OLGU SUNUMU / CASE REPORT

Gülhane Tıp Derg 2014;56:42-44

doi:10.5455/gulhane.11713

Anti IgE tedavi non-atopik astımlılarda kullanılabilir mi: IgE'nin astımdaki rolü hakkında bir olgunun düşündürdükleri

Ali Kutlu(*), Ersin Demirer(*), Sami Ozturk(*), Ali Gunes(*), Ozgur Kartal(*), Ogun Sezer(*), Zafer Kartaloglu(*)

ÖZET

Serum IgE yüksekliği atopi belirtisi olarak kabul edilse de non-alerjik astıma eşlik edebilen yüksek total IgE düzeyi atopiden bağımsız olarak hastalığın patogenezine ve ağırlığına katkı yapabilir. Bu olgu sunumunda alerjik deri testleri ve spesifik IgE'leri negatif olan intradermal testlerde Dermatofagoides pteronysinus'a karşı zayıf pozitiflik saptanan ve bir yıl süreli omalizumab tedavisinden belirgin fayda gören olgu sunulmaktadır.

Anahtar kelimeler: *Astım; İmmunoglobulin E; non allergy; Omalizumab*

Can anti IgE treatment be used in non-atopic asthma patients; thoughts of a case about the role of IgE in asthma

SUMMARY

Although elevated serum IgE is accepted as a sign of atopy, high total IgE level may accompany with non-allergic asthma and contribute to pathogenesis and severity of the disease independently from atopy. In this case report, we present a patient of us whose allergy skin tests and specific IgEs were negative, who was started omalizumab treatment following obtaining weak positivity against Dermatofagoides pteronysinus in intradermal tests repetaed with one year interval and who significantly benefited from treatment.

Key Words: *Asthma; Omalizumab; Immunoglobulin E , non allergy*

* GATA Haydarpaşa Training Hospital,
Ayrı Basım İsteği: Ersin Demirer
Department Of Pulmanary Diseases,
GATA Haydarpaşa Training Hospital,
Istanbul, Turkey;
E-Posta:drersin73@yahoo.com

Makalenin Geliş Tarihi: 07.10.2011 • **Kabul Tarihi:** 14.12.2011 • **Çevrim İçi Basım Tarihi**

Introduction

Bronchial asthma is characterized by inflammation of the lower respiratory tract leading to hyperactivity and a variable degree of reversible airway obstruction. Basically, type of asthma attacks caused by external allergens is defined as extrinsic asthma for decades (1). IgE produced by B cells after sensitization with allergens has a central role in allergic reactions. Despite the relatively short half-life and low serum concentrations, IgE shows immunologically high activity by a number of high-affinity IgE receptors on mast cells and basophils (2). Elevated serum IgE is a sign of atopy which causes bronchial hyperactivity in atopic individuals. Although the role of IgE in non-allergic individuals is not known exactly, high total IgE levels which play a role in the pathogenesis of the disease may increase the severity of asthma (3).

Many studies have shown the central role of IgE in inflammation in asthma disease in which extensive down-regulation causes the suppression of IgE in the large number of effector cells in target organs (4).

Case Report

Thirty-four years old male patient has been diagnosed with asthma for six years. He was followed by our clinic for a year. He was an office staff. He had no history of significant contact with occupational or environmental allergens, smoking and drug allergy. Allergy skin prick test has been performed in a university hospital about four years ago and the result was negative. During the follow-up period in our clinic, there was no sensitivity with a large panel of inhaled allergens in repeated skin prick test. There was also no reaction for house dust mites in intradermal tests. Spirometry results were as follows: FEV1: 3.28 L (83%), FVC: 6:02 L (128%) and FEV1/FVC: 67%.

Despite the treatment with high-dose inhaled steroids (budesonide 1600 mcg / day or Fluticasone 1000 mcg / day), long-acting β2-agonists (formoterol 12 mcg 2x1 or salmeterol 50 mcg 2x1), leukotriene receptor antagonists (montelukast 10mg tablet), theophylline and nasal steroids, the disease was not under control during the follow-up period. Short-term oral steroids were used seven times within one year because of recurrent attacks of asthma. The patient's asthma attacks were usually associated with recurrent sinusitis and upper respiratory tract infections. Patient had septoplasty and endoscopic sinus surgery for chronic sinusitis, and he had experienced short-term recovery of asthma symptoms. However, high dose inhaled steroids and short-term oral steroid treatment were required for controlling the asthma. Since the patients' total IgE level was 203 IU/ml, skin prick

test for inhaled allergens was repeated. The result was negative. Specific IgE tests for house dust mites, molds, pollens (trees, grass-creal and weed) and cat and dog dander were negative. We decided that our patient diagnosed with uncontrolled asthma may benefit fromanti-IgE treatment after evaluating the patient's data and literature, although his allergy tests and specific IgE's were negative. We need to show atopy by skin tests or allergen-specific IgE according to the existing Social Security Institute budget application directive for beginning anti-IgE treatment. We repeated intra-dermal tests in our patient by house dust mites which is the most important perineal allergen and 5x5 mm edema and a concomitant minimal erythema were observed against Dermatofagoides pteronysinus. No reaction in the test made by Dermatofagoides farinea and negative control (saline) was observed. Omalizumab 225 mg every 2 weeks (Xolair c 150 mg flacon) was began considering the patient's weight and IgE level. Inhaled steroid dose was reduced to half dose one month afterthe starting of omalizumab treatment. Although he had experienced several episodes of otitis media and sinusitis in eight-months follow-up period, inhaled steroid dose was needed to be increased only once for a short-term and during this period. While our patient was scored as 7 out of 25 points at the asthma control test before the treatment of anti-IgE, the score was 23 at sixth month of treatment.

Discussion

Elevated serum IgE is a sign of atopy which causes bronchial hyperactivity in atopic individuals. IgE production is not only limited to the respiratory tract of atopic individuals. Although specificity of increased total IgE levels is not known, this may also observed in non-allergic individuals with asthma (5). In a study carried out in our clinic, IgE levels of non-allergic asthma patients had been found higher than that of non-atopic healthy individuals (6). Similar findings were reported by Sears et al. (7). IgE elevation of non-allergic patients may be a nonspecific reaction as a result of stimulation to polyclonal IgE synthesis in B cells due to inflammation in asthma (8). Weak positive reactions may cause a high false-positive results for allergy due to the increased sensitivity in intradermal tests, so positive results which are not supported by clinical history always should be considered as suspicious (9). Despite high level of total IgE in our case, his specific IgE values did not support any allergy. Intradermal test against house dust mites was found to be negative one year ago. Even though the history of our patient didn't suggest house dust mites' allergy, weak positivity in intradermal test repated one year later was enough for legal procedure to start anti-IgE therapy. According to literature discussed in detail below, we thought our patients may benefit from anti-IgE treatment, although the presence of atopy was not thought clinically. We decided to continue treatment for more one year since our patient benefited from 16-weeks initial treatment.

Plasma cells and B cells in respiratory tract mucosa tended to produce IgE intensively in allergic asthma. Cross linking of IgE–FceRI complexes on the mast-cell surface by allergens leads, within minutes, to the so-called 'early phase'

phase starts late phase characterized by accumulation and activation of inflammatory cells in the allergen-sensitive region reaching the peak level after a few hours (10). It was shown that some monomeric IgE molecules have the ability to activate mast-cell signalling in the absence of crosslinking by allergen through some of the same pathways as allergen–IgE complexes (11).

Humanized monoclonal anti IgE antibody reduces levels of circulating free IgE by binding to the constant region (ce3) of the IgE molecule, thus preventing free IgE from interacting with IgE receptors (FceRI and Fc e RII). Omalizumab does not lead anaphylaxis because it does not bind to the variable allergen-specific region of the IgE molecule.

Up-regulation of FceRI receptor expression in high serum IgE concentrations causes mast cell stimulation and mediator release by allergen in a lower concentration (12). The concentration of IgE that required for up-regulation of FceRI receptors in mucosal tissues is higher than normal circulating level, and IgE which are synthesized from local B cells may be active in this regulation (10).

FceRI receptor stimulation in human umbilical cord mast cells causes marked changes on several adhesion molecule expression that provides interaction with cytokine, chemokine and potentially between T and B lymphocytes and dendritic cells (13).

Effectiveness of IgE is very important on FceRI receptor expression. Almost all the free IgE in circulation is required to be removed to achieve results on the mast cell and basophil without Fc eRI receptor down-regulation (4).

In recent years, effectiveness of omalizumab on non-allergic patients with chronic autoimmune urticaria having autoantibody formation on IgG structure is explained by down-regulation effect of Anti-IgE therapy on receptors (14). Similar efficiency is shown in a patient with non-allergic systemic mastocytosis who had episodes of severe anaphylaxis (15).

Omalizumab make FceRI receptor expression of basophils and probably mast cells down-regulated by reducing serum free IgE levels. These receptor changes cause a decrease allergen sensitivity and mediator release of these cells (16).

It was shown that inflammatory cytokines and high-affinity IgE receptor expression have similar features on bronchial biopsies of patients with allergic and non-allergic asthma. Non-allergic asthma patients with IgE> 150 U/mL have lower lung function test parameters than non-allergic asthma patients with normal IgE value. Airway resistance was found high in the first group of patients. Results show that IgE are active in pathogenesis of the disease, and may increase the severity of illness regardless of atopy in non-allergic asthmatic patients (3).

It was observed that there was a tight relationship between serum IgE levels of patients with allergic asthma and FceRI receptor expression on dendritic cells. Omalizumab decreases allergen presentation and Th2 cell activation and proliferation by reducing FceRI receptor expression in circulating dendritic cells (4).

Omalizumab inhibits both early and late asthmatic response against inhaled allergens, and reduces mucus eosinophil count in patients with asthma. These results suggest that IgE contribute both early and late asthmatic response, and regulates tissue eosinophilia in the late asthmatic response and airway narrowing. As a result, omalizumab is effective as potentially on both sensitization phase and phase of allergen-specific immune response.

In recent years, evidences has emerged showing that increasing number of previously diagnosed with nonallergic or idiopathic rhinitis developed a local allergic response

with nasal-specific IgE (sIgE) production and nasal allergen provocation test with a positive response (17).

These findings suggest the presence of local allergic rhinitis (entopy) which could not be revealed by the classic skin tests, and demonstrate itself locally.Local IgE production seen in patients with rhinitis was also shown in bronchial mucosa of patients with atopic and non-atopic asthma (18). We could not find any study reporting that a local allergic response may be seen in patients with non-allergic asthma, such as seen in local allergic rhinitis. Criticism against the presence of local allergic reactions was supported by the claims that it was caused by poor quality allergens (false-negative results of conventional tests) in test material, low sensitivity for detecting IgE and undetectable allergens; however, the data about local allergic reaction limited to nasal mucosa without systemic reactoin has been increasing day by day (17).

As a result, the fore mentioned studies demonstrates that there has been an independent relationship between asthma and serum IgE and IgE plays a central role in asthma.

According to a recently published case study, a patient with severe non-allergic asthma with high serum total IgE levels benefits dramatic response from anti-IgE therapy (19). In that case, intradermal test was not applied. Data about benifit from AntiIg E treatment in at least some patients with non-atopic asthma having high IgE level is increasing day by day.

In patient with high serum Ig E, negative allergy skin tests and serum spesific Ig E and failing to respond to any treatment modality except anti-IgE therapy, for starting omalizumab treatment, even weak positivity of intradermal test against perineal allergen, which is normally met with suspicion, should be evaluated as favor atopy for anti-IgE therapy. It seems that, in a very near future, the range of therapeutic windows in asthma with anti Ig E treatment inevitably will expand.

References

1. Rackemann FM. A working classification of asthma. Am J Med 1947;3(5):601–606.
2. Nowak D. Management of asthma with anti-immunoglobulin E: A review of clinical trials of omalizumab. Respiratory Medicine 2006;100(3):1907–1917.
3. Beeh KM, Ksoll M, Buhl R. Elevation of total serum immunoglobulin E is associated with asthma in nonallergic individuals. Eur Respir J 2000;16(4):609-614.
4. Holgate S, Casale T, Wenzel S, Bousquet J, Deniz Y, Reisner C. The anti-inflammatory effects of omalizumab confirm the central role of IgE in allergic inflammation. J Allergy Clin Immunol 2005;115(3):459-465.
5. Global initiative for asthma (GINA). Global strategy for asthma management and prevention. NHLB/WHO workshop report. National Institute of Health.National Heart, Lung and Blood Institute. Revised 2007.(www.ginasthma.com/download.asp?intid=309).
6. Halisdemir N, Çolak C, Kutlu A, Öztürk S. [The cut-off points of total serum IgE levels in the diagnosis of patients with allergic and non-allergic asthma]. F Ü Sağ Bil Tıp Derg. 2009;23(2):91–94.
7. Sears MR, Burrows B, Flannery EM, Herbison GP, Hewitt CJ, Holdaway MD. Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. N Engl J Med 1991;325(15):1067–1071.
8. Burrows B, Martinez FD, Cline MG, Lebovitz MD. The relationship between parental and children's serum IgE and asthma. Am J Respir Crit Care Med 1995;152(5):1497– 1500.
9. Demirel T. [Diagnostic methods for allergic diseases]. In: Aydilek R, eds. Allerjik Hastalıklar Bronşiyal Astım. 1 st. ed. Istanbul: Bilmedya Grup; 2005.p. 67–76.
10. Gould HJ, Sutton BJ. IgE in allergy and asthma today. Nat Rev Immunol 2008;8(3): 205-217.
11. Kraft S, Kinet JP. New developments in FceRI regulation, function and inhibition. Nature Rev Immunol 2007;7:365–378.
12. Williams CM, Galli SJ. The diverse potential effector and immunoregulatory roles of mast cells in allergic disease. J Allergy Clin Immunol 2000;105(5):847-859.
13. Sayama K, Diehn M, Matsuda K, et al. Transcriptional response of human mast cells stimulated via the FceRI and identification of mast cells as a source of IL-11. BMC Immunol 2002;3:5.
14. Kaplan AP, Joseph K, Maykut RJ, Geba GP, Zeldin RK. Treatment of chronic autoimmune urticaria with omalizumab. J Allergy Clin Immunol 2008;122(3):569-573.
15. Douglass JA, Carroll K, Voskamp A, Bourke P, Wei A, O'Hehir RE. Omalizumab is effective in treating systemic mastocytosis in a nonatopic patient. Allergy 2010;65(7): 926-927.
16. Lin H, Boesel KM, Griffith DT, et al. Omalizumab rapidly decreases nasal allergic response and FceRI on
17. Rondon C, Romero JJ, Lopez S, et al. Local IgE production and positive nasal provocation test in patients with persistent nonallergic rhinitis. J Allergy Clin Immunol 2007;119(4):899–905.
18. Takhar P, Corrigan CJ, Smurthwaite L, et al. Class switch recombination to IgE in the bronchial mucosa of atopic and nonatopic patients with asthma. J Allergy Clin Immunol 2007;119(1):213-218.
19. Van den Berge M, Pauw RG, de Monchy JG, van Minnen CA, Postma DS, Kerstjens HA. Beneficial effects of treatment with anti-IgE antibodies (Omalizumab) in a patient with severe asthma and negative skin-prick test results. Chest 2011;139(1):190-193.