Therapeutic Advances in Chronic Disease

Original Research

Symptoms and exacerbations in asthma: an apparent paradox?

Ther Adv Chronic Dis

2019, Vol. 10: 1–7

DOI: 10.1177/2040622319884387

Jaymin B. Morjaria, Alan S. Rigby and Alyn H. Morice

Abstract

Background: There is a dearth of data on prospectively recorded symptoms in patients with uncontrolled asthma. Asthma symptoms and exacerbation rate are commonly thought to be associated. The aim of this study was to analyse asthma symptoms of cough, wheeze, chest tightness and breathlessness in an uncontrolled asthma cohort. We also examined the effect of maintenance and reliever therapy (MART) on these symptoms and its effect on exacerbation rate.

Methods: Adults with uncontrolled asthma electronically recorded their asthma symptom severity scores twice-daily over a period of 48 weeks following randomisation to beclometasone/formoterol twice daily plus *pro re nata* (prn) salbutamol or MART. Subjects with symptom scores of ⩾2 (ranging from 0 to 3 for each symptom) were considered more symptomatic, whereas those below a score of 2 were considered less severe. The influence treatment on exacerbation frequency and symptom profiles were then correlated.

Results: Of the 1701 subjects in the analyses, 1403 were symptomatic with ⩾100 symptom episodes for one symptom. The remaining 298 subjects were classified as pauci-symptomatic. There was poor association between the frequency and symptom severity score for each symptom. Surprisingly, wheeze was the least reported symptom. Females were more likely to be polysymptomatic. MART compared with prn salbutamol markedly attenuated severe asthma exacerbations. This effect was most notable in subjects with fewer symptoms.

Conclusions: In uncontrolled asthma, there is a poor correlation between reported symptoms and exacerbation frequency. This *post hoc* analysis suggests that MART should not be reserved for symptomatic subjects but achieves the greatest benefit in pauci-symptomatic patients with asthma.

Trial registration: ClinicalTrials.gov identifier: NCT00861926

Keywords: asthma, asthma symptoms, beclometasone/formoterol, breathlessness, chest tightness, cough, maintenance and reliever therapy, wheeze

Received: 29 June 2019; revised manuscript accepted: 27 September 2019.

Correspondence to:
Alyn H. Morice
Hull York Medical School, University of Hull, Castle Hill Hospital, Castle Road, Cottingham, HU6 5JQ, UK
a.h.morice@hull.ac.uk

Jaymin B. Morjaria
Respiratory Medicine, Hull York Medical School, University of Hull, Castle Hill Hospital, Castle Road, Cottingham, UK

Department of Respiratory Medicine, Royal Brompton and Harefield NHS Trust, Harefield Hospital, Hill End road, Harefield, UK

Imperial College, Harefield Hospital, Hill End Road, Harefield, UK

Alan S. Rigby
Respiratory Medicine, Hull York Medical School, University of Hull, Castle Hill Hospital, Castle Road, Cottingham, UK

Introduction

Asthma is characterised by variable airflow limitation and respiratory symptoms.[1] It is a heterogeneous condition in which the observed phenotypes and underlying pathobiological mechanisms (endotypes) are multifaceted as a result of multiple host and environmental interactions.[2] The picture may be further complicated by the presence of other comorbidities, and early life allergen sensitisation and smoking.[2–7]

Over the years, our understanding of the heterogeneity of asthma immunology has progressed; such as the identification of sputum inflammatory cell phenotypes and transcriptomic profiles of high and low type-2 immunity.[8–10] Haldar and colleagues used multivariate techniques to classify asthma populations based on symptoms, age of asthma and body mass index (BMI), as well as eosinophilic inflammation.[11] The clusters identified phenotypes of asthma that had differing responses to therapy. Other symptom-based phenotypes in addition to patient-related factors have also been identified in the literature.[12]

In recent years, a disparity between asthma symptoms and exacerbation frequency has been suggeseted.[12]

The current approach to asthma management, which considers symptoms and exacerbations as synonymous, has been increasingly questioned as an overgeneralization in this multifactorial and heterogeneous condition.[13] Hence, a mechanistic-based approach of the identification of the mechanisms or traits that are treatable has been proposed rather than adopting a one-size-fits-all stepwise approach.

There is a lack of research into individual asthma symptoms in the literature. In patients with uncontrolled asthma, we have recently shown that, whilst symptoms of cough and wheeze were highly correlated, patients who were cough-predominant were largely overweight females whilst those who were wheeze-predominant were older males.[12] In the current analysis, we evaluate the symptoms of dyspnoea and chest tightness and compare them to cough and wheeze in a large group of uncontrolled asthmatic subjects. We examine the effect of as required reliever therapy *versus* maintenance and reliever therapy (MART) on these symptoms. We hypothesised that an asthma symptom-based phenotype may be associated with asthma exacerbation frequency, and hence suggest optimal management of any identifying symptom-based treatable traits.

Methods

We conducted a *post hoc* analysis of the diurnal daily symptom scores recorded in all the subjects recruited in a double-blind, multi-centre randomised proof-of-concept study assessing the efficacy of exacerbation reduction using daily beclometasone/formoterol and as required [*pro re nata* (prn)] salbutamol compared with beclometasone/formoterol as MART.[14] This pharma-designed (Chiesi Farmaceutici) trial recruited uncontrolled adult asthmatics who were previous or never-smokers and were symptomatic despite being on their conventional medication. The primary and secondary, as well as safety, endpoints of the study have been reported previously.[14] The study protocol was approved by the institutional review board at each site and by the central and local ethics committees according to the country's law. Written consent was obtained from all patients. Data from this study give us the opportunity to explore the relationship between symptoms and exacerbations in uncontrolled asthma patients.

The study subjects were provided with electronic devices (Spirotel; Medical International Research, Rome, Italy) capable of contemporaneously recording asthma symptoms on a twice-daily basis prior to conducting their peak flow measurements (PEF). The four asthma-related symptoms reported were cough, wheeze, chest tightness and dyspnoea. Each symptom was rated on a four point scale (0–3). Additionally, for the purposes of the analyses, each symptom episode was defined as an occasion when a symptom of any severity was recorded in the electronic diary. Details of the methodology of the primary study, as well as an initial assessment of two of these symptoms (cough and wheeze), have been reported previously.[12,14]

Patient selection and severity scores

For the purposes of the current analyses, we defined a pauci-symptomatic patient as one who had <100 episodes of any one of the four symptoms recorded in the study period. This was to censor the data and provide a true picture of the symptom severity. Additionally, a severity score of $\geqslant 2$ was considered to represent more severe symptoms.

The data was then subdivided into quartiles depending on the number of episodes recorded.

Statistical methods

Continuously distributed data was summarised by the median (25th/75th percentiles); categorical data by *n* (%). The incidence of symptomatic asthma exacerbations was analysed by Poisson regression (further details are provided the Appendix). Pearson's correlation coefficient (*r*) was used to assess the degree of linear relationships on the scatter plots. Given that this is secondary analysis of an existing dataset, *p*-values (nominally set at 5%, two-tailed) were used sparingly. The data was analysed using StataCorp (Stata Statistical Software, release 10, Stata Corporation, 2007, College Station, TX, USA).

Results

Population sample

A total of 1701 asthmatics made up the intention-to-treat (ITT) population, of whom 1403 (82%) were 'symptomatic' (defined as $\geqslant 100$ symptom

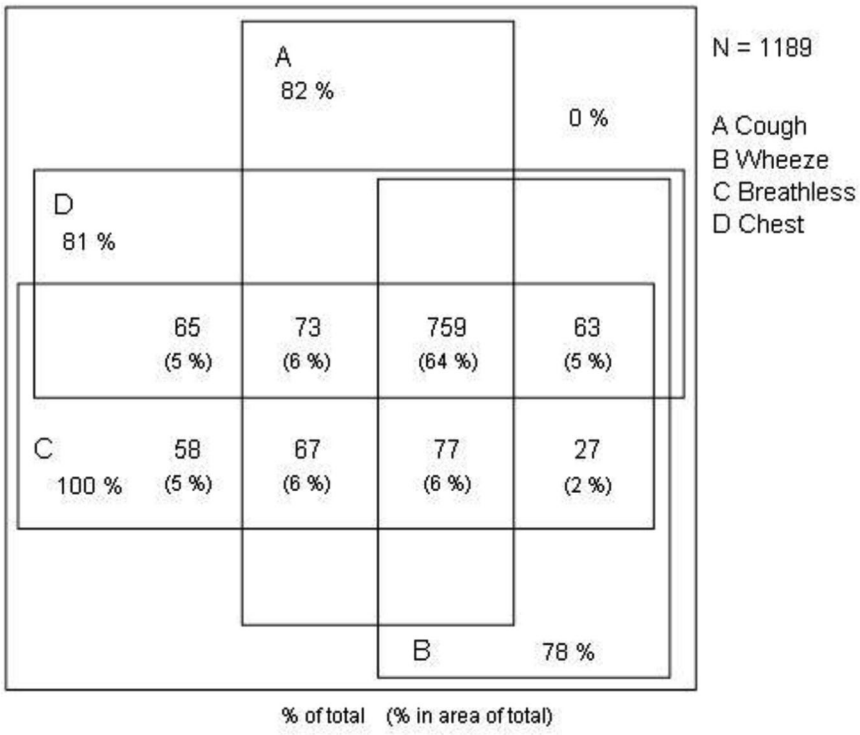

Figure 1. Venn diagram of the ITT population in the study ($n = 1701$) for the presence or absence of each symptoms reported.
ITT, intention to treat.

episodes) for at least one of four symptoms (cough, wheeze, breathless, chest tightness) (Figure 1). The distribution of the symptoms were similar across all four symptom groups (Appendix Table A1). The characteristics of the symptomatic patients were: median age of 50 years (40, 58); median BMI (kg/m^2) of 26.8 (23.9, 29.8); 340 (24%) patients had a BMI $\geq$ 30 kg/m^2; median forced expiratory volume in 1 s (FEV1; % predicted) of 72.2(65.8, 79.1); and 867 (62%) were women.

The remaining 18% ($n = 298$) of the patients were considered pauci-symptomatic. Their characteristics were: median age of 42 (29, 55) years; median BMI (kg/m^2) of 25.5 (22.8, 28.6); 55 (18%) patients had a BMI $\geq$ 30 kg/m^2; median FEV1 (% predicted) of 72.6 (66.7, 79.7); and 182 (61%) were women. Unsurprisingly, the number of episodes scoring zero were approximately twice that in the pauci-symptomatic group compared with the symptomatic (i.e. with a symptom score of $\geq$2). There was no obvious pattern as to which symptom was scored zero.

Symptomatic severity scores

Severity of symptoms was measured on a 4-point scale as described previously. The majority scored symptoms as mild irrespective of symptom (Figure 2a–d). Distribution quartiles are plotted along with severity cut-point of 2 or more. The correlation between frequency and severity symptom was low (Pearson's r 0.18–0.23). Characteristics of those with a severity score $\geq$2 are given in Table 1.

We looked at the frequency of asthmatics with one, two, three or four symptoms with a severity score $\geq$2 (Appendix Table 2). The proportion of women was 57%, 67%, 79% and 71% with one, two, three or all four symptoms, respectively ($p = 0.046$). There was no obvious pattern with age, BMI or FEV1.

Treatment and severe exacerbation rates

Symptomatic patients. There were 294 severe exacerbations in symptomatic patients, contributing to an incidence rate of 0.26 [95% confidence

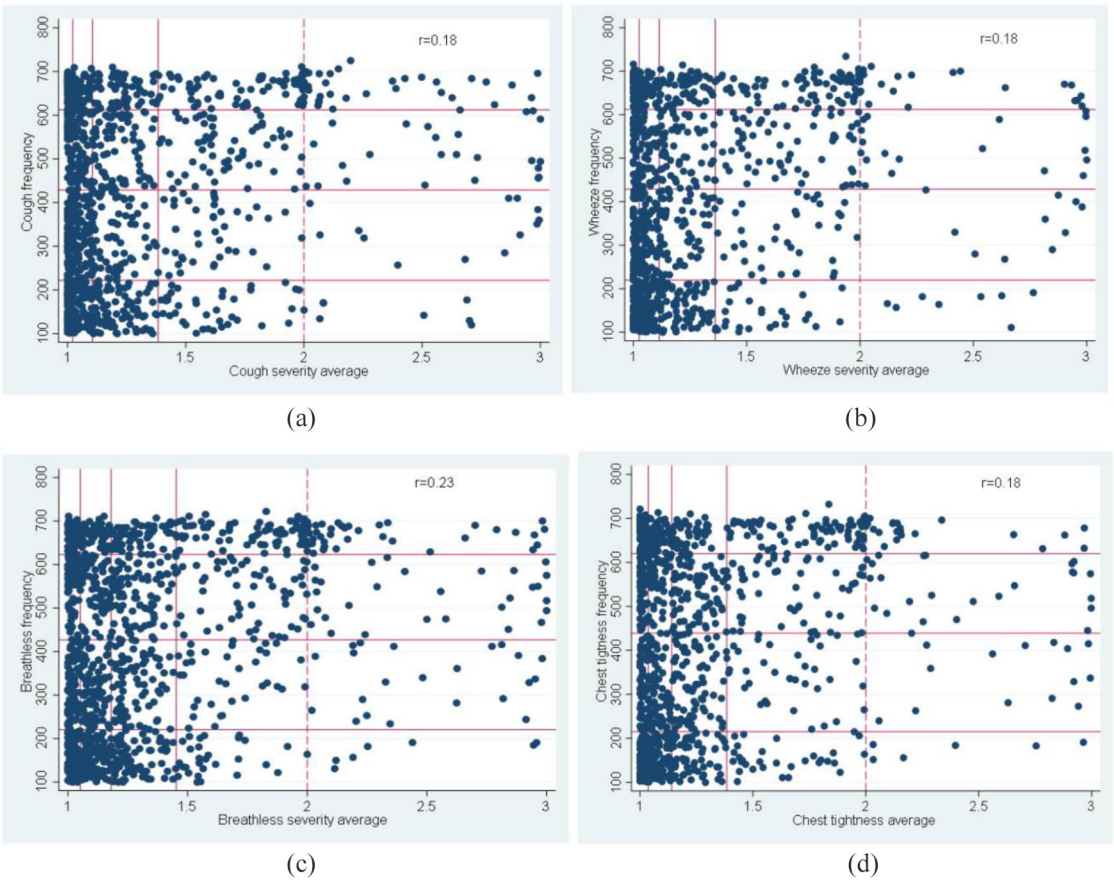

Figure 2. Quartiles of symptom episode frequency and severity (a) cough, (b) wheeze, (c) breathless and (d) chest tightness. Cut-point severity ⩾2 indicated by dashed line. Pearson's correlation coefficient (*r*) top right hand side.

interval (CI): 0.23, 0.29] per-person-years. The incidence rate in MART was (0.21, 95% CI = 0.18, 0.25) and prn salbutamol (0.30, 95% CI: 0.26, 0.35) per-person-years. These were statistically different [incident rate ratio (IRR) = 1.42, $p = 0.003$]. Patients in quartile 4 had the highest exacerbation rate (0.29) but there was no linear relationship with increasing quartiles 1 (0.24), 2 (0.25) and 3 (0.25) and severe exacerbation frequency (Table 2).

Pauci-symptomatic patients. There were 32 severe exacerbations in asymptomatic patients contributing to an incidence rate of 0.19 (95% CI: 0.13, 0.27) per-person-years. The incidence rate in MART was (0.10, 95% CI: 0.05, 0.20) and prn salbutamol (0.28, 95% CI: 0.19, 0.42) per-person-years. These were statistically different (IRR = 2.82; $p = 0.011$). There was a greater distinction between MART and prn salbutamol in the lowest quartile of severe exacerbations (Table 2).

Discussion

This is the first report of prospectively recorded twice-daily symptom scores in patients with uncontrolled asthma over a period of 1 year.

From the current analyses, the vast majority of uncontrolled asthmatics reported few, if any, symptoms. This contrasts to prior retrospective studies that report a high symptom load.[15] A possible explanation for this disparity may be attributed to some element of recall bias in the retrospective analyses. When we examined individual symptoms, patients who were poly-symptomatic were predominantly females. This phenotype has been previously described,[11] and we and others have suggested that this may

be due an increased afferent neuronal airway sensitivity.[12,16,17]

Table 1. Patient characteristics based on symptom episode severity cut-point ⩾2.

Cough (*n* = *81*)	
Age (years)	53 (47, 60)
BMI (kg/m^2)	26.3 (23, 29.8)
Sex (F)	69%
Wheeze (*n* = 57)	
Age (years)	54 (49, 60)
BMI (kg/m^2)	27.3 (23, 31.3)
Sex (F)	74%
Breathless (*n* = 100)	
Age (years)	56 (49, 61)
BMI (kg/m^2)	26.9 (23.9, 31.5)
Sex (F)	67%
Chest tightness (*n* = 68)	
Age (years)	54.5 (47, 60.5)
BMI (kg/m^2)	28.4 (23.6, 60.5)
Sex (F)	79%

BMI, body mass index; F, female; *n*, number or patients; kg/m^2, kilogram/metres squared.

Surprisingly, wheezing was the least reported of symptoms, with cough and breathlessness being the predominant in this patient cohort. This suggests that the main driver of symptoms may be heightened airway sensation rather than bronchoconstriction.[18] In support of this, we found that patients who were highly symptomatic in one domain tended to also be symptomatic in the other three domains. It is widely recognised that cough and bronchoconstriction have different neurophysiological mechanisms. Thus, the presence of polysymptomatic patients would suggest a global increase in airway sensitivity rather than a specific mechanism for each symptom.

Whilst there was a relationship between symptoms and exacerbation rate, this was weak, with polysymptomatic patients being approximately one-fifth more susceptible to exacerbations than pauci-symptomatic patients. Within the symptomatic patients, there appeared to be a little relationship on the exacerbation rate to the number of symptom episodes. Thus, in uncontrolled asthma requiring inhaled corticosteroids (ICS) and long-acting β2 agonists (LABA), there seems to be a weak relationship between symptoms and increasing severe exacerbation rates. This observation calls into question the uncertainty associated with patient-related outcomes and the relevance of symptom diaries in the prediction of exacerbations in patients with uncontrolled asthma.

Table 2. Incidence of severe exacerbations by total symptom episode quartiles, and by treatment.

Symptomatic patients (*n* = *1403*)					
Quartile	**All**	**MART**	**prn Salbutamol**	**IRR**	***p*-value**
Q1	0.26	0.19	0.31	1.63	0.05
Q2	0.24	0.12	0.35	2.82	<0.001
Q3	0.25	0.19	0.29	1.50	0.09
Q4	0.29	0.32	0.25	0.79	0.28
Pauci-symptomatic patients (*n* = *298*)					
–	0.19	0.10	0.28	2.82	0.011

NB: No significant difference *between* Q1 and Q4 (Q1 = lowest, Q4 = highest) noted in the symptomatic patients. The pauci-symptomatic patient group was not subdivided into quartiles.
IRR, incident rate ratio (compares treatment groups *within* a quartile); MART, maintenance and reliever therapy; prn, *pro re nata* (as needed); Q, quartile.

We then went on to compare the effect of treatment on severe exacerbation rates. The effect of MART compared with prn salbutamol was shown to cause a highly significant attenuation in severe exacerbation rate. Indeed, it appeared that the reduction in rate of severe exacerbations was significantly greater in patients with fewer symptoms. In the more symptomatic (Q4), the relationship became insignificant. Thus, in contrast to current practice, where MART tends to be reserved for patients who are polysymptomatic, it should be offered to all patients at risk of exacerbations, irrespective of their symptom profile. This dissociation between improvement in symptoms and reduction in exacerbation rates with MART has previously been reported with another ICS/LABA combination: budesonide/formoterol.[19] More recently, in patients with mild asthma, exacerbation rates were found to be similar with prn budesonide-formoterol when compared with routine twice-daily budesonide, whereas symptom control was found to be superior in the regular ICS maintenance regime.[20] We suggest that regular anti-inflammatory therapy attenuates both symptoms and exacerbation rates, whereas the addition of formoterol has little effect on the symptom profile but reduces the exacerbation rate by up to one-third, particularly in those with fewer symptoms.

There are some limitations to our observations. The reported symptoms were collected subjectively and may represent over- or under-reporting dependent on the individual patient's perception of their asthma. Whilst objective assessments are available for cough, we are unable to objectively assess the other three domains to provide surety in the measurement of each metric. Thus, until improved and easy-to-conduct objective symptom assessments become available, subjective reporting remains our only strategy for assessing asthma symptoms. Uncontrolled asthma patients were recruited onto the study and randomised to beclometasone/formoterol twice daily plus prn salbutamol or MART. Hence, there is no reason to believe that there was any different in either adherence or inhalation technique between the two groups as they were randomly recruited, although we acknowledge that these patient parameters were not studied at the time.

Our analyses of twice-daily symptom scores in uncontrolled asthma patients over 1 year has revealed a surprising disconnect between symptoms and exacerbation rates. The therapeutic implications of the findings are that MART should be used irrespective of the patients' symptom profile, and there is a case for dropping the previous paradigm of two puffs twice a day.

Acknowledgements

We are grateful to Chiesi Farmaceutici SPA for unfettered access to the trial database. We acknowledge the help of Rino Constanza in facilitating this project.

Author contributions

JBM and AHM were involved in the concept, interpretation of the data, writing of the manuscript. ASR was involved in the statistical analyses and the writing of the manuscript.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and publication of this article: This work was funded *via* an educational research grant from Chiesi Farmaceutici SPA.

Conflict of interest statement

The author(s) declared following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: JBM has received honoraria for speaking and financial support to attend meetings/advisory boards from Wyeth, Chiesi, Pfizer, MSD, Boerhinger Ingelheim, Teva, GlaxoSmithKline, Napp, Almirall, AstraZeneca, Trudell Medical International and Novartis Pharmaceuticals UK. ASR has no declarations. AHM has received for speaking and financial support to attend meetings/advisory boards and grants from Boerhinger Ingelheim, Chiesi, Novartis Pharmaceuticals UK, Almirall, Astra Zeneca, GlaxoSmithKline, Reckitt Benckiser, Nexus Communications Group, Pfizer Ltd, Bayer plc, Infirst Healthcare, Afferent Pharmaceuticals Inc, Philips Home Healthcare Solutions, Nycomed, Aerocrine AB, Roche, Genentech, ICON and Patara Pharma.

Data sharing statement (ICJME)

The original study data collected was received from Chiesi Farmaceutici SPA and used for the analyses in this manuscript. We appreciate Chiesi Farmaceutici SPA for the receipt of the data and its unrestricted use for this analyses. This data has not been analysed in the original study or elsewhere. On request to Chiesi Farmaceutici SPA this data may be made available.

ORCID iD

Jaymin B. Morjaria https://orcid.org/0000-0003-1212-3190

Supplemental material

Supplemental material for this article is available online.

References

1. Global Initiative for Asthma. Global strategyfor mangament and prevention, https://ginasthma.org/wp-content/uploads/2018/04/wms-GINA-2018-report-V1.3-002.pdf (2018, accessed August 2018).
2. Papi A, Brightling C, Pedersen SE, *et al*. Asthma. *Lancet* 2018; 391: 783–800.
3. Dixon AE, Kaminsky DA, Holbrook JT, *et al*. Allergic rhinitis and sinusitis in asthma: differential effects on symptoms and pulmonary function. *Chest* 2006; 130: 429–435.
4. Chung KF, Wenzel SE, Brozek JL, *et al*. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43: 343–373.
5. van Maanen A, Wijga AH, Gehring U, *et al*. Sleep in children with asthma: results of the PIAMA study. *Eur Respir J* 2013; 41: 832–837.
6. Parsons JP and Mastronarde JG. Gastroesophageal reflux disease and asthma. *Curr Opin Pulm Med* 2010; 16: 60–63.
7. ten Brinke A, Ouwerkerk ME, Bel EH, *et al*. Similar psychological characteristics in mild and severe asthma. *J Psychosom Res* 2001; 50: 7–10.
8. Simpson JL, Scott R, Boyle MJ, *et al*. Inflammatory subtypes in asthma: assessment and identification using induced sputum. *Respirology* 2006; 11: 54–61.
9. Woodruff PG, Modrek B, Choy DF, *et al*. T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med* 2009; 180: 388–395.
10. Kuo CS, Pavlidis S, Loza M, *et al*. A transcriptome-driven analysis of epithelial brushings and bronchial biopsies to define asthma phenotypes in U-BIOPRED. *Am J Respir Crit Care Med* 2017; 195: 443–455.
11. Haldar P, Pavord ID, Shaw DE, *et al*. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008; 178: 218–224.
12. Morjaria JB, Rigby AS and Morice AH. Asthma phenotypes: do cough and wheeze predict exacerbations in persistent asthma? *Eur Respir J* 2017; 50. pii: 1701366.
13. Agusti A, Bafadhel M, Beasley R, *et al*. Precision medicine in airway diseases: moving to clinical practice. *Eur Respir J* 2017; 50. pii: 1701655.
14. Papi A, Corradi M, Pigeon-Francisco C, *et al*. Beclometasone-formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial. *Lancet Respir Med* 2013; 1: 23–31.
15. Partridge MR, van der Molen T, Myrseth SE, *et al*. Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study. *BMC Pulm Med* 2006; 6: 13.
16. Morice AH, Jakes AD, Faruqi S, *et al*. A worldwide survey of chronic cough: a manifestation of enhanced somatosensory response. *Eur Respir J* 2014; 44: 1149–1155.
17. Millqvist E. The airway sensory hyperreactivity syndrome. *Pulm Pharmacol Ther* 2011; 24: 263–266.
18. Driessen AK, McGovern AE, Narula M, *et al*. Central mechanisms of airway sensation and cough hypersensitivity. *Pulm Pharmacol Ther* 2017; 47: 9–15.
19. Bateman ED, Reddel HK, Eriksson G, *et al*. Overall asthma control: the relationship between current control and future risk. *J Allergy Clin Immunol* 2010; 125: 600–608.e6.
20. O'Byrne PM, FitzGerald JM, Bateman ED, *et al*. Inhaled combined budesonide-formoterol as needed in mild asthma. *N Engl J Med* 2018; 378: 1865–1876.