

Efficacy of immunotherapy in adults with bronchial asthma: a mini-systematic review of randomised clinical trials

T Eltoun and Y Fadelelmoula

Abstract

Bronchial asthma is a chronic disease, characterised by respiratory symptoms, reversible airflow limitation, and/or airway hyperreactivity with symptoms causally related to genetics, environment, viruses, and allergens. The aim of this mini-review is to summarise the body of literature based on studies on efficacy of immunotherapy for the treatment of bronchial asthma in adults. A literature search of the PubMed database was performed using subject headings and keywords related to bronchial asthma and immunotherapy efficacy. Forty studies were identified through this review, of which 30 were immediately considered unsuitable for inclusion. There were 10 controlled trials, reporting on 1780 patients in total. In these studies, asthma manifestations were generally mild to moderate. Allergens tested included: birch pollens, house mite dust, *Dermatophagoides*, grass pollens, and *Parietaria judaica*. The allergen extracts were generally administered in the form of sublingual drops and subcutaneous, local, and depot injections. The main outcomes measured in the trials included: asthma control, drug scores, respiratory function, bronchial hyperresponsiveness, and quality of life. Three birch pollen sublingual immunotherapy trials demonstrated a significant reduction in drug scores and improved asthma control. A second pair of trials examined the effectiveness of *Dermatophagoides* sublingual immunotherapy; while one of these trials reported significant improvement in asthma control, the second trial failed to prove any significant reduction in either asthma control or drug score. House mite dust sublingual immunotherapy proved to be effective in reducing asthma exacerbations and in reducing bronchodilator and steroid use. Grass pollen immunotherapy was carried out using two different methods, namely subcutaneous and depot injections, and both were effective. A single study reported a positive effect for *Parietaria judaica* immunotherapy given sublingually. In conclusion, the data in this review provide evidence for the efficacy of immunotherapy with specific offending allergens in adults with allergic bronchial asthma but a larger systematic review is recommended.

Introduction

Bronchial asthma is a chronic disease, characterised by respiratory symptoms, reversible airflow limitation and/or airway hyperreactivity with symptoms causally related to genetics, environment, viruses, and allergens. Bronchial asthma is a global health problem with rising prevalence in many countries.¹ House dust mite sensitisation is present in up to 50% of patients with asthma² and exposure to house dust mite allergens has been causally related to asthma severity.³

Current asthma treatment (drug and non-drug therapy) is based on the concept of asthma control, which has been shown to improve treatment success. This concept is based on a process of assess, adjust, and review. Symptom control is usually associated with reduced asthma exacerbations, better lung function, and reduced inhaled steroid use. In the case of more severe forms of asthma, symptom control can occasionally not be paired with a reduced exacerbation rate. Therefore it is important to consider both factors of asthma control, i.e. symptoms and exacerbation risk. Other concepts such as therapy based on sputum or fractional exhaled nitric oxide (FeNO) may be used in special cases, e.g. for patients with severe or difficult-to-treat asthma.

Allergen-based immunotherapy is the only treatment option for allergic disease where there is evidence of a disease-modifying effect,³ and thus with a potential for sustained benefits when therapy is terminated. The use of allergen-specific immunotherapy to treat bronchial asthma has been the subject of debate for several decades. Current guidelines offer no clear or unequivocal indications, stating only that allergen-specific immunotherapy is specific for the allergen causing the allergic disease (rhinitis and/or asthma) and not for the disease itself.⁴ Nonetheless, in the majority of clinical trials, the efficacy of allergen-specific immunotherapy has been evaluated separately for the two disorders of rhinitis and asthma⁵⁻¹⁰ and only a few trials have been specifically designed to evaluate the benefits of allergen-specific immunotherapy for asthmatic patients. This is because pure allergic asthma without concomitant allergic rhinitis is rare and more than one third of patients with allergic rhinitis are also diagnosed as having allergic asthma.¹¹ Another problem is that none of the trials evaluating asthma symptoms have been adequately designed and reported. A sample size calculation and a power analysis based on asthma symptoms alone have not been used as the primary outcome in any trial.¹² Moreover, there is no formal consensus on which measurement parameter should be used for evaluating asthma. In this regard, asthma symptoms, rescue medications intake, combined scores, asthma-free days, and asthma exacerbations are all equally reasonable choices;¹³ however, objective functional pulmonary measurements such

T Eltoun and Y Fadelelmoula, Department of Respiratory Care, College of Applied Sciences, Almaarefa Colleges, Riyadh, KSA. Correspondence to: Dr. Tariq Eltoun Yagoub. Associate Professor of Respiratory Medicine, Department of Respiratory Care, Almaarefa Colleges for Science and Technology, Riyadh-Dariyah, Kingdom of Saudi Arabia. P.O.Box 71666 Riyadh 11597. Fax: 014903501. Email: ttoom@mcst.edu.sa

as forced expiratory volume in 1 second (FEV_1) have only been carried out sporadically.¹⁴ Currently, our knowledge on the use of immunotherapy in asthma is based mostly on old clinical trials with subcutaneous immunotherapy, and on a few recent trials conducted with sublingual immunotherapy, in rhinitis patients with concomitant asthma. Regardless of these limitations, and the possible confounding factors, there is some evidence available to derive at least initial conclusions. The aim of this mini-review is to summarise the body of literature based on studies of the efficacy of immunotherapy for the treatment of bronchial asthma in adults.

Methods

A systematic literature search of the PubMed database was performed using subject headings and keywords related to bronchial asthma and immunotherapy efficacy. The studies included in the review were randomised-controlled trials for adult patients with bronchial asthma, written in English. Exclusion criteria were: case reports, systematic reviews, meta-analysis, studies on patients affected by other comorbidities, patients younger than 18 years. The references of each included study were examined to make sure that additional studies were not overlooked. Each reference was manually retrieved from PubMed and its abstract reviewed. No additional studies were identified from assessing the references of the included studies (Figure 1).

The data retrieved from the included studies were as follows:

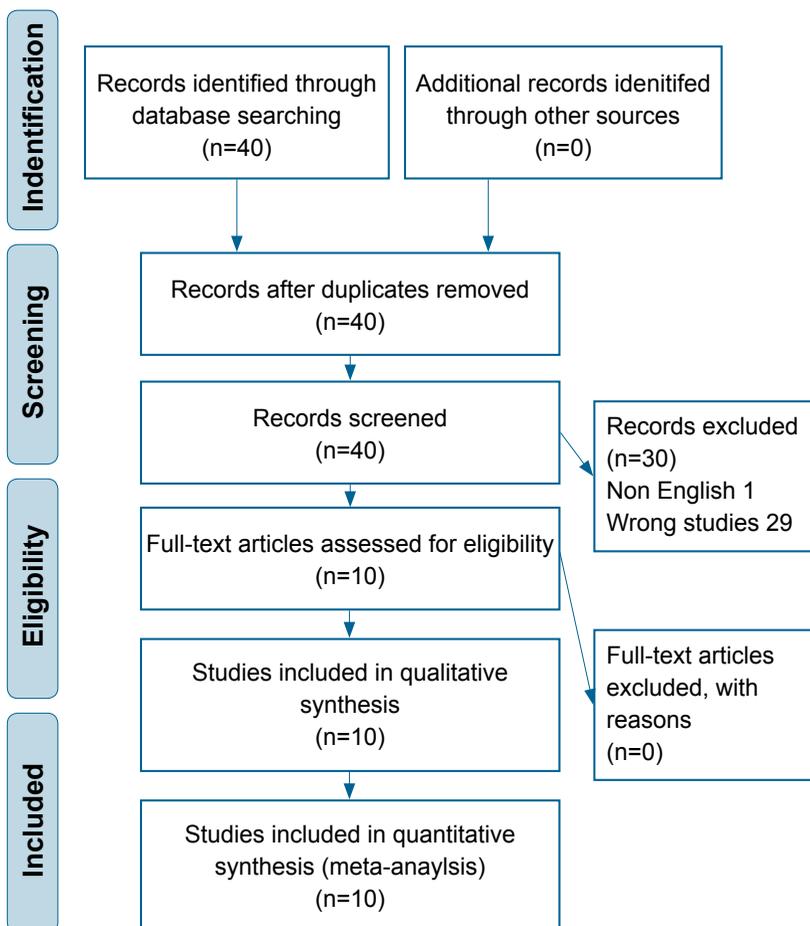


Figure 1 Flowchart representing the inclusion and exclusion criteria of the studies, using preferred reporting items for systematic reviews and meta-analyses (PRISMA)

first author's last name, year of publication, total number of participants, patient demographics, immunotherapy used, clinical and spirometric data.

Results

Forty studies were identified through this review, of which 30 were immediately considered unsuitable for inclusion (review articles, non-randomised or non-controlled trials, studies involving participants with rhinitis and/or conjunctivitis without asthma, and studies without clinically relevant outcomes); 10 controlled trials in adults were identified.

A total of 1780 patients were included in the 10 studies reviewed (Table 1), asthma manifestations were generally mild to moderate. Five types of allergens had been tested (birch pollens in 3 (n=141), house mite dust in 2 (n=919), Dermatophagoides in 2 (n=506), grass pollen in 2 (n=184) and Parietaria judaica in 1 study (n=30). The extracts were administered in the form of sublingual drops (SLIT) in 7 of the studies, the remaining 3 studies used subcutaneous (SIT), local (LIT), and depot injection respectively.

The main outcome measurements in the trials included: asthma control, drug scores, respiratory function, bronchial hyperresponsiveness and quality of life, and the measurements were also used in different combinations. Three birch pollen sublingual immunotherapy trials demonstrated a significant reduction in drug scores and improved asthma control ($p < 0.05$). A second pair of trials examined the effectiveness of Dermatophagoides sublingual immunotherapy; while one of these trials showed a significant improvement in the control of asthma symptoms ($p = 0.244$), the second trial failed to prove any significant reduction in either asthma symptoms control or drug score ($p > 0.05$). In two studies, house mite dust sublingual immunotherapy proved to be effective in reducing asthma exacerbations and in reducing bronchodilator and steroid use after 25 months of treatment. Grass pollen immunotherapy was tried through to different two routes, namely subcutaneous and depot injections, and both were effective ($p < 0.05$). A single study proved the effectiveness of Parietaria judaica immunotherapy given sublingually ($p = 0.04$).

Conclusion

A large number of studies have been carried out over the last decade to investigate allergen-based immunotherapy treatment for different diseases including bronchial asthma and allergic rhinitis. Several systematic literature reviews addressing the use of immunotherapy in bronchial asthma have been conducted to get stronger conclusions out of these studies, but these reviews are of limited use because they include studies in children and patients with allergic rhinitis; in addition, the clinical outcomes of treatments were mostly non-objective. This current review has reviewed the literature in a way that allows evaluating the benefit of immunotherapy in the treatment of adults with bronchial asthma, and only studies that had clear objective clinical outcomes and were blinded

Author	Year	N	Therapy	Clinical and spirometric outcomes measured	Significance
Virchow et al. ¹⁵	2016	834	House dust mite (SLIT)	Risk of a moderate or severe asthma exacerbation compared with placebo	Yes
Bousquet et al. ¹⁶	1999	85	House dust mite (SLIT)	Use of inhaled corticosteroids and beta2-agonists was significantly decreased after 25 months of treatment	Yes
Wang et al. ¹⁷	2014	484	Dermatophagoides (SLIT)	Well-controlled asthma was achieved in patients with moderate asthma but not those with mild asthma	Yes
Crimi et al. ¹⁸	1991	22	Dermatophagoides (LIT)	Symptom score, drug consumption, peak expiratory flow before and during the treatment period	No
Marogna et al. ¹⁹	2013	84	Birch pollen (SLIT)	Improvement of mean monthly asthma control test	Yes
Marogna et al. ²⁰	2010	33	Birch pollen (SLIT)	Bronchial hyperresponsiveness and bronchodilator use decreased significantly in both groups at 5 years, but only in the SLIT group at 3 years	Yes
Voltolini et al. ²¹	2010	24	Birch pollen (SLIT)	The median number of days with asthma at visit 3, 6, 7 and 13.	Yes
Kopp et al. ²²	2008	140	Grass pollen/Depigmented SIT	Symptom load and asthma control (Asthma Control Questionnaire) and quality of life in the case of asthma (Asthma Quality of Life Questionnaire)	Yes
Walker et al. ²³	2001	44	Grass pollen (depot injection)	Reduction in medication scores and seasonal chest symptoms. Impairment of overall quality of life. Methacholine provocation concentration during pollen season	Yes
Purello-D'Ambrosio et al. ²⁴	1999	30	Parietaria judaica (SLIT)	Symptom and drug scores were found especially during the Parietaria pollination period	Yes

Table 1 Summary of controlled trials: type and route of therapy, clinical and spirometric outcomes, statistical significance

control trials were reviewed. The literature search resulted in 10 controlled trials with 1780 patients and 5 different allergen-based immunotherapies. Analysis of the clinical outcomes in those trials has showed a promising efficacy for immunotherapy in bronchial asthma. In conclusion, immunotherapy appears to be an effective treatment for adults with allergic bronchial asthma and this review has clearly supported the usefulness of immunotherapy in the treatment of adults with mild to moderate allergic bronchial asthma in concordance with GINA guidelines.²⁵ In spite of the large number of patients included in this systematic review,

a larger review including more libraries (such as the Cochrane library) and hence a larger number of patients would provide much better results. Synthetic particle immunotherapy, which is a new method in the treatment of allergic diseases, has not been included in this review.

Author Declaration

Competing interests: none.

Any ethical issues involving humans or animals: none.

Was informed consent required: yes - documentation on file.

References

1. Global Initiative for Asthma (GINA). Website: <http://ginasthma.org>. Accessed February, 2017.
2. Kocabas CN, Civelek E, Sackesen C, et al. Burden of rhinitis in children with asthma. *Pediatr Pulmonol* 2005; 40(3): 235–40.
3. Kupczyk M, Kupryś I, Górski P, et al. Aspirin intolerance and allergy to house dust mites: important factors associated with development of severe asthma. *Ann Allergy Asthma Immunol* 2004; 92(4): 453–8.
4. Bousquet J, Lockey RF, Malling HJ. WHO Position Paper. Allergen immunotherapy: therapeutical vaccines for allergic diseases. *J Allergy Clin Immunol* 1998; 102, 558–62.
5. Bonifazi F, Bilò MB. Efficacy of specific immunotherapy in allergic asthma: myth or reality? *Allergy* 1997; 52: 698–710.
6. Cox L. Allergen immunotherapy and asthma: efficacy, safety and other considerations. *Allergy Asthma Proc* 2008; 29: 580–9.
7. Nelson HS. Allergen immunotherapy: where is it now? *J Allergy Clin Immunol* 119: 769–79.
8. Saltoun CA. Update on efficacy of allergen immunotherapy for allergic rhinitis and asthma. *Allergy Asthma Proc* 2002; 23: 377–80.
9. Bousquet J, Demoly P, Michel FB. Specific immunotherapy in rhinitis and asthma. *Ann Allergy Asthma Immunol* 2001; 87: 38–42.
10. Creticos PS. The consideration of immunotherapy in the treatment of allergic asthma. *J Allergy Clin Immunol* 2000; 105: S559–74.
11. Cruz AA, Popov I, Pawankar R, et al. Common characteristics of upper and lower airways in rhinitis and asthma: ARIA update, in collaboration with GA (2)LEN. *Allergy* 2007; 62 Suppl 84: 1–41.
12. Bousquet PJ, Brozek J, Bachert C, et al. The CONSORT statement checklist in allergen-specific immunotherapy: a GA2LEN paper. *Allergy* 2009; 64: 1737–45.
13. Canonica GW, Baena-Cagnani CE, Bousquet J, et al. Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. *Allergy* 2007; 62: 317–24.
14. Passalacqua G, Canonica GW. Specific immunotherapy in asthma: efficacy and safety. *Clin Exp Allergy* 2011; 41: 1247–55.
15. Virchow JC, Backer V, Kuna P, et al. Efficacy of a house dust mite sublingual allergen immunotherapy tablet in adults with allergic asthma: a randomized clinical trial. *JAMA* 2016; 315(16): 1715–25.
16. Bousquet J, Scheinmann P, Guinnee MT, et al. Sublingual-swallow immunotherapy (SLIT) in patients with asthma due to house-dust mites: a double-blind, placebo-controlled study. *Allergy* 1999; 54(3): 249–60.
17. Wang L, Yin J, Fadel R, et al. House dust mite sublingual immunotherapy is safe and appears to be effective in moderate, persistent asthma. *Allergy* 2014; 69: 1181–8.
18. Crimi E, Voltolini S, Troise C, et al. Local immunotherapy with Dermatophagoides extract in asthma. *J Allergy Clin Immunol* 1991; 87 (3): 721–8.
19. Marogna M, Braidì C, Bruno ME, et al. The contribution of sublingual immunotherapy to the achievement of control in birch-related mild persistent asthma: a real-life randomized trial. *Allergol Immunopathol* 2013; 41(4): 216–24.
20. Marogna M, Colombo F, Spadolini I, et al. Randomized open comparison of montelukast and sublingual immunotherapy as add-on treatment in moderate persistent asthma due to birch pollen. *J Invest Allergol Clin Immunol* 2010; 20(2): 146–52.
21. Voltolini S, Troise C, Incorvaia C, et al. Effectiveness of high dose sublingual immunotherapy to induce a stepdown of seasonal asthma: a pilot study. *Curr Med Res Opin* 2010; 26(1): 37–40.
22. Kopp MV, Hamelmann E, Zielen S, et al. DUAL study group. Combination of omalizumab and specific immunotherapy is superior to immunotherapy in patients with seasonal allergic rhinoconjunctivitis and co-morbid seasonal allergic asthma. *Clin Exp Allergy* 2008; 39(2): 271–9.
23. Walker, SM. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. *J Allergy Clin Immunol* 2001; 107: 87–93.
24. Purello-D'Ambrosio F, Gangemi S, Isola S, et al. Sublingual immunotherapy: a double-blind, placebo-controlled trial with Parietaria Judaica extract standardized in mass units in patients with rhinoconjunctivitis, asthma, or both. *Allergy* 1999; 54(9): 968–73.
25. Abramson MJ. Injection allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2010; 8: CD001186.

Call for articles

The Editor welcomes articles on respiratory medicine, and the management of respiratory diseases, from all health professionals, medical and non-medical.

We publish Review Articles, Original Articles, Short Report, Case Reports, and Letters.

Please see 'Guidance to Authors' on page 20 and email your manuscripts to editor@fsg.co.uk.

AJRM
The African Journal of
Respiratory Medicine

THE JOURNAL OF THE PAN AFRICAN THORACIC SOCIETY

www.africanjournalofrespiratorymedicine.com