

The Dilemma: How to Step Down from Step 3 Asthma Treatment?



Ebru Damadoglu, MD^a, and Ahmet Ugur Demir, MD^b *Ankara, Turkey*

Tract 1 in the new Global Initiative for Asthma (GINA) report recommends as-needed low-dose inhaled corticosteroids (ICS)—formoterol for steps 1 and 2 treatment and, as a tract 2 option, low-dose maintenance ICS and as-needed short-acting beta agonist (SABA) for reliever can be chosen for step 2 treatment.¹ Conversely, to step down from step 3 treatment, reducing low-dose ICS—long-acting beta agonist (LABA) to once-daily was recommended based on panel consensus judgment, and discontinuation of LABA was discouraged with a high level of evidence.^{1,2} This implicitly means that, while stepping down from step 3 treatment, both options may lead to undertreatment and loss of asthma control. The researchers of the Step-down of Intervention and Grade in Moderate Asthma (SIGMA) study wanted to address this gap in evidence, and in order to provide more evidence, they aimed to compare 2 step-down approaches with each other and to determine whether the 2 approaches were noninferior to maintaining low-dose ICS/LABA treatment in a pragmatic randomized controlled trial.³ They found that discontinuing LABA or reducing ICS/LABA to once-daily was not noninferior to maintaining ICS/LABA in terms of change in asthma control test (ACT) scores, and the 2 step-down approaches led to similar results. However, the findings should be interpreted carefully.

The design of the SIGMA study was a noninferiority trial, which suggests that one or both of these 2 step-down strategies could be offered to well-controlled asthmatic patients and preferred to the maintenance treatment if they were not worse than the maintenance treatment. The primary outcome was ACT score difference after 6-month follow-up. The authors emphasized that such step-down strategies have not been evaluated in such a trial before. However, the study presents some challenges that, as appreciated in the discussion, could have failed owing to the “conservative strict non-inferiority margin of the study,” and because “about 10% of patients experienced treatment failure following 6 months after step-down.”³ The choice of noninferiority limit for ACT as “−1” was not well

based, given the previous study that found an ACT score change of 3 points as the minimally significant difference.⁴ One of the 2 papers cited as a reference for this choice had a high drop-out rate of almost 50% (from 117 at baseline to 52 at 12 weeks), and had a short duration of follow-up (12 weeks) compared with this study.⁵ However, the authors could defend their choice of a smaller margin of error with the intent of not enlarging the type I error. Second, the findings were not fully conclusive, as evidenced by the confidence interval of the differences also including the range of noninferiority. With a noninferiority margin of −1-point change in ACT, noninferiority was not demonstrated, but the ACT slope showed that, at the end of the study period, most patients were well controlled.³ If it were a superiority trial, this finding, that is, a very small mean difference with a wide confidence interval, could be viewed as evidence of inadequate power, that is, suffering from type II error. Thus, decreasing the type II error might have reached a different conclusion, which would more likely increase the precision of the study findings. Sample size calculated for 90% power was 85 per group, almost 1.5 times the sample size of the study (without correction for loss to follow-up). Third, the 2 outcomes (ie, primary outcome as change in ACT score and secondary outcome as treatment failure, which among the listed possibilities included uncontrolled asthma) were related, were of different type (continuous and binary, respectively), and were analyzed by different approaches (ACT change by per-protocol analysis and treatment failure by intention to treat analysis). In addition, a noninferiority margin for treatment failure was not defined. Because these 2 outcome measures were related but were assessed in different populations, contrasting findings could have been observed. As an example, noninferiority could have been shown in those who continued the treatment arm, whereas a significantly higher proportion of the treatment group could have dropped out owing to uncontrolled asthma, giving rise to a negative secondary outcome.

High SABA use, incorrect inhaler technique and poor adherence, obesity, chronic rhinosinusitis, gastroesophageal reflux disease, confirmed food allergy, pregnancy, smoking, allergen exposure if sensitized, low forced expiratory volume in 1 second (FEV₁), high bronchodilator reversibility, 1 or more severe exacerbation in the last 12 months, and ever intubated or intensive care unit admission for asthma have been defined as risk factors for an asthma exacerbation, and step-down should be performed with close supervision in those who have 1 or more of these risk factors.¹ In the SIGMA study, the enrollment criteria included patients with no severe exacerbations in the previous 6 months instead of 12 at baseline, more than 10% of patients were current smokers, more than 40% were sensitized to inhalant allergens, blood and sputum eosinophil levels were high, over 60% had comorbid rhinosinusitis, and almost 10% of patients in the step-

^aDepartment of Pulmonology, Division of Allergy and Clinical Immunology, Hacettepe University, School of Medicine, Ankara, Turkey

^bDepartment of Pulmonology, Hacettepe University, School of Medicine, Ankara, Turkey

No funding has been received for this study.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication July 12, 2021; accepted for publication July 12, 2021.

Corresponding author: Ebru Damadoglu, MD, Department of Pulmonology, Division of Allergy and Clinical Immunology, Hacettepe University, School of Medicine, 06100 Sıhhiye, Ankara, Turkey. E-mail: edamadoglu@yahoo.co.uk.

J Allergy Clin Immunol Pract 2021;9:3647-8.
2213-2198

© 2021 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2021.07.005>

down groups had an exacerbation in the preceding 12 months before enrollment that required an emergency department visit. Thus, many patients included in the SIGMA study had risk factors for an exacerbation and, therefore, loss of asthma control, and probably were not suitable candidates for step-down. The authors wanted to define risk factors for treatment failure in the step-down groups, but they admit that the group with treatment failure was too small for comparison, and no significant factors were found. GINA recommends consideration of step-down of treatment once good asthma control has been established for 3 or more months, in order to find the lowest effective dose that maintains asthma control and also prevents exacerbations. However, the evidence is based on panel consensus judgment.¹ In case of the presence of 1 or more risk factors for exacerbations, it is preferred to use an ICS-containing inhaler and preferably with as needed ICS-formoterol as a reliever.¹

In a previous randomized controlled pragmatic trial, stable asthma for 3 months was likely to be insufficient criteria to consider a patient suitable for step-down.⁶ The primary outcome in many step-down studies was asthma exacerbations, and studies differ in definitions of loss of asthma control, inclusion criteria, and duration of follow-up.^{2,7,8} Treatment adherence and control of modifiable risk factors, which may be different for each patient, play critical roles in treatment decisions and step-down. In the SIGMA study, short term use of a systemic steroid for 3 to 5 days was permitted once, but in case of a second exacerbation that required systemic steroids, treatment was accepted as failed. However, we do not know how this allowed systemic steroid intervention affected the results and how many patients needed that intervention.

Overall, this study provides an original contribution addressing the important question of the optimal step-down strategy in well-controlled asthma. The challenges brought out by this study invite new studies to build on this evidence. The clinical and molecular predictors of a good response to step-down therapy and how a successful step-down in therapy is best accomplished should be investigated further.

REFERENCES

1. Global Initiative for Asthma. Global strategy for asthma management and prevention; 2021. Available from: <https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf>. Accessed July 9, 2021.
2. Ahmad S, Kew KM, Normansell R. Stopping long-acting beta2-agonists (LABA) for adults with asthma well controlled by LABA and inhaled corticosteroids. *Cochrane Database Syst Rev* 2015;6:CD011306.
3. Kim SH, Lee T, Jang AS, Park CS, Jung JW, Kim MH, et al. Pragmatic randomized controlled trial for stepping down asthma controller treatment in patients controlled with low-dose inhaled corticosteroid and long-acting β 2-agonist: step-down of intervention and grade in moderate asthma study. *J Allergy Clin Immunol Pract* 2021;9:3638-46.
4. Schatz M, Kosinski M, Yarlus AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. *J Allergy Clin Immunol* 2009;124:719-723.e1.
5. Kwon HS, Lee SH, Yang MS, Lee SM, Kim SH, Kim DI, et al. Correlation between the Korean version of Asthma Control Test and health-related quality of life in adult asthmatics. *J Korean Med Sci* 2008;23:621-7.
6. Usmani OS, Kemppinen A, Gardener E, Thomas V, Konduru PR, Callan C, et al. A randomized pragmatic trial of changing to and stepping down fluticasone/formoterol in asthma. *J Allergy Clin Immunol Pract* 2017;5:1378-1387.e5.
7. Mori K, Fujisawa T, Inui N, Hashimoto D, Enomoto N, Nakamura Y, et al. Step-down treatment from medium-dosage of budesonide/formoterol in controlled asthma. *Respir Med* 2016;119:1-6.
8. Reddel HK, Gibson PG, Peters MJ, Wark PA, Sand IB, Hoyos CM, et al. Down-titration from high-dose combination therapy in asthma: removal of long-acting beta(2)-agonist. *Respir Med* 2010;104:1110-20.