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The growing importance of real-life studies in allergen immunotherapy

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Summary
Real-life studies offer the opportunity of obtaining outcomes suitable in clinical practice, as controlled trials do not mirror the real patients' population observed in clinical practice. This concept is particularly appropriate for allergen immunotherapy (AIT). Therefore, the current review will present and discuss the most recent and relevant studies published on this topic. Globally, 15 real-life studies on AIT efficacy are available until now, the total of patients amounts to 9090, with an average number of 699 patients per study. This high number significantly decreases the possibility that the observations from real-life study are casual, and confers to such studies a key role in the next years to assess issues other than efficacy and safety, especially those scantly investigated thus far.

Background

The concept of real-life studies was introduced in the 1970s as an optional approach to laboratory studies (1), but in the following years the actual reference to be used was the randomized controlled trial (RCT), which was pioneered in the 1940s (2) and became the gold standard to establish the efficacy of a medical treatment, such as the "evidence". The basis of an RCT is the random allocation of patients participating to the trial to receive either the treatment under investigation or placebo (a treatment already demonstrated as effective may be also used). The double-blind fashion results in clear advantages in terms of minimization of causality and bias commonly affecting open studies. In 1998, a level II evidence was attributed to a single RCT and a level I (the highest) evidence was attributed to a systematic review of RCTs (3). However, the advantage of the rigid control and patients' selectivity in RCTs is counterbalanced by the unlikely applicability to patients managed in routine clinical practice, because the "highly selected population of RCTs only partially represents the real-life population" (4). This issue plainly concerns also allergen immunotherapy (AIT) for respiratory allergy, which has clear evidence of efficacy and safety as assessed by meta-analyses, but the validity and applicability of the observations resulting from RCTs data, especially in the context of real-life settings, is debatable (5). To confirm the applicability to common practice of AIT products demonstrated as effective in RCTs, real-life (also defined real-world) studies are needed. This model was increasingly used in recent years and, especially when based on large populations of patients, provides very useful data to optimize the prescription and the performance of AIT in clinical practice. Here, we will discuss the significance of the outcomes that were achieved in such studies.

Real-life studies on AIT

The first paper mentioning the term real-life in its title was published in 2004. This study assessed the treatment outcome in 192 patients with allergic rhinitis (AR) with or without asthma treated only with drugs, and in 319 patients treated with sublingual immunotherapy (SLIT) (6). The results showed that SLIT approximately halved the symptom-medication scores compared to the score registered in drug-treated patients. Since then, several real-life studies were performed, including 11 studies on SCIT (7-17), 15 on SLIT (6,18-29) and 5 on both (30-

34). **Tables I** to **III** show the main characteristics of these studies. We analysed the issues highlighted in real-life studies, which are represented by efficacy, safety and tolerability, quality of life, patient adherence and compliance to treatment, economic aspects, and physicians' prescription attitude.

Efficacy and safety of SCIT and SLIT

The major measures to assess efficacy of immunotherapy in RCTs are symptom and medication scores. Actually, in most real-life studies the major aim was efficacy assessment. In 11 studies (3 on SCIT, 7 on SLIT and 1 on both) only efficacy was evaluated, while in 3 studies (1 SCIT and 2 SLIT) also safety was evaluated. In other 2 studies, safety was the only object of assessment. Thus, a global number of 14 real-life studies on efficacy (4 on SCIT, 9 on SLIT and 1 on both) are available. In particular, two studies (1 on SLIT and 1 on SCIT and SLIT) included very large number of patients.
Zielen et al. performed a retrospective multiple regression analysis of data from a German prescription database consisting of 2851 patients treated with grass pollen SLIT tablets, and 71,275 control patients (25) in a time horizon of 7 years. As indicators, changes over time in symptomatic drug consumption after SLIT stopping, use of medications for asthma, and time of asthma onset in patients with AR were used. The results showed a significant difference in favour of SLIT for all comparators. In particular, the use of symptomatic drugs for AR compared to the pre-treatment period was 18.8% lower ($p < 0.01$) in SLIT treated patients than in controls, the asthma medication use decreased by an additional 16.7% ($p = 0.004$) after treatment withdrawal in SLIT treated compared with controls, and the onset of asthma was less frequent (odds ratio 0.696, $p = 0.002$) in SLIT treated patients than in controls. The authors overall conclusions highlighted that the treatment with grass pollen SLIT tablets results in better disease control and less frequent onset of asthma in patients with AR, as well as in slower disease progression in patients with asthma. The other large real-life study included, using the same German prescription database and a time horizon of 2-6 years, a retrospective cohort of 9001 patients treated with SLIT or SCIT for birch pollen-associated

Table I *- Real-life studies on subcutaneous immunotherapy.*

Author, year (ref)	Study population	Issue addressed	Results
Zeldin et al. 2008 (7)	133 pts of all ages	efficacy and safety	significant decrease of symptoms and medication scores, mild to moderate reactions in 8%
Petersen et al. 2010 (8)		willingness to pay	patients with allergy select themselves appropriately according to need
Petersen et al. 2013 (9)	248 pts of all ages	quality of life (QoL)	improvement of QoL and decrease of sick days
Pfaar et al. 2015 (10)	2927 children and adolescents	safety	local reactions in 16.3%, systemic reactions in 1.6%
El-Qutob et al. 2016 (11)	409 pts of all ages	efficacy by physician-completed visual analogue scale (VAS)	58.1% clinical improvement
Droessart et al. 2016 (12)	800 pts of all ages	SCIT efficacy compared to drug treatment after a 3- year course	persistent symptoms in 18% of SCIT vs. 51% of drug treated, drug use in 30% of SCIT vs. 61% of drug treated
Li et al. 2016 (13)	272 pts of all ages	efficacy by symptom severity scores and VAS after 12 months	significant improvement in symptom scores and VAS
Gelincik et al. 2017 (14)	204 adult pts	adherence to SCIT	87.3% of pts were considered adherent
Reiber et al., 2017 (15)	307 adult pts	tolerability	adverse events in 23.3% of pts (mild-moderate in 14.8%, severe in 8.5%)
Allen-Ramey et al. 2017 (16)	6710 pts of all ages	healthcare costs	continued SCIT use associated to lower costs (decreased emergency room visits, inpatient stays, decreased oral corticosteroid use) compared with early discontinuation
Yang et al. 2018 (17)	311 pts of all ages	adherence to a 3-year SCIT course	global adherence rate at year 3 64.6%; 19% of pts dropped out in year 1, 10% in year 2, and 6.4% in year 3; higher adherence in children

AR and asthma and 45,005 matched patients treated only with symptomatic drugs as controls. Six different birch or tree (hazel, alder) pollen extracts were prescribed, including SLIT drops, natural pollen SCIT and 4 SCIT allergoid preparations (36). The multiple-regression analysis showed that at completion of the 6 years follow-up 65.4% of AIT treated patients used no more symptomatic drugs for AR compared with 47.4% of controls ($p < 0.001$), and 49.1% of AIT treated patients used no more drugs for asthma compared with 35.1% of controls ($p < 0.001$). Also, the risk of new-onset asthma was significantly lesser in AIT treated vs. controls (odds ratio 0.83, $p = 0.001$). The very large number of patients analysed in these two studies ensures the reliability of the efficacy data supporting a major role of AIT in the treatment of patients with respiratory allergy. Concerning the safety, though the number of studies was low (2 studies with safety as the only object of assessment, 4 studies

Table II *- Real-life studies on sublingual immunotherapy.*

Author, year (ref)	Study population	Issue addressed	Results
Marogna et al. 2004 (6)	511 pts of all ages	SLIT efficacy compared with drug treatment	significant improvement of clinical scores in the SLIT group
Marogna et al. 2007 (18)	65 adult pts	duration of SLIT efficacy 7-8 years after its stopping	significant difference in symptom-medication scores compared with untreated pts
Sieber et al. 2010 (19)	1052 adult pts	efficacy and safety of high dose SLIT	consistent improvement in symptom and medication score, better results with ultra-rush schedule. Adverse events in 24% of patients during titration with no difference between schedules
Trebuchon et al. 2012 (20)	1289 pts of all ages	SLIT effectiveness on rhinitis and asthma, compliance	symptoms of rhinitis and/or asthma improved in 66% and 63% of pts, respectively, concomitant reduction in medication intake. Compliance 84%
Wessel et al. 2012 (21)	628 pts of all ages	SLIT safety during 3-year treatment with 1-grass tablet	reactions requiring SLIT discontinuation or symptomatic medication: 15 (14 at initiation and 1 at reintroduction); mild- moderate reactions in 46.2%, 14.4% and 1.8% of pts, during the 1st, 2nd and 3rd year of SLIT, respectively
Pastorello et al. 2013 (22)	47 pts of all ages	SLIT efficacy in pts unresponsive to drugs	significant decrease of mean medication score (from 4.2 ± 1.3 before to 2.4 ± 2.0 after SLIT); significant increase in patient satisfaction after SLIT
Shah-Hosseini et al. 2015 (23)	1408 pts of all ages	SLIT effectiveness and safety	significant reduction of symptoms (49.9%) compared with the preceding pollen; mild-moderate reactions in 15.3% of pts
Zielen et al. 2018 (24)	2851 SLIT treated and 71275 untreated pts	SLIT long-term efficacy, asthma onset in pts with rhinitis	medication for rhinitis 18.8% lower and medication for asthma 16.6% lower in SLIT treated at cessation; asthma onset significantly less frequent ($p = 0.002$) in SLIT treated
Janson et al. 2018 (25)	207 adult pts	three-year completion of SLIT	55% of pts completed the SLIT course, 24% were still on treatment, 22% discontinued prematurely; asthma improvement twice as common among pts who completed
Schafer et al. 2017 (26)	253 adult pts	SLIT efficacy and patient's satisfaction	significant improvement of symptoms from baseline, reduced need for medications, good satisfaction
Novakova et al. 2017 (27)	191 adult pts	QoL after a 3-year course of SLIT	significant improvement of QoL compared with baseline
Nadir Bahceciler et al. 2017 (28)	90 children	steroid sparing effects in children with asthma	inhaled corticosteroids avoided in 70% of children; significantly higher avoidance in longer SLIT duration
Kiotseridis et al. 2018 (29)	399 pts of all ages	adherence and QoL in a 3-year course of SLIT	55% of pts completed the SLIT course; improvement of QoL at study end

Table III *- Real-life studies on subcutaneous and sublingual immunotherapy.*

Author, year (ref)	Study population	Issue addressed	Results
Schmidt et al. 2015 (30)	118,754 pts of all ages with allergic rhinitis but without asthma	risk of developing asthma	newly diagnosed asthma in 1.4% of pts treated with AIT for 3 or more years
McDonell et al. 2015 (31)	18,805 pts of all ages	AIT prescription for grass pollen allergy	SCIT is the preferred AIT in Germany but there was a marked increase in prescription of SLIT tablets
Schwanke et al. 2017 (32)	105 adult pts	QoL at initiation of AIT and after 6 d 12 months	improvement of QoL with both SCIT and SLIT but statistical significance only with SCIT
Wahn et al. 2017 (33)	1029 pts of all ages	AIT prescription in polysensitized pts	98% of physicians prescribed SCIT or SLIT, 58% with single-allergen and 42% with multiple-allergens; 74% of them were aware of latest AIT guidelines
Musa et al. 2017 (34)	236 adult pts	compliance at 3-year course of AIT	compliance of 58.7% with SCIT, 11.6% with SLIT
Wahn et al. 2018 (35)	9001 SLIT treated and 45,005 matched untreated pts	SLIT long-term efficacy, asthma onset in pts with rhinitis	significantly reduced AR and significantly decreased risk of new-onset asthma

analysing both efficacy and safety) the overall population investigated included 6148 patients. Such figure guarantees the reliability of the observations that indicate a very good profile of safety in real-life conditions. In fact, most adverse reactions, which ranged from 16.3% to 49.9% in the different studies, concerned local reactions in the oral mucosa, while systemic reactions were rare (7,10,19,21-23). Of interest, no fatal anaphylactic reactions to SCIT were reported. Such reactions have been a critical issue in the past, but the identification of the major risk factors, the highest being associated to the presence of uncontrolled asthma at the moment of the allergen extract injection, made the occurrence of anaphylactic reaction very rare (37). Based on the data from the available studies, it is likely that precautions to prevent anaphylaxis are adopted also in real life.

Other issues investigated

A single study evaluated as a measure of efficacy the steroid sparing effect of SLIT. This issue was previously explored concerning anti-asthmatic drugs, such as montelukast (38) also in controlled trials of allergen immunotherapy (39). The study by Nadir Bahceciler et al. evaluated 90 monosensitised or polysensitised children with asthma treated with single or 2-simultaneous and multiple-pollen-mix allergen SLIT, which resulted in 70% avoidance of inhaled corticosteroids. No significant difference was detected between mono- and poly-sensitized children. The rates of avoidance in mono-allergen, pollen-mixture and 2-simultaneous-allergen SLIT were 93.6, 83.3 and 73.7%, respectively. A significantly higher avoidance ($p = 0.0001$) was observed in children with longer-duration SLIT (28).

Another aspect evaluated in a single study was the ability to prevent the development of asthma in subjects treated for AR. The data were obtained from German National Health Insurance based on a cohort of 118,754 patients with rhinitis but without asthma, who were stratified to received AIT (SCIT or SLIT) or only drugs. In the 2431 AIT treated patients, a new asthma diagnosis was done in 1.4% of subjects, with a risk of asthma was significantly lower in AIT treated (risk ratio 0.60; 95% CI, 0.42-0.84) compared with patients treated only with drugs (31).

The other topics were addressed in multiple studies. The most investigated was adherence and compliance, which was the subject of 5 studies (15,18,26,30). In a short-term study on SCIT, 87.2% of patients were considered adherent (15), while in a 3-year study the adherence at the last year was 64.66% (18). In the two 3-years studies on adherence to SLIT, the same outcome was reported, 55% of patients completing the entire treatment (26,30). The only study comparing SCIT to SLIT reported a compliance rate of 58.7% in SCIT treated and 11.6% in SLIT treated patients (34). Except the first SCIT study, the rate of adherence in real-life is apparently lower than reported in controlled trials, but this is not surprising, based on the much more stringent criteria used to monitor the patients recruited in trials (40). The effects on quality of life (QoL) were analysed in 3 real-life studies. The first was a

prospective assessment of 248 patients with AR on the changes in QoL measured by the disease specific Rhino-conjunctivitis Quality of Life Questionnaire (RQLQ) after a SCIT course. The mean RQLQ-score significantly reduced from 3.02 at baseline to 2.00 at follow-up (9). Novakova et al. prospectively evaluated by RQLQ 191 adult patients with moderate to severe mite-induced or grass pollen-induced undergoing SLIT for 3 years. The mean RQLQ score decreased significantly from baseline to end of treatment for both mite (from 2.95 to 0.76) and grass pollen (from 2.83 to 1.22) SLIT (28). The study by Schwanke et al. used the same questionnaire to compare the variations of QoL in 29 SCIT treated and 11 SLIT treated patients with respiratory allergy from initiation to 6- and 12-months immunotherapy. In both groups of patients there was an improvement in QOL, but the change in the RQLQ score from both baseline to 6 months and baseline to 1 year was significant only in the SCIT group ($p = 0.002$). After 1 year of treatment, both SCIT and SLIT achieved the minimally important difference from baseline in the overall RQLQ score (33).

Economic aspects have increasing importance in any medical treatment. The first real-life study was limited to assessing the willingness to pay for SCIT in patients with respiratory allergy, concluding that subjects with allergy select themselves appropriately according to need and not to other characteristics, such as income or education (8). The more recent study by Allen-Ramey et al. evaluated medical and pharmacy claims from a US Database from January 2009 through February 2014 for adults and paediatric patients with more than 7 or less than 7 injection visits for SCIT within 60 days from starting (17). Each cohort included 6710 patients. Patients receiving more than 7 injections (continuers) used significantly less oral corticosteroids than patients receiving less than 7 injections (27.7% vs. 29.6%, $p = 0.018$). Other significant differences in favour of continuers included less respiratory-related emergency room visit, less outpatient visits in front of higher mean total rhinitis-related costs compared with discontinuers ($ 1918 vs. $ 646, $p < 0.001$). However, when adjusted with a generalized linear model, these costs were significantly lower among continuers ($p < 0.001$).

Lastly, two studies addressed in large populations the physicians prescribing attitudes. The first study, including 18,805 patients, reported that SCIT is the preferred AIT for grass pollen allergy in Germany, though a marked increase in prescription of SLIT occurred when sublingual tablets were made available (31). The other study estimated the AIT prescription in 1029 polysensitized patients. SCIT or SLIT were prescribed by 98% of physicians, using single allergens in 58% and multiple allergens in 42% of cases. The awareness of the updated AIT guidelines was ascertained in 74% of physicians (34).

Conclusions

AIT has received full evidence of efficacy and safety by a number of meta-analyses of placebo-controlled trials. Limiting the examination to the more recent meta-analyses, the evidence concerned both SCIT and SLIT. The analysis by Calderon et al., comprising 51 trials on SCIT in patients with AR, resulted in a highly significant reduction of symptoms and medication scores in active treatment ($p < 0.00001$ in both parameters), while severe systemic reactions requiring adrenaline occurred in 0.13% of patients (41). Radulovic et al. included 49 trials on SLIT in patients with AR: the same level of statistical significance ($p < 0.00001$) was detected for symptoms and medication need, along with the absence of severe systemic reactions requiring adrenaline administration (42). Dhami et al. performed a systematic review and meta-analysis including 89 trials (54 SCIT, 34 SLIT and 1 both treatments) on the efficacy of AIT in allergic asthma. Short-term symptom scores and medication scores were reduced, as shown by a standardized mean difference (SMD) of -1.11 (95% CI -1.66, -0.56) and -1.21 (95% CI -1.87, -0.54), respectively, though with potential publication bias. AIT resulted in a "of adverse events, systemic reactions being more frequent with SCIT but with no fatalities (43). This suggests that AIT in its two routes of administration is clearly indicated as an effective treatment in patients with AR or asthma. However, as hinted above, the efficacy and safety assessed by meta-analyses of rigidly controlled RCTs is unlikely applicable to common clinical practice, the average patient easily lacking the characteristics to be included in a trial. Thus, real-life studies are essential to favour the appropriate choices in daily practice in patients with respiratory allergy. A central aspect is represented by the number of patients: in the meta-analysis of 89 trials on the efficacy of SCIT and SLIT in asthma, a total of 7413 patients were enrolled, resulting in an average number of 83 patients per trial. Instead, in the 13 real-life studies on AIT efficacy available until now, the total of patients amounts to 9090, with an average number of 699 patients per study. This significantly decreases the possibility that the observations from real-life study are casual, and confers to such studies a key role in the next years to assess issues other than efficacy and safety, especially those scantly investigated thus far. Still, the real-life model has its pitfalls. For example, the lack of inclusion and exclusion criteria may result in marked differences in the proportion of patients in the groups to be compared (in the study by Zielen et al. the rate of patients in pediatric age was 48.6% in the SLIT group and 7.5% in the "non-AIT" group) (25).

Conflict of interest

The authors declare that they have no conflict of interest

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