

Desensitization in Interferon- β 1a Allergy: A Case Report

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Established Facts

- Interferon- β , which belongs to the type I interferon family, is used in the treatment of multiple sclerosis.
- Interferon- β decreases T cell activation and interferon- γ production, which may result in an increase in the IgE-mediated response in atopic patients during the treatment for multiple sclerosis.

Novel Insights

- Desensitization is a safe and effective procedure in the treatment of interferon- β 1a hypersensitivity.

Key Words

Desensitization · Drug allergy · Interferon

Abstract

We report a 41-year-old patient with multiple sclerosis (MS) who was successfully desensitized after she developed non-injection-site urticaria and angioedema due to interferon (IFN)- β 1a. Although a few cases of urticaria and anaphylaxis have been reported in the literature, to our knowledge this is the first report of a successful desensitization with IFN- β 1a. Desensitization with IFN- β 1a allowed us to continue with the administration of interferon- β , which is a mainstay in treatment for MS.

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system. Interferon (IFN)- β , which belongs to the type I interferon family, is used as the standard treatment for relapsing-remitting MS. Recombinant IFN- β 1a and IFN- β 1b must be administered continuously to control disease activity. Although the mechanism of action remains incompletely understood, a reduction in active lesions implies anti-inflammatory properties [1]. The most frequently reported side-effects of IFN- β include headache, fever, chills, myalgia and a flu-like syndrome, whereas allergy is uncommon. Cutaneous reactions are usually described as painful erythematous lesions, which have been found to be associated with IFN- β 1b but not with IFN- β 1a [2, 3].

Table 1. Desensitization protocol with IFN- β 1a

	Dilution	Amount, ml
Day 1	11 μ g/ml	
	1:1,000,000	0.5
	1:100,000	0.5
	1:10,000	0.5
	1:1,000	0.5
	1:100	0.5
	1:10	0.5
	Actual dose	0.1
		Total dose = 1.71 μ g
Day 2	11 μ g/ml	0.1
	22 μ g/ml	0.1, 0.2, 0.4, 0.5
	Total dose = 27.5 μ g	
Day 3	44 μ g/0.5 ml	0.125, 0.25
	Total dose = 33 μ g	
Day 4	44 μ g/0.5 ml	0.5
	Total dose = 44 μ g	

Case Report

A 41-year-old woman presented with non-injection-site urticaria and angioedema after IFN- β 1a treatment. She had complained of headache and myalgia for 3 years, and the condition was diagnosed as MS 15 months previously. At first she was treated with oral prednisone along with nonsteroidal anti-inflammatory drugs (NSAIDs). Treatment with continuous self-administered subcutaneous injection of IFN- β 1a was started in July 2007. The treatment schedule was to start with an initial dose of 22 μ g/0.5 ml three days a week for a month, and thereafter to continue with 44 μ g/0.5 ml (Rebif, Serono, Italy). The injections were administered in the upper arms, thigh and abdomen. After the first month, pruritis and urticarial lesions (of which there were approx. 10, and which were 2–3 cm size) started to appear away from the injection sites with each administration of IFN- β 1a 22 μ g/0.5 ml. These lesions usually developed within 1–2 h after the injection and completely resolved within 24 h under an antihistamine treatment. At the third 44 μ g/0.5 ml dose of IFN- β 1a, a generalized urticaria with periorbital and perioral angioedema had developed. IFN- β 1a was discontinued and the urticarial lesions disappeared immediately, with no further relapses.

In her medical history, the patient had perennial mild-intermittent rhinitis for 4 years and an allergy to NSAIDs. Skin prick tests (SPTs) with a battery of common inhalant allergens (ALK, Spain) were positive for house dust mites, consistent with her complaints. The total IgE level was 195 IU/ml. Having excluded NSAID-hypersensitivity to paracetamol, meloxicam and nimesulid with negative oral provocation tests, we performed skin tests with IFN- β 1a, starting at a concentration of 1:10,000 and increasing 10-fold with

intervals of 30 min. All the dilutions were prepared with saline. If negative, SPTs were followed by an intradermal (i.d.) test. Histamine at 10 mg/dl and 0.1 mg/ml were used as positive controls for SPTs and i.d. tests, respectively, whereas phenolated saline was the negative control. A wheal size of 3 mm greater than the negative control was considered positive in SPTs, and the i.d. test was considered positive when the wheal was 10 mm or more. Although no immediate wheal and flare reaction was seen, positive reactions developed after 1 h at a 1:1 dilution in SPTs, and at $\geq$ 1:1,000 dilutions in i.d. tests. Additionally, non-injection site urticarial lesions localized mainly on the patient's arms and trunk appeared within 60 min and lasted less than 12 h.

After written and oral informed consent was completed, a desensitization protocol was arranged as incremental alternating subcutaneous injections of IFN- β 1a, every 30 min on the upper arms, according to the schedule in table 1. No pretreatment with antihistamines was given while the patient was monitored. Desensitization was completed successfully at the end of the 4th day. During the 6-month follow-up period, she received the usual maintenance dose of 44 μ g/0.5 ml IFN- β 1a treatment, 3 times a week, with no adverse reactions.

Discussion

According to the literature, the most commonly reported adverse reactions to IFN- β 1a comprise cutaneous reactions, fever, myalgia, headache, menstrual disorders and flu-like syndrome [2–4]. Cutaneous problems are usually characterized by inflammatory reactions local to the injection site, which can be handled by simple management strategies, such as premedicating with NSAIDs and rotating and precooling the injection sites. Although allergic reactions have been only rarely observed in treatment for MS, the development of a severe urticaria has been reported with IFN- β 1a [5]. A severe IgE-mediated anaphylaxis has also been described after approximately 6 months of IFN- β 1a therapy [6]. Another urticarial reaction over the injection site was reported occurring 9 months after treatment with another form of IFN- β , IFN- β 1b [7]. Ohmoto and Yamamoto [8] presented a case with angioedema after IFN therapy for chronic hepatitis C.

The mechanism by which IFN- β 1a induces allergic reactions is unknown, but the current hypothesis is that IFN- β can increase interleukin-2 which can stimulate a Th2 response [9]. The immunomodulatory mechanism of IFN inhibits the proliferation of T lymphocytes and shifts the Th1 response towards a favorable Th2 type [10]. This effect may result in an increase in an immunoglobulin E (IgE)-mediated response in atopic patients. However, some authors have postulated that the mechanism is not an IgE-mediated reaction because no other proof

of type I allergic reactions has been reported [6]. Others agree that interferon β provokes a specific IgE response with potential clinical manifestations [5]. Nevertheless, anti-IFN neutralizing antibodies may be produced and/or the possibility of intrinsic biological effects of IFN- β may exist [6, 11]. Likewise, Brown et al. [7] showed that immediate positive intradermal testing at a 1:10 dilution confirmed an IgE-mediated allergic response to IFN- β 1b. However, the exacerbation of asthma in their case, was not an allergic reaction, but rather was likely secondary to a biological effect of the IFN.

The onset of reactions long after treatment had begun in our patient suggests that an IgE-mediated allergy may occur with IFN- β therapy in some MS patients. Moreover, delayed occurrence of a vasculitic-like cutaneous reaction to IFN- β 1b was observed 9 months after initiation of therapy [12].

As NSAIDs, which are commonly used to reduce the side effects of IFN, were among the possible triggers of urticaria and angioedema in the present case, oral provocation tests were performed to exclude NSAID hypersensitivity.

There are a number of potential criticisms of this current case report. First, we did not measure specific IgE, which would strengthen the case. Second, we did not have any exposed or healthy control patients.

Successful induction of a tolerance state can also be obtained in non-IgE mediated reactions with immediate type symptoms. Despite the lack of controls, desensitization in the present case is thought to be against an IgE, as the reaction observed is more likely to be IgE-dependent as skin testing (both prick and i.d.) and the clinical history confirmed a late occurring immediate type allergic reaction to IFN- β 1a in this patient. Although a few cases of injection-site reactions and anaphylaxis have been reported in the literature, to our knowledge this is not only one of the few cases reporting non-injection-site urticaria, but also the first case of desensitization with IFN- β 1a.

This case demonstrates that desensitization with IFN- β 1a is a quick and easy solution to a clinically relevant problem, and it has no adverse reactions. This effective and successful procedure should be considered at least in patients with immediate hypersensitivity to IFN- β .

References

- ▶ 1 Yong VW, Chabot S, Stuve O, Williams G: Interferon beta in the treatment of multiple sclerosis: mechanisms of action. *Neurology* 1998;51:682–689.
- ▶ 2 Walther EU, Hohlfeld R: Multiple sclerosis: side effects of interferon beta therapy and their management. *Neurology* 1999;53:1622–1627.
- ▶ 3 Munschauer FE 3rd, Kinkel RP: Managing side effects of interferon-beta in patients with relapsing-remitting multiple sclerosis. *Clin Ther* 1997;19:883–893.
- ▶ 4 García-F-Villalta M, Daudén E, Sánchez J, Fraga J, Ramo C, García-Díez A: Local reactions associated with subcutaneous injections of both beta-interferon 1a and 1b. *Acta Derm Venereol* 2001;81:152.
- ▶ 5 Mazzeo L, Ricciardi L, Fazio MC, Fogliani O, Fedele R, Ferlazzo E, Isola S: Severe urticaria due to recombinant interferon beta-1a. *Br J Dermatol* 2003;148:171–192.
- ▶ 6 Corona T, Leon C, Ostrosky-Zeicher L: Severe anaphylaxis with recombinant interferon beta. *Neurology* 1999;52:425.
- ▶ 7 Brown DL, Login IS, Borish L, Powers PL: An urticarial IgE mediated reaction to interferon beta-1b. *Neurology* 2001;56:1416–1417.
- ▶ 8 Ohmoto K, Yamamoto S: Angioedema after interferon therapy for chronic hepatitis C. *Am J Gastroenterol* 2001;96:1311–1312.
- ▶ 9 Arnason BGW, Reder TR: Interferons and multiple sclerosis. *Clin Neuropharmacol* 1994;17:495–547.
- ▶ 10 Noronha A, Toscas A, Jensen MA: Interferon beta decreases T cell activation and interferon gamma production in multiple sclerosis. *J Neuroimmunol* 1993;46:145–153.
- ▶ 11 Pichler WJ, Campi P: Adverse side effects to biological agents; in Pichler WJ (ed): *Drug Hypersensitivity*. Basel, Karger, 2007, pp 151–165.
- ▶ 12 Cohen BA, Greenberger PA, Saini S: Delayed occurrence of a severe cutaneous reaction in a multiple sclerosis patient taking interferon beta-1b. *Allergy Asthma Proc* 1998;19:85–88.