Immunosuppressive therapy and sarcoidosis

The good, the bad, and the granulomas

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Greetings from the Humidity Belt
General Overview

- Who gets treatment
- Current therapies
- The down side of treatments
- The organ involvement approach
- New directions in immunosuppressive treatment
- Questions and answers
The patient and Doctor experience

It’s a Fan!

It’s a Wall!

It’s a Spear!

It’s a Snake!

It’s a Tree!

It’s a Rope!
Watching and waiting

- Many patients with limited disease and no evidence at diagnosis of organ invasion can be followed with supportive therapy.
- As many as 60-80% patients will have remission of symptoms with supportive care.
- Decision to start immunosuppressive therapy should be based on presence of organ impairment, the degree of symptoms, and the organ location.
Problems with watching and waiting

- Not many reliable prediction criteria on who will progress to more active disease
- Mixed data on whether treatment early leads to remission vs. observation in patients with stage II or III sarcoidosis with limited symptoms
- Some symptoms may actually be made worse by treatment with immune suppressive medications
  - Steroids - depression, fatigue, sleep cycle
  - Methotrexate - fatigue, nausea, depression
**Generally accepted treatment**

- Decline in FVC <15% and or DLCO <20%
- Hypoxemia at time of diagnosis
- Central nervous system involvement
- Cardiac sarcoidosis
- Severe skin involvement (lupus pernio)
- Hypercalcemia
- Solid organ lesions with evidence of organ function impairment
- Spleen enlargement with severe pain
<table>
<thead>
<tr>
<th>What’s available for therapy now</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Antimalarials</td>
</tr>
<tr>
<td>Azathioprine</td>
</tr>
<tr>
<td>Cytotoxic agents (cytoxan)</td>
</tr>
<tr>
<td>Methotrexate</td>
</tr>
<tr>
<td>Other cell cycle inhibitors</td>
</tr>
<tr>
<td>Anti-inflammatory therapy</td>
</tr>
<tr>
<td>Thalidomide</td>
</tr>
<tr>
<td>anti-TNF alpha therapies</td>
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</tbody>
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# Patient experiences in primary care

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*NOTE: The table represents a placeholder for specific patient experiences related to corticosteroids in primary care.*
If all you have is a hammer...
Steroids: What they do

Non Genomic Effects

Genomic effects

- Inhibition of Inflammatory cells
- Downregulation of Cytokines
- Gluconeogenesis
- Fluid retention
- Lymphoid cell Death
Steroids: What they also do

Non Genomic Effects

Genomic effects

Central Obesity
Diabetes
Skin Thinning
Cataracts
Osteoporosis
Corticosteroids: What we know

- Cochrane review of studies of oral steroids in pulmonary sarcoidosis (13 studies)
  - Improved Chest radiographs
  - Improved symptoms
  - Improved functional status
  - No change in lung function
  - No definite disease modification
- Severe CNS, cardiac, solid organ impairment, hypercalcemia still first line of treatment
Corticosteroids: What’s still debated

- Corticosteroids-suppress the inflammatory granulomatous reaction that leads to fibrosis and organ dysfunction vs.
- Corticosteroids-prolong an ineffective inflammatory response and prolong sarcoidosis activity (worse than watching and supportive care)
- More recent studies for pulmonary sarcoidosis suggest lower starting doses of corticosteroids effective with less long term sequelae
Antimalarials

- Chloroquine and Hydroxychloroquine (slightly weaker)
- Extremely lipophilic and have a presumed wide volume of distribution
- Most commonly used for cutaneous sarcoidosis patients
- Chloroquine studied in small trial of pulmonary sarcoidosis with favorable results
- Work well together with other immune suppressive therapies
- Retinal toxicity monitoring required
Antimalarials: what they do

- Allan Genome Biology 2000

APC Dendritic Cells

Allan, Genome Biology 2000
Methotrexate Therapy

- Most widely used steroid sparing agent in sarcoidosis (slow onset of action)
- Delivered orally or subcutaneously
- Usually taken weekly by patients (Lousy Monday syndrome)
- Reported improvement in
  - Pulmonary
  - Cutaneous
  - Hepatic
  - Ocular
  - Cardiac
  - Neurologic
How it works

Adenosine

Increased Polyglutamates

Adenosine

Close monitoring of Liver Function tests during initial therapy

For patients with enteral absorption problems Subcutaneous Drug More effective
Azathioprine and Mycophenolate

- Both now commonly used in sarcoid patients as steroid sparing agents
- Little clinical trial data on either
- Both function as purine synthesis inhibitors
  - Probably modulate the immune system through metabolic impairment of leukocytes
- Liver function tests and WBC counts required
  - Not reported with liver fibrosis
Cyclophosphamide Therapy

- Used with some experience in severe neurosarcoidosis
- Extremely potent immune suppressing agent
- Alkylating agent cross links DNA-RNA and inhibits protein synthesis
- Monitoring for significant side effects
  - Hemorrhagic cystitis
  - Opportunistic infections
  - Increased risk of bladder cancers
Minocycline

- Tetracycline based antibiotic which inhibits protein synthesis
- Most literature for cutaneous sarcoidosis use
- Has both antimicrobial effects and anti-inflammatory
  - In vitro inhibits granuloma formation of irritated macrophages
- Raises the question of whether cell wall deficient bacteria are related to sarcoidosis
- Total body of literature is mixed and trials are scant on evidence, side effects are low
Anti TNF alpha therapies

- **Infliximab (remicaid)**
  - Monoclonal antibody against TNF α
  - Clinical trials on pulmonary function mixed
  - Shown to be useful in refractory neurosarcoidosis, ocular, cardiac, cutaneous
  - Increased risk of tuberculosis and fungal infection rates
  - Host antibodies to infliximab can blunt effectiveness
Anti TNF alpha therapies

- Adalimumab (Humira) and Golimumab (Simponi)
  - Humanized complete monoclonal antibodies
  - Subcutaneous delivery
  - Lower rates of autoantibodies in host
  - Usually given with another agent

- Ustekinumab (Stelara)
  - Monoclonal antibody that binds IL-12 and IL-23
  - Currently approved for psoriasis
  - Part of recently completed trial
The down side of treatments

- Opportunistic infections
  - Corticosteroids-increased risk of common infections
    - UTI’s
    - Cutaneous fungal infections
    - Thrush
  - Combination steroid and DMARDs likely related to increased infections
  - Pneumocystis infections seen with higher doses of prednisone in RA patients
  - What dose requires prophylaxis (?)
The down side of treatments

- Opportunistic infections
  - DMARDs alone?
    - Most literature from rheumatoid arthritis and IBD
    - Methotrexate and Imuran both low risk of opportunistic infections without steroids
  - Anti-TNFα therapies classically associated with increased risk of fungal and mycobacterial infections
  - Increased risk of Pneumocystis infections when TNF inhibitors used with DMARDs.
The down side of treatments

- Sequela of long term therapies
  - Steroids associated with a multitude
    - Osteoporosis
    - Cataracts/Glaucoma
    - Mood disorders
    - Central obesity
    - Acquired diabetes
  - DMARDs
    - Hepatic toxicity
    - Cirrhosis
    - Symptomatic anemia
The down side of treatments

- Concomitant symptom exacerbations
  - Depression and fatigue often made worse with corticosteroids
  - Quality of life scores lower in sarcoid patients after steroid therapy
  - Chronic pain from small fiber neuropathy often does not respond to immune suppressive therapy
- TNF alpha inhibitors have been reported to cause diffuse granulomatous reactions in lung
The organ involvement approach
The organ involvement approach

- Comprehensive investigation into organs involved and degree of impairment
  - Pulmonary function testing
  - Exercise oximetry
  - Imaging
  - Laboratory evaluation for organ dysfunction
- Screening for chronic infectious diseases
  - Viral hepatitis screening
  - Tuberculosis skin testing and quantiferon assay
  - Sexual history
The Organ Involvement Approach

- How many organs are affected by sarcoidosis
  - Direct involvement (CNS lesions)
  - Indirect involvement (Obstructing kidney stones)
- Which drugs penetrate the organs involved
- Which organs are impaired that will metabolize immune suppressive drugs
- What am I likely to make worse in a specific patient with treatments
Many immune suppressive agents used for sarcoidosis complement each other
- Different mechanisms of action
- Lower doses of each by utilizing two agents synchronously
- Different penetration of organs among different agents used in sarcoidosis
- Different onsets of action
  - Rapid nongenomic effects of steroids
  - Slower onset of action of antimetabolites
38 year old male with mild hypertension, night sweats, raised skin lesions on his face and back, recurrent kidney stones and hypercalcemia.

Chest radiograph with hilar lymphadenopathy and upper lobe reticular infiltrates

NKDA

Main complaints are severe joint stiffness, raised disfiguring skin lesions, and several ER visits for kidney stones in the past 24 months.
Tandem Therapy

Corticosteroids
- Rapid onset of action
- Usually effective for joint pain symptoms
- Highly effective for lowering calcium
- Activity for skin lesions

Hydroxychloroquine
- Slower onset of action
- Effective for skin lesions and joint pain symptoms
- Prevents insulin degradation in the liver and suppresses gluconeogenesis
- Increases peripheral utilization of glucose
- Can lower initial starting dose of prednisone required to treat several features of sarcoidosis
Tandem Therapy (other examples)

- Methotrexate and Humira used together
  - Reduces development of host antibodies to humira and prolongs efficacy
  - Both effective for skin lesions
  - Both used for neurosarcoidosis

- Prednisone and mycophenolate
  - Both effective for hepatosplenic sarcoidosis
  - Neither causes hepatic fibrosis
  - Doses of both can be lower
Comorbid disorders

- General assessment of depression/anxiety
  - Significant correlation between lung function and depression scales
  - Immunosuppression more likely to be successful when depression/anxiety treated simultaneously
  - Specific psychiatric disorders associated with steroid therapy exacerbations
    - Bipolar disorder
    - Schizophrenia
Comorbid disorders

- General assessment of chronic fatigue and pain
  - Newer studies that demonstrated treatment of chronic fatigue with stimulants improved quality of life
  - Chronic pain issues related to small fiber neuropathy/myopathy often not improved with immune suppressive therapies
  - Multidisciplinary treatment with immune suppressive therapy and pain management
New directions in therapy

- Stem cell Immunosuppression Techniques
- Randomized trials of Current immunosuppressive agents not previously investigated in sarcoidosis
  - Rapamune and placebo in sarcoidosis (effect unknown)
  - Rituximab and placebo in sarcoidosis (effect unknown)
  - Anakinra and placebo in sarcoidosis (effect unknown)
New directions in therapy

- NOD like receptors and increased innate immunity
  - NOD receptors family of proteins in cells which detect fragments of bacteria in the host and activate immunity
  - NOD gene mutations shared in both Crohn’s disease and familial forms of sarcoidosis
  - NOD gene mutations lead to prolonged immune response after exposure to bacterial fragments
New Directions in therapy

New Inhibitors of NOD 2

- Improved understanding of
  - Relationships between bacterial fragments and development of sarcoidosis
  - Revisiting the roles of antimicrobials and their anti-inflammatory effects in treatment of sarcoidosis
    - Minocycline
    - Anti mycobacterial drugs

Questions and Answers?

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