



Adjustable Maintenance Dosing or Total Asthma Control? Marketing Combination Inhalers

Howard Liss MD*

Rokach Center for the Prevention of Lung Diseases, Clalit Health Services, Jerusalem, Israel

Key words: asthma, inhalers, salmeterol, formoterol, adjustable dosing, fixed dosing

IMAJ 2007;9:635-636

To keep abreast of current advances in treatment, physicians often rely on published clinical trials. Today, pharmaceutical companies underwrite the majority of these studies. With a primary goal of profit, not education, these companies go to great lengths to insure publication of favorable studies [1]. While academic centers have standards for clinical trial agreements with the pharmaceutical industry, they are not always followed [2], and in any case, the majority of clinical studies are done in non-academic centers with the help of for-profit contract research organizations [3]. This results in a publication bias of positive results in industry-sponsored research [4-6]. These industry-sponsored studies are then brought to the attention of physicians by pharmaceutical company representatives. Not surprisingly, these articles have become marketing tools of the pharmaceutical companies.

One example is the current approach to asthma treatment. There are two seemingly different approaches to asthma control in the literature. The first, adjustable maintenance dosing, was promoted by the makers of the budesonide/formoterol combination inhalers and recommended adjusting the dose of a controller medicine up or down according to the clinical condition of the patient. The second, total asthma control, was promoted by the makers of the fluticasone/salmeterol combination inhalers and recommended maintaining the dose of controller medicine needed to prevent exacerbations and keep the patient symptom free. These approaches are based on the pharmacokinetics of salmeterol and formoterol, which have driven the marketing strategies of the pharmaceutical companies.

Adjustable maintenance dosing

Adjustable maintenance dosing fits the favorable dose-response curve of formoterol, which has a significant dose-dependent increase in forced expiratory volume in the first second with increasing doses of 6, 12, 24, and 48 μg [7]. Adjustments, either up or down, can then be made with a single combination inhaler containing formoterol [8,9]. In one study, this resulted in at least 1.2 changes in the subjects' dose of controller medicine during the 12 week study period, suggesting that they may not be adequately controlled with this approach.

* The author has no financial ties or conflict of interest with any pharmaceutical company.

Total asthma control

This approach was promoted because of the poor dose-response curve of salmeterol. Maximal bronchodilatation is achieved with a dose of 50 μg ; a dose of 100 μg only increases the incidence of side effects [10]. With the current fluticasone/salmeterol inhalers, no dose adjustments of either medication are possible with a single inhaler. This approach recommends maintaining the dose that controls the patient rather than adjusting the dose and having to change inhalers [11].

Which approach is preferred? One study, which was sponsored by GlaxoSmithKline, the makers of the fluticasone/salmeterol inhalers, compared adjustable dosing with budesonide/formoterol to fixed dosing with fluticasone/salmeterol during one year of treatment [12]. After 4 weeks, the group receiving the budesonide/formoterol inhaler reduced the use to one puff twice daily. The number of symptom-free days was equal in the two groups for the first 4 weeks of the study, but there were more symptom-free days in the fluticasone/salmeterol fixed-dose group when the dose of budesonide/formoterol was reduced. The authors favored the total asthma control approach of their sponsors. They concluded that there was a minimal amount of controller medicine that was necessary to control patients and it was better to maintain the level of treatment that keeps the patients symptom free instead of responding to short-term changes in symptoms.

The makers of the budesonide/formoterol combination inhaler then revised their approach to adjustable dosing. They combined the need for a minimal amount of controller medicine with the knowledge that it is helpful to increase the dose of the controller medication when asthma control deteriorates. More recent studies used fixed dosing of budesonide/formoterol with additional puffs of the controller inhaler as a reliever medication [13-15]. This approach is only applicable to inhalers containing formoterol and still allows patients to use one inhaler as both controller and reliever medication.

However, close examination of the most recent of these studies reveals several biases that benefit the pharmaceutical company [15]. Patients received low dose combination therapy with budesonide/formoterol, and with terbutaline, formoterol, or budesonide/formoterol as the reliever medication. First, the patients needed to be uncontrolled to some degree in order to evaluate the reliever treatments, and the dose of controller medication was probably lower than what they needed. Secondly,

even though the authors claim an advantage to formoterol over terbutaline as a reliever medication, there was no difference in daily asthma control, mild exacerbations, or emergency room visits, which concurs with other studies comparing formoterol with a short-acting beta agonist [16,17]. Finally, if there was an improvement with the use of a combination inhaler as a reliever medication, perhaps the effect was due to the increase in budesonide. It is known that increasing the dose of inhaled corticosteroids can improve asthma control [18], but there was no group that received budesonide alone as a reliever medication. The purpose of this study was to demonstrate an additional use of the formoterol/budesonide combination inhaler as a reliever medication. Even though the optimal treatment might have been different, the article does broaden the marketing aspects of this particular combination inhaler.

When a patient feels well, should we maintain the dose of controller medicine or try to lower the dose? According to the GINA guidelines (Global Initiative for Asthma), when good control has been achieved for several months, we should try to reduce the dose of maintenance therapy by either slowly reducing the dose of inhaled corticosteroids or removing the long-acting beta agonist [19]. Neither of these recommended approaches actually follows current asthma treatment guidelines. Adjustable maintenance dosing recommends lowering the dose of both controller medicines after a much shorter time of good control and then uses the same inhaler as a reliever medication. Total asthma control does not recommend dose reduction at all. The different approaches are in fact marketing strategies of the companies that manufacture formoterol and salmeterol. Each pharmaceutical company emphasizes different aspects of treatment that are most appropriate to the pharmacology of the long-acting beta agonist in their combination inhalers. Once this is appreciated by physicians, these two seemingly contradictory approaches to asthma treatment become more understandable. The approach of adjustable maintenance dosing using formoterol emphasizes that changes are possible with a single inhaler used as both controller and reliever. The other approach, total asthma control using salmeterol, emphasizes continuing the dose that provides good control so the patient does not have to change inhalers or adjust the dose. Each company found a treatment (and marketing) strategy that fits the pharmacology of their product.

All of the clinical studies mentioned here were sponsored by industry and the authors were employed in a pharmaceutical company. In view of the high degree of involvement in planning, executing, writing and publishing these studies, we must be aware that this literature is also being used as a marketing tool to influence our prescribing behavior and not purely for the dissemination of new information.

References

1. Miller FG, Brody H. Viewpoint: Professional integrity in industry-sponsored clinical trials. *Acad Med* 2005;80:899-904.
2. Steinbrook R. Gag clauses in clinical-trial agreements. *N Engl J Med* 2005;352:2160-2.

3. Dresser R. Private-sector research ethics: marketing or good conflicts management? The 2005 John J. Conley lecture on medical ethics. *Theor Med Bioeth* 2006;27:115-39.
4. Yaphe J, Edman R, Knishkowsky B, et al. The association between funding by commercial interests and study outcome in randomized controlled drug trials. *Fam Pract* 2001;18:565-8.
5. Bhandari M, Busse JW, Jackowski D, et al. Association between industry funding and statistically significant pro-industry findings in medical and surgical randomized trials. *CMAJ* 2004;170:477-80.
6. Lexchin J, Bero LA, Djulbegovic B, et al. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *Br Med J* 2003;326:1167-70.
7. Ringdal N, Derom E, Wahlin-Boll E, et al. Onset and duration of action of single doses of formoterol inhaled via turbuhaler®. *Respir Med* 1998;92:1017-21.
8. FitzGerald JM, Sears MR, Boulet LP, et al. Adjustable maintenance dosing with budesonide/formoterol reduces asthma exacerbations compared with traditional fixed dosing: a five month multicentre Canadian study. *Can Respir J* 2003;10:427-34.
9. Ind PW, Haughney J, Price D, et al. Adjustable and fixed dosing with budesonide/formoterol via a single inhaler in asthmatic patients: the ASSURE study. *Respir Med* 2004;98:464-75.
10. Dahl R, Earnshaw JS, Palmer JBD. Salmeterol: a four week study of a long-acting beta-adrenoceptor agonist for the treatment of reversible airways disease. *Eur Respir J* 1991;4:1178-84.
11. Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? The gaining optimal asthma control study. *Am J Respir Crit Care Med* 2004;170:836-44.
12. FitzGerald JM, Boulet LP, Follows RMA. The CONCEPT trial: a 1 year, multicenter, randomized, double-blind, double-dummy comparison of a stable dosing regimen of salmeterol/fluticasone propionate with an adjustable maintenance dosing regimen of formoterol/budesonide in adults with persistent asthma. *Clin Ther* 2005;27:393-406.
13. O'Byrne PM, Bisgaard H, Godard PP, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005;171:129-36.
14. Vogelmeier C, D'Urzo A, Pauwels R, et al. Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? *Eur Respir J* 2005;26:819-28.
15. Rabe KF, Atienza T, Magyar P, et al. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomized controlled, double-blind study. *Lancet* 2006;368:744-53.
16. Ind PW, Villasante C, Shiner RJ, et al. Safety of formoterol by Turbuhaler® as reliever medication compared with terbutaline in moderate asthma. *Eur Respir J* 2002;20:859-66.
17. Boonsawat W, Charoenratanakul S, Pothirat C, et al. Formoterol (OXIS®) Turbuhaler® as a rescue therapy compared with salbutamol pMDI plus spacer in patients with acute severe asthma. *Respir Med* 2003;97:1067-74.
18. Foresi A, Morelli MC, Catena E. Low-dose budesonide with addition of an increased dose during exacerbations is effective in long-term asthma control. *Chest* 2000;117:440-6.
19. Global Initiative for Asthma. Workshop report, global strategy for asthma management and prevention. National Institutes of Health: National Heart, Lung, and Blood Institute. Bethesda, MD, 2002. Publication No. NIH-NHLI 02-3659 (updated 2005) Accessed at <http://www.ginasthma.org>

Correspondence: Dr. H. Liss, Rokach Center for the Prevention of Lung Diseases, Clalit Health Services, Jerusalem 91000, Israel. Phone: (972-2) 501-7555; Fax: (972-3) 538-5697 email: howardl@clalit.org.il