Is there room for biologicals in sarcoidosis - Real benefit or just expensive?

Martin Brutsche
St. Gallen
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• Standard treatment scheme
• Caveats to longterm treatment
• Alternative treatment choices
• Infliximab – best studied biological
• Conclusions
Granulomatous Lung Diseases

Infection
TB
Fungi
Staph. aureus

Hypersensitivity
Berylliosis
Drugs
EAA

Autoimmunity
Sarcoidosis
Vasculitis
RA

Exposition prophylaxis
Antimicrobial therapy
Immunosuppression

Immunodeficiency
CVID
Hypogammaglobulinaemia
Sec. immunodeficiency

Replacement therapy

Different Prognosis

Chemotherapy
Neoplasia
Metastases
Lymphoma

Kantonsspital St.Gallen
Particularities of sarcoidosis

• Orphan disease
• Heterogenous clinical presentation
  – Mostly thoracic, but all organs can be affected
• Heterogenous clinical outcome
  – 2/3 spontaneous remission, but 5% mortality
• Variable disease activity
  – Single, fatalistic vs. stochastic exacerbation pattern
  – Subacute persistent disease activity

Few RCTs...
No single registered treatment...!
Assessment of disease activity

• Disease severity
  – Lung function testing
  – Rx/CT thorax
  – Extrapulmonary organ manifestations

• Disease progression
  – Rx/CT/lung function over time
  – Fibrosing activity - fibronectin

• Systemic Inflammation
  – Fever, fatigue, weight loss, persistent sweats
  – Elevated sIL-2-receptor +/- ACE-level
Treatment options

- Hydroxychloroquine
  - Pentoxifyllin
- Inhaled Steroids
- Corticosteroids
- Azathioprine
- Methotrexate
  - Cyclosporine
- Leflunomide
  - Thalidomide
  - Golimumab
- Infliximab
  - Rituximab
- Malaria-Drug
  - Pentoxifyllin
  - Lymphocytes ↓
- IL-2 & TNF-α ↓
- IL-2 & TNF-α ↓
- IL-2 ↓
- IL-2 ↓
- IL-2 ↓
- IL-2 ↓
- TNF-α ↓
- TNF-α ↓
- TNF-α ↓
- TNF-α ↓
Indication for systemic steroids

• Severe, active or progressive sarcoidosis
• Specifically in case of:
  – Cardiac sarcoidosis
  – Sarcoidosis of CNS
  – Hypercalcaemia
  – Significantly reduced lung function
  – Sarcoidosis of the posterior eye
Early Treatment of Stage II Sarcoidosis Improves 5-Year Pulmonary Function*

Table 3—Lung Function and Laboratory Test Data in Patients With Initial Stage II(-III) Disease; p Values Indicate Statistically Significant Differences in Changes Between the Groups*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>18-mo Results</th>
<th>5-yr Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Steroid Group</td>
<td>Placebo Group</td>
<td>Steroid Group</td>
</tr>
<tr>
<td>FVC, L</td>
<td>4.48 (0.88)</td>
<td>4.07 (1.03)</td>
<td>4.83 (0.98)</td>
</tr>
<tr>
<td>DLco, mmol/min/kPa</td>
<td>9.17 (1.71)</td>
<td>8.65 (2.24)</td>
<td>10.05 (1.93)</td>
</tr>
<tr>
<td></td>
<td>p = 0.018</td>
<td></td>
<td>p = 0.034</td>
</tr>
<tr>
<td>SACE, U/mL</td>
<td>75 (50)</td>
<td>78 (60)</td>
<td>67 (38)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p = 0.028</td>
</tr>
<tr>
<td>S-Ca, mmol/L</td>
<td>2.35 (0.08)</td>
<td>2.34 (0.12)</td>
<td>2.33 (0.11)</td>
</tr>
<tr>
<td>U-Ca, mmol/24 h</td>
<td>5.1 (2.7)</td>
<td>4.8 (2.7)</td>
<td>5.0 (2.8)</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SD). See Table 2 for expansion of abbreviations.

- Placebo-group: more salvage steroid use (p<0.05), smaller proportion of remissions (24 vs. 38%)
- Stadium I: no differences!

RCT n=189 (Pietinalho et al. CHEST 2002)
Initial therapy for pulmonary sarcoidosis in stages II/III

- 3 months prednisone
  - 20 mg for 8 weeks
  - 15 mg for 2 weeks
  - 10 mg for 2 weeks
- Followed by 15 months budesonide
  - 2x800 μg/d
Sarcoidosis of central airways ➔ obstructive ventilatory defect

Endoluminal stenosis of proximal airways

- Single-center experience: 18/2500 patients
- Patients with relevant respiratory symptoms and extrapulmonary organ manifestations
- The more central airway sites involved the worse the obstruction
- The earlier systemic steroids the better longterm FEV1

Chambellan A. CHEST 2005; 127:472–481
Endoluminal stenosis of proximal airways

Chambellan A. CHEST 2005; 127:472–481
Endoluminal stenosis of proximal airways

Group A: Steroids

Gruppe B: No steroids in the first 3 months

Chambellan A. CHEST 2005; 127:472–481
Are steroids good or bad?

- N=337 patients, cohort study
- Not randomised

Gottlieb JE. CHEST 1997;111:623-31

**Figure 1.** Flow chart illustrating initial categorization based on decision to treat, attainment of remission, and sustenance of remission or relapse. For details, see text.
The shorter the steroid use, the longer the time-to-next-exacerbation...

Gottlieb JE. CHEST 1997;111:623-31
Sarcoidosis mortality (USA)

Figure 1 – Total age-adjusted rate of sarcoidosis-related deaths in the United States, 1999 to 2010.

Figure 3 – Age-adjusted rate of sarcoidosis-related deaths in Caucasians in the United States, 1999 to 2010.

Mirsaeidi M et al. CHEST 2015; 147(2):438-449
Hospitalisations for sarcoidosis (USA)

Gerke et al. BMC Pulmonary Medicine 2012, 12:19
Hospitalisations/Mortality (CH)

- Data from CH-Institute for Statistics (2002-12)
- 8’385/15‘627’573 (0.054%)

Hospitalisations for sarcoidosis

Pohle et al.
PLOS One 2016
Risiks for rehospitalisation (CH)

Pohle et al. PLOS One 2016
Risik for rehospitalisationen (CH)

Pohle et al. PLOS One - accepted
### Steroid-related side effects

- **Self reported side effects**
- **Questionnaire survey in 2446/6517 patients (participation 38%)**

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#### Table 2. Relationship between cumulative prednisone-equivalent dose and self-reported adverse events*  

<table>
<thead>
<tr>
<th>Characteristics/quartile†</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep disturbance (n = 2,146)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>Q2</td>
<td>1.57</td>
<td>1.22–2.02</td>
</tr>
<tr>
<td>Q3</td>
<td>1.68</td>
<td>1.31–2.16</td>
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<tr>
<td>Q4</td>
<td>2.77</td>
<td>2.14–3.59</td>
</tr>
<tr>
<td>Acne (n = 2,040)§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>Q2</td>
<td>1.05</td>
<td>0.69–1.60</td>
</tr>
<tr>
<td>Q3</td>
<td>1.50</td>
<td>1.02–2.20</td>
</tr>
<tr>
<td>Q4</td>
<td>1.63</td>
<td>1.12–2.37</td>
</tr>
<tr>
<td>Skin bruising or thinning (n = 2,144)¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>Q2</td>
<td>1.51</td>
<td>1.18–1.94</td>
</tr>
<tr>
<td>Q3</td>
<td>1.65</td>
<td>1.28–2.12</td>
</tr>
<tr>
<td>Q4</td>
<td>3.04</td>
<td>2.33–3.95</td>
</tr>
<tr>
<td>Weight gain (n = 2,040)#</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>Q2</td>
<td>1.42</td>
<td>1.08–1.85</td>
</tr>
<tr>
<td>Q3</td>
<td>1.79</td>
<td>1.36–2.37</td>
</tr>
<tr>
<td>Q4</td>
<td>2.20</td>
<td>1.65–2.95</td>
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<tr>
<td>Mood problems (n = 2,025)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>Q2</td>
<td>1.65</td>
<td>1.27–2.16</td>
</tr>
<tr>
<td>Q3</td>
<td>1.55</td>
<td>1.19–2.02</td>
</tr>
<tr>
<td>Q4</td>
<td>2.39</td>
<td>1.83–3.12</td>
</tr>
<tr>
<td>High blood sugar (among nondiabetics; n = 1,719)††</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>Q2</td>
<td>0.67</td>
<td>0.33–1.34</td>
</tr>
<tr>
<td>Q3</td>
<td>1.68</td>
<td>0.95–2.99</td>
</tr>
<tr>
<td>Q4</td>
<td>1.82</td>
<td>1.04–3.19</td>
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<tr>
<td>Cataracts (n = 1,869)‡‡</td>
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<td></td>
</tr>
<tr>
<td>Q1</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>Q2</td>
<td>1.19</td>
<td>0.80–1.78</td>
</tr>
<tr>
<td>Q3</td>
<td>1.51</td>
<td>1.03–2.23</td>
</tr>
<tr>
<td>Q4</td>
<td>1.83</td>
<td>1.25–2.69</td>
</tr>
<tr>
<td>Fracture (n = 1,899)§§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>Q2</td>
<td>1.32</td>
<td>0.83–2.08</td>
</tr>
<tr>
<td>Q3</td>
<td>1.73</td>
<td>1.11–2.69</td>
</tr>
<tr>
<td>Q4</td>
<td>1.97</td>
<td>1.27–3.05</td>
</tr>
</tbody>
</table>

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*Curtis JR. Arthritis & Rheumatism 2006; 55:420–426*
### Side effects under $\leq 7.5$ mg/d pred

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>90-day increase in duration of use</th>
<th>95% CI</th>
<th>Average daily dose (per 1-mg/day increase within 0–7.5 mg/day range)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep disturbance†</td>
<td>NS</td>
<td>NS</td>
<td>1.14</td>
<td>1.02–1.28</td>
</tr>
<tr>
<td>Acne‡</td>
<td>1.17</td>
<td>1.04–1.32</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Skin bruising or thinning§</td>
<td>1.17</td>
<td>1.08–1.26</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Weight gain¶</td>
<td>1.09</td>
<td>1.01–1.18</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Mood problems#</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>High blood sugar (among nondiabetics)**</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Cataracts‡‡</td>
<td>1.17</td>
<td>1.06–1.29</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Fracture‡‡</td>
<td>NS</td>
<td>NS</td>
<td>1.26</td>
<td>1.04–1.53</td>
</tr>
</tbody>
</table>

*Curts JR. Arthritis & Rheumatism 2006; 55:420–426*
Granuloma as autochthonous reaction of cell-mediated immune response – access for targeted approaches

Iannuzzi et al. NEJM 2007
Steroid-sparing with MTX and AZA

- N=200 patients, non-randomised
- 145 MTX and 55 AZA
- Mean dose reduction 6.3 mg/d in both groups
- In 70% a dose reduction of 10 mg/d could be made
- Improvement of DLCO, FEV1, FVC after 12 months

Vorselaars ADM. CHEST 2013; 144(3):805–812
Efficacy of mycophenolate mofetil in sarcoidosis

Nabeel Hamzeh c,d,* , Allison Voelker a , Anna Forssén b , E. Brigitte Gottschall a,c,d , Cecile Rose a,c,d , Peggy Mroz c , Lisa A. Maier a,c,d

• N=37, retrospective analysis
• Mycophenolate has steroid-sparing effect comparable to MTX and AZA
• Mycophenolate had not additional effect compared to MTX and AZA
• Mycophenolate is an alternative to MTX and AZA especially in case of side effects

Hamzeh N. Respiratory Medicine 2014;108:1663e1669
Infliximab Therapy in Patients with Chronic Sarcoidosis and Pulmonary Involvement

Robert P. Baughman, Marjolein Drent, Mani Kavuru, Marc A. Judson, Ulrich Costabel, Roland du Bois, Carlo Albera, Martin Brutsche, Gerald Davis, James F. Donohue, Joachim Müller-Quernheim, Rozsa Schlenker-Herceg, Susan Flavin, Kim Hung Lo, Barry Oemar, and Elliot S. Barnathan, on behalf of the Sarcoidosis Investigators

Figure 3. Mean (± SD) changes from baseline in percentage of predicted FVC through Week 52 (randomized patients, no imputation for missing data). *p < 0.05 versus placebo group.

Am J Respir Crit Care Med 2006
Long-Term Treatment with Infliximab in Patients with Sarcoidosis

Total n=25

- Pulmonary n=9
  - Stage II/III n=6
  - Stage IV n=3
- Extrapulmonary n=16
  - CNS n=8
  - Calcium metabolism n=1
  - Lupus pernio n=5
  - Eye n=1
  - Heart n=1

Respiration 2012

Katrin E. Hostettler\textsuperscript{a}  Ueli Studler\textsuperscript{b}  Michael Tamm\textsuperscript{a}  Martin H. Brutsche\textsuperscript{a}
Results - FVC

- >10% improvement: 3/9 (33%)
- 0-10% improvement: 5/9 (56%)
- Worsening: 1/9 (11%)

Baseline FVC: 2.34 L
After treatment FVC: 2.69 L

Baseline FVC, %P: 61%
After treatment FVC, %P: 70%
Effect after 2 treatments with infliximab
## Extrapulmonary sarcoidosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Location</th>
<th>Response</th>
<th>Duration of Therapy (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CNS</td>
<td>complete remission</td>
<td>59</td>
</tr>
<tr>
<td>2</td>
<td>CNS</td>
<td>partial remission</td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>lupus pernio</td>
<td>complete remission</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>CNS</td>
<td>complete remission</td>
<td>20</td>
</tr>
<tr>
<td>13</td>
<td>heart</td>
<td>partial remission</td>
<td>13</td>
</tr>
<tr>
<td>15</td>
<td>heart</td>
<td>no response</td>
<td>13</td>
</tr>
<tr>
<td>17</td>
<td>lupus pernio</td>
<td>no response</td>
<td>4</td>
</tr>
<tr>
<td>20</td>
<td>eye</td>
<td>complete remission</td>
<td>10</td>
</tr>
<tr>
<td>21</td>
<td>CNS</td>
<td>no response</td>
<td>3</td>
</tr>
<tr>
<td>23</td>
<td>CNS</td>
<td>partial remission</td>
<td>3</td>
</tr>
<tr>
<td>24</td>
<td>calcium metabolism</td>
<td>complete remission</td>
<td>2</td>
</tr>
</tbody>
</table>

### Response Rates

<table>
<thead>
<tr>
<th></th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>7 (47%)</td>
</tr>
<tr>
<td>Partial remission</td>
<td>5 (33%)</td>
</tr>
<tr>
<td>No response</td>
<td>3 (20%)</td>
</tr>
<tr>
<td><strong>Worsening</strong></td>
<td>0</td>
</tr>
</tbody>
</table>

Total response rate: 80%
Results - ACE

Serum levels of ACE (U/l)

Elevated ACE
n=2!!

ULN = 68 U/l

Decrease 10/17 (59%)
No change 1/17 (6%)
Increase 6/17 (35%)

All 6 patients with increasing ACE levels had a positive response to infliximab treatment!!
Bosentan does not improve outcome in patients with steroid-resistant pulmonary sarcoidosis – results from the double-blind placebo-controlled Phase 2 BOSSA-trial
Katrin E. Hostettler, Florent Baty, Rebekka Kleiner, Michael Tamm, Martin H. Brutsche
ATS Congress San Diego 5/2014

- Sarkoidosis is associated with pulmonary hypertension
- BAL-Endothelin-1 ↑ (Terashita. Respirology 2006)
  - BAL stimulates fibroblast proliferation, which can be inhibited by ERA
  - Correlation with disease activity (Shahar. Int J Immunopharmacol 1999)
- Blood-endothelin-1 ↑
Mean absolute values ± SD (m0 – m12)
Rituximab for refractory cases?

- Open-label, Phase 1/2-study, n=10
- Inclusion: Persistent symptome in spite of ≥10 mg/d prednisone & relevant organ damage
- Toxicity: 1 hospitalisation due to pneumonia
- 2 deaths due to disease progression
- Inconsistent effects on FVC and 6-MWT after 26 and 52 weeks

Sweiss NJ. Eur Respir J. 2014;43(5):1525–1528
Take Home

1. Sarcoidosis ➤ variable prognosis and presentations
2. No registered treatment available
3. Steroids ➤ unclear disease modification, many side effects
4. Room for treatment alternatives ➤ Biologicals
Is there room for biologicals in sarcoidosis - Real benefit or just expensive?

Martin Brutsche
St. Gallen
There is room for biologicals in sarcoidosis - Real benefit or just expensive?

significant

adapted treatment is likely to reduce disease burden and cost

...treatment alternatives including...

Martin Brutsche
St. Gallen