

Letter to the Editor

**Safety of allergen immunotherapy:
A 10-year prospective study***To the Editor:*

Allergen immunotherapy (AIT) is considered effective and safe when patients are selected and treated in compliance with the relevant standards.¹ When administered correctly, the risk of a severe reaction (grade 3-5 reaction²) is minimal. Nevertheless, the occurrence of even a single anaphylactic shock can be an alarming event for patients and their family and doctors, and causes a misconception about AIT that prevents potential patients from receiving AIT, with no rational justification.

Avoidance of AIT happened on a larger scale after clusters of severe reactions were observed in England (1980) and in Denmark (2003). The National Boards of Health in both countries enforced regulations that led to a sharp decline in the use of AIT in both countries (see Fig E1 in this article's Online Repository at www.jacionline.org). In Denmark, the maintenance dose of grass AIT (~50% of all AIT in Denmark) was limited to 1/10 of the standard maintenance dose (100,000 SQ-U) and injections of different allergens at the same visit had to be separated by 30-minute observation periods between injections followed by the standard 30-minute observation period after the final injection. With few exceptions AIT allergens are not mixed in a single injection in Europe.

We suspected that a main reason for the increase in the number of notified severe reactions was an increase in the total number of AIT treatments (see Fig E1), together with a special Danish practice whereby allergen injections are given as deep subcutaneous injections in the forearm or the upper arm. We were concerned that this method of injection may increase the likelihood of adverse reactions. Notably, AIT injections in the forearm were recommended by the European Academy of Allergology and Clinical Immunology until 2006, and were still recommended by the Danish Society for Allergology and the manufacturer ALK-Abellø in 2016. Table E1 in this article's Online Repository at www.jacionline.org presents selected safety details in different international AIT guidelines.

In 2003, we decided to change our AIT procedures and initiate a surveillance study of severe reactions related to AIT in an effort to detect a root cause of severe reactions. The Joint Task Force on AIT¹ guideline is much more detailed than the European AIT position paper³ and excludes the use of lower-arm injections. We decided to follow the Joint Task Force on AIT guidelines from 2003 instead of the European AIT position paper (1993). Beginning in 2004, we agreed to follow a slow up dosing protocol with weekly injections lasting 15 weeks and ending with a maintenance dose of 100,000 SQ-U. This protocol complies with the manufacturers' "patient information leaflet" but last 2 weeks longer than the protocol in the "summary of product characteristics" (details of the protocol are reported in Tables E2-E7 in this article's Online Repository at www.jacionline.org). Unlike the change in injection site, this protocol modification was not a significant change in our practices because all clinics already used a slow up dosing protocol. However, the agreement secured that a well-defined up dosing protocol was followed during the whole study period.

We invited clinics with a relatively high number of AIT patients per year to participate in a prospective surveillance study of severe reactions. Five clinics agreed to participate and comply

with the Joint Task Force on AIT and updates.^{1,4} In this report, we summarize our 2004-2013 results.

The participating clinics (viz, Allergy and Lung Clinic Hellerup, Helsingør, Charlottenlund, Åbenrå, and Roskilde Hospital) reported the number of injections of aero- and venom allergens to the Study Coordinator (F.M.) on a monthly base. Clinics reported any severe reaction to the study coordinator within 24 hours for root-cause analysis. A *severe reaction* was defined as a grade 3 or 4 reaction according to the European position paper,³ which agreed well with the later World Allergy Organization 2010 classification concerning grades 3 and 4.² By the end of 2013, we had performed 102,274 injections and recorded 3 grade 4 reactions during 7,218 patient-years (note: 1 patient-year is defined as 1 patient treated for 1 year. A single patient continues treatment for 3-5 years and is therefore counted once every year of treatment).

The limitation of this type of study is that its validity relies completely on the validity of the self-reported severe reactions and the grading of severe reactions. Consequently, in 2014, we validated our prospective data using retrospective register data in which we collected data on all patients treated with AIT in all clinics. We recorded all hospital or emergency department admissions from 2004 to 2013 with a diagnosis indicating a severe reaction (see Table E8 in this article's Online Repository at www.jacionline.org). The data were obtained by linking the data from the Danish National Health Service Prescription Database with data from the National Patient Register from which we could obtain the primary diagnosis. From these databases we had information on week of AIT treatment and date of admittance and diagnosis. We were not allowed access to the patients' hospital records.

Both our self-reported data and the validation study confirmed that severe reaction related to AIT was very rare (Table I), corroborating all large studies. Overall, we administered 102,274 injections during 7,218 patient-years of treatment and observed only 3 severe reactions. These are 3 severe reactions per 102,274 injections = 0.0029% (0.0006-0.0085) (exact binomial 95% CI) and 3 severe reactions per 7,218 patient-years = 0.042% (0.0086-0.1214).

The 3 severe reactions observed are described in detail in this article's Online Repository at www.jacionline.org together with our root-cause analyses. We concluded that in the first case there had been an intravascular or intramuscular injection, in the second case there had been excessive exposure to allergen before injection, and in the third case an excessively high dose of allergen was given to a patient with a very strong allergy (clinical judgment). The first 2 cases were probably caused by inadequate education of the staff. The third case likely resulted from the physician's and patient's acceptance of an increased risk for a grade 3-4 reaction due to the patient's strong drive to receive AIT: she had had great benefit from the treatment and wanted to continue AIT even after the reaction.

The register validation study performed after the surveillance study showed that 7 of the AIT patients included in the surveillance study were registered in the National Patient Registry as having been admitted to hospital with a diagnosis indicating a possible severe reaction. Four of the 7 patients were admitted with asthma in the same week that AIT was administered, indicating a possible AIT-related severe reaction. The 3 other patients (1 with

TABLE I. Rate of severe reactions during allergen immunotherapy

Study	Year	No. of patients* or patient-years†	No. of injections* or visits†	SR grade 3-5	Rate of SR grade 3-5/injection (%)	95% CI
Madsen F self-reported data	Present study	7,218†	102,274*	3	0.0029	0.0006-0.0085
Madsen F Register data	Present study	7,218†	102,274*	4	0.0039	0.0011-0.0101
Epstein TG ^{E1}	2016	344,480*	5.6 million†	63	0.0011	Not relevant
Vervloet D ^{E2}	1980	19,739*	151,997*	2	0.0013	0.0016-0.0048
Tinkelman D ^{E3}	1995	4,578*	346,251*	7	0.0020	0.0008-0.0042
Valyasevi MA ^{E4}	1997	NA	79,593*	2	0.0021	0.0003-0.00908
Epstein TG ^{E5,E6}	2014	NA	23 million†	NA	0.0040	Not relevant
Gastaminza ^{E7}	2003	1,212*	29,754*	2	0.0067	0.0008-0.0243
Roy SR ^{E8}	2007	661,123†	1,108,621*	283	0.025	Not relevant
DaVeiga ^{E9}	2008	NA	16,375*	6	0.0366	0.0134-0.0797
Nettis E ^{E10}	2002	555*	36,359*	14	0.0385	0.0211-0.0650
Schiappoli M ^{E11}	2009	1,738*	60,785*	61	0.1004	0.0768-0.1289
Moreno C ^{E12}	2004	423*	17,526*	21	0.1198	0.0741-0.1831
Møllerup MT ^{E13}	2000	657*	10,369*	31	0.2990	0.2032-0.4241
Winther L ^{E14}	2006	1,038*	23,047*	124	0.5380	0.4477-0.6412
Dursun AB ^{E15}	2006	126*	4,705*	38	0.8077	0.5722-1.1069

NA, Not available/applicable; SR, severe reaction.

*Number of individual patients.

†Number of patient-years. One patient-year is 1 patient treated for 1 year. A patient treated for 3 years = 3 patient-years.

asthma, 1 with anaphylactic shock, and 1 with angioedema) were admitted more than 1 week after AIT, indicating that the event was probably not an AIT-related reaction. We therefore calculated that the risk of a severe reaction in this study was at most 4 per 102,274 injections, confirming previous findings from a recent very large study⁵ (Table I).

Our results indicate that AIT performed in compliance with the Joint Task Force on AIT guidelines is safe when administered with slow up dosing (see Tables E2-E6). Severe reaction under this protocol can be considered as “very rare” according to the Medical Dictionary for Regulatory Activities classification⁶ of adverse events. On the basis of our results and results from the very large American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma & Immunology Surveillance Study,⁵ we conclude that severe reaction during AIT should not exceed 0.004% injections/injection-visits when standard up dosing is used. We recommend that continuous surveillance of severe reactions during AIT be incorporated into updates of AIT guidelines. This surveillance could be performed either as a self-reporting system, such as we have described, or as database surveillance with automated monthly reports in settings where databases are available.

This study also showed that AIT performed in compliance with the Joint Task Force on AIT guidelines^{1,4} is safe for patients treated with more than 1 allergen injection per visit and that a mandatory 30-minute interval between injections is not justified. Omitting the interval reduces the number of identification procedures before matching the patient with AIT extracts and also saves time for patients, making the treatment more feasible for both patients and doctors.

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