

REVIEW ARTICLE

Dropouts in sublingual allergen immunotherapy trials – a systematic review

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Keywords

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Abstract

Participant dropouts can reduce the power of allergen immunotherapy clinical trials. Evaluation of the dropout rate and reasons for dropout are important not only in the planning of clinical studies but are also relevant for adherence to immunotherapy in daily clinical practice. A systematic review was carried out in order to establish the overall dropout rate among published double-blind, placebo-controlled randomized clinical trials of sublingual immunotherapy for respiratory allergic diseases. Dropouts were analysed in regards to allergen, formulation, treatment schedule, participant age, study size, number of centres and type of allergic disease. Relative dropout rates in placebo and active groups as well as reasons for dropout were also assessed. A total of 81 studies, comprising 9998 patients, were included. Dropout rates in sublingual immunotherapy controlled studies do not appear to be a major problem with a composite dropout percentage of 14% (95% CI:11.9–16). Furthermore, they are not different for active compared to placebo-treated participants. This lends support to the positive clinical outcomes seen in meta-analyses of these trials.

Sublingual immunotherapy (SLIT) is a long-term treatment for allergic respiratory diseases such as rhinitis, conjunctivitis and asthma and is widely used in Europe. Its efficacy has been demonstrated in controlled trials as well as in meta-analyses (1). However, the importance of dropout rates in the evaluation of controlled studies results has recently been emphasized, as a high dropout rate can weaken positive outcomes (2, 3). Moreover, dropout assessment can have practical implications. In fact, adherence to immunotherapy, sublingual as well as subcutaneous, is generally poor, leading to a reduction in clinical efficacy in the long term (4, 5). Evaluating the reasons for dropouts in clinical studies may provide some suggestions for improving adherence to immunotherapy in daily practice.

The main aim of this study was to establish the overall dropout rate among published double-blind, placebo-controlled randomized clinical trials (DB PC RCTs) of SLIT for respiratory allergic diseases. Furthermore, we aimed to assess whether dropout rates and the reasons for dropout were different between the active and placebo-treated participants.

We also examined whether the dropout rate was influenced by factors including the size of the study, duration, allergen preparation, age of participants, number of study sites, type of respiratory disease being treated and the treatment schedule employed.

Methods

Search strategy

A comprehensive search of the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, MEDLINE, EMBASE, Latin American and Caribbean Literature on Health Sciences (LILACS), Web of Science, Biosis Previews, UK Clinical Trials Gateway and Scopus up to September 2013 was carried out. The search strategy retrieved citations containing the subject heading sublingual immunotherapy and was limited to randomized, double-blind, placebo-controlled trials for allergic asthma, allergic rhinitis or allergic rhinoconjunctivitis. The keywords used were ‘aller-

gen, sublingual immunotherapy, controlled studies, randomized trial'. There were no language restrictions. All published studies up to 30 September 2013 were included in our study. The primary outcome was the overall dropout percentage in each DB PC RCT. Secondary outcomes included the dropout percentage in active and placebo-treated groups and the reasons for dropouts. Data were collected concerning the allergen used, age of participants, the use of drops and/or tablets, the treatment schedule (perennial, preseasonal, pre- and co-seasonal), number of participants, duration of treatment, number of investigative sites and type of allergic disease treated (rhinitis, rhinoconjunctivitis, asthma or combinations of these).

Data collection and analysis

Two independent authors identified all papers reporting DB PC RCTs of sublingual immunotherapy with aeroallergens and assessed whether they met the criteria for inclusion. Following this, each author independently analysed all included papers and recorded the relevant data concerning participant dropouts on a standard proforma. A participant dropout was considered to be any situation causing premature withdrawal from the trial after randomization and before the stated completion of the trial. Comparison was then made between the data recorded by the two researchers. In case of disagreement, the original paper was reanalysed and a consensus decision reached. Studies published as continuations of previously published studies were excluded to prevent repetition of data.

Statistical analysis

For each study, the overall dropout percentage was calculated. The causes for dropouts were recorded into one of five categories: adverse event, lost to follow-up, noncompliance, consent withdrawal and 'other' for those not covered by these four categories. These categories were chosen as they were the most commonly reported causes for dropout in the studies included. Noncompliance was defined as nonadherence to treatment. Population confidence intervals were then calculated alongside the weighting of each study.

A first meta-analysis was conducted using as effect size dropout proportion. A second meta-analysis to assess any differences in dropout between actively treated and placebo groups was also performed using as effect size the relative risk (RR) of dropout (5, 6, 7).

The random-effects model was used, to account for the heterogeneity among studies. The I^2 statistic was used to quantify heterogeneity, considering as homogeneous studies with I^2 values below 25%, low heterogeneity for values between 25 and 50%, moderate heterogeneity for values in the interval 50–75% and high heterogeneity for values over 75%. Subanalyses were conducted for the following variables: allergen used, the age range of participants, the use of drops and/or tablets, the treatment schedule (perennial, pre-seasonal, pre- and co-seasonal), number of participants, number of investigative sites and type of allergic disease treated

(rhinitis, rhinoconjunctivitis, asthma or combinations of these), with an explorative purpose.

The results were presented as Forrest graphs. For the study weights, the inverse variance method was applied. Due to empty cells in some studies (zero dropouts in the treatment group, placebo group or both), we increased by 0.5 the number of cases both in the placebo and in the active treatment arm, both for compliant and dropout cases. This has allowed us to perform both the meta-analyses using the same adjustments on the data, without excluding any study from the analyses (4, 6).

All analyses were performed with Stata 11 (StataCorpLP, College Station, TX, USA) updated with the user-written commands for meta-analysis (*metan*, *metafunnel* and *meta-bias*) (8).

Results

A total of 81 studies, comprising 9998 patients, were initially selected for the meta-analyses (Table 1). 4197 patients were allocated to a placebo arm. 664 (15.8%) of them dropped out, 590 in the first year (14%). A total of 5801 patients were allocated to active treatment arms of which 1003 (17.3%) dropped out, 910 in the first year (15.7%). Only 11 studies had a duration greater than one year. Statistical analyses were therefore restricted to follow-up within 1 year.

Fifty-nine studies used drop formulation immunotherapy, 20 tablets, and 2 studies both drops and tablets. The dropout percentage varied from 0 (14 studies) to 56.5%. At least one dropout occurred in 67 studies. A dropout level of <20% was seen in 65 (80.2%) studies. In 10 of the 67 studies with at least one dropout, dropout reasons were not specified, and in six, they were incompletely described.

A meta-analysis of the dropout percentages was performed for the 81 included studies considering the first year of study. A composite dropout percentage of 14% was observed (95% CI: 11.9–16). The variables potentially affecting the dropout percentage were then analysed: study type (single, multicentre or multinational), age range of patients (children, adults and mixed), place where the study was conducted (Europe, Asia, Canada, USA, Australia), diseases affecting patients (rhinitis, asthma, conjunctivitis), sensitization (monosensitized patients, polysensitized patients), type of allergen used for immunotherapy (cat, ragweed, cypress, house dust mites, olive tree, birch tree, parietaria, grass & olive tree), study size (small: <20 patients; average: 21–40 patients; adequate: 41–100 patients and large: >100 patients) and immunotherapy formulation (drop or tablets), treatment duration (≤ 12 months, 13 months–24 months; more than 25 months) and immunotherapy schedule (perennial, pre-co-seasonal, pre-seasonal and co-seasonal) (Tables 2 and 3).

There was a smaller proportion of dropouts in patients treated with olive immunotherapy (4%, 95% CI: –0.02–0.09), while a greater proportion of dropouts in patients treated with ragweed (22%, 95% CI: 0.16–0.29). Considering the countries where the studies were performed, the study performed in Canada showed the highest proportion of dropouts (36%, 95% CI: 0.26–0.47), although this is based on a

Table 1 Study characteristics

References	Year	First author	N =	% DO	Confidence intervals	% DO active	% DO placebo	% DO adverse events active	% DO adverse events placebo	% DO lost to FU active	% DO lost to FU placebo	% DO NC active	% DO NC placebo	% DO CW active	% DO CW placebo	% DO Other active	% DO Other placebo
9	1986	Seadding	20	10.00	-3.15 -	23.15	10.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	100.00
10	1990	Tari	66	12.12	4.25 -	20.00	11.76	12.50	-	-	-	-	-	-	-	-	-
11	1993	Nelson	44	6.82	-0.63 -	14.27	9.09	4.55	-	-	-	-	-	-	-	-	-
12	1994	Casanovas	15	0.00	0.00 -	0.00	0.00	0.00	-	-	-	-	-	-	-	-	-
13	1995	Feliziani	34	0.00	0.00 -	0.00	0.00	0.00	-	-	-	-	-	-	-	-	-
14	1995	Troise	31	0.00	0.00 -	0.00	0.00	0.00	-	-	-	-	-	-	-	-	-
15	1997	Hirsch	30	3.33	-3.09 -	9.76	6.67	0.00	100.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
16	1998	Horak	41	17.07	5.56 -	28.59	14.29	20.00	-	-	-	-	-	-	-	-	-
17	1998	Hordyk	73	21.92	12.43 -	31.41	23.08	20.59	11.11	-	-	-	-	-	-	-	-
18	1998	Passalacqua	20	5.00	-4.55 -	14.55	0.00	10.00	-	-	0.00	-	100.00	-	0.00	-	0.00
19	1999	Bousquet	85	29.41	19.73 -	39.10	33.33	25.58	35.71	14.29	0.00	42.86	36.36	0.00	0.00	7.14	27.27
20	1999	Clavel	120	0.00	0.00 -	0.00	0.00	0.00	-	-	-	-	-	-	-	-	-
21	1999	La Rosa	41	14.63	3.82 -	25.45	15.00	14.29	66.67	0.00	0.00	33.33	0.00	0.00	0.00	0.00	66.67
22	1999	Mungan	26	0.00	0.00 -	0.00	0.00	0.00	-	-	-	-	-	-	-	-	-
23	1999	Passalacqua	30	10.00	-0.74 -	20.74	6.67	13.33	0.00	0.00	0.00	100.0	100.00	0.00	0.00	0.00	0.00
24	1999	Pradaller	126	5.56	1.56 -	9.56	4.76	6.35	0.00	0.00	0.00	33.33	50.00	0.00	0.00	66.67	50.00
25	2000	Caffarelli	48	8.33	0.51 -	16.15	0.00	16.67	-	-	75.00	-	0.00	-	0.00	-	0.00
26	2000	Guez	72	41.67	30.28 -	53.05	30.56	52.78	0.00	27.27	26.32	0.00	5.26	0.00	0.00	63.64	68.42
27	2000	Paino	24	12.50	-0.73 -	25.73	0.00	25.00	-	-	0.00	-	0.00	-	0.00	-	66.67
28	2001	Ariano	20	0.00	0.00 -	0.00	0.00	0.00	-	-	-	-	-	-	-	-	-
29	2001	Bahceciller	15	0.00	0.00 -	0.00	0.00	0.00	-	-	-	-	-	-	-	-	-
30	2001	Sanchez	40	0.00	0.00 -	0.00	0.00	0.00	-	-	-	-	-	-	-	-	-
31	2001	Volitoli	32	9.38	-0.72 -	19.47	6.25	12.50	0.00	-	-	-	-	-	-	-	-
32	2002	Lima	56	12.50	3.84 -	21.16	7.14	17.86	50.00	0.00	0.00	0.00	0.00	0.00	0.00	50.00	100.00
33	2003	André	110	16.36	9.45 -	23.28	21.82	10.91	33.33	16.67	-	-	-	16.67	33.33	-	-
34	2003	Ippoliti	86	0.00	0.00 -	0.00	0.00	0.00	-	-	-	-	-	-	-	-	-
35	2003	Marcucci	24	0.00	0.00 -	0.00	0.00	0.00	-	-	-	-	-	-	-	-	-
36	2003	Mortemousse	60	25.00	14.04 -	35.96	13.33	36.67	0.00	25.00	9.09	25.00	18.18	0.00	0.00	50.00	72.73
37	2003	Wuthrich	28	21.43	6.23 -	36.63	28.57	14.29	0.00	0.00	0.00	50.00	0.00	0.00	0.00	50.00	100.00
38	2004	Bowen	83	36.14	25.81 -	46.48	44.19	27.50	42.11	15.79	0.00	0.00	9.09	0.00	0.00	42.11	90.91
39	2004	Bufe	161	18.01	12.08 -	23.95	17.07	18.99	-	-	-	50.00	46.67	-	-	-	-
40	2004	Kinchi	47	21.28	9.58 -	32.98	21.74	20.83	20.00	0.00	0.00	80.00	80.00	0.00	0.00	0.00	0.00
41	2004	Roling-Wekinghouse	97	10.31	4.26 -	16.36	10.20	10.42	20.00	0.00	0.00	40.00	40.00	0.00	0.00	0.00	20.00
42	2004	Tonnel	32	43.75	26.56 -	60.94	33.33	52.94	20.00	0.00	0.00	0.00	0.00	20.00	55.56	60.00	33.33
43	2006	Dahl	114	18.42	11.30 -	25.54	17.57	20.00	23.08	15.38	12.50	7.69	0.00	0.00	0.00	53.85	87.50
44	2006	Dahl	634	13.88	11.19 -	16.57	13.29	14.47	38.10	11.90	15.22	9.52	21.74	21.43	8.70	19.05	36.96
45	2006	Di Rienzo	34	5.88	-2.03 -	13.79	5.26	6.67	-	-	-	-	-	-	-	-	-
46	2006	Durham	855	7.60	5.83 -	9.38	7.73	7.34	52.27	14.29	-	-	-	-	-	-	-

Table 1 (Continued)

References	Year	First author	N =	% DO	Confidence intervals	% DO active	% DO placebo	% DO adverse events active	% DO adverse events placebo	% DO lost to FU active	% DO lost to FU placebo	% DO NC active	% DO NC placebo	% DO CW active	% DO CW placebo	% DO Other active	% DO Other placebo
47	2006	Lue	20	0.00	0.00	0.00	0.00	0.00	0.00	42.86	83.33	0.00	0.00	14.29	16.67	42.86	0.00
48	2006	Niu	110	11.82	5.79	17.85	11.11	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
49	2006	Palma Caros	33	39.39	22.72	56.07	56.25	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	2006	Passalacqua	68	17.65	8.59	26.71	17.65	12.50	16.67	0.00	0.00	50.00	83.33	0.00	0.00	37.50	0.00
51	2006	Valovirta	65	21.54	11.54	31.53	18.18	41.18	30.00	0.00	0.00	29.41	30.00	17.65	20.00	11.76	20.00
52	2006	Worm	185	14.59	9.51	19.68	18.09	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
53	2007	Alvarez Cuesta	50	34.00	20.87	47.13	32.00	0.00	0.00	0.00	0.00	55.56	0.00	22.22	0.00	0.00	25.00
54	2007	De Blay	118	14.41	8.07	20.74	14.75	11.11	0.00	11.11	75.00	0.00	0.00	45.76	60.00	11.86	10.00
55	2007	Didier	628	10.99	8.54	13.43	12.50	28.81	0.00	13.56	30.00	0.00	0.00	0.00	0.00	0.00	0.00
56	2007	Moreno	100	15.00	8.00	22.00	19.61	60.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
57	2007	Mosges	101	10.89	4.82	16.97	12.50	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
58	2007	Pham-Thi	111	17.12	10.11	24.12	20.00	9.09	25.00	36.36	12.50	36.36	25.00	9.09	25.00	0.00	12.50
59	2007	Roder	204	26.47	20.42	32.52	25.00	0.00	0.00	0.00	0.00	55.56	77.78	0.00	0.00	44.44	22.22
60	2007	Vervloet	76	7.89	1.83	13.96	5.26	50.00	0.00	50.00	25.00	0.00	0.00	0.00	0.00	0.00	75.00
61	2008	Pfarr	185	14.59	9.51	19.68	18.09	35.29	30.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
62	2008	Stelmack	50	14.00	4.38	23.62	12.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
63	2009	Bufe	253	7.51	4.26	10.76	9.52	33.33	28.57	16.67	0.00	25.00	28.57	0.00	14.29	25.00	28.57
64	2009	Ott	209	56.46	49.74	63.18	59.15	0.00	0.00	0.00	0.00	100.00	100.00	0.00	0.00	0.00	0.00
65	2009	O'Hehir	30	10.00	-0.74	20.74	13.33	50.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00	50.00	0.00
66	2009	Amar	58	8.62	1.40	15.84	7.69	33.33	0.00	0.00	0.00	33.33	50.00	0.00	0.00	33.33	50.00
67	2009	Horak	89	7.87	2.27	13.46	6.67	33.33	50.00	0.00	0.00	0.00	0.00	66.67	50.00	0.00	0.00
68	2010	Voltoini	24	8.33	-2.72	19.39	7.14	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
69	2010	Leonardi	31	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
70	2010	Agostinis	40	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
71	2010	Soner	115	15.65	9.01	22.29	16.00	41.67	16.67	0.00	0.00	33.33	33.33	0.00	0.00	25.00	50.00
72	2010	Cortellini	27	3.70	-3.42	10.83	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00
73	2010	Mosges	116	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.0	100.00	0.00	0.00	0.00	0.00
74	2010	Yonekura	31	9.68	-0.73	20.08	5.00	0.00	0.00	0.00	0.00	100.0	100.00	0.00	0.00	0.00	0.00
75	2010	Halcken	278	3.24	1.16	5.32	5.04	100.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
76	2011	Pfarr	81	1.23	-1.17	3.64	1.54	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
77	2011	Nelson	438	16.21	12.76	19.66	17.84	28.95	24.24	13.16	12.12	31.58	36.36	23.68	24.24	2.63	3.03
78	2011	Bush	31	32.26	15.80	48.71	20.00	50.00	33.33	0.00	0.00	0.00	0.00	0.00	0.00	50.00	66.67
79	2011	Blaiss	344	18.02	13.96	22.09	18.86	39.39	17.24	12.12	0.00	15.15	48.28	30.30	27.59	3.03	6.90
88	2011	Didier	633	19.75	16.65	22.85	21.26	30.68	5.41	0.00	0.00	0.00	0.00	47.73	59.46	21.59	35.14
89	2012	De Bot	251	12.75	8.62	16.88	12.00	0.00	0.00	20.00	5.88	0.00	11.76	93.33	70.59	0.00	0.00
90	2012	Yukselen	21	4.76	-4.35	13.87	9.09	0.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00
91	2012	Wahn	207	13.53	8.87	18.19	16.46	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
92	2012	Stelmack	60	3.33	-2.01	8.67	2.50	0.00	0.00	100.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00

Table 1 (Continued)

References	Year	First author	N =	% DO	Confidence intervals	% DO active	% DO placebo	% DO adverse events active	% DO adverse events placebo	% DO lost to FU active	% DO lost to FU placebo	% DO NC active	% DO NC placebo	% DO CW active	% DO CW placebo	% DO Other active	% DO Other placebo
93	2012	AhmadiAfshar	24	16.67	1.52 –	31.82	16.67	0.00	0.00	0.00	100.00	100.00	0.00	0.00	0.00	0.00	0.00
94	2013	Bozek	108	10.19	4.48 –	15.89	7.84	0.00	0.00	0.00	0.00	75.00	42.86	0.00	0.00	25.00	57.14
95	2013	Creicos	783	22.7	19.8 –	25.67	23.93	31.43	15.79	17.14	7.89	12.86	23.88	38.57	52.63	0.00	0.00
96	2013	Aydogan	18	11.11	–4.54 –	26.76	12.50	100.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00	0.00
97	2013	Wang	120	29.17	21.07 –	37.26	20.00	16.67	4.35	16.67	17.39	0.00	8.70	58.33	65.22	8.33	4.35

N, number of patients; DO, dropout; FU, follow-up; NC, noncompliance; CW, consent withdrawal.

Table 2 Summary of overall dropout rates and relative risk depending on allergen, disease and study size

Parameters	Overall dropout rate (95% CI)*	Relative risk (RR) dropout active vs placebo (95% CI)
Allergen		
Cat	0.14 (–0.01–0.29)	0.97 (0.49–1.93)
Ragweed	0.22 (0.16–0.29)	1.33 (1.03–1.71)
Cypress	0.08 (0.03–0.12)	0.65 (0.20–2.09)
Mites	0.15 (0.11–0.19)	0.77 (0.62–0.95)
Grass	0.14 (0.11–0.17)	1.11 (0.99–1.25)
Olea	0.04 (–0.02–0.09)	0.59 (0.04–8.87)
Silver birch	0.14 (0.04–0.24)	1.00 (0.58–1.73)
Parietaria	0.10 (0.01–0.18)	0.91 (0.32–2.62)
Grass & Olea	0.16 (0.09–0.23)	1.83 (0.71–4.77)
Not specified	0.07 (–0.02–0.16)	0.27 (0.01–6.11)
Disease		
Rhinitis + asthma	0.14 (0.12–0.17)	1.06 (0.96–1.17)
Rhinitis alone	0.08 (0.04–0.13)	1.28 (0.79–2.07)
Conjunctivitis alone	0.26 (0.15–0.37)	0.34 (0.13–0.88)
Asthma alone	0.13 (0.07–0.19)	0.62 (0.09–3.99)
Study size		
<20 patients	0.07 (0.03–0.11)	0.88 (0.30–2.64)
21–40 patients	0.12 (0.08–0.15)	0.69 (0.50–0.97)
41–100 patients	0.16 (0.12–0.20)	0.83 (0.68–1.02)
>100 patients	0.15 (0.12–0.18)	1.19 (1.06–1.32)

*Negative values of the lower limit of the 95% CI are due to the fact that estimates in STATA program were based on SE and provided approximate 95% CI.

single study. Studies performed on patients only suffering from rhinitis had a lower proportion of dropout (8%, 95% CI: 0.04–0.13) compared to studies in patients with asthma and rhinitis (14%, 95% CI: 0.12–0.17), although this did not reach statistical significance. Only a single study evaluated conjunctivitis alone (event rate 26%, 95% CI: 0.15–0.37).

A tendency towards fewer dropouts was observed in small studies (<20 patients: 7%; 95% CI: 0.03–0.11) compared to larger studies (41–100 patients: 16%, 95% CI: 0.12–0.20; more than 100 patients: 15%, 95% CI: 0.12–0.18).

Considering treatment duration, the proportion of dropouts during the first year of treatment was lower in studies length of ≤12 months (12%, 95% CI: 0.09–0.14) compared to longer (13–24 months: 18%, CI 95%: 0.15–0.22).

No differences in the dropout percentages were seen when considering the age range of participants, sensitizations, nor the immunotherapy formulation, schedule and number of study sites.

When dropout risk was compared between placebo and active treatment arms, no differences were found (RR:1.05, 95% CI: 0.96–1.16). Nor was there a significant difference when effects were assessed by the percentage of total dropouts of each study (dropout ≤20%: RR:1.13, 95% CI: 0.99–1.27 and dropout >20%: RR:0.88, 95% CI: 0.71–1.10), assuming that a dropout of more than 20% can weaken the clinical results (5).

Table 3 Summary of overall dropout rates and relative risk depending on age, duration, formulation, schedule, number of centres, sensitizations and geographical area of study

Parameters	Overall dropout rate (95% CI)†	RR dropout active vs placebo (95% CI)
Age		
Children	0.11 (0.08–0.14)	1.10 (0.90–1.34)
Adults	0.15 (0.12–0.18)	1.08 (0.96–1.21)
Children and adults	0.17 (0.08–0.26)	0.60 (0.42–0.86)
Duration*		
≤12 months	0.12 (0.09–0.14)	1.10 (0.98–1.24)
13–24 months	0.18 (0.15–0.22)	0.93 (0.77–1.12)
≥25 months	0.14 (0.08–0.21)	1.16 (0.85–1.59)
Formulation		
Drops	0.14 (0.11–0.17)	0.99 (0.87–1.12)
Tablets	0.13 (0.10–0.16)	1.16 (1.01–1.33)
Not specified	0.24 (–0.13–0.61)	0.68 (0.34–1.36)
Schedule		
Perennial	0.16 (0.13–0.19)	0.87 (0.75–1.02)
Preseasonal	0.09 (0.05–0.13)	0.56 (0.21–1.52)
Co-seasonal	0.22 (–0.09–0.53)	1.14 (0.87–1.48)
Pre/co-seasonal	0.12 (0.09–0.14)	1.20 (1.05–1.36)
Number of centres		
Single	0.13 (0.10–0.15)	0.76 (0.63–0.92)
Multicentre	0.16 (0.12–0.20)	1.12 (0.98–1.28)
Not specified	0.10 (–0.01–0.21)	0.94 (0.46–1.92)
Number of sensitizations		
Monosensitized	0.11 (0.08–0.13)	0.84 (0.69–1.04)
Polysensitized	0.14 (0.05–0.22)	1.08 (0.77–1.51)
Mixed	0.17 (0.13–0.20)	1.12 (1.01–1.25)
Not specified	0.10 (0.02–0.18)	0.70 (0.15–3.24)
Place where study was conducted		
Europe	0.13 (0.11–0.16)	1.04 (0.93–1.16)
Asia	0.12 (0.05–0.18)	0.67 (0.43–1.06)
Canada	0.36 (0.26–0.47)	1.58 (0.87–2.85)
USA	0.16 (0.12–0.19)	1.04 (0.80–1.37)
Australia	0.12 (0.01–0.24)	1.67 (0.25–11.16)
Not specified	0.19 (0.11–0.27)	1.29 (0.97–1.73)

*Meta-analysis of dropout percentages was performed considering only data from the first year.

†Negative values of the lower limit of the 95% CI are due to the fact that estimates in STATA program were based on SE and provided approximate 95% CI.

In the single-centre studies, dropout risk was slightly higher in the placebo arm than in the actively treated arm (RR: 0.76, 95% CI: 0.63–0.92). A higher risk was seen in the placebo group compared to active group for dropouts in patients suffering from allergic conjunctivitis (RR: 0.34, 95% CI: 0.13–0.88); however, this result is based on only a single study.

Concerning the allergen used, in house dust mite studies, the RR of dropout was greater in placebo-treated groups (RR: 0.77, 95% CI: 0.62–0.95); active ragweed-treated patients showed a higher risk compared to placebo-treated patients (RR: 1.33, 95% CI: 1.03–1.71), while a trend towards a higher risk of dropout was observed in grass-treated participants (RR: 1.11; 95% CI: 0.99–1.25; $P = 0.083$).

Moreover, the larger studies (>100 patients) showed a greater risk of dropout in the active arms (RR: 1.19; 95% CI: 1.06–1.32), while studies with a modest number of patients (21–40 patients) had a higher risk in the placebo group (RR: 0.68; 95% CI: 0.49–0.95). A trend towards higher risk of dropout in placebo patients was also observed in studies with 41–100 patients (RR: 0.83, 95% CI: 0.68–1.02; $P = 0.074$).

Regarding age of participants, a significantly higher risk of dropout was observed in the placebo-treated group in studies performed in both adults and children (RR: 0.60; 95% CI: 0.42–0.86). No significant differences were observed in studies performed only in adults or children.

Furthermore, risk of dropout was greater in the active group of studies that enrolled both monosensitized and polysensitized patients (RR: 1.12; 95% CI: 1.01–1.25). A higher risk of dropout in the active group was also seen in pre-co-seasonal schedule studies (RR: 1.20, 95% CI: 1.05–1.36) and also in patients treated with tablets (RR: 1.16; 95% CI: 1.01–1.33). No significant differences in the relative risk of active and placebo groups were found regarding based on treatment duration and countries where studies were performed.

Considering the reasons for dropouts, the risk of dropout due to an adverse event was evaluated in 50 studies with any dropout and in which this information was available. A higher risk was found in actively treated than in placebo-treated patients (RR: 1.53; 95% CI: 1.24–1.90). Regarding the 'non-compliance' and 'Other reasons' category, the risk was higher in the placebo group (respectively: RR: 0.85; 95% CI: 0.67–1.10 and RR: 0.73; 95% CI: 0.61–0.88). No significant differences in the relative risk of active and placebo groups were found regarding: 'lost to follow-up', 'consent withdrawal' and 'noncompliance' reasons.

Discussion

Many controlled trials have recently been performed on sublingual immunotherapy, whose use has become more widespread particularly in Europe. These trials are mainly designed to assess clinical efficacy and safety as the main outcomes, which are of course crucial factors in its successful use in clinical practice. Dropout rates in these studies have been assessed to a lesser extent, and only recently reporting of dropouts and withdrawals have been included in such studies. It is important to note that clinical findings of controlled trials require a low rate of dropouts in order to be considered robust. Furthermore, the conditions of controlled studies can be fairly different to 'real-life' clinical practice. Nevertheless, careful evaluation of the reasons of dropouts in these studies can provide some practical suggestions in improving adherence to immunotherapy.

Our results show an overall low dropout rate, that is, below 20% in the included sublingual immunotherapy-controlled studies. This finding can further strengthen the positive clinical results shown in these trials. Considering the different variables potentially affecting the dropout percentage, no significant differences were found according to the study population size, schedule, age and formulation. This can be relevant in the evaluation of the recent so called 'big

trials' as the clinical benefit is associated with an acceptable low dropout rate. Surprisingly, undergoing a longer schedule does not appear to affect the dropout rate, according to our analysis of the first year of study. A slightly significant increase in dropout was seen in ragweed actively treated patients. Perhaps the shorter pollen season and therefore shorter period of symptoms can justify this finding suggesting a lower adherence in comparison with patients with longer period of symptoms to allergens such as grass, parietaria, house dust mite. On the other hand, the higher dropout rate observed in placebo-treated patients in house dust mite trials could be related to a lack of efficacy of treatment.

According to patient disease, a better compliance was observed in patients with rhinitis in comparison with patients with both asthma and rhinitis. Allergic rhinitis is sometimes considered a trivial disease, but it has a significant impact on patient's quality of life (80), perhaps to a greater extent than asthma (81). Furthermore, this finding may be related to patient selection as patients receiving immunotherapy for rhinitis only tend to be the ones severely affected and may be more motivated to continue on treatment. Moreover, patients could pay more attention to the relationship between rhinitis and allergen exposure, whereas asthma can be elicited by several different triggers besides allergy. The significantly higher dropout rate in patients with isolated conjunctivitis is based on only one study; therefore, no conclusions can be drawn from this.

Comparing active and placebo dropout rates, the only significant difference was reported in adverse reactions, which were a risk factor for stopping treatment in patients receiving active immunotherapy. This is also reflected in the experience from clinical practice where adverse reactions are one of the main reasons for withdrawal in children as well in adults (82, 83). It is important to note that the adverse reactions caused in the trials included in this review were actually local reactions related to tolerability of the treatment rather than concerning its safety. Other factors, such as lack of regular

follow-up and cost, may probably account for the lower adherence in the real-life setting compared to clinical trials (5, 82, 84). Another crucial factor which may affect adherence and sometimes lacking in daily practice is patient education (85, 86). On the contrary in controlled trials, appropriate education and guidance are basic conditions for the enrolment in every patient.

In conclusion, in clinical trials, dropout rates deserve more attention and have to be clearly addressed in order to confirm the strength of the clinical results. The dropout rate in controlled SLIT studies published so far, in contrast to other pharmacological treatments (87), does not appear to be a significant problem. This can therefore further support the positive clinical outcomes seen in these trials and meta-analyses of these.

A careful evaluation of factors affecting the rate of dropout can suggest areas of improvement and potential changes required in the clinical practice of immunotherapy. In well-designed clinical trials, simple instructions at the beginning and regular follow-up assessments positively affect the dropout rate and can be considered as two accessible ways to improve adherence to SLIT in everyday clinical practice.

Author contributions

All of the authors were involved in writing sections of the manuscript, drafting revisions or assisting with data analysis.

Conflicts of interest

S. R. Durham has consultancy arrangements with ALK-Abelló, Circassia, GlaxoSmithKline and Merck; has received one or more grants from or has one or more grants pending with ALK-Abelló; and has received one or more payments for lecturing from or is on the speakers' bureau for Merck. The rest of the authors have no conflicts of interest.

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