of diagnosis.
Studying Natural History in a Retrospective Manner

• Why?
  – Prior studies are single center and tertiary care
  – Rare disease
  – Claims data not ideal (no PFTs, mortality, vitals)
  – Registries not granular enough

  – Need to establish WHAT to collect in large (expensive) prospective studies.
Aims

• Aim 1: Build and validate a retrospective cohort of patients with sarcoidosis in a large population-based dataset.

• Aim 2: Describe natural history of sarcoidosis based on health care utilization and clinical data.

• Aim 3: Based on change in outcomes, calculate sample sizes for particular outcomes.
Study Population

• KPNW Integrated health care system
  – 525K members, low attrition
  – Members can be followed across entirety
  – Vitals, Hospital stays, ER visits, office visits dispensed medications, mental health care, imaging, nursing home admissions, surgeries and lab test results, comorbidities, smoking, PFTs, mortality
Analysis

• Time series of outcome events
  – PFT
  – Medication use (immunosuppression)
  – Frequency of healthcare visits

• Model Cohorts A, B, C: characteristics
Case Definitions

- One ICD 9/10 Code (Inpatient or Outpatient): 1492

- Two ICD 9/10 Codes
  - Patients must have had two years of data pre and post diagnosis.

- Two ICD9/10 codes + Radiograph

- Two ICD 9/10 Codes + Radiograph + Biopsy
<table>
<thead>
<tr>
<th></th>
<th>2 Years Look Back</th>
<th>2 Years Look Back + Chest Imaging + 2 DX</th>
<th>2 Years Look Back + Biopsy + 2 DX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Count</strong></td>
<td>830</td>
<td>745</td>
<td>220</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>53.2 (12.5)</td>
<td>52.8 (12.1)</td>
<td>52.1 (11.9)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>510 (61.4%) [0]</td>
<td>465 (62.4%) [0]</td>
<td>129 (58.6%) [0]</td>
</tr>
<tr>
<td><strong>Hispanic</strong></td>
<td>17 (3.13%) [287]</td>
<td>14 (2.88%) [259]</td>
<td>5 (3.23%) [65]</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Asian</strong></td>
<td>15 (1.8%)</td>
<td>14 (1.9%)</td>
<td>5 (2.3%)</td>
</tr>
<tr>
<td><strong>Black</strong></td>
<td>99 (11.9%)</td>
<td>96 (12.9%)</td>
<td>26 (11.8%)</td>
</tr>
<tr>
<td><strong>White</strong></td>
<td>670 (80.7%)</td>
<td>596 (80.0%)</td>
<td>178 (80.9%)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>16 (1.8%)</td>
<td>14 (1.9%)</td>
<td>5 (2.3%)</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td>31 (3.73%)</td>
<td>25 (3.4%)</td>
<td>6 (2.7%)</td>
</tr>
<tr>
<td><strong>PFT</strong></td>
<td></td>
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<tr>
<td><strong>At Baseline</strong></td>
<td>170 (20.5%)</td>
<td>163 (21.9%)</td>
<td>90 (40.9%)</td>
</tr>
<tr>
<td><strong>9-15 Months</strong></td>
<td>60 (7.2%)</td>
<td>58 (7.8%)</td>
<td>34 (15.5%)</td>
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<tr>
<td><strong>Baseline Spirometry Measures</strong></td>
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<tr>
<td><strong>FEV1 %</strong></td>
<td>84.0 (18.1)</td>
<td>84.7 (17.7)</td>
<td>83.8 (17.2)</td>
</tr>
<tr>
<td><strong>FVC %</strong></td>
<td>92.3 (15.8)</td>
<td>92.8 (15.9)</td>
<td>90.9 (16.2)</td>
</tr>
<tr>
<td><strong>FEV1 / FVC</strong></td>
<td>72.3 (9.4)</td>
<td>72.6 (8.9)</td>
<td>73.5 (8.1)</td>
</tr>
<tr>
<td><strong>Adjusted DLCO %</strong></td>
<td>82.5 (19.1)</td>
<td>82.4 (19.1)</td>
<td>81.3 (20.4)</td>
</tr>
<tr>
<td><strong>Chest CT</strong></td>
<td></td>
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<tr>
<td><strong>At Baseline</strong></td>
<td>212 (25.5%)</td>
<td>195 (26.2%)</td>
<td>105 (47.7%)</td>
</tr>
<tr>
<td><strong>9-15 Months</strong></td>
<td>47 (5.7%)</td>
<td>43 (5.8%)</td>
<td>22 (10.0%)</td>
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<tr>
<td><strong>Chest X-Ray</strong></td>
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<tr>
<td><strong>At Baseline</strong></td>
<td>565 (68.1%)</td>
<td>526 (70.6%)</td>
<td>174 (79.1%)</td>
</tr>
<tr>
<td><strong>9-15 Months</strong></td>
<td>234 (28.2%)</td>
<td>220 (29.5%)</td>
<td>94 (42.7%)</td>
</tr>
<tr>
<td><strong>On Prednisone</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Within 30 Days</strong></td>
<td>176 (21.2%)</td>
<td>162 (21.7%)</td>
<td>63 (28.6%)</td>
</tr>
<tr>
<td><strong>Within 90 Days</strong></td>
<td>215 (25.9%)</td>
<td>198 (26.6%)</td>
<td>79 (35.9%)</td>
</tr>
<tr>
<td><strong>At 1 Year</strong></td>
<td>87 (10.5%)</td>
<td>86 (11.5%)</td>
<td>34 (15.5%)</td>
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</tbody>
</table>
Results

• 20% had PFT at diagnosis, and only 7.2% had second PFT within 24 months of diagnosis.
  – Higher if lung biopsy was obtained (10%)
• The FVC decreased only by 0.32% in those who had PFTs.
• 90% of patients have chest imaging.
• **YET:**
  – 32% were placed on immunosuppression with prednisone (ave 30mg/dy) or steroid-sparing agent.
Daily Dose and Percent Taking Prednisone

Mean Dose (mg/day)

Percent of Cohort on Prednisone

Days since Diagnosis

1 year
Prednisone dose changes after chest imaging.

HR=1.22
Conclusions

- Our finding that 30% of the cohort is treated is consistent with prior observations that about 1/3rd of patients are treated after presentation.

- However, even in those requiring high dose steroids ("progressers"), PFTs are only obtained repeatedly in a small minority of patients, indicating that treatment decisions in current clinical practice are not based on lung function changes (unlike clinical trials).

- Imaging drives, in part, many treatment decisions.

- To assess natural history of pulmonary sarcoidosis, purposefully collected data is necessary and likely includes data that is STANDARDIZED with type and frequency of measures (symptoms, imaging).
Future Directions

- Describe those cohort A with impending worsening course.
- Design of novel repeated frequent outcome measures that would include symptom assessment, imaging, in addition to traditional measurements such as PFTs.
- Prospective cohorts with purposefully collected data.
- Multicenter collaboration with standard protocols.
  - More work must be done to establish meaningful protocols.
Acknowledgements

• FDA
• Jacob Simmering, PhD
• Philip Polgreen, MD
Questions

• Please fill out your PROM survey