Original Article

Impact of Allergen Immunotherapy on Medication Score and Medicine Usage in Patients with Nasobronchial Allergy : A Single Centre, Prospective Observational Study in a Specialty Clinic in Eastern India

Shambo Samrat Samajdar[1], Shatavisa Mukherjee[2], Saibal Moitra[3], Santanu Kumar Tripathi[4]

Background : Allergic diseases constitute a considerable burden on healthcare system in terms of increased cost of care and impaired Quality of Life in affected. To the rescue, Allergen Immunotherapy (AIT) is reported to be an available treatment modality for altering the natural course of allergic disorders. This study tried to assess the impact of medication usage on medication scoring in patients on Allergen Immunotherapy.

Materials and Methods : All consecutive asthma and allergic rhinitis patients prescribed allergen immunotherapy and consenting to join the study were included and interviewed for demographic details and all relevant information, including treatment history. Indication, pattern of prescribing in candidates of allergen immunotherapy, medication score and adherence to therapy were captured in a pre-structured data collection form.

Results : Over 50% patients in both asthma and allergic rhinitis group presented with more than 2 years of symptoms during initiation of AIT. As per reports from Skin Prick Test and specific allergen exposure triggering history, Subcutaneous Allergen Immunotherapy (SCIT) was selected for each patient. Apart from allergen species, drug usage pattern suggested use of antimicrobial, systemic/ inhaled/ intranasal corticosteroids, antihistamines/LTRAs, bronchodilators and beta 2 agonists. AIT causes Th2 mediated reaction conversion to Th1 mediated reaction. In our studied patients, we found that there is decrease in the need of intranasal and inhaled corticosteroids dose with subsequent days.

Conclusion : It is imperative to note that immunotherapy is not competitive with the conventional use of pharmacotherapy and should be administered in the context of general advice regarding overall disease management.

[*J Indian Med Assoc* 2024; **122(11):** 20-5]

Key words **: Allergen Immunotherapy, Prescribing Pattern, Allergic Rhinitis, Asthma, Medication Scoring.**

Allergic disorders like asthma are often under-diagnosed and undertreated, creating a considerable burden on individuals and families. It is responsible for approximately 1% of all disability-adjusted life years lost Worldwide[1]. Allergic disorders and its complications have also been reported to increase health care costs of the individual. Therefore, even though mostly a non-life-threatening condition, they can impair the person's ability to function. It thus has a huge socio-economic impact and can adversely influence psychological wellbeing and Quality of Life[2].

Allergen Immunotherapy (AIT) is the available treatment serving the purpose of altering the natural course of allergic disorders. Currently, it has an established role in the therapy of allergic rhinitis, allergic conjunctivitis, allergic asthma, and insect sting hypersensitivity, based on evidence obtained through randomized controlled trials[3]. Other than conventional Subcutaneous Immunotherapy (SCIT), the role of non-injection routes of immunotherapy such as Sublingual Immunotherapy (SLIT) and oral immunotherapy is not yet established, although there are several observations available showing

Editor's Comment :

- The study found that patients receiving Allergen Immunotherapy (AIT) experienced a reduction in the need for intranasal and inhaled corticosteroids over time, indicating AIT's potential to alter medication dependency in managing allergic diseases.
- More than half of the patients in the study had been experiencing symptoms for over two years before starting AIT, highlighting the chronic nature of allergic disorders and the need for effective long-term treatment strategies.
- While Allergen Immunotherapy can help modify the course of allergic diseases, it should be viewed as a complement to traditional pharmacotherapy rather than a replacement, emphasizing the importance of comprehensive disease management.

[1]MBBS, MD, DM, Assistant Professor, Department of Pharmacology, JMN Medical College and Hospital, Nadia, West Bengal 741222

[2]M Pharm (Pharmacology), MBA (Hospital & Health System Administration), PGDM (Epidemiology & Biostatistics), Department of Clinical & Experimental Pharmacology, School of Tropical Medicine, Kolkata 700073 and Corresponding Author

[3]MD (Respiratory Medicine), PhD, FCCP (USA), DAA (CMC) MNAMS, Professor, Department of Allergy and Immunology, Apollo Gleneagles Hospitals, Kolkata, West Bengal 700054

[4]MBBS, MD, DM, Professor, Department of Pharmacology, Jagannath Gupta Institute of Medical Science and Hospital, Budge Budge, Kolkata 700137

Received on : 10/10/2024
Accepted on : 25/10/2024

therapeutic trend. Newer modalities like anti-IgE therapy (omalizumab) used in combination with immunotherapy have significantly reduced the risk of systemic reactions. Novel immunotherapy approaches through recombinant technology and development of T-cell epitope-based allergy vaccines leading to the production of low-allergenicity extracts are the future goals of improving the outcome of allergic disorders. Allergen specific immunotherapy is a controversial topic in the field of asthma and allergic rhinitis treatment. Various randomized controlled trials demonstrated beneficial effects with some risks of severe and sometimes fatal anaphylaxis[4]. As per GINA 2017, SLIT can be considered as a treatment option in case of house dust mite sensitive adult patients suffering from allergic rhinitis or bronchial asthma who have exacerbation of despite inhalation of corticosteroids (provided FEV1 is >70%). Besides, SCIT is a unique therapy for allergic disease because it provides symptomatic relief while modifying the allergic disease by targeting the underlying immunological mechanism[5]. The present study tried to assess the impact of medication usage on medication scoring in patients on allergen immunotherapy.

Materials and Methods

A prospective, observational, single center study was carried out in a Specialty clinic in Eastern India, where all consecutive asthma and allergic rhinitis patients prescribed allergen immunotherapy and consenting to join the study were included. Permission from Institutional Ethics Committee was obtained prior initiation of the study (CREC-STM/422). Written informed consent was obtained from all participants willing to be a part of the study. Sampling method for this study was convenient sampling, a non-probability sampling method. All consenting patients were interviewed for demographic details and all relevant information, including treatment history. Indication and pattern of prescribing in candidates of allergen immunotherapy were captured in a pre-structured data collection form.

Patients were assessed for their medication score. For medication score, total number of drugs consumed per day for allergic rhinitis and/or asthma was computed for each patient over various time intervals. Assuming one patient is taking Fixed Dose Combination (FDC) of montelukast 10 mg + fexofenadine 120 mg once daily and FDC inhaler of budesonide 200 mcg + formoterol 6 mcg 2 puffs twice daily in initial visit (baseline) and after 6 months he is put on FDC inhaler of budesonide 200 mcg + formoterol 6 mcg 1 puff twice daily and he is taking montelukast 10 mg + fexofenadine 120 mg alternate day as per his own symptoms control requirement.

In this case,

Baseline medication score = [{(1+1) x 30}+{(2 +2) x 30}]/30 = 2+4 + 6 ; while

Medication Score (6 months) = [{(1+1) x 15} + {(1+1) x 30}/ 30 = (30 + 60)/30 = 3

Patients were followed up to one year of allergen immunotherapy initiation. Adherence was checked by using Morisky Medication Adherence Scale (MMAS-8). Data collected was checked for completeness and then statistically analyzed. Descriptive data were represented as mean or percentages. Where possible, demographic and categorical data were analyzed with parametric or non-parametric tests whichever found applicable.

Results

The study included a total of 186 patients with presentations of allergic rhinitis, asthma or both, who were prescribed allergen immunotherapy. Of the total patient population, 57% were males with mean age of the patient population being 37.56 ± 12.09 years. Majority of the study participants belonged to the age group of 40-50 years (40.9%) followed by those in 20-30 years band (26.9%)(Table 1). Patients presented with symptoms like dry cough or cough with mucoid expectoration/ scanty expectoration, running nose, sneezing, breathlessness, wheeze, chest tightness, itchy eyes/ nose/ skin or rash. Most of the patients (over 50%) in both asthma and allergic rhinitis group presented with more than 2 years of symptoms during initiation of AIT. Of total 186 study participants, 47.3% presented with allergic rhinitis, 30.1% were asthma and 22.6% had presentations of both allergic rhinitis and asthma. Subcutaneous allergen Immunotherapy (SCIT) is selected for each patient of asthma and allergic rhinitis with skin prick test positivity, having predominant indoor symptoms,

Table 1 — *Basic Demographics*

Gender Distribution	**Frequency (%)**
Male	106 (57%)
Female	80 (43%)
Age Distribution	**Frequency (%)**
Age in Years	
<20	11 (5.9%)
20 – 30	50 (26.9%)
31 – 40	33 (17.7%)
41 – 50	76 (40.9%)
51 – 60	13 (7%)
>60	3 (1.6%)

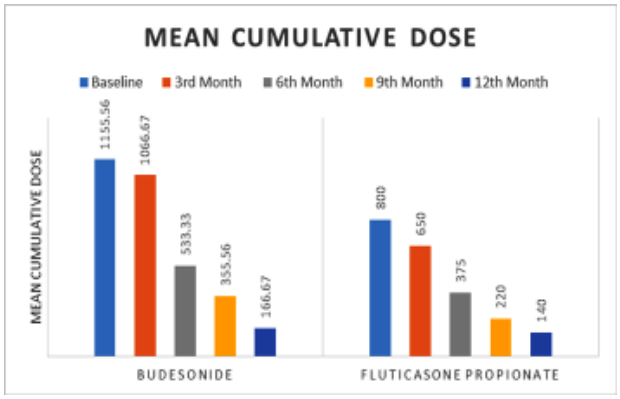
having symptoms triggered by house dust exposure and suffering from perennial allergic rhinitis patients. SCIT for House Dust Mites - (*Dermatophagoides pteronyssinus* 50% + *Dermatophagoides farinae* 50%) was selected for all patients.

Drug usage pattern over the study time period was analyzed in asthma and allergic rhinitis patients (Table 2). In asthma patients, mostly prescribed antimicrobial was cefixime at baseline, which decreased in 6th month. Among systemic corticosteroid, deflazacort was majorly prescribed. Montelukast combined with either fexofenadine or levocetrizine were majorly prescribed. In these patients, mean cumulative dosage of inhaled corticosteroids like budesonide and fluticasone propionate significantly decreased from baseline in subsequent follow ups. Mean cumulative dose of budesonide was 1155.56 mcg at baseline, which decreased gradually to 166.67mcg at 12th month. Similarly for fluticasone propionate, mean cumulative dose was 800 mcg at baseline, which significantly decreased gradually to 140 mcg at 12th month. For allergic rhinitis patients, mostly prescribed antimicrobial was azithromycin at baseline to control flaring up of symptoms assumed to be due to infectious etiology which decreased in 3rd month. Among intranasal corticosteroid, fluticasone furoate (27.5 mcg/actuation) was majorly prescribed, followed by momentasone (50mcg/actuation) and FDC of fluticasone furoate (27.5 mcg/actuation) + azelastine (50 mcg/actuation). Montelukast 10 mg combined with either fexofenadine 120 mg or levocetrizine 5 mg were majorly prescribed. Mean cumulative dosage of intranasal corticosteroids like fluticasone furoate and mometasone significantly decreased from baseline in subsequent follow ups. Mean cumulative dose of fluticasone furoate was 95 mcg at baseline, which decreased gradually to 7.5 mcg at 12th month. Similarly, for momentasone, mean cumulative dose was 172.73 mcg at baseline, which significantly decreased gradually to 13.64 mcg at 12th month. Azelastine + Fluticasone Propionate was prescribed in baseline and 3rd month only, mean cumulative dose being 646 mcg at baseline and 532 mcg at 3rd month respectively (Fig 1).

Table 2 — *Drug Usage Pattern*

Asthma					
	Percentage (%)				
Drugs	**Baseline**	**3rd Month**	**6th Month**	**9th Month**	**12 Month**
Antimicrobials :					
Azithromycin	8.9	-	1.7	1.7	3.6
Moxifloxacin	8.9	-	0.0	3.6	0.0
Ceftriaxone	1.7	-	5.4	0.0	0.0
Cefixime	19.6	-	0.0	0.0	0.0
Cefpodoxime Proxetil	14.3	-	3.6	3.6	3.6
Levofloxacin	10.7	-	0.0	0.0	0.0
Amoxicillin + Clavulanic acid	12.5	-	3.6	5.4	1.7
Clarithromycin	1.7		7.1	0.0	1.7
Systemic Corticosteroid :					
Methylprednisolone	19.6	0.0	0.0	0.0	0.0
Deflazacort	82.1	10.7	3.6	0.0	0.0
Inhaled Corticosteroids and Beta 2 Agonist :					
Budesonide	57.1	58.9	71.4	82.1	82.1
Fluticasone	44.6	42.9	30.4	30.4	30.4
Salmeterol	37.5	23.2	12.5	12.5	12.5
Formoterol	46.4	76.8	89.8	89.8	89.8
Salbutamol	14.3	12.5	0.0	0.0	0.0
Levosalbutamol	14.3	19.6	10.7	7.1	5.3
Ipratropium Bromide	16.1	7.1	5.3	3.6	3.6
Tiotropium	8.9	8.9	5.3	3.6	3.6
Beclomethasone	1.7	7.1	0.0	0.0	0.0
Antihistamines, LTRAs and Oral Bronchodilators :					
Montelukast + Fexofenadine	46.4	57.1	37.5	19.6	16.1
Montelukast + Levocetrizine	37.5	30.4	23.2	7.1	5.3
Montelukast	0.0	0.0	46.4	30.4	19.6
Montelukast + Theophylline	14.3	10.7	1.7	1.7	1.7
Montelukast +Acebrophylline	7.1	5.3	5.3	3.6	1.7
Fexofenadine	16.1	7.1	10.7	5.3	5.3
Levocetrizine	7.1	5.3	5.3	3.6	1.7
Allergic Rhinitis					
Antimicrobials :					
Azithromycin	11.4	2.3	0	0	0
Moxifloxacin	6.8	0	0	0	0
Amoxicillin + Clavulinic acid	4.54	2.3	0	0	0
Intranasal Corticosteroid :					
Fluticasone furoate	68.18	71.6	56.81	32.95	18.18
Momentasone	25	27.27	21.59	17.04	9.09
Azelastine + Fluticasone	6.8	2.3	0	0	0
Antihistamines and LTRAs :					
Montelukast + Fexofenadine	50	50	50	18.18	11.4
Montelukast + Levocetrizine	44.31	45.45	39.77	21.59	18.18
Montelukast	0	0	21.59	18.18	10.22
Bepotastine	4.54	5.68	4.54	0	0
Fexofenadine	3.4	2.3	4.54	4.54	18.18
Levocetrizine	3.4	5.68	9.09	4.54	10.22
Others					
Hydroxypropyl methylcellulose nasal powder	21.59	32.95	18.18	9.09	4.54

(A) Asthma



(B) Allergic Rhinitis

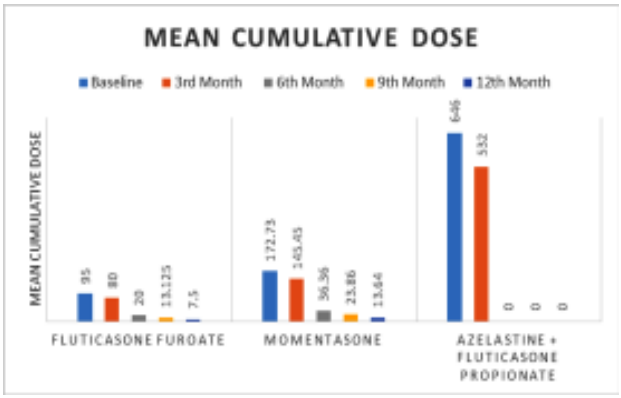


Fig 1 — Mean cumulative dosage of inhaled corticosteroid in Asthma and Allergic Rhinitis patients

Total Medication Score decreased over the study period. In cases of allergic rhinitis, mean medication score was 5.99 ± 0.97 at baseline which gradually decreased to 0.83 ± 0.55 by the end of the study period. In cases of asthma, mean score decreased from 11.89 ± 1.49 at baseline 0.84 ± 0.65 at 12th month visit. In cases of both allergic rhinitis and asthma, mean medication score was 10.69 ± 1.44 at baseline which gradually decreased to 0.99 ± 0.64 by the end of the study period. Decrease in scores were found statistically highly significant at p<0.001. (Table 3) Cumulative medication scoring significantly decreased over the time period (p<0.001)(Fig 2).

Medication adherence of the subjects was assessed using MMAS-8 scale. Total MMAS-8 scores can range from 0 to 8 and have been categorized into three levels of adherence: high adherence (score = 8), medium adherence (score of 6 to <8), and low adherence (score <6). In the present study, majority of the patients were observed to be in medium adherence group for all time points. Adherence levels showed non-significant graded change from low to medium level over the study time frame. (p=0.13) (Table 4)

Discussion

Allergic diseases are among the commonest chronic diseases and encompass atopic eczema/ dermatitis, asthma, allergic rhinitis and allergic rhinoconjunctivitis, food allergy and venom allergy. They frequently start in early childhood and continue throughout adulthood. Allergies can cause a considerable burden to individuals leading to impaired quality of life. On a societal level, they cause additional

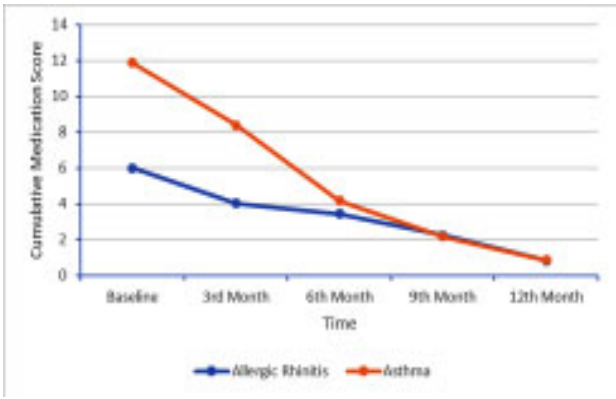


Fig 2 — Cumulative Medication Scoring for patients on AIT

Table 3 — *Medication Score*

	Baseline	3rd Month	6th Month	9th Month	12th Month
Allergic Rhinitis (N=88)	5.99 ± 0.97(4-8)	4.02 ± 0.69**(3-5)	3.43 ± 0.49**(3-4)	2.25 ± 0.81**(1-3)	0.83 ± 0.55**(0-2)
Asthma (N=56)	11.89 ± 1.49(9-14)	8.39 ± 1.33**(6-12)	4.18 ± 0.83**(3-6)	2.16 ± 0.8**(1-3)	0.84 ± 0.65**(0-2)
Allergic Rhinitis+Asthma (N=42)	10.69 ± 1.44(8-13)	8.24 ± 0.93**(7-10)	5.24 ± 0.85**(4-6)	2.17 ± 0.85**(1-3)	0.99 ± 0.64**(0-2)

*Note : Values expressed as Mean ± Standard Deviation (Range)Significance tested considering p<0.05 (using 't-test'); NS- Not Significant, #significant at p<0.05, ##significant at p<0.01, **significant at p<0.001*

Table 4 — *Medication Adherence in Study Subjects*

Adherence Level	Baseline	3 Months	6 Months	9 Months	12 Months	χ^2 Statistics
Low (<6)	32 (17.20)	23 (12.36)	19 (10.21)	20 (10.75)	24 (12.9)	$\chi^2 = 12.55$;
Medium (6-7)	130 (69.89)	145 (77.95)	147 (79.03)	152 (81.72)	151 (81.18)	$p = 0.13^{NS}$
High (8)	24 (12.9)	18 (9.67)	20 (10.75)	14 (7.52)	11 (5.91)	

Note : Values expressed as N (%) ; NS= Non-Significant ; p value (p<0.05 considered significant)

costs, particularly in terms of health care utilization, reduction in economic productivity and impacting on activities of daily living. The latter may include loss of school days, work absence, presenteeism and early retirement. For allergic asthma and allergic rhinitis, many patients respond well to pharmacotherapy, whereas others do not or need treatment with more than one product[6]. However, there is good evidence for the clinical efficacy of AIT for allergic rhinitis, allergic asthma and moderate to severe venom allergy with many patients responding to therapeutic AIT, leading to a sustained reduction in symptoms and requirement for symptomatic treatment. AIT is considered a disease-modifying intervention in IgE-mediated allergic disease, with both a therapeutic, even beyond cessation of AIT and the potential for a preventive effect. It has been shown that children with allergic rhinitis have a 3-fold increased risk of developing asthma and that childhood AD and allergic rhinitis are strongly associated with the incidence and persistence of adult atopic asthma and with allergic asthma persisting into adulthood[7]. Studies assessing the long-term effectiveness of AIT in children with allergic rhinitis indicate that AIT might reduce the risk of developing asthma. AIT has the potential to induce immunological changes that result in immune modification. Immunotherapy is effective against hypersensitivity to pollens, animal allergens, dust mites, molds/fungi and insect stings. The present study aimed to assess the prescribing pattern in candidates for allergen immunotherapy in asthma and allergic rhinitis in a specialty clinic in Eastern India.

The present study included patients with asthma, allergic rhinitis and those with mixed presentation. Over 50% patients in both asthma and allergic rhinitis group presented with more than 2 years of symptoms during initiation of AIT. As per reports from skin prick test and focused history Subcutaneous Allergen Immunotherapy (SCIT) for house dust mites - (*Dermatophagoides pteronyssinus 50% + Dermatophagoides farinae 50%)* was selected for each patient. The commercially available extracts are relatively low in potency. If immunotherapy is prescribed, only glycerinated extracts should be used, and regionally relevant species should be included in the extracts. However, SCIT should only be performed by trained staff in an allergy clinic facility with an appropriate observation area, facilities for vaccine storage at 4ºC, and access to resuscitation facilities, following proper immunotherapy protocols.

Apart from allergen species, drug usage pattern suggested use of antimicrobial, systemic/ inhaled/ intranasal corticosteroids, antihistamines/LTRAs, bronchodilators and beta 2 agonists. In addition, drug usage pattern was assessed for both asthma and allergic rhinitis patients. As in for asthma patients, mostly prescribed antimicrobial was cefixime. Other antimicrobials included azithromycin, moxifloxacin, ceftriaxone, cefixime, cefpodoxime proxetil, levofloxacin, amoxicillin + clavulanic acid, clarithromycin. Systemic corticosteroid prescribing included deflazacort and methylprednisolone. Montelukast combined with either fexofenadine or levocetrizine were majorly prescribed in antihistamines and LTRA group. Other bronchodilators including beta 2 agonists used were salmeterol, formoterol, salbutamol, levosalbutamol, ipratropium bromide, tiotropium, beclomethasone. For allergic rhinitis patients, azithromycin, moxifloxacin, amoxicillin + clavulanic acid were prescribed antimicrobials. Fluticasone, momentasone and fluticasone+azelastine combination were majorly prescribed intranasal corticosteroid. Montelukast combined with either fexofenadine or levocetrizine were majorly prescribed in LTRA and antihistamines group, with hydroxypropyl methylcellulose nasal powder being prescribed throughout the study period. AIT causesTh2 mediated reaction to Th1 mediated reaction. In our studied patients, we found that there is decrease in the need of intranasal and inhaled corticosteroids dose with subsequent days.

The spectra of medication usage have a direct impact on the total medication scoring. Total Medication Score is a prime effectiveness measure in patients of allergic disorders. Medication load signifies the presence of symptoms and need to alleviate it. A true decrease in medication load and eventually medication score is a significant determinant of treatment efficacy. The lower the medication score, the better the therapy. In our study, the cumulative medication score significantly decreased over the study period. Clinical effectiveness of SCIT in management of allergic rhinitis, including 759 patients (546 adults, 53 children, 160 all ages) from 16 studies had suggested that SCIT had produced improvement in medication scores significantly[8]. A Cochrane review including meta-analysis of 51 randomized double-blind placebo controlled trials (2871 subjects with seasonal allergic rhinitis or controls), had indicated that allergen immunotherapy significantly improved overall medication use, and humanistic outcomes[9]. To evaluate the efficacy and safety of SCIT in mite-sensitized subjects with asthma a meta-analysis was

done including a total of 796 subjects from 19 different randomized controlled trials. SCIT had reduced the asthma medication scores compared with the control group significantly[10]. Finding of our study corroborates with these findings. Antihistamine usage was decreased with progression of allergen immunotherapy. Taking a hint from decreased medication score, allergen immunotherapy may be an important option to manage allergic disease. However, we may need further studies specifically double blind randomized clinical trials to test these hypotheses. In the present study, adherence was assessed using MMAS and all subjects were found well adherent throughout all time points of their therapy. In this study, a reduction in medication score was observed after three months of therapy, though different guidelines suggest minimum 3 years of therapy to achieve the same. So, our study sparks the need to further explore whether short duration therapy provides more benefit or not.

An extensive literature search has shown that there exists a dearth of studies assessing the drug prescribing pattern in these AIT candidates. The study may be the first of its kind, however the study being unicentric in nature with a limited sample size, may not be a reflection of the true picture of AIT, but obviously opens up new avenue for further research addressing the limitations.

Conclusion

Unlike anti-allergic drugs, immunotherapy has been shown to modify the underlying cause of the disease, with proven long-term benefits. However, AIT may be combined with appropriate allergen avoidance strategies. It is imperative to note that immunotherapy is not competitive with the conventional use of pharmacotherapy and should be administered in the context of general advice regarding overall disease management.

Source of Funding : Nil
Conflict of Interest : None Declared

References

1 Nitin J, Palagani R, Shradha NH — Prevalence, severity and risk factors of allergic disorders among people in south India. *Afr Health Sci* 2016; **16(1):** 201-9. doi:10.4314/ahs.v16i1.27
2 Lobo F, Lobo B — Quality of Life in Asthmatic Outpatients. *J Asthma* 2008; **45:** 27-32.
3 Viswanathan RK, Busse W — Allergen immunotherapy in allergic respiratory diseases: from mechanisms to meta-analyses. *Chest* 2012; 141(5): 1303-14. doi:10.1378/chest.11-2800
4 Zhang W, Lin C, Sampath V, Nadeau K — Impact of allergen immunotherapy in allergic asthma. *Immunotherapy* 2018; **10(7):** 579-93. doi:10.2217/imt-2017-0138
5 GINA 2017 — Available at https://ginasthma.org/2017-gina/. Accessed on June 20, 2020
6 Galli SJ, Tsai M, Piliponsky AM — The development of allergic inflammation. *Nature* 2008; **454(7203):** 445-54. doi:10.1038/nature07204
7 Papadopoulos NG, Agache I, Bavbek S — Research needs in allergy: an EAACI position paper, in collaboration with EFA. *Clin Transl Allergy* 2012; **2(1):** 21. Published 2012 Nov 2. doi:10.1186/2045-7022-2-21
8 Van Bever HP, Stevens WJ — Evolution of the late asthmatic reaction during immunotherapy and after stopping immunotherapy. *J Allergy Clin Immunol* 1990; **86:** 141-6
9 Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S — Cochrane review: Allergen injection immunotherapy for seasonal allergic rhinitis. *Evid Based Child Health* 2010; **5:** 1279-379
10 Lu Y, Xu L, Xia M, Li Y, Cao L — The efficacy and safety of subcutaneous immunotherapy in mite-sensitized subjects with asthma: A meta-analysis. *Respir Care* 2015; **60:** 269-78.