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Baseline serum CXCL10 and IL-12 levels may predict severe asthmatics' responsiveness to omalizumab

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ABSTRACT

Background: Omalizumab, a humanized anti-IgE monoclonal antibody, is the first molecularly targeted drug for severe asthmatics. However, responses to omalizumab vary widely among patients.
Objectives: This study aimed to assess the potential of baseline serum cytokine levels as predictors of responsiveness to omalizumab.
Methods: Thirty-one patients with severe, persistent asthma were enrolled in this study and administered omalizumab for at least 1 year. Response to omalizumab was assessed based on the physician's global evaluation of treatment effectiveness (GETE) at 48 weeks of treatment. Blood samples were collected at baseline and 16 and 32 weeks after starting omalizumab and measured for 30 cytokines by Luminex 200 and ELISA. Exhaled nitric oxide (FeNO) levels, peripheral blood eosinophil counts, pre-bronchodilator pulmonary functions and Asthma Quality of Life Questionnaire scores were determined at baseline and 16, 32 and 48 weeks after starting omalizumab. The numbers of clinically significant asthma exacerbations in the previous year and during 48 weeks of treatment with omalizumab were assessed.
Results: GETE assessment showed 19 responders (61.3%) and 12 non-responders (38.7%). Responders showed significantly higher levels of CXCL10 and IL-12 at baseline compared to non-responders (CXCL10: responders, 1530.0 ± 315.2 pg/ml vs. non-responders, 1066.0 ± 396.8 pg/ml, P = 0.001; IL-12: responders, 60.2 ± 39.2 pg/ml vs. non-responders, 32.2 ± 26.3 pg/ml, P = 0.04). ROC curves to distinguish responders from non-responders using the baseline serum CXCL10 level showed a good AUC of 0.83. At 32 weeks of omalizumab therapy, serum CXCL10 tended to be increased (1350 ± 412.3 pg/ml at baseline vs. 1529 ± 637.6 pg/ml at 32 weeks, P = 0.16) and serum IL-12 tended to be decreased (49.4 ± 37.0 pg/ml at baseline vs. 43.9 ± 30.9 pg/ml at 32 weeks, P = 0.05). On the other hand, serum IL-5 and PDGF were significantly decreased (IL-5: 54.2 ± 13.8 pg/ml at baseline vs. 49.1 ± 12.5 pg/ml at 32 weeks, P = 0.008; PDGF: 4821 ± 2458 pg/ml at baseline vs. 4219 ± 1951 pg/ml at 32 weeks, P = 0.048).
Conclusions: High baseline serum CXCL10 and IL-12 levels may be useful in predicting a good omalizumab response in severe asthmatics.

1. Introduction

Asthma is a common respiratory disease that is perceived as a heterogeneous clinical syndrome of airway hyperresponsiveness, airway inflammation and airflow obstruction, with various genetic and environmental backgrounds and exacerbating factors, and varying responsiveness to therapeutic agents [1]. About 5–10% of asthma patients are estimated to be severe persistent asthmatics [2,3]. These severe asthmatics suffer from daily symptoms and frequent exacerbations in spite of using nearly maximal doses of inhaled corticosteroids and bronchodilators. Multiple molecularly targeted drugs have been developed and are now widely used to manage severe asthmatics [4–6].

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Omalizumab was the first molecularly targeted drug to be used for asthma treatment [3]. It is a monoclonal anti-IgE antibody, and in clinical settings it significantly reduces asthma exacerbations and use of inhaled corticosteroids [7]. Mechanistically, it inhibits binding of IgE to its high-affinity receptor, FcepsilonRI (FcεRI), on mast cells and basophils, which leads to suppressed release of their inflammatory mediators [8]. Omalizumab rapidly reduces free IgE levels and down-regulates expression of FcεRI on various inflammatory cells, including mast cells, basophils and dendritic cells [8]. It is now widely used to treat severe allergic asthma, but as noted in the guideline of the Global Initiative for Asthma [9], its high cost and different degrees of patient response to omalizumab are sometimes troublesome to both patients and physicians. It is recommended that the effectiveness of omalizumab be evaluated at 16 weeks of use because clinical trials have demonstrated that it takes at least 12–16 weeks for omalizumab to show effectiveness [8]. In addition to the clinical evidence, this timing is also rational in terms of the mechanism of action of omalizumab, i.e., it decreases the free IgE level, which leads to down-regulation of FcεRI expression on basophils over 90 days [10]. As a result, patients who are non-responders may have to suffer from both the symptoms and the cost of this drug for up to 16 weeks. Thus, there is an increasing need for predicting responsiveness to omalizumab before starting its use.

The EXTRA study showed that the peripheral blood eosinophil count and exhaled nitric oxide (FeNO) level at baseline may predict responsiveness to omalizumab as assessed by the rate of asthma exacerbation during the first year of treatment [11]. This observation indicated that the Th2-dominant phenotype responds well to omalizumab therapy. In line with that, baseline serum periostin levels, another Th2 marker, were higher in patients who showed no exacerbations during the first year of omalizumab treatment [12]. On the contrary, there are reports of asthma patients of non-Th2 phenotype who also respond to omalizumab therapy [13,14]. Thus, identification of predictors of a response to omalizumab regardless of the Th1 or Th2 phenotype may be useful for clinical practice, and it may also help us to further clarify the pathogenesis of severe asthma.

This study aimed to assess the potential of the serum cytokine levels at baseline as predictors of responsiveness to omalizumab therapy.

2. Materials and methods

2.1. Subjects

The subjects were 31 patients who had been diagnosed with severe allergic asthma and were then treated with omalizumab for at least 1 year. Twenty-nine of the patients had previously been enrolled in another clinical study (UMIN000002389) [12]. Patients started to receive omalizumab therapy between July 2010 and December 2014 at National Hospital Organization Tokyo National Hospital or Kyoto University Hospital. Asthma was diagnosed according to the criteria of the American Thoracic Society (ATS) [15]. All patients had at least one specific IgE in serum or one positive skin test for common aeroallergens. The study protocol was approved by the Ethics Committee of Tokyo National Hospital and Kyoto University (UMIN000018619), and written informed consent was obtained from all the participants.

2.2. Data and sample collection

All the patients were administered omalizumab every 2–4 weeks depending on their total IgE level. Blood samples were collected at baseline and at 16 and 32 weeks after the first omalizumab dose. Serum was separated by centrifugation and kept frozen at −20 °C until measurement of the serum cytokine levels. The following clinical variables were determined at baseline, and at 16, 32 and 48 weeks of omalizumab therapy: FeNO level, peripheral blood eosinophil count, prebronchodilator pulmonary function, and Asthma Quality of Life Questionnaire (AQLQ) score. FeNO levels during constant exhalation at a flow rate of 50 ml/s were measured using an ozone-chemiluminescence technique (NOA 280; Sievers, Boulder, CO, USA) according to the ATS guidelines [16]. The numbers of clinically significant asthma exacerbations—defined as worsening of asthma requiring treatment with rescue systemic (oral or intravenous) corticosteroids—in the previous year and in 48 weeks of treatment with omalizumab were assessed.

2.3. Responders and non-responders

Response to omalizumab was assessed based on the physician's global evaluation of treatment effectiveness (GETE) at 48 weeks of omalizumab treatment. GETE is a composite measure that includes multiple tools for evaluating a patient's response, such as interviews, review of medical records, spirometry and diaries of symptoms, use of rescue medication and peak expiratory flow (PEF) [17]. Patients with a GETE rating of “excellent” or “good” were classified as responders, whereas those with a GETE rating of “moderate”, “poor” or “worsening” were classified as non-responders.

2.4. Serum cytokine levels

Serum samples were assayed for 27 cytokines (IL-1β, -1RA, −2, −4, −5, −6, −7, −8, −9, −10, −12, −13, −15, −17A, CCL2, 3, 4, 5, 11, CXCL10, basic FGF, G-CSF, GM-CSF, IFN-γ, PDGF-BB, TNF-α and VEGF) by using a Bio-Plex Pro Human Cyokine Panel, 27-Plex (BioRad Laboratories, Hercules, CA, USA) and LUMINEX 200 (Luminex, Austin, TX, USA) according to the manufacturers' instructions. IL-33 (assay range: 6.3–400 pg/ml), thymic stromal lymphopoietin (TSLP) (assay range: 31.2–2000 pg/ml) and chitinase 3-like 1 (CHI3L1) (assay range: 62.5–4000 pg/ml) were measured using ELISA kits from R&D Systems (Minneapolis, MN, USA) according to the manufacturer's instructions.

2.5. Statistical analyses

Univariate analyses were performed using Student's *t*-test for data that passed D'Agostino & Pearson's normality test and the Mann-Whitney *U* test for data that did not. Changes in AQLQ overall scores and the levels of biomarkers at different time points were analyzed using a paired *t*-test. Receiver operating characteristic (ROC) analysis was performed, and the area under each ROC curve (AUC) was calculated. A two-tailed P-value of less than 5% was considered statistically significant. Data were also used for a *post hoc* power analysis ($\alpha = 5\%$) to assess the statistical power for identifying a biomarker able to predict responsiveness to omalizumab. All statistical analyses were performed using GraphPad Prism version 5.0 for MAC OS X (GraphPad Software, San Diego, USA) and IBM SPSS Statistics version 23 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Baseline characteristics of the patients and responsiveness to omalizumab therapy

GETE assessment showed 19 responders (61.3%) (5 “excellent” and 14 “good”) and 12 non-responders (38.7%) (12 “moderate”, 0 “poor” and 0 “worsening”). The demographic and background characteristics, including the doses of both inhaled corticosteroids and oral corticosteroids used to manage the patients, were comparable between the responders and non-responders. However, the responders tended to be older and more often male, and exhibited higher FeNO levels, higher blood eosinophil counts, higher serum IgE, lower FEV_1 and higher in number of clinically significant exacerbations at baseline none of which reached statistical significance (Table 1). The clinical outcomes in the responders and non-responders are also shown in Table 1. The increases in FEV1.0 and AQLQ at 48 weeks were significantly larger in the responders than non-responders (FEV1.0: responders, 0.20 ± 0.26 L vs.