Take a Breath of Real-World Evidence

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Meeting Summary

Allergen immunotherapy (AIT) in the form of subcutaneous or sublingual immunotherapy (SCIT/SLIT) is the only treatment for allergic rhinitis (AR) and/or allergic asthma with long-term efficacy.

Dr Fox considered the benefits for using real-world (RW) evidence in AIT. RW evidence provides the opportunity to explore a wide range of patients, estimate evolving risk benefits, and obtain data on clinical and economic value, as well as allowing comparisons of multiple alternative interventions. In clinical settings, such information allows doctors to provide allergy patients with the best advice, because most patients do not fit the narrow inclusion/exclusion criteria of clinical trials.

The benefits of RW research can be illustrated by two studies that are part of the Bringing Real-World Evidence to Allergy Treatment for Health (BREATH) programme, which was launched by Stallergenes Greer.

Prof Zielen provided an overview of the design of the German Birch AIT and French Grass SLIT Tablets RW studies. The studies are retrospective cohort studies based on IQVIA™ longitudinal prescription databases allowing patient follow-up. Follow-up was up to 9 years in Germany. Both studies share three objectives: looking at progression of AR after treatment cessation, initiation of new asthma medication in patients with AR (not asthma) at baseline, and progression of asthma medication use in patients with asthma (with or without AR at baseline).

Exploring the studies in greater detail, Prof Demoly presented the French Grass SLIT Tablets RW study, which compared 1,099 patients treated with SLIT with 24,475 controls not treated with SLIT. The results for the SLIT cohort versus the control cohort demonstrated long-term benefits for AIT (up to 2 years after treatment cessation), significantly reduced AR medication intake ($p<0.001$), significantly reduced asthma medication intake ($p=0.003$), and significantly decreased initiation of asthma medication ($p=0.0013$).

Prof Wahn presented the German Birch AIT RW study, which compared 9,001 AIT patients with 45,005 control patients not taking AIT. The results showed that AIT patients were significantly more likely to be AR medication-free ($p<0.001$), had reduced risk for initiation of asthma medication during the study ($p=0.001$), and were more likely to be asthma medication-free during 6 years of follow-up ($p<0.001$). Notably, when different types of AIT were compared to control, SLIT was not found to be any less effective than SCIT, opening the way for wider use of sublingual treatments.

Introduction

David Tomlinson

The symposium addressed the question of how to optimise the quantity and quality of RW data for the benefit of patients. For example, the BREATH programme gathered information from >150,000 patients, tracked for 8 years. The audience discussed how RW data like this will change practice.

Time to Think Bigger? Is Real-World Evidence a Game-Changer?

Doctor Adam Fox

While randomised controlled trials (RCT) are considered the gold standard for assessing safety and efficacy, their lengthy inclusion and exclusion criteria have created concerns that it may be difficult to generalise results to wider populations.

Recently, it has become possible to use RW evidence derived from sources outside typical clinical research, with examples including electronic hospital records, billing data, disease registries, and prescription databases. Such sources complement RCT by reflecting use in clinical practice. The approach offers cost-effective possibilities to look at interventions over extended periods of time, creating new data gathering opportunities and changing the way clinicians think about the treatments they prescribe routinely. While RW evidence is increasingly recognised as an important source of information by organisations, such as the National Institute for Health and Care Excellence (NICE) and the U.S. Food and Drug Administration (FDA), in allergy the approach is still in its infancy.

RCT play a critical role in achieving product licences, with RW studies exploring what happens beyond product registration. Real-life populations may vary according to sex, age, ethnicity, comorbidities, disease severity, concomitant medications, and compliance.[1] How such factors affect outcome needs to be explored; this will result in the possibility of using this information to design the next round of RCT.

The benefits of exploring RW data in the context of AIT include:

> A wide range of patients, with possibilities to investigate diverse populations reflecting the range and distribution of patients observed in clinical practice; e.g., polysensitised patients.

> The ability to estimate evolving risk–benefit profiles of AIT, including long-term clinical benefits and risks, such as whether hyposensitising children for AR influences later asthma outcomes.

> Provide evidence related to the clinical and economical value of AIT in addition to safety and proper use. With RW data, it is possible to explore not just whether interventions are effective but where they are most and least effective.

> Possibility for assessment of multiple alternative interventions to inform identification of optimal treatments.

In clinical settings, such information allows doctors to provide patients with the best advice, since most patients do not fit the narrow inclusion/exclusion criteria of clinical trials.

Studies have highlighted the challenges physicians face when treating AIT patients in real practice, which include the problem of selecting the right patient,[2] generalising results from studies to primary care,[3] and the possibility that efficacy may only be achieved for patients with severe symptoms.[4] Even if the right patients are selected, questions remain about whether they will take treatments. It is widely acknowledged that patients in study settings are well motivated and good at taking medications, with a meta-analysis involving 81 SLIT studies and 9,998 patients showing excellent adherence, with only 14% dropping out.[5] Such data are in sharp contrast to a Dutch pharmacy study, which showed only 7% of 3,690 SLIT patients completed their 3-year course.[6]

Study nurses can have a beneficial impact on adherence, with Italian research showing the combination of education, contact, and follow-up reduced drop-out to 5% at 4 months and 12% at 1 year.[7] Such data provide a plausible explanation for differences observed between clinical trials and RW situations.

Despite such challenges, the benefit of AIT treatment in clinical practice was shown recently in a large-scale retrospective RW prescription database analysis using the German longitudinal prescription database, the IQVIA HealthLRx database. The study, which assessed the effectiveness of two grass pollen SLIT tablets, provides a good example of the use of big data. The BREATH large-scale retrospective analysis, which analysed data from 2008–2016, identified 2,851 SLIT patients. They were compared to 71,275 control patients who had seasonal AR; they had been prescribed nasal steroids during the grass pollen season but had not received AIT treatment. The study showed RW treatment of AR patients with grass pollen SLIT tablets versus control was associated with an additional 19% improvement in progression in the use of AR medication, a 30–40% risk reduction of initiating asthma medication, and an additional 17% reduction in asthma medication. These data show grass pollen tablet SLIT prolongs the time to getting asthma and reduces the need for asthma medication.[8]

In summary, RCT remain the gold standard and RW evidence provides data complementing their findings. RW evidence shows how RCT findings can be generalised to broader populations and reflect actual use in practice. However, while RCT evidence supports SLIT efficacy, poor patient selection or poor adherence may impact on effects in clinical practice. BREATH represents the first initiative to develop a substantial RW evidence base around AIT and demonstrates insights into its effects.

What is the Impact of Allergen Immunotherapy on the Disease Evolution of Respiratory Allergy Patients?

Professor Stefan Zielen

Prospective study designs generally require primary data collection, providing a high degree of control over data collected. Disadvantages include studies taking longer and costing more than retrospective designs. Retrospective database studies, looking back in time using secondary data, have the potential to generate

large RW sample sizes quickly and efficiently. Limitations include the fact that the data already exist, allowing for no control over the information collected.

Both the German Birch AIT and the French SLIT Grass Tablets RW data studies are secondary data retrospective studies based on IQVIA longitudinal prescription databases. Patients have a unique ID across all their physicians and the database. Diagnoses are not recorded but are instead inferred from prescriptions. The German study (which retrospectively analysed data from 2008 onwards) involved data from >60% of German pharmacies, while the French study (which retrospectively analysed data from 2012 onwards) involved data from around 35% of French pharmacies.

The main difference was that the German study used birch AIT (in the form of drops, natural SCIT, or chemically modified allergoids) and the French study used grass tablet AIT. Individuals receiving these prescriptions were compared with control patients receiving only symptomatic drugs. For both studies, the three objectives were:

> Progression of symptomatic AR medication after treatment cessation.

> Initiation of new asthma medication in patients with AR (not asthma) at baseline during and after treatment cessation.

> Progression of asthma medication use in patients with asthma (with or without AR at baseline).

For the AIT group, inclusion criteria were ≥5 years of age, ≥2 seasons of treatment with AIT, AR with or without asthma (grass tablets), AR and/or asthma (birch AIT), and ≥1 (grass) or 2 (birch) years follow-up after AIT cessation. The exclusion criteria for the AIT group were perennial and/or severe asthma, and to have received any other AIT in the past. For the control group, inclusion criteria were ≥5 years of age; AR with or without asthma (grass tablets); AR and/or asthma (birch AIT), defined as ≥3 prescriptions of AR; and/or asthma medication for 3 successive grass/birch pollen seasons. The exclusion criteria for the control group were a previous history of AIT and perennial and/or severe asthma.

The German study involved 9,001 AIT patients and 45,005 control patients, and the French study involved 1,099 AIT patients and 27,475 control patients. The key study periods were pre-index (1 year before AIT started representing baseline), index date (date of first AIT delivery), treatment period, and follow-up period (from date of expiry of the last AIT until end of study).

The strengths of the studies are that they reflect clinical practice and the use of AIT, they are nationwide studies representing large cohorts, they allow comparisons of AIT versus standard of care, and different formulations can be tested with the same methodology. Additionally, longitudinal data collection allows patient follow-up over time and the data covers a 9-year period, allowing assessment of long-term effectiveness. Weaknesses include that they are retrospective analyses, the clinical information was obtained via proxies (use of asthma and AR prescription data), and the ability to only detect reimbursed drugs.

New Results from a French Study with Allergen Immunotherapy Tablets for Grass Pollen Allergies

Professor Pascal Demoly

The French study with SLIT tablets for grass pollen allergies was based on a prescription database involving data from one-third of French pharmacies.

Overall, 1,099 AIT patients who received grass pollen tablet SLIT for AR (62% with AR and 38% with AR and asthma) were compared to 27,475 controls who did not receive grass pollen tablet SLIT but had access to symptomatic AR (and asthma) medication (61% with AR and 39% with AR and asthma). For AIT patients, 27.7% were followed for three seasons and 72.3% for two seasons, and controls were followed for a minimum duration of 1 year and a maximum duration of 2 years. The shorter follow-up compared to the German study can be explained by the French prescription database being younger.

Regarding age, for SLIT patients, 43% were aged 5–17 years, 47% 18–45 years, and 10%

>45 years; for the controls, 6% were aged 5–17 years, 24% 18–45 years, and 70% >45 years. The data demonstrate that, overall, AIT patients were younger than controls. However, a post hoc analysis found that even when subjects were paired according to age, the results remained strong.

Regarding the first objective (AR medication progression), the results showed a 50% reduction in SLIT group for AR medication prescriptions after treatment cessation. This was compared to a 30% increase for AR medication use in the control group (p<0.001). Additionally, it was found that 37.4% of AIT patients did not use AR symptomatic drug prescriptions during follow-up, compared to 4.5% of controls. This led to the conclusion that SLIT tablets for grass pollen AR lowered the number of patients using AR symptomatic medication by the end of the study.

Regarding the second objective (initiation of asthma medication), the results showed an additional 36.6% reduction in initiation of asthma medication for the AIT group versus the control group (p=0.003) in the treatment period. In the follow-up period, there was an additional 62.5% reduction in initiation of asthma medication for the AIT group versus control group (p=0.0025). Furthermore, a Cox regression analysis found a significant difference in the length of time AR patients without asthma at baseline did not initiate asthma medication for AIT patients versus the control group (hazard ratio: 0.36; p=0.0013). The findings led to the conclusion that SLIT tablets for grass pollen AR significantly reduce the relative risk of starting asthma medication in real life.

Regarding the third objective (progression of asthma medication), results showed that, during the treatment period, 16% of SLIT patients with asthma at baseline did not use treatments, in comparison to 7.1% of controls. In the follow-up period, 43.1% of the SLIT group with asthma did not use asthma symptomatic medication compared to 10.8% of controls. Overall, there was a 40% reduction in asthma medication in the AIT group after treatment cessation, compared to a 20% increase in the control group (p<0.0001).

In conclusion, the French investigators confirmed the previous German results[8] in a study looking at long-term benefits of grass pollen SLIT tablets with up to 2-years follow-up. The French study showed AR medication, asthma medication, and initiation of asthma medication were all significantly reduced.

New Results from a German Study with Allergen Immunotherapy for Birch Pollen Allergies

Professor Ulrich Wahn

Allergy research is now leaving the ivory tower of academic studies and entering the real world for use in real patients. In the German study on birch pollen allergic patients with AR and/or asthma, investigators compared the six birch-family pollen AIT products available in Germany (one natural SLIT, one natural SCIT, and four allergoid SCIT preparations) with symptomatic drugs. The study set out to understand whether AIT can help patients with AR get better, reduce the 'allergic march of asthma', and influence seasonal asthma; see earlier for the three study objectives.

In the German study, 9,001 AIT patients were matched to 45,005 control patients. The age distribution for both AIT patients and controls was 5–17 years (19.9%), 18–35 years (21.6%), 35–50 years (34.2%), and >50 years (24.3%). The number of seasonal cycles in the treatment period were two (45.1%), three (40.2%), four (13.3%), and five (1.5%). The follow-up duration of the study was an average of 4.4 years, with a minimum of 2 years and a maximum of 6.6 years.

Results for the first objective (AR medication progression) showed significantly more AIT patients (65.4%) than non-AIT patients (47.4%) were AR medication-free (overall response [OR]: 0.51; p<0.001). Furthermore, the proportion of AIT patients not using any AR medication was significantly higher than the control patients for all six different interventional groups.

Additionally, the proportion of patients not using AR symptomatic medication during follow-up was 65.4% for all AIT patients versus 47.4% for controls (OR: 0.51; p<0.001), and the significance was maintained in all AIT treatment groups. After covariate adjustment, the additional reduction in AR medication prescription during

follow-up was -28.6% greater for AIT patients than non-AIT controls (p<0.001).

Taking the second objective (initiation of asthma medication), results showed that during treatment AIT users had a significantly reduced risk of initiation of asthma medication than non-AIT users (OR: 0.83; 95% confidence interval: 0.740–0.930; p=0.001). When different AIT intervention groups were analysed, the effect versus control was stronger for some of the AIT therapies, notably allergoid SCIT-1 (p=0.016) and natural SLIT (p=0.013).

Up to 6 years after stopping treatment, none of the products prevented the occurrence of new-onset asthma medication intake in non-asthmatic patients (OR: 1.02; 95% confidence interval: 0.884–1.182; p=0.765). Over the combined treatment and follow-up period, only SLIT showed a significantly reduced risk of initiating asthma medication use versus non-AIT patients.

Taking the third objective (progression of asthma medication in patients with asthma with or without AR at baseline), at up to 6 years of follow-up, 49.1% of patients in the AIT group using asthma therapy at baseline were asthma medication-free, in comparison to 35.1% of non-AIT patients (OR: 0.60; p<0.001). The difference was statistically significant for all AIT groups. Such data demonstrate it is possible to reduce asthma medication among patients with allergic asthma.

In conclusion, both the German and French studies show that AIT changes the natural history of the patients in the real world, with robust and consistent evidence for reducing both AR and asthma medication intakes and reducing the risk of new asthma medication initiation in those who did not previously have it. AIT is a treatment that now needs to be discussed with patients.

Take-Home Messages

Finally, each of the speakers provided take home messages from the seminar:

> Dr Fox said that RW AIT studies change the way clinicians use the data they produce to inform practice and represent the birth of genuine personalised medicine in allergy.

> Prof Demoly stressed the importance of studies including asthma patients.

> Prof Zielen highlighted the finding that SLIT and SCIT are equally effective.

> Prof Wahn said RW studies show AIT modifies disease and interferes with the 'allergic march', providing long-term benefits.

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