

Letter

RUSH ALLERGEN SUBCUTANEOUS IMMUNOTHERAPY ADMINISTERED WITH INFUSION PUMP

To the Editor: Although rush immunotherapy has many potential benefits, including rapid response, improved compliance, and cost-effectiveness, it is associated with an increased incidence of systemic reactions.¹ We sought to determine whether administration of a new up-dosing subcutaneous immunotherapy (SCIT) schedule with standardized extracts using a subcutaneous infusion pump (IP) could reduce the number of injections, whether the IP is as safe as similar schedules without increasing the rate of local reactions (LRs) or systemic reactions (SRs), and whether it is possible to identify predictors of such reactions.

A prospective, proof-of-concept, pilot study was designed. We studied 81 allergic rhinitis patients with or without asthma who were sensitized to pollens (1 *Cupressus*, 1 *Cupressus* and *Lolium*, 48 grass mix [*Dactylis*, *Festuca*, *Lolium*, *Phleum*, *Poa*, and *Secale*], and 14 grass mix and *Olea*) or pet epithelia (9 cat, 3 dog, and 2 horse) or allergic to Hymenoptera venoms (1 *Polistes dominulus* and 2 *Vespa* spp) who fulfilled the criteria for immunotherapy according to European Academy of Allergy and Clinical Immunology (EAACI) guidelines.² The primary end point was the rate of LRs and/or SRs defined according to the EAACI.² A 30-minute waiting period after infusion was observed. Delayed reactions were monitored after 48 hours by telephone interviews after instructing patients how to monitor adverse reactions or to make an urgent contact if needed to treat any reaction. Patients were not premedicated. All patients or their guardians signed an informed consent form.

A portable, battery-operated pump for subcutaneous infusion (Medis Infusa T1; Medis, Milan, Italy) was used for the administration of the up-dosing phase. An 1-mL syringe and an infusion line (Butterfly-25; Hospira Inc, Lake Forest, IL) was adapted to the pump. Infusions lasted 30 to 45 minutes. Pangramin (pollen extracts), Alutard (epithelia), or Pharmalgen (Hymenoptera venoms) treatments were used with the schedules indicated in Table 1. Up-dosing to reach the maintenance phase consisted of 2 administrations of Pangramin and 3 administrations of Alutard and Pharmalgen extracts given in weekly intervals. After an interim evaluation of the tolerability, a modification was made to the Pangramin pollen schedule to reduce the rate of LRs from 2 to 3 administrations administered fortnightly (n = 26 patients and 102 doses). At least 2 maintenance doses (ranging from 0.8 to 1 mL, depending on the treatment used) were administered with IP, and 2 additional doses were administered without IP in a standard practice (SCIT) 4 weeks apart. All are completing the full course of immunotherapy and are currently undergoing maintenance therapy (1 year). The analysis of the differences in the rate of adverse reactions was performed by the Fisher exact test.

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Table 1. Schedule of Rush Immunotherapy

Week	Dose, mL	Equivalent maximum dose ^a
IP Pangramin (initial; vial B)		
0	0.5	500 STU
1	1	1,000 STU
3	1	1,000 STU
Conventional Pangramin (initial; vial B)		
7	0.8	800 STU
11	0.8	800 STU
IP Alutard (vial 4)		
0	0.1	10,000 SQ
1	0.5	50,000 SQ
2	1	100,000 SQ
4	1	100,000 SQ
Conventional Alutard (vial 4)		
8	1	100,000 SQ
12	1	100,000 SQ
IP Pharmalgen (vial 3)		
0	0.5	5 µg
IP Pharmalgen (vial 4)		
1	0.5	50 µg
2	1	100 µg
4	1	100 µg
Conventional Pharmalgen (vial 4)		
8	1	100 µg
12	1	100 µg
IP Pangramin (modified; vial B)		
0	0.1	100 STU
2	0.2	200 STU
4	0.8	800 STU
6	0.8	800 STU
Conventional Pangramin (modified; vial B)		
10	0.8	800 STU
14	0.8	800 STU

Abbreviation: IP, infusion pump.

^a Equivalent maximum doses: 1,000 STU = 2.5 µg/mL for grasses and 100,000 SQ = 14.6 µg/mL for Fel d 1 and 8 µg/mL for Can f 1.

Patient age ranged from 5 to 57 years, with a mean (SD) of 30.4 (11.9) years. Forty-six patients (56.8%) were female. Thirty-four of 43 patients had well-controlled asthma, and the rest had partially controlled asthma. A total of 278 injections with IP and 119 without it were administered.

During SCIT administration with IP, a total of 18 LRs (6.5% of doses) in 14 patients (17.3%) were observed. All LRs (>10 cm in diameter) appeared after 30 minutes. The rate of LRs from doses administered by IP was 9.2% with pollens (Pangramin), 5.7% with epithelia (Alutard), and 11.1% with venoms (Pharmalgen). The

Table 2. Adverse Reactions After Infusion Pump Injection²

Schedule and treatment	Patients, No.	Doses, No.	LRs, No. (%)		SRs, No. (%)		Grading			Time onset	
			Patients	Doses	Patients	Doses	1	2	3	Immediate	Delayed
Initial											
Pangramin	38	105	7 (18.4)	10 (9.2)	6 (15.8)	6 (5.7)	2	2	2	0	6
Alutard	14	53	2 (14.3)	3 (5.7)	2 (14.3)	2 (3.8)	1	1	0	1	1
Pharmalgen	3	18	2 (66.7)	2 (11.1)	0 (0)	0 (0)	0	0	0	0	0
Modified Pangramin	26	102	3 (11.5)	3 (2.9)	3 (11.5)	3 (2.9)	2	1	0	0	3
Total	81	278	14	18	11	11	5	4	2	1	10

Abbreviations: LRs, local reactions; SRs, systemic reactions.

modified schedule of Pangramin pollen reduced the rate of LRs from 9.2% to 2.9% ($P = .08$). The rate of LRs to maintenance doses by resuming a conventional injection was 7.6%.

A total of 11 SRs (4.0% of doses) in 11 patients (13.6%) were reported after administration with IP (skin and respiratory system involvement in all). One SR appeared within 30 minutes after infusion. The rate of SR from doses administered by IP was 4.3% for pollens (Pangramin) and 3.8% for epithelia (Alutard). No SRs occurred with Pharmalgen. Five SRs were grade 1, 4 were grade 2, and 2 grade 3. All SRs responded well to the treatment (intravenous antihistamines and/or steroids and/or subcutaneous epinephrine). The modified schedule of Pangramin pollen reduced the number of SRs, although not significantly, which changed from 5.7% to 2.9% ($P = .498$). Only 1 SR (0.8% of doses) was observed when SCIT was administered with conventional maintenance injections. A summary of adverse reactions is given in Table 2.

We were not able to identify any clinical feature that could be associated with the appearance of LRs or SRs. In addition, the presence of a previous reaction did not increase the risk of future reactions.

Our results are difficult to compare with other publications because of the method used for monitoring adverse events, with telephone calls 48 hours after injection to register delayed reactions. To our knowledge, delayed reactions have not been so extensively studied in the literature. The most similar rush schedule without premedication concerning number of days for up-dosing and extracts used was published by Justicia et al.³ This article reported a rate of SRs of 22.2% for the 2-day scheduled and 10.6% for the 3-day schedule. Therefore, the incidence of SRs was considerably lower in our study. In other published studies, which used longer schedules, the rate of LRs varied from 0.32% to 4.3% per administered dose (4.5% to 54.0% of patients) and the rate of SR varied from 0.5% to 1.7% of doses (3%–10% of patients).^{4–8}

In conclusion, the use of an IP could shorten the up-dosing phase of SCIT, thereby reducing the number of injections with increase adverse reactions. Although not exempt from SRs, all adverse events were easily controlled by conventional treatment.

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