Editorial

A paradigm shift in the treatment of mild asthma?

Wei Tang[1], Lin Sun[1], J. Mark FizGerald[2]

[1]Department of Pulmonary Critical Care Medicine, Ruijin Hospital, Shanghai Jiaotong University school of Medicine, Shanghai 200025, China; [2]Department of Medicine, University of British Columbia, Vancouver, Canada

Correspondence to: J. Mark FizGerald. Department of Medicine, University of British Columbia, Vancouver, Canada. Email: Mark.Fitzgerald@vch.ca.

Submitted Sep 14, 2018. Accepted for publication Sep 26, 2018.
doi: 10.21037/jtd.2018.09.127
View this article at: http://dx.doi.org/10.21037/jtd.2018.09.127

Mild asthma, often termed mild intermittent or mild persistent asthma, is defined by the Global Initiative in Asthma (GINA) management strategy as patients who meet the criteria for step 1 and step 2 treatment strategies. Although these patients have fewer symptoms, they are the main and largest subgroup of asthma patients. Epidemiological data shows that mild asthma accounts for 70% of the total population of asthma patients, and a large proportion of them are newly diagnosed (1).

Although patients with mild asthma have fewer symptoms than patients with moderate or severe asthma, they also face ongoing chronic inflammation of the lower respiratory tract and the risk of acute exacerbations. According to epidemiological studies, among GINA grade 1 and grade 2 patients, 52.4% and 42.3% of them were uncontrolled (2,3). In addition, up to 25% of patients with mild asthma experienced a severe asthma exacerbation in the previous year (4). All of these data suggest that there are still a lot of unmet needs in the treatment of mild asthma.

Currently, GINA suggests as needed short-acting beta-2 agonists (SABA) as first-line therapy for patients with mild intermittent asthma (step 1) and low-dose inhaled corticosteroids (ICS) maintenance therapy as an alternative approach recommended for long-term anti-inflammatory treatment. For patients with mild persistent asthma (step 2), low-dose ICS maintenance therapy is recommended as the first choice. Leukotriene receptor antagonist is an alternative treatment for these mild persistent asthma patients but this intervention is generally less effective than ICS especially in preventing exacerbations. Low-dose theophylline is another, though less effective, option as well but it has considerable side effects and is not recommended for children under 12 years (5). Although GINA is evidence-based and is updated on an annual basis, there are some contradictions in the management of patients with mild asthma. Firstly, for patients of mild intermittent asthma (GINA step 1), the guideline suggests as-needed use of SABA, which neglects the underlying inflammatory nature of asthma and puts patients at risk of acute exacerbations as is shown in placebo controlled trials where patients receive a SABA compared to ICS. For patients with mild persistent asthma (GINA step 2) who have already accepted the idea of as-needed treatment on step 1, it may confuse them when the severity of the disease progresses to step 2 where we switch the emphasis to using a SABA as the primary treatment to regular ICS and as SABA on an as needed basis. They have to change and accept the long-term anti-inflammatory treatment strategy, which means fixed-dose regular maintenance and preventive therapy. Secondly, beta-2 agonists relieve symptoms rapidly and effectively, giving asthma patients significant improvements, leading to a sense that a SABA is more effective than ICS. These paradoxes in asthma management have been highlighted in a recent commentary (6). Thus patients develop an over reliance on a SABA and are willing to use them as the primary treatment regardless of asthma severity. As earlier studies in Europe revealed, 63% of patients chose SABA as their main therapy, while ICS only accounted for 30%. Even in patients with mild persistent asthma, the number was quite similar, with 75% patients using SABA and only 30% using ICS (7). This approach leads to more uncontrolled asthma, more acute exacerbations and more health care utilization costs (8). Of greater concern an analysis of asthma-related deaths showed that SABA overuse along with ICS underuse is a major contributor to these, in many cases, avoidable events (9). In cohort studies, long-acting beta-2 agonists (LABA) and ICS combination prescriptions were associated with lower hospitalization rates—in those who regularly

prescribed LABA, the rate for asthma-related hospitalization decreased as the number of ICS prescriptions increased. Conversely, in patients prescribed ICS regularly, the number of LABA prescriptions had no effect on the risk of asthma-related hospitalizations (10). In patients with mild asthma, the Kaplan-Meier curve analysis from the ICS use and acute exacerbations has clearly shown that ICS reduces acute exacerbations in mild asthma (11). In the START and OPTIMA studies, two large multicenter studies completed at the beginning of this century, the analysis of results for mild asthma patients reached the same conclusion: use of ICS on a daily basis can reduce acute severe exacerbations in mild asthma, including emergency visits, hospitalizations as well as the lung function loss in patients with severe acute exacerbations (11,12).

Along with the MART (maintenance and reliever anti-inflammatory therapy) strategy, great changes have taken place in the past decade in asthma management. In moderate to severe asthma, irrespective of the comparison compared with the same dose or higher dose of ICS/LABA maintenance plus SABA rescue treatment, MART strategy reduced the rate of exacerbations as well as emergency department and hospitalization rates. In the meta-analysis published recently, it was shown that compared with the same dose of conventional ICS/LABA plus SABA treatment strategy, MART strategy reduced 23% exacerbation rate. Even when compared to a higher dose of ICS in a fixed dose ICS/LABA plus SABA, the MART strategy still reduced the rate of exacerbations by 23% (13). In mild asthma patients, anti-inflammatory treatment is also important, but because their symptoms are often infrequent and not always disruptive on daily activities, it is difficult to motivate patients to take long term ICS to prevent asthma exacerbations and who instead remain over-reliant on the use of as needed SABA. This of course will lead to more symptomatic asthma and experiencing, on an annual basis, severe asthma exacerbations in approximately 20% of mild asthma patients. An intriguing question then is if we could use a similar approach as MART strategy to better manage these mild asthma patients? Recently, two studies addressed this question and were termed the SYGMA studies.

Both SYGMA studies were published in the *New England Medical Journal*. The first multi-center blind placebo controlled study (14) enrolled a total of 3,836 mild asthma patients. After a 2–4 weeks run in period during which used Terbutaline (0.5 mg) as needed, patients were randomly assigned to one of three regimens: twice daily placebo plus terbutaline (0.5 mg) used as needed (terbutaline group), twice-daily placebo plus budesonide-formoterol [200 μg of budesonide PRN and (budesonide-formoterol group], or twice-daily budesonide (200 μg) plus terbutaline PRN (budesonide maintenance group) for 52 weeks. In this study, electronic inhaler monitoring and electronic diaries were used to ensure best adherence. The primary endpoint was to compare the superiority of as-needed budesonide-formoterol to as-needed terbutaline with regard to electronically recorded weeks described as well-controlled asthma weeks (eWCAW). The secondary endpoint was to show the non-inferiority of budesonide-formoterol used as needed to budesonide maintenance therapy with regard to eWCAW and comparing the rates and time to the first severe exacerbation. The demographic and clinical characteristics of the patients at baseline were very similar in the three treatment groups, including age, gender, time since asthma diagnosis, ACQ-5 score, AQLQ score, pre and post bronchodilator FEV1% of predicted value, morning peak expiratory flow ≥80% of the predicted value, bronchodilator reversibility, asthma control according to pretrial treatment, severe exacerbation in previous 12 months. The results showed budesonide-formoterol used as needed was superior to terbutaline used as needed with regard to the primary outcome of the mean percentage of eWCAW. The secondary endpoint showed similar results that non-inferiority of budesonide-formoterol used as needed to budesonide maintenance therapy according to ACQ-5 score and pre-bronchodilator FEV1% improvement. As to asthma exacerbations, budesonide-formoterol used as needed resulted in lower rate exacerbations than terbutaline used as needed (no matter what kind of severity). The rates of severe exacerbations in the budesonide-formoterol group and the budesonide maintenance group did not differ significantly but with the median daily dose of inhaled glucocorticoid in the budesonide-formoterol group being only 17% of that in the budesonide maintenance group. Adherence to the twice-daily, blinded maintenance regimen did not differ significantly across the three trial groups but was exceedingly high and much better than that reported in ICS real world studies: the mean percentage of doses taken were all around 80%. SYGMA1 study showed that budesonide-formoterol used as needed was superior to the SABA terbutaline used as needed both for asthma symptom control and for reducing the risk of asthma exacerbations among patients with physician-assessed mild asthma. Furthermore, budesonide-formoterol used as needed was similar to budesonide maintenance therapy with regard to

reducing the risk of asthma exacerbations, at a substantially lower total glucocorticoid load and without the need for adherence to a twice-daily maintenance therapy schedule.

SYGMA2 after a similar run-in period during which patients only used terbutaline as needed, patients were randomly assigned to receive twice-daily placebo plus budesonide-formoterol (200/6 μg) used as needed or twice-daily budesonide (200 μg) maintenance therapy plus terbutaline as needed. In this study, unlike the SYGMA1 study, only the use of trial inhalers was electronically recorded. Unlike SYGMA1 study, patients did not fill an electronic diary, had only 2 clinic visits, but had telephone call visits at 8, 25 and 42 weeks. The primary end point of SYGMA2 study was that budesonide-formoterol used as needed was non-inferior to regular ICS based on the annualized rate of severe asthma exacerbations. A total of 4,215 mild asthma patients were enrolled into the SYGMA2 study. There was no difference in the baseline demographic and clinical characteristics between the two treatment groups. In the results there was no significant difference in the annualized rate of severe asthma exacerbations as well as the number of patients who had severe exacerbation that led to an emergency department visit or hospitalization between the two groups. Similar to SYGMA 1 there was also no significant difference between the two groups according to pretrial treatment (low dose ICS or LTRA maintenance plus SABA treatment or only treated using SABA). The electronically recorded adherence to each treatment group was similar, the mean percentage of daily doses was 64% and 62%. But the median daily dose of inhaled glucocorticoid was 75% lower in the budesonide-formoterol as needed group than in the budesonide maintenance group. As to lung function and patient-reported outcomes such as ACQ-5 score, budesonide-formoterol as needed treatment was inferior to the budesonide maintenance but the differences were well below the clinically relevant and MCID differences. In conclusion, the SYGMA2 study showed that budesonide-formoterol used as needed was not inferior to the budesonide maintenance therapy with regard to reducing the risk of asthma exacerbations. The budesonide-formoterol as needed therapy used only one quarter of the total exposure of inhaled glucocorticoid which was used in the conventional budesonide maintenance therapy with no safety concerns, and lower reliever-free days (15).

The year of 2018 is potentially a unique time for changing the treatment strategy for mild asthma. Both SYGMA1 and SYGMA2 studies showed that in mild asthma patients, budesonide-formoterol as needed treatment was better than terbutaline as needed treatment in control asthma symptom and in reducing exacerbations. As needed use of budesonide-formoterol was non-inferior to the budesonide maintenance treatment in terms of reducing exacerbations with no need to routinely use a twice daily medication and greatly reduced the exposure to ICS. The SYGMA studies provide a new treatment strategy mild asthma but will require regulatory approval and then acceptance by patients, clinicians and payers. In the overall control of asthma, when airway inflammation is increased leading to patients being more symptomatic and through habit using a SABA with no effect on inflammation, in contrast use of an ICS and a fast acting LABA combination therapy instead leads to the reduction inflammation and relieves symptoms at the same time. This strategy is one that a patient will likely be more adherent to and should be even more effective in a real world setting. These data clearly show that SABA PRN should not be considered as the primary treatment for mild asthma. Future real world studies as well more long-term studies integrating an assessment of airway inflammation are required. It maybe we can identify more accurately patient characteristics that predict patients more likely to respond to this strategy. It should be noted that twice daily ICS remains a strategy that we have the best long-term efficacy and safety data and will remain an option especially for the adherent patient.

Acknowledgements

None.

Footnote

Conflicts of Interest: JM FizGerald: (I) advisory board/membership; personal funds: GSK, Astra Zeneca, BI, Novartis, TEVA, Pfizer, Sanofi Regeneron; (II) peer reviewed funding: CIHR, AllerGen, BC Lung Association; Research funding: GSK, Astra Zeneca, Amgen, Johnson and Johnson, Sanofi Novartis: all paid directly to UBC; (III) speaker/honoraria: Astra Zeneca, BI, Novartis, Pfizer, Merck. In addition he was a co PI for the SYGMA trials. Other authors have no conflicts of interest to declare.

References

1. Dusser D, Montani D, Chanez P, et al. Mild asthma: an expert review on epidemiology, clinical characteristics and treatment recommendations. Allergy 2007;62:591-604.

2. Olaguibel JM, Quirce S, Julia B, et al. Measurement of asthma control according to Global Initiative for Asthma guidelines: a comparison with the Asthma Control Questionnaire. Respir Res 2012;13:50.
3. "Global strategy for asthma management and prevention: GINA executive summary." E.D. Bateman, S.S. Hurd, P.J. Barnes, J. Bousquet, J.M. Drazen, J.M. FitzGerald, P. Gibson, K. Ohta, P. O'Byrne, S.E. Pedersen, E. Pizzichini, S.D. Sullivan, S.E. Wenzel and H.J. Zar. Eur Respir J 2008; 31: 143-178. Eur Respir J 2018;51. doi: 10.1183/13993003.51387-2007.
4. Price D, Fletcher M, van der Molen T. Asthma control and management in 8,000 European patients: the REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey. NPJ Prim Care Respir Med 2014;24:14009.
5. Global Initiative for Asthma (GINA). 2018 GINA report, global strategy for asthma management and prevention. Available online: http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/
6. O'Byrne PM, Jenkins C, Bateman ED. The paradoxes of asthma management: time for a new approach? Eur Respir J 2017;50. doi: 10.1183/13993003.01103-2017.
7. Rabe KF, Vermeire PA, Soriano JB, et al. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. Eur Respir J 2000;16:802-7.
8. Sadatsafavi M, Lynd L, Marra C, et al. Direct health care costs associated with asthma in British Columbia. Can Respir J 2010;17:74-80.
9. Davidsen JR, Hallas J, Søndergaard J, et al. Association between prescribing patterns of anti-asthmatic drugs and clinically uncontrolled asthma: a cross-sectional study. Pulm Pharmacol Ther 2011;24:647-53.
10. Sadatsafavi M, Lynd LD, Marra CA, et al. Dispensation of long-acting β agonists with or without inhaled corticosteroids, and risk of asthma-related hospitalisation: a population-based study. Thorax 2014;69:328-34.
11. Pauwels RA, Pedersen S, Busse WW, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. Lancet 2003;361:1071-6.
12. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. Am J Respir Crit Care Med 2001;164:1392-7.
13. Sobieraj DM, Weeda ER, Nguyen E, et al. Association of Inhaled Corticosteroids and Long-Acting β-Agonists as Controller and Quick Relief Therapy With Exacerbations and Symptom Control in Persistent Asthma: A Systematic Review and Meta-analysis. JAMA 2018;319:1485-96.
14. O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma. N Engl J Med 2018;378:1865-76.
15. Bateman ED, Reddel HK, O'Byrne PM, et al. As-Needed Budesonide-Formoterol versus Maintenance Budesonide in Mild Asthma. N Engl J Med 2018;378:1877-87.

Cite this article as: Tang W, Sun L, FizGerald JM. A paradigm shift in the treatment of mild asthma? J Thorac Dis 2018;10(10):5655-5658. doi: 10.21037/jtd.2018.09.127

