

# Improvement of interferon-beta related skin reactions after diluent halving: first experience of five patients

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**Background:** The spectrum of side effects related to interferon beta-1b (INF-1b) treatment may compromise long-term adherence.

**Methods:** Five INF-1b-treated multiple sclerosis patients with poor skin tolerability and clinical stability were instructed to dissolve the established (250 µg) INF-1b dose in half (0.5 mL) the standard diluent (1.0 mL, 0.54% sodium chloride solution), and were followed for 9 months.

**Results:** Halving the volume of the treatment diluent was associated with significant improvement of skin side effects profile in all patients. The improvement was sustained for 9 months.

**Conclusion:** Halving the volume of the INF-1b diluent could represent a different strategy to optimize skin tolerability and adherence in some multiple sclerosis patients.

**Keywords:** multiple sclerosis, interferon, treatment tolerability, side effects, skin reactions

## Introduction

Immunomodulation with injectable interferon-beta (INF) and glatiramer acetate has been validated in pivotal phase III trials,<sup>1-4</sup> and represents the first-line treatment in multiple sclerosis (MS). However, the side effect spectrum of these drugs has a possible negative impact on patient's quality of life. In turn, this may lead patients to reduce treatment adherence, with obvious negative influence on clinical outcome.<sup>5</sup> Physicians might thus be forced to switch effective MS treatments to other therapies due to relevant local or systemic side effects. New strategies to minimize and manage the known INF-related side effects are thus of major interest in order to guarantee, besides optimal efficacy, the best treatment adherence and acceptance.

In this report, five MS patients – who have clinical and radiological disease stability but suffer severe skin reactions related to INF-1b injections – experienced a marked improvement in skin tolerability after halving the diluent volume while maintaining the same INF-1b dose.

## Representative case

An otherwise healthy 33-year-old female presented with subacute gait ataxia and urinary hesitancy in March 2007. Neurological examination showed an impairment of leg proprioception and mild pyramidal signs. Following appropriate diagnostic work-up, a clinically isolated syndrome was diagnosed. Treatment with steroids led to partial recovery (Expanded Disability Status Score from 3.5 to 2.0). Four months later, the patient presented with a right optic neuritis, which recovered after a high dose steroid course. Treatment with INF-1b 250 µg subcutaneously every other day was started.

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During the following 4 years she had no further attacks, disability progression, or new lesions at follow-up magnetic resonance imaging. Unfortunately, in April 2011 the patient presented with marked erythema and hardened skin changes at injection sites on her abdomen and legs. She was absolutely reluctant to change treatment due to fear of inefficacy and possible severe complications of second-line therapies; she was thus instructed to reconstitute the lyophilized INF-1b to half of the volume of the supplied diluent (0.54% sodium chloride solution), according to anecdotal evidence from patients' and nurses' clinical practice. After this change, the patient much better tolerated the injections with only mild local erythema. During the following 9 months, she remained clinically stable with good treatment compliance. No further severe local or systemic side effects occurred.

Based on this experience, the same treatment regimen was given to four further patients with severe skin reactions and clinical stability under INF-1b treatment. They gave their consent for this treatment change. A nurse specialized in MS injectable treatments instructed patients at home and followed them as necessary. Patients were clinically evaluated every 3 months with standard laboratory assessment for INF-1b treatment; moreover, they had a monthly phone interview for safety monitoring. Severity of skin and systemic side effects before and after treatment change were assessed by visual analog scales and objective medical evaluation (Tables 1 and 2).

## Discussion

Five patients with severe injection site reactions to INF-1b clearly improved after reduction of the volume of the injected INF-1b solution. This was achieved by halving the diluent volume of each injection, thus maintaining the standard INF-1b dose. Skin amelioration generally occurred after  $\geq 3$  months following treatment change and involved tenderness, redness, and local injury and was associated with

an improvement of global patient's satisfaction of treatment as assessed by visual analog scales. Moreover, halving the solution volume was neither associated with a worsening of the systemic side effect profile or with a reduction of clinical efficacy during the follow-up.

Based on clinical trials<sup>6</sup> and patients' experience, local skin reactions and systemic side effects generally increase with INF titration, which represents a standard of care to optimize INF tolerability; nevertheless, higher INF doses are usually associated with more frequent and intense side effects.<sup>1,4,7,8</sup> Until now, no studies have clarified whether this effect is due to the progressively increased injected volume, INF dose, or both.

It was speculated that the injected volume could play a role in INF-1b-associated skin reactions. Five patients were accordingly treated with the standard INF-1b dose in half the standard diluent volume. Intriguingly, this procedure led to a significant improvement of the local inflammatory reactions in all patients after approximately 3 months. The clear temporal association between diluent halving and the improvement of skin symptoms points to a direct role of the injected volume in INF-1b-associated skin reactions. Pathogenetic mechanisms underlying INF-associated injection site reactions are still poorly understood. Injection technique, needle size, depth of injection, and mechanical and inflammatory/immunological changes triggered by the injection process itself or by the injected drug or diluent could represent contributing factors. It has been shown that subcutaneous adipose tissue can release multiple pro-inflammatory cytokines and chemokines such as interleukin-1 beta, interleukin-6, tumor necrosis factor-alpha, and CXCL8 (interleukin-8) even after minimal trauma.<sup>9</sup> Therefore, reduction of the injected volume may lead to less mechanical trauma and reduced activation of the surrounding adipocytes, nerve cells, and immune cells, subsequently leading to a decreased amount of inflammation. It is improbable that diluent components (0.54% sodium chloride solution) play a major role in the

**Table 1** Clinical and demographic characteristics of patients at baseline and at 9 months follow-up

Patient	Baseline clinical and demographics							Clinical course at 9 months	
	Sex	Age	Disease duration	INF-1b duration (years)	EDSS 2 years prior to treatment change/ at baseline	ARR (last 2 years)	Previous treatments (1 year prior to INF-1b)	Number of relapses	EDSS
1	F	37	4	4	2.0/2.0	0	–	0	2.0
2	F	63	33	11	2.0/2.0	0	–	0	2.0
3	F	44	4	4	2.0/2.0	0	–	0	2.0
4	F	60	7	7	2.0/2.0	0	–	0	2.0
5	F	51	2	2	1.0/1.0	0	–	0	1.0

**Abbreviations:** ARR, annual relapse rate; EDSS, Expanded Disability Status Score; F, female; INF, interferon beta-1b.

**Table 2** Evaluation of treatment-related side effects and treatment satisfaction

Pt	Patients' evaluation of local and systemic side effects													Medical evaluation of skin lesions	
	Redness		Tenderness		Necrosis		Pain at injection site		Flu-like symptoms		Headache		Treatment satisfaction	Tenderness T9	Redness T9
	T0	T9	T0	T9	T0	T9	T0	T9	T0	T9	T0	T9	T9		
1	9	3	10	6	0	0	8	5	7	4	8	8	6	Marked improvement	Marked improvement
2	10	5	8	4	2	0	8	4	2	2	0	0	5	Slight improvement	Moderate improvement
3	10	8	10	8	0	0	10	10	0	0	8	8	5	Slight improvement	Slight improvement
4	6	3	3	1	0	0	4	2	0	0	1	1	7	Moderate improvement	Moderate improvement
5	5	2	8	3	0	0	9	0	0	0	3	3	9	Moderate improvement	Moderate improvement

**Note:** Patients' evaluations refer to scoring by visual analog scales (1–10 scoring).

**Abbreviations:** Pt, patient; T0, before treatment change; T9, 9 months after treatment change.

local inflammatory processes as they are standard concentrated constituents of the extracellular spaces.

## Conclusion

Halving the volume of INF-1b diluent could represent an easy and feasible alternative strategy to minimizing poor skin tolerability while continuing a previously efficacious and safe treatment. However, definitive conclusions cannot be drawn from the current case series due to the small number of patients and the descriptive context. Thus, potential employment of this formulation is subject to the positive outcome of an appropriate controlled trial.

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