Behçet’s Disease: The American Perspective

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April 27th, 2018

INTEREST DISCLOSURE

Disclosures

As no medications to treat Behçet’s disease are FDA approved all medications discussed are off-label.

No financial disclosures to report

Learning Objectives

(1) Describe the International Study Group Criteria, the most commonly used diagnostic criteria for Behçet’s disease
(2) Understand how the most serious manifestations of this disease typically manifest
(3) Develop a treatment approach based on organ manifestations of disease
(4) Describe common mimickers
Diagnostic criteria – International Study Group for Behçet’s Disease 1990

Recurrent oral ulcers (at least 3 / yr) plus two of the following

- Recurrent genital ulcers
- Eye lesions (uveitis or retinal vasculitis)
- Skin lesions (E nodosum, papulopustular lesions or acneiform lesions)
- Positive pathergy test

31 yo Caucasian woman with Behçet’s disease (recurrent oral ulcers, erythema nodosum, arthritis of knees /ankles and anterior uveitis) presents with BRBPR

No prior history of vaginal ulcers, pustular skin disease, arthritis, neurologic complaints or a positive pathergy test
Meds: azathioprine 150, naproxen 500 bid

Endoscopy – large well demarcated colonic ulcer, biopsy results pending

Diagnosis?

a) Behçet’s disease with GI involvement

b) Behçet’s disease with NSAID-induced ulceration

c) IBD with extra-intestinal manifestations
Positive Predictive Value of Behçet’s Diagnostic Criteria in American Patients

\[ PPV = \frac{(\text{sensitivity})(\text{prevalence})}{(\text{sensitivity})(\text{prevalence}) + (1 - \text{specificity})(1 - \text{prevalence})} \]

Sensitivity = 0.95  Specificity = 0.98
Prevalence = \(\frac{5}{100,000}\) = 0.2%

Mucocutaneous Disease

Case Study #1

64 yo Caucasian woman with Behçet’s (oral ulcers, anterior uveitis, folliculitis) presenting with resistant oral ulcers. Ulcers began 3y ago, increasing in number with some ulcers present for over a year. Skin pustules over buttocks with small blisters over her chest. Oral ulcers and anterior uveitis steroid and azathioprine responsive.

PMH: fatty liver, osteopenia, glaucoma, gallstones
Meds: colchicine 0.6, azathioprine 200, prednisone 5
Oral Ulceration

Case Study #2

25 yo HLA B51+ Caucasian woman with Behçet’s (oral ulcers, genital ulcers, nodular skin lesions) seen at NIH for second opinion. No ocular, GI, neurologic involvement. Still with recurrent skin nodules, steroid responsive

PMH: celiac sprue, seizure disorder, pyelonephritis

Meds: azathioprine 150, colchicine 1.8, prednisone 25

All: many
Nodular Skin Disease

Pustular Skin Disease
Arthritis
- Knees and ankles most common
- Inflammatory, nondeforming
- Can be arthralgia vs arthritis
- NOT the same as a pain syndrome which can occur concurrently

Pathergy

Colchicine –
24 month placebo controlled RCT

In women (n=39):
- decreased genital ulcers (p=0.004)
- decreased erythema nodosum (p=0.004)
- decreased arthritis (p=0.033)

In men (n=45):
- decreased arthritis (p=0.012)

Yurkdul et al, Arth Rheum, 2001
Azathioprine
RCT Azathioprine vs. Placebo

<table>
<thead>
<tr>
<th></th>
<th>Azathioprine (n=34) Number (%)</th>
<th>Placebo (n=23) Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral ulcers *</td>
<td>4 (12)</td>
<td>8 (35)</td>
</tr>
<tr>
<td>Genital ulcers *</td>
<td>1 (3)</td>
<td>8 (35)</td>
</tr>
<tr>
<td>Pustular lesions</td>
<td>27 (79)</td>
<td>17 (74)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>1 (3)</td>
<td>2 (9)</td>
</tr>
</tbody>
</table>

* p < 0.05

Yazici et al, NEJM, 1990

TNF Inhibitors
RCT etanercept vs. placebo in mucocutaneous disease

** p < 0.01

Melikoglu et al, J Rheum, 2005

Apremilast (Phosphodiesterase 4 Inhibitor) in Mucocutaneous Disease: Trial Design

Study Day

Pre-randomization Phase  Treatment Phase  Extension Phase  Observational Follow-up Phase*

Screening  Apremilast 30 mg BID  Apremilast 30 mg BID  Placebo

Follow-up

* Courtesy of Yusuf Yazici, M.D.
Apremilast: Primary End Point

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo</th>
<th>30 mg BID</th>
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<tbody>
<tr>
<td>wk0</td>
<td>2.9</td>
<td>2.7</td>
</tr>
<tr>
<td>wk2</td>
<td>1.7</td>
<td>0.3</td>
</tr>
<tr>
<td>wk4</td>
<td>1.9</td>
<td>0.7</td>
</tr>
<tr>
<td>wk6</td>
<td>1.9</td>
<td>0.5</td>
</tr>
<tr>
<td>wk8</td>
<td>1.6</td>
<td>0.5</td>
</tr>
<tr>
<td>wk10</td>
<td>1.4</td>
<td>0.7</td>
</tr>
<tr>
<td>wk12</td>
<td>2.1</td>
<td>0.5</td>
</tr>
<tr>
<td>wk14</td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>wk16</td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>wk18</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>wk20</td>
<td>0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>wk22</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>wk24</td>
<td>1.3</td>
<td>1.9</td>
</tr>
<tr>
<td>wk26</td>
<td>1.6</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Mean Number of Oral Ulcers

All patients in the PBO group switched to APR from week 12 visit. APR was discontinued at week 24.

Systemic Steroids?

RCT of 86 patients with active genital ulcers to receive IM 40 mg methylprednisolone every 3 weeks or placebo.

- No significant difference in oral ulcers, genital ulcers, or folliculitis
- Decreased erythema nodosum in steroid group

Mat et al, Rheumatology, 2006

Steroids are overused in mucocutaneous disease!
Mucocutaneous Treatment Stepwise Approach

- Topical steroids. Suggest triamcinolone dental paste for oral and vaginal ulcers
- Colchicine (skin and arthritis > ulcers)
- Azathioprine
- Apremilast vs. TNF inhibitor

Ocular Disease

Hypopyon Uveitis
Eye Disease

Active vitritis (+3 haze OU)

Normal retina and fluorescein angiogram

H. Nida Sen, NEI

Eye Disease – Posterior Uveitis

Retinal vascular leakage veins -> arteries with cotton wool spots

H. Nida Sen, NEI

Azathioprine
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<th>Placebo (n=23) Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New eye disease *</td>
<td>3 (3)</td>
<td>8 (35)</td>
</tr>
<tr>
<td>Recurrence of eye disease *</td>
<td>0 (0)</td>
<td>5 (22)</td>
</tr>
<tr>
<td>Hypopyon uveitis *</td>
<td>1 (3)</td>
<td>7 (30)</td>
</tr>
<tr>
<td>Oral ulcers *</td>
<td>4 (12)</td>
<td>8 (35)</td>
</tr>
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</tr>
</tbody>
</table>

NNT = 2
NNT = 4

p < 0.05

Yazici et al, NEJM, 1990
TNF Inhibitors

Multicenter Study of Infliximab for Refractory Uveoretinitis in Behçet Disease

Table 4. Efficacy of Infliximab by Location and Severity of Ocular Inflammatory Lesions

<table>
<thead>
<tr>
<th>Location</th>
<th>Severity</th>
<th>Before Starting Infliximab</th>
<th>After Starting Infliximab</th>
<th>p Value</th>
<th>p Values</th>
<th>p Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>199 (43)</td>
<td>22 (54)</td>
<td>26 (55)</td>
<td>.015</td>
<td>.42</td>
<td>.42</td>
</tr>
<tr>
<td>Uveoretinitis</td>
<td>14 (40)</td>
<td>10 (30)</td>
<td>10 (30)</td>
<td>.13</td>
<td>.28</td>
<td>.28</td>
</tr>
<tr>
<td>Foveal</td>
<td>10 (30)</td>
<td>3 (10)</td>
<td>5 (15)</td>
<td>.001</td>
<td>.02</td>
<td>.02</td>
</tr>
<tr>
<td>Paracentral</td>
<td>15 (45)</td>
<td>13 (30)</td>
<td>13 (35)</td>
<td>.001</td>
<td>.01</td>
<td>.01</td>
</tr>
<tr>
<td>Pseudophakic eyes</td>
<td>16 (45)</td>
<td>13 (30)</td>
<td>13 (35)</td>
<td>.001</td>
<td>.01</td>
<td>.01</td>
</tr>
<tr>
<td>Unspecified</td>
<td>7 (18)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>.001</td>
<td>.005</td>
<td>.005</td>
</tr>
</tbody>
</table>


Open-Label Gevokizumab Clinical Results

![Day 0](image0.png) ![Day 1](image1.png) ![Day 6](image2.png)

![Day 9](image3.png) ![Day 14](image4.png) ![Day 30](image5.png)

Gul et al, Ann Rheum Dis, 2012

Other Disease Manifestations
Gastrointestinal Disease

Differentiating IBD vs. GI Behçet’s

**Suggestive of IBD**
- "Cobblestone" appearance
- Granulomas, crypt distortion

**Suggestive of Behçet’s**
- Presence of other organ manifestations (genital ulcers, panuveitis)

*Not helpful:* ileocolonic location, anterior uveitis, oral ulcers

United States Prevalence of Disease

Ulcerative Colitis: 238 per 100,000

Crohn’s Disease: 201 per 100,000

Behçet’s Disease: 5.2 per 100,000, 2-40% with GI involvement

Behçet’s is rare
Neurologic Manifestations

- Area of great confusion
- Two types:
  1. Parenchymal white matter lesions typically for brainstem and cerebellum
  2. Dural sinus thromboses
- Controversy over neurocognitive Behçet’s. Usually this is secondary.

Neurologic Disease

Suggested Diagnostic Criteria for Neuro-Behçet’s Disease

A) Fulfilling the International Diagnostic Criteria for Behçet’s Disease
B) Onset of neurological symptoms not otherwise explained by any other known systemic or neurological disease or treatment
C) Presence of at least one of the following:
   - Objective abnormalities on neurological examination (clinical evidence)
   - Abnormal neuroimaging findings suggestive of NBS (imaging evidence)
   - Abnormal cerebrospinal fluid findings suggestive of NBS (laboratory evidence)
   - Abnormal neurophysiological (electromyography or evoked potentials) studies consistent with the current neurological symptoms (neurophysiological evidence)
GI and Neuro Treatment

GI: monoclonal TNF inhibitors similar to IBD

Neurologic disease: Cyclophosphamide vs TNF inhibitors

Deep Vein Thrombosis

Vascular Disease –
Superficial Thrombophlebitis
What is the #1 Cause of Death in Behcet’s Worldwide?

A) Cardiovascular disease
B) Pulmonary arterial aneurysms
C) Budd-Chiari
D) Progressive neurologic disease
E) Infection

> 90% of cases are young men

Kural-Seyahi et al, Medicine, 2003
Saadoun et al, Arthritis Rheum, 2010

How To Approach Diagnosis?

(1) Helpful to use the diagnostic criteria recognizing limitations of PPV of rare disease.
(2) What is objective? Would not treat based on history alone
(3) What is specific? Typical eye disease, typical biopsy, classic neurologic disease. More concerning in patients of typical ethnic background.
(4) What is severe? Try not to immunosuppress for mucocutaneous disease alone

Acknowledgements

NIAMS
Clinical Fellows, Michael Davis, Elaine Novakovich, Elizabeth Jipal, Yin Liu, Raphaele Goldbach-Mansky
NIDDK
Thao Heller, Preet Bagi
NEI
Hatice Nida Sen, Robert Nussenblatt
NHGRI
Melissa Meredith
NI
Ed Cowen
NINDS
Frank Anderson
Clinical Center
Robert Wesley
NYU
Yusuf Yazici
University of Istanbul
Gulen Hatem, Hasan Yalcin
CHSU
Jim Rosenbaum