Journal club

Using biomarkers to adjust corticosteroid dose in patients with severe asthma

Commentary on:
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

In the management of airway disease, escalation of treatment often happens more readily than reduction. In line with this, clinical trials usually focus on the up-titration or addition of medications and few trials are available to also guide reduction in treatment.

Type 2 (eosinophilic) inflammation is the primary target of inhaled and oral corticosteroids in asthma [1], while symptoms can be driven by many factors [2]. Traditionally symptoms have been used to guide changes in treatment, but there are several biomarkers that indicate ongoing T2 inflammation [3], which may be a more accurate guide than using patient reported symptoms.

Heaney et al. [4] present a useful trial from the MRC Refractory Asthma Stratification Programme (RASP) group which helps address this dearth of trial data by comparing a symptom-based approach to a biomarker approach in the adjustment of treatment in severe asthma.

Methods

This was a single-blind randomised controlled trial of participants with severe asthma (Global Initiative for Asthma (GINA) treatment steps 4–5) recruited from severe asthma centres in England, Scotland and Northern Ireland. Participants had an exhaled nitric oxide fraction ($F_{\text{ENO}}$) of <45 ppb (in order to enrich for those likely to be able to reduce treatment), and were block randomised 4:1 into the biomarker guided versus symptom-guided approach, stratified by asthma control and number of rescue corticosteroid courses in the previous year. The biomarker arm used a composite assessment of T2 status using $F_{\text{ENO}}$, blood eosinophils and serum periostin, while the symptom-risk arm used a combination of Asthma Control Questionnaire-7 (ACQ-7) compared to baseline ACQ-7 and recent exacerbations.

Participants were reviewed in clinic every 8 weeks and treatment plans were automatically generated by the electronic study software based on the above information. At the time of clinic review, the biomarker group received an advisory to maintain current treatment, while the symptom group received advice based on the symptom-risk protocol. Once biomarker results were available a further advisory was sent to all participants, to maintain treatment in the symptom-risk group and based on the composite biomarker score for the biomarker group.

The primary outcome measure was the proportion of participants who were able to reduce inhaled corticosteroid burden in severe asthma if treatment advice is followed. T2 low asthma is less common than previously thought. https://bit.ly/3rG7SZ2
their dose of inhaled or oral corticosteroid by week 48. Secondary outcomes included end-study and cumulative corticosteroid doses, asthma control and quality of life. Analyses were performed on an intention-to-treat (ITT) basis with adjustments for age, sex, smoking status, study centre, pre-study exacerbation frequency and baseline ACQ-7. A per-protocol (PP) analysis with identical adjustments was also planned a priori, excluding those who did not follow their treatment advisory or attend clinic.

Main results

Out of 549 potential participants screened, 248 were excluded with the most common reasons being $F_{ENO}$ over 45 ppb and lack of documented reversibility. 240 participants were allocated to biomarker-based treatment while 61 received symptom-based advice. 28.4% of participants in the biomarker group reduced their corticosteroid dose compared with 18.5% in the symptom group (p=0.17). There were similarly no significant differences in the secondary outcomes as per ITT analysis.

The PP analysis, however, did show statistically significant results. While only 40% of the study population ended up included in the PP analysis due to numbers not following their treatment advice, 30.7% of the biomarker arm compared with 5% of the symptom arm managed to reduce their corticosteroid doses (p=0.026). Again, there were no significant differences is secondary outcomes except $F_{ENO}$. Treatment advice adherence varied between study centres, and adherence was less likely when a change in treatment, particularly initiation of oral corticosteroids (OCS) but also a reduction in inhaled corticosteroid dose, was advised.

While no reduction in median OCS doses was achieved, there was a clinically significant median reduction in inhaled corticosteroid (ICS) doses of 1000 μg beclometasone dipropionate equivalents in those who managed to reduce their doses. Exacerbation rates were significantly higher for those who did not follow treatment advisories in the biomarker group (HR 1.64, p=0.01) but not in the symptom group (HR 1.07, p=0.8), and comprised both those refusing to increase and decrease corticosteroid treatment.

An exploratory analysis was performed in patients with uncontrolled asthma at baseline defined by ACQ-7 ≥1.5, which showed that this population was predominantly female, had an elevated body mass index, reduced rates of employment due to asthma-related ill health, higher rates of anxiety and depression, higher OCS usage and lower FEV₁ without lower FEV₁/forced vital capacity ratio. Results from this group showed 26.4% of the biomarker group reduced their corticosteroid dose compared with 5.7% in the symptom group (p=0.027).

Commentary

On the secondary aim of identifying how many participants were T2 low throughout despite reduction in ICS doses, nine (4%) participants achieved the lowest possible ICS dose without demonstrating a T2 signal, while two further participants repeatedly reduced ICS doses as per advice but did not reach the lowest possible dose within the study timeframe. These suggest that around 5% of the study population were genuinely “T2 low”.

Symptoms of asthma, particularly breathlessness and cough, are not specific to airway disease and symptomatic patients will therefore often not respond to escalation in asthma treatment. Unfocused escalation of ICS doses risks worsening underlying drivers of poor asthma control such as infection and gastro-oesophageal reflux disease. These data demonstrate the efficacy of a biomarker approach.

There has long been debate on the proportion of people with asthma who are non-eosinophilic/”T2 low”. The use of inhaled and/or oral corticosteroids has been the major confounder in this area, as corticosteroid therapy will usually reduce T2 biomarkers and make identification of the pathophysiology underlying symptoms more challenging. This study provides good evidence that, within this population of severe asthma patients, genuinely T2 low disease is uncommon at 5% of the study population. Data regarding the stability of treatment advisories, i.e. the frequency of treatment decisions that were reversed at the next decision point would be interesting.

The choice of optimal T2 biomarkers to use is often debated. Peripheral blood eosinophil count is established as a biomarker of T2 disease in asthma [5], but also of corticosteroid responsiveness in COPD [6]. $F_{ENO}$ is also established as a marker of T2 disease [7], but is less commonly measured than eosinophil counts and requires specific equipment. Serum periostin is even less available, but is recognised as a marker of T2 disease [8]. However, the clinical utility of serum periostin is less clear and the evidence base is not sufficient for inclusion in guidelines at this point.

This interesting study also highlights several difficult practical aspects of looking after people with severe asthma. First, no matter how good your approach to treatment is, it cannot help if your patient does not follow your advice as demonstrated by the gap between ITT and PP results. Secondly, patients will often have concerns about changes in treatment that need addressing as demonstrated by the poorer adherence to advisories when they advocate change in treatment compared to no change, and remote instruction as used in this study may be less beneficial than direct discussion of risks and benefits. Thirdly, reduction in corticosteroid...
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Dosing is a slow process, shown by the fact that some T2 low patients did not achieve minimal ICS doses despite 8-weekly reviews for an entire year. Finally, from a research perspective, the significant difference in the PP results highlights a major difficulty in recruitment to clinical trials in severe asthma: trials tend to recruit participants who remain symptomatic and exacerbating despite high-dose treatment, but this study shows that a significant number of symptomatic patients are on more corticosteroid therapy than is required to control their airway inflammation.

Strengths of this study include the simple inclusion criteria and pragmatic nature of the trial design. Data on objective adherence to treatment advice would have been interesting if possible. The inclusion of serum periostin assays within the biomarker strategy may limit usefulness of this approach in nonacademic settings where these may not be available. The lack of adherence to treatment advisories is a common problem in pragmatic studies that do not mandate adherence [9], meaning that further research is required to ensure this approach works in larger populations and how to implement it within clinical practice.

Implications for practice

A biomarker-based approach to adjustment of corticosteroid doses in severe asthma does not appear to result in reduction in corticosteroid doses, with lack of treatment adherence being a problem. The biomarker approach seems to be safe and may allow corticosteroid dose reduction in biomarker low patients who follow treatment advice without loss of asthma control. Genuinely T2 low severe asthma is probably less common than previously thought. Appropriate management of patients who do not follow advice on adjusting treatment remains elusive, and this group are both high-need and high-cost.

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Conflict of interest

T.L. Jones has nothing to disclose.

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