Biologics in Asthma and Chronic Obstructive Pulmonary Disorder

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Several cytokines and chemokines play a potential role in the pathogenesis of asthma and chronic obstructive pulmonary disorder (COPD). Their inhibition by monoclonal antibodies (mAbs) that can block them or prevent their synthesis, antagonize their receptors or affect intracellular signalling pathways may, in the right patient, inhibit the inflammatory process that likely supports the progressive nature of these disorders. These biological agents are divided into those that target type 2 (T2)-mediated inflammation by blocking interleukin (IL)-5 and/or its receptor, preventing IL-4 and IL-13 signalling, affecting the IL-33 pathway and blocking thymic stromal lymphopoietin, and those that target specific pro-inflammatory and pro-neutrophilic cytokines and chemokines such as tumour necrosis factor-α, IL-1, IL-8 and IL-1β. Most biological therapies developed to date target T2 cytokines, alarmins or immunoglobulin E. This article reviews the most recent advances in the potential role of cytokines and chemokines in asthma and COPD, and describes the mAbs already approved to treat T2 inflammation in asthma, the potential benefit of using anti-IL-33 mAbs, and the therapeutic potential of some of these mAbs in COPD. Unfortunately, no biological treatments have been specifically licensed for the treatment of type 1 inflammation.

Keywords

Asthma, COPD, monoclonal antibodies, T1 inflammation, T2 inflammation

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Asthma and chronic obstructive pulmonary disease (COPD) are disorders with predominantly chronic inflammatory airway features. They are increasingly recognized as entities on a heterogeneous obstructive airway disease continuum with distinct phenotypes, various degrees of overlap, and the predominance of asthma in some individuals and COPD in others.[1]

In asthma, chronic inflammation is driven by aberrant type 2 (T2)-high immune pathways strongly linked to atopy and allergy, type I hypersensitivity reactions, eosinophilic inflammation, remodelled airways, and finally, functional derangement.[2] T2-high asthma is orchestrated by T helper 2 (Th2) cells and group 2 innate lymphoid cells (ILC2s) through the secretion of interleukin (IL)-4, IL-5, IL-9 and IL-13, which are regulated by the transcription factor GATA3. T2 inflammation is characterized by alternately activated eosinophils, mast cells and macrophages. IL-4 induces the switching of B cells from immunoglobulin (Ig)G to IgE and the synthesis of IgE. IL-5 increases the proliferation and differentiation of eosinophils in the bone marrow and promotes eosinophil tissue trafficking, activation and survival. IL-9 supports mast cell growth and modulates the properties of T2 inflammation. At the same time, IL-13 activates epithelial expression of inducible nitric oxide synthase, mucus production, airway hyper-responsiveness and fibrosis, linking allergic inflammatory cells to non-immune structural cells.[3–5] Epithelial cells that regulate Th2 cells and ILC2s release upstream cytokines, including the alarmins IL-25, IL-33 and thymic stromal lymphopoietin (TSLP).[3–5] Il-33 is a member of the IL-1 family, which is constitutively and extensively expressed in the nucleus of endothelial cells along the vascular tree, and in epithelial and stromal cells. TSLP, an IL-7-like cytokine triggered in response to environmental antigens in the airway, exerts multipotential pathogenic effects beyond T2 inflammation.[3–5] Conversely, patients with T2-low asthma, who have T2 inflammation levels in the airways comparable to the normal reference range of healthy controls, have no evidence of active type 2 inflammation in their airways, despite evidence of active smooth muscle dysfunction, indicating that the core physiological abnormalities of excessive smooth muscle tone and bronchial hyper-responsiveness in asthma are not driven by type 2 inflammation.[6] T2-low asthma includes very late-onset obesity-associated asthma as well as smoking-related and neutrophilic asthma, and asthma in which affected individuals show slight inflammation.[2]

Chronic inflammation in COPD is characterized by a predominance of macrophages and neutrophils.[7,8] However, the pattern of inflammation is different, mostly driven by T1 and T3 immunity.[5] T1 immunity protects against microbial infections. It is orchestrated by Th1 cells, cytotoxic T cells, ILC1s and the T-box protein expressed in T cells (T-bet or Tbx21) transcription factor, which regulates interferon-γ secretion. T1 immunity is associated with increased activation of pro-inflammatory macrophages. T3 immunity is directed mainly against fungi and is orchestrated by Th17 cells and ILC3s. These cells express retinoic-acid-receptor-related orphan nuclear receptor γ, one of the master regulators in

the development of Th17 cells, and secrete IL-17 and IL-22, which leads to neutrophilic inflammation. However, there is evidence of T2 inflammation in a subset of patients with COPD.[9]

Between 30% and 40% of patients with COPD have increased percentages of eosinophils in sputum during stable periods and acute exacerbations. In contrast, some patients with asthma may have features of COPD with a predominantly neutrophilic pattern of inflammation.[10–12] In addition, several different clinical phenotypes are dictated by the predominant T2 or T1/T17 cytokines.[12]

Given that several cytokines and chemokines play a potential role in the pathogenesis of asthma and COPD, their inhibition could inhibit the inflammatory process that probably supports the progressive nature of these disorders. Putting a stop to their activity usually involves developing monoclonal antibodies (mAbs) that can block these cytokines and chemokines or even their synthesis, antagonize their receptors or target intracellular signalling pathways.[13]

Targeting T2 inflammation

Eosinophilic airway inflammation is an essential feature of chronic airway disease, whether asthma or COPD, and needs to be considered for possible targeted treatment.[11] The treatment of eosinophilic inflammation requires an approach that influences T2 inflammation in its various pathways.[14,15] Most biological therapies developed to date target T2 cytokines, alarmins or IgE.[15]

The following mAbs have been developed to treat T2 inflammation: omalizumab, which is an anti-IgE agent that selectively binds circulating IgE in the blood and interstitial space;[16] mepolizumab and reslizumab, which bind directly to IL-5 and prevent its link with the IL-5 receptor (IL-5R);[17,18] benralizumab, which binds to the α subunit of IL-5R on eosinophils and basophils, thus preventing IL-5 binding and amplifying the antibody-dependent cell cytotoxicity function of these cells by activating natural killer cells to perform apoptosis;[19] dupilumab, an anti IL-4Rα mAb specifically designed to inhibit signalling of IL-4 and IL-13;[20] and tezepelumab, a mAb that blocks TSLP activity by interfering with the interaction of TSLP with its receptor, and subsequent recruitment of IL-7Rα in the signalling complex.[15]

The regulatory authorities of 28 countries across five continents have approved these mAbs to treat severe asthma, although biological prescription criteria differ substantially.[21] The National Heart, Lung, and Blood Institutes/National Asthma Education and Prevention Program guidelines recommend using daily high-dose inhaled corticosteroids (ICS)/long-acting β–2 agonists, and adding low-dose oral corticosteroids (OCS) and as-needed short-acting β2-agonists.[22] The Global Initiative for Asthma (GINA) strategy limits long-term adjunctive therapy with low-dose OCS to step 5 and places it after trials of other more favoured adjunctive treatments (e.g. tiotropium and biological agents), with adverse effects always having to be considered.[23]

Adding asthma biological agents should be evaluated in patients who do not achieve control with current gold standards of care.[24] In contrast, their use in the treatment of COPD is still not ratified, but there are some encouraging data in at least some subgroups of patients.[25]

Omalizumab

Omalizumab is indicated in adults and children 6 years of age and older who have IgE-mediated, moderate-to-severe, persistent allergic asthma that has not been controlled by GINA step 4 treatment, high blood IgE levels, and at least sensitivity to a perennial allergen.[26] Those with a high blood eosinophil count (BEC), fractional expired nitric oxide (FeNO) or periostin in the blood benefit most from omalizumab therapy.[27] Recently, it was observed that in patients with high bronchodilator reversibility, but not in those with low reversibility, omalizumab was more effective than placebo in reducing exacerbations, regardless of fixed airflow obstruction.[28] In addition, patients with fixed airflow obstruction with high bronchodilator reversibility had the best lung function improvement. These findings suggested that asthma with low bronchodilator reversibility may be a more challenging phenotype to treat.

A blood total IgE threshold (IU/mL) is required to initiate treatment with omalizumab. The most common threshold is 30 IU/mL or higher, or 35 IU/mL, followed by 70 IU/mL or higher, 75 IU/mL or 76 IU/mL.[21] The dosage and frequency of omalizumab administration are determined by the blood total IgE level assessed before therapy and body weight (in kilograms).[27] Routine serum measures of free IgE can help identify people who are not responding to omalizumab.[29]

A recent meta-analysis that included 86 publications summarized the real-world effectiveness of omalizumab in severe asthma.[30] Omalizumab significantly reduced the annualized rate of severe exacerbations (risk ratio [RR] 0.41, 95% confidence interval [CI] 0.30 to 0.56), the proportion of patients receiving OCS (RR 0.59, 95% CI 0.47 to 0.75) and the number of unscheduled physician visits (mean difference 2.34, 95% CI 3.54 to 1.13) at 12 months versus baseline. At 16 weeks, 6 months and 12 months, the mean improvement in forced expiratory volume in 1 second (FEV1) was 0.16 L, 0.22 L and 0.25 L, respectively. The Asthma Control Questionnaire score decreased at 16 weeks (1.14), 6 months (1.56) and 12 months (1.13) after omalizumab.

It is also worth reporting on weaning off omalizumab treatment. Omalizumab can be safely removed between 2 and 4 years following commencement of treatment in approximately one-third of patients with allergic OCS-dependent asthma, according to the Omalizumab Dose Reduction (OMADORE) research.[31] There is insufficient evidence for prescribing anti-IgE medication if a patient's asthma is severe enough to require maintenance OCS, as allergies may not cause OCS requirement.[32] However, another study found that withdrawal worsened control.[33]

According to a study that looked at the relationship between serum IgE levels and disease features in two large clinical COPD cohorts, COSYCONET and WISDOM, higher serum IgE was linked to COPD exacerbations and the likelihood of lung function decrease in males with COPD.[34] This discovery suggests that IgE-mediated pathways may be implicated in the pathophysiology of COPD exacerbations in men and progressive airway limitation in individuals with elevated IgE levels. Omalizumab might therefore have beneficial therapeutic implications in these patients. A post hoc analysis of the Prospective observational study to evaluate predictors of clinical effectiveness in response to omalizumab (PROSPERO) cohort analysed patients with asthma–COPD overlap who were treated with omalizumab.[35] Individuals with overlapping asthma and COPD treated with omalizumab had similar clinical outcomes to patients with asthma without overlap in terms of improvements in exacerbation frequency and Asthma Control Test scores.[35] Furthermore, lung function was sustained in the overlap cohort, which was characterized by a medical history of asthma and medical history or self-reported diagnosis of COPD, for the whole 48-week research.

Anti-interleukin-5 monoclonal antibodies

In patients with severe asthma, low IgE and high blood eosinophils, adding an anti-IL-5 biological agent to the standard therapy is reasonable.[36] Patients with a BEC ≥500 cells/μL benefit most from anti-IL-5 mAb treatment.[37] These biological agents are effective also in those with >3% eosinophils in their sputum.[37]

Several meta-analyses evaluating the impact of different anti-IL-5 mAbs in severe asthma have been conducted over time, but none has documented the prevalence of one molecule over the others.[38,39] However, an indirect treatment comparison of the licensed doses of anti-IL-5 treatments suggested that mepolizumab was associated with a significantly greater reduction in clinically significant exacerbations and improvements in asthma control than reslizumab or benralizumab in patients with similar BECs.[40] In addition, another indirect comparison suggested that reslizumab may be more efficacious than benralizumab in patients with eosinophilic asthma in GINA step 4/5 with elevated blood eosinophil levels and two or more exacerbations in the previous year.[41] Most countries require a BEC threshold of 300 cells/μL or greater in the past 12 months (or ever) for mepolizumab and benralizumab, and 400 cells/μL or greater in the past 12 months for reslizumab.[21]

A recent systematic review that aimed to evaluate the real-world efficacy of anti-IL-5 biological agents in severe asthma showed that the annualized exacerbation rate (AER) decreased significantly by 3.79 (95% CI -4.53 to -3.04), 3.17 (95% CI -3.74 to -2.59) and 6.72 (95% CI -8.47 to -4.97) with benralizumab, mepolizumab and reslizumab, respectively, while FEV1 improved by 0.17 L (95% CI 0.11 to 0.24) and 0.21 L (95% CI 0.08 to 0.34) following treatment with mepolizumab and benralizumab, respectively.[42] This latter finding may be indirectly related to the experimental demonstration that mAbs targeting the IL-5–IL-5R axis reduce human airway hyper-responsiveness in response to histamine, parasympathetic activation and mechanical stress.[43] Benralizumab was more effective than mepolizumab in this regard. It must be mentioned that an old study reported that blocking IL-5 in patients with asthma does not reduce airway hyper-responsiveness despite a profound reduction in circulating and sputum eosinophils.[44]

The anti-therapeutic benefits of IL-5 probably occur primarily in patients whose severity of airflow obstruction and symptoms is caused by luminal eosinophils, because the predominant biological role of IL-5 is confined to eosinophil maturation, survival and airway recruitment.[32]

In patients with COPD, IL-5 concentrations in the sputum are linked to the number of sputum eosinophils.[45] Furthermore, during virus-induced exacerbations of COPD, soluble IL-5R is elevated.[46] Therefore, blocking IL-5 may prevent or decrease eosinophil-mediated inflammation because eosinophils rapidly undergo apoptosis without IL-5.[47] According to a Cochrane systematic review that included six studies with 5,542 participants, mepolizumab and benralizumab are likely to reduce the rate of moderate and severe exacerbations of COPD in the highly selected group of people with both COPD and high levels of blood eosinophils.[48] Mepolizumab 100 mg reduced the rate of moderate or severe exacerbations by 19% in those with an eosinophil count of at least 150 /μL (RR 0.81, 95% CI 0.71 to 0.93), whereas mepolizumab 300 mg reduced the rate of exacerbations by 14% in participants who had raised eosinophil levels (RR 0.86, 95% CI 0.70 to 1.06). The rate of severe exacerbations requiring hospitalization in those with an eosinophil count of at least 220 /μL was reduced by benralizumab 10 mg (RR 0.68, 95% CI 0.49 to 0.94) and benralizumab 100 mg (RR 0.63, 95% CI 0.49 to 0.81).

However, the subgroup of patients with COPD that is most likely to have a good response to anti-IL-5 therapy remains to be identified.[49] In any case, a massive clearance of eosinophils from the airways does not provide any meaningful therapeutic improvement in many patients with COPD,[50] perhaps due to the presence of lung-resident eosinophils that are unaffected by IL-5.[51] As a result, airway eosinophilia in COPD may be caused by factors other than IL-5 and may differ from asthma. However, interest in correctly positioning anti-IL-5 mAbs in the treatment of COPD has not waned, and anti-IL-5 mAbs, such as mepolizumab in the MATINEE (Mepolizumab as add-on treatment in participants with COPD characterized by frequent exacerbations and eosinophil level [MATINEE]; ClinicalTrials.gov identifier: NCT04133909)[52] and COPD-HELP (Mepolizumab for COPD hospital eosinophilic admissions pragmatic trial [COPD-HELP]; ClinicalTrials.gov identifier: NCT04075331)[53] trials, and benralizumab in the RESOLUTE (Efficacy and safety of benralizumab in moderate to very severe chronic obstructive pulmonary disease [COPD] with a history of frequent exacerbations [RESOLUTE]; ClinicalTrials.gov identifier: NCT04053634)[54] and ABRA (Acute exacerbations treated with benralizumab [The ABRA Study] [ABRA]; ClinicalTrials.gov identifier: NCT04098718)[55] trials, are still being investigated in patients with COPD.

Dupilumab

Pleiotropic roles are played by IL-4 and IL-13, which share signalling pathways and act through the same IL-4R.[56] They affect eosinophil recruitment, goblet cell hyperplasia, mucus secretion, smooth muscle contraction and hyper-responsiveness. As a result, it is feasible that the therapeutic benefits of anti-IL-4/13 mAb treatment can be seen in a larger range of individuals, not only those with substantial airway eosinophilia.[32] Indeed, regardless of demographics or illness features, a non-specific *post hoc* analysis of the phase III Liberty Asthma Quest study specifically stated that treatment with dupilumab is efficacious in all patients with moderate-to-severe T2 asthma.[57]

Patients with baseline BEC of ≥150 cells/μL and baseline FeNO of ≥25 ppb benefit more from dupilumab treatment,[58] although the group with blood eosinophils >300 cells/μL has the most considerable reduction in asthma exacerbations.[59] Dupilumab is also beneficial for patients not responding to ICS and those with comorbid diseases, including atopic dermatitis, chronic rhinosinusitis with nasal polyposis, and allergic rhinitis.[59] It has been suggested that dupilumab may be a viable therapy option for patients with T2-high severe asthma who do not qualify for or do not respond sufficiently to anti-IgE or anti-IL-5/IL-5R mAbs.[60]

In a small real-life trial conducted in Austria, dupilumab increased the Asthma Control Questionnaire score by 0.57 points after 2 weeks (p=0.014).[60] Similarly, after 4 weeks, the Asthma Control Test score improved by 3.91 points (p=0.024), which was statistically and clinically significant. FEV1 improvement at 2 weeks was not statistically or clinically significant. Improvements were statistically significant and clinically borderline significant at 4 weeks (+0.22 L, p=0.041) and 3 months (+0.23 L, p=0.006).[60]

At 12 months, in a French real-life cohort study of predominantly corticosteroid-dependent severe asthma, dupilumab significantly improved asthma control (median Asthma Control Test score increased from 14 [interquartile ranges (IQR): 7–16] to 22 [IQR: 17–24], p<0.001) and lung function (median predicted FEV1% increased from 58% [IQR: 47–76] to 68% [IQR: 58–88], p<0.001, with a median gain of 0.20 L).[61] Dupilumab also resulted in a reduction in OCS use (median OCS [prednisolone equivalent] dose was reduced from 20 [IQR: 10–30] mg/day to 5 [IQR: 0–7] mg/day, p<0.001, and

24% of patients were weaned off OCS) and the rate of exacerbations (for 78% of patients, the rate of exacerbations was reduced by 50%).

IL-13 activates alveolar macrophages to create matrix metalloprotease-12, and patients with eosinophilic COPD and concomitant emphysema have a high level of matrix metalloprotease-12 in sputum.[62] In addition, ILC2 cells, which can release IL-13, are elevated in patients with stable COPD or after an acute exacerbation.[63] Therefore, two pivotal trials are under way to evaluate dupilumab in patients with COPD with T2 inflammation (Pivotal study to assess the efficacy, safety and tolerability of dupilumab in patients with moderate-to-severe COPD with type 2 inflammation [BOREAS]; ClinicalTrials.gov identifier: NCT03930732) (Pivotal study to assess the efficacy, safety and tolerability of dupilumab in patients with moderate to severe COPD with type 2 inflammation [NOTUS]; ClinicalTrials.gov identifier: NCT04456673).[64,65]

Anti-thymic stromal lymphopoietin monoclonal antibodies

Although permanent decreases in BEC and FeNO levels have been shown in phase II clinical studies, tezepelumab every 4 weeks in patients with moderate-to-severe poorly controlled asthma reduced AERs significantly over 12 months compared with placebo, regardless of BEC, FeNO level or T2 status.[66] The efficacy of tezepelumab was compared with that of dupilumab, benralizumab, mepolizumab and placebo in a network meta-analysis.[67] Tezepelumab had the best overall AER when BEC and FeNO were considered. However, there was no significant difference in AER between tezepelumab and dupilumab except in the subgroup with BEC <150 cells/µL, in which tezepelumab performed much better than dupilumab. Furthermore, in all participants and subgroups examined according to the BEC threshold, there was no significant difference in AER-based efficacy between tezepelumab and mepolizumab. When tezepelumab and benralizumab were compared, tezepelumab had a significantly better efficacy profile than benralizumab in both the total population and the subgroups with BECs of ≥300 cells/µL and ≥150 cells/µL.

Another systematic review, which also compared the efficacy of tezepelumab with other approved biological agents via indirect treatment comparisons, examined 16 randomized controlled trials.[68] All biological agents (tezepelumab, dupilumab, benralizumab, mepolizumab, reslizumab and omalizumab) demonstrated comparable efficacy, with no statistically significant differences in RRs for annualized asthma exacerbation rate (AAER). However, tezepelumab was associated with a numerically lower AAER overall. Tezepelumab versus omalizumab had the highest therapeutic impact, with an RR of 0.60 (95% CI 0.35 to 1.01). RRs were 0.84 (95% CI 0.45 to 1.56) versus dupilumab 200 mg and 300 mg, 0.63 (95% CI 0.35 to 1.09) versus benralizumab, 0.82 (95% CI 0.43 to 1.50) versus mepolizumab and 0.82 (95% CI 0.43 to 1.49) versus reslizumab. Furthermore, tezepelumab ranked first in the network for both AAER and hospitalized AAER, with a surface under the cumulative ranking curve (SUCRA) value of 84% and 95%, respectively.

Several trials are currently under way to confirm the long-term efficacy and safety of tezepelumab in adults and adolescents with severe uncontrolled asthma.[69]

CSJ117 is an antibody fragment that belongs to the immunoglobulin G1/λ isotype subclass and binds to TSLP.[70] It is delivered by inhalation. In 28 patients with mild atopic asthma, it attenuated the allergen-induced late asthmatic response and early asthmatic response at Day 84.[70] It also significantly attenuated the allergen-induced increase in percentage sputum eosinophils after allergen inhalation challenge on Day 84, and reduced FeNO before the challenge at Day 83 but did not affect the allergen-induced change.

A phase IIb study is determining the efficacy and safety of multiple CSJ117 doses (0.5 mg, 1 mg, 2 mg, 4 mg and 8 mg) inhaled once daily, compared with placebo, when added to standard-of-care asthma therapy in adults with uncontrolled asthma (Study of efficacy and safety of CSJ117 in patients with severe uncontrolled asthma; ClinicalTrials.gov identifier: NCT04410523).[71] The primary endpoint is change from baseline in FEV1 after 12 weeks of treatment.[71] Another phase IIb study (Study of safety of CSJ117 in participants with moderate to severe uncontrolled asthma; ClinicalTrials.gov identifier: NCT04946318) is assessing safety and tolerability, pharmacokinetics and immunogenicity data for multiple CSJ117 doses inhaled once daily compared with placebo.[72] Patients included are adults with asthma treated with medium- or high-dose ICS plus long-acting β agonist alone or with additional asthma controllers, who have completed the prior phase IIb study (ClinicalTrials.gov identifier: NCT04410523).[71,72]

The airway smooth muscle of patients with COPD has been shown to express TSLP both constitutively and *in vivo*.[73] As a result, it is indeed possible that TSLP expression influences immune control in COPD airways by interacting with and regulating local immune cells.[74]

Tezepelumab is being tested in individuals with moderate-to-severe COPD who are on inhaled maintenance triple therapy and have had two or more documented exacerbations of COPD within the previous 12 months (Tezepelumab COPD exacerbation study [COURSE]; ClinicalTrials.gov identifier: NCT04039113).[75] A phase II study in patients with COPD is assessing the efficacy, pharmacodynamics/pharmacokinetics and safety of two dose levels of CSJ117 compared with placebo (Study of effect of CSJ117 on symptoms, pharmacodynamics and safety in patients with COPD; ClinicalTrials.gov identifier: NCT04882124).[76]

Anti-interleukin-33 monoclonal antibodies

IL-33 is released from the epithelium in response to epithelial cell damage, stress or necrosis, thus functioning as an alarmin and exerting pro-inflammatory biological functions through its receptor, a heterodimeric complex made up of suppression of tumourigenicity 2 (ST2).[77] It enhances the ILC2 response, which secretes a substantial amount of IL-5 and IL-13 in allergic inflammation by promoting eosinophil recruitment to the airway and maturation in the bone marrow, mainly via ILC2.[78]

Itepekimab, a human mAb against IL-33, was recently evaluated in a phase II trial involving adults with moderate-to-severe asthma receiving an ICS plus a long-acting β agonist.[79] After 12 weeks of treatment, the itepekimab and dupilumab monotherapy groups, but not the combination group (itepekimab + dupilumab), showed a lower risk of asthma control loss events than the placebo group. In addition, FEV1 before bronchodilator use increased with itepekimab or dupilumab monotherapies but not with combination therapy compared with the placebo group. Furthermore, compared with the placebo group, itepekimab treatment improved asthma control and quality of life while significantly lowering the mean BEC. In addition, FeNO, serum total IgE, periostin and plasma eotaxin-4 were reduced by itepekimab alone, albeit to a lesser degree than dupilumab or combined therapy.

As other alarmins, notably TSLP and IL-25, are still active, these data suggest that blocking IL-33 inhibits T2 inflammation only partially.[80] Indeed, astegolimab, a mAb against ST2, lowered asthma exacerbation rates in a large group of patients with poorly managed, severe asthma, including those who were eosinophil-low.[81] This finding suggests that astegolimab

could be helpful in other airway illnesses when T2 inflammation is not the leading cause of tissue destruction.

A first-in-human study that included pharmacokinetic, pharmacodynamic and safety data, has paved the way for more clinical trials with melrilimab (CNTO 7160; GSK-3772847), another anti-ST2 mAb, in patients with asthma.[82] However, a phase II trial in patients with moderate-to-severe asthma and allergic fungal airway disease was terminated due to a high screen failure rate and the feasibility of completing the study in a timely way (Repeat dose study of GSK3772847 in participants with moderate to severe asthma with allergic fungal airway disease [AFAD]; ClinicalTrials.gov identifier: NCT03393806).[83]

Tozorakimab (MEDI3506) is a human anti-IL-33 immunoglobulin G1 mAb that prevents IL-33 signalling.[84] A phase I randomized controlled trial included: 56 healthy adults with a history of mild atopy and sensitivity to house dust mites who received a single ascending dose of tozorakimab or placebo intravenously or subcutaneously; 24 adults with Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade I–II COPD who received multiple ascending doses of subcutaneous tozorakimab or placebo; and eight healthy Japanese adults who received a single intravenous dose of tozorakimab or placebo.[84] The study demonstrated linear, time-independent serum pharmacokinetics with a mean half-life of 12–18 days.[84] The estimated subcutaneous bioavailability was 46.6%. In the multiple ascending doses cohort, partitioning of approximately 0.5% of tozorakimab into the mucosal lining fluid of the nasal airways, collected by nasosorption, was observed. Tozorakimab exhibited target engagement in serum.[85] It raised IL-33–tozorakimab complex levels in serum (all cohorts) and nasal lining fluid (multiple ascending doses cohort) while decreasing IL-33–soluble ST2 complex levels in serum (all cohorts). Tozorakimab reduced IL-33-driven interferon-γ release *ex vivo* in blood from the single ascending dose and multiple ascending doses groups. Compared with placebo, tozorakimab significantly lowered blood IL-5 and IL-13 levels (multiple ascending doses cohort p=0.0037 and p=0.034, respectively). Furthermore, it significantly decreased BEC, which corresponded to decreases in serum IL-5 (r=0.64, 95% CI 0.23 to 0.86) and IL-13 (r=0.75, 95% CI 0.43 to 0.91).

As significant elevations in IL-33 levels have been recorded in serum or plasma, sputum, lung biopsy specimens, and epithelial and endothelial cells of patients with COPD, it is thought that IL-33 may play a role in the pathogenesis and progression of this disorder.[86] Itepekimab as an add-on to the standard of care did not significantly reduce the annualized rate of moderate-to-severe exacerbations of COPD compared with placebo in phase II research over up to 52 weeks of therapy.[87] However, compared with placebo, it dramatically reduced the incidence of exacerbations and improved lung function in former smokers with COPD.[87] Furthermore, in individuals with moderate-to-severe COPD, astegolimab given every 4 weeks throughout a 48-week therapy term did not significantly reduce exacerbation rates but did improve health status and lung function.[88] According to Singh, itepekimab and astegolimab increase FEV1 by reducing eosinophilic airway inflammation.[89]

In addition, tozorakimab is being tested in a phase II proof-of-concept trial in patients with moderate-to-severe COPD and chronic bronchitis to assess how it compares with placebo in terms of lung function after 12 weeks of treatment.[90]

Targeting T1 inflammation

T2-low asthma is characterized by the absence of increased T2 indicators and may represent a neutrophilic or paucicellular disease process; patients with severe refractory asthma have this characteristic.[2] There are no biological therapies that have been specifically approved for patients with T2-low asthma.[91] Previous trials with biological medicines that target T1 pathways, such as anti-tumour necrosis factor (TNF)-α mAbs, have not yielded promising outcomes.[92] Nevertheless, some biological treatments for severe T2 asthma have demonstrated efficacy in patients without apparent T2 biomarker increases in clinical trials.[66,81] Despite being smaller than in T2 asthma, this potential therapeutic impact must still be investigated.

Other inflammatory pathways, such as T17, which orchestrates T3 immunity,[5] may add more complexity to the inflammatory cascade, revealing new therapeutic targets for people with non-T2 asthma.[93] Th17 cells are distinct from Th1 and Th2 cells are characterized by the production of IL-17A, IL-17F and IL-22, which are associated with the most severe asthma phenotypes.[94] These cytokines, which stimulate epithelial cells to generate chemokines and cytokines that attract neutrophils to the site of inflammation, are frequently linked to neutrophilic inflammation.[93] IL-17A and IL-17F are associated with increased neutrophils in the airways and, together with IL-22, increase airway mucus production and smooth muscle mass. In addition, a high level of IL-17A has been linked to more severe forms of asthma in multiple studies.[93] Brodalumab, an anti-IL-17 mAb that binds directly to IL-17R, thereby inhibiting the binding of IL-17 ligands (A and F) to the receptor, was tested in individuals with inadequately controlled moderate to severe asthma.[95] The critical outcome criterion, asthma control as measured by the Asthma Control Questionnaire, revealed no significant differences. However, patients with high FEV1 reversibility at inclusion showed a significant difference in asthma control, suggesting that patients without permanent obstruction and airway remodelling may benefit from an IL-17 blockade strategy in the early stages of airway remodelling.[95]

Secukinumab, a mAb that targets IL-17A, has been tested in patients with uncontrolled asthma, but the full results are not yet available (Safety, tolerability, and efficacy of AIN457 in patients with uncontrolled asthma; ClinicalTrials.gov identifier: NCT01478360).[96] However, patients who responded to secukinumab had considerably lower total IgE levels than non-responders, reduced neutrophilic nasal epithelial inflammation, and downregulated indicators of IgE-driven systemic inflammation, according to a *post hoc* analysis of this study.[97] Furthermore, CJM112, a mAb that targets IL-17A and IL-17F, failed to improve asthma symptoms in patients with severe asthma (Study to assess the efficacy and safety of CJM112 in patients with inadequately controlled severe asthma; ClinicalTrials.gov identifier: NCT03299686).[98]

Brodalumab, secukinumab and CCJM112 have yet to be studied in patients with COPD. Surprisingly, there is no interest in exploring these mAbs in COPD. However, there is evidence that an IL-17-associated airway inflammation signature is elevated in about one-third of patients with COPD and is linked to unique inflammatory, physiological and clinical characteristics.[99] In any case, secukinumab did not diminish the total number of neutrophils in the sputum of healthy individuals who experienced acute neutrophilic airway inflammation following ozone exposure.[100] On the other hand, neutralizing IL-17 activity might cause immunosuppression, which is an issue in patients with COPD because of their vulnerability to lung infections. There is a worry that inhibiting the IL-17–IL-23 axis, which plays a crucial role in defending the lungs against bacterial infections by releasing antimicrobial peptides from airway epithelial cells, may lower infection immunity.[25]

It must be highlighted that, although neutrophilic inflammation is the primary manifestation of COPD, investigations on targeted biological therapy for

neutrophilic inflammation have so far been unsatisfactory.[25] Several mAbs targeting specific pro-inflammatory and pro-neutrophilic cytokines and chemokines, such as TNF-α, IL-1β and IL-8, have been studied for COPD treatment. However, none of these strategies was successful.[25]

Conclusion

The advent of biological therapy has undoubtedly revolutionized the management of severe asthma, whereas it seems to have had less of an impact on COPD therapy.

The success of biological agents in asthma relies primarily on appropriate patient selection. Individual assessment of patients for allergic or eosinophilic asthma is possible using the measurable biomarkers that predict treatment efficacy.[37] Indeed, there is still a need for head-to-head comparison studies of these agents and to identify even more biomarkers, free from error especially as the result of care, for asthma diagnosis, prognosis and response to treatment.[26] It has been correctly pointed out that specific cytokines are more prevalent in some patients than others with a seemingly identical clinical presentation.[5] It is unclear why one cytokine causes inflammation in one patient but not in another. Still, it could be due to a distinct tissue response influenced by genetic and epigenetic variables. Unfortunately, treating T2-low asthma is a therapeutic challenge because its processes are not well known or, at the very least, defined, which is why certain biological agents targeting known pathways, such as those including IL-8, IL-17, IL-1, IL-6, IL-23 and TNF-α, have failed in the past.[101]

Although there is an exciting signal suggesting that biologicals targeting the IL-5 pathway appear to have a weak, albeit significant, effect in patients with eosinophilic COPD,[102] we still stand by what we pointed out 6 years ago, that biological agents generally have little or no effect in patients with COPD, probably because there is no single dominant cytokine in COPD.[103] As a result, it cannot be ruled out that the failure observed while assessing different biological agents in COPD reflects the complexity of the disorder, which includes numerous endo/phenotypic pathways.[104] Therefore, when analysing the effects of biological agents in COPD, the redundancy of signal-induced impacts, particularly the likelihood that other pathways may still create or maintain the inflammatory state even when a specific path is switched off, is a significant aspect that needs to be considered constantly.[105]

We are becoming increasingly certain that biological agents will only be appropriate for a small subpopulation of patients with COPD. However, new studies focusing on outcomes other than exacerbations could provide information that could expand the range of people who can benefit from these drugs if the treatment approach is centred on treatable traits, as suggested for the treatment of COPD in general and eosinophilic forms in particular.[104] ❑

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