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Serum-soluble TRAIL levels in patients with severe persistent allergic asthma: Its relation to omalizumab treatment

PI

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: In this study we compare the Omalizumab treatment modality in the dynamics of cell apoptosis regulating molecules in both severe persistent asthma patients who had no other any allergic disease, newly diagnosed patients with allergic asthma, and healthy volunteers.

Material/Methods: Severe persistent allergic asthma patients were subjected to measurement of serum soluble TRAIL (TNF-related apoptosis-inducing ligand) levels during the active disease phase and the stable phase which occurred 4 months after Omalizumab treatment. Serum sTRAIL concentrations were measured by a solid phase sandwich enzyme-linked immunosorbent assay. Concentration levels were compared with those of age- and sex-matched newly diagnosed patients with allergic asthma, and healthy controls. All assays were carried out in duplicate. Total serum IgE levels, antinuclear antibody (ANA), rheumatoid factor (RF), hepatitis markers, C3, C4 and eosinophil levels were evaluated in all patients.

Results: ANA, RF, hepatitis markers were negative in all patients. Complement 3 and 4 levels were normal in all patients. Prick tests in all patients were detected in mite and grass allergy. These results correlated with specific IgE. There were no differences between the healthy controls, newly diagnosed allergic asthma patients, and non-treated severe persistent allergic asthma patients during the active phase. Interestingly, the levels in variances of the patients who had the effective omalizumab treatment were significantly lower than the healthy controls, while the mean values were not statistically significant.

Conclusions: Our study gives a different perspective on severe persistent allergic asthma and omalizumab treatment efficacy at the cell apoptosis-linked step by the serum sTRAIL levels.

key words: severe persistent allergic asthma • allergic asthma • soluble TRAIL • omalizumab

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Background

Asthma is a chronic inflammatory disease that affects people of all ages, with the increasing total prevalence rate [1,2]. Asthma is a clinical diagnosis that incorporates genetic predisposition and clinical symptoms with objective measures of lung function and disease severity, and is determined by pulmonary function measurements, asthma symptoms, and the need for rescue medication [3,4]. While asthma is classified based on severity, at the moment there is no clear method for classifying different subgroups of asthma beyond this system, and in the most severe form, called 'Severe persistent allergic asthma', diagnosis is based on whether symptoms are precipitated by allergens [5,6]. Different patients will respond differently to the same treatment, thus it is clear that the cases within a classification have significant differences. Finding ways to identify patients who will respond well to different types of treatments is a current critical goal of asthma research.

Omalizumab (trade name *Xolair*), a recombinant humanized monoclonal antibody to IgE, is recommended as a new option for the treatment of severe persistent allergic (IgE mediated) asthma [7,8]. In our previous study, we reported the omalizumab treatment is clinically effective in severe persistent asthma patients with co-morbid allergic conditions [9].

Apoptosis (programmed cell death) is an active physiological process that leads to the ordered destruction of cells without the release of intracellular contents into the extracellular environment (which would cause an inflammatory reaction and tissue damage) [10]. Apoptosis in the immune system is a fundamental process regulating the maturation and homeostasis of the lymphocytes. It can be induced passively through the lack of essential survival signals, or actively, through the ligand induced trimerization of specific death receptors of the tumour necrosis factor (TNF) receptor family, such as Fas, the TNF receptor, or the TNF-related apoptosis-inducing ligand (TRAIL) receptor [11].

The Fas/FasL system plays a crucial role in apoptosis in many diseases, including cancer and inflammatory diseases [12]. The importance of the other death pathways is, however, uncertain. Recent interest has focused on TRAIL, with several studies indicating that sTRAIL is involved in the pathophysiology of different disease states, including cancer, viral infections, autoimmune diseases and inflammation. Defective apoptosis due to its interaction with its ligand preventing signaling for apoptosis may contribute to these diseases [13–23].

Previously, it was reported that allergic rhinitis is a sFas-reduced disease, and it was suggested that sFas might play a new role in allergic rhinitis [24]. Previous studies also showed unexpected difference in serum sFas levels between allergic rhinitis patients and bronchial asthma patients, but no difference in sFas-L between the adults with asthma and healthy controls [24,25]. These studies suggested the possibility of different apoptosis systems in the pathogenesis of the allergic diseases.

TRAIL (APO-2 ligand) is a transmembrane (type II) glycoprotein which also belongs to the TNF superfamily. The extracellular domain of TRAIL is homologous to that of other family members and shows a homotrimeric subunit structure. Like TNF and FasL, TRAIL also exists physiologically in a biologically active soluble homotrimeric form [26].

Table 1. Demographics for newly diagnosed allergic asthma patients (group II) and a healthy control group (group III). Patients in all groups (Tables 1 and 2) were age- and gender-matched.

Patient no.	Group II Age and Gender	Group II Duration of asthma symptoms	Group III Age and Gender
1	57 M	2 years	57 M
2	41 M	1 years	38 M
3	44 F	2 years	46 F
4	42 F	2 years	41 F
5	18 F	2 years	17 F
6	60 F	1 years	56 F
7	48 F	2 years	48 F
8	38 F	1 years	35 F
9	21 M	1 years	16 M
10	57 M	3 years	60 M
11	47 F	1 years	47 F
12	38 F	1 years	40 F
13	50 M	2 years	52 M
14	52 M	1 years	53 M

In this study, our aim was to identify the role of sTRAIL in the pathophysiology of allergic asthma and in omalizumab efficacy as a new treatment modality in severe asthma in general.

Material and Methods

Patients

The study was approved by the local ethics committee, and written consent was obtained from all patients and healthy volunteers. In the first group, 14 patients (6 males and 8 females) with severe persistent asthma were selected whose mean age was 42.4 (±4.6) years and having asthma symptoms more than 5 years, were included in the study. All of these patients received omalizumab therapy for 4 months. Omalizumab was administered according to the product label every 2 weeks. The symptoms and severity of allergic reactions were recorded before and after the omalizumab therapy. Assessments of clinical changes and adverse effects were made at every bimonthly patient visit. For the clinical evaluation, the daytime symptom frequency and night-time symptom frequency was estimated, together with the lung function (PEF and FEV_1 values) (data not shown).

In the second group there were 14 newly diagnosed allergic asthma patients who did not basically overlap with other

Table 2. Demographics for the first patient group (severe persistent allergic asthma – group I).

Patient number	Age (y)	Gender	Duration of asthma symptoms	Duration of severe persistent asthma	Xolair Dose
1	61	M	25 years	5 years	375 mg q. 2 weeks
2	38	M	10 years	2 years	225 mg q. 2 weeks
3	47	F	15 years	4 years	225 mg q. 2 weeks
4	41	F	10 years	4 years	300 mg q. 2 weeks
5	16	F	15 years	2 years	300 mg q. 2 weeks
6	56	F	10 years	2 years	300 mg q. 2 weeks
7	49	F	5 years	1 years	300 mg q. 2 weeks
8	33	F	10 years	2 years	300 mg q. 2 weeks
9	16	M	10 years	2 years	225 mg q. 2 weeks
10	58	M	6 years	1 years	300 mg q. 2 weeks
11	47	F	12 years	2 years	300 mg q. 2 weeks
12	35	F	10 years	2 years	300 mg q. 2 weeks
13	50	M	6 years	1 years	300 mg q. 2 weeks
14	47	M	9 years	4 years	300 mg q. 2 weeks

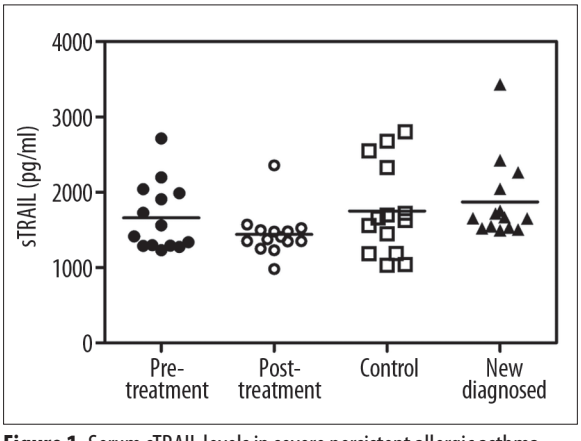

Figure 1. Serum sTRAIL levels in severe persistent allergic asthma patients (before the omalizumab treatment and 4 months after the omalizumab treatment), newly diagnosed allergic asthma patients and in healthy individuals as control.

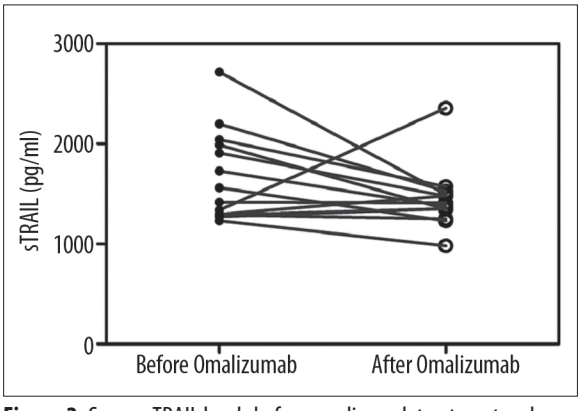

Figure 2. Serum sTRAIL levels before omalizumab treatment and changes in levels in severe persistent allergic asthma patients 4 months after omalizumab therapy, during a stable disease phase.

allergic diseases. Mean age was 43.8 (±4.8) years. All patients were followed in the Immunology and Allergy Clinic of Antalya Education and Training Hospital, and were evaluated by clinical status (Table 1).

In the third group, there were 14 age- and sex-matched healthy individuals with 43.3 (±4.5) years mean age.

Blood collection

Total serum IgE levels, antinuclear antibody (ANA), rheumatoid factor (RF), hepatitis markers, C3, C4 and eosinophil levels were evaluated in all patients.

Total and specific IgE levels were estimated by fluoroenzyme immunoassay (ImmunoCAP-FEIA) using an ImmunoCAP (Phar-macia, Uppsala, Sweden) kit. Values above 100 kU/L and 0.35 kU/L for total and specific IgE levels, respectively, were considered abnormal.

Serum sTRAIL levels were measured by a sandwich enzyme-linked immunosorbent assay (Diaclone, France) in all participants.

Skin-Prick Test (SPT)

Skin prick tests on the forearm were performed in all patients using standardized latex extract containing high ammonia

natural rubber latex, and a full set of 35 common and 35 food allergens. In addition, honey bee venom SPT was performed on 1 patient based on the subject's clinical history. SPTs were performed by skilled nursing personnel. Positive tests were counted as wheals of 3 mm in diameter after 20 minutes. Tests were compared with positive histamine controls and negative saline controls. Commercial extracts used were manufactured by Alyostal ST-IR (Starallergenes S.A.-France). No intradermal tests were performed.

Statistical analysis

The results of patients in both groups were compared with those of healthy subjects. These data were statistically analyzed by using *SPSS version 13.0* for Windows (SPSS Inc., Chicago, IL, USA). Inter-group comparisons were made using the *independent samples T test*. Intra-group comparisons were evaluated with the *Wilcoxon's matched-pairs signed-rank test.*

Results

In this clinical follow-up study, 14 patients had already been receiving omalizumab therapy and these subjects were included for further analysis. The patients had had severe persistent asthma for periods ranging from 2 to 5 years, and had been diagnosed as having allergic asthma for 5–25 years. The study subjects' baseline characteristics are shown in Tables 1 and 2.

The mean total serum IgE levels were as follows: in Group I, 459.785 IU/mL; in Group II, 124.8 IU/mL; and in Group III, 39.88 IU/mL. ANA, RF and hepatitis markers were negative in all patients. Complement 3 and 4 levels were normal in all patients. Prick tests in both patient groups (Group I and II) were positive for mite, and grass allergens. These results correlated with specific IgE.

As shown in Figure 1, there were no differences in the mean values of sTRAIL levels between the severe persistent allergic asthma patients before the omalizumab treatment (n=14; mean ±SD 1663±120.4 pg/ml), newly diagnosed allergic asthma patients (n=14; mean ±SD 1873±142.9 pg/ml), and healthy controls (n=14; mean ±SD 1751±161.6 pg/ml). But in contrast, serum sTRAIL levels in patients with severe persistent allergic asthma after the omalizumab treatment (n=14; mean ±SD 1443±80.93 pg/ml) were lower than those in healthy individuals (n=14; mean ±SD 1751±161.6 pg/ml).

However, 3 of 14 severe persistent allergic asthma patients showed an increase or no change in sTRAIL levels (Figure 2). Those patients (n=3) whose sTRAIL levels were increased or not changed, are the patients in whom the omalizumab treatment was clinically effective after the twelfth dose, while the other patients had a decrease in symptoms, mostly after the second or third dose. The patient whose sTRAIL level was increased about 2-fold was the patient who had newly diagnosed diabetes mellitus after the omalizumab treatment had started. However, the circulating soluble TRAIL is a negative marker for inflammation, and the levels were affected by autoimmune conditions [14,17].

Discussion

As a mechanism in allergic conditions, there was an increase in both T and B cells and eosinophils in both of our 2 patient groups. IT was previously reported that the increase in the eosinophil levels in allergic asthma was due to the increase in peripheral blood eosinophil survival promoted by TRAIL [13]. The exact role of TRAIL *in vivo* still remains unknown. In this study, we showed that soluble TRAIL levels of severe persistent allergic asthma patients were decreased after the anti-IgE treatment using omalizumab. The TRAIL levels of only 1 patient increased after omalizumab treatment. The possible explanation of the 2-fold increase in this patient may be due to the uncontrolled, newly-diagnosed diabetes mellitus (glucose levels were higher than 400 mg/dl and the patient was not using any anti-diabetic drugs).

These results suggest that TRAIL may act as a soluble effector, and the decrease after the omalizumab treatment may be an indicator of clinical improvement.

Omalizumab was evaluated as a treatment for asthma in large, multicenter, double-blind placebo control trials involving patients with moderate to severe asthma who required corticosteroids; when added to oral or inhaled corticosteroids, omalizumab reduced symptoms and exacerbations, improved lung functions and quality of life [27].

Conclusions

The physiological functions of sTRAIL in allergic conditions, and the elucidation of the molecular mechanisms of the TRAIL signaling pathways, will be of significant interest to the scientific allergy community in the coming years.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

ADY was involved in patient recruitment, followed-up the patients, participated in the design of the study and drafted the manuscript. AB carried out the immunoassays, participated in its design and drafted the manuscript. AK researched the literature and participated in coordination. RMG drafted the manuscript and participated in its coordination. All authors read and approved the final manuscript.

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