

REVIEW

Adherence to pharmacological treatment and specific immunotherapy in allergic rhinitis

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Summary

The term compliance simply indicates how much doses of the prescribed medication are taken, whereas the term adherence implies also an agreement between patient and physician about the therapeutic plan, and it is therefore preferred. Adherence is a main problem in all long-term treatments. Thus, it represents a problem also in the case of rhinitis, especially concerning specific immunotherapy that must be assumed continuously for several years. Many factors can affect the adherence, depending on patient, on treatment itself and on the healthcare context, and all those factors usually interact. The adherence measured in controlled trials is usually good, but this does not reflect what happens in real life, where adherence should be preferably measured. There are few data on the adherence in real life for pharmacological treatments of allergic rhinitis (e.g. nasal steroids or antihistamines), whereas more data are available for specific immunotherapy. In this latter case, in real life, adherence seems to be far from optimal, for both sublingual and subcutaneous immunotherapy, although the recent studies agree on the fact that some interventions (i.e. patients' education, strict follow-up, regular contacts) could effectively improve the adherence. In this article, the literature concerning the adherence to pharmacological treatments and immunotherapy in allergic rhinitis was searched and reviewed.

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General context

Usually, the terms 'adherence' and 'compliance' are used interchangeably in the common language. However, their meaning and connotations are somewhat different. The term 'compliance' (the extent to which a person's corresponds to physician's prescription)[1] has been used for a long time to define the observation of the prescriptions (i.e. drugs, medical devices, dietary or behavioural prescriptions) by the patient. More recently, the term 'adherence' has been preferred over the concept of compliance because of the authoritative and paternalistic connotations of the latter one. Adherence has been defined as 'the extent to which a person's behaviour, taking medication, following a diet, and/or executing lifestyle changes, corresponds to the recommendations agreed with a health care provider'[2]. Adherence involves consumer's choice and is intended to be non-judgemental, at variance with compliance, which reinforces patient passivity and blame. Given the

increasing prevalence of chronic diseases (e.g. diabetes, allergies and cardiovascular or degenerative diseases), which require long-term treatments, the problem of non-adherence to therapy has been identified as a major problem facing medical practice. In fact, non-adherence leads to an overall decrease in treatment benefits, with increased hospitalizations, morbidity and mortality. This clearly implies an increased financial burden on patients, healthcare systems and society [3–6]. According to the World Health Organization (WHO) [7], 50% of patients suffering from chronic disease do not follow treatment recommendations. Non-adherence to medical treatment plans is reported to range between 20% and 40% in acute illness, 30–60% in chronic diseases, and reaches 50–80% for preventive treatments [8]. The 2003 WHO report on medication adherence [7] explicitly quotes the statement by Haynes that 'increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific

medical treatments'. From a general point of view, as summarized in Table 1, the major determinants of non-adherence are associated to different variables related to the patient, the disease itself, the treatment, the physician–patient relationship and the healthcare system [3]. All those determinants interact in a complex way [3, 7, 9]. Of note, the complexity of the regimen and the frequency of administration have been formally shown to negatively affect adherence [6, 10–12]. The problem of adherence in the elderly is further complicated by the frequent use of multiple drugs, with increased adverse events that may unfavourably affect the adherence and complicate the disease management [13, 14].

As recently summarized in the World Allergy Organization White Book [15], the worldwide prevalence of rhinoconjunctivitis in adults ranges from 10% to 30%, whereas the ISAAC study [16] reports a prevalence in children ranging from 15% to 37%. In addition to their high prevalence, upper respiratory allergies, which are mostly chronic in their nature and therefore require long-term treatments also produce a socio-economic impact. This is due to both direct costs (pharmacotherapy and visits) and indirect costs, due for instance to loss of productivity (i.e. work and school absence) [17, 18]. Finally, from an epidemiological point of view,

allergic rhinitis and asthma often coexist, and allergic rhinitis is the most important factor for the subsequent development of asthma [19]. Many of the factors mentioned above intervene to decrease compliance in allergic rhinitis: the variability in symptoms (patients stop treatment when symptom free), the complexity of regimens (multiple drugs and immunotherapy) and the duration of treatment (persistent rhinitis).

Based on this background, it is clear that essential elements in the general management of allergic rhinitis to optimize the outcomes are: (1) carefully assessing the adherence to prescriptions, (2) identifying the relevant reasons for non-adherence and (3) implementing strategies for improving adherence.

We searched the literature for articles that assessed the adherence to pharmacological treatment (including nasal corticosteroids, antihistamines, leukotriene modifiers, nasal lavage, cromolin, allergen avoidance) of allergic rhinitis, as well as the adherence to specific immunotherapy.

Adherence: measurement strategies

Accurate and reliable measurement of adherence behaviour is intrinsically difficult. One of the most relevant barriers is the fact that when patients do know that their adherence is under observation, they tend to better adhere. In this connection, the data obtained from clinical trials are partly biased, as also in this case, patients do know they are strictly followed and observed. Some techniques are, in principle, available to overcome this kind of problem, such as the use of hidden electronic devices that count and record the doses dispensed, but those devices are expensive, cannot be used in everyday clinical practice, and are not applicable to all pharmacological treatments [20, 21]. In this regard, measuring the adherence to inhaled drugs, oral medications, injections or preventive measures have to be managed by different approaches and instruments.

Methods for assessing adherence in the clinical or research setting are quite variable, each with its own merits and defects. The available approaches can be roughly divided into:

- 1 Subjective measurements obtained by asking patients (or family members and caregivers) about the medication use. Questioning patients about levels of adherence is an easy method, but it may be fraught with recall difficulties and patient disinclination to reveal poor adherence; patients' medication diaries can be inaccurate and susceptible to misrepresentation;
- 2 Objective measurements obtained by counting pills, examining pharmacy refill records or using electronic medication event monitoring systems. One limitation to calculating adherence using this method is that it

Table 1. Determinants of non-adherence

Factors related to the patient
Presence of physical disorders
Cognitive difficulties
Psychiatric comorbidities
Age (children, adolescents and elderly present high risk of non-adherence)
Knowledge
Expectations
Social and family support
Coping style
Factors related to the disease
Chronicity
Symptom stability
Absence of symptoms
Factors related to the treatment
High number of daily doses taken
Presence of side effects
Complexity of the therapeutic regimes
Ease of use
Factors related to the doctor–patient relationship
Poor relationship
Behavioural inappropriateness by the doctor or the patient
Inadequate patient's involvement
Factors related to the healthcare system
Difficulty of the patients to access health services
Switching to a different formulary
Poor treatment by clinic staff
High medication costs

assumes that the number of pills absent is actually taken by the patients. In addition, this method may not be representative of long-term adherence patterns because patients may exhibit 'white-coat adherence' (patients resume administering a medication shortly prior to an upcoming appointment and continue briefly thereafter) [22, 23]. Electronic monitoring systems are more reliable, and they have been used to monitor the compliance with inhaled corticosteroids [21]. These devices are usually applied to metered dose inhalers, and record the number, date, and time of actuations, without providing any information to the patient. Nonetheless, electronic medication event monitors are expensive, not easily available and not applicable to all medications.

- 3 Biochemical measurements obtained by measuring the concentrations of a drug or its metabolite in blood or urine, and by detecting in blood the biological marker added to the drug formulation. This approach requires sensitive biochemical detection methods to avoid false negative findings. However, for some drugs (e.g. digoxin, antiepileptics, lithium) measuring these levels is a good and commonly used means of assessing adherence.

Currently, various combinations of these measures are used to assess adherence behaviour. Despite this, there is no consensual standard that represents an acceptable adherence rate; patients are generally considered adherent if their medication adherence percentage, defined as the number of doses absent in a given time period, divided by the number of doses prescribed by the physician in that same time period, is greater than 80% [3, 24]. Finally, it is difficult to compare the results of the various trials, due to the fact that different assessment methods are used.

Allergen avoidance strategies and pharmacotherapy for allergic rhinitis

The treatment of allergic rhinitis is based on patient's education, allergen avoidance (when possible), pharmacotherapy and allergen specific immunotherapy [25]. All of those aspects have specific problems affecting the adherence.

There are very few data on the adherence of patients with dust mite avoidance measures (encasing mattresses and pillows, vacuum cleaning, removing carpets, and curtains etc.). An old study conducted with an acaricide product reported that 50–90% of patients complied with the recommended avoidance measures [26]. On the other hand, a more recent study reported that only 35–50% of patients followed the recommendation of encasing pillows and mattresses [27], whereas the adherence to this measure was greater in a paediatric

population, reaching a rate of 96% [28]. The major obstacle to the compliance with dust mite avoidance measures results to be the cost of mite-proof bedding covers, and in fact, it was shown that when encasings are provided without expenses, the adherence rate reaches 90% [29].

The pharmacological treatment is mainly based on antihistamines (topical or systemic) and nasal corticosteroids. Intranasal anticholinergics and cromolyn are second choices, and for those drugs, there are no available data on adherence. Leukotriene receptor antagonists (LTRAs) are licenced for the treatment of allergic rhinitis in some countries, but in other countries, they can be prescribed only when allergic rhinitis is associated with asthma.

Concerning antihistamines, the updated guidelines recommend that only second generation molecules must be used (unless they are not available) [30]. It is generally recommended that antihistamines for persistent allergic rhinitis are taken for prolonged periods [31, 32], as the 'on demand' option is suitable only for intermittent mild rhinitis [25]. In the long-term treatment with antihistamines, the major factor interfering with compliance is the safety (i.e. the presence of side effects, such as somnolence). There are indeed very few data about the compliance with antihistamines in the long-term and in real life, whereas the compliance rates reported in the numerous clinical trials cannot be considered realistic, as happens for all clinical trials where patients are strictly monitored. The most recent open label trial, specifically addressing adherence, reported a rate of 83% over 12 months [33], whereas a real-life French study (considering all the treatment options) involving more than 3500 patients reported an overall adherence rate of 48.7%, with 30% of patients adapting or modifying the prescribed treatment [34].

Concerning intranasal corticosteroids (INCS), which are the most effective drugs acting on both symptoms and inflammation, most of the data on adherence refer to sensory attributes of the products (e.g. taste, smell, aftertaste). According to those studies, the preference of patients is inversely correlated to the intensity of the sensorial attributes, and so is the willingness to adhere [35–37]. One study specifically compared the adherence to INCS therapy reported by patients and by weighting the vials, and found a discrepancy of 87% vs. 65% respectively [38]. The adherence to nasal irrigation with saline in children was recently reported to be greater than 70% [39]. An important consideration to remind is that allergic rhinitis is often sustained by a chronic inflammation, but symptoms vary greatly during time, with symptom-free periods, and this is another relevant determinant for non-adherence.

Overall, it is surprising that given the large diffusion of pharmacological treatments of allergic rhinitis, there

are so few studies specifically addressing and measuring the adherence aspects [40]. As a final remark, it was shown that a structured educational programme was able to increase significantly the compliance with rhinitis therapy and consequently to improve the clinical outcomes [41].

Specific immunotherapy

In allergic rhinitis, specific immunotherapy (SIT) probably represents the most critical problem as far as adherence is concerned. SIT, given either sublingually (SLIT) or subcutaneously (SCIT), is effective in reducing symptoms and medications' use in allergic rhinitis, as demonstrated by numerous clinical trials and meta-analyses [42–44]. In addition, it can modify the natural course of the disease by preventing the onset of new sensitization and by reducing the risk of asthma development [45–47]. On the other hand, SIT is a long-term treatment (recommended duration 3–5 years) [42–44]. This fact obviously implies relevant compliance problems, as happens for all chronic therapies.

It can be expected, in principle, that compliance with SCIT is better than with SLIT, as the first is administered at fixed intervals (usually once monthly) by a physician, whereas the second is self-managed by the patient at home with variable and different schedules of administration [48]. Indeed, looking at the literature, the adherence to SCIT is far from being optimal [49], ranging from 33% to 89% (Table 2). Lower et al. [50] noticed that patients treated according to a time-consuming traditional schedule, reported waste of time and annoyance as the main causes for stopping treatment. The use of accelerated schedules leads to a slight improvement in the compliance rate [51, 52]. In 247 patients treated with SCIT, Ruiz et al.

[53] reported that the major causes of non-compliance were the cost, the worsening of symptoms and the shift to alternative/complementary medicines. A higher SCIT adherence rate was reported by Rhodes [54], though 12% of patients treated with the top dose stopped the therapy before the end of the third year because of side effects, inconvenience or concurrent medical problems. The same reasons for stopping treatment were reported by More and Hagan [55], who studied 381 patients. In a longitudinal and comparative study performed [56] in children, the percentage of patients who abandoned the treatment was 5.6%, 4.5% and 0.8% in the first, second and third year of treatment respectively. Cost was identified as the main cause of withdrawal and poor compliance, also in relation to the treatment's duration. Hankin et al. reported that approximately 39% of patients received immunotherapy for less than 6 months, 14% for at least 6 months but less than 1 year, 18% for less than 2 years, 13% for less than 3 years and only 16% for 3 or more years [57].

In summary, the main reasons reported for non-compliance to SCIT are the inconvenience and the occurrence of side effects. This latter aspect can be partly addressed by reducing the doses of vaccine or with the use of pre-medications, but the inconvenience remains a major problem, with no reasonable solution. In addition, the cost of the treatment is another possible reason for non-compliance, as in many countries SIT is not reimbursed and represents an out of pocket expense for the patient.

Concerning SLIT, the various trials that addressed the adherence aspects suggest a more favourable situation (Table 2), as the adherence rates vary from 75% to more than 95% [56, 58–62]. This has been attributed to the ease of use, to the convenience and to the

Table 2. Studies assessing the adherence to immunotherapy

Author (ref)	Year	Patients*	Duration	Type of IT	Compliance
Lower (50)	1993	315 C	4 years	SCIT	44%
Cohn (51)	1993	217 A	4 years	SCIT	48%
Tinkelman (52)	1995	3349 A	18 months	SCIT	65%
Ruiz (53)	1997	247 A	18 months	SCIT	62%
Rhodes (54)	1999	1033 A	3 years	SCIT	88%
More (55)	2002	361 A	3 years	SCIT	77%
Lombardi (58)	2004	86 A	4–12 months	SLIT	75–97%
Marogna (62)	2004	319 A	3 years	SLIT	80%
Pajno (56)	2005	1886 C	3 years	SCIT	89%
Pajno (56)	2005	806 C	3 years	SLIT	79%
Passalacqua (59)	2006	443 A	6 months	SLIT	76%
Passalacqua (60)	2007	71 C	6 months	SLIT	85%
Roder (61)	2008	154 A	2 years	SLIT	77%
Hankin (57)	2008	3048 C	> 3 years	SCIT	18% 2 years, 13% 3 years, 16% > 3 years
Senna (63)	2010	Not stated	2 years	SLIT	44% 1st year; 28% 2nd year; 13% 3rd year

*C= Children; A= Adults.

overall good safety profile. Nonetheless, as mentioned above, the patient's knowledge about the measurement of his/her compliance introduces an unavoidable bias, which presumably distorts the results in favour of better results. In fact, when the sales data (number of therapies started and refills subsequently sold during maintenance) are analysed, the rates of discontinuation are alarming. In a recent Italian study, with sales data provided by two major manufacturers, more than 50% of patients discontinued SLIT during the first year, and only 13% were still on treatment in the second year. This was independent of the allergen, regimen of administration and reimbursement status [63]. Few studies attempted to identify the reasons for non-compliance with SLIT. A survey, conducted among specialists who routinely prescribed SLIT [64], reported that the absence of perceived efficacy of the treatment was the most frequent reason for withdrawal, followed by cost and tolerability, whereas side effects, patients' education and ease of use were judged to be not particularly relevant to adherence. Those results were essentially replicated in a subsequent survey conducted by means of questionnaires among allergists [65]. The mayor limit of those studies is that data were obtained from physicians and not from patients, who are the main protagonists of the compliance scenario. Some studies attempted to identify the possible interventions to improve adherence. One study in paediatric patients [66] clearly demonstrated that the discontinuation rate is inversely correlated to the frequency of control visits. In that study, the better adherence, although not optimal, was obtained with control visits performed every 3 months. Another study showed that a detailed education (3 h lesson on scopes and effects of SLIT) lead to a significantly better adherence, as compared to a generic information on the treatment [67]. Also, the duration of the treatment (pre-coseasonal or continuous) would play a role in the willingness of patients to adhere. In this regard, concerning seasonal allergies, a seasonal treatment seemed to be better than a continuous (all year long) regimen [68].

In summary, the adherence to SLIT regimens seems to be significantly affected by the frequency of follow-up visits, by the perception of efficacy and by the costs.

Apart from the economic aspects, largely dependent on the local situations, it seems that there is room for improving the adherence to SLIT with a more detailed information/education and with a strict follow-up during the treatment course.

Conclusions

The treatment of allergic rhinitis (rhinoconjunctivitis), as many chronic diseases, is affected by the adherence problem. In general, the effects of adherence have been formally addressed in few real-life studies involving traditional drugs, such as antihistamines or intranasal corticosteroids [39], whereas in clinical trials, the adherence is obviously optimal. In particular, for nasal corticosteroids, the compliance has been formally assessed only on the basis on patients' preference (i.e. taste, aspect, smell), inferring conclusions about the real adherence. Thus, the adherence to therapy remains a major issue under the economic and clinical point of view [69–72]. On the other hand, SIT has been investigated better in detail under the adherence viewpoint and in real life, as in the case of SIT, an optimal compliance is mandatory on the long-term. Also in this case, the results are somewhere discordant, for both SCIT and SLIT, but the general impression is that the compliance is far from being optimal. Only recently, attempts have been made to identify the relevant determinants for non-adherence, and patient's education, costs and perceived (vs. expected) efficacy seem to be the most relevant ones. It is probably difficult, although desirable, to act on the costs, which are determined by the local healthcare systems, whereas a better and more detailed education, especially concerning the efficacy, and a more strict patient–physician relationship are realistic and achievable goals.

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