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ABSTRACT

Objective: In order to understand the role of regular controller inhaled corticosteroids (ICS) versus as-needed ICS-formoterol in managing mild asthma, we performed a modified Delphi procedure.

Methods: Opinions from 16 respiratory experts to three surveys and during a virtual scientific workshop helped to develop final consensus statements (pre-defined as 70% agreement).

Results: Thirteen participants completed all rounds (response rate 81%). At the end of the procedure, there was final consensus on: regular daily ICS being the recommended treatment approach in mild persistent asthma, with better symptom control and robust long-term clinical data compared with as-needed ICS-formoterol (85%); to avoid noncompliance, frequently seen in mild asthma patients, regular ICS dosing should be accompanied by ongoing education on treatment adherence (100%); treatment aims should be targeting asthma control (92%) and reduction of exacerbation risk (85%). No consensus was reached on whether GINA or national guidelines most influence prescribing decisions.

Conclusions: It is important to encourage patients to be adherent and to target both asthma control and exacerbation risk reduction. There is robust clinical evidence to support proactive regular dosing with ICS controller therapy plus as-needed short-acting beta-agonists for the management of patients with mild asthma.

Abbreviations. ACQ-5: Asthma Control Questionnaire-5; BHBIA: British Healthcare Business Intelligence Association; CME: continuing medical education; EphMRA: European Pharmaceutical Market Research Association; FeNO: fractional exhaled nitric oxide; GDPR: General Data Protection Regulation; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroid; SABA: short-acting beta-agonist

Introduction

Asthma is a heterogenous, chronic, respiratory disease characterized by airway inflammation, a history of respiratory symptoms and variable airway obstruction (1). Although the majority of patients with asthma (50–75%) are reported to have mild asthma (2,3), there have been multiple definitions of mild asthma in the past based either on symptoms, airflow limitation and activity limitations or more recently on the intensity of treatment required to control symptoms and prevent future risks (4,5). The definition of mild asthma is still debated and in need of further clarification (1,6). It is well recognized that airway inflammation is present in mild asthma and patients with mild asthma often have suboptimal asthma control, putting them at risk of disease progression, severe exacerbations and

an impaired quality of life (2–5,7–9). A recent large US database study reported that 19.8% of patients with mild asthma (defined as Global Initiative for Asthma (GINA) treatment step 2) had uncontrolled asthma (10).

Inhaled corticosteroids (ICS) are the cornerstone of treatment across all severities of asthma (1,11,12), and early intervention with regular ICS treatment shows benefits in term of achieving asthma control, and in reducing the risk of asthma-related exacerbations, hospitalizations and death (1,13,14). However, adherence with asthma medications in the community is poor (1), and patients with mild asthma are particularly at risk of poor adherence (15). Another challenge in treating patients with mild asthma is that patients frequently do not report their symptoms (16), or have poor perception of their airways obstruction, which may result in under treatment with appropriate ICS or ICS/long-acting beta-agonist regular controller medication and an increased risk of exacerbation (17).

The GINA report recommends two treatment tracks for mild asthma, low dose as-needed ICS-formoterol (preferred option) or regular low dose ICS plus as-needed short-acting beta-agonist (SABA) (1). The 1-year, randomized, double-blind, double-dummy, studies in adults evaluating the as-needed ICS-formoterol treatment strategy demonstrated that treatment with as-needed ICS-formoterol resulted in similar annual severe exacerbation rates but worse asthma symptom control (between treatment difference in mean change from baseline: Asthma Control Questionnaire-5 (ACQ-5): 0.11–0.15) and lower change from baseline in pre-bronchodilator forced expiratory volume in 1 s (FEV_1) (between treatment difference: 33–54 ml) compared with regular maintenance daily ICS and as-needed SABA (18–20). Subsequently, in two 1-year, randomized, open label, controlled trials, one showed better symptom control and one showed similar symptom control with regular maintenance treatment compared with as-needed ICS/formoterol, whilst both showed less severe exacerbations in the ICS-formoterol group as compared to daily ICS and as-needed SABA (20–22). However, around the world, there is not full agreement among several recommendations for the management of mild asthma with some recommending regular daily low dose ICS and as-needed SABA (11,23), and others recommending as-needed ICS-formoterol as an alternative to regular ICS (24–26).

In view of these recommendations, we undertook a modified Delphi procedure, incorporating three rounds of surveys and a scientific workshop, with the aims of understanding asthma specialists' goals in managing and treating mild asthma, focusing on the role of regular controller ICS in managing mild asthma as well as in the use of GINA and other national guidelines.

Methods

Study design

This study used a modified Delphi technique to develop consensus-based statements on factors determining the management of patients with mild asthma. The Delphi procedure is a facilitated group technique that uses structured questionnaires, usually delivered via mail or email, to reach a consensus on a specific topic among a panel of selected experts (27–29). The technique uses anonymity, controlled feedback and group responses to reach consensus. In this study, in addition to the structured, anonymous, Delphi questionnaires, an on-line, virtual scientific workshop was conducted which involved open discussion between the participants and hence we employed a 'modified' Delphi method.

The Delphi survey was run by an independent specialist market research team at Ashfield MedComms, part of Ashfield Health (Macclesfield, United Kingdom). Following a literature search, the research team prepared the survey questionnaire, hosted the online surveys using Decipher software, and analyzed data generated in each survey. The research was designed in compliance with UK General Data Protection Regulation (GDPR) and with the British Healthcare Business Intelligence Association's (BHBIA) Legal & Ethical Guidelines, along with the European Pharmaceutical Market Research Association's (EphMRA). No formal ethical approval was required as this non-interventional physician survey fell outside the remit of the Research Government Framework. All participants provided their informed consent for each survey and any information provided was kept confidential and anonymous.

Participants

Twenty respiratory experts were invited to participate in all rounds of the process. Respiratory physicians with expertise and experience in managing patients with asthma were invited to participate, representing 10 countries (Argentina, Indonesia, Japan, Mexico, Malaysia, Philippines, Spain, Thailand, Turkey, and Vietnam). Participants were selected due to their knowledge of asthma and having an interest in improving patient outcomes, for having experience as an investigator in asthma studies or being a member of international and/or national guideline committees, and, in some cases, due to their own country having national asthma guidelines in place.

The industry sponsors organized and facilitated the scientific workshop but did not complete any of the Delphi surveys.

Stages of the Delphi procedure

The Delphi procedure comprised three stages: (1) development of research questions; (2) Delphi surveys and scientific workshop; and (3) development of final post-survey consensus statements (Figure 1).

Survey questionnaire development

A review of the literature on management of mild asthma in adults, including treatment and management guidelines was used to develop the first survey questionnaire. Subsequent questionnaires were developed based on participant group responses.

Delphi surveys and scientific workshop

Participants were emailed the first Delphi survey which was completed prior to the scientific workshop. The survey consisted of 11 questions (7 close-ended questions and 4 open-ended questions). The objectives of this survey were to: (a) understand prescribers' preferences for the treatment and management of patients with mild asthma; (b) explore the advantages and disadvantages of prescribing daily ICS treatment vs. as-needed ICS-formoterol treatment to patients with mild asthma; and (c) to understand how guidelines and other factors impact the prescribing choices of healthcare professionals.

Participants in the round 1 Delphi survey were invited to participate in an on-line, virtual scientific workshop to discuss the scientific and clinical data for regular ICS dosing versus as-needed ICS/

Stage 1: Development of research questions

- Review of literature
- Develop research questions for first survey

⬇

Stage 2: Modified Delphi procedure

Round 1: Pre-workshop Delphi survey 1
- Expert panel selection (n=16)
- 11 open- and closed-ended questions grouped into two themes ('Treatment choices' and 'Asthma guidelines')

Round 2: Scientific workshop (n=16)
- Virtual scientific workshop to discuss management approach in mild asthma

Round 3: Post-workshop Delphi survey 2 (n=15)
- Modified 10 closed-ended questions (plus open comment on 1 question)
- Analysis to develop consensus statements

Round 4: Delphi survey 3 (n=13)
- Six 5-point Likert questions (plus space for open comment)
- Analysis to develop final consensus statements

⬇

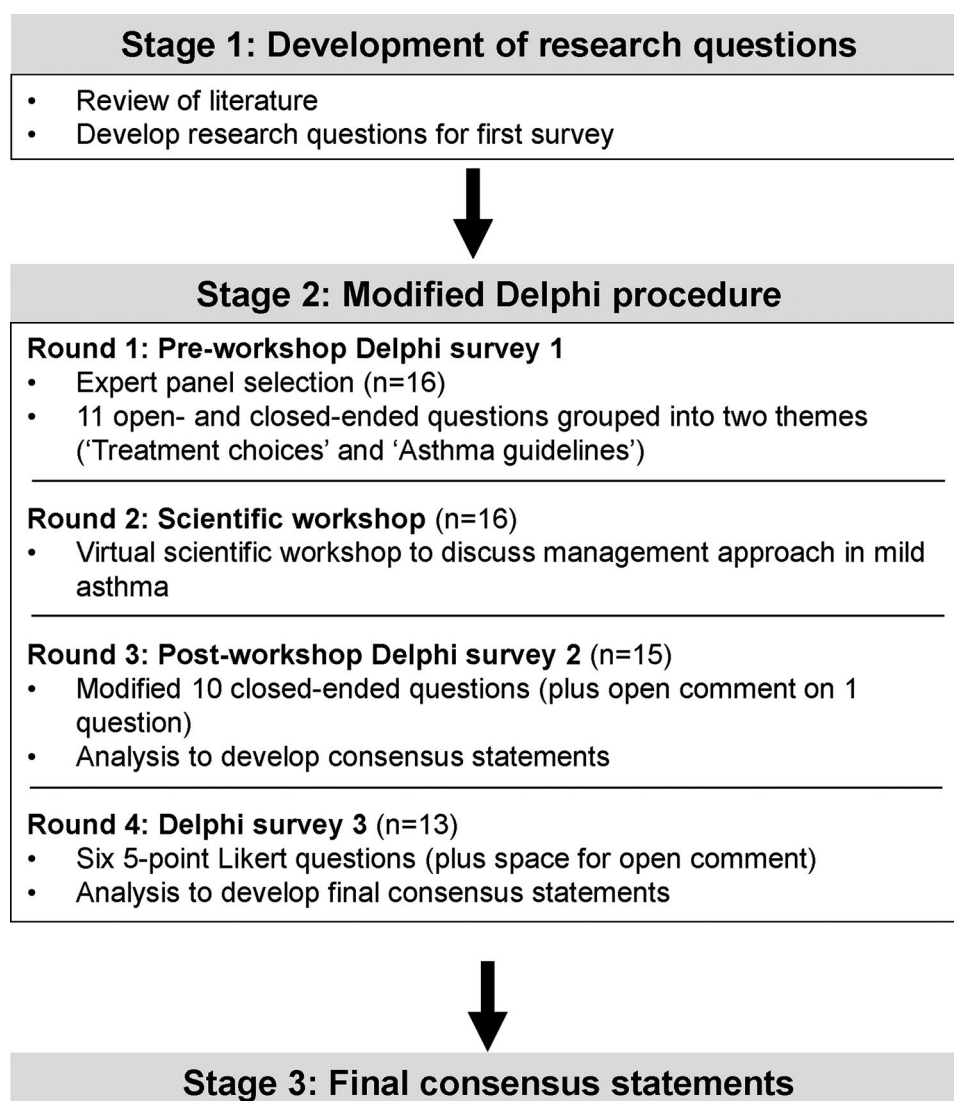## Stage 3: Final consensus statements

Figure 1. Research procedure.

formoterol as well as GINA and national guidelines with respect to management of mild asthma.

Following the scientific workshop, participants were emailed the second Delphi survey which consisted of 10 close-ended questions with space for open comment following 1 question. The objective of the post-workshop survey was to assess level of consensus on key topics following survey 1 results and workshop discussions, specifically, (a) the clinical evidence on the different treatment regimens for controlling mild asthma and differences in outcomes; (b) the extent to which treatment adherence and patient perception of symptoms impact treatment choices and asthma control; and (c) to understand views on using GINA treatment recommendations or local country guidelines for the holistic management of patients with mild asthma

In the last step of the Delphi procedure, participants were emailed final follow-up questions consisting of six 5-point Likert-type questions (Strongly disagree, somewhat disagree, neither agree nor disagree, somewhat agree, and strongly agree). Space for open comment followed each question. The objectives were to obtain a consensus amongst the participants on their understanding and beliefs on, (a) the reasons for recommending regular daily dosing for patients with mild asthma and (b) targeting asthma control or severe exacerbations reduction primarily for asthma management

Data analysis

All data were analyzed descriptively. The results of the first survey and the scientific workshop were subjected to a content analysis to identify and classify common elements in the overall opinion of the panel, and for development of survey 2. A similar approach was used to develop survey 3, the final set of questions. Full feedback on the results of each survey was given to the panelists for consideration and discussion before the next survey was sent out. The phrasing of questions and the rating of responses using a Likert scale were decided by market research experts in line with best practice and other Delphi surveys (27,28,30). For data quality checks, all responses were checked by a data analyst at Ashfield Health to ensure consistency and quality of response.

For the results of surveys 2 and 3, a consensus was pre-defined as achieving 70% agreement. This proportion has been considered appropriate in previous studies that used the Delphi procedure (31–33).

Results

Participants

Twenty respiratory experts were invited to participate and 16 accepted, completed the first Delphi survey and attended the scientific workshop (response rate of 80%) (Figure 1). Of the 16 who accepted the initial invitation, 15 completed the post-workshop Delphi survey 2 (response rate 94%) and 13 completed Delphi survey 3 (response rate 81%). The participant characteristics are summarized in Table S1. Among participants, there was an equal distribution of males and females, their mean age was 56.8 years and they resided across 10 countries. All participants had medical degrees and had been working in the respiratory field for ≥ 15 years.

Delphi survey 1 results

Participants defined mild asthma in a range of different ways, most frequently referring to the GINA definition and based on infrequent symptoms, no impact on daily life, and exacerbations easily controlled by Step 1 or 2 treatment. Participants indicated that 45% of patients with mild asthma currently receive daily ICS (alone or plus another controller) plus as-needed SABA and 25% receive as-needed ICS-formoterol (Table 1). Participants' *preferred* treatment regimen in mild asthma, was indicated as daily ICS (alone or plus another controller) plus as-needed SABA for 44% and as-needed ICS-formoterol for 44% (Table 1).

The most important factors driving treatment choices for mild asthma were efficacy (Figure 2). When considering the advantages and disadvantages of daily ICS versus as-needed ICS-formoterol, the main advantage of daily ICS was efficacy (69% of participants) and the main disadvantage was adherence (56%); whereas the main advantages of as-needed ICS-formoterol were reported as efficacy (31%), convenience (25%) and adherence (25%), and the main disadvantages were cost (44%) and, also, level of efficacy (31%). When asked if there are situations/particular patients for whom as needed ICS-formoterol would be recommended over daily treatment, 56% agreed, while 44% voted against.

Eighty-eight percent of participants strongly or somewhat agreed that there are clear guidelines on the recommended approach to achieving good asthma control in their own country. GINA was most commonly cited as the global document used to guide prescribing decisions for asthma management and most participants also listed their own local/national guidelines as influencing their prescribing decisions.

Table 1. Participants' current and preferred treatments for patients with mild asthma (Delphi survey 1).

Q: Thinking about all your patients diagnosed with mild asthma, please indicate what percentage are currently prescribed each of the following treatments.
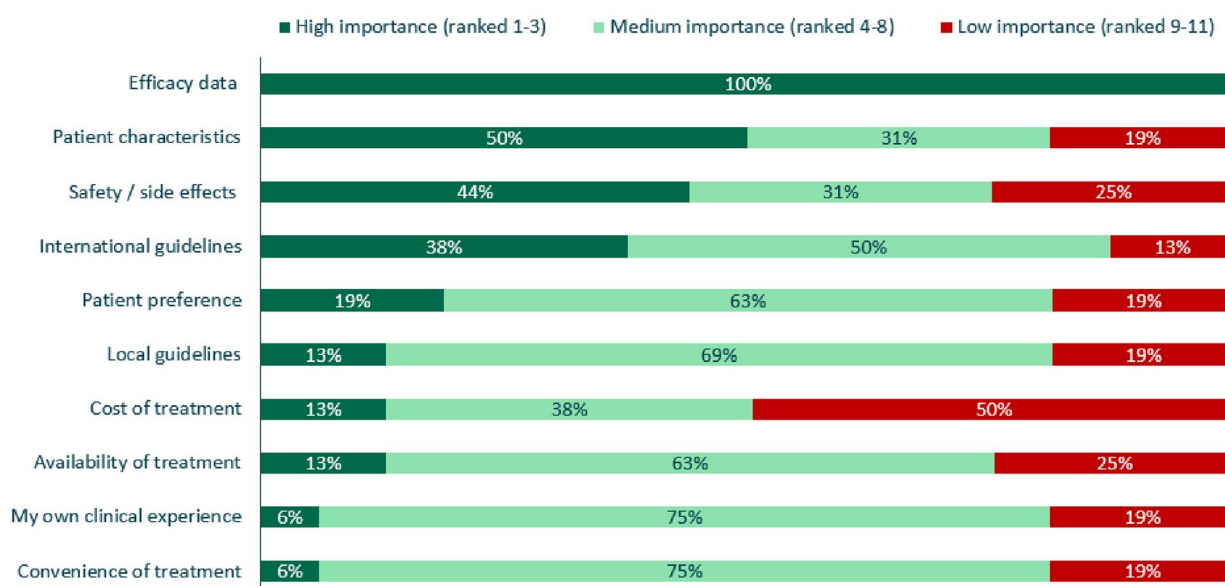
Treatment	Patients (%)
ICS + as-needed SABA	30
As-needed ICS-formoterol	25
Daily ICS + LABA + as-needed SABA	13
As-needed SABA	11
Daily LTRA + as-needed SABA	3
Daily ICS + LTRA + as-needed SABA	2
As-needed ICS and SABA	2
Other*	13

Q: What is your preferred treatment regimen for patients diagnosed with mild asthma (i.e. patients whose asthma can be well controlled with Step 1 or Step 2 treatment, as defined by GINA)?

Treatment	Patients physicians (%)
ICS + as-needed SABA	38
As-needed ICS-formoterol	44
Daily ICS + LABA + as-needed SABA	6
As-needed SABA	–
Daily LTRA + as-needed SABA	–
Daily ICS + LTRA + as-needed SABA	–
As-needed ICS and SABA	–
Other*	13

*Listed as either daily ICS + as-needed ICS-formoterol or as-needed ICS + SABA.
ICS: Inhaled corticosteroid; LABA: long-acting beta-agonist; LTRA: leukotriene receptor antagonist; SABA: short-acting beta-agonist.

Q: Please rank each of the following factors from most important to least important in terms of the extent to which they impact your choice of treatment for patients with mild asthma: Efficacy data; Safety / side effects; Patient characteristics; Patient preference; My own clinical experience; International guidelines; Local guidelines; Convenience of treatment; Cost of treatment; Availability of treatment; Other, please specify

Figure 2. Most important factors driving treatment choices for mild asthma.

Scientific workshop summary

The main findings of the scientific workshop are summarized in Table 2 with examples of individual feedback presented in Table S2. There was general agreement amongst the panel that regular maintenance dosing with ICS is the best asthma management strategy in mild asthma and that the key studies evaluating as-needed ICS-formoterol showed that regular ICS was superior or equivalent to as-needed

ICS-formoterol for asthma control parameters, but not superior for reducing the risk of severe exacerbations. Adherence with regular ICS dosing was raised as an issue and it was agreed by most that it is yet unknown whether a variable dosing regimen would ensure real life adherence in the community.

Most participants agreed that GINA is a good document about asthma, based on the assessment of published literature, although it does not use GRADE methodology (1), and would benefit from being more balanced in this respect. It was also acknowledged that GINA is an outlier in terms of recommending as-needed ICS-formoterol as the preferred treatment option in mild asthma and national treatment guidelines have taken a consensus- and evidence-based approach, with some not recommending as-needed ICS-formoterol at all for mild asthma (11,12,23), some recommending as-needed ICS-formoterol as an alternative to regular ICS in mild persistent asthma (24–26), and some recommending either regular ICS plus as-needed SABA or as-needed ICS-formoterol as a treatment option for mild asthma (34).

Delphi survey 2 results

Following the scientific workshop and completion of the second survey, a number of consensus statements were reached. There was a consensus among participants (80% agreed somewhat or strongly) that they would usually or always recommend daily ICS for patients with mild asthma (Figure 3). In addition,

87% agreed that daily ICS improves lung function and reduces symptom frequency, 73% agreed that the chronic inflammation in mild asthma can only be controlled by regular daily ICS, and 73% agreed that regular ICS is more likely to prevent exacerbations compared with as-needed treatment (Figure 4). Eighty seven percent of physicians reported that the proportion of patients with mild asthma who should be prescribed as-needed ICS-formoterol rather than daily ICS ranges between 0% and 40% (Figure S1), with the main reason given as 'lack of adherence to daily ICS'.

No consensus was reached on which ICS treatment regimen is believed to be most successful for controlling mild asthma (60% favored regular ICS over as-needed ICS-formoterol and 33% regarded both options equally effective), or on the statement, 'as-needed treatment is unlikely to be successful as it is dependent on patients' own accurate perception of symptoms' (53% agreed).
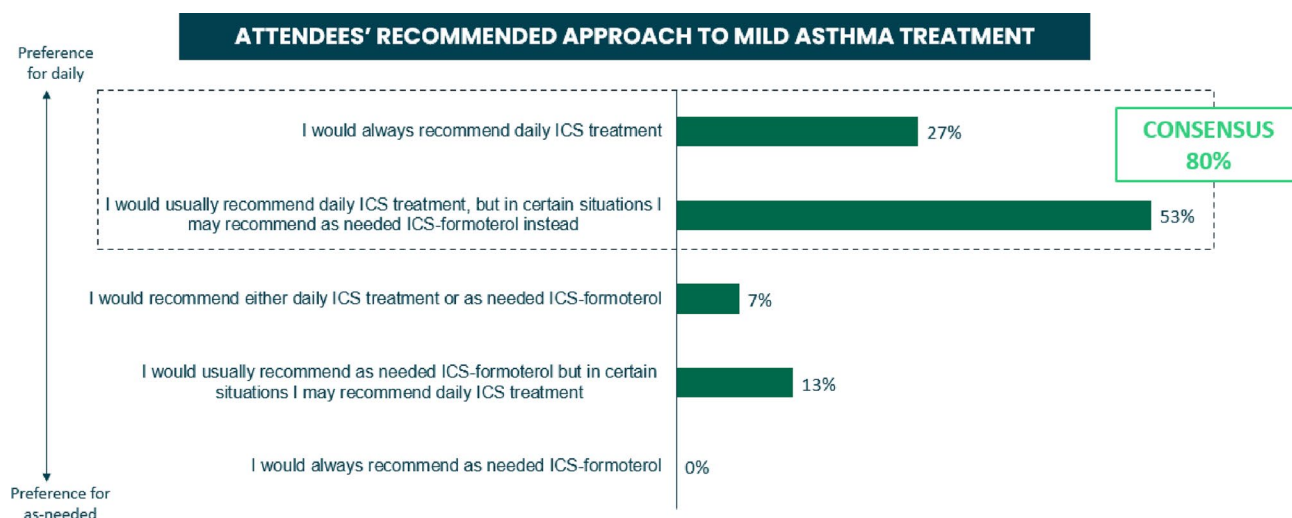
Physicians somewhat or strongly agreed that low adherence is seen across all treatment regimens in asthma management (87%), that patients are less likely to be adherent to treatment if they are feeling well (100%) or to a treatment they need to use every day versus a treatment used less frequently (73%), and that there is wide variation in patients' abilities to accurately assess/perceive their own symptoms (73%).

A consensus was reached on the following statements about GINA: GINA should be treated as an opinion statement rather than a guideline (87%),
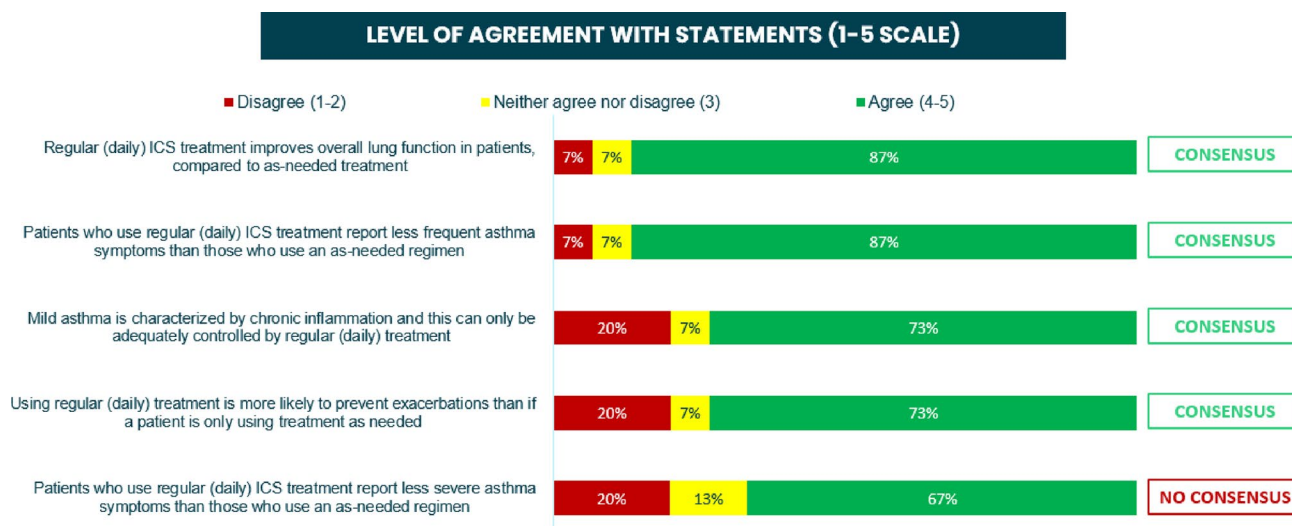
Table 2. Summary of scientific workshop discussions.

Theme discussed	Summary of discussion
Regular dosing versus variable dosing in asthma management: the clinical evidence	• General acceptance that regular maintenance dosing is the best asthma management strategy in mild asthma due to better outcomes in asthma control and inflammation suppression. • Results of RCTs unequivocally stated that regular ICS was superior or equivalent to as-needed ICS-formoterol for asthma control parameters • General agreement that the clinical studies supporting the variable dosing strategy were not conducted in GINA step 1 patients, questioning their scientific validity in relation to patients with mild asthma • The issue of real-world compliance with regular dosing, and use of a variable dosing strategy as an alternative approach, was highlighted by several participants. The question remains whether a variable dosing regimen would ensure adherence. • The importance of considering both asthma control and severe exacerbation risk was emphasized
GINA update for mild asthma and comparison with GEMA 5.0 guidelines	• Most agreed that GINA is a good document about asthma but is an opinion statement, not a guideline; national guidelines are more relevant in individual countries • General agreement that GINA, based on literature review and not GRADE methodology, would benefit from being more balanced in its evidence evaluation to reach consensus recommendations • GEMA 5.0 developed by a multidisciplinary, representative team; uses Delphi panel evaluations and is accredited by AGREE II • In GEMA, three alternatives recommended for Step 1 treatment: SABA only, as-needed ICS-formoterol or as-needed SABA + ICS PRN. Step 2 (persistent mild asthma) recommends regular daily low dose ICS plus as-needed SABA
Discussion on approach by other guidelines	• Other treatment guidelines taken a consensus- and evidence-based approach; some do not recommend as-needed ICS-formoterol at all for mild asthma (Japanese, BTS, NEAPP guidelines) and some recommend as-needed ICS-formoterol as an alternative to regular ICS in mild asthma (Thai and Canadian guidelines) • Guidelines provide consensus- and evidence-based guidance at a group level; individual patient requirements should also be considered

BTS: British Thoracic Society; GEMA: Spanish Guideline on the Management of Asthma; GINA: Global Initiative for Asthma; ICS: Inhaled corticosteroid; RCT: Randomized controlled trial; SABA: short-acting beta-agonist.

ATTENDEES' RECOMMENDED APPROACH TO MILD ASTHMA TREATMENT

Preference for daily

I would always recommend daily ICS treatment — 27%

I would usually recommend daily ICS treatment, but in certain situations I may recommend as needed ICS-formoterol instead — 53%

CONSENSUS 80%

I would recommend either daily ICS treatment or as needed ICS-formoterol — 7%

I would usually recommend as needed ICS-formoterol but in certain situations I may recommend daily ICS treatment — 13%

I would always recommend as needed ICS-formoterol — 0%

Preference for as-needed

Q: During the scientific workshop discussion, it was generally agreed that the results of SYGMA 1 & 2 and Novel START studies showed that regular ICS was superior to as-needed ICS-formoterol for control of mild asthma; however, there was some debate over whether this is always the most appropriate treatment option. With this in mind, please indicate which of the following statements you agree with most, in terms of your approach to mild asthma treatment. (Mild asthma = patients whose asthma can be well controlled with Step 1 or Step 2 treatment, as defined by GINA)

Figure 3. Approach to mild asthma treatment. ICS: inhaled corticosteroid.

LEVEL OF AGREEMENT WITH STATEMENTS (1–5 SCALE)

Disagree (1-2) · Neither agree nor disagree (3) · Agree (4-5)

Regular (daily) ICS treatment improves overall lung function in patients, compared to as-needed treatment — 7% / 7% / 87% — CONSENSUS

Patients who use regular (daily) ICS treatment report less frequent asthma symptoms than those who use an as-needed regimen — 7% / 7% / 87% — CONSENSUS

Mild asthma is characterized by chronic inflammation and this can only be adequately controlled by regular (daily) treatment — 20% / 7% / 73% — CONSENSUS

Using regular (daily) treatment is more likely to prevent exacerbations than if a patient is only using treatment as needed — 20% / 7% / 73% — CONSENSUS

Patients who use regular (daily) ICS treatment report less severe asthma symptoms than those who use an as-needed regimen — 20% / 13% / 67% — NO CONSENSUS

Q: Please indicate the extent to which you agree with the following statements in relation to the benefits of different asthma control regimens for patients with mild asthma (Strongly disagree; Somewhat disagree; Neither agree nor disagree; Somewhat agree; Strongly agree)

Figure 4. Benefits of asthma control treatment regimens. ICS: inhaled corticosteroid.

GINA is a useful document for physicians to refer to for the management of patients with asthma (80%) and there is a need for GINA to include more appropriate clinical evidence in its strategy (73%).

Delphi survey 3 results

A consensus was reached on all six of the final Likert-style questions with physicians agreeing that regular daily dosing with ICS should be the recommended treatment approach in mild persistent asthma, supported by better outcomes and robust long-term clinical data compared with as-needed ICS-formoterol (85%); that a regular daily dosing treatment regimen should be accompanied by ongoing education in the importance of adherence to treatment (100%); that exacerbation reduction is achieved with treatment targeting asthma control (92%) and that asthma control is achieved with treatment targeting moderate to severe exacerbation risk (85%) (Figure 5).

Discussion

The aim of this modified Delphi procedure was to develop consensus-based statements on factors determining the management of patients with mild asthma. After the four-round process, a consensus was reached that, in terms of long-term clinical data and clinical outcomes, regular maintenance dosing with ICS should be the preferred treatment option in mild persistent asthma to achieve symptom control and reduce exacerbations, supported by patient education to encourage treatment adherence. It was also agreed that effective treatment results from targeting both asthma exacerbation reduction and asthma control. There was agreement at the scientific workshop that GINA would benefit from being more methodological in its evaluation of the evidence to reach a consensus on recommendations. Although traditionally GINA recommendations about asthma have been widely accepted, the last proposal regarding step 1 and 2 have not been incorporated by many medicine agencies such as the European Medicines Agency. No consensus was reached on whether GINA or country-specific guidelines are more rigorous or objective, or which have the most influence in driving prescribing habits.

Airway inflammation and airway remodeling are present even in mild asthma (2,35,36), and treatment with ICS leads to decreases in airway inflammation and the airway wall structural changes observed in mild asthma, supporting a treatment strategy for regular daily ICS (35,37). Support for regular treatment also comes from long-term clinical studies that show the benefit of early intervention with ICS on asthma symptoms, in reducing the risk of exacerbations, and on functional changes associated with asthma, (lung function and airway responsiveness) (13,14,38,39). Inflammation and bronchial responsiveness can persist even in the absence of asthma symptoms (40,41), both of which are related to lung function decline (42,43). Jayaram et al. showed in patients with very mild or mild asthma that a clinical control strategy to guide ICS maintenance treatment (based on symptoms and spirometry) was similar to a strategy guided by inflammation (sputum cell counts) in reducing the number of exacerbations (44). A risk of symptom-driven, as-needed therapy is that inflammation and remodeling may persist in periods when symptoms are not apparent. The long-term impact of this strategy on airway inflammation, hyper-responsiveness, remodeling and asthma mortality compared with regular ICS usage is as yet unknown, and further research would be warranted (45). Regular daily ICS therapy with as-needed SABA resulted in better asthma symptom control and similar risk of severe exacerbations compared with as-needed ICS-formoterol, in two double-blind, randomized, controlled trials (18,19). In an open-label, randomized,
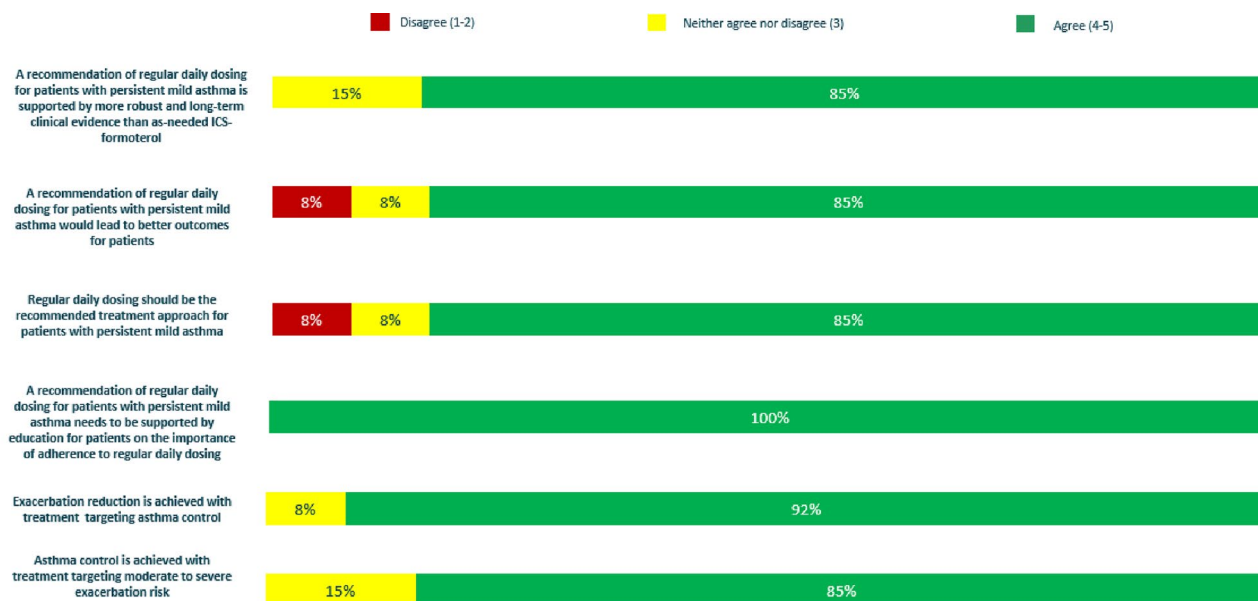
Q: Please indicate to what extent you agree with the following statements (Strongly disagree; Somewhat disagree; Neither agree nor disagree; Somewhat agree; Strongly agree)

Figure 5. Final consensus statements. ICS: inhaled corticosteroid.

controlled trial, regular, daily ICS therapy with as-needed SABA was associated with better suppression of inflammation (fractional exhaled nitric oxide (FeNO), similar symptom control and lung function, but less reduction in the moderate/severe exacerbation rate, compared with as-needed ICS-formoterol (22). In another study comparing regular maintenance dosing with budesonide with intermittent, symptom-guided short courses of corticosteroids (inhaled budesonide or oral prednisolone), Boushey et al. reported similar rates of exacerbations for the two groups but significantly greater improvements in markers of inflammation (bronchial reactivity, the percentage of eosinophils in sputum, and FeNO) following regular daily maintenance treatment (46).

The uncertainty surrounding the long-term impacts of as-needed ICS-formoterol treatment in mild asthma is reflected in the differing treatment recommendations by national guidelines compared with GINA (1,11,12,23–26,34,47), some of which do not recommend or mention as-needed ICS-formoterol at all for the treatment of mild asthma. This indicates a need for clarity in defining mild asthma and in determining the most appropriate treatment for these patients, and may require further development of national guidelines and adaptations to local healthcare systems. The collection of real-life data in different countries will contribute to these discussions. It seems clear that achieving asthma symptom control is not the key objective of as-needed ICS-formoterol therapy, it being more focused on the reduction of severe exacerbations, and there appears to be some acceptance that this treatment strategy would be expected to result in worse symptom control versus regular daily maintenance treatment (21,22). Individual patient characteristics, risk factors, comorbidities and pheno- and endotypes are important factors when considering the effects of a particular treatment on a patient's symptoms and exacerbation risk (1), as well as practical issues such as inhaler technique, adherence and affordability (1,48). Recently, the benefits of type 2 inflammation assessment (FeNO and blood eosinophils) in addition to symptoms and spirometry were reported as useful to determine the effective use of ICS in asthma (49), but these tools are not routinely available in general practice. Certainly, a blanket strategy to treat all mild asthma patients with as-needed ICS-formoterol is not supported by the current available evidence (20).

One of the main problems in maintaining a treatment regimen with regular ICS is that treatment adherence is poor, with reported adherence rates with controller therapies ranging between 22% and 78%

(15,50–52), and having mild asthma is particularly associated with poor adherence (15), putting patients at risk of poorer outcomes, including death due to underuse of ICS (1,4,9). The anti-inflammatory protective effect of ICS treatment builds up over time; this benefit has been shown when ICS are taken regularly and consistently over the long-term (53). Because of the central role ICS play in achieving effective asthma control, addressing poor adherence continues to be of paramount importance. This involves an understanding of a patient's beliefs and perceptions about their asthma and the reasons for their poor adherence – which could be related to technical, behavioral or educational reasons – so that adherence interventions can be implemented and tailored to individual patients (1,15,51,54). Moreover, in some situations primary care physicians are still reluctant to prescribe ICS for prolonged periods, making 'continuing medical education' (CME) an important tool as well. For patients with adherence issues, regular asthma reviews of inhaler technique and adherence (2), and using a personalized action plan (agreed between the patient and healthcare professional) can empower patients to make short-term changes to their medication in response to changes in their symptoms and when to seek professional help (55). Real life adherence to an as-needed dosing strategy in the community is not yet known. A major concern is that as-needed treatment relies on patients perceiving their symptoms and patients who are under-perceivers may delay starting appropriate treatment, increasing the risk of an exacerbation (17). Interestingly, in a one-year open-label study in a real-world setting, regular ICS therapy resulted in better symptom control measured by ACQ-5 and a numerically lower annualized exacerbation rate, despite a low adherence of 56% in this group, compared with as-needed ICS-formoterol (annualized exacerbation rates of 0.175 versus 0.195, respectively) (21).

The Delphi procedure has been well-described as a useful technique for obtaining a group consensus on a specific topic, particularly in circumstances where there is contradictory or insufficient information (27–29). The method is based on the assumption that the opinions of a group are more valid than that of an individual and the use of an independent facilitator and anonymous controlled feedback ensures a robustness in the process. Previous studies in asthma and COPD suggest that a panel with at least 12 members is sufficient to reach a meaningful consensus (56–58). The Delphi procedure used in the current study has some strengths and limitations. A strength of this study is that response rates were relatively high among

the selected panel with 81% of participants completing all four rounds, indicating a good level of interest and engagement in the process. Another strength of this study is that physicians were invited to participate from a broad range of countries and backgrounds (public and private health care), representing different viewpoints. Industry sponsors organized and facilitated the scientific workshop but did contribute to the consensus statements derived from the Delphi surveys. A limitation of this study is that only respiratory specialists were included and their views do not reflect physicians in primary care where most patients with mild asthma are treated. Another limitation is that there is no evidence of reliability with the Delphi methods i.e. that other expert panels would reach the same conclusions (29), and so these results should be interpreted accordingly. Whilst all participants were experts in asthma, their views were not homogenous, suggesting the panel represented a range of views.

Conclusions

The objective of this study was to understand the role of proactive regular controller ICS in the management of mild asthma. The participants in this Delphi study reached the following consensus recommendations: They agreed that regular maintenance dosing with ICS should be the preferred initial treatment option in mild persistent asthma, supported by patient education to encourage treatment adherence. It was also agreed that effective treatment should target both asthma severe exacerbation reduction and asthma control. As no consensus was reached on whether GINA or country-specific guidelines are more rigorous or objective, or which have the most influence in driving prescribing habits, this highlights a need for the development of national guidelines in each country or region which consider local healthcare systems, with a specific focus on mild asthma.

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Author contributions

Declaration of interest

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Data sharing statement

Information on GlaxoSmithKline R&D's data sharing commitments and requesting access can be found at: https://www.clinicalstudydatarequest.com.

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