Sarcoidosis and Biologics

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Sarcoidosis disclosures

• Clinical trials
  – Janssen
  – Pfizer
  – Gilead
  – Actelion
  – Araim

• Research support/consulting
  – Glaxo-Smith-Kline
  – NHLBI
  – Celgene

No medication is FDA-approved for use in sarcoidosis
Rising sarcoidosis mortality in the US

Sarcoidosis vs. other inflammatory diseases in North America
Outline

• Review the experience with traditional anti-TNF medications
• Results of the recent golimumab/ustekinumab trial

Sarcoidosis was first recognized in 1869

Jonathan Hutchinson
1828-1913

“Mortimer’s Malady”

Caesar Boeck
1845-1917
Serum amyloid A hypothesis

Chen ES. Nat Rev Rheumatol 2011
TNF: pleiotropic role in granulomas

Effect of TNF antagonists on MTB-stimulated monocytes

Median IFN gamma reduction

Saliou. J Infect Dis 2006; 194:486
Main immunosuppressive options

Corticosteroids → cyclophosphamide → azathioprine → rituximab

1869

Colchicum
Arsenic
Acid iron
Potassium iodide
Lead/mercury ointment

antimalarials → methotrexate → leflunomide → chlorambucil

Cyclophosphamide
Azathioprine
Leflunomide
Methotrexate
Mycophenolate
Chlorambucil
Thalidomide
Pentoxifylline

2013

Antimalarials
Methotrexate
Leflunomide
Chlorambucil
Thalidomide
Pentoxifylline

Infliximab was effective but not earth-shattering

* Patients with higher SGRQ, disease > 2 years, MRC dyspnea >1 also showed more benefit

Mean change in % predicted FVC from baseline

Placebo Baughman-all Baughman-severe (FVC <59%) Rossman

Rossman MD. SVDLD 2006
How good is the “gold standard” (prednisone)?

- n=53 patients treated with prednisone for 3-8 weeks
- Median FVC improvement 5.4%
- Median DLCO improvement was 10.3%
- >5% improvement of FVC was highly associated with improved MRC dyspnea and with patient global impression of benefit

Effect of infliximab on extrapulmonary sarcoidosis

Judson MA. Eur Respir J 2008; 31:1148
Does ACE help?

Correlation with respiratory functional impairment in 144 non-smoking patients

Rothkrantz-Kos S. Clin Chem 2003

CXR fibrosis does not preclude a response to infliximab

n=43
Main points to date

- We have learned most about how to use these agents by extrapolation
- There are no controlled trials for comparing TNF antagonists
- Infliximab is the current standard for sarcoidosis among the available agents
- There are inter-individual and inter-organ differences in response
Effect of IFX on lupus pernio

Percent with resolution, near resolution, or improvement

Stagaki E. Chest 2008

Infliximab response rates at CCF: four most common indications

>90% able to reduce steroid dose

N=50

Sodhi M. Respir Med 2008
Outline

• Review the experience with traditional anti-TNF medications
• Results of the recent golimumab/ustekinumab trial

Role of IL-12/23 p40 and TNFα in Sarcoidosis

Courtesy of Rosemary Watt
Elevated TNFα and IL-12p40 mRNA in Cutaneous Lesional Skin

Path to identify more responsive subgroup inT48 study

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Compared to Placebo</th>
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<tr>
<td></td>
<td>LS Mean</td>
</tr>
<tr>
<td></td>
<td>∆FVC</td>
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<tr>
<td>All Subjects</td>
<td>(n=138)</td>
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<td></td>
<td></td>
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<tr>
<td>Subjects with more severe pulmonary disease</td>
<td>(n=93)</td>
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<td></td>
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<tr>
<td>Number of years since diagnosis ≥ 2 years</td>
<td>3 mg/kg</td>
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<td></td>
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<tr>
<td>Subjects with chronic sarcoidosis</td>
<td>(n=84)</td>
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</table>

Judson MA. JAAD 2012
Ustekinumab Mechanism of Action

IL-23

Ustekinumab

p19

p40

IL-12

p40

p35

IL-12Rβ1

IL-12Rβ2

NK or T cell membrane

No IL-12 or IL-23 cellular activation

1275148SCD2001 Study Design

180 Pts with Chronic Sarcoidosis

Primary Population: Pulmonary (n≥135)

Secondary Population: Skin (n ≥ 45)

Placebo SC at Wk 0, 4, 8, 12, 16, 20 (n=60)

Ustekinumab (anti-IL12/23) 180 mg SC at Wk 0; 90 mg SC at Wk 8, 16, and 24 with Placebo SC at Wk 4, 12 and 20 (n=60)

Golimumab (anti-TNFα) 200 mg SC at Wk 0; 100 mg sc at Wk 4, 8, 12, 16, 20, 24 (n=60)

Steroid Stable Phase

Steroid Taper Phase

Primary Endpoint

Secondary Efficacy and Safety Assessments
Sarcoidosis Subject Stratification Scheme

Primary Population
Strata 1 + 3 (n ≥ 135) 132

Stratum 1 (lung) 115
Stratum 3 (lung & skin) 17
Stratum 2 (skin) 41

Secondary Population
Strata 2 + 3 (n ≥ 45) 58

Primary Endpoint: Change from Baseline in % Predicted FVC at Week 16

![Graph showing LS Mean (SE) for Placebo (N=44), GLM (N=42), and UST (N=46).]

* Analysis uses last observation carried forward to input missing values
Percent Predicted FVC Responders (≥5%) Over Time

SPGA Responders at Week 28: Secondary Population

Percent of Responders (%)

Placebo (N=20) GLM (N=17) UST (N=21)

p=0.19 p=0.28
It’s never as simple as you think

TNF-α Knockout Models

Form defective granulomas, failing to control infection

C. parvum model: delayed inflammatory response, followed by death

Marino MW. Proc Natl Acad Sci 1997;94:8903-8
Paradoxical granulomatosis

53 year-old female on adalimumab for inflammatory bowel disease develops cough and uveitis

Nascent “sarcoidosis” during TNF therapy

- Probably less than 1% of treated patients
- More commonly reported with ETN
- Usually involve lungs, must may also affect eyes, skin, kidney, other organs
- Typically respond to drug withdrawal

Tong D. Int Med J 2012
Centrality of TNF?

Banchereau J. Immunity 2004

STAT1 plays a central role in sarcoidosis

Crouser ED. AMJRCCM 2009
Transcriptional regulatory analysis

*Interact to promote IFN responses but do not bind each other.*
Rationale for ustekinumab in treatment of sarcoidosis

- Serum concentrations of IL-12p40 and IFN-γ are significantly higher in pulmonary sarcoidosis

- IL-12p40 protein is expressed in epithelioid cells and macrophages of sarcoid lungs

- IL-12p40 levels are significantly higher in BALF and serum from sarcoid patients. IL-12p40 levels paralleled the clinical course of sarcoidosis, with the highest levels detected in BALF from patients with persistent disease

- IL-12 receptor mRNA significantly increased on BAL cells from sarcoidosis patients compared to normal controls

2 Shigehara et al, J Immunol, 2001, 166:642-9
3 Taha et al, AJRCM, 1999, 160:1119-23

Major Inclusion Criteria

- Both Populations (Lung and Skin)
  - Dx of sarcoidosis for ≥ 2 years
  - Histologically proven disease
  - Symptomatic despite current background therapy

- Primary Population (Lung)
  - Stage 2, 3, or 4 [with interstitial infiltrates w/o cavitating disease]
  - FVC ≥45% to ≤80% predicted
  - 6MWD between 100m - 550m
  - MRC dyspnea score >2
Trial Endpoints

• Primary Endpoint:
  – Change from baseline in % predicted FVC at Week 16 in primary population
    • Ustekinumab vs. placebo
    • Golimumab vs. placebo

• Major Secondary Endpoints at Week 28
  – 6 Min Walk (primary population)
  – SGRQ Total Score (primary population)
  – Proportion of responders (“Clear” or “Minimal”) by Skin Physician Global Assessment (in secondary population)
  – % Predicted FVC (primary population)

Number of Subjects by Stratification Factors

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Golimumab</th>
<th>Ustekinumab</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Randomized subjects</td>
<td>58</td>
<td>55</td>
<td>60</td>
<td>173</td>
</tr>
<tr>
<td>Baseline disease organ involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung involvement only</td>
<td>38 (65.5%)</td>
<td>38 (69.1%)</td>
<td>39 (65.0%)</td>
<td>115 (66.5%)</td>
</tr>
<tr>
<td>Both lung and skin involvement</td>
<td>6 (10.3%)</td>
<td>4 (7.3%)</td>
<td>7 (11.7%)</td>
<td>17 (9.8%)</td>
</tr>
<tr>
<td>Skin involvement only</td>
<td>14 (24.1%)</td>
<td>13 (23.6%)</td>
<td>14 (23.3%)</td>
<td>41 (23.7%)</td>
</tr>
<tr>
<td>Prior anti-TNFα use</td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>7 (12.1%)</td>
<td>6 (10.9%)</td>
<td>9 (15.0%)</td>
<td>22 (12.7%)</td>
</tr>
<tr>
<td>No</td>
<td>51 (87.9%)</td>
<td>49 (89.1%)</td>
<td>51 (85.0%)</td>
<td>151 (87.3%)</td>
</tr>
</tbody>
</table>
Distance at Week 28: Primary Population

* Analysis uses last observation carried forward to input missing values

28:
Primary Population
Overall Conclusions

• Neither golimumab nor ustekinumab, at the doses studied, demonstrated efficacy in pulmonary sarcoidosis
• A trend in response following golimumab treatment was observed in skin sarcoidosis
  – However study was underpowered for this endpoint
• A nominally greater proportion of subjects in both active treatment groups were able to reduce OCS dose during the taper phase compared to the placebo