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Improving long-term adherence to sublingual immunotherapy. Results of a proactive patient-centered management planning

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KEY WORDS

Sublingual immunotherapy; allergic rhinitis; allergic asthma; patient compliance; physician-patient relations; shared decision making.

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IMPACT STATEMENT

Long-term adherence to SLIT can be improved by management strategy based on shared decision making followed by proactive and ongoing patients-tailored interventions to support their needs and preferences.

Summary

Background. Long-term adherence to sublingual immunotherapy (SLIT) results very poor in real-life studies. Effective actions are needed. Key point of any policy aimed to overcoming non-cost related barriers to medication long-term adherence is to actively support patients' needs and preferences starting from shared decisions making. **Objective.** To explore SLIT related viewpoints, needs and preferences of a homogeneous group of patients. To assess their priority order and to what extent each of them could affect SLIT adherence. To find a rational basis for a proactive action-plan to support patients' needs and preferences and assess results on SLIT long-term adherence. **Patients and methods.** Preferences and viewpoint of patients in treatment-related decisions and their health-related needs have been explored by structured, direct interview of 65 adult patient. The activities of the hospital outpatient clinic were rearranged to support needs and requests shared by all patients, and to allow tailored interventions integrating them into routine practice. Adherence to SLIT was studied on a different group of 129 patients aged 14 to 42 years and defined as number of patients who completed three years of therapy. **Results.** SLIT was completed by 98 patients (76%). Main cause of discontinuation for 31 remaining patients have been pregnancy (16%), change of work residence (19%), side-effects (10%), perceived inefficacy (26%), and non-compliance (29%). **Conclusions.** To improve adherence, it is necessary to investigate patient-related factors to find a common ground to take actions aimed to remove barriers to long-term SLIT-adherence that virtually can work for all patients, but flexible enough to allow patient-tailored interventions. The substantial differences on disease's perception between patients with only allergic rhinitis and those with asthma entail the necessity of differentiated approaches. Management strategy based on shared decision making followed by proactive and ongoing interventions to support patients' needs and preferences proves effective to ensure a good long-term adherence to SLIT in real-life.

Introduction

Allergy immunotherapy (AIT) is a valuable treatment for allergic respiratory diseases. Modulating the immune response, AIT can modify the natural progression of disease and lead to long lasting efficacy on symptoms reduction (1). However, patient's adherence/compliance (terms often used as synonymous in literature) is a crucial point, as the regular administration of scheduled doses for a prolonged time (not inferior to three years) is mandatory to obtain appreciable outcomes.

The subcutaneous immunotherapy (SCIT) is the traditional method, directly managed by allergists. This should have warranted a good patient's adhesion to therapy. Nevertheless, some studies showed poor compliance in about fifty percent of cases, and even worse (84%) over 3-years course. Inconvenience was the main cause of withdrawal (2-4).

The sublingual immunotherapy (SLIT) is at home, self-administered therapy. An increasing number of clinical trials and meta-analyses have proved its efficacy and showed a better safety pro-

file than subcutaneous method (5). In European countries SLIT is becoming the preferred delivery method. The easy of intake and convenience should have ensured an adequate compliance.

Unlike the optimistic provisions of a better compliance for SLIT against SCIT, post-marketing surveys and real-life studies prove that long-term SLIT adherence is very poor (6). Likewise, a high withdrawal rate was observed in our hospital outpatient clinic. Effective actions to improve adherence are needed. Studies and systematic reviews of non-cost-related barriers to medication long-term adherence (summarized/reviewed by Expert Panel of World Health Organization, RAND Corporation and on Medscape Website) have demonstrated that a key point of any policy aimed to strengthen adherence is to support patients' needs and preferences (7-9).

However, each patient shows a unique cluster of reasons to adhere or not adhere. To find a common ground it is necessary to investigate patient-related factors by homogeneous groups, who are representative of the real, customary population of users. This information is necessary to rearrange the procedures of the outpatient clinics for purpose to remove more substantial barriers to long-term SLIT-adherence by action-plans that could generally work for all patients, but flexible enough to allow patient-tailored interventions.

In the present study we explored needs, preferences and experiences related to SLIT and allergy disease by homogeneous groups of our patients, assessing their relevancies and priority order; then, conceived on patients' needs and preferences, we illustrate our proactive management-plan of the therapeutic program and its results on SLIT long-term adherence.

Patients and methods

This is an observational real-life study, aimed to describe our management strategy of allergy immunotherapy, its rationale, and its outcomes on SLIT compliance. The study is based on the actual, customary patients' population, on data file and routine procedures as established by the care-pathways of the hospital outpatient clinic (Internal Medicine and Allergy Department, Asola Hospital, Azienda Ospedaliera "C. Poma", Mantova, Italy).

Patients' need and preferences

Preferences and feedbacks of patients in treatment-related decisions and their peculiar health related needs have been explored through direct interviews of 65 patients aged 18 to 48 years, mean age 31 ± 9 years, 43 (66%) males. To consider if new needs were arisen over time, 34 out of them (52%) had been on SLIT for one or more years. Forty-eight (75%) were sensitized to pollens, 30 (46%) to mites and 4 (6%) to moulds (*Alternaria spp*). Fifteen (23%) were undergoing two vaccines (tablets for grass; drops and single allergen, for others; pre-co-seasonal for pollens; perennial regimen for mites and *Alternaria*).

Forty-six (71%) suffered from allergic rhinitis and 19 (29%) of them had secondary symptoms of asthma (\leq step 3). Eleven patients (17%) felt asthma as the main clinical manifestation. Forty-three patients (62%) were occupied, 6 (9%) unemployed, 6 (9%) were housewives and 10 (15%) were students. All patients referred to our Allergy Unit and lived in Lombardy Region.

The interviews, hosted with colloquial style, were based on a series of written queries aimed to investigate three interacting domains: 1) social-economic factors, 2) patient-related factor and 3) health system and health-care team related factors.

The questionnaire was not directly administered to the patient but used by interviewer as guidance to explore needs and viewpoints of each of them and establish together value and priority order. The relevance of each issue on the patients' perception has been assessed by a visual analogical scale graded from zero to ten.

SLIT support planning

Based on interviews' results, the routine activities of outpatients clinic were rearranged to support needs and preference which all patients had in common, but flexible enough to allow personalized interventions.

Main areas of interventions were:

1. reengineering of the outpatient hospital clinic organization to support patients' needs and preference (including: practical arrangement to avoid waste of time and bureaucratic hindrances or delays and to ensure adequate and ongoing assistance starting from direct reception to counselling activities);
2. training of team professionals to build partnership and assist patients;
3. enhancement of patients' literacy on allergy disease (including: nature of allergy diseases, their course, co-morbidities and complications; concept of chronic inflammation and its implications);
4. teaching allergy immunotherapy and training to SLIT self-management;
5. flexible patient-tailored work schedule (integration of personal needs into routine practise).

Shared decision-making process (10, 11) was undertaken individually with each SLIT-eligible patient to explain fundamentals on allergy disease and vaccine immunotherapy, and to obtain the agreement on treatment plan and on program of monitoring and controlling of vaccine and drug therapy. Personal request and needs were examined to be integrated into routine practice. The overall SLIT supporting plan is here explained by a concise conceptual framework (**figure 1**). All patients were recalled before starting immunotherapy for educational group session aimed to re-assume information given individually, recall and reinforce training on SLIT self-management, explain again all practical ways for direct access to the service and to receive continuative assistance also by telephonic counselling, ensure compliance with service's regulation

and duties, and reinforce patients' motivation and commitment. Any request for more information or explanations was discussed in group.

Adherence assessment

Adherence was investigated in 129 patients: aged 14 to 42 years, mean age 27 ± 12 years, 91 (70%) males. Thirty-nine patients (30%) received two sublingual vaccines (tablets for grass; drops and single allergen, for others). One hundred-sixty-eight SLITs have been considered, out of them 96 pre-co-seasonal treatments of 7 months duration per year.

The regular intake of the vaccine was directly controlled by the personnel of the allergy service.

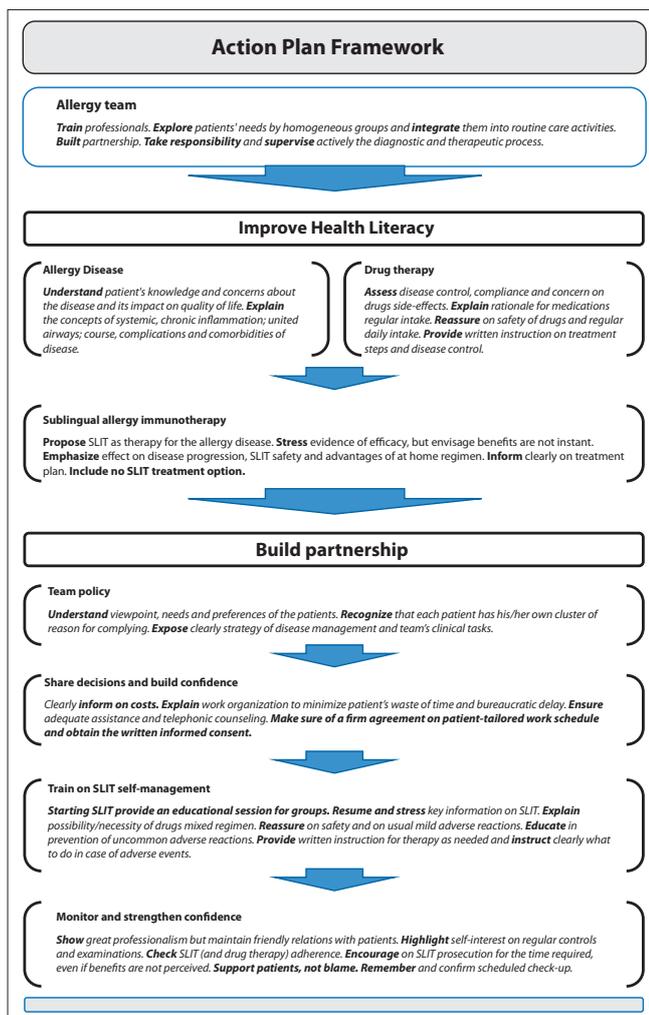
In Lombardy Region vaccines are purchased by hospital pharmacy and given out free of charge. After an educational group session,

patients were invited to take the vaccine starting dose and to stay in the office waiting room for at least 30 minutes. If no significant side effects were observed, the first pack of sublingual vaccine would be filed by date and delivered to each patient by the health-care staff. Patients were recommended to continue daily therapy at home and to make an appointment not later than one week before finishing the box to receive further doses of the vaccine. At this point, one or some packs were provided according to the next appointment, as foreseen by individual periodical control programs. In this way it was possible to check directly, from time to time, the regular intake of the doses and overall adherence to SLIT.

As a purpose of the present study, the adherence to SLIT has been outlined with reference to those patients who completed three years of therapy (grass tablets and other pollens for pre-co-seasonal regimen; mites and *Alternaria* for perennial regimen). Discontinuation reasons have been inquired by direct or telephone interview.

A written informed consent to SLIT and to the present study participation was obtained from all patients. The study, based on routine procedures, was not subject to formal approval of Ethical Committee (Circolare Ministeriale N. 6, 02.09.2002; Decreto della Direzione Generale Sanità Regione Lombardia N.11960 del 13.07.2004; Notification to secretariat: 01.30.2009).

Figure 1 - Action plan conceptual framework: steps and recap of key-points.



Results

Patient-related factors driving adherence

All the patients who assent to vaccines immunotherapy believe that their disease was severe and/or doomed to a progressive worsening.

For patients with allergic rhinitis "progressive worsening" referred to high degree and persistence of symptoms. They were not aware of possible complications of the disease, like chronic sinusitis or asthma. Only patients with bronchial asthma and a part of those who experienced symptoms of secondary asthma had significant concerns for their health status and the risk of progression toward a chronic condition or disability and even the risk of life-threatening events.

All the patients who assent to vaccines immunotherapy experienced a negative impact on quality of life as well as a low control of symptoms in spite of the therapy as prescribed by general practitioner (usually as-needed therapy). Concerns for continuous use of inhaled steroids and hope of dose reduction or withdrawal were an important reason to start immunotherapy for most of the patients with bronchial asthma. In patients with allergic rhinitis, concerns for the prolonged use of anti-histamines or nasal steroids were not a strong motivation for vaccines immunotherapy.

Comprehensive information about SLIT, its rationale, objectives and expected benefits, were required as a prerequisite before the definitive consent. The same could be stated for the education to

the self-management and the prevention and control of possible adverse events. Concerns about the risk of SLIT adverse reaction or side-effect were not considered as a possible cause of non-adherence to immunotherapy. However, all patients deemed periodic controls, ranged from one month to one year, as necessary and advisable. Twenty-seven patients (39%) thought that a specialist check-up should be planned once a year. However, a medical check every two or three months was considered optimal by most of the patients starting SLIT (76%). Actually, regardless any planned check-up, all the patients assigned great relevance to the possibility to contact quickly (at least by phone) the medical staff and to have direct admittance to the allergy unit in cases of need, by-passing the hospital call-center or any waiting-list. Most of the patients believed that allergy vaccines management was a matter of exclusive competence to the allergists (88%), as they supposed general practitioners couldn't have adequate knowledge and skill in immunotherapy.

Adherence-related social-economic factors

Vaccines for immunotherapy are expensive, and direct costs could be a real obstacle to the acceptance and continuation of therapy. In Lombardy immunotherapy is charged by Regional Health Service, but most of the patients (82%) believe that free regimen could only moderately improve adherence, with the sole exception of some jobless or in economic trouble patients. Similarly, private payments (when foreseen as contribution to health expenditure for periodical check-up and examination required by providers) would not have affected adherence to SLIT. The occupational status and consequently the necessity to obtain work permits were not considered as a major deterrent to immunotherapy adherence.

The distance from the allergy clinic was not deemed as a problem for patients live in the neighborhood, whereas patients living far off considered the distance from the allergy office as an important issue to accomplish required medical controls.

The great majority of patients (80%) stressed the necessity to avoid undue waste of time (e.g., for bureaucratic requirements, long wait for medical control and examination and so on). Long waiting time was perceived by the patients in full working business as a significant interference with the daily occupation and activities.

Health system and health-care team factors driving adherence

In this context the dialogue was mainly addressed to realize what actions should be taken to satisfy patients' expectations, to figure out the most suitable program of management and control of SLIT and allergy disease, in order to meet patients' agreement and make shared decisions.

All the patients agreed that a well-planned and shared program of medical controls and examinations was the only way to monitor efficaciously the course of the allergic disease, to grade drug

therapy, and to verify SLIT outcomes. Once again, strong emphasis was placed by most of the patients on the need to avoid unnecessary waste of time and substantial hindrance on their own work and/or others daily tasks.

As reported above, comprehensive information about SLIT and expected benefits, education to the self-management, knowledge, prevention and control of possible adverse reaction or side-effect were felt by all the patients as a primary necessity and a prerequisite for the acceptance of SLIT and its long-lasting therapeutic program.

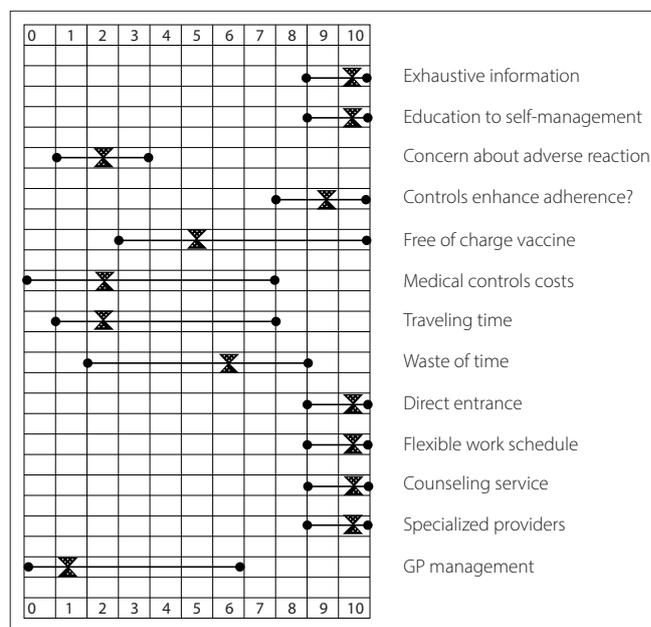
The value and the priority order of the main patient needs and preferences have been shown on the annexed chart (figure 2). No significant differences on needs appraisal have been observed between patients starting SLIT or patients on therapy for a time.

SLIT long-term adherence

A whole cycle of SLIT was completed by 98 patients (76%). Thirty-one patients (24%) discontinued the vaccine therapy. Out of them, 5 because of pregnancy (16%), 2 children because of not well-defined family problems (6%), 6 due to a change of work residence (19%), 3 as a consequence of the persistence of local reactions (10%), 8 for perceived inefficacy (26%), and 7 for admitted non-compliance (23%).

Excluding substantial causes to withdraw the therapy, non-compliance to SLIT could be estimated of about 13% per cent of

Figure 2 - Patients' assessment by visual analogical scale of the relevance of some factors influencing SLIT adherence.



●—●: minimum and maximum value assigned by the patients. X: value assigned by more than 75% of the patients.

the entire population. The adherence profile is therefore comparable to the one issued in double-blind placebo-controlled (DBPC) trials (6).

No difference in SLIT discontinuation has been found between pre-co-seasonal (all pollens, 11 pts) and perennial (other allergens, 9 pts) treatments. Immunotherapy with two vaccines (9 pts) compared to only one vaccine (22 pts) didn't result as a cause of withdrawal.

Based on the delivery time of each vaccine confection, occasional omissions of daily dose did not affect significantly the regular intake of SLIT by the patients who completed the planned cycle of immunotherapy.

Yearly cumulative rate of discontinuation has been 6, 22, 24 percent for the first, second and third year respectively.

Before the reorganization of our care pathways, discontinuation rate was an average of 25 percent in the first year, but it jumped to 56% in the second year and to 68% in the third year (a little lower if compared to other real-life studies) (6).

Discussion

Non-adherence/non-compliance to allergen immunotherapy, as well as any long-term therapy, is a complex phenomenon. A consistent number of studies and systematic reviews (summarized/reviewed by Expert Panel of World Health Organization, RAND Corporation and on Medscape Website) have been identified analyzing a wide range of variables consistently related to long-term compliance/adherence (7-9). It is nowadays clear that in each action-plane to improve adherence it is essential to include patients' perspective and to consider their need and preferences.

In the present study, needs and preferences on SLIT have been investigated by a homogeneous group of patients starting SLIT or on therapy for some years. Most of the results of our study are self-explanatory or easily-understood, but some of them deserve a short discussion.

Large body of data prove that perception of disease severity threat and awareness of disease severity are both strong determinants to patients' compliance (12, 13). The patients who agreed with vaccines immunotherapy believed that their disease was severe and/or doomed to a progressive worsening. However, only patients with bronchial asthma had substantial concerns about the progression and worsening of disease and in general were afraid of significant risks for their own health. For patients with allergic rhino-conjunctivitis, severity mainly referred to symptoms (intensity, persistence, worsening over time and/or poor control by therapy) and impact on life quality, rather than to disease itself. All in all, they were not worried for their own health, neither aware of possible complications of the disease, like chronic sinusitis or asthma. This view/perception of the disease can affect adherence and induce untimely SLIT discontinuation (13). When symptoms disappear, patients feel better and

think that also the disease has disappeared. Hence, they are not prone to a long-term, non-symptomatic therapy.

Concerns for medication possible side-effect or adverse reactions and abstract worries about the long-term consequences of inhaled corticosteroids are well known causes of intentional non-adherence in asthma treatment (14). These concerns seem to be a substantial motivation for patients with allergy asthma to undertake vaccine immunotherapy, which is perceived as a kind of steroid-sparing therapy. That might be a strength of information provided to patients in order to improve SLIT adherence. On the contrary, inhaled corticosteroids seem not to be a source of concern for patients with allergic rhinitis. This dichotomy would deserve to be studied. Lack of comprehensive information about therapy (rationale, objectives, expected benefits, possible adverse-events) and inadequate education to self-management is another well studied cause of unintentional non-adherence (7-9). However, the sole provision of good information is a weak intervention, as a number of patients do not recall what caregivers have advised, and a lot of them justify non-compliance by claiming they did not receive enough information. Moreover, SLIT is not a relief medication, but a long-term therapy, and its effects may not be immediately perceived by patients. Support and assistance interventions are needed to reinforce patients' motivation. It has been proved that frequent and regular monitoring visits, and a firm involvement of patients on therapeutic program enhance SLIT adherence (6). All patients stated to have confidence in safety of SLIT. Nevertheless, they all deemed periodic controls as necessary and advisable, and insisted on the possibility of a quick consultation, if only by phone, in case adverse events. It is worth attention that patients starting SLIT preferred closer controls. We can deduce that these patients need to strengthen their own confidence in allergy immunotherapy and in medical team, and should be supported in their own motivations to confirm adherence.

Most patients deem that the monitoring and the management of their allergy disease and of its specific therapy should not be delegated to the patient and his or her general practitioner. It may induce a feeling of abandonment to their disease; it may generate disappointment, doubts about the actual effectiveness and the benefits of SLIT and, in conclusion, it may erroneously suggest that SLIT might not to be necessary. All these are well known causes of non-compliance and therapy discontinuation (7-9).

In developed countries direct and indirect costs of therapies are not a significant cause of non-adherence, except for jobless or low-income patients (14, 15). This is an outcome also of the present study. Almost all patients agreed to accomplish with a shared plan of periodic check-up and examination (which will be proposed by providers), even if it entail additional direct and indirect costs. However high costs can increase the risk, as low incomes are positively related to poor adherence (14, 16).

On the contrary, particular emphasis has been placed on the need to save time. The allergic patient is usually a young man/woman in

full working business or a student. Students of primary or secondary school cannot live the school without parents. Undue wastes of time (long waiting for medical examinations, bureaucratic delays and problems, poor organization of medical services, trouble to make contact with allergy unit staff, and so on) can significantly interfere with their own job and/or daily tasks. As a matter of fact, retirees and patients who can profit of family members' support show much better compliance than patients who are working (17). As stated above, the thorough knowledge of need and requests of our patients was necessary for reengineer the procedures of the outpatient clinics by putting in place action-plans aimed to overcome the barriers that are most important to SLIT long-term adherence and all patients have in common.

Shared decision-making (SDM) is a key point of supporting plan (10, 11). SDM defines a consultation process aimed to establish a therapeutic alliance between the physician and patient (SDM is a locution which has replaced the term concordance, formerly more used in literature. It can be considered a synonymous of concordance process) (18, 19). SDM is not a further variation of the concept of compliance/adherence. It refers to a work strategy to involve patients in the decision-making procedure and in the choices related to therapy and disease management. The physician and the patient become partners in the therapeutic program. For an effective and successful cooperation, the physician and the patient shall establish a genuine relationship, their respective viewpoints and needs shall be able to be confronted, and decisions shall be shared. It is necessary to resort to a structured communication to explore the patient's knowledge and perception of disease, his/her expectations and concerns and all matters which might affect his/her adherence. Health care providers shall feel responsible for providing exhaustive information, make sure that the patient has understood all the issues, and the prospective barriers to adherence have been clearly discussed in order to overcome them.

SDM is also synonymous with patient-centred care. Patient's autonomy in decision-making must be respected, and primacy of the patient's decisions acknowledged. This is the cornerstone of SDM. Any distortion or stretch to obtain an agreement should be carefully avoided. Most patients want to have clear information about the advice or necessity of long-term therapy and consequently discuss and make decisions in agreement with the physician. In most of this case it might be relatively easy to encourage and implement the partnership on decision-making process, but it is also easy to influence patients taking advantage of the doctor's authority to address them actually to own choices and preferences. It is even more true for patients who completely rely on doctors' decisions. This deceptive way to relate to the patients will entail in many cases the decline of adherence over time. This will happen even more with AIT because this treatment does not replace already existing drug therapy.

However SMD (as pointed by the summary guide of England NHS) (20) is a present-oriented conversation to decide a course of action, whereas it is necessary draw-up a proactive and patient-centered intervention-planning to support adherence throughout the whole SLIT course.

It is quite obvious that the detailed knowledge of patient's needs (but also preferences, expectations and viewpoints) and the foreseeable interactions with the duty of allergy service are the needed basis on which to build an operational partnership and to develop an effective action-plan aimed to improve adherence (**figure 1**).

Improving patient's literacy on AIT and allergy disease is the first step of SDM. A meta-analysis of published studies demonstrates the positive impact of health literacy on adherence and the efficacy of health literacy interventions (21). Health literacy can be defined as the capacity to obtain, understand and use needed information on disease and therapeutic options to make proper decisions. For this purpose, patients' education cannot be limited to the necessary, standard instruction regarding SLIT. Efforts should be made to help patient to understand the concept of desensitization and the rationale, objectives and expected outcomes of SLIT. SLIT is not a relief medication, but a long-term therapy normally given in addition to drugs and other prescriptions and its results are not expected in a short time. For this reason, AIT should be proposed as the main therapy of allergy disease, rather than of symptoms. If benefits are not well perceived patients may believe that allergy vaccines are ineffective and therefore unnecessary.

Patient's perception of inefficacy or poor efficacy is reported in literature as one of the main causes of SLIT withdrawal (6, 22). Allergists should careful avoid that the patients get unrealistic expectations. During the consultation allergist should highlight scientific evidence on SLIT efficacy and safety, and leverage effect on disease progression without giving too much emphasis on the expected symptoms' reduction. The notion that the results are not expected in a short time should be stressed and the prosecution of SLIT for at least one year encouraged even if benefits are not perceived by the patient. Communicate and let them understanding these points is especially important for patients with allergic rhinitis, who (unlike patients with asthma) are less prone to a long-term, non-symptomatic therapy. Allergists should strive to persuade the patients eligible for SLIT that allergic rhinitis is a chronic, not trivial disease and that allergy immunotherapy is a keystone of therapy and prevention of its complications (23).

A strong motivation of patient and a firm involvement of patients on therapeutic program is essential to ensure adherence to vaccine immunotherapy. Studies on long-term adherence to SLIT show that in double-blind, placebo-controlled studies there are no significant differences in withdrawal rates between active and placebo groups. These findings indicate that adherence, compared to perception of poor efficacy of therapy (very likely among placebo-treated patients) or other causes, depends above all on

patients' motivation, that is the decision to participate in the trial and fulfil their commitments with the researchers (6).

A strength of our strategy to improve adherence are the group sessions (**figure 1**). Patients are recalled before starting immunotherapy for educational group session aimed to reassume fundamentals previously given individually to each one, to promote interactive discussion and to reinforce motivation and commitment. During these educational sessions allergists and nurses give practical illustrations on SLIT and train the patients and parents to self-management.

At the group sessions patients were again reassured about at home regimen safety. Usual adverse reactions were explained in detail and patients carefully instructed on prevention and self-medication, but also on what they should do in case of more serious events or emergencies.

The safety profile of SLIT is very good and side-effects uncommon. In our experience however, emphasizing safety beyond measure is something wrong. Perception of side-effects greatly differs in relation with their own literacy, psychology and abstract representation of the symptoms and their possible consequences (14). Patients' concerns about adverse events perceived as potential harmful should be addressed via direct counselling and, where appropriate, by medical examination. In fact, as ranked by 66% of practicing allergists, tolerability proves to be the second or third cause by importance order of SLIT withdrawal (22). SLIT should be compared to a well-tolerated drug therapy not always devoid of adverse events.

There are enough evidences in literature that regular monitoring visits can improve long-term SLIT adherence (6, 24-26). Periodical controls provide the opportunity for communication and interaction with allergy team, and can be a way to strengthen patient's motivation and his/her proactive involvement on therapeutic program. The general plan of management and supervision of SLIT and allergy disease was discussed once again during the group session. The utility of periodic medical-controls and examinations was stressed, emphasizing the mutual interest for both patients and physicians on regular and well-planned follow-up to ensure safety and optimal disease control grading drug therapy. Estimate costs of survey program were reminded to confirm agreement. Special requirement from patients were considered during the group session to show how they could be integrated into routine activities.

Waste of time proves to be one of the major concerns for the patients on SLIT. Even the distance from the allergy office seems to be a problem, as a change of work residence demonstrates to be a significant cause of SLIT withdrawal in the present study. The organization of allergy unit to meet patients' needs and avoid any undue waste of time was explained. Detailed instructions were given to prevent long wait for bureaucratic procedures and reservation lists, current problems with hospital call-center and trouble to make contact with allergy unit staff. The possibility

of admittance during shift change or lunch break was provided for employees how had had difficulty in obtaining work permits. Ongoing assistance and counseling service by allergy unit team, also by phone, and the possibility of direct access to medical controls and examinations, was assured. But at the same time the regulations of the National Health System and duties of resident health services were reminded in order to clearly define the rules to which both healthcare providers and patients have to conform.

Conclusions

There is no doubt that an accurate knowledge of patient-related factor is essential for the development of an effective action-plan to improve adherence.

Of course, patient-related factors are not the only determinants adherence. This is influenced by several other factors, which include social-economic issue, health care system, relationship with medical team, and the characteristics of the disease and related therapy. Each region or local context may have its own specific characteristics. Nevertheless, there is unquestionable evidence that most barriers to "at-home therapy long-term adherence" are fundamentally the same for different settings and pathologies, at least in western countries with high socio-economic development. As a matter of fact, our results are overall consistent with the remarks of most studies and systematic reviews on barriers to medication long-term adherence.

In the present study a proactive management of SLIT starting from SDM process has been applied and tested in the daily clinical practice. SLIT adherence can only be successful if there is an effective cooperation between the patient and health-care provider. The study proves SLIT adherence is an "experiences" that should be supported throughout the whole duration by active, ongoing interventions able to meet patients' needs, preferences and expectations. The intervention strategies here explained are more easily applicable to hospital outpatients clinics, but we have to stress the concept that they may constitute a kind of guide-line applicable in greater or lesser extent to any setting where you can manage allergy immunotherapy.

Of course, SDM process and the other proactive interventions here described seem time-consuming. They might appear too burdensome in term of a lot of work to do, personal commitment, reorganization of processes and working methodologies, and whatever else.

However, the fundamental principles of healthcare management teach that to put users and their needs and expectations at the centre of the healthcare process, is the path to improve the service's performances and effectiveness. Once the scenario is well-defined, the patients' priorities are well established, and the diagnostic and therapeutic care pathways conveniently organized, the timeliness in the problems solving and the service's flexibility (in term of ability to adapt quickly to changes

of needs and context) improve. Despite the issues, disruption, waste of time and human and material resources that a disappointed and non-compliant patient can cause, the reorganization of outpatient facilities, as here suggested, result in “money and time saving”.

Anyway, to assure good SLIT adherence appears to be a worldwide priority: for patients, allergists and allergy vaccines manufacturers. Adherence gets worse over time, and withdrawal rate appears really impressive at third year of therapy (6, 27-29). Non-adherence and untimely discontinuation jeopardize efficacy, discredit and cast doubts about the genuine usefulness of a therapy whose benefits are not instant and neither expected in the short-time. In spite of the progress on vaccine manufacturing and the scientific evidences of efficacy produced by clinical trials, doubts affect not only non-compliant patients, but also a consistent number of family physicians and non-allergy specialists. Understanding and overcoming the many barriers that can hinder adherence is the only way to ensure the effectiveness and the expected results of SLIT.

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Conflict of interests

The author declares that he has no conflict of interests.

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