



Letter

Safety of rush subcutaneous immunotherapy administered in real life using an infusion pump

Rush subcutaneous immunotherapy (SCIT) schedules offer rapid clinical response, improved adherence, and increased cost-effectiveness because of a lower number of visits and doses. However, this therapy is associated with an increased incidence of adverse reactions (ARs).^{1–6} A few years ago, our group described the use of an infusion pump (IP) to administer SCIT according to a rush schedule.⁷ The purpose of this study is to update our data on the safety of this therapy approach and to assess risk factors for ARs in real life using a similar rush schedule with an IP.

The analysis included 112 consecutive patients with allergic rhinitis and/or asthma who were sensitized to pollens or pets or who had Hymenoptera venom allergy with willingness to initiate immunotherapy after receiving accurate information. SCIT indications were based on the guidelines published by the European Academy of Allergy and Clinical Immunology (EAACI).⁸ All patients or their guardians signed an informed consent document. Because this was considered a real-life study on clinical practice, no control group was included.

A portable IP (Infusa T1; Medis, Como, Italy) was used for subcutaneous administration during the up-dosing phase. Treatments with pollen extracts (Avanz and Pangramin); cat, dog, and horse extracts (Alutard); or *Vespa* and *Polistes* venom extracts (Pharmalgen) treatments were used (ALK-Abello, Madrid, Spain). Up-dosing to reach the maintenance phase consisted of 3 doses of the maintenance vials (compared with 12 doses of standard schedule) administered at weekly intervals and at least 2 maintenance doses by injection (Table 1). Infusions lasted 30 minutes, and patients were observed for 30 minutes after completing the infusion. ARs (local, systemic, immediate, or delayed) were recorded according to the EAACI guidelines.⁹ Delayed ARs were monitored by telephone interview after 48 hours of SCIT; for this purpose, patients received instruction on how to monitor ARs and were advised to seek emergency treatment for ARs if necessary. Patients were not routinely premedicated. In the group of patients allergic to pets (n=65), the following determinations were performed: Can f 1, Can f 2, Can f 3, Can f 5, Fel d 1, Fel d 2, Fel d 4, Equ c 1, and Equ c 3 (ImmunoCAP or ISAC, Thermo-Fisher, Stockholm, Sweden). The Fisher exact test and lineal regression were used to analyze differences in the rate of AR occurrence and other parameters.

The population consisted of 57 females and 55 males, and age ranged from 9 to 67 years. Of these individuals, 94.6% had allergic rhinitis, 74% had asthma, and 5% had allergy to Hymenoptera venom.

A total of 543 doses were administered: 470 (87%) with IP and 73 (13%) without IP. A description of the doses is given in Table 2. The initial up-dosing phase was modified in 45 doses (8%) due to

ARs; the highest modification was seen with Pharmalgen (11%) followed by Alutard (10.3%), and finally Pangramin (6.6%). Ninety-one (16.6%) of the doses required premedication (oral antihistamines) due to previous ARs; the highest percentage of premedicated doses was for Pharmalgen (33.3%), followed by Alutard (17%), Pangramin (16.7%), and Avanz (11.5%).

Immunotherapy-related ARs were reported in 66 doses (12%) among 33 patients (29.5%). Forty were local reactions (LRs), 25 were systemic reactions (SRs), and 1 was both an LR and SR. Sixty-two ARs occurred when an IP was used and 4 with standard injections. No ARs were reported in patients receiving olive or *Polistes* extracts.

Regarding LR, 41 (7.5% of doses) were seen in 20 patients (17.8%). Extracts of *Vespa* venom (30.4%) accounted for the highest number of LR, and the lowest number was seen with cat (4.3%) and dog (1.8%) extracts. As for time of appearance, 4 were immediate LR and 36 delayed LR. The most frequent sign was induration (87.8%) followed by erythema (85.4%). The median time of duration of the LR was 48 hours.

Table 1
Schedule of rush immunotherapy

Extract	Week	Vial	Dose, mL	SQ ^a or STU, ^b µg per dose	Administration
Avanz	0	B	0.1	3000 SQ	IP
	2	B	0.2	6000 SQ	IP
	4	B	0.5	15,000 SQ	IP
	6	B	0.5	15,000 SQ	IP
	8	B	0.5	15,000 SQ	Without IP
	10	B	0.5	15,000 SQ	Without IP
Pangramin	0	B	0.1	100 STU	IP
	2	B	0.2	200 STU	IP
	4	B	0.8	800 STU	IP
	6	B	0.8	800 STU	IP
	10	B	0.8	800 STU	Without IP
	14	B	0.8	800 STU	Without IP
Alutard	0	4	0.1	10,000 SQ	IP
	1	4	0.5	50,000 SQ	IP
	2	4	1	100,000 SQ	IP
	4	4	1	100,000 SQ	IP
	8	4	1	100,000 SQ	Without IP
	12	4	1	100,000 SQ	Without IP
Pharmalgen	0	4	0.1	5 µg	IP
	1	4	0.5	50 µg	IP
	2	4	1	100 µg	IP
	4	4	1	100 µg	IP
	8	4	1	100 µg	Without IP
	12	4	1	100 µg	Without IP

Abbreviations: IP, infusion pump; STU, skin test unit; SQ, standard quality unit.

^aEquivalent maximum dose: 100,000 SQ of approximately 14.6 µg/mL for Fel d 1 and approximately 8 µg/mL for Can f 1.

^bEquivalent maximum dose: 1000 STU of approximately 2.5 µg/mL for grasses.

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Table 2
Description of doses and adverse reactions

Extract	Patients	All doses	Doses with IP	LRs, No. (%)				SRs, No. (%)				Grading ^a			Time of onset	
				All LRs		LRs with IP		All SRs		SRs with IP		1	2	3	I	D
				Patients	Doses	Patients	Doses	Patients	Doses	Patients	Doses					
Avanz	20	96	78	4 (20)	11 (11.5)	4 (20)	10 (12.8)	3 (15)	4 (4.2)	3 (15)	4 (5.1)	3	1	0	2	2
Pangramin	6	30	25	2 (33.3)	6 (20)	2 (33.3)	6 (24)	0 (0)	0 (0)	0 (0)	0 (0)	0	0	0	0	0
Alutard	81	390	345	12 (14.8)	17 (4.4)	12 (14.8)	17 (4.9)	10 (12.3)	21 (5.4)	9 (11.1)	18 (5.2)	10	8	0	15	3
Pharmalgen	5	27	22	3 (60)	7 (25.9)	3 (60)	7 (31.8)	1 (20)	1 (3.7)	1 (20)	1 (4.5)	1	0	0	0	1
Total	112	543	470	21 (18.8)	41 (7.5)	21 (18.8)	40 (8.5)	14 (12.5)	26 (4.8)	13 (11.6)	23 (4.9)	14	9	0	17	6

Abbreviations: LRs, local reactions; SRs, systemic reactions; IP, infusion pump; I, immediate; D, delayed.

Extracts administered by doses: 87 grass pollen, 13 grass and olive pollen, 6 olive pollen, 15 other pollen, 258 cat, 106 dog, 31 horse, 23 *Vespula*, and 4 *Polistes*.^aGrading SRs (with IP) according to the European Academy of Allergy and Clinical Immunology guidelines.⁹

SRs were observed in 26 doses (4.8%) in 13 patients (11.6%). SRs were seen with the extracts of grass pollen (Avanz), cat (Alutard), and *Vespula* (Pharmalgen). Regarding time of appearance, 20 were immediate SRs (3.7%) and 6 delayed SRs (1.1%). Symptoms associated with SRs were rhinitis (71.4%) and asthma (71.4%) with cat extracts (Alutard), urticaria (50%) and angioedema (25%) with grass pollen (Avanz), and angioedema (33%) with *Vespula* (Pharmalgen). No cases of hypotension or anaphylactic shock were observed.

Four LRs and 23 SRs required treatment. The LRs required only oral antihistamines, and the 15 individuals with SRs received 2 or more drugs as treatment. The most frequently used drugs were antihistamines (85.2%) followed by salbutamol (44.4%), methylprednisolone (37%), and adrenaline (33.3%). All ARs were successfully treated.

The probability of the same patient having a second LR was 11.6%, and the probability of having a second SR was 4.6%. The appearance of ARs was not associated with asthma diagnosis, severity, or control. However, in the group of patients with LRs or SRs, asthma was observed in 71% of LRs and 71% of SRs; the asthma severity of these patients was mostly moderate persistent asthma, and partially controlled asthma was observed in 60% of SRs.

In the group of patients who received cat extracts (Alutard), no statistically significant association was found with the number positive responses or the intensity of sensitization to the recombinant allergens tested or the type or appearance of ARs.

The ratio of ARs reported in this study performed in real life is similar to those found in our previous study (LRs: 8.5% vs 6.5%; SRs: 4.9% vs 4.0%).⁷ Our results are difficult to compare with other publications. The most similar rush schedule was published by Justicia et al.² In this article, the 2-day schedule reported 22.2% of SRs and 10.6% for the 3-day schedule. In other published studies, but using longer schedules, the rate of LRs varied from 0.32% to 4.3% per administered dose (4.5% to 54% of patients) and the rate of SRs from 0.5% to 1.7% of doses (3% to 10% of patients).^{1–5} The appearance of ARs was not significantly associated with asthma diagnosis, its severity, or its control. Nevertheless, 71% of LRs and 71% of SRs were observed in asthmatic patients, as has been previously described.⁵ In contrast with a recent study,¹⁰ no statistically significant association was found with the animals recombinant allergens tested and the ARs.

In summary, the results of the 2 studies mentioned here suggest that the use of an IP during the up-dosing phase of SCIT according to a rush schedule may be a safe alternative with a faster clinical response. Although this approach does not entirely

prevent ARs, these events were easily controlled by conventional treatment.

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