นิพนธ์ต้นฉบับ

Treatment of chronic urticaria with Allerglobulin(R): preliminary report.

Wiwat Korkij*
Saroj Jirarungreanwong*

Korkij W, Jirarungreanwong S. Treatment of chronic urticaria with Allerglobuline(R): preliminary report. Chula Med J Aug; 35(8): 487-492

Chronic urticaria is defined by the appearance of wheals lasting more than 6 weeks. Over 75% to 85% of patients is idiopathic group. The treatment of chronic urticaria is difficul in some patients especially those who are resistant to antihistamines. The main pathogenesis of urticaria is the triggering of mast cells to release mediators such as histamine by IgE. Allerglobuline(R) is an immune globulin obtained from placenta and has high histamino-therapeutic activity. We studied the efficacy of Allerglobulin in the treatment of chronic urticaria. Ten patients agreed to participate in this study. Each patient was given the diary card to record daily appearance of wheals, severity of pruritus and the number of antihistamines taken each day. A run-in period of 2 weeks before treatment was established to serve as control and records kept as well as during treatment and until 1 week after the last dose of treatment. Allerglobulin was given weekly for 5 weeks and then monthly for 3 months. After treatment, there was no statistical significance in the improvement of all parameters. Allerglobulin has no benificial effects in the treatment of chronic urticaria.

Key words : Chronic urticaria, Allerglobuline, Clacental immune globulin, Immunotherapy.

Reprint request : Korkij W, Department of Internal Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.
Received for publication. May 1, 1991.

*Department of Internal Medicine, Faculty of Medicine, Chulalongkorn University.

วิวัฒน์ ก่อกิจ, สาโรจน์ จิรรุ่งเรืองวงศ์. การรักษาโรคลมพิษเรื้อรังด้วยยาแอลเลอร์โกลบูลิน : รายงานเบื้องต้น. จุฬาลงกรณ์เวชสาร 2534 สิงหาคม; 35(8) : 487-492

โรคลมพิษเรื้อรัง เป็นโรคที่พบบ่อย ใช้เรียกในผู้ป่วยที่เป็นลมพิษมานานเกิน 6 สัปดาห์ขึ้นไป ส่วนใหญ่ (75-85%) ของผู้ป่วยเหล่านี้มักไม่พบสาเหตุ ฉะนั้นการรักษาจึงทำได้ลำบากโดยเฉพาะผู้ป่วยที่ไม่ตอบสนองต่อยา antihistamine พยาธิกำเนิดหลักของลมพิษคือการที่มี IgE ไปกระตุ้น mast cell ให้หลั่ง histamine ออกมา Allerglobulin(R) เป็น immune globulin ที่สกัดมาจากรกของมนุษย์ มีฤทธิ์ในการทำลายและยับยั้งการหลั่ง histamine ที่เกิดจาก IgE ในการศึกษานี้ได้ทดลองรักษาผู้ป่วยที่เป็น chronic urticaria จำนวน 10 ราย โดยผู้ป่วยแต่ละคนต้องนับจำนวนตุ่มที่ขึ้นในแต่ละวัน ความรุนแรงของอาการคันและจำนวนยา antihistamine ที่กินในแต่ละวัน โดยเริ่มบันทึก 2 อาทิตย์ก่อนได้รับ Allerglobuline เพื่อเป็น control ในขณะได้รับยาและหลังได้รับยาครบแล้วต่อไปอีก 1 อาทิตย์ ผู้ป่วยถูกฉีด Allerglobuline อาทิตย์ละครั้ง 5 อาทิตย์ และต่อไปเดือนละครั้ง อีก 3 เดือน ผลการทดลองไม่พบว่าจำนวนผื่นอาการคันหรือจำนวนยา antihistamine ที่ผู้ป่วยกินมีความแตกต่างอย่างมีนัยสำคัญของก่อนรักษาเมื่อเทียบกับหลังการรักษา สรุปได้ว่า Allerglobulin ไม่ได้ผลในการรักษาโรคลมพิษเรื้อรัง

Urticaria is defined by the appearance of wheals of any size and configuration on any part of the skin. It is usually pruritic and disappears within minutes to hours, leaving a basically unaltered, normal appearing skin. Similarly transient, erythematous swellings of the deeper cutaneous and the subcutaneous tissue are called angioedemal and appear in about 50% of patients in association with ordinary urticaria. Urticaria is classified into acute and chronic urticaria. The chronic urticaria is defined by the presence of recurrent episodes of urticarial lesions that come and go over a period of more than 6 weeks.[1] Whereas the cause is often evident in acute urticaria, this is rarely the case in chronic urticaria. The cause is not found in over 75% to 85% of these cases.[1] Chronic urticaria tends to be more common in middle age, particularly in woman.

Urticaria is caused by the triggering of mast cells to release mediators by immunological and nonimmunological mechanisms.[2] The nonimmunological mechanism is induced by direct stimulation of the mast cells by certain stimuli such as aspirin, morphine or physical stimuli. IgE is the major immunoglobulin involved in the immunological mechanism of urticaria. IgE binds to the receptor for IgE on mast cells via its Fc portion. When the certain antigen binds to two adjacent IgE on mast cells it stimulates mast cell to release various mediators such as histamine to produce urticaria.[2] The IgE receptor on mast cells can be blocked by other classes of immunoglobulin especially IgG4. This antibody work as a blocking antibody preventing IgE from binding to its own receptor on mast cells.[3]

Allerglobuline(R) (Institut Merieux, Lyon, France) is an immune globulin obtained from human placenta and chosen by titration based on its high histamino-therapeutic activity.[4] It was launched for the treatment of the allergic condition. Although the precise mechanism of action of Allerglobuline is not yet demonstrated, it could act as blocking antibodies by inhibiting IgE binding to specific receptors on the cell surface or by binding to allergens which in turn blunts the IgE antibody response.[5] Because of these properties Allerglobuline might be useful in the treatment of chronic urticaria.

We conducted a trial to assess the clinical efficacy of Allerglobuline in the treatment of chronic idiopathic urticaria.

Materials and Methods

Ten patients with more than 6 weeks of daily occurrence of urticaria but who were otherwise healthy agreed to participate in the study. Laboratory investigations included complete blood count, urinary analysis, stool examination, VDRL, ASO titer, antinuclear antibodies and hepatitis B surface antigens were performed in all patients. Each patient was given a diary card and were asked to record the dialy occurrence of wheals, severity of pruritus and the number of antihistamines taken each day. Wheal was graded as follow: 0 = no lesion, 1 = 1 – 5 wheals, 2 = 6 – 10 wheals, 3 = 11 – 15 wheals and 4 = more than 15 wheals. Severity of pruritus was graded as follow: 0 = no symptom, 1 = mild pruritus, 2 = moderately pruritus, 3 = severe pruritus, 4 = unbearable pruritus. The records were started 2 weeks before treatment began to serve as a control period, and until 1 week after the last dose of treatment. The patients were given Allerglobuline (5 ml/vial) 2 vials intramuscularly weekly for 5 weeks and then monthly for 3 more months. At the follow up, the patients were asked about the side effects and the efficacy of therapy. The patient was instructed to adjust the amount of antihistamines consumed according to the number of wheals and symptoms.

Statistical analysis

The comparison of nuber of lesions severity of pruritus and the number of antihistamines taken before and after treatment was examined with paired t test.

Results

There were 3 males and 7 females, aged from 16-32 year old (mean = 25.4) who had urticaria ranged from 2 months to 20 years (mean = 53.8 mo.). Four patients also had angioedema before treatment. No systemic diseases were detected in all patients. Laboratory investigations were negative or within normal limit in all patients, except for 2 patients who had elevated eosinophil count (6% and 10%). After treatment with Allerglobulin, the number of lesions (Table 1.) the severity of pruritus (table 2.) and the number of antihistamines used (table 3.) did not show any statistical difference between the before and after treatment.

Table 1. Average grading of lesions/week.

Case	control	1 wk.	2 wk.	3 wk.	4 wk.	5 wk.	9 wk.	13 wk.	17 wk.
1	0.7	0.6	0	1.1	1	1	1.1	1	1
2	3	2.6	3.3	3.3	3.1	2.1	4	4	4
3	3	3.3	2.6	2.6	2.9	2.4	3.1	3.1	3.6
4	4	4	4	4	4	4	4	4	4
5	0.7	1.3	0.7	2.9	0.4	1.1	1	0.7	1
6	1.2	1.1	1.4	2	2	2.1	2.1	0.4	0.9
7	1.4	1.1	1.7	3.6	2.6	3.4	2.9	3.7	2.7
8	1	1 1	1	1.3	1.3	1	1.1	1.7	1.3
9	4	4	4	4	4	4	4	4	4
10	2.4	3	1.8	1.8	1	2.4	2.1	0.7	1.6

*Statistical significance at $\alpha = 0.05$

Table 2. Average grading of pruritus/week.

Case	Control	1 wk.	2 wk.	3 wk.	4 wk.	5 wk.	9 wk.	13 wk.	17 wk.
1	0.4	0.4	0	1.4	1	1.3	1.1	1	1
2	0.4	0.3	0.4	1.1	0.1	0	1	1.1	1.3
3	3	2.7	2	2.1	2.7	1.9	2.1	2.1	2.6
4	3	3	3	3	3	3.6	3.3	3	2
5	0.6	0.7	0.4	1.6	0.3	0.6	0.4	0.4	0.6
6	2	2	2	2	2	2.4	2.4	0.4	0.9
7	0.8	0.9	0.7	1.7	1.3	1.4	1.4	3.3	0.7
8	0.3	0.6	0	0	0.1	0	0	1.1	1.3
9	1	1	1	1	1	1	1.4	1	1
10	1	1	1	1	1.4	1.4	1	0.6	1

*Statistical significance at $\alpha = 0.05$

Table 3. Average number of Antihistamine used/week.

Case	Control	1 wk.	2 wk.	3 wk.	4 wk.	5 wk.	9 wk.	13 wk.	17 wk.
1	3	3	3	3	3	3	3	3	3
2	2	1.6	0.6	1.9	1.9	1.7	2	2	2
3	1	1	1	0.1	0.7	0.7	0.4	1.1	2
4	1	1	1	1	1	1	1	1	1
5	2	1.9	2	2	2	2	2	2	2
6	2.8	2.7	2.9	3	3.3	3	4	2.8	5
7	2	2	2	2	2	3	3	3	3
8	2	2	2	2	1	1	1	1	3
9	6.4	6.1	6.7	10.1	9.4	7.3	6.3	6.6	5
10	2	2	2	2	2	0.5	2	2	2

*Statistical significance at $\alpha = 0.05$

Discussion

The cause of chronic urticaria is infrequently found, however the cause should be searched for in all chronic urticaria patients such as drugs, foods, inhalant allergens, infections, internal diseases and physical factors.[6] Identification and removal of the cause is the ideal treatment for urticaria. This is often impossible in chronic urticaria. If a cause cannot be found then a reduction of various triggering factors should be attempted. This approach is especially applicable in cases of the physical urticaria, although the nonspecific modulating factors that aggrevate cutaneous vasodilatation, such as alcohol, heat, exertion and emotional stress, should also be avoided. The mainstay in the management of urticaria is histamine H_1 receptor antagonists. Hydroxyzine hydrochloride has been demonstrated to be more effective than other antihistamine in the inhibition of wheal-and-flare responses and suppression of histamine-induced pruritus.[7] If it is ineffective, an agent from a different pharmacologic class should be added. The combination of H_1 and H_2 antihistamine may be beneficial in treating some but no all patients with chronic urticaria. In spite of these treatments some patients may be resistant to all antihistamines given. Other drugs with different mechanisms should be tried in this group of patients.

Allerglobuline is a gamma-globulin of placental origin. The principal use derives from the observation by Benda and Urquria.[8] that the injection of 2 ml. of human serum subcutaneously into guinea-pigs protected them against lethal doses of histamine and this protection lasted for several months. The serum of asthmatic patients did not provide this protective activity. Later, after several research programmes, it was established that immune globulins had histamino-protective activity and certain batches of immune globulins had distinctly higher protective activity. Immunoglobulin preparations of placental origin but not plasma origin, inhibited spontaneous IgE production in vitro.[9] The degree of inhibition appeared to related to IgE content in the batch. IgE particularly in dimeric form, induces the appearance of receptors for its Fc fragments on B, T lymphocytes and macrophages. Such induction triggers the production of lymphokines leading to inhibition or stimulation of IgE synthesis.[9] A placental origin for IgE may influence the appearance of these receptors. Besides this activity, Allerglobulin also contains many allergen specific IgG1 including house dust mite, epithelia and moulds.[4] In vitro, this product exhibits a 60-70% inhibition of allergen-induced basophil degranulation. IgG4 or blocking antibody is also one of the component of Allerglobulin. This antibody can interfere with IgE by inhibiting IgE binding to specific receptors on the cell surface.[3] Allerglobuline has been reported in the treatment of hay fever, asthma, allergic rhinopharyngitis, allergic conjunctivitis and atopic eczema.[10] Girard at el.[5] conducted the double blind study of Allerglobuline in hay fever. They found favourable results in 85% of the treated group for rhinitis and 87% for conjunctivitis, versus 20% and 40% respectively in the placebo group. Allerglobuline was used to treat atopic eczema by Pons-Guiraud.[11] Fifty-five percents of patients given Allerglobuline were improved compared with 33% in placebo group. In this study we used Allerglobuline to treat chronic urticaria. At the end of treatment, the number of lesions, pruritus and the number of drugs used did not differ from the control period. The fluctuation of these parameters may reflex the natural course of the disease. The ineffectiveness of Allerglobuline in the treatment of chronic urticaria may be explained in part by:

- The urticaria in our patients was not caused by air born allergens.
- Doses and the frequency of administration of Allerglobuline may not be optimal in this study.

In conclusion, we studied the efficacy of Allerglobuline in the treatment of chronic urticaria. There is no statistical significance in the improvement by using the number of lesions, pruritus and the number of antihistamines used as parameters.

References

1. Adelberg BR. Chronic urticaria In: Lebwohl M ed. Difficult Diagnosis in Dermatology. New York: Churchill Livingstone, 1988. 319-29
2. Czarnetzki BM. Urticaria. Berlin: Springer-Verlag, 1986. 5-24
3. Perelmutter L. IgG4: Non IgE mediated atopic disease. Ann Allergy 1984 Jan; 52(1): 64-8
4. Giannarakos G, Costopoulos E, Christodoulidis A. The therapeutic effect on allergic asthma of immune globulins of placental origin selected for their high anti-allergic activity. Cahiers Medicaux Lyonnais 1972; 18: 4965-70
5. Girard JP, El-Habib G, Granjard P. Treatment of hay fever by Allerglobuline: a randomized double-blind study. Clin Allergy 1988 Jul; 18(4): 393-400

6. Juhlin L. Recurrent urticaria: clinical investigation of 330 patients. Br J Dermatol 1981 Apr; 118(4): 194-201
7. Grant SP. The inhibitory effect of antiallergy drugs on allergen and histamine-induced wheal and flare responses. J Allergy Clin Immunol 1973 Jan; 51(1): 11-15
8. Benda R, Urquia DA. Action antihistaminique du serum humain ou animal chez le cobuye. Communication an 26 congres de la Medecine Francaise. Paris, 1947. 54-64
9. Rigal D, Baboin-Jaubert M, Rousset M, El-Habib FR, Monier JC. Immunomodulation induced by immunoglobulins. I. Action of placental immunoglobulin on in vitro spontaneous synthesis of IgE in Man. Clin Immunol Immunopathol 1988 Oct; 49(1): 1-5
10. Pons-Guiraud A. Interest de l' Allerglobuline(R) dans le traitement de la dermatite atopique de l' enfant et de l' adulte jeune. Etude randomisee en double aveugle. Rev Med Interne 1986; 7: 537-42
11. Pons-Guiraud A, Granjaro P, Fygonnet JP. Interest of Allerglobuline in the treatment of atopic eczema. Gazette Med 1985; 92(1): 1-3