

Review article

Administration regimens for sublingual immunotherapy to pollen allergens: What do we know?

The modalities of administration of sublingual immunotherapy (SLIT), including dosing, build-up phase, duration of the treatment, and frequency of the maintenance dose are largely variable. In the case of pollen (SLIT), the complexity increases, since preseasonal, coseasonal and pre-coseasonal regimens can be used. The administration regimens are of relevance from a practical point of view, but can also have economic implications. We review herein the available literature (randomized double blind controlled studies) on pollen SLIT, in order to derive experimentally-supported suggestions about the regimens of administration that should be preferred.

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Background

Nowadays, there is reliable evidence of the clinical efficacy of sublingual immunotherapy (SLIT) in respiratory allergies, as testified by more than 50 randomized controlled trials and meta-analyses, in adult and pediatric patients, with allergic rhinitis and/or bronchial asthma (1–5). In addition, as a distinctive characteristic, SLIT possesses a very favorable safety profile (1, 6). In fact, the most common side effects are local or gastrointestinal, but they are generally mild and self-limiting, or manageable by temporary dose reduction. The safety profile seems not to be different in very young children (7, 8). Similarly to injection immunotherapy, the literature would suggest that SLIT is capable of preventing the onset of new sensitizations and of reducing the risk of asthma onset in pediatric patients with allergic rhinitis (9, 10). The most recent controlled trials (11–16), involving hundreds of subjects, have clearly demonstrated, at least for grass pollen, a clinical efficacy over placebo far greater than the recommended 20% (17), in addition to a dose-dependent effect.

One of the most important and debated aspects of SLIT is the regimen of administration. Usually, it involves an up-dosing phase with gradual increase of the doses, followed by a maintenance phase. This modality is directly derived by the injection route of immunotherapy. Concerning the maintenance phase, the extract can be given daily, on alternate days or once a week, based on personal experiences and empirical considerations. Also, the dose of allergen is largely variable and there are both positive and negative studies over a wide range of doses (from 2 to 375 times the doses used for injections). Another source of uncertainty is that for pollen allergens, SLIT can be given as *preseasonal* (start before and stop at the beginning of the pollen season), *coseasonal* (start and end with the pollen season), *precoseasonal* (start before the pollen season end continue until the end of it), or *continuous* (all year, independent of the pollen season). Thus, there is an urgent need for definition and unification of doses, regimens and administration schedules, especially for pollen allergens. The regimen of administration and the duration may have also economic implications.

Very recently, the regulatory authorities have started to afford the pharmaco-economic aspects of SLIT, with a special attention paid to the reimbursement modalities. For instance, in Italy the local council of Regione Lombardia has licensed a rule which restricts the reimbursement of pollen SLIT only to short pre-seasonal courses of the duration of 3 months or less. (*Concerning sublingual specific immunotherapy with seasonal allergens (e.g. grass, birch, parietaria, compositae and ragweed), according to the numerous published studies, a pre-seasonal treatment of three months is indicated*) (18).

These restrictions seem to be not justified or supported by the available literature, as detailed below, and could result in the risk of inappropriate treatment, with a consequent loss of the potential benefits of SLIT.

Literature analysis

When making an objective evaluation of the clinical efficacy and dosing regimens of SLIT, only randomized, double blind and placebo-controlled trials must be taken into account, as recommended by the Evidence Based Medicine rules (19). The studies should include patients with ascertained respiratory allergy due to pollens only, and receiving well defined doses.

There are 41 studies of SLIT for pollen allergens (11–16, 20–54), as listed in Table 1. All the 41 studies included patients with seasonal allergic rhinitis, and in 15 trials the patients had also mild to moderate seasonal allergic asthma. The studies were conducted with different allergens: grasses in 25 trials, *Parietaria* in five, cypress-cedar in four, ragweed in two, birch in two, olive in one, trees plus birch in one, and grass plus olive in one. It is not possible to exactly determine or compare in all studies the dose of allergen in micrograms of major allergen, since extracts were quantified in various units, including BU, PNU, SQ-U, SE-U, Aueq, SU/ml, TU, wt/vol and HEP. Nevertheless one firm point is that the dose of extract for SLIT must be higher than for injection immunotherapy (high-dose SLIT). At least for grass pollen, the dose-ranging studies have shown that a monthly maintenance dose of about 600 mcg major allergen(s) achieves the best efficacy (12, 13).

Due to the favorable safety profile, it has become progressively clear that the build-up phase could be not necessary, and that starting with the maintenance dose does not increase the risk of side effects (55, 56). This was confirmed in some of the recent large trials where the no-updosing protocol was used. Moreover, in 21 of the studies an once-daily regimen, instead of each-other-day (13 studies) or less, was used. Of note, the once-daily administration was applied in six studies, including the largest trials (11–16). The no build-up and the once daily administration schedule are more patient-friendly and are expected to improve the compliance and would avoid

dosing mistakes. For this reason, they should be probably preferred.

The duration of treatment, the dosing regimen and the period of follow-up varied considerably among studies. The duration of SLIT courses varied from 3 months (minimum duration) to 3 years (maximum duration). The administration regimen was *preseasonal* in three studies (27, 32, 44), *co-seasonal* in three (15, 42, 47), and *continuous* in eight trials (30, 35, 38, 39, 41, 43, 46, 54), despite the allergen was seasonal. In the remaining 27 trials the adopted regimen was *preseasonal*. All the 'big trials' with grass extracts were conducted with a pre-seasonal schedule of administration, with the exception of one study which used a co-seasonal regimen (15). This latter study, involving a 3-month SLIT was conducted in Germany, where the grass pollen season is usually shorter than in the Mediterranean area. In this area, the grass pollen season is often longer than 1 month, and for other plants, such as *Parietaria*, the pollen season always exceeds 6 months in duration. Moreover, the results of that study with grass pollen cannot be immediately transferred to all the remaining allergens. In addition, it has been clearly demonstrated that a pre-season period of at least 8 weeks is required to achieve an optimal effect with grass pollen (57). Concerning the preventative effects of SLIT, in one of the two studies (9) the treatment was given co-seasonally for 4 months, and in the other one (10) the SLIT was given continuously. One randomized open trial with birch pollen SLIT given continuously achieved a significant benefit in rhinitis and asthma, and the benefit progressively increased over the considered 5-year period (58). Finally, for pollen allergens, there is no study directly comparing the various alternatives (preseasonal, pre-seasonal, co-seasonal or continuous). Nonetheless, the large majority of the trials utilized the pre-seasonal regimen, and therefore this should be considered the optimal choice.

Conclusions

The overall evaluation of the available literature on SLIT would suggest that a pre-seasonal regimen, starting at least 8 weeks before the pollen season would be the best choice for pollen SLIT. Of course a continuous regimen (all year round) for pollen allergens is associated with higher expenditures, although the pharmaco-economy data suggest that also in this case, in the long periods, SLIT is dominant over pharmacotherapy alone (58). The once-a-day administration of the maintenance dose would improve the convenience for the patient, as well as the omission of the induction phase. Policymakers and health authorities should carefully evaluate the evidence from the literature, as well as the characteristics of the local pollen seasons before imposing unjustified restrictions to reimbursement.

Table 1. Characteristics (allergen, duration, regimen, dose/preparation) of SLIT in 41 randomized controlled studies with pollens extracts 1994–2009

Reference	Allergen	Duration	Regimen	Frequency of maintenance	Build-up	Dose/Preparation
(20)	Grass	4 months	Precoseasonal	Daily, then 3/week	40 days	210 µg Dac g 5 Glycerosaline
(21)	Grass	4 months	Precoseasonal	3/week	15 days	19 mcg grass per month. glycerol-phenol
(22)	Parietaria	6 months	Precoseasonal	3/week	50 days	1 µg Par j 1 per month glycerophenol
(25)	Olive	6 months per 2 seasons	Precoseasonal	Daily	2 months	1.215 µg Ole e 1/month. Glycerophenol
(23)	Grass	6 months	Precoseasonal	Daily	25 days	288 mcg Phl p 5/month. Aqueous
(24)	Birch	4 months	Precoseasonal	3/week	28 days	62 µg Bet v 1/month. Glycerophenol
(26)	Grasses	6 months	Precoseasonal	2/week	21 days	4.250 BU/month Glycerinated
(27)	Parietaria	5 months	Preseasonal	Daily	15 days	3.6 µg Par j 1/mo. Cumulative: 16 mcg Par j 1 Glycerophenol
(29)	Grass	4 months	Precoseasonal	Daily	15 days	255 µg Phl p5/month. Cumulat 935 µg Glycerophenol/tablets
(30)	Parietaria	6 months per 2 seasons	Continuous	3/week	40 days	2 730 µg Par j 1/mo; cumulat : 52.5 mg Glycerophenol
(28)	Parietaria	8 months	Precoseasonal	3/week	2 weeks	1.5 µg Par j 1/mo; cumulat 12 mcg Par j 1 Glycerophenol
(32)	Grass (monoid)	14 weeks	Preseasonal	3/week	2 months	12 000 AU/mo. Cumulative 37 000 AU
(31)	Grass	4 months	Precoseasonal	3/week	28 days	Cumul 210 µg Dac g 5; Glycerosaline
(33)	Cypress	8 months	Precoseasonal	3/week	50 days	30 000 RU/mo, Cumulat 300 000 Glycerine-Acque
(34) (second year open)	Birch	24 months per 2 seasons	Precoseasonal	3/week	18 days	90 µg Bet v 1/mo Glycerophenol
(35)	Grass	18 months	Continuous	Daily	6 weeks	0.9 mg Phl p 5 per month Glycerinate
(36)	Ragweed three doses	7 months	Precoseasonal	3/week	28 days updos + 30 days transition	1.4–4.0 mg Amb a 1/month Solution/tablets
(37) (vs plac/control)	Parietaria	13 months	Precoseasonal	3/week	25 days	1.56 µg Par j 1/month; Cumul: 23 µg. Glycerosaline
(38)	Grass	2 years 2 seasons	Continuous	Daily	30 days	6 µg/month glycerol-phenol
(39)	Grass	1 year + 2 open	Continuous	Daily	3 weeks	273 µg Phl p 5/month; Cumul: 9.6 mg. Solution
(40)	Grass	1 year or 2 years	Precoseasonal	3/week	2 months	329 µg Dac g 5/month Solution-tablets
(41)	Grass	3 years	Continuous	3/week	4 weeks	6 µg major/month. Glycerophenol
(42)	Ragweed three doses	4 months	Coseasonal	Daily	17-days	3.1–9.4 mg Amb a 1/month. Solution
(12)	Grass three doses	6 months	Precoseasonal	Daily	No	15 µg (136 pts); 150 µg (139 pts); 450 µg (294 pts) Phl p 5/month tablets
(11)	Grass	5 months	Precoseasonal	Daily	No	450 µg Phl p 5/month. Cumulat. 2.7 mg tablets
(43)	Hazelnut, birch, elm (2 doses)	18 months two seasons	Continuous	Daily	5 weeks	Group 1 3.6 mcg and Group 2 30 mcg per week
(45)	Grass	6 months	Precoseasonal	Daily	NO	450 µg Phl p 5/month. Cumulat. 2.7 mg Tablets
(44)	Grass (monoid)	2 years two seasons	Preseasonal	2/week	14 weeks	8000 AU/month Tablets
(47)	Juniper	4 months per two season	Coseasonal	Daily	1 day	6 mg Jun a 1/month Glycerol-aqueous
(46)	Grass	2 years two seasons	Continuous	2/week	20 days	168 µg Lol p 5/month; cumul 4.5 mg. Solution
(13)	Grass three doses	6 months	Precoseasonal	Daily	5 days	240 µg (157 pts); 750 µg (155 pts); 1.2 mg (160 pts)/month. Tablets
(48)	Jap cedar	7 months	Precoseasonal	1/week	1 month	6 µg Cry j 1/month Solution. Spit
(49)	Grass	10 months	Precoseasonal	3/week	5 weeks	250 µg group 5/month; cumul: 2.5 mg. Solution
(50)	Olive + Grass	10 months	Precoseasonal	Daily	NO	60 µg group 5 and 90 µg Ole e 1/month. Solution
(51)	Grass	9 months	Precoseasonal	Daily	2 months	Cumulative 3.5 mg Phl p 5
(52)	Grass	1 year	Precoseasonal	Daily	50 days	38 µg Lol p 5/month; Cumul 456. Solution; SLIT or supralingual
(53)	Cedar	5 months	Precoseasonal	1/week	6 weeks	2000 JAU
(54)	Grass	2 years 2 seasons	Continuous	Daily	1 day	1.2 mg/month Solution
(14)	Grass	8 months	Precoseasonal	Daily	NO	600 µg major allergen/month. Tablets
(15)	Grass	3 months per 4 years	Coseasonal	Daily	1 day	750 µg major allergen/month tablets
(16)	Grass	6 months	Precoseasonal	Daily	NO	450 mcg Phl p 5/month tablets

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