

A Critical Evaluation of Anti-IL-13 and Anti-IL-4 Strategies in Severe Asthma

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Abstract

Asthma is a high-prevalence disease, still accounting for mortality and high direct and indirect costs. It is now recognized that, despite the implementation of guidelines, a large proportion of cases remain not controlled. Certainly, adherence to therapy and the education of patients remain the primary objective, but the increasingly detailed knowledge about the pathogenic mechanisms and new biotechnologies offer the opportunity to better address and treat the disease. Interleukin (IL)-13 and IL-4 appear as the most suitable targets to treat the T helper 2 (TH2)-mediated forms (endotypes) of asthma. IL-13 and IL-4 partly share the same receptor and signaling pathways and both are deeply involved in immunoglobulin E (IgE) synthesis, eosinophil activation, mucus secretion and airways remodeling. Several anti-IL-13 strategies have been proposed (anrukinzumab, lebrikizumab and tralokinumab), with relevant clinical results reported with lebrikizumab. Such studies facilitate better definition of the possible predictive markers of response to a specific treatment (e.g. eosinophils, total IgE, fraction of exhaled ni-

tric oxide and periostin). In parallel, anti-IL-4 strategies have been attempted (pascolizumab, pitakinra and dupilumab). So far, dupilumab was reported capable of reducing the severity of asthma and the rate of exacerbations. IL-13 and IL-4 are crucial in TH2-mediated inflammation in asthma, but it remains clear that only specific endotypes respond to these treatments. Although the use of anti-IL-14 and anti-IL-13 strategies is promising, the search for appropriate predictive biomarkers is urgently needed to better apply biological treatments.

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Introduction

Asthma is a high-prevalence, chronic disease. In fact, in the USA, it affects about 24.6 million and worldwide about 334 million of people of all ages [1]. Although the mortality for asthma is decreasing overall [2], it still accounts for 90–170 deaths per million. In addition, direct (e.g. hospital care and drugs) and indirect (e.g. loss of work or school days) costs still represent a major burden of the disease. The cost per year for a European patient has been estimated at 509 euros for controlled asthma and 2,281 euros for uncontrolled asthma [3]. Although asth-

ma can be frequently controlled with the standard inhalant therapy, clinical trials report that in about 20% of patients using traditional drugs, asthma remains not controlled [4], and the situation is even worse in real life. On the other hand, the idea that asthma is a single disease has been recently questioned, and it is now considered as a heterogeneous disease with different pathogenic mechanisms, clinical behaviors and responses to treatment.

The process of asthma phenotyping started about 10 years ago, with the aim of identifying homogeneous groups (either clinically or biologically) of patients. More recently, the term 'endotype' was introduced to underline a more in-depth identification of asthma, including the genetic aspects. Nowadays, >100 genes related to the pathogenesis of asthma have been identified, but the road to fully understand the genetic contribution seems to still be long and tortuous, since no 'asthma gene' has been identified so far. In recent years, it was realized that different phenotypes can be characterized by specific molecular patterns, possibly predictive of the response to specific treatments. The most apparent example is the discovery of the role played by T helper 2 (TH2) lymphocyte-mediated inflammation (so-called 'TH2 high') in about half of asthmatic subjects. Subsequently, more clinical trials have been conducted targeting those molecules specifically related to TH2 inflammation. For instance, clinical trials with biological agents against TH2-associated cytokines consistently show a more remarkable efficacy in patients with markers of elevated TH2 inflammation, such as eosinophils [5, 6].

Despite the use of guideline recommendations for management and therapy, a relevant number of patients continue to report an unsatisfactory control of asthma, with impaired quality of life, exacerbations, increased use of rescue medications or systemic corticosteroids and emergency room/intensive care unit admission. It is noteworthy that in about 50% of these patients there is strong evidence of the pathogenic role of TH2 cytokines such as interleukin (IL)-4, IL-5 and IL-13 orchestrating the eosinophilic and allergic inflammatory processes [7].

The Role of IL-13 and IL-4

IL-4 and IL-13 were among the first TH2-related interleukins discovered in the early 1980s and, since then, they have been traditionally associated with atopy and allergic diseases in general but are also involved in pregnancy, fetal development, mammary development, lactation and various neuronal functions including cognitive

and learning processes and memory formation [8–10]. In theory, every cell has the potential to respond to IL-4, IL-13 or both, but some cell types seem to be more susceptible [11].

We have described the relevance of IL-13 and IL-4 in the pathophysiology of asthma, concerning the proliferation of bronchial fibroblasts, myofibroblasts and airway smooth muscle cells, which leads to airway remodeling [12, 13]. An IL-13 induced role in goblet cell differentiation, mucus production, bronchial hyperresponsiveness, immunoglobulin E (IgE) synthesis (a switch of B cell antibody production) and the recruitment of eosinophils and basophils [14–20] has been repeatedly demonstrated [21].

Several clinical trials have highlighted the role of anti-IL-13 biological agents in the control of disease in the 'TH2 high' asthmatic phenotype which is characterized by an overexpression of IL-13 inducible genes such as periostin [6]. The role of TH2 inflammation is apparent in about 50% of asthmatic patients, in whom there is an abnormal production of proinflammatory cytokines, such as IL-4, IL-5 and IL-13, which induce IgE synthesis and eosinophilic inflammation [22]. TH2 effector cells, once activated by stimulating factors such as allergens, pollutants or infectious agents, release the aforementioned cytokines which act on the surface cells. Several studies have demonstrated that the production of IL-4, IL-5 and IL-13 is associated with the response of type-2 innate lymphoid cells (ILC2s) to IL-25, IL-33, thymic stromal lymphopoietin (TSLP) and leukotrienes [23]. High concentrations of ILC2s have been shown in patients with nasal polyposis and/or a high eosinophil blood count [6, 24].

IL-4 was discovered in the 1980s. It is secreted by activated T cells, mast cells, basophils and eosinophils [25]. There is a close link between IL-4 and IL-13 activity: both activate the α -subunit of the IL-4 receptor (IL-4R α), and IL-4 also activates a γ C subunit while IL-13 stimulates the IL-13 receptor α 1 subunit (IL-13R α 1) [26]. The role of IL-4 is linked to TH2 phenotype lymphocytes. It regulates the synthesis of IgE by B cells and the apoptosis and expression of numerous genes involved in the maturation of macrophages, fibroblasts, epithelial and endothelial cells [27] (fig. 1).

Overview of IL-4/IL-13 Receptor Signaling

Circulating IL-4 and IL-13 bind to a specific receptor which is expressed on various cells, including B lymphocytes, eosinophils, basophils, monocytes and macrophages, dendritic cells, endothelial cells, fibroblasts, air-

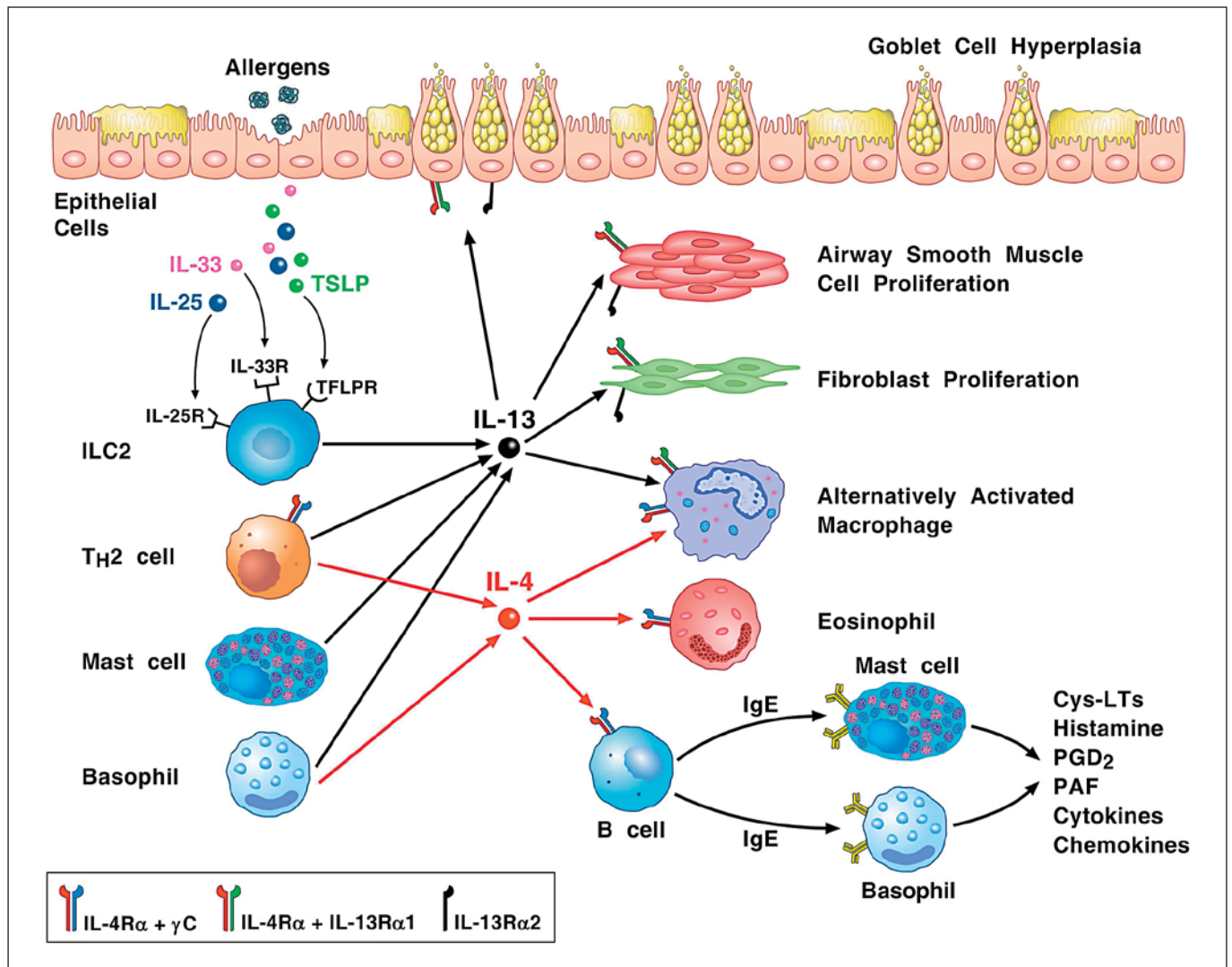


Fig. 1. Diagram of the potential cellular effects of IL-4 and IL-13 on inflammatory and structural cells in asthma. After interaction with noxious agents, including allergens, viruses and proteases, pulmonary epithelial cells can produce TSLP, IL-25 and IL-33. These cytokines activate specific receptors on ILC2s and drive their expansion. Activated ILC2s are central mediators of type 2 immune responses in the lung. Once activated, ILC2s and mast cells produce several cytokines including IL-13. IL-13 induces several cellular changes in the airways including goblet cell hyperplasia and mucus production, airway smooth muscle cell prolifera-

tion, fibroblast proliferation and polarization of alternatively activated macrophages. IL-4, produced by TH2 cells and basophils, activates alternatively activated macrophages and eosinophils and induces IgE synthesis from B lymphocytes and plasma cells. IgE binds to FcεRI receptors on human mast cells and basophils. IgE cross-linking by allergens induces the release of histamine, cys-leukotrienes (Cys-LTs), PAF, prostaglandin D₂ (PGD₂), cytokines and chemokines that are responsible for some of the symptoms of asthma.

way epithelial cells and smooth muscle cells [28]. The receptor is a heterodimer complex of IL-13Rα and IL-4Rα. Circulating IL-13 firstly engages the IL-13Rα1 subunit and this event leads to the recruitment of IL-4Rα. The binding to the IL-13Rα1/IL-4Rα complex initiates the activation of multiple transduction pathways including ty-

rosine kinase 2 (Tyk-2) and Janus kinase 1 (JAK1), which are associated with the IL-13R subunit [29]. The activation of these transduction systems induces the phosphorylation and activation of the proteins, signal transducer and activator of transcription 6 (STAT6) and insulin receptor substrate 2 (IRS-2) [29], which move from the cy-

toplasm to the nucleus, and activate other transduction processes such as that of phosphatidylinositol 3-kinase (PI3-K) [30–32], serine-threonine protein kinase [33–36] and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) [37–39]. IL-13R has another receptor chain, IL-13R α 2, which does not activate transduction processes, but might play a regulatory role in IL-13-induced effects [40] and has been associated with human lung cancer as a potential target for novel therapies [41].

Biomarkers

As the role of specific cytokines in asthma became clearer, specific biomarkers of TH2 airway inflammation were identified. Biomarkers could help to stratify asthma into different subtypes (endotypes), reflecting the predominant pathophysiological mechanism, [42], helping to predict future risk [43] and target TH2-oriented therapies to patients that could respond. TH2-specific biomarkers identified so far include sputum/blood eosinophils, total serum IgE, the fraction of exhaled nitric oxide (FeNO) and bronchial epithelium-derived proteins.

The first biomarker identified and used to predict corticosteroid response was the eosinophil count in sputum and blood. Woodruff et al. [44] found that asthmatic patients with elevated bronchial expression of IL-5 and IL-13 had higher blood eosinophil count than nonasthmatic controls. Some years later, Jia et al. [24] demonstrated a weak correlation between blood and airway eosinophil count, suggesting a limited sensitivity and reproducibility for this biomarker of TH2 inflammation. Furthermore, they presented experimental evidence that periostin is linked to IL-13 and TH2 inflammation.

Asthmatic patients can be classified in 2 main subgroups, as having eosinophilic or noneosinophilic asthma, according to a 2% bronchoscopy-based cut-off of sputum eosinophilia [45–47] found to be positively correlated with IL-13 expression in bronchial submucosa, thus indicating that sputum eosinophil count may be a marker of TH2 inflammation [48].

IL-4 and IL-13 also regulate the synthesis of IgE, and it could be hypothesized that total serum IgE is a biomarker for asthma phenotypes [49]. Unfortunately, total IgE has a low sensitivity and correlates poorly with eosinophilic inflammation [24].

IL-13 promotes NO-synthase activity and NO production, so elevated FeNO is a good index of TH2 inflammation and high levels of IL-13 in bronchial mucosa [50]. In addition, FeNO can also be used as a predictor of steroid

responsiveness more consistently than other parameters. It has been shown that patients with high FeNO levels respond better to steroid therapy, compared to those with lower levels of FeNO [51]. Similarly to FeNO, other evidence shows that the lower the level of eosinophils, the poorer the response to therapy [52, 53].

Other emerging biomarkers which could be helpful to stratify asthma patients are periostin and osteopontin. Both are extracellular matrix proteins associated with TH2 inflammation due to their regulatory role in cell migration, extracellular matrix remodeling, growth and metastasis formation in various malignancies, transforming growth factor beta (TGF- β) concentration and collagen synthesis, that lead to airway remodeling [54–57]. In fact, TH2 high inflammation is characterized by high levels of expression of IL-13 and IL-4 inducible genes, including periostin [58]. Osteopontin and periostin sputum and serum concentration are associated with refractory eosinophilic airway inflammation and an accelerated decline in pulmonary function in patients undergoing inhaled corticosteroid (ICS) therapy [59–61]. Thus, they might be predictive of the response to anti-IL-13 therapy in ICS-insensitive patients, helping to stratify patients in which a relevant improvement of lung function is expected. Nagasaki et al. [62] studied 121 asthmatic patients receiving ICS treatment. They evaluated FeNO levels and serum periostin, and found that among 57 patients with high FeNO, 23 with concomitant high serum periostin had an accelerated decline in pulmonary function and more frequent and severe asthma exacerbations (despite high-dose ICS therapy). These findings suggested that a combined evaluation of FeNO and serum periostin may be useful to identify ICS-insensitive patients.

All these data also suggest that these biomarkers provide complementary information about the different aspects of TH2 inflammation and, consequently, their use should be combined in clinical therapy [63].

Anti-IL-13: Anrukinzumab, Lebrikizumab and Tralokinumab

According to the important role of IL-13 in TH2 inflammation, a potential therapeutic strategy is to block the interaction of IL-13 with the specific receptor. Three monoclonal antibodies are currently under clinical evaluation.

Anrukinzumab is a humanized anti-IL-13 monoclonal antibody which acts to block the cytokine and prevent the activation of IL-13R α 1 and IL-13R α 2. Anrukinzumab has

been tested in asthma and ulcerative colitis in phase II studies [64].

Lebrikizumab is an IgG4 humanized monoclonal antibody that blocks the signaling pathway through the IL-4R α /IL-13R α 1 heterodimer by binding soluble IL-13 and preventing its link to the receptor [65, 66]. Corren et al. [6] performed a randomized, double-blind, placebo-controlled study of lebrikizumab in a population of 219 asthmatic patients with uncontrolled disease according to guidelines-recommended therapy. They found that, compared to the control population receiving placebo, patients on lebrikizumab at a dose of 250 mg monthly for 6 months had a higher increase in forced expiratory volume in 1 s (FEV₁) versus at baseline. Furthermore, patients with higher serum levels of periostin before treatment had a greater improvement in lung function with lebrikizumab than patients with low periostin levels (8.2 vs. 1.6% higher than in the placebo group) and a greater reduction in FeNO levels in the high-periostin subgroup [6]. Another evidence of lebrikizumab efficacy came from Hanania et al. [67], who performed 2 randomized, multicenter, double-blind, placebo-controlled studies and found that treatment with lebrikizumab reduced asthma exacerbations, in particular in the subgroup of periostin-high patients, with a significant 60% reduction, versus the subgroup of periostin-low patients (a 5% reduction). A second study performed by Noonan et al. [68] demonstrated the efficacy of lebrikizumab in terms of variations in FEV₁, though this was not statistically significant, especially in patients with high levels of periostin. These data underlined the potential role of biomarkers, such as periostin, in tailoring an appropriate therapy. It would be of interest to know if all the patients with high periostin were responders or whether there were responders and nonresponders in this high-periostin group. Overall, the mentioned data would further support the discriminating role of high periostin as a predictive biomarker of response to lebrikizumab.

Tralokinumab is a human interleukin-13-neutralizing monoclonal IgG4 antibody which has been tested in severe uncontrolled asthma, ulcerative colitis and idiopathic pulmonary fibrosis. In a first study on moderate-to-severe asthma, Piper et al. [69] show good results about quality of life variation in subjects treated versus placebo group. Brightling et al. [70] performed another randomized, double-blind, placebo-controlled, parallel-group, multicenter, phase 2b study, showing an acceptable tolerability and safety profile for tralokinumab but a nonsignificant reduction of asthma exacerbation rates. Some partially encouraging results were found in a subgroup of patients with a higher baseline amount of dipeptidyl pep-

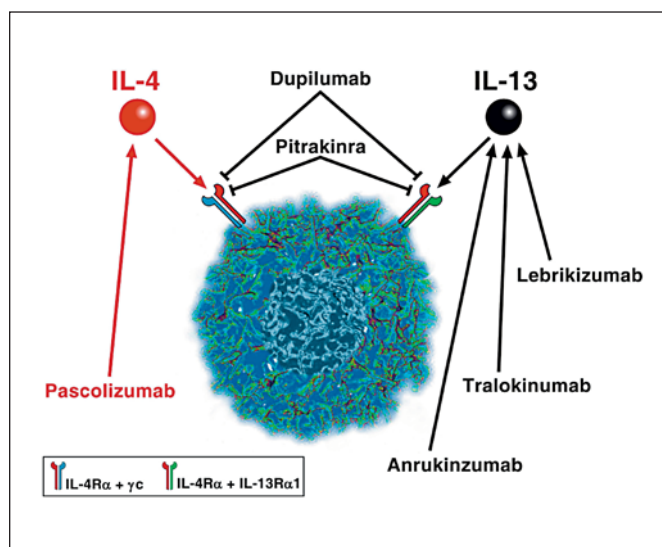


Fig. 2. Novel therapies for asthma targeting IL-4, IL-13 or their receptors. IL-4 signals via type I (IL-4R α + γ c) and type II receptors (IL-4R α + IL-13R α 1) whereas IL-13 binds to type II receptors (IL-4R α + IL-13R α 1) and to IL-13R α 2, which does not contain a transmembrane-signaling domain. Pascolizumab is a humanized anti-IL-4 monoclonal antibody. Dupilumab and pitrakinra prevent IL-4/IL-13 interactions with IL-4R α of the IL-4 and IL-13 receptor complex. Lebrikizumab and tralokinumab are humanized monoclonal antibodies that target IL-13. Anrukinzumab is a humanized anti-IL-13 monoclonal antibody that inhibits the downstream signal of IL-13/IL-13R α 1 through a blocking interaction between IL-13 and IL-4R α .

tidase-4 (DPP-4) and periostin. These findings suggest a possible treatment effect in certain populations. This effect is also currently being analyzed in an ongoing phase 3 trial, together with the possible use of DPP-4 and periostin as biomarkers of interleukin-13 pathway activation. According to the role played by IL-13 in driving airways remodeling and fibroblast proliferation and the positive effect of tralokinumab in reducing IL-13 [12, 13] that contributes to airways inflammation, the use of tralokinumab is also currently being investigated in patients with idiopathic pulmonary fibrosis, especially in the rapidly progressive forms, where IL-13 is overexpressed in the lung tissue [71] (fig. 2).

Anti-IL-4: Pascolizumab, Pitrakinra and Dupilumab

IL-4, produced by T lymphocytes, activated mast cells and basophils, is involved in asthma via its role in many cellular mechanisms such as IgE production, eosinophil

chemotaxis and the development of effector T cell responses [72]. One of the main roles of IL-4 is to promote the differentiation of undifferentiated T helper (TH0) cells to TH2 cells. The TH0 to TH2 skew favors the subsequent production of cytokines and mediators implicated in airway inflammation, obstruction and hyperresponsiveness, typical features of asthma [73]. IL-4 is also implicated in the production of IL-5. Thus, blocking IL-4 could be a reasonable strategy for controlling TH2 inflammation and reducing IL-5-dependent pulmonary eosinophilia [74]. Since IL-4 contributes to collagen production and fibronectin synthesis, fundamental events in airway remodeling, its inhibition could play a relevant role in preventing long-term airway remodeling in patients with severe asthma [75]. Different cells contribute to the production of IL-4 in the airways, particularly eosinophils, basophils, mast cells and ILC2s [23]. Traditionally, TH2 cells are considered the major cellular source of the archetypal TH2 cytokines. Recently, ILC2s have been identified as an alternative source of IL-4, IL-5, IL-9 and IL-13 in response to circulating IL-25, IL-33 and TSLP. These cells are sufficient to induce an allergic response in mice [76]. The role of ILC2s in allergic human diseases characterized by eosinophilic inflammation, such as nasal polyps and atopic dermatitis, has recently been demonstrated [77]. Elevated levels of ILC2s in peripheral blood have also been found in asthmatic patients [78]. Liu et al. [79] have analyzed ILC2 levels in peripheral blood as an alternative and practical biomarker of eosinophilic inflammation in patients with mild-to-moderate asthma who could benefit from a TH2-targeted therapy, and found a 67.7% sensitivity and 95.3% specificity.

IL-4 inhibition can be done either by directly blocking IL-4 or indirectly by blocking the IL-4/IL-13 receptors. Hart et al. [80] evaluated the efficacy and safety of pascolizumab, a humanized anti-IL-4 monoclonal antibody, and its murine parent 3B9. Their study suggested that pascolizumab specifically binds IL-4 with a slow dissociation rate. The *in vivo* studies demonstrate a good tolerability, with a slight accumulation of the drug after chronic administration due to its long half-life. No toxicity or histopathological findings occurred. Although pascolizumab was found to be well tolerated in clinical trials, it did not produce a significant reduction in circulating IgE, so the trials were aborted [81].

Pitrakinra, an IL-4R α /IL-13R α antagonist, was evaluated by inhalation and the subcutaneous route [82]. A double-blind trial with inhaled pitrakinra (10 mg) failed to demonstrate measurable clinical efficacy of the agent, but asthma exacerbations were significantly reduced in a

subgroup of patients with moderate-to-severe asthma with specific amino acid variants in the 3' end of the IL-4R α gene (*IL4RA*) [83]. Another clinical trial on pitrakinra's efficacy in atopic asthma patients demonstrated a lower pulmonary function reduction in the active group than in the control group [84].

Dupilumab is another monoclonal antibody, blocking the alpha subunit of IL-4/IL-13 receptor [85]. Wenzel et al. [86] performed a double-blind, placebo-controlled 2A phase clinical trial with dupilumab in adult patients with moderate-to-severe asthma symptoms and high blood eosinophils (>300 cells/ μ l) or sputum eosinophil level (>3%). The number of asthma exacerbations was significantly lower in the active arm (3 vs. 23), and FEV₁ significantly increased versus baseline. Although dupilumab causes a reduction in the biomarkers of TH2 inflammation, i.e. FeNO, eotaxin-3, thymus and activation-regulated chemokines (TARC), no significant effect on eosinophil blood count could be detected [87].

Another currently ongoing phase 3 trial (NCT02528214) is evaluating the effects of dupilumab in asthmatic patient with severe, systemic, steroid-dependent asthma. Dupilumab has also been proposed for other TH2-related diseases such as atopic dermatitis because of its role in the inhibition of IL-4 and IL-13 pathways. The provisional results of such studies are encouraging, and dupilumab seems to perform better than cyclosporine because of its lower adverse effects and good response to therapy [88]. Other studies assessing dupilumab in TH2-based diseases are investigating its possible use in nasal polyposis, chronic rhinosinusitis [89] and eosinophilic esophagitis (NCT02379052, phase 2) (table 1).

Conclusions

The path to personalized medicine is now a reality and exploring it would guide to a relevant revolution in the prescription modalities for asthma. The new concept is a shift from the era of 'one size fits all' to the era of 'one size does not fit all'. We are currently living in a situation offering multiple solutions to the problem of difficult-to-treat asthma. According to the increasing importance of biomarkers for choosing the right drug, a further desirable therapeutic step would be to have ready-to-go solutions to be applied from the first visit. Rapid measurement of biomarkers (serum periostin, FeNo, eosinophils, etc.) would be fundamental in choosing the more appropriate drug for each individual patient. An alternative could be the use of monoclonal drugs in sequence ('ar-

Table 1. Principal clinical studies with biological drugs anti IL-4 and IL-13 in asthma

Drug	First author [ref.] year	Asthma severity	Patients, n	Dosage	Summary of outcomes
Dupilumab	Wenzel [86] 2013	moderate-to-severe; blood eosinophil count of at least 300 cells/ μ l	52 on dupilumab 52 on placebo	300 mg weekly placebo	↓ asthma exacerbation (3 in dupilumab group, 23 in placebo group) ↑ FEV ₁ change of ACQ5 score ↓ inhalation of albuterol or levalbuterol change in evening asthma score
Pitrakinra	Wenzel [84] 2007	atopic	group 1: 12 on pitrakinra 12 on placebo group 2: 16 on pitrakinra 16 on placebo	25 mg daily s.c. placebo 60 mg 2× daily nebulization placebo	↓ FEV ₁ 17.1 vs. 23.1% (pitrakinra vs. placebo) ↓ FEV ₁ 4.4 vs. 15.9% (pitrakinra vs. placebo)
	Slager [83] 2012	moderate-to-severe	407 non-Hispanic subjects	10 mg 3 mg 1 mg placebo	↓ asthma exacerbation and night waking activity limitation in pitrakinra arm and homozygous for the rs8832 common G allele ↓ (dose-response linked) asthma exacerbation also in subjects homozygous for the common allele in rs1029489 (p = 0.005) and rs8832 (p = 0.009) and the intronic SNPs rs3024585, rs3024622 and rs4787956 (p = 0.03)
Tralokinumab	Piper [69] 2013	moderate-to-severe; uncontrolled	194	150 mg 300 mg 600 mg placebo	modified from baseline in mean ACQ score (-0.76 ± 1.04)
	Brightling [70] 2015	severe uncontrolled	452	(1) tralokinumab every 2 weeks (2) tralokinumab every 4 weeks (3) placebo every 2 weeks (4) placebo every 4 weeks	↓ asthma exacerbation vs. placebo in high-periostin and high-DPP-4 groups FEV ₁ in high-periostin and high-DPP-4 groups
Lebrikizumab	Hanania [67] 2015	moderate-to-severe	463	37.5 mg 125 mg 250 mg placebo s.c. every 4 weeks	↓ asthma exacerbation in high-periostin group no dose response ↑ FEV ₁ in high-periostin group
	Scheerens [66] 2014	mild	29	13 lebrikizumab 16 placebo s.c. every 4 weeks	greater response in high-IgE, high-eosinophil and high-periostin patients
	Noonan [68] 2013	not controlled despite ICS therapy	212	125 mg 250 mg 500 mg placebo s.c. monthly	changes in FEV ₁ were higher in patients receiving lebrikizumab but not clinically significant
	Corren [6] 2011	steroid-dependent	219	250 mg placebo	↑ FEV ₁ in high-periostin group

ACQ = Asthma control questionnaire; s.c. = subcutaneous.

ticulated therapy'), first choosing a drug that acts via a particular immunological mechanism and then a second one that is specific for other pathways. For instance, in patients with an IgE concentration that is too high to use omalizumab, an anti-IL-4 could be proposed, and then once IgE levels are reduced, anti-IgE can be given. Another important unmet need is the duration of therapy. This is clearly emerging for omalizumab, where no standardized protocol is available on when to stop the treatment. An additional open question and possible target of further investigations is the use of molecules targeting different interleukins at the same time, so as to cover multiple therapeutic targets of inflammation simultaneously.

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