

Induction or aggravation of other immune-mediated disorders by disease-modifying therapy in treatment of multiple sclerosis

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Keywords

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Abstract

Interferon beta (IFN- β) and glatiramer acetate (GA) are the primary therapeutic immunomodulatory agents that interfere with relapsing-remitting multiple sclerosis (RRMS), and the most commonly-used drugs as well. Induction or aggravation of other immune-mediated diseases has been reported following IFN- β administration. We have reviewed the reported cases to notify the treating physicians about these rare adverse events. Although co-morbid autoimmune disorders have been reported in patients with MS, the pro-inflammatory role of disease-modifying drugs, especially IFN- β , could affect and enhance this co-occurrence. Clinical or laboratory autoimmunity histories suggest the use of GA over IFN- β as the treatment of choice.

Introduction

Multiple sclerosis is an inflammatory demyelinating disease of the central nervous

system which, in over 85% of circumstances, initially presents as relapsing neurological disability followed by remission phases.¹⁻³ The disease affects young adults and is more common among women.⁴ There is no cure for MS, and treatment concentrates on treating relapses, diminishing the progression of disability and secondary symptom management. Interferon beta (IFN- β) and glatiramer acetate (GA) are the primary therapeutic immunomodulatory agents that interfere with relapsing-remitting multiple sclerosis (RRMS), and the most commonly-used drugs as well.⁵

Isaacs and Lindenmann,⁶ the discoverers of INF, use this term to explain the antiviral replication properties of these biologically-active substances. It features an acceptable risk profile, is well tolerated, and is effective in decreasing the activity of RRMS. This makes INF the first choice for disease-modifying therapy in MS.

GA is a synthetic polypeptide composed of four amino acids in a mixture resembling myelin basic protein.⁷ Many trials have shown that GA can reduce the relapse rate, disability progression and ameliorate the course of the disease as indicated by

MRI findings.⁸ GA is one of the most prescribed disease-modifying-therapies for multiple sclerosis.⁹

Injection site reaction is the most frequent side effect of IFN and GA. Other side effects include a flu-like syndrome, lymphopenia caused by IFN as well as hepatic failure, hepatitis and elevated liver enzymes. These have been reported for both treatments, although they are more common for IFN.¹⁰ Induction or aggravation of other immune mediated diseases have been reported following INF beta administration. Here we have reviewed the reported cases to notify the treating physicians about these rare adverse events. In many instances continuation of INF following appearance of a new autoimmune disease may aggravate the condition and INF therapy should be promptly stopped to prevent further damage.

Review of case reports

Arthritis: A 37-year-old woman with MS presented with isolated temporomandibular joint arthritis two weeks after starting IFN- β 1a therapy. It resolved completely shortly after IFN discontinuation, and did not recur after switching treatment to GA.¹¹ A 38-year-old woman with RRMS presented with left pre-patellar bursitis with no particular involvement three months after initiation of IFN- β 1a.¹¹ A 29-year-old woman with RRMS presented with severe acute-onset arthralgia, swelling of both knees, and inflammatory synovial fluid reaction three weeks after beginning treatment with IFN- β 1b. The condition disappeared a few days after discontinuation of IFN.¹² Seropositive polyarthritis with high erythrocyte sedimentation rate (ESR), elevated C-reactive protein (CRP), and high rheumatic factor (RF) titer was reported in a 42-year-old woman with RRMS after 30 months of treatment with INF- β 1b.¹² Animal experiments have shown that GA could exacerbate autoimmune arthritis. These findings suggest that GA should be used with great caution in patients with MS and other autoimmune complications.¹³

Systemic lupus erythematosus (SLE): A 43-year-old woman with RRMS under treatment with INF- β 1a was diagnosed with drug-induced SLE (DILE) four weeks after developing synovitis, fever, myalgia, and facial edema. Laboratory test results were positive for antinuclear antibodies (ANA) and anti-double stranded DNA antibody (anti-dsDNA). After discontinuation of INF, the symptoms resolved completely.¹⁴ A diagnosis of cutaneous SLE was confirmed by lesional skin

histopathology from arcuate and polycyclic erythematous scaly plaque on the face, trunk, and upper extremities of a 43-year-old woman with RRMS under treatment with intramuscular (IM) INF-b1a who presented with interface dermatitis.¹⁵ Lupus erythematosus profundus (lupus panniculitis) was diagnosed when a 19-year-old woman with RRMS under treatment with INF- β 1b presented with painful nodules on the face, both shoulders, and upper limbs; a skin biopsy suggested lobular panniculitis.¹⁶ Two cases of lupus-like reaction to INF at the injection site were reported in patients with MS being treated with INF- β 1b.¹⁷ SLE induced by INF-b1 therapy was reported in a 34-year-old patient with RRMS who developed myalgia associated with wrist synovitis with no skin involvement.¹⁸

Psoriasis: Case reports have shown an association between psoriasis and MS. In most cases, the psoriasis presented before MS, and it appeared possible to define co-morbidity, but INF-induced psoriasis was not excluded.¹⁹ Exacerbation of cutaneous psoriasis and psoriatic arthritis has been reported in patients with MS.²⁰⁻²²

Inflammatory bowel disease (IBD): Severe colitis caused by Crohn's disease was reported in a patient with MS treated with IFN- β .²³ Aggravation and development of ulcerations was reported after treatment with IFN- β 1a.^{24,25} A case of rapid-onset ulcerative colitis was reported one week after INF- β 1a therapy. The time of onset of ulcerative colitis was from one day after IFN initiation to one week after discontinuation of the therapy.²⁶ Celiac disease was reported in a 36-year old woman with RRMS after one month of treatment with IFN- β 1b.²⁷ MS concomitant with celiac disease has been recently diagnosed more often than expected.²⁷ A 27-year-old woman with RRMS treated with GA for 2 years presented with abdominal pain, diarrhea, fever, and weight loss. A colonoscopy showed diffuse right-sided colitis and ileitis, and the biopsy was compatible with Crohn's disease. This report emphasized that Crohn's disease might be an adverse event related to treatment with GA.²⁸

Sarcoidosis: IFN- β has been reported to induce sarcoidosis. The duration of IFN- β treatment at the time of diagnosis varied from 8 months to three years. The most common presentation included pulmonary manifestations, although hepatic, and bone involvement. Transbronchial, mediastinal, and paratracheal lymph node and skin biopsies confirmed the

diagnoses.^{29,30} Cutaneous and pulmonary sarcoidosis with erythema nodosum in the lower limbs, breast abscesses, and unilateral pulmonary adenopathy were reported in a 33-year-old woman with RRMS treated with INF- β 1b for 2.5 years.³¹

Susac syndrome: Exacerbation of Susac syndrome retinopathy has been reported in a 23-year-old man misdiagnosed with MS who was treated with IFN- β 1a for 15 months. Two weeks after IFN- β discontinuation, the visual field and fluorescein angiography indicated complete recovery.³²

Scleromyxedema: Scleromyxedema was reported in a 37-year-old woman with RRMS under treatment with IFN- β 1a for three years. The patient recovered after discontinuation of IFN- β 1a treatment.³³

Dermatomyositis: A violaceous skin eruption associated with periorbital edema and proximal muscle weakness presented in a 57-year-old man with RRMS under treatment with IFN- β 1a. Skin biopsy diagnosed it as dermatomyositis. Clinical exacerbation occurred after restarting IFN, despite the initial improvement after discontinuation.³⁴

Systemic sclerosis: MS coexisting with systemic sclerosis has been reported.³⁵⁻⁴¹ In most cases, systemic sclerosis presented before MS, but in one case, the systemic sclerosis presented after pulse therapy and initiation of IFN in a patient with MS. It has been postulated that high-dose steroids may be a potent predictor of renal crisis, and that IFN may aggravate Raynaud's phenomenon, and cause vasospasms and vascular occlusion.⁴²

Vitiligo: A 33-year-old woman with MS developed depigmented patches on the dorsal aspects of her hands after 2 years of treatment with IFN- β 1a which was diagnosed as vitiligo. After discontinuation of IFN in preparation for becoming pregnant, the size of the lesions decreased, and significant recovery was noted after three months.⁴³

Urticarial vasculitis: A 48-year-old woman with RRMS who had been treated for three months with GA showed urticarial-like plaques on her body, face, and extremities which skin biopsy confirmed to be leukocytoclastic vasculitis.⁴⁴

Anaphylaxis: IgE-mediated allergy to INF- β 1a was reported in a 34-year-old woman with MS, 15 minutes after injection. It presented with pruritus, urticarial rash, dyspnea, and hypotension, and required emergency hospitalization.⁴⁵ Similar IgE-mediated anaphylaxis has been reported with GA. Two

patients presented with generalized urticaria, nausea, and hypotension upon the first administration of GA. In a third patient, after six months of GA interruption, an immediate reaction presented with eyelid edema 20 minutes after GA administration.⁴⁶

Autoimmune hepatitis (AIH): Features of autoimmune liver disease and primary biliary cirrhosis after 33 months of administration of IFN- β was reported in a 42-year-old woman with RRMS. The strong positivity of antimitochondrial antibodies was consistent with primary biliary cirrhosis and positive ANA along with elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were suggestive of AIH; but clinical symptoms of acute liver injury did not present.⁴⁷ A 20-year-old woman and a 47-year-old man with RRMS treated with IFN- β 1a presented with elevated liver function tests. The first patient presented with asthenia, progressive jaundice, nausea, and abdominal discomfort along with re-elevated liver function tests despite discontinuation of IFN, and was diagnosed with hepatic encephalopathy. The anti-smooth muscle antibody test was positive. The liver function tests and encephalopathy began to recover after 2 days of corticosteroid therapy. In the second case, 37 months after onset of treatment, elevated transaminase levels presented. After re-introduction of IFN, liver function tests were again elevated. The anti-smooth muscle antibody and antimitochondrial antibody tests were negative, but antithyroperoxidase was positive. A liver biopsy documented severe periportal interface hepatitis. Liver function test results recovered rapidly after corticosteroid therapy.⁴⁸

AIH has also been reported with GA. A patient treated with GA presented with malaise and jaundice along with elevated liver function test after two months of treatment. Although the smooth muscle antibody and antimitochondrial antibody were negative, a significantly elevated titer of 1,280 ANA was detected, and the liver biopsy demonstrated AIH.⁴⁹ A biopsy confirmed AIH after switching treatment to GA. This patient developed jaundice and histologically-documented necrotizing hepatitis. IFN was discontinued and after normalization of liver function tests, GA was initiated; however, liver tests again elevated, and a liver biopsy confirmed AIH. It appears that IFN and GA unmasked AIH.⁵⁰

Autoimmune hematologic disease: A 31-year-old patient with RRMS and a positive Coombs

autoimmune hemolytic anemia result presented with fatigue and dizziness two years after starting treatment with INF- β 1b. After other possibilities were ruled out, an association with INF was suggested.⁵¹ A similar scenario has been reported for a 26-year-old woman with RRMS presenting with anemia, jaundice and fatigue 11 months after treatment with INF- β 1b. After discontinuation of INF- β 1b, the symptoms and abnormal lab test disappeared.⁵²

Thrombotic microangiopathy (TMA)-hemolytic uremic syndrome is an unusual side effect of INF. A 37-year-old woman with RRMS and a 20-year history of treatment with INF presented with hypertension, acute renal failure, subnephrotic proteinuria, nausea, and vomiting. A kidney biopsy showed chronic glomerular microangiopathic lesions and moderate interstitial edema with mild inflammatory cell infiltration. TMA secondary to INF- β 1b was diagnosed. Hematological abnormalities and renal function gradually improved after corticosteroid therapy.

It appears that IFN participates in endothelial disruption by interruption and uncontrolled activation of complex pathways of complement regulation.⁵³ In a 48-year-old woman with RRMS treated with INF- β 1b, hemolytic-uremic syndrome (HUS) was diagnosed after she presented with signs of hypertension, asthenia, and loss of muscular strength in the legs. Creatinine levels increased to 1.8 mg/dl and the platelet (PLT) count decreased to $132 \times 10^9/l$. After lack of significant improvement with corticosteroids, she received eculizumab.⁵⁴

A 52-year-old man presented with TMA caused by ADAMTS13 deficiency after treatment with IFN- β .⁵⁵ Three women with RRMS treated with high doses of INF- β 1a were diagnosed with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) when they presented with blurred vision, cephalalgia, confusion, arterial hypertension, seizures, and focal deficits associated with hemolytic anemia and thrombocytopenia.⁵⁶ A 36-year-old patient with RRMS who had been treated with subcutaneous (SC) INF- β 1a was hospitalized due to progressive dyspnea, systolic dysfunction and pulmonary hypertension. Laboratory tests revealed anemia, thrombocytopenia, and high lactate dehydrogenase (LDH). A blood smear showed schistocytes, and TMA was suspected.⁵⁷ A 53-year-old woman with RRMS who had been treated with SC INF- β 1a for 15 years presented

with an epileptic seizure, headaches, confusion, and arterial hypertension. INF- β -associated TMA was diagnosed because of the symptoms of anemia, thrombocytopenia, and elevated LDH, and the presence of schistocytes.⁵⁸ Two cases of INF-associated TMA have been reported, after clinical and laboratory tests showed results similar to the previous scenarios.⁵⁹

Idiopathic thrombocytopenic purpura could be developed secondary to INF- β , and repeated after changing to other forms of INF. In this circumstances, close monitoring of thrombocytopenia is supposed to be considered.⁶⁰

Nephrologic autoimmune adverse events: Glomerulonephritis and nephrotic syndrome was reported in a 40-year-old woman after a long-term INF treatment. Electron microscopy showed immunoglobulin and complement deposits in kidney biopsy. This report suggests that in spite of this INF rare adverse event, physician is supposed to consider of these clinical rare adverse events.⁶¹

Discussion

A combination of blood-brain barrier (BBB) breakdown and immune cell activation terminate in demyelination and axonal injury in MS. It appears that drugs similar to IFN and GA modulate and reduce this inflammatory process. The precise INF and GA mechanisms of action are unclear. Binding of INF- β to its receptors reduces antigen-presenting cells and T-cell proliferation. Its effect on cytokine and matrix metalloproteinase expression potentiates suppressor functions.⁶² IFN- γ antagonism, stop of immune-cell trafficking across the BBB, autoreactive T-cell apoptosis, and induction of anti-inflammatory cytokine shifts have also been theorized as potential mechanisms of INF- β action.⁶³ Induction of T-helper 17 (Th17) cells which may be involved in MS lesions through downregulation of its inflammatory response pathways is another proposed INF- β mechanism of action.⁶⁴ Some evidence of a pro-inflammatory role of INF- β , including an increase in interleukin-6 (IL-6) production in central nervous system astrocytes,⁶⁵ an anti-apoptotic effect on T-cells,⁶⁶ and activation of antigen-presenting dendritic cells,⁶⁷ have been reported.

Several studies showed that a protective action of GA presenting as a switch from Th1 to Th2 (anti-inflammatory cytokine secretion) type responses.⁶⁸ Apart from the effect of GA on CD4+ T-cells, it could cause CD8+ T-cell upregulation,

and enhance suppressor activity of CD8+ T cells.⁶⁹ GA could affect B-cells, and might affect differentiation and polarization of T-cells. GA-activated B-cells enhance secretion of anti-inflammatory cytokines such as IL-10, IL-4, and transforming growth factor beta (TGF- β).⁷⁰ GA has caused notable elevation in IgG4 antibody titers with low pro-inflammatory effects,⁷¹ and increased IgG1 antibodies levels more than IgG2.⁷² On the other hand, antibodies to GA do not affect GA biological activity, as is similar in INF- β .⁷³ GA enhances a natural killer cell cytolytic effect against autologous and allogeneic mature and immature monocyte-derived dendritic cells.⁷⁴

Of 10 comparative studies, only two reported a higher prevalence of rheumatoid arthritis in patients with MS than in matched control groups; eight studies reported no differences.⁷⁵ It appears that the reports of autoimmune arthritis in patients with MS after treatment with INF- β and GA are more pronounced than autoimmune arthritis co-occurrence with MS. The results are similar for SLE.⁷⁵ The incidence of SLE was not significantly different from expectations for the general population. Of five studies, only one showed an increased incidence of SLE in patients with MS.⁷⁵ The incidence and prevalence studies of psoriasis in the MS population showed no meaningful differences with the general population; only one study reported increased prevalence of psoriasis in MS population when compared with the control population.⁷⁵ Most studies reported increased incidence prevalence of IBD before and after of MS diagnosis when compared with the general population. The incidence and prevalence of autoimmune hematologic disease also showed no significant differences between the MS population and a matched control population.⁷⁵ A Danish study reported the prevalence of dermatomyositis in patients with MS to be zero. Its prevalence in other studies was 0.20% to 0.03%. Studies on the incidence and prevalence of vitiligo and AIH in the MS population found no significant differences with control populations.⁷⁵

A recent systemic review documented no increase in risk of co-morbid autoimmune disease with MS. Fewer than 5% of individuals with MS are affected by co-morbid autoimmune diseases. Shared environmental and genetic susceptibility or both may explain this co-occurrence.⁷⁵ These findings suggest that the pro-inflammatory role of INF- β figures in the presentation of autoimmunity

during treatment. In reality, there is a balance between the pro-inflammatory and anti-inflammatory roles of INF- β . Genetic, and immunological and environmental susceptibility may contribute to the pro-inflammatory role in the appearance of a new autoimmune disease. INF composed of highly immunogenic proteins which act on immune system. Flu-like syndrome after the first hours of INF administration defines as immediate reactions, and probably appears due to cytokines release by immune cells. Delayed hypersensitivity can present between 1-2 hours and 14 days after administration. A serum sickness or Arthus-like reactions might be mediated by soluble immune complexes of INF with its antibodies. This type III hypersensitivity reaction may be the pathophysiology of some autoimmune adverse events of INF such as arthritis.⁷⁶⁻⁷⁸

The case reports suggest that if symptoms, signs, or laboratory findings indicate possible autoimmunity in patients with MS, it is better to select GA for treatment over INF- β . The case reports demonstrate that there are fewer adverse autoimmune events related to GA than INF- β . One reason has been shown to be the immunomodulatory effects of GA on autoimmune diseases. Studies indicate that GA decrease experimental autoimmune uveoretinitis,⁷⁹ and has demonstrated a therapeutic effect on IBD.^{80,81} GA may prevent graft-versus-host disease,⁸² and have a potentially therapeutic effect on type 1 diabetes.⁸³ GA has showed no beneficial effects on a spontaneous model of SLE,⁸⁴ and even exacerbated collagen-induced autoimmune arthritis.¹³

Conclusion

Although co-morbid autoimmune disorders have been reported in patients with MS, the pro-inflammatory role of disease-modifying drugs, especially INF- β , could affect and enhance this co-occurrence. A clinical or laboratory autoimmunity history suggest the use of GA over INF- β as the treatment of choice.

Conflict of Interests

The authors declare no conflict of interest in this study.

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References

- Amato MP, Ponziani G, Bartolozzi ML, Siracusa G. A prospective study on the natural history of multiple sclerosis: clues to the conduct and interpretation of clinical trials. *J Neurol Sci* 1999; 168(2): 96-106.
- Scalfari A, Neuhaus A, Degenhardt A, Rice GP, Muraro PA, Daumer M, et al. The natural history of multiple sclerosis: A geographically based study 10: relapses and long-term disability. *Brain* 2010; 133(Pt 7): 1914-29.
- Bordi I, Umeton R, Ricigliano VA, Annibali V, Mechelli R, Ristori G, et al. A mechanistic, stochastic model helps understand multiple sclerosis course and pathogenesis. *Int J Genomics* 2013; 2013: 910321.
- Koch-Henriksen N. The Danish Multiple Sclerosis Registry: A 50-year follow-up. *Mult Scler* 1999; 5(4): 293-6.
- Annibali V, Mechelli R, Romano S, Buscarinu MC, Fornasiero A, Umeton R, et al. IFN-beta and multiple sclerosis: From etiology to therapy and back. *Cytokine Growth Factor Rev* 2015; 26(2): 221-8.
- Isaacs A, Lindenmann J. Virus interference. I. The interferon. *Proc R Soc Lond B Biol Sci* 1957; 147(927): 258-67.
- Teitelbaum D, Meshorer A, Hirshfeld T, Arnon R, Sela M. Suppression of experimental allergic encephalomyelitis by a synthetic polypeptide. *Eur J Immunol* 1971; 1(4): 242-8.
- Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging--measured disease activity and burden in patients with relapsing multiple sclerosis. *European/Canadian Glatiramer Acetate Study Group. Ann Neurol* 2001; 49(3): 290-7.
- Aharoni R. The mechanism of action of glatiramer acetate in multiple sclerosis and beyond. *Autoimmun Rev* 2013; 12(5): 543-53.
- McGraw CA, Lublin FD. Interferon beta and glatiramer acetate therapy. *Neurotherapeutics* 2013; 10(1): 2-18.
- Strueby L, Nair B, Kirk A, Taylor-Gjevve RM. Arthritis and bursitis in multiple sclerosis patients treated with interferon-beta. *Scand J Rheumatol* 2005; 34(6): 485-8.
- Altintas A, Alici Y, Melikoglu M, Siva A. Arthritis during interferon beta-1b treatment in multiple sclerosis. *Mult Scler* 2002; 8(6): 534-6.
- Zheng B, Switzer K, Marinova E, Zhang J, Han S. Exacerbation of autoimmune arthritis by copolymer-I through promoting type 1 immune response and autoantibody production. *Autoimmunity* 2008; 41(5): 363-71.
- Bonaci-Nikolic B, Jeremic I, Andrejevic S, Sefik-Bukilica M, Stojisavljevic N, Drulovic J. Anti-double stranded DNA and lupus syndrome induced by interferon-beta therapy in a patient with multiple sclerosis. *Lupus* 2009; 18(1): 78-80.
- Nousari HC, Kimyai-Asadi A, Tausk FA. Subacute cutaneous lupus erythematosus associated with interferon beta-1a. *Lancet* 1998; 352(9143): 1825-6.
- Gono T, Matsuda M, Shimojima Y, Kaneko K, Murata H, Ikeda S. Lupus erythematosus profundus (lupus panniculitis) induced by interferon-beta in a multiple sclerosis patient. *J Clin Neurosci* 2007; 14(10): 997-1000.
- Arrue I, Saiz A, Ortiz-Romero PL, Rodriguez-Peralto JL. Lupus-like reaction to interferon at the injection site: report of five cases. *J Cutan Pathol* 2007; 34(Suppl 1): 18-21.
- Bahri DM, Khiari H, Essouri A, Laadhar L, Zarea I, Mrabet A, et al. Systemic lupus erythematosus induced by interferon beta1 therapy in a patient with multiple sclerosis. *Fundam Clin Pharmacol* 2012; 26(2): 210-1.
- Fellner A, Dano M, Regev K, Mosek A, Karni A. Multiple sclerosis is associated with psoriasis. A case-control study. *J Neurol Sci* 2014; 338(1-2): 226-8.
- La ML, Capsoni F. Psoriasis during interferon beta treatment for multiple sclerosis. *Neurol Sci* 2010; 31(3): 337-9.
- Webster GF, Knobler RL, Lublin FD, Kramer EM, Hochman LR. Cutaneous ulcerations and pustular psoriasis flare caused by recombinant interferon beta injections in patients with multiple sclerosis. *J Am Acad Dermatol* 1996; 34(2 Pt 2): 365-7.
- Munschauer FE3rd, Kinkel RP. Managing side effects of interferon-beta in patients with relapsing-remitting multiple sclerosis. *Clin Ther* 1997; 19(5): 883-93.
- Samson M, Audia S, Duchene C, Perinet I, Bielefeld P, Besancenot JF. Crohn's disease during the course of multiple sclerosis: role of interferon-beta therapy. *Rev Med Interne* 2009; 30(9): 816-9. [In French].
- Schott E, Paul F, Wuerfel JT, Zipp F, Rudolph B, Wiedenmann B, et al. Development of ulcerative colitis in a patient with multiple sclerosis following treatment with interferon beta 1a. *World J Gastroenterol* 2007; 13(26): 3638-40.
- Rodrigues S, Magro F, Soares J, Nunes AC, Lopes S, Marques M, et al. Case series: ulcerative colitis, multiple sclerosis, and interferon-beta 1a. *Inflamm Bowel Dis* 2010; 16(12): 2001-3.
- Tuna Y, Basar O, Dikici H, Koklu S. Rapid onset of ulcerative colitis after treatment with interferon beta1a in a patient with multiple sclerosis. *J Crohns Colitis* 2011; 5(1): 75-6.
- Fernandez-Salazar L, Alvarez-Quinones M, Gonzalez Hernandez JM, Fraile A, Mayor E, Arranz E, et al. IFN beta 1b induced celiac disease. *Scand J Gastroenterol* 2011; 46(12): 1525-6.
- Charach G, Grosskopf I, Weintraub M. Development of Crohn's disease in a patient with multiple sclerosis treated with copaxone. *Digestion* 2008; 77(3-4): 198-200.
- Chakravarty SD, Harris ME, Schreiner AM, Crow MK. Sarcoidosis triggered by interferon-Beta treatment of multiple sclerosis: a case report and focused literature review. *Semin Arthritis Rheum* 2012; 42(2): 206-12.
- Petousi N, Thomas EC. Interferon-beta-induced pulmonary sarcoidosis in a 30-year-old woman treated for multiple sclerosis: A case report. *J Med Case Rep* 2012; 6: 344.
- Sahraian MA, Moghadasi AN, Owji M, Maboudi M, Kosari F, McGee JC, et al. Cutaneous and pulmonary sarcoidosis following treatment of multiple sclerosis with interferon-beta-1b: A case report. *J Med Case Rep* 2013; 7: 270.
- Laird PW, Newman NJ, Yeh S. Exacerbation of Susac syndrome retinopathy by interferon Beta-1a. *Arch Ophthalmol* 2012; 130(6): 804-6.
- Kumar N, Rodriguez M. Scleromyxedema in a patient with multiple sclerosis and monoclonal gammopathy on interferon beta-1a. *Mult Scler* 2004; 10(1): 85-6.
- Somani AK, Swick AR, Cooper KD, McCormick TS. Severe dermatomyositis triggered by interferon beta-1a therapy and associated with enhanced type I interferon signaling. *Arch Dermatol* 2008; 144(10): 1341-9.
- Trostle DC, Helfrich D, Medsger TA, Jr. Systemic sclerosis (scleroderma) and multiple sclerosis. *Arthritis Rheum* 1986; 29(1): 124-7.
- Igarashi A, Imakado S, Ishibashi Y, Takehara K. Systemic sclerosis associated with multiple sclerosis. *Arch Dermatol* 1989; 125(8): 1145.
- Jawad SH, Askari A, Ward AB. Case history of a patient with multiple sclerosis and scleroderma. *Br J Rheumatol* 1997;

- 36(4): 502-3.
38. Spadaro A, Sensi F, Barrella M, Francia A. Systemic sclerosis and multiple sclerosis. *J Neurol* 1999; 246(6): 497-9.
 39. Chroni E, Paschalis C, Stergiou T, Vlahanastasi C, Andonopoulos AP. Multiple sclerosis in the course of systemic sclerosis. *Ann Rheum Dis* 2002; 61(2): 188.
 40. Gorodkin R, Leahy B, Neary D, Herrick AL. Coexistence of systemic sclerosis and multiple sclerosis. *J Neurol* 2004; 251(12): 1524-5.
 41. Pelidou SH, Tsifetaki N, Giannopoulos S, Deretzi G, Voulgari P, Kyritsis A. Multiple sclerosis associated with systemic sclerosis. *Rheumatol Int* 2007; 27(8): 771-3.
 42. Airo' P, Scarsi M, Rossi M, Mondini M. Onset and enhancement of systemic sclerosis after treatments for multiple sclerosis. *Rheumatol Int* 2008; 28(7): 703-7.
 43. Kocer B, Nazliel B, Oztas M, Batur HZ. Vitiligo and multiple sclerosis in a patient treated with interferon beta-1a: A case report. *Eur J Neurol* 2009; 16(4): e78-e79.
 44. Cicek D, Kandi B, Oguz S, Cobanoglu B, Bulut S, Saral Y. An urticarial vasculitis case induced by glatiramer acetate. *J Dermatolog Treat* 2008; 19(5): 305-7.
 45. Cortellini G, Amadori A, Comandini T, Corvetta A. Interferon beta 1a anaphylaxis, a case report. Standardization of non-irritating concentration for allergy skin tests. *Eur Ann Allergy Clin Immunol* 2013; 45(5): 181-2.
 46. Corominas M, Postigo I, Cardona V, Leonart R, Romero-Pinel L, Martinez J. IgE-mediated allergic reactions after the first administration of glatiramer acetate in patients with multiple sclerosis. *Int Arch Allergy Immunol* 2014; 165(4): 244-6.
 47. Kowalec K, Yoshida EM, Traboulee A, Carleton B, Tremlett H. Suspected autoimmune hepatitis and primary biliary cirrhosis unmasked by interferon-beta in a multiple sclerosis patient. *Mult Scler Relat Disord* 2013; 2(1): 57-9.
 48. Villamil A, Mullen E, Casciato P, Gadano A. Interferon beta 1a-induced severe autoimmune hepatitis in patients with multiple sclerosis: report of two cases and review of the literature. *Ann Hepatol* 2015; 14(2): 273-80.
 49. Neumann H, Csepregi A, Sailer M, Malfetheriner P. Glatiramer acetate induced acute exacerbation of autoimmune hepatitis in a patient with multiple sclerosis. *J Neurol* 2007; 254(6): 816-7.
 50. von K, V, Lohse AW, Schramm C. Unmasking autoimmune hepatitis under immunomodulatory treatment of multiple sclerosis--not only beta interferon. *Am J Gastroenterol* 2008; 103(8): 2147-8.
 51. Alanoglu G, Kilbas S, Arslan C, Senol A, Kutluhan S. Autoimmune hemolytic anemia during interferon-beta-I b treatment for multiple sclerosis. *Mult Scler* 2007; 13(5): 683-5.
 52. Saeedi M, Foroughipour M, Sasannezhad P, Shoebi A. Interferon-beta-1b induced autoimmune hemolytic anemia in a patient with MS: A case report. *Iran Red Crescent Med J* 2011; 13(3): 210-2.
 53. Olea T, Diaz-Mancebo R, Picazo ML, Martinez-Ara J, Robles A, Selgas R. Thrombotic microangiopathy associated with use of interferon-beta. *Int J Nephrol Renovasc Dis* 2012; 5: 97-100.
 54. Milan MS, Virzi GM, Gastaldon F, Proglino M, Brocca A, Ronco C. Brief review and a clinical case of hemolytic uremic syndrome associated with interferon beta treatment. *Blood Purif* 2017; 43(1-3): 136-43.
 55. Orvain C, Augusto JF, Besson V, Marc G, Coppo P, Subra JF, et al. Thrombotic microangiopathy due to acquired ADAMTS13 deficiency in a patient receiving interferon-beta treatment for multiple sclerosis. *Int Urol Nephrol* 2014; 46(1): 239-42.
 56. Larochele C, Grand'maison F, Bernier GP, Latour M, Cailhier JF, Prat A. Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome in relapsing-remitting multiple sclerosis patients on high-dose interferon beta. *Mult Scler* 2014; 20(13): 1783-7.
 57. Azkune C, I, Sanchez Menoyo JL, Ruiz OJ, Garcia Monco JC, Etxeguren U, I. Case report of thrombotic microangiopathy associated with subcutaneous interferon beta-1a: an emerging complication? *Neurologia* 2016; 31(7): 508-9.
 58. Gerischer LM, Siebert E, Janke O, Jungehulsing GJ, Ruprecht K. Favorable outcome of interferon-beta associated thrombotic microangiopathy following treatment with corticosteroids, plasma exchange and rituximab: A case report. *Mult Scler Relat Disord* 2016; 10: 63-5.
 59. Vosoughi R, Marriott JJ. Thrombotic microangiopathy in Interferon Beta treated multiple sclerosis patients: Review of literature and report of two new cases. *Mult Scler Relat Disord* 2014; 3(3): 321-5.
 60. Sahraian MA, Eshaghi A. Concomitant multiple sclerosis and idiopathic thrombocytopenic purpura. *Eur J Neurol* 2010; 17(8): e62-e63.
 61. Wallbach M, Grone HJ, Kitz B, Muller GA, Koziolok MJ. Nephrotic syndrome in a multiple sclerosis patient receiving long-term interferon beta therapy. *Am J Kidney Dis* 2013; 61(5): 786-9.
 62. Markowitz CE. Interferon-beta: Mechanism of action and dosing issues. *Neurology* 2007; 68(24 Suppl 4): S8-11.
 63. Dhib-Jalbut S, Marks S. Interferon-beta mechanisms of action in multiple sclerosis. *Neurology* 2010; 74(Suppl 1): S17-S24.
 64. Hartung HP, Steinman L, Goodin DS, Comi G, Cook S, Filippi M, et al. Interleukin 17F level and interferon beta response in patients with multiple sclerosis. *JAMA Neurol* 2013; 70(8): 1017-21.
 65. Okada K, Kuroda E, Yoshida Y, Yamashita U, Suzumura A, Tsuji S. Effects of interferon- β on the cytokine production of astrocytes. *J Neuroimmunol* 2005; 159(1): 48-54.
 66. Pilling D, Akbar AN, Girdlestone J, Orteu CH, Borthwick NJ, Amft N, et al. Interferon-beta mediates stromal cell rescue of T cells from apoptosis. *Eur J Immunol* 1999; 29(3): 1041-50.
 67. Tak PP. IFN-beta in rheumatoid arthritis. *Front Biosci* 2004; 9: 3242-7.
 68. Miller A, Shapiro S, Gershtein R, Kinarty A, Rawashdeh H, Honigman S, et al. Treatment of multiple sclerosis with copolymer-1 (Copaxone): Implicating mechanisms of Th1 to Th2/Th3 immune-deviation. *J Neuroimmunol* 1998; 92(1-2): 113-21.
 69. Tennakoon DK, Mehta RS, Ortega SB, Bhoj V, Racke MK, Karandikar NJ. Therapeutic induction of regulatory, cytotoxic CD8+ T cells in multiple sclerosis. *J Immunol* 2006; 176(11): 7119-29.
 70. Kala M, Miravalle A, Vollmer T. Recent insights into the mechanism of action of glatiramer acetate. *J Neuroimmunol* 2011; 235(1-2): 9-17.
 71. Basile E, Gibbs E, Aziz T, Oger J. During 3 years treatment of primary progressive multiple sclerosis with glatiramer acetate, specific antibodies switch from IgG1 to IgG4. *J Neuroimmunol* 2006; 177(1-2): 161-6.
 72. Brenner T, Arnon R, Sela M, Abramsky O, Meiner Z, Riven-Kreitman R, et al. Humoral and cellular immune responses to Copolymer 1 in multiple sclerosis patients treated with Copaxone. *J Neuroimmunol* 2001; 115(1-2): 152-60.
 73. Teitelbaum D, Brenner T, Abramsky O, Aharoni R, Sela M, Arnon R. Antibodies to glatiramer acetate do not interfere with its biological functions and therapeutic efficacy. *Mult Scler* 2003; 9(6): 592-9.
 74. Sand KL, Knudsen E, Rolin J, Al-Falahi Y, Maghazachi AA. Modulation of natural killer cell cytotoxicity and cytokine release by the drug glatiramer acetate. *Cell Mol Life Sci* 2009; 66(8): 1446-56.
 75. Marrie RA, Reider N, Cohen J, Stuve O, Sorensen PS, Cutter G, et al. A systematic review of the incidence and prevalence of autoimmune disease in multiple sclerosis. *Mult Scler* 2015; 21(3): 282-93.
 76. Baldo BA, Pham NH. Drug allergy: Clinical aspects, diagnosis, mechanisms, structure-activity relationships. *New York, NY: Springer; 2013. P. 15-35.*
 77. Corominas M, Gastaminza G, Lobera T. Hypersensitivity reactions to biological drugs. *J Investig Allergol Clin Immunol* 2014; 24(4): 212-25.
 78. Cohen BA, Oger J, Gagnon A, Giovannoni G. The implications of immunogenicity for protein-based multiple sclerosis therapies. *J Neurol Sci* 2008; 275(1-2): 7-17.
 79. Zhang M, Chan CC, Vistica B, Hung V,

- Wiggert B, Gery I. Copolymer 1 inhibits experimental autoimmune uveoretinitis. *J Neuroimmunol* 2000; 103(2): 189-94.
80. Aharoni R, Kayhan B, Brenner O, Domev H, Labunskay G, Arnon R. Immunomodulatory therapeutic effect of glatiramer acetate on several murine models of inflammatory bowel disease. *J Pharmacol Exp Ther* 2006; 318(1): 68-78.
81. Aharoni R, Sonogo H, Brenner O, Eilam R, Arnon R. The therapeutic effect of glatiramer acetate in a murine model of inflammatory bowel disease is mediated by anti-inflammatory T-cells. *Immunol Lett* 2007; 112(2): 110-9.
82. Aharoni R, Teitelbaum D, Arnon R, Sela M. Copolymer 1 inhibits manifestations of graft rejection. *Transplantation* 2001; 72(4): 598-605.
83. Cui G, Zhang Y, Gong Z, Zhang JZ, Zang YQ. Induction of CD4+CD25+Foxp3+ regulatory T cell response by glatiramer acetate in type 1 diabetes. *Cell Res* 2009; 19(5): 574-83.
84. Borel P, Benkhoucha M, Weber MS, Zamvil SS, Santiago-Raber ML, Lalive PH. Glatiramer acetate treatment does not modify the clinical course of (NZB x BXSB)F1 lupus murine model. *Int Immunol* 2008; 20(10): 1313-9.