Montelukast and bambuterol combination in the management of asthmatics

ALLERGIC DISEASES AND CYSTEINYL LEUKOTRIENE (LT) ANTAGONISTS

Allergic diseases include a variety of different illnesses (rhinitis, conjunctivitis, asthma, urticaria, and dermatitis) in which the physiological and pathological basis is the release of chemical mediators such as histamine; platelet-activating factor; metabolites of arachidonic acid; and chemotactic factors from mastocytes, basophils, and eosinophils.

Cysteinyl-leukotrienes (CysLTs) are endogenous mediators of inflammation and play an important role in allergic airway disease by stimulating bronchoconstriction, mucus production, mucosal oedema and inflammation, airway infiltration by eosinophils, and dendritic cell maturation that prepares for future allergic response.

Leukotriene modifiers work by several mechanisms. Such mechanisms include:

- **5-lipoxygenase enzyme inhibition** (e.g. zileuton);
- **5-lipoxygenase-activating-protein inhibition** (e.g. quiflapon, BAYx 1005);
- **LTD4-receptor antagonism** (e.g. zafirlukast, montelukast, MK-571, pranlukast).

By competitive binding to the Cys-LT(1) receptor, leukotriene receptor antagonist drugs such as montelukast block the effects of Cys-LTs and alleviate the symptoms of many chronic diseases, especially bronchial asthma and allergic rhinitis.

EFFICACY STUDIES OF LEUKOTRIENE INHIBITORS

In the treatment of persistent asthma, randomized controlled trials have shown leukotriene inhibitors to be more effective than placebo but less effective than inhaled corticosteroids. For exercise-induced asthma, leukotriene inhibitors are as effective as long-acting beta2-agonist bronchodilators and are superior to placebo; they have not been compared with short-acting bronchodilators. Leukotriene inhibitors are as effective as antihistamines but are less effective than intranasal steroids for the treatment of allergic rhinitis.

Recently published studies and case reports have demonstrated beneficial effects of leukotriene receptor antagonists on other diseases commonly associated with asthma (exercise induced asthma, rhinitis, chronic obstructive pulmonary disease, interstitial lung disease, chronic urticaria, atopic dermatitis, allergic fungal disease, nasal polyposis, and paranasal sinus disease) as well as other diseases not connected to asthma (migraine, respiratory syncytial virus postbronchiolitis, systemic mastocytosis, cystic fibrosis, pancreatitis, vulvovaginal candidiasis, cancer, atherosclerosis, eosinophilic cystitis, otitis media, capsular contracture, and eosinophilic gastrointestinal disorders).

MONTELUKAST

Montelukast sodium is a selective and orally-active leukotriene receptor antagonist with demonstrated effectiveness for treating allergic asthma and allergic rhinitis in adults and children as young as 12 months of age for allergic asthma and 6 months of age for allergic rhinitis. It was recently approved in the US for prevention of exercise-induced bronchoconstriction in patients who
are ≥ 15 years of age.5

**MONTELUKAST IN PEDIATRIC ASTHMA MANAGEMENT**

Montelukast is the only leukotriene receptor antagonist approved for use in pediatric patients. Review of existing literature showed that montelukast compared to placebo has proven clinical efficacy in better control of day time asthma symptoms, percentage of symptom free days, need for rescue drugs and improvement in FEV1. Studies also demonstrated improvement in airway inflammation as indicated by reduction in fractional exhaled nitric oxide, a marker of inflammation.

Studies comparing low dose inhaled corticosteroids (ICS) with montelukast are limited in children and conclude that the latter is not superior to ICS. For moderate to severe persistent asthma, when montelukast was compared with long acting beta agonists (LABA) as an add-on therapy to ICS, montelukast was found to be less efficacious and less cost-effective. It has beneficial effects in exercise induced asthma and aspirin-sensitive asthma. Montelukast has onset of action within one hour.

Patient satisfaction and compliance was better with montelukast than inhaled anti-inflammatory agents due to oral, once a day administration. Based on the presently available data, montelukast may be an alternative treatment for mild persistent asthma as monotherapy where ICS cannot be administered. It is also an alternative to LABA as an add-on therapy to ICS for moderate to severe persistent asthma. The other indications for use of montelukast include: allergic rhinitis, exercise induced bronchoconstriction and aspirin-induced asthma.5

**MONTELUKAST IN ADULTS WITH ASTHMA AND ALLERGIC RHINITIS**

The objective of this phase IV study was to investigate the efficacy and safety of montelukast 10mg in adults with both asthma and allergic rhinitis in a real-life setting. Following treatment with 10mg montelukast 86.5% (n=4547) of patients reported a strong or marked improvement in day-time asthma symptoms and 88.5% (n=4367) reported improvement in night-time symptoms. A similarly high proportion of patients had a strong or marked improvement in all symptoms of allergic rhinitis (i.e. sneezing/itching (84%), rhinorrhea (81.7%), nasal congestion (79.3%), watery eyes (78.4%) and red or burning eyes (77.7%). The use of asthma and rhinitis medication was also reduced. 92.3% (n=5685) of all patients intended to continue montelukast therapy.

Overall quality of life (QoL) was “very good” or “good” in 85.2% of patients (n=4991) and a “strong” or “marked” improvement in each of the four domains of sleep, work, everyday life and physical activity were seen. Montelukast was well tolerated. Adverse drug reactions occurred in 14 out of 6158 patients. None of the adverse events was serious. Accordingly, montelukast 10mg is a safe and effective treatment for patients with both asthma and allergic rhinitis.5

**ASTHMA CONTROL WITH ADD-ON MONTELUKAST THERAPY FOR 1 YEAR**

This multicenter, 24-month, pre-post retrospective observational study included patients receiving current inhaled corticosteroid ICS therapy (alone or in combination with long-acting beta-agonist LABA), who received add-on treatment with montelukast for 12 consecutive months.

For the 696 patients from Italy, Poland, and Spain who were included in the analyses, the proportion of patients experiencing an asthma attack declined from 31.5% in the year before to 10.1% (p < 0.001) the year after addition of montelukast to therapy. Proportions of patients with an asthma-related emergency room visit, hospitalization, and oral corticosteroid use declined from 18.7% to 3.9%, from 5.2% to 1.4%, and from 17.5% to 5.9% (all p < 0.01), respectively. The incidence of these outcomes declined in all three countries, regardless of baseline asthma severity or asthma therapy (ICS alone or ICS + LABA).

Addition of montelukast to current ICS therapy improved long-term asthma control and resulted in substantial reductions in asthma-related resource use by patients with mild or moderate persistent asthma and concomitant seasonal AR who were persistent with montelukast therapy in this retrospective observational study.7

**PROTECTION AGAINST EXERCISE-INDUCED BRONCHOCONSTRICTION**

The objective of this double-blind cross-over study was to evaluate montelukast for the prevention of exercise-induced bronchoconstriction (EIB). Sixty-two patients with EIB (post-exercise decrease in forced expiratory volume in 1 second (FEV1) ≥20% at pre-randomization) were randomized to montelukast 10 mg or placebo, followed by exercise-challenge 2, 12, and 24 hours post-dose. Experts concluded that montelukast provided significant protection against EIB at 2 hours after a single dose.8

**MONTELUKAST AS ADD-ON TO BETA-AGONISTS AND AIRWAY RESPONSE**

The present study investigated whether single-dose oral leukotriene receptor antagonists as add-on therapy to short-acting beta-agonists, immediately after allergen challenge, block the late-phase airway response. In total, 35 mild asthmatics (mean age 24 yrs, 19 males) sensitised for house dust mites underwent two courses of bronchial allergen challenge. The results of the present study demonstrate that single-dose leukotriene receptor antagonists given orally right after the early allergic response can significantly inhibit the late allergic response after bronchial allergen challenge.9

**MONTELUKAST IN RECURRENT POST-BRONCHIOLITIS WHEEZING**

In the study group (20 children) treated with montelukast 5 mg/ day for 3 months, the frequency of bronchial obstruction episodes in the 6 months following the start of therapy was significantly lower (p = 0.001) than the 6 months before treatment (1.25 ± 1.41 versus 3.79 ± 2.41).

In the control group (18 children) treated with placebo, the frequency of the bronchial obstruction episodes decreased (from 3.04 ± 1 to 2.41 ± 1.5) in the two analysed periods, but nonetheless the differences were not statistically significant (p = 0.067). The differences between the two groups are present also after excluding

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<td>MONTEY-B 10</td>
<td>Montelukast Sodium eq.to Montelukast 10 mg, Bambuterol HCl BP 10 mg</td>
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the children with atopy. The results suggest the beneficial role of leukotriene receptor antagonists in improving the symptoms of patients with recurrent post-bronchiolitis wheezing.10

Efficacy of Montelukast in Perennial Allergic Rhinitis
This was a double-blind study of 15- to 85-year-old patients randomly allocated to montelukast, 10 mg (n=630), placebo (n=613), or the positive control cetirizine, 10 mg (n=122) for 6 weeks.

The Rhinoconjunctivitis Quality-of-Life score was significantly improved by montelukast (p < 0.05), but not by cetirizine, during 4 and 6 weeks. The treatment effect of montelukast, but not cetirizine, generally remained consistent through the 6 weeks of treatment. In pooled data, montelukast consistently improved DNSS versus placebo during all 6 weeks of treatment (-0.07 [95% CI, -0.10, -0.041]).

In conclusion, montelukast produced numerical improvement in daytime nasal symptoms and significant improvement in quality of life. In a pooled post hoc analysis, montelukast provided consistent improvement in daytime nasal symptoms over 6 weeks, supportive of an overall benefit in PAR.11

Montelukast Reduces Reactions of Allergic Immunotherapy
Experts selected a rush immunotherapy protocol consisting of 19 injections of hymenoptera venom administered over 5 consecutive days, where the majority is developing local reactions (LRs), and counted the number of injections until an LR of >3 cm occurred. The patients were randomized to 3 treatment groups: premedication with placebo, 10 mg montelukast and 5 mg of the antihistamine desloratadine. Compared with placebo, the occurrence of LRs (>3 cm) was significantly delayed by montelukast (p < 0.01, analysis of variance) but not by desloratadine (p = 0.19). The difference between montelukast and desloratadine was close to significant (p = 0.054). Itching, recorded on a scale from 0 to 5, did not differ between the 3 groups.12

Bambuterol
Bambuterol, a biscarbamate ester prodrug of the beta 2 adrenergic agonist terbutaline, has been approved for the treatment of asthma in 28 countries. It is approved for long-term treatment of asthma and other reversible obstructive airways diseases.

Bambuterol is stable to presystemic elimination and is hydrolysed to terbutaline. Peak terbutaline plasma concentrations are reached 1 hour after administration and the pharmacokinetics of the two drugs are similar. The pharmacokinetics of terbutaline is not significantly influenced by concomitant administration of bambuterol. Bambuterol is hydrolysed to terbutaline primarily by butyrylcholinesterase, and lung tissue is capable of this metabolic pathway. It is also oxidatively metabolised to products which can be hydrolysed to terbutaline. Peak terbutaline plasma concentrations occur 3.9 to 6.8 hours after bambuterol ingestion, and the peak: trough terbutaline concentration ratio is lower than that after ingestion of terbutaline.13 The efficacy of bambuterol has been demonstrated to last for 24 hours after ingestion; once-daily administration in the evening is recommended. Maximum therapeutic benefit requires more than 1 week of treatment.

Montelukast and Bambuterol
The rationale of combining montelukast and bambuterol is logical since beta2-agonists are already a proven effective class of drugs causing bronchodilatation. Combining montelukast, an established leukotriene modifier and bambuterol looks to be a logical cause since beta2-agonists are already a proven effective class of drugs causing bronchodilatation.

Bambuterol

Montelukast reduces reactions of allergen immunotherapy


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REFERENCES
Ideal combination

The combination of an oral bronchodilator (bambuterol) and a leukotriene receptor antagonist (montelukast) to take care of both the components of asthma, bronchoconstriction and inflammation which gives greater clinical efficacy.

Montelukast

Orally active compound that binds with high affinity and selectivity to the CysLT 1 receptor. Inhibits physiologic actions of LTD 4 at the CysLT 1 receptor without any agonist activity. Acts as a leukotriene receptor antagonist.

Bambuterol

Is a carbamate prodrug of terbutaline. First once daily oral b 2-agonist with 24-hour duration for the treatment of asthma. Following slow absorption from the GI-tract, the drug is metabolized via hydrolysis (plasma cholinesterase) and gets converted into its active metabolite terbutaline.

Indications

Prophylaxis and chronic treatment of asthma in patients 14 years of age and older.