

SAFETY AND PHARMACOECONOMICS OF A CLUSTER ADMINISTRATION OF MITE IMMUNOTHERAPY COMPARED TO THE TRADITIONAL ONE

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SUMMARY

Accelerated schedules of administration of immunotherapy (rush or clustered) allow to reach the maintenance dosage in shorter times with respect to traditional schedules. Nowadays formal assessments of the safety and economic aspects of those schedule lack for inhalant allergens. We compared in a prospective randomized open study a cluster and a traditional immunotherapy with standardized mite extracts. Thirty eight adult patients with persistent allergic rhinitis due to mites were randomized to receive either a traditional (N= 19) or a cluster (N=19) up-dosing scheme, lasting 13 and 3 weeks respectively. Side effects were carefully evaluated and recorded by physician and costs were calculated as well. In the cluster and traditional up dosing 148 and 241 injections were given respectively. With the cluster up-dosing there were 8 local reactions (15.9% of patients and 5.4% of injections). With the traditional schedule 6 local reactions (31.5 % of patients and 2.4% of injections) occurred. There was no difference between the two treatments in occurrence of side effects per patient and per injection (chi-square 1.31 and 2.23, $p = \text{NS}$). No systemic reaction was recorded. Considering the cost of the extract, the cost of injections and the time spent, the cluster regimen resulted in a global spare of 244.95 euros per patient in the build-up phase. The cluster up-dosing is as safe as the traditional one and allows a significant economical save.

Key-words: Cluster immunotherapy - Traditional immunotherapy - Rhinitis - Mites - Safety - Cost

INTRODUCTION

In the last decades, the standardization of allergenic extracts for diagnosis and treatment has been one of the primary objectives of both manufacturers and scientists. The standardization of an allergenic extract warrants that the allergen content in an extract is stable, and that the potency of the vaccine is identical from batch to batch (1, 2). Vaccines are presently standardized either immunologically or biologically. In many cases the content in micrograms of the major allergen(s) is also available. The quantification of the protein content, in particular, has allowed identifying for most allergens the optimal dosage to be administered (3). Moreover, a proper standardization also implies a better quality of the product and an improved safety. This fact results in the possibility of using schedules of administration that are more comfortable for patients and easier to manage.

In fact, one of the main problems of the traditional specific immunotherapy (SIT) is the need for a long

build-up phase (usually one to three months), with a very slow increase of the amount of allergen given. With standardized extracts "rush" and "cluster" up-dosing phases have become feasible (4). With the rush modality increasing doses of allergen are given every 20-30 minutes on several consecutive days. The cluster schedules involve the injection of increasing doses every 20-30 minutes 2 to 5 times a day, to be repeated after 3-7 day intervals. In general, with the accelerated schedules the maintenance dosage can be reached in less than one month. Rush and cluster immunotherapy have been repeatedly investigated with hymenoptera venom immunotherapy (5, 6), and they are now of clinical use. With respiratory allergens, the available data on the safety and tolerability of accelerated schedules are still few (7, 8).

Aim of the present work was to systematically evaluate the safety, tolerability and pharmaco-economic aspects of a cluster SIT with mite extract, in comparison with a traditional schedule with the same extract.

MATERIAL AND METHODS

This is a prospective, observational, open randomized controlled study, conducted in adult patients with respiratory allergy. Despite the cluster immunotherapy

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was already marketed in Italy (Pangramin™), the Ethical Committees denied the permission to perform the study in a double blind, double dummy and placebo controlled fashion.

Patients and diagnosis

Adult and adolescent patients suffering from respiratory allergy due to house dust mites were enrolled. Mandatory inclusion criteria were: a) history of rhinitis and/or mild to moderate asthma since at least two years; b) skin prick test (> 3 mm) and CAP-RAST (class III or more) positivity for *Dermatophagoides pteronyssinus* and/or *farinae*; c) age between 12 and 60 years. The diagnosis of rhinitis was essentially based on the presence of typical symptoms of sneezing, itching, rhinorrhea and nasal obstruction. Rhinitis had to be persistent, according to ARIA criteria (9). The diagnosis of asthma was based on the presence of one or more of the following: wheezing, shortness of breath, chest tightness, cough, nocturnal awakenings. In the case of asthma, a pulmonary function test was performed. If FEV1 was <80% of predicted, a reversibility test with salbutamol was carried out and considered positive if an increase in FEV1 >12% or >200 ml in absolute value was achieved. In the case of normal spirometry, a methacholine challenge was performed. It was considered positive if the dose of methacholine provoking a fall of FEV1 of 20% was less than 1,200 mcg. Asthma severity was graded according to GINA guidelines (10).

Skin tests were performed (11), with a panel of standardized extracts including: house dust mites, grasses, *Parietaria*, olive, birch, ragweed, hazelnut, *Cladosporium*, *Alternaria*, cat and dog dander. A negative control (saline) and a positive one (histamine hydrochloride 1%) were also used. A wheal diameter greater than 3 mm was considered positive.

Cluster and traditional Immunotherapy

SIT was prescribed according to the most recent guidelines (3, 9). In particular, those patients with severe persistent rhinitis with or without asthma were considered eligible. A careful cost/benefit evaluation was performed, and the patients were informed in detail about the rationale of SIT. The causal role of the allergen was well established through the clinical history (presence of symptoms during almost the whole year). Patients with systemic immunologic disease, malignancies, chronic use of betablockers or corticosteroids were not given immunotherapy, as suggested in the official documents. Both the traditional (Pangramin Depot™, ALK-Abellò S.p.A, Milan) and

the cluster (Pangramin Plus™, ALK-Abellò S.p.A, Milan) were standardized in Biological Units (BU) and Standard Therapeutic Units (STU), and the content of major allergens was also available. The up-dosing scheme of the traditional and cluster SIT are reported in table 1 and 2, lasting 13 weeks and 3 weeks, respectively. In the cluster up dosing, two injections separated by a 30-minute interval were given at each session, for a total of 2 injections weekly in 3 weeks. After the maintenance dose (or the maximum tolerated) was achieved, injections were given monthly.

Safety, tolerability and costs.

All patients were observed for at least 30 minutes after the injection(s). Side effects were classified and graded according to international guidelines as local/systemic and mild to severe. The action taken in the case of side effects was carefully recorded as well. At each subsequent visit, patients were also asked for possible delayed reactions that may have occurred after they had left the clinic. The patients were followed up for at least one year after the up-dosing phase, in order to detect any possible reaction during the maintenance phase.

The pharmaco-economic evaluation included the direct cost of injections (46 € for one group of 8 injections) and the indirect cost of the time spent to go to the clinic and to wait after injection (17.3 €/hour)(12)

DAY	VIAL	VOLUME (mL)	DOSE (BU)
1	A: 100 STU/mL = 1 BU/mL	0.1 + 0.2	0.1 + 0.2
7	0.4 µg/mL Der1+ 0.2 µg/mL Der2	0.4/0.6	0.4 + 0.6
14	B: 1,000 STU/mL = 10 BU/mL	0.1/0.2	1 + 2
21	4 µg/mL Der1 + 2 µg/mL Der2	0.4/0.4	4 + 4

Table 1. Cluster immunotherapy

WEEK	VIAL	VOLUME (mL)	DOSE (BU)
1	1: 10 STU/mL = 0.1 BU/mL	0.1	0.01
2	0.04 µg/mL Der1 + 0.02 µg/mL Der2	0.2	0.02
3		0.4	0.04
4		0.8	0.08
5	2: 100 STU/mL = 1 BU/mL	0.1	0.1
6	0.4 µg/mL Der1 + 0.2 µg/mL Der2	0.2	0.2
7		0.4	0.4
8		0.8	0.8
9	1,000 STU/mL = 10 BU/mL	0.1	1
10	4 µg/mL Der1 + 2 µg/mL Der2	0.2	2
11		0.4	4
12		0.6	6
13		0.8	8

Table 2. Traditional immunotherapy

RESULTS

Nineteen patients (9 female, age range 14-48, mean age 28.8 years) received the cluster SIT for a total of 148 injections in the build-up phase, and 19 (8 female, age range 12-46, mean age 24.9 years) received the traditional dosing schedule, for a total of 241 injections. With the cluster up-dosing there were 8 local reactions in 3 patients (15.9% of patients and 5.4% of injections). The reactions were erythema and swelling at the site of injection, were all delayed (6-8 hours), and occurred after the 2nd cluster. No pharmacological treatment was needed at all. In addition one non specific systemic reaction (non objectivable feeling of vertigo) after the last cluster was reported. This reaction was judged as not ascribable to SIT. With the traditional schedule 6 local reactions in 6 patients (31.5 % of patients and 2.4% of injections) occurred, with swelling and erythema at the site of injection. There was no difference between the two treatments in frequency of side effects per patient and per injection (chi-square 1.31 and 2.23, $p = \text{NS}$), as summarized in table 3. No local or systemic reaction occurred with the two regimens during the maintenance phase. All patients tolerated well the injections, but in general they judged not too comfortable to stay at the clinic for 1 hour with the cluster schedule. The pharmacoeconomic evaluation is shown in table 4. We assumed that each patient had to spent about 1.5 hour (1 hour for moving plus 30 minutes waiting) for the traditional administration, and 2 hours for the cluster administration. Since the cost of the two preparations is identical, the cluster regimen allowed a global spare of 244.95 euros per patient in the build-up phase.

	Pts	Inject	Local reactions		
			N	% patient	% inj
CLUSTER	19	148	8 (3 pts)	15.9	5.4
TRADITIONAL	19	241	6 (6 pts)	31.6	2.4
Chi-square				NS	NS

Table 3. reactions with the two schemes

	CLUSTER			TRADITIONAL		
	Unitary Cost	Number	TOTAL €	Unitary cost	Number	TOTAL €
Injections	46€ per 8 injections	8 inject	46.00	46€ per 8 injections	13 inject.	92.00
Time spent	17.3 € per hour	4 x 2 hrs	138.40	17.3 € per hour	13 x 1.5 hours = 19.5 hrs	337.35
TOTAL			184.40			429.35

Table 4. reactions with the two schemes

DISCUSSION

Specific immunotherapy is a well established treatment for both respiratory allergy and hymenoptera venom hypersensitivity. It acts as a biological response modifier at the earliest stages of the immune reaction to allergens (13), this resulting in improved symptoms and reduced need for medications. Among the practical problems of SIT there is the duration of the up-dosing phase that is traditionally quite long (usually about 3 months, with weekly injections). This slow increase of the dose is dictated mainly by safety reasons, since it has been shown in the past that a rapid dose increasing is associated with a greater occurrence of side effects (14, 15). The improved quality of the extracts and their accurate standardization has allowed exploring different accelerated up-dosing schedules, including the cluster and the rush ones. The accelerated schedules heavily reduce the duration of the build-up phase and are, therefore, time sparing. In fact, the discomfort due to repeated injections is one of the most important reasons for discontinuation (16). Accelerated induction regimens have been used with hymenoptera venom SIT, but few data are available with inhalant allergens. We compared herein the safety of a cluster immunotherapy to mites and a traditional scheme. The overall occurrence of side effects did not differ significantly between the two approaches, although the rates were low with the traditional induction that lasts 13 weeks. The observed side effects were all local and mild, since they did not require pharmacological interventions. Thus, the cluster regimen seems to be a viable and safe alternative to the traditional one. Indeed, the patients have to stay at the clinic at least one hour at each cluster, and this may represent a tolerability problem. On the other hand, the smaller number of injections, concentrated within 4 days allows a not negligible economic spare of about 200 euros per patient in the build-up phase. As a general conclusion, it would be advisable, before prescribing SIT, to inform the patient in detail about the available options, also in term of costs. An optimal treatment should take into account together with efficacy and safety, also the patient's preference and his willingness to pay.

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