SUMMARY

- Anchorage of LABAs in lipophilic receptors gives them their long duration of action
- The addition of LABA to ICS should be given equal weight to increasing ICS
- Do not use LABA as monotherapy
- Several LABAs are under development that may offer once daily dosing lipophilic ICS

LEUKOTRIENE MODIFIERS: LEUKOTRIENE RECEPTOR ANTAGONISTS (LTRA) AND 5-LIPOXYGENASE INHIBITOR
OBJECTIVES

1) Describe the mode of action, therapeutic value and role in the management of asthma.

2) Identify potential adverse effects and strategies for managing patients to minimize side effects

3) Evaluate the cost, barriers and potential benefit of this class of medications.

“PREFERRED” VS. “ALTERNATIVE”

• “If alternative treatment is used and response is inadequate, DISCONTINUE it and use the preferred treatment BEFORE stepping up.”

(EPR3, p. 305, 306 & 343)
CYSTEINYL LEUKOTRIENES

- 1982 Bengt Samuelsson and his team in Stockholm elucidated the formation of cysteinyl leukotrienes and the 5-lipoxygenase pathway
- Products of arachidonic acid metabolism
- Abundantly produced in mast cells, eosinophils and alveolar macrophages
LEUKOTRIENE SYNTHESIS

Leukotrienes are synthesized in the cell from arachidonic acid by 5-lipoxygenase.

Cysteinyl Leukotrienes

- LTC4, LTD4, LTE4
- Bind to CysLT receptors
  - in the airways
  - on other proinflammatory cells
- Important mediators of inflammation and modulate inflammatory response in asthma
CYSTEINYL LEUKOTRIENES

- LTC4, LTD4, and LTE4 are released in the airways after exposure to allergens and are associated with changes in airway hyperresponsiveness

- LTC4 and LTD4 are considerably more potent than LTE4 as a cause of airway smooth muscle constriction

Increased concentrations of CysLTs were not substantially reduced by treatment with inhaled corticosteroids (ICSs), suggesting that the LT pathway is relatively independent of regulation by corticosteroids.


Louis R, et. al., The relationship between airways inflammation and asthma severity., Am J Respir Crit Care Med. 2005;161:5-58
INITIAL THERAPY: ICS VS LTRA

- Two cohorts: patients on ICS or LTRA as initial therapy
- 31,860 patients
- Asthma related charges included
  - ED visits and hospitalizations
  - Office visits
  - Asthma medication use


**Conclusion:**

Across varying degrees of severities, treating asthma with an ICS as initial controller therapy leads to less healthcare resource utilization than does using an LTRA as initial therapy.

EPR-3 RECOMMENDATIONS

- LTRAs are alternative, but not preferred, therapy for the treatment of mild persistent asthma (Step 2 care) [Evidence A]
- LTRAs can also be used as adjunctive therapy with ICS, but in youths ≥ 12 years & adults they are not preferred compared to adding LABA [Evidence A]

MONTELUKAST

Montelukast is a selective leukotriene receptor antagonist that inhibits the CysLT1 receptor, specifically inhibiting the physiologic actions of LTD4 at the CysLT1 receptor
## DOSE OF MONTELUKAST

- Adults and children over 15 years old
  - 10 mg p.o. Q HS
- Children 6 to 14 years old
  - 5 mg, chewed, Q HS
- Children 2 to 5 years old
  - 4mg, chewed, Q HS
- Children 6 to 23 months old
  - 4mg oral granules, mixed, Q HS

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## DOSE OF MONTELUKAST

- Exercise induce bronchospasm (EIB) in adults and in children over 15 years old
  - 10mg Q HS
Montelukast-Induced Adverse Drug Reactions: A Review of Case Reports in the Literature

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LITERATURE REVIEW OF CASE REPORTS MONTELUKAST-INDUCED REACTIONS

Key Words
Montelukast - Adverse drug reaction - Anti-leukotrienes - Allergy - Asthma - Hypersensitivity - Pharmacovigilance - Churg-Strauss syndrome - Toxicity

Abstract

Background: Montelukast, a leukotriene receptor antagonist, binds the cysteinyl leukotriene type 1 receptor. Montelukast is commonly prescribed to asthma patients as add-on therapy to inhaled corticosteroids. Several clinical trials emphasized that montelukast can be considered a safe drug. However, recent evidence reconsidered the benefit/risk ratio of the use of montelukast for both pediatric and adult patients. Summary: The present review analyzed the previous published case reports regarding montelukast-induced adverse drug reactions (ADRs). They included agitation, anxiety, depression, sleep disturbance, hallucinations, suicidal thinking and suicidality, tremor, dizziness, drowsiness, neuropathies and seizures. The immune system can be involved, in particular, cases of Churg-Strauss syndrome have been published. Furthermore, it can induce hypersensitivity reactions, including anaphylaxis and eosinophilic infiltration. In addition, hepatobiliary, pancreatic, and urologic disorders have been observed. Some of these cases are characterized by severe prognosis (i.e., neurological deficit and fatal hepatotoxicity). Key Message: The use of montelukast can be burdened by several ADRs, of which physicians should be aware in their clinical practice. A better understanding of the mechanisms causing ADRs after using montelukast could help researchers and clinicians in defining a risk-reduction strategy aimed to lessen montelukast toxicity. More accurate epidemiological studies, in order to discover risk factors favouring montelukast-associated ADRs, are demanded.

Introduction
Montelukast sodium is a selective leukotriene receptor antagonist (LTRA) that specifically blocks the cysteinyl leukotriene type 1 (CysLT1) receptor. CysLTs (LTC4, LTD4, and LTE4) are important pro-inflammatory lipid mediators binding to CysLT receptors. The CysLT1 receptor is localized in the human airways and synthesized by a variety of cells, including mast cells, eosinophils, bazo-
ZAFIRLUKAST

Zafirlukast is a selective and competitive receptor antagonist of LTD4 and LTE4

DOSE OF ZAFIRULAST

• Adults and children over 12 years old
  • 20mg p.o. BiD on an empty stomach, 1 hr ac or 2 hr pc

• Children 5 to 11 years old
  • 10mg p.o. BiD on an empty stomach, 1 hr ac or 2 hr pc
ADVERSE REACTIONS

- GI: abdominal pain, dyspepsia, nausea, vomiting and diarrhea
- Headache
- Fever
- Asthenia
- Generalized pain

PRECAUTIONS

- May increase liver enzymes
- Coadministration with warfarin increases Prothrombin Time (PT)
ZILEUTON

Zileuton is a specific inhibitor of 5-lipoxygenase and thus inhibits LTB4, LTC4, LTD4, and LTE4 formation. Both the R(+) and S(−) enantiomers are pharmacologically active as 5-lipoxygenase inhibitors in vitro and in vivo.

DOSE OF ZILEUTON

Adults and children over 12 years old

1200mg (2 x 600mg extended release tablets)
p.o. BiD on an empty stomach 1hr ac or 2 hr pc
<table>
<thead>
<tr>
<th>ADVERSE REACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• GI: abdominal pain, dyspepsia, nausea</td>
</tr>
<tr>
<td>• Headache</td>
</tr>
<tr>
<td>• Myalgia</td>
</tr>
<tr>
<td>• Asthenia</td>
</tr>
<tr>
<td>• Unspecified pain</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>PRECAUTIONS</th>
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</thead>
<tbody>
<tr>
<td>• Elevation of ALT, use with caution in patients with significant alcohol consumption and in patients with history of liver disease</td>
</tr>
<tr>
<td>• Monitor liver enzymes once a month x 3 months, then every 2 to 3 months</td>
</tr>
<tr>
<td>• Pregnancy category C</td>
</tr>
</tbody>
</table>
DRUG INTERACTIONS

• Metabolized by CYP3A4
• Known to increase levels of
  • theophylline
  • warfarin
  • terfenadine
  • propranolol
  • pimozide

EPR-3 RECOMMENDATIONS

• Zileuton can be used as an alternative, but not preferred adjunctive therapy in adults [Evidence D]
• Zileuton is less desirable due to limited data on efficacy and the need for liver function monitoring