The Impact of Sublingual Immunotherapy in Quality of Life in Allergic Rhinitis Patients

Abstract

Background: Immunotherapy has proven its efficacy in multiple randomized control trials (RCT) in treating allergic rhinitis (AR) as it induces induces long term remission after discontinuation and prevent new sensitization.

Objective: Our aim is to look into earliest improvement of quality of life (QOL) in AR patient treated with Sublingual immunotherapy (SLIT).

Methodology: Patients who were sensitized to dust mites (*Dermatophagoides farinae*, *Dermatophagoides pteronyssinus* and *Blomia tropicalis*) were enrolled into the study. All patients were treated with SLIT for 6 months. The patients were assessed using rhinoconjunctivitis quality of life questionnaires (RQLQ) and peak nasal inspiratory flow (PNIF) pre-treatment at 1, 3 and 6 months post SLIT. The usage of intranasal corticosteroids (INS) and antihistamine were documented in medication diary. The data for pre and post treatment for RQLQ results were analysed using paired T-test and medication diary were analysed using ANOVA test.

Results: A total of 53 patients were enrolled in the study. The mean RQLQ score showed significant result at 3 and 6 months post SLIT ($p<0.05$). Significant improvement seen in the mean PNIF value pre-treatment (81.54 L/min ±29.36) compared to mean PNIF value at 3 months (92.0L/min ±29.03) and 6 months (96.13L/min ±26.67) post SLIT ($p<0.05$). The dependency of patients towards pharmacotherapy also showed a significant reduction at 3 and 6 months post SLIT ($p<0.05$).

Conclusion: Our study showed a significant improvement of patients' quality of life as early as 3 months of post SLIT treatment.

KEYWORDS

Immunotherapy, quality of life, allergic rhinitis

INTRODUCTION

Allergic Rhinitis (AR) is a highly prevalent, allergy-induced upper-airway inflammatory disease. It is characterized by symptoms of chronicity with periods of acute exacerbation due to immunoglobulin-E (IgE) mediated inflammation of the nasal mucosa after allergen exposure. The clinical presentations are sneezing, watery nasal discharge, nasal obstruction and itchiness. Previously, it was classified into seasonal and perennial AR. However since the introduction of Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines in 2004, its classification has changed to intermittent and persistent AR[1,2].

Allergic march is a sequential progression of atopic dermatitis and food allergy in infants leading to chronic respiratory condition such as AR and asthma in school age children[3]. Sixty percent of allergies appears in the first year of life and 30-40% of children are affected[4]. Moreover, 20%-50% of AR patients are asthmatic suggesting its close relationship with asthma[5]. In Klang Valley, 19.8% of children aged 13-14 are affected and the prevalence of allergic rhinitis in Asia is 8.7%[6] . Most of symptoms manifest before 20 years of age and unlikely after 60 years which it regresses by 59 years[7]. In Malaysia, the commonest aeroallergens are house dust mites (*Dermatophagoides farinae*; DF, *Dermatophagoides pteronyssinus*; DP and *Blomia tropicalis*; BT) due to its tropical climate[8].

Immunotherapy has proven its efficacy in multiple randomized control-trials (RCTs) in treating AR . Its treatment in AR has made it less likely for the subsequent progression into asthma[9,10]. Sublingual immunotherapy (SLIT) has shown to induce long term remission lasting for 7 years after 3 years treatment and it may prevent new sensitizations[9,11]. World Allergy Organization Position Paper 2013 (WAO 2013) by Canonica et al reviewed 77 double-blinded, non-randomized , placebo-controlled trials of SLIT and they concluded that it was clinically effective in rhinoconjunctivitis and asthma[9]. However, it has a low evidence to support its effectiveness on the treatment of eczema[12].

Quality of life (QoL) is a subjective value a person places upon satisfaction with his or her life. AR can be a source of distress for many patients affecting QoL, work habit, sleep disordered breathing in childhood and adolescence[5]. Most of AR patients had their QoL affected and more than 90% of them reported the ability to do daily activity, work and classroom productivity are affected due to the symptoms[13].

Novakova et al., in their study on AR patients who had allergic sensitization to pollens and house dust mites started on sublingual immunotherapy. The study showed significantly increased QoL after completion of a three-year course of treatment[14]. To date, on Pubmed review, there is no data to suggest when is the earliest significance changes of QoL after initiation of SLIT. The aim of our study was to assess the patients' QoL and how long it would take to improve the patients' symptoms significantly post treatment.

MATERIALS AND METHODS

The study was conducted in the otorhinolaryngology clinic, from November 2017 till November 2019. The patients who were diagnosed with moderate to severe persistent AR with positive skin prick test or specific immunoglobulin E (IgE) with a highest sensitization to *Dermatophagoides farinae* (DF), *Dermatophagoides pteronyssinus* (DP) and *Blomia tropicalis* (BT) were enrolled in the study. The exclusion criteria were patients with other nasal conditions causing nasal obstruction such as nasal polyposis, severe deviated nasal septum and sinonasal tumor. Patients with poor lung reserves such as smokers and chronic lung diseases were also excluded.

Study Tools

1. Oraltek® Sublingual Immunotherapy (SLIT) (Immunotek, Spain)

All patient were treated with SLIT extracted from the same manufacturer and allergens used were dust mites (*Dermatophagoides farinae*; DF, *Dermatophagoides pteronyssinus*; DP and *Blomia tropicalis*; BT). There were two preparations of SLIT, either 2 in 1 (DP+DF) or 3 in 1 (DP+DF+BT). SLIT was given according to the skin prick test or specific IgE results. It was either the patients had highest sensitization to two types of dust mites: DP and DF or three types of dust mites: DP, DF and BT. SLIT did not require any dosage adjustment, given two sprays sublingually once daily. The final concentration was 30,000 Therapeutic Units

(TU)/mL in a solution cotaining NaCl 0.9 mg/mL and 50% Glycerol. Each spray delivers 100 µl. The patients had to keep the medication under the tongue for 2 minutes and then swallowed it.

2. Rhinoconjunctivitis Quality of Life Questionnaires (RQLQ)

The QoL was assessed subjectively using RQLQ. It is a disease specific validated questionnaires developed to assess the physical, emotional, and social impact of allergic rhinitis. RQLQ consists of validated 28-item in seven domains (activity limitation, sleep problems, nose problems, non-nose/eye symptoms, practical problems, nose symptoms and emotional function). Patients recorded their nasal symptoms and experiences during the previous 7-day period and chose the responses on a 0 – 6 point scale[15].

3. Peak Nasal Inspiratory Flow (PNIF)

PNIF is an objective assessment of nasal air flow where it measures the cross sectional areas in predetermined point of nasal cavity. Patients needed to be in standing position and measurement was taken in 3 consecutive times with a one-minute interval in-between. PNIF is an inexpensive device, easily applied, fast , portable and simple to measure[16].

4. Medication Diary.

All patients documented the daily usage of intranasal corticosteroids spray and anti-histamine medication in their medication diary during the study period.

5. Safety

The adverse reactions based on the intrinsic properties of the allergen extracts were categorized as immediate when the onset was during the first 30 minutes after the administration and delayed when the onset was afterwards. The systemic reactions were graded according to the WAO grading system on sublingual immunotherapy[9].

All patients were reviewed prior initiation of SLIT. The pre-treatment RQLQ and PNIF were recorded. They were reviewed at 1, 3 and 6 months post SLIT treatment and all were

assessed with RQLQ and PNIF. During the first month of SLIT, the patients were instructed to use both intranasal corticosteroids spray (INS) two puffs in each nostril twice daily and one tablet of antihistamine daily. Following the next five months, the medications were taken as a rescue medication if the AR symptoms were unbearable.

6. Statistical Analysis

The severity of AR, based on ARIA guideline 2008[17], pre and post treatment were analysed using chi-square test. The RQLQ and PNIF pre and post SLIT were statistically analyzed using Paired T-test. The values of INS and antihistamine used every month were analyzed using ANOVA of repeated measures.

RESULTS

Fifty three patients (31 females, 22 males; mean [SD] age, 24.21[±12] years) were recruited into the study. Eight patients were excluded from the study due to grade I adverse effects (WAO grading system) (Table 1). All patients had moderate-severe persistent AR. At six months of SLIT, 44 (95.6%) of patients' symptoms improved to mild-intermittent AR. However, 2 (4.4%) patients had no improvement with SLIT. (Table 2).

QoL assessment by RQLQ showed a significant improvement of the mean score post-SLIT treatment. The mean RQLQ score pre-treatment was 3.19. It reduced to 2.49 at 1 month ($p< 0.05$), 1.67 at 3 months ($p<0.05$) and 1.10 at 6 months ($p< 0.05$). The practical activity (mean=4.07) and nasal symptoms (mean=4.04) were the most affected in which the questionnaires consist of inconvenience of having to carry tissue or hankerchief, needed to rub nose/eye and needed to blow their nose repeatedly (Table 3, Figure 1).

The objective assessment revealed a significant increment of mean PNIF from pre-treatment (84.11; ±36.6) compared to post treatment at 1 month (88.55; ±29.36, $p=0.001$), 3 months (92.00; ±29.03, $p=0.001$) and 6 months (96.13; ±26.67, $p=0.001$) (Table 4, Figure 2).

INS and antihistamine were taken as rescue medications during the period of immunotherapy. During this period, patients may get desentitized to the allergens and the usage of rescue medication will be reduced over the months. ANOVA analysis showed a statistically

significant difference in the usage of INS and antihistamine towards the six months period (p=0.001, 95% CI). (Table 5, Figure 3)

5 patients had Grade 1 systemic complications (World Allergy Organization, WAO) of immunotherapy which were urticaria and worsening of rhinitis symptoms. 3 patients developed urticaria within 5 days of initiation of immunotherapy. All had repeated episode after continuation of therapy and symptoms subsided completely after ceasation of treatment. 5 patients had exacerbation of rhinitis symptoms (Table 1). None of these patients developed anaphylaxis.

DISCUSSION

The QoL of seasonal and perennial AR patients, in both adults and children have been shown to improve after 3 years of SLIT treatment [9,18,19]. In the previous Western studies, the SLIT treatment was given to patients who had dust pollens sensitization. In comparison to the Asian region whereby, 80% of AR patients are sensitized to dust mites (DP/DF/BT) which was the main inclusion criteria in our patients selection[6,8] .

During the early treatment with SLIT, there will be transient increased in antigen–specific IgE and the suppression of allergic Th2-mediated inflammation by regulatory T cells (Tregs) will only takes it effect at 4-12 weeks[9]. The patients may experience worsening of rhinitis symptoms at early period of treatment due to the increase antigen-specific IgE level, hence, in our study, compulsory pharmacological and SLIT combination treatment were initiated during the first month of therapy to alleviate the symptoms. It was also to standardize the treatment and eliminate outcome bias. The significant results at one month may be contributed by the combination of SLIT and pharmacological treatment. Subsequently, on the second month onwards, pharmacological treatment was administered only as a rescue medication. On reviewing the RQLQ at 3 months, the significant result were achieved ($p<0.05$) reflecting the true outcome of SLIT treatment alone. Each of the QoL aspect of RQLQ (activities, non hay fever symptoms, practical problems, nasal symptoms, eye symptoms, sleep, emotion) were significantly improved with SLIT treatment.

Majority of AR patients' QoL are much affected by the nose and eye symptoms as they reported it as annoying and troublesome[20]. Ciprandi et al. found that eye symptoms (itchy eyes/ watery eyes/ sore eyes/ swollen eyes) contributed to impairment of QoL in AR

patients[20]. However, in our study practical problems (inconvenience of having to carry tissue or hankerchief/ need to rub nose or eyes/ need to blow nose repeatedly) and nasal symptoms (stuffy or blocked nose/ runny nose/ sneezing/ itchy nose) scored the highest pre-treatment mean score (nasal score of 4.09 and practical domain score of 4.04). The pre-treatment score was in correlation with severity of AR in which all patients had moderate-severe AR at presentation. At six months of SLIT treatment, the improvement of symptoms showed compelling results with nasal symtoms score of 1.39 ($p=0.001$) and practical domain score of 1.38 ($p=0.001$). This meaningful results reflect that SLIT is clinically relevant and is highly effective.

In treating AR patients, QoL is an important aspect to consider as it has a strong relationship with clinical and functional parameter[21]. Functional parameters signifies the nasal air flow and nasal decongestion and peak nasal inspiratory flow (PNIF) is a useful tool to measure the extend of obstruction[22]. The pre-treatment mean PNIF in our study was 84L/min (±30) followed by mean PNIF 88.14L/min (±29.36) at one month, 92 (±29.03) at 3 months and 96.13 (±26.67) at 6 months post-treatment. Starling-schwanz et al. reported a PNIF cut-off of 115 L/min had moderately high specifity and sensitivity for moderate-severe signs of rhinitis[21]. However, in our study, eventhough the mean PNIF at 6 months was 96.13 (±26.67), the nasal airflow has significant improvement by 9.6% ($p<0.05$) at every follow-up. The improvement of nasal airflow corresponded with the RQLQ further explained the enhancement of patient's QOL. This was demonstrated by Pearson correlation test where there was statistically significant negative linear relationship between PNIF and RQLQ ($p<0.001$) (Figure 4). The PNIF value may be affected by anatomical variants, however, confounding factor such as severe deviated nasal septum, nasal polyposis and chronic lung disease were already excluded, thus our PNIF results were solely contributed by AR features (hypertrophy inferior turbinates, edematous and moist mucosa).

SLIT is a well-tolerated therapy in AR patients. Even though, there were few reported cases of SLIT related-anaphylaxis, to date there are no anaphylactic shock or fatalities reported[9]. In our series, no incidence of asthma attack or anaphylaxis were seen during the 6 months period of SLIT. However, 8 patients had grade 1 systemic adverse reaction, whereby they developed urticaria and worsening rhinitis symptoms (WAO, grade 1 systemic reaction grading system). This may be due to high pre-treatment IgE titre causing the patient to be hypersensitive to the allergens[22]. IgE titre was not tested in these patient as allergic rhinitis

were diagnosed using skin prick test and specific IgE test. None of them received any form of immunotherapy (eg; subcutaenous immunotherapy) prior to SLIT.

Patients on SLIT generally have good compliance rates around 70-80% and treatment drop-out rates due to compliance are only seen after 6 months[23]. Among the reasons for non-compliance are the subjects thought SLIT was not useful anymore due symptoms improvement and the high cost of the medication[24]. Hence, the adherence of SLIT need to be emphasized to complete the recommended 3-year course of therapy.

In analyzing the pharmacological treatment of the patient, there is compelling reduction of antihistamines and INS as rescue medications. At six months, the mean usage of antihistamine and INS are 2.67 (±3.31) and 4.47 (±3.51) , signifying the improvement of QOL in patients who received the SLIT treatment. Danielsson et al conducted a 12-year cross sectional study on 108 allergic rhinitis patients whom 82 of them was treated with pharmacotherapy alone. It was demonstrated that 60% of them will still be dependent on pharmocolotherapy with similar or even worsening severity of symptoms after 12 years of treatment. This may reflect the long term dependency on medication and increment in financial burden in managing AR patients[25]. Berto et al estimated the total cost for patient treated with both SLIT and pharmacotherapy amounted to £1913 as compared to pharmacotherapy alone amounting to £3400. Thus it can be concluded SLIT is less expensive and more effective than pharmacotherapy alone[26].

CONCLUSION

Sublingual immunotherapy does work in treating patients with moderate-severe allergic rhinitis who had allergic sensitization to house dust mites. Our study showed a significant improvement of patients' quality of life as early as 3 months of commencement of treatment.

RECOMMENDATION

We would recommend further studies on long term use (3-5 years) of SLIT and cost benefit analysis of both pharmotherapy and SLIT treatment in patients with AR.

INFORMED CONSENT

The written informed consent was obtained from all the participants.

DISCLOSURES

The authors declares that there are no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

R Luqman, H Salina and Z Farah Dayana are primary reseacher in this study. Statistical analysis was done by MA Mohd Syazwan and contributed in writing up the results. The data collection and final manuscript writing was done by R Luqman and critical revision was done by H Salina.

ETHICAL APPROVAL

The study is in accordance with the Helsinki declaration. The study was approved by Ethics Committee Council of University Kebangsaan Malaysia with a research code of FF-2018-028.

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TABLES

Table 1. Descriptive data showing number of patients excluded from the study

Patients excluded from the study	No
Urticaria	3
Worsening of AR symptoms	3
Worsening of AR + eczema	1
Financial issue	1
total	8

Table 2. Frequency and percentages of AR severity

		Frequency	Percent
AR_Baseline	Moderate-severe persistent	53	100

	Mild persistent	0	0
	Moderate-severe intermittent	0	0
	Mild intermittent	0	0
AR_1m	Moderate-severe persistent	41	83
	Mild persistent	0	0
	Moderate-severe intermittent	1	7.6
	Mild intermittent	3	9.4
AR_3m	Moderate-severe persistent	12	30.2
	Mild persistent	1	3.8
	Moderate-severe intermittent	12	22.6
	Mild intermittent	20	39.6
AR_6m	Moderate-severe persistent	2	4.4
	Mild persistent	0	0
	Moderate-severe intermittent	1	2.2
	Mild intermittent	43	95.6

Table 3. The mean, standard deviation and statistical analysis of each of RQLQ subset and mean of RQLQ scoring during every followup.

	N	Mean	Std. Deviation	t	P
B_Activities	53	3.40	1.34		
M1_Activities	45	2.84	1.31	3.89	0.001*
M3_Activities	45	1.88	1.38	7.73	0.001*
M6_Activities	45	1.33	1.18	11.29	0.001*
B_NHFS	53	2.66	1.31		
M1_NHFS	45	2.32	1.37	2.37	0.022*
M3_NHFS	45	1.56	1.19	5.93	0.001*
M6_NHFS	45	1.09	1.02	9.13	0.001*
B_Practical	53	4.09	1.43		
M1_Practical	45	3.15	1.38	4.67	0.001*
M3_Practical	45	2.15	1.34	8.63	0.001*

M6_Practical	45	1.38	0.92	12.75	0.001*
B_Nasal sx	53	4.09	1.33		
M1_Nasal sx	45	3.00	1.29	6.58	0.001*
M3_Nasal sx	45	2.16	1.32	9.29	0.001*
M6_Nasal sx	45	1.39	1.12	11.94	0.001*
B_Eye sx	53	2.63	1.58		
M1_Eye sx	45	2.12	1.55	2.40	0.020*
M3_Eye sx	45	1.25	1.24	5.90	0.001*
M6_Eye sx	45	0.78	1.04	8.29	0.001*
B_Sleep	53	2.71	1.67		
M1_Sleep	45	1.95	1.49	4.07	0.001*
M3_Sleep	45	1.24	1.41	6.39	0.001*
M6_Sleep	45	0.92	1.22	7.07	0.001*
B_Emotion	53	2.74	1.74		
M1_Emotion	45	2.07	1.56	4.14	0.001*
M3_Emotion	45	1.46	1.44	6.45	0.001*
M6_Emotion	45	0.86	1.03	3.28	0.002*
B_Mean	53	3.19	1.14		
M1-Mean	45	2.49	1.15	5.33	0.001*
M3_Mean	45	1.67	1.12	9.10	0.001*
M6_Mean	45	1.10	0.93	13.22	0.001*

*Significant P<0.05

B = Baseline, M1 = month 1, M3 = month 3, M6 = month 6, NHFS = non hay fever symptoms

Table 4. The mean, standard deviation and statistical analysis of PNIF at baseline, 1month, 3 month and 6 month.

	N	Mean	Std. Deviation	t	P
PNIF_Baseline	53	81.54	30.13		
PNIF_1m	45	88.14	29.36	-2.94	0.005*
PNIF_3m	45	92.00	29.03	-4.09	0.001*
PNIF_6m	45	96.13	26.67	-5.01	0.001*

*Significant P<0.05

PNIF = peak nasal inflow meter. Improvement of PNIF was seen during each followup compared to baseline signifying the improvement in functional parameters (nasal decongestion and nasal airflow).

Table 5. Usage of Phamacotherapy, Nasonex and Aerius during the six month period of SLIT.

	Time	N	Mean	Std. Deviation	95% Confidence Interval for Mean		F	P
					Lower Bound	Upper Bound		
Nasonex	1 Month	53	30.00	0.00	30.00	30.00	319.36	0.001*
	2 Month	44	13.61	5.65	11.90	15.33		
	3 month	43	10.02	4.18	8.74	11.31		
	4 month	43	7.67	3.97	6.45	8.90		
	5 month	43	4.74	3.41	3.69	5.79		
	6 month	43	4.47	3.51	3.39	5.54		
Aerius	1 Month	53	30.00	0.00	30.00	30.00	317.37	0.001*
	2 Month	44	13.05	6.03	11.21	14.88		
	3 month	43	7.33	5.80	5.54	9.11		
	4 month	43	4.35	3.72	3.21	5.49		
	5 month	43	3.33	3.48	2.26	4.40		
	6 month	43	2.67	3.31	1.65	3.69		

*Significant P<0.05

There was significant reduction in the usage of pharmacotherapy from second month onwards ($p < 0.05$)