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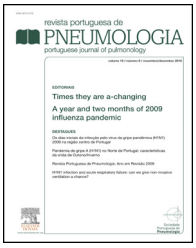

ORIGINAL ARTICLE

Long-term clinical effects of aspirin-desensitization therapy among patients with poorly controlled asthma and non-steroidal anti-inflammatory drug hypersensitivity: An exploratory study

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Nasal polyps

Abstract
Background: According to the Global Initiative for Asthma (GINA), the levels of asthma symptom control can be divided into controlled, partially controlled and uncontrolled asthma. Optional therapy for non-steroidal anti-inflammatory drugs (NSAIDs)-hypersensitive asthmatics uses aspirin desensitization, but until now, this therapy is not established in difficult to treat cases. The aim of this study was to evaluate the efficacy of aspirin desensitization in patients with poorly controlled asthma.
Methods: Patients with poorly controlled asthma, NDAIDs hypersensitivity and aspirin desensitization were included in the retrospective study. The data were compared to those obtained from patients with controlled asthma and aspirin therapy. Lung function, levels of asthma symptom control, asthma medication, the size of nasal polyps (NP) and smell function were evaluated over 18 months.
Results: Thirty-two patients were included in the study (uncontrolled/partially controlled asthma $n = 12$; controlled asthma $n = 20$). After 18 months of follow-up, the patients with poorly

Abbreviations: AERD, aspirin-exacerbated respiratory disease; ASA, acetylsalicylic-acid; FEV1, forced expiratory volume in 1 s; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; LABA, long-acting beta2-agonists; Mo, months; NP, nasal polyp; NSAIDs, non-steroidal anti-inflammatory drugs; PEF, peak expiratory flow; SABA, short-acting-beta2-agonists; VC, vital capacity; V1, visit 1 after 6 months therapy; V2, visit 2 after 12 months therapy; V3, visit 3 after 18 months therapy.

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controlled asthma had significantly increased forced expiratory volume in 1 s (FEV1) values, as compared to the baseline (66–82%; $p = 0.02$), the levels of asthma control improved significantly ($p < 0.01$). The asthma medication was reduced. In the group of controlled asthma the FEV1 values did not increase significantly (91.9–92.4%; $p > 0.05$) and the asthma medication was constant. In relation to nasal parameters the sense of smell improved significantly in both groups, NP-scores did not differ significantly.

Conclusions: Patients with a poorly controlled asthma and NSAIDs hypersensitivity profit from an add-on aspirin therapy.

Introduction

Asthma is a global respiratory health problem affecting 1-18% of the population in different countries.[1] According to the Global Initiative for Asthma (GINA), the levels of asthma symptom control can be divided into controlled, partially controlled and uncontrolled asthma forms.[1] Intolerance to non-steroidal anti-inflammatory drugs (NSAIDs) can be detected among 13–21% of the asthmatics.[2,3] For the asthmatics with nasal polyps (NP), the incidence of NSAIDs intolerance increases to 30%.[4] This association has been termed as ''aspirin triad'', ''aspirin-exacerbated respiratory disease'' (AERD) or ''NSAIDs hypersensitivity''.[5,6] The pathogenesis of the AERD is based on a shift from eicosanoids to leukotrienes.[7] Depending in its severity, asthma can be treated with beta-2 mimetics, corticosteroids, leukotriene receptor antagonists, theophylline or anti-IgE antibodies.[1] A further therapeutic option for asthmatics and NSAIDs hypersensitivity is the aspirin desensitization,[8] where the patient is gradually introduced step by step to aspirin, and a daily maintenance dose is determined. The underlying mechanism of aspirin desensitization has until today not yet been completely clarified. Interestingly, following desensitization, there is an increase in the prostaglandin PGE_2/leukotriene index in patients' blood.[9] To the best of our knowledge, clinical effects of aspirin desensitization in patients with a poorly controlled asthma and NSAIDs hypersensitivity have not yet been reported. For this reason, the aim of our study was to investigate the outcome of aspirin desensitization in patients with NSAIDs hypersensitivity and a poorly controlled asthma. We performed comparative analyses using the data obtained from the patients with controlled asthma and NSAIDs hypersensitivity who underwent aspirin therapy.

Methods

Patients routinely desensitized against at least 18 months in the Department of Pulmonology (Treuenbrietzen, Germany) or the ORL Department of the Charité University Hospital (Berlin) between 2009 and 2013 were included in this retrospective study. All patients enrolled in the study gave their informed consent. The inclusion criteria were NSAIDs sensitivity, nasal polyps, controlled or poorly controlled asthma.

Twelve patients (mean age 48 y, range from 32 y to 73 y, 4 men, 8 women) with poorly controlled asthma and 20 patients with controlled asthma (mean age 57.75 y, range from 44 y to 67 y, 8 men, 12 women) were included. The ''poorly controlled asthma''-group consisted of ten patients with uncontrolled asthma and two patients with partially controlled asthma. Aspirin was recommended to be taken by both groups, in order to improve the nasal and asthma symptoms.

NSAIDs sensitivity was confirmed by oral aspirin provocation test; a positive reaction was a decline of forced expiratory volume in 1 s (FEV1) $\geq$ 20% of baseline and profound rhinorrhea or nasal blockage.[10] The patients were stepwise desensitized to oral aspirin in the hospital with a final daily aspirin maintenance dosage of 500 mg. The following desensitization protocol was used: day 1: placebo/placebo/placebo; day 2: 1/2/4/8; day 3: 10/20/40/80; day 4: 100/100/150; day 5: 200/200/500; from day 6: 500 mg orally administered aspirin.

Following parameters were evaluated:

Levels of asthma symptom control: Assessment of symptom control was done by strictly following the GINA criteria[1] – see Table 1. Following groups of patients were identified:

1. Controlled or stable asthma group: well controlled asthma;
2. Poorly controlled or instable asthma group: partially controlled asthma/uncontrolled asthma.

Pulmonary function values: The peak expiratory flow (PEF) variability was measured before aspirin desensitization. The forced expiratory volume in 1 s (FEV1) and vital capacity (VC) were measured by spirometry before and following aspirin treatment.

Use of asthma medication: The daily use and dosages of the asthma medication were documented. The daily dosages of inhaled corticoids (ICS low/medium/high dosage) and the asthma medication scores were obtained in accordance to GINA criteria.[1] Prednisolone-dependent patients were separated from the dual GINA classification of severity. The medication was not changed 6 months prior to desensitization.

Nasal endoscopy: The Davos-staging of nasal polyps (NP) size was performed (0: no NP; 1: NP in middle meatus; 2: NP beyond middle meatus; 3: obstructing NP).[11]

Sense of smell: The subjective olfactory function was semi-quantitatively documented (0: no sense of smell; 1: mild sense of smell; 2: moderate sense of smell; 3: excellent sense of smell).

Follow-up: The patients were routinely examined before aspirin therapy, 6, 12 and 18 months (visit 1, 2 and 3)