Glatiramer acetate: successful desensitization for treatment of multiple sclerosis

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Background: Glatiramer acetate is an immunomodulatory drug that is widely prescribed for the treatment of multiple sclerosis. It is frequently associated with local injection site reactions and generalized urticaria. It is also associated with immediate postinjection systemic reactions in approximately 10% of patients. To our knowledge, no desensitization protocols for glatiramer acetate have been published to date.

Objectives: To evaluate the safety and efficacy of glatiramer acetate desensitization in a series of patients with multiple sclerosis.

Methods: Six patients with multiple sclerosis and glatiramer acetate–associated local or systemic reactions underwent a 4-hour outpatient desensitization procedure at Cleveland Clinic between 2003 and 2008. Beginning with 20 ng, we administered subcutaneous glatiramer acetate suspension in increasing dosages every 15 minutes. Patient outcomes were monitored by return clinic visit and telephone follow-up.

Results: No episodes of anaphylaxis or serious adverse reactions occurred during or immediately after desensitization. One patient suspended therapy after 14 months due to persistent local injection site reactions. All other patients successfully continued glatiramer acetate therapy.

Conclusion: Glatiramer acetate offers significant benefit to patients with multiple sclerosis. Our experience suggests that patients who suspend its use owing to local or systemic reactions can be successfully and safely desensitized and can resume medication use. To our knowledge, this is the first report of successful desensitization to glatiramer acetate in patients with multiple sclerosis.

Ann Allergy Asthma Immunol. 2010;104:321–325.

INTRODUCTION

Glatiramer acetate (Copaxone; Teva Neuroscience, Kansas City, Missouri) is a pool of synthetic peptides composed of random sequences of 4 amino acids: L-alanine, L-lysine, L-glutamic acid, and L-tyrosine. Its composition is based on the amino acid structure of myelin basic protein. Glatiramer acetate injection is supplied as a single-use syringe prefilled with 1.0 mL of a clear, colorless solution containing 20 mg of glatiramer acetate, 40 mg of mannitol, and no preservative. The recommended dose for the treatment of multiple sclerosis (MS) is 20 mg injected subcutaneously daily.

Glatiramer acetate is one of the immunomodulatory drugs approved and widely prescribed for the treatment of MS,[1–3] a chronic disorder that affects the brain, spinal cord, and optic nerve and is the leading cause of nontraumatic disability in young adults.[3] Glatiramer acetate has been shown to significantly reduce the relapse rate and slow the progression of neurologic disability in patients with MS.[1] The drug has a favorable adverse effect profile compared with other medications used to treat MS, including high-dose corticosteroids and interferon beta.[4] However, approximately 50% of patients may develop local injection site reactions, even though patients are instructed to rotate injection sites regularly. Up to 10% of patients may experience immediate postinjection systemic reactions characterized by flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and urticaria, which may preclude further glatiramer acetate administration due to the severity of the reaction.[4] This poses an obstacle to the treatment of MS, especially in patients who have failed or are not candidates for other therapies.

Desensitization procedures (induction of drug tolerance), including true immunologic desensitization (eg, to penicillin) and graded challenge regimens for non-IgE hypersensitivity reactions (eg, to trimethoprim-sulfamethoxazole), have been successfully used in the management of drug-induced cutaneous reactions.[5–7] However, to our knowledge, no desensitization protocols for glatiramer acetate have been reported to date. The present study retrospectively evaluates the outcome, safety, and long-term utility of glatiramer acetate desensitization in a series of patients with MS who were desensitized at a single institution between January 1, 2003 and December 31, 2008. This study was approved by the institutional review board at the Cleveland Clinic.

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Disclosures: Authors have nothing to disclose.

Funding Sources: This study was supported by the William O. Wagner, MD, Research and Education Fund.

Received for publication July 16, 2009; Received in revised form October 14, 2009; Accepted for publication November 12, 2009.

doi:10.1016/j.anai.2009.11.040

CASE REPORTS

None of the 6 patients had a history of atopy or IgE-mediated reactions to other medications.

Patient 1

A 31-year-old woman with MS developed urticaria on both arms 5 hours after her first dose of glatiramer acetate. She did not report associated cardiovascular, respiratory, or gastrointestinal symptoms. Despite the urticaria, she continued daily glatiramer acetate use. Her urticarial lesions did not improve with antihistamine therapy (diphenhydramine and cetirizine) and became more generalized, involving her legs and trunk. She discontinued glatiramer acetate use after 10 days due to persisting and worsening urticaria. Within 2 days, her urticaria had completely resolved. She was evaluated 1 week after suspending glatiramer acetate use. Examination did not reveal remarkable findings. Skin testing was not performed owing to dermatographism. The patient returned 1 week later for desensitization.

Patient 2

A 43-year-old man with MS developed generalized pruritus followed by urticaria within 30 minutes of glatiramer acetate administration. He had tolerated daily glatiramer acetate therapy for 2 to 3 months without adverse reaction. He sought emergency department management for this reaction, where he received epinephrine, diphenhydramine, and a nebulized bronchodilator. He responded well to this treatment and was advised to suspend glatiramer acetate use. He presented approximately 2 months later. Skin testing was performed, and the patient agreed to return for desensitization.

Patient 3

A 35-year-old man with MS reported almost immediate onset of facial swelling, palpitations, throat constriction, and shortness of breath after glatiramer acetate administration. These symptoms subsided spontaneously within 15 minutes, and the patient reported chills afterward. On another occasion, he reported a sensation of throat constriction along with shortness of breath within 1 minute of administration of glatiramer acetate. These symptoms subsided within 15 minutes. The patient had tolerated glatiramer acetate therapy for approximately 2 years before these episodes without adverse reaction. He was seen approximately 2 months after suspending glatiramer acetate therapy. Skin testing and desensitization to glatiramer acetate were performed.

Patient 4

A 30-year-old woman with MS tolerated glatiramer acetate therapy for 5 years without adverse reaction but then developed respiratory symptoms on 3 occasions after glatiramer acetate administration. During one episode, she experienced chest tightness and difficulty breathing along with headache and facial flushing. Within minutes, she developed hives that she described as pruritic, erythematous, raised areas on her chest, neck, and upper torso. She took diphenhydramine and the symptoms resolved. She elected to discontinue glatiramer acetate use. She was seen approximately 2 months later. Skin testing and desensitization were performed.

Patient 5

A 32-year-old man with aggressive MS was given glatiramer acetate. Five weeks after initiating glatiramer acetate therapy he experienced injection site pruritus within an hour of medication administration followed by the development of local hives and swelling. There was no associated angioedema or urticaria distant from the site of injection and no respiratory or cardiovascular symptoms. Glatiramer acetate therapy was suspended and his symptoms resolved. The patient presented for skin testing and desensitization.

Patient 6

A 25-year-old woman with MS experienced large local reactions after glatiramer acetate administration. She developed local injection site erythema, swelling, and tenderness. These reactions did not involve other organ systems. Despite these reactions the patient continued using glatiramer acetate for several months. She eventually suspended use of the medication and presented after almost a year for skin testing and possible desensitization to glatiramer acetate at the request of her neurologist.

METHODS

Skin Testing

Stock suspensions (20 mg/mL) of glatiramer acetate were prepared. Serial dilutions were formulated at the following concentrations: 0.2 and 2 mg/mL. Percutaneous and intradermal skin tests were performed. The immediate reaction (wheal and flare) was read at 15 minutes. A positive histamine (10 mg/mL) control and a negative saline control were applied in parallel with the test allergens to control for antihistamine premedication and dermatographism.[8] Nine healthy volunteers who had never been exposed to glatiramer acetate also underwent skin testing. During this study, it was found that the 2-mg/mL concentration of glatiramer acetate provoked irritant reactions in most controls. For this reason, further dilutions of 0.02 and 0.002 mg/mL were made from the stock solution. Patients who underwent evaluation early in the study did not undergo skin testing with these dilutions.

Subcutaneous Desensitization

Stock suspensions of glatiramer acetate were prepared by dissolving the contents of the 20-mg stock vial in sterile water to a concentration of 2 mg/mL. Serial dilutions were formulated using 1 mL of sterile water as a diluent in the following concentrations: 0.00002, 0.0002, 0.002, 0.02, and 0.2 mg/mL. Each patient gave informed consent for subcutaneous desensitization in a closely supervised clinical setting beginning with 20 ng and gradually increasing dosages every 30 minutes (Table 1). No premedication was given. After close

Table 1. Standard Glatiramer Acetate Desensitization Protocol

Dose, mg	Preparation	Timing	Route
0.00002	1 mL vial 6	0:00	SC right abdomen
0.0002	1 mL vial 5	0:30	SC left abdomen
0.002	1 mL vial 4	1:00	SC right thigh
0.02	1 mL vial 3	1:30	SC left thigh
0.2	1 mL vial 2	2:00	SC right flank
2	1 mL vial 1	2:30	SC left flank
4	0.2 mL stock vial	3:00	Right abdomen
8	0.375 mL stock vial	3:30[a]	Left abdomen

Abbreviation: SC, subcutaneous.
[a] Observe for 30 minutes after administration of the last dose.

observation for signs and symptoms of adverse reaction for 30 minutes after the last dose, patients were discharged with instructions to take 20 mg of glatiramer acetate subcutaneously the next morning and to continue that dose without a lapse of more than 48 hours between doses. If there was a lapse greater than 48 hours between 2 doses, the patient was advised that he or she would be considered resensitized and would have to return for another desensitization. The patients were provided with self-injectable epinephrine and were instructed in its correct use.

RESULTS

Skin Testing

Skin testing was performed in 5 of 6 patients (patient 1 was dermatographic) and in 9 controls not previously exposed to glatiramer acetate. Of the 5 patients, 3 exhibited remarkable wheal-and-flare reactions at 1:10 dilution (2 mg/mL), and 2 had wheal-and-flare reactions at 1:100 dilution (0.2 mg/mL). One patient was tested at 1:1000 (0.02 mg/mL) and 1:10,000 (0.002 mg/mL) and had wheal-and-flare reactions at 1:1000 (0.02 mg/mL) only. For the controls, percutaneous testing with full-strength glatiramer acetate was performed. One of 9 controls had a wheal-and-flare reaction, and further testing was discontinued in that individual. Intradermal testing was performed in the remaining 8 controls. All 8 controls had wheal-and-flare reactions to glatiramer acetate at 1:10 dilution (2 mg/mL) and 6 at 1:100 dilution (0.2 mg/mL) at the intradermal level, suggesting that these dilutions elicited irritant reactions. Further dilutions of 1:1000 (0.02 mg/mL) and 1:10,000 (0.002 mg/mL) were made in an attempt to find a testing concentration that would not elicit irritant reactions, and intradermal testing was performed with these dilutions in 5 controls. Four of 5 controls exhibited wheal-and-flare reaction to 1:1000 dilution (0.02 mg/mL) and 2 of 5 to 1:10,000 dilution (0.002 mg/mL).

Subcutaneous Desensitization

Successful subcutaneous desensitization was performed in all 6 patients. Patient 5 tolerated the desensitization procedure without adverse reaction. However, the following day when he administered glatiramer acetate, he had a recurrence of local injection site swelling and erythema. These reactions continued despite pretreatment with antihistamines. The patient continued the medication therapy for approximately 14 months after the "desensitization" but eventually suspended glatiramer acetate therapy due to persistent local reactions.

Patients 1 to 4 underwent desensitization to glatiramer acetate and tolerated the procedure well. There were no immediate or subsequent adverse reactions. These patients have continued daily glatiramer acetate administration, with the longest duration of therapy with glatiramer acetate after desensitization without adverse reactions of 39 months (patient 4).

Patient 6 underwent desensitization to glatiramer acetate as well. She reported symptoms of mild dizziness after 3 doses were administered. This resolved in less than 1 hour with 60 mg of oral fexofenadine. The symptom of dizziness was interpreted as a non–IgE-mediated reaction. The desensitization protocol was resumed, and the patient advanced through the remaining doses without further adverse reactions. She was successfully desensitized and continued glatiramer acetate therapy for approximately 8 months. At that time, the patient became pregnant and suspended glatiramer acetate treatment. Table 2 summarizes the patient characteristics and their outcomes.

DISCUSSION

Adverse reactions to glatiramer acetate are common and may lead to suspension of treatment. We demonstrated that this desensitization protocol can be performed safely and can permit resumption of daily glatiramer acetate administration.

The most common adverse effect of glatiramer acetate administration is injection site reaction, including erythema in 66% of patients, induration in 13%, inflammation in 49%, and pain in 73%.[4] Ten percent of patients experienced immediate postinjection systemic reactions characterized by flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and urticaria.[4] The adverse effects to glatiramer acetate reported by patients in this study are consistent with reports in the literature.

In this cohort, patients 3, 4, and possibly 2 had persistent systemic reactions after glatiramer acetate administration. These patients were successfully desensitized to glatiramer acetate. Patient 1 reported a systemic reaction that occurred 5 hours after taking the first dose of glatiramer acetate, which is unlikely to represent an IgE-mediated reaction. Yet, he was successfully desensitized to glatiramer acetate. Patients 5 and 6 had large local reactions at the injection site, and desensitization in one (patient 6) led to the resumption of glatiramer acetate therapy without remarkable local reactions with repeated administration. Bayerl et al[9] reported an unsuccessful attempt to desensitize a patient to glatiramer acetate who had experienced a systemic reaction with previous glatiramer acetate use. To our knowledge, this is the first report of successful desensitization to glatiramer acetate.

In our experience, glatiramer acetate skin testing elicited an irritant reaction in controls and patients. For this reason,

Table 2. Clinical Characteristics and Outcomes[a]

Patient No./Sex/Age, y	Adverse reaction	Skin testing positive at	Reactions during desensitization	Result of desensitization	Clinical course
1/F/31	Generalized cutaneous	Not done	None	No recurrence of urticaria	Tolerating GA
2/M/43	Generalized cutaneous	0.2-mg/mL irritant response	None	No recurrence of urticaria	Tolerating GA
3/M/35	Immediate-onset systemic	0.2-mg/mL irritant response	None	No recurrence of systemic symptoms	Tolerating GA
4/F/30	Immediate-onset systemic	2-mg/mL irritant response	None	No recurrence of systemic symptoms	Tolerating GA
5/M/32	Local injection site	2-mg/mL irritant response	None	Recurrence of local reaction	Patient stopped GA 14 mo later due to persistent reactions
6/F/25	Local injection site	2-mg/mL irritant response	Mild dizziness	No recurrence of local reaction	Continued GA for 8 mo, then stopped due to pregnancy

Abbreviations: GA, glatiramer acetate; MS, multiple sclerosis.
[a] Eight of 8 controls had positive skin test results at 1:10 (2 mg/mL), 6 of 8 at 1:100 (0.2 mg/mL), 4 of 5 at 1:1000 (0.02 mg/mL), and 2 of 5 at 1:10,000 (0.002 mg/mL). This indicates that skin testing is unreliable owing to an irritant response.

wheal-and-flare reaction cannot be interpreted as indicative of sensitization. There may be several reasons for this: (1) the glatiramer acetate preparation is extremely irritating to the skin even at very low concentrations; (2) we used intradermal testing, which has inherent issues with reproducibility and person-person variability; (3) the controls may be sensitized as these sequences are naturally occurring amino acids; and (4) the use of sterile water as a diluent for skin testing may have elicited an irritant reaction. To test the latter hypothesis, skin testing was repeated using normal saline as diluent; however, this was also associated with frequent irritant reactions in controls, which implies that sterile water is not the cause of irritant reactions (data not shown). Based on these findings, we cannot recommend immediate hypersensitivity skin testing in the evaluation and management of patients with adverse reactions to glatiramer acetate. Bayerl et al[9] performed percutaneous and intradermal skin testing in 5 control patients and in 1 patient who had a systemic reaction after subcutaneous use of glatiramer acetate. The patient had wheal-and-flare reactions to full-strength glatiramer acetate on intradermal testing at 15 minutes and 24 hours, which was not observed in the 5 control subjects (data not shown). These results are significantly different than those of the present skin testing, which may be due to the person-person variability seen with intradermal skin testing.

Although immediate postinjection systemic reactions clinically resemble anaphylaxis, they have an unpredictable and sporadic nature, and their pathogenesis is not well understood. Most patients treated with glatiramer acetate develop anti–glatiramer acetate IgG4 without anti–glatiramer acetate IgE antibodies.[2,10] This may be explained by the immunomodulatory actions of the drug. Although glatiramer acetate treatment induces a switch from the T_H1 to the T_H2 phenotype, it also induces regulatory T cells that suppress T_H1 and T_H2 immune responses. That could account for the clinical efficacy and the low incidence of IgE-mediated reactions.[2,11,12] It is also possible that because patients are taking glatiramer acetate daily, they are in a "desensitized" state; perhaps if they then miss 1 or more doses and then administer the medication they could provoke a systemic reaction. That could account for the sporadic nature of the immediate postinjection systemic reaction observed in glatiramer acetate–treated patients. Another possible explanation for these frequent systemic reactions may be a nonimmunologic anaphylactic (anaphylactoid) reaction to glatiramer acetate.

Although anaphylaxis to glatiramer acetate is rare, it has been reported.[9,13] Rauschka et al[13] investigated whether anti–glatiramer acetate IgE antibodies were present in 1 patient with anaphylaxis to glatiramer acetate and found detectable specific IgE levels in the serum, demonstrating that anti–glatiramer acetate IgE can occur in glatiramer acetate–treated patients.

Each vial of glatiramer acetate injection contains 40 mg of mannitol. Mannitol infusion has been reported to cause anaphylactoid reactions.[14] Mannitol inhalation causes increased levels of prostaglandin D_2 and leukotriene C_4, consistent with mast cell activation.[15] We did not evaluate the patients for mannitol hypersensitivity and cannot rule out the possibility that these reactions may be secondary to mannitol. The true mechanism of action underlying glatiramer acetate–induced hypersensitivity reactions requires further study.

Glatiramer acetate administration can reduce the relapse rate of MS by approximately 30% after 2 years of therapy.[1] A double-blind, placebo-controlled study[16] demonstrated a reduction in the number of gadolinium-enhancing lesions in patients receiving glatiramer acetate compared with a placebo. Glatiramer acetate may also have a favorable effect in preventing tissue loss at a later diseased stage.[17,18] Based on these data, subcutaneously administered glatiramer acetate is one of the most widely prescribed drugs for the treatment of

relapsing-remitting MS.[1] Although recurrence and severity of reactions to glatiramer acetate are unpredictable, treating through "hypersensitivity reactions" or rechallenge may be dangerous. The need for a successful desensitization protocol is highlighted by the fact that cutaneous reactions to glatiramer acetate occur in up to 66% and immediate postinjection systemic reactions in up to 10% of patients with MS.

Subcutaneous desensitization to glatiramer acetate using this protocol seems to be safe. We observed no systemic reactions during desensitization or during follow-up of these patients as judged by the ability to tolerate long-term glatiramer acetate therapy after desensitization. The procedure was successful in all 5 patients with systemic reactions and in 1 of 2 patients with large local reactions. The procedure was successful in patients with reactions suggestive of IgE-mediated reactions and in patients with reactions that were clearly not IgE mediated (patients 1 and 6). Experience with more patients is required to confirm the efficacy of this subcutaneous desensitization protocol. We conclude that subcutaneous desensitization is an important option for patients developing cutaneous or systemic reactions to glatiramer acetate, which may permit patients with MS who have achieved benefit with glatiramer acetate therapy to safely resume regular glatiramer acetate treatment.

REFERENCES

1. Weber SM, Hohlfeld R, Zamvil SS. Mechanism of action of glatiramer acetate in treatment of multiple sclerosis. *Neurotherapeutics.* 2007;4: 647–653.
2. Basile E, Gibbs E, Aziz T, Oger J. During 3 years of treatment of primary progressive multiple sclerosis with glatiramer acetate, specific antibodies switch from IgG 1 to IgG 4. *J Neuroimmunol.* 2006;177: 161–166.
3. Fox RJ, Bethoux F, Goldman MD, Cohen JA. Multiple sclerosis: advances in understanding, diagnosing, and treating the underlying disease. *Cleve Clin J Med.* 2006;73:91–102.
4. Langer-Gould A, Moses HH, Murray J. Strategies for managing the side effects of treatments for multiple sclerosis. *Neurology.* 2004;63(suppl 5):S35–S41.
5. Wendel G, Stark B, Jamison RB, et al. Penicillin allergy and desensitization in serious infections during pregnancy. *N Engl J Med.* 1985;312: 1229–1232.
6. Borish L, Tamir R, Rosenwasser LJ. Intravenous desensitization to beta-lactam antibiotics. *J Allergy Clin Immunol.* 1987;80:314–319.
7. Kalanadhabhatta V, Muppidi D, Sahni H, Robles A, Kramer M. Successful oral desensitization to trimethoprim-sulfamethoxazole in acquired immune deficiency syndrome. *Ann Allergy Asthma Immunol.* 1996;77: 304–400.
8. Bernstein IL, Li JT, Bernstein D, et al. Allergy diagnostic testing: an updated practice parameter. *Ann Allergy Asthma Immunol.* 2008;100: 1–148.
9. Bayerl C, Bohland P, Jung EG. Systemic reaction to glatiramer acetate. *Contact Dermatitis.* 2000;43:62–63.
10. Brenner T, Arnon R, Sela M, et al. Humoral and cellular immune responses to Copolymer 1 in multiple sclerosis patients treated with Copaxone. *J Neuroimmunol.* 2001;115:152–160.
11. Weber MS, Hohlfeld R, Zamvil SS. Mechanism of action of glatiramer acetate in treatment of multiple sclerosis. *Neurotherapeutics.* 2007;4: 647–653.
12. Blanchette F, Neuhaus O. Glatiramer acetate: evidence for a dual mechanism of action. *J Neurol.* 2008;255(suppl 1):26–36.
13. 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.
14. Findlay SR, Kagey-Sobotka A, Lichtenstein LM. In vitro basophil histamine release induced by mannitol in a patient with a mannitol-induced anaphylactoid reaction. *J Allergy Clin Immunol.* 1984;73: 578–583.
15. Brannan JD, Gulliksson M, Anderson SD, Chew N, Kumlin M. Evidence of mast cell activation and leukotriene release after mannitol inhalation. *Eur Respir J.* 2003;22:491–496.
16. Comi G, Filippi M, Wolinsky JS; European/Canadian Glatiramer Acetate Study Group. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging: measured diseased activity and burden in patients with relapsing multiple sclerosis. *Ann Neurol.* 2001;49: 290–297.
17. Filippi M, Rovaris M, Rocca MA, Sormani MP, Wolinsky JS, Comi G. Glatiramer acetate reduces the proportion of new MS lesions evolving into "black holes." *Neurology.* 2001;57:731–733.
18. Sormani MP, Bruzzi P, Comi G, Filippi M. The distribution of magnetic resonance imaging response to glatiramer acetate in multiple sclerosis. *Mult Scler.* 2005;11:447–449.

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