Subcutaneous immunotherapy compared with placebo

Casale 2006[159]

Study design	DBPC RCT
Population symptoms	AR (no asthma)
Treatment naive	No 'recent immunotherapy'. 19.5% had previously received SIT
n, age	159 patients (aged between 18 and 50 years); 79 active (two groups, IT with or without omalizumab), 80 placebo (two groups, placebo with or without omalizumab)
Intervention details	*Allergen:* ragweed Nine weeks' pretreatment with active/placebo omalizumab; rush IT with six injections over 3–5 hours with short ragweed extract (ALK-Abelló), 0.012 μg Amb a 1, up to 1.2 μg Amb a 1. Then increasing doses weekly for 4 weeks to 8 μg, followed by 8 weeks of maintenance doses of 12 μg (12 weeks total, including ragweed season)
Outcomes	SSs, AEs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	No details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/personnel	Low risk
Support for judgement	Placebo with increasing concentrations of histamine in order to maintain blinding
Incomplete outcome data	Low risk
Support for judgement	All patients accounted for. Intention-to-treat (ITT) analysis performed
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	Overall, 19.5% previously received SIT, slight imbalance between treatment arms

Ceuppens 2009[160]

Study design	DBPC RCT
Population symptoms	Rhinoconjunctivitis (no or mild asthma)
Treatment naive	Yes. No previous SIT
n, age	62 adults (aged 18–65 years); 31 active, 31 placebo
Intervention details	*Allergen:* birch Glutaraldehyde-modified birch pollen extract adsorbed on to $AlOH_3$ (purethal birch) – 500 µg extract/ml; 52 µg Bet v1 content/ml. Weekly induction (0.05, 0.1, 0.2, 0.3, 0.4 and 0.5 ml); three fortnightly doses of 0.5 ml; maintenance dose 0.5 ml at monthly interval for total of 18–22 months
Outcomes	SMSs, AEs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	No details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/personnel	Low risk
Support for judgement	'Placebo preparations injected subcutaneously'
Incomplete outcome data	Low risk
Support for judgement	Dropouts (4/62; three in active group, one in placebo group) not included in results
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Low risk
Support for judgement	Patients all treatment naive

Chakraborty 2006[30]

Study design	DBPC RCT
Population symptoms	Rhinoconjunctivitis or allergic asthma or both
Treatment naive	Yes. No previous SIT
n, age	35 patients (aged 20–59 years); 18 active, 17 placebo
Intervention details	*Allergen:* date sugar palm Standardised allergen extract *Phoenix sylvestris* (date sugar palm); weekly induction phase for 24 weeks from 0.05 µg to 0.5 µg Fr IIa (fraction 11a of *P. sylvestris*); maintenance phase for 18 months at 2-weekly intervals with 0.5–1 µg Fr IIa. Dose reduced 20–40% in symptomatic patients during pollen season
Outcomes	SMSs, global measure of overall severity
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	No details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/personnel	Low risk
Support for judgement	'Both the subjects and the administering personnel were blinded as to the composition of the injection vials'
Incomplete outcome data	Low risk
Support for judgement	All patients completed the study
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Low risk
Support for judgement	History of IT an exclusion criterion

Charpin 2007[142]

Study design	DBPC RCT
Population symptoms	Rhinoconjunctivitis (possibly associated with moderate asthma)
Treatment naive	Yes. No previous SIT
n, age	40 adults (aged 24–66 years); 22 active, 18 placebo
Intervention details	*Allergen*: cypress Standardised *Juniperus ashei* (cypress) extract (Stallergènes); 54 µg Jun a1 major allergen/ml in 100-index of reactivity (IR) extract. Adsorbed on to $AlOH_3$. Induction phase fortnightly injections followed by maintenance phase at maximum tolerated dose for 15 months (frequency not reported), covering two pollen seasons. Maximum dose of Jun a1 injected was 16.2 µg
Outcomes	SMSs, AEs, QoL
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Computer-generated randomisation
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/personnel	Low risk
Support for judgement	Matched placebo containing histamine
Incomplete outcome data	Unclear risk
Support for judgement	Fairly high number of dropouts (8/22 active and 4/18 placebo); similar reasons for dropout. Not included in 'intention-to-treat (ITT) population'
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Low risk
Support for judgement	All patients were treatment naive

Colas 2006[143]

Study design	DBPC RCT
Population symptoms	Allergic rhinoconjunctivitis with or without asthma
Treatment naive	Unclear, but no IT during last 4 years
n, age	63 adults (aged 18–50 years, mean 33 years); 41 active, 19 placebo
Intervention details	*Allergen*: Russian thistle Depigmented and glutaraldehyde polymerised extract of *S. kali* adsorbed to $AlOH_3$. Cluster schedule: first day 0.1, 0.25 and 0.5 ml × 45-μg extract/ml; 1 week later, 0.1, 0.25 and 0.5 ml × 450 μg/ml; then, starting 1 month later, one injection per month totalling 12 maintenance doses 0.5 ml × 450 μg/ml. Cumulative dose of Sal k 1 during trial was 597.65 μg
Outcomes	SSs, MSs, QoL, AEs, global assessment of health
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	No details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/personnel	Low risk
Support for judgement	'The placebo contained the identical solution as the experimental product, but without active ingredient; the presentation and dosage schedules were identical'
Incomplete outcome data	Low risk
Support for judgement	3/63 patients (two active, one placebo) dropped out prior to pollen season and not due to AEs; not included in analyses
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	No SIT in previous 4 years, but previous history unknown

Creticos 2006[144]

Study design	DBPC RCT
Population symptoms	AR
Treatment naive	Unclear. Exclusion criteria stated that no IT within last 5 years, but 20% were allowed to have had treatment >5 years ago
n, age	25 adults (aged 23–60 years); 14 active, 11 placebo
Intervention details	*Allergen*: ragweed Preseasonal, six injections at weekly intervals, with dose from 0.06 to 12.0 μg AIC (Amb a 1-immunostimulatory oligodeoxyribonucleotide conjugate)
Outcomes	SSs, MSs, rhinitis-VAS, QoL, AEs (all listed as secondary outcomes)
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Random block design provided by Immune Tolerance Network statistical and clinical coordinating centre
Allocation concealment	Low risk
Support for judgement	Blinded coordinator used internet system to receive blinded treatment code
Blinding of participants/personnel	Low risk
Support for judgement	Full details of blinding given in a web appendix
Incomplete outcome data	High risk
Support for judgement	6/14 (active) and 9/11 (placebo) completed year 2; most analyses used only those that had completed. Also used subgroups who reached target dose in analysis
Free of selective reporting	Unclear risk
Support for judgement	All outcomes listed in methodology accounted for in results, although not very detailed. Some further information in web appendix
Free of other bias?	Unclear risk
Support for judgement	No SIT in previous 5 years, but some patients may have had previous SIT

DuBuske 2011[145]

Study design	DBPC RCT
Population symptoms	Moderate to severe AR and/or conjunctivitis
Treatment naive	Excluded if previous treatment unless >3 years ago and with initial success but subsequent symptom recurrence
n, age	1028 adults (aged 18–59 years); 514 active, 514 placebo
Intervention details	*Allergen*: Thirteen-grass mix Grass MATA monophosphoryl lipid (MPL), Pollinex Quattro, Pollinex Complete; Allergy Therapeutics UK. Ultra-short course SCIT – four increasing dose injections [300, 800, 2000, 2000 standardised units (SU)] 13-grass-pollen allergoid mixture in L-tyrosine depot plus 50 μg MPL. Given at approximately weekly intervals pre-season
Outcomes	SMSs, AEs
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Interactive voice randomisation system. Performed in blocks at study and site level
Allocation concealment	Low risk
Support for judgement	Interactive voice randomisation system
Blinding of participants/personnel	Low risk
Support for judgement	Placebo appeared identical apart from active ingredient
Incomplete outcome data	Low risk
Support for judgement	Intention-to-treat (ITT) analysis performed for primary efficacy analysis. Missing data imputed using matched-pair technique. Similar numbers dropped out in both treatment arms
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Low risk
Support for judgement	Excluded if previous treatment unless >3 years ago and with initial success but subsequent symptom recurrence

Francis 2008[146]

Study design	DBPC RCT
Population symptoms	Moderate to severe AR with poor symptom control
Treatment naive	No details
n, age	18 adults (mean age between 30 and 37 years); 12 active, 6 placebo
Intervention details	*Allergen*: timothy grass Modified cluster regimen: weekly visits for 2 months, with two injections per visit in increasing dosage from 100 to 100,000 standardised quality units (SQ-Us) of timothy grass pollen (whole extract, Alutard SQ, ALK-Abelló). Maintenance dose monthly up to 1 year of 1 ml 100,000 SQ-U (20 µg Phl p5) but reduced by 40% z1 during pollen season
Outcomes	Overall clinical assessment, AEs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	No details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/personnel	Low risk
Support for judgement	Placebo with histamine and identical in appearance
Incomplete outcome data	Low risk
Support for judgement	Appears that all participants included in analysis
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	SIT history not reported

Hoiby 2010[148]

Study design	DBPC RCT
Population symptoms	Rhinoconjunctivitis with or without allergic asthma
Treatment naive	No details
n, age	61 adults, adolescents and children (51/5/5, respectively; aged 7–69 years); active 31, placebo 30
Intervention details	*Allergen*: birch Depigoid (Laboratorios LETI SI) standardised depigmented, glutaraldehyde-polymerised *Betula alba* adsorbed on to $AlHO_3$. Updosing at 7-day intervals: 0.2 ml 100 depigmented, glutaraldehyde-polymerised pollen (DPP)/ml, 0.5 ml 100 DPP/ml, 0.2 ml 1000 DPP/ml, 0.5 ml 1000 DPP/ml; maintenance dose 0.5 ml 10,000 DPP/ml every 6 weeks for 18 months; maintenance dose corresponded to 30 μg Bet v 1 before polymerisation
Outcomes	SMSs, AEs, QoL
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Computer-generated randomisation list
Allocation concealment	Unclear risk
Support for judgement	'Within study centres patients were allocated to the treatment in ascending order'
Blinding of participants/personnel	Low risk
Support for judgement	'No visible difference between placebo and Depigoid® vials.' No histamine, but very few reactions in total so unlikely to have interfered with blinding
Incomplete outcome data	Unclear risk
Support for judgement	A 'modified' intention-to-treat (ITT) population was used excluding patients who did not reach maintenance dose, those who did not receive at least one dose during 2006 pollen season and those who did not adhere to study protocol. One patient unaccounted for. Primary analysis conducted on 45/61 patients. All 61 patients accounted for in safety results
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	SIT history not reported

Kettner 2007[149] (abstract only)

Study design	DBPC RCT
Population symptoms	Rhinoconjunctivitis with or without asthma
Treatment naive	No details
n, age	211 patients (age range not stated); 108 active, 103 placebo
Intervention details	*Allergen*: birch rBet v 1-FV recombinant birch extract, dosage increased to 80 µg then maintained 1.5 years (frequency of injections not stated)
Outcomes	SMSs, AEs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	No details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/personnel	Unclear risk
Support for judgement	No details
Incomplete outcome data	Unclear risk
Support for judgement	Results reported for 'full analysis set' only
Free of selective reporting	Unclear risk
Support for judgement	Full methodology not reported, so unclear how many outcome investigated
Free of other bias?	Unclear risk
Support for judgement	SIT history not reported

Klimek 2010[150] (abstract only)

Study design	DBPC RCT
Population symptoms	No details
Symptoms	Allergic rhinoconjunctivitis with or without asthma
Treatment naive	No details
n, age	148 patients (age range not stated); 112 active, 36 placebo
Intervention details	*Allergen*: grasses and rye Coseasonal. Updosing with six injections up to 10,000 SQ-U (Alutard SQ grasses and rye, ALK-Abelló) with 1–3 injection intervals, then two injections of 10,000 SQ-U after 14 and 28 days
Outcomes	AEs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	No details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/personnel	Unclear risk
Support for judgement	No details
Incomplete outcome data	Unclear risk
Support for judgement	No details
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	SIT history not reported

Kuna 2011[152]

Study design	DBPC RCT
Population symptoms	Rhinoconjunctivitis with or without asthma
Treatment naive	Yes. No previous IT
n, age	50 children and adolescents (aged 5–18); active 30, placebo 20
Intervention details	*Allergen*: *Alternaria* $AlOH_3$-adsorbed, standardised *A. alternata* extract 100% (8 μg/ml Alt a 1 in maintenance dose) (Allergopharma) – updosing: 14 injections weekly or fortnightly. Maintenance dose: 1 ml 35,000 therapeutic units (TUs)/ml or highest tolerated dose every 4–6 weeks for up to 3 years
Outcomes	SMSs, AEs, QoL
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Computer-generated random number tables
Allocation concealment	Low risk
Support for judgement	Code concealed by manufacturer
Blinding of participants/ personnel	Low risk
Support for judgement	Placebo containing histamine indistinguishable from active treatment. All personnel at the study site were blinded
Incomplete outcome data	Unclear risk
Support for judgement	Dropouts = 4/30 active and 1/20 placebo. Reason for dropout was difficulties with timings of study for all. Not stated whether 'intention to treat (ITT)' or other
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Low risk
Support for judgement	No previous SIT

Ljorring 2009[153] (abstract only)

Study design	DBPC RCT
Population symptoms	Grass-allergic patients. No further details
Treatment naive	No details
n, age	162 patients. Age and allocation not reported
Intervention details	*Allergen*: grass Alutard SQ® grass, 100,000 SQ-U (ALK-Abelló); 1 year. No further details on treatment schedule
Outcomes	SMSs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	No details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/ personnel	Unclear risk
Support for judgement	No details
Incomplete outcome data	Unclear risk
Support for judgement	Numbers in analysis not reported
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	SIT history not reported

Pauli 2008[154]

Study design	DBPC RCT
Population symptoms	Rhinoconjunctivitis with or without asthma
Treatment naive	Yes. No previous IT
n, age	*n* = 147 (aged 18–50 years); active 98 (three groups), placebo 36
Intervention details	*Allergen*: birch One of three $AlOH_3$-adsorbed extracts: birch pollen extract, natural Bet v 1, recombinant Bet v 1, standardised for Bet v 1 concentration (Stallergènes). Build-up starting 6 months before pollen season by weekly injections from 0.1 ml of 0.5 µg/ml, increasing weekly to 0.3 ml of 50 µg/ml or maximum tolerated dose. Maintenance dose reached at least 7 weeks before pollen season was 15 µg Bet v 1 then given monthly for 2 years
Outcomes	SSs, MSs, AEs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	'Minimisation method considering symptom severity and degree of birch sensitisation'
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding	Low risk
Support for judgement	Placebo containing histamine to maintain blinding
Incomplete outcome data	Low risk
Support for judgement	Between 24% and 27% withdrew from each arm of the four groups, none for AEs. Intention-to-treat (ITT) analysis performed where possible
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Low risk
Support for judgement	Previous SIT considered major protocol violation (*n* = 1)

Pfaar 2010[155]

Study design	DBPC RCT
Population symptoms	Rhinoconjunctivitis with or without asthma
Treatment naive	No details
n, age	184 adults (aged 18–65 years, mean 38 years); 137 active, 47 placebo
Intervention details	*Allergen*: birch, hazel and alder Depigoid® (Laboratorios LETI) standardised depigmented, glutaraldehyde-polymerised tree pollen extract (33% *Corylus avellana*, 33% *Alnus glutinosa*, 34% *B. alba*) adsorbed on to $AlOH_3$. Updosing at 7-day intervals: 0.2 ml 100 DPP/ml, 0.5 ml 100 DPP/ml, 0.2 ml 1000 DPP/ml, 0.5 ml 1000 DPP/ml; maintenance dose 0.5 ml 10,000 DPP/ml every 6 weeks for 18 months; maintenance dose corresponded to 11.0 µg Bet v 1 before polymerisation
Outcomes	SSs, MSs, SMSs, AEs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	No details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/ personnel	Low risk
Support for judgement	'Placebo medication was identical in appearance'
Incomplete outcome data	High risk
Support for judgement	Primary outcomes analysed on intention-to-treat (ITT) and per protocol basis. Secondary outcomes (including SSs and MSs) on per protocol basis only
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear
Support for judgement	Previous SIT history not reported

Powell 2007[156]

Further report of Frew 2006[161] included in Cochrane review, see reported as abstract Krishna 2006.[151]

Study design	DBPC RCT
Population symptoms	Rhinoconjunctivitis inadequately controlled with medication in previous years
Treatment naive	No SIT in previous 5 years
n, age	410 adults (18–60 years, mean 38 years); 203 high dose, 104 medium dose, 103 placebo
Intervention details	*Allergen*: timothy grass Alutard SQ® *P. pratense* 10,000 SQ-U (2 μg Phl p 5) or 100,000 SQ-U (20 μg Phl p 5) (ALK-Abelló); updosing 15 injections (two/visit) over 8 weeks; maintenance phase every 6 ± 2 weeks for approximately 12 months
Outcomes	QoL
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Generated by ALK-Abelló
Allocation concealment	Low risk
Support for judgement	ALK-Abelló maintained sequence; investigators allocated sequential randomisation number from sequence
Blinding of participants/ personnel	Low risk
Support for judgement	'Placebo and active medication were indistinguishable'
Incomplete outcome data	Low risk
Support for judgement	387/410 completed study (169, 87, 91). All randomised subjects included in analysis [intention to treat (ITT)]
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results (note: not all outcomes reported in this publication)
Free of other bias?	Unclear risk
Support for judgement	No SIT in previous 5 years, but unclear if ever treated with SIT

Sahin 2011[157] (abstract only)

Study design	DBPC RCT
Population symptoms	AR and/or conjunctivitis
Treatment naive	No details
n, age	121 adults (aged 18–60 years), 61 active, 59 placebo (1 dropout)
Intervention details	*Allergen*: grass and rye Highly polymerised allergen extract mixture of grass and rye pollen (Clustoid), two injections/day for initiation phase (cluster schedule) then once per month for maintenance (length of treatment not clear)
Outcomes	SSs, MSs, global evaluation by patients, AEs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	No details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/personnel	Unclear risk
Support for judgement	No details
Incomplete outcome data	Unclear risk
Support for judgement	No details
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	Previous SIT history not reported

Ventura 2009[158]

Note: this study has as treatment arms SLIT, SCIT and placebo; there is no direct comparison between SLIT and SCIT.

Study design	DBPC RCT
Population symptoms	Allergic rhinoconjunctivitis
Treatment naive	Unclear (not in treatment at time of study)
n, age	*n* = 20 adults (18–55 years); active *n* = 10, placebo *n* = 10
Intervention details	*Allergen*: cypress 300 IR/ml *J. ashei* extract adsorbed on to aluminium hydroxide phosphate (StaloralR, Stallergènes Sa). Jun a1 MAC 76 μg/ml of the 100-index of reactivity (IR) allergen extract; daily allergen dose in maintenance of 228 μg/ml Twelve-week induction phase with weekly injections and maintenance phase of 9 months with monthly injections
Outcomes	SSs
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Computer-generated code
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding participants/ personnel	Low risk
Support for judgement	The placebo had the same appearance and taste as SLIT. No further details
Incomplete outcome data	Low risk
Support for judgement	Data for all 20 patients reported
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	SIT history of patients not reported

Sublingual immunotherapy compared with placebo

Blaiss 2011[189]

Study design	DBPC RCT
Population symptoms	Moderate to severe allergic rhinoconjunctivitis; 26% history of asthma, 89% multisensitised
Treatment naive	Unclear
n, age	*n* = 345, active *n* = 149, placebo *n* = 158 Children aged 5–17 years; mean age 12.3 years
Intervention details	*Allergen*: timothy grass Once-daily sublingual *P. pratense* grass AIT (allergen immunotherapy tablet) 75,000 SQ-T, 15 µg Phl p5 (Schering Plough) started 16 weeks before pollen season and continued throughout season (23 weeks total)
Outcomes	SMSs, SSs, MSs, QoL, AEs
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	External computer-generated randomisation; stratified by study site and asthma status
Allocation concealment	Low risk
Support for judgement	External randomisation group using an interactive voice response system
Blinding of participants/ personnel	Low risk
Support for judgement	'Subjects and investigators were blinded to treatment by using a matching placebo in identical packaging to the grass AIT treatment. Blinding was maintained until data were locked'
Incomplete outcome data	Unclear risk
Support for judgement	345 randomised; intention-to-treat (ITT) population *n* = 307 (all randomised patients with at least one data entry). Missing data not imputed. Discontinuations 14.6% intervention group and 6.5% placebo group
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear
Support for judgement	SIT history of patients not reported

Cortellini 2010[190]

Study design	DBPC RCT
Population symptoms	Moderate/severe persistent rhinitis with or without intermittent asthma
Treatment naive	Yes
n, age	*n* = 27, adolescents and adults (age 14–42); active *n* = 15, placebo *n* = 12
Intervention details	*Allergen*: *Alternaria* Build-up phase lasted 15 days, starting with one drop from 100-Ru vial, increasing daily by one drop, up to five drops. Repeated with 1000-RU (radioallergosorbent test units) vial and 10,000-RU vial until maintenance dose reached. Maintenance dose was five drops of glycerinated extract, 10,000 RU/ml Alt a 1 (1.5 µg/ml) (Anallergo) every other day for 10 months (January to October)
Outcomes	SSs, MSs, AEs
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Computer-generated randomisation list
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/ personnel	Low risk
Support for judgement	'The placebo was indistinguishable by taste and aspect from the active SLIT.' 'Blinding was maintained until the last patient had completed the study'
Incomplete outcome data	Low risk
Support for judgement	Analysis performed on per-protocol population, not 'intention to treat (ITT)' but only one dropout of 27 randomised
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Low risk
Support for judgement	No previous SIT

Didier 2011[25]

Preliminary results also in Didier 2010 abstract.[199]

Study design	DBPC RCT
Population symptoms	Rhinoconjunctivitis
Treatment naive	No details
n, age	*n* = 633, adults (18–50 years) 2 active (*n* = 207 in both groups), 1 placebo arm (*n* = 219)
Intervention details	*Allergen*: five-grass mix Daily 300-index of reactivity (IR) five-grass pollen tablet (Oralair): either 4 or 2 months' preseasonal treatment, then during the pollen season. Treatment over three consecutive pollen seasons
Outcomes	SSs (adjusted for rescue medication use), SMSs, individual symptoms scores, symptoms and medication-free days, QoL, AEs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	No details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/ personnel	Low risk
Support for judgement	The 2-month group received placebo during the time the 4-month group was receiving their active treatment to maintain blinding
Incomplete outcome data	Unclear risk
Support for judgement	All a patients analyses performed on patients who had at least one dose of investigational product and who had at least one measurement during the pollen season. Frequency of discontinuations was similar between the three groups. Dropouts due to AEs were more frequent in active treatment arms
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	SIT history of patients not reported

Durham 2011[32] (GT–08 trial), Durham 2010,[200] Dahl 2008[270] and Dahl 2006[93]

Note: This study was identified in the Cochrane review; we report on more recent publications with longer follow-up data.

Study design	DBPC RCT
Population symptoms	Significant allergic rhinoconjunctivitis
Treatment naive	Unclear (but no grass pollen SIT within last 10 years or any other allergen within last 5 years)
n, age	$n = 634$ (mean age around 34 ± 10 years)
Intervention details	*Allergen*: timothy grass Grazax® [*P. pratense* 75,000 SQ-T (standardised quality units tablet)/2800 BAU (bioequivalent allergy unit) (ALK-Abelló)]. Treatment started 16 weeks before pollen season and continued daily for 3 years (approximately 15 μg) then 2-year follow-up
Outcomes	SMSs, AEs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	Stated only that patients were randomised but no further details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/ personnel	Low risk
Support for judgement	Placebo tablet similar in taste, smell and appearance. All personnel associated with the study remained blinded
Incomplete outcome data	Unclear risk
Support for judgement	Analyses for all randomised patients where data were available. No imputation of missing data. Similar completion rates at years 1 and 2, and similar reasons for withdrawals. Further loss to follow-up after year 1, as some sites closed and some patients chose not to participate
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	Patients may have had previous SIT (but not in last 10/5 years for grass or other allergen SIT, respectively)

Fujimura 2011[191]

Study design	DBPC RCT
Population symptoms	Moderate or severe symptoms of pollinosis
Treatment naive	Yes
n, age	*n* = 103 adults (age 16–73); active *n* = 58, placebo *n* = 45
Intervention details	*Allergen*: Japanese cedar Standardised Japanese cedar pollen extract (Torii Pharmaceuticals). Updosing from 0.2 ml of 20 Japanese Allergy Unit (JAU)/ml, increasing by 0.2 ml/day for 5 days per week. Maintenance dose was 1.0 ml of 2000 JAU/ml given once weekly over 2 years (two pollen seasons)
Outcomes	SMSs, AEs, QoL
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Random numbers table generated by personnel not directly involved in study
Allocation concealment	Low risk
Support for judgement	Allocation by personnel not directly involved in study
Blinding of participants/ personnel	Unclear risk
Support for judgement	Stated that study was double blind for two seasons; follow-up season was single blind
Incomplete outcome data	Low-risk SMSs, high-risk-QoL data
Support for judgement	Both intention-to-treat (ITT) and on-treatment analysis performed but only on-treatment analysis results presented for QoL data
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Yes
Support for judgement	No previous SIT

Horak 2009[202]

Further publication of study reported in Didier 2007[24] (included in Cochrane review). Horak 2009[202] includes further data on QoL not reported in Didier 2007.[24]

Study design	DBPC RCT
Population symptoms	Moderate to severe allergic rhinoconjunctivitis
Treatment naive	Yes
n, age	*n* = 628 adults (aged 18–45 years); four groups: *n* = 157 given 100 IR, *n* = 155 given 300 IR, *n* = 160 given 500 IR, *n* = 156 given placebo
Intervention details	*Allergen*: five-grass mix 100-index of reactivity (IR), 300-IR or 500-IR standardised lyophilised five-grass pollen tablet (300 IR/ml approximately = 25 mg/ml allergen extracts). Daily tablet. Five days' titration period from 100 IR to assigned dose. Maintenance approximately 4 months prior to pollen season and throughout pollen the season
Outcomes	SSs, QoL, medication-free days, AEs
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Computer-generated randomisation list
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/ personnel	Low risk
Support for judgement	Double blind; blinding maintained during induction phase by giving all patients two tables (presumably using placebo to make up difference), with one tablet from day 6
Incomplete outcome data	Unclear risk
Support for judgement	Only patients with complete data sets included in intention-to-treat (ITT) population (569/628, 91%). Discontinuations due to AE only in active treatment groups. Overall, slightly more withdrawals from active groups
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for; note that clinical outcomes reported in Didier 2007 (in Cochrane review). Additional data in this publication only QoL
Free of other bias?	Yes
Support for judgement	All patients treatment naive

Nelson 2011[192]

Study design	DBPC RCT
Population symptoms	Allergic rhinoconjunctivitis with or without asthma
Treatment naive	Unclear (but stated that no SIT in last 5 years)
n, age	*n* = 438 adults (18–65); active *n* = 213, placebo *n* = 207
Intervention details	*Allergen*: timothy grass Once-daily 2800 BAU standardised *P. pratense*, 75,000 SQ-T, approximately 15 µg Phl p5 (Schering Plough), starting 16 weeks preseasonal plus coseasonal, throughout the pollen season. No build-up dosing
Outcomes	SSs, MSs, SMSs, QoL, AEs
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Computer-generated randomisation schedule
Allocation concealment	Low risk
Support for judgement	External randomisation group using an interactive voice-response system
Blinding of participants/ personnel	Low risk
Support for judgement	'Double-blinding (subjects and investigators) was established by use of a matching placebo tablet.' 'Blinding was maintained until the database was locked'
Incomplete outcome data	Low risk
Support for judgement	391/439 with at least one post-treatment diary entry analysed. Similar numbers and reasons for discontinuation in both treatment arms
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results.
Free of other bias?	Unclear risk
Support for judgement	Some patients may have had previous SIT (but no SIT in previous 5 years)

Panizo 2010[193]

Study design	DBPC RCT
Population symptoms	Rhinitis with or without asthma
Treatment naive	Unclear (but not in last 5 years)
Participant details	*n* = 78 adults (18–65); active = 52, placebo *n* = 26
Intervention details	*Allergen*: timothy grass Daily Grazax® 75,000 SQ-T for at least 8 weeks preseasonal, plus coseasonal, throughout the season
Outcomes	AEs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	Stated that patients were randomised but no further details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/ personnel	Low risk
Support for judgement	'Placebo similar in taste, smell and physical appearance'
Incomplete outcome data	Low risk (for AE outcome)
Support for judgement	All patients included in safety analysis
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	Some patients may have had previous SIT but no SIT in previous 5 years

Pfaar 2011[194]

Study design	DBPC RCT
Population symptoms	Seasonal allergy symptoms
Treatment naive	Unclear (but stated that no SIT in last 3 years)
n, age	*n* = 80 adults (18–65 years); active *n* = 64 (four groups with different doses, *n* = 16 in each), placebo *n* = 16 (four in each group)
Intervention details	*Allergen*: timothy grass Extract of 12 mixed-grass pollens (Allergy Therapeutics, B2 grass mixture), standardised by major allergen, *P. pratense* Phl p 1 ± adjuvant MPL • Group 1: 9.45 µg *P. pratense* • Group 2: 9.45 µg *P. pratense* + 21 µg MPL (monophosphoryl lipid A) • Group 3: 9.5 µg *P. pratense* + 52.5 µg MPL • Group 4: 19 µg *P. pratense* + 52.5 µg MPL Eight-week treatment period; periods varied for the four groups (preseasonal for three, postseasonal for one)
Outcomes	AEs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	Patients were described as randomised, but no further details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/ personnel	Low risk
Support for judgement	'Placebo solutions contained buffered glycerine solution and flavouring to match the active SLIT'
Incomplete outcome data	Low risk
Support for judgement	All subjects accounted for
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	Some patients may have had previous SIT (but no SIT in previous 3 years)

Reich 2011[195]

Study design: RCT	DBPC RCT
Objective diagnosis	Yes
Population symptoms	Moderate to severe rhinoconjunctivitis; 41% with history of asthma
Treatment naive	Unclear (but no SIT in last 5 years)
n, age	*n* = 276, active *n* = 219, placebo *n* = 57 Mean age 35 years
Intervention details	*Allergen*: timothy grass Once daily sublingual *P. pratense* grass AIT 75,000 SQ-T, 2800 BAU (Grazax®, ALK) for 8–10 weeks during pollen season
Outcomes	MSs, AEs, global evaluation
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Computer generated block randomisation. Randomisation list generated by trial-independent statistician
Allocation concealment	Low risk
Support for judgement	Sealed randomisation code envelopes. Patients assigned lowest available randomisation numbers
Blinding of participants/ personnel	Low risk
Support for judgement	'Investigators and patients were blinded throughout the trial.' Matching placebo with taste, smell and appearance similar to the active extract. Drug codes broken only after completion of trial
Incomplete outcome data	Low risk
Support for judgement	All randomised patients included in analyses
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	History of SIT in previous 5 years an exclusion criterion, but unclear if any patients had ever received SIT

Skoner 2010[196]

Study design	DBPC RCT
Population symptoms	Moderate to severe allergic rhinoconjunctivitis
Treatment naive	Unclear (but no SIT for ragweed in last 3 years)
n, age	*n* = 115 adults (aged 18–50 years); *n* = 39 medium dose, *n* = 36 high dose, *n* = 40 placebo
Intervention details	*Allergen*: ragweed Preliminary dosing at first visit: up to four incremental doses of short ragweed pollen extract standardised for Amb a 1 content (medium-dose group 0, 0.48, 1.7 and 4.8 μg Amb a 1; high-dose group 0, 4.8, 17 and 48 μg extract). Maximum tolerated dose used. Daily dose of maintenance dose. Mean maximum tolerated dose was 3.21 (1.64) μg and 30.54 (16.14) μg in medium- and high-dose groups. Average cumulative dose 498 (185) μg/ml and 4941 (1487) μg/ml Pre-and coseasonal treatment. Average duration 17 weeks (±3)
Outcomes	SMSs, AEs
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Central block randomisation with stratification based on asthma diagnosis
Allocation concealment	Low risk
Support for judgement	Sequentially numbered containers, pharmacy control and central randomisation
Blinding of participants/ personnel	Low risk
Support for judgement	Placebo masked with colouring
Incomplete outcome data	Unclear risk
Support for judgement	Patients with missing data excluded from analysis. Data for 90% of patients. Similar proportions missing from different groups, but no reasons stated
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for
Free of other bias?	Unclear risk
Support for judgement	Some patients may have had previous SIT (but no SIT in previous 3 years)

Ventura 2009[158]

Note: this study has as treatment arms SLIT, SCIT and placebo; there is no direct comparison between SLIT and SCIT.

Study design	DBPC RCT
Population symptoms	Allergic rhinoconjunctivitis
Treatment naive	Unclear (not in treatment at time of study)
n, age	*n* = 20 adults (18–55 years); active *n* = 10, placebo *n* = 10
Intervention details	*Allergen*: cypress 300 IR/ml *J. ashei* extract as glycerol saline solution (StaloralR). Daily allergen dose of 228 μg/ml 30-day induction, 11 months' maintenance; drops self-administered three times per week
Outcomes	SSs
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Computer-generated code
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/ personnel	Low risk
Support for judgement	The placebo had the same appearance and taste as SLIT
Incomplete outcome data	Low risk
Support for judgement	Data for all 20 patients reported
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	SIT history of patients not reported

Voltolini 2010[197]

Study design	DBPC RCT
Population symptoms	Moderate/severe persistent rhinitis and slight intermittent to moderate asthma
Treatment naive	No details
n, age	*n* = 24 adults (mean ages 44 and 40 years in active and placebo groups, respectively); active *n* = 14, placebo *n* = 10
Intervention details	*Allergen*: birch Allergen extract of birch at 10 IR/ml and 300 IR/ml (Stallergènes) Build-up from 10 index of reactivity (IR) over 11 days to maintenance dose of 300 IR then daily for 4 months, repeated over two consecutive years
Outcomes	SSs, MSs, asthma days/severity, AEs
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Computer-generated randomisation list
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/ personnel	Low risk
Support for judgement	'Placebo vials matched the active treatment in colour and flavour'
Incomplete outcome data	Low risk
Support for judgement	Analysis of completers only, but only one patient lost to follow-up in each group (reason not stated)
Free of selective reporting	High risk
Support for judgement	MSs measured but not reported. Treatment over two seasons but data reported after 1 year only. SSs recorded for three symptoms but reported for two only
Free of other bias?	Unclear risk
Support for judgement	SIT history of patients not reported

Subcutaneous immunotherapy compared with sublingual immunotherapy

Khinchi 2004[210]

Study design	DBPC RCT
Population symptoms	Rhinoconjunctivitis uncontrolled by conventional pharmacotherapy
Treatment naive	No SIT within last 5 years
n, age	71 adults (20–58 years); 23 SLIT, 24 SCIT and 15 placebo
Intervention details	*Allergen*: birch Birch pollen extract standardised in terms of major allergen Bet v 1 administered as glycerine-saline solution (SLIT, Staloral®) or adsorbed on calcium phosphate (SCIT, Phostal®) *SLIT*: 30-day induction phase, maintenance phase 21–23 months. Drops every other day held under tongue for 2 minutes. Dose between 0.0164 and 49.2 μg *SCIT*: 12-week induction phase (weekly injections) with 0.0164 μg, monthly maintenance phase 3.28 μg
Outcomes	SSs, MSs, QoL, AEs
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Allocation by minimisation
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/ personnel	Low risk
Support for judgement	'All study personnel and participants were blinded to treatment assignment for the 2-year duration of treatment in the study.' Placebo preparations included caramelised sugar for SLIT to ensure identical visual appearance and histamine dihydrochloride for injections to ensure induction of local reactions for SCIT
Incomplete outcome data	Unclear risk
Support for judgement	Similar numbers of withdrawals in the three groups. Only patients completing first treatment season included in statistical calculations. Results not reported in a way that is consistent with most other studies
Free of selective reporting	Unclear risk
Support for judgement	All outcomes listed in methodology accounted for in results. Second season is not included in the evaluation of efficacy (owing to low pollen counts)
Free of other bias?	Unclear risk
Support for judgement	No SIT in previous 5 years but previous treatment history unknown