Association of subcutaneous allergen-specific immunotherapy with incidence of autoimmune disease, ischemic heart disease, and mortality

Allan Linneberg, MD, PhD,[a] Rikke Kart Jacobsen, MSc,[a] Lasse Jespersen, MD,[b] and Steen Z. Abildstrøm, MD, PhD[b] *Glostrup and Copenhagen, Denmark*

Background: Subcutaneous allergen-specific immunotherapy (SCIT) is a well-documented treatment of IgE-mediated allergic disease. Little is known about potential effects of SCIT on the risk of other chronic immune-related diseases. Over the years, a few casuistic reports have caused concern that SCIT might act as a trigger of autoimmune disease.

Objective: We aimed to investigate the association of SCIT with the incidence of autoimmune disease and ischemic heart disease (IHD), as well as all-cause mortality.

Methods: All Danish citizens without other known diseases were linked and followed through central registries on medications and hospital admissions. Persons receiving SCIT and persons receiving conventional allergy treatment (CAT; nasal steroids or oral antihistamines) were compared with regard to mortality and development of autoimmune diseases, acute myocardial infarction (AMI), and IHD. Cox regression (survival analysis) with age as the underlying time scale was used to estimate relative risks (hazard ratios [HRs] with 95% CIs) associated with SCIT compared with CAT adjusted for age, sex, vocational status, and income.

Results: During the 10-year study period (1997-2006), a total of 18,841 and 428,484 persons were followed in the SCIT and CAT groups, respectively. Receiving SCIT was associated with lower mortality (HR, 0.71; 95% CI, 0.62-0.81) and lower incidence of AMI (HR, 0.70; 95% CI, 0.52-0.93), IHD (HR, 0.88; 95% CI, 0.73-1.05), and autoimmune disease (HR, 0.86; 95% CI, 0.74-0.99).

Conclusion: In this registry-based observational study, receiving SCIT compared with CAT was associated with lower risk of autoimmune disease and AMI, as well as decreased all-cause mortality. (J Allergy Clin Immunol 2012;129:413-9.)

Key words: *Allergen immunotherapy, allergy, autoimmune disease, ischemic heart disease, long-term effects, mortality, pharmacoepidemiology, side effects*

Abbreviations used
AMI: Acute myocardial infarction
ATC: Anatomical Therapeutical Chemical
CAT: Conventional allergy treatment
HR: Hazard ratio
ICD-10: International Classification of Diseases, 10th revision
IHD: Ischemic heart disease
SCIT: Subcutaneous allergen-specific immunotherapy

Allergen-specific immunotherapy has been used for treatment of IgE-mediated allergic respiratory disease for more than 100 years.[1] The concept of allergen-specific immunotherapy is that the introduction of increasing doses of allergens to the immune system lowers the threshold for the elicitation of IgE-mediated allergic reactions and increases specific immune tolerance to the offending allergens.[2,3] Over the years, the subcutaneous route of allergen administration has been the most commonly used approach for the induction of allergen-specific tolerance. Cochrane meta-analyses of randomized studies support the hypothesis that subcutaneous allergen-specific immunotherapy (SCIT) reduces symptoms and use of medication in patients with seasonal allergic rhinitis[4] and asthma.[5] Nevertheless, there is evidence that several other routes than the subcutaneous route of allergen administration induce tolerance,[6] and thus the crucial issue might be the dose of allergen introduced to immune-competent cells.[7]

The most frequent adverse effects of SCIT are allergic reactions, including local reactions at the injection site (eg, erythema and swelling of the skin) and systemic reactions (eg, rhinitis, asthma, and anaphylactic shock). Little is known about the long-term effects of SCIT. Because SCIT modulates the immune system, it is theoretically plausible that SCIT might also influence other common immune-related inflammatory diseases, such as autoimmune disease. In fact, the notion that SCIT might trigger the development of autoimmune disease through its effects on the immune system is not new, although the evidence to support this is largely based on casuistic reports. Thus single cases of Sjögren syndrome,[8] multiple sclerosis,[9] localized scleroderma,[10] recurrent pericarditis,[11] and vasculitis[12] have been reported during the course of SCIT. As a principle of caution, immunologic diseases, such as autoimmune diseases, are considered a relative contraindication for SCIT by some international guidelines,[13] whereas others recommend an individual evaluation of the patient.[14]

It is well known that inflammatory mechanisms play a crucial role in the pathogenesis of atherosclerosis and ischemic heart disease (IHD).[15] Mast cells are present in increased numbers in atheromatous plaques, and mast cell activation is known to be able to contribute to coronary artery spasm and atheromatous plaque eruption.[15,16] The co-occurrence of unstable angina pectoris or acute myocardial infarction (AMI) together with an allergic,

From [a]the Research Centre for Prevention and Health, Glostrup University Hospital, and [b]the Department of Cardiology, Copenhagen University Hospital, Bispebjerg.

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Corresponding author: Allan Linneberg, MD, PhD, Research Centre for Prevention and Health, Glostrup University Hospital, 57 Nordre Ringvej, Bldg 84/85, DK-2600 Glostrup, Denmark. E-mail: alllin01@regionh.dk.

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hypersensitivity, or anaphylactic reaction is referred to as the Kounis syndrome.[17-21] Accordingly, mast cell–stabilizing drugs have been proposed as a potential beneficial anti-inflammatory treatment for acute coronary events.[22] To our knowledge, no previous study has made an attempt to evaluate the risk of IHD during or after SCIT.

The randomized, double-blind, placebo-controlled clinical trial remains the gold standard (or the least biased study design) for the assessment of possible beneficial and adverse effects of interventions. One limitation of this type of study, however, is that it is often not possible to assess effects on rare outcomes because of the limited size of the study population, as well as the limited time, incompleteness, or both of longitudinal follow-up. A pharmacoepidemiologic approach taking advantage of linkage between nationwide registries for medications and diseases, thereby obtaining complete follow-up of large populations, might provide the opportunity to study hitherto-unrecognized rare adverse or beneficial effects of medications. Denmark offers an almost perfect setting for pharmacoepidemiologic studies.[23] In the present article we present results from a nationwide pharmacoepidemiologic study investigating the association of SCIT with the incidence of autoimmune disease, IHD, and all-cause mortality. We hypothesized that SCIT, being an immune-modulating treatment, would in some cases be able to act as a trigger of immune-related diseases, such as autoimmune diseases and IHD.

METHODS

Use of Danish registries

All residents in Denmark have a unique and permanent personal civil registration number, which allows linkage on an individual level of data from complete national registers. Information on every dispensed drug prescription from pharmacies in Denmark since 1995 is available in the Danish Register of Medicinal Product Statistics (National Prescription Register). This register holds information on date of dispensing, quantity dispensed, and strength of the medication and the affiliation of the physician issuing the prescription. The drugs are classified according to the international Anatomical Therapeutical Chemical (ATC) system. Because of partial reimbursement of drug expenses by the health care system, pharmacies in Denmark are required to register all dispensed prescriptions in the national prescription register. This ensures a highly accurate register.[24] In the present study we used data from January 1, 1995, to December 31, 2006. The database used for in the present study was established at Statistics Denmark and has been described in a previous article.[25]

Information on chronic diseases was obtained from the Danish National Patient Register, which holds information on all admissions to Danish hospitals since 1978.[26] Each admission is registered by 1 primary diagnosis and, if relevant, 1 or more secondary diagnoses according to the *International Classification of Diseases* (ICD; ie, before 1994, the 8th revision [ICD-8], and since 1994, the 10th revision [ICD-10]). Furthermore, we used the Danish Registry of Causes of Death, which is based on a coding of all death certificates. The Registry of Causes of Death contains the date of death and up to 3 ICD-10 diagnoses suspected to be the cause of death.[27]

Definition of treatment status

The study population was identified among all residents in Denmark aged 18 years or older on January 1, 1997. From this study population, 2 subpopulations were identified.

SCIT group. The SCIT group included all persons who claimed at least 1 drug prescription for SCIT medication (allergen extracts) with ATC codes of V01AAx during the period from January 1, 1997, through December 31, 2006. The most commonly prescribed allergen extracts were grass, birch, house dust mite, cat, and Hymenoptera venoms. During this period, only 1 pharmaceutical company (Alutard SQ; ALK-Abelló, Hørsholm, Denmark) had allergen-specific immunotherapy extracts (and only for the subcutaneous route of administration) registered on the Danish market. Persons in the SCIT group were followed with regard to any registry-based disease outcome from the date of claiming the first prescription during the period from January 1, 1997, through December 2006. In additional sensitivity analyses we excluded persons who claimed a prescription for SCIT medication during the period from January 1, 1995, through December 31, 1996, to exclude prevalent users of SCIT.

Conventional allergy treatment group. The conventional allergy treatment (CAT) group was defined to obtain a comparable control group of persons with probable allergic rhinitis treated with more conventional antiallergic medications, such as oral antihistamines or intranasally administered glucocorticoids. A person was included if he or she had claimed a drug prescription for oral antihistamines (one of the following ATC codes: R06AX13, R06AX18, R06AX22, R06AX26, R06AX27, or R06AE07) or intranasally administered glucocorticoids (one of the following ATC codes: R01AD01, R01AD05, R01AD08, R01AD09, R01AD11, or R01AD12). The dispensing of at least 2 prescriptions (not necessarily the same drug on both occasions) on 2 separate dates within 1 year was required to be included in the CAT group to increase the likelihood that the person actually had allergic rhinitis. Persons in the CAT group were followed with regard to any registry-based disease outcome from the date of dispensing of the second prescription during the period from January 1, 1997, through December 31, 2006. Thus the first prescription might have been dispensed in 1996.

Furthermore, the use of systemic steroids was defined as claiming at least 1 prescription for systemic steroids (ATC codes H02AB04, H02AB01, H02AB06, and H02AB07) during the period from inclusion to the end of follow-up. Similarly, use of statins was defined as claiming at least 1 prescription for statins (ATC codes C10AA) during the period from inclusion to the end of follow-up. The treatment status (SCIT vs CAT status) was treated as a time-dependent variable. Thus persons included in the CAT group were allowed to change status and subsequently be included in the SCIT group. In contrast, it was *a priori* decided that once a person was included in the SCIT group, he or she remained in the SCIT group to ensure that development of any chronic disease was considered as a potential SCIT adverse outcome.

In both groups those who had a diagnosis of chronic disease (any cardiovascular disease, autoimmune disease, or cancer disease) as primary or secondary diagnoses in the Danish National Patient Register during a period of 10 years before the date of inclusion were excluded from all analyses. This was done to eliminate persons with pre-existing diseases that might change the likelihood of being selected for SCIT. This type of selection is also referred to as confounding by indication.[28] Emigration or immigration during the 10-year period before the date of inclusion also resulted in exclusion from the study.

Statistical analyses

All analyses were performed with the statistical program SAS, version 9.1 (SAS Institute, Inc, Cary, NC). Significance testing was 2-sided and based on a 5% probability level.

The statistical method used in all analyses was a Cox regression model with delayed entry and a time-dependent covariate (treatment status: SCIT vs CAT group). Age was used as the underlying time scale to ensure that only persons of the same age were compared. Thus this approach ensures that the effect of treatment status is fully adjusted for age. Cox regression compares the treatment status of each person experiencing an event with the treatment status of persons at risk of an event of the same age (the underlying time scale). The time-dependent covariate (treatment status) was the main covariate and indicated at any time the status of each person (ie, whether a person was in the SCIT or CAT group). We studied 4 different outcomes: death of all causes; AMI (ICD-10 diagnoses I21.x or I22.x, as recorded in the National Patient Registry or the Registry of Cause of Death); IHD (ICD-10 diagnoses I20.x, I21.x, I22.x, I23.x, I24.x, or I25.x, as recorded in the National Patient Registry or the Registry of Cause of Death); and autoimmune disease (≥1 of the diseases listed in Table I). In addition, gastrointestinal cancer (ICD-10 diagnoses C15-16 and C18-21) was used as a control disease in supplemental analyses. Two different setups were used regarding censoring. When looking

TABLE I. List of autoimmune diseases considered in the present study

Autoimmune diseases	ICD-10 codes
Multiple sclerosis	G35-37.x
Rheumatoid arthritis and other forms of polyarthritis	M08.0-9, M05.x, M06.x
Insulin-dependent diabetes mellitus	E10.x
Celiac disease	K90.0
Crohn disease	K50.x
Grave disease	E05.0
Chronic thyroiditis other than E06.3	E06.2
Hashimoto thyroiditis	E06.3
Myasthenia gravis	G70.0
Chronic ulcerative colitis	K51.x
Primary biliary cirrhosis	K74.3
Morbus Addison	E27.1-2
Psoriasis	L40.x
Systemic lupus erythematosus	M32.x
Scleroderma	M34.x
Sjögren syndrome	M35.0

at death of all causes, the only reason for censoring was emigration (and thus lack of registry-based follow-up). When looking at each of the 3 other outcomes, persons were censored on the date of emigration, date of death, or when receiving at least 1 of the above-mentioned diagnoses (cardiovascular disease, autoimmune disease, or cancer disease), whichever date occurred first.

For each outcome, the effect of treatment status (SCIT vs CAT) was examined in 2 models. In the first model the effect of treatment status was adjusted for sex and age of study entry (ie, the age on the date of inclusion in the study). In the second model the effect of treatment status was in addition adjusted for personal income and vocational status (for definition and categorization of variables, see the tables). In a third model additional adjustment for use of systemic steroids or statins was performed.

For each of the 4 outcomes, 3 supplementary Cox regression analyses were performed to further investigate the effect of treatment status on each outcome:

1. The first supplementary analysis was performed to examine whether the effect of treatment status differed between age groups (age 18-30, 30-50, or >50 years at study entry).
2. The second supplementary analysis was performed to separate any potential short- and long-term effects. A new time-dependent treatment status variable was developed including the following categories: "only included in the CAT group at all times," "included in the SCIT group within the last 6 months," or "included in the SCIT group more than 6 months ago."
3. The third supplementary analysis aimed to decrease the influence of a potential "healthy user effect" by excluding persons who received SCIT medication in 1995 or 1996 (ie, persons who were prevalent users ≥2 years before they were included in the SCIT group during the study period from January 1, 1997, through December 31, 2006).

Ethics

Register studies in which individual patients cannot be identified do not require ethical approval in Denmark. The study was approved by the Danish Data Protection Agency (reference 2006-41-6071).

RESULTS

Of the total population of Denmark, during the study period, a total of 18,841 and 428,484 persons were included in the SCIT and CAT groups, respectively. Of the 18,841 persons included in the SCIT group, 8,374 were initially included in the CAT group but changed treatment status from CAT to SCIT. Fig 1 shows the number of persons included in the SCIT group by the calendar year in which they claimed their first prescription for allergen extract from the start of the Danish National Prescription Registry in 1995 through 2006. Since the registry started in 1995, a particularly high number of persons were included as first-time users in 1995 and 1996 because we were not able to distinguish prevalent users (those who also received SCIT before 1995) from new users. Fig 1 also shows the number of persons included in the SCIT group by calendar year when excluding persons who claimed a prescription for SCIT extracts in 1995 or 1996, thereby providing more valid figures of new-incident users of SCIT for each calendar year during 1997 to 2006.

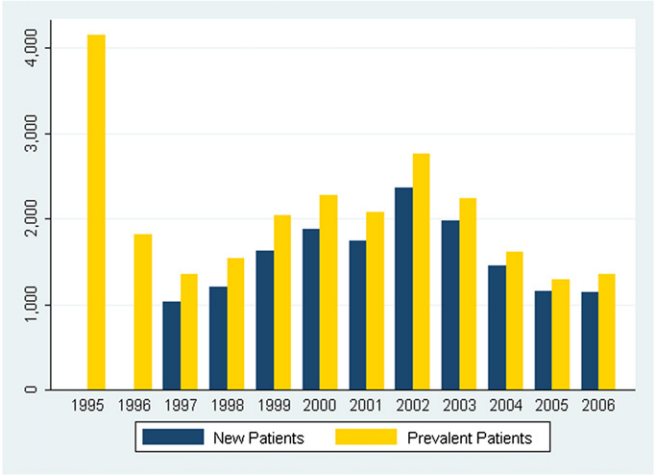

FIG 1. Number of persons *(yellow bars)* included in the SCIT group by the calendar year in which they claimed their first prescription for allergen extract for SCIT from the start of the Danish National Prescription Registry in 1995 and through 2006. The figure also shows the number of persons *(blue bars)* included in the SCIT group by calendar year when excluding persons who claimed a prescription for SCIT extracts in 1995 or 1996, thereby providing more valid figures of new-incident users of SCIT for each calendar year from 1997 to 2006.

During the follow-up, a total of 25,900 deaths were recorded. Of these, 214 and 25,686 deaths occurred among persons included in the SCIT and CAT groups, respectively. Treatment status was significantly associated with mortality (ie, SCIT compared with CAT status was associated with a significantly lower mortality; Table II) after adjustment for age at inclusion, sex, income, and vocational status. Thus SCIT compared with CAT was associated with a 29% mortality relative risk reduction (adjusted hazard ratio [HR], 0.71; 95% CI, 0.62-0.81). In supplemental analyses, as described above, we stratified the analyses by age group and found that the effect of treatment status on mortality was similar across age groups and statistically significant within all 3 age groups (18-30, 30-50, or >50 years at study entry; data not shown). The effect of treatment status differed with time since the start of inclusion. Thus the effect of SCIT on mortality was significantly stronger during the first 6 months of treatment (adjusted HR comparing the effect of SCIT for the first 6 months with no SCIT treatment, 0.30; 95% CI, 0.14-0.69) than after the first 6 months (adjusted HR comparing the effect of SCIT treatment after first the 6 months with no SCIT treatment, 0.74; 95% CI, 0.64-0.85; P for difference = .035). Excluding prevalent users of SCIT (ie,

TABLE II. Association of subcutaneously administered immunotherapy (SCIT) compared with CAT with all-cause mortality

	No. of deaths	Person-years at risk	HR* (95% CI)	HR* (95% CI)
Treatment status				
SCIT group	214	129,294	0.65 (0.57-0.74)	0.71 (0.62-0.81)
CAT group	25,686	2,594,054	1 (reference)	1 (reference)
Sex				
Female	14,891	1,598,132	0.67 (0.61-0.73)	0.61 (0.59-0.62)
Male	11,009	1,125,216	1 (reference)	1 (reference)
Vocational status				
Self-employed or employed	3,274	1,807,092	—	0.39 (0.37-0.41)
Unemployed	283	87,235		0.52 (0.46-0.59)
Student or retired	22,312	821,474		1 (reference)
Other	31	7,516		0.62 (0.43-0.89)
Personal income				
High (>250,000 DKK)	2,849	839,066	—	1 (reference)
Medium (>144,000 DKK)	5,682	969,482		1.29 (1.23-1.35)
Low (<144,000 DKK)	17,369	914,769		1.65 (1.58-1.74)

DKK, Danish krone.
*HR obtained in a Cox regression model with age as the underlying time scale adjusted for variables shown in the table, as well as age at inclusion.

TABLE III. Association of SCIT compared with CAT with the incidence of a registry-based diagnosis of autoimmune disease

	No. of events	Person-years at risk	HR* (95% CI)	HR* (95% CI)
Treatment status				
SCIT group	206	122,914	0.84 (0.72-0.98)	0.86 (0.74-0.99)
CAT group	6,071	2,378,545	1 (reference)	1 (reference)
Sex				
Female	4,387	1,461,881	1.60 (1.52-1.69)	1.46 (1.38-1.54)
Male	1,890	1,039,578	1 (reference)	1 (reference)
Vocational status				
Self-employed or employed	3,529	1,698,389	—	0.73 (0.68-0.79)
Unemployed	213	80,686		0.77 (0.67-0.89)
Student or retired	2,520	715,113		1 (reference)
Other	15	7,240		0.60 (0.36-1.00)
Personal income				
High (>250,000 DKK)	1,475	782,949	—	1 (reference)
Medium (>144,000 DKK)	2,265	893,850		1.24 (1.15-1.32)
Low (<144,000 DKK)	2,537	824,629		1.33 (1.22-1.45)

DKK, Danish krone.
*HR obtained in a Cox regression model with age as the underlying time scale adjusted for variables shown in the table, as well as age at inclusion.

persons who claimed ≥1 drug prescription for SCIT medication in 1995 or 1996) only strengthened the effect of treatment status on mortality (data not shown).

A total of 206 and 6071 cases of autoimmune disease were observed in the SCIT and CAT groups, respectively (Table III). SCIT compared with CAT was associated with a slightly but significantly lower incidence of autoimmune disease. This effect was seen across age groups in the age-stratified analyses. The effect of SCIT tended to be stronger in the first 6 months than after 6 months of treatment, but this difference was not statistically significant (data not shown). Results were similar after exclusion of prevalent users of SCIT in 1995 and 1996 (data not shown).

The effect of treatment status on the incidence of AMI is shown in Table IV. During the 10-year study period, a total of 48 and 3657 cases of a registry-based diagnosis of AMI were observed in the SCIT and CAT groups, respectively. The incidence differed slightly with season, being lower during summertime and higher during wintertime. SCIT compared with CAT was associated with a significantly lower incidence of AMI after adjustment for age at inclusion, sex, income, and social group. In the age-stratified analyses this effect was reasonably similar across age groups, although it did not reach statistical significance within all age groups (data not shown). Furthermore, the effect of SCIT on the risk of AMI appeared to be stronger during the first 6 months of treatment compared with that seen after the first 6 months of treatment, although this difference was not statistically significant (data not shown). Excluding persons who claimed a prescription for SCIT medication in 1995 or 1996 at least 2 years before they were included in the SCIT group only strengthened the effect of treatment status on the incidence of AMI (data not shown). SCIT compared with CAT was associated with a lower incidence of IHD, but this association was not statistically significant (Table V). The effect was similar across age groups and after exclusion of prevalent users of SCIT in 1995 and 1996 (data not shown).

Use of systemic steroids (ie, claiming ≥1 prescription during follow-up) was common, particularly among those who changed status from CAT to SCIT. Thus a total of 26.0% (111,317/428,484), 25.4% (2,662/10,467), and 50.5% (4,226/8,374) had used systemic steroids among those only included in the CAT group, those only included in the SCIT group, and those who

TABLE IV. Association of SCIT compared with CAT with the incidence of a registry-based diagnosis of AMI (ICD-10 diagnoses I21.x and I22.x)

	No. of events	Person-years at risk	HR* (95% CI)	HR* (95% CI)
Treatment status				
SCIT group	48	122,914	0.67 (0.50-0.89)	0.70 (0.52-0.93)
CAT group	3,657	2,378,545	1 (reference)	1 (reference)
Sex				
Female	1,557	1,461,881	0.41 (0.39-0.44)	0.37 (0.35-0.40)
Male	2,148	1,039,578	1 (reference)	1 (reference)
Vocational status				
Self-employed or employed	1,112	1,698,389	—	0.83 (0.74-0.94)
Unemployed	73	80,686		0.93 (0.73-1.19)
Student or retired	2,515	715,113		1 (reference)
Other	5	7,240		0.56 (0.23-1.36)
Personal income				
High (>250,000 DKK)	835	782,949	—	1 (reference)
Medium (>144,000 DKK)	929	893,850		1.15 (1.04-1.27)
Low (<144,000 DKK)	1,941	824,629		1.51 (1.35-1.68)

DKK, Danish krone.
*HR obtained in a Cox regression model with age as the underlying time scale adjusted for variables shown in the table, as well as age at inclusion.

TABLE V. Association of SCIT compared with CAT with the incidence of a registry-based diagnosis of IHD (ICD-10 diagnoses I20.x to I25.x)

	No. of events	Person-years at risk	HR* (95% CI)	HR* (95% CI)
Treatment status				
SCIT group	130	122,914	0.84 (0.70-1.01)	0.88 (0.73-1.05)
CAT group	7,410	2,378,545	1 (reference)	1 (reference)
Sex				
Female	3,612	1,461,881	0.52 (0.49-0.54)	0.47 (0.44-0.49)
Male	3,928	1,039,578	1 (reference)	1 (reference)
Vocational status				
Self-employed or employed	2,336	1,698,389	—	0.80 (0.74-0.87)
Unemployed	162	80,686		0.92 (0.78-1.08)
Student or retired	5,036	715,113		1 (reference)
Other	6	7,240		0.31 (0.14-0.69)
Personal income				
High (>250,000 DKK)	1,640	782,949	—	1 (reference)
Medium (>144,000 DKK)	1,930	893,850		1.19 (1.10-1.27)
Low (<144,000 DKK)	3,970	824,629		1.54 (1.42-1.66)

DKK, Danish krone.
*HR obtained in a Cox regression model with age as the underlying time scale adjusted for variables shown in the table, as well as age at inclusion.

changed treatment status from CAT to SCIT, respectively. However, adjustment for use of systemic steroids in the above statistical models did not change any of the estimates for the association of treatment status with mortality and incidence of disease. A total of 9.1% (38,839/428,484), 5.8% (611/10,467), and 4.1% (347/8,374) had used statins among those only included in the CAT group, those only included in the SCIT group, and those who changed treatment status from CAT to SCIT, respectively. However, adjustment for use of statins in the above statistical models did not change any of the estimates for the association of treatment status with mortality and incidence of disease.

Finally, SCIT compared with CAT was associated (HR adjusted for age at inclusion, sex income, and social group, 0.72; 95% CI, 0.50-1.04) with a lower incidence of gastrointestinal cancer, although this was not statistically significant.

DISCUSSION

To the best of our knowledge, this is the first study investigating the effects of SCIT on mortality and the incidence of immune-related inflammatory diseases. In this nationwide, registry-based, pharmacoepidemiologic study we could not detect any detrimental effects of SCIT in terms of increased risk of autoimmune disease and IHD. In fact, overall, our analyses pointed to a lower risk of these outcomes among persons who had received SCIT compared with CAT.

It should be considered whether the observed negative association between SCIT and mortality/AMI/autoimmune disease could be at least partly due to so-called confounding by indication (ie, persons with a high risk of these diseases are less likely to receive SCIT than persons with a low risk). In Denmark medical consultations are free of charge, but patients must pay a part of the costs for medication. Allergic patients can be referred by their general practitioner to a specialist (eg, an allergologist), who will evaluate the patient and, if relevant, initiate immunotherapy. Because there is a limited number of allergologists in Denmark, patients should be willing to wait for several months for an appointment with the specialist. Confounding by indication could arise from both doctors selecting certain groups of patients for specific treatments or by certain patients themselves selecting

specific treatments or being more willing to wait for a specialist consultation (self-selection).

We made several restrictions in an attempt to decrease the influence of confounding by indication. First, we excluded persons with a diagnosis of chronic disease in the National Patient Registry during a period of 10 years before the date of inclusion in the SCIT or CAT groups.

Second, once a person was included in the CAT group, the person was censored if receiving a diagnosis of a chronic disease not included as an outcome in that specific analysis. The latter was decided because if a person had a chronic disease, he or she might be less likely to commence a course of SCIT as a treatment of allergy. In contrast, once persons were included in the SCIT group they were not allowed to change status to the CAT group, and as a consequence, any development of chronic disease was accounted for as an effect of SCIT, even when the disease developed years after discontinuation of SCIT.

Third, in supplemental analyses we aimed to exclude prevalent users of SCIT (those receiving SCIT in 1995 or 1996), who might be at lower risk of side effects than new users.

Fourth, we performed multivariable analyses, taking into account a few but important determinants of chronic disease and mortality (ie, use of systemic steroids, use of statins, socioeconomic status [vocational status and income], age, and sex). In this regard the lack of information on lifestyles (eg, smoking and alcohol use) is a clear limitation of these analyses.

In summary, in spite of our attempts to reduce the influence of potential confounding and biases, the negative associations between SCIT and the incidence of disease/mortality remained statistically significant. However, these associations should still be interpreted with caution because completely comparable study groups (SCIT vs CAT) with regard to all important determinants of disease/mortality cannot be guaranteed in a nonrandomized study. A randomized study considering the above end points would indeed be desirable but does not seem feasible. Nevertheless, from a clinical practice point of view, it is reassuring that our data did not indicate that SCIT is associated with increased risk of autoimmune disease or IHD. Thus we were not able to confirm the *a priori* hypothesis that SCIT is a risk factor for (or trigger of) incident autoimmune disease, as has been indicated by several case reports over the years.

If we assume that the observed negative association between SCIT and IHD is causal, it is of interest to consider the possible underlying biologic mechanisms. It is generally accepted that inflammatory processes play an important role in atherosclerosis and IHD. Of note is that it has been proposed that atherosclerosis fulfills the criteria to define a condition as being autoimmune in nature.[29] The known involvement of mast cells in patients with atherosclerotic coronary artery disease is of potential interest because mast cells are key effector cells in IgE-mediated allergic immune responses. Recent data strongly suggest a role of mast cells in the metabolic syndrome and diabetes, both of which are major risk factors for IHD. Thus in mice fed a westernized diet, genetically induced deficiency of mast cells, or their pharmacologic stabilization, reduces body weight gain in concert with improved glucose homeostasis and energy expenditure.[30] Furthermore, levels of serum tryptase, a major product of mast cells, appear to be increased in persons with the metabolic syndrome[31] and have even been proposed as a new biomarker of coronary artery disease.[32] The precise immunologic mechanisms by which SCIT influences the allergen-specific immune response and the immune system in general are not completely understood. However, immunotherapy-induced suppression of mast cells and their release of proinflammatory mediators is among the known effects and possible mechanisms of SCIT.[2] Thus mast cells and their products might represent a possible pathway of the potential effects of SCIT on IHD. It seems feasible to provide some proof of concept by including metabolic and cardiovascular risk biomarkers in randomized trials of SCIT.

Although it is obvious that SCIT targets the allergen-specific immune response, a nonspecific effect of SCIT and other vaccines has been discussed over the years. In this context it should be noted that the SCIT product that was used for treatment of all patients in the SCIT group contains aluminum hydroxide as an adjuvant for depot vaccination. Aluminum hydroxide has been widely used for injection immunotherapy to increase the immune stimulation and reduce the risk of anaphylaxis. Aluminum hydroxide has been shown to reduce the allergen-induced production of the T_H2-type cytokines IL-5 and IL-13 without influencing the IL-10 production in human immune cells.[33] It is not known whether aluminum hydroxide in itself has non–allergen-specific effects on the immune system.

SCIT compared with CAT was found to be associated with the incidence of very different chronic diseases, such as IHD and autoimmune disease. To investigate this further, we examined whether SCIT had a similar effect on gastrointestinal cancer, which we *a priori* hypothesized would not be associated with SCIT and might therefore function as a "control" disease. Moreover, gastrointestinal cancer is not significantly influenced by smoking, thereby decreasing potential confounding by smoking. However, the nonspecific effects of SCIT appeared to include gastrointestinal cancer, although this effect was not statistically significant. This observation might support the hypothesis that the effect of SCIT on chronic disease is nonspecific.

In conclusion, in this observational study receiving SCIT compared with CAT was associated with lower mortality and a lower incidence of AMI and autoimmune disease. Whether these effects reflect a beneficial immune-modulating effect of SCIT or biases inherent in the study design (eg, confounding by indication) remains to be elucidated. From a clinical point of view, it might be of particular interest that we did not find evidence to support the hypothesis that SCIT is associated with increased risk of development of autoimmune disease, as has been indicated by a few previous case reports.

Key messages

- **Little is known about the long-term effects of SCIT.**
- **There has been concern that SCIT might act as a trigger of autoimmune disease.**
- **This pharmacoepidemiologic study does not support that SCIT is associated with increased risk of autoimmune disease or IHD or increased mortality.**

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