ANTILEUKOTRIENES IN UPPER AIRWAY INFLAMMATORY DISEASES

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Introduction

• Leukotrienes (LTs) are inflammatory mediators, previously known as slow-reacting substances of anaphylaxis, produced by a number of cell types including:
  o mast cells
  o eosinophils
  o Basophils
  o Macrophages
  o monocytes
Introduction

- LTs are synthesised from arachidonic acid (AA) by the 5-lipoxygenase (5-LO) pathway

- Synthesis of these mediators results from the cleavage of AA in cell membranes
Introduction

• LTs exert their biologic effects by binding to and activating specific adaptors
• This occurs in a series of events, leading to
  • contraction of human airway smooth muscle
  • cell chemotaxis
  • increased vascular permeability
Introduction

• The LT family consists of:
  - LTA4 (unstable intermediate product converted to LTC, LTD and LTE)
  - LTB4
  - LTC4
  - LTD4
  - LTE4 called cystenlyle LT
cysteinyl leukotrienes

- CysLTs are potent pro inflammatory mediators produced from AA through the 5-LO pathway.
- They have important pharmacological effects by interacting with at least two different receptors:
  - CysLT1
  - CysLT2
cysteinyl leukotrienes

• By competitive binding to the cysteinyl LT1 receptor
• LT receptor antagonist (LTRA) drugs, such as
  • montelukast
  • Zafirlukast
  • pranlukast
• block the effects of cysteinyl LTs improving the symptoms of some chronic respiratory diseases, particularly bronchial asthma and allergic rhinitis
cysteinyl leukotrienes

• CysLT\textsubscript{1} mediates:
  ▪ sustained bronchoconstriction
  ▪ mucus secretion
  ▪ Oedema in the airways

• Selective antagonists of CysLT\textsubscript{1} approved for the treatment of asthma block the pro-asthmatic effects of CysLT\textsubscript{1}
cysteinyl leukotrienes

- Experiments in mice that are deficient in CysLT2, or that overexpress CysLT2 in the lungs, have indicated that CysLT2 does not mediate bronchoconstriction but rather contributes:
  - Inflammation
  - vascular permeability
  - tissue fibrosis
Introduction

The two classes of LTs
  • LTB4
  • peptidylcysteinyl LT

promote:
  • inflammatory cell recruitment
  • Activation (primarily of eosinophils)
  • Fibrosis
  • airway remodelling
  • smooth muscle and epithelial cell proliferation.
Introduction

CysLTs promotes:

• increase the expression of adhesion molecules like P selectin
• airway remodelling by increasing the deposition of collagen
• enhancing collagen synthesis and degradation by fibroblasts
• Proliferation of bronchial epithelial cells and smooth muscle cells
Receptors activation

- LTs act by binding to specific receptors of the rhodopsin class that are located on the outer plasma membrane of structural and inflammatory cells.
- Once ligated by the LT, these receptors interact with G proteins in the cytoplasm.
Receptors activation

- eliciting an increase in intracellular calcium and a reduction in intracellular cyclic AMP
- proximal signals activate downstream kinase cascades in ways that alter various cellular activities
Receptors activation

• During the **early-phase** response to antigens, CysLTs are released by mast cells and basophils
• in the **late phase**, they are synthesised by eosinophils and macrophages
Antileukotrienes

Antileukotriene drugs are classified into two groups based on their mechanism of action:

- **LT receptor antagonist** (zafirlukast, pranlukast, montelukast), which block the LT receptor and thus block the end-organ response of LTs

- **LT synthesis inhibitors** (zileuton, ZD2138, Bay X 1005, MK-0591), which block the biosynthesis of cysteinyll LTs and LTB4
Zafirlukast

- Zafirlukast is an LTD4 receptor antagonist that has been used for LTD4-induced
  - bronchoconstriction
  - exercise challenge
  - cold-induced asthma
  - chronic asthma
Zileuton (Zyflo) 5-lipoxygenase inhibitor
• indicated for asthma
• recommended for adults
• It is administered twice daily or four times daily
• Adverse effects include
  ▪ dyspepsia (8.2 %)
  ▪ transaminase elevation (1.9 %).
Montelukast (Singulair, Pluralair, Montecarlo, Lovetas)

- **CysLT1 antagonist**
- indicated for asthma and rhinitis
- recommended for adults and children aged 6 months and older
- administered as once daily
- Adverse effects are not observed.
Pranlukast

- Pranlukast (Onon, Azlaire)
- CysLT1 antagonist
- Indicated for asthma and rhinitis
- recommended for adults and children aged 1 year and older
- administered twice daily
- Adverse effects are not observed.
Zafirlukast (Accolate)

- CysLT1 antagonist
- indicated for asthma and rhinitis
- recommended for adults and children aged 5 years and older
- administered twice daily
- Adverse effects are not observed except single reports of hepatoxicity.
ANTILEUKOTRIENES IN CHRONIC RHINOSINUSITIS AND NASAL POLYPS
In CRS and NP

• CysLTs demonstrate important pro-inflammatory and Profibrotic effect contribute to the extensive hyperplastic rhinosinusitis and nasal polyposis

• these patients have :
  ▪ CysLTs Overproduction
  ▪ enhanced sensitivity to CysLTs
    • by over expression of CysLT receptors
    • including two well-characterised receptors (CysLT1 and CysLT2) and newly described selective LTE4 receptors
In CRS and NP

• In Chronic hypereosinophilic rhinosinusitis the sinus tissue demonstrates a marked increase in cells that express:
  • cytokines (e.g., IL-5 and GM-CSF)
  • chemokines (e.g., CCL5, CCL11, and CCL24)
  • proinflammatory lipid mediators (e.g., CysLTs)

• that are responsible for the differentiation, survival, and activation of eosinophils
In CRS and NP

In Pérez-Novo et al.’s study samples were prepared from sinonasal tissue of patients with

- **CRS with polyps** (CRS-NP group, n=13)
- **CRS without nasal polyposis** (CRS group, n=11)
- **nasal polyposis and aspirin sensitivity** (CRS-ASNP group, n=13)
- **normal nasal mucosa from healthy subjects** (NM group, n=8)
In CRS and NP

- IL-5 and eosinophil cationic protein were increased in both groups of nasal polyp tissue compared with in the NM and CRS groups
- correlated directly with LTC4, LTD4, and LTE4 concentrations
- Inversely correlated with PGE 2 concentrations

- They concluded that changes of tissue eicosanoid metabolism do occur in CRS, even in the absence of clinical aspirin sensitivity
- and these changes appear to be related to the severity of eosinophilic inflammation.
In CRS and NP

- Ulualp et al. studied 18 patients who had all undergone previous sinus surgery
  - Sixteen received zafirlukast
  - Two received zileuton
- evaluated by questionnaires and postoperative sinus endoscopies
In CRS and NP

- Overall benefit on the questionnaire was positive in 12 out of 15 patients (80%).
- Endoscopic findings demonstrated:
  - No abnormalities in 8 (53%) patients.
  - Nasal crusting in 6 (40%) patients.
  - Erythema with nasal crusting in 1 (7%) patient.

- In this uncontrolled study, the authors concluded that anti-LT therapy seemed to be an effective treatment for most patients whose symptoms of CRS persist following sinus surgery.
In CRS and NP

- Parnes and Chuma investigated the effects of anti-LT added to the standard treatment in 36 patients with CRS with or without NP
  - 26 received zafirlukast
  - 5 received zileuton
  - 5 switched from zafirlukast to zileuton

- A statistically significant improvement was noted with respect to:
  - headache, facial pain and pressure, ear discomfort, teeth pain, purulent nasal discharge, postnasal drip, nasal congestion and obstruction, olfaction, and fever
In CRS and NP

- Overall improvement was noted by 72% of the patients
- Side effects occurred in 11% of the patients

- An objective improvement, or at least stabilisation, of NP was seen in 50% of the patients
# Antileukotrienes in chronic rhinosinusitis and nasal polyps

<table>
<thead>
<tr>
<th>Authors</th>
<th>Main comments</th>
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<tbody>
<tr>
<td>Pérez-Novo et al. [29••]</td>
<td>IL-5 and eosinophil cationic protein increased in nasal polyp tissue and correlated directly with LTC 4, LTD 4, and LTE 4</td>
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<tr>
<td>Ulualp et al. [30]</td>
<td>Anti-LT therapy seemed to be an effective treatment for most patients whose symptoms of CRS persist following sinus surgery</td>
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<tr>
<td>Parnes and Chuma [31]</td>
<td>In patients with CRS with or without NP, a statistically significant improvement was noted with respect to headache, facial pain and pressure, ear discomfort, teeth pain, purulent nasal discharge, postnasal drip, nasal congestion and obstruction, olfaction, and fever who received zafirlukast or zileuton</td>
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<td>Kutting et al. [32]</td>
<td>Montelukast (10 mg daily) associated with oral steroids (oral methylprednisolone 40 mg) in nine patients with severe NPs; and no evidence of NP recurrence in five (56 %) patients, one (11 %) with NP reduction, and three (33 %) without changes by nasal endoscopy</td>
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Antileukotrienes in chronic rhinosinusitis and nasal polyps

<table>
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<th>Reference</th>
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<tr>
<td>Mullol et al. [33••]</td>
<td>Montelukast may contribute to the reduction of eosinophilic inflammation in upper-airway inflammatory diseases such as rhinitis and nasal polyposis</td>
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<td>Ragab et al. [34]</td>
<td>Clinical response to montelukast appeared to be more impressive with respect to asthma than NP, possibly suggesting that LTs are more relevant in the lower than in the upper airway</td>
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<td>Kieff et al. [37]</td>
<td>Patients with perennial allergies and NPs seem more likely to respond to the montelukast treatment than those without allergy</td>
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<td>Wentzel et al. [38••]</td>
<td>LTAs are an effective tool for treating CRSwNP, with limited benefit as an adjunctive therapy</td>
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<tr>
<td>EPOS 2012 consensus [39•]</td>
<td>In adults with chronic rhinosinusitis with nasal polyps, antileukotriene treatment was mentioned as “negative outcome with no relevance”</td>
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</table>
Grundmann and Topfner studied 18 patients with AIA diagnosed by oral provocation and treated with montelukast after undergoing sinus surgery.

- Evaluation by:
  - endoscopic assessment
  - determined the eosinophilic cationic protein (ECP) levels in serum.

- Findings:
  - significant reduction in ECP levels
  - beneficial effect on nasal and pulmonary symptoms
  - significant reduction in the number of polyps noted on endoscopic examination
In CRS and NP

• A prospective, double-blind study on 40 patients compared the effects of the LTRA montelukast (10 mg daily) and nasal beclomethasone (400 μg daily) on the postoperative course of patients with NPs.

• Significant reduction in the symptom scores between these two postoperative treatments in the year following surgery.

• Montelukast group improvement was more marked in itching, post-nasal discharge and headache.
In CRS and NP

- The control of sneezing and rhinorrhea was comparable in both groups with a marginal advantage of montelukast
- Steroids had a more marked effect on smell disturbances and obstruction
- No differences in the recurrence rate or need for rescue medications between the groups throughout the study period
In the EPOS 2012 consensus, in adults with chronic rhinosinusitis with nasal polyps, antileukotriene treatment was mentioned as “negative outcome with no relevance”.

- Antileukotrienes were not recommended for adults or children with chronic rhinosinusitis with or without nasal polyps.
ANTILEUKOTRIENES IN ALLERGIC RHINITIS
Allergic rhinitis

- clinically expressed by sneezing, rhinorrhea, nasal itching, and congestion
- Allergen driven mucosal inflammatory disease that is modulated by immunoglobulin E
In AR

• CysLTs promote various proinflammatory actions, including
  ▪ microvascular leakage
  ▪ inflammatory cell chemotaxis (particularly eosinophils)
  ▪ mucus hypersecretion,
  ▪ neuronal stimulation
• all of which are relevant to the pathophysiology of AR
In AR

- CysLTs receptors are located in nasal tissue
- CysLTs are increased in patients with AR and are released following allergen exposure
- Nasal administration of CysLTs reproduces the symptoms of AR
• **Histamine** has long been implicated as a major mediator of AR, primarily causing sneezing, nasal itching, and rhinorrhea.

• In contrast to histamines, **LTs** such as **LTC4** and **LTD4** contribute to **vascular permeability and vasodilation**, resulting in mucosal swelling, which causes rhinorrhea and nasal congestion
In AR

• the nasal allergen challenge induced release of CysLTs has been correlated with allergic symptoms
• nasal congestion in the early phase and late phase is accompanied by a significant increase in CysLTs in nasal lavage fluid from AR patients

• Therefore, CysLTs play an important role in AR
In AR

- **Histamine** nasal challenge induces neurological responses, such as itching and sneezing, but affects nasal congestion to a lesser degree.

- Therefore, **LTs** contribute to the pathophysiology of AR and potentially increase both mucus production and congestion.
In AR

• Both Antihistamine and LTRAs have:
  • antiallergic
  • anti-inflammatory properties
• including effects on mediator release and chemo attraction of inflammatory cells.
• These findings suggest that administering antihistamine and LT modifiers together might result in an amplified effect for the treatment of allergic rhinitis
In AR

- In recent animal studies, nasal LTD4 challenge was shown to increase nasal airway resistance, and anti-LT can inhibit the antigen-induced increase in nasal resistance.
• Lu et al evaluated the treatment outcomes of LTRAs as a monotherapy or combined with second-generation oral H1-histamines for the treatment of allergic rhinitis

Treatment outcomes, including:
  • the daytime nasal symptom score (DNSS)
  • Night time symptom score (NSS)
  • composite symptom score (CSS)
  • daytime eye symptom score (DESS)
  • rhinoconjunctivitis quality of life questionnaire (RQLQ)

• used to evaluate the therapeutic effects of LTRAs on seasonal and perennial AR
Montelukast statistically significantly reduced the NSS, but not the DNSS, in patients with seasonal AR compared to loratadine.

The combination therapy of montelukast and loratadine statistically significantly improved the CSS compared to either montelukast or loratadine monotherapy.

Montelukast, a representative LTRA, can be used as first-line therapy for AR, with comprehensive improvement of nasal and ocular symptoms and quality of life in AR patients.
In AR

• The LTRA montelukast is FDA-approved for the treatment of symptoms of seasonal AR in adults and paediatric patients 2 years of age and older and perennial AR in adults and paediatric patients 6 months of age and older.

• While several other LTRAs are available in the USA, montelukast is the only LTRA approved by the FDA for AR.
In AR

• meta-analyses (predominantly based on controlled studies of montelukast in adults with seasonal AR)

• have concluded that LTRAs are more effective at controlling symptoms and improving the quality of life than placebo

• While some studies have shown that LTRAs are as effective as oral antihistamines

• others have shown that LTRAs are less effective than oral antihistamines and INS
In AR

• In a single randomised, double-blind study, montelukast had a similar effect to pseudoephedrine in reducing the symptoms of AR except the symptoms of nasal congestion, for which pseudoephedrine was more effective.
In AR

- Montelukast is generally well tolerated and is not associated with drowsiness.
- Some reports have demonstrated rare drug-induced neuropsychiatric events (including aggression, depression, suicidal thinking, and behaviour (1 in 9929).
In AR

- Montelukast has traditionally been more expensive than oral antihistamines.
- A subset of patients who have AR and asthma may benefit from this medication.
- Three studies with arms that compared INS to INS+LTRA did not show a significant benefit to adding LTRA in their primary outcome. The largest trial enrolled 102 patients.
In AR

- The concomitant use of loratadine and zafirlukast is significantly more effective for diminishing the response to an inhaled allergen challenge than the use of loratadine or zafirlukast alone.
In AR

- Montelukast, was studied during the spring of 2000 in 1302 subjects with seasonal AR to a relevant allergen
- Subjects were randomised to treatment with
  - 10 mg montelukast,
  - 10 mg loratadine
  - Placebo

- The primary efficacy variable, change from baseline in the daytime nasal symptom scores as well as secondary end points (night time and composite symptom scores) significantly (p<0.01)
- favoured the treatment groups over placebo
In AR

- multicentre pilot study in California investigated the hypothesis of combination mediator LT and histamine antagonist therapy in patients with seasonal AR

- Four hundred sixty subjects were randomised to in the spring of 1997
  - 10 mg montelukast combined with 10 mg loratadine
  - 10 mg montelukast
  - 20 mg montelukast, and 10 mg loratadine
  - placebo
In AR

- The combination group showed significant improvement in
  - the daytime
  - Night time
  - composite symptom scores

- The rhinitis quality of life improved (p<0.05) in
  - the combination group
  - Loratadine
  - montelukast (10 mg)
ARIA

• Should oral leukotriene receptor antagonists be used for treatment of allergic rhinitis?
  
  • suggest oral leukotriene receptor antagonists in adults and children with seasonal allergic rhinitis (conditional recommendation | high quality evidence)
  
  • In preschool children with perennial allergic rhinitis (conditional recommendation | low quality evidence).
• Should **oral leukotriene receptor antagonists** be used for treatment of allergic rhinitis?

• In adults with **perennial allergic rhinitis** we suggest that clinicians **do not administer** and patients do not use oral leukotriene receptor antagonists (**conditional recommendation** | high quality evidence).
• Should **oral leukotriene receptor antagonists** versus **oral H1-antihistamines** be used for treatment of allergic rhinitis?

• **suggest oral H1-antihistamines** over oral leukotriene receptor antagonists in patients with **seasonal allergic rhinitis** *(conditional recommendation | moderate quality evidence)*

• And in **preschool children** with **perennial allergic rhinitis** *(conditional recommendation | low quality evidence)*
Conclusion

• CysLTs (LTC4, LTD4, and LTE4) promote various pro inflammatory actions, including:
  • microvascular leakage
  • inflammatory cell chemotaxis (particularly eosinophils),
  • mucus hypersecretion
  • neuronal stimulation

Antilukotrines

• are effective for asthma and in selected cases of chronic rhinosinusitis with nasal polyposis.
• not recommended in adults and children with chronic rhinosinusitis without nasal polyps
Thank you