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Supplementary information

Allergen immunotherapy: past, present and future

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SUPPL. TABLE 1. RANDOMIZED CONTROLLED, CLINICAL TRIALS SHOWING LONG-TERM EFFICACY OF ALLERGEN IMMUNOTHERAPY FOR ALLERGIC RHINITIS

AUTHOR [REF], YEAR, COUNTRY	SCIT	SLIT	PLACEBO	PATIENTS' CHARACTERISTICS	ALLERGEN	UNITS	MAINTENANCE DOSE AND FREQUENCY	TOTAL STUDY DURATION (Y)	AIT DURATION (Y)	YEARS AFTER CESSATION	YEARS BLINDED AFTER CESSATION	OUTCOME AT THE END OF THE TREATMENT PERIOD	OUTCOME AT THE END OF THE OFF-TREATMENT OBSERVATION PERIOD
DURHAM [1] 1999 UNITED KINGDOM	21	-	19	**Age:** 19-52 years **Dx**: Severe SAR associated with grass pollen **Asthma**: Patients with chronic asthma were excluded	*Phleum pratense*	SQ-U	**Dose**: 100,000 SQ-U (20 µg of *Phl p* 5) **Freq**: Monthly	7	Up to 7	3	3	**TSS** Year 4 **Maintenance group:** AUC 626 (70–3528) **Discontinuation group:** 798 (0-2289) **No immunotherapy:** 2615 (609–10,416)	**TSS** Year 7 **Maintenance group:** AUC 921 (0–2299) **Discontinuation group:** 504 (45–4567) **No immunotherapy:** 2863 (774–12,033)
JACOBSEN [2] 2007 DENMARK	103	-	102*	**Age:** 6 to 14 years **Dx**: Grass and/or birch-pollen induced ARC **Asthma**: 0%	*Phleum pratense* and/or *birch pollen Betula verrucosa*	SQ-U	**Dose:** 100,000 SQ [20 µg of Phl p 5 (grass) / 12 µg of Bet v 1 (birch)] **Freq**: 6 weeks (± 2 weeks)	10	3	7	0	**Rhinitis VAS –** Year 3 Active vs Control p <0.01	**Rhinitis VAS –** Year 10 Active vs Control -19.9 (A) vs -11.5 (C) mm p <0.05
BOZEK [3] 2020 POLAND	33	-	29	**Age:** 65 to 75 years **Dx**: Moderate or severe intermittent allergic rhinitis **Asthma**: 0%	Grass mix	AUM	**Dose**: 13.1 µg *Phl p* 5 **Freq**: Every 2 weeks **Schedule**: Pre-seasonal (Jan-Apr)	6	3	3	3	**CSMS Year 3** Baseline: 2.15 ± 1.04 SCIT: 1.13 ± 0.73 (p=0.03) Baseline: 2.31 ± 1.13 Placebo: 2.08 ± 0.65 (p=0.28)	**CSMS Year 6** SCIT: 1.41 ± 0.72 Placebo: 2.41 ± 1.11
DURHAM [4] 2012 UNITED KINGDOM	-	316	318	**Age:** 18-65 years **Dx**: 2-year history of grass-pollen induced ARC **Asthma**: Patients with *perennial* asthma were excluded.	*Phleum pratense*	SQ-T	**Dose**: 75,000 SQ-T (15 µg *Phl p* 5) **Freq**: Daily	5	3	2	2	**RCSS** Reduction relative to placebo **Season 3** -29% (p <0.001)	**RCSS** Reduction relative to placebo **Follow-up season 5** -25% (p <0.004)
DIDIER [5] 2015 FRANCE	-	207 **(2M)** 207 **(4M)**	219	**Age:** 18-50 years **Dx**: 2-year history of grass-pollen induced ARC **Asthma**: 11-16%	5 grasses mix	IR	**Dose**: 300 IR (25 µg group 5 major allergen) **Freq**: Daily	5	3	2	2	**DRTSS** Reduction relative to placebo [4M] **Year 3** -38.5% (p <0.0001)	**DRTSS** Reduction relative to placebo [4M] **Follow-up year 5** -23.5%

OTT [6] 2009 GERMANY	-	142	67	**Age**: 7-64 years **Dx**: ARC associated with grass pollen **Asthma**: 11-14%	5 grasses mix	IR	**Dose**: 300 IR/mL (21 µg/mL of *Phl p* 5) **Freq**: Daily	4	3	1	1	**SLIT** CHANGE **Season 3** -1.02±4.54 p = 0.0004	**PLACEBO** CHANGE **Season 3** +1.32±4.40	**SLIT** CHANGE **Follow-up** -1.94±5.05 p = 0.015	**PLACEBO** CHANGE **Follow-up** -0.30±4.40
BERGMANN [7] 2014 GERMANY	-	169 **(500 IR)** 170 **(300 IR)**	170	**Age:** 18-50 years **Asthma**: 29-32%	*D pteronyssinus and D farinae*	IR	**Dose**: 300 IR or 500 IR (16 or 28 µg *Der p* 1) **Freq**: Daily	2	1	1	1	**AAdSS - Year 1** **500IR:** −0.78 (−1.34 to −0.22) p = 0.0066, % −20.2 **300IR:** −0.69 (−1.25 to −0.14) p = 0.0150, %−17.9		**AAdSS - Year 2** **500IR: %** −19.1, p <0.05 **300IR: %** −17.0, p <0.05	
VALOVIRTA [8] 2018 FINLAND	-	398	414	**Age:** 5 to 12 years **Dx**: 2-year history of grass-pollen induced ARC **Asthma**: 0%	*Phleum pratense*	SQ-T	**Dose**: 75,000 SQ-T (15 µg *Phl p* 5) **Freq**: Daily	5	3	2	2	**ARC VAS score Year 3** -9.23 (5.7 - 12.8) -30%, p <0.001		**ARC VAS score Year 5** -5.8 (2.2 - 9.4), -23%, p = 0.002	
YONEKURA [9] 2021 JAPAN	-	2K: 260 5K: 264 10K:259	259	**Age:** 5 to 64 years **Dx**: ARC symptoms for 2 consecutive seasons **Asthma**:	Japanese cedar	JAU	**Dose**: 5,000 JAU **Freq**: Daily	5	3	2	2	**TNSMS** Reduction relative to placebo **Year 3** 3.04 (2.21 to 3.87) - 46.3% (36.6% to 54.8%) p <0.001		**TNSMS** Reduction relative to placebo **Year 5** 2.62 (1.58 to 3.66) -34.0% (22.4% to 44.1%) p <0.001	
SCADDING [10] 2017 UNITED KINGDOM	36	36	34	**Age:** 18 to 65 years **Dx**: Moderate to severe ARC **Asthma**: Mild asthma	*Phleum pratense*	SQ-T SQ-U	**Dose SCIT**: 100,000 SQ-U (20 µg of *Phl p* 5) **Freq**: Monthly **Dose SLIT**: 75,000 SQ-T (15 µg *Phl p* 5) **Freq**: Daily	3	2	1	1	**TNSS (**10-hour AUC) vs placebo NAC Year 2 **SLIT** −1.42 (−2.61 to −0.22) p = 0.02 **SCIT** −2.11 (−3.22 to −1.01) p < 0.001		**TNSS** (10-hour AUC) vs placebo NAC Year 3 **SLIT** −0.30 (−1.52 to 0.92) p = 0.62 **SCIT** −0.90 (−1.96 to 0.16) p = 0.10	

2M: two-month pre-coseasonal schedule; 4M: four-month pre-coseasonal schedule; AAdSS: average adjusted symptom score; AIT: allergen immunotherapy; ARC: allergic rhinoconjunctivitis; AU: allergy units; AUC: area under the curve; AUM: allergy unit milliequivalent; CSMS: combined symptom medication score; DCS: daily combined symptoms medication score; Dx: disease; IR: index of reactivity; JAU: Japanese allergy unit; NAC: nasal allergen challenge; PP: per protocol; RCSS: rhinoconjunctivitis symptom score; SAR: seasonal allergic rhinitis; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy; SQ-T: standardised quality units tablets; SQ-U: standardised quality units; TNSMS**:** total nasal symptom and medication scores; TNSS: total nasal symptom scores; TSS: total symptom scores; VAS: visual analogue scale.

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