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RESEARCH ARTICLE

Effects of omalizumab on eosinophil cationic peptide, 25-hydroxyvitamin-D, IL-1β and sCD200 in cases of Samter's syndrome: 36 months follow-up

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Abstract

Contex: The historic triad of nasal polyposis, asthma and intolerance to aspirin and related chemicals, recently designated as Samter's syndrome, is an inflammatory condition of unknown pathogenesis. This study surveyed the levels of chosen serum eosinophil cationic peptide (ECP), soluble CD200 (SCD200), interleukin (IL)-1β, high sensitive C-reactive protein (hs-CRP) and 25-hydroxyvitamin-D (25(OH)D) in the aspirin-induced asthmatic patients treated with anti-IgE therapy to investigate their roles in the pathogenesis of disease perpetuation and anti-IgE therapy's impact on them.

Methods: Medical history, lung function tests and measurement of fractional exhale nitric oxide concentrations were performed on the same day. Concentrations of IL-1β and SCD200 in the serum samples were quantified using ELISA kits. Total and specific IgE and hs-CRP levels were enumerated by fluoroenzyme immunoassay. Serum levels of 25(OH)D were quantified by a radioimmunoassay.

Results: We had three patients of severe persistent allergic asthma with Samter's syndrome. Levels of total IgE, ECP, fractional exhale nitric oxide concentrations, SCD200, IL-1β and hs-CRP were decreased while 25(OH)D was increased after starting the treatment of anti-IgE.

Conclusions: To our knowledge, this is the first time an association between omalizumab use and Samter's syndrome has been documented. As a conclusion allergic nasal symptoms (sneezing, postnasal drip) and asthma symptoms were decreased in patients, but no change was seen on nasal polyposis development after omalizumab treatment.

Keywords

Anti-IgE, aspirin-induced asthmatic patients, eosinophil cationic peptide, fractional exhale nitric oxide concentrations, 25-hydroxyvitamin-D, IL-1β, omalizumab, Samter's syndrome, soluble CD200

History

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Introduction

The historic triad of nasal polyposis, asthma and intolerance to aspirin and related chemicals, recently designated as Samter's syndrome, is an inflammatory condition of unknown pathogenesis[1,2]. Patients with Samter's triad were significantly more likely to have a recurrence and undergo a second surgery following reccurence than were patients without asthma or with only asthma from the triad[3–5]. On average, patients with Samter's triad had undergone approximately 10 times as many previous endoscopic sinus surgery procedures as had the patients without Samter's triad. At six months following the most recent surgery, patients with Samter's triad had significantly higher rates of symptom recurrence (nasal obstruction, facial pain, postnasal drip and anosmia) and a recurrence of nasal polyps[6].

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The development of anti-IgE therapy (omalizumab, Xolair) over the past 20 years provides an interesting example of the emergence of a conceptually new therapeutical class for allergic asthma. It is conceivable that mast cells residing in the nasal lining, lower airway, other areas of the mucosal tracts and in the skin differ in tryptase and chymase content, sensitivity, receptor regulation and life span[7–9].

In Turkey, omalizumab was approved for treating patients 14 years and older with severe allergic asthma in 2006 and a payment policy was issued by the Health Insurance Bureau in the same year. Moreover, our knowledge about the omalizumab in use of asthma and other allergic diseases has improved to such an extent that we can now better understand the treatment influence on levels of oxidative stress markers, high-sensitive C-reactive protein (hs-CRP) and inflammatory markers such as T cell related cytokines (interleukin (IL)-17, IL-8, IL-10, transforming growth factor-β, granulocyte colony-stimulating factor)[10–12]. When nasal poliposis patients with asthma is divided into subgroups as aspirin-induced asthmatic (AIA) patients and aspirin-tolerant asthmatic (ATA) patients, AIA patients had more extensive sinonasal disease

than ATA patients. After surgery, CT improvement with worse CT scores were seen in AIA patients[13].

Also, it is not yet known what the potential long-term effects of Xolair use may have on people who are prone to getting cancer (such as the elderly). While it would appear that omalizumab has potentially severe side effects, it must be remembered that anaphylaxis and cancer formation occurred only in a very small number of patients. We showed that omalizumab therapy increases blood glucose levels in allergic asthma patients with diabetes mellitus. Although we do not know the exact mechanism behind this relationship, it might be related with vial containing of omalizumab[14].

This is a pilot study that surveyed the levels of chosen serum eosinophil cationic peptide (ECP), soluble CD200 (SCD200), IL-1β, hs-CRP and 25-hydroxyvitamin-D (25(OH)D) in the AIA patients treated with anti-IgE therapy to investigate their roles in the pathogenesis of disease perpetuation, and anti-IgE therapy's impact on them.

Methods

Experimental procedures

Blood samples were drawn at first diagnosis (pre-omalizumab period) and after 36 months of treatment during disease remission (post-omalizumab period). Blood samples measurement were always taken in the morning between 8 and 10 am. Participants abstained from caffeinated drinks and food for 12 h before testing. Medical history, lung function tests and measurement of fractional exhale nitric oxide (FENO) concentrations (ppb) were performed on the same day. FENO concentrations were assessed following ATS/ERS guidelines[15]. Concentrations of IL-1β, SCD200 in the serum samples were quantified using ELISA kits (DEIA234-Creative Diagnostics, Shirley, NY). Total and specific IgE levels were enumerated by fluoroenzyme immunoassay (ImmunoCAP-FEIA) using an ImmunoCAP (Pharmacia, Uppsala, Sweden) kit. Values above 100 and 0.35 kU/L for total and specific IgE levels were considered abnormal. Serum hs-CRP levels were measured using a hs-CRP assay (Behring-Latex-Enhanced using the Behring Nephelometer, BN-100; Behring Diagnostics, Westwood, MA). The sensitivity of the assay ranged 0.04–5.0 mg/L. Serum levels of 25(OH)D were quantified by a radioimmunoassay (Cobra-Quantum, Packard, MN) and categorized into sufficient ($\geq$30 ng/mL), insufficient (20–<30 ng/mL) or deficient (<20 ng/mL).

A spirometry was performed at each visit. Reference values for the Mediterranean population were used[16].

Skin prick tests (SPTs) on the forearm were performed in all patients using standardized latex extract containing high ammonia natural rubber latex, and a full set of 70 common and food allergens. SPTs were performed by skilled nursing personnel. Positive tests were counted as wheals of 3 mm in diameter after 20 min. Tests were compared with positive histamine controls and negative saline controls. Commercial extracts used were manufactured by Allergopharma (Reinbek, Germany). No intradermal tests were performed. The specific IgE levels were correlated with the SPTs. Autologous serum skin test was performed by injecting 0.05 mL of the patient's own serum intradermally into the left flexor forearm, 2 in below the antecubital crease and a saline control into the right forearm. A reading of the wheal was taken after 30 min. A wheal and flare of more than 1.5 mm diameter than that of the control was considered positive.

Treatment control and protocol

Patients were asked to describe their asthma treatment at each outpatient visit, and the total monthly oral corticosteroid dose was recorded. In the case of exacerbation, patients were asked to come to the hospital, if possible to the outpatient center at our allergy service during business hours rather than the emergency room (ER) in order to facilitate treatment control. Nonetheless, data for patients who came to the ER and discharge treatment were recovered, since the clinical histories at the hospital are computerized. Best Standard Care following the recommendations of the Global Initiative for Asthma included inhaled fluticasone 500 mg bid, inhaled salmeterol 50 mg bid and oral methyl-prednisolone. Prior to starting omalizumab treatment, patients underwent a run-in period of at least 36 months. The protocol followed for decreasing oral steroid administration was as follows: the daily dosage was decreased by 2 mg/d; if the patient remained stable, at the end of the two weeks the daily dosage was decreased by a further 2 mg for the following weeks. Steroid dosage was then increased to the previous level and the process was repeated.

The study was approved by the local ethics committee, and written informed consent was obtained from all patients and healthy volunteers.

Results

Their asthma was not under control and frequent emergency department admissions lead us to use omalizumab treatment. All of the patients had an asthma control test score (pre-omalizumab period) of <20, indicating that asthma was not well controlled on previous treatment, before the omalizumab therapy.

It is found that evidence of misdiagnosis of asthma in subjects who were obese[18]. Our patients were not obese (Table 1).

Case I: body temperature (BT) was 36.7 °C with heart rate of 92 beats/min and 120/70 mmHg arterial blood pressure with tachypnea and wheezing. He was operated eight times because of nasal polyposis. Previously, he was diagnosed of Hashimato's, thyroiditis and aspirin allergy. Thyroid antibodies were positive in patient. His past history revealed angioedema and otoimmune urticaria exacerbations for seven years which sometimes associated with larynx edema. Patient's autologous serum skin prick test was positive. After the third round of omalizumab, frequency of exacerbations decreased and after 11th round it was completely disappeared.

Case II: BT was 36.6 °C with heart rate of 88 beats/min and 110/65 mmHg arterial blood pressure with tachypnea and wheezing. She was operated five times because of nasal polyposis. The patient had previously reported nonsteroidal anti-inflammatory drug induced anaphylaxis.

Case III: BT was 36.9 °C with heart rate of 90 beats/min and 120/60 mmHg arterial blood pressure with cyanosis, tachypnea and wheezing. She was operated two times because

Table 1. Laboratory and clinical findings of the patients.

	Case I	Case II	Case III	
Age (years) and gender	39 male	56 female	34 female	
BMI (kg/m^2)	25	29	26	
DSA	6	7	7	
F.period	3	3.5	3	
Number of injection/dose of omalizumab (mg per 2 weeks)	52/225	64/300	48/300	
SPTs	Grass, mite, cockroach.	Grass, tree, mite, shrimp, perch, egg, latex.	Grass, tree, mite, kiwi, orange.	
		Pre-omalizumab/post-omalizumab		
Daily ınhalant steroid Doses (μg)	2000/1000	3000/1000	2000/1000	
Daily oral steroid doses (mg)	8/0	6/0	6/0	
FVC (%)	62/91	57/94	71/110	
FEV1 (%)	55/67	52/84	72/91	
PEF (%)	62/67	67/75	65/78	
MEF 25–75 (%)	33/45	42/51	67/79	
ACTS (0–24)	16/23	14/22	16/23	
FENO (ppb)	51/28	62/29	48/31	
Laboratory markers		Pre-omalizumab/post-omalizumab		Normal range
ECP (ng/mL)	84/31	248/55	119/32	6–24
SCD200 (pg/mL)	52/21	59/22	42/13	
IL-1β (pg/mL)	28/12	39/11	27/9	
Hb (g/dL)	13.5/12.9	13.9/13	12.4/12.9	12–16
WBC (mL)	5400/8200	4800/4400	7940/6300	4800–10 800
Eosinophil (%)	7.9/1.5	9.9/1.5	6.4/0.6	0.9–2.9%
Basophil (%)	2.4/0.1	0.9/0.1	1.6/0.0	0.2–1%
Platelet (mL)	220 000/170 000	180 000/150 000	410 000/370 000	150 000–450 000
MPV (fL)	12.5/12.4	11.5/12.0	10.1/10.1	6.5–11.6
Hs-CRP (mg/L)	6.2/5.1	9.9/5.3	8.5/3	0–6
Total IgE (IU/L)	446/124	135/90	249/128	0–100
25(OH)D (ng/mL)	15/22	8/25	20/22	

DSA: duration of severe persistent asthma years; BMI: body mass index; F.period: followed-up for years ACTS: asthma control test score; ECP: eosinophilic cationic peptid; SPTs: skin prick tests; hs-CRP: high sensitive C-reactive protein; 25(OH)D: 25-hydroxyvitamin D; FENO: fractional exhale nitric oxide concentrations.

of nasal polyposis. Previously, she was diagnosed of multi-drug allergy.

Anti nuclear antibody, hepatitis markers, HIV and rheumatoid factor were negative in all patients. Liver and renal function tests, complement-4 levels were within normal ranges.

Blood levels of total IgE, ECP, SCD200, FENO concentrations, IL-1β and hs-CRP were decreased while 25(OH)D was increased after starting the treatment of anti-IgE. Their routine blood counts, pulmonary function test findings and other biochemical tests were given in Table 1.

Discussion

Many patients with Samter's syndrome also have a marked eosinophilia of both bronchial and nasal secretions as well as the circulating blood. Approximately 10% of the patients have urticaria–angioedema, alone or in combination with respiratory inflammation. As with all allergic diseases, the cornerstone of treatment is environmental control with avoidance of respiratory irritants, aspirin and aspirin-like medications. Management of upper airway disease requires careful prescription of medication supplemented by judicious selection of surgery[1,2]. In this follow-up, omalizumab significantly improved asthma control test scores and pulmonary function in patients with Samter's syndrome.

Asthma is associated with increased levels of eosinophils in tissues, body fluids and bone marrow. Elevated levels of ECP have been noted in asthma patients. ECP, with low RNase activity, is widely used as a biomarker for asthma. ECP inhibits cell viability and induces apoptosis to cells[17]. Toxic epidermal necrolysis pathogenesis in immunological symptoms are similar to graft versus host disease. We found that sCD200 levels were higher in blister fluid than serum[19]. *In vivo* testing in a murine model of passive cutaneous anaphylaxis revealed that inhibition *in vivo* by CD200R1 cross-linking was much more sensitive than that seen *in vitro*, perhaps reflecting a higher constitutive expression of CD200R1 on mast cells *in vivo* compared with cells maintained in culture, and/or the existence of other cell–cell interactions *in vivo* which could lower the threshold for CD200R1-mediated suppression. The data from these *in vivo* studies were taken to imply a potential clinical utility for CD200:CD200R1 in regulation of allergic inflammatory disease[20]. 25(OH)D is a steroid hormone that is now widely accepted to exert several extraskeletal actions. In relation to the lung, evidence from observational studies, animal models and *in vitro* cell culture suggest that 25(OH)D may play a beneficial role in pulmonary inflammation[21]. 25(OH)D has effects on the innate and adaptive immune system. 25(OH)D levels are associated with poor asthma control, reduced pulmonary function, increased medication intake and exacerbations. Little is known about 25(OH)D in adult asthma patients or its association with asthma severity and control[22]. In autoinflammatory as well as allergic diseases such as hypersensitivity and bronchial asthma, dysfunctional inflammasome processing has been demonstrated to account for IL-1β-induced inflammation[23]. We investigated soluble

CD200 that can also be linked to apoptosis and is an immunosuppressive ligand[20]. Blood levels of total IgE, ECP, SCD200, IL-1β, FENO concentrations and Hs-CRP were decreased while 25(OH)D and IL-8 were increased after starting the treatment of anti-IgE. We think that decreased oral steroid usage is the reason of increased 25(OH)D levels.

Omalizumab demonstrated clinical efficacy in the treatment of nasal polyps with comorbid asthma, supporting the importance and functionality of local IgE formation in the airways[24], but in our study, no changes was seen on nasal polyposis after omalizumab treatment. Nasal polyps from patients with Samter's triad had a significantly higher inducible nitric oxide synthase activity when compared with the nasal polyp patients without Samter's syndrome[25].

To our knowledge, this is the first time an association between omalizumab use and Samter's syndrome has been documented. As a conclusion allergic nasal symptoms (sneezing and postnasal drip) and asthma symptoms (cough, dyspnea) were decreased in patients, but no change was seen on nasal polyposis development after omalizumab treatment operated once more.

Author contribution

ADY contributed substantially to conception and acquisition of data, and followed-up the patients. Laboratory works were taken care by SG and ADY. ADY, SU and LGS drafted the article critically for important intellectual content and gave final approval of the version to be published.

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Declaration of interest

The authors declare that they have no conflict of interest.

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