

## Research Article

# Chronic Urticaria: A Novel Approach in Treatment

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### Abstract

**Rationale:** To investigate the prevalence of pollen sensitization in patients with chronic spontaneous urticaria (CSU) and to observe the clinical efficacy of specific immunotherapy in patients when pollen sensitization was the only identifiable cause.

**Methods:** Patients who were diagnosed with CSU between 2005 and 2012 were included in a prospective study. Only patients who had urticaria at least 5/7 days of the week were included. Patients were evaluated by history, duration, severity and frequency of symptoms, drugs used, total and specific IgE for local pollens. Those who were pollen sensitive were observed for 2 weeks before starting specific immunotherapy (SCIT) and monthly follow up at least for one year. The end point was asymptomatic at least for 6 months compared to controls who did not receive SCIT.

**Results:** Thirty three patients, 23 females and 10 males were included and 15 patients controls. Seven patients had urticaria alone and 26 patients had urticaria with AR or BA or both. Four patients were lost to follow up. Seven patients (24%) became symptom-free compared to 15 controls ( $p < 0.0001$ ), 22/29 (76%) their urticaria became far spaced or went into remission with  $p < 0.001$ , Visual analogue for 7/24 was 100% and 22/29 visual analogue was between 50% and 95%. In 4 patients there was no improvement. The overall improvement in SCIT patients for one year or more was 80% (25/29).

**Conclusion:** Patient with CSU, were pollen sensitization is the only identifiable cause may benefit from SCIT. This study is the first to show the benefit of IT in CSU.

### Background

Urticaria is a common problem especially among females. The underlying cause/causes are numerous and sometimes cannot be

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identified. Some report showed that pollen sensitization to mugwort and birch pollens is more common in chronic urticaria. Treatment at present is symptomatic, with several recent drugs including biologics, but none has been claimed to be curative.

### Objective

To investigate the prevalence of pollen sensitization in patient with chronic urticaria and to observe the clinical efficacy of specific immunotherapy in patient where pollen sensitization was the only identifiable cause of their urticaria.

### Methods

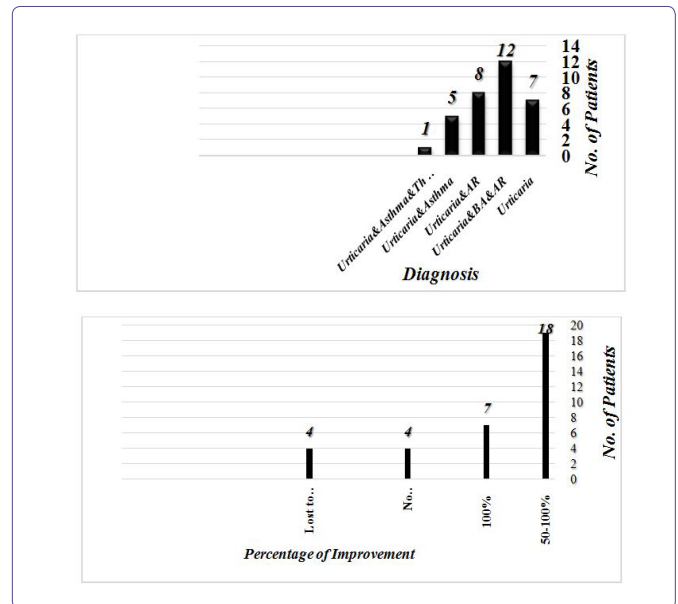
Patients who were diagnosed with chronic urticaria between 2005 and 2012 were included in a prospective study. Only patients who had urticaria at least five days out of seven days of the week were included. Patients who had identifiable cause such as drugs or thyroid problems were excluded. Also, patients whose course was characterized by periods of intermittent remission and flare ups were excluded. Only patients who had daily or at least five days per week symptoms were included. All patients were evaluated by complete history regarding duration, severity, parts of the body involved and drugs used. Laboratory investigations included total and specific IgE by skin test and or in vitro measurement using UNICAP (RAST-pharmacia), for local pollens and foods; thyroid profile for TSH, antithyroglobulin and microsomal antibodies were measured. 33 patients who met the criteria for inclusion were followed up regularly at least for one year. Those who were pollens positive were started on specific Subcutaneous Immunotherapy (SCIT) with increasing concentration of vaccine (Greer lab), in an accelerated schedule twice weekly, starting with 1:100,000 w/v and increasing to maintenance dose of once every two weeks of 1:500 w/v, with 0.5ml injection. The maintenance of 1:500 w/v was chosen because our patients were very sensitive and did not tolerate higher concentration. The patients were followed up monthly and were evaluated for symptoms, the use of antihistamines, number of days with skin lesions and visual analogue by patients and physicians and compared to 15 patients who decided to stay on symptomatic treatment. Immunotherapy was discontinued after patient became symptom-free at least for six months.

### Results

Table (1) is a demographic characteristic of the 33 patients with chronic allergic urticaria. There were 23 females and 10 males' age range 8-56 years with average of 30.68 years. The duration of urticaria was 10-17 years in eight patients and less than one year in 12 patients and 1-3 years in three patients and between six weeks and three months in six patients, while in four patients the duration was not well defined. Figure 1 illustrates the diagnosis and other allergic symptoms associated with urticaria. Only seven patients had urticaria alone while 26 patients had other allergies including rhinitis and or

asthma associated with urticaria. Four patients were lost to follow up and 29 patients were available for analysis. Seven patients 24% (7/29) became symptom-free compared to the 15 patients who did not receive SCIT ( $P < 0.0001$ ), while 22/29 (76%) patients their urticaria either became far apart spaced or went into remission compared to those who did not receive SCIT ( $P < 0.05$ ) with marked reduction or discontinuation of symptomatic treatment 22/29 with ( $P < 0.001$ ). Visual analogue for 7/29 was 100% by patients evaluation and 22/29 (76%) patients the visual analogue was between 50% and 95%. In four patients (14%) there was no improved  $P < 0.7$  (Figure 2). Patient who received SCIT for three or more years improved the most. Some patients who became asymptomatic, decided to continue immunotherapy on monthly basis for a period longer than three years. They were afraid if they stop SCIT the urticaria might relapse.

Table (2) shows the characteristics of patients who were lost to follow up and (Table 3) shows the characteristics of patients who did not improve with immunotherapy. The overall improvement in patients who received SCIT for one year or more was 86% (25/29) patients. Table (4) is the characteristics of patients who had 100% improvement. Some patients started to show significant improvement as early as seven months of after the start of treatment.



### Discussion

Treatment of chronic urticaria is essentially symptomatic. Many drugs have been used but none is curative. This includes antihistamine blockers, anti-leukotrienes, corticosteroids, cyclosporin, hydroxychloroquine, dapsone, sulfasalazine, methotrexate, IV gamma globulin and omalizumab [1,2]. Other biological agents such as Rituximab has been claimed to be successful in treating chronic autoimmune refractory urticaria [3]. Recently, Kocaturk E, et al., showed that investigational substance P antagonists, C5a/C5a receptors inhibitors, Anti IL4, Anti IL5 and Anti IL13 and others may target urticaria treatment [4]. Most recently, more biologic agents have been proposed to treat urticaria, such as Ligelizumab, and molecules targeting intracellular signaling pathways such as spleen tyrosinase kinase inhibitors and others [5]. Other alternative treatment for chronic urticaria that has been tried includes Adalimumab, vitamin D, probiotics, histaglobin, injection of autologous whole blood or serum [6] and phototherapy [7].

Male	Female	Total of Patient
10	23	33
Age Range:		Average:
8-56 years old		30.68 years
Duration of Urticaria		Patient
10-17 years		8
< 1 year		12
1-3 years		3
6 weeks-3 months		6
Unknown		4

Table 1: Demography of patients with chronic allergic urticaria.

	Age	Sex	Total IgE	Specific IgE	Duration of Disease	Duration of IT	Other Diagnosis
1	42 y	F	106 KU/L	Weeds + Grass	6 M	8 Months	Eczema for 6 months
2	52 y	M	4055 KU/L	Weeds + Grass Multiple Foods	10 M	4 Months	AR, BA, High Anti Thyroid Antibody
3	42 y	F	151.5 KU/L	Weeds	2 M	2 months	AR
4	13 y	F	399 KU/L	Weeds + Grass	3 Y	4 months	AR, BA

Table 2: Characteristics of 4 patients lost to follow up.

	Age	Sex	Total IgE	Specific IgE	Duration of Disease	Duration of IT	Other Diagnosis
1	56 y	M	1574 KU/L	Weeds + Grass	?	14 Months	AR, Hypothyroid
2	40 y	F	407 KU/L	Weeds + Grass	10 years	43 Months	BA, AR, Drug Allergy
3	43 y	F	174 KU/L	Weeds	7 Months	29 Months	
4	40 y	M	254 KU/L	Weeds + Mesquite	?	12 Months	AR, BA

Table 3: Characteristics of 4 patients lost to follow up.

	Age	Sex	Total IgE	Specific IgE	Duration of Disease	Duration of IT	Other Diagnosis
1	31	F	142	Weeds + Mesquite	14 years	15 Months	Mild AR, No Treatment
2	39	F	50.5	Weeds + Grass	2 years	36 Months	BA, ARAsypmtomatic No treatment
3	35	M	260	Weeds	10 years	36 Months	AR Asypmtomatic No treatment
4	33	M	38.8	Weeds + Grass	9 months	30 Months	Asypmtomatic No treatment
5	33	F	ND	Weeds + Grass + Mesquite + Cat	15 months	60 months	Asypmtomatic No treatment
6	12	F	1215	Weeds + Grass	2 years	19 months	Asypmtomatic No treatment
7	21	M	141	Weeds + Grass + Food	3 months	36 months	BA, ARAsypmtomatic

**Table 4:** Characteristics of patients with 100% improvement.

Most recently, more biologic agents have been proposed to treat urticaria, such as Ligelizumab, and molecules targeting intracellular signaling pathways such as spleen tyrosinase kinase inhibitors and others [5]. Other alternative treatment for chronic urticaria that has been tried includes Adalimumab, vitamin D, probiotics, histaglobin, injection of autologous whole blood or serum [6] and phototherapy [7].

None of these modes of treatments gave long lasting remission of chronic urticaria. We asked ourselves what to do with patients with chronic urticaria, where the only identified cause is sensitivity to pollens, especially when urticaria is associated with other symptoms of allergy such as allergic rhinitis, or allergic asthma or both. The most common sensitizing allergens in our patients were Mugwort, Russian Thistle, Amaranthus and Atriplex. Some patients were sensitized to weeds, grasses and Mesquite trees. Because sunshines 12 months a year in our region, plants pollinate all year around. Therefore, we decided to treat those patients with local allergens vaccine starting with the low concentration the patient can tolerate without reactions. We are aware some allergist use higher concentrations of vaccine for maintenance, our patient were unable to tolerate concentration more than 1:500 w/v without reaction. This may be due to the fact that pollen is in the air all the time, in addition to the finding that pollens are crushed by sand particles which make them more potent. All patients were informed that this is a new approach before we got their consent. In one year after starting SCIT the majority of our patient had remarkable improvement and most stopped symptomatic treatment. Xing DR, et al., [8] treated 2885 patients who had chronic urticaria and dust mite allergy, with immunotherapy with good to excellent results; with efficacy of 91.1% (226/248) with 66.1% of excellent or good results. Collins found more mugwort and birch sensitization in patients with chronic urticaria compared to allergichrhinitis but no allergy vaccine was given [9]. Similar studies by other authors showed the same [10,11]. There is one case report by Kasperska-Zajak where a patient with respiratory allergy and CU his Urticaria flared up during Immunotherapy with dust mite suggesting that Immunotherapy is beneficial in sensitized chronic urticaria [12].

Mahesha, et al., found high sensitivity among patients with urticaria to dust mite suggesting that allergy may play a role in the cause of chronic urticaria [13]. Our patients had overall efficacy of immunotherapy of 86% with 14% (4/29) patients showed 100% remission of their urticaria compared to patient who stayed on symptomatic treatment. Although some cases of chronic urticaria go into remission even without treatment, our patients were symptomatic all the time and they did not benefit from other forms of treatment. Furthermore, we observed the continuity of their urticaria two weeks before SCIT. Their remission after SCIT cannot be attributed to natural course of

remission and relapse. We believe our study proves that chronic urticaria is amenable to treatment with allergy vaccine when pollens are the main or the only underlying cause. This novel approach has no previous similar study in the English literature. Therefore, more studies are needed to confirm our findings. Although some authors mentioned that chronic urticaria is not allergic [14].

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