Sarcoidosis Case

Robert P. Baughman
Interstitial Lung Disease and Sarcoidosis Clinic
University of Cincinnati, USA

© WASOG: educational material
Sarcoidosis Case

• patient is a Caucasian male
• age 46 was diagnosed with sarcoidosis
  - positive mediastinoscopy
• skin lesions on arms and back
• no pulmonary symptoms
Question 1: Would you treat this patient?

1. yes because he has lung involvement
2. yes because he has skin disease
3. no because he is not short of breath
4. no because his skin lesions are not on his face
5. I would let the patient decide
Question 2: Which systemic therapy would you initiate?

1. none
2. prednisone
3. hydroxychloroquine
4. methotrexate
5. infliximab
Symptoms

- none
  - observe
- single organ
  - treat topically
- multi-organ
  - prednisone, 20-40 mg qd
    - no response
      - consider other agents
    - response
      - taper to ≤10mg qd
        - yes: continue regimen
          - response: taper off prednisone
        - no: treat with MTX
          - no response: consider other agents

Extensive skin: Hydroxychloroquine
Antimalarials in sarcoidosis

Pulmonary

- Chloro (response: 40, no response: 10)

Cutaneous

- Chloro (response: 15, no response: 5)
- Hydroxy (response: 20, no response: 5)
- Chloro (response: 10, no response: 10)
- Chloro (response: 15, no response: 5)

Citations:

Treatment course

• for two years skin did well with hydroxychloroquine and topical steroids
• presents in 2004 with worsening skin lesions despite hydroxychloroquine
• has no pulmonary symptoms, although still has thoracic sarcoidosis
Sarcoidosis Case: 2004
Question 3: Which systemic therapy would you initiate?

1. stop all therapy
2. prednisone
3. stay with hydroxychloroquine
4. methotrexate
5. infliximab
Refractory skin lesions

- no response to hydroxychloroquine
- patient would like to avoid prednisone at this point
- started on methotrexate
  - 10 mg once a week
- skin lesions improve
Chronic disease

tolerates prednisone

yes

continue prednisone

no

cytotoxic agent: MTX; AZA; Leflunomide

response to single agent

no

add second cytotoxic agent

yes

taper off prednisone

consider adding anti-TNF agent
Methotrexate (MTX) vs azathioprine (AZA)

• retrospective study of treatment of these agents as steroid sparing agents

• two sites employing different therapy
  o one site: methotrexate
  o 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%)
Outcome of treatment

• reduction of dose of prednisone
  o for those on >1 year treatment: 10 mg
  o no difference between groups

• improvement in FVC
  o 95 ml/year
  o no difference between groups

• infections more likely for those on azathioprine
  o methotrexte 18.1%
  o azathioprine 34.6%
  o p=0.01
Treatment with MTX for > 2 years: response to MTX

Effectiveness of MTX for specific organ involvement

- **Neurologic disease (CNS)**
  - non responders to methotrexate usually treated with cyclophosphamide

- **Eye disease**
  - non responders to methotrexate usually responded to combination cytotoxic drugs

Steroid sparing effect of MTX for acute sarcoidosis

- methotrexate (MTX) 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

Methotrexate therapy for sarcoidosis

- initial and follow-up laboratory data
  - CBC
  - hepatic function
  - renal function
- initial dose
  - 10 mg per week
- maximal dose 15-20 mg per week
- to reduce toxicity
  - half dose one day, rest next day
  - folate 1 mg per day


- reduction of dose for neutropenia
1606 sarcoidosis patients seen during 13,576 clinic visits

869 patients (8732 visits)
On MTX treatment currently or in past

746 patients (5265 visits)
with available blood work

607 patients (3600 visits)
currently on MTX and with available blood work

572/607 (94.2%) patients
(3407/3600 (94.6%) visits)
with available liver function tests

ALT > 1.5 times ULN
73/572 (12.8%) patients
116/3405 (3.4%) visits

ALT > 3 times ULN
9/572 (1.6%) patients
10/3405 (0.3%) visits

587/607 (96.7%) patients
3534/3600 (98.2%) visits
with available white blood counts

WBC <3800 cells/cu mm
70/587 (11.9%) patients
162/3534 (4.6%) visits

WBC <1500 cells/cu mm
1/587 (0.2%) patients
2/3534 (<0.001%) visits
## Leukopenia in MTX treated patients

<table>
<thead>
<tr>
<th></th>
<th>Leukopenia (WBC&lt;3800 cells/cu mm)</th>
<th>No Leukopenia (WBC&gt;3800 Cells/cu mm)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>70 (11.9%)</td>
<td>517 (88.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>50 ± 9.5 *</td>
<td>50 ± 10.7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>47 (67%)</td>
<td>387 (75%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td><strong>African American</strong></td>
<td>§ 39 (56%)</td>
<td>215 (42%)</td>
<td>0.027</td>
</tr>
<tr>
<td><strong>Serum creatinine &gt;1.2 mg/dL</strong></td>
<td>4 (5%)</td>
<td>28 (6%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td><strong>Hepatic sarcoidosis</strong></td>
<td>5 (7%)</td>
<td>47 (9%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td><strong>MTX dosage mg/week</strong></td>
<td>9.0 ± 2.5</td>
<td>9.9 ± 2.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Concurrent prednisone</strong></td>
<td>36 (51%)</td>
<td>307 (60%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>LTA (ALT &gt;1.5 time ULN)</td>
<td>no LTA (ALT&lt;1.5 times ULN)</td>
<td>p value</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------------------------</td>
<td>---------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>total</td>
<td>73 (12.8%)</td>
<td>499 (87%)</td>
<td></td>
</tr>
<tr>
<td>age, years</td>
<td>48 ± 9.8 *</td>
<td>50 ± 10.8</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>female §</td>
<td>63 (86%)</td>
<td>324 (72%)</td>
<td>0.01</td>
</tr>
<tr>
<td>African American</td>
<td>33 (46%)</td>
<td>219 (44%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>serum creatinine &gt;1.2 mg/dL</td>
<td>3 (4%)</td>
<td>22 (95%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>liver sarcoidosis §</td>
<td>13 (8%)</td>
<td>36 (8%)</td>
<td>0.008</td>
</tr>
<tr>
<td>MTX dosage mg/week</td>
<td>9.9 ± 2.6</td>
<td>9.8 ± 3.1</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>concurrent prednisone</td>
<td>50 (68%)</td>
<td>260 (58%)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>
Most LFT abnormalities grade 1-2

<table>
<thead>
<tr>
<th></th>
<th>Alanine aminotransferase (ALT)</th>
<th>Asparate aminotransferase (AST)</th>
<th>Alkaline phosphatase (ALP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.5 times ULN</td>
<td>73 (12.8%) *</td>
<td>18 (3.2%)</td>
<td>22 (3.9%)</td>
</tr>
<tr>
<td>&gt;3 times ULN</td>
<td>9 (1.6%)</td>
<td>4 (0.7%)</td>
<td>6 (1.1%)</td>
</tr>
<tr>
<td>&gt;5 times ULN</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
<td>2 (0.04%)</td>
</tr>
</tbody>
</table>
Methotrexate course

- patient takes methotrexate
  - total resolution of skin lesions after six months
- after two years of methotrexate stop drug
- recurrence of skin lesions
- restart methotrexate
- lesions improve
- liver biopsy performed
  - no methotrexate toxicity
Methotrexate second time

- after six months of methotrexate
  - skin lesions improved
- patient develops cough
- now dyspneic
- worsening of chest roentgenogram
Sarcoidosis case

2004

2007
Question 4: What would you do now?

1. add prednisone to methotrexate
2. switch from methotrexate to leflunomide
3. stop methotrexate and initiate infliximab
Cough and dyspnea

• stop methotrexate
  o cough associated with methotrexate was reported in 6 of 54 patients treated for two or more years of methotrexate

• added prednisone

• cough resolved
Stopping methotrexate

- cough improved
- dyspnea persisted
- worsening of chest roentgenogram
Sarcoidosis case

2007

2009
Sarcoidosis case: CT 2009
Chronic disease

1. taper prednisone to < 10 mg/d
   - yes: continue prednisone
   - no: cytotoxic agent: MTX; azathioprine; leflunomide
     - response to single agent
       - no: add second cytotoxic agent
       - yes: taper off prednisone
         - consider adding anti-TNF agent
Tumor Necrosis Factor

- TNF is a central cytokine in chronic inflammatory conditions

- It is secreted by several effector cells
  - Especially macrophages

- It has multiple effects in the cytokine cascade
  - Initiation of the granulomatous reaction
  - Neutrophil chemotactic
TNF release of BAL retrieved alveolar macrophages

![Bar graph showing TNF pg/ml/24 hr]

- **Controls**
- **No therapy, stable**
- **No therapy, progressive**
- **On therapy, progressive**
Anti-TNF therapy for sarcoidosis

- a large randomized trial demonstrated benefit for treating chronic pulmonary sarcoidosis
  - 135 patients in a double blind randomized trial 2:1 infliximab to placebo
  - primary endpoint improvement in FVC
- this study to confirm observations made by case series and a smaller clinical trial

138 pts with chronic pulmonary sarcoidosis

138 pts with chronic pulmonary sarcoidosis

Studies drug

Randomization

Primary Endpoint

Safety Follow ups

Study Design

Study Design

Primary Endpoint

Randomization

Study drug

placebo (n = 45)

infliximab 3 mg/kg (n = 46)

infliximab 5 mg/kg (n = 47)
Total daily dose of corticosteroid at baseline: prednisone equivalent (mg)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 45)</th>
<th>3 mg/kg (n = 46)</th>
<th>5 mg/kg (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>number on</td>
<td>42</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>corticosteroids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (SD)</td>
<td>13.9 (9.3)</td>
<td>12.1 (6.9)</td>
<td>12.2 (5.6)</td>
</tr>
<tr>
<td>range</td>
<td>(2.5, 50.0)</td>
<td>(2.5, 40.0)</td>
<td>(3.3, 25.0)</td>
</tr>
</tbody>
</table>
Everything you’ve always wanted to know about the use of MTX in sarcoidosis...

Help is at hand. There’s an app for that!

The app was developed on behalf of the ild care foundation (www.ildcare.eu) and the WASOG.

You can find it in the Apple Store or Google Play Store. Download it for free!

## Multinational Recommendations

<table>
<thead>
<tr>
<th></th>
<th>Indications for MTX in sarcoidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>Second-line agent</strong></td>
</tr>
<tr>
<td></td>
<td>In steroid-refractory cases</td>
</tr>
<tr>
<td></td>
<td>In steroid-associated adverse effects</td>
</tr>
<tr>
<td></td>
<td>As steroid-sparing agent</td>
</tr>
<tr>
<td></td>
<td><strong>First-line agent</strong></td>
</tr>
<tr>
<td></td>
<td>MTX/steroid combination therapy</td>
</tr>
<tr>
<td></td>
<td>Monotherapy in exceptional situations</td>
</tr>
<tr>
<td></td>
<td><strong>Recommended initial MTX dosage 5-15mg weekly</strong></td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Folic acid with MTX is recommended</strong></td>
</tr>
<tr>
<td></td>
<td>• at least 5 mg weekly or 1 mg daily</td>
</tr>
</tbody>
</table>
## Multinational Recommendations

<table>
<thead>
<tr>
<th></th>
<th>Pre-administration work-up before starting MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>• AST, ALT, ALP, bilirubin</td>
</tr>
<tr>
<td></td>
<td>• CBC, creatinine</td>
</tr>
<tr>
<td></td>
<td>• When indicated: serology for HIV, hepatitis B/C and IGRA test</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Consider some contraindications before starting MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>• Renal disease</td>
</tr>
<tr>
<td></td>
<td>• Hepatic disease other than sarcoidosis</td>
</tr>
<tr>
<td></td>
<td>• Bone marrow depression</td>
</tr>
<tr>
<td></td>
<td>• Acute or chronic infection</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>When starting MTX or increasing the dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>• Monitor ALT/AST, creatinine and CBC every 3-6 weeks</td>
</tr>
<tr>
<td></td>
<td>• After a stable dose every 1-3 months</td>
</tr>
<tr>
<td></td>
<td>• After stabilization every 6 months</td>
</tr>
</tbody>
</table>
# Multinational Recommendations

|   | **Gastrointestinal side-effects** |
|---|--|---|
| 7 | • Splitting the oral dose with ingestion within a 12-h period  
   • Parenteral administration  
   • Alternative immunosuppressive drug |

|   | **Confirmed increase in ALT/AST** |
|---|--|---|
| 8 | • Exclude other causes  
   • MTX dose reduction or withdrawal  
   • Liver biopsy  
   • Additional folic acid supplementation  
   • After normalization alternative immunosuppressive drug |

|   | **MTX is appropriate for long-term use** |
|---|--|---|
| 9 |   |

|   | **MTX should not be used** |
|---|--|---|
| 10 | • By men or women for 3 months before planned pregnancy  
   • During pregnancy or breast feeding |
Possible misconceptions

- ‘MTX is not useful as anti-inflammatory agent due to major toxicity’
  - 11% of pulmonologists do not prescribe MTX
  - in sarcoidosis discontinuation of MTX only 0-10%
    - GI complaints most reported reason
  - in RA MTX less frequently discontinued than other DMARDs

- ‘MTX p.o. is as effective as s.c.’
  - only 42% of experts prescribed MTX subcutaneous in GI toxicity
  - parenteral MTX higher effectiveness en less GI toxicity
  - other option: splitting oral dose

- ‘Males with child wish need to stop MTX because of the risk of malformations/teratogenicity’
  - we don’t know yet

---

Conclusion

- MTX is first-choice second-line agent in sarcoidosis
- optimization of its use is important
- multinational recommendations serve to promote this
- future research
  - establishment possible misconceptions
  - revealing mechanism of anti-inflammatory action
Recommendations use of TNF-α inhibitors specifically targeting sarcoidosis

**Recommendation dosage:**
- Infliximab: dosage of 5 mg/kg i.v. at week 0, 2, 6 and every 4 weeks thereafter
- Adalimumab: dosage of 80-160 mg s.c. at week 0, 40 mg at week 1, and 40 mg once every week thereafter

**Discontinuation in case of:**
- severe uncontrolled side-effects
- primary ineffectiveness during 3-6 months treatment
- secondary ineffectiveness due to antibody formation
- or stable disease during treatment with TNF-α inhibitors for at least 6-12 months discontinuation should be considered.

Summary

- Sarcoidosis is a granulomatous disease affecting multiple organs.
- Its therapeutic management is very challenging.
- Curative treatment is currently not available for sarcoidosis.
Summary

• nonspecific immunosuppression with prednisone remains the first-choice therapy

• chronic use of corticosteroids is accompanied with severe adverse events

• timely implementation of appropriate steroid-sparing cytotoxic agents is important
Acknowledgements

• Dr. Elyse Lower, Co-director of ILD/Sarcoidosis Clinic
• Dr. Peter Engel, Co-Director of PH Clinic
• Research coordinator, Rebecca Ingledue
  University of Cincinnati, USA
• Our patients
WASOG

Join us: become a member!

World Association for Sarcoidosis and Other Granulomatous Disorders

www.wasog.org