IgG_4 cross-reactivity induced by the SQ tree SLIT-tablet extends the immune modulating effect to the entire birch homologous group

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Background

In Europe and North America, allergic rhinoconjunctivitis is commonly caused by allergens from the birch homologous group. The birch homologous group includes birch, oak, alder, hazel, hornbeam, beech, and chestnut, all characterized by having Bet v 1 homologous allergens. The high sequence identity between the Bet v 1 homologues within this group leads to extensive cross-reactivity.

Here, we characterize the IgE sensitization and IgG_4 responses induced by the SQ tree SLIT-tablet (containing birch extract) with respect to cross-reactivity toward allergens in the birch homologous group to investigate whether the significant clinical effect determined previously for both birch and oak exposure may extend to the entire birch homologous group.

Methods

Blood samples were collected from adults with moderate to severe birch pollen induced rhinoconjunctivitis who had been treated with the SQ tree SLIT-tablet for 24 weeks during the TT-03 trial (ClinicalTrials.gov Identifier NCT02481856). The study was approved by the Ontario IRB, approval number 12069.

Serum IgE (pre-treatment) and IgG_4 (treatment-induced) specific for birch, oak, alder, hazel, hornbeam, beech, and chestnut were measured by standard ImmunoCAP. Correlation analyses and inhibition assays were performed to evaluate immunological cross-reactivity. Olive served as a negative control as it does not belong to the birch homologous group.

Results

The analyses demonstrated strong correlation between IgE reactivity (pre-treatment) toward birch and alder, hazel, hornbeam, oak, and beech (Fig 1). Correlation levels ranged from r=0.37 for chestnut and birch to r=0.98 for birch and alder.

The analyses also demonstrated strong correlation between IgG_4 reactivity (treatment-induced) toward birch and alder, hazel, hornbeam, oak, and beech (Fig 2). Correlation levels ranged from r=0.15 for chestnut and birch to r=0.95 for birch and alder.

Inhibition experiments revealed that in the majority of patients, alder-, hazel- and oak-specific IgE and IgG_4 reactivity was inhibited by more than 80% by birch allergen extract, confirming that the observed correlations result from true antibody cross-reactivity (Fig 3).

Funding: This study was funded by ALK.
Conflict of Interest: MC Arseneault is an employee of ALK Canada.

Pre-treatment IgE

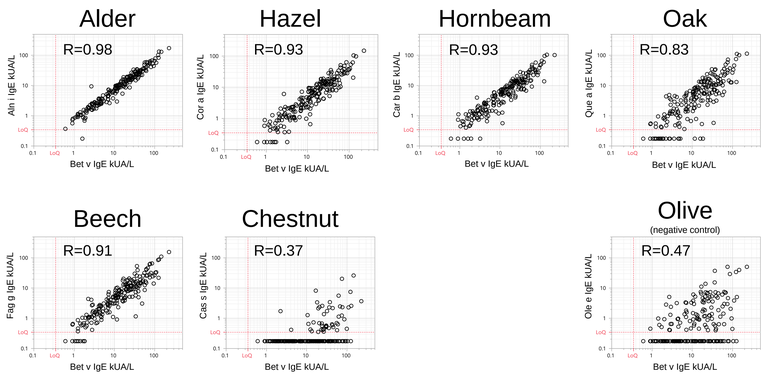

Figure 1. Pre-treatment IgE reactivity to birch correlates with pre-treatment IgE reactivity to homologous allergens. Serum IgE reactivity to birch is displayed on all x-axes and serum IgE reactivity to alder, hazel, hornbeam, oak, beech, chestnut, and olive on the respective y-axes. Correlation calculations included samples with a positive value for both Bet v and the homologue; correlation coefficients are displayed in each panel.

Treatment-induced IgG_4

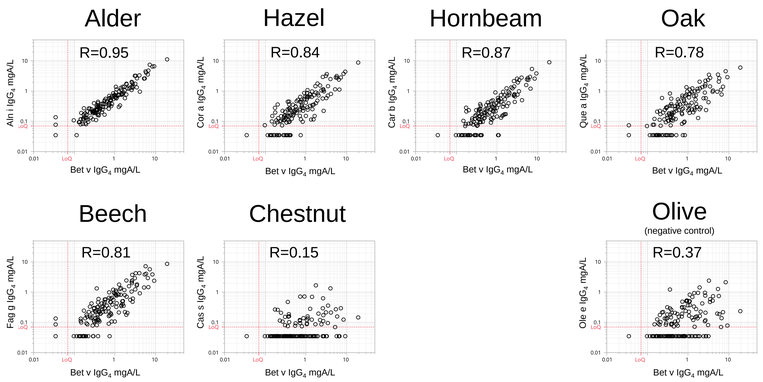

Figure 2. Treatment-induced IgG_4 reactivity to birch correlates with treatment-induced IgG_4 reactivity to homologous allergens. Serum IgG_4 reactivity to birch is displayed on all x-axes and serum IgG_4 reactivity to alder, hazel, hornbeam, oak, beech, chestnut, and olive on the respective y-axes. Correlation calculations included samples with a positive value for both Bet v and the homologue; correlation coefficients are displayed in each panel.

IgE inhibition *IgG_4 inhibition*

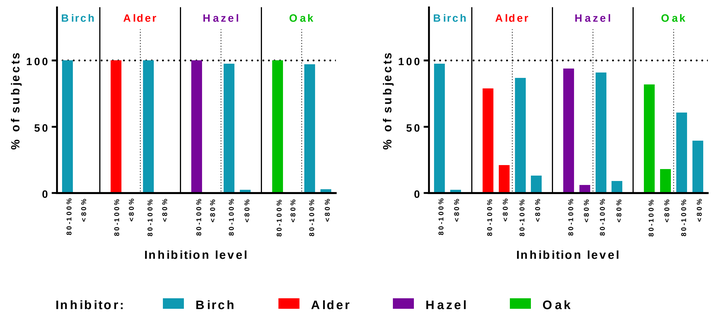

Figure 3. Alder-, hazel-, and oak-specific IgE and IgG_4 reactivity is inhibited by birch allergen extract in most subjects. Proportion of subjects showing 80-100% inhibition or <80% inhibition of allergen-specific IgE or IgG_4 reactivity in response to inhibition with birch, alder, hazel, or oak. Only subjects with quantifiable levels of IgE or IgG_4 binding are included in the panels.

Conclusion

A high level of cross-reactivity toward birch and allergen extracts from other trees in the birch homologous group was observed for both IgE sensitization and treatment-induced IgG_4.

This suggests that the significant clinical effect determined previously for both birch and oak exposure may extend to other members of the birch homologous group.