

REVIEW

ARTICOLO DI AGGIORNAMENTO

Pre-seasonal or perennial multiple allergen extract based immunotherapy: hypothesis of therapeutic approach to treatment of symptomatic polysensitised allergic patients

Immunoterapia pre-stagionale o perenne a base di estratti allergenici multipli: ipotesi di un approccio al trattamento di pazienti allergici polisensibilizzati sintomatici

R.E. ROSSI, G. MONASTEROLO*, L. ROSSI**

Allergy Unit, National Health Service, Rete di Allergologia Regione Piemonte, Cuneo 1, Italy; * Dipartimento di Analisi Chimico-Cliniche e Microbiologia, Ospedali di Fossano e Savigliano, Italy; ** Department of General Pathology, University of Genoa, Italy

Key words

Allergen • Sublingual immunotherapy • Subcutaneous immunotherapy

Parole chiave

Allergene • Immunoterapia sottocutanea • Immunoterapia sublinguale

Summary

Symptomatic allergic patients are often polysensitised. In order to discover symptom causative allergens and to discriminate between apparent and genuine polysensitisation cases, component resolved diagnosis is the correct approach toward the selection of an appropriate allergen extract for immunotherapy. Different allergen vaccines could be administered to patients before the pollen season over different periods and with various modalities in order to respect patient's sensitisation profile and symptom onset.

Allergic disorders represent the second cause of chronic systemic illness after cardiovascular diseases. Nowadays more than 75% of symptomatic allergic patients are polysensitised ¹. In these cases, when an allergen extract-based diagnosis is utilized, the choice of an allergen vaccine may be cumbersome. Component-resolved diagnosis has been greatly improved with the recent commercial availability of allergen molecule-based immuno-assays (e.g. CAP-System, Immuno-Solid-phase Allergen Chip); allergists can now define the sensitisation profiles of their patients in order to facilitate an allergen-comprehensive immunotherapy ²⁻⁴. This innovative approach has aided in ascertaining patients' cross- or co-sensitisation status so that symptom causative allergens may be identified. It is well known that allergen-specific immunotherapy induces a state of antigen-

Riassunto

I pazienti allergici sintomatici sono spesso polisensibilizzati. Per individuare gli allergeni che causano la malattia e per distinguere casi di polisensibilizzazione vera o apparente, l'approccio diagnostico corretto deve essere basato sull'impiego di componenti definiti per poter scegliere l'estratto allergenico per immunoterapia più appropriato. Prima della pollinazione possono essere somministrati ai pazienti vaccini allergene-specifici, in periodi differenti e con varie modalità, rispettando il profilo di sensibilizzazione del paziente e la comparsa della sintomatologia.

specific non-responsiveness, particularly in allergic rhino-conjunctivitis and/or asthma and Hymenoptera venom allergy ⁵. Co-sensitised patients require an allergen vaccine containing the relevant allergens responsible for the symptoms. In addition, mixtures of allergens with protease activities should be avoided (e.g. groups 1, 3, 6, 9, 15 of mite allergens which may destroy the structure of pollen allergen molecules with consequent loss of their immunogenicity) ⁶. Once the patient's specific IgE profile has been established by component-resolved diagnosis, various allergen vaccines can be administered prior the pollen season (indeed throughout multiple pre-pollination periods according to need), utilizing different modalities of administration. Although there is no experimental proof or clinical trial that multiple immunotherapies given prior to different pollen seasons are effective,

we have previously documented a good safety profile of sublingual allergen vaccines when administered at high doses before the pollen season ⁷⁻⁹; these doses have been much higher than those administered in controlled studies in which efficacy of SCIT/SLIT was well established ⁵. This might enable allergists to administer allergen vaccine sequentially at high doses over short periods in order to treat the patient's prevailing sensitisations. Recent allergen immunotherapy studies have demonstrated a dose dependency on clinical efficacy ¹⁰⁻¹⁵. In order to achieve a good clinical outcome, a cumulative dose of at least 100-200 $\mu\text{g}/\text{year}$ should be administered with subcutaneous allergen vaccines ^{5,16}. Similarly, with sublingual vaccine a dose of 2-6 mg/year of major allergen is recommended ^{7,10-12,17}. Table I shows the recommended doses for main major allergens in different controlled studies.

Consistent with these studies we suggest that poly-allergic patients, on the basis of their persistent symptoms and patterns of sensitisation, could be conveniently treated with different allergen immunotherapy regimens as depicted in Figures 1-4. This approach

could be advantageous because the allergic patient can receive different allergen extracts via different administration routes and this is a satisfactory alternative to renouncing allergen immunotherapy altogether ³⁸. Further, it allows the allergist to customise any given patient's immunotherapy regimen throughout the year according to season and environmental presence of allergens. Last but not least, it has been observed that patients who receive high dose sublingual vaccine over a short period (weeks) without significant side effects, are particularly pleased with the results compared to the administration of low dose vaccine regimens over longer periods. Given that allergen immunotherapy is the only curative approach to treatment of respiratory allergic disease ³⁹, allergen vaccines could have significant economic advantages over antiallergic drug treatment in the long term ⁴⁰ with negligible side effects.

In conclusion poly-allergen immunotherapy could confer an immunological advantage ^{41,42}, as well as beneficial clinical outcomes and long-term economic savings for patients.

Tab. I. Recommended major allergen doses administered to allergic patients in different controlled vs. placebo studies.

	Duration (months)	Monthly Dose (μg)	Daily Dose (μg)
Hirsch et al., 1997 ¹⁸	12	47.5	1.5 (Der p 1)
Vourdas et al., 1998 ¹⁹	5	337.0	11.1 (Ole e 1)
Clavel et al., 1998 ²⁰	6	576.0	19.2 (Phl p 5)
Bousquet et al., 1999 ²¹	24	1.04	0.034 (Der p 1)
Passalacqua et al., 1999 ²²	8	2.0	0.06 (Par j 1)
Pradallier et al., 1999 ²³	4	255.0	8.50 (Phl p 5)
Purello D'Ambrosio et al., 1999 ²⁴	8	1.50	0.05 (Par j 1)
Pajno et al., 2000 ²⁵	24	100.0	3.33 (Der p 1)
Guez et al., 2000 ²⁶	24	91.66	3.05 (Der p 1)
Bahceciler et al., 2001 ²⁷	6	93.33	3.11 (Der p 1)
Ippoliti et al., 2003 ²⁸	6	57.0	1.58 (Der p 1)
Bufe et al., 2004 ²⁹	36	263	8.76 (Phl p 5)
Khinki et al., 2004 ¹⁷	24	465.91	15.53 (Bet v 1)
Marogna et al., 2004 ³⁰	36	10.83	0.36 (Der p 1)
Smith et al., 2004 ³¹	24	2.91	0.097 (Phl p 1)
	32	2.18	0.072 (Par j 1)
Rollinck-Wernighouse et al. 2005 ³²	12	15.6	0.52 (Phl p 1)
Bahceciler et al., 2005 ³³	36	174.0	5.8 (Dac g 5)
Marogna et al., 2005 ³⁴	4	913.0	30.45 (Lol p 1)
Rossi et al., 2005 ^{7-9*}	4	720.0	24.0 (Phl p 5)
	4	600.0	20.0 (Bet v 1)
	4	6300.0	210.0 (Par j 1)
Durham et al., 2006 ¹⁰	2	900.0	15.0 (Phl p 5)
Valovirta et al., 2006 ³⁵	12	128; 15.3	4.2; 0.51 (Bet v 1)
Savolainen et al., 2006 ³⁶	24	128.0; 15.3	4.2; 0.51 (Bet v 1)
Niu et al., 2006 ³⁷	6	283.3	9.4 (Der p 1)

* Open studies

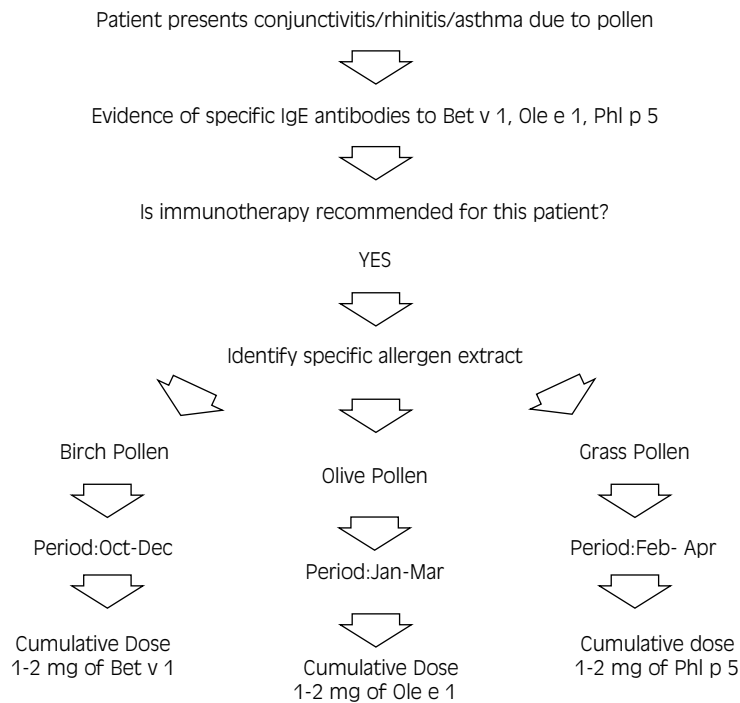
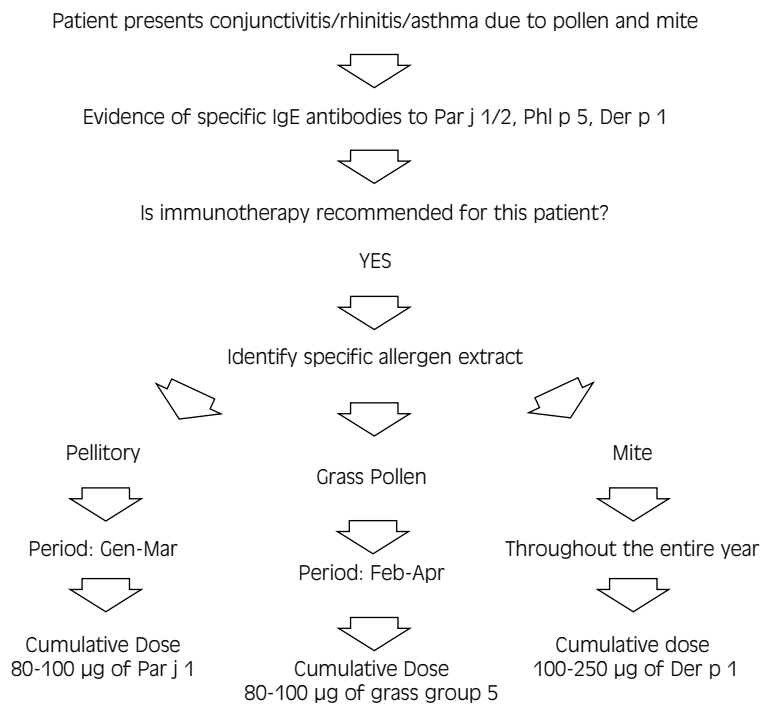
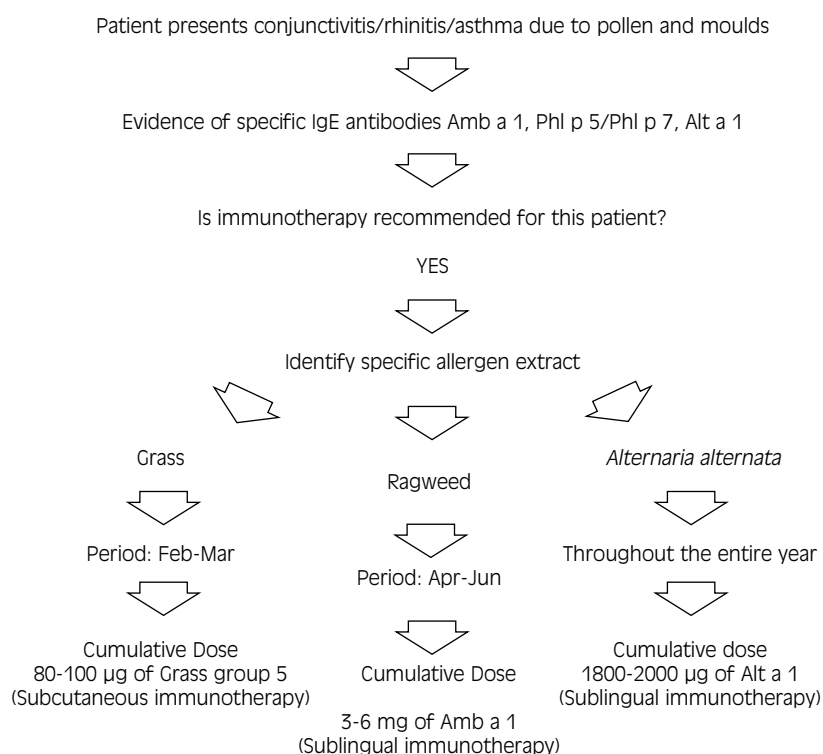
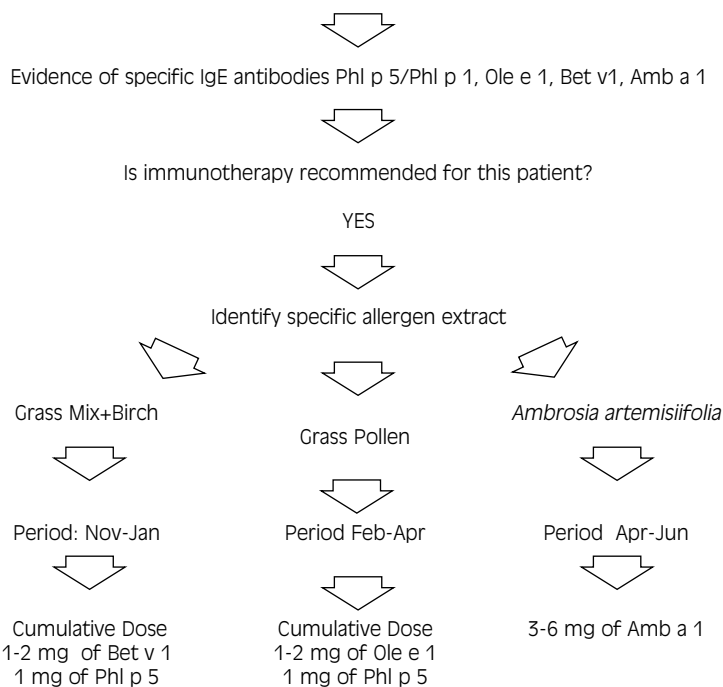
Fig 1. Algorithm for sequential sublingual allergen immunotherapy.**Fig 2.** Algorithm for sequential subcutaneous allergen immunotherapy.

Fig 3. Algorithm for sequential combined subcutaneous/sublingual allergen immunotherapy.**Fig. 4.** Algorithm for sequential sublingual allergen immunotherapy.

Patient presents conjunctivitis/rhinitis/asthma due to pollen poly-sensitisation with a prevalence of symptoms on May-June



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