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DECREASED USE OF ASTHMA AND ALLERGY DRUGS IN ITALIAN ASTHMATIC CHILDREN RECEIVING MONTELUKAST VERSUS OTHER CONTROLLERS

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BACKGROUND

- Leukotrienes are leukocyte-generated lipid mediators that promote eosinophil and mast-cell induced bronchoconstriction and inflammation associated with asthma.
- Recognition of the importance of leukotrienes in the pathogenesis of asthma has led to the development of leukotriene synthesis inhibitors and leukotriene receptor antagonists (LTRA). Montelukast is the only LTRA with proven efficacy in children 6 month–14 years.
- Montelukast improves pulmonary function, reduces symptoms, decreases night-time awakenings, and decreases the need for rescue medications as compared to placebo.
- Therapy with inhaled corticosteroids (ICS) is the recommended first choice treatment to reduce inflammation and symptoms in children with mild to severe asthma according to the GINA guidelines. However, people with asthma who remain symptomatic despite use of ICS should receive additional controller therapy. The dose of ICS can be increased or long-acting B-agonists (LABA) or LTRA can be added on to ICS treatment.
- Montelukast offers significant benefits when added to inhaled corticosteroids (according to secondary endpoint analyses) and may allow for tapering off of ICS and reduction in B-agonist use
- A randomized non-blinded study in 6-11 year old children showed that compliance and patient satisfaction was greater with montelukast than with sodium cromoglycate or inhaled beclomethasone

RATIONALE

- Clinical trial data assess the efficacy of a drug under protocol-driven circumstances with better adherence than in real life practice. Observational studies supplement clinical trial data since they provide information on effectiveness in a real-world clinical practice setting with more heterogeneous patient populations and poorer adherence.
- There is limited evidence from observational studies on effectiveness of Montelukast added to ICS vs. other asthma controllers in children with asthma initiating GINA stage 3 therapy requiring high dose ICS, addition of LABA to ICS or addition of Montelukast to ICS

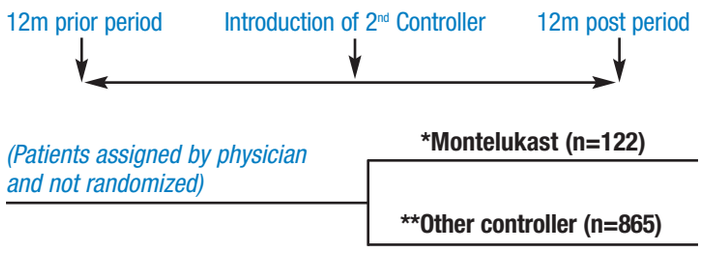
OBJECTIVES

- Evaluate and compare the following asthma outcomes in children receiving either montelukast [MON] or other asthma controller [OTHER], comprising high-dose inhaled corticosteroid (h-d ICS) or ICS + long-acting beta agonist (LABA):
  - Asthma exacerbations
  - Asthma-related hospitalizations
  - Asthma-rescue/acute and allergy medication use and cost

METHODS

Study Design

- 2-year retrospective pre-post cohort study in asthmatic patients <14 yrs



* ~75% of this group also received ICS
**Other Controller (h-d ICS, ICS+LABA)
n=All children

Setting

- Italy is one of the few countries in which a specific primary care system is devoted to children up to the age of 14 years. Within the framework of the National Health Service (NHS), every child is registered at birth and receives free medical care from one of the approximately 6,000 family paediatricians working for the NHS.
- PEDIANET is a network of family paediatricians who share a common project of epidemiological and clinical research on the care of children. They all maintain computerized medical records.
- A central PEDIANET database is kept in the city of Padua with the longitudinal medical records of children who are or have been registered with the collaborating pediatricians (n=109).
- For the purpose of this study, the data were collected and handled anonymously in compliance with the Italian law on privacy.

Population

- Italian children (<14 years) with asthma
- Registered for ≥2 years with pediatrician during period July 2001–October 2004
- Received ≥2 consecutive asthma-controller prescriptions* after July 1, 2001 in addition to existing therapy
  - *Controllers: high-dose ICS defined as 800 μg beclomethasone, > 400 μg budenoside, > 1250 μg flunisolide and > 500 μg fluticasone per day (www.gina.org), LABA (formoterol, salmeterol) or LTRA (only montelukast during study period)

METHODS (CONT'D)

- Continuous eligibility (>1 year of follow-up prior and after the index date)
- No chronic obstructive pulmonary disease, cystic fibrosis or bronchopulmonary dysplasia

Outcomes

- Asthma exacerbations (pre, post and difference) defined as either oral steroid use, hospitalization or bronchitis with bronchospasm, or unscheduled asthma-related visits with cough, dyspnea and/or wheezing
- Pre-post differences in mean per-child-per-year hospitalization rates
- Pre-post differences in mean per-child-per-month prescription costs and rates of
  - Rescue medications [RM] (short-acting beta agonist)
  - Acute medications [AM] (antibiotics, oral corticosteroids)
  - Allergy medications [ALM] (antihistamines, nasal steroids)
  - Other respiratory medications [ORM] (e.g. cromones)
- All data were obtained from the computerized medical charts and costs were obtained from the Italian drug tariff (2004 values). In order to extract data on exacerbations, a manual review of the records was required to ensure complete understanding of physician notes and correct coding.

Statistical Analyses

- Multivariate linear regression adjusting for baseline differences including age, gender, severity (derived via algorithm based on prior medication use), concomitant allergic rhinitis (AR) and sinusitis

RESULTS

Table 1: Baseline Treatment Patterns

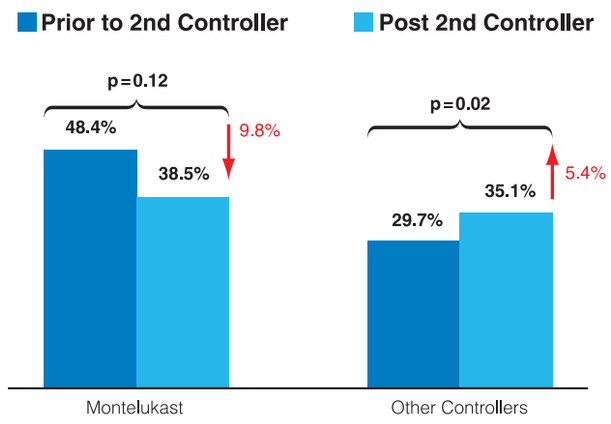
	N (% within group)	% (of total)
MONTELUKAST	**122**	**12%**
ICS+Montelukast	91 (75%)	9%
Montelukast monotherapy	31 (25%)	3%
OTHER	**865**	**88%**
High-dose ICS	677 (78%)	69%
ICS+LABA	187 (22%)	19%
LABA monotherapy	1 (<1%)	–
TOTAL	**987**	

Table 2: Baseline[1] Patient Characteristics

	Montelukast* N=122	OTHER** N=865	P-value
Female (%)	29.5%	40.2%	0.023
Age (mean, SD)	7.3	5.3	<0.001
Asthma severity			
Intermittent	44%	72%	<0.001
Mild	33%	19%	
Moderate	10%	6%	
Severe	13%	3%	
Allergic rhinits	19%	8%	<0.001
Sinusitis	4%	12%	0.008
Prior hospitalizations for asthma	2.5 %	0.8 %	0.008

NOTES: [1]At the time of 2nd asthma controller introduction
*75% added to ICS
**Includes h-d ICS and ICS+LABA; LABA alone negligible

Figure 1: Change in Asthma Exacerbations between Post and Pre Controller Treatment Periods – Children (<14) [% patients/per year]



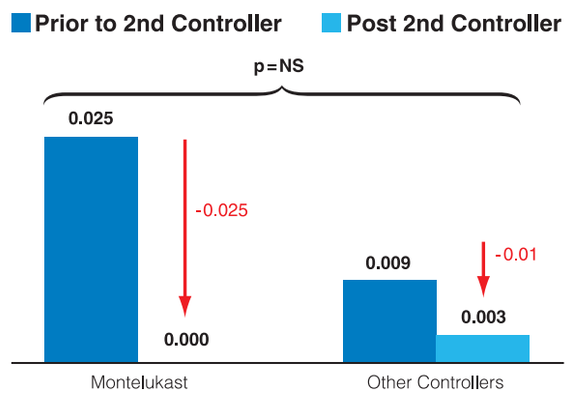
NOTES: ~75% children in Montelukast group also received ICS
Other controllers are hdICS or ICS+LABA

RESULTS (CONT'D)

Change in Asthma Exacerbations between Post and Pre Controller Treatment Periods – Multivariate Analysis

- After adjustment for age, asthma severity, concomitant allergic rhinitis and sinusitis:
  - Children on montelukast experienced a 5% decrease in risk of exacerbations compared to children on either h-d ICS or ICS+LABA controllers (p=NS).

Figure 2: Change in Asthma Hospitalizations between Post and Pre Controller Treatment Periods – Children (<14) [% patients/per year]



NOTES: ~75% children in Montelukast group also received ICS
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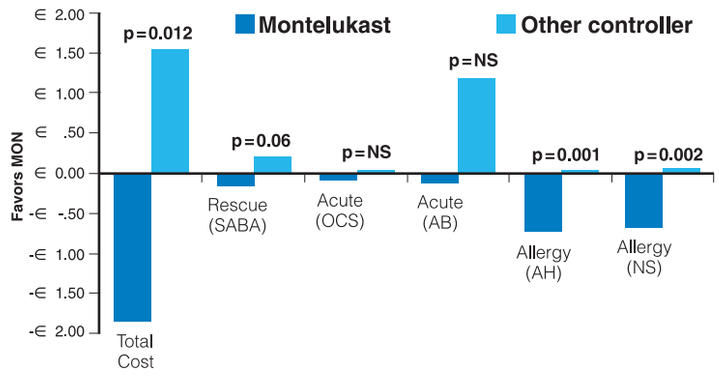
Figure 3: Cost Difference between Post and Pre Controller Treatment Periods — Children (<14) [Mean Euro per patient/per month]



NOTES: Total includes rescue, acute, allergy medications.
Rescue includes SABA. Acute includes oral corticosteroids and antibiotics.
Allergy includes antihistamines and nasal steroids.

CONCLUSIONS

- Children treated with montelukast (75% of patients received ICS at baseline) had more severe asthma and higher rates of concomitant allergic rhinitis at baseline compared to children treated with either h-d ICS or ICS+LABA.

DESPITE THIS:

- Children adding montelukast had similar reductions in asthma exacerbations and asthma-related hospitalizations compared to children who either received h-d ICS or added LABA to ICS.
- Significant decreases in total use and costs of asthma-rescue/acute and allergy medication were observed over a 2-year period among asthmatic children adding montelukast compared to those treated with either h-d ICS or ICS+LABA.

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