Safety And Efficacy Of Two Days Of Rush Immunotherapy Among Patients With Allergic Rhinitis And Asthma

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Abstract

This study was done to assess the safety and efficacy of rush immunotherapy (RIT), and was conducted in the Allergy Centre of Kempegowda Institute of Medical Sciences Hospital & Research Centre, Bangalore, India. Twenty patients in the age group of 18-50 years were included, of which thirteen patients had allergic rhinitis, and seven patients had allergic rhinitis with asthma. All of these patients were positive for skin prick test for house dust, dust mites, tree pollens, grass pollens, and weed pollens, either singly or in combination. They received RIT as per the protocol. Among these patients, the safety of RIT was assessed based on reactions during RIT and efficacy was assessed by estimating total serum IgE and IgG at baseline, after two weeks, and after six weeks. Local reactions were observed in five patients, which subsided without any medication. Systemic reaction was observed only in one patient following a 9th injection on Day 2. This patient responded satisfactorily to Inj. Chlorpheniramine maleate, Inj. Hydrocortisone, and Oxygen inhalation and completed RIT. Late systemic reactions were not noted in any of the patients. Estimation of total serum IgE showed a significant reduction and total serum IgG showed a significant increase after six weeks. It was concluded that rush immunotherapy was tolerated by most patients with a systemic reaction rate comparable to conventional immunotherapy. All patients were able to reach maintenance dose months sooner than weekly schedules. With refinement of this procedure, Rush Immunotherapy may become a widely used method for desensitizing patients with inhalant allergens, and could make immunotherapy less expensive and more convenient to the patients.

INTRODUCTION

Immunotherapy has been shown by numerous investigators to be an effective treatment for allergic rhinitis, [1] allergic asthma, [2] and Hymenoptera sensitivity[3] in appropriate individuals. Traditionally, its administration consisted of weekly subcutaneous injections of small amounts of clinically relevant allergen extracts in slowly increasing doses until “maintenance” or therapeutic doses are reached. The optimal dose necessary for efficacy should be immunogenic and ideally should not induce a systemic reaction[4]. The schedules consisted of once or twice weekly injections, usually achieving a maintenance dose at 4 to 6 months.

Compliance with this regimen requires a great deal of discipline and effort by the patient. In addition, it is costly, inconvenient, uncomfortable, and one generally must wait for many months before experiencing improvement in symptoms. All of these factors contribute to reduced compliance with this type of therapy.[5]

Several studies have shown that by decreasing treatment complexity and personal involvement, compliance is improved. Reduced cost and increased tolerability of rush immunotherapy (RIT) in comparison to conventional immunotherapy was recently reported in a bee venom study in Australia[6] and the results were extrapolated to include non-venom immunotherapy.

Rush immunotherapy is a technique for advancing an allergic patient through a series of injections to an immunizing “maintenance” dose of all allergic extract in a short period of time. Previously reported rush immunotherapy studies required 3 to 7 or more days to complete,[7,8] with the most rapid non-venom RIT protocol taking 1½ days.[9] A major concern about regular use of rush immunotherapy is its increased risk of systemic reactions. This incidence has been reported to range from 15.4% to 73% with aqueous extracts.[8, 10-12] Premedication demonstrated a decrease in the incidence of systemic reactions with a range of 7.3% to 27% in rush immunotherapy patients.[13] These systemic reaction rates are comparable to those seen with conventional schedules, which are associated with rates ranging from 0.8% to 46.7%[15] or 14% to 30% in other

reports.[15, 16]

Studies on immunotherapy itself are limited in this part of the country there is a complete lack of research regarding safety and efficacy of rush immunotherapy with premedication. Hence, the present study was undertaken to alleviate the needs of allergic rhinitis and asthma patients. The purpose of this report is to describe our experience using a two day rush immunotherapy protocol.

MATERIAL AND METHODS

A total of 20 patients between ages 18 and 50 years, who were positive for skin prick test (13 allergic rhinitis and 7 allergic rhinitis with asthma), were recruited for the two day rush immunotherapy after obtaining informed consent. The study was conducted at the Allergy Centre, Kempegowda Institute of Medical Sciences Hospital and Research Centre, Bangalore. The protocol was approved by the institutional ethics committee.

Rush immunotherapy was performed as per Modified Joy Portnoy et al[13]protocol (Table 1& 2). The clinical diagnosis of allergic rhinitis and asthma was made according to ARIA guidelines[17] and GINA guidelines, [18] respectively. Among these patients, safety of RIT was assessed based on reactions during RIT. The patients were subjected to a baseline estimation of total serum IgE and IgG by ELISA method (prior to the initiation of rush immunotherapy) and after two weeks and six weeks (i.e., on Day 0, Day 14 and Day 42).

Preparation of extract for Rush Immunotherapy

A modified Joy Portnoy et al[13] protocol was used as a reference in preparation of the extract. Aqueous allergen extracts (Credisol, Navi Mumbai) were used in graded strengths of 1-4 and standardized using w/v ratio as per the manufacturer instructions.

Strength 1 : 0.004%w/v

Strength 2 : 0.04%w/v

Strength 3 : 0.4%w/v

Strength 4 : 2%w/v

Maintenance treatment set : (1 vial of 4.5ml), this vial contained extract of strength 4.

PROCEDURE OF RUSH IMMUNOTHERAPY

One week preceding rush immunotherapy, patients were subjected to general physical examination, baseline spirometry, and orientation towards the procedure. A premedication with Tab. Prednisolone-20 mg B.D., Tab. Loratadine-10 mg O.D. and Tab. Ranitidine -150 mg B.D, was given to all the patients the previous day and during two days of the procedure. On day one of admission, the patients were subjected to a physical examination, peak expiratory flow rate was recorded and an intravenous line was placed as a precautionary measure. The procedure was done in the presence of a crash cart equipped with emergency medicines like Inj. epinephrine, oxygen, intubation tube, ambu bag etc. Before each injection, blood pressure, pulse rate, respiratory rate and peak expiratory flow rates of all patients were measured. Patients were also observed for two hours after the last injection on both day one and two. (Table 1 & 2).

Figure 1

Table 1 Protocol for rush immunotherapy (Day 1)

Strength	Time	Volume	Concentration
Vial 1	9.00 am	0.2 ml	1:25,000
	9.30 am	0.4 ml	1:25,000
	10.00am	0.6 ml	1:25,000
After one hour interval			
Vial 2	11.00 am	0.2 ml	1:2,500
	11.30 am	0.4 ml	1:2,500
	12.00 noon	0.6 ml	1:2,500
+ Two hours of observation			

Figure 2

Table 2 Protocol for rush immunotherapy (Day 2)

Strength	Time	Volume	Concentration
Vial 3	9.00 am	0.2 ml	1:250
	9.30 am	0.4 ml	1:250
	10.00am	0.6 ml	1:250
After one hour interval			
Vial 4	11.00 am	0.2 ml	1:50
	11.30 am	0.4 ml	1:50
	12.00 noon	**0.6 ml**	1:50
+ Two hours of observation			

Reactions to rush immunotherapy were graded on a scale of 0+ to 6+. It was done before each injection, and at any time that a reaction occurred. Local reactions were graded as 0+ and 1+ no matter how large they were, provided there were no associated systemic reactions. Systemic reactions were graded 2+ and above (refer Table 5).

RESULTS

Among the 20 patients studied, a majority of the patients, 11 (55%), were in 18-30 years age group. The mean age of the patients was 33.05±10.76 years . Out of 20 patients, 11 were males and 9 were females (Table 4).

Figure 3

Table 4 Socio-demographic characteristics and allergen positivity of the patients who received Rush Immunotherapy

Sl. No.	Pt code	Age	Sex	Rhinitis	Asthma	Reaction grade	Dose at reaction
1	GAY	42	F	+	Moderate	1+	10th inj
2	CHA	27	F	+	-	1+	5th inj
3	KRI	45	F	+	-	-	-
4	FAZ	47	M	+	Moderate	1+,0+	5th & 9th inj
5	MON	24	M	+	-	-	-
6	BAS	28	M	+	-	-	-
7	VIN	22	M	+	-	-	-
8	GUP	25	M	+	-	-	-
9	GAN	24	F	+	-	-	-
10	RAJ	30	F	+	-	-	-
11	PRA	34	M	+	Moderate	-	-
12	DEV	43	F	+	-	-	-
13	ANI	24	M	+	-	-	-
14	ROT	50	M	+	Moderate	-	-
15	SOU	18	F	+	-	-	-
16	SHA	50	F	+	-	1+	10th inj
17	MAD	44	M	+	-	0+	4th inj
18	GAR	20	M	+	Moderate	-	-
19	REJ	42	F	+	Mild	-	-
20	NAT	22	M	+	Moderate	-	-

Local reactions: 0+ No significant reaction, small area of erythema <12mm without swelling or wheal formation.
1+ Erythema >12mm and/ or swelling or wheal formation.

Systemic reactions: 2+ **Cutaneous only**: such as urticaria. 3+ Generalized pruritis and/ or sneezing: may consist of increased allergy symptoms such as nasal congestion, sneezing, or pruritis especially in the mouth or throat. 4+ Pulmonary: consists of wheezing, shortness of breath, tightness. May be associated with decreased pulmonary function tests. 5+**Anaphylaxis:** a sensation of not feeling right is a frequent prelude. May consist of hypotension, laryngeal edema, severe wheezing, and cramping. 6+ **Cardiopulmonary arrest**.

SKIN PRICK TEST RESULTS

Out of 20 patients, 11 patients were allergic to one or more than one weed pollens (Brassica nigra, Dodonae viscose, Ageratum conyzoides, Xanthium strumarium, Parthenium hysterophorus, Cassia siamea). 10 patients were allergic to one or more than one tree pollens (Prosopis juliflora, Cocos nuciferus, Typhus angustata, Carica papay, Eucalyptus tereticornis, Ailanthus excelsa). 6 were allergic to grass pollen (Cynodon dactylon) and 12 patients were allergic to house-dust and house dust mites (Dermatophagoides farinae and Dermatophagoides pteronyssinus). Individuals showing skin reactions to specific allergens with more than 2+ reactions were considered as a positive skin prick test (according to Agarwal et al 2003 criteria). Those specific allergens were included in the rush immunotherapy (Table 4).

Figure 4

Table 5 Systemic and local reactions following Rush Immunotherapy

Sl. No.	Pt code	Reaction Grade	Reaction symptom	Time to Reaction, Minutes	H_1	H_2	Beta agonist	Others	Late Reaction
1	GAY	4+	Sneezing Difficulty in breathing Decrease PFR	5min after the dose	+		-	Inj Efcorlin O_2 inhalation	Nil

Figure 5

Table 6 Treatment for systemic reactions

Titers	Base Line µ	SD[1]	After 2nd Week*	SD[2]	p-value	After 6th Week**	SD[3]	p-value
IgE	239.19	2.6	210.15	2.56	<0.05	174.61	2.51	<0.003
IgG	0.4010	1.94	0.37	2.85	>0.27	0.52	1.55	<0.045

* shows a significant change in IgE titre as compared to base line levels ($p< 0.05$)
** further reduction in IgE titre after 2nd week ($p<0.003$)

Among 20 patients who underwent rush immunotherapy, 5 (25%) patients developed local reactions, which subsided spontaneously without any medication (Table 5). Systemic reactions were observed only in one patient following the 9 th injection on Day 2. This patient responded satisfactorily to Inj. Chlorpheniramine maleate. Inj. Hydrocortisone was given as the patient was a diabetic and in whom Inj. Epinephrine was a relative contraindication[19]. In addition, Oxygen inhalation was given, and RIT was completed. No late systemic reactions were noted in any of the patients (Table 6).

TOTAL IGG AND IGE TITRES

Table 7 Statistical inference between total serum IgE and IgG – baseline, after 2 weeks and after 6 weeks using paired t –test

Three blood samples were collected from all 20 patients for estimation of total IgE and IgG titre. There was a significant decrease in the IgE titre value from baseline to 2 nd week ($t=1.67$, $df=19$, $p<0.05$) and baseline to 6 th week ($t=3.067$, $df=19$, $p<0.003$), which was found to be statistically significant.

It was observed that there was initial dip in the IgG titrevalue from the baseline to 2 nd week (t=0.62, df=19, p>0.272), which was not statistically significant and baseline to 6 th week (t=1.82, df=19, p<0.045), which was found to be statistically significant.

Following initial rush immunotherapy, patients received a maintenance immunotherapy once in two weeks consisting of 0.6 ml of 1:50.

DISCUSSION

Immunotherapy is an important therapeutic modality for treating allergic patients who have rhinitis or asthma. Compliance is also a major issue with respect to the efficacy of immunotherapy. A substantial amount of time has to be invested by the patient, which is inconvenient. In addition, clinical relief occurs after a long time, particularly in patients on traditional schedules. Rapid dosage schedule, as used in rush immunotherapy, offers many advantages over traditional schedules in selected patients. An additional advantage to patients who receive rush immunotherapy is the ability to achieve bimonthly, or less frequent, injections more rapidly.

Other potential advantages of rush immunotherapy over conventional schedules include (1) reduction in the vulnerable time between induction of decreased IgE and increased IgG responses, (2) it is more cost effective since fewer total injections are required, (3) it reduces dosage errors as most patients can achieve their maintenance dose in two days. An increase in the incidence of systemic reactions is a major disadvantage reported with rush immunotherapy. To address this concern, the use of premedication before and during rush immunotherapy has shown to reduce the risk of systemic reaction rate when compared to that seen with traditional immunotherapy. Systemic reactions in one study were seen in 7.3% of patients using combined premedication with preventative measures.[11] Other studies using premedication have described systemic reaction rates ranging from 14.7%[8] to 27%,[13] although the studies by Hejjaoui also included both children and adults and evaluated only a single antigen. The 5% systemic reaction rate seen in this study was less, compared to the rates in those studies. There are no other studies of two-day rush immunotherapy protocol in adults; therefore, it is not known whether our results can be extrapolated to this population.

The mechanism behind rush immunotherapy is not well understood, although it is reasonable to postulate that a form of desensitization does occur during the first few weeks. After that, there is no reason why rush immunotherapy should be different from conventional immunotherapy, as demonstrated by an increased IgG response within 4 weeks in a previous study .[13] We feel that the prednisone used for premedication may protect against late occurring systemic reactions. More data are required to define the risk of late phase systemic reactions and even then, one could never conclude that such reactions would not occur.

We observed only 1 (5%) systemic reaction among our patients. This suggests that the premedication used prior to rush immunotherapy was not masking severe systemic reactions that might recur after the premedication was discontinued. The premedication also may have served to attenuate the systemic reactions that were seen since no severe reactions were noted.

CONCLUSION

Two days rush immunotherapy with premedication is a well-tolerated procedure in most patients. Maintenance immunization levels are achieved more rapidly than with traditional immunotherapy or previously reported rush schedules. Due to a reduction in time commitment by the patient, a decrease in the total number of injections, and rapid achievement of maintenance dose, rush immunotherapy will eventually increase compliance and improve quality of life in these patients.

We therefore propose that rush immunotherapy could be used as an alternative to weekly immunotherapy to improve convenience and to help reduce treatment costs. Further studies are necessary to confirm these results. In this study, specific IgE estimations could not be done due to financial constraints.

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