

A MODEL FOR MANAGEMENT OF SUBLINGUAL IMMUNOTHERAPY

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Summary

High dose sublingual immunotherapy (SLIT) is generally well tolerated, since most side effects are local reactions involving the oral or gastrointestinal mucosa. However, such reactions, if not adequately managed, may lead the patient to stop SLIT.

■ **Objective :** We introduce a method to manage side effects of SLIT, which was successfully applied on a group of children undergoing SLIT.

■ **Methods :** SLIT was performed with Staloral 300® (Stallergenes, Antony, France) by the schedule in 11 days indicated by the manufacturer with a top dose of 8 pressures of the 300 IR concentration. The treatment was managed by flow charts suggesting adjustment of dose, regimen, or kind of assumption depending on the kind of reactions (oral, gastrointestinal, respiratory).

■ **Results :** An overall number of 200 children (120 males, 80 females, mean age 9 yrs, range 3-14 yrs) were treated. Of them, 155 (77.5%) had no reaction, while 45 (22.5%) had side effects, consisting of 20 oral itching or burning, 15 gastrointestinal symptoms and 10 rhinitis. No systemic reaction was observed. All side effects were successfully managed by the proposed method, thus reaching the maintenance dose in all patients but one, reporting repeated intense oral itching, who stopped SLIT.

■ **Conclusions :** High dose SLIT is well tolerated in treated patients. In most patients with side effects, which are mainly oral itching or gastrointestinal disturbances due to contact with the allergen extract, a proper management allows to reach the maintenance dose with no further reactions.

Key-words : Immunotherapy - SLIT - Side effects - Management.

INTRODUCTION

Allergen specific subcutaneous immunotherapy (IT) is an effective treatment of respiratory allergy (1, 2), but is somewhat limited by the problem of adverse reactions, which in some countries led to a negligible use of this treatment (3).

Administering the allergen extracts by ways different from the subcutaneous and particularly by local ways, was seen as a possible solution to this problem.

Among them, sublingual immunotherapy (SLIT) has emerged as the most suitable local IT, and recent consensus documents indicate it as a therapeutic option in adults and children with allergic rhinitis, conjunctivitis and asthma, provided adequate cumulative doses, 100 or more times greater than those received by subcutaneous IT, are administered (4).

Still, side effects may occur with SLIT, mainly consisting of local reactions in the mouth or in the gastrointestinal tract (5-7), while no anaphylactic reactions was reported thus far. Such reactions are mostly light/moderate but when repeated may lead the patient to stop SLIT, thus denying an effective treatment.

We propose in this article a method to manage SLIT by using flow charts designed for the different kinds of side effects encountered, which were successfully applied on patients treated with high dose SLIT.

METHODS

PATIENTS

We evaluated the tolerability of high dose SLIT in 200 children (120 males, 80 females, mean age 9 years, range 3-14 years). Most patients were treated with grass pollen extract or house dust mites extracts (150 patients), the remaining were treated with tree pollen extracts (30 patients), *Parietaria* pollen extracts (10 patients), and *Alternaria* (10 patients).

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EXTRACTS

SLIT was performed with Staloral 300® (Stallergènes, Antony, France) with a treatment schedule in 11 days for the initial phase as indicated by the manufacturer culminating in a top dose of 8 pressures 3 times a week of the 300 IR concentration except treatment with alternaria which was performed with Staloral 100 with a treatment schedule in 28 days for the initial phase as indicated by the manufacturer culminating in a top dose of 20 drops 3 times a week of the 100 IR. The doses were administered in the morning before breakfast (before breakfast and dinner when half-doses were used), holding the extract for at least two minutes under the tongue.

ASSESSMENT OF SIDE EFFECTS

Each side effect was registered and classified according to a scale from 0 to 5 as reported in table 1. The management of side effects was done according to the flow-charts reported in figures 1 to 4, particularly for the reactions with oral itching or burning (figure 1), with gastrointestinal symptoms (figure 3), and with systemic symptoms (figure 4).

Grade of symptoms	Kind of symptoms
0	Absent
1	light, perceived by the patient but not requiring consult with physician
2	Moderate, perceived more greatly and requiring consult with physician but with no need of drug treatment
3	Intense, perceived very intensely and worrying for the patient, modifying quality of life and requiring changes in SLIT regimen or possible drug treatment
4	Marked, requiring an intervention by the physician or by E.R. and momentary suspension of SLIT
5	Severe, with life-threatening reactions requiring early intervention or hospitalization

Table 1 : Grading of side effects to SLIT.

RESULTS

One hundred-fifty-five patients (77.5%) tolerated SLIT with no reaction, while 45 (22.5%) had side effects, consisting of 20 oral itching or burning, 15 gastrointestinal symptoms, and 10 rhinitis.

The reactions were equally distributed between the build-up (23 reactions) and the maintenance phase (22 reactions). No oedema of the mouth and lips, nor skin reactions, asthma or other kinds of severe sys-

temic reactions were observed. Two patients reported ear disturbances, and thus underwent to a tympanogram which gave normal result.

Most side effects were classified as graded 1 or 2 according to the reported grading scale, and none required urgent medical intervention.

All side effects were successfully managed with the flow-charts indicated above and it was thus possible to reach the maintenance phase in all patients but one, who had repeated intense oral itching despite the dose adjustment and refused to continue SLIT.

DISCUSSION

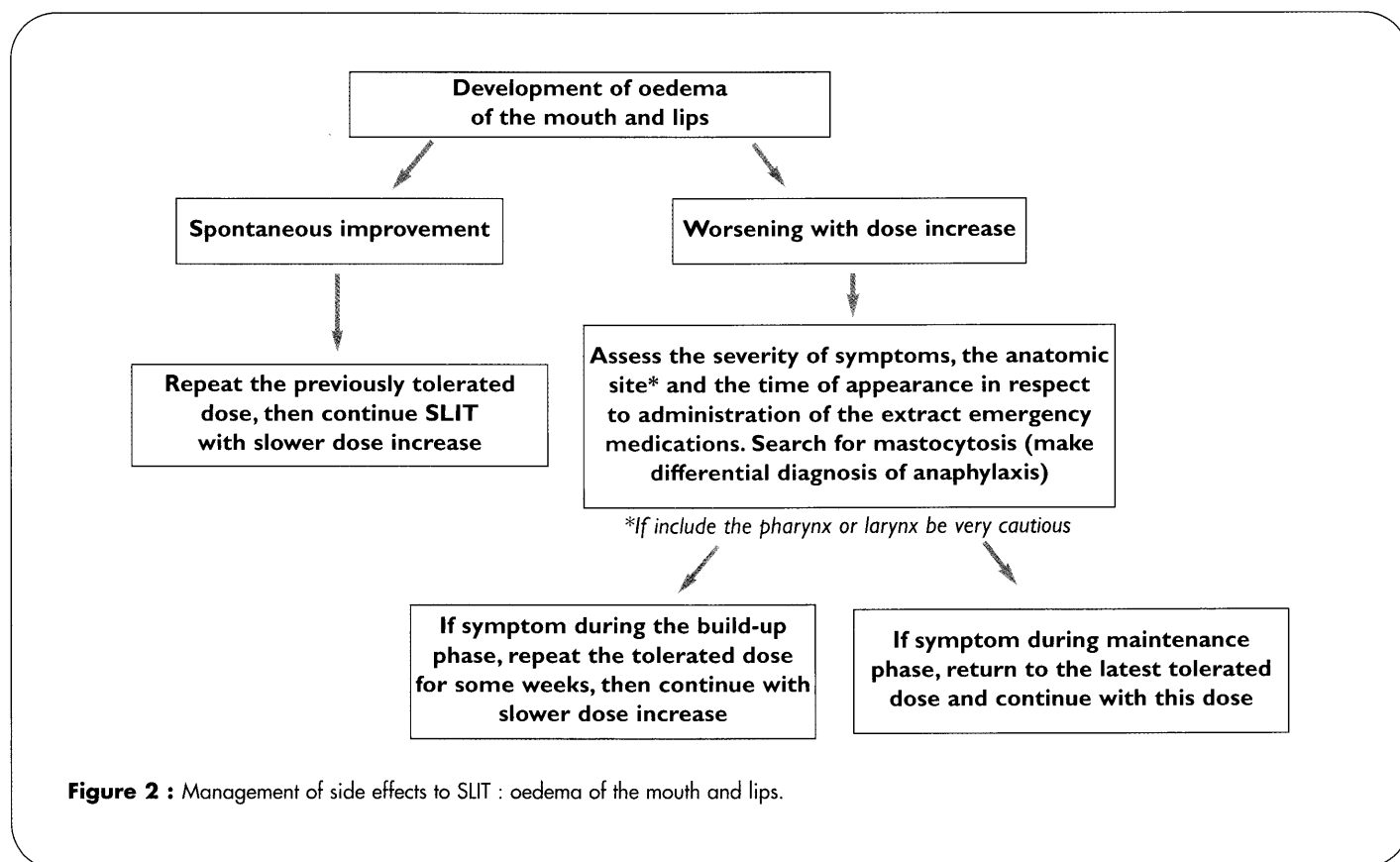
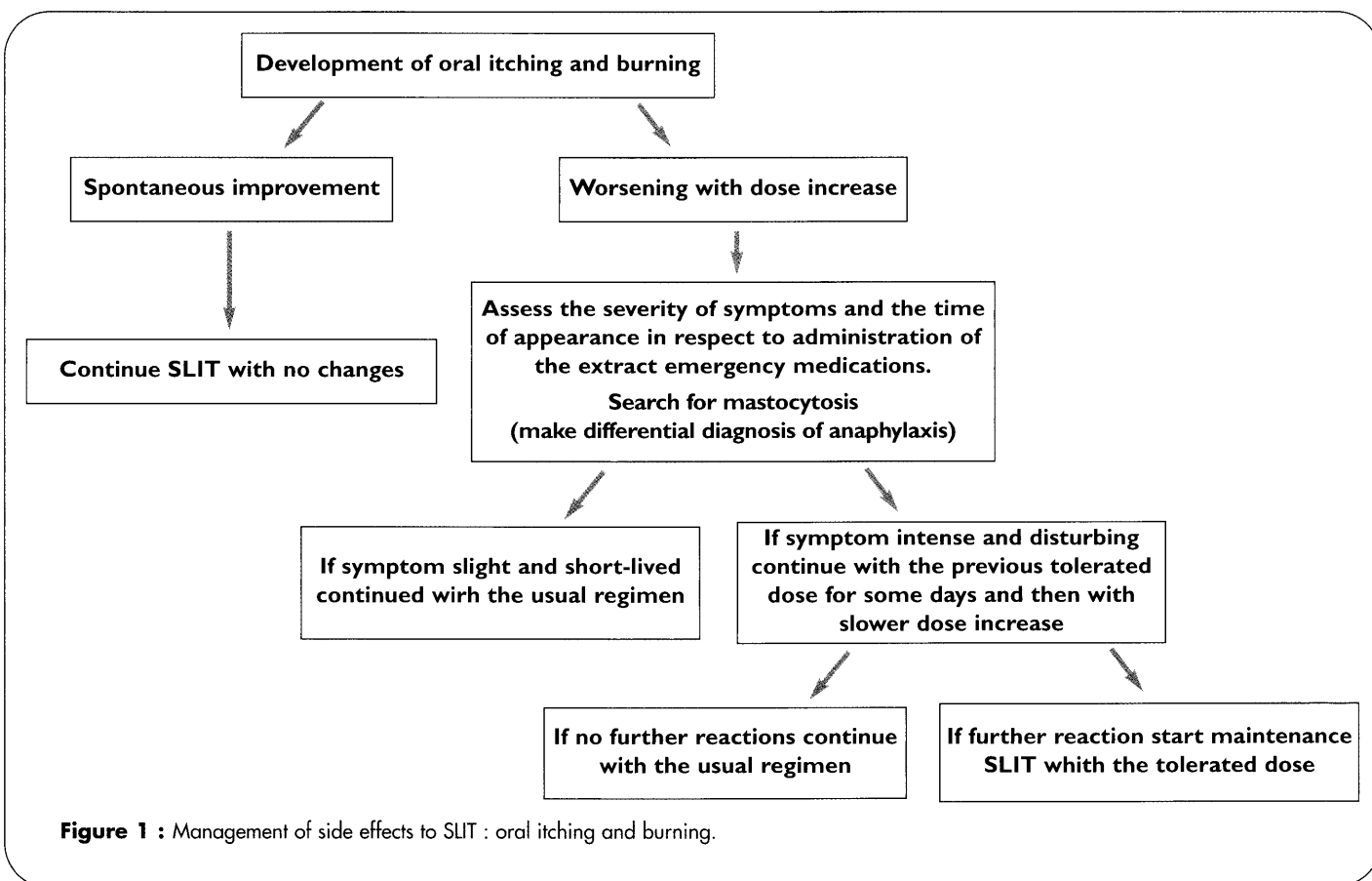
SLIT was introduced in 1986 with a study based on homeopathic doses (8), but trials conducted with therapeutic dosages were conducted in the first half of the 90s (9-12).

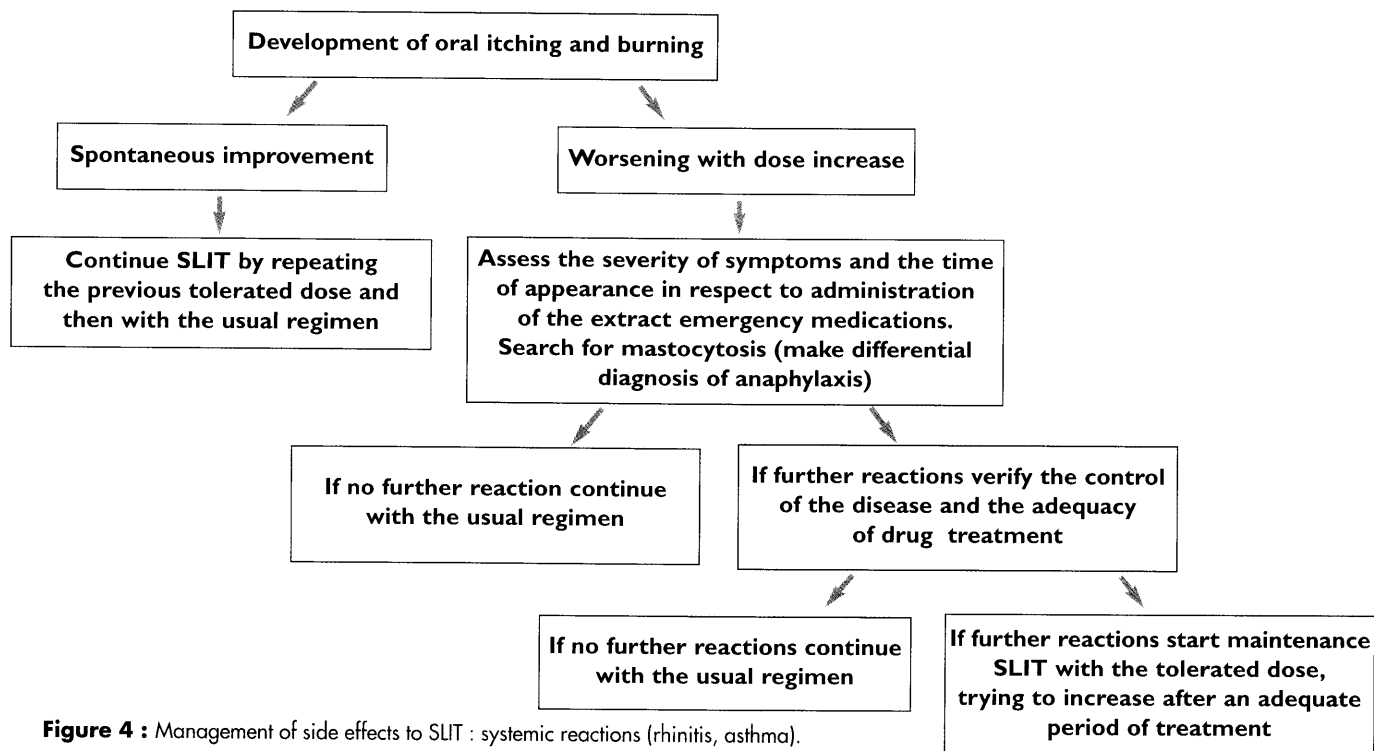
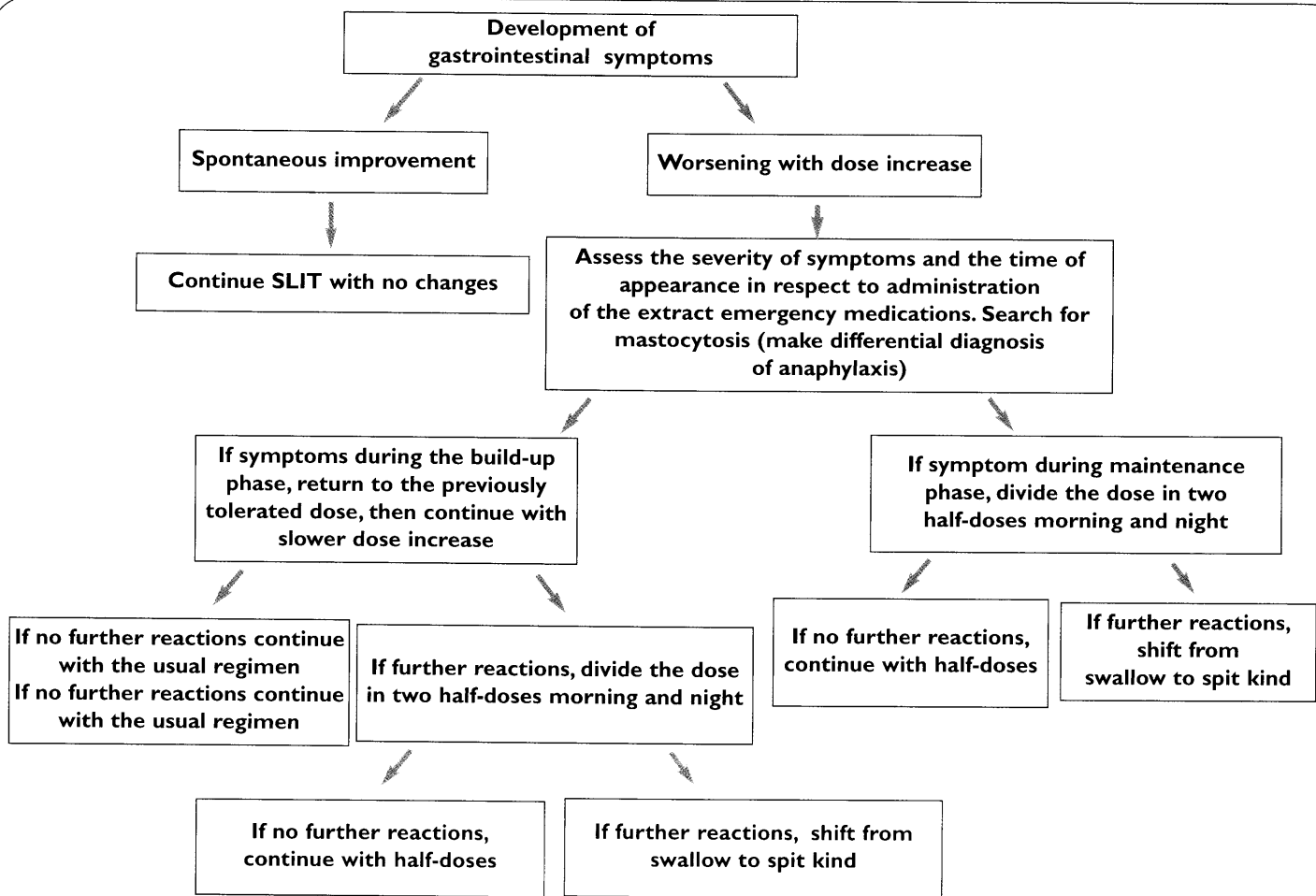
From one study it seemed apparent that the tolerability of SLIT was controversial because much lower in children even though conducted with low doses (9) but subsequent accurate analysis and studies did not confirm such observation (5, 6) and currently this treatment is equally indicated in adults and children (4).

From all the available controlled studies it is evident that SLIT is generally well tolerated, and that systemic reactions, such as rhinitis, asthma or urticaria, are more frequent in placebo treated (probably for the bad control of the allergic disease) than in actively treated patients (6). The only side effects significantly related to SLIT are local, with involvement of the oral cavity and of the gastrointestinal tract. They may be compared to the local reactions in the arm with subcutaneous IT, however when repeated and disturbing may be a cause for treatment withdrawal. André found that repeated or intense buccal phenomena and abdominal pain were the main cause of dropout in both adults and children (13).

In the present study we treated 200 children with high dose SLIT, assessing every side effect according to their kind and to a grading of severity. The rate of reactions was 22.5%, somewhat lower than that observed in controlled studies (6), with no severe reaction requiring drug treatment.

The most commonly reported side effects were oral itching or burning, followed by gastrointestinal symptoms, which are those commonly described in all SLIT controlled trials irrespective of the magnitude of the dosage administered.





These results confirmed the safety of high dose SLIT and are in agreement with a recent placebo-controlled study analysing three regimens of SLIT with different dose increase, that showed that there was no statistical difference in the rate of such reactions between the actively treated groups with low or higher dose of SLIT (14).

The major aim of this study was to assess whether side effects to SLIT can be managed to reach the maintenance phase and prevent treatment dropouts.

The data we obtained indicate that the described management model is able to achieve such a goal. In particular, all oral reactions but one and most gastrointestinal were overcome by dose adjustment, while gastrointestinal symptoms required in a few cases (2 patients) the shift from swallow to spit kind.

This shift proved to be effective in managing the two rare cases of very sensitive patients and in avoiding drop out.

However, clinical efficacy of sublingual spit IT has yet to be demonstrated in controlled trials and sublingual swallow IT remains currently the only form of SLIT treatment clinically validated (15).

One must consider that the difference between the sublingual and the oral route, no more considered an effective treatment (4), is in the prolonged contact with the oral mucosa, which ensures the characteristics of the kinetics of the allergen extract (16).

In particular what must be clinically validated in controlled trials is the fact that once the tolerance to the administered allergen takes place, it is possible to return to the swallow kind, as we experimented with success in the patients we studied.

Concerning the management of reactions with angioedema or asthma, the model we propose remain theoretical, as we did not observe such reactions, but it is conceivable that the dose adjustment to the individual reactivity is able to achieve in most patients an adequate treatment performance. In any case, our model is suitable with the regimen and doses of the extracts we used, and different materials deserve other investigations.

In conclusion, high dose SLIT has been well tolerated in treated children. The encountered side effects are those described in controlled trials, mainly oral itching and burning or gastrointestinal disturbances due to contact with the allergen extract, and can be easily managed with some simple measures which allows to reach the maintenance dose with no further reactions.

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