Personalized Medicine in Allergy

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Allergic disease is among the most common pathologies worldwide and its prevalence has constantly increased up to the present days, even if according to the most recent data it seems to be slightly slowing down. Allergic disease has not only a high rate of misdiagnosis and therapeutic inefficacy, but represents an enormous, resource-absorbing black hole in respiratory and general medicine. The aim of this paper is to summarize principal therapeutic innovations in atopic disease management befallen in the recent years in terms of personalized/precision medicine.

Key Words: Personalized/precision medicine; allergy; monoclonal antibodies; omalizumab; mepolizumab

INTRODUCTION

The allergic response is currently defined as "*the result of immune reactions to antigens known as allergens,*" characterized by the production of specific Immunoglobulin E (IgE) as a consequence of this exposure.[1] Nowadays, according to several authors, allergic diseases are going through a stationary or even a decreasing phase in terms of prevalence, although the increasing prevalence persists in developing countries, especially those in which allergic pathologies were not so common in the past.[2] An Italian statistic performed in 2005 reports that allergic disease is positioned at the third place of chronic pathologies with an incidence of 10.9%, with a higher prevalence in females (12.9%) vs males (9.6%).[3]

Allergic disease often deeply affects patients' quality of life and absorbs an important part of health care resources in every country. Undeniably, one of the most represented in terms of both the number of patients and importance is asthma. Accordini *et al.*[4] stated that in 2010, the annual expenditure for any European asthmatic patient was 509 € for controlled asthma and 2,281 € for uncontrolled asthma. Not only is asthma one of the most prevalent allergic diseases, but it is estimated that worldwide, urticaria occurs lifetime with a prevalence of above 20%,[5] and it is also approximated that in 2012, about 8.8 millions of children reported skin allergies in a 12-month observation period.[6] The high incidence the social burden of these diseases require us to pay more attention to what concerns the diagnosis and therapy in these kind of patients. New therapeutic approaches have recently been put under investigation. What

happened to severe uncontrolled asthma with anti-IgE therapy has happened to difficultly controlled chronic urticaria also with good results in terms of clinical effect[7] and safety.[8] The importance of precision medicine in other allergic diseases opens numerous questions on the need to evaluate the possibility of searching several biomarkers for asthma able to predict the response to these biological treatments that could be used possibly in the nearest future.

FROM "ONE SIZE FITS ALL" TO PRECISION MEDICINE

Allergic and chronic respiratory diseases have an important socioeconomic impact and represent an important burden of missed or wrong diagnosis. Consequently, adequate diagnosis and treatment are unsatisfactory. Precision medicine could represent a novel, revolutionary approach,[9] ideally capable of resolving or at least reducing this burden, implementing physicians' awareness of these critical issues.[1]

The "one size fits all" principle on which asthma therapy was

based on is radically changing for several years. Actually, one size does not fit all. Atopy's therapy is moving from blockbusters to a phenotype/endotype-driven precision medicine, currently based on monoclonal antibodies directed against specific and selected cytokines/interleukins involved in airway remodeling and inflammation in chronic severe asthma and at the base of several other allergic pathologies. This change in route is even deeper than thought before, implying a transition from general practitioners, who traditionally treated these diseases, to specialists.[10] In fact, patients eligible for monoclonal antibodies follow a narrow therapeutic path: specialists are allowed to administer biological drugs, whereas general practitioners take care of the classical management of allergic diseases, as it actually is the case for other medical specialties like oncology or rheumatology.

A few years ago, we described a "target medicine like" approach called "the magic bullets which seek their own targets" starting from omalizumab, the first and at that time unique biologic available.[11] Conceptually, we described the same process of the "Personalized Medicine" targeting with the biologic the mechanism of the diseases, as predicted by the immunologist Paul Ehrlich one century ago.[12]

The definition of Precision Medicine given by Passalacqua *et al.*[13] could be reassumed as a "structural model aimed at customizing healthcare, with medical decisions and products tailored on an individual patient at a highly detailed level." Precision medicine's mantra could be summarized with "prescribing the optimal treatment to the right patient," since no other allergy treatment, excluding possibly monoclonal antibodies, has these specific characteristics (Fig. 1).[14]

Allergen immunotherapy (AIT) represents an optimal model of tailored therapies because etiological agents responsible for the symptomatological cortege are described at a molecular level.

Focusing on asthma, traditional anti-asthma therapy was based on bronchospasm-relieving (beta-2-agonists) and anti-inflammatory drugs (corticosteroids) to control symptoms and reduce inflammation.[15] The reason why we are now moving from non-specific drugs to monoclonal antibodies is the fact that whereas most people are adequately controlled in their pathology, many asthmatic people still present an uncontrolled symptomatic asthma despite the evidence provided by international guidelines and maximal therapy.

Hence, this has been necessary to expand our knowledge on the physiopathological bases of asthma, rhinitis, and other allergic pathologies and brought to unveil the path to different phenotypes of the same disease, forcing to reconsider allergic diseases as multifaceted, not static, and invariable entities that could benefit from precision medicine.

Deeping our knowledge about TH2 inflammation and TH2 cytokines/interleukins permitted us to develop alternative treatment strategies based on intervening directly on the molecules responsible for the pathogenesis of allergic diseases and establishing the bases for molecularly targeted therapies.

At the present days, omalizumab, a humanized monoclonal antibody directed to circulating IgE, is the only targeted monoclonal antibody approved in severe uncontrolled asthma and chronic urticaria treatment.

FIRST TARGETED DRUGS IN ASTHMA: OMALIZUMAB AND MEPOLIZUMAB

In the recent years, a new approach in asthma therapy is catching on, trying to match the right treatment to a specific mechanism of disease. Several studies have been conducted to master asthma physiopathology, defining the specific characteristics of asthma phenotypes, and finding each ideally appropriate therapy. Nowadays, the majority of new anti-allergic biologic drugs have not been approved yet for routine use, and further studies and clinical trials are necessary before they could be routinely used.

The first biological target identified in allergic disease was IgE, and the first targeted biologic drug, actually the only one available for routine use, is omalizumab, a humanized, murine-derived, IgG1 monoclonal antibody which is presently approved only in severe asthma and chronic urticaria. Omalizumab binds to circulating IgE in the Cε3 region hindering their link to their receptors FcεRI and FcεRII on basophils and mast cell membrane, and therefore this avoids degranulation and release of allergic inflammation mediators.[16]

Several studies on the efficacy and safety of omalizumab showed a reduction in allergens' effect on the airways,[17] a better control of asthma symptoms[18] and a significant reduction in the number of exacerbations,[19] even in subjects poorly responsive to maximal therapies.[20] Other studies also showed significant benefits in allergic asthmatic children[21] and a significant reduction in systemic corticosteroid dosage in subjects with refracto-
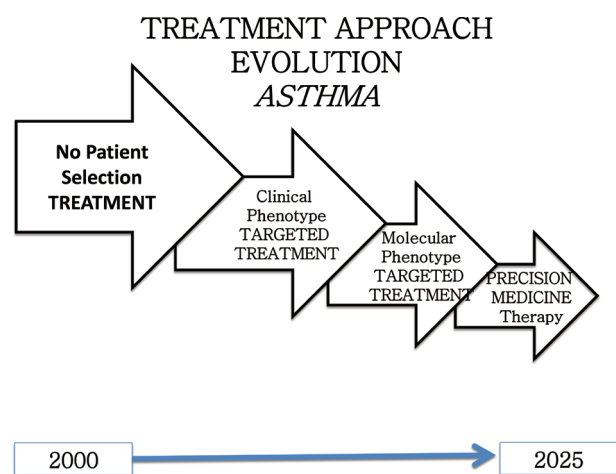
Fig. 1. Evolution of treatment in asthma, from a therapy applicable to any patients to a precision medicine.

ry disease.[22] Omalizumab's treatment inclusion criteria for asthmatic patients, adults, and children (6-12 years old) are persistent severe asthma for more than 12 months not adequately controlled with high doses of ICS and (long acting beta 2 agonists (LABAs), evidence of the sensitization to a perennial allergen at by detection of specific IgE or skin tests, incomplete control of respiratory symptoms, high levels of serum IgE, and reduced baseline pulmonary function (FEV1<80%).[23] Omalizumab represents the first and only example of a drug dedicated to a specific subtype of asthmatic patients and can be considered the first tile of asthma target therapy's articulated mosaic. However, some other interesting data seem to reveal a connection between omalizumab responders and periostin levels,[24] similar to anti-IL-13 drugs, showing that some mechanisms still have to be clarified.

In the literature, there are also some off-label uses in several diseases in which IgE actually plays an important role in determining their pathogenesis, such as allergic rhinitis, atopic dermatitis, anaphylasix, food and drug allergy, eosinophilic granulomatosis with polyangioitis (Churg-Strauss syndrome), eosinophilic pneumonia, allergic bronchopulmonary aspergillosis, larynx angioedema, skin diseases, and ocular/ear disorders. The evidence of clinical efficacy is still too weak, but they are noteworthy.

The first clinical trial on the efficacy and safety of omalizumab goes back to 2001.

The food and Drug Administration (FDA) approved omalizumab in 2003 for treating patients aged 12 years and older suffering from moderate to severe allergic asthma. Moreover, omalizumab has recently been approved in chronic urticaria treatment strategies. At the present days, omalizumab is soon going off patent, opening the drug market to biosimilars, and shortly 2 other anti-IgE monoclonal antibodies, quilizumab and ligelizumab, will be available.[25,26]

If the light of the research has immediately been pointed at IgE as the keystone of the allergic response since the beginning of asthmatic phenotype characterization, the role of eosinophils and the role of IL-5 in their maturation, recruiting, and survival processes establishes another pillar of today's developing target therapy: anti-IL-5 biological drugs and eosinophil count as biomarker.

Mepolizumab was the first anti-IL-5 drug tested and its connection with eosinophil cells quickly emerged from clinical studies. One of the first clinical trials showed poor efficacy on reducing asthma symptoms or increasing pulmonary function.[27] However, further trials revealed the bias behind these results and gave more positive findings. In the first studies, there was a lack in selection of patients with high count of eosinophils. Other studies successfully reached this objective, collecting very interesting data and demonstrating, in a population of asthmatic patients with high sputum/blood eosinophil count, a significant reduction in acute exacerbations frequency, a drop

in eosinophil count, and a significant reduction in systemic corticosteroids dosage.[28,29] Such findings were very relevant, highlighting the evident connection between a targeted drug and an easy-to-evaluate biomarker, potentially leading to a really effective targeted therapy for some asthmatic patients. As eosinophils are also involved in other diseases than asthma, related trials were subsequently performed. Studies in patients with Churg-Strauss disease and with hypereosinophilic syndrome were conducted, showing good clinical results.[30,31] Even in nasal polyposis, mepolizumab showed a good efficacy, with a significant reduction in polyp size,[32] and similar good results were obtained in patients with eosinophilic esophagitis.[33] Conversely, although a reduction in eosinophilic count, no clinical benefit seems to come from mepolizumab's use in atopic dermatitis.[34] On the way of blocking the IL-5 pathway, several trials were run to evaluate the clinical efficacy and safety of reslizumab, another anti IL-5 drug, and benralizumab, an anti-IL-5R monoclonal antibody. A couple of studies were undertaken to evaluate reslizumab's efficacy and safety on OCS-controlled, hypereosinophilic asthmatic patients and showed a better control of disease exacerbation rate in the treated group versus the placebo population.[35] Similar results were achieved in benralizumab's clinical trials which also showed a benefit in pulmonary function and a reduction in symptoms, with a tight correlation with eosinophil count.[36] Other trials demonstrated a cell-mediated cytotoxicity against bone marrow eosinophil's immature progenitors, "opsonized" by benralizumab.[37] About the other eosinophil-related diseases, a trial on children and adolescent patients with eosinophilic esophagitis seemed to show a significant reduction in intraepithelial eosinophilic granulocytes, but failed to show a significant benefit in symptomatology versus placebo.[38] Reslizumab was also significantly able to reduce nasal polyp size, with a correlation between efficacy and nasal IL-5 levels.[39] A trial conducted on patients affected by COPD, characterized by high eosinophil count, failed to demonstrate clinical improvement, even if a not statistically significant benefit in FEV1 and specific questionnaires in patients with blood eosinophil >200 cells/mcL seemed to leave an open door for further similar studies.[40]

Unfortunately, nowadays none of anti-IL-5 monoclonal antibodies can be used yet for routine clinical use, although mepolizumab has already been approved by the EMA and the FDA and could probably be available in the future.[41]

BIOMARKERS AS ESSENTIAL ADJUVANTS IN THERAPEUTIC STRATEGY CHOICE

Several studies have recently underlined that asthma is a complex disease with different clusters of symptoms. Since different pathophysiological mechanisms are involved in the disease development, a single therapy cannot be applied to all patients.[42] Uncertainty remains on why only some patients' phe-

notypes and endotypes show an encouraging response to biological treatments. However, the use of biomarkers specific for each phenotype/endotype of asthma could help select patients eligible for determinate treatments, for whom a positive response could be expected from the utilization of monoclonal antibodies.

For these reasons, it is a clear need to find valid biomarkers for stratifying patients and to establish appropriate personalized therapy. According to the NIH Biomarkers Definitions Working Group, a biomarker could be defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention."

An ideal biomarker is low-invasive, specific, sensitive, simple-to-obtain, cheap, and highly reproducible; moreover, it should be related to clinical features and not influenced by other diseases.[43,44]

Various pro-inflammatory stimuli are able to induce nitric oxide (NO) by bronchial epithelial cells. Increased fractional exhaled nitric oxide (FeNO) is associated with eosinophilic inflammation, poor disease control, and aspirin-induced asthma. On the other hand, NO is reduced in patients with non-atopic asthma or neutrophilic inflammation, and obese patients.[45]

FeNO is non-invasive, simple-to-obtain, and highly reproducible. FeNO measurement can be used to predict steroid response in patients with eosinophilic inflammation. Moreover, FeNO is more influenced by asthma control than by severity, and this peculiarity makes this test useful for disease management.[46] Several attempts have been made to standardize FeNO measurement and to develop guidelines that could help the physicians in clinical practice. Guidelines suggest the following cutoff points: low FeNO <25 ppb (<20 ppb in children), intermediate FENO between 25 and 50 ppb in adults (20-35 ppb in children), and high FENO >50 ppb in adults (>35 ppb in children).[47]

FeNO is influenced by factors not directly related to asthma, such as age, weight, gender, rhinitis, and smoking; moreover, it is an expensive technology and not all centers can afford it. Another FeNO disadvantage is the lack of association with some asthma phenotypes, for example neutrophilic inflammation. Although a unique marker of asthma does not exist at present, FeNO could be used in association with clinical evaluation, sputum analysis, and pulmonary function tests to draw a correct management plan of asthma therapy and at follow up.[48]

Exhaled breath condensate (EBC) is another noninvasive technique that could be used to evaluate pulmonary inflammation. EBC is obtained by condensation of exhaled aerosols. EBC permits us to obtain various markers that correlate with treatment's response and asthma severity; moreover, EBC is simple and can also be obtained from children without train. In asthmatic patients, EBC analysis shows increased concentrations of endogenous reactive oxygen species (ROS), adenosine, arachi-

donic acid metabolites, nitrogen reactive products, ammonia, and pro-inflammatory cytokines.[49]

Unfortunately, EBC analysis has not been standardized yet, and we have no guidelines. Furthermore, another critical issue is that EBC results are influenced by smoking, alcohol, infections, exercise, and other factors that should be taken into count.[50]

Periostin is a matricellular protein that binds to several other proteins, such as collagen, fibronectin, and tenascin-C, with an important role in the maintenance of inflammatory processes. Sidhu *et al.*[51] demonstrated that periostin is produced by epithelial lung cells by the stummulation of IL4 and IL-13, and it could be suppressed with the use of corticosteroids. This means that although periostin may also be present at non-physiological quantities in other diseases, it could be used as a biomarker in some forms of severe asthma.[51]

The characteristics that make periostin a good biomarker are its facility in passing from inflamed tissues to the blood and the low serum basal level in physiological conditions.[52]

A study conducted by Corren *et al.*[53] demonstrated that high serum periostin levels are associated with a greater response to lebrikizumab, a humanized monoclonal antibody that blocks IL13 reducing the release of signaling molecules and prevents airway remodeling. The variables taken into count to evaluate the response to therapy were the changes in pulmonary function and the lowering of exacerbations rate.[53]

Nevertheless, there are some critical issues that actually limit the use of periostin as a biomarker for asthma. Periostin levels rise in several diseases which have an increased basal cellular activity, such as cancers with metastatic spread and several other ones, highlighting the role of clinicians in properly evaluating comorbidities. Moreover, at the present days, we do not achieve any standardization of periostin measurement, and cutoff values have not yet been established (Fig. 2).

Eosinophils play a central role in asthma, being involved in the development of allergic processes and in the maintenance of inflammatory phenomena. Eosinophil are recruited by various proteins secreted by epithelial cells; eotaxin1 (CCL-11) is one of the most potent chemoattractants and a correlation has been demonstrated between CCL-11 and asthma severity.[54] Eosinophil count can be considered a good marker of asthma as it is related to clinical manifestation. A previous analysis conducted has demonstrated the reduction in the number of eosinophil count in the peripheral blood of asthmatic patients under treatment with omalizumab. High eosinophil counts in sputum might be related to the thickening of the reticular basement membrane, showing that the number of eosinophil can go hand in hand with airway remodeling.[55]

Though eosinophil count is a simple, non-invasive test, there is a weak correlation between sputum eosinophils and response to treatment with mepolizumab.[56]

Eosinophil count alone is not a complete biomarker; in order
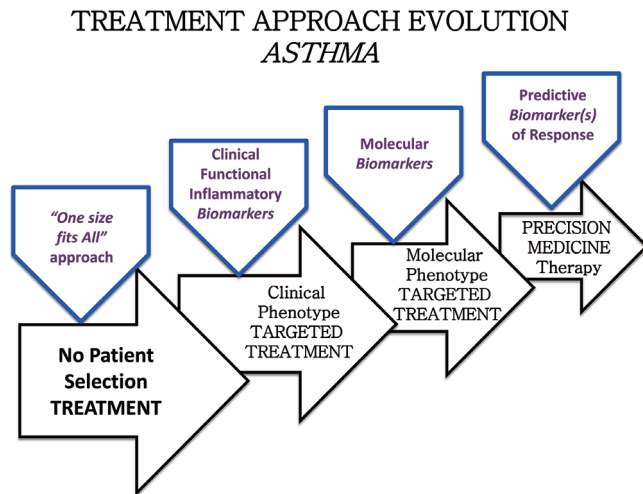
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to better follow the trends of asthma, it could be useful to associate eosinophil count with other biomarkers, such as periostin, FeNO, and pulmonary function tests.

In conclusion, there is no single biomarker valid to be used alone as the gold standard. A biomarker capable of predicting airway inflammation degree may not be valid for predicting the response to therapy. It is therefore necessary to the combined use of biomarkers to improve asthma management strategies.[56]

TARGET DRUGS IN ANGIOEDEMA

Angioedema is a localized and self-limiting edema of the subcutaneous or submucosal tissue, due to a temporary increase in vascular permeability caused by the release of different vasoactive mediators.[57] Organs involved include the skin, oropharynx, upper respiratory airways, and gastrointestinal tract. Different types of acquired and hereditary angioedema are now identified. Acquired angioedema can be secondary or a side effect in approximately 1% of patients treated with angiotensin-converting enzyme inhibitors (ACE-I) and is a common cause of hospitalization for allergic disease after asthma.[58,59]

Idiopathic acquired angioedema can be histaminergic (IH-AAE) or non-histaminergic (INH-AAE). Angioedema with C1-INH deficiency can be acquired (no family history and onset after 40 years) or hereditary in association with a genetic C1-INH deficiency. Hereditary angioedema due to C1-INH deficiency (C1-INH-HAE) is an autosomal dominant condition with prevalence of approximately 1.5/100.000 inhabitants.[60,61] HAE is caused by the overproduction of bradykinin and the activation of the bradykinin β-2 receptor.[61] Recent evidence suggests that VEGF-A, previously known as Vascular Permeability Factor, could contribute to increased vascular permeability in HAE patients.[62]

C1-INH-HAE is manifested by recurrent, localized subcutaneous, or submucosal edema lasting 2-7 days. The clinical expression is highly variable among patients. Patients with C1-INH present with low C4, and measurement of C4 levels is used to screen C1-INH-HAE because it is decreased between attacks and can be only exceptionally normal.[63] Diagnosis is confirmed by plasma levels of C1-INH below 50% of the normal value. Two phenotypic variants of C1-INH-HAE have been described: 85% of cases are characterized by low antigenic and functional levels of C1-INH; 15% of patients have normal quantitative levels of C1-INH and diagnosis requires measurement of C1-INH activity in plasma. Edema of the larynx is the most fearsome feature of this disorder and can be life-threatening.[64]

HAE-affected individuals carry a mutation in the *C1-INH* gene. *C1-INH* maps on chromosome 11q12-q13.1; it is arranged in 8 exons, the first one containing 38 bp of non-coding sequence and the second having a 22 bp-long signal peptide before the first methionine.[65] More than 300 *C1-INH* deficiency-causing mutations leading to failure in production or activity of C1-INH protein have been identified. This explains the phenotypic heterogeneity of hereditary angioedema. Approximately 25%-30% of these mutations occur as *de novo* events.[66]

The phenotype of HAE is extremely variable and includes different degrees of severity and number of attacks, and their localization. Interestingly, there does not seem to be a correlation between gene mutations, C1-INH levels, and phenotypes in patients with HAE.[65,67] The care of patients with HAE is neither optimal nor uniform in Europe,[68,69] Canada,[70] and worldwide. Management of HAE can also be divided into various approaches due to the heterogeneity of the disorders. The aim of treatment of acute attacks, also referred to as "on-demand therapy," is to minimize their severity, including potentially fatal upper airway edema, and associated with impaired quality of life (QoL). The heterogeneity of the phenotype of HAE therapy should be personalized.

Acute treatment includes plasma-derived C1 inhibitor (pdC1-INH) (Berinert⃰, Cinryze) recombinant human C1-INH (rhC1-INH, Ruconest⃰),[71] and antagonist of bradykinin β2-receptor Icatibant (Firazyr⃰),[72] which are all acceptable options for acute treatment. Icatibant may be particularly useful in enabling self-administration as intravenous access is not necessary. The inhibitors pdC1-INH and rhC1-INH are administered intravenously. Regular profilactic treatment with C1-INH may be necessary for patients having 2 or more attacks per week. Recent evidence suggests that self-administration of C1-INH is emerging as an effective treatment to improve clinical outcomes and reduce costs in HAE.[73] Ecallantide (Kalbitor⃰, Dyax Corp) is a 60-amino acid recombinant protein approved by the FDA, but not by the EMA, as s.c. injection in the treatment of acute attacks of angioedema.[74] Due to the uncommon risks of anaphylaxis, Ecallantide must be administered by healthcare professionals.

In patients with frequent attacks or on demand therapy is in-

adequate to achieve control of the disease, long-term prophylaxis should be considered. Similar to the treatment of acute attacks, the long-term prophylaxis of angioedema must be personalized. Attenuated androgens are effective in long-term prophylaxis for most people. Stanozolol (Winstrol®, Winthrop, Bridgewater, NJ) can be administered orally (2 mg/or less). Danazol (Danatrol®, Sanophi-Aventis, Paris, Fr) can also be administered orally (200 mg/or less). Stanozol® and Danazol®, particularly at high doses, carry a potential cardiovascular risk.[75] In addition, these drugs should not be used in children and pregnant patients. Risk-benefit balance of long-term administration of androgens should always be carefully evaluated, and treatment should be individualized according to individual risk factors, response to treatment, contraindications, and possible adverse events.

Finally, because HAE is a rare disease, patient information and support should be comprehensive and consistent. Psychological support should be provided by specialists and healthcare professionals.[76]

Chronic Spontaneous (idiopathic) Urticaria (CSU) is characterized by itchy wheals and flare reactions, angioedema, or both for greater than 6 weeks.[77] CSU has been estimated to affect approximately 0.5%-1% of the general population. Antihistamines are the first-line therapy for acute and chronic urticaria. Unfortunately, approximately 50% of patients to respond CSU fail with this therapy and require additional medications. Some of these patients have IgE autoantibodies against autoantigens, whereas in the majority of cases the nature of the abnormalities cannot be identified.[78] Two phase II and phase III multicenter, randomized, placebo-controlled clinical trials[7,8,79] have established that omalizumab is safe and efficacious for treating recalcitrant patients with CSU that cannot be adequately treated with conventional therapy. Different from asthma[80] and EGPA,[81] omalizumab rapidly acts in patients with CSU. The mechanisms of action of omalizumab in chronic urticaria are largely unknown. It has been suggested that omalizumab blocks IgE antibodies with cross-reactivity to low concentrations of self-antigens.[78]

FUTURE PERSPECTIVES (OFF–LABEL USES)

Off-label use of omalizumab in allergic b disease showed interesting results. These type of studies can enlarge the treatment possibilities of various disease, which are uncontrolled, partially controlled, or controlled at the cost of relevant side effects, maybe allowing a progressive enlargement of official clinical indications as it happened for chronic urticaria. Although its IgE-binding activity, omalizumab has also been tested even in subjects with non-allergic asthma, anecdotally showing good results in long-term treatment,[82] with significant reductions in exacerbation frequency and improvements in pulmonary functions.[83] A study conducted on 10 patients affected by occupa-

tional asthma and treated with omalizumab showed a reduction in exacerbation rate and a decrease in corticosteroids (both inhaled and systemic) dose.[84] Actual knowledge about the efficacy of anti-IgE therapy in allergic bronchopulmonary aspergillosis is still insufficient as significant benefits shown in some studies[85] were not confirmed in other clinical trials.[86] Chronic urticaria is not the only dermatologic disease in which omalizumab's efficacy and security have been explored. Hotze *et al.*[87] performed a trial of 20 patients affected by atopic dermatitis and demonstrated a connection between the absence of a primary deficit in mechanic cutaneous barrier, high levels of some glicerophospholipides, and a good response to omalizumab. Nevertheless, they concluded that despite the positive results obtained with omalizumab, further investigations are necessary to demonstrate anti-IgE therapy's efficacy in atopic dermatitis. Interesting results also came from the application of omalizumab in bullous pemphigoid, with a significant decrease in the eosinophilia that tipically accompanied this cutaneous disease.[88] In association with desensitizing immunotherapy, omalizumab showed clinical efficacy in reducing symptoms in polysensitized children and adolescents with seasonal allergic rhinitis,[89] showing discordant results in patients with chronic rhinitis and nasal polyposis,[90,91] both entities which are hypothetically present in asthmatic patients.

Eosinophilic otitis media (EOM) is an intractable chronic otitis characterized by highly viscous effusion that contains plenty of eosinophils, IgE, eosinophil cationic protein, and IL-5.[92] EOM has frequently been associated with asthma and shown a good response to omalizumab[93] together with an interesting reduction in eosinophil's proteins in middle ear fluids.[94] The efficacy of association of omalizumab and immunotherapy in allergic patients was also demonstrated in another study,[95] in which the addition of anti-IgE allowed for escalation of therapeutic allergen doses. Similar trials showed the same efficacy in association with desensitizing therapy in food allergy.[96] One of these trials showed an interesting link between omalizumab's onset of action and basophil count, opening a possible path to the discovery of a new biomarker.[97] The scientific literature is full of single-patient case reports showing the efficacy of an anti-IgE therapy in several other allergic diseases. More extended and accurate studies, together with a meticulous analysis of the biochemical basis of these diseases, finalized, to look for new valid biomarkers that could lead many of these pathologies actually treated with unspecific drugs (*i.e.*, corticosteroids) and to have valid target therapies. More knowledge of biomarkers and mechanisms understating allergic disease could allow us to consider different therapeutic approach from a single drug approach, to an "articulated therapy" where physicians could use a sequence of biological products able to act on different pathophysiological disease's steps,[98] for instance, omalizumab associated by allergen immunotherapy (AIT) (Fig. 3).[99]

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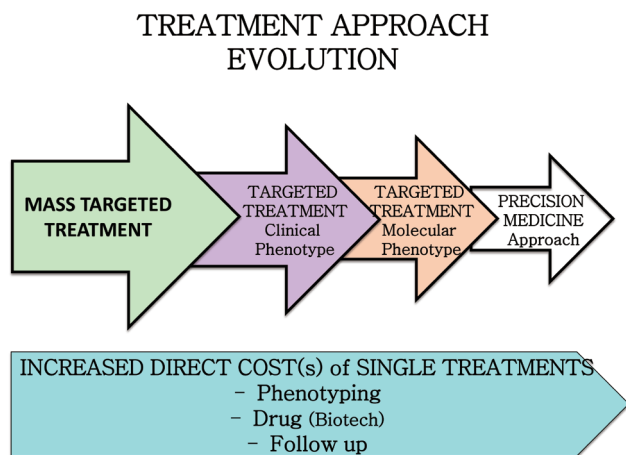
Fig. 3. New findings in asthma therapy increase possibility of therapy approach as well as costs.

CONCLUSIONS

Writing this paper, maybe for pure curiosity, we conducted a medline using the word "allergy" and the name of the principal monoclonal antibodies. We decided to restrict the research field to clinical trials performed from 2001, year of the first clinical trial on omalizumab, until today. The aim was to have an esteem of how many clinical trials have been conducted on the application of monoclonal antibodies in allergic diseases' therapeutic strategies since nowadays. Interestingly, we found that 151 clinical trials were run involving omalizumab: 21 trials involving mepolizumab, 3 trials regarding reslizumab, 4 trials using lebrikizumab, 10 trials concerning benralizumab, 2 trials about pitrakinra's use, 1 trial on tralokinumab, and 3 trials on dupilumab's potentially relevant role in severe uncontrolled asthma therapy. The first clinical trial performed on a monoclonal antibody (omalizumab) goes back to 2001, and after more than 15 years, our knowledge on omalizumab and its possible further applications are still too narrow and have to be enlarged, possibly including other allergic diseases. Hence, the use of the other monoclonal antibodies needs to be further investigated, our knowledge on their use has to be deepened, and other clinical trials have to be performed on allergic subjects before we could utilize target therapies in therapeutic treatment strategies.

The application of these issues might possibly reduce the burden of refractory allergic disease that places allergic pathologies at the third place of the list of chronic diseases and makes them a blackhole of economic resources.

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