Respiratory Medicine (2013) 107, 981–986

Available online at www.sciencedirect.com

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Long-term follow-up after two years of asthma treatment guided by airway responsiveness in children

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Received 17 October 2012; accepted 18 March 2013
Available online 11 May 2013

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0954-6111/$ - see front matter
http://dx.doi.org/10.1016/j.rmed.2013.03.008

KEYWORDS
Asthma;
Child;
Airway hyperresponsiveness;
Follow-up

Summary
Introduction: Children with persistent asthma may have diminished lung function in early adulthood. In our previous study ('CATO') we showed preservation of lung function in asthmatic children, during 2 years of treatment that was guided by airway hyperresponsiveness (AHR). The aim of the present prospective follow up study was to investigate whether the positive effect of the AHR strategy on lung function had persisted beyond the duration of the intervention study, after several years of usual care by paediatrician and general practitioner.
Methods: With a mean interval of 4.4 y after the last visit, 137 subjects (67% of the original CATO population) participated in this follow-up study. Evaluation consisted of spirometry ($n = 137$), a methacholine challenge test ($n = 83$), data on inhaled steroid treatment and asthma exacerbations ($n = 137$), and an asthma symptom diary during 6 weeks ($n = 90$).
Results: At follow-up, lung function, % symptom-free days and exacerbation rates of both treatment strategy groups was similar. The mean dose of inhaled corticosteroids had diminished from 550 μg/day at the end of CATO to 235 μg/day at follow-up. The decrease in AHR measured at the end of CATO was maintained at follow-up for both treatment strategy groups.
Conclusion: The beneficial effect on lung function of 2 years treatment guided by AHR was lost after 3–7 years of usual care. This suggests that an AHR-guided treatment strategy may need to be sustained in order to preserve lung function.

Introduction

Some longitudinal studies have shown that children with persistent asthma have a lower lung function in young adulthood.[1,2] This seems independent of therapy with inhaled corticosteroids (ICS).[3] The outcome of asthma depends on the duration of the disease,[4,5] airflow obstruction,[6,7] level of airway hyperresponsiveness (AHR),[8] and gender.[1] Treatment with ICS reduces airway inflammation and symptoms and improves lung function.[9,10] Treatment strategies that titrated the dose of ICS on the presence and severity of eosinophilic airway inflammation showed marked reduction of asthma exacerbations[11,12] and AHR.[13] Long-term effects of such treatment strategies have not been reported. We previously documented preservation of lung function in asthmatic children in whom treatment was guided by AHR during a period of 2 years (CATO study clinical trial number NCT00158834 at clinicaltrials.gov).[14] This benefit was especially seen in those children who had low symptom scores and high levels of AHR. We hypothesized that the benefit of a treatment strategy that takes AHR into account would not persist beyond the duration of the intervention, because treatment would again be solely based on symptoms, and children may have bad perception. For this purpose we performed a prospective follow up study (clinical trial number NTC00441675 at clinicaltrials.gov) 3–7 years after the end of the CATO study.

Methods

Patients

All patients who participated in the CATO study ($n = 206$) were asked to take part 3–7 years after they finished CATO. At start of the CATO study, subjects were 6–16 y old and had moderately severe allergic asthma. They were symptomatic and/or had marked AHR.[14] Thus, there were 3 predefined subgroups, characterized by symptoms, AHR or both, and these were analyzed separately.[14] Subjects and/or parents (if children were younger than 18 years) gave written informed consent. The study was approved by the medical ethical committees of the participating centres.

Design

The mean interval between inclusion in the CATO study and follow-up was 4.4 years (range 3–7 years). Originally, patients were randomized and treated either on the basis of symptom scores (reference strategy) or on symptoms and AHR (AHR strategy).[14] After the study, patients received usual care based on guidelines of the Dutch Pediatric Respiratory Group,[15] largely corresponding to the GINA guidelines.[16]

Primary endpoint at follow-up was change in FEV_1 (%pred) from baseline at randomization. Secondary endpoints were PD_{20}, symptom scores and exacerbations, and ICS dose.

At follow-up, patients were seen twice. At the first visit, spirometry was performed (FEV_1, FVC and bronchodilator response 20 min after inhalation of 400 μg salbutamol; Masterscreen, Jaeger, Würzburg, Germany).[17] Data on the use of asthma medication were collected from pharmacists data records. An asthma exacerbation was defined as a deterioration of asthma requiring treatment with oral corticosteroids.[14] Data on oral corticosteroid prescription were collected from pharmacist records and patients or parents reports. On the second follow-up visit 6 weeks later, the % symptom-free days was determined, and a methacholine challenge test was performed using the same dosimeter protocol as in CATO.[14] Short acting β-agonists were stopped for 8 h, and long-acting β-agonists for 36 h before both visits.

Symptom scores

During the 6 weeks between the first and the second follow-up visit children recorded asthma symptoms twice daily on a diary card as used in CATO. Questions on cough, wheeze and shortness of breath were each scored on a 0–3 point scale, and the number of puffs of rescue β-agonists was

recorded. A symptom-free day was defined as 24 h with score 0 for cough, wheeze and shortness of breath.

Statistical analysis

Data at follow-up were compared with data of the same individuals during the CATO study period. As the use of age-specific reference equations for spirometry might affect the comparisons at follow-up that included children and young adults, we additionally analyzed FEV_1 normalized for a wide age range.[18] Comparison of categorical data was done with the Chi-square test. Continuous data were compared between or within groups using the Mann–Whitney and Wilcoxon test, respectively. For the evaluation of exacerbation rates, taking account of the duration of observation of individual patients, Poisson regression analysis was used. The highest dose of methacholine in the provocation tests was 1570 ug. If children had no 20% decrease of FEV_1 at this dose, the PD_{20} value was set at 1570 ug but was considered a right-censored observation, i.e. the true PD_{20} value will be larger than 1570 ug but remains unknown. Stata software (procedure Cnreg), which allows for such censored data, was used to evaluate the log-transformed PD_{20} outcomes. Profiles of changes of FEV_1 were calculated using repeated measurements Anova, which allows for occasional missing values. Correlation coefficients given are Spearman's. Data given are mean ± sem, unless indicated otherwise. $P = 0.05$ (two-sided) was considered the limit of significance in all analyses.

Results

One hundred and eighty-nine children and adolescents of the original CATO study population ($n = 206$) were asked to participate, 17 could not be traced. One hundred thirty-seven children (67% of the original study population) participated in the first follow-up visit, 100 patients completed both visits. The main reasons for nonparticipation were lack of time and other priorities. The distribution of the participants over the original subgroups was the same for both studies (CATO and CATO follow up). The mean time interval between the last visit in the CATO study and the first follow-up visit was 4.4 years (range 3–7); Age and lung function of the population who participated differed significantly from those of the children who did not (Table 1).

Lung function and AHR

FEV_1 and postbronchodilator FEV_1 were similar in children from the AHR and reference strategy groups (97.5% (sd 14.7) and 98.0% (15.7), $p = 0.69$). Postbronchodilator FEV_1 was 105.9% (14.6) and 105.1% (16.0) for the AHR and reference strategy groups ($p = 0.76$). FEV_1 changes from initial CATO baseline were not different between the treatment strategies: −1.6% (2.2) and −0.7% (1.7) for the AHR and reference strategy groups ($p = 0.37$). FEV_1 changes since the end of the 2-years intervention were −1.4% (2.1) and +0.6% (1.6), respectively (Fig. 1 A). Changes in FEV_1 at the first follow-up visit were similar for the 3 subgroups (Fig. 1B–D). A borderline-significant difference in change in FEV_1 was seen in the subgroup that had benefited most from the AHR strategy initially (Fig. 1B). Mean FEV_1 change since end of CATO study period in this subgroup was −6.0% (3.3) for the AHR strategy versus +1.7% (2.5) for the reference strategy ($p = 0.08$). Repeated analysis using reference equations for a wider age range[18]

Table 1 Characteristics of the children in the CATO-follow-up study and those who did not participate in the follow-up study, as measured at enrolment in the CATO[14] intervention study. Data given are numbers (%) of patients, mean (sd), or median (range).

	Follow-up population $n = 137$	No follow-up $n = 69$	p-Value
Gender (%)			
Male	74 (54)	43 (62)	0.32
Female	63 (46)	26 (38)	
Age at enrolment[a] (yrs)	10.4 (2.4)	11.8 (2.2)	<0.001
Age at follow-up (yrs)	16.8 (2.4)	18.2 (2.2)	<0.001
FEV_1 (%pred) at enrolment	98.7(14.9)	92(12.8)	0.002
FEV_1/FVC (%) at enrolment	82.7 (8.4)	80.4 (9.2)	0.17
PD_{20} (μg methacholine) at enrolment	219 (0.8-> 1570)[b]	233 (0.8-> 1570)[b]	0.13
% Symptom free days at enrolment	47.3 (37.2)	50.6 (35.9)	0.48
Treatment strategy (%)			
AHR	76 (55)	28 (41)	0.06
Reference	61 (45)	41 (59)	
Subgroup in CATO			
AHR	58 (42)	33 (48)	0.75
Symptoms	32 (23)	14 (20)	
AHR + symptoms	47 (34)	22 (32)	
Drop-out during CATO study			
Yes	5 (4)	16 (23)	<0.001
No	132 (96)	53 (77)	

[a] At randomisation in the original CATO study.
[b] Upper limit of testing (1570 ug = highest dose).

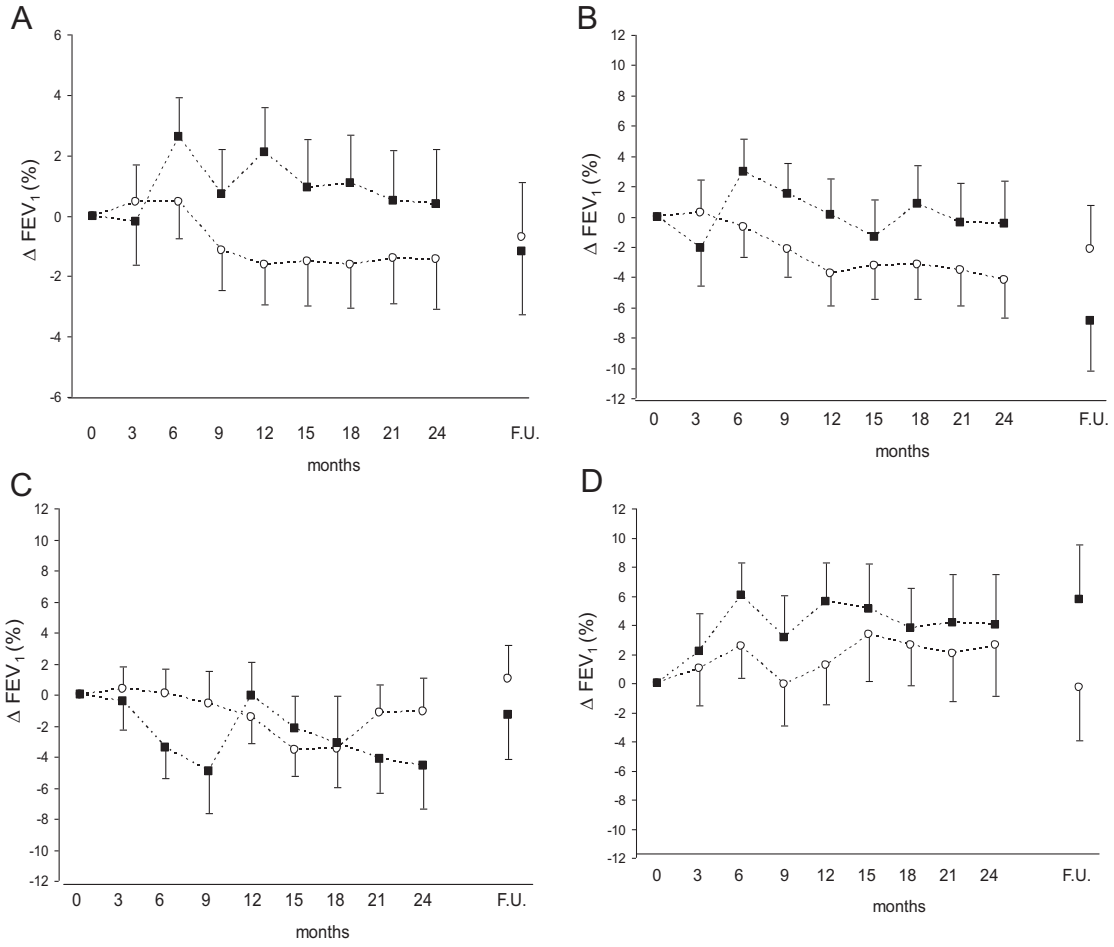

Figure 1 Mean change from baseline of FEV_1 (%pred) during the 2 years CATO intervention study[14] in patients who completed the follow up study after the CATO trial, and at follow-up. Month 0 is time of enrolment, F.U. represents the follow-up assessment. Error bars represent standard errors and solid and open symbols depict the AHR and reference strategy group, respectively. A: Total group of 137 patients. B: Subgroup airway hyperresponsiveness, 58 patients. C: Subgroup symptoms, 32 patients. D: Subgroup with airway hyperresponsiveness + symptoms, 47 patients.

produced similar results, with no significant differences in FEV_1 at follow-up between treatment strategies in the total population and in subgroups. No correlation was found between FEV_1 and time interval of follow-up visit or age at follow-up. A significant correlation between FEV_1 at start of the original CATO study and FEV_1 at follow-up existed ($r = 0.45$, $p < 0.001$). However, a lower FEV_1 did not correlate with FEV_1 decline.

PD_{20} at follow-up was assessed in 83 patients (36 from the AHR group and 47 from the reference strategy group). The increase of PD_{20} during the CATO study was maintained at follow-up for both treatment strategy groups (Fig. 2). No differences between treatment strategy arms and subgroups were found. The mean change from baseline of PD_{20} at CATO—FU was 3.3 and 2.8 doubling doses for the AHR and reference strategy, respectively ($p = 0.59$).

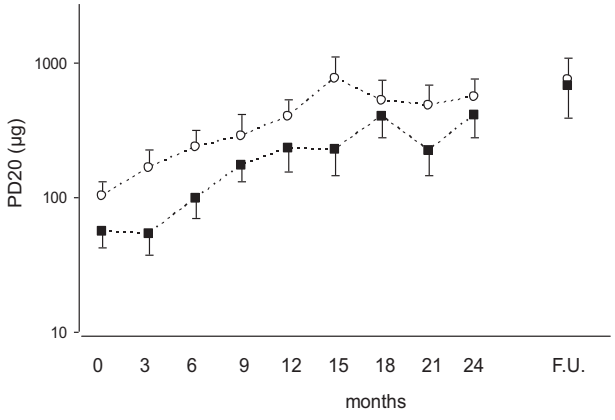

Figure 2 Geometric mean PD_{20} values during the 2 years CATO intervention study[14] in patients completing CATO-follow up study and at CATO-follow-up study according to treatment strategy. Month 0 is time of enrolment, F.U. represents the follow-up assessment. Error bars represent standard errors and solid and open symbols depict the AHR and reference strategy group, respectively. Error bars represent standard errors.

Symptoms and exacerbations

Ninety patients returned evaluable diary cards (at least 20 completed days in the 6 weeks period). The mean %

symptom-free days was 63 (5) and 67 (4) for the AHR and reference strategy groups, respectively (NS). The increase in % symptom-free days from CATO baseline was maintained at follow-up (Fig. 3).

During the CATO study 50 exacerbations requiring oral steroids occurred in 33 patients. During the follow-up years, 59 exacerbations were reported in 30 patients and another 4 exacerbations in 4 patients were reported between the 2 follow-up visits. The mean annual exacerbation rates were 0,26 in the year before- and 0.14 during the CATO study, and 0.10 in the follow-up years. The exacerbation rates during the intervention and follow-up years did not differ, and were significantly lower than before entering CATO. Baseline FEV_1 was inversely related to the exacerbation rate: per 10% points increase in FEV_1, the exacerbation rate decreased by 0.84 ($p = 0.03$).

Medication use

At follow-up, all but 5 children reported to have asthma symptoms, although only 93 out of 137 (68%) still used ICS with a mean daily reported dose of 248 μg fluticasone equivalent. There was no difference in FEV_1, AHR or symptom scores in those with or without ICS at follow-up. The ICS dose, based on pharmacy registrations, gradually diminished over the years from 550 μg at the end of CATO to 235 μg at follow-up.

Discussion

We prospectively assessed the long-term effects of 2 years of AHR-guided asthma treatment in children in whom we previously found a better evolution of lung function as a result of this intervention. After a mean interval of 4.4 years, range 3—7 years, the effect of AHR-guided treatment on lung function was lost. Overall, AHR and symptom-free days had remained at the same level as at the end of the 2-year intervention, despite the use of much lower doses of ICS and irrespective of the initial treatment strategy. We speculate that this reflects the natural history of asthma, which tends to improve during adolescence.[1] The subgroup of children with AHR and low symptom scores at baseline benefited most from the AHR strategy in the CATO study. This benefit was also lost at follow-up.

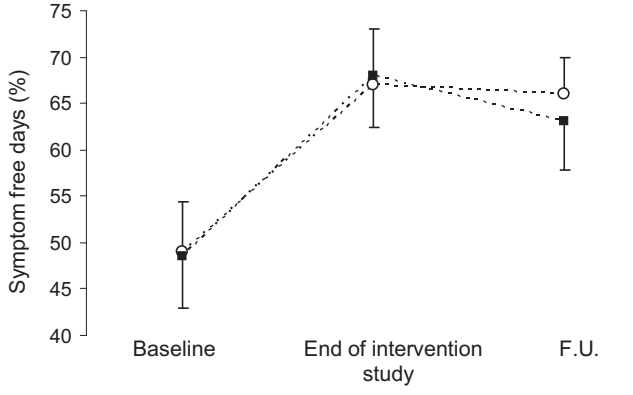

Figure 3 Mean values of % symptom-free days at CATO[14] enrolment, at the end of the 2-years CATO intervention study in patients completing CATO-follow up study and at CATO-follow-up study. (FU) error bars represent standard errors. Solid and open symbols depict the AHR- and reference strategy groups, respectively.

To our knowledge this is the first study which focuses on long-term effects of a phenotype-specific treatment strategy. Few studies have examined the persistence of effects of treatment strategies.[19] Recent data from the CAMP follow-up study showed that the positive effects of treatment with ICS on AHR, lung function and asthma control had disappeared 4 years after discontinuation of ICS.[20] Waalkens et al. reported similar findings already within 6 months after discontinuation of inhaled corticosteroids.[21] Contrary to the data of the CAMP follow-up study our data show that improvement in AHR and reduction of asthma exacerbations were maintained at the level reached during the intervention study, and we speculate that this is because of the continuous treatment with ICS. Contrary to the CAMP study the majority of children in our study continued their ICS.

That the subgroup with low symptom perception, that initially improved most from the AHR strategy, showed no lasting benefit beyond the duration of the intervention study is remarkable. One could imagine that participation in a 2-year intervention study with regular assessments of AHR and lung function might well improve symptom perception, and that this could specifically help children in the subgroup with low symptom scores despite AHR. This was apparently not the case, suggesting that there was no long-term effect of 2 years of AHR-guided treatment on symptom perception.

As can be expected in an adolescent population, a substantial number of the original study population could not be persuaded to co-operate in the follow-up. Our results may therefore have been biased by selection. Children in the follow-up study were younger and had higher FEV_1 values than those of the original study population. Adolescence, with a concomitant loss of interest and low priority of attending, may well have accounted for the younger age of those who participated at follow-up. We think it is unlikely that high FEV_1 values interact with the willingness to participate. However, as children who did not participate indeed had a lower baseline FEV_1, such an effect could have influenced our results.[6] It might be that children with lower FEV_1 benefited more from an intensive treatment strategy. It could be argued that expressing lung function as % predicted at follow-up becomes problematic when separate adult and paediatric reference equations for spirometry are used. We think that this has not affected our findings, as additional analyses using reference equations for a wide age range produced similar results.[18]

What could be the impact of our finding for clinical practice? The long-term evolution of lung function suggests that an AHR-guided treatment strategy may need to be sustained for longer than 2 years in order to preserve lung function. In view of the relatively low ICS doses at the end of the intervention, such a strategy would seem to be safe. It remains to be shown that such a strategy would be feasible and has the desired long-term effects.

In conclusion, we found that the beneficial effect on lung function of 2 years' asthma treatment guided by AHR

was lost after 5 years of usual care, based on international guidelines. It remains to be shown if continuation of the experimental treatment strategy could have maintained the initial effect or might have further improved lung function.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.rmed.2013.03.008.

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