



Inhaled corticosteroids and asthma control in adult-onset asthma: 12-year follow-up study

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ARTICLE INFO

Keywords:

Asthma

Adult

Inhaled corticosteroids

Asthma-control

Prescription

Cumulative dose

ABSTRACT

Background: Prescribed inhaled corticosteroid (ICS) doses in asthma have been studied in cross-sectional settings whereas long-term follow-up studies have not been carried out.

Objective: To evaluate prescribed medication longitudinally by calculating cumulative ICS doses and dose changes in a cohort of new-onset adult asthma during 12 years and in different groups of asthma control.

Methods: A total of 203 patients were followed for 12 years as part of Seinäjoki Adult Asthma Study (SAAS). All asthma-related visits and prescribed medication over the study period were collected from medical records.

Results: Total cumulative ICS dose for the 12-year follow-up period was 3.4g ($\pm$ SEM 0.1) per patient. Both respiratory specialists and GPs prescribed step-ups and step-downs in ICS treatment and in total 649 dose changes were noted during the follow-up (median 3(1–5) per patient). Patients with uncontrolled asthma received higher ICS doses throughout the follow-up period, and therefore, cumulative 12-year ICS dose ($3.8\text{g} \pm \text{SEM } 0.2$) in this group was higher than that in those with partially controlled ($3.4\text{g} \pm \text{SEM } 0.2$) or controlled disease ($2.9\text{g} \pm \text{SEM } 0.2$) ($p = 0.0001$). Patients with uncontrolled asthma were also prescribed a higher number of ICS dose changes than patients with controlled disease.

Conclusion: Despite frequent dose changes and high ICS doses during the 12-year follow-up, the level of asthma control remained poor in patients with uncontrolled asthma. This suggests that high ICS doses may not be effective enough for management of disease in patients with uncontrolled adult-onset asthma and novel targeted treatments are required.

1. Introduction

Asthma is a heterogenic disease occurring in both adults and children worldwide [1,2]. Age at disease onset has been shown to have a significant role in distinguishing the phenotypes of asthma [3,4]. Recent findings indicate that the majority of new-onset asthma cases occur in adults [5,6]. The early-onset (childhood-origin) and adult-onset asthma appear to be different with respect to several disease characteristics [3,4]. For example, over 70% of the early-onset asthma patients have been predicted to remit while only < 5% remission rates have been observed in patients with adult-onset asthma [7–9]. This suggests that data from studies among patients with asthma-onset at childhood may not be applicable to adult-onset forms of the disease.

Current guidelines recommend inhaled corticosteroids (ICS) as the basis of initial controller treatment [2]. Control-based management of

asthma means that treatment is adjusted based on a continuous cycle of assessment, treatment, and review of the patient's response in both symptom control and future risks [2]. In patients with increased asthmatic symptoms and/or exacerbations of the disease, step-up of the treatment is recommended. Before the era of different add-on therapies such as long-acting bronchodilators or leukotriene antagonists, an increase in the dose of ICS was the recommended step-up in the therapy and this option remains an effective second line option even in the current guidelines [2] and especially if exacerbations of asthma prevail [2,10]. Several factors such as correct use of inhalers and adherence to the treatment affect the outcome of the disease and have been described to be major barriers for successful treatment [11,12]. Another factor less studied is adherence to treatment guidelines, i.e. whether correct treatment is prescribed. This has been examined in some register-based and cross-sectional studies which have indicated that the prescribing

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<https://doi.org/10.1016/j.rmed.2018.02.025>

Received 13 December 2017; Received in revised form 26 February 2018; Accepted 28 February 2018

Available online 02 March 2018

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Abbreviations

ACT	Asthma control test
AQ20	Airways questionnaire 20
BD	Bronchodilator
BMI	Body mass index
FeNO	Fraction of NO in exhaled air
FEV ₁	Forced expiratory volume in 1 s

FVC	Forced vital capacity
HFA	Hydrofluoroalkane propellant
ICS	Inhaled corticosteroid
LABA	Long-acting β_2 agonist
LTRA	Leukotriene receptor antagonist
OCS	Oral corticosteroids
SABA	Short-acting β_2 -agonist

practices of ICS may need further improvement [13–17]. It appears that the adherence to the guidelines may also be different between specialists and general practitioners (GPs) [16,17]. Discontinuation of the controller treatment has been reported to be common in children managed in primary care [18]. However, there is paucity of information concerning ICS therapy in long-term settings. It may, however, be expected that because the remission rate is low in patients with adult-onset asthma [8,9] the prescribed ICS dose should increase cumulatively over the years.

In light of the fact that the achievement of good disease control is the target of asthma management, relatively little is known on the long-term variability in asthma control. Even though some interventional studies have shown that good asthma control can be achieved by stepping up treatment or by follow-up interventions [19,20], surprisingly large proportion of patients remain uncontrolled after stepping up the therapy [12]. Factors such as smoking and concurrent chronic obstructive disease, obesity, male sex and rhinitis have been reported to associate with an increased risk of uncontrolled asthma [8,21]. This suggests that a poor disease control may result from several events occurring longitudinally. Therefore, it can be hypothesized that the status of current uncontrolled asthma can be traced back by following prescribed medication for asthma over the past years. Moreover, our aim was to assess the extent to which the initial ICS therapy is changed in real-life in new-onset adult-asthma patients.

2. Methods

2.1. Patients and study design

The current study was part of Seinäjoki Adult Asthma Study (SAAS), which is a prospective single-center (Seinäjoki Central Hospital, Seinäjoki, Finland) 12-year follow-up study containing 257 consecutive patients with diagnosis of new-onset adult asthma. All adult age (≥ 15 years) newly diagnosed patients were included during the period of 1999–2002. Institutional permissions were obtained and study participants gave written informed consent of the study protocol approved by the Ethics committee of Tampere University Hospital, Tampere, Finland.

The schematic presentation of the study is shown in Fig. 1. The study protocol has been published separately [22]. Patients were consecutively included in the study if all of the following criteria were fulfilled: 1) new-onset asthma diagnosed by respiratory specialist 2) confirmation of diagnosis by lung function measurements showing reversible obstruction 3) symptoms of asthma 4) age ≥ 15 years. Patients with comorbidities, other lung diseases, and history of smoking were included. The study was divided into two parts: collection of the original cohort and the 12-year follow-up visit (Fig. 1). At the baseline visit data was collected on symptoms, lung function, demographics and initial medication as previously described [23,24]. Patients were followed up for 12 years (mean 12.2 years, range 10.8–13.9 years) after the diagnostic visit. From the original cohort of 257 patients, 203 returned to the 12-year control visit in which asthma status, medication, control, and lung function were evaluated [8,23–25]. Asthma-related visits [24] and medication information were collected from the whole 12-year follow-up period from medical records (Fig. 1).

2.2. Medication information and ICS dose calculations

Prescribed medications and dose calculations were carried out based on the data obtained from all asthma-related visits (Fig. 1). Focus in this study was in ICS (including ICS-LABA combination inhalers). All ICS doses were converted into budesonide equivalents [2,26]. High dose was determined as daily dose over 800 μg and medium dose over 400–800 μg^2 . If medication information was inadequate, it was calculated based on previous confirmed information. If the prescribed dose ranged the calculations were made by using the smallest dosing possibility (e.g. 1 or 2 inhalations twice daily was calculated as 1 inhalation twice daily). Medication gaps over 9 days and medication changes over 14 days were taken into consideration.

2.3. Asthma control

Patients were separated into three groups by their asthma control at follow-up visit which was defined according to the Global Initiative for Asthma (GINA) 2010 guideline [27] as previously reported [8]. Patients with controlled asthma were defined by fewer symptoms, normal lung

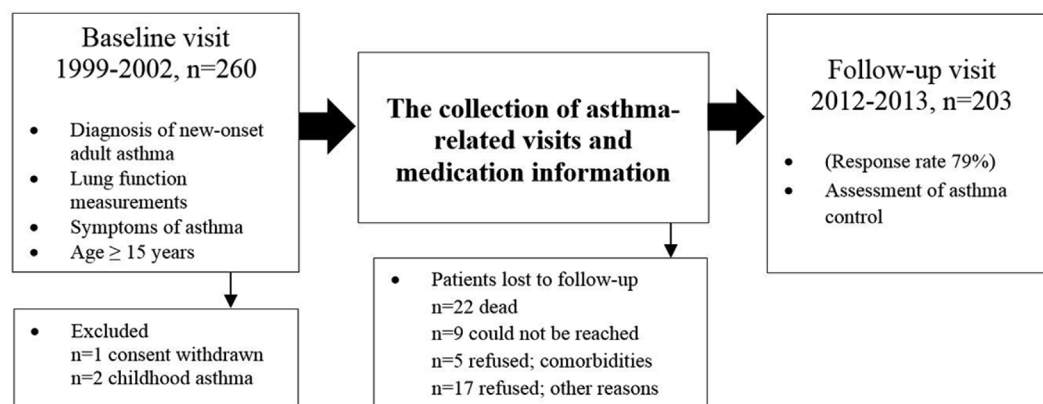


Fig. 1. Flow chart of Seinäjoki Adult Asthma Study (SAAS).

function and rare usage of reliever medication. Patients with partially controlled asthma may have had 1–2 of the following features: day or nighttime symptoms, need for rescue treatment, decreased lung function or limitation of activities due to asthma. When defining patients with uncontrolled asthma, three or more of those features were required.

2.4. Statistical analysis

The results are shown as mean $\pm$ SD, or median (interquartile range) but annual cumulative and daily doses are represented as mean $\pm$ SEM for clarity. Baseline and follow-up values were compared by using paired samples *t*-test, related samples Wilcoxon signed rank test or McNemar test. Comparison of three control groups were analyzed by using one-way ANOVA with Tukey's post hoc test, Pearson Chi-Square test or independent samples Kruskal-Wallis test. To analyze differences in cumulative dose of ICS and annual daily ICS dose between three control groups two-way ANOVA was used. A *P*-value < 0.05 was regarded as statistically significant. Statistical analysis were performed using SPSS software, version 24 (IBM SPSS, Armonk, NY, USA) and GraphPad Prism software, version 7.03 (GraphPad, La Jolla, CA, USA).

3. Results

3.1. Characteristics of the study patients

The main characteristics of the study population ($n = 203$) are shown in Table 1 [8]. The majority of patients were non-atopic (63%) and females (58%) and half of the patients were current or ex-smokers. Patients were more obese, had better spirometry values and lower blood eosinophil count at the 12-year follow-up visit than at baseline. Symptom score (AQ20) was lower at the follow-up visit than at baseline. During the diagnostic visit (baseline), 8% of the patients used inhaled corticosteroids (ICS) whereas 76% reported to be daily ICS users at the follow-up visit [8].

3.2. Annual prescribed daily and cumulative ICS doses

To visualize prescribed anti-inflammatory medication for asthma in the whole study population, the average annual daily inhaled corticosteroid (ICS) dose and cumulative dose were calculated (Fig. 2). The highest average annual ICS dose was $939 \mu\text{g}$ ($\pm$ SEM 25) among the study population which was reached one year after the diagnosis (Fig. 2). The average total cumulative dose of ICS for the whole 12-year follow-up period was 3.4 g ($\pm$ SEM 0.1) per patient. The annual cumulative averages consist of individual patient profiles (eFigures 1–4) where each change in slope represents the change in dose of ICS and the steeper the change in slope the bigger the change in dose. Of the study cohort 87.2% ($n = 177$) had at least one change in ICS dose. Taking all increases and decreases into account 649 dose changes occurred among study population (median 3 (1–5) per patient) in 12-year study period. Of the increases ($N = 281$) 38.4% were prescribed by respiratory specialist and 61.6% by GP (general practitioner) and of the decreases ($N = 368$) 56.5% were prescribed by respiratory specialist and 43.5% by GP. Daily ICS was discontinued and ICS were continued on as needed basis until follow-up visit in 9 patients (4%). In addition, 13 patients (6.4%) had a period when ICS were used on as needed basis but later on regular daily ICS was prescribed again.

3.3. Asthma control

At the 12-year follow-up visit asthma control was evaluated and the patients were divided into three groups according to their asthma management level: controlled ($n = 69$), partially controlled ($n = 74$) and uncontrolled ($n = 60$) [8]. Characteristics of the groups are shown

in Table 2. Patients with uncontrolled asthma were more often males, older and used higher dose of inhaled corticosteroids than patients with controlled asthma [8]. Daily add-on drugs were more often used in patients with uncontrolled than in patients with partially or controlled asthma. Lung function was higher in patients with controlled asthma than patients with partially or uncontrolled asthma. However, no difference was found in inflammatory parameters such as blood eosinophil counts, FeNO or total IgE between the three groups.

3.4. Annual cumulative and daily ICS doses in asthma subgroups

To evaluate how the level of asthma control affects prescribing of medication for the patient, we studied average annual cumulative and daily doses of ICS in the study subgroups. Patients with controlled, partially controlled and uncontrolled asthma had significantly different ($p < 0.0001$) cumulative doses of ICS during the 12-year study period (Fig. 3). Patients with controlled asthma had the lowest total cumulative dose of ICS ($2.9 \text{ g} \pm \text{SEM } 0.2$) whereas patients with uncontrolled asthma had the highest total cumulative dose of ICS ($3.8 \text{ g} \pm \text{SEM } 0.2$). Patients with uncontrolled asthma had higher annual daily dose of ICS versus patients with controlled asthma from 2 to 12 years after diagnosis ($p < 0.05$) (Fig. 4). When comparing patients with controlled and partially controlled asthma, the average annual daily ICS dose differed significantly only at two follow-up years (2 and 12- years after diagnosis). The highest annual daily average dose of ICS was $981 \mu\text{g}$ ($\pm$ SEM 72) with uncontrolled asthma patients at tenth year after diagnosis and the lowest was $635 \mu\text{g}$ ($\pm$ SEM 48) with controlled asthma patients 12 years after diagnosis. The current guideline [2] suggests that asthma therapy should be stepped down once good asthma control has been achieved and maintained for about 3 months. Even though current control-based treatment strategy was not in use during the early phase of this study, the decrease in the mean ICS dose in the second year in the group having currently well-controlled asthma suggest that in this group relatively good symptom control was achieved and the ICS dose was reduced (Fig. 4).

Table 1
Characteristic of the study patients ($n = 203$).^a

	Baseline ($n = 203$)	Follow-up ($n = 203$)	<i>p</i> value
Age (y)	46 (14)	58 (14)	< 0.001
Female gender <i>n</i> (%)	118 (58.1)	118 (58.1)	
BMI, kg/m ²	27.1 (24.2–29.8)	28.1 (24.4–31.3)	< 0.001
Smokers (incl. ex) <i>n</i> (%)	103 (50.7)	107 (52.7)	0.125
Post-bd FEV ₁ % pred	88 (77–99)	90 (80–98)	0.013
Post-bd FVC % pred	94 (82–102)	98 (88–107)	< 0.001
Post-bd FEV ₁ /FVC	0.79 (0.75–0.85)	0.75 (0.69–0.81)	< 0.001
Blood eosinophils ($10^9/\text{l}$)	0.28 (0.15–0.42)	0.17 (0.10–0.27)	< 0.001
Total IgE (kU/l)	84 (35–174)	61 (24–163)	0.046
AQ20 score	7 (4–10)	4 (2–7)	< 0.001
Daily ICS use <i>n</i> (%)	16 (8.0)	155 (76.4)	< 0.001
Daily ICS dose, μg budesonide equivalents of daily users		800 (400–1000)	
Daily LABA <i>n</i> (%)		96 (47.3)	
Daily add-on drug <i>n</i> (%)		103 (50.7)	
Daily LTRA <i>n</i> (%)		27 (13.4)	
Daily theophylline <i>n</i> (%)		4 (2)	
Daily tiotropium <i>n</i> (%)		8 (3.9)	

^a A part of the data has been previously reported [8]. Data are presented as *n* (%), mean (SD) or median (interquartile range), unless otherwise stated. BMI = body mass index, ICS = inhaled corticosteroid, BD = bronchodilator, LABA = long-acting β_2 -agonist, LTRA = leukotriene receptor antagonist, FEV₁ = forced expiratory volume in 1 s, FVC = forced vital capacity, AQ20 = airways questionnaire 20.

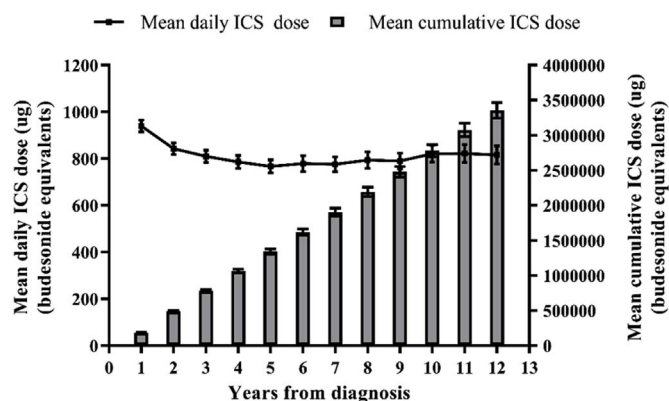


Fig. 2. Average prescribed annual daily inhaled corticosteroid (ICS) dose and cumulative dose among study population ($n=203$). The data are presented as mean $\pm$ SEM.

3.5. Dose changes in asthma subgroups

To analyze other possible differences in prescribed ICS medication according to the status of asthma control, we compared the number of changes in ICS dose between the subgroups. Of the patients with uncontrolled asthma, 87% had at least one change in dose, and altogether 235 dose changes were needed to these patients within 12 year follow-up period. The differences between dose changes in control groups are shown in Fig. 5 where each change in slope indicates a change in ICS dose. The median number of dose changes was 4 (2–6) per patient with uncontrolled asthma and 2 (1–4) per patient with both partially controlled as well as controlled asthma. Statistically significant difference was seen in the number of dose changes between patients with uncontrolled and controlled asthma ($p = 0.016$) and also a similar tendency ($p = 0.055$) was observed between the patients showing uncontrolled and partially controlled disease. Respiratory specialist increased ICS dose significantly more often in patients with uncontrolled asthma than in controlled asthma (Table 3).

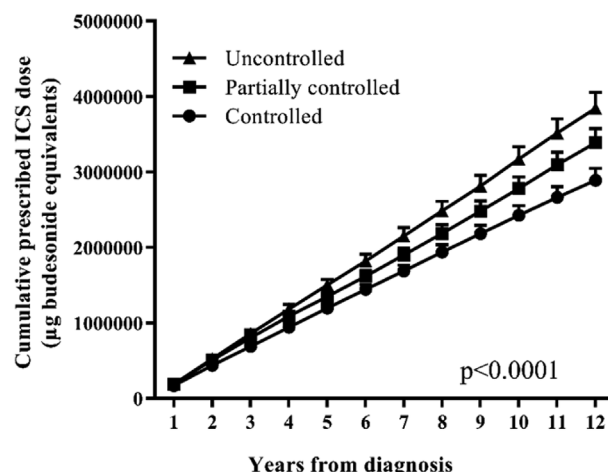


Fig. 3. Average of annual prescribed cumulative dose of inhaled corticosteroid (ICS) in asthma subgroups based on different level of asthma control. The data are presented as mean $\pm$ SEM. P-value indicates the difference between three slopes analyzed by two-way ANOVA.

4. Discussion

In this study we evaluated annual daily and cumulative doses of ICS from diagnosis to 12-year follow-up visit in patients with adult-onset asthma, in the total cohort and in patients having different levels of disease control. Concordant with the low rate of remission in adult-onset asthma the prescribed ICS dose increased in a cumulative manner. Cumulative and average annual daily dose of ICS were significantly higher in patients with uncontrolled asthma when compared to patients with controlled asthma through the 12-year study period. Patients with uncontrolled asthma also needed higher numbers of ICS dose changes. These results suggest that in adult-onset asthma the status of uncontrolled disease is not a momentary event but rather reflects poor asthma control long-term which may not be responsive to current therapeutic strategies.

Cross-sectional studies have revealed trends in ICS prescribing for adults and children [13–15,17,18] but follow-up studies concerning

Table 2
Characteristics of asthma patients at 12-year follow-up visit ($n = 203$).^a

	Controlled $n = 69$	Partially controlled $n = 74$	Uncontrolled $n = 60$	p value
Age (y)	54 (14)	60 (12)*	61 (13)*	0.005
Female gender n (%)	48 (69.6)	42 (56.8)	28 (46.7)*	0.030
BMI, kg/m ²	27.7 (4.8)	28.9 (5.8)	29.1 (6.1)	0.324
Smokers (incl. ex) n (%)	25 (36.2)	45 (60.8)*	37 (61.7)*	0.003
Daily ICS use n (%)	47 (68.1)	57 (77.0)	51 (85.0)	0.078
ICS daily dose μ g budesonide equivalents of daily users	550 (400–1000)	800 (713–1000)	1000 (400–1350)*	0.016
Daily SABA n (%)	2 (2.9)	7 (9.5)	14 (23.3)*	< 0.001
Daily LABA n (%)	19 (27.5)	36 (48.6)*	41 (68.3)*	< 0.001
Daily add-on drug n (%)	20 (29)	38 (51.4)*	45 (75)*#	< 0.001
Daily LTRA n (%)	4 (5.8)	11 (14.9)	12 (20.3)*	0.049
Daily theophylline n (%)	0 (0)	2 (2.7)	2 (3.3)	0.338
Daily tiotropium n (%)	0 (0)	0 (0)	8 (13.3)*#	< 0.001
Use of oral corticosteroid courses for asthma n (%)	15 (22.1)	24 (32.4)	26 (44.8)*	0.025
Comorbidities	1 (0–2)	1 (0–2)	2 (1–3)*#	< 0.001
Post-bd FEV ₁ % pred	96 (91–102)	89 (79–98)*	81 (64–94)*#	< 0.001
Post-bd FVC % pred	102 (93–110)	96 (85–105)	95 (83–105)*	0.007
Post-bd FEV ₁ /FVC	0.77 (0.73–0.83)	0.76 (0.69–0.81)	0.71 (0.61–0.78)*#	< 0.001
Blood eosinophils (10^9 /l)	0.16 (0.12–0.28)	0.18 (0.09–0.28)	0.19 (0.09–0.27)	0.870
FeNO (ppb)	12 (6–19)	10 (5–20)	11 (5–18)	0.533
AQ20 score	2 (0–4)	4 (2–6)*	8 (5–11)*#	< 0.001
ACT score	24 (22–25)	22 (20–24)*	18 (14–21)*#	< 0.001

^a Part of the data has been previously reported [8]. Data is presented as n (%), mean (SD) or median (interquartile range). * indicates $p < 0.05$ versus controlled and # indicates $p < 0.05$ versus partly controlled. BMI = body mass index, ICS = inhaled corticosteroid, BD = bronchodilator, SABA = short-acting β_2 -agonist, LABA = long-acting β_2 -agonist, LTRA = leukotriene receptor antagonist, FEV₁ = forced expiratory volume in 1 s, FVC = forced vital capacity, FeNO = fraction of NO in exhaled air, AQ20 = airways questionnaire 20, ACT = asthma control test.

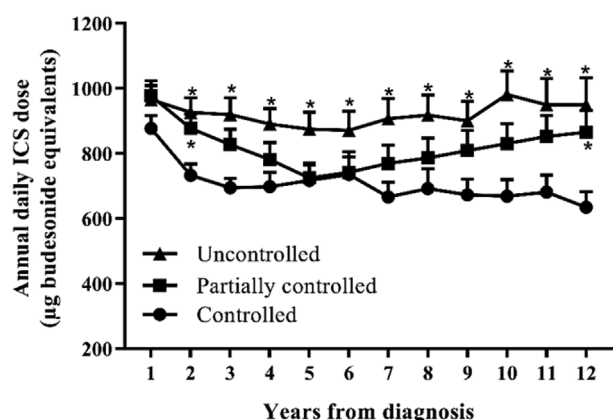


Fig. 4. Average of annual daily prescribed dose of inhaled corticosteroid (ICS) in asthma subgroups based on different level of asthma control. The data are presented as mean $\pm$ SEM. * indicates $p < 0.05$ versus controlled group analyzed by one-way ANOVA with Tukey's post hoc test or independent samples Kruskal-Wallis test.

individual patient's medication use longitudinally have not been carried out so far. The remission rate in childhood asthma have been evaluated and it appears to be significantly higher than in patients with adult-onset asthma [7,8]. Discontinuation of asthma medication has been reported to be common in children reflecting the low use of medication longitudinally in patients with early-onset asthma [18]. In our patients with adult-onset asthma cumulative dose of ICS increased during the 12 year follow-up and this combined with relatively low remission rate may indicate more persistent and difficult manifestations of the disease. Moreover, this is supported by the observed low rate (4%) of discontinuation of prescribed daily ICS treatment in all patients with adult-onset asthma.

Patients with uncontrolled asthma were treated with higher ICS doses than patients with partially and controlled asthma almost for the entire 12-year follow-up period, and therefore the cumulative dose of

ICS increased most steeply in patients with uncontrolled disease. The average total cumulative prescribed dose of ICS 12 years after diagnosis in these patients was 33% higher than that in patients with controlled disease. In addition, the average annual daily dose was the highest in patients with uncontrolled asthma when compared to patients with controlled or partially controlled asthma 12 years from the diagnosis. The average annual daily dose ranged from 872 μ g to 981 μ g in patients with uncontrolled asthma, indicating that most patients were treated with high ICS dose throughout the 12-year study period. Partially controlled patients started with high dose of ICS but the dose declined during the first five years after diagnosis and then began to increase. Treatment with high dose ICS was started also in controlled patients but the annual daily dose decreased to medium level during the first two years from diagnosis. These results are in line with guidelines [2] recommending to increase the controller medication if asthma remains uncontrolled by the current therapy and to decrease the dose when asthmatic symptoms have remained well-controlled for 3 months.

The need for high cumulative and average annual daily ICS doses in patients with uncontrolled asthma suggest that the status of disease control is not a momentary event but develops longitudinally as a result of several precipitating factors. The determinants which may contribute to inadequate asthma control include obesity, smoking and non-adherence to treatment [2,8,21]. Also incorrect use of inhaler devices and poor inhaling techniques are possible reasons leading to worsening of the asthma control [12]. It is commonly known that adherence to ICS treatment is unsatisfactory affecting management of asthma [11,28]. The risk factors for poor adherence have been studied and patients with milder asthma seem to be more non-adherent to the treatment compared with patients having moderate to severe symptoms of asthma [29,30]. This study was not planned to evaluate adherence to asthma treatment but to establish basis for these studies by observing prescribing practices of ICS in detail in long-term follow-up.

While assessing controller treatment and possible changes to ICS therapy the disease control, responsiveness to treatment and future risks must be taken into account for finding the appropriate step-up or

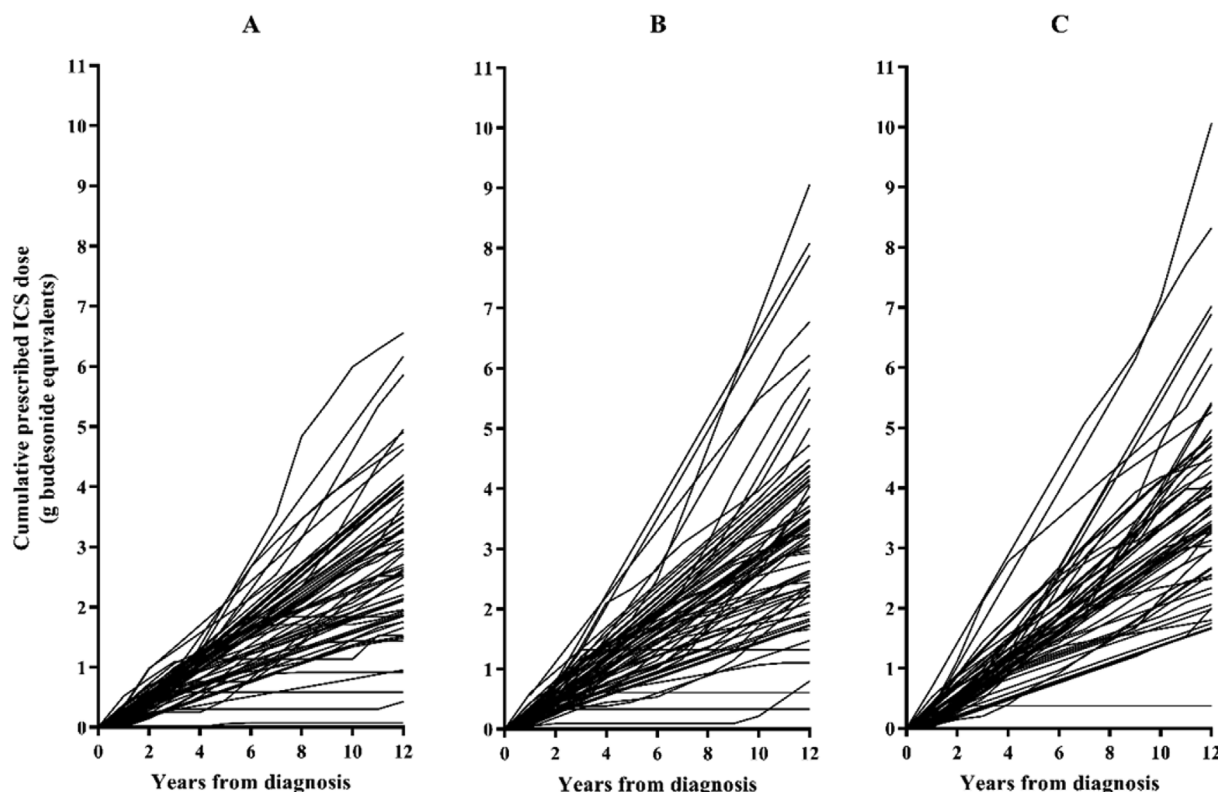


Fig. 5. Cumulative dose of prescribed inhaled corticosteroid (ICS) for individual patients in controlled A ($n = 69$), partially controlled B ($n = 74$) and uncontrolled C ($n = 60$) subgroups.

Table 3

Changes in ICS doses among patients with different level of asthma control and the proportion of changes made by respiratory specialist.

	Controlled n = 69	Partially controlled n = 74	Uncontrolled n = 60	p value
Dose changes N	195	219	235*	0.012
Increase in dose N (%)	77 (39)	98 (45)	106 (45)*	0.010
Increase in dose made by respiratory specialist N (%)	24 (31)	39 (40)	45 (42)*	0.035
Decrease in dose N (%)	118 (61)	121 (55)	129 (55)#	0.034
Decrease in dose made by respiratory specialist N (%)	60 (51)	81 (67)	67 (52)	0.470

Data are presented as N (%). * indicates $p < 0.05$ versus controlled and # indicates $p < 0.05$ versus partially controlled analyzed by one-way ANOVA with independent samples Kruskal-Wallis test. n, number of patients, N, number of dose changes.

step-down phases in treatment [2,15]. A previous study examined the effects of step-up treatment to uncontrolled adult asthma patients and showed that in spite of the optimization of the treatment most patients continued to show inadequately controlled asthma [12]. In our study patients with uncontrolled asthma had significantly more ICS dose changes and increases in ICS dose than patients with controlled asthma during 12-year follow-up period suggesting that physicians have tried to improve the management of asthma by changing the ICS dose of uncontrolled patients. On the other hand, in patients with stable asthma the reduction of medication has not been connected to increased risk to recurrence of symptoms and loss of asthma control [31–33]. In our study both respiratory specialists and general practitioners had prescribed reductions in ICS treatment for all study subgroups. Moreover, we showed that patients received more decreases than increases in dose during follow-up.

Seinäjoki Adult Asthma Study is a 12-year follow-up study of real-life new-onset adult asthma patients revealing information on prescribed ICS to consecutive adult asthma patients in a long-term follow-up setting. Many of the previous studies concerning prescribing practices are cross-sectional by nature. These studies included populations from different databases indicating that the cohort may be selected, and therefore patients or physicians outside these databases are excluded from the study cohort [13,16,18]. SAAS represents an extensive 12-year follow-up of patients including information on all asthma-related visits and prescribed medication over the years. Moreover, all new-onset adult asthmatics including patients with comorbidities, other lung disease, and history of smoking were included, and therefore the study cohort well represents the general adult population with asthma [8,23,24].

Our real-life setting establishes some possible sources of error into the results. Because physician's markings were not always complete in medical records, some shortage of information was observed. On the other hand, this kind of shortage is part of the treatment of every asthma patients in real-life. In case of inadequate information on medication, the calculations had to be made based on general assumptions. However, the study is a long-term follow-up, and therefore single shortcomings in medication information do not presumably have a major effect on the results. In the previous study concerning association between prescribing practices and uncontrolled asthma the level of asthma control was evaluated without lung function tests while we elucidated the level of asthma control with GINA 2010 recommendations where lung function tests were systematically a part of the disease assessment [27,34]. The questionnaire-based tests are clinically useful but when evaluating asthma control without lung function tests inaccuracy of assessment is possible [35,36].

Our findings show that prescribed longitudinal medication in patients with uncontrolled asthma differs markedly from partially and controlled patients. The annual average daily dose was significantly higher in patients with uncontrolled asthma than in patients with controlled asthma for almost the entire 12-year study period. Despite having many dose changes and treatment with high ICS dose during the 12-year follow-up, the level of asthma control remained poor in these patients at the 12-year follow-up visit. Current guidelines underline the adjustment of controller treatment to achieve good asthma control but

our patients with poorly controlled asthma remained uncontrolled despite of high dose ICS treatment suggesting its limited benefit [2]. These findings indicate that general recommendations are not suitable for all patients with asthma. Our results also raise a question on the need for development of phenotype-specific drug treatment for those adult asthmatics being unresponsive to ICS. Steps towards phenotype-specific treatment of asthma have been recently taken since the uncontrolled allergic asthma patients have anti-IgE (omalizumab) as one of the treatment options and patients with severe eosinophilic asthma can be treated with anti-IL-5 antibodies (mepolizumab or reslizumab) [2,37–39]. In addition to allergic and eosinophilic asthma, our results suggest that the development of novel targeted therapies is needed also for other phenotypes to achieve good asthma control. Our previous cluster analysis concerning patients with adult-onset asthma showed that patients with phenotypes of obesity-related or smoking asthma had more often uncontrolled asthma as compared to patients with non-rhinitic, female or atopic asthma [24]. Step-up in treatment did not seem to improve the outcome of asthma in uncontrolled patients, therefore patients with obese-related or smoking asthma may benefit more of changes in lifestyle than increase in ICS dose [3,24,40]. Even though the benefits of higher dose of ICS have been shown to prevent exacerbations, the effects are shown to be limited in enhancing lung function and symptom-control [10]. This may be one of the explanations why high ICS dose seems to have only limited benefits in patients with uncontrolled asthma.

Taken together, we showed for the first time that in adult-onset asthma patients followed over a period of 12 years the prescribed ICS dose increased in a cumulative manner and prescription discontinuation was rare. This is in line with the low remission rate in adult-onset asthma. Patients with uncontrolled asthma received higher ICS doses throughout the follow-up period, and as a consequence, cumulative ICS dose 12 years after diagnosis was higher than in those with partially controlled and controlled disease. This suggest that the increase in ICS dose may not to be effective enough for the management of asthma in patients with uncontrolled adult-onset disease and novel targeted treatments are required. Consequently, the patients with uncontrolled asthma should receive special attention in asthma follow-ups.

Funding

This study is supported by the Tampere Tuberculosis Foundation (Tampere, Finland), the Finnish Anti-Tuberculosis Association Foundation (Helsinki, Finland), the Research Foundation of the Pulmonary Diseases (Helsinki, Finland), the Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital (Tampere, Finland) and the Medical Research Fund of Seinäjoki Central Hospital (Seinäjoki, Finland). None of the sponsors had any involvement in the planning, execution, drafting or write-up of this study.

Competing interests

The authors report no conflict of interest related to this study.

Contributors

IV analyzed and interpreted the data, and wrote the manuscript. HK, LET and ON designed the study. PI contributed to the study design, interpretation of the data, writing of the manuscript and provided statistical advice. HK, PI, ON, and LET commented on drafts of the manuscript. All authors accept full responsibility for the conduct of the study, had access to the data, and controlled the decision to publish.

Clinical Trials

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

Acknowledgements

Mrs Aino Sepponen, RN, is gratefully acknowledged for her help through all stages of this work.

Transparency document

Transparency document related to this article can be found online at <http://dx.doi.org/10.1016/j.rmed.2018.02.025>

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.rmed.2018.02.025>.

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