Internet-based tapering of oral corticosteroids in severe asthma: a pragmatic randomised controlled trial

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ABSTRACT

Background In patients with prednisone-dependent asthma the dose of oral corticosteroids should be adjusted to the lowest possible level to reduce long-term adverse effects. However, the optimal strategy for tapering oral corticosteroids is unknown.

Objective To investigate whether an internet-based management tool including home monitoring of symptoms, lung function and fraction of exhaled nitric oxide (FeNO) facilitates tapering of oral corticosteroids and leads to reduction of corticosteroid consumption without worsening asthma control or asthma-related quality of life.

Methods In a 6-month pragmatic randomised prospective multicentre study, 95 adults with prednisone-dependent asthma from six pulmonary outpatient clinics were allocated to two tapering strategies: according to conventional treatment (n=43) or guided by a novel internet-based monitoring system (internet strategy) (n=52). Primary outcomes were cumulative sparing of prednisone, asthma control and asthma-related quality of life. Secondary outcomes were forced expiratory volume in 1 s (FEV1), exacerbations, hospitalisations and patient’s satisfaction with the tapering strategy.

Results Median cumulative sparing of prednisone was 205 (25-75th percentile −221 to 777) mg in the internet strategy group compared with 0 (−497 to 282) mg in the conventional treatment group (p=0.02). Changes in prednisone dose [mixed effect regression model] from baseline were −4.79 mg/day and +1.59 mg/day, respectively (p<0.001). Asthma control, asthma-related quality of life, FEV1, exacerbations, hospitalisations and satisfaction with the strategy were not different between groups.

Conclusions An internet-based management tool including home monitoring of symptoms, lung function and FeNO in severe asthma is superior to conventional tapering in reducing total corticosteroid consumption without compromising asthma control or asthma-related quality of life.

Clinical trial registration number Clinical trial registered with http://www.trialregister.nl (Netherlands Trial Register number 1146).

INTRODUCTION

Despite the regular use of high doses of inhaled corticosteroids (ICS) and long-acting bronchodilators, patients with severe asthma may require frequent bursts or even depend on daily oral corticosteroids. In the majority of these patients the use of systemic corticosteroids leads to serious adverse effects including osteoporosis, bone fractures, diabetes, hypertension, cataract and muscle weakness. These adverse effects may seriously affect patients’ quality of life and have considerable public health implications. Since adverse effects are dose- and time-dependent, systemic corticosteroids should be used in the lowest possible dose.

Tapering oral corticosteroids in patients with severe asthma remains a challenge. These patients—although relatively few—generally require considerable time and resources because their disease is often complicated by comorbidities, steroid resistance and fixed airflow limitation. Moreover, patients with a suppressed hypothalamic-pituitary-adrenal axis or psychological dependencies may have unpredictable or unsuspected responses to tapering. This is why patients are often prescribed higher doses of oral corticosteroids than are strictly indicated, which leads to unnecessarily high cumulative doses of oral corticosteroids.

Currently, there are no guidelines on how to taper oral corticosteroids safely in severe asthma. Clinicians generally make occasional attempts to reduce the dose of oral corticosteroids based on...
symptoms, physical signs and lung function. Ideally, tapering should be a continuous, dynamic and personalised process based on frequent evaluations, objective parameters of disease severity and constant monitoring of risks. In conventional settings it can be quite complicated to achieve this ideal situation, both for patients and physicians. Internet-based management strategies have therefore been developed to enhance the feasibility and effectiveness of intensive monitoring. Many examples of internet-based applications can be found in the management of chronic diseases and severe patients including HIV, diabetes, hypertension, asthma and lung transplantation. The recent development of hand-held devices to measure lung function and exhaled biomarkers at home also provide new opportunities for more frequent and accurate adjustments of asthma therapy.

Comparative effectiveness research is increasingly applied in asthma to evaluate the outcome of clinical interventions. It provides the basis for rational decision-making about the care of individual patients with asthma and how best to deliver this care in real-world settings. We therefore designed this pragmatic randomised clinical trial to assess the outcome (cumulative dose of oral corticosteroids, asthma control and asthma-related quality of life) of an internet-based management tool in comparison with conventional asthma treatment over a period of 6 months.

METHODS

Subjects
Eligible patients were adults (18–75 years) with a diagnosis of severe refractory asthma according to the major and minor criteria recommended by the American Thoracic Society. They had uncontrolled asthma despite intensive follow-up by an asthma specialist for at least 1 year, chronic treatment with oral corticosteroids and high doses of ICS plus long-acting bronchodilators. All were non-smokers with a maximum smoking history of 15 pack-years and had access to internet or mobile telephone.

Study design
We conducted a 6-month pragmatic prospective randomised controlled study involving outpatients from two academic tertiary care hospitals and four large community hospitals in The Netherlands. The study was designed according to the CONSORT recommendations for pragmatic trials. Patients were randomly allocated to one of two strategies: dose adjustment of oral corticosteroids guided by an internet-based management tool (internet group) or according to conventional asthma treatment by the pulmonologist (conventional management group). All patients were followed for 6 months and had the same monthly follow-up visit at their own pulmonologist. Pulmonologists were instructed not to change the maintenance dose of ICS during the study unless strictly necessary on clinical grounds.

Internet group
The internet-based management tool comprised (1) an electronic diary; (2) treatment decision support for the patients; and (3) monitoring support by a study nurse.

Electronic diary
Patients recorded symptoms, registered their dose of oral corticosteroids, lung function using a hand-held spirometer (Piko-1; Ferraris Respiratory, Hertford, UK) and exhaled nitric oxide (FE\textsubscript{NO}) using a hand-held NO analyser (Niox Mino; Aerocrine AB, Solna, Sweden) before medicine intake on a daily basis.

Asthma control questionnaires (ACQ) were completed weekly and asthma-related quality of life questionnaires (AQLQ) were completed at baseline and every 3 months thereafter. Patients registered their data via a validated asthma monitoring service using an internet application or SMS messages. They also registered every event related to asthma such as antibiotic intake, emergency room visits or deterioration of symptoms. At the end of the study patients rated their global satisfaction with the tapering strategy on a 7-point scale ranging from ‘absolutely not satisfied’ to ‘completely satisfied’.

Treatment decision support
Patients had daily information about their asthma graphically on the web page and received weekly instructions via the web page for stepwise corticosteroid dose adjustments according to a built-in algorithm (table 1). The decision rule of this algorithm was based on week-to-week changes in mean levels of FE\textsubscript{NO} and ACQ as follows. If asthma remained controlled (change in ACQ < +0.5), the algorithm recommended down-titration by one dose step. If asthma control deteriorated, the algorithm recommended up-titration of the corticosteroid dose only in case of a concomitant increase in FE\textsubscript{NO}>10 ppb; this was to avoid an increase in the dose of oral corticosteroids for reasons other than a flare-up of asthmatic airway inflammation.

Monitoring support
A study nurse was responsible for coaching the patients, monitoring the data entered at the web page and facilitating the communication between patients and pulmonologists.

The pulmonologists were not aware of any of the data registered on the study website but were contacted by the study nurse in case of an imminent exacerbation (decrease in morning FE\textsubscript{V}1 of at least 10% compared with mean FE\textsubscript{V}1 from the week before). In case of an exacerbation they could overrule the internet dose prescription. The tapering algorithm was then interrupted and immediately restarted at the end of the steroid burst.

<table>
<thead>
<tr>
<th>Panel A</th>
<th>Δ ACQ ≥ +0.5</th>
<th>Δ ACQ &lt; +0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔF\textsubscript{NO} &gt; +10 ppb and &gt;10%</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>ΔF\textsubscript{NO} &gt; +10 ppb and ≤10%</td>
<td>=</td>
<td>↓</td>
</tr>
<tr>
<td>ΔF\textsubscript{NO} ≤ −10 ppb</td>
<td>=</td>
<td>↓</td>
</tr>
<tr>
<td>ΔF\textsubscript{NO} &lt; −10 ppb</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Panel B</th>
<th>Maintenance dose (mg/day)</th>
<th>Dose steps (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;25</td>
<td>Increase or decrease 10 mg</td>
<td></td>
</tr>
<tr>
<td>20–25</td>
<td>Increase or decrease 5 mg</td>
<td></td>
</tr>
<tr>
<td>10–20</td>
<td>Increase or decrease 2.5 mg</td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>Increase or decrease 2.5 mg every other day</td>
<td></td>
</tr>
</tbody>
</table>

Panel A shows the criteria for dose adjustment of prednisone based on daily FE\textsubscript{NO} values and weekly ACQ score. Panel B shows the dose steps for the adjustment of prednisone maintenance dose. Δ ACQ denotes difference of Asthma Control Questionnaire scores between 2 weeks. Δ F\textsubscript{NO}= difference of mean fraction of exhaled nitric oxide between 2 weeks (in parts per billion). ↑ denotes increase of prednisone dose by one step; = denotes no change in prednisone dose; ↓ denotes decrease in prednisone dose by one step.

Table 1 Criteria for dose adjustment of oral corticosteroids in the internet-based management group with corresponding dose steps

Conventional management group

Patients in the conventional management group visited the pulmonology outpatient clinic every month and had their oral corticosteroids down-titrated according to the prescription by the pulmonologist. Pulmonologists followed the Global Initiative for Asthma (GINA) guidelines for treatment of patients with severe asthma and were instructed to down-titrate the dose of oral corticosteroids whenever possible on clinical grounds.

For research purposes the patients in the conventional management group were asked to enter their daily dose of corticosteroids in the study website and, for safety reasons, they also registered symptoms and lung function which were accessible to the study nurse only.

Randomisation and masking

Randomisation was stratified for study centre and initial oral corticosteroid dose (lower or higher than 10 mg prednisone equivalent/day). Patients were randomised by a computer random number generator and remained on the same allocation throughout the study. The treatment assignments were unblinded after randomisation to allow monthly corticosteroid dose adjustments according to conventional treatment by the physician or weekly adjustments according to the internet algorithm.

Outcome measures

The primary outcomes were cumulative sparing of oral corticosteroids (actual cumulative dose minus the expected cumulative dose) and (equivalence in) ACQ and AQLQ. Secondary outcomes were global satisfaction scale and (equivalence in) FEV₁, number of exacerbations and days of hospitalisation. The actual cumulative dose was calculated from the doses registered daily on the website and the expected cumulative dose was extrapolated from the daily dose at study entry. An exacerbation was defined as a decrease in morning FEV₁ of at least 10% compared with the mean FEV₁ from the week before, or a respiratory event requiring an increase in prednisone equivalent to at least 10 mg/day, or a course of antibiotics, with or without hospitalisation.

Newly diagnosed severe adverse effects of corticosteroid use during the study were documented for safety reasons.

Figure 1

Assessment, randomisation and follow-up of the study patients.

Randomisation was stratified but without blocking, which explains the unequal number of patients in each study group.
analysed with mixed effects regression models including time, treatment strategy and their interaction as covariates, and with random patient effects for the intercept and the regression weight of time on oral corticosteroid treatment. The effect of time was modelled with a linear model and the goodness of fit was checked by introducing higher order polynomial terms of time into the model. The fit of the covariance structure of the residuals was checked by extending the model with an autoregressive structure. Histograms of the residuals were further inspected for normality. The main trend in the average change with time of the average corticosteroid usage was summarised with the change rate estimated from the linear model.

The repeated measurements of the ACQ and AQLQ were analysed in a similar fashion but the dependent variables were the change from baseline ACQ and AQLQ, respectively. The effect of time on average change in ACQ and AQLQ was modelled non-parametrically and summarised with the change from baseline ACQ and AQLQ averaged over all repeated measurements during follow-up.

RESULTS

Ninety-five patients were randomised from November 2007 to October 2008. Five patients in the conventional management group withdrew consent before the study had started and one patient was excluded from the study because of poor adherence to the trial protocol (figure 1). Eighty-nine patients were included in the intention-to-treat analysis (table 2); 51 and 38 patients were randomised to internet-based and conventional management, respectively. Randomisation was stratified without using allocation blocks, which explained the unequal number of patients in each study group.

The median dose of prednisone equivalent at study entry was 10 (25–75th percentile 5–15) mg/day in the internet group and 10 (5–15) mg/day in the conventional management group (p = 0.26). Other baseline characteristics of the study groups were equally similar (table 2).

Sparing of oral corticosteroids

The median cumulative sparing of prednisone equivalent in 6 months was 205 (25–75th percentile −221 to 777) mg in the internet group compared with 0 (−497 to 282) mg in the conventional management group (p = 0.02, table 3).

Mixed effects regression model analysis showed a total decrease in daily prednisone requirement from baseline of −4.79 mg/day (daily decrease of −0.019 (SE 0.0014) in the internet group compared with +1.59 mg/day (daily increase +0.001 (SE 0.0032)) in the conventional management group (p < 0.001, figure 2). Ten of 51 patients in the internet group and none of the patients in the conventional management group (p = 0.004) managed to taper their oral corticosteroid dose to 0 mg, with a mean (SD) duration of 79.7 (12.8) oral corticosteroid-free days over 6 months.

ACQ and AQLQ

Asthma control remained stable in both groups with a mean change in ACQ score of 0.26 (95% CI 0.07 to 0.45) and 0.12 (95% CI −0.12 to 0.36) in the internet group and conventional management groups, respectively (p = 0.57).

Similarly, changes in asthma-related quality of life did not differ between the study groups (table 3) with mean changes in the AQLQ score of −0.05 (95% CI −0.24 to 0.18) and 0.14 (95% CI −0.13 to 0.41) in the internet and conventional management groups, respectively (p = 0.50).

Secondary and additional outcomes

Changes in FEV₁, number of asthma exacerbation, days of hospitalisation and patients’ global satisfaction with the strategy were not different between the two groups (table 3).

The median (range) change in dose of ICS was 125 (−250 to 250) μg/day in the conventional management group versus no change (0 to 250) μg/day in the internet strategy group (p = 0.01).

Monitoring adverse events

Three patients had newly diagnosed severe adverse effects (diabetes in two patients and glaucoma in one patient).

Internet algorithm

Compliance with measuring FEV₁, FENO, ACQ and entering the data into the website was very high (88.8% in the conventional treatment group, 89.6% in the internet strategy group and 89.3% in the whole group).

The computer algorithm was overruled by the pulmonologist in 57 of 1023 decisions. The main reasons for these were to slow down the pace of steroid tapering (65%), to treat an exacerbation (9.7%) or to increase the oral corticosteroid dose based on clinical grounds (9%). On eight occasions the patients themselves decided not to follow the computer advice for a variety of reasons.

ACQ and FENO contributed to the decisions of the computer algorithm in 859 (84%) and 164 (16%) cases, respectively (table 4). There was no difference in total tapering dose of oral

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**Table 2**  Baseline characteristics of subjects in the intention-to-treat population

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Internet group (n=51)</th>
<th>Conventional management group (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.8 (±12.4)</td>
<td>52.4 (±11.7)</td>
</tr>
<tr>
<td>Male sex, n (% total n)</td>
<td>23 (45)</td>
<td>18 (47)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>28.3 (±5.4)</td>
<td>30 (±8.8)</td>
</tr>
<tr>
<td>Atopy, n (% total n)</td>
<td>23 (45)</td>
<td>19 (50)</td>
</tr>
<tr>
<td>Age of asthma onset (years)</td>
<td>26 (4–42)</td>
<td>24.5 (3–40)</td>
</tr>
<tr>
<td>Duration of OCS use (months)</td>
<td>36 (12–132)</td>
<td>46 (12–120)</td>
</tr>
<tr>
<td>Dose of prednisone (mg/day)</td>
<td>10 (5–15)</td>
<td>10 (5–15)</td>
</tr>
<tr>
<td>Dose of ICS (μg/day)*</td>
<td>1250 (750–1500)</td>
<td>1000 (750–1500)</td>
</tr>
<tr>
<td>Never smokers, n (% total n)</td>
<td>30 (58.8)</td>
<td>21 (55.3)</td>
</tr>
<tr>
<td>Pack-years (only ever smokers)</td>
<td>3 (3.1–9.7)</td>
<td>5 (3.6–12)</td>
</tr>
<tr>
<td>Pre-bronchodilator FEV₁†</td>
<td>2.52 (±1.02)</td>
<td>2.40 (±1.42)</td>
</tr>
<tr>
<td>% Predicted</td>
<td>76.3 (±24.7)</td>
<td>71.3 (±21)</td>
</tr>
<tr>
<td>Change in FEV₁ after β₂ ( % )†</td>
<td>7.2 (1.3–13.5)</td>
<td>8.5 (3.1–18)</td>
</tr>
<tr>
<td>Pre-bronchodilator FVC †</td>
<td>3.24 (±1.5)</td>
<td>3.58 (±0.9)</td>
</tr>
<tr>
<td>% Predicted</td>
<td>113 (±11.1)</td>
<td>94 (±15.5)</td>
</tr>
<tr>
<td>FVC/FVC ratio</td>
<td>0.63 (±0.18)</td>
<td>0.69 (±0.49)</td>
</tr>
<tr>
<td>Exhaled nitric oxide (ppb)†</td>
<td>38 (18–81)</td>
<td>34 (13–75)</td>
</tr>
<tr>
<td>Juniper ACQ score‡</td>
<td>2.2 (±1.11)</td>
<td>2.5 (±0.95)</td>
</tr>
<tr>
<td>Juniper AQLQ score§</td>
<td>5.0 (±1.06)</td>
<td>4.6 (±1.18)</td>
</tr>
</tbody>
</table>

Data are presented as median (25–75th percentile) or mean ± SD unless otherwise stated. Atopy is defined as at least one positive radioallergosorbent test for common aeroallergens. All p values are >0.05.

*The doses of all ICS were converted to the equivalent dose of fluticasone.
†FEV₁, FVC and exhaled nitric oxide measured at study baseline visit.
‡The Juniper Asthma Control Questionnaire score ranges from 0 to 7, with higher scores indicating worse control.
§The Juniper Quality of Life Questionnaire score ranges from 1 to 7, with higher scores indicating better quality of life.

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroids; OCS, oral corticosteroids; ppb, parts per billion.
The use of airway responsiveness, 26 eosinophils in prolonged use. The adjustment of ICS guided by objective how to taper oral corticosteroids safely in asthma after
considered as a safe and feasible way to adjust the dose of oral monitoring of objective measures of asthma control should be
These results suggest that a strategy based on intensive internet
compromising asthma control or asthma-related quality of life.
conventional treatment over a period of 6 months without
patients with steroid-dependent asthma compared with
This study shows that an internet-based management tool has
dosing and effect of OCS guided by objective
patients’ rate for their satisfaction with the tapering strategy from 1 (absolutely not satisfied) to 7 (really satisfied).

**DISCUSSION**

This study shows that an internet-based management tool has the potential to decrease total corticosteroid consumption in patients with steroid-dependent asthma compared with conventional treatment over a period of 6 months without compromising asthma control or asthma-related quality of life. These results suggest that a strategy based on intensive internet monitoring of objective measures of asthma control should be considered as a safe and feasible way to adjust the dose of oral corticosteroids in patients with severe asthma.

There is very little information available in the literature on how to taper oral corticosteroids safely in asthma after prolonged use. The adjustment of ICS guided by objective parameters of airway disease has been addressed in several other studies. The use of airway responsiveness, 26 eosinophils in induced sputum27 and FE\textsubscript{NO}28 29 appear to be superior over usual care in most studies, although for FE\textsubscript{NO} there has been some controversy.30—32 In contrast to these previous studies, the aim of our study was not to evaluate the use of ACQ or FE\textsubscript{NO} in adjusting the corticosteroid dose but to use these measures as part of an integrated multifaceted approach including internet-supported monitoring and continuous supervision by a specialised asthma nurse.

We compared the effectiveness of two clinical strategies using a pragmatic approach19 according to CONSORT guidelines.22 In this approach the use of placebo or sham is not recommended to assess the relative benefits versus harms of different treatment strategies in order to make it more representative of actual practice.19 Patients in our study were aware of their randomisation group and knew that they would receive tapering instructions either on a weekly basis from the computer or by the treating physician on a monthly basis. Blinding the patients would therefore not only be futile but also diverge from the pragmatic concept.

One could argue that belief in the novel internet approach, extra effort and optimism might have positively influenced the effectiveness of the internet-based management tool. However, given the fact that the patients’ global satisfaction with both tapering strategies was similar and even tended to be in favour of conventional asthma treatment, this seems highly unlikely. The

| Table 3 Primary and secondary outcomes according to treatment group |
|--------------------------|-------------------------|--------------------------|--------------------------|--------------------------|
| Variable                             | Internet group (n = 51) | Conventional management group (n = 38) | Absolute difference* (%95 CI) | p Value |
| Sparing of prednisone in 6 months (mg) (median, 25–75th percentile)† | 205 (−221 to 777) | 0 (−497.5 to 282) | 205 (45 to 365) | 0.02 |
| Mean (SE) ACQ change from baseline†‡ | 0.26 (0.09) | 0.12 (0.12) | 0.14 (−0.14 to 0.42) | 0.37 |
| Mean (SE) AQLQ change from baseline†‡ | −0.03 (0.10) | 0.14 (0.13) | 0.17 (−0.14 to 0.48) | 0.30 |
| Slope FEV\textsubscript{1} (12) | −0.0009 | −0.0007 | 0.0002 (−0.0012 to 0.0018) | 0.73 |
| Exacerbations per patient (median, 25–75th percentile) | 1 (0 to 1) | 1 (0 to 1) | 0 | 0.78 |
| Exacerbations per year (median, 25–75th percentile) | 1.68 (0 to 3.9) | 1.82 (0 to 2.5) | −0.14 | 0.95 |
| Days of hospitalisation per patient (median, 25–75th percentile) | 0 (0 to 7) | 0 (0 to 7) | 0 | 0.25 |
| Days of hospitalisations per patient/year (median, 25–75th percentile) | 0 (0 to 17) | 0 (0 to 7) | 0 | 0.25 |
| Mean (SE) global satisfaction scale†‡ | 5.58 (0.2) | 6.08 (0.18) | 0.5 (−0.07 to 1.06) | 0.09 |

*Absolute difference is the difference in median or means between the groups.
† Sparing of prednisone is the difference between the expected cumulative dose (daily dose at study entry multiplied by the number of days in the study) and the actual cumulative dose. For the calculation of the actual cumulative dose we used the dose registered daily on the website by each patient.
‡ Values are model estimates of mixed effects regression models.
The Juniper Quality of Life Questionnaire (AQLQ) score ranges from 1 to 7, with higher scores indicating worse control.
† The Juniper Asthma Control Questionnaire (ACQ) score ranges from 0 to 7, with higher scores indicating better quality of life.
** Incidence of exacerbations/year (number of exacerbations per patient divided by the number of days in the study and multiplied by 365).
†† Incidence of days of hospitalisations/patient/year (number of days of hospitalisation per patient divided by the number of days in the study multiplied by 365).
‡‡ Patients’ rate for their satisfaction with the tapering strategy from 1 (absolutely not satisfied) to 7 (really satisfied).

| Table 4 Contribution of fraction of exhaled nitric oxide (FE\textsubscript{NO}) and Asthma Control Questionnaire (ACQ) to algorithm decisions |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Δ ACQ ≥ 0.5 | Δ ACQ < 0.5 |
| ΔFE\textsubscript{NO} > +10 ppb and >10% | OCS ↓ | OCS ↓ |
| 36 (3.5%)* | 128 (12.5%)* |
| ΔFE\textsubscript{NO} > +10 ppb and ≤10% | No change in OCS | OCS ↓ |
| 1 (0.1%)* | 3 (0.3%)* |
| −10 < ΔFE\textsubscript{NO} ≤ +10 ppb | No change in OCS | OCS ↓ |
| 105 (10.3%)* | 621 (60.7%)* |
| ΔFE\textsubscript{NO} < −10 ppb | OCS ↓ | OCS ↓ |
| 22 (2.2%)* | 107 (10.5%)* |

*Number of observed decisions (and their relative percentage to the total number of interventions) corresponding to the different algorithm possibilities in the internet management group over a 6-month period.
ΔACQ difference in Asthma Control Questionnaire scores between 2 weeks; ΔFE\textsubscript{NO} difference in mean fraction of exhaled nitric oxide (in parts per billion) between 2 weeks; OCS, increase in prednisone dose by one step; OCS, decrease in prednisone dose by one dose step.
success of the internet-based strategy therefore does not seem to be biased by enthusiasm for the new intervention.

The design of the tapering algorithm was such that stable symptoms (increase in ACQ <0.5) would always lead to a reduction in corticosteroid dose and increased symptoms (increase in ACQ ≥0.5) only to a step-up in dose if there was a concomitant increase in FE_{NO}. This was to avoid overtreatment in patients with corticosteroid withdrawal symptoms or discordance between symptom expression and in

Aerocrine-AB in April 2007. The funding sources had no role in the study design, data collection, analysis or interpretation, or in the decision to submit this article for publication.

Competing interests None.

Patient consent All patients provided written informed consent.

Ethics approval The study was approved by the ethics committee of all participating institutions (Academic Medical Centre, University of Amsterdam, Amsterdam; Medical Center Leeuwarden, Leeuwarden; HagaZiekenhuis, Den Haag; Medisch Spectrum Twente, Enschede; Leiden University Medical Center, Leiden; St Franciscus Gasthuis, Rotterdam, The Netherlands).

Contributors The authors were solely responsible for the study design, data analysis and interpretation and for the writing of the manuscript. All authors had equal participation.

Provenance and peer review Not commissioned; externally peer reviewed.

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Thorax published online April 7, 2011

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