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Original article

Investigation of an adequate immunotherapy induction schedule with an *Alternaria tenuis* extract

Background: The optimal induction schedule for immunotherapy with fungal extracts has not yet been established. The present study investigates the safety of induction schedules with a biologically standardised *Alternaria tenuis* extract using progressive cluster schedules in patients selected according to the criteria established in the international guidelines. **Methods:** A historical cohort study was carried out on 108 patients (4-28 years of age; 97% asthmatics) who had received immunotherapy with Pangramin Depot (*A. tenuis*)® using either of the following schedules: Schedule 1: 4 visits / 10 injections ($N = 60$); Schedule 2: 4 visits / 8 injections ($N = 9$); Schedule 3: 3 visits / 9 injections ($N = 6$), and Schedule 4: 3 visits / 6 injections ($N = 33$). The European guidelines for controlled administration were applied, at three Spanish allergy centres, and the reactions elicited were recorded according to the same guidelines. **Results:** Overall, the 108 patients had 402 visits and received 944 doses. With Schedule 1 there were one local and two mild systemic reactions (Grade II) within the 30-minute observation period, with rapid response to standard therapy. There were no reactions with the other three schedules. All the patients reached the maintenance dose recommended by the manufacturer. **Conclusions:** The four schedules assessed were well tolerated. The simplest one (Schedule 4: three visits / six injections) represents a valid alternative for the routine administration of immunotherapy to well-selected patients under controlled conditions.

Key words: *Alternaria*. Asthma. Immunotherapy. Adverse reactions.

Búsqueda de una pauta idónea para iniciación de inmunoterapia con un extracto de *Alternaria tenuis*

Fundamento: No se ha establecido la pauta de iniciación óptima para un extracto de hongos. En este trabajo se estudia la seguridad de la iniciación con un extracto de *Alternaria tenuis* estandarizado biológicamente, mediante pautas agrupadas progresivas, en pacientes seleccionados de acuerdo con los criterios establecidos en las guías internacionales. **Métodos:** Se realiza un estudio de cohortes históricas con 108 pacientes (4-28 años; 97% asmáticos) que recibieron tratamiento con Pangramín Depot (*A. tenuis*)® mediante los siguientes esquemas: pauta 1 4 visitas/10 inyecciones ($n = 60$); pauta 2: 4 visitas/8 inyecciones ($n = 9$); pauta 3: 3 visitas/9 inyecciones ($n = 6$), y pauta 4: 3 visitas/6 inyecciones ($n = 33$). Se apli-

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Table I. Dosing schedules used.

DAY	SCHEDULE 1		SCHEDULE 2		SCHEDULE 3		SCHEDULE 4	
	VIAL	VOLUME	VIAL	VOLUME	VIAL	VOLUME	VIAL	VOLUME
1°	1	0,2	2	0,1	2	0,05	2	0,2
		0,4		0,2		0,1		0,4
		0,8		0,2				
7°	2	0,2	2	0,4	2	0,5	3	0,1
		0,4		0,4		0,1		0,2
		0,8		0,2				
14°	3	0,1	3	0,1	3	0,2	3	0,4
		0,2		0,2		0,2		0,4
						0,4		
21°	3	0,4	3	0,4				
		0,4		0,4				
VISITS	4		8		3		3	
DOSES	10		4		9		6	

caron las guías europeas de administración controlada en tres centros españoles de alergia y se procedió al registro de reacciones mediante la misma normativa. **Resultados:** Los 108 pacientes realizaron 402 visitas y recibieron 944 dosis. En la pauta 1 aparecieron una reacción local y dos sistémicas leves (grado II) dentro de los 30 minutos de observación, con rápida respuesta al tratamiento. No hubo reacciones en las otras tres pautas. Todos los pacientes alcanzaron la dosis de mantenimiento recomendada por el fabricante. **Conclusiones:** Las cuatro pautas valoradas han mostrado ser bien toleradas. La más sencilla de ellas (3 visitas / 6 dosis) es una alternativa válida para el tratamiento de rutina de pacientes bien seleccionados, en condiciones controladas.

Palabras clave: *Alternaria*. Asma. Inmunoterapia. Reacción adversa.

INTRODUCTION AND BACKGROUND

The efficacy of allergen immunotherapy is well established and is already a demonstrated fact¹. Nevertheless, there is still debate as to its benefit/risk ratio. The established and proven opinion is that this ratio is based on the three factors of "Patient", "Extract" and "Administration schedule".

Academic and scientific reports that have constituted international reference guidelines in the last few years^{2,3} state that the patient who is to receive immunotherapy must be carefully selected and must conform to a clinical profile of

allergic respiratory or anaphylactic disease, with IgE-mediated hypersensitivity to an allergen that is relevant in his/her environment and which cannot be eliminated by usual procedures, and who evidences a clear impact on his/her quality of life for that reason. The disease must be stable and reversible, and no formal contraindications to the use of epinephrine or any other intercurrent conditions should exist. Those same reports recommend the use of extracts of proven quality manufactured by legally licensed and authorised laboratories. The extracts should be mono- or oligocomponent ones, they should be biologically standardised and their major allergen contents should be preferably expressed in micrograms (μg). It is desirable that the extracts maintain a constant major allergen / total extract ratio. As regards the administration schedule, the ideal schedule has yet to be defined. Nevertheless, some of its main features are already known: an ideal induction schedule should reach the optimum dose⁴ with maximum safety, and low-dosage schedules that are patently useless should be avoided⁵; this ideal schedule should also be able to be administered within the shortest possible time, so as to prevent patient discomfort and reduce health care costs.

In the present study we investigate the adequacy of a number of cluster dosage schedules for induction of immunotherapy with an *Alternaria tenuis* extract.

PATIENTS AND METHODS

We have analysed four historical cohorts of patients receiving specific *Alternaria tenuis* immunotherapy accor-

Table II. Numbers of visits, numbers of doses and incidences in the patients studied

	No. of visits	No. of doses	No. of patients
SCHEDULE 1	243	605	
Conventional	780	780	60
SCHEDULE 2	36	72	
Conventional	117	117	9
SCHEDULE 3	18	54	
Conventional	78	78	6
SCHEDULE 4	99	198	
Conventional	429	429	33
INCIDENCES	6	15	
Total	402	944	
Conventional	1.404	1.404	108

ding to the international guidelines at the Outpatient Allergy Clinics of three Spanish hospitals: the "Reina Sofía" Hospital in Córdoba, the "Virgen de la Cinta" C.P.E. in Huelva, and the "Conxo" Hospital in Santiago de Compostela. The four cohorts comprised 108 patients, 40 (37%) females and 68 (63%) males. Three patients (2.8%) had only rhinitis and 105 (97.2%) persistent mild-to-moderate bronchial asthma⁶ with or without associated rhinitis. Hypersensitivity to *A. tenuis* was diagnosed by skin prick test (wheal diameter equal to or greater than that of the 10 mg/ml histamine diphosphate positive control) and specific IgE quantitation (CAP class 3 or higher, CAP System, Pharmacia, Uppsala, Sweden). The mean age of the study population at the time of beginning immunotherapy was 12.7 years (range, 4 to 28 years; median age 11 years).

In all cases an aluminium hydroxide-adsorbed, biologically standardised *Alternaria tenuis* extract was used that is marketed at a maximum concentration of 1 Biological Unit (B.U.)/ml (Pangramín Depot B.U.®, ALK-ABELLÓ, Madrid, Spain).

The four dosage schedules used (Table I) were progressively introduced, with no predetermined assignment criteria.

All patients gave their informed consent for receiving their immunotherapy treatments under controlled conditions, under direct supervision by the authors. The 1993 European Guideline³ for immunotherapy administration and adverse reaction assessment was applied, which has been confirmed by the WHO in 1998¹; the same Guideline was followed for the administration of corrective treatment when required.

For the statistical study, the SPSS software package for scientific data was used.

RESULTS

Table II summarises the number of visits to the Allergy Clinics by the study patients, the incidences, and the numbers of doses received. The same table also states the theoretical numbers of visits and doses for the same numbers of patients if they had received a conventional schedule with no incidences.

The adverse events observed were associated to Schedule 1. One immediate local reaction of assessable size was recorded, which did not lead to any modification of the schedule, and two Grade II systemic reactions: one case of rhinoconjunctivitis and one of mild bronchospasm. The one rhinoconjunctivitis episode occurred in a 17-year-old female diagnosed of rhinoconjunctivitis without associated asthma, 15 minutes after the administration of a 0.1 ml dose from Vial 3. This reaction remitted with antihistamines. The bronchospastic episode occurred in a 10-year-old girl with a diagnosis of bronchial asthma, 10 minutes after the second 0.4 ml dose from Vial 3, and subsided adequately after administration of an aerosolised β -agonist. In the first case the immunotherapy schedule was increased by one visit and two doses, and in the second one by two visits and three doses.

In addition, there was an overall increase by six visits and fifteen doses over the programmed duration and dose numbers of the schedules for a number of reasons other than adverse events, mostly irregularities in therapy compliance.

No immunotherapy course was interrupted, and there were no withdrawals or dropouts. All 108 patients progressed to the maintenance phase with the 0.8 B.U. dose recommended by the manufacturer.

DISCUSSION

The occurrence of systemic reactions under immunotherapy has been ascribed to reasons related to the patient (severity of the treated condition, extreme hypersensitivity), to the extract used (excessive potency, badly controlled composition, component instability) or to the administration schedule (induction phase, rapid schedules)¹. Most of the fatal reactions reported in the literature

have been associated to avoidable factors (errors in dosage, incompatibilities that had not been considered, clinical instability, delayed identification and management of the reaction, batch disparities, and others)⁷. The number and severity of the adverse reactions during immunotherapy decreases considerably when controlled administration is performed according to the European guidelines⁸, even to the point of elimination of Grade IV reactions^{9,10}. Furthermore, it is in the mind of all present day Allergologists that the safety of immunotherapy, and not only its efficacy, increases with the specificity of the extract. The concept that "innocuousness equals safety" is by now obsolete⁸, as demonstrated by the fact that hymenoptera venom extracts, which are well known to be not at all innocuous, have been the subject of only a single report of a fatal adverse reaction¹¹.

The routine modality of administration of immunotherapy has come under self-critical review in recent years, based on the fact that the conventional schedules, with 12-to-16-week induction phases, had actually been arbitrarily proposed and had not been questioned for decades, as they were considered to be safer than the cluster and quick immunotherapy ones.

The 108 patients reported in the present paper had received *Alternaria tenuis* immunotherapy according to any one of four cluster schedules. The results achieved with Schedule 1, the so-called "Roman" schedule, with depot *Dermatophagoides pteronyssinus* extracts have been reported previously¹². This same schedule, with slight modifications, has been applied with aqueous grass pollen and *Olea europaea* pollen extracts of two different manufacturers¹³. In both cases, the numbers of patients evidencing systemic reactions (all of them mild) were similar to those reported in other series with controlled administration of conventional schedules^{9,14}. The results have been reported of a large series¹⁵ of patients treated with the same *Alternaria* extract using the "Roman" schedule, in which inflammatory reactions of varying intensity occurred in 1.17% of the injections and Grade II systemic reactions in 0.2%. In the present series there were two Grade II reactions in the 60-patient, 605-dose subgroup, equivalent to 3.3% of the patients and 0.3% of the doses (the latter percentage is slightly lower if the increased number of doses due to incidences in this group is considered).

The present results may be considered to represent a guarantee of the safety of the "Roman" schedule with the extract used. However, the intention of the authors is to improve any safe schedule by achieving, in the induction

phase, the lowest possible number of visits and of doses. Schedules 2 and 3 represent stepwise improvements on Schedule 1, and they have evidenced a good safety level despite the low numbers of cases; they thus constitute an adequate transition to Schedule 4. The technique for their development has included adjustment, among other parameters, of the initial starting dose. If correction of the Th2 – Th1 dysbalance is accepted as the probable mechanism of action of immunotherapy, we must also accept that those who postulate that the administration of low doses of allergen adsorbed on aluminium hydroxide are not a desensitisation technique, but quite the reverse, are right¹⁶. The present proposal, together with the manifest lack of need of the lowest dosages for guaranteeing the safety of the patient receiving immunotherapy¹⁷, constitutes an invitation to all Allergologists to begin their immunotherapy courses with doses higher than those habitually used. Even so, other clinical groups with recognised experience in immunotherapy prefer to cluster their schedules and give lower starting doses, although this implies a greater number of injections and of visits¹⁸.

A conventional immunotherapy induction schedule of 13 visits, for 108 patients, would have taken up 1,404 visits and as many doses. The present series has taken up 402 visits and 944 doses. This represents savings of 1,002 visits for the Health Care System and of 460 injections for the patients, who are mostly very young people. The numbers of visits and injections decrease gradually from Schedule 1 to Schedule 4, which allows for a 50% reduction in the number of doses and a 75% one in the number of visits as compared to a conventional schedule.

In summary, the *Alternaria tenuis* extract used in the present study has evidenced excellent safety in cluster initiation schedules which range from four visits and ten doses to three visits and six doses; the latter one shall probably provide clinical benefit for the patients and considerable savings for the Health Care System.

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