New Orleans Saints
2010 Superbowl Champions
FLUTICASONE, AZITHROMYCIN, AND MONTELUKAST THERAPY IN REDUCING STEROID EXPOSURE IN BRONCHIOLITIS OBLITERANS SYNDROME AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT
Bronchiolitis obliterans syndrome

- New fixed airflow obstruction developing 1-2 years after transplant
- Presents with nonspecific respiratory symptoms
- Develops in the presence of active chronic GVHD
- 5-year posttransplant survival of BOS patients: 10%

H&E stain

Trichrom stain
Bronchiolitis Obliterans Syndrome

“Chronic scarring process affecting the small airways of the lung which results in progressive obliteration of the small airways with resultant obstructive lung disease.”

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Proliferative bronchiolitis

- BOOP
- COP
- Alveolar lining damage
- Epithelial necrosis
- Inflammatory infiltrate
- Peribronchiolar interstitial inflammation
- Concentric peribronchiolar fibrosis
- Cicatrization

Constrictive bronchiolitis

- BO
- BOS
- OB

Migrating fibroblasts
Matrix proteins and organization
Mucous plug
Findings on HRCT: air trapping, bronchial wall thickening, bronchiectasis, and bronchial dilations
Onset of airflow obstruction is likely well before clinical symptoms
BOS Risk Factors – Univariate Analysis

- Recent study by our lab:
  - All 63 (100%) BOS cases had cGVHD
  - HR 10.3 (95% CI (3.24,33.06))
  - On multivariate analysis, only cGVHD was statistically significant.
  - Very low IgG levels (<363) were approaching significance.

- Prior studies have shown that sex matching (M:F, F:M), stem cell source (peripheral vs. marrow), and conditioning regimen (myeloablative vs. non-myeloablative) were associated with increased risk of BOS after transplantation.3-6

<table>
<thead>
<tr>
<th>Variable</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Age at transplant</td>
<td>0.104</td>
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<tr>
<td>Gender match</td>
<td>0.238</td>
</tr>
<tr>
<td>Race</td>
<td>0.141</td>
</tr>
<tr>
<td>Disease risk</td>
<td>0.618</td>
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<tr>
<td>Source of stem cells</td>
<td>0.096</td>
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<tr>
<td>HLA match</td>
<td>0.970</td>
</tr>
<tr>
<td>CMV serostatus</td>
<td>0.404</td>
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<tr>
<td>Conditioning regimen</td>
<td>0.393</td>
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<tr>
<td>Busulfan based regimen</td>
<td>0.979</td>
</tr>
<tr>
<td>Methotrexate use</td>
<td>0.407</td>
</tr>
<tr>
<td>Baseline FEV1</td>
<td>0.035</td>
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<tr>
<td>Baseline FEV1/SVC ratio</td>
<td>0.001</td>
</tr>
<tr>
<td>IgG level</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking history</td>
<td>0.495</td>
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<tr>
<td>Acute GVHD</td>
<td>0.324</td>
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<tr>
<td>Chronic GVHD</td>
<td>&lt;0.001</td>
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BOS prevalence based upon modified NIH Consensus Guidelines

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Pre NIH Consensus</th>
<th>Post NIH Consensus</th>
</tr>
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<tbody>
<tr>
<td>All patients</td>
<td>2-3%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Patients with cGVHD</td>
<td>6%</td>
<td>14%</td>
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- Median time to meeting NIH spirometric criteria from transplant: 440 days (range 274-1690)
- 70% occurred within the first 2 years
- 30% developed between 2-4 years after HCT
Implications of BOS

- **Mortality**
  - Studies have shown that mortality rates after diagnosis of BOS are 9%, 12%, and 18% at three-, five-, and ten-years after transplantation, respectively.\(^7\)
  - Also, the presence of early airflow decline independently increased the risk of mortality 2.3-fold following transplant.\(^7\)

- Significant morbidity and effect on quality of life.

- Treatment of BOS also associated with significant morbidity
Conventional Treatment of BOS

- Cornerstone of treatment is high dose, 1mg/kg/day Prednisone therapy that is then tapered over a long period of time, typically 12-18 months.
  - FHCRC taper: 1mg/kg/day prednisone for a period of two weeks, followed by a 25% per week taper to 1mg/kg/qod dose that is maintained for a period of 3 months. If tolerated, a 10-20%/month taper is then initiated.
  - Typical six month Prednisone dosing is 5000-7000mg
Conventional Treatment of BOS

- Non-Corticosteroid Immunosuppression is commonly used, but not in an organized fashion.
  - Tacrolimus
  - Sirolimus
  - MMF
  - CSA
  - Azithromycin
  - Montelukast
  - Inhaled Corticosteroids
  - Extracorporeal Photophoresis

- High dose corticosteroids carry high morbidity.
Corticosteroid Morbidity

- Corticosteroid related morbidity is a function of both cumulative dose and average daily dosing.⁸
- Three of the most common complications of glucorticoid therapy are decreased bone mineral density and fracture, opportunistic infection, and glucose intolerance.
  - A meta-analysis showed increase in cumulative prednisone dose from 1.5g to 13.9g, there was a decrease in Z-score from -0.5% in the spine to -4.7% and from -0.7% to -6.1% in the hip. In addition, with the same change in cumulative dose, relative risk of fracture doubled in both the hip and spine.⁹
  - When the dose of daily prednisone was increased from 20mg/day to 40mg/day, there was an OR of 2.1 of developing a serious infection.¹⁰
  - One study has shown that 47% of HCT patients with GVHD are treated with prednisone for >12 months and, of those, 68% developed hypertension and 30% developed diabetes mellitus. Prednisone exposure over this time frame of > 0.25mg/kg/day was associated with a RR of 4.1 of developing persistent diabetes mellitus at 2 years post transplant.¹¹
Given the implications of high dose steroids, it is important to find alternate or adjunctive therapies for treatment.

Recent reports in both the stem cell and lung transplant literature suggest that inhaled corticosteroids, macrolides and leukotriene inhibitors may have anti-inflammatory and antifibrotic effects that might be beneficial in the treatment of BOS.
Study Design and Hypothesis

- Interim analysis and case series with comparison to retrospective group of standard patients identified from a pre-existing database.
- **FAM therapy will reduce prednisone exposure in BOS patients over a 6 month period without decrement in FEV$_1$ or increase in rates of treatment failure.**
FAM Rationale

- **Fluticasone:**
  - There have been studies in transplant and HCT patients with BOS in which inhaled CS have stabilized or improved FEV\(_1\) and improved clinical symptoms.\(^{11,12}\)
  - Inhaled Corticosteroids have 1/10\(^{\text{th}}\) the effect on AM cortisol than that of oral prednisilone (Lipworth 1999).

- **Azithromycin:**
  - Several studies have found that azithromycin use is associated with an improvement in FEV\(_1\) with either reversal of AFO in or a slower progression of established BOS after lung transplantation\(^{13-15}\) and suggest that azithromycin has anti-inflammatory activity that may stop the progression of BOS after HCT.

- **Montelukast:**
  - Leukotrienes have been implicated in immune mediated bronchiolitis in animal and human models\(^{16}\) and have also been implicated as a factor in lung fibrosis\(^{17}\). A small pilot study showed benefit of montelukast therapy in cGVHD patients with low side effect profile\(^{18}\).
Methods

- Nine patients evaluated between June 2008 and November 2009 at the Fred Hutchinson Cancer Research Center (FHCRC)/Seattle Cancer Care Alliance (SCCA)

- “FAM” therapy was Fluticasone INH 440mcg twice daily, Azithromycin 250mg orally every Monday, Wednesday, and Friday, and Montelukast 10mg orally every day.

- FAM patients had their prednisone dose increased to 1mg/kg/day for the first 2 weeks, followed by a 2 week taper to 0.25 mg/kg/day equivalence by 4 weeks, then guided by manifestations of chronic GVHD.

- Comparison patients had their prednisone taper guided by a local chronic GVHD taper schedule, such as the FHCRC taper schedule.
Methods (Cont)

- Data obtained by chart review of FHCRC and UWMC medical record.
- Six month cumulative prednisone and average daily prednisone dose were calculated.
- FEV₁ values were recorded at 3 and/or 6 month post diagnosis (+/- 1 month).
- FEV₁ change was calculated by subtracting FEV₁ at diagnosis from the FEV₁ at 6 months or 3 months.
- Treatment failure was defined as a decrease in FEV₁ of > 10% during the six month period of follow-up and worsening of clinical symptoms.
Statistical Analysis

- Median 6 month prednisone, Median mg/day prednisone, FEV$_1$ change, and incidence of treatment failure were compared, with P-values generated for each.

- Two sided p values <0.05 were considered statistically significant. All categorical variables were compared using $\chi^2$ analysis and continuous variables were compared using Student’s T-test.

- FAM and comparison group were compared based on 10 clinical variables to ensure the two populations were similar.
A total of 9 patients received FAM therapy. One patient was lost to follow-up.

Except for donor type ($p=0.006$), there was no significant difference in the distribution of patient age ($p=0.143$), sex match ($0.278$), race ($p=0.798$), disease risk ($p=0.533$), stem cell source, CMV serostatus ($p=0.529$), conditioning regimen ($p=0.181$) and GVHD score ($p=0.226$), and lung score ($p=0.139$) between the two groups.

Note that lung score encorporates pre-transplant FEV$_1$. 
Results

Cumulative Six Month Steroid Dose

- FAM Patients
- Control Patients

mg Prednisone

Patients
Results

Median mg/day Steroid Dose

- **FAM Patients**
- **Control Patients**
## Results

<table>
<thead>
<tr>
<th></th>
<th>FAM Group (interquartile range)</th>
<th>Comparison Group (interquartile range)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median 6-month cumulative prednisone exposure</td>
<td>1819mg (0-4036mg)</td>
<td>7163mg (6551-7829mg)</td>
<td>0.002</td>
</tr>
<tr>
<td>Median average mg/day</td>
<td>13mg/d (0-23mg/d)</td>
<td>40mg/d (36-46mg/d)</td>
<td>0.001</td>
</tr>
<tr>
<td>Median FEV1 change</td>
<td>2% (-4% to 5%)</td>
<td>1% (-4% to 5%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>1</td>
<td>1</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Study Flaws and Weaknesses

- Most glaring weakness is small sample size.
- Three FAM patients were not started on any steroids
  - No increase in treatment failure and all three had stable PFTs
- Lack of standardization of steroid tapering in comparison patients.
- Comparison patients variably on multiple non-corticosteroid immunosuppressive agents, including one or more of the study drugs.
- Given rarity of the condition and its high morbidity and mortality, formal RCTs are very difficult.
- Problems are being addressed by an ongoing multi-center trial.
Conclusions

- BOS is an under recognized complication of HSCT and carries high morbidity and mortality.
- Old estimates of incidence are probably far lower than actual incidence.
- New diagnostic criteria most likely diagnose the disease late in its course.
- New therapies are needed that can be initiated early and carry lower side effect profiles.
Conclusions

- Our data challenges two current clinical approaches to BOS:
  - First, it challenges the precept that high dose corticosteroids for prolonged periods are necessary for all BOS patients.
  - Second, it provides evidence suggesting that alternative less toxic therapies should be investigated for the management of BOS.
- While these data are not definitive, they suggest for the first time that there might be treatment alternatives for BOS that can help reduce the quantity of corticosteroids used in this setting while maintaining stable lung function.
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- Carina Moravec, R.N. - FHCRC
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Questions?