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Successful combined therapy for refractory chronic urticaria in a 10-year-old boy

D. Vita, G. Passalacqua, L. Caminiti, G. Barberio, G. B. Pajno*

Key words: chronic urticaria; ϵ aminocaproic acid; montelukast; ranitidine.

Urticaria lasting more than 6 weeks is defined as chronic, and in the majority of cases its etiology remains unknown. Chronic idiopathic urticaria is usually quite frustrating for the patient, as it heavily impairs the quality of life, and for the physician, as it is difficult to

Chronic idiopathic urticaria is a difficult to treating disease, therefore we describe a combination therapy which may be considered an useful treatment.

treat. H1-antihistamines are the first-line treatment (1), and in those patients with an unsatisfactory response to antihistamines, the addition of other antimediator (e.g. leukotriene modifiers or anti-H2 antihistamines) can be of benefit. For refractory cases, long-term treatments with systemic steroid or immunosuppressants are used as second choice (1, 2), whereas the role of intravenous gamma-globulins or plasmapheresis is controversial. We describe the case of a child with severe and refractory chronic urticaria (CU), successfully treated with a new combination therapy.

A 10-year-old boy was referred for severe chronic urticaria. He had been well until the age of 8, when episodes of generalized urticaria began to occur. His clinical history was negative for allergic diseases: asthma, atopic dermatitis, hay fever. A detailed study for the possible common causes of urticaria was under-

Table 1. Posology of the combined regimen

Drugs			
Month 1	ϵ -Aminocaproic acid (100 mg/kg/day)	Montelukast (5 mg/day)	Ranitidine (6 mg/kg/day)
Month 2		Montelukast (5 mg/day)	Ranitidine (6 mg/kg/day)
Month 3			Ranitidine (6 mg/kg/day)

taken. Routine laboratory parameters (including blood cell counts, clinical chemistry and urinalysis) were all within the normal range, as well as thyroid hormones and thyrothrin. Erythrocyte sedimentation rate was 16 mm/h. Antinuclear autoantibodies and rheumatoid factor were negative and complement fractions and circulating immune complexes were normal. Repeated stool assays for parasites and eggs gave negative results. A detailed allergologic study was also carried out, but skin prick tests and radioallergosorbent test with aeroallergens and common food allergens were negative; total serum IgE was 179.5 U/ml. No local reaction after intradermal injection of autolog serum could be demonstrated. Additional studies included hepatitis B surface antigen and antibody, and paranasal sinuses CT, that provided negative results as well. The C1qINH, measured by radial immunodiffusion, resulted within the normal range. The patient was repeatedly treated with H1 and H2 antihistamines in various combinations, with only marginal benefit. A satisfactory, although not full, control of symptoms could be obtained only with repeated courses of prednisone (1 mg/kg/day). Nevertheless, when the systemic steroid was tapered, urticaria invariably relapsed within 1–2 weeks. During 2 years, the patient underwent nine courses of systemic prednisone.

Before giving immunosuppressant agents we attempted an empirical therapeutic approach, combining an anti-fibrinolytic agent (ϵ aminocaproic acid) plus montelukast plus the H2 antihistamine ranitidine. This regimen induced a full remission of urticaria in about 48 h. The treatment was gradually tapered in the subsequent months, and no relapse of symptoms occurred (Table 1). At present, after about 13 months, the patient still remains completely symptom-free.

Treating chronic idiopathic urticaria represents a challenge for physicians, as no avoidable cause can be detected. Therefore, the therapy can only have the goal of controlling symptoms. Nevertheless, in several patients the recommended first-line drugs are not effective, and the second-line drugs (steroids, cyclosporine) provoke severe systemic effects. These problems are of major relevance in the pediatric age. These are the reasons why numerous empirical attempts have been proposed and described. For instance, antiprotease drugs (e.g. tranexamic acid or ϵ -aminocaproic acid) that are commonly used for prophylaxis of hereditary angioedema are effective in chronic urticaria (3, 4). In children, these anti-fibrinolytic agents are always of first choice for long-term treatments, because they are safer than attenuated androgens (5). On the contrary, the efficacy of leukotriene receptor antagonists has been demonstrated in several studies, although the role of leukotrienes in urticaria is not completely clarified. Finally, H2 antihistamines are often considered as useful adjuncts in the treatment of urticaria (1).

In the case herein described, our main aim was to avoid, if possible, the use of long-term corticosteroids or cyclosporin A (6). For this reason we carried out an exploratory attempt with a combination of relatively safe drugs which, in turn, seldom are effective when used alone.

This case report suggests the described combination therapy may be considered as an alternative to standard medications.

*Divisione di Pediatria II – Servizio di Allergologia Pediatrica
Università di Messina
Via Consolare Valeria – Gazzi
98125 Messina
Italy
Tel: +39 090 2935007
Fax: +39 090 2212143
E-mail: giovanni.pajno@unime.it

Accepted for publication 19 January 2004
Allergy 2004; 59:1021–1022
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Dendritic cells present neuromuscular blocking agent-related epitopes to T cells from allergic patients

N. Aubert, P. M. Mertes*, M. Janaszak, D. A. Moneret-Vautrin, M. C. Laxenaire, G. Kanny, F. Lavaud, J. Bernard

Key words: allergen presentation; allergy; anaphylactic reaction; dendritic cells; NMBA.

Anaphylactic reactions to neuromuscular blocking agents (NMBA) remain a major

life-threatening and unpredictable complication during anaesthesia (1).

Dendritic cells (DC) are considered to be the most powerful antigen-presenting cells (2).

They can skew CD4⁺ T-cell differentiation towards a Th2 cytokine secretion pattern, which induces humoral responses dominated by an enhanced IgE production such as in allergic diseases.

We undertook a case-control study to assess whether DC from patients having presented an anaphylactic reaction to an NMBA during anaesthesia were able to present the incriminated drug and to stimulate T cells.

Ten patients sensitized to an NMBA and eight control subjects were involved in the study (Table 1). Monocytes and T lymphocytes were purified from fresh heparinized blood. Monocyte-derived DC (3) were generated in a 5-day culture with GM-CSF and IL-4, then matured for 2 additional days with TNF- α and PGE₂ in the presence or absence of NMBA. Both NMBA-pulsed and control DC were co-cultured (ratio 1 : 10) with T lymphocytes from the same donor. After 5 days, proliferative responses were quantified by the mean [³H]-thymidine incorporation. Stimulation indices (SI) were calculated as 'cpm in coculture with NMBA-pulsed DC/cpm in coculture with unpulsed DC' and were considered as

Dendritic cells from patients allergic to neuromuscular blocking agents are able to present the allergen and stimulate autologous T cells *in vitro*.

positive when SI > 2. In addition, lymphocyte transformation tests (LTT) were performed in the presence of the incriminated NMBA for each patient and in the presence of succinylcholine for healthy donors.

No proliferative response was observed using LTT either in patients or in healthy donors. In contrast, NMBA-pulsed DC induced a significant proliferative response of T cells in two patients sensitized to succinylcholine and in one patient sensitized to atracurium. These specific responses demonstrate for the first time the capacity of DC to present NMBA-related epitopes that are recognized by T cells.

Several mechanisms could explain how DC might process and present the incriminated NMBA (4). The drug might undergo covalent binding to soluble proteins processed by DC and consequently modified peptide might be expressed in association with MHC molecules. Another possibility is a covalent or noncovalent interaction of NMBA with the MHC-peptide complex directly at the surface of the DC. Nevertheless, experimental conditions for optimal NMBA presentation by DC remain to be defined, and this could be of particular importance for the development of DC-based assays for the characterization of NMBA-specific T-cell clones and for the *in vitro* diagnosis of an allergy to these drugs.

This work was supported in part by a grant from the Société française d'Anesthésie et de Réanimation, France.

Table 1. Clinical and immunological characteristics of allergic patients

Patient	Birth year	Sex (M/F)	Incriminated NMBA	Time since last exposure	Skin test response	LTT (SI)	DC-T (SI)
1	1944	F	Atracurium	20 years	+	0.3	2.1
2	1964	F	Atracurium	3 months	+	0.4	0.7
3	1941	F	Atracurium	1 year	+	0.9	0.7
4	1940	M	Succinylcholine	22 years	+	0.7	3.2
5	1948	F	Succinylcholine	10 months	+	ND	2.4
6	1932	M	Rocuronium	6 years	+	1.0	1.4
7	1966	F	Rocuronium	2 years	+	0.8	0.9
8	1956	F	Rocuronium	10 months	+	0.8	0.8
9	1930	M	Pancuronium	15 years	+	1.5	1.1
10	1969	F	Mivacurium	1 year	+	0.3	0.8

NMBA, neuromuscular blocking agent; LTT, lymphocyte transformation test; DC, dendritic cell; SI, stimulation index; ND, not done.