



Recurrent Arthritis and Anti-cyclic Citrullinated Peptide Positivity during Interferon-beta 1a Treatment in Two Patients with Multiple Sclerosis

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Received: 03 November 2015

Revised: 30 December 2015

Accepted: 30 January 2016

ARTICLE INFO

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Keywords:
Arthritis;
Multiple sclerosis;
Interferon-beta

ABSTRACT

Interferon (IFN) beta is the most widely prescribed disease-modifying drug for multiple sclerosis (MS). However, some adverse reactions are observed in course of IFN-beta therapy. This article presents two cases of female patients diagnosed with relapsing-remitting MS who developed inflammatory musculoskeletal manifestations, following IFN-beta 1a therapy. In the first patient recurrent arthritis developed a week after initiation of IFN-beta, which improved few weeks after a switch to glatiramer acetate. The second patient developed recurrent arthritis 1 month after IFN-beta 1a therapy who suffered painful arthritis despite discontinuation of the medication. Both patients were seropositive for anti-cyclic citrullinated peptide; the first patient was a positive rheumatoid factor (RF) and the second patient was both positive RF and anti-Ro. The role of IFN-beta in the setting of inflammatory musculoskeletal disease remains unclear. To minimize its side effects, review of these antibodies may be required in patients who are candidates for this therapy.

Citation: Cheraghmakani H, Mobini M, Baghbanian M. **Recurrent Arthritis and Anti-cyclic Citrullinated Peptide Positivity during Interferon-beta 1a Treatment in Two Patients with Multiple Sclerosis.** Case Rep Clin Pract 2016; 1(2): 33-7.

Introduction

A number of different interferon (IFN) beta preparations have been investigated for the treatment of

relapsing-remitting multiple sclerosis (RRMS) including IFN-beta 1b and beta 1a. Beside therapeutic effects, there are known side effects such as flu-like symptoms and

injection site reactions. There have also been reports of thyroid dysfunction, development of livedo reticularis and secondary raynaud phenomenon, arthritis and bursitis, and systemic lupus erythematosus (SLE) during IFN-beta treatment (1-6). However, the occurrence of arthritis has rarely been observed during IFN-beta 1a treatment.

This article reports the development of recurrent arthritis in two patients with RRMS, following the start of therapy with IFN-beta 1a and reviews other cases with rheumatologic side effects of this treatment.

Case Report

The first patient was a 35-year-old woman who was referred to a rheumatologist with a 2 years history of right leg pain and limping. Furthermore, she had an episode of painful right eye blurred vision, right hemiparesis, and sphincter dysfunction separately in the past 2 years; but no any history of rash, fever, oral ulcer, arthralgia, or Raynaud phenomenon. In physical examination, increased deep tendon reflexes, Babinski sign and impaired position sense was seen in the right limb.

To evaluate the systemic vasculitis syndromes, laboratory and imaging studies were requested including mild anemia (hemoglobin = 11.1), erythrocyte sedimentation rate (ESR) = 35, a positive anti-cyclic citrullinated peptide (CCP) = 210 [upper limit of normal (ULN) = 5], and rheumatoid factor (RF) = 85 (ULN = 31). The results for antinuclear antibodies (Ab) (ANA), anti-dsDNA, anti-C and perinuclear-anti-neutrophil cytoplasmic Ab, C-reactive protein (CRP), and anti-cardiolipin Ab were all negative. There was not any bone or joint lesion in whole body bone scan. The patient was referred to a neurologist who diagnosed her with MS based on relevant cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) findings. Treatment by IFN-beta 1b was started, but 4 months later it was switched to IFN-beta 1a (high dose, high frequency) because of severe side effects (flu-

like syndrome and local injection site reaction). After 1 week, the patient experienced five episodes of arthritis in hands and knee joints which lasted 1-2 days and repeated after each injection. Laboratory investigations revealed elevated ESR = 58 and CRP = 16 (ULN = 3.8). The liver and kidney function tests were normal and viral markers for hepatitis B surface antigen and hepatitis C virus Ab were negative. Because of recurrent arthritis, IFN was stopped and treatment was continued by prednisolone (7.5 mg/day) and methotrexate (7.5 mg) for short term, glatiramer acetate and calcium-D. The patient was followed for 6 months without any episode of arthritis.

The second case was a 42-year-old woman with a history of upper limb pain and paresthesia and right eye blurred vision separately in the past 4 years. The diagnosis of MS was made based on relevant CSF and MRI findings. She did not have any history of arthritis, Raynaud phenomenon, rash, oral or ophthalmic dryness.

One month after treatment by IFN-beta 1a, the patient experienced acute and recurrent attacks of arthritis, so therapy was changed to Glatiramer acetate. Laboratory findings included: mild anemia, ESR = 59, CRP = 25 (ULN = 5), anti-CCP = 64 (ULN = 18), anti-Sjögren's syndrome A antigen (SSA)/Ro = 46 (ULN = 18). ANA, RF, anti-ds DNA, HIV Ab, and anti-cardiolipin Ab were all negative and serum complement levels were normal. Despite discontinuation of IFN-beta 1a for 2 months, the patient suffered recurrent arthritis which happened every 2-3 days and persisted for hours. In this time, lab tests including negative ANA, positive anti-SSA/Ro and anti-CCP and normal complement were done. Ophthalmologic exam (Schirmer test) was normal. The patient was diagnosed as having early undifferentiated connective tissue disease (7) and treatment with low dose of prednisolone, hydroxychloroquine, and methotrexate was started.

Table 1 shows rheumatologic manifestation and patient's outcome after IFN-beta 1a.

Table 1. Some rheumatologic side effects of IFN-beta 1a in patients with MS

Author/year	Age/sex	Duration of treatment	Rheumatologic manifestation	Rheumatologic lab and imaging tests	Patient outcome
Levesque et al./1999 (11)	69/F	8 weeks	seronegative, symmetric polyarthritis	Low titer ANA, negative RF, positive HLA-DRB1*0404	After 14 months treatment by prednisolone and methotrexate, arthritis were controlled
Russo et al./2000 (12)	14/F	2 months	Symmetric polyarthritis	Negative ANA, positive RF, positive HLA-DRB1*0404	Some clinical improvement by NSAID, the patient discontinued IFN by own decision, and arthritis was resolved some weeks later
De Santi et al./2005 (10)	48/F	5 years	Primary Sjögren's syndrome	Negative ANA	Low dose of prednisolone and then hydroxychloroquine was prescribed and oral and ocular symptoms were ameliorated
Bahri et al./2012 (6)	34/F	9 months	Drug-induced lupus erythematosus	Positive ANA, anti-dsDNA	Under corticosteroids treatment, the patient did not develop any other lupus manifestations
Chakravarty et al./2012 (16)	39/F	3 years	Sarcoidosis	Negative ANA, elevated ACE level, hilar and mediastinal lymphadenopathy	IFN was discontinued, hydroxychloroquine, methotrexate and prednisolone were prescribed, and sarcoidosis manifestations were resolved 6 months later
Buchanan et al./2013 (15)	33/F	1 week	Drug induced subacute cutaneous lupus erythematosus	Positive ANA, anti-SSA/Ro and then anti-SSB/La	Avonex was discontinued, did not response to topical management, hydroxychloroquine and prednisolone were prescribed
Toussirot et al./2014 (9)	54/F	9 months	Psoriatic arthritis	Negative RF and anti-CCP	Avonex was continued, sulfasalazine, methotrexate and leflunomide were ineffective, low dose of prednisolone and hydroxychloroquine were partially effective
Cheraghmakani et al.	35/F	1 week	Seropositive recurrent arthritis	Negative ANA, positive RF and anti CCP	IFN was discontinued, prednisolone was started, arthritis was resolved
	42/F	1 month	Undifferentiated connective tissue disease	Negative ANA, RF anti ds DNA, positive anti-SSA/Ro and anti-CCP	IFN was discontinued, prednisolone, hydroxychloroquine and methotrexate were started, arthritis was resolved

CCP: Cyclic citrullinated peptide, SSA: Sjögren's syndrome A antigen, ANA: Antinuclear antibodies, RF: Rheumatoid factor, ACE: Angiotensin converting enzyme, NSAIDs: Non-steroidal anti-inflammatory drugs, IFN: Interferon

Discussion

We described two patients with recurrent arthritis in association with IFN-beta 1a during MS treatment.

IFN-beta is the most widely prescribed disease-modifying drug for MS (8) and it was rarely reported with development of autoimmune disorders such as increased prevalence of thyroid dysfunction and autoimmunity (1), vasoconstrictive and procoagulant effects (2), Raynaud's phenomenon, livedo-reticularis and digital necrosis (3), arthritis and bursitis (5), psoriatic arthritis (9), Sjögren's syndrome (10), and SLE (6). In some reports, arthritis happened during IFN-beta 1a (9, 11, 12) or IFN-beta 1b (4, 13, 14). Duration of IFN therapy to the first rheumatologic manifestation was different, from 1 week to 5 years (10, 15). In most cases, rheumatologic manifestation was resolved after IFN discontinuation (5, 6, 9, 12), however, in some it lasted for months (11, 16).

Data in literature support a possible pathogenic role for Type I IFN in RA and MS, based on demonstration of an IFN signature in blood in RA and MS. In these cases, while systemic Type I IFN might play a contributing role in induction of autoimmunity, but its anti-inflammatory role might be more significant (17). In contrast, it was found that IFN-beta is ineffective and might worsen clinical status in diverse diseases such as RA, SLE, and psoriasis when a Th17 immune response is prominent (18). In a randomized, double-blind, placebo control study in patients with active RA no clinical or radiological effect was seen in the treatment with IFN-beta 1a 3 times weekly in combination with methotrexate (19).

IFNs may cause drug-induced lupus (15). Expression of an IFN signature is also seen in highly related syndromes characterized by systemic autoimmunity, including Sjögren's syndrome (20). The occurrence of sarcoidosis while using these agents is perhaps due to a dysregulation in the modulatory role played by IFN-beta expression in chronic inflammation (16).

In susceptible individuals, IFN-beta 1a may certainly induce or exacerbate the concomitant systemic autoimmune diseases and rheumatologic manifestation. Clinicians should consider this possibility when treating patients with MS.

It is suggested that in patients who are candidate for IFN-beta (specially INF-beta 1a) therapy, evaluations are conducted before starting the drug by performing physical examination, special lab tests (RF, anti-CCP, ANA subtypes), and chest X-ray.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

The authors would like to thank the patients for their cooperation.

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