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Research Article

EFFICACY OF SUBLINGUAL IMMUNOTHERAPY FOR COW MILK ALLERGY IN PATIENTS WITH CHRONIC URTICARIA

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ABSTRACT

Background: defining the etiology of chronic urticaria is difficult and complicated. This study designed to define the prevalence of CM allergy in patients with chronic urticaria and determine the efficacy of Sublingual immunotherapy for patients with chronic urticaria allergic to CM.

Method: 147 patients (mean age 34.3 years, 60 males) with chronic urticaria after exclusion of systemic diseases underwent skin prick test then complete restriction of CM for 2 weeks then open challenge with CM to determine the prevalence of CM allergy in those patients. Only patients with complete remission of symptoms with milk elimination and re-appearing of symptoms with re-challenge are diagnosed to have CM allergy. After that patients who diagnosed to have CM allergy submitted to 6 weeks of sublingual immunotherapy for CM then re-challenged with CM to determine the efficacy with this modality of therapy.

Results: 53 patients (36%) diagnosed to have CM allergy by the diet elimination and re-challenge test. From the 53 patients 51 agreed to administer Sublingual immunotherapy for CM. After the 6 weeks another 2 patients dropped out through the follow up and 49 patients completed the trial to the end; from those 34 patients (69%) showed complete remission after re-challenge with CM and maintained that remission for another 2 months follow up 32 (60.4%) maintained on remission after 1 year and 31 (58.5%) maintained after 3 years.

Conclusion: CM allergy is an important cause of chronic urticaria, and the Sublingual immunotherapy for CM is the promising way to treat that group of patients proved to have CM allergy.

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INTRODUCTION

Chronic Spontaneous Urticaria (CSU) defined as the occurrence of urticarial wheals and/or angioedema without apparent cause for more than 6 weeks[1]. It is differentiated from the chronic inducible urticaria in which the cause can easily attributed by history & simple examination the examples of chronic inducible Urticaria are: symptomatic dermographism, cold induced urticaria, solar urticaria, vibratory angioedema, delayed pressure urticaria, heat urticaria, contact urticaria, cholinergic urticaria and Aquagenic urticaria[2].

The prevalence of Chronic Urticaria varies from 0.5-5% in general population[3], in children it was estimated to be 1.8%[4].

The adverse reaction to Cow Milk (CM) could be non-allergic (CM intolerance) or allergic. The allergic type require the

activation of immune mechanism which could be IgE mediated and/or non-IgE mediated[5].

Food elimination was considered to be the standard method for managing Food allergy, Recently published studies on CM, egg and peanut allergy recommend the trial of food introduction even early in infancy (before the age of 6 months) in allergic patients and who has a strong family history of allergy in order to avoid the development of such food allergy [6-8].

And the use of food immunotherapy may be a good alternative for managing the documented food allergy.

METHOD

Patients

Patients with CSU defined by occurrence of spontaneous urticarial wheal +/- angioedema for more than 6 weeks with no apparent relevant cause at the ages (12 -60ys).

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Exclusion criteria

Patient with other known dermatological diseases (as atopic dermatitis, psoriasis, pemphigus, etc...)

Patients with history of previous anaphylaxis either to drugs or food or even of unknown cause.

Patients with other chronic diseases (chronic liver diseases, viral hepatitis, hypertension, Diabetes mellitus, thyroid disorder, chronic renal disorders, autoimmune diseases, chronic infections, blood diseases, malignancies, etc...) by history, examination and appropriate lab investigations.

Patients on chronic medications.

Objectives

To identify the prevalence of CM allergy in patients with chronic spontaneous urticaria, and the efficacy of sublingual specific allergen immunotherapy for CM allergy.

Intervention

Antihistamine Cetrizine 10 mg tablet prescribed as on demand treatment for one week at the dose of 1 tablet up to four tablets / day, then the drug stopped for another 1 week before performing Skin Prick Test (SPT) and re-prescribed again through the remaining of the study as the same on demand method.

SPT performed with drop of freshly prepared milk in Glycerin (1:1) solution with positive control of Histamine and negative control of Saline 0.9% in Glycerin (1:1).

The SPT Performed on internal side of forearm with more than 5 cm space between each drop and the others. The longest diameter of weal was measured after 20 min, expressed in millimeters. All the skin-prick tests were performed and measured by the same person.

All patients (either with +ve or -ve skin test) subjected to complete CM protein restriction for 2 weeks then open food challenge with CM performed to confirm the presence of CM allergy , patients with complete remission at the 2nd week with reappearance of Urticaria symptoms after re-challenge considered as allergic to CM by food elimination –open challenge test.

Patients with confirmed CM allergy by food elimination –open challenge test are instructed to complete elimination of CM for 2 weeks then submitted to 6 weeks of CM-SLIT(patients instructed to leave the drops under the tongue for about 30 seconds then swallow the remaining), then re-challenged with CM to determine the efficacy of CM-SLIT.

The immunotherapy was performed by using serial dilutions of cow milk in Glycerin (1/500, 1/50, 1/5) each concentration for 2 weeks starting from 1 drop/ day increasing 1 drop daily (concentration 1/500) until reaching 14 drops then starting the next dilution.

All patients after completion of the 6 weeks CM immunotherapy underwent open food challenge with recording of the symptom score for 2 months period to identify the (responders) patients achieving complete remission, another follow up after 1 year & 3 years to identify the long term tolerance.

Assessment of patient response

Patients scored their symptoms daily using the Urticaria Activity Score 7 (UAS 7), recording daily number of hives (0 indicating none, 1 indicating <20 wheals/24 h, 2 indicating 20-50 wheals/24 h, 3 indicating >50 wheals /24 h or large confluent area of wheal), and score of pruritus (0 indicating none, 1 indicating mild not bothering, 2 indicating mild annoying but not interfere with life activity , 3 indicating sever interfere with life activity). The total daily score calculated on scale from 0-6, UAS 7 calculated by the sum of the daily score over the week (on scale from 0 -42)[1]

UAS 7 recorded for the patient at base line (1 week before milk elimination), at the 2nd week of diet elimination and the week 4 & 8 after the completion of immunotherapy and the re-introduction of milk in food.

The patient considered allergic to cow milk if the symptoms disappeared at the 2nd week of elimination (UAS 7 of 0) & recurrence of symptoms after open challenge with CM in food.

Complete remission defined by the absence of the urticarial wheals (UAS 7 of 0) at the weeks 4& 8 after the completion of immunotherapy, without the need of rescue anti histaminic drugs.

Another visit or phone call after 1 and 3 years to assess the long term tolerance is followed.

Informed Consents were obtained from all subjects.

RESULTS

147 patients mean age 34.3 Standard Deviation (SD) 12.21 years, 60 males were enrolled in the study, of which 28 (19%) patients had +ve skin prick test to CM,

As the food elimination & re-challenge test is the standard test for diagnosis both types of CM allergy (IgE mediated and non IgE mediated) so we considered it as the reference test.

The prevalence of CM allergy according to CM elimination& re-challenge was 36% (53 patients).

18 of the patients who confirmed to be CM allergic by the elimination& re-challenge test had +ve skin prick test reaction to milk. Ten of the patients with +ve SPT to CM proved to be non-allergic by the food elimination & re-challenge test.

The sensitivity, specificity Positive Predictive value (PPV) and Negative Predictive value (NPV) for CM-SPT are shown in the table 1.

Table 1 The sensitivity, specificity, PPV, NPV for CM-SPT

for CM-SPT	% (95% CI)
Sensitivity	34 (21.9-48.4)
PPV	64.3 (44.1-80.7)
Specificity	89.4 (80.9-94.5)
NPV	70.6 (61.4-78.4)

By comparing the age of the CM allergic versus the non CM allergic, we found that the mean age of CM allergic patients was 30.4 (95% CI 27.20-33.66) years, the non CM allergic 36.5 (95% CI 34.03-38.88).

The mean difference between the two groups was -6.02 (95% CI -10.06 to -1.8), which was statistically highly significant (p = 0.0037, t= -2.95).

The mean & SD baseline UAS7 for the CM allergic patients was 20.98 +/- 8.23 and for the non CM Allergic was 19.54 +/- 8.2 with insignificant mean difference between the two groups -1.44 (95% CI -1.35 to +4.23) p = 0.31.

From the 53 patients who proved to be allergic to CM by Food elimination & re-challenge test 51 agreed to start the CM-SLIT, there were no difference in the gender distributing in between these two groups, the number of males in the CM patients was 23 (43.4%) and in the CM non allergic was 37 (39.36%).

49 patients completed the 6 weeks course of CM-SLIT (two patients dropped out through this period due to distant residence).

From those 49 patients the responders were 34 (response rate 69.4%) Figure 1.

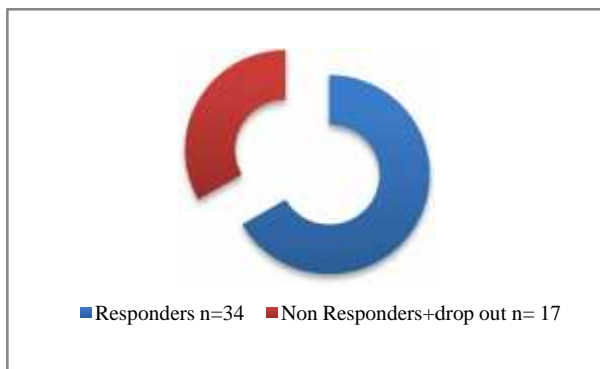


Figure 1 Rate of responders to CM-SLIT

There was no statistical difference in the mean & SD baseline UAS7 for the responders (21.38 +/- 7.7) and non-responders (22.07 +/- 9.54) p=0.79

With mean difference - 6.88 (95% CI -5.85 to +4.49)

From that 34 patients 32 (60.4%) maintained on remission after 1 year and 31 (58.5%) maintained after 3 years

DISCUSSION

Food allergy defined as “adverse reaction to food protein through activation of the immune system” [9].

For that the allergic reaction of food extended to be a broad range of IgE mediated allergy & non IgE mediated allergy, while the skin prick test is a valuable test for the diagnosis of IgE mediated allergy [10].

In a systemic review and meta-analysis for the diagnosis of food allergy Soares-Weiser *et al.* found that results of the sensitivity & specificity of SPT in diagnosing food allergy is widely heterogeneous according to criteria of inclusion & exclusion of the patients in each individual study, the specificity of SPT to CM founded to be 67.5 (CI 95% 56-77.2) [11].

In our study the specificity was higher 89.4 (CI 95% 80.9-94.5), we relate that to the use of fresh drop method in the SPT for CM. it was reported that the sensitivity & specificity of SPT for food allergy is different with the using of commercial extract versus the fresh drop method, with more relevant results with the fresh drop method [12].

By using the fresh drop SPT Verstige *et al.*, found that the specificity of SPT for CM was 75% with NPV 83% which is more related to our findings [13].

The sensitivity of SPT to IgE mediated hyper sensitivity is well known [14,15], in the case of food allergy the IgE mediated type is easily identified by the patient with occurrence of symptoms with minutes to two hours after ingestion of the provoking food [16], in our study we excluded this type of patients (with obvious cause of urticaria).

We found the CM allergic patients were younger than the CM non allergic in the study population, although a large meta-analysis on the prevalence of food allergy couldn't identify the difference between age groups in the prevalence of food allergy due to the heterogeneity and the difference between the self-reported food allergy & the objective measures [17].

In one multi-center study on the prevalence of the food allergy in adults the range varied from country to country (4.6% in Spain up to 19.1% in Australian adult population) [18].

Using allergen immunotherapy for food allergy was 1st reported and published at 1908 when Schofield described the management of a child with egg anaphylaxis by gradual increasing dose of hen egg [19,20]. It was reported that a high proportion of patients could tolerate the food challenge after immunotherapy by heated and raw food [20].

Another randomized double blind placebo controlled trial on CM allergen immunotherapy revealed the efficacy of this modality for children to tolerate significantly larger amount of milk (5140 mg) than the placebo arm (40 mg) P = .0003 [21].

In our study the success rate was 69% for follow up of 2 months, 60.4% at one year and 58.5% at 3 years. Also Salmivesi *et al.* found a supporting results of achieving 89% success in desensitization that maintained in 79% of the patients up to 3.5 years after CM allergen immunotherapy [22].

Many of other studies also support that the patients once primarily achieve desensitization, it will be maintained for long duration [23,24].

Even the desensitization can be conducted in a rush escalation in some patients with 2 hourly doubling the dose of the CM (in 3-5 dose/day) to reach 120 mL of CM within only 3-7 days [25].

CONCLUSION

CM allergy is an important cause of chronic urticaria, and the Sublingual immunotherapy for CM is the promising way to treat that group of patients proved to have CM allergy.

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