PRIMING-LIKE EFFECT AND SUCCESSFUL DESENSITIZATION AFTER ANAPHYLACTIC SHOCK BY LATEX SUBLINGUAL IMMUNOTHERAPY

A. Antico (1), M. Pagani (1), A. Crema (1)

The present report deals with some unusual events observed restarting allergy vaccine in a case of anaphylactic shock which occurred giving the maximum scheduled dose (25 drops) of rush sublingual immunotherapy (SLIT) to latex.
Restarting SLIT by usual (not rush) scheme we observed long-lasting fall of reactivity threshold. The maximum tolerable dose was reduced to 2 drops, a dose fivefold smaller than the one well tolerated during previous rush phase (10 drops).
We have excluded a possible nocebo effect and proved that the reduced tolerance was real by double blind placebo-controlled challenge test. We have considered this effect in some ways similar to priming effect.
SLIT was continued with two drops every day. After about twenty months we could demostrate a significant reduction of skin reactivity by end-point technique and an improved response to the controlled exposition to latex by use-tests. In the same time the tolerance to vaccine was improved to three drops.
The better safety profile allowed us to restart and continue with SLIT also in the reported case of anaphlicatic shock by latex vaccine and, after about two years, to induce valuable hyposensitization. Latex SLIT is confirmed as a safe and effective method.

Immunological tolerance - Latex allergy - Priming effect - Sublingual immunotherapy - Systemic hypersensitivity reaction.

INTRODUCTION

Evidence based studies demonstrate that sublingual (swallowed) immunotherapy (SLIT) is effective and safe without the risks of severe systemic reactions observed with subcutaneous allergen-specific immunotherapy (SCIT) (1, 2). As a matter of fact, the high safety of the method allows home therapy.
Moreover, a number of published studies prove that rush therapy has no more adverse reactions than the usual one, so that more and more allergists are using rush SLIT as it allows to reach within days the maintenance dose and to achieve a reduction of symptoms (3, 4).
As a rule, rush SLIT can be practised without hazards. But exceptions to the rule can exist and uncommon cases of systemic reactions, sometime severe, have been observed during SLIT (5-7).
Recently we have reported a case of severe life-threatening anaphylactic shock during rush sublingual immunotherapy (SLIT) to latex (8).
Later on, we decided to try latex SLIT by usual (not rush) scheme. Restarting SLIT we observed some unusual events not previously described in literature which we refer in the present case-report.

(1) Azienda Ospedaliera 'C. Poma' - MN - SC di Medicina Interna ed Allergologia - Ospedale Civile - 46041 Asola, MN (Italy)

CASE REPORT

A 36-year-old woman with latex allergy, affected by urticaria and asthma challenged by handling or exposition to latex articles was treated with rush SLIT (Alk-Abello', Milan, Italy). About twenty minutes after taking the higher dose the patient showed cutaneous rash and spreading urticaria followed at once by an asthma attack and a serious condition of anaphylactic shock which required treatment in emergency room.
This reaction occurred giving the maximum scheduled dose of rush phase, a dose (25 drops) fivefold higher than that one used as maintenance dose (5 drops). For this reason and taking into account the severity of clinical manifestations challenged by handling or exposition to latex articles of which the patient suffered, compared to proved good tolerability of SLIT (9,10), we considered the opportunity to begin SLIT by usual (not rush) scheme. So, after informed consent, we restarted latex immunotherapy. For safety reasons, during build-up phase we planned to repeat three times the scheduled doses with vial at higher concentration (Tab. 1).
Reached the dose of three drops of vial 4, the patient noticed mouth and throat hitching followed after few minutes by general malaise, sweating, abdominal pain nausea and vomiting. No seriuos changes in vital

signs were observed. The symptoms were well controlled administering antihistamine and steroids.
Next attempts to give three drops provoked the same symptoms. This was very surprising because during previous rush phase of latex SLIT she had well tolerated a dose more than three times higher (10 drops). For this reason we decided to check whether the aforesaid complaints were in some way the result of nocebo effect. So, informed written consent obtained, the patient was submitted to double-blind placebo-controlled challenge-test. Because of the special taste of latex extract, we used as placebo some drops of a commercial compound of metoclopramide laced with citrus fruits juice as well as the vaccine. Five healthy people were unable to detect difference between active and placebo. The challenge test gave a positive result, the same dose reproducing the same symptoms. In this way we were able to demonstrate that the threshold of tolerance was really reduced to two drops.
SLIT was continued with two drops every day, a cumulative dose lower than the optimal maintenance dose scheduled, but in any case considered by the producer as enough to induce immunological tolerance.
The efficacy of SLIT was monitored measuring skin reactivity by end-point technique (11) and performing "use-tests" (12, 13). No changes of reactivity were seen at the first controls, but after twenty months a significant reduction of end-point (from 1:16 to 1:4) and an improved response to controlled exposition to latex were demonstrated. In the same time we observed that also the tolerance to vaccine was improved to three drops. Thus the patient is now pursuing latex SLIT with a maintenance dose of three drops every day, a cumulative dose equal to the one suggested by the producer as optimal.

DISCUSSION

The reported case suggests the following remarks.
At the best of our knowledge, long-lasting fall of tolerance threshold to dose of allergen-vaccine after systemic side effects or anaphylactic shock during immunotherapy has never been reported. As a rule, when a mild to moderate systemic reaction adverse event occurs during build-up phase of SCIT or SLIT the dose is reduced by one or two steps before restarting up-dosing. During maintenance phase dose is reduced of a certain extent with respect to clinical severity of adverse reactions (14). In any way we expecte to be able to go back to the previous higher well tolerated dose.
In the case here reported, we were instead compelled to reduce the maintenance dose to a fifth of the dose before tolerated by the patient. Any attempt to increase this dose proved to be vain. We have demonstrated by double blind placebo-controlled challenge test that the reduced tolerance was real, excluding a possible nocebo effect.
We have considered this effect in some ways similar to priming effect because, likewise to what happens during nasal challenge with pollens, since the symp-

Day	Vial	Dose (drops)	Concentration (mg/ml)	Interval (between doses)
Up-dosing phase				
1	0	1	5×10^{-8}	1 day
2-5			increase 1 drop a day up to 5 drops	1 day
6	1	1	5×10^{-5}	1 day
7-10			increase 1 drop a day up to 5 drops	1 day
11	2	1	5×10^{-2}	1 day
12-15			increase 1 drop a day up to 5 drops	1 day
16	3	1	5	1 day
17-20			increase 1 drop a day up to 5 drops	1 day
21-23	4	1	500	1 day
24-26		2		1 day
25-29		3		1 day
30-32		4		1 day
33		5		
Maintenance phase				
35	4	5		2 days

Table 1: Planned treatment for latex SLIT based on standard schedule.

toms have been provoked, reactivity threshold and provocative dose are both greatly reduced (15,16). We cannot exclude that this effect might be peculiar to latex SLIT. We would speculate that, as far as latex SLIT concerns, the sublingual route causes a mucosal contact and perhaps an allergy response analogous to natural exposition of mucosae to latex allergens.

Another matter is worthy of remark. An analysis of published studies yielded the surprising result that SLIT with high doses is safer than SLIT with usual lower doses (4). In other words it seems there is no correlation between dose increase and increased risk of adverse reactions.

As far as the reported case concerns, we have demonstrated with no doubt, by double blind placebo-controlled test, that the provocation of the observed adverse reactions was dose-dependent. This observation is in line with the results of systematic review of published studies which demonstrate that adverse reactions related to SLIT practice are dose- and allergen-related (1).

For this reason, in our opinion rush phase of SLIT to latex should always be performed in protected setting where emergency treatment and intensive care room access must be available.

As afore said , when late local or mild to moderate systemic side effects occur during SCIT the maintenance dose is properly reduced. In case of severe, lifetrheatening systemic reaction or anaphylactic shock the continuation of immunotherapy shoud be carefully evaluated in terms of risks versus potential benefits, but we know that in most cases immunotherapy by subcutaneous route is stopped.

The rules for dose modifications and discuntinuations of SCIT are quite similar to the ones of SLIT (14). However they are less compelling, if considering the higher safety level of sublingual route. As far as we know, when a severe reaction occours during SCIT most allergists decide to shift with sublingual route because of its better safety profile, instead of renouncing to immunotherapy.

Since in the case reported anaphylactic shock occurred after maximum scheduled dose of rush phase, we have decided there are no substantial contra-indication to restart SLIT. As a matter of fact we have been able to restart and to continue with SLIT even if at lower dose and, after about two years, to induce valuable hyposensitization, improving tolerance to exposition to and handling of latex objects.

In conclusion, we can state that latex SLIT, as well as other allergens, is confirmed as a safe and effective method.

References

1. Wilson D.-R., Torres L.-I., Durham S.-R. - Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 2005;60:4-12.
2. Olaguibel J.-M., Alvarez Puebla M.-J. Efficacy of sublingual allergen vaccination for respiratory allergy in children. Conclusion from one meta-analysis. *J Invest Allergol Clin Immunol* 2005;15:9-16.
3. Gidaro G.-B., Marcucci F., Sensi L. *et al.* - The safety of sublingual-swallow immunotherapy: an analysis of published studies. *Clin Exp Allergy* 2005;35:1407-1408.
4. Bousquet J. - Sublingual immunotherapy: from proven prevention to putative rapid relief of allergic symptoms. *Allergy* 2005;60:1-3.
5. Rolinck-Werninghaus C., Wolf H., Liebke C. *et al.* - A prospective, randomized, double-blind, placebo-controlled multi-centre study on the efficacy and safety of sublingual immunotherapy (SLIT) in children with seasonal allergic rhinoconjuntivitis to grass pollen. *Allergy* 2004;59:1285-1293.
6. Grosclaude M., Bouillot P., Alt R. *et al.* - Safety of various dosage regimens during induction of sublingual immunotherapy. A preliminary study. *Int Arch Allergy Immunol* 2002;129:248-253.
7. Lombardi C., Giargioni S., Melchiorre A. *et al.* - Safety of sublingual immunotherapy with monomeric allergoid in adults: multicenter post-marketing surveillance study. *Allergy* 2001 56:989-992.
8. Antico A., Pagani M., Crema A. - Anaphylaxis by latex sublingual immunotherapy. *Allergy* 2006;61:1236-1237.
9. Cistero Bahima A., Sastre J., Enrique E. *et al.* - Tolerance and effects on skin reactivity to latex of sublingual rush immunotherapy with latex extract. *J Invest Allergol Clin Immunol* 2004;14:17-25.
10. Savi E., Maffini I., Burastero S.-E.. - A latex-containing hepatitis-B vaccine administered in a severely latex allergic paediatric patients after specific sublingual immunotherapy: a case report. *Allergy* 2004;59:1014-1015.
11. Bordignon V., Parmiani S. - Variation of the skin end-point in patients treated with sublingual specific immunotherapy. *J Investig Allergol Clin Immunol* 2003;13:170-176.
12. Kurtz K.-M., Hamilton R.-G., Adkinson N.-F. Jr. - Role and application of provocation in the diagnosis of occupational latex allergy. Ann Allergy Asthma Immunol 1999;83:634-639.
13. Hamilton R.-G., Peterson E.-L., Ownby D.-R. - Clinical and laboratory-based methods in the diagnosis of natural rubber latex allergy. *Ann Allergy Asthma Immunol* 2002;110(2 Suppl):S47-56.
14. Alvarez-Cuesta E., Bousquet J., Canonica G.-W. et al. - Standard for practical allergen-specific immunotherapy. *Allergy* 2006;61(Suppl 82): 1-20.
15. Connel J.-T. - Quantitative intranasal pollen challenges. II. Effect of daily pollen challenge, environmental pollen exposure and placebo challenge on the nasal membrane. *J Allergy* 1968;41:123-129.
16. Connel J.-T. - Quantitative intranasal pollen challenges. 3. The priming effect in allergic rhinitis. *J Allergy* 1969;43:33-44.