Clinical Communications

Long-term adherence to inhaled corticosteroids in clinical phenotypes of adult-onset asthma

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Clinical Implications

- Long-term adherence to inhaled corticosteroids was 75% or greater in phenotypes with the poorest outcome but did not differ significantly among clusters. Poor outcome in the most severe phenotypes was not related to poor adherence to inhaled corticosteroid medication.

In our previous cluster analysis, we identified five phenotypes of adult-onset asthma with variable long-term prognoses: smoking, obese, atopic, nonrhinitic, and female asthma.[1] Smoking and obese clusters showed the poorest 12-year outcome for asthma control, lung function, hospitalizations, and exacerbations. Previously, medication adherence data were not combined with clinical phenotypes, which made it difficult to assess the role of adherence in phenotype outcome. Therefore, our aim was to study adherence to inhaled corticosteroids (ICS) and its long-term variability in previously established clinical phenotypes of adult-onset asthma.

This study is part of the Seinäjoki Adult Asthma Study (ClinicalTrials.gov ID NCT02733016), a prospective, single-center study at Seinäjoki Central Hospital in Seinäjoki, Finland, where 203 patients with new-onset adult asthma (≥15 years) were observed for 12 years. Asthma was diagnosed by respiratory specialists and confirmed by lung function measurements. We excluded 20 patients with missing parameters related to cluster assignment and 19 patients with ICS prescribed only periodically at any point. The prescribed ICS dose was calculated based on medical records.[2] Dispensed doses were obtained from the Finnish Social Insurance Institution. Adherence was computed as previously described by comparing cumulative dispensed ICS doses (in micrograms) to corresponding prescribed doses (in micrograms)[2] (see Methods in this article's Online Repository at www.jaci-inpractice.org).

Main features of the previously identified clusters are listed in Table E1 (in this article's Online Repository at www.jaci-inpractice.org).[1] Obese and smoking clusters were dispensed the highest cumulative dose of ICS, and nonrhinitic and atopic clusters the lowest (Figure 1) ($P = .005$). However, long-term adherence showed no statistically significant difference between clusters, although they tended to differ ($P = .075$) (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Usually 80% is the most common cutoff for good adherence,[2] the obese cluster showed a long-term mean adherence of 86%, the smoking cluster 75%, the female cluster 69%, the atopic cluster 62% and the nonrhinitic cluster 63% (Table I). Fully nonadherent years (no dispensed ICS) were most common in the nonrhinitic cluster ($P = .006$), and 35% in this cluster were fully nonadherent to ICS in the last follow-up year (Table I). Sense of improved asthma was the most common reason for not taking drugs in the atopic and nonrhinitic clusters ($P = .020$) (Table I) (see adherence-related questions in the Online Repository). Nonadherence was uncommon in the obese cluster, but unlike in the other clusters, the reasons were more often related to financial matters ($P = .040$). When clusters were divided into controlled and noncontrolled groups,[3] no significant differences were found in adherence (data not shown).

To the best of our knowledge, this study is the first to combine clinical phenotypes with medication adherence data. Our results show that the obese and smoking phenotypes were dispensed the most ICS during the 12-year follow-up, consistent with previous findings that patients in severe obese and smoking clusters often used the highest doses of ICS.[4] These clusters showed overall relatively good long-term adherence to ICS medication (≥75%), but their outcome was still the poorest based on asthma control, lung function, hospitalizations, and exacerbations. Despite these findings, our results should not be to mean that ICS treatment is not beneficial for gaining asthma control. Regularly used glucocorticoid medication may be insufficient to control airway inflammation in some patients, partly owing to less steroid-sensitive T2-low inflammation.[5,6] However, it is possible that overuse of glucocorticoids has a role in the poor outcome of the obese cluster, because high-dose ICS treatment may have harmful effects in those with non-eosinophilic obese asthma.[7] Obese patients could also benefit from weight loss, and current smokers from smoking cessation.

In the nonrhinitic cluster with milder asthma, patients had the most fully nonadherent years regarding ICS use overall, but the asthma was rarely uncontrolled at the 12-year follow-up visit (8%). Sense of improved asthma was the most common reason for not taking drugs in atopic and nonrhinitic clusters, which suggests seasonal symptoms, intermittent remission, or low perception of symptoms. However, it is possible that patients were using other controller treatment (eg, leukotriene receptor antagonist) during ICS nonadherent years to maintain asthma control, thus improving their outcome. In addition, it has been proposed that there are cases in which low adherence is not critical for asthma control, especially in milder disease forms.[8] For good ICS adherence, there are also benefits beyond asthma control. For example, noncontrolled asthma combined with less than 80% adherence to ICS has been associated with faster lung function decline versus noncontrolled asthma with 80% or greater adherence.[9]

Of the patients in the obese cluster, 96% were not currently working, 60% were receiving a disability pension, 28% had depression, and the average income was the lowest of any cluster. Socioeconomic status was the lowest in the obese and smoking clusters, and financial issues were often associated with poor adherence in the obese versus other clusters, even in Finland, which has a special asthma medication reimbursement system and relatively low medication expenses for patients. Considering possible a relation of depression and adherence, we had too few patients with depression to reach a conclusions.

Strengths of this study were an extensive 12-year follow-up with data that included information on all prescribed and refilled ICS

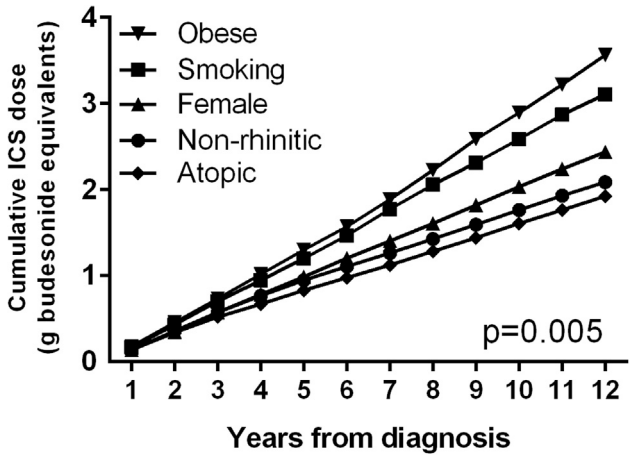

FIGURE 1. Cumulative dispensed inhaled corticosteroid (ICS) dose in phenotypes of adult-onset asthma. *P* values were obtained by using two-way analysis of variance.

doses and dose changes, a cohort representing real-life adult asthma patients, and an asthma diagnosis based on objective lung function testing. This study was limited by sample size, although extensive and reliable data were available from each patient. Moreover, the possibility exists that medication was dispensed but not used, or patients may have had an incorrect inhalation technique, although the technique was carefully instructed to all patients at the start of therapy, according to the principles of the Finnish Asthma Program.

Overall, our data provides reasons to believe that phenotype may affect adherence to ICS. Our data show that obese and smoking clusters with the poorest outcome were dispensed the most ICS medication during the 12-year follow-up, and long-term adherence to ICS medication was at an acceptable level (≥75% to 80%). The poor outcome of these patients raises questions about the assumed wisdom of the impact of ICS adherence on outcome and suggests that this phenomenon needs to be investigated further. Our results also suggest that more effective treatments combined with nonpharmacologic approaches (weight loss, smoking cessation, and diet) are needed to

TABLE I. Inhaled corticosteroid (ICS) use and adherence to ICS treatment in asthma clusters*

Variable	Atopic	Nonrhinitic	Female	Obese	Smoking	*P*
Subjects	33	37	49	25	20	
Total prescribed ICS during 12-y follow-up, g budesonide equivalent	3.3 (1.3)	3.3 (1.1)	3.4 (1.4)	4.1 (2.1)	4.3 (1.9)	.04
Total dispensed ICS during 12-y follow-up, g budesonide equivalent	1.9 (1.5)	2.1 (1.5)	2.4 (1.7)	3.6 (2.7)	3.1 (1.2)	.003
Average prescribed daily ICS dose during 12-y follow-up, μg budesonide equivalent	817 (527-961)	800 (611-962)	800 (576-999)	811 (615-1169)	910 (736-1187)	.18
Average dispensed daily ICS dose during 12-y follow-up, μg budesonide equivalent	411 (247-728)	389 (245-763)	570 (297-796)	736 (384-1201)	695 (503-881)	.01
Average 12-year adherence to ICS (%)	62 (40)	63 (38)	69 (38)	86 (46)	75 (22)	.12
Adherence to ICS in 2 last years of follow-up (%)	67 (52)	59 (50)	66 (42)	89 (52)	78 (34)	.13
Years with 0% adherence to ICS, n (%)						.006
None	20 (60.6)	16 (43.2)	36 (73.5)	18 (72.0)	13 (65.0)	
1-2	5 (15.2)	8 (21.6)	2 (4.1)	3 (12.0)	7 (35.0)	
≥3	8 (24.2)	13 (35.1)	11 (22.4)	4 (16.0)	0	
0% adherence to ICS in last year of follow-up, n (%)	8 (24.2)	13 (35.1)	6 (12.2)	3 (12.0)	2 (10.5)	.046
≥3 y with >100% adherence, n (%)	15 (45.5)	13 (35.1)	20 (40.8)	17 (68.0)	6 (30.0)	.065
Self-reported daily use of ICS, n (%)	26 (78.8)	28 (75.7)	40 (81.6)	23 (92.0)	19 (95.0)	.25
Self-reported ICS dose of daily users, μg budesonide equivalent	800 (400-1000)	800 (400-1000)	800 (550-1000)	1000 (475-1525)	1000 (800-1200)	.25
Adherent by self-report, n (%)	23 (69.7)	23 (62.2)	36 (73.5)	20 (80.0)	17 (85.0)	.35
Reason for nonadherence, n (%)						
Sense of improved asthma/no drug use	8 (24.2)	6 (16.2)	3 (6.1)	1 (4.0)	0	.02
Sense of improved asthma, less/no drug use	9 (27.3)	8 (21.6)	5 (10.2)	1 (4.0)	1 (5.0)	.04
Financial reasons	1 (3.0)	0	3 (6.1)	4 (16.0)	0	.04
Suspects or has experienced side effects	4 (12.1)	4 (10.8)	4 (8.2)	3 (12.0)	1 (5.0)	.90

*Continuous variables are shown as mean (SD) or median (interquartile range). Group comparisons were performed by one-way analysis of variance (total prescribed/dispensed ICS, adherence), Kruskal-Wallis test (ICS dose, average daily dispensed/prescribed) or chi-square test (all categorical variables).

improve the outcome of asthma in the most severe phenotypes, because poor outcomes in these phenotypes were not related to poor adherence to ICS.

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Conflicts of interest: P. Ilmarinen is an employee of GlaxoSmithKline and reports grants and personal fees from AstraZeneca, personal fees from Mundipharma, personal fees from GlaxoSmithKline, and personal fees from Novartis, outside the submitted work. H. Kankaanranta reports grants, personal fees and nonfinancial support from AstraZeneca, personal fees from Chiesi Pharma AB, personal fees and nonfinancial support from Boehringer-Ingelheim, personal fees from Novartis, personal fees from Mundipharma, personal fees and nonfinancial support from Orion Pharma, personal fees from SanofiGenzyme, and personal fees from GlaxoSmithKline, outside the submitted work. L. E. Tuomisto reports nonfinancial support from Chiesi, personal fees and nonfinancial support from Boehringer-Ingelheim, personal fees from Astra Zeneca, and nonfinancial support from Teva, outside the submitted work. The rest of the authors declare that they have no relevant conflicts of interest.

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METHODS

Study design and patients

This study is part of Seinäjoki Adult Asthma Study (ClinicalTrials.gov ID NCT02733016), a prospective, single-center study at the Seinäjoki Central Hospital in Seinäjoki, Finland, where 203 patients with new-onset adult asthma (≥15 years) were observed for 12 years. Institutional permission was obtained and participants gave written informed consent for the study protocol, which was approved by the Ethics Committee of Tampere University Hospital, Tampere, Finland. Over 94% of patients with a diagnosis of novel asthma at the study site were recruited to the study. The only exclusion criteria were childhood-onset asthma and physical or mental inability to provide signed informed consent. Asthma was diagnosed by respiratory specialists based on typical symptoms during 1999 to 2002 and confirmed by lung function measurements. After diagnosis, the patients were treated and monitored according to the principles of the Finnish Asthma Program and guidelines. The total cohort consisted of 257 patients, 203 of whom returned for the 12-year follow-up visit (79% response rate). At this visit, asthma status and control, comorbidities, medication, and socioeconomic factors were evaluated using structured questionnaires, and lung function and inflammatory parameters were measured. Data were gathered from all asthma-related visits to health care (primary care, private health care, and hospital clinics), exacerbations, acute respiratory tract infections, and hospitalizations during the whole 12-year follow-up. Compared with our previous cluster analysis (n = 171), missing data were completed from medical records for 12 patients and clusters were assigned using discriminant analysis (total n = 183). Twenty patients were still excluded from analyses owing to missing data regarding cluster assignment. Furthermore, we excluded patients for whom inhaled corticosteroids (ICS) were prescribed only periodically at any point of the follow-up, to ensure the inclusion of only patients with regular ICS medication prescribed.

Structured questionnaire and self-reported adherence

At the 12-year follow-up visit, patients filled out a structured questionnaire with adherence-related questions. The patient was regarded adherent based on self-report with an affirmative answer to "I have used asthma medication as was prescribed." Reasons for nonadherence were evaluated by the question "If you have used asthma medication less than prescribed, for what reasons?" Options were defined as:

Sense of improved asthma. Affirmative answer to "Asthma has improved and you do not feel like [there is a] need for drugs anymore" or to "other reason, please describe," and the patient described an improvement in asthma and a reduction in the use of drugs.

Suspects or has experienced side effects. Affirmative answer to "You have experienced side effects when using medication" and/or "You suspect side effects at long-term use of the medication."

Financial reasons. Affirmative answer to "The medical treatment has been difficult to accomplish [owing] to financial reasons."

Statistical analysis

Continuous data are expressed as means ± SD or median and interquartile range. Comparisons among five groups were performed by using one-way analysis of variance with Tukey's post hoc, Kruskal-Wallis, or chi-square test. To analyze differences in time-dependent cumulative dispensed ICS and time-dependent adherence between clusters, two-way analysis of variance was used. Statistical analyses were performed using SPSS software (version 25, IBM SPSS Statistics, Armonk, NY). *P* less than .05 was regarded as statistically significant.

Assessment of lung function and inflammatory parameters

Lung function measurements were performed with a Vmax Encore 22 spirometer (Viasys Healthcare, Palm Springs, CA) that was calibrated daily. Finnish reference values were used. Post-bronchodilator measurements were taken 15 minutes after inhalation of salbutamol (400 μg). We determined venous blood was collected and white blood cell differential counts. Laboratory assays were performed in an accredited laboratory (SFS-EN ISO 15189:2013) of Seinäjoki Central Hospital.

Asthma control, Asthma Control Test, comorbidities, and socioeconomic data

Asthma control was based on Global Strategy for Asthma Management and Prevention 2010. Noncontrolled asthma included patients with partially or uncontrolled asthma who had at least one of the following features: daytime symptoms more than twice per week, any limitation of activities, any nocturnal symptoms, the need for reliever or rescue treatment more than twice per week and/or lung function (peak expiratory flow or forced expiratory volume in 1 second) less than 80% of predicted. Patients filled an Asthma Control Test questionnaire and structured questionnaire with questions on comorbidities, medications in use, income, educational level, working situation, and reasons for not currently being employed. Depression was based on self-reported disease and medication data.

Computation of adherence

The prescribed dose for each patient and each year of follow-up was calculated based on medical records. All drug and dose changes were considered for each patient and all doses were converted to budesonide equivalents. Dispensed doses of ICS were obtained from the Finnish Social Insurance Institution, which records all dispensed medication from any Finnish pharmacy. By comparing dispensed doses with prescribed ICS doses, we evaluated adherence of a single patient during the 12-year follow-up. In the case of ranged doses prescribed (eg, 1-2 puffs two times daily), we interpreted that to mean that patients were adherent when the minimum ICS doses were dispensed. Prescription renewals are cost-free, and if patients continue with the same medication and dosing, the prescription is usually renewed for another year. If the doctor wants to meet the patient, a smaller amount (eg, 3-month prescription) is renewed, which lasts until the next visit. Therefore, there would not be a situation in which a patient is without a prescription. Long-term medication is usually prescribed for 1 to 2 years in Finland.

The 12-year adherence was calculated by comparing the total cumulative dispensed doses of ICS with the total cumulative 12-year prescribed doses. To obtain the variability of adherence at long-term follow-up, we calculated the annual adherence for

TABLE E1. Patient characteristics in clusters at 12-year follow-up visit*

Variable	Atopic	Nonrhinitic	Female	Obese	Smoking	*P*
Subjects, n	33	37	49	25	20	
Female, n (%)	17 (51.5)	16 (43.2)	49 (100)	16 (64)	3 (15)	<.001
Age at onset, y	34 (11)	51 (11)	44 (13)	57 (8)	54 (9)	<.001
Body mass index, kg/m^2	27.5 (3.8)	29.2 (5.3)	27.0 (4.5)	32.8 (5.3)	28.1 (4.8)	<.001
With smoking history, n (%)	16 (48.5)	18 (48.6)	18 (36.7)	11 (44)	16 (80.0)	.03
Pack-years of smokers	9 (8)	22 (11)	10 (9)	17 (10)	33 (17)	<.001
Current smokers, n (%)	5 (13.5)	5 (13.5)	8 (16.3)	0	4 (20.0)	.28
Atopic, n (%)	21 (65.6)	8 (25.8)	20 (42.6)	2 (9.1)	5 (31.3)	<.001
Rhinitis, n (%)	32 (97.0)	3 (8.1)	44 (89.8)	24 (96)	14 (70.0)	<.001
Depression, n (%)	2 (6.1)	2 (5.4)	3 (6.1)	7 (28.0)	1 (5.0)	.01
Coexisting chronic obstructive pulmonary disease,§ n (%)	3 (9.4)	9 (24.3)	2 (4.1)	3 (12.0)	14 (70.0)	<.001
Drugs in use other than asthma/allergy-related, n	0 (0-2)	1 (0-4)	1 (0-3)	6 (4-7)	3 (2-9)	<.001
Asthma control,† n (%)						<.001
Controlled	17 (51.5)	14 (37.8)	15 (30.6)	4 (16.0)	2 (10.0)	
Partially controlled	10 (30.3)	20 (54.1)	21 (42.9)	9 (36.0)	1 (5.0)	
Uncontrolled	6 (18.2)	3 (8.1)	13 (26.5)	12 (48.0)	17 (85.0)	
Asthma Control Test score	23 (21-25)	22 (21-24)	21 (19-24)	19 (15-22)	19 (13-21)	<.001
Asthma Control Test score categories, n (%)						<.001
>19	28 (84.8)	31 (83.8)	34 (69.4)	10 (40.0)	10 (50.0)	
16-19	4 (12.1)	4 (10.8)	11 (22.4)	8 (32.0)	2 (10.0)	
<16	1 (3.0)	2 (5.4)	4 (8.2)	7 (28.0)	8 (40.0)	
Two or more oral steroid courses per previous 2 y, n (%)	2 (6.1)	2 (5.4)	9 (18.8)	7 (29.2)	5 (25.9)	.035
One or more hospitalization owing to respiratory-related reason during follow-up, n (%)	6 (18.2)	8 (21.6)	9 (18.4)	12 (48.0)	11 (55.0)	.002
Pre-bronchodilator FEV_1, % reference	86 (12)	86 (15)	95 (13)	79 (17)	64 (19)	<.001
Annual decline in FEV_1, mL‡	−63 (38)	−52 (32)	−32 (25)	−46 (30)	−77 (52)	<.001
Blood eosinophils, $\times 10^9$/L	0.22 (0.13-0.28)	0.14 (0.09-0.25)	0.16 (0.10-0.28)	0.13 (0.06-0.25)	0.23 (0.13-0.41)	.048
Visits to health care during 12-y follow-up	11 (7-19)	11 (9-20)	16 (8-23)	20 (13-30)	21 (15-26)	.009
Monthly gross income (euros)	2500 (1813-3500)	1900 (1200-2925)	2079 (1343-2400)	1300 (830-2026)	1700 (1500-2400)	.001
Level of education, n (%)						.001
Tertiary	8 (24.2)	3 (8.1)	9 (18.4)	0	2 (10.0)	
Secondary	18 (54.5)	16 (43.2)	30 (61.2)	9 (36.0)	6 (30.0)	
Primary	7 (21.2)	18 (48.6)	10 (20.4)	16 (64.0)	12 (60.0)	
Not employed, n (%)	10 (30.3)	21 (56.8)	19 (39.6)	24 (96.0)	14 (70.0)	<.001
Retirement pension	2 (6.1)	11 (29.7)	9 (18.8)	6 (24.0)	8 (40.0)	
Disability pension	0	5 (13.5)	6 (12.5)	15 (60.0)	6 (30.0)	
Old unemployed	2 (6.1)	2 (5.4)	0	3 (12.0)	0	
Other age unemployed	0	2 (5.4)	0	0	0	
Student	1 (3.0)	0	1 (2.1)	0	0	
Other (parental leave, etc.)	5 (15.2)	1 (2.7)	3 (6.3)	0	0	

FEV$_1$, forced expiratory volume in 1 s.

*Continuous variables are shown as mean (SD) or median (interquartile range). Group comparisons were performed by one-way analysis of variance, Kruskal-Wallis test, or chi-square test.

†Asthma control based on Global Strategy for Asthma Management and Prevention 2010.

‡Annual decline from maximum point of FEV_1 within 2.5 y after diagnosis and start of treatment to 12-y follow-up visit.

§Defined as post-bronchodilator FEV_1/forced vital capacity less than 0.7 and 10 or more pack-years' smoking history.

each patient for each year by dividing the patient's yearly dispensed ICS doses by yearly prescribed ICS doses (microgram budesonide equivalents). Altogether, the extensive 12-year follow-up and the fact that long-term medication is prescribed continuously enhanced the evaluation of 12-year ICS adherence, including the initiation of medication and periods of persistence and temporary nonpersistence. All patients had an individual 12-year time-varying scope of adherence; when combined, it was possible to compare both average 12-year adherence and annual adherence of patients.

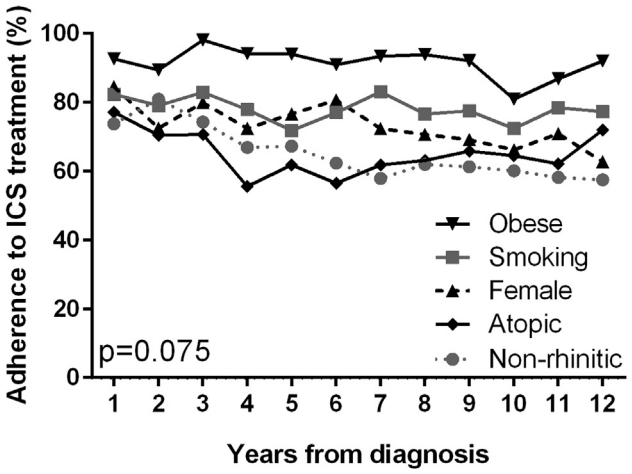

FIGURE E1. Long-term adherence to inhaled corticosteroid (ICS) treatment in phenotypes of adult-onset asthma. *P* values were obtained using two-way analysis of variance.