ORIGINAL ARTICLE

Quality Assurance of Allergen-Specific Immunotherapy During a National Outbreak of Anaphylaxis: Results of a Continuous Sentinel Event Surveillance System

F Madsen,[1] L Frølund,[2] M Christensen,[3] A Frost,[4] U Søes Petersen[5]

[1] Allergy and Lungclinic Helsingør. Sct. Olai Gade 39 1, 3000 Helsingør, Denmark
[2] Allergy and Lungclinic Hellerup, Bernstorffsvej 20, 2900 Hellerup, Denmark
[3] Lung and Allergy Clinic Aabenraa, Madevej 11, 6200 Åbenrå, Denmark
[4] Specialist Clinic Hellerup, Hans Edvard Teglersvej 9, 2920 Charlottenlund, Denmark
[5] Roskilde Hospital, Department of Internal Medicine, Roskilde, Roskilde Sygehus Køgevej 7-13, 4000 Roskilde, Denmark

Abstract

Background and Objective: Subcutaneous allergen-specific immunotherapy (SCIT) is an effective treatment for patients with allergic asthma and rhinitis. SCIT may be performed in many different ways and good safety profiles have been published. Other studies, however, have reported high frequencies of severe adverse events (SAEs) but without identifying the causes. After an increase in SCIT-related SAEs in Denmark between 2003 and 2004, strict performance regulations were imposed by the authorities. Because safety data from national databases were not available, we implemented a surveillance system aimed at identifying the causes of SAEs.
Methods: We prospectively registered the number of injections and SAEs during SCIT. A slow up-dosing regimen was used and adherence to international standards was optimized.
Results: No SAEs were observed with 28 992 injections. The maximal risk per injection was calculated at <1.3 per 10 000 injections.
Discussion: Our results confirm the good safety profile of SCIT. We applied a sentinel SCIT surveillance system that may offer a means of guaranteeing safety by providing online feedback to all participating clinics when SAEs occur in order to explore their causes by root course analyses performed by all participants. Furthermore, such quality assurance documentation may facilitate wider acceptance of SCIT by health care administrators, clinicians, and patients.

Key words: Safety. Risk management. Allergen immunotherapy. Risk. Immunotherapies. Allergen. Sentinel surveillance.

Resumen

Antecedentes y objetivo: La inmunoterapia alérgeno-específica subcutánea (ITSC) es un tratamiento efectivo para pacientes con asma y rinitis alérgica. La IAES podría realizarse de muchas maneras diferentes y se han publicado perfiles buenos de seguridad. Otros estudios, sin embargo, han comunicado alta frecuencia de efectos adversos graves (EAGs) pero sin causas identificadas. Después de un aumento de las EAGs relacionadas con ITSC en Dinamarca entre 2003 y 2004, las autoridades han impuesto estrictas regulaciones de actuación. Dado que no se encontraban disponibles los datos de seguridad de las bases de datos nacionales, implementamos un sistema de vigilancia destinado a identificar las causas de EAGs.
Métodos: Registramos prospectivamente el número de inyecciones y los EAGs durante SCIT. Se empleó un régimen de reducción de dosis y optimizó la adherencia a los estándares internacionales.
Resultados: No se observaron EAGs con 28 992 inyecciones. Se calculó el riesgo máximo por inyección siendo <1,3 por 10 000 inyecciones.
Discusión: Nuestros resultados confirman el perfil de buena seguridad de la ITSC. Aplicamos un sistema de vigilancia centinela de ITSC

que podría ofrecer un medio de seguridad garantizada facilitando una retroalimentación en línea a todos los participantes clínicos cuando los EAGs ocurren para explorar sus causas mediante el análisis de la causa raíz por todos los participantes. Además, esta confirmación de la calidad en la documentación podría facilitar una aceptación más extensa de la ITSC por los administradores del cuidado sanitario, clínicos y pacientes.

Palabras clave: Seguridad. Manejo de riesgo. Inmunoterapia de alérgeno. Inmunoterapias. Alérgeno. Vigilancia centinela.

Introduction

There is ample evidence that subcutaneous specific allergen immunotherapy (SCIT) is an effective treatment for allergic rhinitis and asthma [1,2] (Cochrane reviews) and severe hymenoptera venom allergy [3]. Evidence of the same quality, however, is not available for the risk of severe adverse events (SAEs) during SCIT.

Whether SCIT is over- or underutilized is difficult to determine since the risk of SAEs seems to vary considerably, not only between countries, but also between settings [4]. International position papers have reported SAE frequencies ranging from less than 1% (conventional SCIT) to 36% (rush SCIT) [5].

At present there is no consensus on what constitutes an acceptable upper limit for the risk of SAEs during SCIT and it probably depends on the severity of the disease being treated and the likelihood of treatment success. Because risk monitoring has not formed an integral part of SCIT to date, the treatment has come under varying levels of pressure at different points in time following the observation of clusters of fatalities and SAEs.

Pressure from authorities has resulted in the imposition of strict performance regulations, which seems reasonable when there is clear evidence of substandard performance. These regulations, however, have had unintended effects in the United Kingdom [6] and in Denmark, where the number of patients offered SCIT fell. In Denmark the situation also led to a marked fall in the sales of vaccines [7].

The integration of safety monitoring into SCIT procedures would make it possible to identify centres where treatment has gone out of control. The expressions *out of control* and *in control* are common terms in safety and process monitoring. The implementation of treatment procedures, whether in SCIT or heart surgery [8,9] permits the continuous monitoring of quality. The most common way to do this is to establish control limits (such as 95% tolerance limits) between which the process has to run to be acceptable. With such a system, results (such as the number of patient deaths per surgeon or of SAEs per allergy vaccination clinic) can be continuously monitored. This set-up has the advantage that in the event of anomalies, only certain centers have to stop or correct their activities. Centers that are in control, in contrast, can continue their activities and even provide a benchmark for safety management procedures as data accumulate.

This study was initiated following an outbreak of unexplained SAEs in Denmark between 2003 and 2004 during SCIT with timothy grass. Following an increase in the number of SAEs reported to the Danish Medicines Agency, this agency, in conjunction with the Danish Society of Allergy and the allergen extract manufacturer, ALK-Abelló, recommended reducing the maximal dose of timothy grass and the Danish Health Board imposed stringent regulations on the performance of immunotherapy. It was agreed that the main problem was the lack of data on the number of patients treated, the true number of SAEs in Denmark, and the standard of physician performance. In 2004 it was decided to establish a national database for allergen-specific immunotherapy but this database has not yet been launched. Since SCIT treatment had gone out of statistical control in Denmark [10], we decided to implement a sentinel event surveillance system and an alert system for SAEs resulting from SCIT. This system is well known and is described in a position paper by the Joint Commission [11]. In the words of the Joint Comission, a sentinel event is "an unexpected occurrence involving death or serious physical or psychological injury, or the risk thereof. The phrase, "or the risk thereof" includes any process variation for which a recurrence would carry a significant chance of a serious adverse outcome. Such events are called "sentinel" because they signal the need for immediate investigation and response."

We report the set-up of this system and the results following 28 992 injections.

Methods

Five clinics participated in the study. The clinics had a relatively high SCIT volume compared to the national average based on figures from hospitals (National Health Board data) and primary care centers (national health insurance data), and all the participating physicians had at least 20 years' experience with SCIT. Every month, the clinics reported the number of patients that received SCIT, as well as the allergen type, number, and dose administered. Each SAE was defined according to the European Academy of Allergy and Clinical Immunology (EAACI) guidelines [12] as either grade 3 (non-life-threatening urticaria, angioedema, or asthma responding well to usual treatment) or grade 4 (life-threatening anaphylactic shock requiring more intensive treatment). All SAEs had to be reported to all participating clinics within 24 hours. The participating physicians had all declared that they were prepared to complete a full root cause analysis [13] of all SAEs, including on-site inspection within a week of each incident. (Because no SAEs occurred, however, this analysis was not necessary).

Grade 1 reactions (unspecific symptoms, probably not immunoglobulin E-mediated, such as discomfort, headache,

and arthralgia) and grade 2 reactions (mild systemic reactions, mild rhinitis or asthma, responding well to antihistamines and adrenergic ß2-agonists) [12] were not recorded because they do not constitute a health risk to patients or signal a safety problem, unless they develop into grade 3 reactions. The feasibility of including a safety study as an integrated part of SCIT was also a concern and therefore only grade 3 and 4 reactions were registered since grade 1 and 2 reactions are not considered to represent a health risk to the patient.

The results were e-mailed to the program coordinator every month and entered in a Microsoft Excel spreadsheet. A cumulative risk-adjusted mean chart analysis [9] of SAEs was also to be reported monthly. However, as no grade 3 or 4 reactions occurred, the statistical analysis was replaced with an estimate of the maximal risk of an event that had not yet occurred [14]. Within a few hours of receiving the data, the maximal risk was calculated and returned to the participating clinics. Analyses of data were performed with the statistical software package SPSS 14.0 (SPSS Inc. Chicago, Illinois, USA).

Immunotherapy Protocols and Technique

Only biologically standardized depot allergen formulations with a high content of relevant major allergens were used (Alutard; ALK-Abelló, Hørsholm, Denmark). SCIT was performed according to the recommendations of the allergen extract manufacturer and the Danish Medicines Agency specified in the corresponding summaries of product characteristics [15], with the following exceptions and clarifications. A slow up-dosing phase with 1-weekly injections and increments from 10 standardized quality units (SQ-U) to 100 000 SQ-U over 15 weeks was used, and a maintenance dose was to be given every 6 to 8 weeks for 3 to 5 years. Before the first injection, the patients were asked if they had experienced any symptoms (particularly rhinitis and asthma symptoms) since the previous visit and also if they had started any new medications. During the pollen season, 2 clinics (clinics 2 and 3) routinely reduced the allergen dose as recommended by EAACI [3,12]; the other clinics only reduced the dose if the patient showed symptoms during the pollen season. Ventilatory capacity was routinely measured in all patients prior to injections in order to exclude uncontrolled asthma, which is the main risk factor for death. The interval between injections of 2 or more allergens per patient on the same day was lower than the 30-minute interval recommended by the EAACI [3,12]. In our case, it was approximately 5 to 7 minutes, which is the time needed to check the patient–allergen match, prepare the dose, fill the syringe, and perform the injection(s). Doses were not divided when a new vial of allergen was used. The injections were performed subcutaneously at an angle of 10º to 25º (and not at 40º as recommended by the EAACI [3,12]), with a flow of 1 mL/min, a 1-mL syringe, and aspiration every 0.2 mL. If blood was aspirated, the injection was stopped and the patient was observed closely for the following 30 minutes. If no symptoms

Table 1. Number of Patients, Injections, Doses, and Allergens by Clinic

2004-2006 Clinic	Clinic 1	Clinic 2	Clinic 3	Clinic 4	Clinic 5	Total
Patients, No.	487	120	102	244	170	1123
Injections, No.						
Single allergen						
<10 000, SQ-U	660	187	240	598	410	2095
10 000-<100 000, SQ-U	1373	532	631	490	521	3547
100 000, SQ-U	3067	208	292	930	1547	6044
≥2 allergens						
< 10 000, SQ-U	681	402	501	436	92	2112
10 000-<100 000, SQ-U	741	1251	902	445	208	3547
100 000, SQ-U	117	323	235	924	556	3155
Total injections 2004-2006, No.	7639	2903	2801	3823	3334	20 500
2007-2008						
Patients, No.	293	85	118	170	175	548
Injections, No.	2485	1152	1475	1715	1665	8492
2004-2008						
Total injections 2004-2008, No.	10 124	4055	4276	5538	4999	28 992
Total patients 2004-2008, No.	780	205	220	414	345	1964

Abbreviations: SQ-U, standardized quality unit.

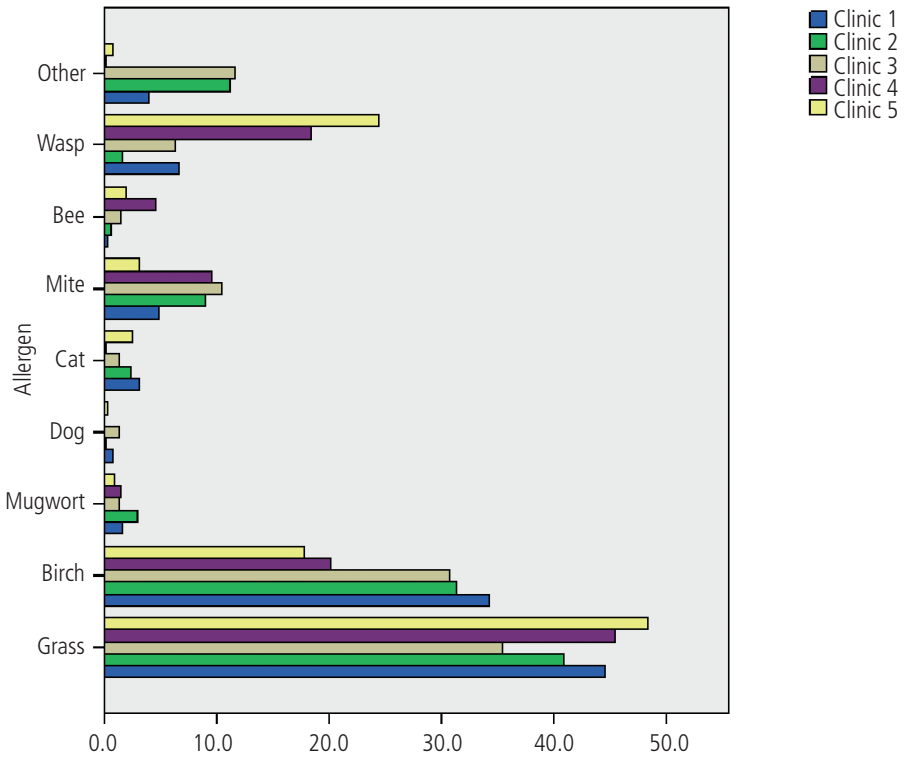

Figure 1. Distribution of allergens per clinic (20 500 injections per clinic, % of total).

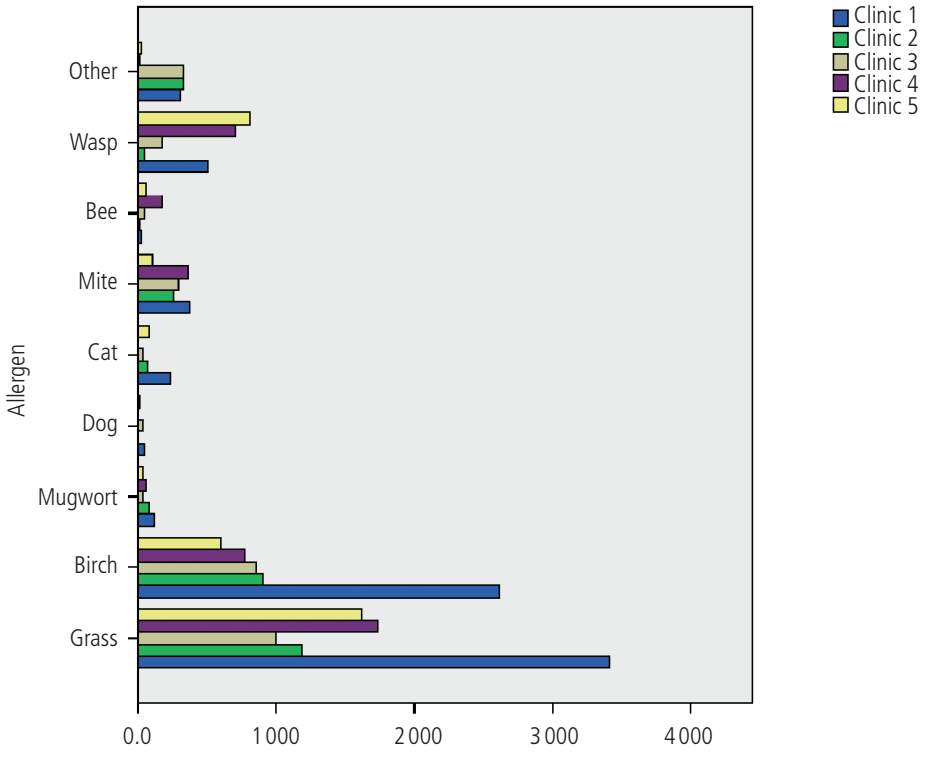

Figure 2. Number of allergens per clinic (20 500 injections per clinic, % of total).

Table 2. Absolute Risk of Severe Adverse Events[a] (SAEs) per 10 000 Injections

	No. of Patients	No. of Injections	No. of Injections per Patient	No. of SAEs	Risk (95% CI)
Tinkelman et al [23]	4578	346 251	76	98	2.8 (2.3-3.4)
Lin et al [19]	4810	513 368	107	139	2.7 (2.3-3.2)
Ragusa et al [22]	2206	192 505	87	115	6.0 (4.9-7.2)
Mellerup et al [24]	657	10 369	16	31	29.9 (20.3-42-4)
Nettis et al [21]	555	36 359	66	14	3.9 (2.3-6.5)
Moreno et al [20]	488	17 368	41	21	12.1 (7.5-18.5)
Dursun et al [25]	126	4705	37	38	81 (59-111)
Winther et al [18][b]	1038	30 728	30	124	40.4 (33.7-47.9)
Madsen et al (current study)	1671	28 992	17	0	0[c] (0.0-1.3)

[a] Grade 3 or 4 event according to the European Academy of Allergy and Clinical Immunology guidelines [12].
[b] According to an e-mail from the authors, the exact number of injections in the study could not be calculated. Based on data extrapolated from the yearly number of injections, the total number of injections may have been 30 728 at most.
[c] Maximal risk of an event that has not yet happened.

developed during this observation period, a new injection was performed. During the study, the syringes and injection sites were changed according to EAACI and the American College of Allergy Asthma and Immunology (ACAAI) guidelines: syringes with fixed needles were used instead of syringes with removable needles and the injection site was moved from the forearm and upper arm to the posterior part of the middle third of the upper arm at the junction of the deltoid and the triceps muscles exclusively.

Treatment with systemic antihistamines was recommended from 2007 onwards, but some patients preferred not to take any medication. Special attention was paid when questioning patients on allergy symptoms and changes in medication before injections.

From May 2004 to December 2006 detailed data were collected, as described above, and from January 2007 to January 2008 the total number of injections and patients were reported. All SAEs were still to be reported within 24 hours. This study did not require approval from the Danish ethics committee system.

Results

The number of patients, injections, and doses per clinic from May 2004 to January 2008 are reported in Table 1. Figure 1 shows the distribution of allergens per clinic. When more than 2 allergens were injected during a single visit, allergens number 3 and 4 were registered as "other combinations". Timothy and birch alone or in combination accounted for approximately two thirds of all injections (Figure 2). The distribution of allergens was comparable between clinics except for the number of wasp allergen injections, which was higher in the more rural clinics 4 and 5 (Figure 1). The number of "other combinations" was relatively higher in clinics 2 and 3 as they had a greater frequency of multiple (>2) allergen injections per patient (Figure 2).

No SAEs (grade 3 or 4 reactions) were observed (Table 2). Based on 28 992 injections, the maximal risk of a grade 3 or 4 reaction was estimated at 0.013%, which is the equivalent of fewer than 1.3 SAEs per 10 000 injections or 1 SAE per 7860 injections.

Discussion

The primary outcome of this study was the documentation of sentinel event surveillance as a simple measure to bring SCIT safety under control after a national outbreak of SAEs in Denmark. Such a surveillance system should be considered for routine inclusion in future immunotherapy standards. Existing national drug safety surveillance systems are considered inappropriate. Indeed, in response to criticism of its drug and medical device safety monitoring systems, the United States Food and Drug Administration is launching a new electronic system for identifying safety problems once a drug is on the market [16,17]. Such a system might solve many problems but until proven efficient we will have to rely on simpler but already proven systems.

The secondary outcome of this study might seem trivial but it is satisfactory. No SAEs occurred during the first 28 992 allergen injections performed and the calculated maximal risk of SAEs was 1.3 per 10 000 injections. The main strength of our study was its simplicity, fast feedback to participants, and rapid achievement of clinically useful data. Although international standards were largely followed, it is impossible to transcribe the sum of varying clinical judgements and subprocedures underlying our results. These medical subcultures are neither identical to the EAACI guidelines nor to the recommendations of the ACAAI; they rather follow more local traditions and recommendations, a fact which should be taken into consideration when extrapolating results. It is likely that these medical subcultures hold the key to further improvements in safety. In the present study, SCIT was the sole responsibility of specialists, and this is the case in many countries.

We expected a higher frequency of SAEs as, with the exception of our slower up-dosing schedule, our methods and patients were comparable to those described in previous Danish studies [18]. To compare the prevalence of SAEs between studies calls for some hesitation as details of methods used and definitions of SAEs may vary or be obscured. Table 2 summarizes the results from studies using different dosing schemes, allergen preparations, and techniques. Most SCIT studies performed have observed a SAE frequency of 6 per 10 000 injections [19-23]. Our results are broadly consistent with this figure, which is derived from large prospective and retrospective studies. In contrast, a large safety study by Winther et al [18] and a smaller one by Mellerup et al [24] observed a relatively high frequency of SAEs. In the second study, 3 clustered SCIT regimens were used. In 1 group, aqueous allergen extracts produced a high rate of side effects, but even in the largest group, treated with depot extracts, the number of SAEs was high. The use of aqueous extracts is generally believed to carry a high risk of systemic reactions, but this is not necessarily so [23]. Dursun et al [25] reported results for patients treated with rush, clustered, and conventional SCIT protocols. The frequency of SAEs was relatively high in all groups (Table 2) but grade 4 reactions were only seen during rush up-dosing. The study by Winther et al reported SAE data from 4 allergy clinics in Copenhagen, Denmark: 3 hospital-based clinics, which used different types of clustered SCIT, and 1 private allergy clinic, which used the same slow up-dosing protocol as we did. In the private clinic, the use of 3 to 4 allergens in a single patient during a visit was not unusual, and most of the data is derived from this clinic. Exact information on the frequency of SAEs is not reported; the majority of SAEs were classified as grade 3, but there were 8 grade 4 reactions. The findings reported do not support the theory that the number of allergens applied per patient is a major risk factor for SAEs in SCIT. The patients, allergens, and clinic set-ups are largely similar to those in our study, possibly suggesting that a fast up-dosing protocol may be a risk factor for SAE. This would be consistent with previous findings, such as those reported by Mosbech et al [26] in 2000. When dealing with SCIT, however, it is important to avoid violation of international standards concerning preinjection patient status, especially negligence of lack of asthma control [3-5] and obvious human failures, such as failures relating to the identification and matching of allergens and patients, dosing, injection technique, patient observation, and rapid action on observation of symptoms [27]. It is not easy to validate the impact of factors such as injection site (upper or lower arm), technique (subcutaneous or deep subcutaneous), size and type of syringe (with or without a removable needle), and the use of a 30-minute interval between injections (2-hour observation for 4 injections). These factors are described in guidelines and may influence results, but most studies on SCIT safety do not describe the methods in sufficient detail to evaluate their significance. There would certainly seem to be room for improvement in this area.

Our results show that the combination of sentinel surveillance, a slow up-dosing protocol, and adherence to standard medical practice and professional recommendations [28] can result in safe SCIT. In treatments such as SCIT, where SAEs are rare, root cause analyses provide a means of identifying problems and instituting correctional procedures. Lockey et al [29,30] produced invaluable information from large-scale root cause analyses, but some details may have been lost as the data were collected retrospectively. We believe that all SAEs should be explored and a root cause analysis performed immediately. It is important to understand that SCIT on the whole is very complex and involves multiple procedures. It is not yet possible to deal with all aspects in an operational fashion, and guidelines should be considered general recommendations as they may not be applicable to certain patients with unique clinical characteristics. Instead, we should focus on the cause of each SAE. Could it have been prevented had standard procedures been followed? A root course analysis must be done to gain information that will be of use for future patients.

The European recommendation of a 30-minute interval between injections of 2 or more allergens in a patient in a single visit [3,12] would make sense if SAEs were a common complication in SCIT. It is not based on scientific evidence, however, and will oblige clinicians to handle several procedures twice (eg, patients need to be identified and extracts performed before both the first injection and the second one 30 minutes later). This interval could possibly even increase risk by increasing the rate of mistaken patient identity, which is one of the major risk factors together with dosing failures [31]. We therefore suggest using a modified sentinel surveillance system, at least in cases where SCIT is out of control or, in settings such as the UK, where debates about the efficacy of immunotherapy have been overshadowed by concerns about safety [6]. In our opinion, the issue of the 30-minute demand is unresolved and more data are needed to substantiate this recommendation, at least when slow up-dosing schemes are used. Slow up-dosing protocols might be a problem for both patients and clinics. The time needed for multiple appointments should be weighed against safety. At present a slow up-dosing protocol can be considered very safe. The high safety level identified in our study (<1.3 SAEs per 10 000 injections) may serve as a reference limit for clinics exploring faster protocols with higher risk [18,24]. Future SCIT standards for quality assurance should include measurements of outcome as part of good practice [8] so that it can be determined where those outcomes lie with respect to others [8]. Publication of national and international results is considered right and proper [8]. The practical solution is likely to be a new electronic system for identifying safety problems once a drug is on the market [16], but until this is running, our simple model might suffice.

In conclusion, we applied a sentinel surveillance system to monitor SAEs related to SCIT in 5 clinics using a slow up-dosing protocol. We did not observe any SAEs during the first 28 992 allergen injections and the calculated maximal risk of SAEs was 1.3 per 10 000 injections. Our system of providing online feedback to participating clinics when SAEs occur in order to investigate their causes may secure the safety of patients even further. Finally, such quality assurance documentation may facilitate wider acceptance of SCIT by health care administrators, clinicians, and patients.

Acknowledgements

The data was presented in a poster at the European Respiratory Society annual congress [32]. The study was funded by the participating clinics and the Danish foundation for the improvement of quality in specialist practice.

References

1. Abramson MJ, Puy RM, Weiner JM. Is allergen immunotherapy effective in asthma? A meta-analysis of randomized controlled trials. Am J Respir Crit Care Med. 1995;151:969-74.
2. Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. Cochrane Database Syst Rev. 2007;24;(1):CD001936. Review.
3. Álvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E. Standards for practical allergen-specific immunotherapy. Allergy. 2006;61 Suppl 82:1-20.
4. Bernstein DI, Wanner M, Borish L, Liss GM. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. J Allergy Clin Immunol. 2004;113:1129-36.
5. Cox L, Li JT, Nelson H, Lockey R. Allergen immunotherapy: A practice parameter second update. J Allergy Clin Immunol. 2007;120:S25-S85.
6. Frew AJ. Immunotherapy: how safe is safe? Clin Exp Allergy. 2006;36:251-3.
7. Danish Pharmacy Agency. Consumption and Statistics. Accessed May 30, 2009. http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=11739.
8. Keogh B, Spiegelhalter D, Bailey A, Roxburgh J, Magee P, Hilton C. The legacy of Bristol: public disclosure of individual surgeons' results. BMJ. 2004;329:450-4.
9. Sismanidis C, Bland M, Poloniecki J. Properties of the cumulative risk-adjusted mortality (CRAM) chart, including the number of deaths before a doubling of the death rate is detected. Med Decis Making. 2003;23:242-51.
10. The Joint Commission. Looking at the ORYX Data. [Cited 2008 Jun 26]. Available from: http://www.jointcommission.org/AccreditationPrograms/BehavioralHealthCare/ORYX/looking_at_oryx_data.htm
11. The Joint Commission. Reporting of Medical/Health Care Errors. [Cited 2009] May 11]. Available from: http://www.jointcommission.org/SentinelEvents/errors.htm
12. Malling HJ, Weeke B. Immunotherapy. Position paper. Allergy. 1993;48 Suppl.14:9-35.
13. Vincent C, Taylor-Adams S, Chapman EJ, Hewett D, Prior S, Strange P, Tizzard A. How to investigate and analyse clinical incidents: Clinical Risk Unit and Association of Litigation and Risk Management protocol. BMJ. 2000;320:777.
14. Eypasch E, Lefering R, Kum CK, Troidl H. Probability of adverse events that have not yet occurred: a statistical reminder. BMJ. 1995;311:619-20.
15. Danish Pharmacy Agency. [Summary of product characteristics]. ALK 225 Phleum pratense. [Cited 2008 Jun 26]. Available from: http://www.produktresume.dk/docushare/dsweb/Get/Document-19295/ALK+225+Phleum+pratense%2C+injektionsv%C3%A6ske%2C+suspension+til+subkutan+anvendelse+%28Alutard+SQ%29.doc
16. Kuehn BM. FDA Turns to Electronic "Sentinel" to Flag Prescription Drug Safety Problems. JAMA. 2008;300:156-7.
17. Kondro W. Adverse reaction database has minimal information. CMAJ. 2005;173:137.
18. Winther L, Arnved J, Malling HJ, Nolte H, Mosbech H. Side-effects of allergen-specific immunotherapy. A prospective multi-centre study. Clin Exp Allergy. 2006;36:254-60.
19. Lin MS, Tanner E, Lynn J, Friday GAJ. Nonfatal systemic allergic reactions induced by skin testing and immunotherapy. Ann Allergy. 1993;71:557-62.
20. Moreno C, Cuesta-Herranz J, Fernandez-Tavora L, Alvarez-Cuesta E. Immunotherapy safety: a prospective multi-centric monitoring study of biologically standardized therapeutic vaccines for allergic diseases. Clin Exp Allergy. 2004;34:527-31.
21. Nettis E, Giordano D, Ferrannini A, Tursi A. Systemic reactions to allergen immunotherapy: a review of the literature. Immunopharmacol Immunotoxicol. 2003;25:1-11.
22. Ragusa FV, Passalacqua G, Gambardella R, Campanari S, Barbieri MM, Scordamaglia A, Canonica GW. Nonfatal systemic reactions to subcutaneous immunotherapy: a 10-year experience. J Investig Allergol Clin Immunol. 1997;7:151-4.
23. Tinkelman D, Cole W, Tunno J. Immunotherapy: A one-year prospective study to evaluate risk factors of systemic reactions. J Allergy Clin Immunol. 1995;95:8-14.
24. Mellerup MT, Hahn GW, Poulsen LK, Malling HJ. Safety of allergen-specific immunotherapy. Relation between dosage regimen, allergen extract, disease and systemic side-effects during induction treatment. Clin Exp Allergy. 2000;30:1423-9.
25. Dursun AB, Sin BA, Oner F, Misirligil Z. The safety of allergen immunotherapy (IT) in Turkey. J Investig Allergol Clin Immunol. 2006;16:123-8.
26. Mosbech H, Muller U, behalf of the Study Group*. Side-effects of insect venom immunotherapy:results from an EAACI multicenter study. Allergy. 2000;55:1005-10.
27. Borchers AT, Keen CL, Gershwin ME. Fatalities following allergen immunotherapy. Clin Rev Allergy Immunol. 2004;27:147-58.
28. Li JT, Lockey RF, Bernstein IL, Portnoy JM, Nicklas RA. Allergen Immunotherapy: A Practice Parameter. Ann Allergy Asthma Immunol. 2003;90 s1:1-40.
29. Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). J Allergy Clin Immunol. 1987;79:660-77.
30. Lockey RF, Nicoara-Kasti GL, Theodoropoulos DS, Bukantz SC. Systemic reactions and fatalities associated with allergen immunotherapy. Ann Allergy Asthma Immunol. 2001;87:47-55.
31. Aaronson DW, Gandhi TK. Incorrect allergy injections: allergists' experiences and recommendations for prevention. J Allergy Clin Immunol. 2004;113:1117-21.
32. Madsen F, Christensen M, Frolund L, Soes-Petersen U, Frost A. Sentinel surveillance of risk associated with specific allergy vaccination (SAV). Quality assurance of a clinical procedure with few but serious side effects. Eur Respir J 26[Suppl. 49], 526s. 2005.

Manuscript received September 6, 2008; accepted for publication December 16, 2008.

Flemming Madsen

Allergy and Lungclinic Helsingør
Sct. Olai gade 39 1
3000 Helsingør, Denmark
E-mail: fm@allergia.dk