Recent developments in the management of severe asthma

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Fevipiprant is unlikely to be implemented as a future treatment for severe asthma, while tezepelumab may be a future treatment option for patients with severe asthma with and without eosinophilic inflammation https://bit.ly/3KE1BH4

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Commentary on:

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- Brightling CE, *et al*. Effectiveness of fevipiprant in reducing exacerbations in patients with severe asthma (LUSTER-1 and LUSTER-2): two phase 3 randomised controlled trials. *Lancet Respir Med* 2021; 9: 43–56.
- Heaney LG, *et al*. Composite type-2 biomarker strategy *versus* a symptom–risk-based algorithm to adjust corticosteroid dose in patients with severe asthma: a multicentre, single-blind, parallel group, randomised controlled trial. *Lancet Respir Med* 2021; 9: 57–68.

Context

Although they constitute only 3–10% of the adult asthma population [1, 2], patients with severe asthma account for more than 60% of the total costs associated with the disease. In addition, patients with severe asthma have markedly reduced quality of life due to symptoms, medication side-effects and hospitalisations [3, 4].

With the introduction of biologic treatments for T-helper cell type 2 (T2)-driven asthma, the treatment options for severe asthma have improved substantially [5]. Treatment with biologics can reduce the rate of exacerbations [6] and emerging evidence suggests a beneficial effect of biologics on the symptom burden, as well as improving the quality of life for asthma patients with T2 inflammation [7]. However, the currently available biological treatments are not administered to patients who exhibit no evidence of allergy or eosinophilic inflammation [8], and other treatment options are needed for patients with non-T2 inflammation.

Two recent trials have addressed this unmet need. First, the NAVIGATOR trial tested a monoclonal antibody that targets thymic stromal lymphopoietin (TSLP) [9], which is a key regulator of the T2 immune response in the skin and the respiratory and gastrointestinal tracts [10, 11]. TSLP is an upstream epithelial cytokine that is released in response to triggers and stimulates mast cells to produce key T-helper cell (Th)2 inflammatory cytokines such as interleukin (IL)-5, IL-4, and IL-13 [12]. A role for TSLP in asthma pathogenesis is also suggested by the correlation between TSLP expression and both airway obstruction and disease severity [12]. Further, TSLP may drive neutrophilic inflammation upon activation of dendritic cells, inducing a Th17 response [13]. Thus, targeting TSLP may have immunomodulatory effects in patients with T2-high or non-T2 asthma.

Second, the two phase 3, randomised, double-blind, placebo-controlled replicate trials LUSTER-1 and LUSTER-2 assessed the effects of an oral antagonist of the prostaglandin D_2 receptor 2 [14]. Prostaglandin D_2 is released from mast cells, eosinophils and several airway structural cells, and it has potent effects on eosinophils, neutrophils, mast cells, Th2 cells, and innate lymphoid cells [15]. An early phase 2 study showed that fevipiprant reduced sputum and bronchial eosinophils, compared with placebo, suggesting that fevipiprant may have beneficial effects in patients with T2-high asthma [16]. The LUSTER-1 and LUSTER-2 trials investigated whether fevipiprant reduced asthma exacerbations in patients with either eosinophilic or non-eosinophilic severe asthma.

Finally, the multicentre, single-blind, parallel group, randomised controlled RASP-UK trial investigated using a biomarker strategy to adjust the corticosteroid dose for patients with severe asthma [17]. The study compared a composite score based on exhaled nitric oxide fraction (F_{ENO}), blood eosinophil and serum periostin measurements with a standardised symptom–risk-based algorithm. The rationale for the study was that the current treatment guidelines recommend increasing the inhaled corticosteroid (ICS) dose whenever asthma symptoms worsen, although symptoms can also occur in the absence of T2 inflammation [18]. The therapeutic benefits of ICS treatment are less in patients with non-T2-high asthma than in patients with T2-high asthma, and high doses of ICS are associated with side-effects [19]. Hence, this biomarker-based strategy has the potential to decrease the use of unnecessary ICS in patients with Th2-low asthma.

Methods

NAVIGATOR

The NAVIGATOR trial was a phase 3, multicentre, randomised, double-blind, placebo-controlled trial. Patients aged 12–80 years with physician-diagnosed asthma who had received a minimum daily dose of 500 µg fluticasone propionate (or equivalent) for at least 12 months before screening were randomised to 210 mg tezepelumab or placebo every 4 weeks for 52 weeks [9]. Patients who were treated with approved and non-investigational biological drugs were also permitted to participate in the study if the last dose had been administered more than 4 months or five half-lives prior to screening. The primary endpoint was the 1-year rate of asthma exacerbations over the 52-week period and this was assessed in the subgroup of patients with baseline eosinophil counts of both less than and above 300 cells·µL^{-1}. The predefined key secondary endpoints were changes in pre-bronchodilator forced expiratory volume in 1 s (FEV_1), the Asthma Control Questionnaire (ACQ) score, the Asthma Quality of Life Questionnaire, and the Asthma Symptom Diary.

LUSTER-1 and LUSTER-2

The LUSTER-1 and LUSTER-2 trials were two phase 3, double-blind, placebo-controlled, parallel-group, replicate studies that assessed the effects of oral fevipiprant in adolescents and adults with severe asthma (Global Initiative for Asthma (GINA) steps 4 and 5) [14]. The inclusion criteria were: age ⩾12 years; diagnosed with asthma for at least 24 months prior to inclusion; a history of two or more asthma exacerbations within the 12 months prior to entering the study; and FEV_1 ⩽90% predicted for patients aged 12–18 years and FEV_1 ⩽80% predicted for patients aged >18 years. Patients were randomised to 52 weeks of once-daily oral treatment with 150 mg or 450 mg fevipiprant or placebo in a 1:1:1 ratio. Recruitment was stratified so that two-thirds of the patients had blood eosinophil counts of ⩾250 cells·µL^{-1} and the remaining patients had blood eosinophil counts <250 cells·µL^{-1}. The primary endpoint was the 1-year rate of moderate-to-severe asthma exacerbations exhibited by patients who had 150 mg or 450 mg once-daily doses of fevipiprant, compared with placebo over 52 weeks. This endpoint was assessed in patients with high levels of blood eosinophils (⩾250 cells·µL^{-1}) and in the overall study population.

RASP-UK

The RASP-UK trial was a single-blind, randomised trial that included 301 patients with severe asthma (GINA step 4 or 5), from 12 specialist severe asthma centres across the UK, who were aged 18–80 years and had F_{ENO} concentrations of <45 ppb [17]. All patients were randomly assigned in a 4:1 ratio to one of the following two strategies, designed to monitor and adjust their corticosteroid dose over a period of 48 weeks: 1) a biomarker strategy intervention group in which blood eosinophil counts, F_{ENO} concentrations and serum periostin measurements were recorded; and 2) a standardised symptom–risk-based algorithm control group. The patients were assessed at a clinic every 8 weeks. For the intervention group, treatment was adjusted according to a prespecified composite biomarker scoring system based on F_{ENO}, blood eosinophil count, and serum periostin measurements. For the control group, treatment was adjusted according to a symptom–risk-based scoring system based on the ACQ-7 and post-bronchodilator FEV_1 measurements. The primary endpoint was the proportion of patients who exhibited a reduction in ICS or oral corticosteroid (OCS) dose from baseline to week 48. Key secondary

endpoints were the ICS dose at the end of the study, the proportion of patients who were on maintenance OCS at the end of the study, and the cumulative dose of ICS. When comparing the two groups, the authors considered a 20% difference in the proportion of patients receiving a lower ICS dose to be clinically relevant.

Results

In the NAVIGATOR trial, 2420 patients were screened of which 1061 were randomised to either tezepelumab (n=529) or placebo (n=532) [9]. In the overall population, patients treated with tezepelumab had a lower 1-year asthma exacerbation rate than those given placebo (0.93, 95% CI 0.80–1.07 *versus* 2.10, 95% CI 1.84–2.39) and the rate ratio was 0.44 (95% CI 0.37–0.53; p<0.001). Tezepelumab also reduced the exacerbation rate in patients with baseline blood eosinophil counts less than 300 cells·μL^{-1} (rate ratio 0.59, 95% CI 0.46–0.75; p<0.0001). A prespecified minimum clinically important difference (0.1 L) in pre-bronchodilator FEV_1 was observed in the tezepelumab group (0.23 L) but not in the placebo group (0.09 L) and the group difference was 0.13 (95% CI 0.08–0.18; p<0.001). No clinically or statistically significant changes were observed for the remaining key secondary outcomes. Not surprisingly, significant and clinically relevant changes were observed for T2 inflammatory biomarkers such as F_{ENO} (−13.8 ppb, 95% CI −17.1 to −10.6), blood eosinophil count (−130, 95% CI −156 to −104), and total serum IgE (−208, 95% CI −303.7 to −112.3).

In the LUSTER-1 and LUSTER-2 trials, 894 and 877 patients, respectively, were randomly assigned to either 150 mg fevipiprant, 450 mg fevipiprant or placebo. In both trials, the authors found no statistically significant difference in the annual asthma exacerbation rate between either dose of fevipiprant and placebo. Patients receiving 450 mg fevipiprant experienced modest, but not statistically significant reductions in exacerbation rate in both the overall population and the high-eosinophil group (LUSTER-1: 0.78 (95% CI 0.61–1.01) and 0.83 (95% CI 0.61–1.14), respectively; LUSTER-2: 0.76 (95% CI 0.58–1.00) and 0.72 (95% CI 0.52–1.01), respectively). The authors also found numerically, but not statistically, significant improvements in post-bronchodilator FEV_1 in the intervention groups, with the greatest change in the 150 mg fevipiprant, high-eosinophil group (least-squares mean: 0.119; 95% CI 0.065–0.173). The changes in ACQ-5 were neither clinically nor statistically significant.

The RASP-UK study randomly assigned 240 patients to the biomarker strategy intervention group and 61 patients to the control group. The per-protocol population consisted of only 40% of the intention-to-treat population due to patients not following at least one treatment advisory, withdrawing from the trial, or missing a study visit. In the intention-to-treat population (n=264), 28.4% of the patients in the intervention group reduced their ICS dose compared with 18.5% in the control group (odds ratio 1.71, 95% CI 0.80–3.63; p=0.17). In the prespecified per-protocol population (n=121), a significantly greater proportion of patients in the intervention group reduced their ICS dose compared with the control group (30.7% *versus* 5.0%; odds ratio 11.48, 95% CI 1.35–97.83; p=0.026). In the intention-to-treat population, there were no significant differences in secondary outcomes between the two groups. In the per-protocol population, there were no significant differences observed between the intervention and control groups, except for F_{ENO} concentrations (21.0 ppb, 95% CI 19.0–24.0 *versus* 13.5 ppb, 95% CI 9.0–25.0, respectively; odds ratio 1.39, 95% CI 1.07–1.80; p=0.014).

Commentary

The management and treatment guidelines for asthma are under constant review as new monitoring and treatment options are being introduced [5, 18]. The current guidelines recommend a stepwise increase in ICS to achieve symptom control and reduce exacerbations, regardless of the level of blood eosinophils [18]. However, eosinophilia is a strong predictor of treatment response and can be used to guide treatment in both asthma and COPD [20]. Furthermore, only half of patients with asthma have eosinophilic inflammation [21] and all the currently available biological treatments are approved for patients with signs of T2 inflammation [22]. In this context, the NAVIGATOR, LUSTER-1 and LUSTER-2 trials investigated new therapeutic options for patients with severe asthma that remained uncontrolled despite a systematic approach and GINA step 4 or 5 treatment, but who were not eligible for any of the available biological treatments.

In a phase 2 study, a once-daily dose of 500 mg fevipiprant was not associated with significant changes in FEV_1 or ACQ-7 score. However, subgroup analyses showed that patients with FEV_1 <70% of the predicted value exhibited a significant increase in trough FEV_1 (difference=207 mL, 95% CI 96–319) and a statistically, but not clinically, relevant change in ACQ-7 score (difference= −0.41, 95% CI −0.61 to −0.13) [23]. In another phase 2 study, a twice-daily dose of 225 mg fevipiprant reduced the sputum eosinophil count, compared with placebo [24].

In the two phase 3 trials described here, treatment with fevipiprant did not result in any statistically significant changes in the primary endpoint, which was the annual exacerbation rate in the overall populations and high-eosinophil groups. Further, no clinically relevant changes were observed in the key secondary outcomes, such as FEV_1 and ACQ scores. Early studies had shown a reduction in eosinophils, and it was expected that treatment with fevipiprant in the phase 3 studies would reduce the number of exacerbations, particularly in the high-eosinophil group. Although the patients were randomly assigned within randomisation strata based on high and low levels of blood eosinophils, the median baseline level of blood eosinophils was at least 320 cells·μL^{-1} across all the groups. The numerical reductions in exacerbation rates were generally lower in the LUSTER-2 trial, but there was no consistency in the magnitude of reductions relative to the level of blood eosinophils or the dose of fevipiprant. The LUSTER-trials had a number of limitations that could explain the lack of efficacy. First, the dose-ranging study investigated the change in FEV_1 over a 12-week period [25] and showed that the 150 mg dose was optimal, whereas the primary endpoint in the LUSTER-trials was the exacerbation rate over a 52-week period and the efficacy seemed to increase with the 450 mg dose. Second, the authors used blood eosinophils and F_{ENO} as markers of eosinophilic inflammation rather than samples from the airways, and although widely used as such, these biomarkers do not always correlate in asthmatic individuals [26, 27]. Based on the main findings of the LUSTER-trials, it seems unlikely that fevipiprant will be implemented in the treatment of severe asthma, but have we seen the end of fevipiprant? There are currently 14 registered studies on clinicaltrials.gov that include fevipiprant, and all of them are completed, but do not have results yet. The next step for fevipiprant can be determined by these unpublished studies or if future *post-hoc* analyses of the LUSTER-trials reveal subgroups of asthma patients who benefit from fevipiprant more convincingly and this is subsequently proven in new phase 3 trials.

The NAVIGATOR trial investigated the efficacy of tezepelumab on the 1-year rate of asthma exacerbations in patients receiving GINA step 4 or 5 treatment. Notably, the patients who were included in this trial did not necessarily reflect a real-life population because they also had to meet the following criteria: documented evidence of FEV_1 reversibility of at least 12% and 200 mL within 12 months prior to screening; the occurrence of at least two asthma exacerbations, despite high-dose ICS treatment, during the previous 12 months; and the addition of at least one controller medication, with or without OCS, for at least 3 months before inclusion. The main analyses showed that treatment with 210 mg tezepelumab every 4 weeks for 52 weeks reduced the 1-year exacerbation rate, compared with placebo, by 56% in the overall population and by 41% in the group with blood eosinophils <300 cells·μL^{-1}. Among the key secondary outcomes, only pre-bronchodilator FEV_1 was significantly improved in the tezepelumab group compared with placebo, with a difference of 130 mL. The strengths of the NAVIGATOR trial are both the multinational and large sample size and the consistency in the improvements of asthma-related outcomes in patients treated with tezepelumab. However, the study is limited by its duration (52 weeks), although it is comparable with other similar studies. Further, patients who were current smokers, had more than 10 pack-years smoking history, or a pulmonary or systemic comorbidity were excluded. These strict criteria reduce the generalisability of the main results. Although fevipiprant is unlikely to be implemented in future asthma treatment guidelines, the NAVIGATOR trial showed that anti-TSLP treatment may be a feasible option for patients with severe asthma and a history of exacerbations, as well as for patients with low blood eosinophil counts.

These trials with novel treatments raise several questions regarding future studies. For example, how do we as researchers and respiratory physicians design future studies on biological treatments to include patients who have uncontrolled asthma, exacerbations and impaired quality of life despite GINA step 4 or 5 treatment when such patients may be eligible for effective approved biological treatments? Notably, some patients included in the NAVIGATOR trial had previous treatment with biologics; thus, participation in the trial did not prevent these patients from being treated with currently available monoclonal antibodies. Interestingly, the reduction in asthma exacerbation rate observed in patients with high blood eosinophil counts who were treated with tezepelumab is similar to that observed for treatment with other monoclonal antibodies, such as mepolizumab and benralizumab [28, 29].

Finally, the RASP-UK study investigated whether a biomarker strategy could be used more effectively than a standardised symptom–risk-based algorithm approach to adjust the corticosteroid dose administered to patients with severe asthma. Previous randomised clinical trials showed that using F_{ENO} to guide asthma treatment could reduce the rate of asthma exacerbations [30] and also led to a faster reduction in the level of airway hyperresponsiveness [31]. The RASP-UK study showed that patients who had their treatment adjusted using the biomarker strategy reduced their corticosteroid dose by 30.7%, compared with a reduction of only 5.0% in the control group.

Interestingly, only 40% of the included patients followed the protocol and the main reason for this was a failure to follow at least one treatment advisory. Patients in both the biomarker strategy group and the

control group showed reluctance to reduce their ICS, which surprised the authors as the patients were fully informed regarding the study design. A *post-hoc* analysis among the symptomatic patients (ACQ-7 $\geqslant$1.5) showed that a significant proportion of the patients could reduce their use of corticosteroids when treatment was tailored according to the biomarker strategy, and without worsening of asthma control.

Adjusting the dose of OCS and ICS remains an important ongoing clinical consideration, and this should be based on biomarkers that predict the treatment response [20]. One important secondary aim in the RASP-UK study was to estimate the proportion of patients who could reduce the ICS dose to the lowest dose and remain composite T2 biomarker-low, and the authors found that this group accounted for only 5% of the patients who were assigned to the biomarker strategy group and completed the study. This finding suggests that previously the prevalence of T2-low asthma might have been overestimated.

Implications for practice

The management of asthma should be based on a systematic approach to identify the many possible triggers, phenotypes and comorbidities that can influence the prognosis. The current asthma treatment guidelines recommend a stepwise approach, with ICS as the cornerstone. Both initiation of ICS treatment and reduction of ICS dose are important control points in asthma management. The RASP-UK trial showed that a biomarker strategy, which involved measuring F_{ENO} concentrations, serum periostin levels and blood eosinophil counts, could be successfully used to guide reductions in ICS dose. However, implementing and maintaining such a strategy may be challenging, and patients must be committed and well informed. The study found that patients in both the biomarker strategy group and the control group showed reluctance to reduce their ICS. Patients in the biomarker-low group that were reluctant to reduce the treatment were characterised by being more symptomatic and with a lower lung function. This could partly explain the lack of willingness to reduce treatment, as asthma patients are more likely to use inhalers in the presence of symptoms and *vice versa* [32]. Given the variation and role of T2-inflammation in asthma and the possibility to measure predictive biomarkers of treatment response, using a biomarker-directed strategy to adjust the dose of corticosteroids could be particularly relevant for patients whose symptoms do not correlate with T2-biomarkers. These patients in the RASP-UK trial who were willing to reduce the treatment, could reduce their ICS dose without worsening of asthma symptoms. One important question is how should clinicians inform and encourage symptomatic, but biomarker-low asthma patients to reduce their ICS?

The introduction of monoclonal antibodies has resulted in a marked improvement in the treatment options for some patients with severe uncontrolled asthma that fails to respond adequately to high-dose ICS and controller medications. The LUSTER-1 and LUSTER-2 trials found no significant improvements in asthma exacerbation rates, FEV_1 or ACQ scores in patients treated with the prostaglandin D_2 receptor 2-antagonist fevipiprant. Therefore, fevipiprant will probably not be a future treatment option for patients with asthma. However, treatment with tezepelumab reduced the 1-year asthma exacerbation rate in the overall study population by 56%. Interestingly, a clinically relevant reduction in exacerbation rate (41%) was also observed in patients with blood eosinophil counts <300 cells·μL^{-1} who were treated with tezepelumab, compared with placebo. In spite of the limitations in the NAVIGATOR trial, tezepelumab will most likely be a future treatment option for patients with severe asthma. Treatment with anti-IgE, anti-IL-4/IL-13, and anti-IL-5 are only indicated for patients with signs of T2-inflammation. Tezepelumab differs from other available biologics as it is an upstream cytokine that plays an important role for both Th2 and Th17 immune responses. Thus, tezepelumab may be relevant for patients with severe T2-high or non-T2 asthma, and in particular the latter patient group for whom the currently available biologics are not a treatment option.

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