7

House Dust Mite Immunotherapy in Iraqi Patients with Allergic Rhinitis and Asthma

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1. Introduction

Respiratory allergy (allergic rhino conjunctivitis and allergic asthma), is community encountered medical condition that cause substantial morbidity and mortality worldwide [1]. Asthma is still remains a concerning and coasty epidemic that is largely unexplained [2]. In Iraq, both allergic rhinitis and asthma cause poor performance at work and school and diminished quality of life [3]. Suspected allergen(s) avoidance is the first-line treatment for these conditions. However, in many cases, exposure to a particular allergen cannot be completely avoided [4]. Pharmacotherapy, whether that reversing inflammation or controlling the effect of released mediators are not always fully effective or well tolerated [4]. Allergen immunotherapy is widely accepted as an efficacious treatment in allergic rhinitis and asthma [5-9]. Well characterized dust mite extracts have shown significant benefit by reducing symptoms, medication requirements and sensitivity to dust mite allergens [10]. Recent studies of specific immunotherapy using standardized extracts also showed improvement in symptoms, medication and bronchial hyperresponsiveness [10-13]. However, Adkinson et al [14] were unable to show any significant improvement in symptoms, medication use, peak flow rate, BHR or rate of asthma remission following multiple allergens SIT in asthmatic children.

More recent studies in children and adults show additional positive outcomes of SIT which are decreased tendency for additional environmental sensitization [15], as well as a decreased incidence of asthma in treated allergic rhinitis patients [16]. Although the documented effectiveness of SIT in the treatment of allergic rhinitis and allergic asthma, the real life efficacy and use of this treatment option is severely limited by perceived low patient compliance [17, 18], adverse local and systemic side effects [19, 20] and significant delay in effect after the initiation of therapy, all of which may lead to relatively low adherence rate [8].

Although there is much and convincing evidence for SIT effectiveness and efficacy from international studies only single study has prospectively investigated the real-life efficacy in Iraqi patients [21]. This prospective study of patients undergoing SIT in an office setting to produce practical data of efficacy of house dust mite extracts for allergic patients in Iraq.

Objectives: To

1. Determine the therapeutic efficacy of house dust mite immunotherapy in Iraqi patients with allergic rhinitis and asthma.
2. Clarify whether specific immunotherapy of therapeutic benefits in patient with asthma and allergic rhinitis.

2. Patients and methods

2.1 Patients

From January 2000 to December 2008, we selected 822 patients with allergic rhinitis and asthma to receive subcutaneous specific immunotherapy according to European Academy of Allergy and Clinical Immunology (EAACI) guidelines [22] in a double blind placebo controlled clinical trial. Subjects were recruited from asthma clinic in the city of Tikrit, Iraq, only subjects who fulfilled the GINA guidelines for mild to moderate asthma and/or allergic rhinitis [23] and had positive skin prick-test to *Dermatophagoides pteronyssinus* and/or *D. farines* were included.

Subjects excluded if their PEER of <80% of predicted value recorded on 3 occasions during the 2 week prior to randomization, with positive SPT to animals and pets at home; asthma exacerbation during the last month prior to first visit, forced expiratory volume at 1 second (FEV1) of <60% predicted during the screening visits, had any serious chronic underlying illness. Patients were evaluated by medical history, clinical examination and skin prick test with common allergen. All data were collected prospectively, including information on exposure, social factors, additional diagnosis and medication usage, family history of allergic diseases, exposure to house pets, active or passive smoking, measures of treatment efficacy, and patients' satisfaction as well as local and systemic reactions to the SIT shots. The protocol was approved by Tikrit University College of Medicine Ethical Committee and informed written consent taken from each patient. After patient selection, they were randomized to SIT and/or placebo and pharmacotherapy. The two groups were comparable at baseline (Table-1).

Variable	Immunotherapy	Placebo	P value
Patients no.	411	411	NS
Female/Male	198/213	194/217	NS
Defaulted	73(18%)	94(23%)	NS
Patients for analysis	338(82%)	317(77%)	NS
Age range	6-65	6-65	NS
Age mean	32±15	31±18	NS
Clinical history			
AR	52(15%)	54(17%)	NS
Asthma	115(34%)	107(34%)	NS
AR+ Asthma	171(51%)	156(49%)	NS
Use of medication			
Antihistamine	270(80%)	269(85%)	NS
Glucocorticoids	135(39%)	127(40%)	NS
B2-mimetics	166(49%)	149(47%)	NS
Mast cell stabilizer	101(30%)	111(35%)	NS

Table 1. Patient characteristics.

2.2 Asthma and allergic rhinitis diagnosis

The diagnosis of asthma and classification was performed by specialist physicians based on the National Heart Blood and Lung Institute / World Health Organization (NHLBI/WHO) workshop on the Global Strategy for Asthma [24]. Allergic rhinitis diagnosis was performed according to previously reported guidelines [25].

2.3 Lung function test

Computerized Spirometer (Autosphiror, Discom-14, Chest Corporation, and Japan) was used for measurement of FEV1 predicted percent of the patients at their enrollment in the study and when indicated according to studies design.

2.4 Skin prick test

The skin prick tests were performed for all patients and control and evaluated in accordance with European Academy of Allergy and Clinical Immunology subcommittee on allergy standardization and skin tests using standards allergen panel (Stallergen, France). The panel for skin test include: dust mite (Dermatophagoides farina, Dermatophagoides peteronyssinus), Aleternaria, Cadosprium, Penicillum mixture, Aspergillus mixture, Grasses mixture, Feather mixture, Dog hair, Horse hair, Cat fur, Fagacae, Oleaceae, Betulaceae, Plantain, Bermuda grass, Chenopodium and Mugworth. All tests were performed in the outpatient Asthma and Allergy Centre, Mosul by a physician using a commercial allergen extracts (Stallergen, France) and a lancet skin prick test device. A wheal diameter of 3 mm or more in excess of the negative control was considered as positive test result.

2.5 Allergen extracts for SCIT

Therapeutic vaccines containing allergen extracts were purchased from Stallergen, France. Both aqueous and glycenerated extracts were used to achieve a concentrate of 1:100 w/v of the mixed extract. In standardized extracts the stock formulation was prepared by tenfold dilution. Separate vial was used for allergen extract to reduce proteolysis degradation. All extracts were stored at 8 ^{0}C . Therapeutic vaccine varied with each individual patient based on specific allergen identified during testing. Moist patients received a variety of aeroallergen combination.

2.6 SCIT protocol

The treatment protocol is of two stage, the attack and maintenance stages. The attack treatment with gradual increase in dose and concentration of vaccine content were carried weekly for a period of 20 weeks. The vaccine is injected by deep subcutaneous route in the posterior aspect of upper arm. The maintenance treatment dose given in a constant dose every 15 days and then every 4 or 6 weeks interval. The interval between two maintenance injections must not exceed 6 weeks. Local reaction size was measured 20 minutes after each injection. Observed large local reactions (more than 20 mm wheal size) mandated a repeat of the same dose on the next visit, while systemic allergic reactions (skin, respiratory, cardiovascular, and / or gastrointestinal) required a two fold reduction in vaccine concentration. Maintenance dose was set in most cases at 0.5 of the stock standardized extracts.

2.7 Immunotherapy schedule

Immunotherapy was given in term of conventional schedule. Conventional Immunotherapy build- up was typically given as injection per week until the maintenance dose was reached and it was given once monthly. Allergen vaccines were administered subcutaneously according to EAACI guidelines [26] after the patients had given their informed consent.

3. Evaluation of treatment efficacy

3.1 Symptom score

A 10 cm visual analogue scales from 0=absent to 10=sever symptoms, for each symptom: rhinorrhoea, nasal congestion, nasal itching, ocular itching, sneezing, asthma symptoms (chest tightness, shortness of breath, cough) and wheezing as recommended by the ARIA review [27]. A change of 2 or more points on this scale is considered a clinically significant change with consequent significant change in the patient quality of life.

3.2 Medication score

Medication usage was recorded by patients on a VAS from 0=no medication to 10=repeated daily use of nasal corticosteroids, antihistamine oral medication, eye drops, inhaler corticosteroids, systemic corticosteroids, and beta agonists.

Patients graded their symptoms retrospectively at each visit. The use of rescue medication was recorded on the diary card in addition to regular medications.

3.3 Determination of serum eosinophil cationic protein

Serum ECP was determined by ELISA kit (MBL MESCACUP ECP TEST) from Medical and Biological Laboratories Co. LTD, Japan. Serum ECP determined by ELISA kit (MBL MESCACUP ECP TEST) from Medical and Biological Laboratories Co, LTD, Japan. This ELISA detects s human ECP with a minimum detection limit of 0.125 ng/ml. The test performed according to the instruction of manufacturer. Briefly, In the wells coated with antihuman ECP monoclonal antibody, 100 ul of diluted serum samples (1:5 sample diluents) or standards were added and incubated for 60 minutes at room temperature (20 - 25 0C). After washing for 4 times, a 100ul of peroxidase conjugated antihuman ECP polyclonal antibody is added into the wells and incubated for 60 minutes at room temperature. After another 4 times washing, a 100 ul of peroxidase substrate reagent is added to each well and the plate incubated for 10 minutes at room temperature. The add 100 ul of stop solution (0.5 mol/l H_2SO_4) and read the absorbance at 450 nm using a microplate reader. The concentration of ECP is calibrated from a standard curve based on reference standards.

3.4 Statistical analysis and data collection

The results of the study are reported as ratios and/or percentage of the entire cohort. Paired sample t-test was used for the comparison of symptoms and medication scores. Chi square test was used for comparison of the SPF and pulmonary function test in both groups, using SPSS computer package. P values of < 0.05 were considered significant.

4. Results

A total of 822 patients were randomized into two treatment groups (411 for each). Of them 167 subject defaulted during the trial (73 subjects, 18% in the SIT group; 94 subjects, 23% in placebo group). In most cases this was due to logistical barriers, work schedule, travel distance to the clinic and patients and some doctors wrong opinion regarding SIT. Thus 655 subjects were eligible for analysis (338 subjects, 82% in the SIT group; 317 subjects, 77% in the placebo group), with age range of 6-65 years (Mean 32±15 for SIT group and 31±18 for the placebo group), completed at least 3 years of treatment. There was no significant difference in the frequency of AR, Asthma and AR with asthma between immunotherapy and placebo groups.

4.1 Asthma group

A negative PFT was demonstrated in 87% of asthmatic patients receiving SIT and in 91% of patients in placebo group (P=0.0001). In addition PFT improvement was demonstrated in 67% in SIT group and in 19% of placebo group (P=0.0001). Symptom score reduced from 7.56±1.84 to 3.30±1.74 in SIT group (P=0.0001), while it was reduced from 7.63±1.66 to 7.11±2.65 in placebo group (P=0.08). Medication score significantly declined from 5.38±1.12 to 2.20±0.90 in SIT group. While in placebo it was reduced from 5.30±1.41 to 4.94±1.31 in the placebo group (P=0.05). Combined symptom and medication score significantly (P=0.0000) declined from 6.64±1.48 to 2.73±0.97 in SIT group. In placebo group the reduction was not significant (P=0.99). Serum ECP reduced significantly (P=0.000) in both SIT (29.3±7.21 to 15.3±4.11) and placebo (27.1±6.14 to 17.2±3.27). Table -2.

Variables	Immunotherapy	Placebo	P value
No of patients	115	107	
SPT negative	87%	9.1%	0.0001
PFT improvement	67%	19%	0.0001
Symptom score			
Pre- treatment	7.56(0.84)	7.63(0.66)	0.49
Post-treatment	3.30(0.74)	5.56(0.65)	0.0001
P value	0.0001	0.0004	
Medication score			
Pre-treatment	5.38(1.12)	5.30(1.01)	0.94
Post-treatment	2.20(0.90)	3.84(1.11)	0.001
P value	0.0003	0.002	
Combined symptom and medication score			
Pre-treatment	6.64(1.48)	6.47(1.47)	0.39
Post –treatment	2.73(0.97)	4.70(1.25)	0.0001
P value	0.0001	0.0001	
ECP			
Pre –treatment	29.3(7.21)	27.1(6.14)	0.01
Post –treatment	15.3(4.11)	17.2(3.27)	0.0002
P value	0.0001	0.0001	

Table 2. Response to SCIT in patients with asthma.

4.2 Allergic rhinitis group

After 3 years of intervention, negative SPT demonstrated in 81% of patients receiving SIT and in 19% of placebo group (P=0.000). Symptom score reduced significantly (P=0.0001) from 6.61±1.62 to 2.71±0.74 in SIT group. The reduction of symptom score in placebo group was not significant (6.67±1.37 to 6.00±1.16, P=0.99). Furthermore, medication score declined significantly (P=0.0001) from 5.35±1.85 to 2.21±1.87 in SIT group, while the reduction was not significant (P=0.98) in placebo group.

In addition, combined medication and symptom score was significantly reduced (P=0.0001) from 6.12±1.7 to 2.52±1.78 in SIT group, while the reduction in placebo group was not significant. Serum ECP reduced significantly in both SIT (19.3±7.01 to 14.2±5.10, P=0.0001) and placebo group (20.1±5.30 to 17.3±6.31, P=0.014) Table -3.

Variables	Immunotherapy	Placebo	P value
No of patients	52	54	
SPT negative	81%	19%	0.0001
Symptom score			
Pre-treatment	6.61(1.62)	6.67(1.37)	0.76
Post -treatment	2.71(0.74)	5.64(1.16)	0.0001
P value	0.0001	0.0001	
Medication score			
Pre –treatment	5.35(1.85)	5.3(2.27)	0.85
Post –treatment	2.21(0.87)	4.10(2.44)	0.0001
P value	0.0001	0.009	
Combined symptom and medication score			
Pre-treatment	6.12(1.7)	6.16(1.75)	0.86
Post -treatment	2.52(0.78)	5.10(1.80)	0.0001
P value	0.0001	0.002	
ECP			
Pre-treatment	19.3(7.01)	20.1(5.30)	0.37
Post -treatment	14.2(5.10)	17.3(6.31)	0.0001
P value	0.0001	0.014	

Table 3. Response to SCIT in patients with allergic rhinitis.

4.3 Patients with both allergic rhinitis and asthma

PFT improvement was demonstrated in 65% of SIT group while it was 25% in placebo group (P=0.0001). In addition, negative SPT was demonstrated in 78% of patients receiving SIT, while the corresponding value was 23% in placebo group (P=0.0001).

Symptom score declined significantly (P=0.0001) from 7.56±1.87 to 3.42±1.55 in SIT group, while the reduction in placebo group was not significant (P=0.052).

Medication score reduced significantly (P=0.0001) from 5.22±2.72 to 2.72±1.53 in SIT, but the reduction in placebo group was not significant (5.30±1.99 to 4.99±1.86, P=0.10).

Combined symptom and medication score reduced significantly (P=0.0001) from 6.72±1.51 to 3.18±1.63 in SIT, while the reduction in placebo group was not significant (6.32±2.72 to 6.32±1.99, P=0.31).

Serum ECP reduced significantly (P=0.0001) in both SIT (34.2±13.2 to 16.3±6.72) and placebo group (31.1±11.7 to 19.2±5.4) Table -4.

Variables	Immunotherapy	Placebo	P value
No of patients	171	156	
SPT negative	78%	23%	0.0001
PFT improvement	65%	25%	0.0001
Symptom score			
Pre –treatment	7.56(0.87)	7.35(0.84)	0.06
Post – treatment	3.43(0.55)	5.69(0.87)	0.0001
P value	0.0001	0.0001	
Medication score			
Pre –treatment	5.22(0.89)	5.30(0.79)	0.48
Post –treatment	2.72(0.53)	4.26(0.86)	0.0001
P value	0.0001	0.0001	
Combined symptom and medication score			
Pre-treatment	6.72(1.51)	6.62(1.29)	0.59
Post -treatment	3.18(0.63)	5.19(1.10)	0.0001
P value	0.0001	0.0001	
ECP			
Pre –treatment	34.2(13.20)	31.1(11.7)	0.34
Post -treatment	16.3(6.72)	19.2(5.4)	0.0005
P value	0.0001	0.0001	

Table 4. Response to SCIT in patients with asthma and allergic rhinitis.

4.4 All patients

We combined the data of the three groups together. There was a significant decline (P<0.0001) in symptom score from baseline value to that of after 3 years intervention in the SIT (P=0.0001, 7.29±1.2 to 3.18±1.54), but not in the placebo treated subjects (7.23±2.89 to 6.93±1.85, P=0.12). Medication score significantly (P=0.0001) declined in SIT (5.38±1.05 to 2.42±1.66), and placebo (5.31±2.38 to 4.82±2.14, P=0.03).

The SIT resulted in significant (P=0.0001) decline in combined symptom and medication score (6.61±1.46 to 2.91±1.68). In addition, placebo group demonstrated a significant reduction (P=0.03) in combined medication and symptom score (6.27±2.37 to 5.88±2.2).Serum ECP reduced significantly (P=0.0001) in both SIT (30.2±7.9 to 15.6±2.32) and placebo (27.9±6.37 to 18.2±5.8) groups. Table -5.

Variables	Immunotherapy	Placebo	P value
No of patients	338	317	
SPT negative	82%(5)	17%(7)	0.0001
PFT improvement	66(2)	22(4)	0.0001
Symptom score			
Pre –treatment	7.29(1.20)	7.23(0.99)	0.48
Post –treatment	3.18(0.54)	5.63(0.85)	0.0001
P value	0.0001	0.0001	

Variables	Immunotherapy	Placebo	P value
Medication score			
Pre –treatment	5.38(1.05)	5.31(1.08)	0.62
Post treatment	2.42(0.66)	4.10(1.15)	0.0001
P value	0.0001	0.0001	
Combined symptom and medication score			
Pre –treatment	6.61(1.46)	6.54(1.37)	0.71
Post –treatment	2.91(0.68)	5.10(1.20)	0.0001
P value	0.0001	0.0001	
ECP			
Pre –treatment	30.2(7.9)	27.9(6.37)	0.01
Post -treatment	15.6(2.32)	18.2(5.8)	0.0001
P value	0.0001	0.0001	

Table 5. Response to SCIT in all patients.

4.5 Percentage and amount of score changes

The SIT resulted in significantly (P=0.0001) greater subjective rating of improvement than placebo treatment in all four parameters (symptom score, medication score, combined symptom and medication score, and serum ECP). Whether the analysis performed for each disease condition alone (allergic rhinitis, asthma, both allergic rhinitis and asthma) or combined in one group (all patients).

The results are summarized in Table -6.

Variables	Immunotherapy	Placebo	P value
No of patients	338	317	
SPT negative	277	54	0.0001
PFT improvement	223	70	0.0001
Asthma group			
Symptom score	4.17(55.2%)	2.07(27%)	0.0001
Medication score	3.18(59.1%)	1.46(27.5%)	0.0001
Both scores	3.73(56.2%)	1.77(27.4%)	0.0001
ECP	15.3(52.2%)	9.9(36.5%)	0.0001
Allergic rhinitis group			
Symptom score	3.91(59.2%)	1.03(15.4%)	0.0001
Medication score	3.14(59%)	1.20(22.6%)	0.0001
Both scores	3.60(59%)	1.06(17.2%)	0.0001
ECP	5.10(26.4%)	2.80(14%)	0.0001
Allergic rhinitis and Asthma group			
Symptom score	4.13(55%)	1.66(22.5%)	0.0001
Medication score	2.50(48%)	1.04(20%)	0.0001
Both scores	3.54(53%)	1.43(22%)	0.0001
ECP	17.90(52.3%)	11.90(38.3%)	0.0001
All patients			
Symptom score	4.11(56.4%)	1.60(22.1%)	0.0001

Variables	Immunotherapy	Placebo	P value
Medication score	2.96(55%)	1.21(23%)	0.0001
Both scores	3.7(56%)	1.44(22%)	0.0001
ECP	14.60(48.3%)	9.70(35%)	0.0001

Table 6. Reduction in clinical scores following SIT in patients with asthma and allergic rhinitis.

5. Discussion

Despite numerous studies, the role of IT in the management of asthma remains controversial [28, 29], and interpretation of published reports varies considerably, presumably because of personal bias [30]. The variability in response to SIT in allergic diseases as reported in the literature may be due to uncontrolled factors that differ for people receiving the same therapy [30]. These factors are environmental control measures, degree of allergen exposure, type of allergen exposure, presence of allergenic sensitivities not incorporated into the treatment; non-allergenic triggers of asthma such as infection or exposure chemical sensitizer, genetic influence and source of vaccine used in IT. Furthermore, the outcome of the treatment trial influenced by allergen specificity used in the treatment as well as the dose and treatment schedule employed in the course.

This is the first clinical trial that evaluated the effectiveness of SIT in Iraq, and includes a large treatment group, in which the outcome measured using objective criteria.

The current study shows conclusively that house dust mite SIT results in significant improvement in allergic rhinitis and asthma, symptoms and reduction in rescue medication requirement. The results of this study differ from that of less successful studies [14, 31] with a population more heterogeneous in their allergen sensitivities. In our study we used a single allergen for treatment, as the house dust mite, Dermatophagoides, was by far the most important allergen in our study population. However, this study finding was in agreement to that reported by others [10, 32-36].

Immunotherapy has been established as efficacious treatment for allergic rhinitis by seasonal pollens, dust mite, and animal allergens, some studies show controversial findings [30]. A recent review [37] concluded that immunotherapy is highly effective in the treatment of allergic rhinitis. Several reported studies have shown that immunotherapy is effective for the treatment of AR, both in adults and children [14, 38, 39].

This study indicated that HDM immunotherapy significantly reduced symptom score, medication score and serum ECP level. Furthermore, in patients with both AR and asthma, HDM IT significantly reduced the symptom score, medication score and serum ECP mean level. However, the response was superior in group of patients with AR alone as compared to group of patients with AR and asthma. This finding is consistent with that reported by others [33].

Avoidance and medication provide suboptimal control of AR in up to 40% of some patient populations [40]. However, this study demonstrated that HDM IT induced a 59% reduction in combined symptom & medication score in patients with allergic rhinitis, while the corresponding value was 53% for patients group with asthma and AR. The reported studies

indicated efficacy of SIT in AR in adults and children [9, 41-45]. There are clinical and immunological evidence that supports the long term efficacy of SIT [46].

In our study we don't use BHR to a direct stimulus such as methacholine or histamine since it has poor correlations with indices of airway inflammation such as sputum eosinophils [47-49]. Thus we used serum ECP because it is a better marker of airway inflammation in asthma as in correlates with sputum eosinophils [49] and PFT following IT and medication [50]. Serum ECP level decreased after 2 years of immunotherapy in perennial allergic rhinitis [51] and asthma [50]. However, the rise in serum ECP after allergen challenge was significantly attenuated after just 1 year of immunotherapy in asthmatic patients [52]. Our study indicated a significant decrease in serum ECP in both SIT and placebo treated subject. However, the reduction was significantly higher in SIT group as compared to placebo group for patients with AR, Asthma, and AR with Asthma and when the data of patients pooled together. In placebo treated group decline in serum ECP may be due to treatment with inhaled corticosteroids.

When the data of three disease groups pooled together, the symptom score, medication score, combined score and serum ECP significantly reduced in SIT as compared to placebo treatment group. Furthermore, SPT negative results and PFT improvement were significantly higher in SIT compared to placebo group.

In this study SIT induces a significant reduction in all parameters used in the study whether the patients were with AR, asthma or both combined together. SIT shows overall percent reduction of 54%, while it was 17.5% in placebo group.

Based on the finding of this and other studies, single allergen SIT is likely to be beneficial to patients with AR, asthmatic and with both, sensitized to a dominant allergen. However, there are other drugs such as inhaled long acting B_2-agonist and anileukotriens agents that might be better at symptom control and lung function improvement, SIT has some unique benefits [10].

Haugaard et al [53], reported that SIT reduce airway sensitivity to allergens, which may lead subsequently to reduction in frequency of exacerbation and severity of asthma triggered by allergen exposure. In addition, the effect of SIT may persist for at least 5-6 years after the end of treatment [53]. Furthermore, SIT reduces the conversion of AR to asthma [51] and prevents the development of new sensitization [44].

Different studies show controversial outcome for SIT. Failure to respond to SIT may be due to: inadequate dose of allergen, missing allergens not identified during the allergy evaluation, inadequate environmental control, and exposure to non allergenic triggers.

Systemic adverse reactions were developed in 62 (15.1%) individuals from the 411 subjects included in the study. None of the developed systemic reactions had life threatening reactions. House dust mite was with a predictive value for development of systemic adverse reactions (OR=2.3, p=0.0001) [54]. However, this study indicated that HDM specific immunotherapy was with good tolerance

6. Conclusion

HDM immunotherapy for 3 years significantly reduced symptom and medication use in AR, asthma and patients with both conditions, and prevent the consequent development of

asthma in patients with AR. This was associated with a greater subjective improvement in asthma control.

7. References

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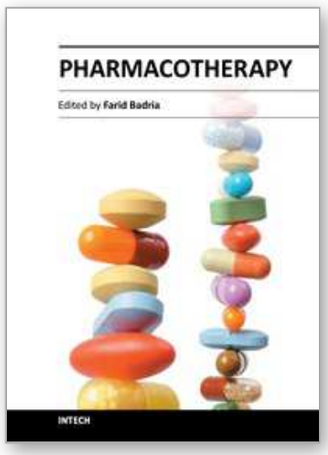

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The intent of this book is to provide an overview of current conceptualizations of Pharmacotherapy. The book focuses on three major areas; diagnosis, treatment, and prevention for a wide array of diseases; Cognitive and Psychological disorders (Schizophrenia and Nicotine addiction), Inflammatory disorders (New Chemical anti-inflammatory and Immunotherapy), updated antihypertensive therapy and healing of ulcers with venous origin. A separate chapter is dedicated to the rationality of drug use in earthquake injuries. The last chapter deals with Imaging of potential therapeutic or diagnostic agents in animal models in the early stage of research. We hope this book is useful to a wide range of people, from students first learning about Pharmacotherapy, to advanced clinicians and researchers.

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