PILOT STUDY: SPECIFIC IMMUNOTHERAPY IN PATIENTS WITH PAPULAR URTICARIA BY CIMEX LECTULARIUS

ABSTRACT:

Background: Papular urticaria is a chronic allergic reaction induced by insect bites. In México the most common causative arthropods reported are bed bugs, fleas and mosquitoes. Approximately 70% of people who are bitten by *Cimex Lectularius* (*C. Lectularius)* experience hypersensitive reactions, papular urticaria, extensive erythema, urticaria, and even anaphylaxis has been reported, Pruritus is the major complaint, impairing quality of life and sleep. Immunotherapy has been used in mosquito bite papular urticaria resulting in improvement of skin lesions and possibly protecting against reactions to subsequent exposures to mosquitoes.

Methods: Children, 4-10 years of age, with recurrent papular urticaria due to bedbugs not responsive to multiple treatments were included. An initial allergy assessment included clinical history, skin prick test (SPT), and specific IgE sensitisation was performed to confirmed bedbug sensitization. Twenty children were randomized to receive subcutaneous specific immunotherapy (SSI) with whole body bed bug extract or conventional treatment. The treatment was carried out over twelve months and the response was assessed using the Dermatology Quality of Life Index (DLQI), the immunotherapy satisfaction questionnaire (ESPIA questionnaire) and the 12-Item Pruritus Severity Scale (12-IPSS). The results from both the treated and control groups were compared.

Results:

The twenty patients were randomized, 12 to receive immunotherapy and 8 to receive conventional treatment for 12 months. Quality of life improved with a reduction in the DLQI score of 19.83 in the immunotherapy group versus 9 in the conventional treatment group (p=.03). Itch improved with a reduction in the 12-IPSS of 16.5 in the immunotherapy group versus 9.63 in the conventional treatment group (p=0.02). After twelve months of treatment, all 12 patients who received immunotherapy, reported a decrease of persistent cutaneous lesions but the 8 on conventional treatment did not. A mean score of 95.75 (SD 3.3) was recorded for satisfaction with immunotherapy.

Conclusions. Patients with papular urticaria by *C. lectularius* receiving allergen immunotherapy for 1 year showed a significant improvement compared with baseline and patients receiving conventional treatment regarding skin lesions, quality of life impairment, intensity of pruritus and satisfaction with immunotherapy.

INTRODUCTION:

Papular urticaria also called **lichen urticatus or prurigo simplex acuta** (insect bites) is a chronic allergic reaction induced by insect bites, which is common in the tropics, in urban regions and in spring and summer. It is one of the most common dermatoses of childhood, with reported frequencies of 20% and 25% in Colombia and Venezuela respectively have been published.[1-2]

In Mexico the most common agents reported to cause papular urticaria are bed bugs, fleas and mosquitoes. Bed bugs are bloodsucking arthropod parasites of the *Hemiptera* order. Four genera are known: *Cimex, leptocimex, oeciacus* and *haematasiphon* comprising 91 known species. Only three species cause bites in humans*: Cimex hemipterus*, *Cimex lectularius* and *Leptocimex boueti*. *Cimex lectularius* is most prevalent in temperate regions, whereas *Cimex hemipterus* is found mainly in tropical and subtropical regions and *Leptocimex boueti* predominates in Western Africa and South America.[3] Bed bugs have been a persistent and scorned pest of humans, as referenced in recorded narratives dating back to classical Greek writings (Aristoteles in the year 400 BC), medieval European texts and the Jewish Talmud. In London, in 1930, one-third of the population (approximately 4 million people) was estimated to be affected. The introduction of modern insecticides such as the organochlorine dichloro-diphenyl trichloroethane (DDT) provided a fast and an inexpensive method to control insect pests, including bed bugs.[3] Unfortunately, bed bug infestations have rapidly increased worldwide over the last 20 years. Various factors have been postulated to be responsible for this reappearance. Overcrowded cities, a greater reliance on communal laundries, unregulated sale of second-hand clothing, use of previously owned furniture and furnishings, lack of family health care, a worldwide increase in secondary hosts including rodents, poultry, dogs and cats, lack of knowledge about the disease from the patient and from the health provider, an increase in local and international travel and migration, high costs of extermination processes coupled with insecticide resistance and toxicity of some others.[5-9.]

A variety of clinical reactions to bed bugs have been reported. Approximately 70% of the victims of *C. lectularius* bites will develop a cutaneous reaction and rarely a systemic reaction. These allergic reactions can vary from itchiness, an erythematous rash, urticaria, asthma and in the worst-case scenario, anaphylaxis. Pruritus is usually the cause of the impaired quality of life and sleep disturbances.[10-11] Cutaneous lesions usually start as small red macules that evolve to very pruritic wheals that last for several days causing the patient to enter an itch-scratch-itch cycle, which may lead to secondary bacterial infections. The lesions characteristically appear in exposed areas of the skin, such as the face, neck, hands and arms. The bites and pruritic papules display patterns that help identify the offending agent; appearing in pairs (dumbbells), following a linear or grouped triangular pattern with the lesions separated by a few millimeters, known as the "breakfast, lunch, and dinner" pattern. The bite itself is painless. Dependent on prior exposure, bites become symptomatic within minutes in those with prior sensitization or symptoms are delayed until sensitization has occured in first time exposed individuals. Lesions occur in crops in sensitized individuals with new local reactions developing while the old lesions heal. The most frequent complications of papular urticaria include ecthyma, cellulitis, cutaneous hyperpigmentation lymphangitis and impetigo. The reactions are sometimes complicated by insomnia and psycho-affective conditions such as anxiety, depression and psychotic states.[12-14]

The diagnosis and identification of the responsible biting insect is clinical. *In vivo* analyses with skin prick test using the *C. lectularius* salivary gland solution can be used to confirm sensitization to *Cimex* in difficult cases. potential protein antigens present in the saliva of *C. lectularius*. [15-16]

Specific treatment involves removal from exposure and eradication of the insects which may prove to be difficult. Management should be based on education of the patient, improvements in personal hygiene, environmental hygiene and home hygiene and medical measures. Firstly, the control of the bed bugs is challenging but the nature of the condition should be carefully explained, and the patient and family empowered to eradicate the insect. Hygienic-environmental measures include a deep cleaning of the house, personal and bed clothes; and the eradication of the bed bugs through the application of insecticides (pyrethrin, permethrin, organophosphates and carbamates). Thirdly, medical treatment is symptomatic. If there is superadded infection, an antiseptic or topical or systemic antibiotic is used dependent on the extent and severity of the infection. For acute bites mild steroids, such as hydrocortisone are recommended according to Mexican guidelines.[17] Oral antihistamines are given for intense itching. The preventive use of repellents, such as citronella fragrances or 5% benzyl benzoate, help to reduce bites while the total eradication takes place.[18]

Immunotherapy for papular urticarias caused by insect bites (mosquito) has been shown to be effective in improving skin lesions and increasing levels of the subclass of IgG4 that may have a protective role against subsequent reactions to exposures to the same insects.[19]

MATERIAL AND METHODS:

We recruited children aged 4–15 years old, from the allergy clinic at Hospital General de Mexico Eduardo Liceaga, an urban, tertiary referral center. We identified children who had recurrent papular urticaria caused by bed bugs in whom multiple previous treatments had been used without response (eradication of the bed bugs through the application of insecticides in their homes, topical corticoids, antihistamines). Written consent and written assent were obtained from the parents and child. Ethics approval was given by the Internal Committee of Hospital Bioethics.

The participants who fitted the selection criteria underwent an initial allergy assessment including clinical history, SPT and specific IgE to determine bed bug sensitization. Additional aeroallergens that were tested included mosquito, flea, *Dermatophagoides Pteronyssinus* house dust mite, *Periplaneta Americana, Alternaria* mould, *Aspergilus Niger, Amaranthus Palmeri, Atriplex Bracteosa, Chenopodium Album, Salsola Kali, Fraxinus Americana, Ligustrum, Artemisia* spp., Ambrosia spp., *Cosmos Bipinnatus, Hellianthus Annus,* Quercus spp., Alnus spp., *Prosopis* spp., *Schinus Molle, Populus Alba, Cynodon Dactylon, Lolium Perenne, Phleum Pratense,* cat and dog dander based on the Mexican immunotherapy guidelines.[20] Prick testing was performed according to the method of the subcommittee on Skin Test of the American Academy of Allergy, Asthma & Immunology using standardized lancets. The participants were interrogated and classified in a socioeconomic stratum based on the Mexican Association of Research Agencies and Public Opinion A.C. (AMAI) in High Class (A / B), High Middle Class (C +), Middle Class (C), Middle Low Class (D +), Low Class (D), Extreme Poverty (E)

Twenty children were randomized to receive subcutaneous specific immunotherapy with a whole-body bed bug extract or conventional treatment (antihistamines, topical steroids, citronella fragrance).

C. lectularius extract was prepared from 4 g of dried *C. lectularius* were obtained from three homes of families affected by bed bugs in Mexico City and from the Penitentiary Center ("Reclusorio Preventivo Varonil Norte") in Mexico City, by degreasing the samples with sulfuric ether and subsequently drying in the sun for a period of 12 hours and grinding them to powder using mortar and pestle

The bed bug allergen preparations was based on Good Manufacturing Practice with the references given in the work of Price et al. in Journal Allergy Clinical Immunology in 2012. The allergenic extract of bed bug was defined as 100 I.R./ml. (67 mcg/ml.)

Immunotherapy was initiated with the whole-body bed bug extract at a concentration of .0001 wt/vol given subcutaneously. Thereafter biweekly subcutaneous injections, of progressively increasing doses were administered for three months (induction phase). The dose was then maintained after 12 weeks of treatment (maintenance phase) till the end of the study period (Table I).

The response to immunotherapy was assessed using scores of quality of life (Dermatology Quality of Life Index), scores of satisfaction to immunotherapy (ESPIA questionnaire) and intensity scores of pruritus (12-Item Pruritus Severity Scale). These were performed before the start of immunotherapy, at 3 months, at 6 months and at 12 months of treatment.

The DLQI score range is 0-30, the higher the score the higher the impairment of the QOL. Scores of 0-1 are defined as having no effect on the patient´s QOL, scores of 2-5 a small effect, scores of 6-10 a moderate effect, scores of 11-20 a very large and scores of 21-30 extremely large effects on patient´s QOL.

The intensity of pruritus was assessed using the 12-Item Pruritus Severity Scale. The score ranges from 3 (minimal pruritus) to 22 (most severe pruritus).

The satisfaction of treatment with immunotherapy was evaluated based on the ESPIA questionnaire that consists of 16 items distributed in 4 dimensions: perceived efficacy, activities and environment, cost-benefit balance, and general satisfaction. The final score ranges from 0 (low satisfaction) to 100 (high satisfaction).

Statistical analysis: Statistical evaluation was done by Mann-Whitney U-Test (two tailed probabilities), for the intergroup comparisons and the Wilcoxon signed rank for intragroup comparison at the different time of observation. The chi-square test was used to test the significance of differences among the overall evaluation stated at the end of the trial. The level of significance chosen was $p < 0.05$.

RESULTS:

A total of 20 patients were included for this study from 24 recruited, corresponding to a response rate of 83.3%. Three patients did not meet inclusion criteria (response to conventional treatment) and 1 patient refused participation. All 20 enrolled patients had recurrent papular urticaria caused by bed bugs which was not responsive to multiple previous treatments and which was affecting QOL. The mean age of the recruited children was 6.2 years (SD 1.73) and 100 % (n = 20) were male, none of the females having met inclusion criteria. A mean DLQI score of 23.60 (SD 2.34) and mean 12 item PSS score of 20.35 (SD 1.3) were recorded for the group on enrollment.

Twenty patients were randomized by coin toss, 12 to receive immunotherapy and 8 to receive conventional treatment. There were no significant differences between the two groups with regard the age, IgE (median 121 kU/l versus 140 kU/l), socioeconomic stratum, comorbidities and positive skin prick tests to aeroallergens. (TABLEII).

Quality of Life

Patients who received immunotherapy showed an improved mean DQLI score of 23.83 (SD 2.51) before starting treatment to 4.00 (SD 1.41) after 12 months of treatment. Compared to patients receiving conventional treatment who showed an initial mean DLQI score of 23.25 (SD 2.18) and 14.25 (SD 2.25) after 12 months of treatment. Overall the reduction in the DLQI score of 19.83 in the immunotherapy group versus 9 in the conventional treatment group was significant (p=.0012) (Figure I).

Intensity of Pruritus

Patients who received immunotherapy experienced a reduction in the intensity of pruritus evaluated with the 12-Item Pruritus Severity Score (12-IPSS) from 20.5 (SD 1.24) to 4 (SD 1.41) after 12 months of treatment. Compared to patients with conventional treatment who presented an initial 12-IPSS of 20.13 (SD 1.45) and a final of 10.5 (SD 3.4) after 12 months. Overall the reduction in the 12-IPSS of 16.5 in the immunotherapy group versus 9.63 in the conventional treatment group was significant. (p=0.02)
(Figure II)

The satisfaction of the immunotherapy was assessed using the ESPIA Questionnaire and a mean satisfaction of 95.75 (SD 3.3) was recorded.

The yearly cost analysis of the immunotherapy was $60 on average for each patient which was accompanied by a reduction in the conventional medicines (antihistaminics, steroids, insect repellents) used, compared to the control group receiving conventional treatment with an average cost of $180 for each patient without a decrease in the use of medications during the study period.

After twelve months of treatment, all 12 patients who received immunotherapy, reported a decrease of persistent cutaneous lesions (papular urticaria). (Figure 3) On the contrary the

other 8 patients with conventional treatment did not present a significant reduction of cutaneous lesions (papular urticaria).

Discussion

Papular urticaria is a manifestation of recurrent pruritic papules or vesicles and varying degrees of local edema. Reactions are thought to be the result of a hypersensitivity reaction to biting, stinging, or urticating insects (mosquitoes, flies, gnats, mites, ticks and bed bugs).[18]

Cuellar et al. demonstrated that papular urticaria was a chronic allergic disease where there was a genetic predisposition with an increased expression of molecules such as CD83, CD86 and HLA-DR which are related to antigen presentation and there are lower levels of regulatory cytokines such as interleukin-6 and IL-10 leading to an increase in the production of Th-2 cytokines ending in the production of a skin allergic reaction to exposure to an allergen in the sting or bite of an insect (saliva).[19]

Penneys et al. demonstrated human antibody binding to salivary gland and foregut endothelial protein antigen in mosquitoes. Previously sensitized sites also erupt following the appearance of new lesions, suggesting that circulating antigen triggers the reactivation of sensitized sites. [20]

Price et al. demonstrate the development of an IgE response to *C. lectularius* following bed bug bites and Leverkus et al. identified the allergen as nitrophorin in the bed bug's saliva.[21.]

Allergen specific immunotherapy (SIT) has been studied and used since Noon's first report in 1911. SIT is the only treatment option that modifies fundamental allergic mechanism by inducing desensitization. Immunological changes associated with immunotherapy result in clinical tolerance (decrease in antigen-specific responsiveness) and immunologic tolerance (specific immune deviation from a TH2 to a TH1 cytokine profile).

Until now, 6 studies on mosquito immunotherapy have been conducted based on clinical variables such as skin reactivity, nasal reactivity, symptom and drug scores and immunological variables such as increase in IgG4 antibody levels. No study has been carried out in bed bug immunotherapy. Both insects causes have been shown to be allergic hypersensitivity reactions to the saliva allergen found in both insects.[22,23.]

In the present study patients in the active group receiving immunotherapy with whole-body bed bug (*C. lectularius*) extract for 1 year demonstrated significant improvement in clinical variables (skin lesions, improvement in quality of life, intensity pf pruritus and satisfaction with treatment) compared with the conventional treatment group.

In this study, with the progression of immunotherapy 100% of patients showed improvement in quality of life with a DQLI with a reduction from 23.86 to 11.91 (51%) in the Score at month 3 of treatment and from 23.86 to 4.13 (83%) at month 12 of treatment, being the maximum improvement in the first three months of treatment. The decrease in the intensity of pruritus was 74% in the third month of treatment and 80% after 12 months of treatment being the maximum intensity of pruritus reduction in the first three months of treatment.

Satisfaction with immunotherapy using the ESPIA questionnaire was greater than 88 in the 12 patients with an average satisfaction of 95, supporting a high satisfaction with the treatment.

The medical treatment for bed bug papular urticaria is with topical steroids at the site of the bite and on acute lesions. The medical treatment for pruritus is with antihistamines. The most specific and curative management is the eradication of the bed bugs and thus exposure, but

this can be challenging. Bed bugs are very resistant insects, that can survive for up to a year without food and are able to extend their territory through walls and ceilings. Eradication is best performed by a professional, but this is expensive often a change in household furniture is recommended and thus an unaffordable option for the vast majority of affected patients.[21]

Limitations

The limitations of this study include small sample size recruited in a tertiary allergy clinic, which makes it difficult to extrapolate results to the general population. *In vitro* tests are not available to identify specific IgE against bed bugs saliva antigens. The treatment is focused on the reduction of symptoms and improvement in quality of life, does not reduce the transmission of the disease therefore it does not replace the definitive treatment that is the extermination of the bed bugs.

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Conclussions:

This pilot study demonstrates that subcutaneous immunotherapy with a whole body, bed bug extract is effective in reducing the number of skin lesions and pruritus intensity while improving quality of life in patients with recurrent papular urticaria caused by bed bug bites who had failed multiple previous adequate and appropriate treatments. It was rated as a highly satisfactory treatment by patients.

The objective of this preliminary study was to determine the feasibility for a larger, future study in collaboration with first level services focused on populations of low socioeconomic level, with a large number of patients using a standardized extract.

Conflict of Interest:

The authors declare that they have no conflict of interests.

Table I Subcutaneous specific immunotherapy scheme.		
Induction Dose	**Schedule (Biweekly)**	**Week**
0.001 wt/vol	0.1	1
	0.2	1
	0.4	2
	0.8	2
0.01 wt/vol	0.1	3
	0.2	3
	0.4	4
	0.8	4
0.1 wt/vol	0.1	5
	0.2	5
	0.4	6
	0.8	6
1 wt/vol	0.1	7
	0.2	7
	0.4	8
	0.8	8
10 wt/vol	0.1	9
	0.2	9
	0.4	10
	0.8	10
100 wt/vol	0.1	11
	0.2	11
	0.4	12
Maintenance Dose	**Weekly**	
50 mcg/ml	0.50 cc	
Mixed non-standardized whole-body extract of *C. lectularius* (bed bug).		

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TABLE II: DEMOGRAPHIC CHARACTERISTICS OF EXPERIMENTAL GROUP AND CONTROL GROUP

N	G	AGE	ADDRESS	SEST	IGE	OTHER ALLERGENS SPT	COMOR-BIDITIES	DLQI				12I PSS				ESPIA
EXPERIMENTAL GROUP								0	3	6	12	[illegible]	3	6	12	93
1	M	8	**MEXICO CITY, IZTAPALAPA.**	D+	45	PER, DER.	AR	21	14	9	5	20	10	8	4	94
2	M	6	**MEXICO CITY, IZTAPALAPA.**	D+	80	PER, MOS.	NONE	25	13	11	6	22	12	6	5	96
3	M	4	**MEXICO CITY, GUSTAVO A MADERO**	D	67	DER, CYN, LOL.	NONE	26	[illegible]	8	4	19	11	7	3	100
4	M	6	**MEXICO CITY, GUSTAVO A MADERO**	D	167	DER, MOS.	NONE	24	10	6	4	20	8	6	3	100
5	M	7	**MEXICO CITY, GUSTAVO A MADERO**	D	79	NONE	[illegible]ONE	19	8	4	2	21	14	10	4	88
6	M	8	**MEXICO CITY, IZTACALCO**	D+	212	AMA, FRAX, H[illegible]	NONE	23	16	11	5	22	10	10	8	96
7	M	5	**MEXICO CITY , IZTACALCO**	D+	95	[illegible]	AD	21	12	6	3	18	8	6	4	96
8	M	9	**MEXICO CITY, IZTACALCO**	D+	[illegible]	CAN, FEL.	NONE	24	11	6	2	21	12	8	3	98
9	M	5	**MEXICO, NAUCALPAN**	C	345	DER, PER, CYN.	AR	25	11	7	5	20	14	10	3	96
10	M	10	**MEXICO, NAUCALPAN**	C	98	NONE	NONE	28	9	4	3	20	9	5	4	93
11	M	7	**MEXICO, TLALNE[illegible]ANTLA**	D+	188	CAN, FEL.	NONE	26	16	10	6	21	15	7	4	94
12	M	5	**MEXICO, [illegible]TLALNEPA[illegible]NTLA**	D+	75	NONE	NONE	24	11	6	3	22	14	8	3	94
CONTROL GROUP																
1	M	5	**MEXI[illegible] CITY, CUAUTEMOC**	C	<5	NONE	NONE	26	20	18	15	20	15	12	8	DNA
2	M	7	**MEXICO CIT , CUAUTEMOC**	C	245	FRAX, HEL, CYN.	AR	24	18	16	17	18	16	12	10	DNA

3	M	6	**MEXICO CITY, ALVARO OBREGON**	D	130	CAN.	NONE	26	17	18	15	19	14	[illegible]	14	DNA
4	M	5	**MEXICO CITY, ALVARO OBREGON**	D	56	DER, PER.	AD	23	19	16	12	21	[illegible]	10	6	DNA
5	M	8	**MEXICO CITY, ALVARO OBREGON**	D	78	NONE	NONE	20	18	15	10	[illegible]	18	15	15	DNA
6	M	4	**MEXICO CITY, ALVARO OBREGON**	D	53	NONE	NONE	22	20	16	14	20	16	12	13	DNA
7	M	5	**MEXICO, AZCAPOTZALCO**	D+	200	DER, PER.	AR	24	[illegible]	20	15	22	16	12	10	DNA
8	M	4	**MEXICO, ECATEPEC**	D	353	FRAX, AMA, QUER, ALN, CYN.	AR	21	19	18	16	19	14	10	8	DNA

N: NUMBER, G: GENDER, M: MALE, F: FEMALE, SEST: SOCIOECONOMICC STRATUM.

E: EXTREME POVERTY, D+: MEDIUM-LOW CLASS , D: POVERTY, C: MEDIUM CLASS, C+: MEDIUM-HIGH CLASS , A/B: HIGH CLASS, PER:*PERIPLANETA*, DER:*DERMATOPHAGOIDES,* CYN:*CYNODON*, MOS:MOSQUITO, AMA: A*MARANTHUS*, FRAX:*FRAXINUS*, QUER: Q*UERCUS*, ALN: *ALNUS*, HEL:*HELLIANTHUS*, LOL:*LOLLIUM*, CAN: DOG, FEL: CAT, AR: ALLERGIC RHINITIS, AD: ATOPIC DERMATITIS, SPT (SKIN PRICK TEST)

12I-PSS: 12-ITEM PRURITUS SEVERITY SCALE, DQLI (DERMATOLOGY QUALITY OF LIFE INDEX), ESPIA (SATISFACTION IMMUNOTHERAPY QUESTIONNAIRE). DNA (DID NOT APPLY).