TARGET – Real-World-Evidence study on the long-term benefits of MCT ® -associated pollen allergoid SCIT on AR and asthma

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Abstract

Background: Allergen immunotherapy (AIT) may have a long-term disease modifying effect. The aim of this study is to demonstrate the long-term benefit of MCT®-associated allergoid pollen SCIT (MCT®-associated -AIT) on allergic rhinitis (AR) and asthma in clinical practice. Methods: In this retrospective Real-World-Evidence (RWE) study the impact of AIT on the progression of AR and onset of need for asthma medication was analyzed using a German longitudinal database. Anonymized prescription data of AR patients and exactly matched control patients aged from 5-65 years were analyzed. Results: Significantly less patients treated with MCT®-associated-AIT did receive prescriptions for symptomatic AR medication in the follow up period vs. control group (OR: 0.27; $p < 0.001$). Further, significantly less asthmatic patients under MCT®-associated-AIT did receive prescriptions for asthma medications (OR: 0.48; $p = 0.004$). In addition, the prescriptions of AR and asthma medication for MCT®-associated-AIT patients were significantly reduced in the follow-up vs. baseline and control group (24.2% and 35.6%, respectively, $p < 0.001$).The probability of asthma medication onset in non-asthmatic patients during follow-up was significantly reduced for AIT patients compared to controls (OR: 0.77, $p = 0.001$). All endpoints were significant for children/adolescents and adults in the individual analyses. Conclusions: This study gives evidence for long-term benefits up to 9.5 years of MCT®-associated-AIT on the need for AR and new-onset asthma medication in AR patients and asthma medication in asthmatics in an RWE setting.

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Short title: TARGET: Tyrosine-Allergoid – RWE in Germany – Effectiveness in AIT

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Results: Significantly less patients treated with MCT®-associated-AIT did receive prescriptions for symptomatic AR medication in the follow up period vs. control group (OR: 0.27; $p < 0.001$). Further, significantly less asthmatic patients under MCT®-associated-AIT did receive prescriptions for asthma medications (OR: 0.48; $p = 0.004$). In addition, the prescriptions of AR and asthma medication for MCT®-associated-AIT patients were significantly reduced in the follow-up vs. baseline and control group (24.2% and 35.6%, respectively, $p < 0.001$).The probability of asthma medication onset in non-asthmatic patients during follow-up was significantly reduced for AIT patients compared to controls (OR: 0.77, $p = 0.001$). All endpoints were significant for children/adolescents and adults in the individual analyses.

Conclusions: This study gives evidence for long-term benefits up to 9.5 years of MCT®-associated-AIT on the need for AR and new-onset asthma medication in AR patients and asthma medication in asthmatics in an RWE setting.

Keywords: AIT, allergic rhinitis, allergoids, asthma occurrence, asthma progression

Background:

Over the last 50 years the number of patients with allergies has increased rapidly . Children are affected with a 12-month prevalence of AR of 8.8% increasing to 15.3% in adolescence . Allergic rhinitis (AR) commonly precedes asthma and about 85% of asthma patients also have AR . In Germany, about 1 million children and adolescents are affected by AR, about 0.5 million of adolescents by asthma and among adults the 12-month prevalence of asthma is 6% . The increasing number of adult patients affected by allergies emphasize the importance of effective and causal, disease modifying therapies nowadays and in the future.

Allergen immunotherapy (AIT) has a long-term disease modifying effect as a causal and preventive approach regarding allergic progression or new sensitizations . As the relative risk of developing bronchial asthma within less than 10 years is 3.5-fold higher for patients with AR and the risk of a change from AR to allergic asthma is greatest for children with hay fever, an early initiation of AIT for children and adolescents is recommended with focus on products, for which appropriate effects have been shown . For AIT several standardized products are available, differentiated by the route of application as subcutaneous (SCIT) or sublingual immunotherapy (SLIT).

SCIT allergoids are chemically modified allergens with reduced IgE binding capacity allowing fast updosing with a good safety profile demonstrated for children and adults . In addition, SCIT is well investigated in controlled, intermittent and mild persistent asthma . The most common adjuvant to strengthen the AIT immune response is aluminium hydroxide . An alternative adjuvant, microcrystalline tyrosine ($MCT^{(r)}$), shows a favourable safety profile inducing even less anaphylactic reactions in mice and induces less TH2 related cytokines which should be suppressed in AIT .

AIT patients should be treated for at least 3 years, SCIT must be administered by a physician and requires regular visits during the maintenance phase. Thus, patient adherence is essential for efficacy, especially in clinical practice routine. In real life, a low level of compliance and persistence, particularly when using SLIT

is observed . According to the German S2k AIT Guideline, insufficient compliance is a contraindication to AIT with allergens).

Double-blind placebo-controlled studies (DBPCSs) are classified as gold standard evaluating the efficacy of medical treatments, although it has to be considered that e.g. in SLIT DBPC trials a complete blinding is not possible . This may have an influence on the placebo effect.

The efficacy and safety has been proven for various SCIT allergoids preparations including MCT(r)-associated allergoids in DBPC studies and meta-analyzes under ideal clinical study conditions .The efficacy of MCT(r)-associated SCIT allergoid was demonstrated recently in a meta-analysis providing strong evidence on the efficacy of SCIT in pollen allergy-induced allergic rhino conjunctivitis (ARC), showing significant reduction of allergic symptoms and medication use . In addition to DBPC studies Real-world evidence (RWE) data increase corroboration by allowing insights into the therapeutic effectiveness, especially in children and adolescents, particularly after AIT completion. RWE studies are playing an increasingly important role. Health authorities in US and Europe have recognized the added value of RWE studies and are working on the framework of the "Real-World Evidence Program" .

The aim of the "Tyrosine Allergoid - Real World Evidence in Germany - Effectiveness in AIT" (TARGET) study is to demonstrate the long-term benefit of MCT$^{(r)}$-associated allergoid pollen SCIT on AR and asthma in adults, children and adolescents (5-65 years) in clinical practice routine.

Methods

Study design

This study was a retrospective data analysis using a German longitudinal prescription database (LRx, IQVIA, Frankfurt am Main, Germany). The overall analysis period was January 2008 to June 2020 (see Figure 1).

The index period for the study was defined from September 2009 to August 2013, including four allergy seasons (September to August). For the AIT group, eligible patients were initiated on the respective SCIT products at index date during this period. A pre-index period of 12 months before SCIT initiation was determined. Treatment period lasted from index date until expiry of the last prescription of the respective product followed by the follow-up period of at least two years until end of the study in June 2020.

For the control group, index date was defined as the first prescription in the second allergy season during the index period. Treatment period was from index date until expiry of the last prescription of the respective product within a maximum of five years followed by the follow-up period of at least two years until end of the study in June 2020.

Three authorized allergoids in Germany containing grass or tree pollen were analysed: one MCT$^{(r)}$-associated allergoid and two aluminium hydroxide adjuvanted allergoids (allergoid 2 and 3, respectively). For the control group symptomatic AR medications were defined in accordance with the ARIA guideline 2019 .

Database

The analyses are conducted with IMS$^{(r)}$ LRx, a German database accessing nationwide pharmacy data collection centres processing anonymized prescription data of all German patients within the statutory health insurance system allowing a patient follow-up over time. The coverage for back data since 2008 is about 35% of all German statutory prescriptions.

Patients

Patients meeting the following criteria were included in the overall AIT group: age [?]5 and [?]65 years; received at least one prescription of a symptomatic AR medication during the pre-index period (see Figure 1); received treatment with one of the selected AIT products with at least four prescriptions in [?]3 consecutive pollen seasons between index date and end of year 5; initiated treatment with one of these products between September 2009 and August 2013; and [?]2 years of follow-up after treatment.

Each AIT group has a matched control group with patients between the age [?]5 and [?]65 years with AR and/or asthma with at least three prescriptions of symptomatic AR medication in three successive allergy seasons (September to August) and with at least two years of follow-up.

Patients were excluded if they had received any specific immunotherapy in the entire database history (January 2008 to June 2020); had severe asthma (defined as having prescriptions of biologics for asthma) or perennial asthma [defined as [?]3 prescriptions of inhaled corticosteroids (ICS), long-acting ss2-agonists (LABA) in combination with inhaled corticosteroids, Theophylline or leukotriene receptor antagonists (LTRA), distributed over any three successive 4-month periods before the index date]; if they had COPD-specific maintenance medication in the entire database history; if they had extreme (0.25% of largest) values in terms of number of AR, allergic conjunctivitis (AC) or anti-asthmatic prescriptions during pre-index or follow-up period or if they had prescriptions of allergens of the focus product of both grass and tree pollen (Table S 1 and Table S 2).

Patients in the different control groups underwent exact matching with those in each AIT group. More than 58% of the patients were matched based on all defined covariates. Subsequently in separate matching steps covariates were removed to match the remaining patients. Details can be found in the supplemental Table S3.

Outcomes

The impact on the progression of AR was measured by symptomatic AR medication prescription after expiry of AIT treatment considering the probability of requiring symptomatic AR medication in the follow-up period and the number and reduction of AR prescriptions in the follow-up period standardized by year compared to the pre-index period.

For asthmatic patients, defined as patients treated with two prescriptions of an anti-asthmatic medication in the same or two sub-sequent allergy seasons, the impact of the study products on the progression of asthma was measured analogously. The other patients were classified as non-asthmatic at baseline. After expiry of AIT treatment the impact of the study products on the progression of asthma was measured by the probability of requiring anti-asthmatic medication and number and reduction of anti-asthmatic prescriptions in the follow-up period standardized by year after AIT compared to the pre-index period.

For non-asthmatic patients at index date, the impact on asthma incidence was measured analogously by the occurrence and by time to prescription of anti-asthmatic medication in the follow-up period.

Statistical analysis

Descriptive statistics were presented for all outcome variables and covariates. Analyses of progression of AR, progression or occurrence of asthma were carried out using a general linear regression model, with the ratio of annual number of prescriptions in the follow-up period vs the pre-index period used as the outcome variable. Analysis of AR and asthma medication intake was achieved by logistic regression with a stepwise selection of significant covariates. The individual length of the analytical time span was included as a covariate. Time to asthma medication intake was investigated using survival analysis. The proportion of patients with any level of treatment between the AIT and non-AIT control groups was also analysed by logistic regression. Statistical analyses were based on two-way testing without exception. For all statistical tests, significance level was set to 5% ($P < 0.05$). Analyses were performed using SAS 9.4 software SAS Institute, Inc., Cary, NC, USA.

Results

Patient population

Within the index period 181,496 patients received prescriptions within the AIT group. 5,959 patients fulfilled the inclusion criteria. Of these 44.8% received grass and 55.2% tree pollen allergoids. 504 of these patients received the MCT$^{(r)}$-associated allergoid, 3,329 patients allergoid 2 and 2,126 patients allergoid 3. The same number of matched control patients were included for each group. For each study product about half of

the patients were classified at index as adults (3,256 patients >18-65 years), followed by a high number of children (1,958 patients 5-12 years) and adolescents (745 patients 13-18 years). Baseline characteristics are summarized in Table 1. AIT therapy was mainly prescribed by Specialists (ENT specialist, dermatologist, pulmonologist, 58.9%), followed by Paediatricians (26.5%) and Generalists (14.5%). Only slightly more than half of the children and adolescents received AIT therapy through Paediatricians (56.1%), 59.0% of those treated with the MCT$^{(r)}$-associated allergoid, 52.9% with allergoid 2 and 59.6% with allergoid 3. The second most frequent prescribers of AIT therapy in this age group were Specialists. Before initiation of an AIT therapy 26.6% of the patients already had received asthma medication. The proportion of asthma was higher for patients initiated on the MCT$^{(r)}$-associated allergoid (31.9%) than for patients initiated on allergoid 2 or 3 (25.5% and 27.1%, respectively). The percentage of juvenile asthma patients was higher (30.6%) than in adults (23.3%, age >18 years). This proportion was highest in children and adolescents treated with MCT$^{(r)}$-associated allergoid, at 36.8%. The percentage of asthma patients was lower for allergoid 2 (29.2%) and allergoid 3 (30.8%).

AIT Effectiveness on AR progression

With 27.8%, significantly more patients treated with MCT$^{(r)}$-associated allergoids did not receive prescriptions for symptomatic AR medication in the follow up period vs. control group (covariate adjusted Odds Ratio (OR): 0.27; $p < 0.001$). Significant differences were also shown for allergoid 2 (19.0%, OR: 0.41; $p < 0.001$) and allergoid 3 (20.4%, OR: 0.33; $p < 0.001$) and therefore for the entire AIT treatment group (20.3%, OR: 0.37; $p < 0.001$, see Figure 2).

In addition, the prescriptions of symptomatic AR medication in the MCT$^{(r)}$-associated allergoid treatment group were significantly reduced by 24.2% in the follow-up vs. baseline and control group ($p < 0.001$). These effects could also be demonstrated for the allergoid 2, allergoid 3 and entire AIT treatment group (21.2%, 16.9%, 20.0%, $p < 0.001$, see Table 2).

All endpoints were significant for children/adolescents and adults in the individual analyses.

AIT effectiveness on asthma progression

Progression of asthma was analysed for asthmatic patients at baseline. With 17.8%, significantly more patients treated with MCT$^{(r)}$-associated allergoids did not receive prescriptions for symptomatic asthma medication in the follow up period vs. control group (OR: 0.48; $p = 0.004$). Significant differences were also shown for the treatment group of allergoid 2 (16.2%, OR: 0,47; $p < 0.001$) and allergoid 3 (14.3%, OR: 0.48; $p < 0.001$) and therefore for the entire AIT treatment group (15.6%, OR: 0.48; $p < 0.001$, see Figure 3a).

In addition, the prescriptions of symptomatic asthma medication in the MCT$^{(r)}$-associated allergoid treatment group were significantly reduced by 35.6% in the follow-up vs. baseline and control group ($p < 0.001$). These effects could also be demonstrated for the allergoid 2, allergoid 3 and entire AIT treatment group (28.3%, 30.1%, 29.1%, $p < 0.001$, see Table 2).

AIT effectiveness on onset of asthma

Onset of asthma was analysed for non-asthmatic patients at baseline. The probability of asthma medication onset during follow-up was significantly reduced for patients treated within the AIT group compared to controls (OR: 0.77, $p = 0.001$ (all patients, 5-65 years); OR: 0.78, $p = 0.017$ (adults, <18-65 years), see Figure 4a). The probability of not being prescribed symptomatic asthma medication was significantly greater for patients treated with AIT compared to the control group (see Figure 4b).

AIT effectiveness on asthma progression and onset of asthma in children and adolescents

The progression of asthma was analysed for asthmatic children and adolescents at baseline. With 16.3%, significantly more patients treated with MCT$^{(r)}$-associated allergoids did not receive prescriptions for symptomatic asthma medication in the follow up period vs. control group ($p = 0.037$). Significant differences were also shown for the treatment group of allergoid 2 (15.0%, $p < 0.001$) and allergoid 3 (11.6%, $p < 0.001$) and therefore for the entire AIT treatment group (13.8%, $p < 0.001$, see Figure 3b).

In addition, the prescriptions of symptomatic asthma medication in the MCT$^{(r)}$-associated allergoid treatment group were significantly reduced by 33.7% in the follow-up vs. baseline and control group ($p = 0.016$). These effects could also be demonstrated for the allergoid 2, allergoid 3 and the entire AIT treatment group (22.8%, 25.7%, 24.7%, $p < 0.001$, see Table 2).

Onset of asthma was analysed for non-asthmatic children and adolescents at baseline. The probability of asthma medication onset during follow-up was significantly reduced for children and adolescents treated within the AIT group compared to controls (OR: 0.74; $p = 0.02$, see Figure 4a). The probability of not being prescribed symptomatic asthma medication was significantly greater for children and adolescents treated with AIT compared to the control group (see Figure 4c).

Discussion

The TARGET study demonstrates that grass or tree pollen AIT is associated with significantly reduced AR progression, i.e. less symptomatic medication prescriptions in the total AIT group and different allergoid SCIT groups. These results are in line with the results of other RWE studies published by Wahn et al and Vogelberg et al . The beneficial effect was demonstrated for MCT$^{(r)}$-associated SCIT allergoid with a higher percentage of patients without AR medication prescription in comparison to the control group. The percentage of patients without AR medication prescription is in line with other RWE studies . In addition, a significant reduction of AR medication prescription in the follow-up vs. baseline and control group was observed for the MCT$^{(r)}$-associated allergoid. Beneficial effect was also observed for allergoid 2 and 3.

The TARGET study also showed a significant decrease in the probability of requiring anti-asthmatic medication and amount of anti-asthmatic mediation prescribed during follow up. This beneficial effect was also observed for the different analysed AIT products including a higher percentage of patients without asthma medication in comparison to the control group. As for AR medication, the control group also requires less anti-asthmatic medication. The proportion of asthmatic children/adolescents not requiring anti-asthmatic medication during follow-up is even greater compared to adults. Again, this effect was also seen for the AIT subgroup analysis. In terms of the additional reduction in asthma medication during follow-up vs pre-index compared to the control group, the TARGET study revealed a reduction of 29.1% points for the total AIT population. Wahn et al. reported a reduction of 32.0% points overseeing a shorter follow-up period of up to 6 years.

The Kaplan-Meier curves for AIT patients and patients without AIT are very close in the first five years of follow-up, however, afterwards the probability of asthma free survival is greater for AIT patients compared to control patients. Importantly, the beneficial effect of an AIT on the occurrence of asthma was statistically significant overall as well as for adults and children/adolescents which is in contrast to the study by Wahn et al. This might be due to the higher proportion of children and adolescents in the TARGET study (˜45% vs ˜20%) as it has been proposed that onset of asthma can be best prevented starting therapy early in childhood and adolescence . The European Academy of Allergy and Clinical Immunology (EAACI) recommend AIT for children and adolescents in order to prevent asthma . Further, another retrospective RWE LRx database study by Devillier et al. point out the consistent long-term benefits of an AIT in patients with AR with or without associated asthma in terms of slower progression of AR and asthma medication intake, and reduced risk of new-onset asthma medication use, mirroring the efficacy findings in RCTs in the real-world setting . The findings of the TARGET study are supported by a recent retrospective cohort study by Fritzsching et al., REACT, using claims data of a German health insurance fund database . Fritzsching et al. also found AIT patients to be associated with greater reductions in AR and asthma prescriptions and a reduction in asthma treatment compared to control subjects. It must be considered that real-world studies should not be directly compared due to different in- and exclusion criteria, data source, matching of patients and further aspects of differing study design.

The present real-world findings add to the current body of clinical evidence extending existing RCT evidence for AIT. Becker et al. performed a meta-analysis on RCTs recently showing a significant improvement of allergic symptoms and reduction in medication use in patients treated with MCT$^{(r)}$-associated allergoids .

Showing a reduction in AR and asthma medication prescription of 24.2% and 35.6% compared to control group after SCIT with MCT$^{(r)}$-associated allergoids, the results of the TARGET study are highly valuable data to complement the efficacy data of MCT$^{(r)}$-associated SCIT allergoids.

This RWE study had several limitations. Clinical information had to be obtained via proxies like for AR diagnosis by prescription of symptomatic AR medication . Some patients with AR might have not been detected, because a large proportion of AR medication is available over-the counter. Furthermore, from 2017 onwards some intranasal corticosteroids were not reimbursed. However, for children up to the age of 12 years non-prescription AR drugs can be prescribed at the expense of the statutory health insurance funds which should minimize this effect in this age group. Moreover, all anti-asthmatic medications are prescription-bound. In total, any such bias should affect both the AIT and non-AIT control groups equally, thus not impacting the relative comparisons between the groups.

Importantly, the unmet need for an appraisal of the quality of RWE in AIT has been addressed by Paoletti et al. who recently initiated a systematic review of observational studies of AIT to provide an essential source of real-world data and improve quality in clinical decision making . RWE will likely prove to be of enormous value to synthesize evidence from the different sources RCTs and RWE studies, a position which is already changing with regard to evolving regulatory opinions, guidance frameworks, and with growing recognition of the value of using RWE that is acceptable for regulatory decision-making . The FDA and EMA is already developing guidance that defines how regulators consider RWE in their decision-making - both for new and existing approvals .

The main strengths of this study are that it was conducted in a real-world, large and inclusive patient cohort, with the longest follow up period (after AIT completion) shown in AIT RWE studies (up to 9.5 years, O 6.3 years). The current study used a stringent patient-matching process with at least 58% of eligible patients being matched to appropriate controls. Each AIT group was matched separately to their controls ensuring high data quality and a good comparability of the study cohorts with their controls. This reduced confounding, avoided possible bias from intergroup differences and ensured robustness of findings.

Conclusions

RWE studies are playing an increasingly important role. Health authorities in US and Europe have recognized the added value of RWE studies. In addition to DBPC studies RWE data increase corroboration by allowing insights into the therapeutic effectiveness after AIT completion, especially in children and adolescents. The TARGET study has the longest follow-up period (after AIT completion) shown in AIT RWE studies so far and demonstrates the long-term benefit of pollen (grasses or trees) allergoid SCIT including MCT$^{(r)}$-associated allergoids on the progression of AR and progression and occurrence of asthma up to 9.5 years of follow-up in clinical practice. Importantly, also the prevention of asthma was demonstrated. Results were significant for all patients (5-65 years) but also for children/adolescents and adults in the individual analyses. The results of the TARGET study substantiate the findings of other RWE studies in patients with pollen-induced allergies and demonstrate the effectiveness of authorized SCIT allergoids including MCT$^{(r)}$–associated allergoids in AR and asthma under real-world conditions.

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