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Anti-IgE Therapy Combined with Specific Immunotherapy: Pro

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The binding site of IgE for the high-affinity receptor FcεRI is located within the third domain of the heavy chain, C3. A murine antibody, MAE1, was generated, that recognizes the same residues in the C3 domain of IgE that are responsible for binding to FcεRI. To avoid sensitization with foreign proteins, a humanized version, containing 95% of a human IgG1 antibody and only 5% of the murine IgE-specific epitope, was constructed and named recombined humanized monoclonal antibody (rhuMAb)-E25 or omalizumab.

The main features of anti-IgE are that it

- I. recognizes and binds IgE, but not IgG or IgA;
- II. inhibits the binding of IgE to FcεRI;
- III. does not bind to IgE bound to mast-cells or basophils and thus, does not cause degranulation ("non-anaphylactic antibody");
- IV. blocks mast cell degranulation following passive sensitization *in vitro* or challenge with allergen *in vivo*;
- V. is unspecific for the allergen-specificity of the IgE antibody, meaning that it binds to any IgE molecule.

Anti-IgE has been demonstrated to be safe and effective in controlling birch pollen-induced seasonal allergic rhinitis (SAR) compared with placebo, with less use of rescue medication and improved quality of life (QOL).

Anti-IgE in combination with SIT in children with SAR (Phase III study)

SIT is considered as the only curative treatment for SAR and allergic asthma, as long as its prerequisites are fulfilled: small scale of sensitizations, administration of adequate doses of standardized allergens. Beneficial effects of SIT can be observed even years

after discontinuation. Especially in children, administration of SIT may prevent the extension of upper airway disease to the lower airways. However, SIT carries the risk of side effects. Since anti-IgE reduces the serum concentration of IgE and thereby reduces IgE-mediated reactions, it was hypothesized that concomitant treatment of anti-IgE and SIT could improve the risk/benefit ratio of SIT in polysensitized patients during the consecutive pollen seasons and thereby would prove clinically superior to treatment with SIT alone. Therefore, a randomized, double-blind placebo-controlled study in children with SAR was initiated to investigate whether combined therapy with SIT and anti-IgE is favorable to single treatment alone.

In the study, 221 patients (6–17 years) with moderate-to-severe SAR and sensitization to birch- and grass-pollen (history ≥ 2 years, IgE specific to birch and grass CAP class ≥ 2 , total serum IgE levels 30–1300 IU/ml) were included. There were four treatment arms: each subject was started on SIT-birch (2 groups) or SIT-grass (2 groups) for ≥ 14 weeks prior to start of birch-pollen season (Build up phase: 12 injections, 1-week intervals. Maintenance phase: 5 injections, 4-week intervals). After SIT titration (12 weeks), placebo or anti-IgE was added for 24 weeks to either one of the two groups of the respective SIT arms. When analyzed separately by season, the two groups receiving unrelated SIT were considered as placebo controls. Anti-IgE was administered s.c. at 2- or 4-week intervals at a dose equivalent to a minimum of 0.016 mg/kg/IU IgE/ml serum in 4 weeks. As primary outcome the "Symptom load" (sum of mean daily symptom severity score plus mean daily rescue medication use) was chosen.

As a result, combination therapy of anti-IgE and SIT was found to reduce the symptom load over the entire pollen seasons (birch and grass) by 48% compared to SIT alone ($p < 0.001$). Reduction was highly significant for both analyses, SIT-birch + anti-IgE vs. SIT-birch + placebo, and for SIT-grass + anti-IgE vs. SIT-grass + placebo.

In the birch pollen season, the addition of anti-IgE to the relevant SIT-birch reduced symptom load by 50% compared to SIT alone (median symptom score 0.46 vs. 0.23, $p = 0.003$). Anti-IgE reduced symptom load in comparison with the irrelevant SIT-grass alone by 39% (0.44 vs. 0.27, $p = 0.1$). Unexpectedly, the patients treated with SIT-birch (+ placebo) alone showed a comparable symptom load of 0.46 versus 0.44 ($p = 0.43$) compared with the group treated with SIT-grass (+ placebo). This may be caused by pollen exposure before adequate cumulative SIT doses were administered and may also reflect the very modest symptom load scores in this group.

In the grass-pollen season, the relevant SIT-grass reduced symptom load by 32% compared to irrelevant SIT-birch + placebo (0.61 vs. 0.89, $p = 0.1$). The addition of anti-IgE to the relevant SIT-grass had a highly significant effect with 57% decrease in mean symptom load compared to SIT-grass alone (0.26 vs. 0.61, $p = 0.001$). Addition of anti-IgE to the unrelated SIT-birch (considered as treatment with anti-IgE alone) reduced symptom load by 45% compared with unrelated SIT-birch alone (0.49 vs. 0.89, $p < 0.001$).

Over both pollen seasons, addition of omalizumab resulted in reduction of the median rescue medication score of 78% compared to SIT-birch groups (0.06 vs. 0.27, $p < 0.001$) and by as much as 81% compared to SIT-grass groups (0.03 vs. 0.16, $p = 0.001$).

The results of the treatment of SAR with anti-IgE required a further study.

In comparison with SIT, anti-IgE recruited less patients to the study. The unexpected results already 45 days after start of the study sizes have been observed in another placebo-controlled study.

For the future, a study with SIT with anti-IgE during the first year of the pollen season and the safety of allergen immunotherapy with an additional year of SIT.

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The results of the study strongly support the primary hypothesis, that the combined treatment of SIT and anti-IgE is more effective than SIT alone. Patients receiving anti-IgE required almost no additional symptomatic rhinitis medication.

In comparison to the study on SAR in adults (1), where 44% of patients were recruited less than one week and 10% of patients were recruited even after the start of the unexpected early pollen season, in the study in children, anti-IgE was administered already 45 days prior to the start of the birch-pollen season. Recently the same effect sizes have been described in a Japanese cohort of cedar pollen allergy adults with SAR in another placebo controlled trial (2).

For the future it seems to be justified to further evaluate the combined approach of SIT with anti-IgE-treatment. Apart from increasing the effect of SIT particularly during the first year of treatment, anti-IgE might also offer the possibility to increase the safety of allergen specific vaccination. Further more as a non-specific approach it offers an additional therapeutic option for patients with multiple allergies.

References

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