

# Anaphylactic Reaction after Injection of Glatiramer Acetate (Copaxone®) in Patients with Relapsing-Remitting Multiple Sclerosis

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Dear Sir,

Glatiramer acetate (GA, Copaxone®) is one of the approved drugs for immunomodulatory therapy of relapsing-remitting multiple sclerosis (RRMS) [1–4]. Of the few adverse effects known to be associated with GA therapy, the most common is a local reaction at the site of injection, while another side effect is an immediate postinjection systemic reaction (IPISR). This is characterized by flushing, chest tightness, palpitations and dyspnea, and occurs immediately after injection, with spontaneous resolution after about 20 min [5]. Little has been documented about the occurrence of a systemic anaphylactic reaction to GA. We report 6 cases in which patients developed such a reaction. In all patients, diagnosis of RRMS according to the McDonald criteria was confirmed [6]. According to published guidelines [7], anaphylactic reactions are subclassified into four grades of severity (table 1).

## Case Series (table 1)

### Case 1 (Anaphylactic Reaction Grade 1)

Diagnosis of MS was confirmed in a 34-year-old female patient in June 2007, and therapy with GA was started in July 2007. While exanthema occasionally appeared at the site of injection, no further side effects occurred until October 2007, at which time the patient developed general-

ized pruritic exanthema over the whole body immediately after injection of Copaxone. This improved after a few days without therapy and no further symptoms such as dyspnea or hypotension were evident. Following this systemic allergic reaction, therapy with GA was discontinued. Apart from MS, the patient also suffers from recurrent depressive episodes; additional diseases, co-medication or allergies are not evident.

### Case 2 (Anaphylactic Reaction Grade 2)

Diagnosis of MS was confirmed in a 23-year-old female patient in August 1999. In the years thereafter, the patient received different immunomodulatory drugs, all to no avail and eventually resulting in severe non-allergic adverse effects. Therapy with GA was therefore started in April 2007. Although the patient occasionally suffered from exanthema at the injection site, further side effects did not occur. In May 2007, after an injection of GA, the patient developed an allergic reaction with extensive generalized erythema, which then spontaneously improved after a few hours. Therapy was continued until the second occurrence in October 2007 of an allergic reaction characterized by hypotension and dyspnea for several hours and generalized exanthema over the whole body. These symptoms persisted for several days before spontaneous improvement. We stopped

therapy with GA after the second adverse reaction. The patient is not known to suffer any other diseases or allergies.

### Case 3 (Anaphylactic Reaction Grade 2)

Diagnosis of MS was confirmed in a 39-year-old female patient in December 2006, and therapy with GA was started soon after. The patient suffered from mild, transient depressive symptoms under GA treatment. In May 2007, a mild reaction with erythema, dyspnea and hot flushes occurred and was subsequently classified as IPISR. After injection of GA 1 month later, the patient suffered from dyspnea, nausea, orthostatic dysregulation, abnormal fatigue and systemic erythema, which persisted for more than 1 day and then slowly improved without medication. Apart from MS, the patient suffered from allergic bronchial asthma during childhood.

### Case 4 (Anaphylactic Reaction Grade 3)

Diagnosis of MS was confirmed in a 21-year-old female patient in November 2005, and therapy with interferon- $\beta_{1b}$  was started in December 2005. However, this therapy was aborted after a few weeks due to the occurrence of a mild allergic reaction. Alternative therapy with interferon- $\beta_{1a}$  was not tolerated either, so the patient then received GA from May 2006 onwards. GA therapy was well tolerated and no

**Table 1.** Grades of severity of anaphylactic reactions [7]

Grade 1	General symptoms, systemic reaction of the skin with erythema
Grade 2	Additional hypotension and tachycardia or gastrointestinal symptoms, mild dyspnea
Grade 3	Additional bronchial spasm, shock, infrequently laryngeal edema with inspiratory stridor
Grade 4	Cardiac and respiratory arrest

**Table 2.** Summary of patient history and characteristics

	Anaphylaxis severity	Gender	Age at time of MS diagnosis	Date of MS diagnosis	Initiation of GA therapy	IPI SR	Other medication	Date of anaphylaxis	Treatment duration	Side effects	Other drug allergies
Patient 1	grade 1	female	34 years	06/2007	07/2007	no	no	10/2007	3 months	occasional exanthema	no
Patient 2	grade 2	female	23 years	08/1999	04/2007	no	yes	10/2007	6 months	occasional exanthema	no
Patient 3	grade 2	female	39 years	12/2006	12/2006	yes	no	06/2007	6 months	mild depressive symptoms	no
Patient 4	grade 3	female	21 years	11/2005	05/2006	no	yes	08/2006	3 months	no	yes
Patient 5	grade 3	male	21 years	01/2003	07/2007	no	no	10/2007	3 months	no	no
Patient 6	grade 3	female	25 years	11/2001	04/2002	no	yes	07/2002	3 months	occasional exanthema	no

IPI SR occurred. In August 2006 the patient suffered from a severe anaphylactic reaction immediately following an injection of GA. Symptoms included nausea, facial edema, paraesthesia and bronchial spasm, and could only be ameliorated by administration of steroids. The patient was in intensive care for 1 day. The patient is known to have additional allergies to several different drugs.

#### Case 5 (Anaphylactic Reaction Grade 3)

Diagnosis of MS was confirmed in a 21-year-old male patient in January 2003. Immunomodulatory therapy was not administered at that time point. Although no further relapses occurred in the following years, we found via electrophysiological and MRI assessment in July 2007 that sub-clinical progression of the disease had taken place. The patient was therefore started on immunomodulatory therapy with GA, which was initially well tolerated; there were also no signs of an IPI SR. Three months later, in October 2007, the patient developed after injection of GA a severe anaphylactic reaction with scalp pruritus, nausea, vomiting and symptoms of shock with severe hypotension. These symptoms slowly improved after treatment with dimetidine, dexamethasone, cimetidine and adrenaline. The patient was in inten-

sive care for 1 day. Apart from a mild allergic rhinitis, the patient harbors no other allergies.

#### Case 6 (Anaphylactic Reaction Grade 3)

Diagnosis of MS was confirmed in a 25-year-old-female patient in November 2001. Immunomodulatory therapy with interferon- $\beta_{1a}$  was started immediately, but then interrupted in March 2002 because of severe non-allergic adverse effects. Therapy with GA was started in April 2002. Although the patient occasionally suffered from exanthema at the injection site, further side effects did not occur. In July 2002, a severe systemic allergic reaction appeared after injection of GA; here, the patient experienced heat sensation, angioneurotic edema of the face and the neck, exanthema of the arms and the body, and a bronchial spasm. The symptoms slowly improved after the injection of steroids and clemastine. The patient has no known additional diseases or allergies.

### Discussion

We report a case series of 6 patients with RRMS, each of whom developed anaphylactoid or anaphylactic reactions under treatment with GA (table 2). Therapy

was interrupted in all patients between 3 and 6 months after treatment initiation after the occurrence of the anaphylactic reaction. Because the therapeutic effect of GA is usually only first apparent about 6 months after the initiation of treatment, it is not possible to evaluate the potential benefits of GA in these patients. In general, we treat about 500 MS patients per year. Table 2 provides an overview of patient details.

GA is known to be a very well-tolerated drug for immunomodulatory therapy of RRMS. Since its approval for clinical use, the most common adverse effects of GA are injection site reactions and IPI SR [5]. There are also reports by the manufacturer (Aventis, Austria) describing very rare non-fatal allergic reactions. Furthermore, Rauschka et al. [8] reported a patient who developed under GA therapy a severe anaphylactic reaction that occurred about 1 year after treatment initiation. Drug-specific IgE serum antibodies against GA were detected in this patient, while prick and intracutaneous tests with GA showed positive results. In our patients, the levels of serum antibodies against GA were not obtained.

It is striking that the anaphylactic reaction in our patients, as well as in the patient described by Rauschka et al. [8], appeared

after a latency of 3–6 months of well-tolerated GA therapy and following a lack of prodromi. According to the classification criteria of Coombs and Gells [7], the clinical manifestation of exanthema, angio-neurotic edema and bronchial spasm corresponds to an allergic reaction type 1. In accordance with this, Rauschka et al. [8] found IgE antibodies against GA in the reported patient. This type of allergic reaction usually appears soon after the initiation of treatment. A type 1 reaction after a latency period of several months of daily GA application, as described in this report, is therefore remarkable, although the underlying pathomechanisms are not yet clear. Beside GA, also hypersensitivity against mannitol, which is a relevant ingredient of Copaxone and well known to be an allergenic substance [9, 10], should be considered as a potential cause for the allergic reactions in our patients. A possible mechanism could be gradual accre-

ment of IgE antibody titers against GA or mannitol in predisposed patients, which might lead to an anaphylactic reaction after the concentration of antibodies reaches a critical level. This reaction could be triggered by an accidental intravenous application of Copaxone that induces histamine release, which has also been discussed as a possible pathomechanism of an IPISR [5, 11]. Nevertheless, the factors leading to an IPISR or a severe anaphylactic reaction after accidental intravenous application of Copaxone are not known. The presence of an atopy does not seem to be a relevant factor, since only 1 of our patients suffered from other allergies.

In summary, the effect of GA on the immune system seems to be more complex than initially expected. In particular, an allergic reaction to Copaxone after a long period of continuous therapy, as reported here, has not been reported as an adverse effect of GA.

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