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Case Report

Effectiveness of House Dust-mite Subcutaneous Allergen Immunotherapy (HDM-SCIT) Combined with Omalizumab (Anti-IgE) in Five Cases of Steroid-Dependent Allergic Rhinitis with Asthma

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Abstract

Allergen Immunotherapy (AIT) offers a potential to be a disease modifying therapy by inducing allergen specific regulatory T (T reg) cells, allergen specific IgG4 and T-cell tolerance. However, the frequency & duration of therapy and potential for Systemic Allergic Reactions (SARs) have limited its use. Our five patients of steroid dependent (Basal cortisol <3.3 ug/dl) Allergic Rhinitis with Asthma, who were at greater risk for SARs and had difficulty in achieving the maintenance dose of AIT, were given combined House Dust Mite Subcutaneous Allergen Immunotherapy (HDM-SCIT) with Omalizumab which enabled them to achieve the target maintenance dose of SCIT without adverse events and increased tolerance to specific Dust mite allergen. The outcome was well-controlled asthma with reduction of Oral Corticosteroids (OCS) in one case and discontinuation of OCS in four cases with steroid-sparing effect.

Keywords: Steroid-dependent; Asthma; Rhinitis; Allergen immunotherapy (AIT); House dust mite (HDM); Subcutaneous immunotherapy (SCIT); Omalizumab (Anti-IgE); Adrenal insufficiency (AI); Oral corticosteroids (OCS); Inhaled corticosteroids (ICS); Dermatophagoides pteronyssinus (Dp); Dermatophagoides farinae (Df)

Abbreviations: AIT: Allergen Immunotherapy; HDM: House Dust Mite; SCIT: Subcutaneous Immunotherapy; OCS: Oral Corticosteroids; ICS: Inhaled Corticosteroids; LABA: Long-Acting Beta Agonist; LAMA: Long-Acting Muscarinic Agonist; Dp: Dermatophagoides pteronyssinus; Df: Dermatophagoides farina; SARs: Systemic Allergic Reactions; RCAT: Rhinitis Control Assessment Test; ACT: Asthma Control Test; AI: Adrenal Insufficiency

Introduction

Specific Allergen Immunotherapy (AIT) is the only therapeutic method with positive impact on natural course of allergic diseases affecting clinical development (including the progression of Rhinitis to Asthma) and new sensitization. However, the frequency and duration of therapy and the potential for Systemic Allergic Reactions (SARs) have limited its use, especially in patients with symptomatic persistent Allergic Asthma, who are at a greater risk for severe reactions due to AIT [1]. Glucocorticoids are the mainstay of therapy for a variety of chronic inflammatory diseases including asthma. Its therapeutic effect is achieved by inducing apoptosis and decreasing activation of the main effector cells in asthma- the eosinophils and the T lymphocytes [2]. Any patient who requires daily OCS (or very high dose of high potency ICS) to minimize the frequency of

asthma exacerbations are defined either steroid-dependent (normal pulmonary function maintained only on taking OCS) or steroid resistant (poor pulmonary function despite treatment with OCS) [3]. Omalizumab is recommended for patients with moderate to severe uncontrolled allergic asthma with IgE level of 30-700 ku/l in USA (30-1500 ku/L in Europe). It reduces free IgE by 89% to 99% soon after administration and low levels persist throughout treatment [4]. According to the Global Initiative for Asthma (GINA guidelines step IV & V), high dose ICS and OCS are required to ensure asthma control during treatment. Treatment with Omalizumab should be considered for patients aged >6 years with uncontrolled moderate to severe steroid-dependent persistent Asthma as per guidelines (Global Initiative for Asthma-GINA 2019 Step V, National Asthma Education and prevention program expert panel Report 3: NAEPPEPR-3, Step V and VI) and with a history of positive skin test or *in vitro* reactivity to a perennial aero-allergen [5].

House dust mite (HDM) is a predominant source of indoor aero-allergen worldwide, are found mainly in mattresses, sofa and carpets throughout the year. These allergens on inhalation cause a sensitization reaction, through the epithelial leakage into the respiratory system by cleavage of the tight junctions in between the epithelial cells [6]. Dust-mite Immunotherapy provided an alternate option for treating HDM-driven allergic Asthma for a long-term symptom relief [7]. In order to decide the adequate treatment of severe allergic asthma, patients should be explored for potential immediate type reactions to inhalant allergen sources like pollens and HDM. HDM-SCIT can be applied in patients of Asthma as long as the Asthma is controlled. HDM-SCIT might facilitate achieving asthma control while stepping up drug treatment [Long-Acting Beta Agonist (LABA), Long-Acting Muscarinic Agonist (LAMA), ICS] as per AIT guidelines. Several trials have been performed with pre-administration or co-administration of biologicals and HDM-AIT for HDM-driven Allergic Asthma [8]. Therapy with anti-IgE (Omalizumab), using the humanized monoclonal anti-IgE antibody Omalizumab, acts to reduce circulatory level of free IgE, inhibits early and late phase response to allergens, and decreases tissue eosinophil and Th2 lymphocytic cytokines, IL-4 & IL-13[9]. Clinically, treatment with Omalizumab (Anti-IgE) is well tolerated and can reduce the requirement for Inhaled Corticosteroids (ICS), the need for systemic steroids and protects against disease exacerbations [10]. Therefore, AIT acts to induce a population of regulatory immuno-protective antibodies while anti-IgE has a passive action on IgE inflammation. Combining AIT with Omalizumab results in enhanced efficacy and better safety, faster symptom relief, persistent serum inhibitory activity of allergen IgE binding to Antigen Presenting Cells (APC) and also might result in prolonged down regulation of Th2 lymphocytic activity [11]. We describe five cases that were successfully treated with a combination of HDM-SCIT [D. pteronyssinus (Dp 50% & D. farinae (Df)50%] with Omalizumab (Anti-IgE), have significant Immuno-regulatory activity and were found to be efficacious, safe with steroid sparing effect.

Case Description

Case 1: 30 years female, Steroid-dependent Allergic Rhinitis with Asthma has had history of recurrent episodes of sneezing, rhinorrhea, watering eyes and shortness of breath since 6-7 years. Symptoms aggravate on exposure to dust, change of season, drugs (NSAIDS), more at night. She was on symptomatic treatment (LABA, LAMA, high dose ICS with on & off low dose OCS).

Case 2: 11years female, Steroid-dependent Allergic Rhinitis with Asthma with complaints of recurrent cough, breathlessness, sneezing, nasal congestion and watering eyes along with history of drug allergy (Penicillin /Aspirin) on and off since 4-5 years. She was on symptomatic treatment (LABA, LAMA, High dose ICS with on & off low dose OCS). Symptoms aggravated during change of season and exposure to dust.

Case 3: 16 years female, Steroid-dependent Allergic Rhinitis with Asthma presented with recurrent episodes of sneezing, rhinorrhoea, cough and sore throat on and off since 6-7 years. Symptoms are perennial and exacerbate during exposure to dust, change of climate and at night. She took symptomatic (LABA, LAMA, high dose ICS with on & off low dose OCS) and indigenous treatment.

Case 4: 14 years male, Steroid-dependent Allergic Rhinitis with Asthma presented with complaints of cough, sneezing, rhinorrhoea, nasal congestion on and off since 6 years. He took indigenous ayurvedic treatment along with multiple courses of OCS, LABA, LAMA and high dose ICS.

Case 5: 49 years male, Steroid-dependent Allergic Rhinitis with Asthma with hypothyroidism and Drug (Disprin and Ciprofloxacin) & food allergy (sesame seeds, dry fruits, milk and wheat) since 20-25 years. He has had recurrent episodes of rhinitis, sneezing, watering from eyes, cough, shortness of breath and migraine. Was given multiple courses of antibiotics, anti-histamines, montelukast, OCS along with indigenous treatment.

Recommendation of cases

All the five cases were given combined HDM-SCIT (HDM, 10000 AU per ml SCIT Greer Laboratories, Inc.) with effective dose [gradual up-dosing protocol of build-up phase to achieve Maintenance Dose (MD)- 500 AU per month] and Anti-IgE [Inj Omalizumab (150 mg) X 15 days before AIT followed by once a month for variable duration] [case 1 for 10 months, case 2 for 17 months, case 3 for 11 months, case 4 for 25 months, case5 for 15 months] (Table 6) with supportive therapy for 3 years. Asthma symptoms were well controlled with discontinuation of OCS in Case 1-4 while there was marginal reduction of OCS in Case-5

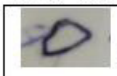
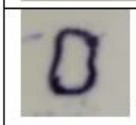
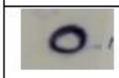
along with improvement in lung function, Specific IgE to Dp/ Df and serum cortisol as shown in Tables 1-5.

	Case 1			
	2016		**2019**	
RCAT/ACT scoring	12/12 Baseline		20/21	
FEV1	63%		87%	
FEV1/FVC	86.9%		87.6%	
PEFR (variability)	300-400 L/mts (25%)		420-450 L/mts (6.6%)	
Total IgE	542 IU/ML		762 IU/ml	
Eosinophil % / AEC	1.9 % / 139 cells/ul		2.5% / 253 cells/ul	
Serum cortisol / OCS	2.7 mcg/dl / on 16 mg MP		7.43 mcg/dl	
	SPT wheal size	**Specific IgE**	**SPT wheal size**	**Specific IgE**
Histamine	 5mm	N/A	 5mm	N/A
D. pteronyssinus	 8mm	50.0 kua/l	 3mm	6.21 kua/l
D. farinae	 9mm	95.5 kua/l	 4mm	27.80 kua/l
Cockroach	 3mm	0.20 kua/l	 <3mm	0.11 kua/l

RCAT-Rhinitis Control Assessment Test, ACT-Asthma Control Test, FEV-Forced Expiratory Volume, FVC-Forced Vital Capacity, PEFR-Peak Expiratory Flow Rate, AEC-Absolute Eosinophil Count, OCS-Oral Corticosteroids, MP-Methyl Prednisolone.

Table 1: Clinical characteristics of case 1.

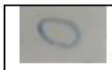
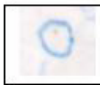
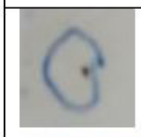
	CASE 2	
	2016	**2019**
RCAT/ACT scoring	10/11 Baseline	21/21
FEV1	90%	102%
FEV1/FVC	84.1%	88.5%
PEFR (variability)	200-300 L/mts (33%)	330-350 L/mts (5.7%)
Total IgE	2327 IU/ML	1010 IU/ml
Eosinophil % / AEC	0.9 % / 68 cells/ul	1.5 % /169 cells/ul
Serum cortisol / OCS	<0.5 mcg/dl / on 8 mg MP	5.6 mcg/dl

	SPT wheal size	**Specific IgE**	**SPT wheal size**	**Specific IgE**
Histamine	 5mm	N/A	 5mm	N/A
D. pteronyssinus	 7mm	2.24 kua/l	 4mm	1.55 kua/l
D. farinae	 7mm	2.5 kua/l	 4mm	1.71 kua/l
Cockroach	 3mm	0.91 kua/l	 <3mm	0.81 kua/l

RCAT-Rhinitis Control Assessment Test, ACT-Asthma Control Test, FEV-Forced Expiratory Volume, FVC-Forced Vital Capacity, PEFR-Peak Expiratory Flow Rate, AEC-Absolute Eosinophil Count, OCS-Oral Corticosteroids, MP-Methyl Prednisolone.

Table 2: Clinical characteristics of case 2.

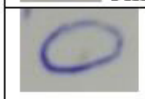
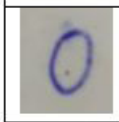
	CASE 3	
	2017	**2018**
RCAT/ACT scoring	12/12 Baseline	22/20
FEV1	77%	97%
FEV1/FVC	80%	90.6%
PEFR (variability)	300-400 L/mts (25%)	450-500 L/mts (10%)
Total IgE	2597 IU/ML	3100 IU/ml
Eosinophil % / AEC	7.4 % / 363 cells/ul	3% / 157 cells/ul
Serum cortisol / OCS	1.2 mcg/dl / on 8 mg MP	6.2 mcg/dl

	SPT wheal size	**Specific IgE**	**SPT wheal size**	**Specific IgE**
Histamine	 5mm	N/A	 5mm	N/A
D. pteronyssinus	 10mm	>100.0 kua/l	 5mm	52.0 kua/l
D. farinae	 10mm	93.30 kua/l	 5mm	50.3 kua/l
Cockroach	 7mm	11.20 kua/l	 3mm	4.7 s kua/l

RCAT-Rhinitis Control Assessment Test, ACT-Asthma Control Test, FEV-Forced Expiratory Volume, FVC-Forced Vital Capacity, PEFR-Peak Expiratory Flow Rate, AEC-Absolute Eosinophil Count, OCS-Oral Corticosteroids, MP-Methyl Prednisolone

Table 3: Clinical characteristics of case 3.

	CASE 4	
	2016	**2018**
RCAT/ACT scoring	10/11 Baseline	23/23
FEV1	60%	84% without OCS
FEV1/FVC	76.8%	86%
PEFR (variability)	240-300 L/mts (33%)	320-350% (8.5%)
Total IgE	1417 IU/ML	591 IU/ml
Eosinophil % / AEC	17.20 % / 1980 cells/ul	6.2 % /601 cells/ul
Serum cortisol / OCS	<0.50 mcg/dl / on 12mg MP	5.4 mcg/dl

	SPT wheal size	**Specific IgE**	**SPT wheal size**	**Specific IgE**
Histamine	 5mm	N/A	 5mm	N/A
D. pteronyssinus	 8mm	1.02 kua/l	 4mm	0.44 kua/l
D. farinae	 8mm	1.4 kua/l	 4mm	0.69 kua/l
Cockroach	 7mm	0.16 kua/l	 2mm	0.17 kua/l

RCAT-Rhinitis Control Assessment Test, ACT-Asthma Control Test, FEV-Forced Expiratory Volume, FVC-Forced Vital Capacity, PEFR-Peak Expiratory Flow Rate, AEC-Absolute Eosinophil Count, OCS-Oral Corticosteroids, MP-Methyl Prednisolone.

Table 4: clinical characteristics of case 4.

	CASE 5	
	2017	**2020**
RCAT/ACT scoring	$12/13_{Baseline}$	22/23
FEV1	78% / 96% after bronchodilator	84%
FEV1/FVC	67.7% / 82.3% after bronchodilator	86.6%
PEFR (variability)	400-500 L/mts (20%)	550-600 L/mts (8.3%)
Total IgE	69.1 IU/ML	20 IU/ml
Eosinophil % / AEC	10.7 % / 1059 cells/ul	2 % /220 cells/ul
Serum cortisol / ACTH/ OCS	0.7 mcg/dl / <5 pg/ml/ on 16mg	1.73 mcg/dl /<5 pg/ml/ on 8 mg AD
	SPT wheal size **Specific IgE**	**SPT wheal size** **Specific IgE**
Histamine	 5mm N/A	 5mm N/A
D. pteronyssinus	 8mm <0.1 kua/l	 4mm 0.03 kua/l
D. farinae	 8mm <0.1 kua/l	 4mm 0.03 kua/l
Cockroach	 3mm <0.1 kua/l	 4mm 0.01 kua/l

RCAT-Rhinitis Control Assessment Test, ACT-Asthma Control Test, FEV-Forced Expiratory Volume, FVC-Forced Vital Capacity, PEFR-Peak Expiratory Flow Rate, AEC-Absolute Eosinophil Count, OCS-Oral Corticosteroids, MP-Methyl Prednisolone, ACTH-Adrenocorticotropin Hormone, AD-Alternate Day

Table 5: Clinical characteristics of case 5.

No. of Visits	**1st Visit**	**2nd Visit**	**3rd Visit**	**4th Visit**	**5th Visit**	**6th Visit**
Cluster Dose AIT (500 AU per 0.5ml per MD) Combined with ***Inj Omalizumab (150mg)****	0.05/0.05ml @ 60 mts interval (100 AU)	0.1/0.1 ml @ 60 mts interval (200 AU)	0.2/0.2 ml @ 60 mts interval (400 AU)	0.3/0.2 ml @ 60 mts interval (500 AU)	0.5 ml (500 AU)	0.5 ml (500 AU) M.D (500 AU)
Cluster Dose frequency	First day	10-12 days	10-12 days	15-20 days	20-30 days	Every 4 weeks
Inj Omalizumab (150mg) X 15 days before AIT followed by once in a month in variable duration ***[case 1 for 10 months, case 2 for 17 months, case 3 for 11 months, case 4 for 25 months, case5 for 15 months X omalizumab given]***						

AU-Allergy Unit, MD-maintenance dose (500 AU), conc.-concentration, AIT-Allergen Immunotherapy, HDM-Hose Dust Mite

Table 6: Schedule and duration of Combined House Dust Mite Subcutaneous Cluster Immunotherapy (HDM-SCIT) (Dp-50%, Df-50% 500 AU per MD) along with Inj Omalizumab therapy.

Discussion

Steroid-dependency generally occurs following uninterrupted steroid intake for more than a year at a dose of 0.3 mg/kg/day with basal serum cortisol <3 mcg/dL (PPV 93%) [12]. Adrenal Insufficiency (AI) is defined as basal cortisol <85 nmol / L/ 3.1 ug/dL

(specificity of 99.7%) and Serum cortisol level >350 nmol/L / 12.7 mcg/dL (sensitivity 98.9%) will rule-out AI [13]. Our five cases were clinically defined as Steroid-Dependent Allergic Rhinitis with Asthma, when OCS was added then symptom control was achieved with normal lung function despite the maximum dose of LABA, LAMA, ICS. This definition however is ambiguous (Difficult-to-control asthma). The diagnosis of HDM- driven Allergic Asthma in our five cases relies on the proof of HDM (Dp/ Df) sensitization together with a detailed clinical history showing typical symptoms of asthma induced by HDM exposure. In addition, the gold standard diagnosis of dust mite allergy could be perfect asthma control in HDM-FREE environment [7]. These patients underwent Skin Prick Test (SPT) (AllergoPharma, Germany/ Greer Lab, USA) and Specific IgE (Thermofisher, ImmunoCap) to aeroallergens after giving an informed consent. HDM-SCIT with effective dose could not be started because of fear of adverse reaction to allergen extract, so Omalizumab was prescribed 15 days before the start of build-up dose of HDM extract by cluster-immunotherapy (the schedule of administration involve effective concentration of 1000 AU per ml with increasing concentration 0.05-0.05 ml , 0.1/0,.1 ml, 0.2/0.2 ml, 0.3/0.2 ml till maintenance dose (MD) of 0.5 ml of 1000 AU per ml) was achieved. Further MD of HDM-SCIT was continued every 4 weeks for 3 years along with Inj Omalizumab 150 mg given every 4 weeks varying from 10-25 months as shown in Table 6. In four of our cases (Case 1-4), combined HDM-SCIT with Omalizumab led to significant steroid-sparing effect and discontinuation of OCS along with 50-60% reduction in the use of ICS after 12 months with relative improvement in RCAT & ACT scoring, FEV1, FEV1/FVC ratio, PEFR variability and increase in serum cortisol levels after 12 months (Tables 1-4). While in Case 5, there was marked improvement in lung function and quality of life but the reduction in OCS was marginal (Table 5) even after 15 months of taking Omalizumab, which could be due to Hypothalamus-Pituitary-Adrenal Suppression (HPA Suppression) [serum cortisol (0.7 mcg/dl BASELINE/ 1.73 mcg/dL) and ACTH levels (<5 pg/mL) were persistently low].

In clinical practice it is often challenging to discontinue Omalizumab and AIT in patients with steroid-dependent Allergic Rhinitis with Asthma. Four of our patients were successfully treated to achieve steroid-free clinical remission after 12 months of combined HDM-SCIT along with Omalizumab (Anti-IgE). We have three years follow-up of these four cases showing an improvement in Lung function and serum cortisol.

Conclusion

Combined Allergen Immunotherapy with Omalizumab was found to be efficacious, safe with steroid-sparing effect. We hypothesize, both have synergistic-significant immune-modulatory activity. More studies are necessary to investigate the combined treatment of HDM-SCIT and Omalizumab with reference to efficacy, safety, synergistic patho-physiological mechanism.

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