

2

ALLERGEN IMMUNOTHERAPY FOR INSECT VENOM ALLERGY

A SYSTEMATIC REVIEW AND META-ANALYSIS

🌀 Supplementary materials 🌀

Sangeeta Dhama¹, Hadar Zaman², Eva-Maria Varga³, Gunter J Sturm^{4,5}, Antonella Muraro⁶, Cezmi A Akdis^{7,8}, Darío Antolín-Amérigo⁹, M Beatrice Bilò¹⁰, Danijela Bokanovic⁴, Moises A Calderon¹¹, Ewa Cichocka-Jarosz¹², Joanne NG Oude Elberink^{13,14}, Radoslaw Gawlik¹⁵, Thilo Jakob¹⁶, Mitja Kosnik¹⁷, Joanna Lange¹⁸, Ervin Mingomataj^{19,20}, Dimitris I Mitsias²¹, Holger Mosbech²², Markus Ollert²³, Oliver Pfaar^{24,25}, Constantinos Pitsios²⁶, Valerio Pravettoni²⁷, Graham Roberts^{28,29,30}, Franziska Ruëff³¹, Betül Ayşe Sin³², Miqdad Asaria³³, Gopal Netuveli³⁴, Aziz Sheikh³⁵

AFFILIATIONS

- ¹ Evidence-Based Health Care Ltd, Edinburgh, UK
- ² School of Pharmacy, University of Bradford, Bradford, UK
- ³ Department of Pediatric and Adolescent Medicine, Respiratory and Allergic Disease Division, Medical University of Graz
- ⁴ Department of Dermatology and Venerology, Medical University of Graz, Graz
- ⁵ Outpatient Allergy Clinic Reumannplatz, Vienna, Austria
- ⁶ Department of Women and Child Health, Food Allergy Referral Centre Veneto Region, Padua General University Hospital, Padua, Italy
- ⁷ Swiss Institute of Allergy and Asthma Research (SIAF), Switzerland Servicio de Enfermedades del Sistema Inmune-Alergia, University of Zurich, Zurich, Switzerland
- ⁸ Christine Kuhne–Center for Allergy Research and Education (CK-CARE), Davos, Switzerland
- ⁹ Universidad de Alcalá, Madrid, Spain
- ¹⁰ Allergy Unit, Department of Internal Medicine, University Hospital of Ancona, Ancona, Italy
- ¹¹ Section of Allergy and Clinical Immunology, Imperial College London, National Heart and Lung Institute, Royal Brompton Hospital, London, UK
- ¹² Department of Pediatrics, Jagiellonian University Medical College, Krakow, Poland
- ¹³ Department of Allergology and Internal Medicine, University of Groningen, University Medical Hospital Groningen
- ¹⁴ Groningen Research Center for Asthma and COPD (GRIAC), Groningen, The Netherlands
- ¹⁵ Department of Internal Medicine, Allergy and Clinical Immunology, Medical University of Silesia, Katowice, Poland
- ¹⁶ Department of Dermatology and Allergology, University Medical Center Gießen and Marburg (UKGM), Justus Liebig University Gießen, Gießen, Germany
- ¹⁷ Medical Faculty Ljubljana, University Clinic of Respiratory and Allergic Diseases Golnik, Golnik, Slovenia
- ¹⁸ Department of Pediatric Pneumonology and Allergy, Medical University of Warsaw, Warsaw, Poland
- ¹⁹ Department of Allergology and Clinical Immunology, Mother Theresa School of Medicine
- ²⁰ Department of Paraclinical Disciplines, Faculty of Technical Medical Sciences, Medicine University of Tirana, Tirana, Albania
- ²¹ Department of Allergy and Clinical Immunology, 2nd Pediatric Clinic, University of Athens, Athens, Greece
- ²² Allergy Clinic, Copenhagen University Hospital Gentofte, Gentofte, Denmark
- ²³ Department of Infection and Immunity, Luxembourg Institute of Health (LIH), Strassen, Luxembourg
- ²⁴ Department of Otorhinolaryngology, Head and Neck Surgery, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany
- ²⁵ Center for Rhinology and Allergology, Wiesbaden, Germany
- ²⁶ Medical School, University of Cyprus, Nicosia, Cyprus
- ²⁷ UOC Clinical Allergy and Immunology, IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
- ²⁸ The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport Isle of Wight
- ²⁹ NIHR Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust
- ³⁰ Faculty of Medicine, University of Southampton, Southampton, UK
- ³¹ Klinik und Poliklinik für Dermatologie und Allergologie, Klinikum der Universität München, Munich, Germany
- ³² Department of Pulmonary Diseases, Division of Immunology and Allergy, Faculty of Medicine, Ankara University, Ankara, Turkey
- ³³ Research Fellow Centre for Health Economics, University of York, UK
- ³⁴ Institute for Health and Human Development, University of East London, London
- ³⁵ Asthma UK Centre for Applied Research, Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, UK.
-

APPENDIX 2.1 SEARCH STRATEGY

Search strategy 1: MEDLINE, EMBASE

1	insect sting.mp. or exp insect sting/	29	subcutaneous immunotherapy.mp. or exp subcutaneous immunotherapy/
2	insect bite.mp. or exp insect bite/	30	(intradermal immunotherapy or intralymphatic immunotherapy).mp.
3	insect allergy.mp. or exp insect allergy/	31	specific immunotherapy.mp.
4	exp immediate type hypersensitivity/ or exp delayed hypersensitivity/ or exp hypersensitivity/ or hypersensitivity.mp.	32	exp systematic desensitization/ or exp desensitization/ or desensitization.mp.
5	hypersensitivity reaction.mp. or allergic reaction/	33	dose response.mp. or exp dose response/
6	anaphyla\$.mp.	34	hyposensitization.mp.
7	systemic anaphylaxis/ or exp anaphylaxis/ or anaphylaxis.mp.	35	or/21-34
8	exp allergy/ or allergy.mp.	36	intervention study.mp. or exp intervention study/
9	allergic.mp.	37	intervention studies.mp.
10	swelling.mp. or exp swelling/	38	(analytical stud* or experimental stud*).mp.
11	edema.mp. or exp edema/	39	exp "clinical trial (topic)" / or exp "controlled clinical trial (topic)" / or exp "randomized controlled trial (topic)" / or trial.mp. or exp controlled clinical trial/
12	systemic reaction.mp.	40	(uncontrolled trial or randomi?ed controlled trial or quasi-randomi?ed trial or non-randomi?ed trial).mp.
13	shock.mp. or anaphylactic shock/ or exp traumatic shock/ or exp shock/	41	placebos.mp. or exp placebo/
14	hives.mp. or exp urticaria/	42	random allocation.mp. or exp randomization/
15	laryngeal obstruction.mp. or exp larynx stenosis/	43	double blind procedure/
16	death.mp. or exp death/ or exp sudden death/	44	(double-blind or double blind).mp.
17	angioedema.mp.	45	(single-blind or single blind).mp.
18	airway obstruction.mp. or exp airway obstruction/	46	(triple-blind or triple blind).mp.
19	exp Hymenoptera venom/ or exp Hymenoptera/ or hymenoptera.mp.	47	random*.mp.
20	or/1-19	48	search:.tw.
21	immunotherapy.mp. or exp subcutaneous immunotherapy/ or exp immunotherapy/	49	review.pt.
22	exp adrenalin/ or adrenalin.mp.	50	systematic review.tw.
23	(epipen or epinephrine).mp.	51	meta analysis.mp.pt.
24	exp immunotherapy/ or venom immunotherapy.mp.	52	case series.mp. or exp case study/
25	allergen immunotherapy.mp.	53	(case\$ and series).tw.
26	specific immunotherapy for hymenoptera venom.mp.	54	(case\$ adj2 stud\$).tw.
27	immunomodulation.mp. or exp immunomodulation/	55	or/36-54
28	immunologic response.mp. or exp immune response/	56	20 and 35 and 55

57	exp bee venom/ or exp bee/ or bee.mp.
58	honey bee.mp. or exp honeybee/
59	wasp venom.mp. or exp wasp venom/
60	exp ant sting/ or ant.mp. or exp ant/ or exp ant venom/
61	sawfl*.mp.

62	(apis mellifera or vespid or vespula or white hornet or yellow jacket or yellow hornet or polistes or arthropod venom or solenopsis invicta or myrmecia pilosula).mp.
63	or/57-62
64	56 and 63

Search strategy 2: Cochrane library, HTA, EED, CINAHL, ISI Web of Science, TRIP

(Insect sting or insect bite or insect allergy or venom allergy or insect venom allergy or hypersensitivity or immediate type hypersensitivity or delayed hypersensitivity or allergic reaction or severe allergic reaction or anaphylaxis or anaphylactic shock)

AND

(Immunologic, desensiti* or immunotherapy or venom immunotherapy or specific immunotherapy for hymenoptera venom or subcutaneous immunotherapy or intradermal immunotherapy or intralymphatic immunotherapy or specific immunotherapy)

AND

(Analytical stud* or intervention stud* or experimental stud* or trial or clinical trial* or controlled clinical trial or uncontrolled trial or randomi* controlled trial or quasi randomi* or non randomi* or random allocation or single blind method or double blind method or triple blind method or random* or systematic review or meta-analysis or meta analysis or case-series or case series)

APPENDIX 2.2 EXPERTS CONSULTED

1	Patrizia Bonadonna: no reply
2	Ronit Confino-Cohen: no reply after two reminders
3	David Golden: additional studies recommended
4	Carmen Moreno: additional studies recommended
5	Axel Trautmann: not aware of additional studies or research

APPENDIX 2.3 PRISMA CHECKLIST

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	35
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	37
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	38
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	38-39
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	41
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	38-39
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	38-39
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	E9-10
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	38-39
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	40
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	39
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	41
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	40
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	40
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	41
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	41

Section/topic	#	Checklist item	Reported on page #
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	41-42
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	43-53
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	54-55
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	43-53
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	57-58
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	41-57
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	59
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	59-60
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	59-60
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	60
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	60