The Role of Inflammation and Its Treatment in Cystic Fibrosis

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Pro-inflammatory cytokines are one of the major causes of human morbidity and mortality

Overwhelming production of pro-inflammatory cytokines (interferon- (INF), tumour-necrosis factor (TNF), interleukin 1 (IL-1) and high-mobility group box 1 (HMGB1)) can be more dangerous than the original stimuli and cause the characteristic cardiovascular collapse and multiple organ failure associated with severe sepsis.

Anti-inflammatory strategies to control the production of these pro-inflammatory cytokines represent a therapeutic approach for infectious and inflammatory disorders.
Abnormal CFTR and the Pathophysiology of CF

Increased or dysregulated CFTR leads to:

- Decreased Cl⁻ conductance
- Increased amiloride-sensitive Na⁺ conductance
- Raised potential difference across the CF airway epithelium
- Defective transepithelial fluid transport in the CF airway

Boucher RC. *Eur Respir J.* 2004.
Role of Inflammation in the Pathophysiology of CF Lung Disease

Defective CFTR gene

Defective/deficient CFTR

Abnormal airway surface environment

Bronchial obstruction

Infection

Inflammation

Bronchiectasis
Mucus Impaction in CF

The Lung in Cystic Fibrosis

Courtesy of M. Konstan 2011.
Adverse effects of elastase on host defense mechanisms and inflammation. In the cystic fibrosis airway
Infection and Inflammation in BAL of Healthy-Appearing Infants with CF

Non-CF Control

Cystic Fibrosis

Courtesy of F. Accurso, J. Wagener.
Infection and Inflammation in BAL

1. NON-CF AIRWAY.
- Mucociliary clearance and cough
- Bacteria
- IL-10
- Antimicrobial substances
- Macrophage
- Neutrophil

2. CF AIRWAY.
- Increased bacterial colonisation of epithelia.
- Increased neutrophils and macrophages
- IL-10
- Proinflammatory Cytokines
CFTR and Innate Immune Response to *Pseudomonas*

- (a) Antimicrobial factors and NO
- (b) CFTR binding and internalization of Pa
- (c) Desquamation and (d) Removal by mucus clearance or (e) Apoptosis and ingestion by dendritic cell
- (f) Pro-inflammatory signals
- (g) PMN infiltration
- (h) Apoptosis and ingestion by dendritic cell
- (i) T-cell response

The Role of Neutrophils in CF Airway Disease

PMN

LTB₄, IL-8

PMN

↑ Mucus secretion

Elastin degradation

Elastase

CR1, C3bi cleavage

Failure of opsonophagocytosis (bacterial persistence)

IL-8

Epithelial

IgG cleavage

O₂⁻, H₂O₂

DNA

Plugging of airways

Structural damage

Bronchiectasis

Approaches to Decreasing Inflammation in the CF Lung

- **Inhibit pro-inflammatory signals**
  - Cytokine priming: TNF, IL-1
  - Chemoattractants: IL-8, LTB$_4$, C5a

- **Inhibit PMN response**
  - Activation
  - Adhesion: CD11b/CD18, ICAM-1

- **Neutralize PMN products**
  - Elastase and other proteases
  - Oxidants
  - DNA and actin
Drugs That Inhibit PMN Signaling or Response

- **Broad-based (multispecific) drugs**
  - Corticosteroids, NSAIDs

- **Specific drugs and biologic agents**
  - Inhibitors/antagonists of pro-inflammatory cytokines and eicosanoids
  - NF-κB and p38 MAPK inhibitors
  - Adhesion molecule inhibitors
  - IL-10

## Anti-inflammatory Properties of Corticosteroids

<table>
<thead>
<tr>
<th>Effect on gene targets</th>
<th>Physiological effects specific to CF</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ IL-1, TNF-α, GM-CSF</td>
<td>↓ Cytokine-mediated inflammation</td>
</tr>
<tr>
<td>↓ IL-3, IL-4, IL-5, IL-8</td>
<td></td>
</tr>
<tr>
<td>↓ Phospholipase A&lt;sub&gt;2&lt;/sub&gt;</td>
<td>↓ Prostaglandins</td>
</tr>
<tr>
<td>↓ Cyclooxygenase type 2</td>
<td>↓ Leukotrienes</td>
</tr>
<tr>
<td>↑ Lipocortin-1</td>
<td></td>
</tr>
<tr>
<td>↓ Adhesion molecules</td>
<td>Reduced infiltration of neutrophils</td>
</tr>
<tr>
<td>↑ Endonucleases</td>
<td>Induction of apoptosis in lymphocytes and eosinophils</td>
</tr>
</tbody>
</table>
NF-κB Plays a Pivotal Role in Inflammatory Response

Glucocorticoids Inhibit NF-κB
## Prednisone Trials in CF

<table>
<thead>
<tr>
<th>Authors</th>
<th>Auerbach</th>
<th>Eigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study duration, yr</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Number of subjects</td>
<td>45</td>
<td>285</td>
</tr>
<tr>
<td>Age of subjects, yr</td>
<td>1-12</td>
<td>6-14</td>
</tr>
<tr>
<td>Prednisone dose, mg/kg QOD</td>
<td>2</td>
<td>1 or 2</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary function ↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Growth ↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalizations ↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>None</td>
<td>Growth retardation, diabetes, and cataracts</td>
</tr>
</tbody>
</table>

Risk of Persistent Growth Retardation in Boys After Prednisone Therapy

**BOYS**
- Placebo (n = 35)
- Low-dose prednisone (n = 46)
- High-dose prednisone (n = 45)

**GIRLS**
- Placebo (n = 38)
- Low-dose prednisone (n = 29)
- High-dose prednisone (n = 31)

## Lung Function (FEV$_1$% Predicted) After Prednisone Therapy

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>1 mg/kg</th>
<th>2 mg/kg</th>
<th>$P$ value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End of study</strong></td>
<td>76</td>
<td>85</td>
<td>76</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>6-7 yrs later</strong></td>
<td>71</td>
<td>71</td>
<td>66</td>
<td>0.51</td>
</tr>
</tbody>
</table>

*Low-dose vs high-dose or placebo

Summary of Systemic Prednisone Therapy in CF

- Provides some benefits to lung function during treatment
- Benefits do not persist after discontinuation
- Severe adverse effects limit its use
- Adverse effects tend to be long-lasting
- The risks of systemic steroid therapy appear to outweigh the benefits for patients with CF
Use of Anti-inflammatory Therapies in CF Patients

Usage of routine therapies (%)

Year

Inhaled corticosteroids
Mast-cell stabilizers
Oral corticosteroids
All NSAIDs
Ibuprofen

ESCFT Database. 2002.
Could Inhaled Corticosteroids Be a Good Alternative to Prednisone?

• Increase in ICS use (25% to 45%)
• Efficacy in slowing progression of lung disease not demonstrated
  – Several studies of short duration and small sample sizes
• Positive safety profile not established
• Further studies required to evaluate efficacy and safety

Rationale for Ibuprofen Use

• Inhibits activation, adhesion, chemotaxis, and degranulation of PMN
• Effective in an animal model of chronic *Pseudomonas* infection and inflammation
• Effective in a 4-year clinical trial in CF patients
• Safer than systemic corticosteroids
Ibuprofen Inhibits NF-κB
Clinical Trial of Ibuprofen

STUDY DESIGN:
- 4-year DB/PC
- N = 85, age 5 to 39 years
- Mild CF lung disease
- Ibuprofen 20 to 30 mg/kg BID

RESULTS:
- Delayed decline in lung function
- Delayed CXR deterioration
- Preserved IBW
- Reduced hospitalizations
- Reduced use of other medications

Slowing Decline in Lung Function May Improve Survival

Increase FEV$_1$ without change in rate of decline

CFF Patient Registry: Clinical Use of Ibuprofen

Registry period: 1996 to 2000  (avg N = 19,733)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Patients Using Ibuprofen (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>29</td>
</tr>
<tr>
<td>5-12</td>
<td>599</td>
</tr>
<tr>
<td>13-17</td>
<td>424</td>
</tr>
<tr>
<td>&gt;17</td>
<td>246</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FEV1 (% predicted)</th>
<th>Patients Using Ibuprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>80</td>
</tr>
<tr>
<td>40-60</td>
<td>132</td>
</tr>
<tr>
<td>&gt;60</td>
<td>871</td>
</tr>
</tbody>
</table>

Registry period: 1996 to 2000  (avg N = 19,733)

Potential Barriers to Ibuprofen Use

- Beneficial effect on lung function not fully accepted
- Concerns regarding safety
- Poor adherence may increase PMN migration
- Establishing individual dose through pharmacokinetic testing is logistically difficult
- No marketing by pharmaceutical industry

## Complications from Ibuprofen Therapy: All Patients

CFF patient registry: 1996 to 2000  (avg N = 19,733)

<table>
<thead>
<tr>
<th></th>
<th>IBU</th>
<th>Non-IBU</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcers</td>
<td>0.32%</td>
<td>0.22%</td>
<td>1.44 (0.86 to 2.44)</td>
</tr>
<tr>
<td>GI bleeds</td>
<td>0.49%</td>
<td>0.23%</td>
<td>2.12 (1.40 to 3.21)*</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0.06%</td>
<td>0.21%</td>
<td>0.30 (0.11 to 0.85)**</td>
</tr>
</tbody>
</table>

*P = 0.004; **P = 0.02 IBU vs non-IBU

### Complications from Ibuprofen Therapy: Pediatric Patients

CFF registry period: 1996 to 2000  
Age 5 to 12 yr; FEV$_1$ ≥60% predicted  (avg N = 4505)

<table>
<thead>
<tr>
<th></th>
<th>IBU</th>
<th>Non-IBU</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcers</td>
<td>0.18%</td>
<td>0.08%</td>
<td>2.42 (0.84 to 6.97)</td>
</tr>
<tr>
<td>GI bleeds</td>
<td>0.32%</td>
<td>0.10%</td>
<td>3.19 (1.30 to 7.85)*</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0.00%</td>
<td>0.01%</td>
<td>0.30 (0.11 to 0.85)</td>
</tr>
</tbody>
</table>

*P = 0.01 IBU vs non-IBU

The Trans-Canadian Ibuprofen Trial

- 2-year randomized, double-blind, placebo-controlled multicenter trial
- 145 CF patients: age 6-18 years, FEV$_1$ >60% predicted
- Ibuprofen 20-30 mg/kg BID vs placebo
- Primary outcome measure: annual rate of change in lung function (FEV$_1$ and FVC)

# The Trans-Canadian Ibuprofen Trial: Adverse Events

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patient</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>1</td>
<td>Abdominal cramps, nausea, diarrhea</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Conjunctivitis</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Nausea, dizziness, tinnitus</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Gastrointestinal bleeding</td>
</tr>
<tr>
<td>Placebo</td>
<td>1</td>
<td>Epigastric pain, nausea, diarrhea</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Reactive arthritis</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Abdominal pain (hepatitis)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Abdominal pain (reflux esophagitis)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Abdominal pain (gastritis)</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>High liver enzymes</td>
</tr>
</tbody>
</table>

Summary of Ibuprofen Therapy in CF

- Ibuprofen slows the decline in lung function
- Increase in risk for GI bleed (RR 2-3), but absolute risk is small
- Mechanism of anti-inflammatory effect needs to be elucidated—specific agents may offer better safety profile
- The benefits far outweigh the risks, especially for young, relatively well patients
Approaches to Neutralizing PMN Products

- Anti-elastases and other protease inhibitors
  - $\alpha_1$-PI, SLPI, N/MEI, EPI-HNE-4, elafin
- Antioxidants
  - $\beta$-carotene, $\alpha$-tocopherol, glutathione
- DNase, gelsolin

Bronchoalveolar Lavage in the Evaluation of Anti-inflammatory Treatment: The BEAT Study

N = 105
Mean age 11.8 yr
FEV₁ >80% predicted

N = 85; elevated baseline neutrophils
N = 20; normal baseline neutrophils
N = 46; rhDNase 2.5 mg QD
N = 39; no treatment
N = 20; control

3 years

- BAL performed at baseline, 18 months, and 36 months
- Outcome measures: neutrophils, IL-8, elastase, myeloperoxidase, FEV₁, FVC, FEF₂₅-₇₅

The BEAT Study: Effect of rhDNase on Inflammation

PMN %

- rhDNase-treated
- Untreated

IL-8

- rhDNase-treated
- Untreated

Elastase

- rhDNase-treated
- Untreated

The BEAT Study:
Effect of rhDNase on FEV₁ Decline

![Chart showing the effect of rhDNase on FEV₁ decline.
Controls: n = 20, rhDNase-treated: n = 46, Untreated: n = 39.](image)
Summary of rhDNase as an Anti-inflammatory Therapy

- rhDNase therapy stabilized the levels of inflammatory markers in patients with elevated baseline neutrophil counts
- rhDNase therapy prevented an increased rate of decline in lung function ($\text{FEV}_1$)
Approaches to Inhibiting PMN Signaling and Response

• Broad-based (multispecific) drugs
  – Corticosteroids, NSAIDs

• Specific drugs and biologic agents
  – Inhibitors/antagonists of pro-inflammatory cytokines and eicosanoids
  – NF-κB and p38 MAPK inhibitors
  – Adhesion molecule inhibitors
  – IL-10
Schematic of possible effects of drug candidates on sputum markers of inflammation and infection and associated clinical consequences.

<table>
<thead>
<tr>
<th>△ Infection (log₁₀ cfu)</th>
<th>Beneficial or harmful</th>
<th>Harmful</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 2</td>
<td>IV</td>
<td>III</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ 2</td>
<td>II</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>△ Inflammation – Elastase/IL-8 (log₁₀)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
</tr>
</tbody>
</table>

Scott D. Sagel; James F. Chmiel; Michael W. Konstan; Proc Am Thorac Soc 2007, 4, 406-41
Future Studies in Anti-inflammatory Therapies in CF Should Address:

• Mechanism of action
• Specific agents
• Local vs systemic therapy
• Optimal timing and patient selection
Благодарю за внимание