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RESEARCH LETTER

Severe repeated anaphylactic reactions to sublingual immunotherapy

KEYWORDS

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Abstract Sublingual immunotherapy (SLIT) for allergic rhinitis is a well-established and effective therapy. To date only 11 reports of anaphylaxis to SLIT have been published. Our case relates to a female patient receiving SLIT to *Olea europaea* pollen and House Dust Mites (HDMs). She had an unremarkable medical history, apart from persistent, perennial rhinoconjunctivitis and controlled asthma with seasonal aggravation. During the build-up phase of immunotherapy our patient suffered severe anaphylactic episodes during every attempt to increase the dose of *Olea* extract, according to ordinary regimen. Therefore, we adopted a modified build-up protocol administering incremental doses of saline dilution of original extract, in 30-min intervals. Following this modified scheduled regimen we managed to advance SLIT and a maintenance dose of three drops per day (lower than the ordinary dose) was reached. On the contrary, SLIT to HDMs advanced with no reaction, and the maintenance dose was reached in five days. Although SLIT seems to have an excellent safety profile this does not rule out the possibility of an anaphylactic reaction even if current guidelines have been followed precisely. Our case indicates that SLIT schedules with large doses of allergens, omitting up-dosing phase, could be not safe enough for a minority of high sensitive patients to whom a more gradual dose increase may be necessary.

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To the Editor,

Sublingual immunotherapy (SLIT) for allergic rhinitis is a well-established and effective therapy, currently considered to be safer and almost equally effective alternative to classical subcutaneous immunotherapy (SCIT).

Regarding the safety of SLIT, recent meta-analyses and systematic reviews suggest a remarkably safe profile without any severe systemic reactions, anaphylaxis or use of adrenaline in 49 studies, reviewed by Radulovic et al.¹ So far, only 11 cases of anaphylaxis to SLIT have been published.²⁻⁷

We present a case of a 35-year-old female suffering from persistent, perennial rhinoconjunctivitis and well-controlled asthma with seasonal aggravation. Symptoms appeared 15 years ago, and were becoming more severe each year, while symptomatic relief medications had been partly effective during the pollen season.

Sensitivity to *Olea europaea* pollen, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* were identified by SPTs and serum s-IgE measurement. SLIT was carried out during the pollen season (in September) with standardised extracts of Sublivac (HAL, Netherlands)

Table 1 Anaphylactic reactions to SLIT – modification of ordinary regiment.

Time	<i>Olea</i> regiment administration	Outcome	Therapy	Following administration at home	Premedication
Day 1	1 drop of ordinary regiment	Anaphylaxis (flushing, hoarseness, dyspnoea, dizziness and mild hypotension)	Adr sc, H1-AH, H2-AH, C/S iv	–	–
Day 7	Drop dilutions: 1/5, 2/5, 3/5, 5/5	No reaction	None necessary	1 drop/day	H1-antihistamine p.o.
Day 14	2 drops of ordinary regiment	Anaphylaxis (flushing, hoarseness, dyspnoea, dizziness and mild hypotension)	Adr sc, H1-AH, H2-AH, C/S iv	1 drop/day	H1-antihistamine p.o.
Day 21	Drop dilutions: 1 + 1/3, 1 + 2/3, 2	No reaction	None necessary	2 drop/day	H1-antihistamine p.o.
Day 28	3 drops of ordinary regiment	Anaphylaxis (flushing, hoarseness, dyspnoea, dizziness and mild hypotension)	Adr sc, H1-AH, H2-AH, C/S iv	2 drop/day	H1-antihistamine p.o.
Day 35	Drop dilutions: 2 + 1/3, 2 + 2/3, 3	No reaction	None necessary	3 drop/day	H1-antihistamine p.o.
Day 42	4 drops of ordinary regiment	Anaphylaxis (flushing, hoarseness, dyspnoea, dizziness and mild hypotension)	Adr sc, H1-AH, H2-AH, C/S iv	3 drop/day	H1-antihistamine p.o.

In-hospital attempts to increase dose during build-up phase, outcomes and self-administered doses at home the subsequent days. Dilutions of ordinary regiment were prepared using saline and administered in 30 min intervals. AH, antihistamines.

(10,000 allergy units/ml, 500 AU/drop) *Olea europaea* and Sublivac *D. pteronyssinus* 50%, *D. farinae* 50%.

Induction of immunotherapy was initiated on two consecutive weeks. During the first week SLIT with HDM extract was advanced without any side-effect and the following week we proceeded to SLIT with *Olea*. The patient was administered the first drop of *Olea* extract and was attended in our department according to current guidelines. Within 10 min, she developed an anaphylactic reaction (flushing, hoarseness, dyspnoea, dizziness and mild hypotension) and was treated with epinephrine, antihistamines and corticosteroids. In every attempt to increase the dose according to ordinary regiment she suffered a severe anaphylactic reaction (in all five reactions). Therefore, we adopted a modified build-up protocol (Table 1) and educated our patient to use autoinjectable adrenaline (no reaction occurred at home, where the dose remained unchanged).

The step-up process with SLIT to olive was quite difficult to advance because she could not tolerate more than three drops of extract per day. On the contrary, SLIT to House Dust Mites advanced with no reaction, and the maintenance dose was reached in five days.

Although our patient did not have to withdraw from SLIT, she eventually remained on a lower maintenance dose (3 drops/day), because she had got tired and refused to consent to any subsequent dose increase. That maintenance dose proved to be effective, as she reported a 50% decline on symptom-medication score during the next pollen season.

Despite the fact that the safety of SLIT is well-established, adverse reactions may occur, mainly during the

build-up phase. Furthermore all previously published reports of anaphylaxis during SLIT, were characterised either by a deviation from international guidelines,^{1,3} or by previous frequent reactions during SCIT.^{4,6}

In our case, anaphylactic episodes occurred in-hospital following the first dose and also after any subsequent dose increase, in a young female asthmatic patient lacking any history of anaphylaxis. During the build-up phase, asthma was well controlled and no predicting factor for a subsequent anaphylaxis was present. Despite these reactions, we managed to increase the tolerated dose, by administering premedication (antihistamine p.o.) during the build-up phase, increasing gradually the dose only in-hospital and maintaining the same dose for seven consecutive days at home (Table 1).

The remarkable safety profile of SLIT allowed the recent modification of SLIT schedules, omitting the up-dosing phase and starting with the maintenance dose. However, it seems that there is a subgroup of sensitive patients who need a more conservative build-up schedule in order to avoid a severe anaphylactic reaction.

Although SLIT seems to have an excellent safety profile this does not rule out the possibility of an anaphylactic reaction even if current guidelines have been followed precisely. It is imperative to administer the first dose under medical supervision and be vigilant to immediately recognise any possible systemic reaction. Our case indicates that SLIT schedules with a large dose of allergens, omitting up-dosing phase, may not be safe enough for a minority of high sensitive patients to whom a more gradual dose

increase could be necessary. So far, the majority of studies focus mainly on effectiveness of SLIT and, to a lesser extent, on side-effects (usually considered as secondary outcomes). Therefore, more studies primarily focused on adverse reactions to SLIT are needed.¹

Conflict of interest

The authors have no conflict of interest to declare.

Ethical disclosures

Patients' data protection. Confidentiality of data. The authors declare that they have followed the protocols of their work centre on the publication of patient data and that all the patients included in the study have received sufficient information and have given their informed consent in writing to participate in that study.

Right to privacy and informed consent. Right to privacy and informed consent. The authors declare that no patient data appears in this article.

Protection of human subjects and animals in research. Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

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