

ORIGINAL ARTICLE

Tolerability and efficacy of house dust mite AIT

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Abstract

Sublingual immunotherapy based on grass pollen allergy immunotherapy tablets is an efficacious and well-tolerated treatment for rhinoconjunctivitis, and subcutaneous house dust mite (HDM) immunotherapy is effective against allergic asthma. Three studies have investigated a new ALK tablet for HDM allergy: two studies on tolerability in adults and children, and one on efficacy and safety in adults and adolescents with asthma. Treatment was well tolerated, mainly with mild-to-moderate local reactions pertaining to the administration site, such as temporary oral pruritus. The primary efficacy endpoint was a significant reduction in inhaled corticosteroid dose compared to baseline after 1 year of daily treatment. A positive therapeutic effect on asthma was demonstrated by a reduction of more than 80 µg/day inhaled budesonide for a group receiving six developmental units daily compared to the placebo group.

House dust mite (HDM) allergy immunotherapy tablets (AIT) have not yet been marketed, but the tablets are in development and the constituents and concept of use are similar to Grazax[®], except that the grass pollen allergens are substituted with an extract of HDMs. The HDM AIT is also for sublingual use, and the tablets are rapidly dissolving and require no up dosing. The active ingredient is a mixture of allergens from cultures of HDMs, *Dermatophagoides pteronyssinus* and *D. farinae*. The content of the major allergens Der p 1 and 2, as well as Der f 1 and 2, are expressed in developmental units (DU), so they are not at present directly comparable to milligram or microgram quantities.

House dust mite allergy immunotherapy tablet tolerability

Two studies have been conducted on tolerability in adults and children (1), MT01 and MT03, followed by a quantitative study on efficacy and safety in adult and adolescent asthma patients (2), MT02. The first tolerability study enrolled 71 adults and the second 72 children, aged 5–14 years. Patients were suffering from asthma and rhinoconjunctivitis and were treated for 1 month with different doses: from 1 to 32 DU in adults and 1 to 12 DU in children. Side-effects were similar to those reported for the Grazax[®] studies, mainly oral pruritus and throat irritation. One adult patient in the highest dose group reacted with vomiting. After this occurrence, the group was discontinued, so the full study is

up to 16 DU, with one withdrawal because of mouth oedema and throat tightness in one patient at 16 DU. The pediatric study had no withdrawals because of adverse events.

The treatment and tolerability study, MT-02 (2), included 602 subjects. The top dose was 6 DU, so this was a considerably lower dose compared to the MT-01 tolerability study. The treatment period was 1 year. Patients were adolescents older than 14 years or adults, all with a clinical history of HDM-induced asthma and mild-to-severe allergic rhinitis. All had documented HDM allergy by both skin-prick test and specific IgE. Withdrawals because of adverse events were few. A clear dose response in side-effects was not observed. The observed side-effects were mostly oral pruritus with some patients experiencing itching in the throat or ears. Side-effects were at the same level and type as observed in the Grazax[®] studies.

House dust mite allergy immunotherapy tablet efficacy

In the treatment and tolerability study, MT-02, all patients were required to be able to control asthma with inhaled corticosteroids, have had corticosteroids for at least 6 months, and be stable for at least 3 months before the trial. Up to 800 µg/day budesonide was accepted. All had documented asthma by reversible airway obstruction, by Global Initiative for Asthma guidelines. Therefore, asthma was documented and controlled at entry.

Participants were from all over Europe. Groups were placebo and three doses, 1, 3, and 6 DU (Fig. 1). To prevent

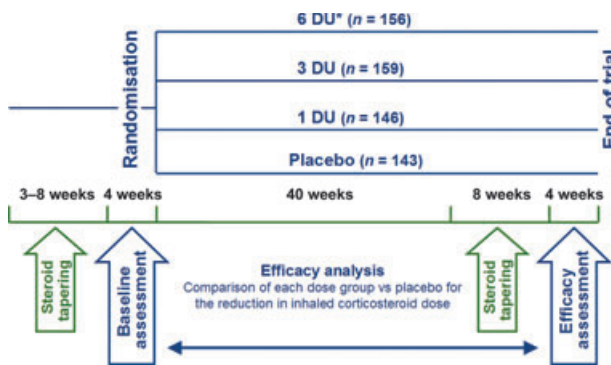


Figure 1 Trial design MT-02.

overmedication and allow effects to be seen, patient steroid dose was tapered down during a run-in period until patient asthma was no longer stable. Steroid use was increased again until asthma was stable, before randomization. Baseline assessment was followed by treatment with tablets for 40 weeks. Steroid tapering was repeated to determine whether subjects required the same amount of corticosteroid. When the asthma became unstable, steroid dose was increased until stability was obtained again.

Efficacy was determined as reduction in inhaled corticosteroid dose between assessments at baseline and after 1 year. Controlled asthma was defined by a combination of symptom, medication, and quality-of-life scores, but not including dose of inhaled corticosteroid. In this way, we tended to keep all other factors such as symptoms and lung function constant. This is different from most hay fever studies where efficacy is determined from change in symptom and medication scores. Here, we used those scores to make the patients comparable and used inhaled corticosteroid dose as the primary efficacy endpoint, with some included secondary endpoints for measuring general effectiveness. The groups had comparable characteristics in mean age and other parameters. Secondary parameters used to make patients comparable included number of asthma exacerbation and others. Nose symptoms were measured as secondary parameters but were not used to make patients comparable before treatment.

References

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Inhaled corticosteroid reduction after AIT

The primary endpoint of inhaled corticosteroid reduction was reached. The placebo group also showed an improvement (median reduction from 400 to 280 µg/day) but the highest dose group showed a significant further decrease of over 80 µg/day of inhaled budesonide compared to the change seen in the placebo group (median reduction from 400 to 200 µg/day). The change in the two lower dose groups was not significantly different from the placebo group.

Thus, the study showed a successful reduction in inhaled corticosteroids with AIT. The secondary endpoints that were used to obtain comparability among patients showed a small improvement in rhinoconjunctivitis quality-of-life scores. Changes, if any, in other secondary endpoints were the same among groups. No new sensitivities occurred during the study period. A conjunctival provocation test was not conclusive, as only some patients were tested and many dropouts occurred. Rhinoconjunctivitis scores improved by 0.2 in the highest treatment group compared to the placebo group. The asthma quality-of-life scores were comparable, as intended to keep the asthma symptoms 'constant'. A slight, nonsignificant trend in improvement was seen in the highest treatment group.

In summary, the HDM AIT tablets were well tolerated in adults up to 16 DU and up to 12 DU in children. A few asthma and rhinoconjunctivitis adverse events were observed, with a few dropouts because of side-effects. The treatment was efficacious. We obtained a highly significant reduction in the use of inhaled corticosteroids in the 6 DU treatment group compared to placebo and the reduction in, inhaled corticosteroid use did not compromise asthma control, quality-of-life or lung function.

Conflict of interest

Holger Mosbech has received a research grant from ALK-Abelló, consultancy fees from ALK-Abelló as well as lecture fees from ALK-Abelló and AstraZeneca.