Biomarker-based corticosteroid adjustment in severe asthma: a modified Delphi consensus

To the Editor:

Asthma is managed using "step-wise" adjustment of corticosteroid therapy to achieve asthma control. When corticosteroid treatment is adjusted using sputum eosinophil count or exhaled nitric oxide fraction, exacerbations are reduced [1, 2]; however, implementation in clinical care has been slow. In parallel, airway transcriptomic analysis has demonstrated that type 2 eosinophilic inflammation is absent in many patients with minimal response to corticosteroid treatment [3–5]. The UK Refractory Asthma Stratification Programme (RASP-UK) (http://rasp.org.uk/) is exploring non-sputum biomarker-based strategies to target corticosteroid treatment in severe asthma [6, 7], and sought to determine clinician and patient views on clinically relevant reductions in corticosteroid treatment.

Three expert physician groups in severe asthma management participated in an online anonymous modified Delphi process [8] (three rounds): 1) RASP-UK Investigators (n=21), 2) UK severe asthma physicians not in RASP-UK (n=16) and 3) the European Respiratory Society Severe Asthma Clinical Research Collaboration [9] (n=22). 41 out of 59 physicians completed the process to achieve final statement consensus (>75% agreement) (figure 1). An identical process using a patient-focused questionnaire was sent to severe asthma patients from Asthma UK's Expert Patient Group (two rounds achieved consensus; 16 out of 23 completed the first round and 12 completed the second round). A RASP-UK investigator and statistician composed the questions. After the first round, the questions of subsequent rounds were adapted based on the responses from the previous round.

The final consensus statements and levels of agreement were as follows.

Statement 1

Do you believe that biomarker-based adjustment of corticosteroid dose is currently the optimal way to adjust corticosteroid treatment in patients with severe asthma compared to symptoms, lung function and exacerbation history?

Consensus not achieved

Physician view
Only 39% of the European group (group 3) agreed, compared to 68% of the RASP-UK (group 1) and 67% of the UK non-RASP (group 2) physicians. Currently, 44% of European physicians use biomarker-based corticosteroid adjustment routinely compared with 95% (group 1) and 100% (group 2).

Patient view
No consensus was reached on patient preference on corticosteroid adjustment using symptoms or biomarkers (50% each). The majority (75%) believed their corticosteroid was currently adjusted using symptoms/lung function.
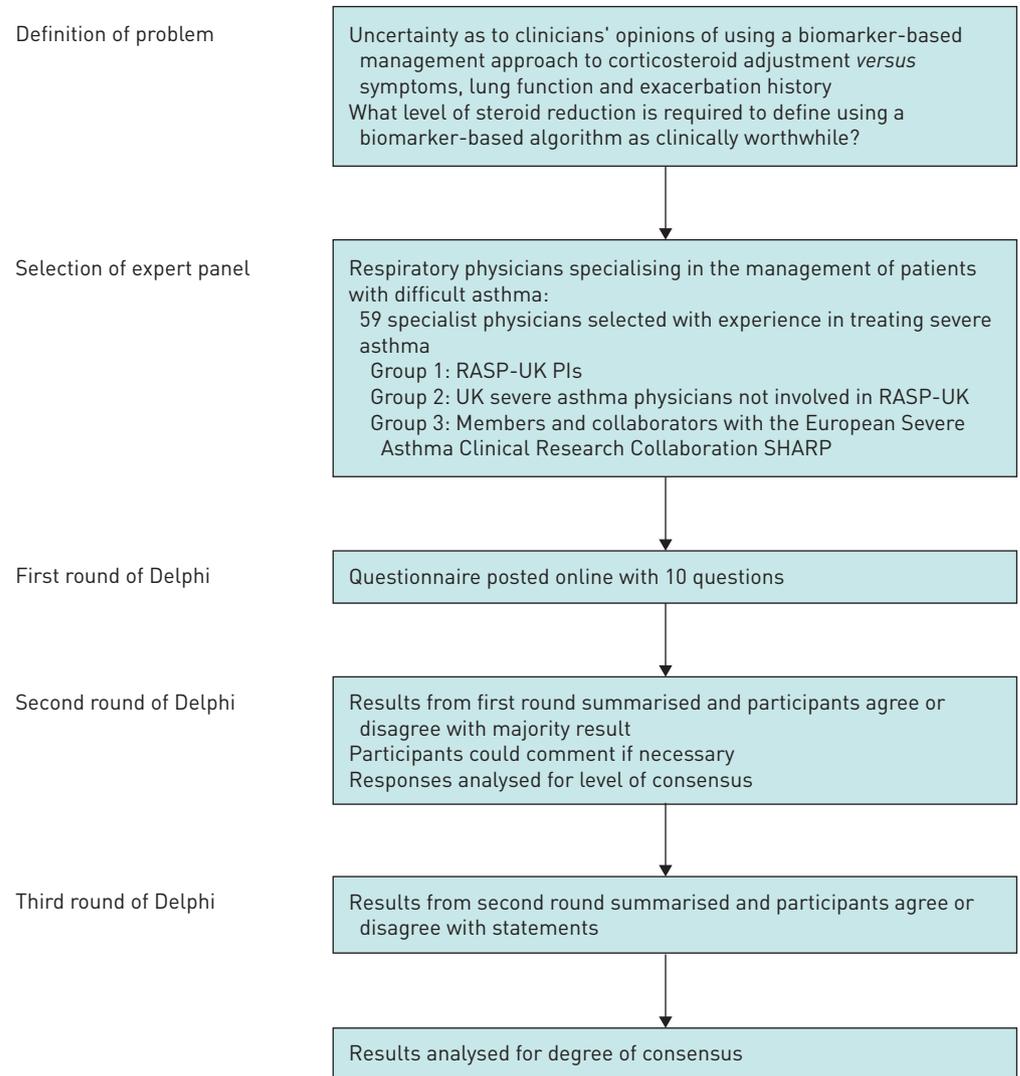
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UK asthma physicians are supportive of biomarker-based steroid adjustment, but European physicians need more evidence http://ow.ly/sTrf30my3jw

Definition of problem	Uncertainty as to clinicians' opinions of using a biomarker-based management approach to corticosteroid adjustment *versus* symptoms, lung function and exacerbation history What level of steroid reduction is required to define using a biomarker-based algorithm as clinically worthwhile?
Selection of expert panel	Respiratory physicians specialising in the management of patients with difficult asthma: 59 specialist physicians selected with experience in treating severe asthma Group 1: RASP-UK PIs Group 2: UK severe asthma physicians not involved in RASP-UK Group 3: Members and collaborators with the European Severe Asthma Clinical Research Collaboration SHARP
First round of Delphi	Questionnaire posted online with 10 questions
Second round of Delphi	Results from first round summarised and participants agree or disagree with majority result Participants could comment if necessary Responses analysed for level of consensus
Third round of Delphi	Results from second round summarised and participants agree or disagree with statements
	Results analysed for degree of consensus

FIGURE 1 Modified Delphi process used to reach a consensus among experts in severe asthma regarding the degree of benefit of biomarker-based adjustment of corticosteroid treatment required to make the conversion to a biomarker algorithm from current standard care worthwhile. RASP-UK: UK Refractory Asthma Stratification Programme; PI: principal investigator; SHARP: Severe Heterogeneous Asthma Research collaboration, Patient-centred.

Statement 2

Accepting that nonadherence may be both intentional and unintentional, do you agree that between 30% and 50% of severe asthma patients in the most severe and difficult asthma clinics are poorly adherent with *inhaled* corticosteroid treatment as the primary clinical problem?

Consensus achieved

Physician view
Group 1 felt this proportion was 30–50%, group 2 thought 25–50% and group 3 thought 20–50%.

Patient view
94% of patients reported they would never miss taking their inhalers.

Statement 3a

Do you agree that *at least* 5 mg (or 2.5 mg if on $\leqslant$10 mg·day^{-1}) reduction in daily *oral* prednisolone would be regarded as a *clinically* meaningful reduction?

Consensus achieved

Statement 3b

If you treat patients with asthma on maintenance oral steroids, do you agree that at least 25% of patients would be required to be on this optimised "lower" dose of daily oral prednisolone treatment to justify routine use of biomarker-based corticosteroid treatment adjustment in routine clinical care?

Consensus achieved

Physician view

All expert physician groups agreed that at least 5 mg (or 2.5 mg if $\leqslant$10 mg·day^{-1}) reduction in prednisolone was clinically meaningful. Group 1 thought that at least 25% of patients would need to make this reduction to justify a biomarker-based strategy, whilst groups 2 and 3 thought at least 20%.

Patient view

91% of patients felt any reduction in oral corticosteroids would make blood/breath tests worthwhile.

Statement 4a

Do you agree that in a severe asthma population on high-dose inhaled steroids (2000 µg beclomethasone dipropionate equivalent dose) that at least a 500 µg reduction in daily inhaled corticosteroid treatment would be regarded as a clinically meaningful dose reduction?

Consensus not achieved

Statement 4b

Do you agree that at least 30% of patients would be required to be on this optimised "lower" dose of daily inhaled corticosteroid treatment to justify routine use of biomarker-based corticosteroid treatment adjustment in routine clinical care?

Consensus not achieved

Physician view

Group 1 agreed that at least 500 µg reduction was clinically meaningful and group 2 thought this was at least 250 µg reduction. For group 3, 62% felt that at least 250 µg reduction was clinically meaningful (no consensus). Groups 1 and 2 agreed that at least 30% of patients would need to be on this optimised lower dose to justify using a biomarker-based adjustment strategy; for group 3, 54% felt that at least 40% of patients would need to achieve this (no consensus).

Patient view

73% of patients felt that additional blood/breath tests would be worthwhile if they led to any reduction in inhaled corticosteroid treatment.

Statement 5

Accepting at least three exacerbations per year (requiring oral corticosteroid rescue therapy), do you agree that at least a 30% reduction per year would be an acceptable reduction to justify routine use of biomarker-based corticosteroid treatment adjustment?

Consensus achieved

Physician view

Group 1 agreed that at least a 30% reduction in asthma exacerbations per year would justify routine use of biomarker-based corticosteroid treatment adjustment whereas groups 2 and 3 agreed that at least a 20% reduction would justify routine use.

Patient view

44% of patients had three or more asthma attacks in the previous year requiring oral corticosteroids. All patients thought that having regular blood and breath tests would be worthwhile if this prevented one attack.

Statement 6

Excluding patients where persistent symptoms of cough, wheeze and breathlessness are due to comorbid conditions (*e.g.* obesity, vocal cord dysfunction, dysfunctional breathing, rhinosinusitis, *etc.*), do you agree that *at least* 25% of remaining severe asthma patients in your clinic have persistent symptoms *due to asthma* that are *not* corticosteroid responsive?

Consensus achieved

Physician view

Groups 1 and 2 agreed at least 25% and group 3 agreed at least 20% of severe asthma patients have persistent symptoms due to asthma that are not corticosteroid responsive.

Patient view

91% of patients agreed that not all their symptoms responded to inhaled or oral steroids.

The RASP-UK programme is exploring if a non-sputum biomarker-based adjustment of corticosteroid treatment is clinically more beneficial than standard care [7]. In this modified Delphi exercise, consensus was reached on all issues for groups 1 and 2. However, for group 3, consensus was not reached on a number of issues, including clinically meaningful dose reduction in inhaled corticosteroid treatment and proportion of patients reducing inhaled corticosteroid treatment to justify routine use of biomarkers. Overall, European experts appeared less supportive of biomarker-based corticosteroid adjustment compared to UK physicians and correctly stated that although sputum eosinophil count was evidence based, delivery was difficult in routine care and the optimal combination of non-sputum-based biomarkers was unknown [10, 11].

Patient views are critical in understanding acceptance of treatment strategies and there was no consensus on corticosteroid treatment adjustment using symptoms *versus* biomarkers, suggesting education may be required on the utility of biomarkers in targeting treatment. The majority felt any reduction in inhaled/ oral corticosteroid dose or eradicating one severe exacerbation would make biomarker tests worthwhile. Patients felt regular blood and breath tests were unlikely to improve adherence; however, this small motivated group reported never missing medication. The group of patients who took part in this survey volunteered for Asthma UK and some were also involved in the Patient Input Platform for the RASP-UK programme. These patients may, therefore, have had greater knowledge regarding severe asthma and biomarkers.

In conclusion, we present a consensus view of severe asthma expert physicians on non-sputum biomarker-based corticosteroid adjustment and the scale of benefit that would persuade them to use biomarkers in routine clinical care. A small number of nonconsensual issues were identified, where European group experts appeared to be less supportive of biomarker-based adjustment of asthma treatment compared to UK physicians.

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