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Original article

Efficacy of oral tolerance induction to raw apple using an ultra-rush protocol in 28 patients allergic to rosaceae fruits: RAAP study

Efficacité de l'induction de tolérance orale à la pomme crue selon un protocole ultra-rush chez 28 patients allergiques aux rosacées : étude RAAP

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ABSTRACT

Background. – The aim of this study was to describe an ultra-rush (UR) protocol of Raw Golden Apple (RGA) in 28 patients with Oral Allergy Syndrome (OAS) which resulted in avoidance of raw rosaceae fruits, in order to demonstrate the safety of the protocol and follow-up of patients at 2 months and 1 year.

Methods. – The UR protocol was administered with RGA in a daycare hospital starting with 1 gram (g) of RGA, then by regularly doubling the dose until 128 g, to reach a 255 g cumulative dose in a 3-hours' period. During the post-hospitalization period, patients had to eat half of a RGA a day during one month, then 1 RGA a day during one month. An assessment consultation was performed at two months follow-up and a telephone interview at one year.

Results. – Duration of OAS to raw rosacea ranged from 6 months to 20 years. All 28 patients received the 255 g cumulative dose. Tolerance was very good in 25 of the 28 patients. No major allergic incident was recorded. After two months, all the patients were eating a RGA. After one year, 21 patients continued eating all types of raw rosacea fruits.

Conclusion. – This study shows that resumption of RGA intake by patients with OAS to raw rosacea fruits, part of a cross-allergy with birch pollen is possible within 3 hours' after use of an UR protocol. This protocol is simple, safe and easy to administer. Follow-up at 2 months and at one year was positive.

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R É S U M É

Background. – Le but de cette étude était de présenter un protocole accéléré « *ultra-rush* » (UR) de remise en contact avec la pomme golden crue (PGC) chez 28 patients porteurs d'un syndrome oral (SO) ayant abouti à l'éviction des rosacées crus, de démontrer sa sécurité et de réaliser un suivi à deux mois et un an.

Matériel et méthode. – Le protocole UR a été réalisé avec une PGC lors d'une hospitalisation de jour en débutant avec 1 gramme (g) de PGC, les doses étant régulièrement doublées jusqu'à 128 g pour atteindre une dose cumulée de 255 g en trois heures. Après l'hospitalisation, les patients devaient manger ½ PGC par jour pendant un mois, puis 1 PGC par jour pendant un mois. Une consultation de suivi était réalisée à deux mois et un entretien téléphonique à un an.

Mots clés :

Allergie à la pomme

Allergie aux rosacées

Syndrome oral

Induction de tolérance

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Résultats. – La présence du SO précédant la réalisation du rush variait de 6 mois à 20 ans. Vingt-huit patients ont été inclus atteignant tous la dose cumulée de 255 g. La tolérance était très bonne pour 25 des 28 patients. Aucun accident allergique majeur ne fut observé. Après deux mois, tous les patients remangeaient une PGC. Après un an, 21 des 28 patients continuaient de manger tous les fruits crus de la famille des rosacées.

Conclusion. – Cette étude montre que la re-consommation de PGC par des patients porteurs d'un SO aux fruits de la famille des rosacées, issue d'une réaction allergique croisée avec le bouleau, est possible en 3 heures en utilisant un protocole accéléré dit « *ultra-rush* » qui est simple, sécurisé et facile à réaliser. Les résultats du suivi à 2 mois et à un an sont positifs.

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1. Introduction

The prevalence of food allergy has increased by almost 50% over the last 20 years and now affects many Western countries, of which 8% of children and 5% of adults [1].

In patients starting from the age of 5, plant allergens are the first to be involved in food allergy [2]. Rosaceae (apple, peach, pear, cherry, apricot, plums, and nectarines) are responsible for more than 30% of allergies starting from this age [3].

These fruits are responsible for a particular type of food allergy, which usually causes symptoms limited to the oropharyngeal tract, called oral allergy syndrome or pollen-food allergy syndrome (PFAS) [4]. These symptoms follow the consumption of raw fruits [5,6]. OAS is observed mainly in central, eastern and northern Europe [2]. The clinical signs are oral pharyngeal pruritus, tingling of the mouth and lips, edema and sometimes discomfort with swallowing. These symptoms occur within 15 minutes after eating the offending fruit, and last 30 minutes, then stop [7]; but they tend to worsen over time, leading patients to avoid eating raw rosaceae fruit, as well as nuts, peanuts, kiwis and many other raw fruits and vegetables.

This clinical presentation evolves concurrently with birch pollen allergy [2,8]. Indeed, the major birch allergen called Bet v 1, is the one involved in almost 95% of patients with birch allergy in terms of sensitization [9]. In addition, Bet v 1 has a strong structural homology with one of the major apple allergens, Mal d 1, since it belongs to the pathogenesis related (PR) proteins group, specifically the PR10 group [10,11]. Over 70% of patients with birch allergy suffer from a PFAS to rosaceae, particularly to raw apple [12].

Therapeutic management is limited [6,13], based on avoidance of trigger foods [14] in case of a relevant clinical history or a positive oral provocation test [15].

Several studies have evaluated the outcome of PFAS after betulaceae pollen immunotherapy. Although some studies seem to show effectiveness [16,17], results remain limited [18,19] and need to be confirmed by further studies [20–22]. Thus, Kinacian et al. in a 2007 study showed that one year of sublingual desensitization did not improve the oral apple syndrome, while decreasing the seriousness of rhinitis related to Betulaceae allergy [23]. Raw golden apple desensitization has already been described by Nucera et al. in 2010 [24] in 2 patients with apple/birch syndrome by sensitization to PR 10. Likewise, raw golden apple tolerance induction in the same population was described in 2012 by Kopac et al., [25] and in 2014 by Bouvier et al. [26] according to slow protocols.

This article presents an accelerated protocol or ultra-rush (UR) for resumption of RGA intake performed in a half-day hospital stay in 28 patients suffering from PFAS with raw rosaceae, which resulted in avoidance of this entire family of fruit. The tolerance of this protocol is discussed as well as two months after the ultra-rush protocol and the maintenance of the tolerance at one year. The clinical and biological profile of the population was analyzed, together with the effect of UR on resumption of intake of other rosaceae.

2. Methods

This was a retrospective observational impact study of 28 patients seen in an allergy practice between June 2016 and October 2017. The UR method was performed in the outpatient clinic in two hospitals of the Lyon region (France), i.e. the Charcot clinic (69110 Sainte-Foy-Lès-Lyon) and the Beaujolais clinic (69400 Arnas). The study was appropriately registered (ClinicalTrials.gov Identifier: NCT04116580) and conducted in accordance with the principles of the declaration of Helsinki.

2.1. Inclusion criteria

Eligible patients were 10 years of age and older with allergic rhinitis or asthma related to birch pollen-associated PFAS for raw rosacea. They avoided these fruits for at least 6 months and suffered from significant quality of life impairment.

The allergy assessment was based on positive Skin Prick Tests (SPT), IgE to Bet v 1 (>0.10 kU/L) and a positive IgE assay to apple (>0.10 kU/L). Subjects were excluded from the study in case of a severe allergic reaction to rosacea, greater than grade 2 according to Ring and Messmer's classification [27] and uncontrolled asthma with FEV1 $<70\%$. Pregnant women were also excluded, as well as immunocompromised patients, patients with a malignancy, or ongoing infectious disease or serious cardiovascular disease and patients unable to give informed consent.

2.2. Study endpoints and assessments

The primary endpoint was evaluation of tolerance of ultra-rush protocol in a selected population presenting a PFAS who received a 255 g cumulative dose of raw golden apple ingested in 3 hours.

Secondary endpoints were the evaluation of safety of the ultra-rush method, and tolerance to daily consumption of raw golden apple during the two months following the ultra-rush method, assessment of possible resumption of eating of other raw rosaceae two months after the ultra-rush procedure when carried out between mid-April to mid-July, the evaluation of maintenance of this tolerance at 1 year, and to determine the biological sensitization profile of treated patients.

2.3. Implementation of the protocol

The protocol was administered in 4 phases (T) (Fig. 1).

2.3.1. First consultation – selection of the patients (T1)

During the first consultation, each patient's medical history was collected including current history (date of onset of seasonal rhinoconjunctivitis, date of avoidance of raw rosaceae, as well as for other fruits because of the OAS). Asthma screening has been routinely done. Prick tests with airborne allergen were performed (including five grass pollens and birch) and native raw golden apple testing

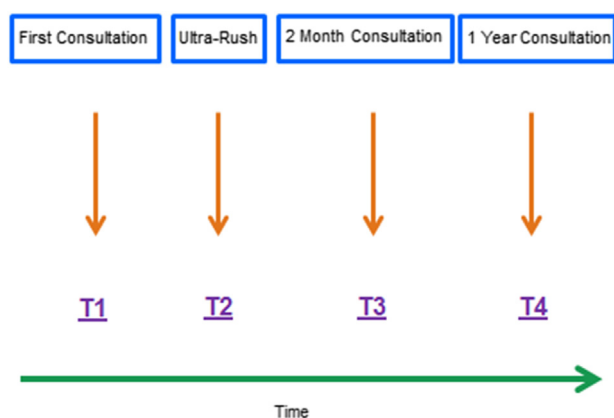


Fig. 1. Schematic overview of the protocol.

according to the prick-prick technique [28]. After a lung function tests, other laboratory tests were ordered to evaluate specific IgE for apple, PR 10 Bet v 1 protein, Bet v 2 profilin and lipid transfer protein (LTP), Pru p 3, by immunoCap technique [29]. In total, the inclusion of patients was based on a clinical history with concomitant seasonal allergic rhino-conjunctivitis and an OAS to raw rosacea with avoidance of this family of fruits for at least 6 months.

2.3.2. Ultra-rush (T2)

The UR was administered in a daycare hospital. Patients were not on antihistaminic drug, and a peripheral venous line was installed.

First, the Mother Solution (MS) (Fig. 2) was prepared from 10 g of raw apple mixed with 90 mL of water for 40 seconds according to the oral tolerance induction technique published in 2014 [26]. In total, 10 mL were extracted and placed in a plastic cup marked with the patient's name (Fig. 2). At time 0 (T0), prick tests were performed with RGA (prick-prick) and MS [26].

Secondly, dose escalation started (Fig. 3). At T0 +20 minutes, patients took 1 g of food (10 mL of MS), then by doubling the doses from 2 g to 128 g, patients consumed unpeeled RGA every 20 minutes at first up to 32 g, then every 30 minutes for the last 2 doses to reach a 255 g cumulative dose within a period of 3 hours. The MS was used only for the initial prick test and to administer the first dose of raw apple.

At each dose-increase, the patient was re-evaluated and the intensity of side effects based on manifestation of OAS was measured according to a three-color rule based on the Hansen et al. classification [30]. On a 0 to 10 graduated scale, green corresponded to no or mild side effects (0 to 3 on the scale); orange to moderate side effects (4 to 6 on the scale) and red to severe side effects (7 to 10 on the scale) (Fig. 4).

One hour after the last dose intake, patients were allowed to snack on 300 g of boiled potatoes. One hour after taking this light meal, an assessment consultation with medical report was made. An explanation on continuation of the protocol was provided on an information sheet and patients were provided with a booklet dedicated to record tolerance for daily RGA consumption using the same rule of 3 colors. An antihistaminic drug and a short-acting beta 2 mimetic drug were prescribed in case a patient had an allergic reaction at home.

2.3.3. Post-hospital time (T3 and T4)

Half of an unpeeled RGA was consumed at home on a daily basis at any time of the day for one month. RGA dose intake was doubled the following month, in order to reach one whole RGA per day. For the patients who underwent the UR procedure between mid-April and mid-July, intake of other raw rosacea (peach, cherry, apricot,

plum, mirabelle, nectarine) was permitted at the end of week 5 post UR. A two-month evaluation consultation was conducted (T3) with assessment of compliance and tolerance to raw golden apple and other raw rosacea (when possible) reintroduction, using the previously described three-color rule.

Afterwards, patients had to maintain their tolerance by consuming at least half a raw apple of any type three times a week. A telephone interview was performed at 1 year of the UR (T4) to evidence tolerance and compliance with the protocol. This post-hospital time was the same for all the patients.

3. Results

Population profile. Twenty-eight patients were included (23 women and 5 men); average age was 30.6 years (range: 10–51 years). All had birch pollen-related allergic rhino conjunctivitis, classified as severe and persistent according to the ARIA classification [31]. Fourteen of them were asthmatic and 8 had a history or current atopic dermatitis (AD), 14 had OAS for at least one other food: kiwi for 8 of the patients and hazelnut for 7 of them.

OAS has been evolving on average for 6.8 years for extremes ranging from 6 months to 20 years and occurred 8.6 years on average after respiratory symptoms; for 8 patients only, food allergy occurred the same year as rhinitis. In addition to systematic birch sensitization, 15 patients were sensitized to grass pollens (Fig. 5).

Allergy testing. For all patients, prick tests with MS were positive; 26 of the 28 patients included had a positive native apple prick test. The results of the biological investigations found rBet v 1 IgE recombinant positive for all patients with an average rate of 37.99 kU/L; IgE rBet v 2 positive for 11 patients with an average of 7.67 kU/L; apple IgE positive for 27 out of 28 patients with an average of 4.15 kU/L; 4 patients had rPru p 3 positive IgE (range between 0.19 to 4.43 kU/L) (Fig. 5).

3.1. Tolerance of the UR and the first two months post-rush

All patients reached the cumulative dose of 255 g of RGA. Tolerance was very good for 25 of the 28 patients. One patient had severe oral pruritus (red zone) at each dose. 2 patients did not tolerate the last dose; the first had an episode of isolated vomiting; the second had lower lip edema treated with an antihistaminic tablet.

During the course of the ultra-rush procedure, several patients had moderate side effects (orange zone) similar to an oral syndrome (4 patients with 16 g, 6 patients with 32 g and 64 g and 7 patients with 128 g) (Fig. 6).

During the post-hospitalization phase, all patients were able to consume half of an RGA a day for one month, and all of them consumed 1 raw apple a day during the 2nd month. Adverse effects of OAS were mainly concentrated during the first two weeks affecting 25.5% of the population (50/28 × 7 or 50/196 days) during the first week, and 15.3% of the population during the second week to finally fall to 0.02% at S3 and 0.01% at S4 and S5 (Fig. 7). Eleven out of 12 patients who had the rush between May and July reconsidered other raw rosacea at two months.

3.2. Results at 1 year

Of the 28 patients, 26 were reassessed, the remaining 2 patients were lost to follow-up. Five had stopped the protocol, 2 for compliance difficulties, 2 for the persistence of a serious and uncomfortable OAS, and 1 for gastroparesis attacks. No particular biological sensitization profile was demonstrated in the event of failure. At least 21 patients or 75% consumed all rosacea (apple, pear, peach, apricot, nectarine, cherry) at 1 year.

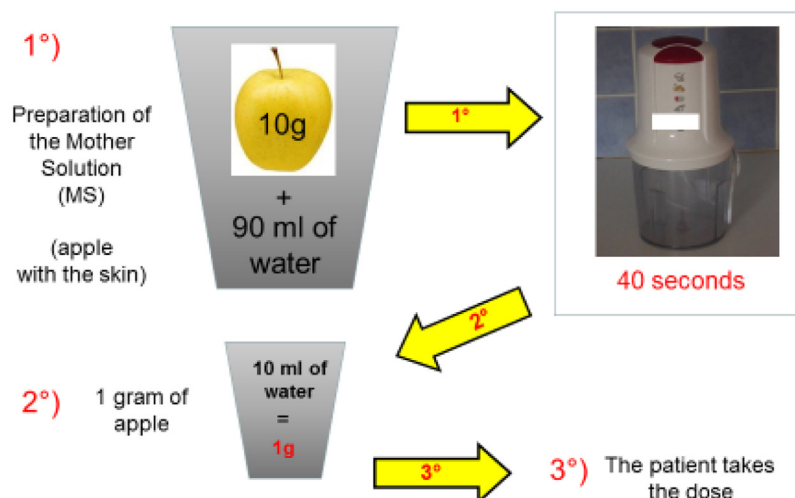


Fig. 2. Preparation of the Mother Solution to get 1 g of apple.

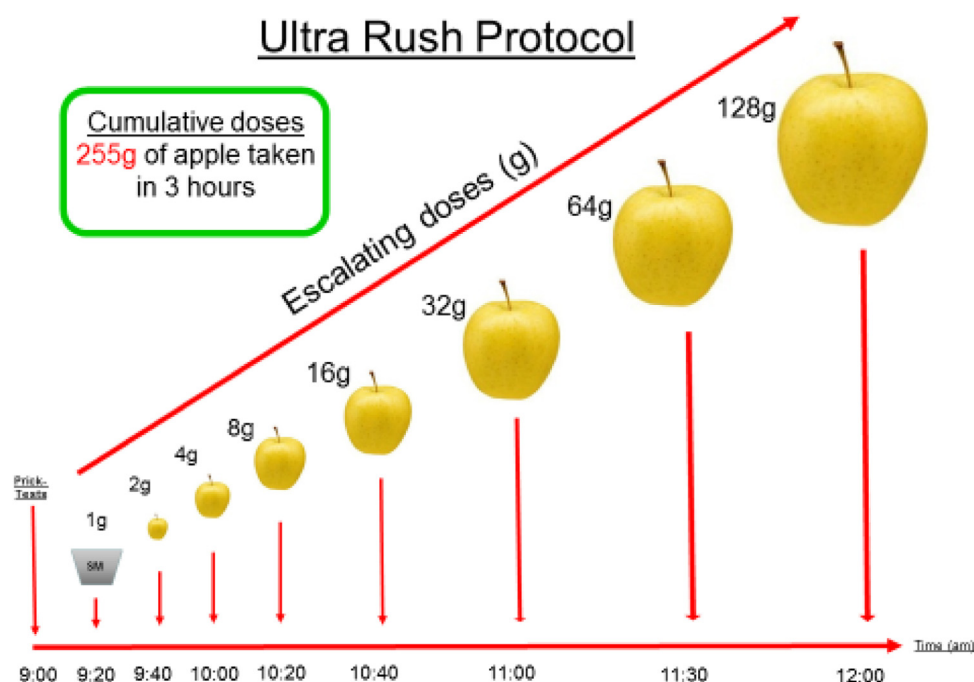


Fig. 3. Schematic overview of the ultra-rush method.



Fig. 4. Overview of the 3 color rule.

4. Discussion

4.1. Implementation – tolerance

We chose the golden apple for its high PR10 and LTP content compared to other varieties like escolette or priscilla [32,33]. While Oral Induction Tolerance (OIT) to RGA was first studied by Nucera et al. [24] in 2008 in two patients; its implementation was carried out by Kopac et al., [25] in 2012 and by our own team in 2014 [26] with a slow protocol on 52 patients. In this study, we showed that an ultra-rush protocol with accelerated dose escalation is possible in patients not receiving antihistaminic treatment.

They started with ingestion of 1 g of raw apple to reach a final dose of 128 g for a cumulative dose of 255 g in 3 hours. This protocol is simple, safe and easy to administer. It is faster to perform than those described above [24–26] where the maintenance dose was reached over several months, based on the premise that the increase in dose should be slow and regular [25,26]. Tolerance of the UR was good. All patients were able to take the last dose. The three colors rule has been very helpful to us at this level. In total, 82.1% of the patients had no symptoms at 16 g (green zone); 23/28 patients. This rate has dropped to 64.3% for the 128 g dose, (18/28 patients). At this dose, 7 patients had moderate OAS. No severe anaphylactic reaction (grade II or III according to the Ring and Messmer classification) [27] was observed. Adrenaline has never been used.

The main interest of the MS appears in its best sensitivity for the realization of the native food test prick (100%) versus 92% for the prick test with the native apple. It appears that the first dose of 1 gram can be given directly with the PGC.

n	Sex	Age	RC	A	DA	kiwi	hazel nut	IgE Bet v 1 kUA/l	IgE Bet v 2 kUA/l	IgE Pru p 3 kUA/l	IgE Apple kUA/l	Prick Apple (mm)	Prick MS (mm)	Histamin Control (mm)
1	W	24	1	1	1	0	0	60,5	<0,10	<0,10	7,16	10	11	10
2	W	25	1	0	0	0	1	8,7	4,18	<0,10	3,22	3	5	6
3	W	39	1	0	0	0	0	70,5	<0,10	<0,10	1,04	7	10	6
4	W	12	1	0	0	0	0	>100	<0,10	<0,10	14,38	8	7	7
5	W	25	1	0	0	0	0	12,6	<0,10	<0,10	1,37	6	6	10
6	W	32	1	0	0	1	0	99,3	<0,10	<0,10	3,09	6	5	6
7	W	23	1	0	0	1	1	19,6	<0,10	<0,10	1,18	8	10	8
8	W	27	1	0	0	1	0	18,3	<0,10	<0,10	2,26	13	7	8
9	M	39	1	0	0	0	0	70	<0,10	4,43	4,43	8	6	7
10	W	46	1	1	0	0	0	0,53	<0,10	<0,10	0,31	6	6	6
11	W	14	1	1	1	1	0	96,5	<0,10	<0,10	9,12	4	5	5
12	W	47	1	0	1	1	1	13,5	<0,10	<0,10	0,49	5	10	6
13	W	29	1	1	0	0	1	74,6	17,1	2,82	25,4	6	8	6
14	W	35	1	0	1	0	0	11,3	<0,10	<0,10	<0,10	0	5	5
15	M	45	1	0	0	1	0	13,7	2,7	<0,10	1,19	7	7	6
16	W	19	1	1	0	0	0	20,4	8,12	<0,10	3,41	6	8	6
17	M	28	1	1	1	0	0	24,6	20,9	<0,10	6,52	0	7	4
18	W	28	1	1	0	0	0	1,16	5,3	<0,10	1,11	5	5	5
19	W	45	1	0	0	0	0	46,5	<0,10	<0,10	4,86	15	8	8
20	W	10	1	1	0	0	0	9,36	11,4	0,20	1,71	5	5	8
21	W	42	1	1	0	0	0	8,52	<0,10	0,19	1,14	8	6	10
22	W	38	1	0	1	1	1	14,3	<0,10	<0,10	1,93	5	6	6
23	W	25	1	0	0	0	0	4,53	<0,10	<0,10	2,60	7	6	6
24	W	36	1	1	1	1	1	37,1	3,22	<0,10	2,13	8	8	6
25	M	27	1	1	0	0	0	26,8	7,15	<0,10	3,15	7	8	6
26	W	51	1	1	0	0	0	>100	<010	<0,10	2,07	7	6	10
27	W	30	1	1	0	0	0	21,6	2,82	<0,10	2,72	8	7	6
28	M	16	1	1	1	0	0	79,5	1,5	<0,10	4,24	8	12	8
μ	W+M	30,6	1	0,5	0,25	0,28	0,21	37,99	7,67	1,91	4,15	6,64	7,14	6,82

Fig. 5. Population profile and allergologic results.

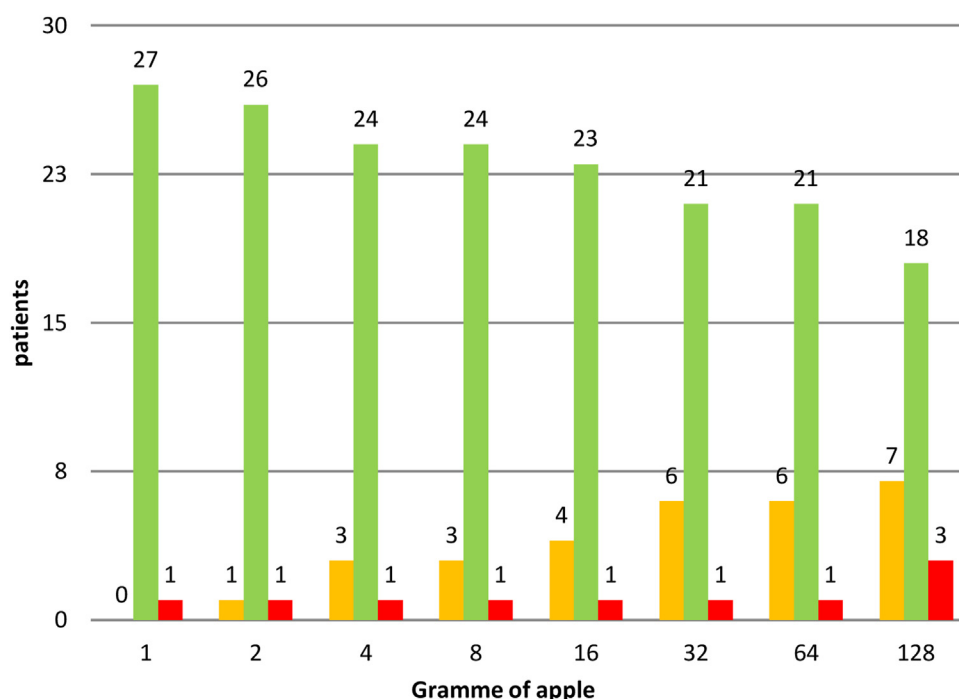


Fig. 6. Tolerance of the ultra-rush according to the three-color rule.

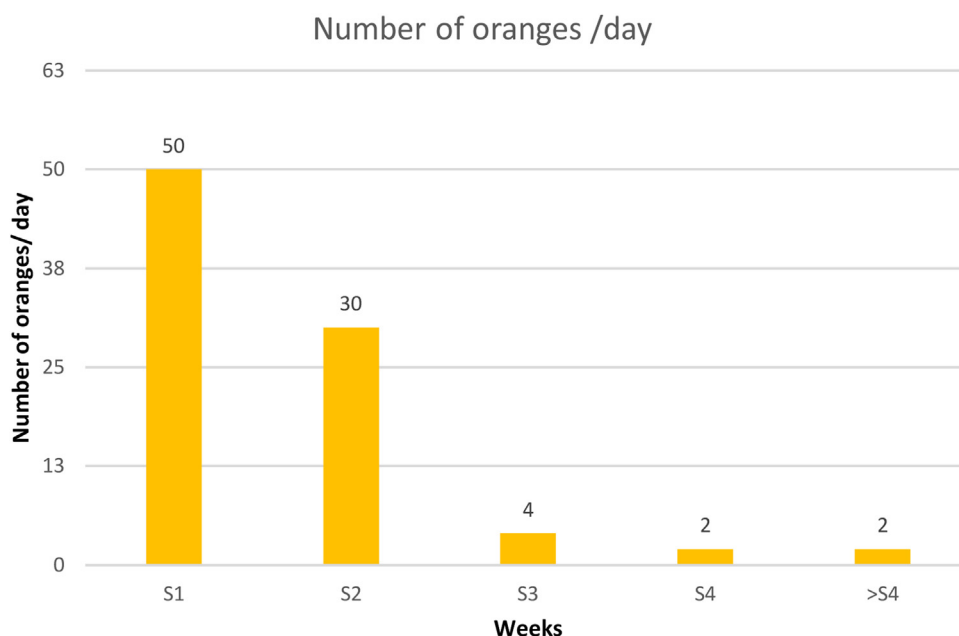


Fig. 7. Tolerance of the first 2 months post-ultra-Rush.

During the first two months post UR, the number of “orange” days decreased with time, mainly present during the first two weeks affecting 25.5% of the population the first week and 15.5% the second week, to finally become insignificant (1%). Our data showed that at two months, all patients were responders, consuming one raw apple daily. No serious allergic reaction was recorded. Eleven of the 12 patients who followed the UR between mid-April and mid-July consumed other raw rosaceae fruit (peach, plum, apricot, cherry and nectarine) at two months compared to the 6 months of other study [26]. This time interval could be the ideal period to carry out the UR. The result seems durable over time. At 1 year, 75% of patients (21 out of 28) ate all raw rosaceae. For the 7 patients who have been lost in sight or who have had to stop the protocol,

there is no appearance of a particular allergological or biological profile, including no particular severity of OAS. This rate of positive result is superimposable on what we find in our 2014 study where 41 out of 52 patients reconsumed all rosacea at 48 weeks as well as the dropout rate at 1 year (25% versus 23%) [26].

Finally, although outbreaks of atopic dermatitis have been reported in children allergic to birch, challenged with a birch pollen-related food [34], we did not observe any case.

4.2. Oral allergy syndrome

According to our data, OAS to rosacea affected young subjects with an average age of 30.6 years, compared with 30.1 years in

other studies [25]. The female predominance remains high, 82% in our cohort, which is also found in other studies [25,26], even though it seems more pronounced here. Birch allergy rhinitis preceded OAS in 71% of cases, with an average time interval of 8.6 years versus 4 years in our 2014 study [26]. Rhinitis was associated with seasonal asthma in 50% of cases, the same rate that we found in 2014 [26] and quite the same as a pediatric study in Italy by Mastroianni on about 1271 children [35]. OAS may appear as a sign of severity of rhinitis. It seems necessary to look for asthma in the presence of this type of symptoms, confirming earlier work [26], but the presence of associated asthma does not mean a stronger severity of OAS and does not influence the success or failure of the OIT. OAS by allergy to rosacea can reach other fruits. The two most common being the kiwi (33.7%) and the hazelnut (31.2%) in our data.

All patients were sensitized to Bet v 1; the IgE rate is highly variable (0.53 kU/L to 20.4 kU/L) for an average of 37.99 kU/L. This rate is independent of the severity of the symptoms. The apple/birch oral syndrome by mono sensitization to Bet v 2 is possible, however, it is rare [26]. We did not observe any case of it. Co-sensitization with LTP is possible, the rate remains low. In this study, it was between 0.11 kU/L and 4.43 kU/L for 4 patients. It is not a significant element of clinical severity and it is not a contraindication for the realization of the UR method. PR10/LTP co-sensitization appears as a biological marker for protection against severe allergic reaction [36]. This confirms what we had highlighted in 2011 in our first study on apple OIT involving 18 patients, 7 had a co-sensitization to Pru p 3 [37] without a reaction, unlike patients who had pure LTP sensitization [38,39] or the LTP expresses itself producing severe allergic reactions. In this case, the level of IgE to Pru p 3 was higher [40]. In the case of LTP/profilin co-sensitizations, the clinical picture varies according to the studies, which can lead to severe allergic adverse events according to Mota [41], or protect against severe adverse reactions according to recent studies [42,43].

4.3. Birch pollination

Four patients followed the protocol during the birch pollination period without severe allergic incident. During the course of the UR, we did not observe more adverse events. Three out of 4 patients were constantly in the green zone; 1 patient had a pronounced oral syndrome for all doses taken (red zone). For the two months post UR, 1 patient had no reaction. For the other three, the tolerance was satisfactory without differences compared to other patients. At no time was severe discomfort noted (red zone) during this period for these 4 patients.

With regard to respiratory symptom outcome, 2 out of 4 patients suffered from chronic mild seasonal asthma. No particular exacerbations were observed during this period. It seems that we can administer this protocol during the birch pollination period.

The current retrospective study naturally has some limitations. The cohort may appear modest with no control group. Another limitation is related to the follow-up study or the fact that we didn't follow the patient after one year.

5. Conclusion

We demonstrated in a cohort of 28 patients that resumption of eating raw apple in patients with oral allergy syndrome related to raw rosacea associated with persistent and severe allergic rhinitis to birch on rBet v 1 positive is possible with an ultra-rush protocol initiated in an hospital setting to reach a cumulative dose of 255 g in 3 hours.

This simple, fast and safe protocol, is easy to administer and allows to acquire tolerance that is quickly maintained by the consumption of half an apple a day during the first month then an apple

a day during the second month. At two months, all the patients consumed a raw golden apple with or without the skin. The tolerance of this UR protocol is good as well as the first two months post UR. It appears that this protocol may be offered to all patients who suffer from raw rosacea OAS associated with an allergy to birch. That should supplant in future slow protocols.

The effects are positive with the disappearance of the oral allergy syndrome, clearly improving patient quality of life. This protocol allows consumption of other raw rosacea at the end of the week 5 if the UR protocol is administered between mid-April and mid-July, which seems to be the best period for its use. However, it is feasible during the birch pollination phase without destabilizing underlying asthma.

In all, the results of this study are encouraging, the disappearance of the oral syndrome was maintained over time if patients continue to consume raw rosacea fruit regularly. The effects are very positive including effects on the quality of life. It now remains to evaluate in this cohort or another, the adverse effects of resumption of ingestion of raw golden apple on rhinitis related to birch pollen allergy. Finally the next phase could be further simplified and faster starting directly at 2 grams of apple. Other studies may supplement the findings of this study.

Ethics committee approval and consent to participate

The Ethics committee's approval was obtained by the university of Lyon hospital. Consent to participate was collected by sending an information letter to each patient and non-objection to collection of their personal data. The study complied with national ethical and regulatory requirements (including data protection).

Disclosure of interest

Dr Bouvier report personal fees from Alk Abello, Chiesi, Stallergene Greer, Menarini and AstraZeneca unrelated to this work.

Dr Hacker report personal fees from Alk Abello and Stallergene unrelated to this work.

Dr Lefevre declares that he has no competing interest.

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