Diagnosis and treatment of sarcoidosis

Robert P. Baughman
Interstitial Lung Disease and Sarcoidosis Clinic
University of Cincinnati
Pharmacologic Support in Sarcoidosis for Dr. Baughman

– Centocor
– Celgene
– Actelion
– Cephalon
– Genetech

– Gilead
– Forest
– United Therapeutics
– Pfizer
– Mallinkrodt
Off label drug use

• Only two drugs FDA approved for pulmonary sarcoidosis
  – Prednisone
  – Repository corticotropin

• No drug approved for extra pulmonary sarcoidosis

• All other drugs listed are “off label” indications
Prevalence of Sarcoidosis in America

Prevalence of Sarcoidosis in America

How to diagnose sarcoidosis

• Find noncaseating granulomas
  – No other cause for granulomas
    • TB
    • Beryllium

• Appropriate clinical setting

• Never can be 100% sure of the diagnosis
ACCESS 736 patients

Number of cases with a specific organ involvement undergoing biopsy of that organ

<table>
<thead>
<tr>
<th></th>
<th># Cases</th>
<th># Biopsied</th>
<th>% Biopsied of number cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrathoracic</td>
<td>699</td>
<td>567</td>
<td>81%</td>
</tr>
<tr>
<td>Skin</td>
<td>117</td>
<td>74</td>
<td>63%</td>
</tr>
<tr>
<td>Peripheral lymph node</td>
<td>112</td>
<td>61</td>
<td>54%</td>
</tr>
<tr>
<td>Otolaryngeal</td>
<td>22</td>
<td>11</td>
<td>50%</td>
</tr>
<tr>
<td>Liver</td>
<td>85</td>
<td>19</td>
<td>22%</td>
</tr>
</tbody>
</table>

Time until diagnosis of Sarcoidosis
ACCESS

Time until diagnosis of Sarcoidosis
Symptoms make difference

Diagnosed within 6 months

Suspected pulmonary sarcoidosis

Initial appearance on CXR/CT scan

Adenopathy (stage I / II)
- Löfgren Syndrome; Asymptomatic BHL
- Definite pulmonary sarcoidosis

Infiltration
- EBUS; TBNA; Mediastinoscopy
- TBB; Cryo-TBB

Fibrosis
- VATS lung biopsy

Atypical patterns
- TBB; Cryo-TBB; CT-guide percutaneous lung biopsy; VATS lung biopsy

Skin or superficial lymph nodes involvement

Biopsy

How Specific is Noncaseating Granuloma for Sarcoidosis?

• In liver, granulomas are almost always noncaseating.
• In skin, noncaseating granulomas can be seen as reaction to foreign body (e.g. splinter)
• Not all granulomas are due to sarcoidosis
  – Histoplasmosis
  – Tuberculosis
  – Cancer
  – Lymphoma (especially Hodgkin’s)
Patient with fever, cough, weight loss

- EBUS demonstrates non caseating granulomas
- Cryo biopsy negative
Treated for *M. kansassii* for 18 months
How to diagnose sarcoidosis

• Find noncaseating granulomas
  – No other cause for granulomas
    • TB
    • Berrylium

• Appropriate clinical setting
  – More organs identified, the more confident the diagnosis

• Never can be 100% sure of the diagnosis
Ocular:
- Uveitis
- Pars planitis
- Optic neuropathy
- Mutton fat keratic precipitates

Skin:
- Lupus pernio
- Erythema nodosum
- Maculo-papular lesions
- Papules within tattoo

Liver:
- Increased alkaline phosphatase
- Hepatosplenomegaly

Abnormal calcium metabolism:
- Hypercalcemia or hypercalcuria (with or without nephrolithiasis)
- with an increased 1,25-OH dihydroxy vitamin D level

Thoracic:
- Bilateral hilar adenopathy
- Bilateral upper lobe infiltrates
- Perilymphatic nodules on HRCT
- Peribronchial thickening on HRCT
- Lymphocytic alveolitis on BAL

Neurologic:
- Seventh cranial nerve palsy
- Lymphocytic meningitis
- Gallium enhancing lesion on MRI

Cardiac:
- PET enhancement of myocardium
- Gallium enhancement of myocardium
- Ventricular arrhythmias
- Cardiomyopathy

Patient gave written permission for use of photograph of face
Judson MA, Sarcoidosis Vasc Diffuse Lung Dis 2014; 31:19-27
The WASOG Sarcoidosis Organ Assessment Instrument: An Update of a Previous Clinical Tool


¹Albany Medical College; Albany, New York USA; ²Ruhrlandklinik, University Hospital, University Duisburg-Essen, Essen, Germany; ³Gelderse Vallei Hospital Ede; Maastricht University, Maastricht, The Netherlands; ⁴Royal Brompton Hospital, London; ⁵National Jewish Health, Denver, Colorado USA; ⁶University of California, San Francisco, San Francisco, CA USA; ⁷University of Southern California Keck School of Medicine, Los Angeles, California USA; ⁸Cleveland Clinic, Cleveland, Ohio USA; ⁹AP-HP, Hôpital Avicenne, Université Paris 13, Sorbonne Paris Cité, France; ¹⁰University of Illinois College of Medicine at Chicago, Chicago, Illinois USA; ¹¹The Ohio State University Medical Center, Columbus, Ohio USA; ¹²Icahn School of Medicine at Mount Sinai; New York, New York USA; ¹³University of Cincinnati Medical Center; Cincinnati, OH, USA; ¹⁴Nippon Medical School, Tokyo, Japan; ¹⁵Department of Ophthalmology and Visual Science, Yokohama City, Japan; ¹⁶Aoyama General Hospital, Tokyo, Japan; ¹⁷Japan Railway Tokyo General Hospital, Tokyo, Japan; ¹⁸JR Sapporo Hospital, Sapporo, Japan; ¹⁹St. Antonius Hospital, Utrecht, The Netherlands; ²⁰University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania USA; ²¹Tongji University, School of Medicine, Shanghai, China; ²²Azienda Ospedaliera Universitaria Senese, Italy; ²³Kinki-Chuo Chest Medical Center; Osaka, Japan; ²⁴University Hospital, Freiburg, Germany; * see appendix 1
Sarcoidosis Diagnostic Score (SDS)

• Assigned points for each organ involvement
  – Biopsy=5
  – Highly probable=3
  – At least probable=2

• Calculated scores for a total of initial 600 patients seen in University of Cincinnati Sarcoidosis clinic over a six month period

<table>
<thead>
<tr>
<th></th>
<th>Initial Cohort</th>
<th>Validation Cohort</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>600</td>
<td>380</td>
<td>980</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>450</td>
<td>103</td>
<td>553</td>
</tr>
<tr>
<td>Other diagnosis</td>
<td>150</td>
<td>277</td>
<td>437</td>
</tr>
</tbody>
</table>

Bickett A, Lower EE, Baughman RP.
Receiver Operator Curves

SDS biopsy: 6 points
sensitivity 100%, specificity 100%
AUC of 1.000.

SDS clinical: 3 points
Sensitivity of 94.2%, specificity of 88.8%
AUC of 0.977.
Likelihood ratio for a patient to have sarcoidosis: SDS clinical 3 or more was 7.89; 4 or more was 54.69
Löfgren's syndrome
Periarticular arthritis
Swedish patients who present with hilar adenopathy and periarticular arthritis

- 144 patients followed for at least two years
- 70% were DQB1*0201/DRB1*0301 positive
  - 103 of the 104 patients had resolution within two years.
- 30% were DQB1*0201/DRB1*0301 negative
  - 22 of 40 resolved within two years.

Patients with Lofgren seen between 1994 and 2008 at Karolinska University

301 patients

DRB1*03

Positive: 205 (68%)

60% men

Negative: 96 (32%)

45% men *

170 with EN
126 arthritis without EN

• Differs from DRB1*03 positive p<0.05
Two Year Follow-up

- 275 patients followed for at least two years
- Divided into three groups
  - Resolving
  - Non-resolving
  - Relapsing

Supportive diagnostic tests

• ACE
  – Elevated in 60% with active disease
  – Elevated in 20% with chronic disease
  – Affected by genetic polymorphisms

• BAL
  – Relatively specific, not sensitive

• CT scan
  – Adenopathy and peribronchial thickening
    • Nonspecific

• PET scan
  – Identify multi organ involvement

• MRI
  – Cardiac and bone disease
PET scan demonstrating multi organ involvement, including Bone
MRI showing bone involvement
Patient had lump on finger biopsy and had tender nodule on wrist
Sarc in Wrist

Radial Head lesion

Ulnar Lesion pushing outward
Cardiac Sarcoidosis

- Significant cause of morbidity and mortality
- Most common cause of sarcoidosis death in Japan
- Can be identified by PET and/or MRI scan
Cardiac Sarcoidosis

Cardiomyopathy
- Echocardiogram
- Heart cath *
- Immunosuppressive

Arrhythmias
- 12 lead ECG
- Holter monitor
- EPS testing
- Pacemaker
- Defibrillator
- Immunosuppressive
Cardiac sarcoidosis at University of Cincinnati

LVEF<50% 9 (15.0%)
Both 31 (51.7%)
Arrhythmia 20 (33.3%)

2 patients with LVEF>=50% and no arrhythmia

More You Look, More You Find
More Recent Studies may be Looking Harder

- Teirstein AS. Sarcoidosis 1992; 9(S1):155-159.
More You Look, More You Find
More Recent Studies may be Looking Harder

## WASOG criteria of cardiac involvement

<table>
<thead>
<tr>
<th>Highly probable</th>
<th>Cardiac biopsy positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable</td>
<td>Treatment responsive CM or AVNB</td>
</tr>
<tr>
<td>Probable</td>
<td>Reduced LVEF in the absence of other clinical risk factors</td>
</tr>
<tr>
<td>Probable</td>
<td>Spontaneous or inducible sustained VT with no other risk factor</td>
</tr>
<tr>
<td>Probable</td>
<td>Mobitz type II or 3rd degree heart block</td>
</tr>
<tr>
<td>Probable</td>
<td>Patchy uptake on dedicated cardiac PET</td>
</tr>
<tr>
<td>Probable</td>
<td>Delayed enhancement on CMR</td>
</tr>
<tr>
<td>Probable</td>
<td>Positive gallium uptake</td>
</tr>
<tr>
<td>Probable</td>
<td>Defect on perfusion scintigraphy or SPECT scan</td>
</tr>
<tr>
<td>Probable</td>
<td>T2 prolongation on CMR</td>
</tr>
<tr>
<td>Possible</td>
<td>Reduced LVEF in the presence of other risk factors</td>
</tr>
<tr>
<td>Possible</td>
<td>Atrial dysrhythmias</td>
</tr>
</tbody>
</table>
Cardiac sarcoidosis at University of Cincinnati: WASOG criteria *

*Only included highly probable or probable. Patients could have more than one criteria
Diagnosis of Cardiac Arrhythmias: Delphi Consensus

• In suspected cardiac sarcoidosis, testing
  – 12 lead EKG 84%
  – Holter monitor 65%
  – EPS studies
    • Routine 39%
    • Only if have arrhythmias 42%

## Screening for Cardiac Sarcoidosis

<table>
<thead>
<tr>
<th></th>
<th>Prevalence</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Pos LR *</th>
<th>Neg LR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History of cardiac symptoms</strong></td>
<td>12 (19%)</td>
<td>46</td>
<td>95</td>
<td>8.7</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td>3 (5%)</td>
<td>8</td>
<td>97</td>
<td>3.2</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Holter</strong></td>
<td>13 (21%)</td>
<td>50</td>
<td>97</td>
<td>19</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Echo</strong></td>
<td>8 (13%)</td>
<td>25</td>
<td>95</td>
<td>4.8</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Any variable</strong></td>
<td>29 (47%)</td>
<td>100</td>
<td>87</td>
<td>7.6</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Two or more variables</strong></td>
<td>7 (11%)</td>
<td>25</td>
<td>97</td>
<td>9.5</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Three or more variables</strong></td>
<td>1 (2%)</td>
<td>4</td>
<td>100</td>
<td>3.2</td>
<td>1</td>
</tr>
<tr>
<td><strong>All variables abnormal†</strong></td>
<td>0 (0%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Pos LR: positive likelihood ratio  
Neg LR: negative likelihood ratio
Treating sarcoidosis

- Wells’ Law

Athol Wells
Only treat sarcoidosis to avoid danger or improve quality of life.
Danger

• Organ failure
  – Respiratory
  – Cardiac
  – Neurologic
  – Liver
  – Ocular

• Death
Treatment of Danger: Respiratory Failure

- **Anti-inflammatory**
  - Prednisone
  - Cytotoxics
    - Methotrexate
    - Azathioprine
  - Anti-TNF
    - Infliximab
  - Others
    - Rituximab
    - Corticotrophin

- **Pulmonary hypertension**
  - Vasodilator therapy
    - Bosentan
    - Riociguat
    - Sildenafil

- **Fibrosis**
  - Pirfenidone

- **Infections**
  - Aspergilloma
  - Bronchiectasis

- **Transplant**
Taper to lowest tolerable dose

Prednisone or prednisolone 1A

Progression and/or toxicity

No

Taper to lowest tolerable dose

FVC Change in Absolute Percent in Randomized Clinical Trials

- Pietinalho Subset: Prednisolone plus Budesonide vs Placebo
- Gibson: Prednisone all versus Prednisone subset

Progression and/or Toxicity on Prednisone

Yes

6 months of either methotrexate, azathioprine, leflunomide, or mycophenolate

Avoid Prednisone Side Effects

Consider a Switch
Changes in Quality of Life associated with prednisone usage

• Compared response for those receiving more or less than 500 mg prednisone in previous year
  – 62 patients <500 mg in previous year
  – 52 patients >500 mg in previous year
  – 5 mg every other day = 912 mg/year

• Corrected for severity of disease using propensity analysis

Comparison of Quality of Life using Sarcoidosis Assessment Tools

- Patients on <500 mg prednisone in previous year scores indicating
  - Less fatigue
  - Better satisfaction
  - Better able to perform daily activities
- All three changes were greater than the Minimal Important Difference (MID)

Taper glucocorticoids to prednisone <10 mg/day or equivalent

Yes:
Continue glucocorticoids alone

Not able to taper

Rule out other causes of symptoms *

Cytotoxic drugs
Methotrexate: Level 1A
Azathioprine Level 1C
Leflunomide Level 1C
Mycophenolate 2C

* Pulmonary hypertension, CHF, muscle weakness, fatigue, infection
Taper glucocorticoids to prednisone <10 mg/day or equivalent

Yes:
Continue glucocorticoids alone

Not able to taper

Which Cytotoxic Drug?

Cytotoxic agents
Methotrexate: Level 1A
Azathioprine Level 1C
Leflunomide Level 1C
Mycophenolate 2C

* Pulmonary hypertension, CHF, muscle weakness, fatigue, infection
Steroid Sparing Effect of Methotrexate for Acute Sarcoidosis

- Methotrexate patients had a significant lower prednisone dose in the last six months of study.
- This was associated with significantly less weight gain for patients on MTX.

Baughman et al Sarcoidosis 2000; 17: 60-66
Methotrexate vs Azathioprine

• Retrospective study of treatment of these agents as steroid sparing agents
• Two sites employing different therapy
  – One site: Methotrexate
  – Other site: Azathioprine

Comparison of Methotrexate to Azathioprine

Chronic sarcoidosis

Methotrexate
- N=145
- Stopped due to side effects: N=23 (15.8%)

Azathioprine
- N=55
- Stopped due to side effects: N=14 (25.5%)

No difference between groups:
- Reduction of prednisone
- Improvement in FVC
Outcome of Treatment

• Reduction of dose of prednisone
  – For those on >1 year treatment: mean of 10 mg
    • No difference between groups

• Improvement in FVC
  – 95 ml/year
    • No difference between groups

• Infections more likely for those on azathioprine
  – Methotrexte 18.1%
  – Azathioprine 34.6%
    • P=0.01
Mycophenolate (MMF) for sarcoidosis

- Ten patients received MMF for >6 months. Four improved, six remained stable.

- MMF appears to offer no extra benefit to sarcoidosis patients unresponsive to previous steroid-sparing agents, but may be beneficial in patients intolerant to their previous steroid-sparing agent.
Neurosarcoidosis: Methotrexate versus Mycophenolate

• Treated 40 neurosarcoidosis patients with either agent for at least 3 months
  – Methotrexate (MTX): 32 patients
  – Mycophenolate (MMF): 14 patients

• Adverse events
  – Methotrexate: 11
  – Mycophenolate: 1
    • P=0.12

Daily prednisone dose initially and at Relapse/End of Follow-up

Mycophenolate                               Methotrexate

Both groups had significant fall in prednisone dose
Treatment Algorithm for Symptomatic Sarcoidosis

- Organ-threatening disease
- 6 months of cytotoxic therapy
  - Disease progression or toxic effects
    - Yes
      - Add infliximab or adalimumab
      - Disease progression or toxic effects
        - Yes
          - Consider alternatives: corticotropin, CLEAR, VIP
        - No
          - Taper glucocorticoids to lowest tolerable dose
  - Yes

Complicated Sarcoidosis: Third Line Therapy

- Failure/Toxicity Cytotoxic Drugs
  - Infliximab Level 1A
  - Adalimumab Level 1B
  - Rituximab Level 1B
  - Repository corticotropin 1B
  - Consider other treatments *

* Minimal studies and may not be commercially available
Who should be considered for infliximab therapy?

- Chronic advanced pulmonary disease
- Evidence for ongoing inflammation
  - Elevated CRP
  - Increased soluble IL-2 receptor
  - Positive PET scan
- TNF-α G 308A polymorphism
- Lupus pernio
- Neurologic disease
- Refractory eye disease

Infliximab treatment for 26 weeks
48 patients studied

Change in FVC % predicted versus $\text{SUV}_{\text{max}}$ pulmonary parenchyma

TNF-α G-308A polymorphism associated with response to infliximab

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Total</th>
<th>Improved</th>
<th>Stabilised/worsened</th>
<th>Relative risk (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG</td>
<td>78</td>
<td>73 (93.6)</td>
<td>5 (6.4)</td>
<td>3.09 (1.84–5.20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GA</td>
<td>31</td>
<td>9 (29.0)</td>
<td>22 (71.0)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>2</td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

First Report of use of Infliximab for sarcoidosis: before and after three months of Infliximab

Baughman and Lower Sarcoidosis 2001; 18: 70-74.
Treatment of *lupus pernio*

- Retrospective report of one institution’s experience of treating 54 patients with *lupus pernio*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSS: corticosteroids alone</td>
<td>35</td>
</tr>
<tr>
<td>AG: drugs other than prednisone or infliximab</td>
<td>19</td>
</tr>
<tr>
<td>CSS+ AG: combined therapy</td>
<td>49</td>
</tr>
<tr>
<td>IFX: Infliximab</td>
<td>13</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>116</strong></td>
</tr>
</tbody>
</table>

Treatment of *lupus pernio*

* Resolution: Complete or Near Complete resolution
CSS: Corticosteroids;
AG: hydroxychloroquine, methotrexate, other steroid sparing agents
IFX: Infliximab
Number of patients randomized
N=138

Placebo
N=45

Number with Chronic facial lesions
N=5

Received all treatments and were evaluated at each time point
N=5

Infliximab
3 mg/kg
N=48

Number with Chronic facial lesions
N=5

Received all treatments and were evaluated at each time point
N=4

Infliximab
5 mg/kg
N=47

Number with Chronic facial lesions
N=9

Received all treatments and were evaluated at each time point
N=8

Before and after infliximab therapy
Significant improvement in Desquamation:
24 weeks of infliximab versus placebo

P<0.005

Significant improvement in Induration: 24 weeks of infliximab versus placebo

Lower the better

P<0.01

Response to Infliximab for ocular disease

• 14 patients with chronic ocular inflammation studied
• 13 of 14 had improvement
  – Global assessment by ophthalmologist
  – The one non responder was non compliant
• Prednisone while treated with infliximab
  – Discontinued in 3 patients
  – Reduced dose in 4 patients
  – Not on prednisone 7 patients

Limitations of Infliximab therapy

• Cost
• Allergic reactions to medication
  – 10% of UC patients withdrawn from infliximab because of reactions
• Increased rate of infections
  – TB, fungus
• Can not use in advanced CHF
• Increased rate of malignancy
• May lead to sarcoidosis like reaction
Adalimumab for pulmonary sarcoidosis

- Prospective study of adalimumab in patients with refractory pulmonary sarcoidosis
  - 11 patients enrolled
    - 1 patient dropped out when moved from area
- Patients treated with adalimumab 40 mg weekly
- Eighty percent were stable or improved at 12 months
  - Change in FVC, 6MWD, or steroid dosage
- No significant adverse reactions occurred

Other anti-TNF agents for sarcoidosis

• Etanercept less effective
  – TNF receptor antagonist
  – Limited benefit in treating progressive pulmonary disease
  – No different from placebo in treating eye disease

• Golimumab no improvement in pulmonary disease
Biosimilars

Biosimilars in sarcoidosis

• While several studies in other indications, no published study in sarcoidosis

• Since there is variable response to anti-TNF agents (e.g. infliximab vs golimumab) one needs to prescribe with caution

• One approach is not to switch patients but to start all new cases on biosimilar

• A database of cases started on biosimilars would be useful
Failure/Toxicity Cytotoxic Drugs

- Infliximab Level 1A
- Adalimumab Level 1B

Consider other treatments *

- Rituximab Level 1B
- Repository corticotropin 1B

* Minimal studies and may not be commercially available
Rituximab for Sarcoidosis

• T-reg cells may play a role in chronic sarcoidosis

• Rituximab modifies T-reg function

• Rituximab has a different toxicity profile than the anti-TNF regimens
  – Less cardiotoxic
  – No carcinogenicity

• Has been reported as effective in ocular and cardiac sarcoidosis
Granulomatous disease of eye orbit
Before and after 4 months of Rituximab therapy

Prednisone 60 mg                      Prednisone 15 mg

Patient with Li Fraumeni syndrome (p53 mutation) leading to increased risk for cancer

Rituximab for Pulmonary Sarcoidosis

• Investigators
  – Nadera Sweiss MD University of Chicago
  – Robert Baughman MD and Elyse Lower MD Cincinnati

• Open label trial of therapy
  – Two treatments (1 gram) given 2 weeks apart and patients then monitored for one year
  – Regimen used for rheumatoid arthritis

• Outcome was change in FVC
  – Weeks 24 and 48 after first dose

Changes in FVC% with Rituximab
Five of Ten &gt;5% improvement at week 24

Refractory Sarcoidosis

**Failure/Toxicity Cytotoxic Drugs**

- Infliximab Level 1A
- Adalimumab Level 1B

Consider other treatments *

- Rituximab Level 1B

* Minimal studies and may not be commercially available
Repository Corticotropin Injection (RCI) Experience in Refractory Sarcoidosis

- Two centers in United States
  - University of Alabama, Birmingham
    - Dr Joseph Barney
  - University of Cincinnati Medical Center
    - Dr Robert Baughman
    - Dr. Elyse Lower
- Summarized experience of patients treated up to January 2015

Treatment Response Was Assessed in Patients Treated ≥3 Months of Corticotropin

Relapsed

- Worsening of target organ when prednisone was reduced and patient maintained on initial or higher dose of glucocorticoids

Stable

- No clinically significant target organ improvement, but reduction in glucocorticoid dosage

Improved

- Clinically significant target organ improvement

- Reduced inflammation (chest imaging or PET scan)
  - or
  - >10% FVC improvement
  - or
  - >50% improvement in other organ abnormalities

CNS = central nervous system.

Baughman RP et al. Respir Med 2016; 110:66-72
47 patients started on therapy

Treated for less than 3 months
N=18

Death
N=2

Cost
N=4

SAE
N=11

Non compliance
N=1

Treated for at least 3 months
N=29

Improvement
N=11

Reduce prednisone ≥ 50% *
N=8

Stable
N=16

Reduce prednisone ≥ 50%
N=16

Relapse
N=2

Reduce prednisone ≥50%
N=0

*Two patients did not take prednisone, One reduced cyclophosphamide

Baughman RP et al. Respir Med 2016; 110:66-72
Prospective trial of RCI for chronic pulmonary sarcoidosis

18 patients enrolled

1 withdrew prior to starting therapy

RCI 40 units twice a week
N=9

Stopped treatment within 2 weeks because of toxicity
N=1

Finished 24 weeks of therapy
N=8

Reduced dose by half
N=2

RCI 80 units twice a week
N=8

Reduced dose by half
N=5

Finished 24 weeks of therapy
N=8

1 withdrew prior to starting therapy

Results for all patients treated with RCI for 24 weeks

P<0.01

P<0.05
Significant improvement in King’s Sarcoidosis Health Questionnaire
What’s next?

- **Aprelimast**  

- **CLEAR**  
  - Drake WP et al. Sarcoidosis Vasc Diffuse Lung Dis 2013; 30(3):201-211.

- **Transdermal nicotine**  

- **Placental derived mesenchymal-like cells**  
  - Baughman RP et al. Sarcoidosis 2015; 32:106-114

- **Vasoactive intestinal peptide**  

- **Somatostatin receptor blockade**  

- **Interleukin-1 receptor antagonism (anakinra)**  
  - Successful treatment of Blau’s syndrome  
Treatment of Danger: Respiratory Failure

- Anti-inflammatory
  - Prednisone
  - Cytotoxics
    - Methotrexate
    - Azathioprine
  - Anti-TNF
    - Infliximab
  - Others
    - Rituximab
    - Corticotrophin

- Pulmonary hypertension
  - Vasodilator therapy
    - Bosentan
    - Riociguat
    - Sildenafil

- Fibrosis
  - Pirfenidone

- Infections
  - Aspergilloma
  - Bronchiectasis

- Transplant
Prevalence of sarcoidosis associated pulmonary hypertension (SAPH)

- Echo alone
- Right Heart Cath

- All patients attending clinic
- Patients referred for evaluation of dyspnea
- Patients listed for transplant
University of Cincinnati Experience

130 Sarcoidosis patients with persistent dyspnea

- Normal PA pressure, No PH, N=60
  - 3 (5.5%) Died

- Elevated PA pressure, Left ventricular dysfunction, PH/LVD, N=20
  - 3 (15%) Died

- Elevated PA pressure, No left ventricular dysfunction, PH without LVD, N=50
  - 18 (36%) Died

Patients with SAPAH had significantly shorter predicted survival compared to other two groups (P<0.02).
6 Minute walk <450 meters

- **No**
  - Follow

- **Yes**
  - **Echo**
    - TR < 2.5
    - TAPSE > 1.8
    - Normal right ventricle
    - Watch
    - Desat <90% on 6 MW test
    - TR >2.5
    - TAPSE < 1.8
    - Evidence of right ventricular dysfunction
    - Echo indeterminate
    - Mean PA/ascending aorta>1
    - Right heart catheterization
Only treat sarcoidosis to avoid danger or improve quality of life
Quality of life issues

• Pulmonary
  – Cough
  – Dyspnea
• Eye
  – Visual loss
• Cosmetically important skin lesions
• Calcium dysregulation
• Fatigue
• Small fiber neuropathy
Treatment of Quality of Life

- **Anti-inflammatory**
  - Prednisone
  - Hydroxychloroquine
  - Cytotoxics
    - Methotrexate
    - Azathioprine
  - Anti-TNF
    - Infliximab
  - Others
    - Rituximab
    - Corticotrophin

- **Fatigue**
  - Neurostimulants

- **Small fiber neuropathy**
  - IV Ig

- **Acute events**
  - Antibiotics
  - Short course prednisone
Sarcoidosis Specific Fatigue

- Poor disease control
  - Granulomas may increase fatigue

- Treatment side effects
  - Corticosteroids
    - Altered moods
    - Increase weight
    - Elevate blood sugar
  - Higher prednisone doses may impair QOL
Sleep Problems are Common in Sarcoidosis Patients

• UC experience
  • Turner G. Sarcoid Vasc Diffuse Lung Dis 1997;14:61-64

• Sarcoid patients referred for sleep studies
  – 46/62 (74%) experienced sleep apnea (OSA)
  – 34/62 (60%) noted daytime sleepiness
    • Patterson K. Chest 2013;143:1562-1568

• OSA = 15/29 (52%) Turkish patients
Poor Sleep Habits Common in Sarcoidosis Patients

• 67% of 1200 German patients experienced poor sleep quality (PSQI >5)
• Twice as common as in general population
• Poor sleep associated with
  – Female sex
  – Dyspnea
  – Fatigue, depression, and anxiety

• Bosse-Henck. Sleep Med 2015;16:570-576
Measuring Fatigue

• Multiple instruments to measure Quality of Life and fatigue

• No perfect testing

• General instruments for chronic illness
  – FACIT-F, SF-36
  – WHO-QOL

• Specific sarcoidosis instrument
  – Fatigue Assessment Scale (FAS)
Comparison of Fatigue
Dutch versus Cincinnati Patients

• Overall incidence the same
• Dutch patients had more severe fatigue
• Cincinnati patients
  – Lower FVC
  – Less fatigue for those receiving hydroxychloroquine

Intervention Trials for Persistent Sarcoidosis Fatigue

- Measuring fatigue is difficult
- Placebo effect is powerful
- Fatigue varies from person to person
Neurostimulant Therapy for Sarcoid Associated Fatigue

- Case reports suggest benefit for methylphenidate (Ritalin®) for chronic sarcoidosis patients with persistent fatigue.

- Other neurostimulants, including dex-methylphenidate (Focalin®), can improve fatigue in cancer patients with “chemo” brain.
A Randomized Double Blind, Placebo Controlled Trial of Dexmethylphenididate Hydrochloride ($d$-MPH) for Sarcoidosis Associated Fatigue

Elyse E. Lower, MD
Stacy Harman
Robert P. Baughman, MD
University of Cincinnati
Sarcoidosis Interstitial Lung Disease Clinic

Double Blind, Placebo-Controlled, Cross Over Study

Treatment 1: d-MPH or Placebo
Treatment 2: Placebo or d-MPH (opposite of treatment 1)
FAS: Lower Score, Less Fatigue

Difference between d-MPH and placebo p<0.02

Significantly less fatigue when treated with d-MPH

Weeks of Therapy

FAS Score

Baseline 1 2 3 4 5 6 7 8

Difference between d-MPH and placebo p<0.02
Treating sarcoidosis

• Wells’ Law

Athol Wells
Only treat sarcoidosis to avoid danger or improve quality of life
Conclusion

- Diagnosis of sarcoidosis is a combination of clinical features, including biopsy
- Several agents are available for treating the inflammation seen in sarcoidosis
- A step wise approach to therapy seems appropriate
- Steroid sparing agents should be used to minimize long term steroid toxicity
- Newer agents are being explored
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Become a WASOG Sarcoidosis Clinic:

https://www.stopsarcoidosis.org/become-sarcoidosis-clinic