Behcet’s Disease

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Disclosures

• No personal disclosures relevant to this talk

• Support for the VF Symposium provided by Celgene
  • Will be discussing Apremilast
Description of 3 patients in 1937

Triad:
- Aphthae
- Genital ulcers
- Hypopyon uveitis

Earlier description
Hippocrates
5th Century BC

Worldwide Prevalence of Behcet’s

Disease of the Silk Roads

http://www.orexca.com/silk_road.html
Comparison to other forms of Vasculitis

- **Immune Complex Small Vessel Vasculitis**
  - Cryoglobulinemic Vasculitis
  - IgA Vasculitis (Henoch-Schönlein)
  - Hypocomplementemic Urticarial Vasculitis
    - (Anti-C1q Vasculitis)

- **Medium Vessel Vasculitis**
  - Polyarteritis Nodosa
  - Kawasaki Disease

- **Anti-GBM Disease**

- **ANCA-Associated Small Vessel Vasculitis**
  - Microscopic Polyangiitis
  - Granulomatosis with Polyangiitis
    - (Wegener’s)
  - Eosinophilic Granulomatosis with Polyangiitis
    - (Churg-Strauss)

- **Large Vessel Vasculitis**
  - Takayasu Arteritis
  - Giant Cell Arteritis

Chapel Hill Consensus Conference 2013
Quick facts:

Demographics:
• Median age of onset in 3^{rd} decade of life
  • Rare to start in childhood or > 50 years old
• Males equally as effected as females
• More severe course in young males

Clinical course
• Course can have cycles of exacerbations and remissions
• For some, symptoms can disappear over time

Strongest Genetic Association
• HLA-B51
Limited information on etiopathogenesis

Genetic susceptibility

Behçets disease

- Innate immune system
  - Nonspecific self-tolerant inflammation

- Adaptive immune system
  - Self-reactive autoinflammation
    - Secretion of proinflammatory cytokines (IL1, IL8, TNF-α)
      - Activation of self-destructive T cells
      - Production of anti-endothelial cell autoantibodies
        - Vasculitis-induced tissue damage
          - Reduced expression of CTLA-4, CD86, PD-L1

Environmental factors

- Herpes simplex virus
- Streptococcus sanguis
- Pollutants

HLA-B*51

IL10

IL23R-IL12B2

Manifestations

- Mucocutaneous (Skin, oral, genital)
- Eye
- Musculoskeletal (muscles/joints)
- Vascular/Cardiac
- Central Nervous System
- Gastrointestinal
- Other, less common
Mucocutaneous: Oral sores

- Most commonly minor aphthous ulcers
  - < 10mm
  - 85%
- Typically multiple at a time
- Painful
- Indistinguishable from other causes
Oral ulcers: Other causes

Important things to think about:
• Herpes simplex virus
• Vitamin deficiencies (e.g. Zinc and Vitamin C)
• Iron, B12, folate deficiencies
• Systemic Lupus Erythematosus
• ANCA associated vasculitis
• Inflammatory bowel disease (i.e. Crohn’s and Ulcerative Colitis)
• Celiac disease
• HIV
• Stress/diet induced
Mucocutaneous: Genital ulcers

Males
• Typically on scrotum
• Less commonly on other sites
• Not the urethra

Females
• Major or minor labia

Most commonly heal in about 2-4 weeks
Large ulcers may scar
Mucocutaneous: Skin

- 80% of patients
- Acne-like lesions
  - Face, upper chest, upper back, legs, arms
- Papulopustular lesions
- Erythema nodosum (left picture)
- Superficial Thrombophlebitis (right picture)
- Usually subsides in 2-6 weeks
- Hyperpigmentation possible
- Ulceration possible

https://www.mayoclinic.org/diseases-conditions/thrombophlebitis/symptoms-causes/syc-20354607

Mucocutaneous: Pathergy (Test)

Occurrence of a small red bump or pustule at the site of needle insertion, 1 to 2 days after the test, constitutes a positive test.

The pathergy test is helpful in diagnosing Behçet’s Disease. It is a simple test in which the forearm is pricked with a small, sterile needle.


Eye Involvement

- 50% of patients
- More frequent/severe in males and younger patients
- Usually w/n 3 years of disease onset
- Vision threatening
- Uveitis (inflammation within eyes)
- Retinal occlusive vasculitis
- Conjunctivitis (rare)
- Concerning symptoms:
  - Redness, pain, light sensitivity, blurred vision, dark floating spots in vision
Musculoskeletal

- 50% of patients
- Generally effects only 1 or few joints at a time
- Not deforming
- Most frequent joints include:
  - Knees
  - Ankles
  - Wrists
  - Elbows
- Enthesitis (inflammation at the attachment of tendon to bone)
- Association with acne lesions
Vascular/Cardiac Involvement

• Veins or arteries
• Various size blood vessels
• More common in males
Venous (Vein) Involvement

- 33% develop thrombo-phlebitis (clot-inflammation of veins) of either superficial (near skin) or deep (larger veins)

- Deep vein thrombosis (DVT):
  - Different from regular DVTs:
    - Lower risk of thromboembolism (traveling to other organs such as lungs)
    - Adheres to vein wall
    - Requires immunosuppression

- Budd-Chiari Syndrome
  - Involvement of veins around liver (supra-hepatic veins)
Artery Involvement

- Less than 5%
- Pulmonary artery aneurysm **
  - Can have hemoptysis – coughing blood
  - 3cm or larger life threatening
  - CT or MRI can confirm
- Other areas of aneurysm/occlusion
  - Abdominal aorta
  - Carotid arteries
  - Femoral arteries
  - Popliteal arteries
  - (rarely) coronary arteries

Heart Involvement

- Valvular lesions
- Myocarditis (upper picture)
- Endomyocardial fibrosis – scarring on inner part of heart
- Pericarditis (lower picture)
- Intracardiac thrombosis – clot in heart
- Coronary vasculitis
- Ventricular aneurysms

http://www.secondscount.org/pediatric-center
https://medlineplus.gov
Central Nervous System Involvement

- 5-10% of individuals
- Parenchymal brain involvement (80%)
  - Brain itself
- Nonparenchymal brain involvement (20%)
  - Vascular system of brain
  - Dural vein thrombosis
  - Intracranial hypertension
- Possible symptoms:
  - Cognitive changes, behavioral changes, headaches, vision changes, loss of control of bowel/bladder, sensory loss

https://www.osteopath-west.co.uk/what-is-central-sensitization/
https://www.sciencedirect.com/topics/neuroscience/great-cerebral-vein
Gastrointestinal Involvement

- Mucosal ulcerations
  - Common areas: Ileum, cecum, colon
- Difficult to distinguish from inflammatory bowel disease (i.e. Crohn’s and ulcerative colitis)
- Symptoms:
  - Anorexia, vomiting, abdominal pain, diarrhea, blood or dark tarry stools

Other features

• Glomerulonephritis (kidney) is uncommon
• Amyloidosis
  • Deposition of abnormal proteins in tissue
• Epididymitis
  • Inflammation around testis in males
Disease Clusters

• Deep vein thrombosis & Dural sinus thrombosis
• Acne & Arthritis & Enthesitis
• GI predominant disease

Could there be more then 1 disease mechanism?
Regional Difference

Gastrointestinal Manifestations
• More frequent in Far East
• Less frequent in Turkey

Pathergy
• More frequent in Turkey, Mediterranean, Japan
• Less frequent in Northern Europe and USA

HLA-B51 association
• Most pronounced in Middle and Far East
Treatment Principles

• In many patients, Behcet’s goes into remission with time

• In non-severe manifestations (e.g. mucocutaneous disease) treatment is conservative

• Consider topical therapies for oral and genital ulcers

• Aggressive treatment of eye disease and organ threatening manifestations
  • Currently only 10-15% vision loss with eye involvement compared to around 75% 20-30 years ago

• Males and younger patients are more likely to have more severe disease

• Unfortunately, there are limited studies
Treatments: Colchicine

In trials, shown to be effective:
  • Females: genital ulcers, erythema nodosum and arthritis
  • Males: arthritis only

Tablet generally taking 1-2 times daily

Caution in those with kidney or liver problems

Possible side effects:
  • Diarrhea and other GI symptoms
  • Neuropathy
  • Low blood counts

Treatments: Dapsone

- In trials, shown to be effective:
  - Oral/genital ulcers, skin involvement
- Oral
- Consider screening for glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Monitor for anemia and liver function tests
- Avoid if Sulfa allergic

Possible side effects:
- Anemia
- Low white blood cell count
- Skin reactions (occasionally severe)
- Liver
- Peripheral neuropathy
Treatments: Azathioprine

- In trials, shown to be effective:
  - Eye disease (RCT), oral/genital ulcers, arthritis, DVT prevention
- Weight based dosing
- Use for at least 3 months
- Caution with liver issues
- Dose adjustment with kidney disfunction
- TPMT testing (blood test)
  - Risk of side effects

Possible side effects:
- GI symptoms (nausea)
- Infections
- Low blood counts
- Liver
- Malignancy (lymphoma)
- Progressive multifocal leukoencephalopathy (PML)
  - Rare
  - Severe
  - Reactivation of brain virus (JC)

Treatments: TNF inhibitors

- In trials, shown to be effective:
  - Oral ulcers, nodular skin lesions, papulopustular skin lesions (Etanercept)
- Subcutaneous or intravenous
- Used frequently in other autoimmune diseases
- Etanercept, Infliximab, Adalimumab
- TB and viral hepatitis panel generally recommended prior

Possible side effects:
- Infections
- Injection/infusions reactions
- Reactivation of tuberculosis
- Lupus-like reactions

Caution:
- History of congestive heart failure
- History of multiple sclerosis
Treatments: Methylprednisolone

• In trials, shown to be effective:
  • Erythema Nodosum
• Subcutaneous
• Steroid (similar to prednisone)
• Short term use
  • Long term use associated with multiple possible side effects

Possible side effects:
• Mood changes
• Insomnia
• Osteoporosis
• Infections
• Cataracts/glaucoma
• Hypertension
• Diabetes
• Weight gain
• Easy bruising
• Other
Treatments: Cyclosporine

- In trials, shown to be effective:
  - Eye and mucocutaneous lesions
- Oral
- Quick acting
- Caution in kidney and liver dysfunction

Possible side effects:
- Gingival hyperplasia
- Infections
- Liver
- Increase potassium
- Hypertension*
- Increased uric acid
- Malignancy (skin)
- Kidney dysfunction*
- Neurotoxicity*
- Thrombotic microangiopathy

*close monitoring required
Treatments: Thalidomide

- In trials, shown to be effective:
  - Treatment resistant oral/genital ulcers, papulopustular skin lesions
- Recurrence usual when withdrawn
- Oral
- Due to side effects, short duration use
- High pregnancy risk

Possible side effects:
- Bone marrow suppression
- Low heart rate
- CNS effects
- Skin reactions (e.g. Steven Johnson’s syndrome)
- Hypersensitivity reactions
- Orthostatic hypotension
- Constipation
- Hepatotoxicity
- Neuropathy
- Malignancy
- Seizure
- Thrombosis
Treatments: Interferon-α-2a

- In trials, shown to be effective:
  - Reducing frequency of oral ulcers, genital ulcers, papulopustular lesions
- Expert opinion:
  - Effective in ocular disease
- Subcutaneous
- Frequent side effects
- Not well tolerated

Possible side effects:
- Flu-like symptoms
- Fevers
- Joint pains
- Injection site reactions
- Low white blood cells
- Hair loss
- Depression
Treatments: Cyclophosphamide

• No large trials
  • Effective in severe forms of vasculitis
• Used in organ/life threatening disease
• Oral or intravenous
• Close monitoring of blood counts
• Short term use recommended

Possible side effects:
• Infections
• Bone marrow suppression
• Cardiotoxicity
• Infertility
• GI
• Hepatotoxicity
• Pulmonary toxicity
• Impaired wound healing
• Hemorrhagic cystitis
• Malignancies (e.g. bladder cancer)
  • Risk based on lifetime dose
Apremilast: Phase II study


No. at Risk
- Placebo: 56, 56, 53, 51, 44, 42, 45, 45, 36, 34, 45, 38, 38, 54
- Apremilast, 30 mg: 55, 55, 50, 53, 48, 47, 50, 49, 41, 49, 38, 37, 47, 40, 54

Mean No. of Oral Ulcers
- Placebo: 2.9, 1.7, 1.9, 1.9, 1.6, 1.4, 2.1, 0.4, 0.4, 0.6, 0.6, 0.5, 0.3, 0.4, 1.3, 1.6
- Apremilast, 30 mg: 2.7, 0.3, 0.7, 0.5, 0.5, 0.7, 0.5, 0.6, 0.6, 0.6, 0.7, 0.2, 0.6, 1.9, 1.7

Placebo crossover to apremilast
Apremilast discontinuation

Week of Visit
Treatments: Apremilast

- Phase III study ongoing
- Best evidence in oral lesions
- Oral
- Does not suppress immune system (i.e. does not increase risk of infection)

Possible side effects:
- Gastrointestinal (e.g. nausea, diarrhea)
- Mood (e.g. depression)
- Weight loss
Behcet’s: The Future

Needs:
• More randomized treatment studies
• Clarification: One disease or multiple diseases?
  • Wide regional and sex differences
• Better tests for diagnosis

Apremilast phase III preliminary results encouraging
• Possible FDA approval (¿This month)
Summary

• Highest prevalence in Mediterranean and Far East
• Mucocutaneous symptoms are the most common manifestations
• Topical therapies can be effective for oral and genital lesions
• Eye disease is one of the most serious manifestations, requiring treatment
• Deep vein thrombosis requires immunosuppressive treatments
• Apremilast phase III studies ongoing