

Immediate reactions with glatiramer acetate

Diagnosis of allergy and desensitization protocols

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Abstract

Purpose of review

Diverse adverse events have been associated with administration of glatiramer acetate (GA), mainly local reactions at the injection site. Other, less frequent generalized reactions include isolated post-injection reactions and anaphylaxis, which may lead to discontinuation of GA.

Recent findings

Close collaboration between the allergy and neurology departments is needed to study adverse reactions to GA. The allergy study should include a detailed history and skin prick and intradermal tests with GA and, if possible, determination of specific IgE levels. Furthermore, the implication of other drugs should be ruled out.

Summary

An accurate diagnosis of reactions to GA is essential if we are to confirm or rule out allergy to GA. When an allergy diagnosis is confirmed or firmly suspected based on clinical evidence, desensitization protocols are increasingly seen as safe methods for reintroduction of GA.



Multiple sclerosis (MS) is one of the most common causes of neurologic dysfunction among young adults.¹ Glatiramer acetate (GA) (Copaxone; Teva Pharmaceuticals Ltd, United Kingdom) was the first effective treatment and was tested initially in an animal model of MS, where it suppressed autoimmune encephalomyelitis.² GA resembles the basic myelin protein, which acts as an autoantigen of MS. Since its regulatory authorization in Europe in 2000, GA has led to a reduction in relapse rates, hospital admissions, and courses of corticosteroids.³

Adverse events have been reported after daily subcutaneous administration of GA 20 mg. Most involve erythema and pruritus at the injection site (80%–90%). In addition, 10%–15% of patients present with isolated postinjection reactions (IPIRs), which include a combination of chest tightness, shortness of breath, palpitations, anxiety, and flushing for 15–30 minutes that resolve spontaneously. No cardiovascular consequences or other adverse events have been demonstrated after IPIR. Thus, it is not usually an indication for discontinuation of therapy.^{3–6}

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Anaphylaxis attributable to GA is a rare phenomenon (0.8% worldwide).⁷ Two mechanisms of anaphylaxis have been described in mice, and both seem to be valid for humans. The first is an IgE-dependent mechanism, via which patients sensitized to a particular allergen develop allergen-specific IgE. Reexposure to allergen results in cross-linking of specific IgE bound to high-affinity IgE receptors (FcεRI) on mast cells and basophils. It induces activation of these cells, which release histamine, tryptase, platelet-activating factor (PAF), and other mediators. In the second mechanism, antigen-IgG complexes cross-link FcγRIII receptors on mast cells, basophils, and macrophages with secretion of PAF. Higher amounts of antigen are needed in the IgG-dependent mechanism. Although IgE anaphylaxis in humans is well established, the existence of IgG-mediated anaphylaxis in humans remains unproven.⁸

As the overall safety and efficacy profiles of GA are favorable, many patients with allergic reactions to GA may wish to continue GA. Therefore, an accurate diagnosis of allergic reactions should be made. For those patients who are not candidates for other therapies, desensitization procedures are increasingly seen as an excellent and safe method for administering this first-line drug. Desensitization protocols were originally developed for antibiotics, although in recent decades, they have been applied to many other agents, including GA.^{8,9}

Drug desensitization is achieved via gradual introduction of a drug so that it causes cross-linking of drug-specific IgE on the surface of mast cells, thereby maintaining the intracellular signal below a clinical threshold and preventing clinically significant mast cell degranulation. An alternative theory is that univalent drug-carrier protein molecules prevent cross-linking of surface IgE and transmission of an intracellular signal.⁸ The goal of desensitization is to induce tolerance with few or no adverse effects while escalating to the therapeutic dose. Desensitization is drug specific and is sustained only as long as the drug is administered continuously.⁸

In reactions to GA, clinical symptoms of IPIR are not always easy to distinguish from anaphylactic reactions. It is important to conduct an appropriate allergy study to avoid unnecessary discontinuation of GA and complex and expensive procedures such as desensitization.

The present study analyzes the clinical outcomes and diagnostic methods used in 6 patients who were sent to our Allergy Unit for evaluation of adverse reactions to GA between 2007 and 2014. Desensitization protocols were performed in 4 patients.

Methods

We present 6 patients who experienced severe adverse reactions to GA and were sent for an allergy workup (table 1).

Patient 1

A 37-year-old man diagnosed with relapsing-remitting MS (RRMS) was prescribed daily subcutaneous administration of GA (20 mg) in 2004. He initially experienced local symptoms (pruritus and papules at the injection site), which resolved spontaneously in 48 hours. He subsequently experienced an episode of tachycardia and dyspnea during the administration of GA; this resolved after a few minutes, and therapy was continued. After 3 years of treatment, he complained of tachycardia and dyspnea—again, immediately after his GA dose—which resolved after a few minutes. Thirty minutes later, he developed generalized urticaria, intense pruritus (palms, soles, and ears), angioedema (labial, palpebral, and lingual), dyspnea, and, finally, loss of consciousness. He received epinephrine, corticosteroids, and antihistamines in the emergency department. GA was withdrawn. He had a personal history of allergic rhinoconjunctivitis due to pollen and delayed pressure urticaria.

Patient 2

A 36-year-old man was previously diagnosed with anaphylaxis induced by methylprednisolone succinate and trimethoprim/sulfamethoxazole, urticaria-angioedema due to diclofenac, and urticaria-angioedema due to *Anisakis simplex*. In 1999, he was diagnosed with RRMS and was treated with interferon beta-1b for 10 years, which was replaced by GA owing to disease progression. The patient was treated daily with GA for 1 year without adverse reactions. In December 2010, immediately after administration of the drug, he experienced nausea and vomiting, dysphagia, upper airway dyspnea, erythema, and facial angioedema, pruritus affecting the head, and labial angioedema. He was referred to the emergency department, where he received epinephrine, corticosteroids, and antihistamines. GA was withdrawn.

Patient 3

A 37-year-old man was diagnosed with RRMS in 2002. He was treated with GA, which he tolerated for 5 years. Then, immediately after a GA injection, he experienced nonpruritic facial erythema, dyspnea, and dizziness. His symptoms disappeared in 20 minutes, and no treatment was required. A second similar episode occurred some weeks later. GA was well tolerated between both events. GA was discontinued.

Patient 4

A 31-year-old woman had been diagnosed with rhinoconjunctivitis due to pollen, pet epithelium, and mite. In 2006, she was diagnosed with RRMS and initiated interferon-beta therapy, which was suspended owing to side effects. Consequently, she started therapy with GA. Local reactions appeared but resolved in 24 hours. She tolerated this treatment for a further 3 years when, immediately after a GA injection, she experienced generalized erythema, conjunctival erythema, dyspnea, anxiety, dizziness, and blurry vision. These symptoms resolved spontaneously in 10 minutes. GA was withdrawn.

Table 1 Clinical characteristics

Patient/sex	Personal atopic background	Local reactions	IPIR	Systemic reaction (severity of anaphylaxis ¹⁰)	Symptoms during the anaphylactic reaction
P1/M	Allergic rhinoconjunctivitis and pressure urticaria	Yes	Yes	Grade 3	Dyspnea, generalized urticaria, angioedema, and loss of consciousness
P2/M	Drug-induced anaphylaxis <i>Anisakis simplex</i> -induced U-AE	No	No	Grade 2	Nausea, vomiting, throat tightness, erythema, and angioedema
P3/M	No	No	Yes	No	NA
P4/F	Allergic rhinoconjunctivitis	Yes	Yes	No	NA
P5/M	No	Yes	Yes	Grade 1	Erythema and urticaria
P6/F	No	Yes	No	Grade 3	Presyncope, diaphoresis, throat tightness, dyspnea, abdominal pain, and hypotension

Abbreviations: Ax = anaphylaxis; IPIR = generally isolated postinjection reaction; NA = not applicable; U-AE = Urticaria-Angioedema.

Patient 5

A 34-year-old man was diagnosed with inflammatory white matter disease in the right cerebral hemisphere and MS. He started therapy with GA in April 2012. At the beginning of treatment, he experienced an episode of dyspnea, which resolved spontaneously. During the course of his treatment, he experienced recurrent local reactions. In May 2014, 5 minutes after receiving a dose of GA, he experienced palmo-plantar and genital erythema and pruritus followed by urticaria on the trunk. He received corticosteroids and antihistamines. GA was suspended.

Patient 6

A 32-year-old woman was diagnosed with RRMS. She received interferon-beta therapy for 8 years and remained clinically asymptomatic. Owing to progression of the disease, treatment with interferon was replaced by GA. Local reactions appeared but resolved in 24 hours without treatment. Five months after starting therapy with GA, immediately after administration, she experienced cold sweats, instability, vertigo, light-headedness without loss of consciousness, throat tightness, dyspnea, and heartburn. Symptoms resolved in 10–15 minutes without treatment. During the night, she experienced leg tremors, tension headache, and hypotension (90/30). Identical reactions appeared 2 days after administration of GA. Eventually, GA was discontinued.

Standard protocol approvals, registrations, and patient consents

The study was approved by the Ethics Committee (PTM-GLA-2018-01) and adhered to the Declaration of Helsinki (Brazil 2013). All patients signed the informed consent document.

The allergy workup included a complete blood test, skin prick test (SPT) with GA (20 mg/mL), and an intradermal test (IDT) with GA diluted to 0.2 and 0.1 µg/mL. As the commercial preparation Copaxone includes 40 mg of mannitol as

an excipient,¹¹ IDT with mannitol was also performed (10 mg/mL). Histamine was used as a positive control and saline as a negative control.

Specific IgE (dot blot) was determined in the first 2 patients. Briefly, 3 µL of GA (20 and 2 mg/mL, respectively) was spotted onto each nitrocellulose membrane, left to dry, and blocked with 5% bovine serum albumin (Sigma-Aldrich)–phosphate-buffered saline (BSA-PBS) for 1 hour. Then, after washing with 0.05% Tween-PBS, the membrane was incubated with the patients' serum diluted 1:5 in 0.5% BSA-PBS overnight. The following day, it was incubated with horseradish peroxidase-labeled anti-IgE. Finally, it was treated with 3,3',5,5'-tetramethylbenzidine. The same procedure was performed with a healthy patient, who was included as a negative control. As an internal control for the technique, *Lolium perenne* was spotted onto a nitrocellulose membrane and incubated with serum from a *Lolium*-allergic patient. In addition, all 6 patients underwent a drug challenge with 100 mg of IV mannitol.

Drug challenge with GA was performed in those cases in which an allergic reaction was not suspected. The challenge was performed with increasing doses until the therapeutic dose was reached (i.e., 2.5 and 5 mg on the first day and 10 and 10 mg on the second day). The doses were administered at 1-hour intervals, and patients remained under observation for 2 hours after the full dose.

Finally, a desensitization protocol was followed in 4 of 6 patients (table 2). Specific informed consent was given before the procedure, and patients were closely supervised. First, patients 1 and 2 followed desensitization protocol “A.” In protocol “A,” an initial dose of 0.01 mg was given, and further increasing doses were administered every 20 minutes until 20 mg was reached. No premedication was given.

Table 2 Desensitization protocols “A” and “B”

Time (min)	Interval (min)	Protocol A		Protocol B	
		Dose administered (mg)	Cumulative dose (mg)	Dose administered (mg)	Cumulative dose (mg)
0	20			0.00002	
20	20			0.0002	
40	20			0.002	
60	20	0.01		0.02	
80	20	0.05		0.05	
100	20	0.1		0.1	
120	20	0.2		0.2	
140	20	0.5		0.5	
160	20	1.0		1.0	
180	20	2.0		2.0	
200	20	4.0		5.0	
220	20	6.0		6.0	
240	20	7.0	20.86	6.0	20.87

Owing to an allergic reaction during the desensitization process in patient 2, the protocol was modified based on Bains et al.¹² In this desensitization protocol “B,” the initial dose was 0.00002 mg, and further increasing doses were administered gradually every 20 minutes until 20 mg was reached. In addition, premedication was given with 300 mg of oral acetylsalicylic acid and 10 mg of oral montelukast per day (from 48 hours before and on the desensitization day).

Data availability

Anonymized data not published within this article will be made available by request to any qualified investigator.

Results

In all cases, the complete blood count, biochemistry values, and total serum IgE were within normal ranges, and specific IgE levels to *Anisakis simplex*, *Echinococcus granulosus*, and *Ascaris lumbricoides* were negative. Basal serum tryptase levels were 4.10 and 4.33 µg/mL in the first and second cases, respectively.

SPTs with GA were negative in all patients. IDT with GA at 0.1 µg/mL was positive in patient 2 (9 × 8 mm wheal diameter) and negative in the remaining 5 cases. Ten healthy volunteer patients who had previously received Copaxone underwent the same skin testing procedure. SPT and IDT with GA were all negative in control patients. IDT with mannitol was also negative in all patients (table 3).

Specific IgE (dot blot) was determined in the first 2 patients and was found to be positive in blood serum from patient 2 at both GA concentrations (20 and 2 mg/mL) (figure) and

negative in patient 1. The anaphylactic reaction was then confirmed to be of allergic origin in patient 2.

Drug challenge with 100 mg of IV mannitol proved negative in all 6 patients (table 3). As symptoms resolved rapidly and spontaneously, IPIR was suspected in patients 3 and 4, and drug challenge with GA was scheduled to rule out an allergic reaction. Drug challenge with 20 mg of subcutaneous GA was negative in both patients (table 3). The patients continued treatment with GA, which was well tolerated.

A desensitization protocol was undertaken in 4 patients. Although specific IgE was not demonstrated, the clinical histories of patients 1, 5, and 6 suggested degranulation of mast cells or basophils, and owing to the severity of the anaphylactic reaction, GA challenge testing was not performed. In patient 2, an IgE-mediated response was established by positive IDT and dot blot.

Patient 1 tolerated the desensitization protocol “A” well, and no reactions were observed. The patient continued treatment with daily GA for a further 5 months. Then, immediately after a GA injection, he developed tachycardia, dyspnea, dry cough, chest tightness, dysphagia, generalized urticaria, and labial and palpebral angioedema. He was referred to the emergency department, where he received epinephrine, corticosteroids, and antihistamines. His symptoms resolved in 1 hour. GA was suspended, and the patient initiated treatment with interferon beta-1-alpha.

In patient 2, the desensitization protocol “A” was initiated with 0.01 mg of subcutaneous GA. Fifteen minutes after the

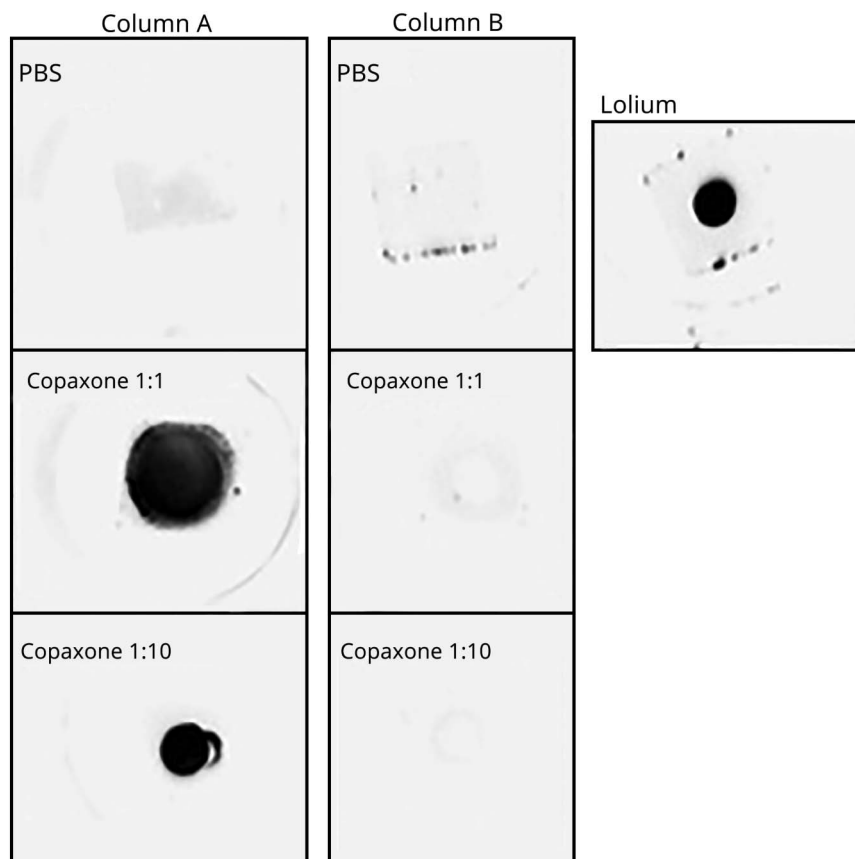
Table 3 Summary of allergy studies

Patient/sex	Skin testing			slgE dot blot	Challenge test		GA desensitization protocol
	SPT	IDT			GA	Mannitol	
		GA	Mannitol				
P1/M	Neg	Neg	Neg	Neg	ND	Neg	Yes
P2/M	Neg	Positive	Neg	Positive	ND	Neg	Yes
P3/M	Neg	Neg	Neg	ND	Neg	Neg	ND
P4/F	Neg	Neg	Neg	ND	Neg	Neg	ND
P5/M	Neg	Neg	Neg	ND	ND	Neg	Yes
P6/F	Neg	Neg	Neg	ND	ND	Neg	Yes

Abbreviations: GA = glatiramer acetate; IDT = intradermal test; ND = not done; Neg = negative; slgE = specific IgE; SPT = skin prick test.

0.1 mg dose (accumulated dose of 0.16 mg), he developed generalized erythema, dysphagia, upper airway dyspnea, genital pruritus, and uvular angioedema. The desensitization was aborted, and the patient was treated with epinephrine, corticosteroids, and antihistamines. Sixty minutes after the onset of the anaphylactic reaction, the serum tryptase level was 4.83 µg/mL. Owing to medical necessity, desensitization

was reattempted 1 week later. The protocol was modified based on Bains et al.¹² (protocol “B”) and restarted with an initial dose of 0.00002 mg (table 2). In addition, premedication was given with 300 mg of oral acetylsalicylic acid and 10 mg of oral montelukast per day. Desensitization was well tolerated, and no reactions were observed. The patient tolerated daily GA for a further 18 months and continued

Figure Immunoblot performed in patient 2

If the balance of GA is favorable compared with other alternative therapeutic options, a desensitization procedure could be attempted.

receiving acetylsalicylic acid and montelukast every day. Eighteen months after the desensitization protocol, IDT with GA (0.1 µg/mL) was repeated and remained positive.

The desensitization protocol “B” was also used successfully on patients 5 and 6, who tolerated GA well with no reactions. These patients did not receive premedication.

Discussion

Diagnosis and management of adverse reactions to GA are complex. A careful study should be performed to determine whether the patient should continue with treatment or if a desensitization procedure should be recommended.

We present 6 cases of adverse reaction to GA, most of them in men diagnosed with MS at age 21–39 years. Of these, 4 patients presented with IPIR and 4 experienced local reactions at the injection site. Four patients developed systemic allergic reactions, anaphylaxis, or generalized urticaria. Most of the anaphylactic reactions occurred after a long period of treatment with GA (from 5 months to 3 years).

Diagnosis was based on the clinical history and an allergology workup. Different therapeutic approaches were followed in each case (table 3). The most frequent adverse effects to GA are local irritant reactions, which do not require an allergology workup.

Isolated IPIRs are uncommon. As IPIRs constitute an unpredictable nonallergic reaction that always resolves in a few minutes without sequelae, administration of GA can be continued. Two of our patients experienced symptoms compatible with IPIR, and a graded challenge test with GA ruled out an allergy diagnosis. Because these patients continued their treatment with no new reactions, GA was not discontinued. Nevertheless, IPIRs may be misdiagnosed as anaphylaxis.^{3–6} IPIRs do not predict anaphylactic reactions, which are infrequent.^{5,9,13–15} Patients may have both IPIRs and anaphylaxis at different times.

In our series, 4 patients presented with moderate-severe systemic reactions. Patients presenting with a clinical history of anaphylaxis should undergo an *in vivo* study. IDT with GA at 0.1 µg/mL was positive in patient 2. Other authors reported IDT with GA as positive at concentrations ranging

from 2 to 20 mg/mL.^{5,9,12,13,15–21} However, as some of these concentrations became irritant in some controls, skin tests were of limited value in most cases. Of interest, we found a positive IDT result at GA concentrations 20 times lower than previously reported, although the IDT result was negative in the 10 controls; therefore, we concluded that this concentration was nonirritant.

Owing to the irritant effects in the skin tests described above, some authors conducted *in vitro* studies. Increased immunoglobulin (Ig) G₁, IgG₄, and IgE to GA were detected by ELISA in patients who experienced anaphylaxis with GA.^{5,15} The increase in IgG subclasses of GA-reactive antibodies in patients with MS receiving GA, especially IgG₂ and IgG₄, had previously been described by Farina et al.²² GA induces GA-reactive T cells to produce Th2 cytokines, such as interleukin (IL) 13, IL-5, and IL-4, which are known switch factors for IgG₄. Furthermore, T cells produce nerve growth factor, which stimulates B cells to produce IgG₄. Nevertheless, no association has been found between GA-antibody response and therapeutic activity.²² Of interest, no IgE levels were obtained in the patients.^{5,15} Recently, the result of the basophil activation test was positive in 2 patients with GA-induced anaphylaxis.¹⁵ Similarly, our dot blot demonstrated the presence of an IgE mechanism in an anaphylactic reaction.

As Copaxone contains 40 mg of mannitol as an excipient and a mannitol-specific IgE reaction was recently reported in a case of anaphylaxis,²³ the allergy study should include mannitol in GA reactions. Therefore, we applied IDTs with mannitol (10 mg/mL). The negative results in the skin tests and challenge enabled us to rule out mannitol allergy, as reported by other authors.^{9,13,15,17}

The low sensitivity of *in vivo* and *in vitro* study impairs the allergy diagnosis. In our series, 3 anaphylactic reactions were most likely due to mast cell and/or basophil degranulation, although no IgE-mediated mechanism could be demonstrated. In those cases in which systemic reactions appear, the risk-benefit assessment of GA for each patient should be taken into account. If the balance of GA is favorable compared with other alternative therapeutic options, a desensitization procedure could be attempted.

Desensitization procedures are reported to be effective and safe methods for administering first-line drugs in patients who are not candidates for other therapies.⁸ Bains et al.¹² reported the first successful desensitization protocol to GA in 6 patients with MS who had experienced systemic reactions. No premedication was needed. Minor reactions were observed, and 5 of 6 patients tolerated GA. Sheth et al.¹⁸ used this protocol in 1 patient; however, she experienced a mild hypersensitivity reaction during the protocol, which was subsequently aborted. The authors then developed a modified desensitization protocol including premedication with oral prednisone and diphenhydramine for 10 days, and

Desensitization carries a risk of triggering anaphylactic reactions.

additional steps were added. The patient developed mild facial flushing after the last dose, although this resolved without treatment. Prednisone and cetirizine were suspended, respectively, 10 and 21 days later. Crestani et al. recently reported the first successful desensitization protocol in a pediatric patient, and Syrigou et al. described a modified desensitization protocol that was started with a 10-fold lower dose than that described by Bains et al.^{9,12,20} In our study, the desensitization procedure was performed in 4 patients who had experienced anaphylactic reactions.

Initially, we used an adapted protocol (protocol “A”) (table 2), which was modified (protocol “B”) after an adverse reaction appeared during the procedure in patient 2. We also added premedication with acetylsalicylic acid and montelukast, which have proven effective at blocking hypersensitivity reactions, especially in patients with more severe cutaneous reactions.²⁴ This procedure enabled desensitization to be completed with no side effects in 3 patients.

Desensitization carries a risk of triggering anaphylactic reactions. In some cases, when a desensitization procedure fails, it is suitable to reattempt a second desensitization protocol starting with lower doses, including premedication to prevent possible reactions, or introducing new steps in the protocol.⁸ It is noteworthy that in our study, 1 patient, who underwent the desensitization protocol safely and continued with GA for several months, eventually experienced a new anaphylactic reaction. Thus, we should provide patients with epinephrine autoinjector devices and training in how to use them.

In conclusion, we present our experience in the management of reactions to GA, including local side effects, IPIR, and anaphylactic reactions. Although specific IgE may only be present in a small group of patients, we strongly recommend that it be investigated. Last, we describe a safe desensitization protocol, which enabled treatment to be continued in patients for whom no alternative therapeutic options were available.

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Disclosure

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TAKE-HOME POINTS

- Adverse reactions to GA range from local injection site reactions to generalized reactions such as IPIR and anaphylaxis.
- Incorrect diagnosis of adverse reactions may lead to unnecessary discontinuation of GA or complex and expensive procedures such as desensitization.
- We demonstrated specific IgE to GA by IDT and dot blot in 1 of 6 patients. The diagnosis of allergy to GA was firmly suspected based on the clinical history in 4 of 6 patients.
- Two desensitization protocols were safely and successfully performed in 4 of 6 patients. Only 1 patient subsequently developed an anaphylactic reaction, leading to suspension of GA. The other 3 patients continued to receive GA daily with no adverse reactions.

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Appendix Authors

Name	Location	Contribution
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Appendix (continued)

Name	Location	Contribution
Maria Luisa Baeza, MD, PhD	Hospital Gregorio Marañón, Madrid	Performed the allergology workup, desensitization protocols, and IgE dot blot analysis; read and approved final manuscript

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