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Benefit from anti-inflammatory treatment during clinical remission of atopic asthma

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Remodeling

Summary *Study objectives*: Subjects with atopic asthma often experience a disappearance of symptoms around puberty. However, airway inflammation and remodeling may persist. It is unknown whether those findings warrant prolonged anti-inflammatory treatment despite the absence of symptoms. In this study, we investigated whether a short course of combined anti-inflammatory treatment would, also in this specific patient population, diminish airway inflammation and/or remodeling.

Design: A double-blind, randomized placebo-controlled trial was conducted in 28 asymptomatic subjects with a history of atopic asthma, with established bronchial hyperresponsiveness to methacholine (MCh) as non-invasive indicator of ongoing airway pathology.

Interventions: Intervention consisted of the salmeterol/fluticasone propionate combination (SFC) product (50/250 μg bid via the Diskus™ inhaler) or placebo for 3 months.

Measurements: The change in lung function (FEV_1), bronchial response to MCh and adenosine monophosphate (AMP), the fraction of nitric oxide in exhaled air (FENO) and quality of life (QOL) scores were measured. Also, bronchial biopsies were taken and cryo sections immunostained for eosinophils (major basic protein, MBP) and mast cells (tryptase and chymase) before and after treatment. The change in

Abbreviations: AMP, adenosine-5′-monophosphate; BAL, bronchoalveolar lavage; FENO, fraction of nitric oxide in exhaled air; LABAs, long-acting β_2-agonists, MBP, major basic protein; MCh, methacholine; PD_{20}, cumulative provocative doses causing a 20% fall in FEV_1; QOL, quality of life; RBM, reticular basement membrane; SFC, salmeterol/fluticasone propionate combination product

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reticular basement membrane (RBM) thickness, one of the parameters of airway remodeling, was also determined.

Results: SFC treatment improved hyperresponsiveness to MCh ($P = 0.014$) as well as AMP ($P = 0.011$), and reduced FENO ($P < 0.001$) significantly as compared with placebo. Lung function tended to improve (NS). Furthermore, SFC treatment reduced tryptase in the subepithelium of bronchial biopsy specimens ($P = 0.01$), and slightly reduced RBM thickness ($P = 0.05$). However, eosinophils in (sub)epithelium were not significantly affected; neither were chymase levels, blood eosinophils or QOL scores.

Conclusions: We found that 3 months of treatment with fluticasone propionate and salmeterol reduced airway hyperresponsiveness, FENO and tryptase density in the airway mucosa as markers of airway inflammation. MBP density in the airway mucosa and QOL were, however, unchanged. The clinical relevance of these findings, especially with respect to the long-term outcome, has not been determined yet.

Introduction

Atopic asthma commonly starts in childhood and often seems to disappear in early adolescence.[1,2] The term ''clinical remission'' is widely used to identify subjects with apparently outgrown asthma. Unfortunately, a substantial proportion those subjects will have a relapse later in life, mostly before the age of 30.[2] Recently, airway inflammation and structural airway changes were demonstrated in airway biopsy specimens and bronchoalveolar lavage (BAL) fluid from young adults with a longstanding clinical remission of atopic asthma.[3,4] Ongoing inflammation and remodeling possibly contribute to irreversible airway narrowing[5] and bronchial hyperresponsiveness, thereby probably providing a basis for a future relapse of asthma.

It is unclear whether the long-term prognosis of subjects in clinical remission of asthma, but with evidence of ongoing disease, can be altered positively with prolonged anti-inflammatory therapy. There is ample evidence that inhaled steroids decrease airway inflammation,[6] whereas the effect on remodeling is less evident.[7,8] An effect on subepithelial collagen deposition[9] and airway wall vascularity[10] was, however, documented. It has also been shown that in very mild asthmatic subjects, anti-inflammatory therapy with fluticasone propionate reduces airway inflammation and remodeling after 3 and 12 months of therapy, respectively.[11] Besides, De Kluijver[12] demonstrated that low-dose allergen exposure in asymptomatic asthmatic subjects led to airway inflammation without worsening of symptoms, which could be prevented by inhaled steroid treatment. Hence, the question is whether persistent airway inflammation and remodeling warrant the use of prolonged anti-inflammatory treatment in otherwise asymptomatic subjects with a history of atopic asthma.[9,13,14] To provide an answer to this question, it should at first and foremost be evaluated whether anti-inflammatory therapy indeed has a direct diminishing effect on airway inflammation and/or remodeling in this specific patients' population. Subsequently, future studies should elucidate whether prolonged anti-inflammatory therapy will positively alter the long-term prognosis from subjects in clinical remission of asthma.

When it comes to the treatment of choice, there is a rationale for combining inhaled steroids with long-acting β_2-agonists (LABAs) in the present study population. After all, a novel anti-neutrophilic effect of the LABA salmeterol in mild asthma has been reported recently,[15] next to an anti-eosinophilic effect of the LABAs salmeterol[16] and formoterol.[17]

Therefore, it was the aim of this study to investigate the effect of a short course of combination treatment with salmeterol and fluticasone propionate on indices of airway inflammation and remodeling in young adults in longstanding clinical remission of atopic asthma, who had hyperresponsiveness to methacholine (MCh) as non-invasive indicator of ongoing airway disease.

Subjects, study design and methods

Subjects

Young adults, 18–30 years of age, were selected from the Sophia Children's Hospital discharged atopic asthma patients files. Clinical remission of atopic asthma was defined as to two independent investigators repeatedly reported complete absence of asthmatic symptoms while not taking any asthma or allergy medication for at least 12 months prior to the study. Subjects with perennial rhinitis