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Article type : Letter to the Editor

Title

Potential treatment effect of the SQ tree SLIT-tablet on pollen food syndrome caused by apple

Capsule summary

Pollen food syndrome (PFS) is common and interferes with daily living. The results of this apple challenge suggest a potential treatment effect of birch AIT on PFS related to tree pollen.

Keywords

Pollen food syndrome, food challenge, apple, sublingual immunotherapy, tree SLIT-tablet

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Main text

To the editor

In adolescents and adults up to 60% of all food allergies are associated with a respiratory allergy [1]. Around 70 percent of birch allergic individuals develop allergic symptoms against certain foods such as nuts and apples containing homologous cross-reactive allergens to the major birch allergen Bet v 1 [2,3,4]. The symptoms are manifested as a condition called pollen food syndrome (PFS), and its occurrence typically involves pre-sensitisation to pollen allergens from the *Fagales* order. PFS is IgE-mediated and is caused by cross-reactivity between Bet v 1 and other protein family 10 (PR-10) proteins in a number of common food items such as apple, hazelnut, carrot and peach [2,3]. PFS interferes with activities of daily living, as patients will experience local oral symptoms such as itching, tingling, swelling in the mouth, or oral angioedema after intake of a number of common food items [2,5]. Some patients may also experience systemic reactions [2,3], but PR-10 triggered PFS is not a severe condition in most cases [3].

Birch allergen immunotherapy treatment (AIT) could be beneficial in the treatment of PFS due to the cross reactivity between Bet v 1 and common PR-10 allergens [6]. In a recently published position paper from EAACI on PFS, the authors concluded that trials were needed to assess the effect of birch AIT on PFS [1].

The original purpose of the study presented here investigates the potential treatment effect on PFS of a sublingual immunotherapy tablet for the treatment of tree pollen allergy, the SQ tree SLIT-tablet (12 SQ-Bet, ALK, Hørsholm, Denmark).

The treatment effect was measured in an open-label apple challenge conducted at the end of a double-blind, placebo-controlled phase III trial in a subgroup of the trial participants after 6.5-9.5 months of once-daily treatment with the SQ tree SLIT-tablet or placebo. The primary phase III trial results were reported previously [7]. In total, 124 participants (63 placebo, 61 SQ tree SLIT-tablet) from 12 centres in Germany and 12 centres in Poland with tree pollen allergy accepted to participate. They were challenged with apple slices (cut by standardised apple slicer) in 5 steps with increasing amounts corresponding to 4, 8, 16, 32 and 64 g given in intervals of 15 minutes. Objective and subjective PFS symptoms in response to the challenge were recorded. Participants reported a global evaluation of efficacy on PFS symptoms after intake of apple by comparing subjective PFS symptoms before and after treatment (see also online addendum). Specific IgE and IgG_4 responses to the apple PR-10 allergen Mal d 1 were measured throughout the trial.

The majority of participants in both groups (75% for SQ tree SLIT-tablet and 68% for placebo) managed to consume the highest dose of apple (64 g) without relevant objective symptoms. The subject-reported PFS symptoms by VAS during the apple challenge were generally low and many participants reported no symptoms (**Figure 1**). However, the mean levels of PFS symptoms after apple intake were lower for participants in the active group compared with placebo. Especially the increase in symptoms from before the apple challenge to after the first dose of apple (4 g) was more pronounced for participants in the placebo group, suggesting improved tolerance in the active group. This tendency was similar for individual symptoms and the overall PFS VAS score. A global evaluation of efficacy on PFS symptoms showed that more participants in the active group reported improved PFS symptoms after treatment compared with placebo (87% vs. 64%, OR=0.27, p=.0028).

Treatment with the SQ tree SLIT-tablet increased serum levels of apple specific IgE and IgG_4 compared with placebo at all measured time points (changes from baseline, **Figure 2**). Apple specific IgE increased in the active group until the off-season visit, after which it began to decrease. However, at end of trial serum levels of apple specific IgE (log-transformed) were still significantly higher in the active group than for placebo (p<.001 for difference in change from baseline).

The change from baseline in apple specific IgG_4 (log-transformed) increased throughout the duration of the trial in the active group (p<.001 for difference between groups at end of trial). No increases in apple specific IgE or IgG_4 were seen for the placebo group.

The apple specific immunological responses resembled that seen for birch. The ratio of IgG_4/IgE showed that the immunoglobulin production was in favour of Mal d 1 reactive IgG_4 over IgE from 4 weeks of treatment (**Figure 2**).

The apple challenge did not lead to any serious adverse events, severe local swellings and/or systemic allergic reactions. A summary of adverse events reported during the entire trial period showed that a slightly higher proportion of participants with PFS reported adverse events regardless of treatment group compared with participants without PFS (placebo: 59% vs. 50%, 12 SQ-Bet: 84% vs.77%). This was primarily driven by more events of oral pruritus. The main safety phase III trial results have been published previously [7].

It is a limitation of this study that no baseline challenge was conducted. A study is warranted where participants are pre-selected specifically for PFS (e.g. by challenge) to confirm the findings of the present study. This would ensure distinct PFS symptoms and allow for a better detection of differences in desensitisation between the groups. However, despite the majority of participants reported no PFS symptoms in the present study, the results point at a potential treatment effect: we saw a significant difference between the groups in the global evaluation and a trend towards improved PFS symptoms in the active treatment group for each dose step (Figure 1).

It has been suggested that higher allergen doses are needed to reduce food-induced reactions than to reduce pollen-induced reactions [8]. The present study suggests, that the SQ tree SLIT-tablet is of sufficiently high-dose to elicit an effect on PFS symptoms, and to modulate the antibody responses towards apple allergens (i.e. apple-specific IgE and IgG_4).

The results of the apple challenge suggest a potential treatment effect of the SQ tree SLIT-tablet on PFS related to tree pollen. Participants in the active group on average experienced less symptoms during the apple challenge, were more likely to reach the highest dose of apple and rated their global evaluation of PFS symptoms better than participants in the placebo group. In conclusion, this exploratory study indicated a potential improvement of PFS and increased tolerance to apple in participants with a history of apple induced symptoms treated with the SQ tree SLIT-tablet, compared with placebo. Treatment resulted in changes in serum levels of apple specific IgE and IgG_4 with the similar kinetics as seen for birch specific IgE and IgG_4. These results should be confirmed in a study with participants pre-selected specifically for PFS.

Figure legends

Figure 1 Reported overall PFS VAS score

The symptoms were measured on a VAS scale ranging from no symptoms to severe symptoms. No symptoms corresponded to 0 cm and severe symptoms corresponded to 10 cm. –: mean, –: median

Figure 2 Change from baseline of apple specific IgE and IgG_4 (log transformed)

Approximate time points: Randomisation: 0 months; Off-season: 1 month of treatment; Pre-tree pollen season: 4 months of treatment; Pre-birch pollen season: 7 months of treatment; End of trial: 9 months of treatment

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Author contributions

All authors made substantial contributions to conception and design of, or acquisition of data or analysis and interpretation of data. All authors revised the manuscript critically for important intellectual content. All authors gave final approval of the version to be published. TB were signatory investigator in the trial, SJT and IS were involved in designing the apple challenge and BSS was involved in trial design and responsible for reporting of trial results.

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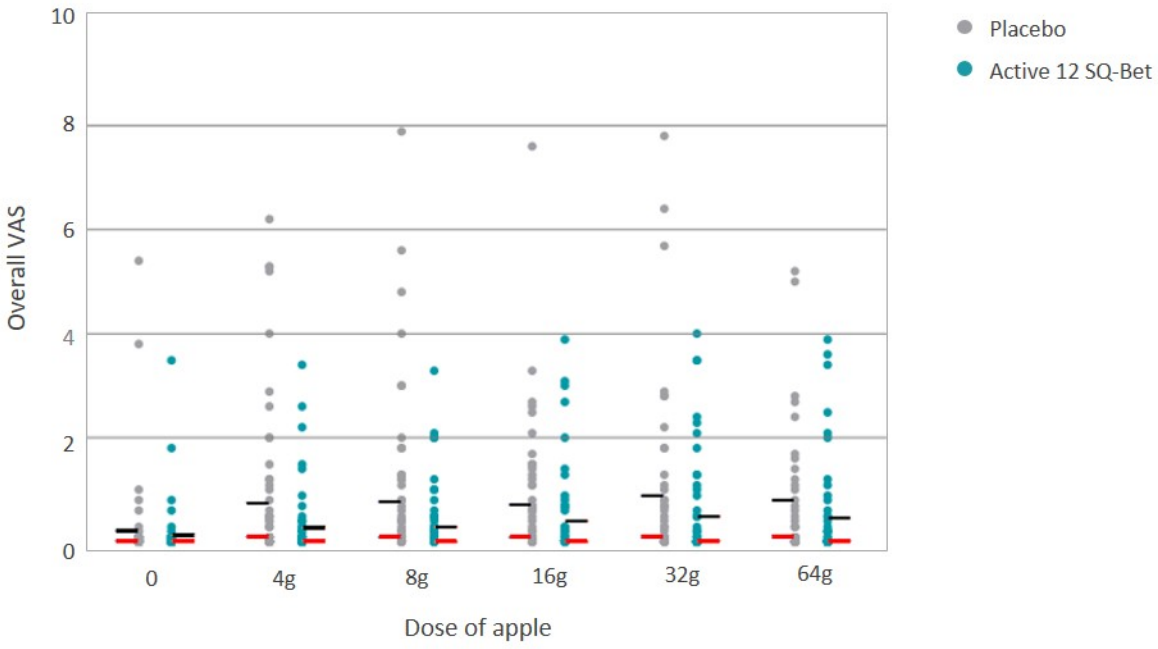

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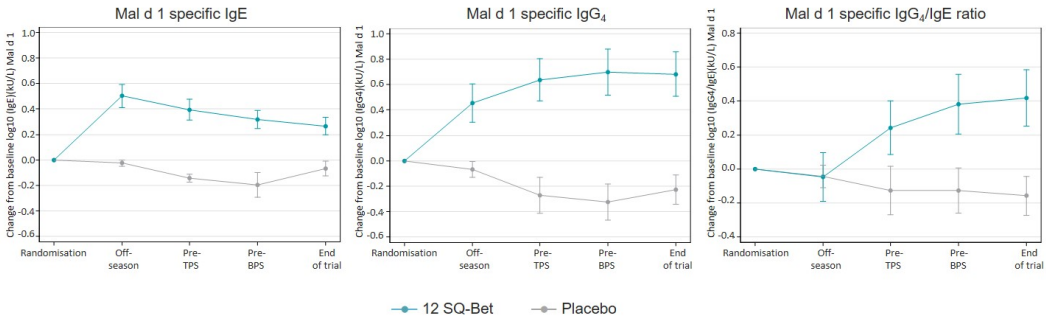

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