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Patient-Oriented Application of New Monoclonal Antibodies for Severe Asthma

Şiddetli Astım için Yeni Monoklonal Antikorların Hasta Odaklı Uygulanması

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Abstract

Asthma is a chronic lung disease that occurs due to many genetic and environmental factors. In the Global Initiative for Asthma (GINA) guideline, anti-immunoglobulin E (anti-IgE) (omalizumab) for patients with allergic asthma, anti-interleukin-5 (mepolizumab and reslizumab) or anti-interleukin 5 receptor (benralizumab) for patients with severe eosinophilic asthma are recommended as add-on treatment if the patients remain uncontrolled on STEP-4 treatment. Omalizumab, a humanized monoclonal antibody, inhibits the immunologic effects of immunoglobulin E (IgE) that binds to circulating high affinity IgE receptor. Mepolizumab acts by binding to interleukin-5 (IL-5), a cytokine required for the development of eosinophils, and reduces eosinophil levels. Although the mechanisms of action are similar, the magnitude of the patient's airway inflammation, the severity of the disease, and the phenotypic differences of the patients may be important for the treatment decisions. Even though in GINA, omalizumab is recommended as add-on treatment in STEP-5 for ≥6 years of age moderate to severe allergic asthma, in our country it was approved for the same phenotypic patients who were over 12 years of age. Both clinical trials and real world experience data support efficacy and safety of omalizumab for the treatment of moderate-to-severe allergic asthma. Evidence for clinical use in non allergic asthma as well as other investigational uses are already limited.

Keywords: Asthma, immunoglobulin E, mepolizumab, omalizumab

Öz

Astım, birçok genetik ve çevresel faktörden dolayı ortaya çıkan kronik bir akciğer hastalığıdır. Astım için Küresel Girişim (GINA) kılavuzunda belirtildiği gibi, BASAMAK-4'te verilen tedaviye rağmen kontrol edilemeyen durumlarda; allerjik astım hastalarında anti-immunglobulin E (anti-IgE) (omalizumab), ciddi eosinofilik astım hastalarında ise anti-interlökin-5 (mepolizumab ve reslizumab) veya anti-interlökin 5 reseptör (benralizumab)'ün tedaviye eklenmesi önerilmektedir. İnsan monoklonal antikoru olan omalizumab, immünoglobulin E'nin (IgE) dolaşan yüksek affiniteli IgE reseptörüne bağlanmasının immünolojik etkilerini inhibe eder. Mepolizumab, eozinofillerin gelişimi için gerekli olan bir sitokin olan interlökin-5'e (IL-5) bağlanarak etki eder ve eozinofil seviyelerini azaltır. Bu iki ilacın etki mekanizması benzer olsa da, hastanın hava yolu inflamasyonunun büyüklüğü, hastalığın ciddiyeti ve hastalar arasındaki fenotipik farklılıklar tedavi seçiminde önemli olabilir. GINA kılavuzunda omalizumabın ≥6 yaş orta-ağır astımlı olguların tedavisine BASAMAK-5'te eklenmesi önerilmekle birlikte, ülkemizde aynı fenotipten hastada 12 yaş üzeri kullanımı onaylanmıştır. Hem klinik deneyler hem de dünya deneyimlerinden toplanmış veriler, orta-şiddetli allerjik astımın tedavisi için omalizumabın etkinliğini ve güvenilirliğini desteklemektedir. Nonallerjik astımda ve diğer araştırma amaçları için kullanımlarına dair klinik veri halen kısıtlıdır.

Anahtar Kelimeler: Astım, immünoglobulin E, mepolizumab, omalizumab

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Introduction

Asthma is a heterogeneous chronic disease that may interfere with patients' every day works a lot, and effects patients of all ages.[1] It occurs due to inflammation of the airways resulting from allergic reactions triggered by the binding of an inhaled allergen such as pollen to antigen-specific IgE, that causes airways to swell and get inflamed. The inhaled antigen binds to IgE, and this antigen-bound IgE cross-links to high-affinity IgE receptors on the surface of basophils and mast cells, thus causing the release of mediators.[2] The attack of asthma is the most common and bare symptom. The attack forms from these IgE binding inhaled substances, creating immunologic effect and block the breathing.

In the pathogenesis of asthma, T helper (Th2) cells are thought to play an important role by producing cytokines as an immunological response. In asthmatic patients, Th2-type cytokines such as IL-4, IL-5, IL-13, which they express, play a crucial role in the pathogenesis of the disease. IL-4 and IL-13 provide IgE production in B cells, while IL-5 is responsible for eosinophil activation. In addition, IL-4 and IL-5 are known to be responsible for airway hyper-reactivity and eosinophilia in patients with asthma.[3]

The exact pathogenic pathway of severe allergic asthma is not exactly known yet but many genetic and environmental factors are thought to be the cause of it. Causes may be atopic, respiratory infections that individuals had in childhood or connection to allergens and viral infections in early childhood when the immune system is developing. It has been known that great numbers of cytokines and inflammatory cells are included, and eosinophils perform as key inflammatory cell mediators. Different causes diversify the severity and course of the disease. Current drugs for asthma are predominantly non-specific inhaled corticosteroids, and long-acting β-agonists. Although they affect the high prevalence of asthma, one in ten patients does not reply to any treatment even at high doses or with the use of oral corticosteroids.[4] Poor responses can be caused by multiple factors such as poor adherence with treatment, untreated co-morbidities, dysfunctional breathing or psychological problems. Phenotypes that analytical clustering methods have revealed dependence on high-dose corticosteroid treatment, severe airflow obstruction and exacerbations are related to an allergic background and late onset of disease.[2] Different phenotypes offer the scientists a field for searching asthma and the differentiation of the treatments.[5]

A phenotype evolves from variety of genetic and environmental factors in conjunction with characteristics for asthma or specific IgE responsiveness to particular allergens.[6] Recently, different phenotypes have been recognized such as allergic asthma which is a widely identified group of patients, including non-allergic, aspirin-exacerbated. Individual treatment decisions in asthma involves the seeking of the best ratio between efficacy and feasibility, using patient characteristic phenotypes and guided by biomarkers (called "endotypes").[7,8] Novel endotyping strategy for personalized treatment of asthma should be included as "omics" based signatures but they not yet emerged in the clinical practice. Several noninvasive biomarkers such as blood eosinophils, serum IgE, exhaled nitric oxide, sputum eosinophils, pointing Th2 driven eosinophilic inflammation that are currently used to drive treatment decisions but they need to be validated in the extensive use of clinical practice.

In the GINA guideline, anti-immunoglobulin E (anti-IgE) (omalizumab) for patients with moderate-to-severe allergic asthma, anti-interleukin-5 (mepolizumab, reslizumab and benralizumab have been approved in December 2015, March 2016, and November 2017 respectively) for patients with severe eosinophilic asthma are recommended as add-on treatments in STEP-5. Patients with severe asthma have persistent symptoms or exacerbations requiring the use of high-dose inhaled corticosteroid together with the second controller. They would be a candidate for optimized personalized treatment whether with anti-IgE for allergic, or with anti-interleukin-5 for eosinophilic phenotypes.

Clinical and research consequences

In the early 1990's, Th1 and Th2 immunity hypothesis have been identified, and led to the hypothesis that asthma/allergies were primarily driven by Th2 immunity involving the cytokines IL-4, IL-5, and IL-13.[9–12] Eosinophilic bronchitis is a prototype of the type-2 driven inflammatory process which will be responsible to the corticosteroids or target therapies against T2 cytokines such as IL-4, IL-5, and IL-13. Omalizumab for allergic and mepolizumab for eosinophilic asthma patients were validated treatment options in moderate to severe asthma petients who have persistent symptoms with the optimal medical treatment, recommended in STEP-4 GINA. In this review, we searched the previously made clinical trials on omalizumab and mepolizumab treatments. In the studies we examined, morphometric, eosinophilic, and Multidimensional Protein Identification Technology (MudPIT) proteomic analyses were used for investigating the bronchial specimens.[13] We further eliminated some data that we obtained from these studies. We used the following terms for the search: "Personalized medicine", "IgE treatment", "asthma", and "mepolizumab". Recently, the anti-IgE and anti-IL-5 are the two monoclonal antibodies available, but selection criteria between the two have not been demonstrated yet. This study focuses on the changes in usage of these drugs. In spite of the multifaceted effectiveness of asthma pharmacotherapy in mild and moderate forms of the disease, the clinical trials were made generally in severe cases.[14] The exacerbations in patients with severe asthma leave them in a situation

that may require hospitalization, and due to the dose of the drugs, the side effects leave patients in a more complicated situation. Also, their treatment is more expensive compared to the mild and moderate asthma. This requires more "severe patient oriented" searches to be in progress. Omalizumab was first licensed in 2005 for severe allergic asthma in patients aged 12 years or older. In 2009 the licence was extended for the patients that are at least 6 years of age for poorly controlled severely persistent allergic asthma.[15] The dose and dose frequency of omalizumab are dependent to the serum total IgE level (IU/mL) and the patient's body weight (kg).[16] According to the calculations, omalizumab is given by a subcutaneous injection every 2 or 4 weeks; mepolizumab is also administered every 4 weeks.

Mechanism of activity for mepolizumab

Mepolizumab was the first anti-IL-5 humanized monoclonal antibody described over 15 years ago.[17] It is a monoclonal antibody against interleukin-5, a signaling protein of the immune system. Most recently, monoclonal antibodies targeting IL-5 or its receptors such as mepolizumab, reslizumab, and benralizumab have been studied for the treatment of eosinophilic asthma.[17] An important clinical effect has been detected in non-eosinophilic asthmatics besides eosinophilic phenotype with benralizumab. But no data is available for mepolizumab or reslizumab in non-eosinophilic participants.[17] Mepolizumab binds to IL-5 with high affinity, and prevents binding of IL-5 to the surface of eosinophils and basophils, selectively inhibiting eosinophilic inflammation. It decreases the number of eosinophils in both blood and sputum (Table 1), and also reduces the exacerbations.[14,18]

Studies on mepolizumab

In the first studies that researchers worked on, anti-IL-5 treatment did not give the expected results. It was seen that although the blood eosinophil levels decreased, the clinical outcomes gave no different results than the placebo receivers. The cause of this was discovered lately: the first searches were on patients with controlled asthma, receiving drugs already and patients were given low dose.[14,19] After many clinical trials and researches, the appropriate dose and the suitable patient population that mepolizumab will be effective was determined. In a study that Flood-Page et al. made, it was indicated that mepolizumab creates no significant difference in the quality of life, symptom scores and exacerbation rates of the patients in differentiating doses; but also in that study, mepolizumab had induced a substantial decline in sputum eosinophils at two different doses (p=0.006, 250 mg; p=0.004, 750 mg).[19] In another study comparing 3 patient groups (intravenous-mepolizumab group, subcutaneous-mepolizumab group and the placebo receiver group), it was found that the mepolizumab receiving patients' exacerbation rates were more significant in active treatment groups than those in the placebo group. Compared to the placebo, the relative reduction in exacerbation rate of the intravenous-mepolizumab group was 47% (95% Confidence Interval [CI], 28 to 60), and of the subcutaneous-mepolizumab group was 53% (95% CI, 36 to 65). The use of anti-IL-5 was found to be associated with reduction in

Table 1. There are some statements below about the effects of these two drugs

Target	Biologic therapies used	Type of study	Major outcome
IgE	Anti-IgE mAb (omalizumab)	Allergen challenge: mild-to-moderate allergic asthma	↓ Early and late asthmatic response, ↓ serum free IgE
		Chronic moderate-to-severe allergic asthma	↓ Asthma exacerbations, ↓ serum free IgE
		Chronic severe allergic asthma	↓ Asthma exacerbations greater when sub analyzed by type 2–high phenotypes (↑ blood eosinophil counts, or serum periostin levels)
IL-5	Anti–IL-5	Allergen challenge: mild allergic asthma	No effect on clinical asthma outcomes despite ↓ in blood and sputum eosinophil counts
	Anti–IL-5 (mepolizumab)	Mild-to-moderate allergic asthma	No effect on clinical asthma outcomes despite ↓ in blood, sputum, bone marrow, and airway eosinophil counts
	Anti–IL-5 (mepolizumab; reslizumab)	Chronic, refractory, severe asthma with type 2–high phenotype (sputum eosinophils >3%, or ↑ blood eosinophil counts)	↓ Asthma exacerbations, ↓ blood/sputum eosinophils, ↑ FEV_1

eosinophil numbers and asthma control.[20] The DREAM trial was a large multicenter, placebo-controlled study showing reducing asthma exacerbations and eosinophilic inflammation.[21] An important finding of the study was that mepolizumab reduced the number of exacerbations and blood and sputum eosinophils, despite a small effect on FEV1 and Asthma Control Questionnaire (ACQ) scores compared with the placebo.[22] Extra-large mepolizumab trial in patients with severe asthma taking high-dose combination of an inhaled corticosteroid (ICS)/a long-acting beta-agonist (LABA) treatment with inflammation showed, three different applied doses forms of mepolizumab were equally effective in reducing asthma exacerbations compared with the placebo. The greatest reductions were seen in those with the highest blood eosinophil counts, and greatest prior exacerbation history. Several studies demonstrated that mepolizumab is well tolerated and efficacious in adults with severe eosinophilic asthma; a recent study showed us the cessation of mepolizumab resulted in a rapid increase of blood eosinophils followed by an increase in asthma symptoms and exacerbations. Those studies showed the importance of maintaining suppression of eosinophilic inflammation in these cases.[22,23]

Mechanism of activity for omalizumab

Omalizumab is a recombinant DNA-derived humanized monoclonal antibody that selectively binds to circulating human IgE, and prevents the IgE binding to mast cells by high and low affinity receptors.[24] It reduces the cell activation and generation of inflammatory mediators. The airway mast cells are important in the formation of asthma because they secrete an array of cytokines such as the two Th2 cytokines namely IL-4 and IL-5, tumor necrosis factor-α and this creates the main problem that forms asthma.[24,25] was defined to be the first nonsteroidal agent with major anti-inflammatory activity in the airways of patients with allergic asthma.[26] Also, omalizumab is the only biological anti-IgE agent currently licensed for usage. In the studies we examined, omalizumab was found to be very effective and safe to use.[26] It improved asthma control in allergic asthmatics compared to a placebo controlled patient.[26] Patients showed reductions in corticosteroid requirements.

Features of omalizumab

As one of the most important findings, omalizumab was shown to reduce eosinophils levels (to one-tenth of control group).[24] Also it was found that smooth muscle proteins such as tropomyosins, myosins, and actins were reduced to very low levels. In an another study, omalizumab decreased corticosteroid requirements compared with the placebo after a fluticasone reduction phase in patients with severe atopic asthma receiving corticosteroids and long-acting β-agonists (LABAs).[16,27] On the contrary, the other severe asthma trial, add-on omalizumab did not significantly decrease asthma exacerbations.[27,16] It was observed that quality of life and symptom scores of the patients taking omalizumab has improved. Regarding forced expiratory volume in 1 sec (FEV1), different results were published.[13,18] Also in a different study it was found that patients with severe asthma had greater reductions in asthma exacerbations with omalizumab therapy.[7] These findings led the researchers to study more on the patients who have severe asthma. Another reason that omalizumab is used on the patients with severe asthma is that it has fewer side effects. It may cause a severe allergic reaction called anaphylaxis.[28] The reaction may occur after the initial dose, or after many doses. Also, cases of cancer and inflammation in blood vessels are rarely observed with the patients taking omalizumab.[28] Severe inflammation was reported in patients using lowered dose of corticosteroids or in patients who stopped to have them.[28]

Conclusion

Omalizumab and mepolizumab are approved drugs by Food and Drug Administration (FDA) for the treatment of allergic asthma in many countries. Omalizumab is recently the recommended treatment for allergic asthma. New treatments have been being tested and are becoming available for severe asthmatics.[25] The most recent one is anti-IL-5 which was found to be effective especially in severe eosinophilic asthma. The difference between their utilization creates a new field of personalized medicine. These agents are yet to be used by every asthma patient. For all patients, the lowest dose is recommended because of the detrimental adverse effects that may occur but for the patients with allergic asthma who are poorly controlled with inhaled steroids, omalizumab may provide symptom control and allow them to be managed with lower inhaled steroid doses. There are no clinically or immunologically definitive factors that consistently predict a good therapeutic response to omalizumab or mepolizumab in allergic asthma. According to the current knowledge, the duration of treatment is unclear. The effects are different in every patient. The dose of the agent should be determined depending on the clinical caharacteristics

of the patients. The evolution of asthma treatment, and biologic therapies specifically targeted to the right patients will improve efficacy and reduce risk.[7]

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