Time to spirometric and exercise response in a 4-week oral corticosteroid trial for stable COPD patients

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Summary

Objective: Little evidence supports the commonly recommended 2-week duration for an oral corticosteroid trial in stable COPD patients. We aimed to assess the time to spirometric and exercise responses in stable COPD patients undergoing an oral corticosteroid trial.

Methods: In a pilot study a 28-day trial with prednisone 0.5 mg/kg bodyweight was performed in all outpatients meeting entry criteria during one calendar year. Response was assessed by spirometry (twice weekly) and 6-minute walk distance (6MWD, weekly). Of 36 moderate to severe COPD patients started on prednisone, 30 completed the study according to the protocol.

Results: The mean post-bronchodilator forced expiratory volume in 1 second (FEV1) was 49.5% predicted and the 6MWD was 444 m at baseline. On the basis of spirometry (post-bronchodilator FEV1 ≥15% and ≥200 ml) 12 patients were responders. Five additional patients improved their 6MWD by ≥55 m (exercise responders). Of all 17 responders six (35%) responded between day 17 and 28 (4 spirometric and 2 exercise responders). Responders and non-responders showed a maximum FEV1 increase from baseline on day 24 of 264 ml and 70 ml, respectively.

Conclusion: An oral corticosteroid trial of only 2 weeks’ duration may miss a clinically significant number of corticosteroid-responsive stable COPD patients.

Key words: COPD; corticosteroids; exercise tests; spirometry; prednisone

Introduction

The role of corticosteroids in stable chronic obstructive pulmonary disease (COPD) patients has been investigated extensively in recent decades. Guidelines reflect the perception that a subgroup of patients responds to this treatment, although identification of characteristics associated with a positive response to treatment with corticosteroids has proven difficult [1, 2]. In the light of the published evidence the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend that regular treatment with inhaled corticosteroids be prescribed only for symptomatic COPD patients with a documented spirometric response to corticosteroids or for those with FEV1 <50% predicted and repeated exacerbations [3]. Since the early 1980s many guidelines have recommended evaluation of corticosteroid responsiveness in COPD patients by a two-week trial of oral corticosteroids (usually 30–40 mg prednisolone) with spirometric documentation of response [4–7]. There has been no general consensus on how to perform an oral corticosteroid trial (OCT), a fact reflected in variations in the recommended dose, duration and the definition of a positive response [1]. An FEV1 increase of at least 15% and 200 ml from baseline represented a positive response to corticosteroids in the COPD guidelines published by the British Thoracic Society (BTS) in 1997 [5], whereas responders were defined by a 20% increase in FEV1 from baseline in a meta-analysis by Callahan and co-workers [6]. Treatment response has also been defined as ≥20% increase from baseline in FEV1, forced vital capacity (FVC) or mean daily or weekly peak expiratory flow (PEF) [8–10]. The evidence in favour of a two-week duration for an OCT is limited. One time-response study in patients with chronic airway obstruction showed the highest mean PEF on the eighth day of prednisolone treatment [11]. This frequently cited study is of limited value to COPD patients, as the majority of the subjects were asthmatic [11]. Another time-response study compared oral with inhaled corticosteroids in a crossover design in 121 patients with non-asth-
mastic chronic airway obstruction. Fifty patients (41.3%) showed a full or partial response to oral prednisolone and in 8 responding patients the mean PEF was still rising at day 14. The authors concluded that a trial of corticosteroid treatment should last more than 14 days [8]. Frequently only a minority of patients assessed by OCT (often as few as 10–20%) are found to be corticosteroid-responsive [5, 6]. Whether an OCT of longer duration would detect a higher percentage of corticosteroid-responsive COPD patients has yet to be investigated [1, 12]. As evidence mounted that 2-week OCTs were not reliably predicting the COPD patients who benefit from long-term inhaled corticosteroids, we conducted a critical evaluation of the manner in which OCTs have been performed and considered a longer duration and a functional outcome assessment as possible improvements. In view of the costs and potential adverse events associated with prolonged inhaled corticosteroid use, the concept of a short, low-cost improved OCT to identify corticosteroid responsiveness in COPD patients seemed an attractive concept, particularly in the context of limited health care resources (South Africa).

In recent years most guidelines have ceased recommending an OCT because of mounting evidence that a short course (2 weeks) of oral corticosteroids was a poor predictor of the long-term response to inhaled corticosteroids in COPD [3, 13]. Newer guidelines recommend a trial of inhaled corticosteroids for 6–12 weeks in patients who are symptomatic despite established bronchodilator treatment. Inhaled corticosteroids are also recommended for patients with FEV1 <50% predicted and repeated exacerbations [3, 13]. Some patients not falling into the last-mentioned category (i.e. without repeated exacerbations) may potentially benefit from inhaled corticosteroids, but the challenge remained of how to select these patients with the limited resources available. We therefore decided to evaluate the duration of the OCT by means of a time-response study. On the basis of previous work highlighting the importance of exercise testing for therapy evaluation and our own pilot experiments, we hypothesised that a differential response would be detectable with spirometry and 6-minute walk distance (6MWD), resulting in a clinically significant number of patients responding beyond 2 weeks of oral corticosteroid treatment [14–16]. We therefore conducted a pilot study to investigate the time needed to reach spirometric and exercise response criteria during 4 weeks of prednisone treatment in stable, moderate to severe COPD patients.

Patients and methods

Entry criteria and baseline evaluations

Over a one-year period (2003) all COPD outpatients at the Tygerberg academic hospital with persistent symptoms despite established bronchodilator therapy were considered for this pilot study. Of 48 consecutive patients without current corticosteroid treatment, 36 met all the entry criteria: age ≥40 years, established COPD diagnosis [3] for at least 2 years, ≥10 pack years’ smoking history, no treatment change in 4 weeks prior to the study and post-bronchodilator FEV1 <80% and FEV1/FVC ratio <70% [3]. We excluded patients if they had a clinical diagnosis of asthma or allergic rhinitis with onset before age 40, seasonal or episodic dyspnoea, significant cardiovascular or other respiratory disorders, thoracotomy with pulmonary resection, COPD exacerbation within the previous 4 weeks or a history of drug or alcohol abuse. The presence of airflow reversibility to inhaled bronchodilators was not adopted as an exclusion criterion as long as patients fitted the COPD definition in the GOLD guidelines [3, 17]. Twelve COPD patients did not fulfil the entry criteria for the following reasons: 4 no informed consent, 2 recurrent cardiac failure, 2 transport problems, 2 frequent exacerbations, 1 unable to perform lung functions, 1 recent inhaled corticosteroid treatment.

We assessed the bronchodilator response before and 30 minutes after inhalation of 400 mcg salbutamol (Ventolin®, Glaxo Wellcome, Midrand, South Africa) from a metered dose inhaler and large volume spacer. During the study no beta-blockers, antihistamines or inhaled corticosteroids were permitted. Maximum bronchodilator therapy was continued throughout the study, which included continued use of oral theophylline where applicable. Inhaled medicines were withdrawn prior to lung functions in accordance with recommended time limits [18]. The study was approved by the Institutional Review Board of the University of Stellenbosch and all patients gave written informed consent.

Study protocol

The OCT was preceded by 3 baseline visits in a 2–4 week run-in period with 3 spirometry evaluations, 3 clinical examinations and three 6MWD tests performed on different days, and a skin prick test to common aeroallergens. The best baseline result of spirometry and 6MWD obtained in this period was used as the baseline value. This leads to high baseline values and subsequently tends to minimise improvements seen during the OCT. Only patients with a variability of <15% of FEV1 during the run-in period and no clinical evidence of respiratory exacerbation (increased dyspnoea or sputum) [19] were started on 0.5 mg/kg bodyweight prednisone as a once-daily morning dose for 4 weeks. This dose was chosen in approximation to the generally recommended fixed dosage of 30–40 mg/d. Compliance was checked by pill count. At the end of the 28-day OCT the dose was tapered to zero within a week. Responders were then started on inhaled corticosteroids. All visits were in the morning at the same time on day 1, 7, 10, 14, 17, 21, 24 and 28 with assessment of spirometry, vital signs, current medications, smoking status (verified by sealed carbon monoxide), signs of exacerbations or adverse events. Weekly assessments by the two study physicians (MMS, PB) included clinical examination, transitional dyspnoea index (TDI) and post-spirometry 6MWD with a standardised encouragement...
A follow-up visit was done on day 56. American Thoracic Society (ATS) guidelines were adhered to concerning 6MWD, spirometric assessments, calibration and equipment maintenance [18, 20]. A Jaeger Masterscope 4.0 spirometer (Würzburg, Germany) was used by a trained lung function technologist. Responders were defined spirometrically by an increase in post-bronchodilator FEV₁ ≥15% and ≥200 ml from best baseline result [3, 5, 12]. Exercise responders were defined as patients who increased their 6MWD by ≥55 m from best baseline result [15, 16]. Spirometric responder definition was the primary definition of response and only where these criteria were not met was the exercise definition of response used. To allow comparison with other trials a 20% increase in FEV₁ from baseline was also analysed [6, 10, 22].

### Statistical analysis

Results are presented as means with 95% confidence intervals (upper; lower limits) or standard deviation unless indicated otherwise. Reporting of statistical significance has been limited to the main outcome: number of responders detected on 2-week OCT versus 4-week OCT. A *p*-value of <0.05 was considered significant. A one-sided McNemar chi-square test was used on the basis of the directional hypothesis. Due to the small sample size the power of this study is insufficient to detect differences in baseline characteristics or possible predictors of response to corticosteroids. The statistical package Statistica, version 6.1 (Statsoft, Inc. Tulsa, OK, USA) was used.

### Results

Thirty-six stable COPD patients fulfilled all the entry criteria and were started on prednisone treatment. Of these, 6 subjects were excluded from analysis due to COPD exacerbations (2 patients), discontinuation of treatment (2) and missed visits (2). Thirty patients completed the trial with full data; their baseline characteristics are shown in Table 1.

The time required to reach the response criteria of these patients is depicted in Figure 1A: 8 patients responded spirometrically between day 7 and 14, two on day 17 and two on day 28 of treatment. These spirometric responders had an increase in 6MWD of 55 m from baseline (at the respective time-points). Five additional patients improved their 6MWD by ≥55 m on day 14 (3 patients), on day 21 (1 patient) and day 28 (1 patient).

Overall 17 patients (57%) were considered responders. Six of these patients (35%) responded between day 17 and 28 (4 spirometric and 2 exercise responders, figure 1A). The increase in the number of responders detected by extending the OCT from 2 weeks to 4 weeks (12 versus 17) was statistically significant (*p* = 0.04).

If spirometric and exercise response criteria are given equal diagnostic weight and the first time-point at which either is reached is recorded, 11 responders are detected within the first 2 weeks and 13 within 3 weeks of starting prednisone treatment (figure 1B). In the 3rd and 4th week of the OCT 6 responders (3 spirometric and 3 exercise) were identified.

If an increase in FEV₁ of ≥20% from baseline is considered an alternative spirometric response

### Table 1

<table>
<thead>
<tr>
<th>Subjects (n)</th>
<th>all</th>
<th>responders</th>
<th>non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years</td>
<td>58 (9)</td>
<td>58 (53; 62)</td>
<td>59 (54; 64)</td>
</tr>
<tr>
<td>Male %</td>
<td>70</td>
<td>59</td>
<td>85</td>
</tr>
<tr>
<td>Skin prick positive %</td>
<td>17</td>
<td>12</td>
<td>23</td>
</tr>
<tr>
<td>Current smokers %</td>
<td>53</td>
<td>65</td>
<td>39</td>
</tr>
<tr>
<td>Exhaled CO ppm</td>
<td>8.9 (7.5)</td>
<td>10.2 (6.5; 13.9)</td>
<td>7.31 (3.1; 11.5)</td>
</tr>
<tr>
<td>Pack years (n)</td>
<td>35 (18)</td>
<td>31 (22; 40)</td>
<td>40 (10; 51)</td>
</tr>
<tr>
<td>Height cm</td>
<td>168 (10)</td>
<td>168 (163, 173)</td>
<td>169 (164, 175)</td>
</tr>
<tr>
<td>Weight kg</td>
<td>64 (13)</td>
<td>63 (56, 70)</td>
<td>66 (59; 74)</td>
</tr>
<tr>
<td>Body mass index kg/m²</td>
<td>23 (6)</td>
<td>23 (20, 27)</td>
<td>23 (20, 25)</td>
</tr>
<tr>
<td>Theophylline use %</td>
<td>63</td>
<td>71</td>
<td>54</td>
</tr>
<tr>
<td>FEV₁ pre-BD L</td>
<td>1.26 (0.5)</td>
<td>1.27 (1.02; 1.53)</td>
<td>1.24 (0.94; 1.54)</td>
</tr>
<tr>
<td>FEV₁ pre-BD % predicted</td>
<td>44 (17)</td>
<td>46 (37; 54)</td>
<td>41 (32; 51)</td>
</tr>
<tr>
<td>FEV₁ post-BD L</td>
<td>1.44 (0.5)</td>
<td>1.42 (1.15; 1.69)</td>
<td>1.46 (1.16; 1.77)</td>
</tr>
<tr>
<td>FEV₁ post-BD % predicted</td>
<td>49 (18)</td>
<td>50 (42, 59)</td>
<td>48 (18, 59)</td>
</tr>
<tr>
<td>ΔFEV₁ post-pre BD L</td>
<td>0.18 (0.16)</td>
<td>0.17 (0.09; 0.25)</td>
<td>0.19 (0.1; 0.28)</td>
</tr>
<tr>
<td>FVC post-BD L</td>
<td>2.86 (0.71)</td>
<td>2.76 (2.41; 3.12)</td>
<td>3.00 (2.60; 3.41)</td>
</tr>
<tr>
<td>FVC post-BD % predicted</td>
<td>79 (17)</td>
<td>79 (71, 88)</td>
<td>80 (70; 89)</td>
</tr>
<tr>
<td>FEV₁/FVC post-BD %</td>
<td>0.49 (11)</td>
<td>0.51 (45; 56)</td>
<td>0.48 (42, 54)</td>
</tr>
<tr>
<td>6MWD m</td>
<td>444 (68)</td>
<td>448 (411, 481)</td>
<td>442 (402, 481)</td>
</tr>
</tbody>
</table>
criterion [6, 22], then 11 of the 12 above-defined spirometric responders reached this cut-off; 8 patients within the first 2 weeks, one on day 24 and two on day 28.

Towards the end of the OCT improvements from baseline in FEV₁ and 6MWD were more pronounced (figures 2–5): responders and non-responders showed a maximum FEV₁ increase from baseline on day 24 of 264 ml and 70 ml, respectively. 6MWD improvements at 21 and 28 days were 56 m and 72 m for responders and 14 m and 12 m for non-responders, respectively.

Figure 1
Time to positive spirometric and/or exercise responses during an oral corticosteroid trial. Black bars represent spirometric responders, white bars depict exercise responders, grey bars show subjects who were both spirometric and exercise responders at the same time-point. The number of subjects is shown. Total n = 30. A. Time-points at which subjects meet spirometric response criteria for the first time (increase in post-bronchodilator FEV₁ ≥15% and ≥200 ml from baseline). In addition, 5 exercise responders are shown (increase in 6MWD ≥55 m from baseline). B. Time-points at which subjects first met spirometric or exercise response criteria for the first time.

Figure 2
Change of postbronchodilator FEV₁ from baseline in ml during oral corticosteroid trial. Mean ± 95% confidence interval. FEV₁ = forced expiratory volume in 1 second. Responders n = 17; non-responders n = 13.

Figure 3
Change of postbronchodilator FEV₁ from baseline in percent during oral corticosteroid trial. Mean ± 95% confidence interval. FEV₁ = forced expiratory volume in 1 second. Responders n = 17; non-responders n = 13.

Figure 4
Change of 6-minute walk distance from baseline during oral corticosteroid trial. Mean ± 95% confidence interval. 6MWD = six-minute walk distance. Responders n = 17; Non-responders n = 13.

Figure 5
Total transitional dyspnoea score during an oral corticosteroid trial. Mean ± 95% confidence interval. Responders n = 17; non-responders n = 13.
The mean total SGRQ score at baseline was 54 (22) and 56 (24) for responders and non-responders, respectively. The respective total scores on day 28 were 42 (21) and 49 (22). The mean total baseline dyspnoea index for responders and non-responders was 5.6 (3) and 5.4 (3), respectively. The change in total TDI over time is depicted in figure 5. Medication compliance was excellent for all but 4 patients: a total of 3–5 doses were missed by each of these patients during the 28 days of treatment. None of these patients were excluded from the analysis. Two were responders. None of the glucose measurements showed hyperglycaemia on day 28 of treatment. Mean weight increased for all patients from the baseline 64 kg (13) to 65 kg (14) at day 14 and remained at that level until day 28. The following adverse events were noted: dyspepsia (6 patients), COPD exacerbations (4), oral thrush (2), recurrence of anal thrush (1), chest pain (1), and restlessness (1). Most adverse events occurred in the last week of treatment and some after completion of the steroid trial (documented on day 56). One patient was diagnosed with transverse myelitis and advanced-stage prostate cancer after missing the last trial visit (day 28) and abruptly withdrawing from prednisone. The transverse myelitis was fully reversible after hospitalisation and was considered paraneoplastic. The onset may have been related to the sudden withdrawal of prednisone.

Discussion

This study shows that a significant number of corticosteroid-responsive COPD patients may meet response criteria only after the commonly recommended 2-week duration of an OCT. The extended duration of the OCT and the inclusion of exercise responders resulted in more than half the patients being identified as corticosteroid-responsive. If the OCT had been limited to two weeks’ duration, 6 of the 17 responders (35%) would have been missed.

Little data is available on time to spirometric or exercise response in stable COPD patients undergoing an OCT. Blair and Light compared once daily and alternate daily administration of prednisolone during a 10-day OCT [23]. On day 5 of treatment the mean spirometric response was similar to placebo, whereas on day 10 it had increased 2–3 fold with 28% of patients considered responders (>25% increase in FEV1). Another study investigated a 1-week OCT with 20 mg prednisolone daily. None of the 26 patients were considered responders by the authors [24]. However, 4 of these patients (15%) did show a >20% increase in FEV1 after one week. In the current study 7% and 20% were spirometric responders by day 7 and 10 respectively, and the maximum spirometric improvement was attained on day 24 (figure 1A, figure 2–3). The meta-analysis did not generate data allowing the optimum duration of a steroid trial to be determined [6, 25]. Using a 20% improvement in FEV1 to define response to treatment, they subtracted the proportion of responders in the placebo group from that of the active treatment group. The benefit of oral corticosteroid treatment then ranged from 0% to 38%, with a weighted mean treatment effect of 10% [6]. Twelve of the 15 studies included in the meta-analysis had treatment durations of 14 days or shorter. The current study shows a substantially higher percentage of corticosteroid-responsive patients compared to the studies considered in the meta-analysis [6]. Chanez et al. reported a 48% response rate in subjects treated with prednisolone 1.5 mg/kg/bodyweight for 15 days [1]. This result is in the order of magnitude of the current study. Possible explanations for the higher percentage of responders in our study are the longer duration of the corticosteroid trial, the inclusion of exercise responders, repeated outcome assessments and the high percentage of patients on theophylline treatment. Theophylline appears to reverse the corticosteroid resistance commonly encountered in COPD patients through effects on histone deacytelase 2 [26]. In the current study 63% of the patients were under treatment with theophylline and, unlike in most other protocols, theophylline was not withdrawn for study visits.

The inclusion of exercise responders was based on the fact that some patients clearly benefit functionally without meeting spirometric cut-off values. These patients should not be denied the possible benefit of corticosteroid treatment. To date only 4 studies have performed exercise tests in this context, of which only one has shown a significant improvement of 20 m after 2 weeks in the most responsive patient group [2, 25]. It remains to be determined why some patients show a clear increase in exercise tolerance without substantial improvement in FEV1. A positive influence on static lung volumes (dynamic hyperinflation) is a possibility, but this was not investigated here. Repeated outcome assessments are likely to detect more responders than one-off measurements, owing to the spontaneous fluctuations in spirometric function [24]. This has prompted some authors to question whether a single measurement is a reliable aid in determining appropriate long-term treatment [12, 17, 27].

The majority of the patients participating in the ISOLDE trial were evaluated by an uncontrolled 2-week OCT prior to receiving inhaled corticosteroids for 3 years [22]. The response to prednisolone was unrelated to the subsequent change in FEV1 over the following years on either
may have been observed in an OCT with less frequency and may have resulted in better 6MWD results than expected. The Hawthorne effect and the training effect may not show significant effects on pulmonary function main outcome measures, as a previous study did claim to be responsible for the subjective improvement observed. Such an effect may have influenced the secondary outcomes (SGRQ, dyspnoea scores), but is unlikely to have influenced the secondary outcomes (SGRQ, dyspnoea scores). The Hawthorne effect and the training effect may have resulted in better 6MWD results than may have been observed in an OCT with less frequent examination time-points [29]. Both effects are possible limitations of the exercise response criterion.

We take the view that evaluation of the response to an OCT should not only be done by spirometry but also by an exercise test such as the 6MWD. This allows the functional benefit to be quantified by a second method and may identify corticosteroid-responsive patients otherwise missed due to an insufficient increase in FEV1. On the basis of this pilot study no definite recommendation can be made regarding the best duration and time-points of assessment during an OCT. However, two weeks was too short for 35% of responders in this population. Extension of an OCT may be advisable in subjects showing some improvement in spirometry and/or 6MWD but not attaining response criteria by the two weeks’ deadline. Whether an improved OCT will better identify the patients who will benefit from long-term inhaled corticosteroid treatment remains to be investigated [30].

In conclusion, we have shown that a two-week OCT missed a significant percentage of corticosteroid-responsive patients with stable, moderate to severe COPD, that the percentage of such responders may be considerably higher than previously reported when the duration of the trial is extended, and an improvement of ≥55 m in 6MWD is adopted as an additional response criterion.

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