Coccidioidomycosis in Rheumatologic Patients

Susan E. Hoover, MD
The problem

Prevalence of rheumatoid arthritis is 1%
Population of Arizona is 6 million
At least 150,000 new cocci infections yearly
DMARDs and BRMs improve disease outcomes
There are no guidelines for managing cocci in these patients
13 cases of cocci in patients taking TNF antagonists
   12 infliximab (11 with methotrexate)
   1 etanercept
All had pneumonia
4 had disseminated disease
2 had a prior history of cocci and their disease was thought to represent reactivation

2. Retrospective cohort study 2000-2003
985 patients with RA, JRA, psoriatic arthritis, reactive arthritis
11 developed symptomatic cocci (1%)
   7/247 on infliximab
   4/738 on etanercept
Studies of cocci in rheumatic disease
Mertz and Blair Ann NY Acad Sci 2007

Retrospective chart review 2000-2006
854 rheumatology patients
16 developed cocci (1.9%)
   6 on infliximab
   1 on etanercept
   2 were disseminated (both articular, neither on TNF inhibitor)
   2 were asymptomatic
Most common rheumatic dx was RA

The seasonal pattern and increasing incidence 2000-2006 suggested that most cases were new infections
Chart review of 298 patients on BRMs
20 developed cocci (6.7%)
   13 on infliximab (10.6%)
   3 on etanercept (2.9%)
   4 on adalimumab (3.3%)
3 were asymptomatic
4 were disseminated

“Control group” of 225 patients on methotrexate
4 developed cocci (1.3%)

Limitations: capturing the denominator?
Conclusions and questions

There is a significant (1% or higher) incidence of cocci in patients on TNF inhibitors and other drugs for rheumatic diseases.

Disseminated disease appears more common than in the general population.

How should we manage these patients during and after cocci infection?

Can we resume BRM or DMARD therapy?
Subsequent Therapy of Patients with Biologic Response Modifiers or Disease-Modifying Antirheumatic Drugs after Coccidioidomycosis

Susan Knowles MD, Sara Taroumian MD, Jeffrey Lisse MD, James Yanes MD, Neil M. Ampel MD, Eric Gall MD, Rafael Grau MD, Barbara Bode MD, Berchman Vaz MD, PhD, John Galgiani MD and Susan Hoover MD, PhD

1University of Arizona Health Care Network, 2Southern Arizona VA Health Care System, 3Arizona Arthritis Center, 4Catalina Pointe Rheumatology, 5Valley Fever Center of Excellence

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Methods

Retrospective chart review

Developed cocci while on DMARDs or BRMs

Seen at least once in a University-affiliated or Veterans Administration outpatient rheumatology clinic in Tucson, Arizona between 2007-2009

Charts were reviewed up to June 1, 2011

Mode of diagnosis, clinical manifestations, antifungal therapy and duration, and management of BRM/DMARDs
Results

485 charts reviewed (344 University, 144 VA)

44 patients developed cocci during treatment with a BRM and/or DMARD

6 Asymptomatic

29 Pulmonary

9 Disseminated

Skin: 4

Joint: 2 (knee, ankle)

Meningitis: 1

Lymph node: 1

Larynx: 1
Results

20 Male, 24 Female
60-79 yrs
Caucasian
Rheumatoid Arthritis
33 RA
4 AS
3 PsA
2 IBD SpA
1 SLE
1 other
Medications at time of diagnosis

- BRM alone: 11
- BRM + DMARD: 25
- DMARD alone: 8
**BRMs at time of diagnosis**

Most common: Infliximab

<table>
<thead>
<tr>
<th>Biologic Response Modifier (total)</th>
<th>BRM alone</th>
<th>BRM in combination with DMARD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab (21)</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Etanercept (6)</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Adalimumab (8)</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Abatacept (1)</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

No particular agent seemed to be associated with dissemination
DMARDs at time of diagnosis

Most common: Methotrexate (MTX) alone or in combination

<table>
<thead>
<tr>
<th>DMARD (total)</th>
<th>DMARD alone</th>
<th>In combination with BRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate (26)</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>Azathioprine (5)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Leflunomide (2)</td>
<td>0</td>
<td>2</td>
</tr>
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</table>
Initial BRM/DMARD Management

- BRM & DMARD held (26) 59%
- BRM held, but DMARD cont (8) 18%
- No change in therapy (10) 23%
Initial Antifungal Therapy

All but 3 patients had antifungal therapy initiated for 3 months or longer (fluconazole 400 mg/day)

Median duration was 12 months

Range 0 – 96 months

Duration of antifungal therapy

- More than 12 mo: 18
- 6-12 mo: 12
- 3-6 mo: 4
- 3 mo or less: 4
- None: 4

Number of patients
Subsequent BRM/DMARD Management

Follow-up data were available for 38/44 patients. 33/38 patients had resumed or continued BRM and/or DMARD:

- 23 restarted BRM +/- DMARD; 10 DMARD alone
- Disseminated disease:
  - 4 BRM + DMARD
  - 4 DMARD alone
- 5 patients did not restart BRM/DMARD: remission of rheumatic disease (4), dissemination (1)

No complications from cocci to date (median f/u 30 mo)
BRM/DMARD Rationale

BRM/DMARD continued at time of initial infection
  Cocci asymptomatic
  Active rheumatic disease

BRM/DMARD later restarted
  Active rheumatic disease
Time to Restart DMARD/BRM

DMARD
- Range: 0-48 months
- Median: 1 month

BRM
- Range: 0-72 months
- Median: 10 months
Antifungal Therapy

16/33 received BRM/DMARD WITH antifungal therapy
  5 DMARD alone
  11 BRM +/- DMARD

17/33 received BRM/DMARD WITHOUT antifungal therapy
  5 DMARD alone
  12 BRM +/- DMARD
Antifungal Therapy Rationale

Continuing antifungal while on BRM/DMARD:
  Persistent positive serologies
  Dissemination

Stopping antifungal while on BRM/DMARD:
  Negative serology
  Adverse reaction
Cocci can be serious infection in patients on BRM/DMARDs
How do I manage the initial infection?
Can I resume BRM/DMARD therapy?
Initial Cocci Infection

**Asymptomatic**
- Consider continue BRM/DMARD if rheumatic disease active
- Antifungal therapy 6-12 months
- Closely monitor

**Pulmonary**
- Hold BRM
- Consider continue DMARD if mild infection and rheumatic disease active
- Antifungal therapy at least 6-12 months or until resolved
- Closely monitor

**Disseminated**
- Hold DMARD & BRM
- Antifungal therapy indefinitely
- Closely monitor
Subsequent BRM Therapy

Is Cocci Active?
Persistent Symptoms
AND
Imaging not resolved / stable

NO

Serology NEGATIVE

Cocci Resolved
• Consider restart BRM
• Antifungal therapy 6-12 mo or lifelong if disseminated
• Closely monitor

Serology POSITIVE

Low Titer Serology (IDCF < 1:16)
• Consider restarting BRM after consultation with ID
• Risk vs Benefit
• Continue antifungal
• Closely monitor

High Titer Serology
• Do not restart BRM
• Continue antifungal
• Reeval in 1-3 months

YES, cocci still active
Conclusions

Treating with a BRM and/or DMARD after cocci infection appears to be safe in some patients.

All patients should receive initial antifungal therapy; however, concomitant antifungal when resuming BRM/DMARD must be an individualized decision.

Larger studies with longer follow up are indicated to further characterize the relationship between BRM/DMARD therapy and this endemic fungal infection.