

EXPERT OPINION

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Omalizumab is effective in treating severe asthma in patients with severe cardiovascular complications and its effects on sCD200, d-dimer, CXCL8, 25-hydroxyvitamin D and IL-1 β levels

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Background: There have been concerns about the cardiovascular safety of omalizumab.

Objectives: In this study, the clinical status of the omalizumab receiving severe asthma patients and the cytokine expressions patterns were investigated.

Materials and methods: In a pilot study described below we examined the levels of serum eosinophil cationic peptid (ECP), CD200, d-dimer, 25-hydroxyvitamin D (25(OH)D), CXCL8 and IL-1 β in asthma patients treated with anti-IgE therapy, to explore their relationship with disease activity, and the impact of anti-IgE therapy impact on those levels. Exercise stress testing and blood samples were taken at all follow up visits from the time of first diagnosis and after 20 months of treatment during the disease remission.

Results: Fractional exhaled nitric oxide concentrations and serum levels of sTRAIL, sCD200, D-dimer, ECP, total IgE, IL-1 β and Hs-CRP were decreased while CXCL8, 25(OH)D were increased after starting the treatment of anti-IgE. Our first case of a patient, who had both protein C and S deficiency and hence a high risk for thromboembolism, documents for the first time the safety of omalizumab for asthmatic patients with concurrent risk factors contributing to arteriothrombotic events.

Conclusion: Omalizumab might be used carefully in patients with cardiovascular diseases.

Keywords: 25-hydroxyvitamin D, asthma, cardiovascular risk, CXCL8, IL-1 β , omalizumab, protein C and S deficiency, sCD200

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1. Introduction

Since the discovery of IgE in 1967, the mechanisms of immediate-type hypersensitivity and allergy have been increasingly unraveled. IgE binds to the high-affinity IgE-Fc receptor on mast cells and basophils and mediates inflammatory cascades of the allergic response [1]. The mechanism of action of omalizumab in the treatment of asthma is believed to be multifactorial and includes effects mediated through altered production of redox metabolites and regulation of production of known inflammatory proteins [2-5]. It is conceivable that mast cells residing in the

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Table 1. Clinical findings and omalizumab dose schemes in asthmatic patients.

Case (C)	C-I	C-II	C-III	C-IV	C-V
Age (year) and gender	48 male	53 female	54 female	63 male	38 female
ADY	31	12	34	15	19
F. period (months)	26	21	22	23	43
BMI (kg/m ²)	21.6	27.2	26.6	24.8	25.3
Smoker	NO	NO	NO	NO	NO
Comorbidities	PS-CD, irregular emphysema and MPE	Nasal polyposis, multidrug allergy, HT, CHF and IC	HT, MVP, MVR, HST and CHF	AA and autoimmune urticaria	HT, RA and HST
SPT	Mite and mold	Grass, mite, cockroach and cat	Grass, wheat, mold, tree, mite, dog and cat	Grass, wheat, mold, cockroach and mite	Mite, barley mixture and molds
NOI/DAI (mg per in 2 weeks)	47/375	26/300	24/375	22/375	65/300
DISD (µg)	2000/2000	2000/1000	4000/2000	2000/500	1000/1000
Pre/post-anti-IgE					
DOSD (mg)	60/4	16/0	40/4	24/0	20/4
Pre/post-anti-IgE PFT	Pre-anti-IgE/post-anti-IgE				
FVC (%)	66/90	71/90	40/64	75/89	46/93
FEV1 (%)	56/72	56/74	35/58	54/66	43/82
PEF (%)	75/74	64/71	39/46	64/68	55/72
MEF 25 – 75 (%)	34/36	36/39	22/30	37/42	53/58
ACT	7/18	14/22	6/14	14/20	6/21
SOA	27/14	22/11	26/17	23/10	25/16

AA: Aortic aneurysm; ACT: Asthma control test score; ADY: Asthma diagnosis year; BMI: Body mass index; CHF: Congestive heart failure; DAI: Dose of anti-IgE; DISD: Daily inhalant steroid doses; DOSD: Daily oral steroid doses; F.period: Followed-up for a period; HST: Hashimoto's thyroiditis; HT: Hypertension; IC: Intracranial embolus; MPE: Multiple pulmonary embolus; MVP: mitral valve prolapse; MVR: Mitral valve replacement; NOI: Number of injection; PFT: Pulmonary function test; PS-CD: Protein-C, protein-S deficiency; RA: Rheumatoid arthritis; SOA: Severity of asthma; SPT: Skin prick test.

nasal lining, lower airway, other areas of the mucosal tracts and in the skin, differ in tryptase and chymase content, sensitivity, receptor regulation and lifespan [6,7].

Most asthmatic individuals respond satisfactorily to inhaled corticosteroids and β -adrenergic agonists; however, 5 – 10% of them have severe, persistent symptoms that respond poorly to such treatment [8,9]. Those patients, who cannot be adequately controlled with even high doses of corticosteroids and often require repeated emergency visits and hospitalization, are approved to use omalizumab by the health insurance systems in many countries. There have been concerns about the cardiovascular safety in patients initiating omalizumab therapy, due to the most recent study that analyzed the association between omalizumab and arterial thrombotic events [10-12]. Herein, we report five cases, wherein allergic asthma patients with comorbid severe cardiovascular complications were effectively treated with omalizumab, with improvements both in pulmonary and cardiovascular functions. To our knowledge, no similar report has been published.

In a pilot study described below, we examined the levels of serum eosinophil cationic peptide (ECP), soluble CD200, TNF-related apoptosis inducing ligand (sTRAIL), d-dimer, 25-hydroxyvitamin D (25(OH)D), CXCL8 and IL-1 β in

allergic asthma patients treated with anti-IgE therapy, to explore their relationship with disease activity, and the impact of anti-IgE therapy impact on those levels.

2. Materials and methods

Exercise stress testing and blood samples were taken at all follow-up visits from the time of first diagnosis and after 20 months of treatment during the disease remission. Blood samples for CXCL8, IL-1 β , sTRAIL, ECP, high sensitive C-reactive protein (hs-CRP), d-dimer, sCD200, 25(OH)D total and specific IgE measurement were always taken in the morning between 08.00 and 10.00 h. The results were reported as means of duplicate measurements. Participants abstained from caffeinated drinks and food for 12 h before testing. Medical history, lung function tests, measurement of exhaled nitric oxide concentrations (FENO) were performed on the same day.

Assessment of clinical changes and adverse effects were evaluated at each bimonthly patient visit, including vital signs, full physical examination, details of any allergy incidents, total and specific IgE levels, serum ECP levels, pulmonary function tests (FEV1/FVC rates), FENO concentrations and asthma control test (ACT) (Quality Metric Inc.). The severity of

asthma score (SOA) was used as a measure of asthma severity. All ongoing usage of medication was recorded for all patients, and asthma severity and control was defined based on symptom load and treatment intensity. The use of additional steroid therapy and the doses given are recorded in Table 1.

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-Immunology Service during business hours rather than the emergency room in order to facilitate treatment control.

Best standard care, following the recommendations of GINA, included inhaled corticosteroids (fluticasone 500 mg b.i.d.), inhaled long-acting β -agonists (salmeterol 50 mg b.i.d.) and oral methylprednisolone. Prior to starting omalizumab treatment, patients underwent a trial period of at least 42 months. The protocol followed for decreasing oral steroid administration was as follows: the daily dose was decreased by 2 mg/day; if the patient remained stable, at the end of the 2 weeks, the daily dose was decreased by a further 2 mg for the following weeks; steroid dose 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.

Skin prick tests (SPT) 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. The commercial extracts used were manufactured by Allergopharma (Germany). No intradermal tests were performed. The specific IgE levels were correlated with the SPTs.

2.1 Experimental procedures

Concentrations of sCD200 in the serum samples were quantified using enzyme-linked immunosorbent assay (ELISA) kit (Sino Biological, Inc., Catalog Number: SEK10886). IL-1 β levels were measured using ELISA kit (Diacclone, Catalog No: 851.610.005). CXCL8 levels in culture supernatants were determined using a 'sandwich' ELISA with paired antibodies purchased from Endogen, Inc. (Woburn, MA, USA). The ELISA was performed using the Diacclone, France sTRAIL ELISA kit according to the manufacturer's instructions. Total and specific IgE levels were enumerated by fluoroenzyme immunoassay (ImmunoCAP) using an ImmunoCAP (Pharmacia, Uppsala, Sweden) kit. Values > 100 and 0.35 kU/L for total and specific IgE levels, respectively, were considered abnormal. Serum hs-CRP levels were measured using a hs-CRP assay kit (Behring Latex-enhanced using the Behring Nephelometer BN-100; Behring Diagnostics, Westwood, MA, USA). The sensitivity of the assay ranged from 0.04 to 5 mg/l. Serum levels of 25(OH)D were quantified by a radioimmunoassay (Cobra Quantum, Packard, MN, USA) and categorized into sufficient ($\geq$ 30 ng/ml),

deficient (< 20 ng/ml) or insufficient (20 to < 30 ng/ml) based on previous recommendations.

3. Results

3.1 Case I

A 48-year-old white Caucasian male who had protein C and protein S deficiency had been followed up by our Allergy-Immunology Unit. Previously, he had been diagnosed with irregular emphysema with an abnormal density in left lower lobes. Moreover, non-homogeneous lung aeration with persistently aerated lung units, parenchymal densities in apical segment of the upper lobe subpleural bullous lesions and bronchial wall thickening were reported in phase-contrasted tomography. Also, an 8 mm subpleural nonspecific nodule was detected at the posterior of the left lower lobe with pleural tags. Echocardiogram revealed left atrial dimensions in normal range and normal left ventricular function within normal dimensions. Alpha 1-antitrypsin (AAT) level was estimated in this case and resulted as 1.29 g/l and the normal reference range as 0.9 – 3 g/l. He was also evaluated with Doppler ultrasonography and subacute thrombosis was determined in vena saphena parva and in left vena perforantes cruris. Bilateral pulmonary thromboembolism was observed in multiple segments by Tc99m DTPA/MAA radioaerosol ventilation-perfusion scintigraphy. In addition, homogenous emphysema was determined by computed tomography (CT). According to the clinical findings, lung transplantation was suggested due to the survival benefit.

3.2 Case II

The female patient was diagnosed with congestive heart failure (CHF) and hypertension (HT). She used calcium channel blocker (CCB) and clopidogrel (CP). Two years ago she suffered an intracranial embolus with resultant facial palsy.

3.3 Case III

Previously, the patient was diagnosed with CHF, HT, Hashimoto's thyroiditis (HST). Because of mitral valve prolapse, she had required mitral valve replacement 5 years ago. She was using LT4, CCB and CP. Thyroid antibodies (anti-TPO) were positive in the patient.

3.4 Case IV

The patient was diagnosed with an aortic aneurysm 8 years ago. Patient's autologous serum SPT was positive. Antinuclear antibody (ANA) and hepatitis markers (HBsAg, HBsAb and anti HCV), HIV, rheumatoid factor (RF) and anti-TPO were negative in patient. His past history revealed angioedema and autoimmune urticaria exacerbations for 9 years, which was sometimes associated with larynx edema.

3.5 Case V

The patient was diagnosed with a rheumatoid arthritis (RA), HT and HST 19 years ago. She was on LT4, CCB and non-

Table 2. Laboratory findings.

Laboratory markers	Pre-anti-IgE/Post-anti-IgE					Normal range
	C-I	C-II	C-III	C-IV	C-V	
Case (C)						
WBC (mm ³)	7930/8100	5960/6900	5800/6400	5900/6300	9.980/6200	4800 – 10800
Eosinophil (%)	19/3.4	19.3/4.9	26.8/8.4	22.4/5.6	21/2.8	0.9 – 2.9
Basophil (%)	1.8/0.6	0.6/0.1	1.9/0.7	1.5/0.1	1.9/0.4	0.2 – 1
Platelet (mm ³)	301,000/230,000	220,000/190,000	310,000/280,000	218,000/180,000	250,000/ 242,000	150,000 – 450,000
MPV (fL)	9.9/10.7	10.5/10.4	10.9/11	10.9/11.2	10.2/11.4	6.5 – 11.6
PT	12.3/12.5	13/13.5	14.4/14.2	12.3/12.5	12.3/12.5	11.8 – 15.3
INR	0.845/0.718	0.79/0.88	0.9/0.9	0.845/0.718	0.825/0.9	0.8 – 1.2
aPTT	28/29	32/31	38/37	34/32	29/29	25 – 40.3
d-dimer (U/L)	769/432	416/408	589/492	349/337	569/321	0 – 500
hs-CRP (mg/l)	9.3/2.5	7.9/3.5	12.5/4.8	7.9/3.8	31.2/5.5	0 – 6
Total IgE (U/L)	716/594	120/104	1050/1013	598/510	618/397	0 – 100
ECP (ng/ml)	267/62	167/84	86/65	48/38	310/67	6 – 24
25(OH)D (ng/ml)	17/22	22/31	28/33	23/28	19/29	
FENO (ppb)	78/41	47/29	49/37	52/36	61/26	
sTRAIL (pg/ml)	813.4/258	1218.3/586.2	1143/593.5	1391.5/892	1220.5/438	
SCD200 (pg/ml)	30.3/15.4	42.6/24.5	46.9/30.2	29.5/12.4	48.5/16.9	
CXCL8 (pg/ml)	15.5/24.8	8.2/14.5	10.2/19.6	6.7/18.4	9.5/28.9	
IL-1 β (pg/ml)	29.8/22.3	27.4/20.1	35.8/29.9	17.9/16.6	26.5/28.7	
Protein C (%)	57.1/71.1	-	-	-		70 – 140
Protein S (%)	56.7/94.6	-	-	-		60 – 130
APC-NR	0.50/0.63	-	-	-		0.8 – 2
AIII (%)	107.1/126	-	-	-		75 – 125

25(OH)D: 25-hydroxyvitamin D; AIII: Antithrombin III; APC-NR: Activated protein-C resistance; ECP: Eosinophil cationic peptide; FENO: Fractional exhaled nitric oxide concentrations; hs-CRP: High sensitive C-reactive protein; MPV: Mean platelet volume.

TNF disease-modifying anti-rheumatic drugs. RF and anti-TPO were positive. High-resolution CT showed bronchiectasis.

Fractional exhaled nitric oxide concentrations and serum levels of sTRAIL, sCD200, d-dimer, ECP, total IgE, IL-1 β and hs-CRP were decreased, while IL-8, 25(OH)D were increased after starting the treatment of anti-IgE. The ACT scores, SOA and quality of life measurements improved generally in the four patients.

4. Discussion

In the first case, deficiencies of the endogenous anticoagulants, protein C, protein S and antithrombin III, are usually polygenic and have an autosomal dominant inheritance with variable penetrance. Protein C requires protein S as a cofactor and is activated by thrombin, and their deficiency increases the risk of thromboembolism. Also, protein S levels modulate the activated protein C resistance phenotype induced by elevated prothrombin levels. The male patient was a heterozygous carrier of factor V Leiden and prothrombin G20210A mutation, which is related to high risk of thrombosis [13,14]. The relevance of the heterozygosity for hereditary protein S/C deficiency as a risk factor for thrombosis has been disputed, because heterozygotes without symptoms have been identified among blood donors and relatives of homozygotes [13]. Harper *et al.* showed that successful prevention will require protein C replacement together with

antithrombin supplements up to, but not exceeding, normal plasma activity [14]. After anti-IgE therapy, Doppler ultrasonography revealed that it did not reveal any thrombus and the patient did not require lung transplantation and that serum protein S/C levels increased to normal ranges. Exercise stress testing was normal. In the second case, after initiation of anti-IgE treatment, neither cranial emboli event nor any neurologic complications did occur. In the third case, patient did not report any cardiac arrhythmias after initiation of anti-IgE therapy. Besides, exercise stress testing was normal, while the patient was treated with anti-IgE. In the fourth case, after third rounds of omalizumab, frequency of exacerbations decreased and after eleventh round it completely disappeared. Aneurysm enlargement or complications were not detected during the treatment with anti-IgE. In the fifth case, the patient did not report any side effects and complication did not occur during this long follow-up period. No change was noted in our patient's RA activity scores 28 (DAS28). Lung involvement is common in RA, affecting 5 – 10% of RA patients and is often their major cause of morbidity and mortality [15]. Clinical and laboratory data are shown in Tables 1 and 2.

The development of anti-IgE therapy over the past 20 years provides an interesting example of the emergence of a conceptually new, biotechnology-produced pharmaceutical [16]. Our knowledge concerning the use of omalizumab in treatment of asthma and other allergic diseases has improved to include our

understanding that treatment acts on many levels, including affecting levels of oxidative stress markers, the interaction of oxidants and antioxidant balance and regulating levels of inflammatory proteins including cytokines (IL-8, IL-10, TGF- β , GCSF, IL-17), hs-CRP and sTRAIL [2-5]. Asthma is associated with increased levels of eosinophils in tissues, body fluids and bone marrow. Higher levels of ECP are also associated with exacerbated asthmatic conditions [17-19]. In patients with chronic and/or severe asthma, FENO levels are helpful in determining whether or not eosinophilic airway inflammation is currently active [20]. The SOA score was found to be a valid measure of asthma severity [21]. Objective pulmonary function testing was done around the time of diagnosis [22,23] and our patients were not obese.

FENO were assessed following ATS/ERS guidelines [17,24]. In autoinflammatory as well as allergic diseases such as bronchial asthma, dysfunctional inflammasome processing has been demonstrated to account for IL-1 β -induced inflammation [25]. CD200 is a novel immunosuppressive molecule [26,27]. Thus, the increased levels seen in patients with active disease presumably represents a manifestation of a homeostatic response directed at control of inflammation, with the diminished levels than seen in well-controlled patients, thus reflecting, in turn, the successful suppression of the inflammatory response. 25(OH)D has effects on both the innate and adaptive immune system and levels of 25(OH)D are predictive of pulmonary function [28,29]. It was previously shown that 25(OH)D plays an immunomodulatory role in inflammatory diseases. In our study, the increase in 25(OH)D might be associated with a decrease in the use of systemic steroids.

While there was a small decrease in thrombocyte count, thromboembolism was not observed. Our clinical experience together with international coordination on performing the omalizumab treatment in large number of patients with different clinical status helped us to relate this knowledge to clinical application in thromboembolism. These data suggested that routine clinical measurement of ECP, IL-1 β , 25(OH)D, sTRAIL and sCD200 may provide useful additional information to conventional clinical measures, which can help us understand the current clinical status of asthmatic patients. In Turkey, omalizumab was approved for treating patients 13 years and older with severe allergic asthma in 2006 and a payment policy was issued by the Health Insurance Bureau in the same year. Approximately 600 patients with severe

allergic asthma have been treated with omalizumab to date in major medical centers with response rates estimated to be ~ 80 – 95%. In Turkey, a small number of patients with other allergic conditions have also been treated with omalizumab in off-label uses with generally good results. Except the one patient who had a temporary thrombocytopenia, there was no change of mean platelet volumes in severe asthma patients without cardiovascular risk. Moreover, the patient with Samter's syndrome had a significant asthma score during 36 months of follow-up time [30,31]. The patients did not develop any side effect or a complication during this long follow-up time conversely to the expectations of recent literature.

It has previously been reported that exposure to omalizumab might be associated with an increased risk of arterial thrombotic events in asthmatic patients. Our first case of a patient, who had both protein C and protein S deficiency and hence a high risk for thromboembolism, documents for the first time the safety of omalizumab for asthmatic patients with concurrent risk factors contributing to arteriothrombotic events. In cases when the risk of cardiovascular diseases was high, no complication was observed. In conclusion, omalizumab might be used safely in patients with cardiovascular diseases but definite conclusions cannot be drawn since this is quite a short case series. To address this issue and still the most recent study in the literature highlighting the arteriothrombotic events, larger case series are need to be further tested [12].

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Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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