

Specific immunotherapy can greatly reduce the need for systemic steroids in allergic rhinitis

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Abstract

Background: Worldwide, more than 400 million individuals have allergic rhinitis, which has a significant impact on the individual's general health. Most patients self-medicate with over-the-counter drugs, but severe cases need treatment with topical corticosteroids and/or immunotherapy (SCIT). Although the ARIA guidelines discourage the use of systemic corticosteroids, this treatment is often used by general practitioners.

Aims: To investigate the use of systemic steroids to treat allergic rhinitis in Denmark and the role of SCIT as an alternative.

Methods: A retrospective study based on Danish National Registry databases 1995–2009. Steroid use was defined as a minimum of one steroid injection during April–July for at least three consecutive years. SCIT treatment against grass (*Phleum pratense*), birch (*Betula verrucosa*) or both was included.

Results: Overall, 39 173 individuals were treated with either SCIT or steroids; 93.1% received only steroids, and 6.9% received SCIT and/or steroids. The steroid-to-SCIT ratio was 14 : 1 ($P < 0.0001$). The mean annual steroid injections were 1.6 in the steroid-only group and 1.0 in the SCIT group ($P < 0.0001$). Of the SCIT-treated individuals, 84% did not need steroids after SCIT treatment ($P < 0.0001$). The hazard ratios of receiving steroids after SCIT against grass, birch or both were 0.65, 0.83 and 0.72, respectively ($P < 0.0001$), when compared with the steroids-only group. The maximum hazard reduction was obtained if patients responded well to SCIT treatment after one to 3 years.

Conclusions: Systemic steroid injections are still widely used to treat pollen allergy. Specific immunotherapy can greatly reduce the need for steroids.

Allergy is an increasing problem in western societies, with children and young adults being particularly affected (1, 2). About 400 million people worldwide have allergic rhinitis (rhinitis) (3). Moderate and severe rhinitis has a significant impact on the individual's general health (4), often resulting in sick leave and repercussions on school or workplace performance (5–7). In Denmark, at least 20% of the population aged 15–41 years has skin-prick-test-verified rhinitis (8). Awareness of allergic disease is important for general health, not least in the 60% of patients with both asthma and rhinitis; incorrect classification of rhinitis and asthma can prevent the start of relevant treatment (9, 10). Accordingly, knowledge of rhinitis is crucial, especially because a potentially curative treatment is available in the majority of cases.

For symptoms progressing from mild/intermittent to severe/persistent, rhinitis patients should first be treated with oral antihistamines or leukotriene receptor antagonists (or a combination), then with intranasal steroids (with an optional combination of any/all of the previously mentioned treatments) and lastly with short-term systemic steroids. Immunotherapy should be considered from moderate/intermittent and mild/persistent symptoms through to severe/persistent symptoms. Large depot injections of steroids are inadvisable owing to the well-known potential side effects (11, 12).

Although antihistamines, leukotriene receptor antagonists and topical steroids are widely used and are generally well tolerated, they are all purely symptomatic and seldom sufficiently alleviate severe symptoms. Accordingly, general

practitioners tend to subscribe systemic steroids, which are the most potent symptomatic treatment, despite steroids being indicated only for short-term treatment of difficult cases of rhinitis.

The use of systemic steroids is somewhat surprising as immunotherapy is available as an alternative treatment. Several studies have demonstrated the symptom-alleviating effect of immunotherapy as well as its generally good tolerability and safety profile. Immunotherapy is the only disease-modifying treatment available; moreover, it has the potential to cure rhinitis for a prolonged period.

The aims of the present nationwide study were to investigate the use of systemic steroids administered as depot injections for rhinitis treatment in Denmark and to illustrate the impact of subcutaneous immunotherapy (SCIT) in relation to the use of steroids in allergic rhinitis to assess the potential steroid-reducing benefits of immunotherapy.

Methods

Design

The study was designed as a registry-based, retrospective study using Danish National Registry databases. All Danish citizens and residents in Denmark are assigned a permanent, personal and unique civil-registration number, which enables individual linkage of nationwide registers. The main registry used for this study was the Danish Register of Medicinal Product Statistics (here termed prescription register, NPR), which contains all information on dispensed prescriptions from Danish pharmacies since 1995, where drugs are classified according to the Anatomical Therapeutic Chemical (ATC) system. Because the government-financed healthcare system partially reimburses drug expenses, all Danish pharmacies are obliged to register all dispensed drug prescriptions, ensuring a valid and accurate register (13). The prescription register was combined with the Central Person Registry to ascertain fatalities during the study period.

Study population

The data used in this study originated from the NPR based on data collected during 1995–2009. Inclusion criteria were (1) SCIT treatment against grass (*Phleum pratense*), birch (*Betula verrucosa*) or both; (2) only one start-up kit for each unique allergen (i.e. no failed updosing) followed by at least one maintenance kit; (3) only kits with aluminium solution; and/or (4) at least one steroid injection during April–July for three consecutive years during 1995–2009.

Sublingual immunotherapy treatment with Grazax (the only product registered in Denmark) was omitted from the analyses, because Grazax was only to a limited extent launched in 2007 with major restrictions on indications, whereas the release was more general from 2010. In total, no more than 55 individuals in Denmark received SLIT treatment for at least 1 year during 2007–2009, and only one of them completed the recommended treatment length of 3 years.

Exclusion criteria were (1) SCIT against any allergen other than grass or birch; (2) therapy kits in aqueous solution; (3) more than one SCIT updosing during 1995–2009; and (4) SCIT updosing started outside 1995–2009.

Individuals treated with systemic corticosteroid (steroids)

All individuals were included who had a prescription with an ATC code beginning with H02 and the common name of the only prolonged effect (depot) steroid drugs available in Denmark, namely 'Depo-medrol', 'Diprosan' or 'Lederspan'.

Individuals treated with specific immunotherapy

All individuals were included who had a prescription with an ATC code beginning with V01AA (i.e. allergen extracts) and the common name of the only therapeutic drug available in Denmark for specific immunotherapy (SCIT) against grass [*'ALK (225) Phleum pratense' (ALK225)*] or birch [*ALK108 Betula verrucosa (ALK108)*].

Symptomatic treatment

Leukotriene receptor antagonists, intranasal corticosteroids and oral antihistamines were included as symptomatic treatment. The vast majority of antihistamines are available as over-the-counter drugs, and only the smaller part of oral antihistamines available as prescription drugs are listed in the NPR. Only drugs registered in the NPR could be included in this study. All intranasal corticosteroids and all leukotriene receptor antagonists were included.

Statistics

All data were extracted and examined using the SAS Statistical Software Package version 9.2 (SAS Institute Inc., Cary, NC, USA) for Windows. Years in SCIT were calculated as the number of days from first start-up kit to last maintenance kit plus 300 days (i.e. a maintenance kit will last about 300 days), divided by the average number of days in a year: 365.2. Time to event was analysed with survival-type models. Graphs of time to event used Kaplan–Meier estimates. Hazard ratios were calculated with proportional hazard models.

P-values < 0.05 were considered significant.

Ethics

The Danish Data Protection Agency approved the present study (2007-58-0015, int. ref: GEH-2010-001). Register-based retrospective studies do not require ethical approval in Denmark.

Results

Total population

In total, 1 744 629 individuals received steroid injections or SCIT during 1995–2009. Of these, 1 705 456 (97.8%) did not

have three steroid injections over three consecutive years or SCIT treatment during the same period and were therefore excluded (the 'rheumatic group'); 39 173 (2.2%) had at least three steroid injections over three consecutive years and/or received SCIT treatment and were included for further analyses (the 'allergic group') (Table 1). None of the 39 173 died during 1995–2009.

The distribution of the total number of steroid injections during 1995–2009 showed that the 'rheumatic group' received injections evenly distributed over each month of the year (Fig. 1), with an average of 4 993 (95% CI: 4783–5204)

steroid injections per month. For the 'allergic group', the average number of steroid injections was 2181 (95% CI: 1773–2589) per month. The distribution of injections for the 'allergic group' was skewed towards an increase beginning in April, peaking in June and then dropping to almost average levels in July (Fig. 1). The maximum mean number of steroid injections was reached in June with an average of 7607 for the 'rheumatic group' vs 9113 for the 'allergic group' ($P = 0.0041$). In the 'rheumatic group', the male-to-female ratio was 1 : 0.8, and for the 'allergic group', the ratio was 1 : 1.4 ($P < 0.0001$).

Table 1 Population overview ('Steroid dependent' is defined as individuals who had at least one corticosteroid injection during April–July for at least three consecutive years 1995–2009)

		Male		Female		Excluded (%)	Included (%)
SCIT		Steroid dependent (%)	Nonsteroid dependent (%)	Steroid dependent (%)	Nonsteroid dependent (%)		
None		21 269 (1.2)	741 637 (42.5)	15 208 (0.9)	946 168 (54.2)	1 687 805 (96.7)	36 477 (2.1)
Birch, grass or both	Completed	605 (<0.1)	896 (<0.1)	336 (<0.1)	859 (<0.1)		2696 (0.2)
	Updosing not completed	225 (<0.1)		174 (<0.1)		399 (<0.1)	
	Only steroid after SCIT	12 (<0.1)	64 (<0.1)	16 (<0.1)	29 (<0.1)	121 (<0.1)	
Other (cat, dog, house dust mite, etc.)		888 (<0.1)	8003 (0.5)	584 (<0.1)	7656 (0.4)	17 131 (1.0)	
Total		22 999 (1.3)	750 600 (43.0)	16 318 (0.9)	954 712 (54.7)	1 705 456 (97.8)	39 173 (2.2)
						Total individuals	1 744 629 (100.0)

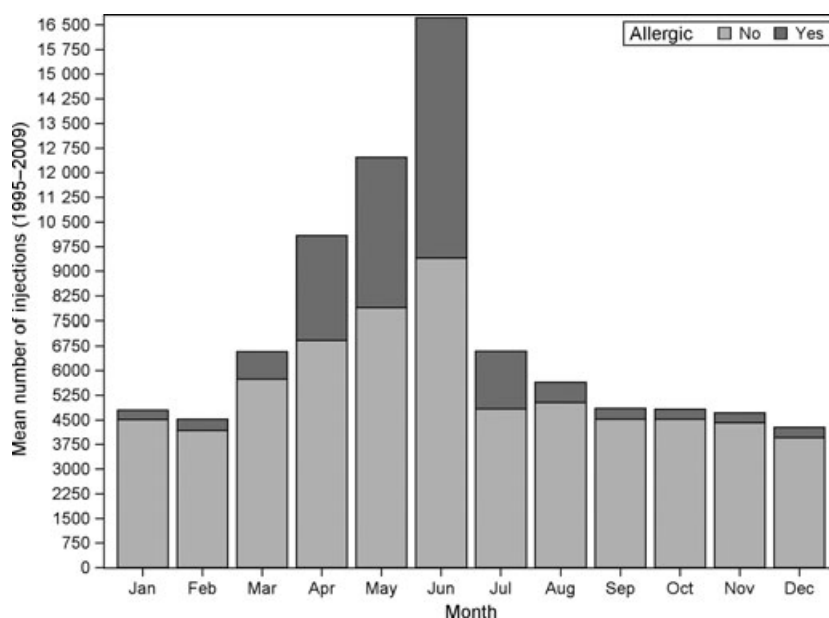


Figure 1 Steroid injections during 1995–2009; 'allergic' is defined as an individual receiving at least three injections of

systemic corticosteroids during April–July over three consecutive years.

The number of consecutive steroid injections (defining the 'rheumatic'/'allergic' group) was adjusted with both two and 4 years as definition. Three years was found to be the most appropriate, based on the shape of Fig. 1. We also excluded the nonsteroid-dependent SCIT group (869 males and 859 females), which did not change the overall trend in the data.

Systemic steroid injections increased from 1995 to 2000, remained high from 2000 to 2007 and then decreased rather rapidly from 2007 to 2009. Intranasal corticosteroids remained stable from 1995 to 2007 and then increased from 2007 to 2009. Prescription oral antihistamines topped in 1998 and then decreased in 1998–2001, remained stable in 2001–2007 and finally increased in 2007–2009. Leukotriene receptor antagonists were introduced in 1998 and then increased slightly all the way to 2009. Specific immunotherapy increased slowly from 1995 to 2003. In 2003, a sudden increase in side effects because of uncertain guidelines in

Denmark caused the treatment to drop in 2003–2004. From 2004–2009, a slight increase was seen again. Overall, the drop in systemic steroids in 2007–2009 corresponds to an increase in nonsystemic steroid symptomatic treatment in the same period (Fig. 2).

Annual seasonal corticosteroid injections in relation to SCIT

Of the 39 173 individuals included, 36 477 (93.1%) received only steroid injections and no SCIT; 2696 (6.9%) received SCIT for birch, grass or both, of whom 941 were also 'steroid dependent', that is, had at least one steroid injection during April–July for three consecutive years (Table 1).

The mean annual steroid injections during April–July in the group that received steroid injections only were 1.6 injections (95% CI: 1.5–1.6). For the group receiving SCIT against grass, birch or both, the mean annual steroid injection use was 1.0

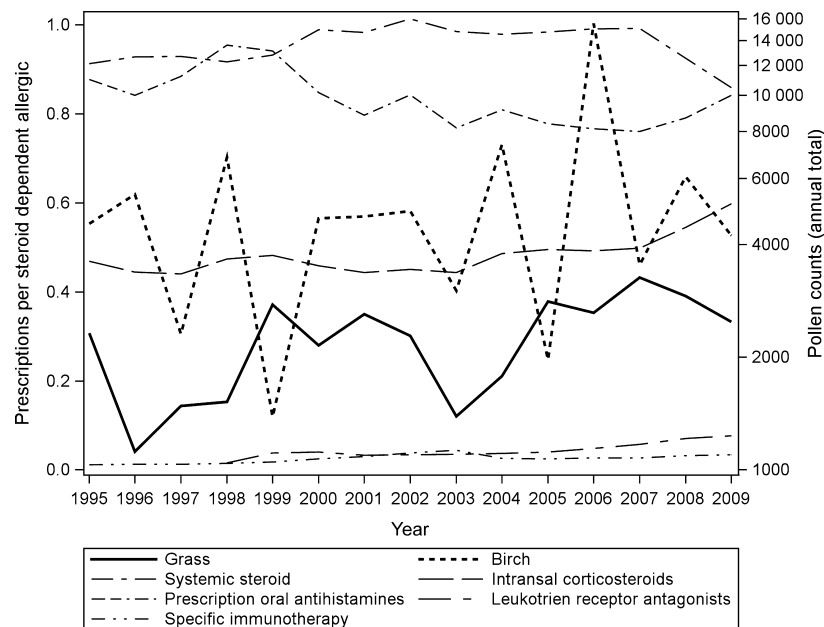


Figure 2 Overall trend in allergy-related treatment alternatives for pollen-allergic individuals during 1995–2009. Only prescription oral antihistamines are shown. Specific immunotherapy includes birch

and grass. Pollen counts are kindly provided by the Danish Meteorological Institute (<http://www.dmi.dk>) and Asthma and Allergy Denmark (<http://www.astma-allergi.dk>).

Table 2 Annual systemic steroid injections before and after SCIT treatment

SCIT treatment	N Obs (%)	Died between 1995 and 2009 (% of N Obs)		Mean number of injections	95% CI for mean	Mean change (before/after SCIT)
		$P < 0.0001$	Before/after SCIT			
None	36 477 (93.1)	1788 (4.9)	Before	1.6	1.5–1.6	–
Phleum prat.	1383 (3.5)	6 (0.4)	Before	1.0	1.0–1.0	–0.8 (95% CI: –0.8 to –0.8)
			After	0.2	0.2–0.2	$P < 0.0001$
Betula verr.	529 (1.4)	3 (0.6)	Before	0.8	0.8–0.9	–0.7 (95% CI: –0.8 to –0.7)
			After	0.1	0.1–0.1	$P < 0.0001$
Phleum prat. and Betula verr.	784 (2.0)	10 (1.3)	Before	1.0	0.9–1.0	–0.8 (95% CI: –0.9 to –0.8)
			After	0.2	0.1–0.2	$P < 0.0001$

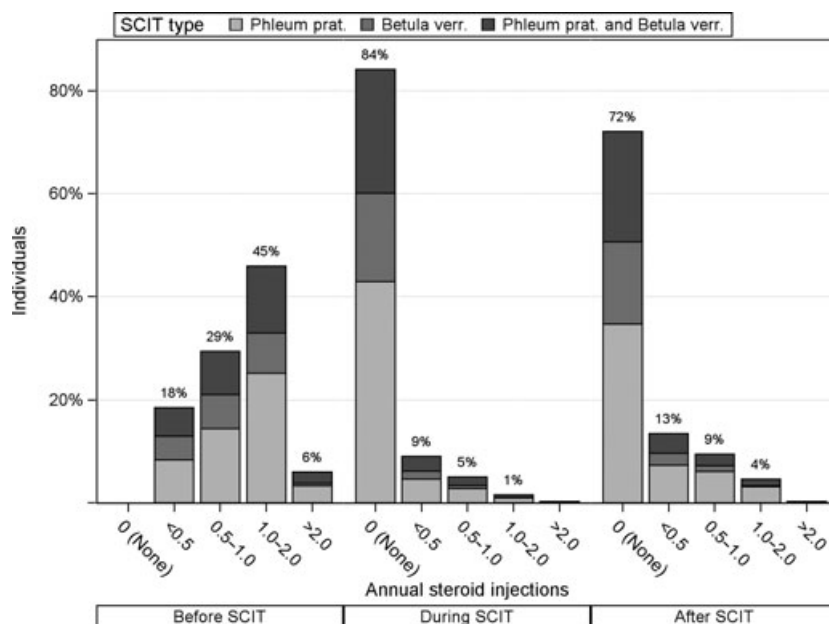


Figure 3 Average annual steroid use in relation to SCIT treatment. Most steroid use ceases after SCIT treatment. Colour

coding distinguishes between SCIT for Phleum prat., Betula verr., or both.

(95% CI: 1.0–1.0), 0.8 (95% CI: 0.8–0.9) and 1.0 (95% CI: 0.9–1.0), respectively (Table 2). All three SCIT groups showed significant drops between 0.7 and 0.8 in annual steroid use after SCIT treatment ($P < 0.0001$; Table 2).

In the SCIT group, 605 males and 859 females were steroid dependent and received steroid injections annually during April–July. Of these individuals, 84% received no steroid injections during SCIT treatment and 72% remained off steroids after SCIT treatment ended (Fig. 3).

Risk of receiving a corticosteroid injection after completed SCIT treatment

To assess the risk of receiving a steroid injection after completed SCIT treatment, the 2696 SCIT-treated individuals were included in a time-to-event analyses at the time of their last SCIT maintenance. The response was defined as the time from entry until the event occurred (i.e. a steroid injection during April–July), or the individual was censored (i.e. reached 31 December 2009 without receiving a steroid injection or died). The 36 477 who received only steroid injections were included at the time they were defined as steroid dependent (i.e. had received at least one steroid injection during April–July for three consecutive years). Event and censoring in this group were done using the same criteria as in the SCIT group.

For the group receiving SCIT against grass, the risk of receiving a steroid injection after SCIT treatment completion was the lowest for the group receiving 1 year of SCIT treatment, with a significant and gradually increasing risk with increasing length of treatment (Fig. 4). The group receiving SCIT against grass and birch showed a similar pattern. How-

ever, the group receiving SCIT against birch had no significant difference between one, three and 5 years of treatment.

The corresponding Cox regression hazard ratios showed a significant decrease in risk for SCIT against grass, birch or both for all treatment lengths, except 5 years' SCIT against both birch and grass (Table 3). The highest reduction was obtained from 1 year of SCIT against grass (HR: 0.65; 95% CI: 0.59–0.72), and the risk reduction diminished with increasing length of SCIT treatment for all groups. Again, the birch group had no significant difference between the different lengths of SCIT treatment.

Discussion

We showed that a large group of individuals received systemic steroid annually during April–July, with a peak in June. If pollen-allergic individuals are defined based on either (1) treatment with SCIT or (2) at least one steroid injection during April–July for a minimum of three consecutive years, 39 173 individuals had rhinitis triggered by pollen during 1995–2009. Of these individuals, only 2696 (6.9%) were treated with SCIT compared with 36 477 (93.1%) treated with steroid injections only.

The symptomatic treatment with subscription drugs (steroids, some oral antihistamines, leukotriene receptor antagonists) showed fluctuations over time, but no apparent visual correlation with pollen counts. Interestingly, from 2007 and onwards, there seems to be a paradigm shift from systemic steroid injections towards nonsystemic steroid symptomatic treatment. No sure increase in immunotherapy could be observed in the same period (Fig. 2). Ideally, the graph in Fig. 2 should show actual days-in-treatment, instead of the number of subscriptions. Unfortunately, the NPR does not

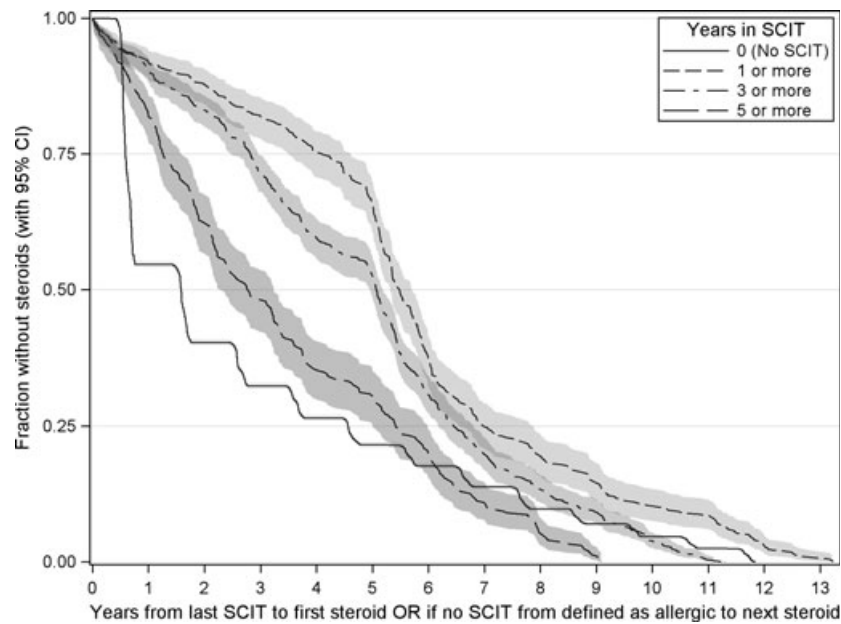


Figure 4 Grass (*Phleum pratense*): Kaplan–Meier curve of time from last SCIT to first steroid injection during April–July (with 95% confidence intervals as bands).

Table 3 Hazard ratios for receiving another steroid injection after immunotherapy (SCIT) when compared to individuals that did not receive SCIT (i.e. the “None” group)

SCIT type	Years in SCIT	Hazard ratio	95% CI	P-value
None	0 (No SCIT)	1.00	–	–
Phleum prat.	1 or more	0.65	0.59–0.72	<0.0001
Phleum prat.	3 or more	0.80	0.74–0.86	<0.0001
Phleum prat.	5 or more	1.06	0.95–1.19	0.3123
Betula verr.	1 or more	0.83	0.68–1.02	<0.0001
Betula verr.	3 or more	0.87	0.78–0.98	0.0221
Betula verr.	5 or more	0.98	0.83–1.15	0.7803
Phleum prat. and Betula verr.	1 or more	0.72	0.62–0.83	<0.0001
Phleum prat. and Betula verr.	3 or more	0.89	0.80–0.98	0.0236
Phleum prat. and Betula verr.	5 or more	1.09	0.95–1.24	0.2160

contain information about dose and frequency for the individual prescription.

We were able to show that individuals treated with SCIT against birch, grass and a combination of both had the largest decrease in steroid injections when receiving 1 year of treatment; the decrease diminished with increasing length of treatment from 1 to 5 years. Lastly, we showed that patients who no longer needed steroid injections after the first year of immunotherapy retained this lack of need for longer than those who required immunotherapy for up to 5 years.

The number of rhinitis patients was low, but it covered only those treated with prescribed medication and did not include the vast majority presumably using over-the-counter medication. The numbers indicate that for every 15 patients with rhinitis, only one is treated with SCIT, whereas 14 are regularly prescribed systemic steroids during the peak pollen season – in direct opposition to the ARIA guidelines.

The study showed that on average 1.6 steroid injections are prescribed annually for those with rhinitis. The SCIT against grass, birch or both can postpone the need for further steroids for about 2 years, providing the initial treatment is stopped within the first year. However, all groups tended towards an increasingly short steroid-free period with increasing length of SCIT treatment (1, 3, 5 years), probably because individuals needing long-term SCIT treatment (i.e. more than 3 years) are not responding so well to the treatment.

Minimizing the need for steroid treatment against rhinitis is probably a desirable outcome because numerous studies have shown serious side effects of long-term systemic steroid use (14). Nevertheless, to our knowledge, treating rhinitis with steroid injections once or twice a year has not been shown to have adverse effects. The allergologists’ general rejection of this highly effective but strictly symptomatic treatment seemingly stems from the term ‘do no harm’ (15–19).

The safety and efficacy of SCIT treatment have been demonstrated numerous times. The treatment can not only postpone, but also sometimes prevent development and/or exacerbation of asthma and rhinitis in children. No similar benefits have been associated with steroid injections. Because rhinitis is highly associated with asthma, this should be taken

into consideration when GPs choose between continuous use of steroids and SCIT treatment.

Further studies are needed to evaluate the safety and efficacy of both short- and long-term steroid treatment. Annual steroid injections still seem to be the 'drug-of-choice' for many GPs when treating rhinitis in young adults, with a 14 : 1 ratio. Ideally, such studies should be performed as randomized placebo-controlled double-blinded, and focus on the possible differences in safety and efficacy of SCIT, SLIT and steroid injections.

The main limitation of this study is the definition of rhinitis patients treated with steroid injections. The definition chosen (i.e. at least one steroid injection during April–July for a minimum of three consecutive years) could be unreliable because we did not know the real reason why these patients received steroids. It could have been to treat another disease, most likely a rheumatic illness. Figure 1 demonstrates this, as the 'nonallergic' group still has a slight upward slope during April–June.

Another limitation is the exclusion of all participants receiving SCIT treatment beginning before 1 January 1995 and those who received only uposing during 1995–2009.

A third limitation is the lack of proper sublingual immunotherapy (SLIT) data. Owing to delays in general government approval, the NPR does not contain proper data for SLIT until from 2010 and onwards. And because of the registry legislation in Denmark, the data have not yet been released for research use. SLIT may affect the need for steroid injections in a similar pattern, and further studies should examine the role of SLIT in relation to steroids.

Finally, we did not include the possibility that a large group of steroid-treated individuals could achieve the same benefit with intranasal corticosteroids (ICS), which are also prescription drugs in Denmark. The ARIA guidelines clearly state that ICS should be tried before moving to SCIT, and therefore, we do not know whether SCIT was strictly indicated to treat rhinitis.

Rather than the emphasis being on the efficacy and safety of steroids, it should be on what benefits the patients gain from steroids compared with immunotherapy.

Conclusion

The use of steroids to treat rhinitis is still highly prevalent in Denmark. SCIT has been shown to significantly reduce the need for steroids in individuals with rhinitis, but only if an appropriate effect of treatment is obtained within the first three treatment years.

Because the safety and efficacy of steroids in treating rhinitis remain to be fully established, in contrast to SCIT, which has the added benefit for children of inhibiting development and exacerbation of asthma and allergy, we recommend SCIT as an alternative to steroids for the treatment of rhinitis.

Conflict of interest

The authors have received financial support for their research from ALK (Hoersholm, Denmark).

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