

Original article

Stability of asthma control with regular treatment: an analysis of the Gaining Optimal Asthma controlL (GOAL) study

Background: Uncontrolled asthma is characterized by variability. Current asthma guidelines recommend focussing on the achievement and maintenance of control but few studies have examined in detail, using composite measures of control, the stability and potential duration of control once achieved. In this *post-hoc* analysis of the results of the Gaining Optimal Asthma controlL (GOAL) study, we examine the association between the level of asthma control achieved during the step-up phase of the study and the stability of control experienced during the maintenance phase.

Methods: GOAL was a 1-year, randomized, stratified, double-blind study of 3421 patients with uncontrolled asthma, which compared salmeterol/fluticasone propionate combination with fluticasone propionate in achieving two composite, guideline-based measures of control: totally controlled and well-controlled asthma. We analysed the proportion and duration of time spent in control, the effect of treatment on asthma stability, and the impact of asthma control stability on unscheduled use of healthcare resources.

Results: In patients achieving well-controlled or totally controlled asthma, at least well-controlled asthma was maintained for a median of almost 3 and 6 months, and for more than 85% and 95% of weeks of follow-up, respectively. A high level of stability was confirmed in a Markov analysis investigating transitional probability of change in control status. Variability in control was associated with increased probability of an unscheduled healthcare resource use (odds ratio: 1.06, $P < 0.001$).

Conclusions: Most patients achieving guideline-defined control can maintain at least a similar level of control with regular, stable dosing, with little likelihood of losing control.

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The goal of asthma treatment is to achieve and maintain control of asthma (1–6). With this aim, the recently revised Global INitiative for Asthma (GINA) guidelines recommend a management strategy that involves regular assessment, with adjustments made to maintenance treatment based on control status (4). This means increasing treatment if asthma is uncontrolled or partially controlled, and once control is achieved, maintaining or stepping down treatment to the lowest dose that maintains control. To date, however, few studies have used composite measures to examine in detail the level of stability and potential duration of control that can be maintained following constant treatment over a period of months. Such information could be beneficial when advising patients what to expect once control is achieved, and when deciding how long to continue with stable dosing until step-down is attempted.

The concept of stability as an outcome measure has received little attention in the literature; however, it has recently been recognized as a component of 'future risk' in the guidelines, alongside severe exacerbations, lung function decline and long-term side effects of asthma treatment (7). Stability of asthma control could also be viewed as the converse of variability, aspects of which are diurnal variation in peak expiratory flow (PEF) (8, 9), periodic breakthrough symptoms and intermittent use of rescue bronchodilator. In clinical trials, these have been reported as poorly controlled asthma days or asthma exacerbation days (10, 11), but the current version of the GINA guidelines suggests the use of a simple composite measure for this purpose, assessed either weekly or monthly (4).

The Gaining Optimal Asthma controlL (GOAL) study, which was designed to determine the proportion of patients that can achieve a guideline-defined level of

control (12), also provided the opportunity to examine the nature of asthma control, and the stability of control once it was achieved. The control levels achieved during the last 8 weeks of Phase I were defined as totally controlled, well-controlled or not well-controlled asthma. In Phase II of the study, which began when patients achieved a predefined level of control (total control) or had increased treatment to the highest specified dose, patients continued on a stable dose until the end of the 52-week study. In this report, we examine the relationship between the level of control achieved during Phase I (the current level of control) and 'future risk' of instability (weeks in which control is lost), exacerbations, and unscheduled healthcare resource use (13–15).

Methods

Study design

Details of the GOAL study design have been published previously (12), and are briefly summarized here. Patients aged between 12 and 80 years, with at least a 6-month history of asthma and reversible airflow limitation, were recruited by investigators from general practice and hospital clinics across 44 countries. During a 4-week run-in period, patients continued on their usual dose (if any) of inhaled corticosteroid (ICS); patients with less than two well-controlled weeks were randomized to receive either SFC (Seretide®/Advair®, Viani®; GlaxoSmithKline, Middlesex, UK) or FP (Flixotide®/Flovent®; GlaxoSmithKline). Patients were stratified according to their previous ICS use: Stratum 1, no ICS; Stratum 2, ≤ 500 µg beclomethasone dipropionate daily or equivalent; or Stratum 3, > 500 –1000 µg beclomethasone dipropionate daily or equivalent.

During Phase I of the study (dose escalation), treatment was stepped up every 12 weeks until asthma was totally controlled or the maximum dose of study drug was reached (12). Patients who achieved total asthma control entered Phase II, and for the remainder of the study, continued on the dose at which their asthma had become totally controlled. Patients whose asthma did not become totally controlled entered Phase II after 12 weeks at the maximum study dose, and remained on that dose until the end of the study. Therefore, the duration of Phase II could be 16, 28 or 40 weeks.

Definitions of totally controlled and well-controlled asthma

A week of totally controlled asthma was defined as none of the following each week: daytime symptoms, use of rescue salbutamol/albuterol, night-time awakenings, exacerbations (defined as a deterioration in asthma requiring treatment with an oral corticosteroid or an emergency department visit, and/or hospitalization), emergency visits or treatment-related adverse events (AE) enforcing a change in therapy. In addition, patients had a morning PEF of $\geq 80\%$ predicted for every day. A patient was considered totally controlled if these criteria were met for 7 out of the 8 weeks.

To have had a week of well-controlled asthma, a patient had to meet the same criteria as total control for night-time awakenings, exacerbations, emergency visits, and treatment-related AE. Patients also had to achieve two out of the following: ≤ 2 days with a daytime symptom score > 1 ; ≤ 2 days and ≤ 4 occasions of rescue

medication use; or morning PEF $\geq 80\%$ predicted every day. A patient was considered well controlled if these criteria were met for 7 out of the 8 weeks. Patients whose asthma did not meet the criteria for at least well controlled were considered to have asthma that was not well controlled.

Statistical analyses

Proportion of time controlled in Phase II. Weekly assessments of control during Phase II were used to determine the mean proportion of time that patients achieved the specified levels of asthma control (i.e. totally controlled or at least well controlled), according to control status at the end of Phase I.

Proportion of patients maintaining control in Phase II. The proportion of patients whose asthma stayed totally controlled or well controlled (i.e. at least well controlled) was calculated by treatment group and control status in Phase I on a week-by-week basis throughout Phase II.

Duration of uninterrupted control in Phase II. The number of consecutive weeks that patients remained at the specified level of asthma control that they achieved in Phase I without slipping to a lower level of control, or in the case of well-controlled asthma, either totally or well controlled was calculated. The time until the first week that patients were not well controlled during Phase II was also calculated.

Probability of maintaining or improving weekly control status. The probabilities of achieving asthma control during any given week in Phase II were calculated using an alternative logistic regression model with exchangeable log odds ratios (OR). Age, sex, forced expiratory volume in 1 s (FEV₁) at baseline, treatment dose during Phase II, stratum, control status at the end of Phase I and treatment group were all included in the model as covariates. An alternative logistic regression accounts for the association between the measurements within a given patient and models the associations between pairs of responses with log OR, which correspond to the coefficients. This contrasts with traditional generalized estimating equations that model associations with correlations. The model was fitted using SAS Proc Genmod (sas v8.2, Cary, NC, USA).

Probability of moving to or remaining at a given level of weekly control status. Weekly transition probability was defined as the probability of a patient moving from one level of control to another or remaining at a particular level after having been at that level of control for 1 week. Four disease control levels were defined: totally controlled, well controlled, not well controlled without exacerbation, and not well controlled with exacerbation. Transition probabilities between the control levels were computed using a Markov model (Fig. 1) (15).

Unscheduled healthcare resource use. The impact of asthma control stability on unscheduled healthcare resource use was investigated by determining the probability of an unscheduled resource use event (an unscheduled general practice or hospital visit, or a home visit by the general practitioner) occurring during Phase II. This probability was modelled using a logistic regression analysis, adjusting for age, sex, baseline FEV₁, stratum, geographical region, treatment received, mean level of control, and variability in control. The weekly probability of having an unscheduled healthcare resource-use event was modelled using an alternative logistic regression

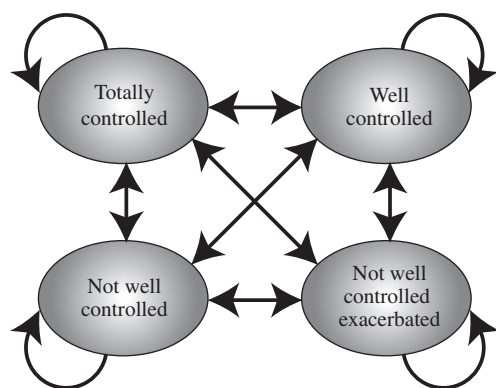


Figure 1. Markov model: transitional probability [transitional probability independent of time (homogeneous)] of changing control status. Totally controlled week: no daytime symptoms, use of rescue salbutamol/albuterol, night-time awakenings, exacerbations, emergency visits or treatment-related adverse events enforcing a change in therapy and morning PEF $\geq 80\%$ predicted every day; well-controlled week: no night-time awakenings, exacerbations, emergency visits or treatment-related adverse events; plus, two of the following: ≤ 2 days with a daytime symptom score > 1 ; ≤ 2 days and ≤ 4 occasions of rescue medication use; or morning PEF $\geq 80\%$ predicted every day; not well controlled: did not meet criteria for totally or well controlled; not well controlled exacerbated: did not meet criteria for totally or well controlled with asthma exacerbations.

analysis with repeated measures, adjusting for age, sex, baseline FEV₁, mean level of control, and variability in control over the weeks of the evaluation period preceding the week of interest. Mean level of control was defined as the mean score for each patient during Phase II. Patients were scored as not well controlled with exacerbation (0); not well controlled without exacerbation (1); well controlled (2); or totally controlled (3). Variability in control was computed as the coefficient of variation of the scores for each patient reported during Phase II.

Results

Patient characteristics

Baseline characteristics for the intention-to-treat population ($n = 3416$) were similar between treatment groups within each stratum as previously reported (12). Further details of patient characteristics, including reasons for withdrawal in each phase of the study are described elsewhere (12), along with results relating to response to treatment (12), improvements in health status (16), and individual clinical endpoints (17).

Proportion of time controlled in Phase II

Across all three strata, patients whose asthma was totally controlled in Phase I remained totally controlled for most of the time in Phase II (Fig. 2). For example, patients in Stratum 1 (steroid-naïve) who were totally controlled at the end of Phase I remained totally controlled for a mean

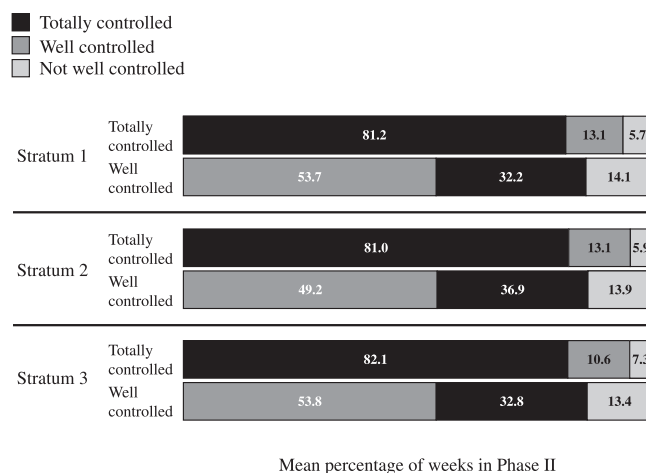


Figure 2. Proportion of time that asthma was controlled during Phase II according to control status at the end of Phase I. Patients who were totally controlled in Phase I: Stratum 1, $n = 391$; Stratum 2, $n = 302$; Stratum 3, $n = 153$. Patients who were well controlled in Phase I and had data in Phase II: Stratum 1, $n = 314$; Stratum 2, $n = 385$; Stratum 3, $n = 318$.

of 81.2% (standard deviation [SD]: 23.4%) of the weeks in Phase II. In Stratum 1, patients who were previously well controlled remained well controlled for 53.7% (SD: 34.9%) of the time and, for 32.2% (SD: 36.2%) of the time, the level of control improved, such that these patients' asthma was considered to be totally controlled. Therefore, this group was considered to be at least well controlled for a mean of 85.9% (SD: 22.8%) of the time. Similar results were seen for other strata.

Proportion of patients maintaining control in Phase II

Most patients whose asthma was either totally or well controlled at the end of Phase I remained at least well controlled each week (Fig. 3). Approximately 35–45% of the patients whose asthma was not well controlled at the end of Phase I had a week of at least well-controlled asthma at the end of Phase II.

Duration of uninterrupted control in Phase II

Once total control had been achieved in Phase I, patients maintained that level of control for at least 3 months (mean number of weeks [SD]: 12.6 [12.3], 12.2 [12.3] and 14.3 [13.4]) weeks for patients in Strata 1, 2, and 3, respectively, and 20.3–23.0% of the patients remained totally controlled until the end of the double-blind period, depending on the stratum.

The mean number of weeks to first week of not well-controlled asthma was longer for patients who were totally controlled at the end of Phase I, compared with those who were well controlled. Patients who had achieved total asthma control at the end of Phase I

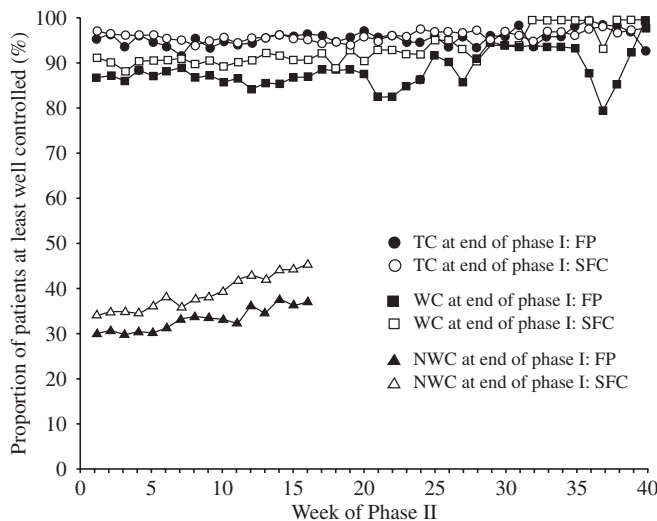


Figure 3. Proportion of patients with at least well-controlled asthma during Phase II. Patients who were totally controlled (TC) in Phase I and had data in Phase II (pooled data from all strata): fluticasone propionate (FP), $n = 328$; salmeterol/fluticasone propionate combination (SFC), $n = 518$. Patients who were well controlled (WC) in Phase I and had data in Phase II: FP, $n = 495$; SFC, $n = 522$. Patients who were not well controlled (NWC) in Phase I and had data in Phase II: FP, $n = 668$; SFC, $n = 507$.

maintained at least well-controlled asthma for approximately 5–6 months (mean 21.4–23.8 weeks, depending on the stratum). Patients whose asthma was well controlled at the end of Phase I spent approximately 3 months with at least well-controlled asthma (mean 11.1–14.0 weeks, depending on the stratum).

Probability of maintaining or improving weekly control status

The achievement of a higher level of control at the end of Phase I was predictive of an increased likelihood of being controlled during Phase II. Patients who were totally controlled at the end of Phase I were 31 times more likely to be totally controlled during Phase II than were patients who were not well controlled at the end of Phase I (OR: 30.5; 95% confidence interval [CI]: 24.46–38.02; $P < 0.001$). Similarly, totally controlled patients were seven times more likely to be totally controlled during Phase II than were patients who were only well controlled at the end of Phase I (OR: 6.63; 95% CI: 5.56–7.92; $P < 0.001$). The type of treatment received was found to have a significant impact on the weekly probability of being totally controlled. After adjustment for control status at the end of Phase I, patients receiving SFC were 1.2 times more likely to be totally controlled than those receiving FP alone (OR: 1.2; 95% CI: 1.05–1.37; $P = 0.007$), and 1.27 times more likely to be at least well controlled compared with FP alone (OR: 1.27; 95% CI: 1.12–1.45; $P < 0.001$).

Table 1. Transitional probability (%) of control status in any week of Phase II according to control status in the previous week, by stratum

Control status in previous week	Control status in any week of Phase II				Total
	TC	WC	NWC (–E)	NWC (+E)	
Stratum 1					
TC	89.4	7.8	2.8	0.1	100.0
WC	18.8	70.0	11.1	0.1	100.0
NWC (–E)	7.0	17.1	75.5	0.4	100.0
NWC (+E)	4.6	21.5	16.9	56.9	100.0
Stratum 2					
TC	88.0	8.9	3.1	0.1	100.0
WC	16.6	72.4	10.9	0.2	100.0
NWC (–E)	4.9	14.5	80.3	0.3	100.0
NWC (+E)	15.2	10.9	14.1	59.8	100.0
Stratum 3					
TC	83.7	12.2	3.9	0.2	100.0
WC	12.1	73.4	14.1	0.4	100.0
NWC (–E)	2.8	12.2	84.4	0.6	100.0
NWC (+E)	5.6	9.4	21.3	63.7	100.0

TC, totally controlled; WC, well controlled; NWC, not well controlled; –E, without exacerbation; +E, with exacerbation.

Table 2. Logistic regression modelling of unscheduled healthcare resource use during Phase II

	Odds ratio	95% CI	P-value
Intra-patient CV	1.06	1.05–1.07	<0.001
Mean level of control	0.74	0.54–1.01	0.061
Patients treated with SFC vs FP	1.06	0.77–1.46	0.715
Patients in Stratum 1 vs Stratum 3	0.41	0.27–0.63	0.009
Patients in Stratum 2 vs Stratum 3	0.49	0.33–0.72	0.141

Results from a logistic regression with age, sex, FEV₁ at baseline, dose over Phase II, treatment, geographical region, stratum, mean level of control and variability in control (measured by the intra-patient coefficient of variation [CV]). CI, confidence interval; FP, fluticasone propionate; SFC, salmeterol/fluticasone propionate combination.

Probability of moving to or remaining at a given level of weekly control status

Table 1 shows the results of Markov modelling to determine the transitional probabilities of a given level of control in any week of Phase II, according to patients' control status the previous week. Patients whose asthma was controlled at any given week were more likely to remain at the same level of control the following week.

Unscheduled healthcare resource use

The number of unscheduled visits was 102 with FP and 94 with SFC. Variability in asthma control was found to be associated with an increasing probability of an unscheduled healthcare resource use event ($P < 0.001$) (Table 2). As the within-subject variability increases, there is a corresponding increase in the probability of an unscheduled healthcare resource use event. Variability in control

was also statistically significantly predictive of the presence of an unscheduled healthcare resource-use event on a weekly basis ($P < 0.001$).

Discussion

The findings from this analysis of the GOAL study demonstrate that once asthma control is achieved for 8 weeks, the 'future risk' of instability, measured as weeks during which patients are uncontrolled, is greatly reduced. The probability of becoming uncontrolled is inversely associated with the level of control achieved. Higher stability (lower variability) in asthma control is also associated with a lower future probability of unscheduled healthcare resource use, a finding that is likely to translate into better Quality of Life (QoL) and cost savings for patients with asthma.

Stability of control – meaning sustained prevention of symptoms with low or no reliever use and no exacerbations for long periods of time – was analysed in three ways, each providing a different dimension of control. Patients who achieved total asthma control during dose escalation maintained guideline-defined control continuously for a median duration of approximately 6 months, and patients who achieved well-controlled asthma maintained control for a median duration of approximately 3 months. Patients who had achieved total control spent more than 90% of weeks at least well controlled, but patients who were well controlled at the end of Phase I spent more than 80% of weeks well controlled.

It is notable that patients who were well controlled at the end of Phase I improved to being totally controlled during more than one-third of the weeks in Phase II, indicating that with stable dosing patients tend to improve further. In the group of patients who were not well controlled during the assessment period at the end of Phase I, up to 45% of patients were at least well controlled each week during Phase II, confirming the benefit of sustained treatment in patients who have difficulty in achieving control (18).

The week-by-week transitional probabilities, relating to the likelihood of a patient's control status changing from one level of control to another, represent asthma control stability in a way that is relevant to patients. Specifically, the information indicates how likely it is that a patient's asthma will be controlled in the next 7 days, on the basis of control status in the previous 7 days. Patients achieving guideline-defined control were highly likely to remain controlled, with an approximately equal probability (~10%) of improving or deteriorating from one level to another. Perhaps even more important to patients, for whom the unpredictability of asthma reduces QoL, is the knowledge that if in the previous week they were well or totally controlled, the probability (as predicted by Markov modelling) of experiencing a week in which control is lost and accompanied by a severe exacerbation is very low

(probabilities of $\leq 0.2\%$ and $\leq 0.4\%$, respectively, for previously totally and well-controlled asthma).

Patients were stratified on the basis of prior treatment with ICS during the last 6 months, and all were not well controlled at entry. A greater proportion of patients in Stratum 1 (no prior ICS use) achieved control during the dose-escalation phase with either treatment than did those in Strata 2 and 3 (prior low- or moderate-dose ICS users). However, for those who achieved control (either well or totally controlled), the differences between strata were relatively small, whether expressed as median weeks of continuous control, percentage weeks controlled, or in the Markov model (Table 1; Fig. 2). The only difference was a significantly higher rate of unscheduled healthcare resource use in patients in Stratum 3 (prior moderate-dose ICS users) compared with Stratum 1 (no prior ICS use). These results confirm that stability is largely a function of control, and relatively independent of asthma severity or treatment responsiveness.

Significantly more patients receiving SFC entered Phase II totally or well-controlled than did patients receiving FP alone (12). The current analysis provides insights into the relative efficacy of the two treatments in maintaining asthma control when continued at a stable dose for a period of months. No significant difference was observed in the time spent controlled during Phase II, or in unscheduled healthcare resource use, suggesting that reduction in these outcomes is related to the level of control achieved, rather than the treatment received. When adjustment was made for control status at the end of Phase I, the treatment difference was reduced; however, SFC was still associated with a higher overall probability of being either totally controlled or well controlled during each week of follow-up in Phase II than was FP. This shows that more patients receiving SFC than FP improved their level of control during Phase II.

This study provides new data relating to maintenance of control once it is achieved that is relevant to recommendations made in the current version of the GINA guidelines (4). First, control can be maintained with great stability in most patients following stable dosing with the same treatment with which control was achieved, and that this is associated with reduced unscheduled healthcare resource use. Second, the degree of stability achieved correlates with the level of control achieved, i.e. future risk of instability and exacerbations is predicted by the current level of control. Finally, the results confirm that treatment with SFC results in more weeks with higher levels of control during follow-up than is achieved with FP alone, and with lower probability of losing control. This stabilizing effect of a long-acting β_2 -agonist in reducing minor breakthrough of asthma symptoms is consistent with the results of other studies (19).

Although the GOAL study did not attempt to examine guideline recommendations for stepping down treatment once control is achieved, this analysis does provide some information relevant to decisions regarding treatment

step-down. Based on our findings, the guideline recommendation that an attempt to step down treatment be made after 3 months of controlled asthma appears appropriate (4, 7). There might be some benefits in maintaining treatment for longer in patients who are well controlled, these include greater number of weeks with total control and potentially improving features such as airway hyper-responsiveness (a parameter that was not measured in this study) (20). However, studies on step-down of treatment provide evidence that most patients with well-controlled asthma can do so without losing control, although fewer lose control if SFC rather than FP is used (12).

The analyses presented here have several limitations. First, the defined levels of control, although based on the goals of treatment of GINA guidelines, were arbitrary and are not identical to the categories of 'controlled', 'partly controlled', and 'uncontrolled' subsequently presented in the current version of the guidelines (4). However, the categories are similar, and the quantitative differences in observations between the three levels of control observed in this study support the validity of such subdivisions. The GOAL definitions of control have been validated and published (21). Second, these analyses are *post hoc*, although they utilize prospectively collected data. A third limitation of the analysis is the low level of

exacerbations during Phase II. This limited examination of the relationship between control level and future risk of an exacerbation, in spite of the large size of the study.

In conclusion, this analysis demonstrates that with the regular use of treatment at a stable dose, most patients who achieve guideline-defined control can maintain it for prolonged periods. Patients achieving the highest levels of control were most likely to remain at a high level of control, and conversely, patients who were not well controlled, and therefore experiencing variable asthma control, were those most likely to require unscheduled healthcare resources. This highlights the potential benefits of treatment to achieve and maintain asthma control as recommended by international management guidelines.

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