GOAL: What Have We Learned?

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A recent study entitled "Can Guideline-Defined Asthma Control Be Achieved?"[1] stands out as one of the most noteworthy clinical studies of the past year because of the important concepts it confirms and because of the many significant questions it raises. Published online in July 2004 and in print in October of the same year, it is referred to by most as the GOAL trial (from the now familiar acronym for "Gaining Optimal Asthma controL"). Based on what we have learned from the GOAL trial, it is likely that the next iteration of asthma guidelines will be somewhat more stringent in their acceptance of symptoms that define "well-controlled asthma" or "acceptable control."

To fully appreciate the study, it is necessary to highlight two previous hypothesis-generating studies[2,3] that led to the development of the GOAL trial protocol. In the first of the two studies, the authors pooled data from eight trials using inhalers containing combined salmeterol and fluticasone propionate.[2] The data were reanalyzed with a new endpoint based on a composite measurement of asthma control as defined in guidelines published by the Global Initiative for Asthma (GINA). This was the first time a composite endpoint based on current asthma guidelines was used, as opposed to the majority of asthma studies to date, which have selected single-variable endpoints. The results of this analysis indicated that guideline-defined asthma control can be achieved and led to the development of a prospective protocol using the composite measure as the endpoint. The second hypothesis-generating study also indicated that improved quality of life was realized as the level of control improved, control again being defined by a guideline-based composite measure.[3] A significant observation across both studies was that similar proportions of individuals were achieving the same levels of asthma control[2,3] and improvements in quality of life[3] in the populations studied, regardless of the severity of asthma. This suggests that patients with more severe asthma should be taught to expect the same level of control and the same quality of life as those with milder asthma.

The GOAL trial was then developed as a "proof of concept" that asthma control according to the GINA guideline-based definition is achievable. The primary objective of the study was to compare the proportion of individuals who achieved a composite guideline-based measure of well-controlled asthma by using an inhaled corticosteroid alone with the proportion of those who achieved the same by using an inhaled corticosteroid in combination with a long-acting β agonist. The patients were stratified before randomization, according to their prior exposure to inhaled corticosteroids. Patients in each stratum were started on an initial dose of fluticasone, and approximately half were also given salmeterol in a combination device. There were up to three treatment steps, depending on the stratum, during which the dose of inhaled corticosteroid was escalated to a maximum of 1,000 μg of fluticasone propionate per day if patients did not meet the protocol-defined criteria for total control. If the composite measure of total control was achieved, the patient remained on the same dose until the completion of the 52-week study. If protocol-defined total control was not achieved by the time the patient reached the maximum dose, the maximum dose was continued until the end of the study.

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Individual parameters used by various worldwide asthma guidelines in defining asthma control have, for the most part, been separately validated in previous studies. However, until this study was completed, the determination of which parameters were used to create a composite definition of asthma control was based primarily on expert opinion. The GOAL trial is the first large-scale (n = 5,068) long-term (1 year) prospective trial that proves that guideline-defined composite measures of asthma control are achievable.

The results of this study may change our practice by asking us to reconsider our current acceptance of the presence of some symptoms as "adequately controlled." The study creates confidence that high levels of control not only can be achieved but can be maintained for up to a year, with the association of significant improvements in quality of life. Bateman and colleagues, quoting Cockroft and Swystun, stated that "for patients with more severe disease, many physicians equate therapeutic success with a reduction in symptom severity, rather than aiming for optimal control."[2,4] Clearly, this is no longer acceptable. It is likely that there will now be an increase in the stringency of asthma guidelines in their definition of control. A measure of an amount of improvement from baseline may show statistically (and sometimes clinically) relevant results, but a more meaningful measure of a treatment's success is how close a patient can get to the "ceiling" (ie, the extent to which the goal of therapy has been met).[2] As Bateman and colleagues discussed, this will lead not only to better clinical management of asthma but also to the use of a composite measure to define asthma control in future studies, which would allow better comparisons of study results and treatment modalities.[2] The use of single criteria as markers of response to treatment favours a positive response whereas a composite measurement of asthma control is more stringent. The latter may be a truer measurement of asthma control, but it is important to note that it may also problematically underestimate a true positive response to treatment. In a recent editorial, Reddel pointed out that with a composite measure, there is a "lack of specificity of most of the clinical features of asthma, manifest by overlap with concurrent conditions."[5] In Reddel's examples, cough from postnasal drip or shortness of breath from lack of physical fitness would cause an individual to fail the composite measure of control as defined by the GOAL trial but would not respond to increased doses of inhaled corticosteroid.[5] Clearly, a more stringent composite measure of asthma control does not negate the importance of good clinical judgment in practice. Asthma is a syndrome (ie, a collection of symptoms) that may have different causes and an underlying pathophysiology (eg, eosinophilic versus neutrophilic inflammation, allergic versus nonallergic). Therefore, asthma may not respond equally well in all individuals to the same treatment modalities. In addition, although the GOAL study challenges one to strive for total control in the management of asthma, it is important to note that a significant portion of study participants did not achieve total control. It is clear that an inhaled corticosteroid and long-acting β agonist alone are not sufficient for all patients and that other treatment modalities may be necessary.

It is important to note that the GOAL study was not designed to validate a certain strategy for dose escalation or frequency of patient follow up, and it did not compare different strategies for gaining control. The protocol used for escalating therapy in the GOAL study was meant to mirror common practice and guideline recommendations, but the results should not be taken to indicate that the same regimen is universally appropriate. The results actually reveal that there was continued improvement in each group over time even while subjects were taking lower doses of inhaled corticosteroid, suggesting the possibility that longer intervals of treatment are needed before increasing or stepping up therapy.

The GOAL study indirectly confirms the prior understanding of the advantage of add-on therapy with a long-acting β agonist as opposed to mere increased doses of inhaled corticosteroid. A similar proportion of individuals achieved control with lower doses of inhaled corticosteroid, using combined inhaled corticosteroid and long-acting β agonist. However, although a similar proportion of individuals also reached comparable levels of control more quickly with the combination, the study does not confirm that the more expensive

combination inhaled corticosteroid/long-acting β agonist devices are needed as initial therapy for all individuals. As Barnes discussed in an accompanying editorial, the differences in rates of improvement were small, and the results seen in the steroid-naive group reinforces current recommendations that inhaled corticosteroids alone be used as initial treatment.[6] He added that "it will be a matter of debate whether these differences justify the additional cost" of a combination device.[6]

In addition, although initial attempts to achieve total control as defined by the study may necessitate escalating doses of inhaled corticosteroid, the GOAL study was not designed to justify prolonged maintenance on high doses. As previously mentioned, there was a noted continual improvement over the 52 weeks of the study and a similar rate of improvement across all groups, suggesting a steroid effect. The study results also show that the high doses used contributed to a measurable clinical benefit, as a greater proportion of patients achieved better control by 52 weeks. Further benefits were also found during a final treatment phase that included oral corticosteroids and high-dose combination inhaled therapy for those whose asthma was not totally controlled as defined by the study. This challenges the thought that there is no benefit to escalating inhaled corticosteroid doses beyond the moderate-dose range. Admittedly, the degree of benefit decreased as the dose increased, and it is important to recognize that maintaining individuals indefinitely at higher corticosteroid doses not only increases the potential for adverse effects but also increases asthma care costs by using more medication. What is not clear from this study is how high to escalate doses or how long to continue high-dose inhaled corticosteroid therapy before accepting the level of control achieved and stepping back to maintain it. Further study is certainly needed to determine how high to go and when to begin stepping down the dose. One must also be mindful that because the study does not compare different medications within the same class and does not compare different types of delivery devices, one cannot infer from the results that one medication of the same class or a certain delivery device is superior to another.

We are clearly in a phase of understanding asthma in which we can begin to fine-tune asthma management rather than focusing merely on the palliation of a chronic incurable condition. The GOAL trial may begin to shift our current definition of acceptable asthma control, causing the development of more stringent guidelines and challenging us to strive for better levels of symptom control in our patients.

References

1. Bateman ED, Boushey H, 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.
2. Bateman ED, Bousquet J, Braunstein GL. Is overall asthma control being achieved? A hypothesis-generating study. Eur Respir J 2001;17:589–95.
3. Bateman ED, Frith LF, Braunstein GL. Achieving guideline-based asthma control: does the patient benefit? Eur Respir J 2002;20:588–95.
4. Cockroft DW, Swystun VA. Asthma control versus asthma severity. J Allergy Clin Immunol 1996;98:1016–8.
5. Reddel HK. Goals of asthma treatment: how high should we go? Eur Respir J 2004; 24:715–7.
6. Barnes NC. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. Am J Respir Crit Care Med 2004;170:830–1.