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REVIEW

Practice parameters for sublingual immunotherapy

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ABSTRACT: ***Practice parameters for sublingual immunotherapy. C. Ortolani, F. Agostinis, S. Amoroso, R. Ariano, A. Barbato, M. Bassi, G. Cadario, P. Campi, F. Cardinale, G. Ciprandi, R. D'Anneo, M. Di Gioacchino, V. Di Rienzo, A. Fiocchi, M. Galimberti, E. Galli, M. Giovannini, C. Incorvaia, S. La Grutta, C. Lombardi, F. Marcucci, G. Marseglia, M. Minelli, A. Musarra, E. Nettis, E. Novembre, G. Pajno, G. Patriarca, F. Pezzuto, P. Piras, S. Pucci, A. Romano, C. Romano, O. Quercia, G. Scala, D. Schiavino, G. Senna, G. Sforza, M. Tosca, S. Tripodi, F. Frati.***

The efficacy and safety of sublingual immunotherapy (SLIT) are currently supported by clinical trials, meta-analysis and post-marketing surveys. Practice parameters for clinical use of SLIT are proposed here by a panel of Italian specialists, with reference to evidence based criteria.

Indications to SLIT include allergic rhinoconjunctivitis, asthma, and isolated conjunctivitis (strength of recommendation: grade A). As to severity of the disease, SLIT is indicated in moderate/severe intermittent rhinitis, persistent rhinitis and mild to moderate asthma (grade D).

SLIT may be safely prescribed also in children aged three to five years (grade B), and its use in subjects aged more than 60 years is not prevented when the indications and contraindication are ascertained (grade D).

The choice of the allergen to be employed for SLIT should be made in accordance with the combination of clinical history and results of skin prick tests (grade D). Polysensitisation, i.e. the occurrence of multiple positive response does not exclude SLIT, which may be done with the clinically most important allergens (grade D).

As to practical administration, co-seasonal, pre co-seasonal, and continuous schedules are available, being the latter recommended for perennial allergens or for pollens with particularly prolonged pollination, such as Parietaria (grade D). For pollens with relatively short pollination, such as grasses and trees (cypress, birch, alder, hazelnut, olive) the pre co-seasonal and perennial schedules are preferred (grade C).

The build-up phases suggested by manufacturers can be safely used (grade A), but they can be modified according to the patient's tolerance (grade C). A duration of SLIT of 3-5 years is recommended to ensure a long-lasting clinical effect after the treatment has been terminated (grade C). ***Monaldi Arch Chest Dis 2006; 65: 1, 44-46.***

Keywords: Sublingual immunotherapy, rhinitis, asthma, conjunctivitis.

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Introduction

Sublingual immunotherapy (SLIT) has received great interest since its introduction [1-3], and is currently considered a viable alternative to subcutaneous immunotherapy (SCIT). In recent years the scientific evidence on SLIT was further integrated by a meta-analysis study of efficacy [4], by reviews and large surveys on the safety [5-8], and other clinical aspects were investigated as well. As to efficacy, the meta-analysis in adults could yield the number of patients needed to ensure the strongest evidence [4] while the few studies addressed with children prevent as yet to reach similarly sound conclusions [9] though a clear benefit was reported in single studies [10, 11]. In addition, clinical effectiveness was apparent concerning mite-induced asthma also from systematic review [9].

A panel of Italian specialists accomplished in allergen immunotherapy was formed to propose practice parameters of SLIT to be used to perform such treatment, considering all the literature and, when unavailable, their clinical experience. Regarding the latter, the statements were derived from the specialist's answers to a questionnaire dealing with the practical aspects of SLIT. These parameters are specifically addressed with practical use of SLIT, regarding the indications, the choice of allergens to employ, the schedules of administration, the duration and monitoring of treatment, and refer to the commonly used form of sublingual/swallow immunotherapy, in which the allergen extract is kept under the tongue for a few minutes and then swallowed, since the so called sublingual/spit form, in which the extract is spat out, has been insufficiently studied.

The scientific evidence was classified according to Shekelle *et al.* [12], who introduced four grades of recommendation of strength of based on six categories of evidence (table 1).

Table 1. - Classification of scientific evidence

CATEGORY OF EVIDENCE	
Ia:	evidence from meta-analysis of randomised controlled studies
Ib:	evidence from at least one randomised controlled study
IIa:	evidence from at least one controlled study without randomisation
IIb:	evidence from at least one other type of quasi-experimental study
III:	evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV:	evidence from expert committee reports or opinions or clinical experience of respected authorities, or both
STRENGTH OF RECOMMENDATION	
A:	directly based on category I evidence
B:	directly based on category II evidence or extrapolated recommendation from category I evidence
C:	directly based on category III evidence or extrapolated recommendation from category I or II evidence
D:	directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

Indications to SLIT

According to placebo-controlled studies, SLIT has a grade A strength of recommendation for treating allergic rhinitis/rhinoconjunctivitis [4] and allergic asthma [13], and this completely agrees with the current concept of rhinitis and asthma as manifestations of a same allergic syndrome. Similar recommendation is also available for isolated allergic conjunctivitis [14].

Regarding the severity of the disease, rhinitis is currently classified in intermittent and persistent, both divided into mild and moderate/severe [3]. Intermittent allergic rhinitis is eligible for SLIT when moderate/severe, persistent allergic rhinitis also when mild, due to the duration of symptoms (grade D).

Asthma is similarly classified in intermittent, mild, moderate, and severe persistent [15]. Intermittent and mild to moderate persistent asthma is eligible for SLIT, while severe asthma must not be treated for safety reasons, unless drug treatment induces a step down of the disease to lower levels (grade D).

Concerning the patient's age, recent data has shown that the occurrence rate and severity of adverse events in children aged 3-5 years [16-18] does not differ from other age ranges. Therefore, the age of 3 years or greater can be considered adequate to start the treatment (grade B). In adults, there is, in principle, no upper limit of age for starting SLIT, but over 60 years the allergic mechanism and the causal role of allergen (s), must be clearly documented and other causes of respiratory diseases must be ruled out (grade D).

When deciding to use SLIT instead of SCIT, some important factors must be considered: the fact that SCIT is relatively contraindicated in children younger than 5 years, the patient's preference, and the expected compliance, recently evaluated in SLIT treated subjects [19, 20] and in one study [20] compared to SCIT (grade C).

Choice of the allergen (s)

The choice of allergen to be employed for SLIT should be made, as for SCIT, according to the combination of clinical history and results of skin prick tests; a combination of clinical history and *in vitro* IgE tests are acceptable when skin prick tests cannot be performed (grade D).

The presence of polysensitization, i.e. of multiple positive response to diagnostic tests does not exclude SLIT: in such case the clinically most important allergen (s) must be used for treatment, and mixtures of several allergens must be avoided (grade D). If the use of only one allergen is decided, it is preferable to perform SLIT with the perennial instead of the seasonal allergen (grade D).

Schedules of administration

Co-seasonal (which commences at the beginning of pollen season and is interrupted at the end of the season each year), pre-co-seasonal (which commences before the pollen season and is interrupted at the end of the season each year), and continuous (which can commence at any time and is continued without interruption) schedules are available. The continuous administration is recommended for perennial allergens such as house dust mites, animal epithelia, and moulds, but also for pollens with particularly prolonged pollination, such as Parietaria (grade D). For pollens with relatively short pollination, such as grasses and trees (cypress, birch, alder, hazelnut, olive) the pre-co-seasonal schedules have to be preferred (grade C).

The build-up phases suggested by manufacturers can be safely used (grade A), but they can be modified according to patient's tolerance and following some general rules [21], which essentially regard local reactions in the mouth or at gastrointestinal level (grade C).

In case of momentary interruption of SLIT, it is advisable to restart the treatment from the build-up phase if more than 40 days have passed from the latest administration (grade D).

Duration of treatment and monitoring

According to follow-up studies [22] a duration of SLIT of 3-5 years can be recommended to ensure a long-lasting clinical effect after stopping the treatment (grade C). This can be applied to any allergen used for treatment (grade D).

To monitor the efficacy of the treatment, clinical data (severity and duration of allergic symptoms, drug consumption, and quality of life) is adequate. Among immunological parameters, the possible reduction of the skin prick test response to the specific allergen can be used as an indicator of decrease of sensitivity induced by SLIT, while *in vitro* measurement of specific IgE or IgG antibodies are of secondary importance (grade D).

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