The Treatment of Asthma with Leukotriene Receptor Antagonists

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Completion of Assessment Questions following this article entitles members to one credit towards C.E. requirement.

Over the past three decades the pharmacotherapy of asthma has been based on glucocorticoids, ß$_2$ agonists and theophyllines. Research conducted over the past 10 years has led to greater understanding of the cellular and molecular basis of asthma, particularly the role of the underlying inflammatory process.

Both national and international guidelines stress the importance of switching off the inflammatory cascade (Figure 1). Glucocorticoids are the most effective anti-inflammatory agents available and in many countries, including Malta, they are used as first line treatment. However, despite their proven safety and efficacy, there are still a number of patients whose asthma is not adequately controlled and as a consequence have a poor quality of life.

The search for alternative pharmacological agents that target airway inflammation and ease the problem of compliance has led to a novel class of non-steroidal anti-asthma drugs which are effective over a wide range of asthma severity, have a high therapeutic index, are orally active and have a once daily or twice daily regimen. Leukotriene receptor antagonists are a hybrid between a preventer of inflammation (antagonism of inflammatory activities of leukotrienes) and bronchodilating reliever (antagonism of leukotriene induced smooth muscle bronchoconstriction). Currently available on the local market is zafirlukast (Accolate®, Zeneca) which is a cysteinyl leukotriene antagonist. Another drug within this class, however not as yet available locally, is montelukast (Singulair®, Merck).

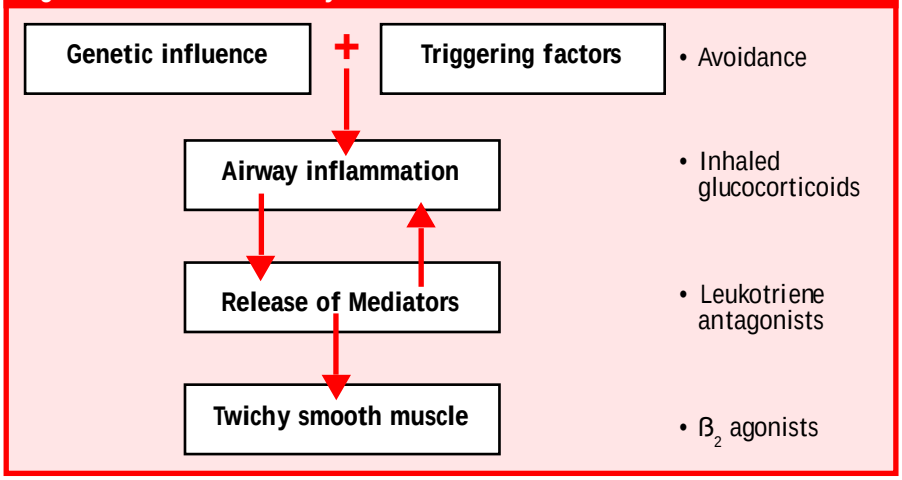
What are leukotrienes?

Leukotrienes are a group of arachidonic acid derivatives that are produced during asthmatic reactions by cells involved in the pathogenesis of asthma and other inflammatory diseases. The cysteinyl leukotrienes C_4 (LTC_4), D_4 (LTD_4) and E_4 (LTE_4) are important mediators of inflammation. They are formed in many cells including mast cells and eosinophils and are potent inducers of bronchoconstriction, plasma exudation and mucus production.

How do the new anti-leukotriene drugs work?

There are currently four classes of anti-asthma and anti-inflammatory drugs which interfere with leukotriene synthesis or activity which are under development as seen in Figure 2. These are 5-lipoxygenase inhibitors and 5-lipoxygenase activating protein (FLAP) inhibitors which block the synthesis of cysteinyl leukotrienes and the

Figure 1 The inflammatory cascade in asthma



leukotriene B_4 (LTB_4). The third class are competitive antagonists of LTB_4. The drugs which are currently available in Malta and the UK are those of the 4th class and act by competitively blocking the activity of cysteinyl leukotrienes at the LTD_4 receptor. They are termed cysteinyl leukotriene receptor antagonists.

When should leukotriene receptor antagonists be used?

The local guidelines on the management of asthma issued by the Malta Lung Study Group do not mention the use of leukotriene receptor antagonists. However, these guidelines are in the process of being revised. The position of these drugs in the international guidelines is still unclear due to the lack of published data at the time of drawing up these guidelines. It is debatable whether these drugs should be used as first-line preventive monotherapy instead of low dose inhaled corticosteroids in patients with mild persistent asthma or as an alternative to long-acting bronchodilators, i.e. second-line therapy, in addition to inhaled corticosteroids in patients with moderate to severe persistent asthma.

It is important to note that leukotriene receptor antagonists should be taken on a regular basis to achieve benefit, even during symptom free periods and should normally be continued during acute exacerbations of asthma. However, they are not indicted to relieve an attack of acute severe asthma.

In the UK, zafirlukast is licensed for use in patients aged 12 years and over. It may be used as first line therapy instead of inhaled corticosteroids in mild persistent asthma. Montelukast is licensed in patients aged 6 and over as second line asthma treatment in combination with inhaled corticosteroids and as monotherapy in exercise induced asthma.

Clinical considerations

Zafirlukast and montelukast both achieve peak plasma concentrations approximately 3 hours after oral administration. There is a 40% decrease in the bioavailability of zafirlukast when taken with food; it is therefore recommended that the tablets should not be taken with food as this could lead to a decreased pharmacological response. Co-adminstration of zafirlukast with erythromycin, theophylline or terfenadine results in a decrease in the plasma concentration of zafirlukast, while an increase results when it is co-administered with aspirin. In smokers the clearance of zafirlukast may be increased by about 20%. Prescribing information regarding the use of zafirlukast states that the safety of this drug in pregnancy has not been established and since it is excreted in breast milk it should not be administered to lactating mothers.

The literature suggests that leukotriene receptor antagonists may be of particular use in:

- **exercise induced asthma**
- **asthmatics who are intolerant to aspirin and other non-steroidal anti- inflammatory drugs**
- **nocturnal asthma**
- **asthmatics who concomitantly present with allergic rhinitis.**

Official montelukast prescribing information advises that the use of montelukast is avoided in pregnancy and lactation unless essential.

Conclusion

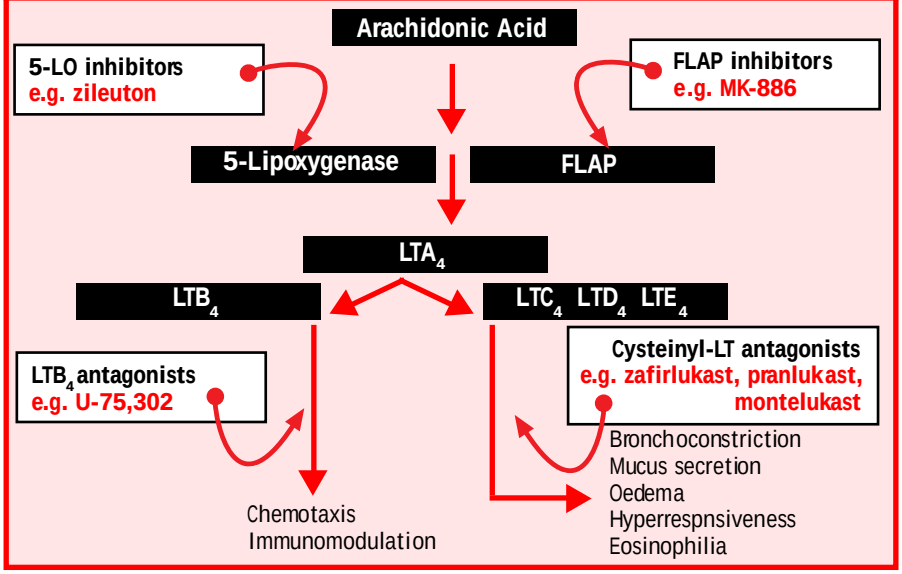
Leukotriene receptor antagonists represent an important advance in asthma therapy. They are active over a wide range of asthma severity and have both an anti-inflammatory and a bronchodilator property. They are active orally, therefore overcoming the potential problems with compliance when using inhalers.

They also act within the first 24 hours while inhaled corticosteroids take a much longer time to achieve maximal

Table 1 Leukotriene Receptor Antagonists

Generic	Propriety	Oral dose	Other information
Zafirlucast	Accolate (Zeneca)	20 mg bd	Take 1hr before or 2hr after eating.
Montelukast	Singulair (Merck)	Adults: 10 mg at night Paed: (6-12yr): 5 mg at night	Paediatric dose available as chewable tablets.

Figure 2 The four groups of anti-asthma and anti-inflammatory drugs directed against LT synthesis and activity



response. However, when compared to inhaled beclomethosone 400 micrograms daily both the above mentioned drugs appear to be less effective in mild to moderate asthmatics. They are comparable in cost to long acting $ß_2$ agonists but more expensive than low dose inhaled steroids.

While further long term studies are required to determine the position of these drugs in asthma treatment guidelines, they provide oral, safe and effective therapy. ✶

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The Treatment of Asthma with Leukotriene Receptor Antagonists

Select only ONE option in each question by ticking the respective box on the Response Sheet (page 39).

Assessment Questions:

1. The inflammatory process in asthma is:

a. of secondary importance
b the main pathological process in asthma
c the target of all anti-asthma drugs
d all of the above.

2. Which of the following statements is true?

a. Leukotrienes are arachidonic acid derivatives
b. Leukotrienes are only involved in the pathogenesis of asthma
c. Leukotrienes are only produced in mast cells
d. Leukotrienes are not involved in mucus production.

3. Leukotriene receptor antagonists are
a. non-steroidal drugs
b. enhance the inflammatory process
c. steroidal drugs
d a combination of answers a and b.

4. Leukotriene receptor antagonists
a. have anti-inflammatory activities
b. act in the same way as $ß_2$ agonists
c. have bronchodilating effects
d. a combination of answers a and c.

5. Leukotriene receptor antagonists currently available on the local market are
a. pranlukast
b. montelukast
c. zafirlukast
d. salbutamol

6. The cysteinyl leukotriene receptor antagonists act by
a reducing arachidonic production
b. reducing FLAP synthises
c. competing with the LTB_4 receptor
d. blocking the LTD_4 receptor.

7. Which of the following statements is true
a. an example of a 5-lipoxygenase inhibitor is montelukast
b. LTD4 is a not cysteinyl leukotriene
c. zafirlukast is a cysteinyl leukotriene receptor antagonist
d. cysteinyl leukotriene receptor antagonists are ineffective if taken with inhaled corticosteroids.

8. The recommended use of cysteinyl leukotriene receptor antagonists
a. as reliever therapy i.e. instead of short acting (2 agonists
b. instead of oral prednisolone
c. instead of inhaled steroids in mild persistent asthma
d. instead of nebulised therapy.

9. Zafrilukast is also licensed for use in
a. COPD
b. bronchitis
c. emphysema
d. none of the above.

10. Leukotriene receptor antagonists are of particular use in
a. aspirin sensitive asthmatics
b. asthmatics allergic to salbutamol
c. persons presenting with occupational asthma
d. none of the above.

11. Which of the following statements is false?
a. cortocosteriods are the most effective anti-inflammatory agents available
b. zafirlukast is the only cysteinyl leukotriene receptor antagonist available locally
c. montelukast is licensed for use in the UK
d. leukotriene receptor antagonists only have a bronchodilating effect.

12. Which of the following statements is true?
a. zafirlukast is licensed only for use in patients over 12 years of age.
b. zafirlukast is also licensed for use in children over 6 years of age
c. montelukast is of no use in exercise induced asthma
d. montelukast has a low therapeutic index.

13. Zafirlukast and montelukast achieve peak plasma concentrations how long after administration?
a. after 30 minutes
b. after 1 hour when taken with food
c. after 3 hours
d. none of the above

14. Zafirlukast is available as
a. an inhaler
b. nebuliser solution
c a tablet
d. a combination of answers a and b.

15. Montelukast is available as
a. chewable tablets for children
b. suspension
c. tablets for adults
d. a combination of answers a and c.

16. The dosage regimen for zafirlukast is
a. 20 mg bd. with food
b. 20 mg bd. 2 hours after food
c. 20 mg bd. 1 hour before food
d. a combination of answers b and c

17. The use of cysteinyl leukotriene receptor antagonists in pregnancy and lactation
a. is absolutely safe.
b. is recommended after the 2nd trimester
c. is not recommended
d. none of the above.

18. One of the major advantages of cysteinyl leukotriene receptor antagonists is
a. their low cost
b. that they over come the problem of compliance with inhalers
c. that they can safely be used in children of all ages
d. that they have no side effects.

19. When used in mild to moderate asthma leukotriene receptor antagonists
a. are the most effective anti-inflammatory agents
b. are less effective than inhaled beclomethosone 400(g daily
c. are just as effective as any anti-asthma drug
d. are of no use.

20. Which of the following statements is true?
a. cysteinyl leukotriene receptor antagonists should be taken on a prn basis
b. cysteinyl leukotriene receptor antagonists should be taken on a regular basis
c. cysteinyl leukotriene receptor antagonists should only be taken in conjunction with salmeterol
d. cysteinyl leukotriene receptor antagonists should not be taken if cough is present.

"To loose one's health renders science null, art inglorious, strenght effortless, wealth useless and eloquence powerless."

Adversus Ethicus