

Clinical and radiological response and side effects of beta interferon in Iraqi patients with relapsing and remitting multiple sclerosis

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ABSTRACT

Objective: To determine the efficacy and tolerability of subcutaneous Interferon beta 1a (IFN β -1a) among Iraqi patients with relapsing remitting multiple sclerosis (RRMS).

Methods: The study was held at the Multiple Sclerosis clinic at Baghdad Teaching Hospital, Baghdad, Iraq from January-October 2004. Thirty-seven patients with clinically definite RRMS and disability status scale below 6.5 were enrolled in this study. Patients received IFN β -1a, 22 μ g subcutaneously 3 times a week. Clinical measures, including number of relapses and disability progression, with MRI measures including number, size activity of lesions, and brain atrophy were used for evaluation of response to treatment. Side effects were also looked for.

Results: Patient ages ranged between 17-60 years with a mean age of 34.85 years, with 20 female patients and 17 male patients. After 2 years of treatment, there was a significant reduction in relapse rate (54.1% were relapse

free, and 21.6% had reduction in relapse rate). There was also a significant effect on disability progression (the mean expanded disability status scale (EDSS) before treatment was 3.22 and mean EDSS after treatment was 2.84). Significant effects on MRI measures were also shown, presented by a reduction in the number of lesions, which was seen in 64.9% of the patients, and a reduction in the size of lesions, which was seen in 64.9% of the patients. Also, significant effects on the activity of lesions was seen, as 67.6% of the patients had non-active lesions before treatment and remained non-active after treatment, and 29.7% of the patients had active lesions before treatment, which became non-active after 2 years of treatment. Mild adverse reactions were seen, mainly influenza like reactions and injection site reactions.

Conclusion: Interferon β -1a was effective in the treatment of RRMS with minimal side effects.

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Multiple sclerosis (MS) is a disease of the central nervous system of unknown etiology,¹ reported from Iraq since 1958.² A recent report of a large series from the newly established MS clinic at Baghdad Teaching Hospital, concluded that MS in Iraq has the same features encountered in Western countries.³ Beta interferon (IFN- β) has been used in the treatment of MS. Multicenter, double blind and placebo-controlled

trials of IFN- β have confirmed that the treatment resulted in a moderate reduction in relapse rate, and a pronounced decrease in accumulation of disease burden as measured by MRI after 2 years of follow up.^{4,5} Interferon β -1a has been available in the MS clinic in Baghdad Teaching Hospital since 2001. In this report we assess the response of Iraqi patients to IFN β -1a and compare it with published reports.

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Methods. A retrospective and prospective study conducted at the MS clinic at Baghdad Teaching Hospital. The study lasted from January-October 2004, and included 37 patients with clinically definite relapsing remitting MS (RRMS). Ethical approval was given to conduct the study by the ethical committee at the College of Medicine, University of Baghdad, and the study was explained to each patient and informed consent was obtained. Patients with clinically definite RRMS according to Poser's criteria,⁶ attending the MS clinic at Baghdad Teaching Hospital comprised the study population. Four hundred RRMS patients were registered at the MS clinic at the time of study. Only patients who satisfied the following criteria were included: Patients above the age of 15 years were enrolled, those who had at least one relapse in the preceding 2 years, those who were ambulatory with Kurtzke's expanded disability status scale scores (EDSS)⁷ of 0-6.5, and patients who were on IFN β -1a treatment for more than one year without interruption. Patients with the following criteria were excluded: Patients with treatment duration of less than one year, patients on irregular treatment.

The patients received IFN β -1a (Rebif® 22, Industria Farmaceutica Sero S.P.A., Italy). It came in prefilled syringes, each syringe containing 22 μ g of IFN β -1a in 0.5 ml. Each patient received Rebif 22 μ g 3 times a week sub-cutaneously preceded by 500 mg paracetamol. From the beginning of 2001 until the end of the study, this was the only IFN β available. In addition to IFN β -1a, patients were treated with baclofen, carbamazepine or antidepressants. Methylprednisolone pulse therapy was used only during relapse. Patients had already been followed up at the MS clinic before the study. During the study the follow up was completed and patients were seen monthly, and the following points were recorded: 1. History: detailed history of the following points: regular intake of treatment, any symptoms suggesting the side effects listed in a special sheet and any positive symptoms were recorded, any new symptoms suggesting a relapse, then at the end of the study the number of relapses from starting the treatment until the end of the study was calculated and compared with number of relapses in the last 2 years before starting the treatment from the patient's records at the MS clinic. A relapse was defined as any new neurological signs and symptoms or worsening of pre-existing symptoms for more than 24 hours, preceded by stability for at least 6 weeks, in the absence of metabolic causes such as fever.⁶ 2. Examination: the following points were assessed: injection sites, any erythema, bruises or skin necrosis. Neurological examination was carried out by a specialist neurologist for any new

neurological deficit. 3. The EDSS score assessment: The EDSS score⁷ was recorded at the end of 2 years of treatment, and was compared with that before starting the treatment obtained from the patient's records. Investigations were carried out for all the patients in the same laboratory of Baghdad Teaching Hospital and included the following: 1. Complete Blood Picture (CBP): carried out every 3 months looking for the following: white blood cell (WBC) and platelet counts. 2. Liver function test (LFT) carried out every 3 months looking for the following: total serum bilirubin (TSB), serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT), and alkaline phosphatase (ALPH). Results were recorded from the beginning of treatment until the end of 2 years follow up. 3. Thyroid function test (TFT) carried out once yearly, so during the 2 years course of treatment it was carried out 3 times; once at the beginning of the treatment course, the second at the end of the first year, and the third at the end of the second year. 4. Magnetic Resonance Imaging (MRI) carried out 2 times, one just before starting the treatment course to make a definite diagnosis of MS, and the second at the end of the second year, to assess the difference between the MRI before treatment and MRI after 2 years of treatment. The following points were looked for on MRI: 1. Number of lesions on both MRIs. The results were categorized as either: Reduction in number, same number, increased number (namely, new lesions). 2. Size of lesions. The results were categorized as: reduction in size, the same size, increased size. 3. Activity of lesions. The results were categorized as: lesions changed from active to non-active, lesions that were active and still active, lesions changed from non-active to active, and lesions that were non-active and still non-active. 4. Brain atrophy. The results were categorized as: if there is some degree of brain atrophy and this remained the same, if there was no or some degree of brain atrophy and this increased, if there were no brain atrophy and still no brain atrophy.

Statistical analyses were carried out using the Statistical Package for Social Sciences, version 10. Descriptive statistics were used to express the mean and standard deviation of age, duration from onset of disease until starting treatment, EDSS before and after treatment, and relapses before and after treatment. Frequency and percentages were used to express gender and MRI measures. Paired Student's t-test was used to assess the differences between relapses before and after treatment and EDSS before and after treatment. Z-test of proportion was used to assess the difference between MRI measures before and after treatment; $p < 0.05$ was considered the minimal for statistical significance.

Results. Thirty-seven patients were included in the study, 20 (54.1%) females and 17 (45.9%) males. Their ages ranged from 17-60 years with a mean age of 34.85 years. The duration from the diagnosis of the disease until starting the treatment with β -interferon ranged from 1-28 years with mean duration of 7.45 years. The duration of treatment ranged from 1-3 years of treatment with mean duration of 2.5 years. Interferon β -1a significantly reduced the number of relapses, and the mean number of relapses within 2 years before treatment was 1.76, while the mean number of relapses within 2 years of treatment was 0.71. The mean difference was significant ($p < 0.0005$). Twenty patients (54.1%) were relapse free after 2 years, 8 patients (21.6%) had reduction in their number of relapses, 7 patients (18.9%) had the same number of relapses, and 2 patients (5.4%) had an increased number of relapses. There was a statistically significant difference in the mean EDSS score. At the start of treatment, the mean EDSS score was 3.22, while the mean EDSS score after 2 years of treatment was 2.84, the mean difference was statistically significant ($p < 0.0005$). The scores during acute relapses were excluded. Twenty-one patients (56.8%) had no change in their EDSS scores before and after treatment, 14 patients (36.8%) had >1 point reduction in their EDSS score, and 2 patients (5.4%) had >1 point worsening in their EDSS score. Interferon β -1a treatment had a significant effect on number of lesions. Twenty-four patients (64.9%) had a reduction in their number of lesions after 2 years of treatment, 10 patients (27%) had the same number of lesions, and 3 patients (8.1%) had new lesions. By Z-test of proportion, $p < 0.01$. Interferon β -1a treatment also had a significant effect on size of lesions. Twenty-four patients (64.9%) had reduction in the size of their lesions, 13 patients (35.1%) had the same size of lesions before and after treatment. No increase in the size of lesions was observed in any patient. By Z-test of proportion, p -value was < 0.01 . Interferon β -1a had a good effect on the activity of lesions. Twenty-five patients (67.6%) had non-active lesions on the first MRI, which remained non-active in the last MRI, 11 patients (29.7%) have active lesions, which became non-active, one patient (2.7%) had an active lesion before treatment and another active lesion after treatment. Interferon β -1a treatment showed no significant effect on brain atrophy. Nineteen patients (51.4%) had no brain atrophy before or after treatment, 17 patients (45.9%) had some degree of brain atrophy, which remained the same, and one patient (2.7%) had no brain atrophy previously, and developed brain atrophy later on. The most common adverse effect was mainly influenza like illness, which was seen

in 20 patients (54.1%), and most of these reactions were fatigue, malaise, and high temperature, which occurred 6-8 hours after injection, and in the first few months of treatment. The other major reactions were injection site reactions, which occurred in 25 patients (67.5%) as pain, erythema and hyper pigmentation at the site of injection, but none had skin necrosis or skin nodule. There were no effects on psychological status, except 2 patients (5.4%) with mood alteration and insomnia, which responded to tricyclic antidepressants, there were no suicidal attempts. Three (15%) of the female patients had menstrual disturbances in the form of irregular cycles but none had infertility. Only one patient (2.7%) had mildly elevated transaminases, which were transient and returned to normal spontaneously, serum bilirubin and ALPH levels were normal. There were periodical changes in WBC count and platelet count in the form of neutropenia and thrombocytopenia, which were also transient and returned too normal spontaneously. Four (10.8%) patients had leucopenia and 3 (8.1%) patients had thrombocytopenia. Four patients (10.8%) had infrequent attacks of palpitation after taking the injection. No patient had thyroid function abnormalities.

Discussion. Interferon β is a long-term treatment for MS. It was introduced to Iraqi patients with RRMS in October 2001. Certain outcome measures were used in different MS clinical trials,⁸ and these measures were also used in this study, including both clinical and MRI measures. Relapse rate or attack rate was preferred as the primary outcome measure of clinical trials.^{4,5,7,9,10} Such an approach is attractive for several reasons, first, it seems to measure a relevant clinical aspect of the disease, second, it is an objective clinical measure, especially in circumstances where minor fluctuations in function are eliminated from the definition of an attack, third, patients typically experience several attacks during the course of clinical trials so that statistical power to detect differences before and after treatment is generally adequate. On the basis of several studies, IFN β has been demonstrated to reduce the attack rate in patients with MS,⁹⁻¹³ and results of the current study confirm this observation. The mean number of relapses was significantly reduced from 1.75 relapses in 2 years before treatment to 0.7 relapses in 2 years of treatment. Percentages of relapse free patients, and that of patients with reduction in relapse rate were approximately similar to those of the previous studies.

The assessment of disability is a critical part of a clinical trial design. The EDSS has been the most

widely employed scale for this purpose and this scale has been used in almost all recently published studies.^{9,10,14} The EDSS is complicated to score and at lower degrees of disability, the scale is subjective and has poor interrater.^{15,16} Moreover, it is very non-linear over its range in comparison with the actual level of function. Some recent studies,^{17,18} have tried to make the scale more reliable by measuring the so called confirmed 1-point EDSS change (namely, a change of one or more EDSS point sustained on 2 consecutive assessments performed 3 or 6 months apart), and we used this scale in this study. Several recent trials showed that IFN β -1a causes a reduction in a confirmed 1-point EDSS progression,^{9,10,19} and these results were confirmed by this study, where there was reduction in mean EDSS score from 3.2162 before treatment to 2.8378 after 2 years of treatment.

Magnetic resonance imaging measures are objective measures that can be used to provide objective support for a clinical outcome that is of primary interest. Several recent trials have used MRI measures of disease activity (new lesions, enhancing lesions) to support therapeutic claims relating to clinical attack rate.^{10,14,17,20,21} Similarly MRI measures of disease severity, such as change in total volume of disease burden and cerebral atrophy, have been used to support claims of therapeutic benefit for clinical measures of disease severity such as confirmed disability progression. In this study, both measures of disease activity as number of lesions, and measures of disease severity as changes in the total volume and brain atrophy were used. The results found that both measures were significantly affected by IFN β -1a treatment, as the number of new lesions and active lesions, which indicate significant effects on disease severity and support the significant effects on relapse rate. There were also significant effects on sizes of lesions, which support the effect on disability progression. These results were confirmed by other studies.^{9,10} There were no significant effects on brain atrophy, since brain atrophy could occur in patients with MS in spite of IFN β treatment.

Increases in the efficacy of a therapy are only clinically beneficial if they are associated with acceptable tolerability and safety.²² The adverse effects most directly attributable to treatment with IFN β are flue like syndromes, injection site reactions, asymptomatic reduced WBC count and asymptomatic elevation of liver enzymes. Flue like symptoms are associated with all IFN β products. This study recorded an incidence of 54% in patients during 2 years of therapy, this was similar to other studies.^{9,17} This side effect was managed by educating the patients to take paracetamol 500 mg prior to injection and to

take the injection at bedtime.²³ Injection site reaction was the other frequent side effect, with the proportion of patients with injection site reaction being 67.5%, nearly similar to other studies.⁹ Educating patients and revising techniques of injections and the use of ice could manage this side effect locally before and after injection, together with changing the injection site.⁹

It was shown that asymptomatic laboratory abnormalities occurred frequently in IFN β treated patients. Elevated liver enzymes can be seen in up to 60% of patients receiving IFN β -1a, but these are generally mild and often spontaneously remit while still on treatment.²³ This study showed that only one patient had mildly elevated transaminases, and none showed elevated serum bilirubin or ALPH, which may be due to race or genetic factors. Asymptomatic cytopenia predominantly of WBC occurs commonly, but it is not associated with clinical problems and rarely requires dose adjustment and frequently spontaneously remits without the need for stopping therapy.²² This study showed that 10.8% of patients had transient leukopenia and 8.1% of patients had transient thrombocytopenia, which is less than previous studies.²² Menstrual disturbances as polymenorrhea (frequent menstrual cycles) and menorrhagia (heavy menses) occurred in 15% of the female patients. Although some reports showed that patients with severe vaginal bleeding responded to treatment with conjugated estrogens, the exact mechanism for the development of these menstrual disorders is unknown. Reports of menstrual disorders associated with IFN β are rare.²⁴ Depression increased spasticity and mental abnormalities have been reported, although these symptoms also occur as part of the underlying disease and their relationship to medication is unclear.¹ Some studies showed that there might be a course of depression during initiation of treatment, which is related to level of depression before treatment.²⁵ In this study there was no effect on psychological status, except in 2 patients with mood alteration and insomnia, which responded to tricyclic antidepressants, this was also seen in other studies.²⁶ Seizures were not seen in our patients, in other studies seizures have seldom been described.²² Interferon β treatment is associated with synthesis of thyroid autoantibodies and development of autoimmune thyroid disease. Some studies show that thyroid dysfunction can occur in approximately 7% of patients.²⁷ None of our patients had thyroid dysfunction.

In this study, IFN β has been convincingly demonstrated to reduce the attack rate in patients with MS in up to 60%. Treatment with IFN β also slows

the sustained disability progression. Beneficial effects on MRI measures of disease activity and disability progression have been clear after INF β treatment through reduction of lesion number, size, and activity. Side effects of IFN β are not serious, and they are simple and easily manageable. These results indicate that Iraqi patients respond to IFN β similarly to other Western patients and confirm the earlier report that MS in Iraq has the same features as those encountered in Western countries.³

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