Monoclonal Antibodies and JAK-Inhibitors for Type 2 Inflammation

Subjects: Allergy

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Bronchial asthma and its frequent comorbidity chronic rhinosinusitis (CRS), are characterized by an inflammatory process at lower and upper respiratory tract, with a variability in terms of clinical presentations (phenotypes) and distinct underpin pathophysiological mechanisms (endotypes). Based on the characteristics of inflammation, bronchial asthma can be distinguished into type 2 (eosinophilic) or nontype 2 (noneosinophilic) endotypes. In type 2 asthma endotype, the pathogenic mechanism is sustained by an inflammatory process driven by Th2 cells, type 2 innate lymphoid cells (ILC2) and type 2 cytokines, which include interleukin (IL)-4, IL-5, IL-9 and IL-13.

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1. Monoclonal Antibodies Targeting Type 2 Inflammation

During the past decade, the development of biological agents targeting type 2 cytokines or their receptors represents a landmark advancement in the treatment of inflammatory diseases in which these factors play a central role, such as severe asthma and more recently CRSwNP and atopic dermatitis [1][2][3][4]. According to the International Severe Asthma Registry, type 2 asthma represents approximately 70% of severe asthma cases [1]. In eosinophilic asthma, eosinophils increase in the peripheral circulation and accumulate in the airway wall and lumen, causing mucus hypersecretion, bronchoconstriction and airway remodeling [5].

Given the association of IL-4, IL-5, IL-9, IL-13 and TSLP to asthma pathologies, all have been targeted with antibody-based therapeutics that bind either directly to the cytokines or their receptors. Biological agents targeting type 2 inflammation include anti-IgE (omalizumab), anti-IL-5 (mepolizumab and reslizumab), anti-IL-5Rα (benralizumab) and anti-IL-4/IL-13Rα (dupilumab) [6][7][8][9][10][11][12][13]. Presence of a specific type 2 endotype is assessed in clinical practice using blood eosinophil count, FENO, and total and specific IgE to identify the dominant driver (type 2 cytokines or IgE) [14]. Biological agents are more likely to be efficacious in patients with asthma, particularly those with higher FENO levels and blood eosinophils, atopic dermatitis, CRSwNP, allergies and OCS use. Omalizumab, a recombinant humanized IgG1 monoclonal antibody, selectively binds to free IgE molecules, independent from the specificity, blocking the binding site (Cε3 domain) for FcεRI, modulating and acting upstream of the IgE network and slowing or preventing both the early and late allergic inflammatory cascade [15]. The depletion of free IgEs induces a downregulation of FcεRI expression not only on mast cells and basophils, but also on dendritic cells, reducing their antigen presenting activity to T lymphocytes [16][17][18]. By interrupting the IgE-mediated inflammatory cascade at an early stage, thus reducing both early and late asthmatic responses, omalizumab improves exacerbations, lung function and asthma control, with greater effect on exacerbations

demonstrated for patients with high FENO levels, circulating eosinophils and periostin [19][20][21][22]. The clinical use of omalizumab has been recently extended to the treatment of patients with refractory CRSwNP. Omalizumab, indeed, improves nasal polyp score (NPS), nasal congestion score (NCS) and sinu-nasal outcome test (SNOT)-22, and shows an overall good impact on patients' quality of life (QoL) [23].

Mepolizumab, reslizumab and benralizumab are three mAbs that reduce eosinophilic inflammation and are recommended as add-on therapies for the treatment of patients with severe, uncontrolled asthma who exhibit an eosinophilic phenotype [24][25][26]. These biological agents have been designed taking into account the central role of IL-5 in the differentiation, maturation and survival of eosinophils [26][27][28]. While the effect of the anti-IL-5 mAbs has been related to their ability to indirectly target eosinophils, benralizumab, a humanized afucosylated mAb recognizing the α-subunit of the IL-5 receptor, exerts its effect directly by depleting eosinophils through antibody-dependent cell-mediated cytotoxicity (ADCC) [29][30].

Mepolizumab, by blocking the effect of IL-5, reduces exacerbation rates, improves lung function and reduces oral corticosteroid (OCS) exposure in severe asthmatic patients with a blood eosinophils count of ≥150 cells/μL. For mepolizumab, better clinical outcomes have also been observed in patients with a higher percentage of blood and sputum eosinophilia, with severe asthma forms associated with CRSwNP, and lower maintenance OCS requirement [7][31][32][33][34][35]. In fact, concerning CRSwNP, positive results in terms of improvement of nasal symptoms have been obtained in a recent clinical trial with mepolizumab [3]. As noted above, benralizumab, an anti-IL-5 receptor alpha (IL-5Rα) mAb, exerts the therapeutic effects by inducing a direct, rapid and nearly complete depletion of eosinophils via enhanced ADCC, providing enhanced clinical benefits for patients with late onset asthma, increased peripheral blood eosinophils, greater exacerbation history, poor lung function, OCS use and CRSwNP as comorbidity [36][8][9][29][30][31]. More recently, taking into account the complex but partial interplay between eosinophilic inflammation, remodeling and the role of the various type 2 cytokines, a deep attention has been dedicated to other type 2 cytokines as IL-4 and IL-13. Indeed, they have been clearly identified as preferential therapeutic targets since they play a central role in the pathogenesis of type 2 inflammation disorders, including BA, CRSwNP and atopic dermatitis [37][38][39][40]. In fact, dupilumab, a fully human mAb directed toward the α chain of IL-4 receptor used by both cytokines, has been recently introduced for treating all the type 2 related diseases. Dupilumab has been demonstrated to significantly reduce the rates of severe asthma exacerbations and OCS use and to improve lung function, effects particularly observed in patients with high peripheral blood eosinophils counts and FENO levels [7][38]. The beneficial effects are very pronounced in patients suffering from CRSwNP treated with dupilumab who display a rapid decrease of polyp size, radiological sinus opacification and symptoms severity [39]. Even though all the biologicals available exert significant clinical benefits in patients with type 2 diseases (asthma and/or CRSwNP and/or atopic dermatitis), clinical trials and real-life studies have highlighted a variable response to treatment [41]. In addition, while dupilumab is highly effective in controlling atopic dermatitis, no data are available regarding anti-IL-5/IL-5R monoclonal antibodies. We can hypothesize that, in atopic dermatitis, the axis IL-4-IL-13 is crucial in the pathogenesis of skin inflammation while IL-5/eosinophyl pathway is dispensable.

Airway epithelial cells represent the first line of defense in the mucosal surfaces. In response to injury due to allergens and pathogens, airway epithelial cells secrete cytokines such as IL-25, IL-33, TSLP and granulocyte

macrophage colony stimulating factor (GM-CSF) [42]. These cytokines can activate dendritic cells and ILC, promoting production of Th2 cytokines and provoking a T2 high inflammation [42]. These cytokines have therefore been studied as useful targets for BA. Indeed, tezepelumab, a fully human anti-TSLP monoclonal antibody, has been shown to improve asthma control and FEV1 and reduce exacerbations, blood eosinophyl count, FENO and total serum IgE in phase II trials [43][44]. An anti-IL-33 monocloclonal antibody, REGN3500, has been shown to prevent airway remodeling in a murine model of house dust-mite-induced asthma and to reduce eosinophyls infiltration and airway hyperreactivity in an ovalbumin induced asthma murine model [45][46][47]. IL-25 blockade has also displayed promising results in murine models of ovalbumin-induced and house dust-mite-induced asthma, but clinical trials on humans are still awaited [48][49].

Another attractive target for asthma therapy was IL-13, which has an important role in goblet cells hyperplasia and airway remodeling [50]. Unfortunately, several monoclonal antibodies targeting IL-13 (lebrikizumab, tralokinumab, GSK679586) were not able to reduce exacerbations in clinical phase-2 and phase-3 trials [51][52][53]. Lastly, anti-IL9 monoclonal antibody, MEDI-528, which was developed considering the role of IL-9 in mast cell biology, also failed to show efficacy in phase-2 trials [54].

The existence of a range of response among biologicals is likely due to differences in target and patients' baseline features. After all, during the type 2 inflammatory process, the role of the individual cytokines is not exclusive and each can participate to a greater or lesser extent in the initiation, maintenance and amplification of the inflammatory process [55]. Furthermore, the role of individual cytokines and of the cells they affect may be different at the individual level, in the different phases of the disease and in the different tissues (bronchial and nasal mucosa, skin). In addition, histological alterations of the airways wall in asthma and CRS change over time at least in partly because of the effect of treatment [55]. For this reason, despite the therapeutic success of biologics, it has become evident that targeting a single cytokine does not completely abrogate the type 2 disorder in the great majority of patients.

2. JAK-Inhibitors Targeting Type 2 Cytokine Pathways

Although the focus of JAK inhibitors for the treatment of chronic inflammatory conditions has been on RA and IBD, there are other conditions in which JAK inhibitors could serve as therapeutic options. In fact, also taking into account the role of the JAK pathways in the transmission of intracellular signals of type 2 cytokines involved in asthma pathogenesis, new therapeutic strategies interfering with JAK appear at the horizon for treating patients suffering from the severe form of bronchial asthma, CRS and atopic dermatitis. Actually, many JAK inhibitors, which also inhibit STAT phosphorylation, have been developed for treating inflammatory diseases [56][57]. Tofacitinib is a potent pan-JAK antagonist that is notably more selective against JAK1 and JAK3, which are critical in Th2 signaling, than against JAK2 and TYK2 [58]. Experimental data obtained in mouse model of pulmonary eosinophilia, show that systemic administration of the JAK3 inhibitor tofacitinib (CP-690550), approved for the treatment of rheumatoid arthritis, ulcerative colitis and moderate-to-severe chronic plaque psoriasis [59][60][61][62][63][64][65], effectively inhibited antigen-induced pulmonary eosinophil influx, IL-13 and eotaxin expression [61]. These data are consistent with the previous demonstration that $JAK3^{-/-}$ mouse models failed to exhibit efficient recruitment of Th2

cells to the lungs following antigen challenge [66]. In addition, by considering that IL-9 uses the JAK3 pathway for the signal transmission and has also been implicated in the development of allergic pulmonary inflammation, the effects of JAK3 block could be related to the downstream inhibition signal [67][68]. More recently, topical tofacitinib effectively reduced overall inflammation in a murine model of CRSwNP by suppressing Th2-dominant inflammation [69]. The possible use of topical JAK inhibitors has also been evaluated in asthma patients. In fact, in adult subjects with mild asthma and FENO higher than 40 parts per billion (ppb), inhaled tofacitinib induced dose-dependent reduction of FENO [70]. In the group of type 2 diseases, JAK inhibitors have been largely evaluated in patients suffering from atopic dermatitis. In moderate-to-severe atopic dermatitis, a small open-label clinical trial with oral tofacitinib in six patients who were refractory to standard treatment showed a decrease in SCORAD from 36.5 at week 8 to 12.2 at week 29, with no adverse events [70]. More importantly, 2% topical tofacitinib in mild-to-moderate atopic dermatitis patients showed a significantly decrease of EASI score compared with the control group (–81.7% vs. −29.9%) [61]. In addition, baricitinib, an oral small molecule with potent JAK1 and JAK2 antagonism, has been demonstrated to be effective in reducing the skin lesions and pruritus in atopic dermatitis patients and improving HRQoL [71]). The JAK1 inhibitor abrocitinib, which reduces IL-4 and IL-13 signaling, is being investigated for the treatment of atopic dermatitis. The 200 mg dose of abrocitinib was superior to dupilumab with respect to itch response at week 2 but not with respect to most other key clinical features of the disease [72]. Taking this into account, it could be hypothesized that JAK inhibition in type 2-low asthma endotype may also be effective in a proportion of asthmatic patients; the endotype is represented by the type 2-low pattern. This observation seems to suggest that tezepelumab, a monoclonal anti-TSLP antibody being studied in patients with asthma, proves to be effective regardless of type 2 endotype in producing a consistent reduction in asthma exacerbations, considering that TSLP exerts its biological effects through the JAK1/JAK2 pathway [43]. One of the major concerns during treatment with biological agents has been related to the safety profile. Data obtained from the clinical trials and in real-life studies have been clearly confirmed not only the efficacy but also the safety of the biological agents targeting type 2 cytokines [73]. In addition, the high safety profile is also confirmed by the authorization to administer omalizumab, the first biological agent for treating severe asthma, in pregnant women [74]. To date, the safety profile of JAK inhibitors represents a key point of discussion specifically when these drug are used systemically for the treatment of immune-mediated diseases such as asthma and atopic dermatitis. Most of the safety data come from the large trials of in rheumatic and inflammatory bowel diseases. In recently published analysis using data from long-term extension studies in patients suffering from rheumatoid arthritis and treated with tofacitinib, emerges a major incidence for severe infections but similar to those observed biologics as anti-TNF-α monoclonal antibodies, currently used in clinical practice for the treatment of this disease, as noted in [75]. However, an increase of the risk of herpes zoster infection compared with biologics is observed [76]. Cardiovascular risk was one of the concerns raised about JAK inhibitors, largely related to the alterations in lipid profile noted with this class of drugs [77]. To avoid rapid absorption across the lung and into systemic circulation, design of lung-restricted molecules must include a lung retention strategy. To maximize this objective, inhaled design must contemplate not only retention of the compound within the lung, but also access of the drug to the relevant biological target. In addition, to reduce the possible negative impact of a systemic treatment, a selective potent inhaled JAK inhibitor (GDC-0214) has been used in patients with mild asthma. The biological effect caused dose-dependent reductions in FENO for mild asthma. There were no major imbalances in adverse events or laboratory findings, or evidence of systemic JAK

inhibition. As the authors mentioned, however, subsequent trials will be needed to confirm whether or not the observed reduction in FENO will translate to improvements in airflow obstruction, symptoms and exacerbations among populations with a broader spectrum of asthma severity [78].

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