The Global Initiative for Asthma guidelines (2019): Change in the recommendation for the management of mild asthma based on the SYGMA-2 trial – A critical appraisal

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ABSTRACT

The Global Initiative for Asthma (GINA) recently released their updated Global Strategy for Asthma Management and Prevention Guide (2019). The pocket guide for practicing clinicians states that "the 2019 GINA strategy report represents the most important change in asthma management in 30 years." An important recommendation is the change in treatment strategy for the management of mild asthma where the guideline recommends that" all adults and adolescents with asthma should receive either symptom driven (in mild asthma) or daily low dose inhaled corticosteroid (ICS) containing controller treatment to reduce the risk of serious exacerbations." Our study critically appraises the SYGMA-2 trial, a key trial that largely formed the basis of this recommendation and discusses the potential consequences of using only long-acting beta-2-agonist + ICS as needed as against regular, daily low-dose ICS with as-needed short-acting beta-2-agonist. Our critique covers airway inflammation, disease heterogeneity, understanding the noninferiority margin and its consequences, the Hawthorne effect, and conflict of interest. It is our view that statement of this magnitude will have far-reaching implications for clinical practice which will be in the interests of some patients but also against the interests of others.

KEY WORDS: Critique, Global Initiative for Asthma 2019 guidelines, ramifications

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BACKGROUND AND RATIONALE

The Global Initiative for Asthma (GINA) recently released their updated Global Strategy for Asthma Management and Prevention Guide (2019). The pocket guide for practicing clinicians states that "the 2019 GINA strategy report represents the most important change in asthma management in 30 years."[1] Among the several new recommendations that have been incorporated in the guidelines, a significant one is the change in treatment strategy for the management of mild asthma (Steps 1 and 2). The guideline states that "all adults and adolescents with asthma should receive either symptom driven (in mild asthma) or daily low dose inhaled corticosteroid (ICS) containing controller treatment to reduce the risk of serious exacerbations." This change as stated in the preface of the main document is based on a 12-year search for evidence to address the management of patients with mild asthma.[1]

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A statement of this magnitude can have far-reaching consequences in the way clinicians treat their patients with mild asthma as also the way in which patients perceive and respond to the treatment prescribed. Both of these can and will eventually impact the global burden of the disease. We present in this paper our critical appraisal of the SYGMA-2 trial,[2] a key trial which largely formed the basis of this recommendation and discuss the potential consequences of using only long-acting beta-2-agonist (LABA) + ICS as needed as against regular, daily low-dose ICS with as-needed short-acting beta-2-agonist (SABA).

A SUMMARY OF THE SYGMA-1 TRIAL

The May 17, 2018, issue of the New England Journal of Medicine (NEJM) carried two studies: SYMGA-1[3] and SYGMA-2. The former study was a 52-week, double-blind, randomized, multicenter, parallel group, Phase III study in participants (n = 3849) over the age of 12 years with a diagnosis of mild asthma and evaluated efficacy and safety of three interventions: budesonide-formoterol (160/4.5 μg) "as needed" versus terbutaline (0.4 mg) "as needed" versus budesonide (200 μg) twice daily + terbutaline (0.4 mg) "as needed." The rationale for the study was that while guidelines recommend regular, daily, low-dose inhaled glucocorticoids as maintenance treatment to reduce airway inflammation, help control symptoms, and reduce the risk of exacerbations, patient adherence to inhaled glucocorticoids in real life is low across all severities of asthma. Patients largely rely on SABAs for symptom relief. Thus, using a combination of a SABA with an inhaled glucocorticoid could potentially address this problem. This study by O'Byrne *et al.* showed the superiority of "as-needed" budesonide-formoterol to "as-needed" terbutaline with regard to its primary outcome of asthma symptom control. The combination, however, was inferior to budesonide maintenance therapy + as-needed terbutaline (0.4 mg), but resulted in a significantly lower glucocorticoid exposure.[3]

A SUMMARY OF THE SYGMA-2 TRIAL

In the same issue of the NEJM, Bateman *et al.* report the SYGMA-2 study designed in parallel to SYGMA-1. Here, n = 4215 patients were randomly assigned to receive 52 weeks of treatment with either (a) twice daily placebo + budesonide-formoterol used as needed (ICS + LABA) or (b) budesonide alone (ICS alone) + as-needed terbutaline.[2] The reasoning for the SYGMA-2 trial was identical to the SYGMA 1 trial (poor adherence in real life to the daily, low-dose inhaled glucocorticoids). The budesonide-formoterol combination was shown to be noninferior to maintenance treatment with ICS in terms of prevention of exacerbations, the primary outcome measure. The secondary outcome measures such as symptom control, quality of life, and spirometric assessment were better in the maintenance ICS group. Similar to the SYGMA-1 trial, the use of the combination resulted in a significantly lower glucocorticoid exposure.

CRITIQUE OF THE SYGMA-2 TRIAL

The challenge of airway inflammation

Airway remodeling, a process whereby structural changes occur in both small and large airways has been documented in all stages of asthma severity and even in the face of adequate symptom control.[4] These changes are believed to result from an ongoing chronic inflammatory process that involves the activation of CD4+ T cells, eosinophils, neutrophils, and mast cells[5] and can consequently result in airway hyperresponsiveness and bronchoconstriction. The 2018 GINA guidelines themselves endorse the use of daily, regular low-dose ICS as maintenance therapy. In addition, in the SYGMA-2 study, symptom control was better in the group that received regular, low-dose ICS – a secondary outcome. The nonassessment of inflammatory markers by Bateman *et al.* as well as the lack of evaluation of the long-term outcomes of the potential airway remodeling that could have occurred in the 52 weeks in patients[6] who only received as-needed budesonide-formoterol makes this recommendation tenuous.

Disease heterogeneity in mild asthma

Mild asthma is defined as disease that is well controlled with Step 1 or Step 2 treatments, i.e., with "as-needed" reliever medications alone or with low-dose controller treatment such as low-dose ICS, leukotriene receptor antagonists, or chromones. Patients who qualified for either of the steps would have been enrolled in the study. What will remain unknown is the number of patients belonging to the Step 2 category, i.e., needing low-dose ICS who would be the most susceptible to the risk of exacerbations. As the authors themselves have stated in the introduction, the underuse of ICS in patients with mild asthma is associated with risk of severe exacerbations and even death.[7]

Understanding the noninferiority margin and its potential consequences

The SYGMA-2 trial started as a superiority trial and was eventually converted to a noninferiority trial. The intent of a noninferiority trial is to show that the product that is being tested is "no worse" or "not materially worse than control."[8] These studies answer the question as to whether we are willing to accept a new intervention that may be clinically worse yet beneficial to patients by way of, for example, lower costs, better compliance, or fewer side effects. The interest in any noninferiority study is, therefore, always "one sided" or asymmetric.[9,10] There are three primary reasons why a noninferiority study is run: (a) the two interventions are truly efficacious leaving noninferiority testing as the only option, (b) the test product has a very small advantage that makes the conduct of a large trial impractical, and (c) the test product has a disadvantage but that disadvantage is smaller than the proposed noninferiority margin.[10] SYGMA-2 likely falls into Categories b and c.

The editorial accompanying the SYGMA-2 trial by Lazarus[11] in the same issue states that "as needed treatment was similar, or at least, noninferior to regular maintenance therapy with inhaled glucocorticoids with prevention of exacerbations." It would be inappropriate to interpret noninferiority as "similar" when the ideal interpretation of noninferiority in statistical terms is "no worse than." The interest in the lesser objective of noninferiority arises only when the superiority trial fails to detect a significant difference between the two treatments being compared. For a superiority trial, the lower bound of the 95% confidence interval for the treatment difference provides a quantitative estimate of the minimum expected difference between the test and the reference products.[12,13] Downgrading a superiority to a noninferiority trial is acceptable methodologically only when the original protocol had envisaged this and the margin for noninferiority was defined *à priori*.[10] This is particularly important for licensing purposes. The SYGMA-2 trial which downgraded its superiority objective to noninferiority does not give reasons for the same either in the manuscript or in the protocol.[14] The CONSORT guidelines for reporting studies[9] clearly state under point 3b in the Methods section that "important changes to methods after trial commencement should be listed with reasons." The protocol merely states that blinded sample size review permitted testing of the noninferiority hypothesis without loss of power and does not give clear reasons for the change. Another important aspect of this change is its impact on the sample size. Because the margin of difference by default is much higher in superiority trials, they have lower sample sizes and noninferiority trials with their smaller margins have higher sample sizes.[13] No change in the sample size post downgrading the objective is alluded to either in the study or the protocol.

The noninferiority limit set by the authors was 20% (rate ratio of the two groups = 1.2) assuming a rate of 0.1 exacerbations per patient-treatment year in the population under study which the authors felt would be clinically relevant. The biggest challenge with SYGMA-2 lies in the 95% confidence interval of the difference finally seen between the two groups. This is 0.97 (NA, 1.16). The value of 1.16 is dangerously close to 1.2, and as is known with noninferiority studies, it is very easy for the test product to become "inferior" when the intervention is used in the general population. This is one of the reasons why opponents of noninferiority trials argue that the noninferiority design allows new products to compete with older ones on the basis of small differences seemingly beneficial to patients.[14]

Understanding the Hawthorne effect and its consequences on the noninferiority design

The Hawthorne effect refers to change in people's behavior when they are participants in an experiment as they are aware that they are under observation/scrutiny. The authors themselves have stated that adherence to ICS was actually much higher in the study (approximately 60%) than they anticipated (real-world studies estimate compliance around 35%).[2] This could be attributed to the Hawthorne effect. It is also well known that researchers rarely appreciate the value of the Hawthorne effect in Randomized controlled trials [RCTs] leading to overtly optimistic estimates of the success of interventions.[15] The adherence in the real world to asthma medications is known to be <50% in children[16] and ranges from 30% to 70% in adults.[17] This is likely to be the extent of adherence in the general population where patients are not "under" observation unlike in a clinical trial. Real world data (based on true adherence rates) would need to be evaluated to find the true difference between the treatment groups.

Appreciating Conflict of Interest

While the study data were collected by the investigators, the analysis was done by employees of the sponsor and not by the investigators themselves or an independent agency. In the listing of conflict of interest, all authors but two have listed some form of support from the sponsor. One of the authors also serves on the Board and Science Committee of the GINA. While the COI itself has been declared, how it was addressed is not mentioned.

OUR PERSPECTIVE OF THE GLOBAL INITIATIVE FOR ASTHMA RECOMMENDATIONS BASED ON A CRITICAL APPRAISAL OF THE SYGMA-2 TRIAL

The SYGMA-2 trial was begun on the premise that patients with mild asthma often only rely on SABAs for symptom relief and have poor adherence to maintenance therapy with ICS. Both the SYGMA studies in fact showed good adherence in both the arms with the difference not being statistically significant. In fact, the adherence in the SYGMA study was about 60%, which is much higher than real-life adherence (as the authors have mentioned) – this actually could argue in favor of a need-based approach. However, mild asthma is no longer mild as severe exacerbations in mild asthma represent 30%–40% of asthma exacerbations requiring emergency consultation and can even be fatal.[7] A study by Ding and Small evaluated the disease burden of mild asthma using both patient and physician surveys in Step 1 and Step 2 patients and found that 19% of all patients experienced one or more exacerbations.[18] Step 2 patients also experienced more exacerbations requiring treatment intensification, an emergency department visit, or hospitalization. An Australian study found that 33% of childhood deaths from asthma occurred in children who have asthma classified as "mild."[19]

It is our view that maintenance ICS remains relevant and "as-needed budesonide-formoterol" should be prescribed to patients as first line only after a detailed explanation of how airway remodeling can occur in the absence of maintenance low-dose ICS. It is also our view that patients who are prescribed such therapy should be carefully screened for their ability to perceive their asthma symptoms and their

ability to recognize signs of an impending exacerbation. In countries such as India, most patients with asthma do not use (and are often not even recommended) regular peak flow meters for monitoring, and this can be a significant impediment to picking up warning signs of an early exacerbation. The use of daily low-dose ICS has been established in a *post hoc* analysis of the START trial where $n = 3577$ patients who received daily low-dose budesonide had decreased severe asthma related events (SARE) risk, reduction in decline of lung function, and improved symptom controls cross all subgroups.[20] One counter argument against the use of daily low-dose ICS + as-needed SABA could be that in SYGMA 2, the group that received "as-needed ICS + LABA" required only one quarter of the ICS. This could be a significant cost-saving exercise, as the mean daily dose of steroids in most of the studies using this approach has been considerably less (BEST, TREXA, SYGMA, and PRACTICAL).[2,3,21-23] The trade-off with the low-dose ICS + as-needed SABA group will be the potential greater risk adverse events (a patient behavior that is associated with a perception of risk associated with daily use of ICS) in the group that received daily low-dose ICS. The SYGMA 2 study, however, found that the adverse events in the two groups were comparable, consistent with the long-standing safety record of these drugs. However, if such studies are conducted longer, there may be reduction in inhaled steroid side effects – as mentioned earlier, the cumulative annual dose of inhaled steroids in the need-based approach is significantly less. It is a well-known fact that regular beclomethasone usage in children has demonstrated short-term growth retardation.[24]

Evidence that as-needed ICS + LABA is superior to as-needed SABA was elegantly established in children and adolescents with beclomethasone and salbutamol in the TREXA study[22] – a trial that is yet to be replicated so well, owing largely (we believe) due to the lack of studies with beclomethasone, a much cheaper steroid. The TREXA and BEST[23] studies were early data in this space. Studies with as-needed ICS and formoterol in Step 1 are lacking in children, and therefore, this recommendation for need-based ICS + LABA is not included in the GINA 2019 statement for children below 12 years of age.

Finally, ACQ-5 scores and lung functions were clearly better in the maintenance budesonide group than the as-needed budesonide + formoterol group in the SYGMA-2 trial. This is something we all need to reflect on. A study by Panizza *et al.* showed that in a cohort of 89 asthmatics who were followed up over 17 years in Perth, Australia, it was poorer lung function but not initial symptom severity that predicted mortality better.[25] The risk of death was higher with decreased FEV1 and increased FEV1 variability, age, and treatment requirements. Lung function impairment is also known to contribute to all-cause mortality.[26,27]

The GINA statement emphasizes that it is not a guideline but rather an evidence-based strategy that helps focus on translation into clinical practice. This strategy needs to be placed in perspective as the current 2019 statement can have far-reaching implications for clinical practice, both in the interests of some patients and against the interests of others. Only time will tell us the impact of this sweeping change in recommendation on the management of mild asthma.

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Conflicts of interest
There are no conflicts of interest.

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