Patient's compliance with allergen immunotherapy

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Background: Allergen immunotherapy (IT) is an effective treatment of respiratory allergy, but requires strict rules of performance. This makes compliance particularly relevant, but thus far only a few studies have investigated this issue.

Methods: We reviewed all the available articles on compliance and adherence with IT in its different forms of administration, ie, subcutaneous (SCIT), sublingual (SLIT), and local nasal (LNIT).

Results: Early studies, when only SCIT was available, reported a low compliance, ranging from 45% to 60%, but the demanding schedules used, with very frequent injections, accounted for this outcome, as shown by patients' recognition of inconvenience as the major cause of noncompliance. The most recent studies reported a good compliance, estimated in 75% to 90%, to both SCIT and SLIT, inconvenience remaining the major cause of noncompliance, followed by cost of the treatment. The only study addressing LNIT found a very poor compliance (27%), the major cause being the side effects, with repeated nasal reactions to the allergen extract.

Conclusions: Adequate education of patients and optimization of administration schedules, with fine balancing between dose effectiveness and cost, are the factors most likely to achieve further improvement of compliance with IT.

Keywords: allergen immunotherapy, subcutaneous, sublingual, local nasal, compliance, adherence

Introduction

Allergen immunotherapy (IT) is the practice of administering gradually increasing doses of the specific causative allergen to reduce the clinical reactivity of allergic subjects. IT has a central role in the management of respiratory allergy with rhinitis and asthma, because it is the only treatment acting on causes and not simply on symptoms as drugs do (Bousquet et al 1998; Frew 2003). Moreover, the capacity to alter the natural history of allergy offers long-lasting efficacy once IT is discontinued (Durham et al 1999).

Subcutaneous IT (SCIT) has long been the conventional way of giving the treatment, but in recent years other routes of administration were introduced, mainly for safety reasons, and today sublingual IT (SLIT) and local nasal IT (LNIT) are suggested as viable treatment options when considering hyposensitization (Bousquet and van Cauwenberge 2001; Canonica and Passalacqua 2003).

However, IT in any form requires substantial commitment by the patients, who must undergo regular (usually monthly) injections when SCIT is chosen, and daily (or very frequent) administration of the allergen extract when SLIT is chosen, for a prolonged time, generally stated as at least three years. In fact, this is the minimal time required to achieve the immunological changes needed to ensure long-lasting clinical effects following the end of treatment (Frati et al 2007).

This makes compliance issues particularly relevant, but thus far little attention has been paid to this aspect, with only a few studies investigating compliance with SCIT (Cohn and Pizzi 1993; Lower et al 1993; Tinkelman et al 1995; Rhodes 1999; More and Hagan 2002), compliance or adherence to SLIT (Lombardi et al 2004; Pajno et al 2005;

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Passalacqua et al 2006, 2007), and one study investigating also compliance to LNIT (Pajno et al 2005).

According to established definitions, compliance is "The extent to which a patient's behavior matches the prescriber's advice" and adherence is "The extent to which the patient's behavior matches agreed recommendations from the prescriber" (Haynes 1979). Measurement of adherence includes the number of doses actually used by the patient and this may result in technical problems, unless the rigid boundaries of a double-blind, placebo-controlled study are present. Of course this affects SLIT and LNIT self-administered by patients at home, but not SCIT. The studies measuring adherence to SLIT approached the problem by contacting the patients through unscheduled phone calls, not leaving the time to calculate and adjusting the doses to please the prescriber.

Compliance to SCIT

Since SCIT is administered directly by physicians or trained nurses, the compliance aspects would appear of secondary importance, but the first studies published in the 1990s reported rates of lack of compliance surprisingly high, corresponding to about 50%, in both adults (Cohn and Pizzi 1993) and children (Lower et al 1993). The protocol used, based on injections at weekly interval the first year and fortnightly interval the second year, was probably the causative factor for such a bad result. In particular, the study by Cohn and Pizzi (1993) analyzed practice records of 217 patients treated with SCIT for allergic rhinitis or allergic asthma and found that 50% of subjects with rhinitis and that 48% of those with rhinitis and asthma discontinued the treatment. Inconvenience was identified as the major cause of discontinuation (55% of cases) in rhinitis, while in rhinitis and asthma only 22% of patients indicated such an issue. The first cause of stopping SCIT in these patients (25%) was feeling better with drug treatment, which was not reported by any patient with only rhinitis.

In the same year, the study by Lower and colleagues (1993) reviewed 315 patients aged 5 to 18 years who were prescribed SCIT for allergic rhinitis or asthma. Of them, 44% were noncompliant, with males slighly more compliant than females, and private patients more compliant than nonprivate patients.

In the ensuing years more favorable results were reported, also because of the development of less demanding schedules. A study evaluated SCIT-treated subjects in a private practice in Atlanta, USA, and found a significantly higher compliance in patients receiving the injections in the allergist's office compared to those receiving the injections in facilities outside the clinic, who had a noncompliance rate of about 35% (Tinkelman et al 1995).

A similar rate was detected in a population of 247 allergic patients undergoing SCIT in Mexico, who were noncompliant in 38% of cases. The major cause of noncompliance were the early feeling of improvement and the high cost of the treatment, but also the feeling of worsening with SCIT and the change to alternative medicine (Ruiz et al 1997).

Rhodes (1999) found that 12% of patients receiving optimal doses of allergen extracts discontinued SCIT before completion of the suggested three-year duration of treatment. The most common reasons for premature stopping were concurrent medical problems, inconvenience, and adverse reactions to treatment (Rhodes 1999). The safety issue is important, because it is established that to be effective SCIT requires the administration of sufficiently high doses of allergen extracts, but this exposes the patients to the risk of adverse reactions (Bousquet et al 1998), which in turn may associate to compliance problems.

A recent study analyzed the compliance to three forms of IT, SCIT, SLIT, and LNIT administered in hospital or in private office settings in 2774 children (Pajno et al 2005). SCIT was used, by a build-up phase in 12 weeks followed by maintenance injections every 3–4 weeks, in 1886 subjects. Of them, 207 (10.9%) were noncompliant, with no significant difference between the two settings. Concerning the hospital setting, most patients withdrew from SCIT during the build-up phase or during the second year of treatment, while in private office setting most patients withdrew from SCIT after the first year of treatment. The major reason for withdrawing was the cost (35%), followed by family problems (21%), inconvenience (20%), lack of efficacy (16%), and adverse reactions (7%).

It is apparent that in the latest studies, which used optimal allergen extracts and less challenging schedules, the compliance to SCIT was much better than in previous investigations, both in adults (12%) and in children (11%). For the latter, the parents' role in collaborating with physicians during the treatment must be obviously considered.

Compliance to SLIT

SLIT has different compliance issues than SCIT, because it is administered at home by patients themselves and thus it is not affected by most causes reported for noncompliance to SCIT, having instead compliance problems similar to drug treatment, which were already recognized more than thirty years ago (Blackwell 1973) and more recently analyzed in

their relationship with patient's characteristics, quality of life, and costs (Billups 2000).

In some studies not specifically designed for compliance (for instance safety and tolerability analyses) was reported that treatment withdrawal is frequently caused by repeated local reactions in the mouth or at gastrointestinal level (André et al 2000; Wilson et al 2005). Moreover, as previously noted in SCIT studies, it was observed that a lack of compliance to SLIT may be caused by the erroneous perception that once allergic symptoms are improved, SLIT is no more needed (Novembre et al 2004). Concerning specific compliance and adherence studies, the available data indicate quite satisfactory results.

In a study on 319 patients mainly addressing the efficacy of SLIT, the adherence to treatment (assessed by measuring the consumed allergen extracts) was estimated to be good, ie, >80% in 72% of patients, and fair, ie, >60% in 18% of patients (Marogna et al 2004).

The approach of evaluating the adherence by measuring the consumption of allergen extracts was used in other three studies, which were facilitated by the fact that preparations in tablets or in liquid monodoses were employed. In the first of these, adult patients under SLIT treatment were asked by phone (without being warned in advance) to count the remaining tablets in the box; the phone interview was done during the first year in patients treated for dust mite allergy and during the first pollen season in patients treated for pollen allergy. The adherence value was comprised between 75% and 97% (Lombardi et al 2004). The other two surveys were real-life studies investigating the compliance to SLIT in 443 adult and adolescent patients (Passalacqua et al 2006) and in 71 children (Passalacqua et al 2007), respectively. In the study on adults, data on compliance were obtained (by unscheduled phone calls) after three months in all patients, while after six months data were obtained on 266 patients because the remaining 217 had received a preseasonal SLIT of 3–4 months duration; 76.3% of patients after three months and 74.8% after six months had a compliance higher than 90%; in 4% of patients SLIT was discontinued for various reasons unrelated to treatment; and in 1% for side effects possibly related to treatment (Passalacqua et al 2006).

Similarly, in the study on children with the same product in monodoses, parents were interviewed by unscheduled phone calls at the third and sixth month of SLIT and asked to count at once the remaining doses; a compliance rate higher than 75% was found in 85% of children at the third month and in 84% of children at the sixth month; the major cause of withdrawal (5.6% of cases) was the cost of treatment, while side effects accounted for 1.4% of stopping (Passalacqua et al 2007).

In the already cited study on compliance to SCIT, SLIT, and LNIT in children, data on SLIT concerned 806 patients, 173 of whom (21.4%) were noncompliant, with a highly significant difference ($p < 0.0001$) for a better compliance in hospital setting (90.5%) compared to private office setting (61.2%); the most common reason of withdrawal was the cost of treatment, reported globally in 36.4% of cases, followed by inconvenience, feeling of inefficacy, and side effects (Pajno et al 2005).

Compliance to LNIT

The only study addressing this issue is that by Pajno and colleagues (2005) which evaluated 82 children, all treated in private offices, and found a compliance value of 27%; the major reason of noncompliance to LNIT were the side effects, with repeated nasal reactions to introduction of the allergen extract reported as reason for withdrawing in 56.6% of cases; other causes were inefficacy and cost, concerning 18.3% and 13.3% of cases, respectively (Pajno et al 2005). By these findings, the nasal route of administration, though scientifically demonstrated as effective and thus accepted in consensus documents (Bousquet et al 1998; Bousquet and van Cauwenberge 2001), seems unlikely to represent a true option for immunotherapy.

Comprehensive analysis of compliance with IT

Currently, compliance, cost, and quality of life are considered important issues in management of respiratory allergy (Blaiss 2003). From the literature on compliance with IT, summarized in Table 1, it is apparent that in early studies, when only SCIT was available, compliance was low, ranging from 45% to 60%, but the demanding schedules used, with very frequent injections, accounted for this outcome, as clearly shown by patients' recognition of inconvenience as the major cause of noncompliance. Another critical aspect in compliance is patient's knowledge and access to information about the treatment. A study from Israel showed that patients undergoing SCIT have a very poor knowledge of the treatment and, consequently, incongruous expectations. In fact, about 40% of patients expected a complete recovery of their allergies and about 20% expected an improvement within days or weeks from starting. One fourth of the study group did not know which allergens were administered and one third were aware of the potential side effects (Sade et al 2003).

Table 1 Studies on compliance with immunotherapy

Author study	Kind of IT	Kind of patients	Compliance
Cohn and Pizzi 1993	SCIT	Adults	48%
Lower et al 1993	SCIT	Children	44%
Tinkelman et al 1995	SCIT	Adults	65%
Ruiz et al 1997	SCIT	Adults	62%
Rhodes 1999	SCIT	Adults	88%
Pajno et al 2005	SCIT	Children	89%
Marogna et al 2004	SLIT	Adults	80%
Lombardi et al 2004	SLIT	Adults (with seasonal or perennial allergies)	75%–97%
Pajno et al 2005	SLIT	Children	79%
Passalacqua et al 2006	SLIT	Adults and adolescents	76%
Passalacqua et al 2007	SLIT	Children	85%
Pajno et al 2005	LNIT	Children	27%

Abbreviations: SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; LNIT, local nasal immunotherapy.

In a report on two small groups of patients undergoing SLIT and receiving standard instructions or a complete programme for education and training to SLIT, respectively, a lower compliance was found in the former, mainly because of common local side effects (oral itching and burning, abdominal pain) they were not able to manage (Incorvaia et al 2003).

Analyzing the most recent studies, one may think that patient's information on IT, in both its subcutaneous and sublingual forms of administration, is improved, because a good compliance, estimated in 75% to 90%, was reported. Considering SLIT in children, sociological factors, such as the educational and economic status of the family, should be taken in consideration when prescribing the treatment, because successful adherence is dependent on the parents' understanding and motivation.

Also in recent studies the two major causes of noncompliance were inconvenience – in SCIT, it was the need to go to hospital or to the physician's office to have the shots and in SLIT, it was the need of very frequent administrations – and cost. Concerning SLIT, which was introduced much more recently in respect to SCIT, it is likely that the individuation of optimal dosage and the modifications of current schedule may favor a further improvement of compliance and adherence. For example, it was recently demonstrated that in patients treated with SLIT for dust mite allergy, an intermittent schedule, while maintaining comparable efficacy and safety, had a better compliance than the usual continuous schedule (Cadario et al 2008).

Conclusive considerations on compliance with SLIT must take into account a comparison with antiallergic drugs, which seems particularly appropriate for topically administered preparations. For example, adherence rates to prescribed inhaled drugs in asthma are surely problematic, corresponding to a range from 30% to 70% in general (Bender et al 1997), with a rate lower than 50% in children (Milgrom et al 1996). Compliance with SLIT is much better and is likely to further improve following the approaching introduction of more friendly preparations in tablets and expanding patient's knowledge and education.

Disclosure

The authors report no conflicts of interest in this work.

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