

Efficacy of doxycycline as add-on to interferon beta-1a in treatment of multiple sclerosis

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Mehrdokht Mazdeh¹, Ahmad Reza Mobaien²

¹Department of Neurology, Farshchian Hospital, Hamedan University of Medical Sciences, Hamedan, Iran

²Department of Infectious Diseases and Tropical Medicine, Valiasr Hospital, Zanjan University of Medical Sciences, Zanjan, Iran

Keywords

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Abstract

Background: Available evidence shows that tetracycline family has cellular and molecular mechanisms to protect neurons and oligodendrocytes by modulating matrix metalloproteinases. We tried to compare the effectiveness of intramuscular and subcutaneous interferon beta-1a (INF- β 1a) in combination with oral doxycycline among patient with relapsing remitting multiple sclerosis (RRMS) and secondary progressive multiple sclerosis (SPMS).

Methods: A double-blind clinical trial study was conducted at Hamedan University of Medical and Health Sciences in Iran. Sixty patients with definite diagnosis of RRMS or SPMS were treated with doxycycline and 44 μ g subcutaneous INF- β 1a three times a week or 30 μ g intramuscular INF- β 1a once a week for six months. Neurologic examinations were performed monthly until the end of the treatment. Changes in expanded disability status scale (EDSS) scores, brain magnetic resonance images (MRIs), and frequency of receiving corticosteroid pulse were evaluated before and after the treatment.

Results: Women constituted 88.3% of the participants. The mean age of the patients was 32 years. The mean EDSS

scores reduced from 4.5 to 3.0. Based on the frequency of receiving corticosteroid pulse, relapse rate decreased from 3.2 to 0.8. MRI showed that the number, volume, and activity of the lesions decreased among 13.3% of the participants, increased among 15%, and remained persistent among 71.7%.

Conclusion: Combination of doxycycline and IFN- β 1a can decrease relapse rate and improve EDSS scores in patients with RRMS and SPMS. However, it does not affect MRI changes. Further controlled clinical trials on greater number of patients with MS are needed to evaluate the efficacy of combination therapy.

Introduction

Multiple sclerosis (MS) is an inflammatory autoimmune disease of central nervous system (CNS) and spinal cord. Plaques of white matter, caused by demyelination and loss of axon in this area, are characteristics of MS.¹ Exact pathogenesis of MS is not well understood. However, various theories including immune defect, genetic capacity, infectious diseases, mental stress, biochemical agents, diet, vitamin deficiency, and allergic reaction have been suggested.²

There are 5-10 cycles of hidden action in the course of MS that can be uncovered with magnetic

resonance imaging (MRI). In addition, the disease manifests with clinical signs.³ The most important factor in determination of disease process is relapse rate. Relapse is defined as acute or subacute clinical disorders that usually occur days to weeks after a cycle of recovery. Nearly 15% of the patients do not experience relapse.⁴ Recurrent relapses in the first two years, advanced progress from beginning, male gender, and cerebellar or motor disorders can predict a poorer clinical course of the disease. On the other hand, female gender, dominant sensorial symptoms, and optic neuritis may have better prognosis.⁵ Based on disease pattern and progression, MS is categorized as relapsing-remitting MS (RPMS), primary-progressive MS (PPMS), secondary-progressive MS (SPMS), and progressive-relapsing MS (PRMS). Nowadays, the most common scales to assess disability of patients with MS is Kurtzke expanded disability status scale (EDSS).⁴

The aim of treatment in patients with MS is to regulate the clinical course and reduce the complications of the disease. While acute attacks are usually treated with corticosteroid, interferon beta-1a (IFN- β 1a) is reserved for the regulation of the clinical course. Probable mechanisms for MS treatment with IFN- β 1a include the inhibition of adhesion, synthesis, and transfer of matrix metalloproteinases (MMPs) and antigen blocking.³

There is accumulating evidence that MMPs play a key role in the pathogenesis of many neuroinflammatory diseases. MMPs can be subdivided into collagenase, gelatinase A and B, stromelysins-1, and inhibitors like plasminogen activator inhibitor-1 (PAI-1). The activity of other MMPs is closely regulated by tissue inhibitors of metalloproteinase.⁶ MMP-9 is a well-known gelatinase B which is the most known protease.^{7,8} The roles of MMP-9 are disruption of blood-brain barrier (BBB), prevention of T cell migration into the CNS, and myelin destruction.^{9,10} Increased MMP-9 serum levels and decreased tissue inhibitor of metalloproteinase-1 (TIMP-1) serum levels provoke BBB rupture and T cell entrance to the nervous system which result in the formation of new lesions.^{6,11,12}

Nearly all previous studies have focused on T cell penetration to the nervous system. However, the role of B-cells in the nervous system cannot be overlooked. In fact, although T cells appear in the beginning of inflammation, there will be no demyelination in the absence of B-cells.¹³ Treatment with IFN- β 1a decreases MMP mRNA. It thus reduces T cell penetration to the CNS and cures the disease.^{11,14}

Boz et al. showed that body can rebalance MMP-9/TIMP-1 after six months of treatment with IFN- β 1a.⁹ Milanese et al. reported 20.5% decline in disability

progression following beta interferon therapy.¹⁵ Multiple studies in many regions have reported that the use of beta interferon in MS for two years significantly reduced MRI changes, clinical relapses, and yearly attacks.¹⁶ A systematic review article on 21 studies from 1993 to 2001 reported IFN- β 1a (Rebif, Avonex) to be significantly more effective than interferon beta-1b (IFN- β 1b; Betaferon) in reducing the disability course of MS.¹⁷

In recent years, neuroprotective effects of tetracycline have been clearly shown in animal models with acute or chronic neurodegeneration.¹⁸ This recent finding presented a new point of view about the cellular and molecular mechanisms through which tetracycline protects neurons and oligodendrocytes. However, only the second generation of tetracyclines is usable since they contain minocycline and doxycycline which are semisynthetic. Among the characteristics of these drugs are passing BBB easily and inhibiting MMP.¹⁹ Doxycycline is absorbed rapidly and completely from the gastrointestinal tract. Since it is lipid soluble, it highly penetrates to cerebrospinal fluid (CSF). Doxycycline is tolerated much better than minocycline and is a strong MMP inhibitor. Since MMP-9 can cleavage and deactivate IFN- β , it can cause relapse during treatment. Therefore, relapse reduction can be expected following treatment with doxycycline.²⁰

Minagar et al. investigated combined therapy with IFN- β 1a and doxycycline in 15 patients with RRMS. Individuals with RRMS taking IFN- β 1a with breakthrough disease activity took 100 mg doxycycline daily for four months. During the study, only one patient experienced a relapse and adverse effects were little. There were no unexpected or synergistic adverse effects associated with combination therapy. The authors thus concluded that a combination of intramuscular IFN- β 1a and oral doxycycline treatment is effective, safe, and well tolerated.²⁰

Until now, evidence about latest treatments to prevent the progressive course of MS has been contrasting. Therefore, we designed a trial to evaluate the effectiveness of a combination of doxycycline and IFN- β 1a in treatment of MS.

Materials and Methods

On the base of Poser et al.²¹ and McDonald et al.²² diagnostic criteria, 14-51 year-old patients with definite diagnosis of MS were enrolled. Patients were included if they had RRMS or SPMS and had not responded to therapy (at least two relapses or one point increase on the EDSS before during the past year). All subjects had EDSS scores of 0-5.5 and could walk.

Relapse was defined as appearance or recrudescence of one or two neurological defects without fever which last for at least 24 hours with a 30-day interval between the two attacks. SPMS was defined as a deteriorative course and independent relapse that lasted for at least six months following one course of RRMS. Inclusion criteria for SPMS patients was EDSS scores less than 5.5, more than two relapses in the history of patients, and one point increase on the EDSS during the past two years.

Patients in both groups were excluded in case of receiving corticosteroid therapy during the three months before the study, receiving immunosuppressive therapy with cytotoxic agents, pregnancy, breastfeeding, or intolerance or sensitivity to doxycycline.

Demographic and clinical characteristics of the participants were recorded in a questionnaire after obtaining informed consents from all 60 patients (7 men and 53 women). The subjects received 44 µg subcutaneous IFN-β1a (Rebif) three times a week or 30 µgintramuscular IFN-β1a (Avonex or Cinnovex) once a week. Both methods were combined with 100 mg doxycycline once daily for six months. Patient outcomes were evaluated with relapse rate on the basis of corticosteroid pulse and EDSS point changes.

Changes and deterioration in clinical disability after of six months of treatment were assessed by brain MRI before and after therapy. Standard brain MRI was taken from each patient with a 1.5-T scanner (imaging protocol: T1 sagittal, T1 and T2 axial, fluid attenuated inversion recovery images). A neuroradiologist who was blinded to patients' clinical data counted the number of contrast-enhancing lesions on brain MRIs.

Results

Sixty patients with RRMS or SPMS who were taking IFN-β1a and had experienced breakthrough disease activity were enrolled. The mean age of participants was 32.0 ± 1.8 years. Women constituted 88.3% of the population. The mean disease duration was 51.0 ± 41.2 months. The mean EDSS scores before and after treatment were 4.5 ± 0.9 and 3.0 ± 1.3, respectively. Based on corticosteroid pulse, the mean relapse rates before and after treatment were 3.2 ± 3.3 and 0.8 ± 0.8, respectively (Tables 1 and 2).

Table 1. Frequency of corticosteroid pulse therapy in patients before and after combination therapy with interferon beta-1a and doxycycline

Steroid pulse	Before therapy	After therapy
0-3	35 (58.3)	58 (96.7)
4-5	15 (24.9)	2 (3.3)
6-10	8 (13.3)	0 (0)
11-19	2 (3.5)	0 (0)

Values are expressed as n (%).

Table 2. Expanded disability status scale (EDSS) scores and steroid pulse in patients before and after combination therapy with interferon beta-1a and doxycycline

Clinical evaluation	Before therapy	After therapy	P
EDSS score	4.5 ± 0.9	3.0 ± 1.3	< 0.001
Steroid pulse	3.2 ± 3.3	0.8 ± 0.8	< 0.001

Values are expressed as mean ± SD.

The mean number, volume, and activity of contrast-enhancing lesions on brain MRIs decreased in 13.3% of participants and increased in 15%. No changes were observed in 71.7% of the study subjects. No serious adverse effects, laboratory disturbance, or unexpected adverse events were reported.

Discussion

There is growing interest in combination therapy to stabilize the clinical course, reduce the rate of clinical relapses, and decelerate the progressive course of the underlying pathologic mechanisms of MS.²³ This study evaluated the efficacy, tolerability and safety of combination therapy with IFN-β1a and oral doxycycline, a potent inhibitor of MMP, in patients with RRMS or SPMS. We found that a combination of intramuscular IFN-β1a and oral doxycycline could reduce relapse rate and EDSS scores in MS patients. However, the combination could not reduce contrast-enhancing lesions on brain MRI.

An open-label study assessed 11 patients with RRMS who had received doxycycline and intramuscular IFN-β1a for at least six months. The authors reported that lower number of lesions on brain MRI and reduced mean EDSS score (3.9 vs. 1.4) after treatment.²⁰ Another research surveyed the effectiveness of a 4-month combination therapy with doxycycline and IFN-β1a among 15 patients with RRMS. It showed decreased number of lesions and EDSS scores after treatment.²⁰ Investigating the effects of doxycycline on MMP-9 suppression in brain arteriovenous malformations showed that serum levels of MMP-9 were significantly reducing following doxycycline therapy.²⁴

Changes in the appropriate balance of MMP-9/TIMP-1 are pathological effects that lead to inflammation and demyelination. As MMP-9 increases and TIMP-1 decreases, BBB rupture occurs and T cells arrive into the nervous system and make damage. In course of active MS, IFN-β therapy increases serum level of MMP-9. However, MMP-9 can reduce the effectiveness of interferon. Since doxycycline is a potent inhibitor of MMP-9, its usage is expected to decrease relapse rate.

Conclusion

Overall, data from this cohort study suggest that the

combination of oral doxycycline and IFN- β 1a may reduce relapse rate and EDSS scores in patients with MS. Nevertheless, it was not found to reduce the number of lesions on the brain. Further controlled

clinical trials with larger sample size are warranted to demonstrate the safety and efficacy of the mentioned combination over a longer period.

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