

*Short Communication***Rapid exacerbation of multiple sclerosis following the initiation of interferon- $\beta$ : report of nine cases***Masoud Etemadifar,<sup>1</sup> Amir Hossein Sarrami<sup>2</sup>***Abstract**

**BACKGROUND:** Interferon- $\beta$  (IFN- $\beta$ ) is an effective drug in multiple sclerosis (MS) but it may cause acute exacerbation of MS following the initiation of treatment. This study evaluated patients with rapid exacerbation of multiple sclerosis (REMS) following the initiation of IFN- $\beta$ .

**METHODS:** We retrospectively reviewed the clinical records of 2350 patients with multiple sclerosis who started treatment with IFN- $\beta$  and were registered with Isfahan MS Society (IMSS). Patients with rapid exacerbation of multiple sclerosis within 24 hours after initiation of IFN- $\beta$  treatment were selected and their demographic and clinical data were extracted.

**RESULTS:** We identified nine patients with rapid exacerbation of multiple sclerosis following the initiation of IFN- $\beta$ . Their mean age at the time of treatment with IFN- $\beta$  was  $37.3 \pm 6.28$  years. Seven patients had rapid exacerbation of multiple sclerosis after initiation of IFN- $\beta$  1a and two patients after IFN- $\beta$  1b. The course of disease in all of these patients was relapsing-remitting. However, all had converted into secondary progression within the first year after occurrence of rapid exacerbation of multiple sclerosis following the initiation of IFN- $\beta$ .

**CONCLUSIONS:** This study may indicate that the effects of IFN- $\beta$  are not purely anti-inflammatory and a small percentage of MS patients experience rapid exacerbation of multiple sclerosis following the initiation of IFN- $\beta$ . Future studies are needed to validate our findings.

**KEYWORDS:** Multiple Sclerosis, Interferon- $\beta$ , Rapid Exacerbation, Central Nervous System.

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Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system, resulting in clinical relapses and disability. Interferon- $\beta$  (IFN- $\beta$ ) is an effective immunomodulatory agent that has been used to reduce relapse rate and to delay disability progression in patients with relapsing-remitting MS.<sup>1</sup> On the other hand, the effects of IFN- $\beta$  may be occasionally desirable. IFN- $\beta$  may induce the onset or exacerbation of some autoimmune diseases, such as systemic lupus erythematosus, dermatomyositis, ulcerative colitis and autoimmune hyperthyroidism.<sup>2-6</sup> Acute exacerbation of demyelinating diseases is a possible adverse effect of IFN- $\beta$ , recorded occasionally in the literature.<sup>7-10</sup>

This study was designed to identify patients

with rapid exacerbation of MS (REMS) following the initiation of IFN- $\beta$  and to study their demographic and clinical characteristics. Here, we present our findings on nine patients with REMS following the initiation of IFN- $\beta$  and try to provide new insights regarding clinical aspects surrounding this paradoxical response to IFN- $\beta$  in patients with MS.

**Methods**

We retrospectively reviewed the clinical records of 2350 MS patients who started treatment with IFN- $\beta$  (IFN- $\beta$  1a and IFN- $\beta$  1b) and were registered with Isfahan MS Society (IMSS). Details of the database were published before.<sup>11</sup> Those with REMS within 24 hours after initiation of IFN- $\beta$  treatment were selected. REMS following

1- Professor, Department of Neurology, Isfahan University of Medical Sciences, Isfahan, Iran.

2- Student of Medicine, Isfahan Neurosciences Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.

Corresponding author: Amir Hossein Sarrami

E-mail: a\_sarrami@edc.mui.ac.ir

the initiation of IFN- $\beta$  was defined as a new functionally disabling neurological symptom which appeared within 24 hours of first injection of IFN- $\beta$ , associated with a disability of at least one system which lasted more than 24 hours and led to cessation of IFN- $\beta$  and administration with corticosteroid. Among these patients, each case that had any evidence meeting the criteria of neuromyelitis optica (NMO)<sup>12</sup> would be excluded. Patients with REMS following the initiation of IFN- $\beta$  were assessed for demographic and clinical data.

## Results

We identified ten patients with REMS following the initiation of IFN- $\beta$ . One of them met the criteria of NMO, so was excluded. Table 1 shows demographic and clinical characteristics of remained nine patients. Five patients were males and four patients were females. Their ages at the time of treatment with IFN- $\beta$  ranged from 26 to 46 years, with the mean of  $37.3 \pm 6.28$  years. None of these patients had any underlying disease. Duration of MS before initiation of

IFN- $\beta$  in these patients ranged from 1 to 10 years, with the mean of  $5.4 \pm 3.2$  years.

Seven patients had REMS following the initiation of IFN- $\beta$  1a and two patients after IFN- $\beta$  1b. Despite treatment of acute relapse with high dose corticosteroids, there were residual disability left, thus treatment with IFN- $\beta$  was switched to more aggressive therapeutic options in order to control the progressing disease course. The course of MS in all these nine patients was relapsing-remitting, but they had converted into secondary progressive within the first year after occurrence of REMS following the initiation of IFN- $\beta$ . Lower limb weakness and ataxia were two more frequent presentations which were occurred in 66.6% and 44.4% of the patients, respectively.

New REMS plaques detected by magnetic resonance imaging (MRI) following the initiation of IFN- $\beta$  were as follows: new periventricular plaques in 88.8% of subjects, juxtacortical plaques in 55.5%, spinal plaques in 55.5%, brainstem plaques in 22.2% and cerebellar plaques in 11.1% of patients.

**Table 1.** Patient's demographic and clinical characteristics

Patient	Sex	Age	Duration of MS before initiation of IFN- $\beta$ (years)	Last EDSS before initiation of IFN- $\beta$	Treatment (Type of IFN- $\beta$ )	Onset symptom	New MRI plaques after REMS	Maintenance treatment after REMS	Progression of MS after REMS	Duration of MS in our survey (years)	Last EDSS in our survey
1	M	43	4	2	IFN- $\beta$ 1b	Lower limb weakness	Periventricular, juxtacortical, thoracic	Methotrexate	Secondary progressive	7	4.5
2	M	40	1	2	IFN- $\beta$ 1a	Ataxia	Periventricular, juxtacortical, cervical	Cyclophosphamide pulse (monthly)	Secondary progressive	9	9
3	M	34	6	2.5	IFN- $\beta$ 1a	lower limb weakness	Periventricular, juxtacortical, cervical	Azathioprine	Secondary progressive	1	4
4	M	43	10	2.5	IFN- $\beta$ 1a	Ataxia & left hemiparesis	Periventricular, cervical	Azathioprine	Secondary progressive	1	4.5
5	M	26	7	3.5	IFN- $\beta$ 1a	Ataxia & lower limb weakness	Periventricular, juxtacortical	Mitoxantrone	Secondary progressive	3	5.5
6	F	46	9	2.5	IFN- $\beta$ 1a	Lower limb weakness	Periventricular	Methotrexate	Secondary progressive	1	4.5
7	F	33	1	1.5	IFN- $\beta$ 1a	Lower limb weakness	Cerebellar, brainstem, cervical	Mitoxantrone	Secondary progressive	2	6.5
8	F	37	4	3	IFN- $\beta$ 1b	Ataxia	Periventricular, brainstem, cervical	Mitoxantrone	Secondary progressive	3	5.5
9	F	34	7	2.5	IFN- $\beta$ 1a	Lower limb weakness	Periventricular, juxtacortical	Methotrexate	Secondary progressive	3	5

EDSS: Expanded Disability Status Scale

M: Male

F: Female

## Discussion

Rapid exacerbations of autoimmune diseases in the initiation or during the treatment with IFN- $\beta$ <sup>2-6</sup> suggest that IFN- $\beta$  acts not only as an immunomodulatory drug but also as a potential autoimmunity stimulating agent. Generally, treatment with IFN- $\beta$  is associated with diverse responses in MS patients, probably due to genetics or disease heterogeneity.<sup>1,13</sup> REMS following the initiation of IFN- $\beta$  is a paradoxical response which indicates an accelerated worsening of the disease as a result of treatment.

Rudge et al. after a small double-blind study on patients with IFN- $\beta$  1a suggested that there may be worsening of the disease course during the first months after initiation of IFN- $\beta$  1a.<sup>8</sup> Shimizu et al. reported 7 patients who showed severe exacerbations of neuromyelitis optica between 2 to 60 days after the initiation of IFN- $\beta$  1b and suggested that IFN- $\beta$  1b may trigger the exacerbation in some patients with the neuromyelitis optica.<sup>9</sup>

Although these phenomena and also exacerbations of other autoimmune diseases mainly occur some months after the onset of treatment<sup>5</sup> but they may also present within first hours of IFN- $\beta$  injection.<sup>2-4</sup> After a single dose injection of IFN- $\beta$ , serum levels of the drug peak at 12-16 hours.<sup>1</sup> The gene expression of myxovirus resistance protein A (MxA) which is a sensitive measure of the biological response to IFN- $\beta$ , up-regulates within 3 hours of IFN- $\beta$  injection, and peaks at 12 hours after injection.<sup>14</sup> Hence, REMS following the initiation of IFN- $\beta$  is not incompatible with the pharmacokinetics and reported biological activity of the drug.

For proper explanation of REMS following the initiation of IFN- $\beta$ , we should consider the important role of IFN- $\gamma$ . IFN- $\gamma$  is a T helper cytokine which has a significant increase during exacerbation of MS.<sup>7</sup> Moreover, IFN- $\gamma$  administration may also trigger the exacerbation of MS.<sup>15</sup> Interestingly, treatment with IFN- $\beta$  may cause transient increase in the number of IFN- $\gamma$  secreting cells.<sup>7,8</sup> In support of this, there are evidences that *in vitro* addition of IFN- $\beta$  to naive lymphocytes lead to up-regulation of IFN- $\gamma$  secretion.<sup>15,16</sup>

However, rapid pro-inflammatory effects of IFN- $\beta$  are not only relevant to IFN- $\gamma$  production. Nakatsuji et al. documented the significant increase in IL-6 level at first hours after IFN- $\beta$  administration which was associated with progression of disability.<sup>17</sup> In addition, Boylan et al. documented a transient elevation in four serum pro-inflammatory biomarkers included of serum amyloid A protein, C reactive protein,  $\beta$ 2-microglobulin and neopterin following IFN- $\beta$  1a administration which can induce inflammatory process in patients with MS.<sup>18</sup> Taken together, these evidences suggest that IFN- $\beta$  in addition to anti-inflammatory properties might even exert transient pro-inflammatory effect.<sup>18</sup> However, how these pro-inflammatory effects of IFN- $\beta$  just in some patients would initiate a neurological dysfunction is uncertain.

Despite all these evidences, one could argue that these neurological dysfunctions may also reflect the natural course of MS, unrelated to treatment with IFN- $\beta$ . Moreover, in such a large group, REMS after initiation of IFN- $\beta$  may be developed as a result of chance. Definitive answer to this dilemma needs large-scale clinical trials; however, considering the exacerbations of further autoimmune events after administration of IFN- $\beta$ ,<sup>2-6</sup> occurrence of this reaction in MS patients may not be impossible. Our study had also the limitations of retrospective studies. It is probable that some of the patients with REMS following the initiation of IFN- $\beta$  might be missed or not be recorded.

As all these nine patients converted to secondary progressive MS in short time, it should be considered that patients with REMS following the initiation of IFN- $\beta$  have poor prognosis. Therefore, in order to delay disability progression, we should initiate a competent immunosuppressive drug for them as soon as possible.

## Conclusion

We presented our findings on nine patients with REMS following the initiation of IFN- $\beta$ . This study may indicate that the effects of IFN- $\beta$  are not purely anti-inflammatory and a small percentage of MS patients experience REMS

following the initiation of IFN- $\beta$ . Future studies are needed to find the exact causes of this paradoxical response.

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### Conflict of Interests

Authors have no conflict of interests.

### Authors' Contributions

M E participated in evaluation of patients and writing the article. AHS participated in collecting the data and writing the article.

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