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Early View

Original article

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Long-term adherence to inhaled corticosteroids and asthma control in adult-onset asthma

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Conception and design, H.K., L.E.T., O.N., and P.I.; Data analysis, I.V. and P.I.; Data collection, H.K., L.E.T., O.N., P.I., and I.V.; Manuscript writing, I.V., P.I., and H.K.; Manuscript review and editing, I.V., P.I., H.K., L.E.T., O.N., and L.L.

Competing interests

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Abstract

Background

In short-term studies poor adherence to inhaled corticosteroids (ICS) has been associated with worse asthma control but the association of long-term adherence and disease control remains unclear.

Objective

To assess the relationship between 12-year adherence to ICS and asthma control in patients with adult-onset asthma.

Methods

As part of Seinäjoki Adult Asthma Study (SAAS), 181 patients with clinically confirmed new-onset adult asthma and regular ICS medication were followed for 12 years. Adherence (%) to ICS was assessed individually ((µg dispensed / µg prescribed)x100) during the follow-up. Asthma control was evaluated after 12-years of treatment according to GINA 2010 guideline.

Results

Asthma was controlled in 31% and not-controlled (partly or uncontrolled) in 69% of the patients. Patients with not-controlled asthma were more often males, older, non-atopic and used higher doses of ICS than those with controlled disease. The mean 12-year adherence to ICS was 63% (SD 38%) in patients with controlled asthma and 76% (SD 40%) in patients with not-controlled disease (p=0.042). Among patients with not-controlled asthma, those with lower 12-year adherence (<80%) had more rapid decline in FEV_1 (-47mL/year) compared to patients with better adherence (≥80%) (-40mL/year) (p=0.024). In contrast, this relationship was not seen in patients with controlled asthma.

Conclusions

In adult-onset asthma, patients with not-controlled disease showed better 12-year adherence to ICS treatment than those with controlled asthma. In not-controlled disease, adherence <80% was also associated with more rapid lung function decline underscoring the importance of early recognition of such patients in routine clinical practice.

Running head: Adherence and asthma control in adult-onset asthma

Abstract word count: 248/250

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Take home message (255/256 characters): Patients with not-controlled asthma and poor adherence showed increased FEV_1 decline. Special emphasis on ICS adherence should be paid on subjects who do not have controlled asthma, as they seem to be in higher risk of developing fixed airway obstruction.

This study is registered at www.ClinicalTrials.gov with identifier number NCT02733016.

Abbreviations

ICS: inhaled corticosteroid

MPR: Medication Possession Ratio

PDC: Proportion of Days Covered

SMART: single maintenance and reliever therapy

FEV_1: forced expiratory volume in one second

GINA: Global Initiative for Asthma

BDP: beclomethasone dipropionate

FVC: forced vital capacity

BD: bronchodilator

FeNO: exhaled nitric oxide

IgE: immunoglobulin E

IL-6: interleukin 6

hsCRP: high-sensitivity C-reactive protein

AQ20: airways questionnaire 20

ACT: asthma control test

AUC: area under curve

BMI: body mass index

SABA: short-acting β_2-agonist

LABA: long-acting β_2-agonist

LTRA: leukotriene receptor antagonist

MARS: Medication Adherence Rating Scale

Morisky: Morisky Medication Adherence Scale

INCA: INhaler Compliance Assessment

Introduction

Successful asthma treatment plays a pivotal role in preventing exacerbations, enhancing patients´ quality of life and decreasing health-care costs[1]. Asthma often remains poorly controlled despite effective pharmacological treatment strategies[2-4] and current guidelines emphasize the importance of finding out the reason behind not-controlled asthma in each patient[5]. Age of asthma onset has been shown to differentiate the phenotypes of asthma[6,7] but very little information exists on the disease control characteristics of the late-onset asthma phenotype[3].

To gain optimal benefits from pharmacotherapy, patients should be adherent to treatment, which has unfortunately been shown to be often suboptimal[1,8]. Only two studies so far have evaluated long-term adherence to inhaled corticosteroids (ICS): Childhood Asthma Management Program (CAMP) (4-year follow-up)[9] and Seinäjoki Adult Asthma Study (SAAS) (12-year follow-up)[8]. In these studies, mean adherence to ICS was 52% and 69%, respectively. Previous studies assessing asthma control and adherence have been either cross-sectional or with short follow-ups[10-18]. In addition, the evaluation of adherence and asthma control has mostly been questionnaire-based and information concerning diagnostic criteria, duration and age of onset of asthma are often missing, potentially influencing the results[4,13,15]. Poor asthma control has been associated with higher risk of exacerbations, lower quality of life and increased health-care use[2,4,10,19]. Previous studies have suggested that suboptimal adherence to pharmacological therapy impairs asthma control[4,10-13,20]. In contrast, a recent study identified that patients with uncontrolled asthma were more adherent to ICS treatment.[21] However, the adherence was determined from prescriptions issued reflecting the physician's prescription manners, not the adherence of the patient. It should be noted that in previous

studies Medication Possession Ratio (MPR) and Proportion of Days Covered (PDC) formulas have been regularly used for estimating adherence[1,21]. Unfortunately the data used in these formulas is usually lacking details, such as did patients have continuous prescription for ICS and how were dose ranges and single maintenance and reliever therapy (SMART) regarded, all being relevant issues in treatment of asthma.

Inadequate use of preventer medication is suggested to be related to decline in lung function but there are no data on the association between long-term adherence and lung function decline stratified by asthma control. An Australian study[22] found accelerated lung function in patients not taking adequate preventer therapy. Furthermore, in previous short-term (1-year) follow-up study conducted in UK[23], patients with difficult-to-control asthma and sub-optimal ICS adherence had reduced FEV_1. In our recent study, poorer 12-year adherence was related to lung function decline in long-term but patients with good adherence used more add-on drugs, oral corticosteroid courses, had more hospital days, and used more health-care services, i.e. had features suggesting not-controlled asthma[8]. Thus, we hypothesized that not-controlled asthma is not a direct consequence of poor adherence and that lung function decline does not depend on poor adherence only but may be affected by asthma control. Hence this study aimed to assess the relation between 12-year adherence to ICS and asthma control in patients with adult-onset asthma, especially concentrating on whether the effect of poor adherence on lung function decline is affected by asthma control. In this study, we used full coverage dispensing data and information on prescribed ICS offering the possibility to assess real-life adherence based on dispensed and prescribed amounts of ICS[8,24].

Methods

Study design and patients

The current study is part of SAAS, which is a prospective 12-year follow-up study of patients with diagnosis of new-onset adult asthma. All new adult (age ≥15 years) patients in Seinäjoki Central Hospital were included during the period of 1999-2002. Diagnostic criteria, inclusion and exclusion criteria have been reported earlier[25] (eTable 1). Patients with comorbidities or smoking history were not excluded. Study participants gave written informed consent to the study protocol approved by the Ethics committee of Tampere University Hospital, Tampere, Finland.

The study was divided into two parts: baseline visit and 12-year follow-up visit (Figure 1). At the baseline visit, data was collected on symptoms, lung function and demographics as previously described[25]. Furthermore, regular ICS medication was prescribed and each patient received asthma education, advice to use inhaler correctly and self-management instructions according to Finnish Asthma Programme[26]. From the original cohort of 257 patients, 203 (79%) returned to the 12-year follow-up visit in which asthma control, medication and lung function were evaluated (online supplement). All asthma-related visits and medication information were collected for the whole 12-year follow-up period from medical records[24]. To ensure that the study population included only patients with regular ICS medication, we excluded patients for whom ICS was prescribed only periodically (often GINA step 1 and ICS use during pollen season) at any point of the follow-up (Figure 1).

Asthma control and lung-function

Asthma control was defined according to GINA 2010[27] and not-controlled included both partially and uncontrolled asthma (online supplement). Lung function measurement points were: 1) baseline (diagnosis), 2) the maximum lung function (Max0–2.5) during the first 2.5 years after diagnosis (after start of therapy) and 3) 12-year follow-up visit (online supplement). Decline in lung function during the 12-year follow-up period was defined as change in pre-bronchodilator FEV_1 from Max0-2.5 to 12-year time point.

Assessment of adherence

The prescribed ICS dose in each patient for the 12-year period was calculated based on medication records as previously described[24]. Shortly, we converted all prescribed ICS doses (ICS in both single and combination inhalers) to beclomethasone dipropionate (BDP) equivalents, and based on that information, calculated annual prescribed ICS medication for each patient. The dispensed ICS doses were obtained from the Finnish Social Insurance Institution that records all purchased medication from any Finnish pharmacy. All drug and dose changes were taken into account individually. In the case of ranged doses prescribed (e.g. 1-2 puffs 2 times daily) we interpreted that patients were adherent when the minimum ICS doses were dispensed. Adherence to ICS was determined as recently described[8], consisting of initiation, implementation and persistence (online supplement). The 12-year adherence was calculated by comparing cumulative dispensed doses of ICS (µg) to cumulative prescribed doses of ICS (µg) and annual adherence by comparing yearly dispensed doses of ICS (µg) to yearly prescribed doses of ICS (µg). This adherence calculation combines elements from both MPR and PCD formulas (online supplement)[8,28] and we estimated the time-variance of the adherence according to a recent publication[29].

Statistical analyses

The results are shown as mean (SD), or median (interquartile range) but annual adherence is represented as mean ± SEM for clarity. Comparison of groups with ≥80% or <80% adherence to ICS were analyzed by using independent samples t-test and Mann-Whitney U test for normally and non-normally distributed continuous variables, respectively, and Pearson Chi-Square or Fisher´s exact test for categorical variables. To analyze differences in annual adherence over the 12 year period between controlled and not-controlled patients, annual adherence was plotted against time for individual patients and mean area under curve (AUC) values were compared by using independent samples t-test. A multivariable binary logistic regression analysis was performed to analyze factors associated with not-controlled asthma. A multiple linear regression analysis was performed to analyze factors associated with FEV_1 decline as previously described[30]. The correlation matrix was analyzed and covariates not strongly correlated ($r<0.7$) (age, gender, BMI at follow-up, FeNO >20 ppb, pack years ≥10 at follow-up, ΔFEV_1 (baseline-$max_{0\text{-}2.5}$) and average 12-year adherence (<80%) to ICS) were included in the analysis and outliers were removed to ensure homoscedasticity (online supplement). A P-value <0.05 was regarded as statistically significant. Statistical analyses were performed by using IBM SPSS statistics software, version 24 (IBM SPSS, Armonk, NY, USA) and GraphPad Prism software, version 7.03 (GraphPad, La Jolla, CA, USA).

Results

Patient characteristics

Majority of the study patients were females (60%), average age was 59 (SD 13) years at the follow-up visit and half of the patients were current or ex-smokers (eTable 2). At the follow-up visit patients had higher BMI, better lung function, lower blood eosinophil counts and fewer symptoms (AQ20) compared to the baseline visit (eTable 2).

Asthma control

At the 12-year follow-up visit, asthma control was evaluated and the patients were divided into two groups: controlled (n=56) and not-controlled (n=125). Group characteristics are shown in Table 1. Patients with not-controlled asthma were more often males, older and were prescribed higher doses of ICS than patients with controlled asthma. As previously reported, lung function was better and smoking was less common in patients with controlled asthma vs. not-controlled asthma[3]. Patients with not-controlled asthma used more daily add-on drugs, had more days in hospital and were dispensed higher doses of oral corticosteroids (Table 1). In addition, patients with not-controlled asthma were less often atopic and had a higher number of asthma-related contacts to healthcare. No difference was found in inflammatory parameters.

Table 1. Characteristics of asthma patients at 12 years after diagnosis according to their level of asthma control (n=181)[£].

	Controlled (56)	Not-controlled (125)	p-value
Age (y)	56 (14.6)	61 (12.4)	0.011[a]
Female gender n (%)	41 (73.2)	67 (53.6)	0.014[b]
BMI, kg/m2	27.6 (3.8)	29.1 (6.0)	0.079[a]
Smokers (incl. ex) n (%)	18 (32.1)	73 (58.4)	0.001[b]
Smoking history, pack-y	7 (2-12)	20 (10-32)	<0.001[c]
Pack-y >=10 and post-BD $FEV_1/FVC<0.7$ n (%)[Ʊ]	4 (7.1)	29 (23.4)	0.011[b]
Pre-bd FEV_1% pred	92 (86-99)	82 (70-93)	<0.001[c]
Pre-bd FEV_1/FVC	0.75 (0.70-0.79)	0.73 (0.64-0.78)	0.016[c]
Post-bd FEV_1% pred	96 (90-101)	84 (75-96)	<0.001[c]
Post-bd FEV_1/FVC	0.77 (0.73-0.83)	0.73 (0.65-0.79)	0.002[c]
Blood eosinophils ($\times 10^9 \cdot L^{-1}$)	0.17 (0.12-0.28)	0.18 (0.09-0.27)	0.353[c]
Total IgE ($kU \cdot L^{-1}$)	51 (28-161)	71 (24-172)	0.617[c]
FeNO (ppb)	12 (6-19)	10 (5-18)	0.392[c]
Blood neutrophils ($\times 10^9 \cdot L^{-1}$)	3.7 (3.0-4.6)	3.9 (2.9-4.9)	0.522[c]
Prescribed daily dose of ICS (µg BDP)	751 (502-939)	838 (664-1023)	0.014[c]
Dispensed daily dose of ICS (µg BDP)	411 (246-625)	602 (354-838)	0.002[c]
Daily SABA n (%)	2 (3.6)[£]	19 (15.2)	0.024[b]
Daily LABA n (%)	18 (32.1)	77 (61.6)	<0.001[b]
Self-reported use of oral corticosteroid courses for asthma n (%)	12 (21.4)	48 (39.0)	0.026[b]
Dispensed oral corticosteroid for asthma per year (mg)[#]	44 (0-127)	92 (0-240)	0.013[c]
Comorbidities	1 (0-2)	1 (0-3)	0.057[c]
Co-medications (non-respiratory)	1 (0-4)	2 (0-4)	0.124[c]
AQ20 score	2 (0-4)	6 (3-9)	<0.001[c]
ACT score	24 (22-25)	20 (17-23)	<0.001[c]
Asthma-related visits to health care	12 (6-19)	16 (10-26)	0.014[c]
Atopy n (%)[Ω]	27 (50.9)	34 (30.6)	0.016[b]
Hospital in-patient periods, ≥1, asthma-related (unplanned) n (%)	1 (1.8)	15 (12.0)	0.024[b]

Data is presented as n (%), mean (SD) or median (interquartile range). BMI= body mass index, Smoking history, pack-y= pack years of smokers, FEV_1= forced expiratory volume in 1 second, FVC= forced vital capacity, IgE= immunoglobulin E, FeNO= fraction of NO in exhaled air, BD= bronchodilator, ICS= inhaled corticosteroid, BDP= beclomethasone dipropionate equivalents, Daily SABA= self-reported daily use of short-acting β2-agonist, Daily LABA= self-reported daily use of long-acting β2-agonist, AQ20= airways questionnaire 20, ACT= asthma control test, Asthma related visits to health care= all respiratory related scheduled and unscheduled contacts to healthcare due to asthma. Self-reported use of oral corticosteroids, asthma related visits to healthcare and hospital in-patient periods have been examined during whole 12 years follow-up period. [#]Dispensed doses of oral corticosteroids (mg) were obtained from the Finnish Social Insurance Institution and were divided by the years of follow-up. [Ʊ]Baseline Pack-y >=10 and post-BD FEV1/FVC<0.7 n (%)= 2 (3.6) with controlled and 13 (10.7) in patients not-controlled asthma (p=0.150). [Ω]Atopy was defined as at least one positive response (≥ 3 mm) in skin prick towards common aeroallergens[31]. [£]These 2 patients were not dispensed SABA at the year when asthma control was determined and therefore they were considered to belong to group of controlled patients. However, they self-reported daily use of SABA and more SABA was dispensed on preceding years of the follow-up. Statistical significances were evaluated by independent samples t-test ([a]), Fisher´s exact test ([b]) or by independent samples Mann-Whitney U test ([c]). [£]The results of lung function and inflammatory parameters have been previously published in patients with controlled, partially controlled and uncontrolled asthma[3].

Adherence and asthma control

The mean 12-year adherence to ICS was 63% (SD 38) in patients with controlled asthma and 76% SD (40) in patients with not-controlled disease (p=0.042) (Figure 2A). Patients with not-controlled asthma had significantly higher adherence (p=0.037) compared to patients with controlled asthma in the whole 12-year study period (Figure 2B). Furthermore, 34% of the study patients had not-controlled asthma despite having ≥80% adherence to ICS treatment during 12-year follow-up (Table 2). The association between ≥80% adherence and not-controlled asthma remained in binary logistic regression analysis adjusting for age ≥60, BMI ≥30, gender, COPD and rhinitis. When evaluating long-term ICS use, it was found that 76.8% of the patients with not-controlled asthma and 60.7% of the patients with controlled asthma were more than 50% adherent to their ICS treatment each year during the 12-year follow-up (p=0.032).

Not-controlled asthma

A large variation in the ICS adherence was found in the not-controlled asthma group. Therefore we considered that there may be two different groups of patients with suboptimal asthma control; a) those having not-controlled asthma due to low adherence to ICS and b) those having not-controlled asthma despite good adherence to ICS. To see, whether clinical differences exist between these groups, we evaluated asthma-related parameters in patients having not-controlled asthma but ≥80% or <80% 12-year adherence (Table 2 and eTable3). The patients having not-controlled asthma and ≥80% adherence had a higher number of asthma-related contacts to healthcare, higher blood neutrophil count and used more often LABA or LTRA (Table 2).

Table 2. Characteristics of patients with not-controlled asthma at 12 years after diagnosis according to their level of 12-year adherence (n=125).

	Not-controlled asthma n=125		
	Good adherence (≥80%) n=61	Poor adherence (<80%) n=64	p-value
Age (y)	62 (12)	60 (13)	0.242[a]
Female gender n (%)	36 (59.0)	31 (48.4)	0.283[b]
BMI, kg/m^2	28.4 (24.6-32.5)	28.5 (24.5-32.3)	0.286[c]
Smokers (incl. ex) n (%)	35 (57.4)	38 (59.4)	0.857[b]
Smoking history, pack-y	19 (9-34)	20 (12-30)	0.977[c]
Pre-bd FEV_1% pred	84 (71-99)	80 (70-90)	0.200[c]
Pre-bd FEV_1/FVC	0.73 (0.65-0.78)	0.72 (0.63-0.78)	0.797[c]
Post-bd FEV_1% pred	84 (75-99)	84 (75-92)	0.386[c]
Post-bd FEV_1/FVC	0.73 (0.66-0.79)	0.73 (0.65-0.80)	0.888[c]
Blood eosinophils ($\times 10^9 \cdot L^{-1}$)	0.15 (0.08-0.25)	0.19 (0.10-0.29)	0.118[c]
Total IgE ($kU \cdot L^{-1}$)	61 (23-138)	79 (29-197)	0.140[c]
Blood neutrophils ($\times 10^9 \cdot L^{-1}$)	4.2 (3.4-5.2)	3.5 (2.7-4.6)	0.022[c]
Prescribed daily dose of ICS (µg)	841 (704-1062)	834 (642-995)	0.412[c]
Dispensed daily dose of ICS (µg)	831 (728-1103)	375 (210-520)	<0.001[c]
Daily SABA n (%)	13 (21.3)	6 (9.4)	0.082[b]
Daily LABA n (%)	46 (75.4)	31 (48.4)	0.003[b]
Daily LTRA n (%)	16 (26.2)	6 (9.5)	0.019[b]
Self-reported use of oral corticosteroid courses for asthma n (%)	26 (44.1)	22 (34.4)	0.355[b]
Dispensed oral corticosteroid for asthma per year (mg)[#]	125 (10-273)	70 (0-193)	0.176[c]
Co-medications (non-respiratory)	2 (1-5)	2 (0-4)	0.116[c]
AQ20 score	6 (3.5-8)	5.5 (2-10)	0.822[c]
ACT score	21 (18-23)	20 (16-23)	0.795[c]
Allergy and/or rhinitis n (%)	45 (73.8)	46 (71.9)	0.843[b]
Asthma-related visits to health care	19 (13-28)	13 (9-22)	0.005[c]

Data is presented as n (%), mean (SD) or median (interquartile range). BMI= body mass index, Smoking history, pack-y= pack years of smokers, FEV_1= forced expiratory volume in 1 second, FVC= forced vital capacity, IgE= immunoglobulin E, BD= bronchodilator, ICS= inhaled corticosteroid, BDP= beclomethasone dipropionate equivalents, Daily SABA= self-reported daily use of short-acting β_2-agonist, Daily LABA= self-reported daily use of long-acting β_2-agonist, Daily LTRA= self-reported daily use of leukotriene receptor antagonist, AQ20= airways questionnaire 20, ACT= asthma control test, Asthma related visits to health care= all respiratory related scheduled and unscheduled contacts to healthcare due to asthma. Self-reported use of oral corticosteroids and asthma related visits to healthcare have been examined during whole 12 years follow-up period. [#]Dispensed doses of oral corticosteroids (mg) were obtained from the Finnish Social Insurance Institution and were divided by the years of follow-up. Statistical significances were evaluated by independent samples t-test ([a]), Fisher´s exact test ([b]) or by independent samples Mann-Whitney U test ([c]).

Controlled asthma

Assessment of patients with good asthma control revealed that patients with ≥80% adherence had lower BMI, higher total IgE and peripheral blood neutrophil counts and lower FEV_1

reversibility (mL) than patients with <80% adherence and controlled asthma (Table 3 and eTable 4). In addition, patients with controlled asthma and ≥80% adherence reported using oral corticosteroids more often and had tendency to increased asthma-related visits to healthcare compared to <80% adherent patients.

Table 3. Characteristics of patients with controlled asthma at 12 years after diagnosis according to their level of 12-year adherence (n=56).

	Controlled asthma n=56		
	Good adherence (≥80%) n=21	Poor adherence (<80%) n=35	p-value
Age (y)	58 (11)	54 (16)	0.266[a]
Female gender n (%)	16 (76.2)	25 (71.4)	0.764[b]
BMI, kg/m^2	26.3 (3.4)	28.3 (3.8)	0.045[a]
Smokers (incl. ex) n (%)	5 (23.8)	13 (37.1)	0.382[b]
Smoking history, pack-y	10 (3.7-14.8)	5.3 (1.3-9.3)	0.383[c]
Pre-bd FEV_1% pred	91 (86-100)	92 (86-98)	0.939[c]
Pre-bd FEV_1/FVC	0.74 (0.68-0.80)	0.75 (0.71-0.79)	0.460[c]
Post-bd FEV_1% pred	96 (90-100)	96 (91-102)	0.826[c]
Post-bd FEV_1/FVC	0.75 (0.71-0.82)	0.78 (0.73-0.83)	0.285[c]
Blood eosinophils ($\times 10^9 \cdot L^{-1}$)	0.25 (0.13-0.37)	0.15 (0.11-0.26)	0.095[c]
Total IgE ($kU \cdot L^{-1}$)	93 (39-214)	43 (23-95)	0.022[c]
Blood neutrophils ($\times 10^9 \cdot L^{-1}$)	3.9 (3.6-5.5)	3.6 (2.6-3.9)	0.016[c]
Prescribed daily dose of ICS (µg BDP)	620 (488-1017)	800 (541-925)	0.565[c]
Dispensed daily dose of ICS (µg BDP)	628 (476-983)	301 (90-402)	<0.001[c]
Daily SABA n (%)	0 (0)	2 (5.7)	0.523[b]
Daily LABA n (%)	8 (38.1)	10 (28.6)	0.558[b]
Daily LTRA n (%)	2 (9.5)	2 (5.7)	0.626[b]
Self-reported use of oral corticosteroid courses for asthma n (%)	8 (38.1)	4 (11.4)	0.040[b]
Dispensed oral corticosteroid for asthma per year (mg)[#]	48 (6-203)	0 (0-99)	0.060[c]
Co-medications (non-respiratory)	0 (0-4)	1 (0-4)	0.472[c]
AQ20 score	2 (0-3.5)	2 (1-4)	0.724[c]
ACT score	24 (22-25)	24 (22-25)	0.593[c]
Allergy and/or rhinitis n (%)	14 (66.7)	24 (68.6)	>0.999[b]
Asthma-related visits to health care	17 (8-27)	9 (6-17)	0.062[c]

Data is presented as n (%), mean (SD) or median (interquartile range). BMI= body mass index, Smoking history, pack-y= pack years of smokers, FEV_1= forced expiratory volume in 1 second, FVC= forced vital capacity, IgE= immunoglobulin E, BD= bronchodilator, ICS= inhaled corticosteroid, BDP= beclomethasone dipropionate equivalents, Daily SABA= self-reported daily use of short-acting β_2-agonist, Daily LABA= self-reported daily use of long-acting β_2-agonist, Daily LTRA= self-reported daily use of leukotriene receptor antagonist, AQ20= airways questionnaire 20, ACT= asthma control test, Asthma related visits to health care= all respiratory related scheduled and unscheduled contacts to healthcare due to asthma. Self-reported use of oral corticosteroids and asthma related visits to healthcare have been examined during whole 12 years follow-up period. [#]Dispensed doses of oral corticosteroids (mg) were obtained from the Finnish Social Insurance Institution and were divided by the years of follow-up. Statistical significances were evaluated by independent samples t-test ([a]), Fisher´s exact test ([b]) or by independent samples Mann-Whitney U test ([c]).

Decline in lung function

Next we evaluated the change in lung function in patients with controlled and not-controlled asthma and in groups of ≥80% and <80% 12-year adherence. The patients with not-controlled asthma and <80% 12-year adherence had more rapid decrease in lung function (FEV_1) compared to patients with ≥80% adherence (p=0.024) (Table 4, Figure 3). However, no difference was found in patients with controlled asthma between the adherence groups (Table 4). We carried out multiple linear regression analysis to find out whether poor adherence predicts accelerated lung function decline in patients with not-controlled asthma when adjusted for age, BMI at follow-up, gender, FeNO >20 ppb, pack-years ≥10, and ΔFEV_1(baseline-$Max_{0\text{-}2.5}$) (Table 5). After adjustments, poorer adherence (<80%) remained a significant predictor for FEV_1 (mL) decline.

Table 4. Lung function change (ΔFEV_1 from $max_{0\text{-}2.5}$ to 12-year follow-up visit) in patients with controlled and not-controlled asthma and different level of adherence (n=181).

	Good adherence ≥80%	Poor adherence <80%	p value
Not controlled asthma (n=125)			
ΔFEV_1 mL·year^{-1}	-40 (-56 to -20)	-47 (-83 to -32)	0.024
ΔFEV_1 % pred·year^{-1}	-0.47 (-0.98 to 0.25)	-0.76 (-1.40 to -0.17)	0.029
Controlled asthma (n=56)			
ΔFEV_1 mL·year^{-1}	-39 (-59 to -24)	-35 (-67 to -25)	0.859
ΔFEV_1 % pred·year^{-1}	-0.31 (-0.76 to 0.54)	-0.34 (-1.10 to 0.07)	0.271

ΔFEV_1= change in pre-bronchodilator-FEV_1 from the maximum value during the first 2.5 years after diagnosis and start of treatment to 12-year follow-up visit. Statistical significances were evaluated by independent samples Mann-Whitney U test. When patients with COPD were excluded from the analysis, ΔFEV_1 mL·year^{-1} was -36 (-54 to -18) in patients with >80% adherence and -43 (-78 to -28) in patients with <80% adherence and not-controlled asthma (p=0.058).

Table 5. Predictors for annual decline of FEV_1 (mL) (ΔFEV_1 from $max_{0\text{-}2.5}$ to 12-year follow-up visit) in 12-year follow-up in patients with not-controlled asthma as evaluated by multiple linear regression analysis (n=100).

	Unstandardized B coefficient (95% CI)	p value
Age at follow-up	-0.10 (-0.53 to 0.33)	0.638
Female gender	12.46 (1.03 to 23.89)	0.033
BMI at follow-up	-1.03 (-2.05 to -0.00)	0.049

Pack-years ≥10 at follow-up	-7.92 (-19.01 to 3.16)	0.159
ΔFEV_1 mL[#] (baseline-$Max_{0-2.5}$)	-0.024 (-0.04 to -0.01)	0.005
FeNO >20 ppb	-23.48 (-35.99 to -10.97)	<0.001
Average 12-year adherence (<80%) to ICS	-10.36 (-20.37 to -0.36)	0.042

BMI= body mass index, ICS= inhaled corticosteroid, FeNO= fraction of NO in exhaled air. [#]change in pre-FEV_1 from baseline to the maximum value during the first 2.5 years after diagnosis and start of treatment. In univariate analysis, unstandardized B coefficient (95% CI) for average 12-year adherence (<80%) to ICS is -11.23 (-22.15 to -0.32), p=0.044.

Discussion

In this study we evaluated both annual and 12-year adherence to ICS from diagnosis to 12-year follow-up visit in patients with adult-onset asthma and different categories of asthma control. The mean adherence to ICS was better in patients with not-controlled than controlled asthma (76% vs 63%). Considering patients with not-controlled asthma, good 12-year adherence (≥80%) was associated with daily use of LABA and higher number of peripheral blood neutrophils and asthma-related contacts to healthcare. Importantly, in patients with not-controlled asthma <80% adherence predicted more rapid lung function decline in adjusted analyses.

Although previous studies have suggested better ICS adherence to be associated with good disease control[4,11-13,20], in this study patients with not-controlled asthma had higher 12-year adherence to long-term ICS treatment compared to patients with controlled disease. The higher proportion of adherent patients in the former group may be explained by more severe symptoms and associated need of medication[16,21]. On the other hand, patients with controlled asthma may have themselves stepped-down their ICS therapy after achieving disease control, which would appear as lower adherence rates during the follow-up. In group comparisons, 58% of the patients with not-controlled disease were current or ex-smokers and had significantly more pack-years than those with controlled asthma. This is in line with previous studies which have related smoking to worse asthma control[3,4,12,32]. Furthermore, patients with not-controlled asthma were more often older, males and less often atopic compared to those

with controlled disease. In addition, there was a tendency between poorer asthma control and higher BMI. In patients with adult-onset asthma, phenotypes related to obesity and smoking are currently recognized, these phenotypes being at risk of poorer asthma outcomes and disease control[33-35]. Even though patients with not-controlled asthma had mean 12-year ICS adherence as high as 76%, factors such as smoking and obesity may induce insensitivity to ICS and poor response to treatment[34,36,37]. Furthermore, in recent studies the average age of patients has been lower in comparison to our study population[10,13,14] indicating that previous studies have included more patients with allergic asthma showing predominantly type 2 inflammation. Therefore, ≥80% adherence to long-term ICS treatment appears not to be effective enough to control asthma, since these patients may have had non-type 2 inflammation or untreated co-morbidities.

While it seems to have been taken for granted that poor adherence is one common reason behind not-controlled asthma, previous studies in this field have usually been cross-sectional or short-term follow-ups and no long-term studies have been conducted[10-17]. These cross-sectional studies mostly included patients having asthma diagnosis but the information on age of asthma onset, diagnostic criteria or duration of asthma were often lacking[10-12,14,16-18]. Moreover, in previous studies asthma control has been defined as asthma symptom control assessed by ACT (Asthma Control Test) or ACQ (Asthma Control Questionnaire) and not including both symptoms and lung function defined by GINA guideline. Further, adherence has been evaluated with MARS (Medication Adherence Rating Scale) or Morisky (Morisky Medication Adherence Scale) questionnaires[4,12,14-16,18]. Such self-reports are widely used for assessing adherence but may be vulnerable to the shortcomings of these memory-dependent channels. We found one 3-month clinical trial on inhaler adherence in patients with uncontrolled asthma where control was assessed according to GINA guidelines and adherence

monitored with INCA (INhaler Compliance Assessment) device, in which 27% of patients stayed refractory despite being adherent to salmeterol/fluticasone treatment and having correct inhaler technique[38]. A similar result was found in the current study where 34% of the study patients remained not-controlled despite having ≥80% adherence to ICS treatment during 12-year follow-up. To our knowledge, this is the first study where asthma control is determined according to GINA guidelines in unselected patient population and adherence is confirmed longitudinally by comparing each patient´s dispensed ICS medication to truly prescribed doses of ICS[8]. Furthermore, all patients with objectively confirmed diagnosis of new-onset adult asthma were included meaning e.g. patients with comorbidities and history of smoking.

When assessing lung function decline during 12-year follow-up in patients with not-controlled asthma, those with lower (<80%) 12-year adherence had more rapid decline in FEV_1 compared to patients with ≥80% adherence (p=0.024). This difference was not seen in patients with controlled asthma. The observed difference may also be clinically meaningful since the patients with adult-onset asthma rarely remit and a level of 7ml/year would correspond to 140ml in 20 years and 210ml in 30 years. Smoking and exacerbations are also important factors associated with the decline in lung function[30]. Even though the two adherence groups with not-controlled asthma did not differ by smoking, we adjusted our analyses for smoked pack-years and found that poorer adherence (<80%) remained a significant predictor for FEV_1 decline in patients with not-controlled asthma. The finding underscores the importance to determine patients´ asthma control by GINA guidelines and to assess treatment adherence. Early recognition of patients with not-controlled (partially or uncontrolled) asthma and sub-optimal (<80%) adherence should allow us to detect those patients who may be at risk for steeper lung function decline at long-term. Moreover, it may

also allow the opportunity to motivate them towards better adherence and thereby avoid undesirable outcomes in lung function. On the other hand, this may help to identify patients whose asthma is not-controlled despite high adherence to treatment. These patients may show non-type 2 inflammation since they have higher blood neutrophil counts and current medications may not be effective enough to control their disease. These results further suggest that patients with late-onset asthma and insufficient therapeutic response need new treatment strategies and possibly other interventions such as support in smoking cessation and weight loss.

In the current study, medical records and pharmacy dispensation data were used in adherence calculations, and therefore some limitations must be addressed. The dispensed medication is not a guarantee of the actual use of inhaler and therefore patient´s adherence to treatment may be overestimated. Although patients had guidance to correct inhaler use when medication was initiated, the correct inhaler technique could not be ensured. Furthermore, asthma control was measured at follow-up visit and not regularly during the follow-up. However, the current study with an exceptionally long follow-up period is based on objectively calculated adherence data, and assessment of asthma control includes also lung function according to GINA guidelines[3,8]. Recently, it was suggested[38] that an assessment of adherence with electronical device could be beneficial in patients with severe asthma. According to our results such approaches could also be used in patients with not-controlled disease. Future studies should assess how guidance on adherence focused to subjects with poor adherence to ICS and not-controlled asthma affects long-term changes in lung function.

In conclusion, we combined, for the first time, long-term adherence to ICS with asthma control determined according to GINA guideline[27]. The mean 12-year adherence to this treatment was especially high in patients with not-controlled disease. New treatment strategies combining pharmacological and non-pharmacological approaches may be needed in patients with insufficient therapeutic response. Importantly, our results showed that patients with not-controlled asthma and poor adherence (<80%) had more rapid decline in FEV_1 during 12-year follow-up compared to patients with higher adherence (≥80%), which must be recognized to avoid negative consequences. In clinical practice, careful evaluation of patient´s asthma control and adherence to treatment enhances the recognition of those patients at risk of rapid lung function decline at long-term.

Acknowledgements

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Figure legends

Figure 1. Flow-chart of the study.

Figure 2. Long-term adherence to ICS in patients with controlled and not-controlled asthma. (2A) The average 12-year adherence to ICS in study subgroups (mean, SD). Adherence >100% means that patients were dispensed more than regular individually prescribed minimum dose of ICS. (2B) The average annual adherence (mean ± SEM) in patients with controlled and not-controlled asthma during the 12-year follow-up period. P-value represents difference in annual ICS adherence between not-controlled and controlled patients as defined by area under the curve method and independent-samples t-test. Significant difference was also seen when patients with COPD were excluded from the analyses (2A p=0.021 and 2B p=0.019).

Figure 3. Schematic presentation of the changes in forced expiratory volume in 1 s (FEV_1) (mL) during 12 years of follow-up in patients with not-controlled asthma and ≥80% or <80% adherence. Model based on group medians. At the year 0 patients were steroid-naïve and ICS treatment was initiated (diagnostic visit). Origin for lung function decline is the maximal point of lung function within 2.5 years after start of treatment.

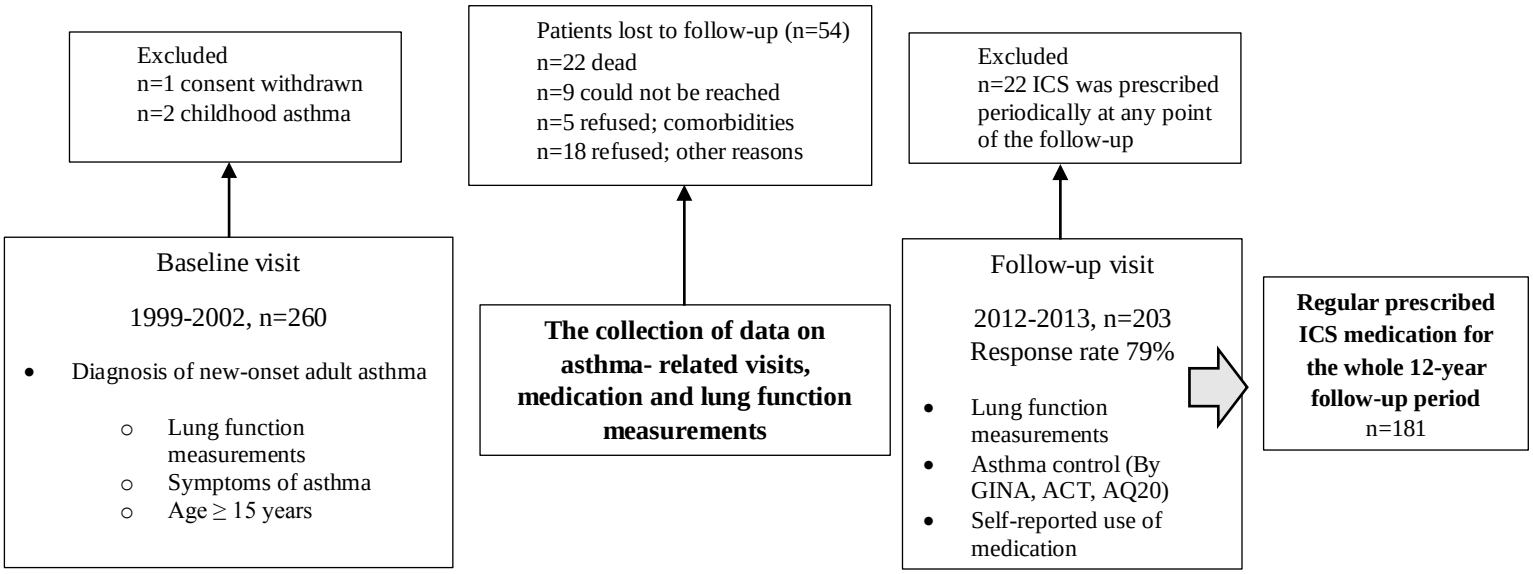
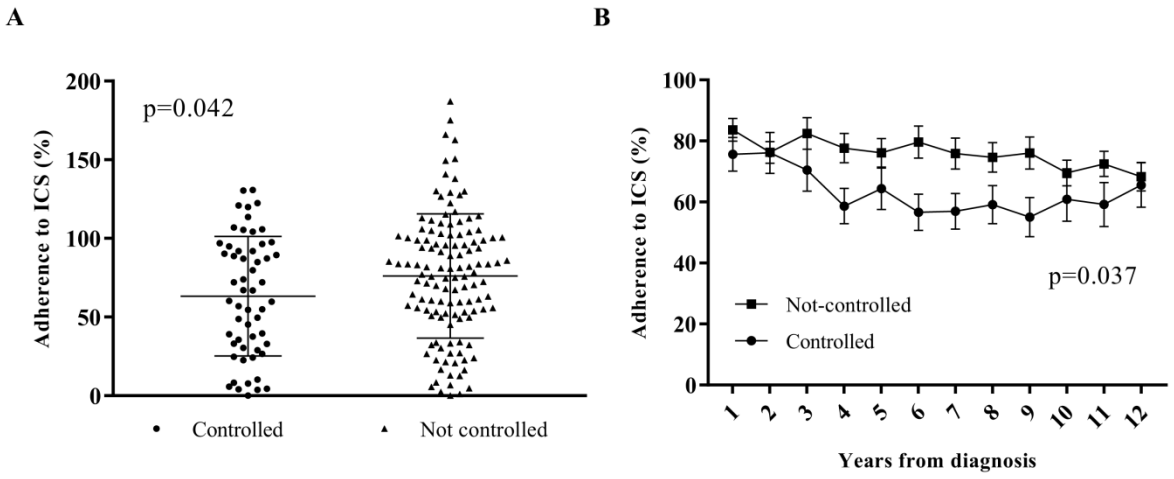


Figure 1. Flow-chart of the study.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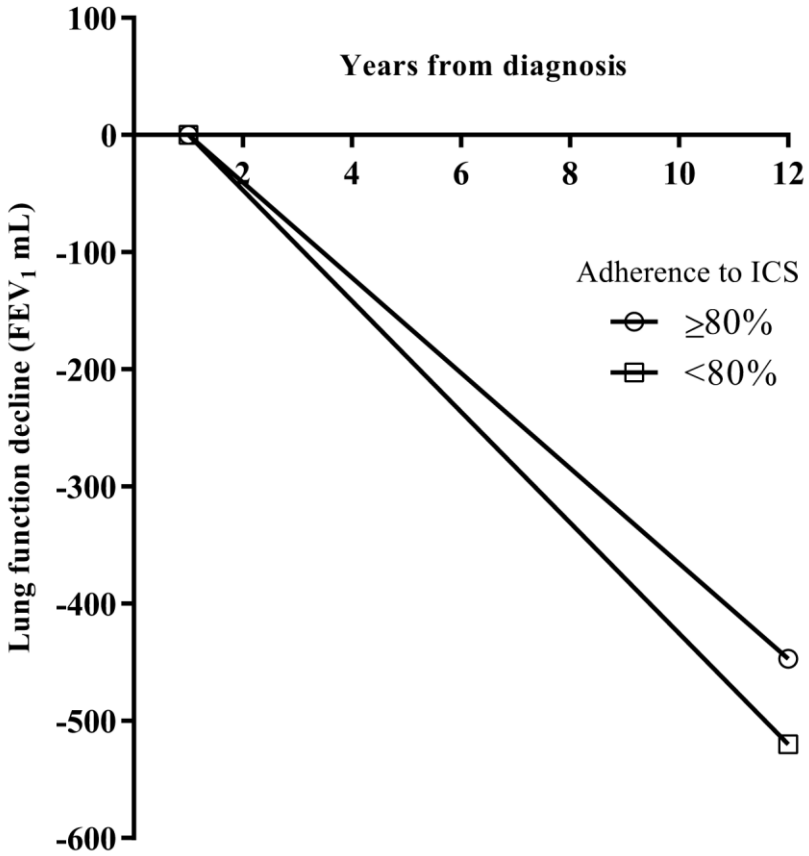
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Lung function decline (FEV1 mL)
Adherence to ICS
≥80%
<80%

Long-term adherence to inhaled corticosteroids and asthma control in adult-onset asthma

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Supplementary material

Lung function measurements

Lung function measurements were performed using a spirometer (Vmax Encore 22, Viasys Healthcare, Palm Springs, CA, USA) according to international and national recommendations and Finnish reference values[E1-E3]. Lung function measurement points were: 1) baseline (i.e. time of asthma diagnosis), 2) the maximum lung function (Max0–2.5) during the first 2.5 years after diagnosis (i.e. after start of anti-inflammatory therapy) based on the highest pre-bronchodilator forced expiratory volume in 1 s (FEV1) % pred and 3) after 12 years of follow-up (figure 1). Lung function measurements after the diagnosis of asthma were taken while patients were on medication, without pauses or withholding on the therapy.

Laboratory measurements

Fraction of exhaled nitric oxide (FeNO) was measured with a portable rapid-response chemiluminescent analyzer according to American Thoracic Society standards (flow rate 50 mL·s−1; NIOX System, Aerocrine, Solna, Sweden)[E4]. Venous blood was collected and white

blood cell differential counts were determined. Total immunoglobulin (Ig)E levels were measured by using ImmunoCAP (Thermo Scientific, Uppsala, Sweden)[E4]. Serum levels of IL-6 were determined by ELISA (R & D Systems, Minneapolis, MN, USA) and hsCRP was measured using particle-enhanced immunoturbidometric method on Roche Cobas 8000 automated clinical chemistry analyser (Roche Diagnostics, Basel, Switzerland).

Evaluation of symptoms and dispensed oral corticosteroids

Patients filled out the Airways Questionnaire 20 (AQ20) at baseline visit and during the follow-up visit symptoms were measured both with AQ20[E5] and Asthma Control Test (ACT)[E6]. Dispensed doses of oral corticosteroids (OCS) (mg) were obtained from the Finnish Social Insurance Institution and were divided by the years of follow-up as previously described[E7]. Regarding dispensed OCS, only those having indication for asthma were taken into account.

Asthma control

Patients were separated into two groups by their asthma control at follow-up visit which was defined according to the Global Initiative for Asthma (GINA) 2010 guideline[E8] as previously reported[E9]. Patients with not-controlled asthma (partially or uncontrolled asthma) had at least one of the following features: symptoms of asthma or need for rescue treatment more than twice weekly, decreased lung function (<80% predicted) or limitation of activities due to asthma.

Linear regression analysis

The correlation matrix was analyzed and explanatory variables not strongly correlated ($r<0.7$) (age, gender, BMI, pack years ≥10, ΔFEV_1 (baseline-max0-2.5), average 12-year adherence (<80%) to ICS, FeNO >20 ppb) were included in the analysis. Patients whose FEV_1 annual decline and ΔFEV_1 (baseline-max0-2.5) differed over 2.9-3SD from mean were removed as outliers to ensure homoscedasticity, as well as patients whose age differed over 2.1SD and BMI differed over 2.3SD from mean. We did an additional sensitivity analysis by including also those patients whose age and BMI differed over 2.1SD and 2.3SD from mean and the result regarding adherence remained similar.

Computation of adherence

Prescribed dose for each patient and each year of the follow-up was calculated based on medical records[E7,E10]. All drug and dose changes were taken into account individually for each patient and finally all doses were converted to beclomethasone dipropionate (BDP) equivalents (Example 1)[E10]. Patients´ dispensed doses of ICS were obtained from the Finnish Social Insurance Institution that records all purchased medication from any Finnish pharmacy (Example 1)[E7]. By comparing dispensed doses to prescribed ICS doses, it was possible to evaluate adherence of a single patient during 12-year follow-up period as previously reported[E7]. In the case of ranged doses prescribed e.g. 1-2 puffs 2 times daily we interpreted that patients were adherent when the minimum ICS doses were dispensed. Taking into account, that the renewing of prescription is cost-free and in the case patient continues with the same medication and dosing the prescription is renewed usually for another year (if doctor wants to meet the patient she/he renews smaller amount e.g. 3 months prescription which lasts until the next visit), and therefore there would not be a situation where patient is without prescription. Long-term medication is usually prescribed for 1-2 years in Finland.

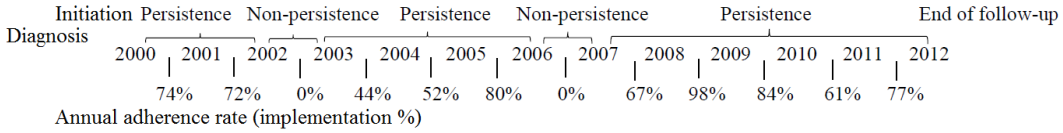
The 12-year adherence was calculated by comparing total cumulative dispensed doses of ICS to total cumulative 12-year prescribed doses[E7]. The most commonly used cut-off point (≥80%) in respiratory literature was set also in this study to distinguish the differences between patients with better (≥80%) and poorer (<80%) 12-year adherence[E11-E13]. To obtain a view on the variability of the adherence at long-term follow-up, annual adherence was calculated for each patient individually for each year by dividing patients yearly dispensed ICS doses by yearly prescribed ICS doses (µg BDP equivalents)[E7]. All in all, the extensive 12-year follow-up period and the fact that long-term medication is prescribed continuously, enhanced the evaluation of 12-year ICS adherence including initiation of medication and periods of persistence and temporary non-persistence (Example 2). Moreover, recent publication has used time-varying adherence to describe patient´s adherence behavior and this method was also adapted in the present study[E14]. (Example 2). However, time-varying PDC cannot take into account the dose ranges of asthma medication and therefore we modified the form by using the ug/ug and described the time-varying behavior in year of the follow-up (Example 3). In conclusion, all patients have their individual 12-year time-varying scope of adherence and when combined these together was possible to compare both average 12-year adherence and annual adherence of the patients.

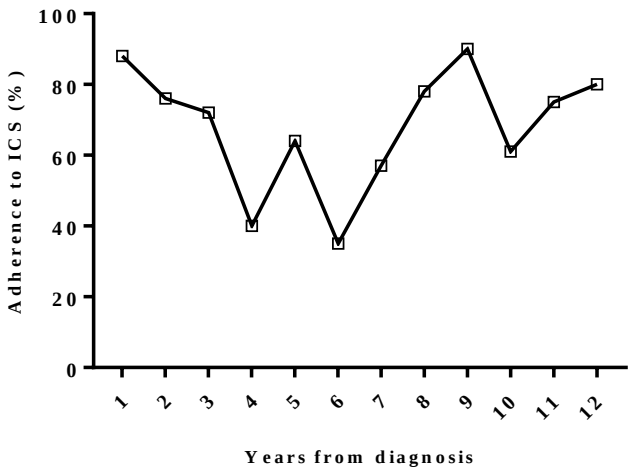
Example 1. 1-year adherence of one example patient.

		SUM
Prescribed doses of ICS (µg) in year 2008	1.1.2008-18.5.2008 (138 days) Pulmicort 200µg 1-2 puffs[£] 2 times a day =138 days*400µg=**55200µg** 19.5.2008-27.8.2008 (101 days) Pulmicort 400µg 1 puff 2 times a day =101 days*800µg=**80800µg** 28.8.2008-31.12.2008 (126 days) Symbicort Turbuhaler 200µg/6µg 1-2 doses 2 times a day =126 days*400µg=**50400µg**	**186 400 µg**
Dispensed doses of ICS (µg) in year 2008	Pulmicort Turbuhaler 200µg 1x200 puffs (=one inhaler bought) =200µg*200puffs= **40 000µg** Pulmicort Turbuhaler 400µg 1x200 puffs (=one inhaler bought) =400 µg*200 puffs= **80 000µg** Symbicort Turbuhaler 200µg/6ug 2x120 puffs (=two inhalers bought) =200 µg*2 inhalers*120puffs= **48000µg**	**168 000µg**
	Adherence = dispensed ICS µg / prescribed ICS µg *100	168 000 / 186 400 =90.1%

[£]In the case of ranged doses prescribed we interpreted that patients were adherent when the minimum prescribed ICS doses were dispensed.

Example 2. 12-year ICS adherence of one example patient.





Example 3. Time-varying adherence of one example patient (The average 12-year adherence of the example patient is 68%).

eTable 1. The inclusion and exclusion criteria used in SAAS.

Inclusion criteria	- A diagnosis of new-onset asthma made by a respiratory specialist - Diagnosis confirmed by at least one of the following objective lung function measurements:[a] - FEV_1 reversibility in spirometry of at least 15% and 200 mL after 400 µg of salbutamol - Diurnal variability (⩾20% on at least three days) or repeated reversibility (⩾15%/60 l/min on at least three occasions) during a two-week PEF monitoring - A significant decrease in FEV1 (15%) or PEF (20%) in to exercise or allergen challenge test - A significant reversibility in FEV_1 (at least 15% and 200 mL) or mean PEF (at least 20%) in response to a trial with oral or inhaled glucocorticoids - Symptoms of asthma - Age ≥15 years
Exclusion criteria	- Physical or mental inability to provide signed informed consent - Diagnosis of asthma below the age of 15 years - Of note: - Patients with comorbidities, either other lung disease or any other significant disease, were not excluded - Patients were not excluded because of smoking, alcohol use or any other lifestyle factor - Respiratory symptoms or any other disease during childhood was not a reason to exclude patients, but a diagnosis of asthma at age <15 years was an exclusion criteria

FEV_1= forced expiratory volume in one second, PEF= peak expiratory flow, SAAS= Seinäjoki Adult Asthma Study. Published earlier Kankaanranta et al. 2015[E15]

eTable 2. Characteristics of the study population (n=181).

	Baseline (n=181)	Follow-up (n=181)	p value
Age (y)	47 (13)	59 (13)	<0.001
Female gender n (%)	108 (59.7)	108 (59.7)	
BMI, kg/m^2	27.2 (24.3-30.1)	28.6 (24.5-31.4)	<0.001
Smokers (incl. ex) n (%)	88 (48.6)	91 (50.3)	0.250
Smoking history, pack-y	15 (6.6-21)	18 (7.3-30)	<0.001
Pack-y ≥ 10 and post-BD $FEV_1/FVC<0.7$ n (%)	15 (8.3)	33 (18.2)	<0.001
Pre-bd FEV_1% pred	81 (70-92)	86 (75-96)	<0.001
Pre-bd FVC % pred	90 (78-100)	97 (87-106)	<0.001
Pre-bd FEV_1/FVC	0.75 (0.68-0.80)	0.73 (0.66-0.79)	<0.001
Post-bd FEV_1% pred	87 (76-98)	89 (80-98)	0.012
Post-bd FVC % pred	94 (82-102)	98 (88-107)	<0.001
Post-bd FEV_1/FVC	0.79 (0.73-0.84)	0.75 (0.68-0.81)	<0.001
Blood eosinophils ($\times 10^9 \cdot L^{-1}$)	0.28 (0.17-0.40)	0.18 (0.10-0.28)	<0.001
Total IgE ($kU \cdot L^{-1}$)	84 (36-165)	61 (25-168)	0.187
Daily ICS user n (%)	14 (7.7)	148 (81.8)	<0.001

AQ20 score	7 (4-10)	4 (2-7)	<0.001

Data is presented as n (%), mean (SD) or median (interquartile range). BMI= body mass index, Smoking history, pack-y= pack years of smokers, ICS= inhaled corticosteroid, BD= bronchodilator, FEV_1= forced expiratory volume in 1 second, FVC= forced vital capacity, Daily ICS use= self-reported daily use of ICS, AQ20= airways questionnaire 20. Age is analyzed by paired samples t-test and lung function measurements, inflammatory markers, BMI, pack-years and AQ20 score by related samples Wilcoxon Signed Rank test. Daily ICS users and smokers were analyzed by McNemar test.

eTable 3. Characteristics of patients with not controlled asthma at 12 years after diagnosis according to their level of 12-year adherence (n=125).

	Not-controlled asthma n=125		
	Good adherence (≥80) n=61	Poor adherence (<80) n=64	p-value
Lung function at follow-up			
Pre-bd FVC % pred	95 (84-106)	93 (81-101)	0.182[a]
Post-bd FVC % pred	98 (84-108)	95 (84-102)	0.199[a]
FEV_1 Reversibility mL	70 (5-140)	95 (43-178)	0.059[a]
FEV_1 Reversibility % of initial FEV_1	2.7 (0.19-5.2)	3.8 (1.7-8.3)	0.085[a]
Lung function change			
ΔFVC mL pred·$year^{-1}$	-31 (-56 to -8)	-41 (-63 to -14)	0.245[a]
ΔFVC % pred·$year^{-1}$	0.13 (-0.48 to 0.85)	-0.24 (-0.8 to 0.44)	0.073[a]
ΔFEV_1/FVC·$year^{-1}$	-0.005 (-0.009 to 0.0)	-0.006 (-0.010 to -0.002)	0.180[a]
Markers of inflammation			
FeNO (ppb)	10 (5-15)	10 (5-23)	0.443[a]
IL-6 (pg/mL)	2 (1.2-4.2)	1.9 (1.2-4.2)	0.552[a]
hsCRP	1.2 (0.5-2.4)	1.5 (0.67-3.2)	0.281[a]
Burden of asthma			
At least one hospitalization due to asthma n (%)	12 (19.7)	9 (14.1)	0.476[b]
Visits due to acute upper respiratory tract infection or asthma flare-up	6 (2-12)	2 (1-8)	0.053[a]
Asthma control visits	7 (4-12)	6 (3-10)	0.149[a]
Add-on drugs			
Daily add-on drug n (%)	49 (80.3)	33 (51.6)	0.001[b]
Daily theophylline n (%)	4 (6.6)	0 (0)	0.054[b]
Daily tiotropium n (%)	5 (8.2)	3 (4.7)	0.485[b]
Comorbidities			
Comorbidities (altogether)	1 (0-3)	1 (0-3)	0.487[a]
Treated hypertension	29 (47.5)	18 (28.1)	0.028[b]
Treated dyspepsia	10 (16.4)	3 (4.7)	0.041[b]
Diabetes	11 (18)	10 (15.6)	0.813[b]
Coronary artery disease	9 (14.8)	8 (12.5)	0.797[b]
Depression/Mental health medication	8 (13.1)	8 (12.5)	>0.999[b]
Painful condition	6 (9.8)	8 (12.5)	0.779[b]
Other			
Pack-y >=10 and post-BD FEV1/FVC<0.7 n (%)[£]	10 (16.4)	19 (30.2)	0.090[b]
Fulfils severe asthma criteria according to ERS/ATS n (%)	6 (9.8)	5 (7.8)	0.759[b]
Allergy and/or rhinitis n (%)	45 (73.8)	46 (71.9)	0.843[b]
Atopy n (%)[Ω]	14 (26.4)	20 (34.5)	0.413[b]

Data is presented as n (%), mean (SD) or median (interquartile range). FEV_1= forced expiratory volume in 1 second, FVC= forced vital capacity, Lung function change: From max0–2.5 (point of highest lung function during the first 2.5 years after baseline) to 12-year follow-up visit, IL-6= Interleukin 6, hsCRP= High-sensitivity C-reactive Protein, FeNO= fraction of NO

in exhaled air, BD= bronchodilator, Daily add-on drug= self-reported daily use of long-acting β2-agonist, leukotriene receptor antagonist, theophylline or tiotropium, ERS= European Respiratory Society, ATS= American Thoracic Society. Severe asthma was defined according to the ATS/ERS 2014 criteria[E16]. Hospitalizations, asthma control visits and hospital days were examined during the whole 12-year follow-up period. [£]Baseline Pack-y >=10 and post-BD FEV1/FVC<0.7 n (%)= 6 (10) with controlled and 7 (11.3) in patients not-controlled asthma (p= >0.999). [Ω]=atopy was assessed based on skin-prick test. Statistical significances were evaluated by independent samples Mann-Whitney U test ([a]) or by Fisher´s exact test ([b]).

eTable 4. Characteristics of patients with controlled asthma at 12 years after diagnosis according to their level of 12-year adherence (n=56).

	Controlled asthma (n=56)		
	Good adherence (≥80) n=21	Poor adherence (<80) n=35	p-value
Lung function at follow-up			
Pre-bd FVC % pred	104 (96-111)	103 (91-110)	0.767[a]
Post-bd FVC % pred	102 (94-109)	102 (92-111)	0.966[a]
FEV_1 Reversibility mL	60 (10-95)	110 (30-160)	0.033[a]
FEV_1 Reversibility % of initial FEV_1	2.7 (0.4-4.6)	3.5 (0.9-6.5)	0.204[a]
Lung function change			
ΔFVC mL pred·year^{-1}	-34 (-56 to -13)	-30 (-67 to -11)	0.939[a]
ΔFVC % pred·year^{-1}	0.07 (-0.46 to 0.73)	-0.08 (-0.97 to 0.49)	0.271[a]
ΔFEV_1/FVC·year^{-1}	-0.005 (-0.006 to -0.001)	-0.004 (-0.006 to –0.002)	>0.999[a]
Markers of inflammation			
FeNO (ppb)	12 (7-20)	12 (5-16)	0.537[a]
IL-6 (pg·mL^{-1})	1.3 (1.1-2.3)	1.4 (0.91-2.5)	0.735[a]
hsCRP (mg·L^{-1})	0.93 (0.42-1.6)	1.2 (0.47-2.4)	0.441[a]
Burden of asthma			
At least one hospitalization due to asthma n (%)	2 (9.5)	4 (11.4)	>0.999[b]
Visits due to acute upper respiratory tract infection or asthma flare-up	5 (0-10)	1 (0-5)	0.152[a]
Asthma control visits	5 (3.5-11.5)	5 (3-7)	0.123[a]
Add-on drugs			
Daily add-on drug n (%)	8 (38.1)	11 (31.4)	0.772[b]
Daily theophylline n (%)	0 (0)	0 (0)	
Daily tiotropium n (%)	0 (0)	0 (0)	
Comorbidities			
Comorbidities (altogether)	0 (0-2.5)	1 (0-2)	0.857[a]
Treated hypertension	8 (38.1)	10 (28.6)	0.558[b]
Treated dyspepsia	2 (9.5)	0 (0)	0.136[b]
Diabetes	3 (14.3)	4 (11.4)	>0.999[b]
Coronary artery disease	0 (0)	4 (11.4)	0.286[b]
Depression/Mental health medication	4 (19.0)	5 (14.3)	0.715[b]
Painful condition	2 (9.5)	2 (5.7)	0.626[b]
Other			
Pack-y >=10 and post-BD FEV1/FVC<0.7 n (%)[£]	2 (9.5)	2 (5.7)	0.626[b]
Fulfils severe asthma criteria according to ERS/ATS n (%)	0 (0)	1 (2.9)	>0.999[b]
Allergy and/or rhinitis n (%)	13 (68.4)	24 (68.6)	>0.999[b]
Atopy n (%)[Ω]	11 (55.0)	16 (48.5)	0.779[b]

Data is presented as n (%), mean (SD) or median (interquartile range). FEV_1= forced expiratory volume in 1 second, FVC= forced vital capacity, Lung function change: From max0–2.5 (point of highest lung function during the first 2.5 years after baseline) to 12-year follow-up visit, IL-6= Interleukin 6, hsCRP= High-sensitivity C-reactive Protein, FeNO= fraction of NO

in exhaled air, BD= bronchodilator, Daily add-on drug= self-reported daily use of long-acting β2-agonist, leukotriene receptor antagonist, theophylline or tiotropium, ERS= European Respiratory Society, ATS= American Thoracic Society. Severe asthma was defined according to the ATS/ERS 2014 criteria[E16]. Hospitalizations, asthma control visits and hospital days were examined during the whole 12-year follow-up period. [£]Baseline Pack-y >=10 and post-BD FEV1/FVC<0.7 n (%)= 0 (0) with controlled and 2 (5.7) in patients not-controlled asthma (p=0.523). [Ω]=atopy was assessed based on skin-prick test. Statistical significances were evaluated by independent samples Mann-Whitney U test ([a]) or by Fisher´s exact test ([b]).

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