Management of Bronchial Asthma in Adults

...emerging role of anti-leukotriene

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Bronchial Asthma

Chronic persistent Airway inflammation

Structural change

Pro-inflammatory cells
- Eosinophils
- T lymphocytes
- Macrophages
- Mast cells

Pro-inflammatory mediators

Airway Hyperresponsiveness

Epithelial shedding
Smooth muscle hypertrophy/hyperplasia
Mucus metaplasia
Subepithelial fibrosis

Episodic Bronchospasm

Triggers
Acute and Chronic Persistent Airway Inflammation

Eosinophils: ECP, EDN, MBP

CD4+ T lymphocyte (Th2):
- IL-3, IL-4, IL-5, GM-CSF,
- IL-13

macrophages

CD8+ T lymphocyte

Sloughing epithelium

Endothelin-1 (bronchoconstrictor)

RANTES, GM-CSF, Ed

(chemotaxis)

Airway smooth muscle

GM-CSF, IL-8, RANTES,

Eotaxin

COX-2, NO, ROS
Neuropeptides released from sensory nerve endings (C-fiber)

- Toxic particles
- Noxious gas

Mucus plug

- Nerve activation

Epithelial shedding

- Subepithelial fibrosis

- Sensory nerve activation

- Cholinergic reflex

- Bronchoconstriction
  - Hypertrophy/hyperplasia

Mucus hypersecretion
- Hyperplasia

Vasodilatation
- New vessels

Plasma leak
- Oedema

Neuropeptides released from sensory nerve endings (C-fiber)
Airway Inflammation in Asthma

- IgE related immunological inflammation
  - *Antigen elicited mast cell activation* (early phase),
  - *Eosinophil, basophil, Th2 lymphocyte secreted cytokines*
    - mediated responses (late phase)
- Pro-inflammatory mediators released from structural cells
- Neurogenic inflammation: sensory C-fiber released neuropeptides (tachykinins)
- *Irritant induced non-immunological inflammation* (RADS)
Airway Inflammation Persists Despite Corticosteroid Use

In a clinical study of 74 patients

- Eosinophil × 10³/g sputum

ICS=inhaled corticosteroids; OCS ± ICS=received oral corticosteroids with or without ICS

Adapted from Louis R et al Am J Respir Crit Care Med 2000;161:9-16.

- ICS=mild to moderate (n=10)
- ICS=high-dose (n=15)
- OCS (n=10)
- OCS ± ICS (n=7)

Mild to moderate

Severe asthma

Residual airway inflammation (corticosteroid insensitive)
Airway Inflammation in Asthma

IgE mediated immunological inflammation
- Antigen elicited mast cell activation (early phase),
- Eosinophil, basophil, Th2 lymphocyte secreted cytokines mediated responses (late phase)

Neurogenic inflammation: sensory C-fiber released tachykinins

Irritant induced non-immunological inflammation

Pro-inflammatory mediators released from structural cells

Corticosteroid Sensitive

Corticosteroid Insensitive

Varies with individuals
ICS vs Airway Hyperresponsiveness

ICS fails to completely reverse airway hyperresponsiveness

1. Structural factors
2. Residual inflammation
3. Autonomic dysfunction

Kuo et al., Eur Respir J 1994
Structural change and Airway Hyper-responsiveness

Concerning about airway remodeling is increasing……..

- Airway smooth muscle Hypertrophy/hyperplasia
  - Enhanced contractility
  - Synthesis of Pro-inflammatory mediators
  - Enhanced Airway Hyper-responsiveness
  - Exaggerate Clinical responses
- Subepithelial fibrosis
  - Loss of compliance
Variation of Airway Structure

Collagen 1

Collagen 3

Similar severity of asthma
Different level of airway remodeling
Diversity of Asthma

• Variable in structural changes
• Variable in airway inflammation magnitude and composition
• Variable in the nature of triggers

Individualized treatment
Therapeutic Approach to Bronchial Asthma

- Anti-inflammatory agents
- Avoid or Treat concomitant diseases
- Bronchial protective agents (LABA)

- Steroid sensitive
  Steroid insensitive

- Allergic rhinitis/sinusitis
  GERD
  Aspirin sensitive asthma
  Virus infection etc.,

- Structural factors
  (airway remodeling)
Effect of Salmeterol on glucocorticoid receptors

- Fluticasone
- Salmeterol

β2 adrenoceptor

Glucocorticoid receptor

Synergistic Effect

Enhance anti-inflammation
Provide bronchodilator effect on airway hyperresponsiveness

GRE

Steroid-responsive gene

mRNA

protein

PKA

cyclic AMP

Modified from P J Barnes
Combination therapy is more effective than a higher dose of ICS

Most effective decreasing acute exacerbation stabiling clinical course

Severe                     moderate                 mild persistent         mild intermittent

Combination therapy

Systemic steroids

Inhaled steroids

Rescue bronchodilators

GLOBAL INITIATIVE FOR ASTHMA
Despite ICS or ICS plus LABA therapy, 74% of patients used rescue therapy each day (INSPIRE study)

SABA use (inhalations/day in the last week)

- None: 26%
- 1–2: 38%
- 3–4: 21%
- 5–8: 11%
- 9+: 5%

SABA = short-acting $\beta_2$-agonist
Base: all respondents (n=3,415)

Despite ICS or ICS plus LABA therapy, only 28% of patients were well controlled according to the Asthma Control Questionnaire (ACQ).

**ACQ-6 summary score**
- Well controlled: 0.0 to 0.74
- Not well controlled: 0.75 to 1.5
- Uncontrolled: >1.5

GINA 2006 guidelines

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Intermittent</th>
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<tbody>
<tr>
<td>None</td>
<td>Low-dose ICS (theophylline, leukotriene modifier, cromolyn)</td>
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<table>
<thead>
<tr>
<th>Step 2</th>
<th>Mild persistent</th>
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<tbody>
<tr>
<td>Low-dose ICS (theophylline, leukotriene modifier, cromolyn)</td>
<td>Low-to-medium-dose ICS + LABA (theophylline, leukotriene modifier, oral $\beta_2$-agonist)</td>
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<thead>
<tr>
<th>Step 3</th>
<th>Moderate persistent</th>
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<tbody>
<tr>
<td>Step 3</td>
<td>Low-to-medium-dose ICS + LABA (theophylline, leukotriene modifier, oral $\beta_2$-agonist)</td>
</tr>
<tr>
<td>Step 3</td>
<td>High-dose ICS + LABA plus if needed</td>
</tr>
<tr>
<td>Step 3</td>
<td>Anti-IgE</td>
</tr>
<tr>
<td>Step 3</td>
<td>Leukotriene modifier</td>
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<tr>
<td>Step 3</td>
<td>Oral $\beta_2$-agonist</td>
</tr>
<tr>
<td>Step 3</td>
<td>Oral corticosteroid</td>
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<tr>
<td>Step 3</td>
<td>Theophylline-SR</td>
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<tr>
<th>Step 4</th>
<th>Severe persistent</th>
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<tr>
<td>Step 4</td>
<td>Outcome: Asthma Control</td>
</tr>
<tr>
<td>Step 4</td>
<td>Outcomes: best possible results</td>
</tr>
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</table>

ICS = inhaled corticosteroid; LABA = long-acting $\beta_2$-agonist

Leukotriene modifier
Effective in some patients
Decrease dosage of ICS

Adapted from GINA Workshop Report 2006
CASIOPEA Study
Montelukast + Budesonide

Significantly Reduced Asthma-Exacerbation Days

Median percentage of asthma-exacerbation days

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median Percentage of Asthma-Exacerbation Days</th>
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<tr>
<td>Budesonide + placebo (n=308)</td>
<td>35%</td>
</tr>
<tr>
<td>Montelukast + budesonide (n=317)</td>
<td>35%</td>
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</table>

Adapted from Vaquerizo MJ et al Thorax 2003;58:204-211.
CASIOPEA Study
Montelukast + Budesonide

Significantly Increased Asthma-Free Days

Median percentage of asthma-free days

- **Budesonide + placebo** (n=308) - 42.3%
- **Montelukast + budesonide** (n=317) - 66.1%

56% increase, p=0.001

Adapted from Vaquerizo MJ et al Thorax 2003;58:204-211.
The percentage of patients who awoke during the night because of asthma

Adapted from Vaquerizo MJ et al *Thorax* 2003;58:204-211.

**CASIOPEA Study**
**Montelukast + Budesonide**

Significantly Reduced Nocturnal Awakenings

Least square mean % of patients with nocturnal awakenings*

20% p=0.01

Budesonide + placebo
(n=308)

Montelukast + budesonide
(n=317)

*The percentage of patients who awoke during the night because of asthma
Adapted from Vaquerizo MJ et al *Thorax* 2003;58:204-211.
CASIOPEA Study
Montelukast + Budesonide

Significantly Reduced Beta$_2$-Agonist Use*

% change from baseline in beta$_2$-agonist use

A more rapid onset of action than budesonide + placebo

First 7 days in active treatment

* $p = 0.05$ vs. budesonide alone
Adapted from Vaquerizo MJ et al Thorax 2003;58:204-211.
Central Role of CysLTs in Asthma

- Increased Mucus Secretion
- Edema
- Blood Vessel
- Inflammatory Cells (mast cells, eosinophils)
- Airway Smooth Muscle
- Sensory Nerves (C fibers)
- Eosinophil Influx
- Contraction and Proliferation
- Cationic Protein Release, Epithelial-Cell Damage
- Decreased Mucus Transport

Stable Acute exacerbation

Pro-inflammatory cells

Am J Respir Cell Mol Biol 2005, 531-
Residual Airway Inflammation

*(Steroid insensitive)*

Cells:
- Neutrophil
- Cytotoxic T cells (CD8, Tc2 cells)
- Structural cells

Pro-Inflammatory mediators:
- Leukotrienes
- Neuropeptides
- Growth factors
- Reactive oxygen species
Effect of Inhaled Fluticasone Propionate on Urinary LTE$_4$ Excretion

Urinary LTE$_4$ excretion (ng/mmol creatinine)

- Fluticasone propionate: 18.7
- Placebo: 18.4

$p = \text{NS between groups}$

Effect of Oral Prednisone on Urinary LTE₄ Excretion

*Urinary LTE₄ (ng/mg creatinine)*

- **Baseline**
  - Control
  - Prednisone

- **Post-allergen challenge**
  - Control
  - Prednisone

*p<0.05 vs. baseline

Adapted from Dworski R et al Am J Respir Crit Care Med 1994;149:953-959.
Oral Prednisone Did Not Suppress CysLT Levels Recovered from BAL Fluid

Eicosanoids in Asthmatics

BAL = bronchoalveolar lavage
Adapted from Dworski R et al Am J Respir Crit Care Med 1994;149:953-959.
When low dose ICS fails to control asthma.....

(n=75)
Budesonide 800 µg/day

2 weeks
Incomplete control

Budesonide 1600 µg/day

Budesonide 800 µg/day + Montelukast 10 mg

12 weeks

Respiratory Medicine 2007 online
ICS+Montelukast vs DS ICS

- Anti-leukotriene vs High dose steroids
- Compared with baseline
- Equal efficacy in PFT & QoL
- No change in inflammatory markers

Leukotriene: A major mediator in heightened airway inflammation

ΔamPEFR (L/min)

- 6 weeks
- 12 weeks

Eosinophilia on sputum
- 29%
- 26%

*Respir Med 2007, online*
Diverse Immune and Inflammatory stimuli

Inflammatory cells

PLA2

Arachidonic acid

FLAP

5-LO

LTA4

Leukotrienes

LTB4

LTA4 hydrolase

LTC4 synthase

LTC4

LTD4

LTE4

CysLT1

Leukocyte

BLT1

BLT2

CysLT2

Leukotrienes

Macrophages

Endothelium

Bronchospasm
Mucus production
Vascular permeability
Tissue edema
Chemotaxis for pro-inflammatory cells

Smooth muscle

Diverse Immune and Inflammatory stimuli

Leukocyte

Ubiquitous cell

LTA4

BLT1

BLT2

CysLT1

CysLT2

Leukotrienes

Macrophages

Endothelium
Specific Forms of Persistent Asthma

- Allergic rhinitis and Asthma
- Aspirin sensitive asthma
- Exercise induced asthma
- Sinusitis complicated asthma
- Pre-menstruation asthma
Allergic rhinitis aggravates Asthma severity


<table>
<thead>
<tr>
<th>Asthma symptoms</th>
<th>Moderate/severe AR</th>
<th>mild to nil AR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; One attack/week</td>
<td>64.0%</td>
<td>44.3%</td>
</tr>
<tr>
<td>Nocturnal attack</td>
<td>19.6%</td>
<td>11.8%</td>
</tr>
<tr>
<td>Inable to work</td>
<td>24.2%</td>
<td>12.1%</td>
</tr>
<tr>
<td>Moderate/severe asthma</td>
<td>60.3%</td>
<td>51.2%</td>
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</tbody>
</table>
Similar Immunological Responses between Allergic Rhinitis and Asthma

Allergen → IgE → Mast cells

Histamine

New synthesis
Leukotrienes
PGs, PAF

Eosinophils

Cytokines

Lymphocytes

CysLT1 receptor
On nasal mucosa

Chronic allergic responses

edema
Inflammatory cells
hyperresponsiveness

Allergic rhinitis
→ sneezing
→ rhinorrhea
→ mucus secretion
→ nasal stuff
→ airway edema

Asthma
→ bronchospasm

CysLTs=cysteinyl leukotrienes; PGs=prostaglandins; PAF=platelet activating factor

Anti-leukotriene concomitantly improves
Allergic rhinitis & Asthma

**Allergic rhinitis**

![Graph showing change from baseline score](image)

- Placebo (n=352)
- Montelukast 10 mg once daily at bedtime (n=348)

\[ p<0.001 \text{ montelukast vs. placebo} \]

Adapted from Reiss TF et al. *Arch Intern Med* 1998;158:1213-1220

Multicenter, randomized, 12-week double-blind trial of montelukast vs. placebo in patients 15 years and older with asthma

**Asthma**

![Graph showing morning FEV\textsubscript{1} mean % change from baseline](image)

- Montelukast 10 mg once daily (n=408)
- Placebo (n=273)

\[ p<0.001 \text{ montelukast vs. placebo} \]

Adapted from Malmstrom K et al. Poster presentation at the 57th AAAAI Annual Meeting, March 16–21, 2001.

Multicenter, 12-week double-blind, randomized trial in patients 15 to 81 years with seasonal allergic rhinitis.
Aspirin Sensitive Asthma

• Severe asthma attack min-3 hrs after taking aspirin or NSAIDs
• 15-20% of asthmatics
• Usually with nasal polyps, sinusitis
• Anaphylactic reaction
• No latency
Aspirin Sensitive Asthma

- Arachidonic acid
  - Cyclooxygenase
    - Aspirin
    - NSAIDs
    - Thromboxane
    - LTC4
    - LTD4
    - LTE4
  - Lipoxygenase
    - PGE4
    - Histamine release

- Leukotrienes

Montelukast protects from Aspirin Challenge
Aspirin (or NSAID) sensitive Asthma

- Masked by URI
  - Severe attack after anti-pyretics

- Chronic persistent asthma
  - Rheumatoid arthritis
  - Degenerative arthritis
**EIA**

% Change from Pre-exercise FEV₁

Max % Fall in FEV₁

**Time to Recovery from Max % Fall in FEV₁ to within 5% of Pre-exercise FEV₁**

End of Exercise

Return to 5% of Pre-exercise FEV₁

**AUC₀₋₆₀ₘᵣᵣᵣ**

AUC_{0-60min}

Time (Minutes)
Effect of anti-leukotriene therapy on exercise-induced bronchoconstriction

Significant difference in mean maximum fall in FEV$_1$, p<0.01

Finnerty et al (1992)
Fig 1 Cumulative percentage of patients with an asthma exacerbation (P=0.599 by log rank test)
Leukotrienes and Airway Remodeling
Airway smooth muscle proliferation

Airway fibrosis

Am J Respir Crit Care Med 2006, 173:718-728
Allergen challenge

+Montelukast

Control

+Steroid

OVA challenge

+MK+Steroid

+Montelukast

Mucus metaplasia/hyperplasia

Am J Respir Crit Care Med 2006, 173:718
TGF-β1 and Fibrosis

- TGF-β1
  - Fibroblasts
    - Proliferation
    - Differentiation JNK pathway
  - Myofibroblasts
    - Delayed apoptosis
    - Extracellular Matrix
    - Collagen deposition

The most effector molecule in airway fibrosis
Synergistic Effect between TGF-β1 and Leukotrienes

- Proliferation of mesenchymal cells
- Broncho-constriction
- Pro-inflammatory effect

Immunology and Cell Biology advance online publication, 27 February 2007
TGF-β1

Int Arch Allergy Immunol 2005, 137(suppl 1)17-20
Mobilization of stem cells from bone marrow to circulation after response to lung injury

Lung Injury

Bone Marrow

- Release of injury and recruitment signals

Chemokines such as CCL2 and CXCL12 are released and form a chemotactic gradient for fibrocyte recruitment. Once *in-situ*, autocrine and paracrine profibrotic factors likely drive the differentiation of fibrocytes into effector fibroblasts and myofibroblasts.

Chemokine-receptor-bearing fibrocytes leave the bone marrow and enter the circulation.

Blood Vessel
Patients with rapid decline in FEV1 within 5 years of follow up

Circulating fibrocyte

- Patients with rapid decline in FEV1 within 5 years of follow up.
- Normal Asthma vs. Chronic Asthma with Obstructive asthma AESubjects.
- Percentage of fibrocyte in NANT cells, %
- Decline of FEV1 in 5 years (%)
- Circulating fibrocyte

Graphs showing distribution and correlation:

- Scatter plot with linear regression:
  - n=9, r=0.812, p=0.0024
  - P<0.0001
Culture for 14 days

Cell count of myofibroblast (10^4 cells/ml)

- Normal Subjects
- Asthma Normal PFT
- Chronic Obstructive Asthma

30% FCS + Montelukast

p = 0.0007
p = 0.0012
p = 0.001

myofibroblasts

Montelukast

Adipose cells
When asthma symptoms persists despite of use of inhaled corticosteroid….

Long-acting $\beta_2$-agonists or

Leukotriene modifiers (especially when specific triggers exists) are the best-fit add-on therapy.