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Treating allergic rhinitis with depot-steroid injections increase risk of osteoporosis and diabetes

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KEYWORDS

Rhinitis;
Immunotherapy;
Steroid;
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Summary

Background: In Denmark, 23% of the adult population have allergic rhinitis. We have previously demonstrated that a majority of hay fever patients are treated with depot-steroid injections in violation of the guidelines. It has been hypothesised that 1–2 annual depot-steroid injections are not harmful to the patient.

Objectives: Investigate if the depot-steroid treatment of allergic rhinitis instead of immunotherapy increases risk of steroid-related diseases.

Methods: A retrospective study based on Danish National Registries 1995–2011 covering diagnoses, medications, as well as clinical outcomes. The main analysis was time dependent poisson regression models with results presented as rate ratios (RR), and incidence per 1000 patient years.

Steroid use was defined as minimum one injection during April–July for at least three consecutive years. Treatment with specific immunotherapy against grass, birch or both was used as non-steroid control group. Relative risk of adverse outcomes such as osteoporosis, infections, diabetes and/or tendon rupture was investigated.

Results: We identified 47,382 individuals with rhinitis; 55.8% treated with steroids, 37.6% with immunotherapy, and 6.7% with both. No significant differences in infections or tendon rupture were observed. For steroid treatment RR of diabetes was 1.5 (95% CI: 1.3–1.8; $P < 0.001$),

Abbreviations: AR, allergic rhinitis; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; AIT, allergen immunotherapy tablets; SIT, specific immunotherapy; ARIA, allergic rhinitis and its impact on asthma; ATC, Anatomical Therapeutic Chemical Classification; ICD, International Statistical Classification of Diseases and Related Health Problems ICD; RR, rate ratios; COPD, chronic obstructive pulmonary disease.

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incidence 3.9 (95% CI: 3.5–4.3), and RR of osteoporosis was 1.2 (95% CI: 1.0–1.5; $P = 0.023$), incidence 2.8 (95% CI: 2.5–3.1). Risk of diabetes culminated within the first two years of treatment start.

Conclusions: Compared to immunotherapy regular use of depot-steroid injections to treat allergic rhinitis is associated with increased risk of being diagnosed with diabetes and osteoporosis.

Clinical implications: Treating seasonal allergic rhinitis with depot-steroid injections should be abandoned and replaced with immunotherapy, as annual depot-steroid treatment is associated with increased risk of diabetes and osteoporosis.

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Introduction

Allergic respiratory diseases have increased over the past decades, and currently 500 million people worldwide suffer from allergic rhinitis (here termed rhinitis) [1], and 23% of the adult population in Denmark have allergic rhinitis [2]. One of the most comprehensive classification and treatment recommendations for rhinitis is described in The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines. ARIA recommends initial treatment with over-the-counter drugs like oral or intranasal antihistamines, followed by intranasal corticosteroids, and in the case of moderate-severe rhinitis specific immunotherapy (SIT) [3]. The efficacy and safety of SIT is well documented, both for subcutaneous treatment [4] and for the new sublingual tablet alternative [5]. Systemic corticosteroids are only recommended in the most severe cases of rhinitis and solely on a short-term oral treatment. However, we have previously shown that depot-injections of corticosteroids are regularly used to treat rhinitis caused by birch (*Betula Verrucosa*) and grass (*Phleum pratense*) pollen in Denmark, with an immunotherapy to steroid ratio of 1:14 respectively [6]. Severe adverse events like necrosis and hypocorticism, due to depot-steroid injections, have been reported previously [7–11]. However, firm knowledge of the risk of developing tendon ruptures, infections and common endocrine diseases including diabetes and osteoporosis are urgently needed [12,13].

The present nationwide study aimed to investigate if compared to immunotherapy the use of depot-steroid injections increased the relative risk of developing common steroid-related diseases [13].

Methods

Design

The study was designed as a registry-based, retrospective study using different Danish National Registry databases. All residents in Denmark are assigned a permanent, personal and unique civil registration number, which enables individual linkage of all nationwide registers. The main registry used for this study was the Danish Register of Medicinal Product Statistics (hereafter termed the prescription register), which contains all information on dispensed prescriptions from Danish pharmacies since 1995, where drugs are classified according to the Anatomical Therapeutic

Chemical Classification (ATC) system. Because the state-financed healthcare system partially reimburses drug expenses, all Danish pharmacies are obliged to register all dispensed drug prescriptions, ensuring a valid and accurate register [14]. The prescription register was combined with the Central Person Registry to ascertain fatalities during the study period. This civil registration number is connected to The Danish National Patient Registry, which contains information on hospital admissions with diagnoses coded according to the International Statistical Classification of Diseases and Related Health Problems (ICD) [15].

Study population

The data used in this study originated from registries based on data collected 1995–2011.

Inclusion criteria were: 1) Subcutaneous or sublingual-tablet immunotherapy against grass (*Phleum pratense*), subcutaneous immunotherapy against birch (*Betula verrucosa*) (no sublingual tablet currently available in Denmark against birch pollen), or both; and 2) at least one steroid injection during April–July for three consecutive years 1995–2011.

Exclusion criteria were: a) Immunotherapy against any allergen other than grass or birch, b) diagnosis of chronic obstructive pulmonary disease, c) diagnosis of rheumatic disease, d) less than two of the following treatments: oral or intranasal antihistamines, or intranasal corticosteroids, and e) diagnosis of malignant disease.

A subgroup was defined as individuals who were 18–45 years old at the time of treatment start.

Definition of diagnosis based on registry data

The ICD and ATC codes used in this study to identify groups are shown in Table 1. ICD codes used to establish diagnosis was used as is. Drug prescriptions by ATC codes were used by identifying prescription patterns as described in the following.

Rhinitis treatment with depot-steroid injections was defined as individuals receiving at least one depot-steroid-injection in April–July for three consecutive years [6]. Rhinitis treatment with immunotherapy, symptomatic rhinitis treatment drug class, and diabetes diagnosis were all included based on first prescription. Diabetes follow-up was based on last occurrence of prescriptions 1995–2011. Asthma diagnoses were established as three consecutive years with prescriptions.

Table 1 Overview of International Statistical Classification of Diseases and Related Health Problems (ICD) and Anatomical Therapeutic Chemical Classification (ATC) of drugs used to identify diseases.

Group definition	Diagnosis		Drugs	
	Codes beginning with		ATC	Description
	ICD-9	ICD-10		
Asthma	493	J45	R03A, R03B	Inhalant steroids, beta-2-agonists and/or muscarinic-antagonists
Cancer	140–209	C	—	—
Chronic Obstructive Pulmonary Disease (COPD)	492, 494, 496	J44	—	—
Diabetes	24900, 24908–25000	D10, E11	A10A, A10B	Human insulin (commonly used to treat Type I diabetes) or oral anti-diabetic drugs (commonly used to treat Type II diabetes)
Osteoporosis	72309	M81–83	—	—
Respiratory tract infection	46602–48499	J01–18	—	—
Rheumatic disease	725–729	M35	—	—
Rhinitis Symptomatic treatment	—	—	R01AD, R06AE, R06AX, R01AC	Intranasal corticosteroids, Subscription antihistamines (over-the-counter drugs is not registered in the database), Intranasal antihistamines
Depot-steroids	—	—	H02AB01, H02AB04, H02AB08	Depot-injection corticosteroids
Immunotherapy Grass (<i>Phleum pratense</i>)	—	—	V01AA02	Subcutaneous immunotherapy or Grazax allergen immunotherapy tablets
Birch (<i>Betula verrucosa</i>)	—	—	V01AA05	Subcutaneous immunotherapy drug
Tendon rupture	84500–84501	M66	—	—

Statistics

All data were extracted and examined using the SAS Statistical Software Package version 9.2 for Windows (SAS Institute, Cary, NC, USA). Poisson regression models (SAS proc genmod) were used to examine risk following therapy with either steroid or immunotherapy in a time dependent manner. Patients entered the analyses at the time when steroid therapy or immunotherapy was established. Time ended with a relevant event or was censored at unrelated death, any cancer diagnosis or on 31-Dec-2011. Time was split in 5 year intervals by both calendar year and age. Calendar year and age were entered into models as continuous parameters, other variables as class variables. The assumption of linearity of continuous variables was tested by demonstrating no importance of further inclusion of quartiles of variables. The assumption of constant risk in intervals was tested by demonstrating nearly identical results with split at 1 year intervals. Interactions were tested and the only relevant interaction found was with time after start of steroid therapy. Therefore time after steroid therapy was subdivided in the first 2 years and later years.

Ethics

The Danish Data Protection Agency approved the present study 2007-58-0015. Register-based retrospective studies do not require ethical approval in Denmark.

Results

Total population

In the period 1995–2011 a total of 86,368 individuals received steroid injections April–July for three consecutive years, or immunotherapy against grass or birch. The following were excluded: 2171 (2.5%) with a diagnosis of chronic obstructive pulmonary disease, 2955 (3.4%) diagnosed with rheumatic disease, 15,747 (18.2%) who did not have at least two classes of symptomatic drug prescriptions (intranasal/oral antihistamines, or intranasal corticosteroids), and lastly 18,113 (21.0%) who received immunotherapy for other allergies (e.g. insect venom or house dust mites) (Table 2). The final study population totalled 47,382 (54.9%) individuals; of these 31,135 were 18–45 years old.

The mean age was 40.5 years (95% CI: 40.4–40.7) in the steroid group, and 30.0 years (95% CI: 29.8–30.2; Wilcoxon $P < 0.001$) in the immunotherapy group. In the 18–45-year-old group the mean age in the steroid group was 33.3 years (95% CI: 33.1–33.4), and in the immunotherapy group it was 31.7 years (95% CI: 31.6–31.9; Wilcoxon $P < 0.001$). A total of 610 individuals died, and 1784 subjects were diagnosed with cancer.

Incidence and risk of steroid-related diseases

Risks are presented as rate ratios (RR) for individuals treated with steroids compared to immunotherapy,

Table 2 Population overview. Steroids is defined as at least three steroid injection for three consecutive pollen seasons (April–July). “Other allergy treatment” is either oral antihistamines, intranasal antihistamines, and/or nasal corticosteroids. At least two “Other allergy treatment”s are required. Specific immunotherapy (SIT) is for either birch, or grass (subcutaneous or Grazax) or for both.

Reason for exclusion	Steroids	SIT for birch and/or grass	Steroids and SIT for birch and/or grass	All
(None; included in study)	26428 (55.8%)	17798 (37.6%)	3156 (6.7%)	47382 (54.9%)
Diagnosed with COPD	1492 (68.7%)	652 (30.0%)	27 (1.2%)	2171 (2.5%)
Diagnosed with rheumatic disease	1804 (61.0%)	1050 (35.5%)	101 (3.4%)	2955 (3.4%)
No other allergy treatment than steroids and no SIT	15747 (100.0%)	—	—	15747 (18.2%)
Received other SIT than birch and/or grass	—	17438 (96.3%)	675 (3.7%)	18113 (21.0%)
All	45471 (52.6%)	36938 (42.8%)	3959 (4.6%)	86368 (100.0%)

incidences as number per 1000 patient years. All results were adjusted for calendar year, age, sex and asthma. Results are shown in Table 3. No significant increase in RR was seen for either respiratory tract infections or tendon rupture. In the total population, RR of diabetes for steroid treatment was 1.5 (95% CI: 1.3–1.8; $P < 0.001$) with an incidence of 3.9 (95% CI: 3.5–4.3). For osteoporosis the RR for steroid treatment was 1.2 (95% CI: 1.0–1.4; $P = 0.023$) with an incidence rate of 2.8 (95% CI: 2.5–3.1). For 18–45-year olds, RR for diabetes for steroid treatment was 1.4 (95% CI: 1.1–1.7; $P = 0.003$), and RR for osteoporosis was 1.6 (95% CI: 1.2–2.1; $P = 0.002$). In the total population treated with depot-steroids 1015 cases of diabetes and 640 cases of osteoporosis occurred during the period 1995–2011.

Time-dependency of risk in relation to treatment

Survival analyses indicated that the largest risk increase for diabetes and osteoporosis was seen within the two years following treatment with steroids (Figs. 1 and 2). These results were confirmed by a risk analysis of the interaction between steroid treatment and years (<2 years after treatment versus >2 years after treatment). Adjusted risk for diabetes within first two years after treatment was 1.4 (95% CI: 1.2–1.7; $P = 0.007$).

Diabetes follow-up

Follow-up data for diabetes treatment showed that 92.3% of patients in the steroid group and 93.3% of patients in the immunotherapy group received anti-diabetic treatment during the first year after diagnosis ($P = 0.658$). At the one-year follow-up, the percentages for patients with diagnosed diabetes who were still receiving anti-diabetic treatment in the steroid and immunotherapy groups were 56.9% and 62.2%, respectively ($P = 0.180$). At the two-year follow-up the corresponding percentages were 40.1% and 51.2% respectively ($P = 0.004$).

Discussion

We confirmed our previous findings that a large proportion of individuals with allergic rhinitis are treated with depot-injections of corticosteroids regularly throughout the pollen season (Table 2). Furthermore, we demonstrated a 50% increased risk of being diagnosed with diabetes ($P < 0.001$), and a 20% increased risk of being diagnosed with osteoporosis ($P = 0.023$) among individuals treated with steroids when compared to immunotherapy (Table 3). In a subpopulation of 18–45-year-old individuals, we demonstrated a similar risk of developing diabetes (40%; $P = 0.003$), whereas the risk of being diagnosed with osteoporosis

Table 3 Incidence and risk of steroid-associated diseases. Numbers in parentheses are 95% confidence intervals. Relative risks are adjusted for calendar-time, age, sex, and asthma diagnosis.

Diagnose	Steroid-treated	Count (all)	Incidence per 1000 patient years	Relative risk	P-value	Count (18–45 years of age)	Incidence per 1000 patient years	Relative risk	P-value
Diabetes	No	283	1.8 (1.6–2.1)	1.0	.	175	1.7 (1.5–2.0)	1.0	.
	Yes	404	3.9 (3.5–4.3)	1.5 (1.3–1.8)*	<0.001	191	2.4 (2.1–2.8)	1.4 (1.1–1.7)*	0.003
Osteoporosis	No	202	1.3 (1.1–1.5)	1.0	.	98	0.9 (0.8–1.1)	1.0	.
	Yes	294	2.8 (2.5–3.1)	1.2 (1.0–1.5)*	0.023	106	1.3 (1.1–1.6)	1.6 (1.2–2.1)*	0.002
Respiratory tract infection	No	253	1.6 (1.5–1.9)	1.0	.	166	1.6 (1.4–1.9)	1.0	.
	Yes	240	2.3 (2.0–2.6)	1.2 (1.0–1.4)	0.063	139	1.8 (1.5–2.1)	1.1 (0.9–1.4)	0.382
Tendon rupture	No	11	0.1 (0.0–0.1)	1.0	.	8	0.1 (0.0–0.2)	1.0	.
	Yes	13	0.1 (0.1–0.2)	1.3 (0.6–3.0)	0.555	7	0.1 (0.0–0.2)	1.1 (0.4–3.2)	0.847

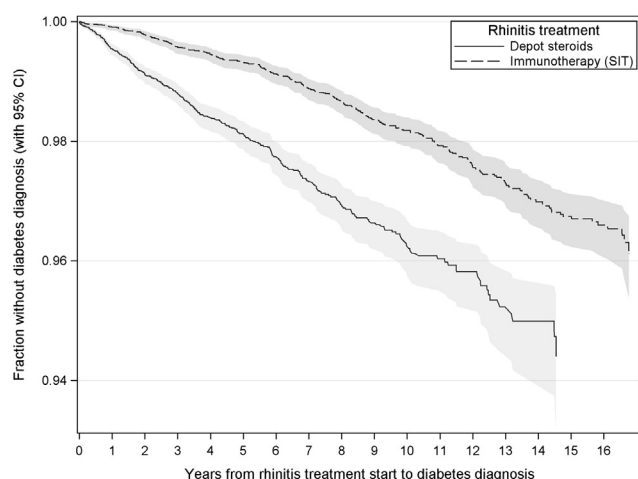


Figure 1 Time-dependent risk of diabetes when subjects receive depot-steroid injections for rhinitis, when compared to immunotherapy. Risks adjusted for calendar-time, sex, age, and asthma diagnosis.

among the young group was 60% increased and thus even more pronounced (Table 3). These data suggest that of the 1015 cases with diabetes and 640 cases with osteoporosis related to depot-steroid treatment, 451 cases of diabetes and 213 cases of osteoporosis might have been prevented during the years 1995 and 2011 if rhinitis was treated with immunotherapy instead of steroids.

We believe that this study provides strong evidence for the association between depot-steroid injections and increased risk of the unwanted side-effects of osteoporosis and diabetes. Although incidence rates were generally low, the relative increments in the diabetes and osteoporosis diagnoses were surprisingly significant and tended to increase with the length of treatment (Figs. 1 and 2). With respect to diabetes, the follow-up data showed that immediately following a diagnosis there was no difference

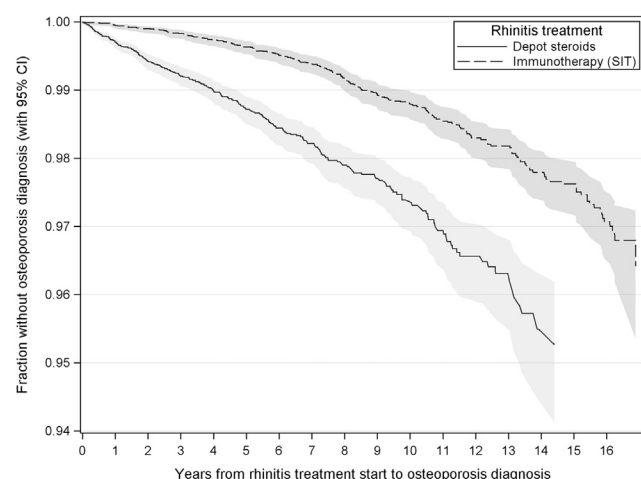


Figure 2 Time-dependent risk of osteoporosis when subjects receive depot-steroid injections for rhinitis, when compared to immunotherapy. Risks adjusted for calendar-time, sex, age, and asthma diagnosis.

between steroid and immunotherapy treated individuals in the use of anti-diabetic treatments. Among the cases diagnosed with diabetes based on the prescription of glucose lowering drugs, the numbers who remained on glucose lowering treatment decreased in both groups during the two years observation period, ending up at only 40% and 51% for steroids and SIT respectively ($P = 0.004$). This difference indicates that steroid-induced diabetes to a large extent is self-limiting and thus disappears after steroid treatment is discontinued. Surprisingly, no increased risk of respiratory-tract infections was demonstrated with steroid treatment. One reason for this may be that the diagnosis of infections applied in this study required hospitalisation, and thus only the most severe cases with infections are detected. Interestingly, no increased risk with steroid treatment was observed for tendon rupture, possibly because of the low number of cases (24 out of 47,382 individuals).

In our initial analysis we also investigated the risk of neoplasms and cancer, and found increased relative risks for both in the group receiving steroid treatment. As this random finding surprised us, we decided to exclude individuals diagnosed with cancer to eliminate the possibility that the cancer disease by itself would result in increased steroid treatment. However, it cannot be ruled out that the immunosuppressive effect of repeated steroid injections might interfere with normal cell-lifecycles and thus inducing cancer.

A limitation of this study is that although increasing prevalence of osteoporosis and diabetes is observed among rhinitis patients treated with depot-steroids, we do not know if the cumulative effect of several steroid injections plays a role. However, our previous findings indicate that individuals that have become adjusted to treatment with depot-steroids seldom change to immunotherapy at a later stage [6].

A general potential bias of any epidemiological study based on retrospective registry data is contamination in the group by other diseases and/or incorrect diagnosis. Whereas the diagnosis captured in the Danish National Patient Registry are generally reliable [15], diagnosis based on prescription drugs can be more troublesome as there is an assumption that drugs are used appropriately by doctors as well as patients. However, the diagnosis of allergic rhinitis is made only rarely in a hospital setting, and is much more common in general practice and specialist practice outside hospital. For this reason, unfortunately, the diagnosis of allergic rhinitis does not appear in the Patient Registry. This issue does not, however, appear to concern individuals undergoing specific immunotherapy, assuming that immunotherapy is not used on non-allergic individuals. Consequently, the accuracy of the rhinitis diagnosis may mainly concern the steroid treated individuals. The elimination of rheumatic as well as chronic obstructive pulmonary diseases and the introduction of prescription antihistamines or intranasal corticosteroids as a prerequisite only refine the population, thus ensuring a correct diagnosis.

Another potential bias is the significant differences in the mean age between steroid- and immunotherapy-treated individuals. As expected, the mean age difference in the total population was around ten years. Since the prevalence of most diseases increases with age, we decided

to try to minimise the bias by singling out a subgroup of 18–45-year-old individuals most likely to have atopic diseases and calculating incidence and risk for steroid-related diseases. Again we observed significant increases in both diabetes and osteoporosis, although with fading prevalence. These data all together does not suggest that the differences in age between groups may explain the extensive differences in diabetes and osteoporosis.

A possible confounder in our study approach is that doctors might initiate screening for osteoporosis and/or diabetes following treatment with steroids compared to immunotherapy which is not associated with the same risk factors. Accordingly, more individuals might be diagnosed when treated with steroids as a result of the screening. The extent to which this may have influenced the current results is unknown, but at least for diabetes, the issue may not be trivial due to our knowledge of the disease being very common and asymptomatic in its earliest stages, leaving around 50% of type 2 diabetes patients undiagnosed in most populations.

Another limitation of the study is that diabetes patients with mild disease not requiring glucose lowering medical treatments were not included in the study. As discussed in our previous publications using the definition of diabetes based on use of glucose lowering drugs [16,17], we believe that this definition include the majority of patients with diabetes in Denmark, and most importantly it includes the most severe cases. In that respect, is need to be emphasized that the diagnostic criteria for type 2 diabetes are arbitrarily defined, that the criteria have changed over the years gradually becoming more inclusive, and that the day-to-day variation of a diagnostic oral glucose tolerance test is around 40% meaning that some randomness exists as to whether a person with mild glucose intolerance is being diagnosed with diabetes or not.

In conclusion; generally the side-effects of corticosteroids are well documented [13,18]. Although some studies have suggested that depot-steroid injections are a safe alternative when treating allergic rhinitis [19], several others, including the international GA(2)LEN corporation and the ARIA guidelines [3,20], have disputed even the basic efficacy of steroids in treating rhinitis [21–23] compared to other treatment alternatives. Furthermore, there are confirmed reports of steroid-associated tissue necrosis [7,10], skin atrophy [9], reduction of cortisol levels [24], and suppression of the hypothalamic-pituitary-adrenal axis [11].

Conclusions

The use of depot-injection corticosteroids should be abandoned due to serious long-term side effects and be replaced by immunotherapy, as we have previously demonstrated that immunotherapy reduces the need for systemic-steroid injections [6] and the safety, and efficacy of immunotherapy has been documented in large-scale randomized placebo-controlled trials [4,25].

Conflict of interest

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