

IgE-Mediated Allergic Reactions after the First Administration of Glatiramer Acetate in Patients with Multiple Sclerosis

Mercè Corominas^a Idoia Postigo^d Victoria Cardona^c Ramon Lleonart^a
Lucía Romero-Pinel^b Jorge Martinez^d

^aDivision of Allergology, Department of Internal Medicine, and ^bDivision of Multiple Sclerosis, Department of Neurology, Hospital Universitari de Bellvitge, IDIBELL, L'Hospitalet de Llobregat, ^cDivision of Allergology, Department of Internal Medicine, Hospital Universitari de la Vall d'Hebron, Institut de Recerca Vall d'Hebron, Barcelona, and ^dDepartment of Pharmacology, Pais Vasco University, Vitoria, Spain

Key Words

Anaphylaxis · Glatiramer acetate · IgE · Multiple sclerosis · Myelin basic protein

Abstract

Background: Immediate adverse reactions to glatiramer acetate (GA), a drug used in the treatment of patients with multiple sclerosis (MS), have been poorly investigated. We studied 3 MS patients who presented adverse reactions following GA administration. Two of them experienced severe anaphylactic reactions after the first administration and the other an eyelid edema upon reintroduction 6 months after GA withdrawal. **Methods:** Skin prick tests (SPT) to GA and mannitol were performed on all 3 patients and in 10 atopic controls. Specific IgE (slgE) levels to GA, myelin basic protein (MBP) and MBP fragments were assessed in all 3 patients, 6 MS patients treated with GA for more than 6 months and 10 healthy donors. Specific IgG (slgG) to GA was also quantified in the three study groups. Both slgE and slgG were determined by means of the UniCAP 100 assay. **Results:** SPT and slgE to GA were positive only in the 3 patients with adverse reactions while slgE to mannitol was negative in all. slgE tests

against MBP and its fragments were negative in all individuals. Similar levels of slgG to GA were found in all studied subjects. **Conclusion:** These results demonstrate the significance of slgE in allergic reactions to GA presented by these patients and suggest the importance of strict surveillance during administration of the first GA doses.

© 2015 S. Karger AG, Basel

Introduction

Multiple sclerosis (MS) is an autoimmune demyelinating inflammatory disease of the central nervous system with an uncertain etiopathogenic mechanism, although it has been associated with impaired T cell function, which focused on Th1, regulatory T cells and Th17 cells, in recent years [1]. Different proteins, such as myelin basic protein (MBP), proteolipid protein, myelin oligodendrocyte glycoprotein and myelin-associated oligodendrocytic basic protein, are considered target antigens.

Glatiramer acetate (GA) is one of the drugs approved for the treatment of relapsing-remitting MS. The molecular structure is based on MBP and consists of acetate salts

Table 1. Levels of sIgE to GA, MBP and MBP fragments and GA sIgG in the 3 patients

Patient No.	sIgE, kU/l						sIgG, mg/ml
	GA	GA + BSA	BSA	MBP	MBP ¹ (frag. 4–14)	MBP ¹ (frag. 104–118)	GA
1	0.98	1.17	<0.1	<0.1	<0.1	<0.1	5
2	54.20	78.20	<0.1	<0.1	<0.1	<0.1	4.1
3	7.33	11.70	<0.1	<0.1	<0.1	<0.1	3.72

¹ Antigen from human brain (Sigma M0689); [pGlu⁴]-MBP 4–14 (Sigma P2186) and [Ala¹¹³]-MBP 104–118 (Sigma M8309).

of synthetic polypeptides composed of four amino acids (L-glutamic acid, L-alanine, L-tyrosine and L-lysine). Studies suggest an immunomodulatory effect of GA in MS, competing with myelin antigens for T-cell activation and inducing the generation of T_{reg} cells, a Th2 response and expansion of CD8⁺ T cells [2].

Allergic reactions to GA are rare, with the incidence of anaphylaxis being estimated at less than 0.1% of treated patients; IgE-mediated mechanisms have been described in few cases [3, 4].

We studied 3 patients with MS presenting immediate reactions to GA. Two of them experienced anaphylaxis (generalized urticaria, nausea and hypotension) upon the first administration of the drug. One patient developed elevated serum tryptase during the event (45 µg/l, basal 6 µg/l). The third patient experienced eyelid edema 20 min after GA re-administration, which had been interrupted for 6 months.

The Hospital's Ethic Committee approved the study and participants gave written informed consent.

Patients and Methods

Skin prick tests (SPT) were performed with GA (20 mg/ml) and mannitol (40 mg/ml; a potential immunogen contained in the solvent) on the 3 patients and 10 atopic subjects. Histamine (10 mg/ml) and glycerol saline were used as positive and negative control, respectively. SPT were considered positive if the mean diameter of the wheal induced by GA was >3 mm larger than the negative control.

Specific IgE (sIgE) to GA to MBP and MBP fragments, as well as specific IgG (sIgG) to GA was assessed (ImmunoCAP, Thermo-fisher) in the 3 patients, 6 patients with MS treated with GA for more than 6 months and 10 healthy donors.

GA covalently bound or not to 1% bovine serum albumine (BSA), and MBP fragments and MBP were biotinylated according to Sander et al. [5] assuming a molar ratio 1:5. Binding of labeled antigens to Streptavidin ImmunoCAP to measure sIgE and sIgG was performed according to Sander et al. [5] and Rodrigo et al. [6], respectively.

Table 2. GA-specific IgG (mg/ml)

Subjects (n)	Mean	Min.–max.
GA-allergic patients (n = 3)	4.27	3.72–5
GA-treated MS patients (n = 6)	5.34	4.20–6.02
Healthy donors (n = 10)	4.98	3.20–7

Results

GA SPT was positive in the 3 patients and negative in the 10 atopic subjects. Mannitol SPT was negative in all. GA sIgE was only positive in the 3 patients with adverse reactions, with sIgE levels being higher when GA was bound to BSA (table 1). sIgE against MBP and MBP fragments was negative in all groups while GA sIgG was detected in all (table 2).

Discussion

We report 3 patients with adverse reactions after GA administration in whom an allergic mechanism has been demonstrated by means of positive SPT and sIgE. Previous reports of patients with immediate reactions to GA show different results for GA SPT and sIgE [3, 4, 7, 8]. In our patients, intradermal tests were not performed as all of them already had a positive SPT, which was negative in the control subjects.

It is noteworthy that in the 2 patients who developed anaphylaxis, the reaction happened after the first administration of the drug. To explain this, one might hypothesize that certain patients with MS would be reactive to myelin antigens, inducing IgE production. In this sense, Mikol et al. [9] found sIgE against peptides derived from myelin in patients with MS. The administra-

tion of drugs that mimic these antigens, such as GA, would be able to induce anaphylaxis even in patients naive to the drug. On the other hand, in experimental autoimmune encephalomyelitis models, Smith et al. [10] demonstrated that intravenous administration of soluble peptide or peptide oligomers is sufficient to induce an IgE-mediated anaphylaxis.

One possible explanation for not detecting sIgE antibodies against MBP or MBP fragments in the patients may be that the IgE-specific epitopes were not accessible to antibody binding [9]. Moreover, the fact that the marketed MBP fragments (4–14 and 104–118) do not correspond with the MBP epitope on which GA acts (82–100) [11] would explain the negative sIgE against these fragments.

Some studies have shown GA sIgG only in GA-treated patients [12], while others have also found them in some nontreated MS patients and in healthy donors [13]. In our study, we have detected GA sIgG not only in GA-treated MS patients, but also in all healthy subjects. MS patients have proteolytic IgG autoantibodies against MBP [14]. As

GA structure is based on MBP, patients with MS may have cross-reactive IgG antibodies [15]. However, other authors found GA sIgG, but not against MBP, in treated patients [16]. As GA is composed of synthetic polypeptides of four amino acids, it is possible that these polypeptides share not only epitopes with MBP but also with other proteins. This hypothesis could explain the detection of GA sIgG in healthy donors.

The importance of the results lies not only in demonstrating GA sIgE in patients treated with the drug, but also in that some of these patients may present an allergic reaction due to the presence of GA sIgE antibodies prior to the first drug administration. This finding stresses the need for strict surveillance during the administration of the initial doses of GA.

Acknowledgments

The authors thank Ms. Anna González and Ms. Concepción Martín for their valuable assistance in the organization of blood samples.

References

- ▶ 1 Venken K, Hellings N, Liblau R, Stinissen P: Disturbed regulatory T cell homeostasis in multiple sclerosis. *Trends Mol Med* 2010;16: 58–68.
- ▶ 2 Racke MK, Lovett-Racke AE, Karandikar NJ: The mechanism of action of glatiramer acetate treatment in multiple sclerosis. *Neurology* 2010;74(suppl 1):S25–S30.
- ▶ 3 Bayerl C, Bohland P, Jung EG: Systemic reaction to glatiramer acetate. *Contact Dermatitis* 2000;43:62–63.
- ▶ 4 Rauschka H, Farina C, Sator P, Gudek S, Breier F, Schmidbauer M: Severe anaphylactic reaction to glatiramer acetate with specific IgE. *Neurology* 2005;64:1481–1482.
- ▶ 5 Sander I, Kespohl S, Merget R, Goldscheid N, Degens PO, Bruning T, Raulf-Heimsoth M: A new method to bind allergens for the measurement of specific IgE antibodies. *Int Arch Allergy and Immunol* 2005;136:39–44.
- ▶ 6 Rodrigo MJ, Postigo I, Wangenstein O, Guisantes JA, Martinez J: A new application of Streptavidin ImmunoCAP for measuring IgG antibodies against non-available commercial antigens. *Clin Chim Acta* 2010;411: 1675–1678.
- ▶ 7 Sanchez-Lopez J, Rodriguez del Rio P, Cases-Ortega B, Martinez-Cocera C, Fernandez-Rivas M: Allergy workup in immediate-type local reactions to glatiramer acetate. *J Investig Allergol Clin Immunol* 2010;20:521–523.
- ▶ 8 Soriano Gomis V, Perez Sempere A, Gonzalez Delgado P, Sempere JM, Niveiro Hernandez E, Marco FM: Glatiramer acetate anaphylaxis: detection of antibodies and basophil activation test. *J Investig Allergol Clin Immunol* 2012;22:65–66.
- ▶ 9 Mikol DD, Ditlow C, Usatin D, Biswas P, Kalbfleisch J, Milner A, Calenoff E: Serum IgE reactive against small myelin protein-derived peptides is increased in multiple sclerosis patients. *J Neuroimmunol* 2006;180:40–49.
- ▶ 10 Smith CE, Eagar TN, Strominger JL, Miller SD: Differential induction of IgE-mediated anaphylaxis after soluble vs. cell-bound tolerogenic peptide therapy of autoimmune encephalomyelitis. *Proc Natl Acad Sci U S A* 2005;102:9595–9600.
- ▶ 11 Aharoni R, Teitelbaum D, Arnon R, Sela M: Copolymer 1 acts against the immunodominant epitope 82–100 of myelin basic protein by T cell receptor antagonism in addition to major histocompatibility complex blocking. *Proc Natl Acad Sci U S A* 1999;96:634–639.
- ▶ 12 Brenner T, Arnon R, Sela M, Abramsky O, Meiner Z, Riven-Kreitman R, Tarcik N, Teitelbaum D: Humoral and cellular immune responses to Copolymer 1 in multiple sclerosis patients treated with Copaxone. *J Neuroimmunol* 2001;115:152–160.
- ▶ 13 Farina C, Vargas V, Heydari N, Kumpfel T, Meinel E, Hohlfeld R: Treatment with glatiramer acetate induces specific IgG4 antibodies in multiple sclerosis patients. *J Neuroimmunol* 2002;123:188–192.
- ▶ 14 Ponomarenko NA, Durova OM, Vorobiev II, Belogurov AA Jr, Kurkova IN, Petrenko AG, Telegin GB, Suchkov SV, Kiselev SL, Lagarkova MA, Govorun VM, Serebrykova MV, Avale B, Tornatore P, Karavanov A, Morse HC, Thomas D, Fibroulet A, Gabibov AG: Autoantibodies to myelin basic protein catalyze site-specific degradation of their antigen. *Proc Natl Acad Sci U S A* 2006;103:281–286.
- ▶ 15 Teitelbaum D, Aharoni R, Sela M, Arnon R: Cross-reactions and specificities of monoclonal antibodies against myelin basic protein and against the synthetic copolymer 1. *Proc Natl Acad Sci U S A* 1991;88:9528–9532.
- ▶ 16 Karussis D, Teitelbaum D, Sicsic C, Brenner T: Long-term treatment of multiple sclerosis with glatiramer acetate: natural history of the subtypes of anti-glatiramer acetate antibodies and their correlation with clinical efficacy. *J Neuroimmunol* 2010;220:125–130.