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Review

Future Biologic Therapies in Asthma☆

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ABSTRACT

Despite the administration of appropriate treatment, a high number of patients with asthma remain uncontrolled. This suggests the need for alternative treatments that are effective, safe and selective for the established asthma phenotypes, especially in patients with uncontrolled severe asthma. The most promising options among the new asthma treatments in development are biological therapies, particularly those monoclonal antibodies directed at selective targets.

It should be noted that the different drugs, and especially the new biologics, act on very specific pathogenic pathways. Therefore, determination of the individual profile of predominant pathophysiological alterations of each patient will be increasingly important for prescribing the most appropriate treatment in each case. The treatment of severe allergic asthma with anti-IgE monoclonal antibody (omalizumab) has been shown to be effective in a large number of patients, and new anti-IgE antibodies with improved pharmacodynamic properties are being investigated.

Among developing therapies, biologics designed to block certain pro-inflammatory cytokines, such as IL-5 (mepolizumab) and IL-13 (lebrikizumab), have a greater chance of being used in the clinic. Perhaps blocking more than one cytokine pathway (such as IL-4 and IL-13 with dulipumab) might confer increased efficacy of treatment, along with acceptable safety.

Stratification of asthma based on the predominant pathogenic mechanisms of each patient (phenoendotypes) is slowly, but probably irreversibly, emerging as a tailored medical approach to asthma, and is becoming a key factor in the development of drugs for this complex respiratory syndrome.

Futuras terapias biológicas en el asma

Palabras clave:
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RESUMEN

Un porcentaje elevado de pacientes con asma no está controlado, incluso a pesar de seguir un tratamiento adecuado. Esto indica que son necesarios tratamientos alternativos que sean eficaces, seguros y selectivos para los fenotipos de asma descritos, especialmente en pacientes con asma grave no controlada. De los nuevos tratamientos en desarrollo para el asma, las opciones más prometedoras son las terapias biológicas, en particular los anticuerpos monoclonales frente a dianas selectivas.

Es importante tener en cuenta que los diferentes fármacos, pero especialmente los nuevos tratamientos biológicos, actúan sobre vías patogénicas muy específicas, y por lo tanto cada vez va a ser más importante determinar el perfil individual de alteraciones fisiopatológicas predominante en cada paciente para prescribir el tratamiento más adecuado en cada caso. El tratamiento del asma grave alérgica con un anticuerpo monoclonal anti-IgE (omalizumab) ha mostrado ser eficaz en un número elevado de pacientes, y nuevos anticuerpos anti-IgE con mejores propiedades farmacodinámicas están siendo investigados.

Entre las terapias en desarrollo, los medicamentos biológicos dirigidos a bloquear ciertas citoquinas proinflamatorias, como IL-5 (mepolizumab) e IL-13 (lebrikizumab), son los que tienen más visos de ser utilizados clínicamente. Tal vez el bloqueo de más de una vía de citoquinas (como IL-4 e IL-13 con dulipumab) pueda ofrecer una mayor eficacia del tratamiento, junto con una seguridad aceptable.

La estratificación de asma en función de los mecanismos patogénicos predominantes en cada paciente (fenoendotipos) está abriendo paso, de forma lenta pero probablemente irreversible, a la medicina personalizada para el asma, y se está convirtiendo en un factor clave en el desarrollo de fármacos para este complejo síndrome respiratorio.

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Introduction

Drugs currently used for the treatment of asthma reduce inflammation of the respiratory tract and relieve bronchospasm, but do not offer a cure, so symptoms reappear when treatment is discontinued. International[1] and national[2] guidelines for the management of asthma underline the importance of effective treatment for achieving and maintaining control. Despite the wide availability of effective treatments, and uniform treatment guidelines,[1,2] achieving control of their asthma remains a constant challenge for many patients. Recent studies indicate that over 50% of patients with asthma are not controlled,[3,4] even on regular maintenance treatment with a combination of inhaled corticosteroids (IC) and a long-acting beta-2 agonist (LABA).[5]

These data suggest that there is a need for alternative treatments, particularly for patients with severe uncontrolled asthma. However, it is important to remember that different drugs, particularly biologics, act on specific pathogenic pathways, so the individual profile of the predominant physiopathological alterations of each patient must be determined in order to prescribe the most appropriate treatment in each case.[6]

Asthma management, both current and future, must include the stratification of patients into the recently defined phenotypes (clinical, inflammatory, molecular)[7] and endotypes (allergic asthma, aspirin-sensitive asthma, late-onset hypereosinophilic asthma, *etc.*)[8] that can be grouped under "phenoendotypes". Moreover, in the last 10 years, significant efforts have been made to identify the characteristics that differentiate severe asthma from mild to moderate asthma, preparing the ground for the development of new selective treatments.

Among the new asthma treatments the most promising are biological therapies, and in particular, selectively targeted monoclonal antibodies (mAb).[9] Biologics at a more advanced stage of development are reviewed below (Table 1), some of which, such as the new anti-IgE, anti-IL-5 and anti-IL-13 mAbs, may find their place in clinical practice in the not too distant future.

Table 1
Biologics Currently Under Development for the Treatment of Asthma.

New anti-IgE monoclonal antibodies
Quilizumab (MEMP1972A)
8D6
Anti-IL-5 biologics
Anti-IL-5 monoclonal antibodies
Mepolizumab (anti-IL-5)
Reslizumab (anti-IL-5)
Benralizumab (anti-IL-5Rα)
TPI-ASM8 (anti-IL-5Rβc and anti-CCR3 receptor antisense oligonucleotides)
IL-4/IL-13 antagonist
Pascolizumab (anti-*IL-4 mAb)*
Altrakincept (soluble human recombinant IL-4R)
Pitrakinra (IL-4 mutein)
Anti-IL-13 monoclonal antibodies
Lebrikizumab
Anrukinzumab
Tralokinumab
Dulipumab (anti-IL-4Rα mAb)
Anti-IL-9 monoclonal antibodies
MEDI-528
Anti-TNF-α treatments
Etanercept (TNFR2/p75 fusion protein and human IgG1 Fc)
Anti-TNF-α monoclonal antibodies
Infliximab
Adalimumab
Golimumab
Anti-T-cell monoclonal antibodies
Daclizumab (anti- IL-2 receptor α chain)
Keliximab (anti-CD4)
Oxelumab (OX40 ligand blocker)
KB003 (anti-GM-CSF)

mAb: monoclonal antibody; GM-CSF: granulocyte and macrophage colony stimulating factor; IL: interleukin; TNF-α: tumor necrosis factor α.

New Anti-IgE Monoclonal Antibodies

Protein–protein interaction between IgE and its high-affinity receptor (FcεRI) is a key component in the allergic response. At present, omalizumab is the only mAb approved for the treatment of asthma. Clinical studies in omalizumab have further defined the role of IgE in allergic asthma. Moreover, it is important to take into consideration certain entities in which IgE may also play a part even if allergic etiology is not well established, such as nasal polyposis or non-allergic asthma. Nasal polyposis may be present in asthma with or without concomitant atopy, but it is particularly associated with non-allergic aspirin-sensitive asthma, and is one of the most common comorbid conditions in patients with severe asthma. Most studies on the pathogenesis of nasal polyposis show inflammatory eosinophilic proliferation and elevated local IgE, in addition to elevated degranulated mast cells. Omalizumab has shown clinical efficacy in the treatment of polyposis in patients with asthma, suggesting that local production of IgE in the respiratory tract may be important in these patients.[10,11]

In non-allergic asthma, the bronchial inflammatory process, while not fully clarified, appears to resemble that of allergic asthma, with an increase in Th2 lymphocytes, mast cell activation and eosinophil infiltration. The lack of therapeutic alternatives in these patients occasionally means that omalizumab for "compassionate use" is prescribed. Two preliminary studies[12,13] have shown that omalizumab is effective in the treatment of non-allergic asthma.

New anti-IgE molecules, discussed below, are being developed that will probably be superior to the currently available agent. A new human anti-IgE mAb (8D6) possesses a unique set of binding specificities. This mAb binds to a conformational epitope on the CH3 domain of human IgE and can compete with omalizumab for IgE binding.[14] Like omalizumab, 8D6 does not bind to IgE already bound to the high-affinity IgE receptor (FcεRI) on basophils and mast cells, but unlike omalizumab, it can bind to IgE already bound to the low-affinity receptors (FcεRII or CD23).[14] Since previous studies have shown that anti-CD23 mAb can inhibit IgE synthesis in *in vitro* lymphocyte cultures and inhibit IgE production, 8D6 may offer pharmacological mechanisms in addition to those mediated by omalizumab for the neutralization of IgE.

Quilizumab (MEMP1972A, Genentech/Roche) is another anti-IgE mAb currently under study in a phase IIb, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of 3 doses (150, 300 and 450 mg subcutaneously) in adults with allergic asthma not controlled with IC and a second maintenance medication (NCT01582503).

Using small molecules to inhibit the IgE–FcεRI receptor interaction is an attractive strategy in the treatment of allergic diseases. Cyclic peptides and small proteins that interfere with the IgE–FcεRI system are under development and may be effective in this area.[15]

Anti-IL-5 Biologics

Interleukin (IL)-5 is a hematopoietic cytokine produced by various cells such as Th2 lymphocytes, eosinophils, basophils, mast cells and natural killer T-cells, and is the main eosinophil modulator cytokine.[16] IL-5 enhances eosinophil chemotaxis, activation and degranulation, while reducing apoptosis and prolonging survival. The IL-5 receptor (IL-5R) is expressed on both basophils and eosinophils and is made up of 2 subunits: an α-subunit (IL-5Rα) that is IL-5-specific and a βc-subunit (IL-5Rβc) that is responsible