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Formoterol used as needed improves health-related quality of life in asthmatic patients uncontrolled with inhaled corticosteroids

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Summary Clinical benefits have been shown to occur when using the long-acting β_2-agonist formoterol 4.5 μg for as-needed medication rather than terbutaline 500 μg in patients with unstable asthma taking an inhaled corticosteroid. This study compared their effects on health-related quality of life and the relation with conventional clinical indices in the same population. 362 asthmatics were randomized to use either formoterol 4.5 μg or terbutaline 500 μg as needed, both inhaled via Turbuhaler®. The Asthma Quality of Life Questionnaire (AQLQ) was practised at enrolment and completed by 341 patients after randomization and at 4, 8, and 12 weeks. Clinical indices were measured at the same time points. Mean overall AQLQ scores were comparable at baseline, being 4.90 in the formoterol and 4.82 in the terbutaline group and improved during treatment by 0.41 and 0.17 units, respectively (mean difference 0.24, 95% CI 0.08, 0.39, $P < 0.005$). Mean improvement in the symptom domain was 0.49 units when using formoterol. Correlations between changes in clinical indices and changes in AQLQ scores during the 12-week period were weak (maximum r value=0.37). When used for as-needed medication, formoterol 4.5 μg provided an improvement in asthma-specific quality of life and to a somewhat greater extent than the widely used terbutaline 500 μg. The symptom domain in AQLQ showed almost 0.5 units improvement after formoterol, a change that is considered to be clinically relevant.
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Introduction

Over the last 10 years, health-related quality of life (HRQL) has become an important outcome in clinical studies and disease management programs for various diseases, including asthma. Recognition of the importance of HRQL, its weak correlation with conventional clinical indices and the availability of validated HRQL instruments means that many clinical studies now include patient HRQL values as one of the end-points. Asthma-specific HRQL measures have been developed over the past few years, including the Asthma Quality of Life Questionnaire (AQLQ), which has been used in clinical studies worldwide.[1] Several studies have shown that the use of a long-acting β_2-agonist twice daily is associated with improvements in asthma-related quality of life.[2–6]

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The use of short-acting β_2-agonists for symptom relief in patients with asthma is well established. The long-acting β_2-agonist formoterol has a rapid onset similar to that of the short-acting β_2-agonists.[7–10] Short-term studies showed its safety when compared with the short-acting β_2-agonists, salbutamol and terbutaline.[11,12] A recent long-term study showed that formoterol reduces the number of exacerbations and the time to the first exacerbation when used as-needed, without any safety issues.[13] This suggests that formoterol may be used on an as-needed base. The current study investigates the effects of formoterol and terbutaline as needed on asthma-related quality of life in the latter study, which included patients with moderate to severe asthma not adequately controlled on inhaled steroids alone.

Methods

The methodology of this double-blind, randomized, parallel-group study has already been published.[13] Patients ($\geqslant 18$ years) with asthma for at least 6 months and treatment with a constant dose of inhaled corticosteroids for at least 4 weeks participated. The forced expiratory volume in one second (FEV_1) at baseline had to be >50% predicted, with >12% increase after inhaling 1.5 mg terbutaline via Turbuhaler®. The mean daily need for rescue treatment (Bricanyl® Turbuhaler 500 μg dose^{-1}) had to be 3–8 times/day on any 7 days of the 2-week run-in period. Approval was obtained from regulatory agencies and ethics committees at all the four centres, and patients gave written informed consent.

Study design

Patients visited the clinic before and after a 2-week run-in period, and after 4, 8 and 12 weeks treatment. After run-in, patients were randomized to use either 4.5 μg formoterol (Oxis® Turbuhaler) or 500 μg terbutaline (Bricanyl Turbuhaler) for as-needed medication during 12 weeks. Pre-bronchodilator FEV_1 was measured at all visits. Severity of asthma symptoms was rated on a 0–3 point scale each morning and evening: 0=no symptoms, 3=severe symptoms. Peak expiratory flow (PEF) was recorded with a Vitalograph® Peak Flow Meter (Buckingham, UK).

Asthma Quality of Life Questionnaire (AQLQ)

Patients completed the self-administered AQLQ at each clinic visit before any other measurements.[1] A practice questionnaire at the first visit was discarded. Baseline values were obtained at the start of the treatment period. The AQLQ comprises four domains of HRQL: activity limitation (11 items), symptoms (12 items), emotional function (5 items), and environmental stimuli (4 items). Patients are asked to recall their experiences during the previous two weeks and score each item on a 7-point Likert scale: 1=severe, 7=no impairment. Scores for the four domains and overall score are computed as averages of the item scores. A change of 0.5 point is judged as the minimal important difference (MID).[14,15]

Statistical analysis

The analysis is based on all patients with health-related quality of life data available after randomization, using the last-value-carried-forward principle to estimate missing values. The changes in overall AQLQ scores from the start to the end of treatment as well as changes in the four domain scores were compared between treatment groups, using analysis of variance with treatment and centre as fixed factors and overall AQLQ score at the start of treatment as covariate. Mean differences and 95% confidence limits between treatments were calculated. The number needed to treat (NNT) was calculated using the MID. The NNT is the number of patients who need to be treated with a new intervention (formoterol) for one patient to have a clinically important improvement over that which one would have experienced with the control intervention (terbutaline). Associations between changes in AQLQ scores and changes in clinical indices over 12 weeks treatment were examined using the Pearson's correlation coefficient.

Mean values of PEF and symptoms for the last 7 days in the run-in period and the last 28 days of the treatment period were analysed. Mean change in FEV_1 from randomization to the last visit was calculated.

Results

Of 362 patients randomly assigned to the two treatment groups, 341 patients were eligible for the AQLQ assessments. Demographic and baseline data were comparable in the two groups (Table 1).

Changes in AQLQ

Baseline data for AQLQ score were similar in both groups (Table 1). The overall AQLQ score improved

Table 1 Patient characteristics at baseline.

Variable	Formoterol		Terbutaline	
Number of patients	182		180	
Men/women (no.)	88/94		69/111	
Age (years)	46	(18–70)	48	(18–75)
Duration of asthma (years)	16	(1–66)	17	(1–60)
FEV_1 (L)	2.36	(1.13–4.30)	2.27	(1.00–4.65)
FEV_1 (% predicted)	73.7	(4–162)	74.2	(40–130)
Reversibility (% from baseline)	19	(2–77)	19	(−3–98)
Inhaled daily steroid dose (μg)	890	(200–2800)	860	(100–2400)
AQLQ				
Overall	4.90		4.82	
Activity limitation	4.82		4.67	
Symptoms	4.81		4.75	
Emotional function	5.35		5.35	
Environmental exposure	4.85		4.78	

Values are presented as means with ranges between brackets=( ).

during treatment (visit 2–visit 5) in both groups, with a significantly greater improvement in the formoterol group than in the terbutaline group (improvement 0.41 vs. 0.17, respectively, $P = 0.0003$, Fig. 1). The greatest improvements were seen in the symptom domain of AQLQ, with a change of 0.49 in the formoterol group and 0.21 in the terbutaline group ($P = 0.002$)(Fig. 2). The domain for emotional function reached only a borderline significance (increase of 0.37 in the formoterol group and 0.20 in the terbutaline group, $P = 0.074$). 68 patients (38%) in the formoterol group and 51 (29%) in the terbutaline group increased in the overall score of AQLQ more than 0.5 unit. The NNT for the formoterol group was 9.1 with regard to the overall AQLQ and 7.7 for the symptom domain of the AQLQ.

Changes in clinical characteristics

Mean morning and evening PEF and symptoms were similar in both groups during the run-in period. Mean morning and evening PEF improved significantly more in the formoterol group than in the terbutaline group during the study ($P = 0.009$ and 0.043, respectively). Improvements in symptoms were similar in the two groups (Table 2). Mean FEV_1 changed from 2.31 L at the start of the study to 2.38 L at the last visit in the formoterol group and from 2.20 to 2.18 L in the terbutaline group, the difference between the groups being statistically significant (mean ratio 105%, 95% CI 101, 108, $P = 0.004$). The mean number of rescue inhalation medications fell more in the formoterol group than in the terbutaline group (1.15 inhalations vs. 0.40 inhalations, and mean change 0.76, 95% CI 1.18, 0.33, $P = 0.0005$).
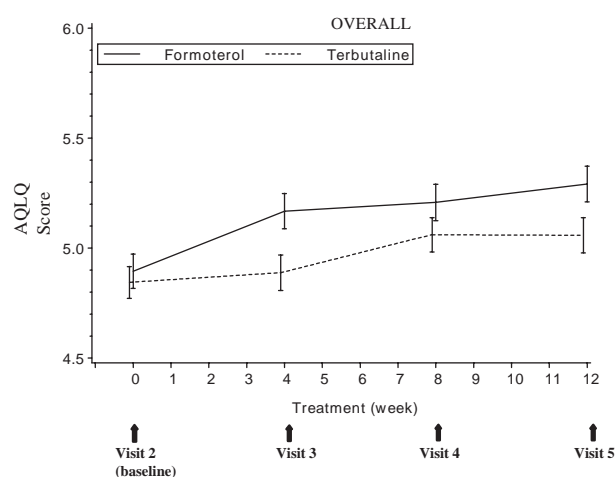

Figure 1 Mean values ($\pm$SEM) in overall AQLQ from baseline to week 12. Higher score means better HRQL.

Correlations

Correlations between changes in AQLQ scores and changes in the clinical measures were weak to moderate, both for overall scores and for the specific AQLQ domains (Table 3, Fig. 3).

Discussion

The present study shows that use of formoterol 4.5 μg as-needed medication in patients inadequately controlled when using inhaled corticosteroids improves HRQL to a greater extent than the use of terbutaline 500 μg. The two groups were comparable with regard to the doses of inhaled corticosteroids. Formoterol improved overall HRQL
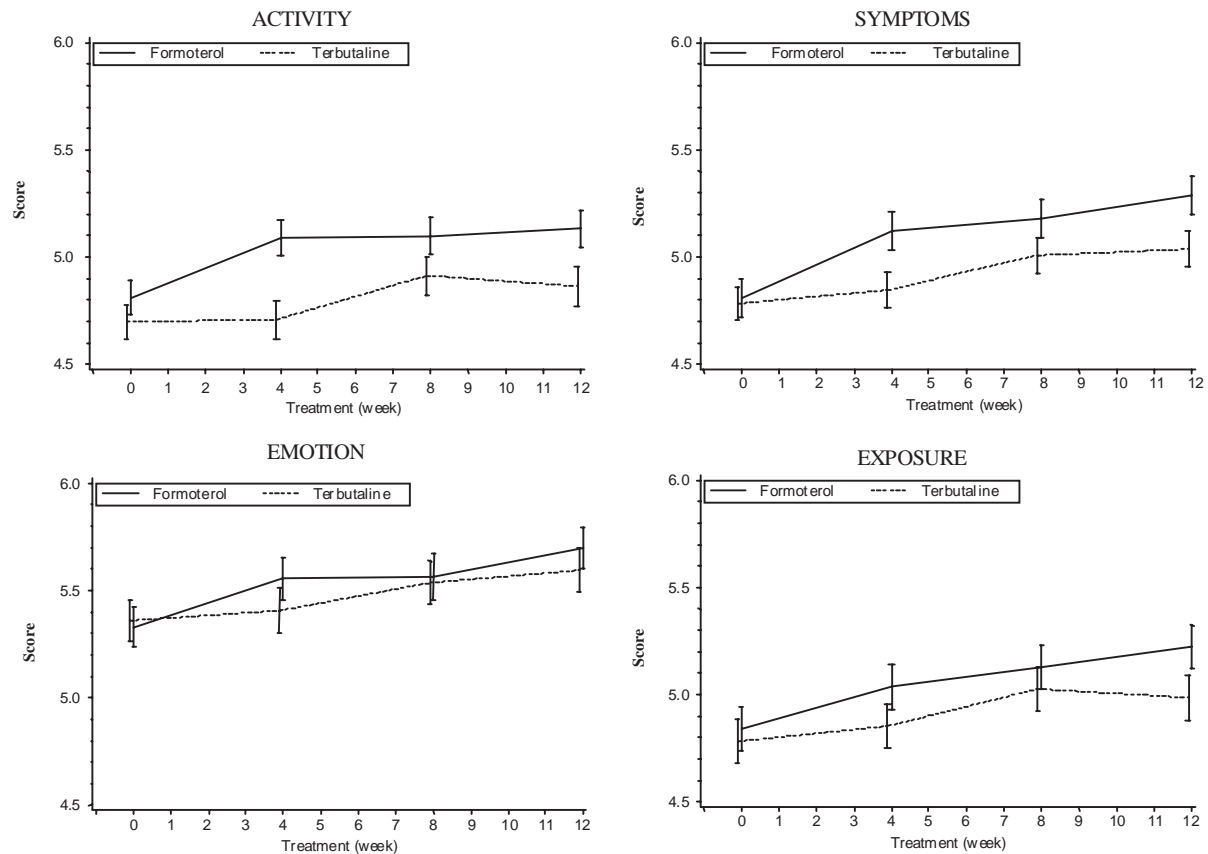
Figure 2 Mean values ($\pm$SEM) in symptoms, activity limitation, emotional function, environmental exposure in AQLQ from baseline to week 12. Higher score means better HRQL.

Table 2 Change in asthma control, diary variables, during formoterol and terbutaline treatment for 12 weeks.

*	Formoterol			Terbutaline			Formoterol-terbutaline		
	Baseline	Treatment	Change	Baseline	Treatment	Change	Mean change	95% CI	P-value
Symptoms day (score 0–3)	1.18	0.99	−0.20	1.21	1.04	−0.17	−0.04	−0.15, 0.08	0.5
Symptoms night (score 0–3)	0.51	0.44	−0.08	0.55	0.49	−0.06	−0.02	−0.11, 0.07	0.7
PEF morning (l/min)	369	376	8	357	354	−4	11	3,20	<0.01
PEF evening (l/min)	387	391	3	376	373	−5	8	0,15	<0.05

*Adjusted mean values.

compared with baseline and each of the domains of the AQLQ as well (symptoms, activity limitation, emotional function and environmental exposure). Mean improvement in the symptom domain was almost 0.5 units (0.49), a change that patients consider being important and which therefore can be interpreted as clinically relevant. The overall score for improvement in AQLQ was 0.41 in the formoterol group. The NNT calculation showed that the number for this overall AQLQ was 9.1 for the formoterol group. This means that one in

nine patients experienced a clinically important improvement in their HRQL over and above that which they would have had using terbutaline as needed. The NNT for the formoterol group was 7.7 (eight patients) for the symptom domain of AQLQ.

The reason for the improvement in HRQL when using a long-acting instead of a short-acting β_2-agonist can be debated. Patients required their inhalers less often with formoterol and were thus not reminded about having asthma as frequently, although the difference between the two

Table 3 Correlation coefficients (r) between change in HRQL measures and changes in FEV_1, symptoms and PEF with treatment.

	Overall*	Activity*	Symptoms*	Emotions*	Environment*
FEV_1 (L)*	0.15	0.11	0.19	0.08	0.07
Symptoms[†] (day)	−0.37	−0.30	−0.42	−0.21	−0.23
Symptoms[†] (night)	−0.29	−0.22	−0.34	−0.19	−0.13
PEF[†] (morning)	0.24	0.19	0.27	0.17	0.14
PEF[†] (evening)	0.24	0.17	0.29	0.16	0.13

*Mean change from visit 2 to visit 5.
[†]Mean change from run-in to end of treatment.
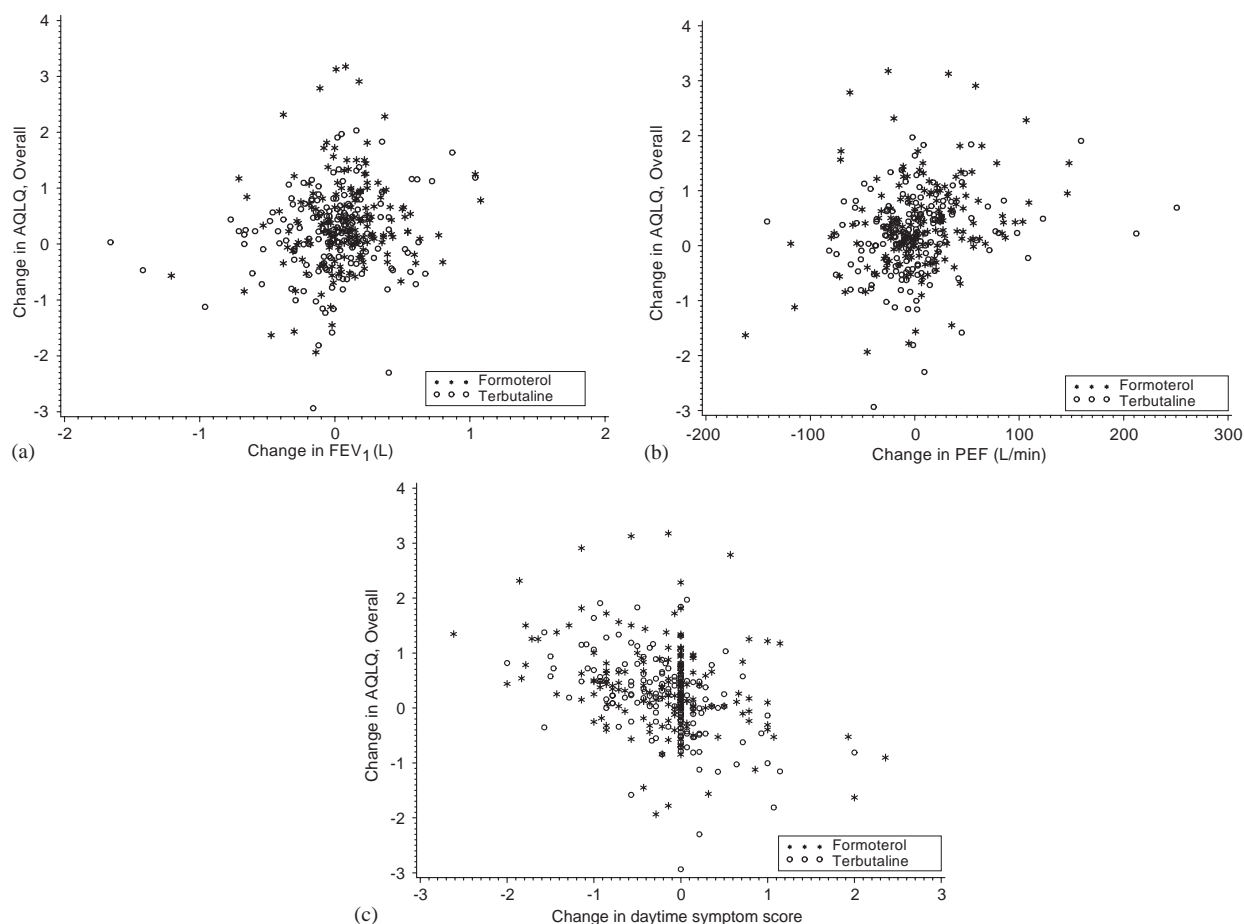
Figure 3 (a) Plot of change in AQLQ, overall vs. change in FEV_1. (b) Plot of change in AQLQ, overall vs. change in PEF. (c) Plot of change in AQLQ, overall vs. change in symptoms.

treatments was not large.[13] Another reason could be that the long duration of formoterol may result in a better exercise tolerance and thus increase the patient's HRQL. Better stabilization of the airway function with better PEF values may also have affected patient's HRQL, as will have the decrease in the number of exacerbations.[13] The difference in improvements in PEF between the groups was small; however, the favour was for formoterol.

Long-acting β_2-agonists have been shown to improve cognitive performance in patients with nocturnal asthma, who then sleep better through the night.[16] In our study, nocturnal symptoms did not improve to a larger extent than daytime symptoms and correlations between nocturnal symptoms and HRQL scores were weak. The improved HRQL with formoterol is therefore not easily explained by better asthma control at night.

Our data suggest that, in patients with asthma who are still unstable despite adequate doses of an inhaled corticosteroid, the use of formoterol as needed may be preferable to terbutaline as-needed

from a patient's point of view. Although there was an overall improvement in mean AQLQ scores and clinical measures of asthma control, the pattern within patients varied greatly as shown by the weak correlations between the changes in clinical measurements and AQLQ scores (Table 3; Fig. 3a–c). These data emphasize the fact that the benefits perceived by patients cannot be derived from spirometry or symptom scores, but are manifested in patients' day-to-day functioning. No single conventional clinical variable correlated well with HRQL data, as has been shown in previous studies including the 1-year FACET study.[17] Other publications have shown weak correlations between HRQL and FEV$_1$.[18,19] There must presumably be differences in patients' perception of changes in their airway calibre or in their lifestyle to explain the weak correlation between FEV$_1$ and AQLQ scores. This means that patients with the same change in FEV$_1$ may be affected by their disease with a great variation and if so score their HRQL differently. This scenario has also been highlighted in a paper by Juniper.[20]

It has to be emphasized that the patients in the present study all received moderate to high doses of inhaled corticosteroids and in addition had a daily need for rescue treatment of at least three times/day at randomisation, which means that according to present guidelines, this patient group would be prescribed a maintenance use of long-acting β_2-agonists.

In conclusion, this study has shown that formoterol 4.5 μg when used for as-needed medication provides an improvement in asthma-specific quality of life and to a somewhat greater extent than the widely used rescue medication, terbutaline 500 μg. The main benefit from formoterol was seen in the symptom domain. Further studies in patients with mild to moderate asthma are needed to confirm the use of an as-needed treatment with the rapid- and long-acting β_2-agonist, formoterol, as an alternative to the rapid- and short-acting β_2-agonists.

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