Response to beta interferon 1b among Saudi patients with multiple sclerosis

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ABSTRACT

Objectives: To determine the efficacy and tolerability of subcutaneous beta interferon 1b (B_{1F1b}) among Saudi patients with remitting-relapsing multiple sclerosis (R-R MS).

Methods: An open label study held at the Neurology Division of the Armed Forces Hospital, Riyadh from March 1997 until December 2001. Thirty-two consecutive patients below the age of 50 years with clinically definite R-R MS according to Poser's Criteria and expanded disability status scale below 5.5 were enrolled in treatment with subcutaneous B_{1F1b} 8 million IU 3 times a week. The primary outcome measures used were: reduction in annual relapses, proportion of relapse-free patients, and the mean time to the first relapse after treatment was started. The secondary outcome measures used were the time to progression in disability, tolerability and safety of the beta interferon.

Results: Only 28 patients were analyzed to assess the outcome measures, the other 4 patients dropped out and were followed-up. Twenty were women and 8 were men (female:male ratio of 2.5:1). There was a significant reduction in relapse-rate in all patients, 32.5% were relapse-free, while 37.5% showed reduction in the number of relapses. None of our patients showed progression of disability ($P<0.0249$). Mild adverse reactions were seen in 38.5%, influenza-like illness occurred in 53.6%, and injection-site reaction in 35.7%.

Conclusion: Subcutaneous B_{1F1b} is effective in patients with R-R MS, especially in reducing relapse rate, probable disability, and it is well tolerated. However, longer follow-up is necessary to evaluate the role of B_{1F1b} in preventing disability.

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Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) of unknown etiology. In Arabic countries, the disease was more prevalent in the Middle East, and it was found to be in the medium zone[1] especially in the Kingdom of Saudi Arabia (KSA) in which the prevalence is 8 per 100,000.[2] No differences were found in the age of onset, clinical pattern and disability compared with those reported in Europe and North America. Therapeutic advances have been slow to develop, partly because of incomplete understanding of the pathogenesis of the disorder, highly variable course of the disease and lack of objective markers of treatment effect, particularly in the short-term.[3-5] Recently, encouraging results from multicenter, double-blind and placebo-controlled trials of interferon beta showed that beta interferon 1b (IFN-B1b) is effective in patients with relapse-remitting (R-R) MS at a high dose of 8 million IU administered every other day subcutaneously.[6,7] The interferon treatment resulted in a modest reduction in relapse rate by up to 34% and a pronounced decrease in accumulation of disease burden as measured by magnetic resonance image (MRI) after 2 years of follow-up, but its effect on the progression of disability was not significant.[6-8] We used interferon Beta-1b in Saudi patients with a disease pattern of R-R MS and similar clinical symptomatology to Western population but probably of a different natural history. We present the results of the major outcome measures, which include relapse rate, disability, safety and tolerability of the treatment with interferon.

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Methods. ***Population.*** We studied 32 consecutive patients with clinically definite R-R MS according to Poser's criteria.[9] It is an open-label prospective study held at the Neurology Division at the Armed Forces Hospital, Riyadh, in which patients were recruited from the outpatient departments, accident and emergency rooms, and other referral centers in KSA from March 1997 until December 2001. Patients above the age of 12 years, who were clinically stable (namely, either not in relapse or started 3 months after relapse), were enrolled if they had at least 2 relapses in the preceding 2 years and were ambulatory with Kurtzke's expanded disability status scale scores (EDSS) of 0 to 5.0.[10] Also, we included those patients who had the illness for a duration of less than 10 years. We excluded any patient with primary or secondary progressive MS, isolated demyelinating syndromes (for example Devic's or optic neuritis), pregnancy, severe depression or psychiatric disease, patients who received previous systemic treatment with interferon, immunosuppressive agents in the preceding one year (prior to enrollment), and patients with serious hypersensitivity reactions to natural or recombinant interferon or human albumin. All patients were assessed clinically by one neurologist, including the clinical pattern of the disease progression, number of relapses, and baseline EDSS scores according to diagnostic criteria used by Schumacher.[11] Magnetic resonance imaging brain studies were carried out, including axial T1- and T2-weighted images and proton density in all patients.[12,13] Patients presenting with symptoms of myelopathy also had spinal cord imaging. Evoked potential studies that included pattern-shift visual evoked potentials, brainstem auditory evoked potentials, and somatosensory evoked potentials were carried out. Also, cerebrospinal fluid (CSF) immunological studies, such as oligoclonal bands or Immunoglobulin (Ig) G-index was carried out.[13] Complete and differential hematological tests and biochemical tests, including liver function tests, brucella titers, hepatitis screen, collagen, autoimmune and vasculitis screens were also performed. The need for medication was discussed with the patient and their families. The efficacy, adverse effects and necessity of family planning were also discussed. The patients were taught how to inject themselves under the supervision of a well-trained nurse and by using videotape and brochures from the drug manufacturer. Each patient received IFN-B1b, 8 million units, 3 times per week subcutaneous, preceded by 1 gram of paracetamol orally.

Clinical data (outcome measures). 1. The primary outcome measures used were: (a) The reduction in annual exacerbation's, which were assessed by the mean reduction in the annual relapse rate. The acute relapse was defined according to Schumacher's and Poser's criteria[8,9,11,14] as new neurological symptoms and signs or worsening of pre-existing symptoms for more than 24 hours, preceded by stability for at least 6 weeks in the absence of metabolic cause such as fever.[9,14] (b) The proportion of exacerbation–free patients. (c) The mean time to the first relapse after treatment was started. 2. The Secondary outcome measures included were: (a) We assessed the time to progression in disability, which is defined as a persistent change in EDSS[7,15,16] of at least one point sustained over 3 months that indicates improvement, stability or worsening. The lower the scores the better the outcome is. The disability scores measured during relapses were not included. (b) The tolerability and safety of the drug was assessed by the number of dropouts due to inconvenience or adverse reactions that necessitates drug withdrawal.

Follow-up. All patients were followed-up in the outpatient department (OPD) monthly for the first 3 months, then every 3 months. During each visit, patients were reassessed clinically and the injection sites were re-examined. During relapses, patients were first assessed clinically and their EDSS scores were tabulated. Then, MRI was carried out to support the clinical impression of acute relapses.[17] The relapse was treated with high dose of methyl-prednisolone 1 gram per day for 5 days in an outpatient or inpatient setting depending on the severity of the attack. Complete blood counts and blood chemistry was repeated during every follow-up visit. Those who developed reactions at the site of injection, their techniques were re-evaluated, including the dose and needle size.[11] All other adverse reactions, their frequency, time of occurrence following injection, duration of the symptoms and their management were all tabulated. The dropouts were followed every 3 months, the number of relapses they had, time of stopping the treatment, their EDSS and the reasons for withdrawal were also recorded.

Statistical method. The sample size analyzed was 28 patients using ANOVA and t-test.

Results. A total of 32 patients of clinically definite R-R MS were enrolled in treatment with IFN B1b. Four patients dropped out, and the remaining 28 patients were analyzed regarding their age, sex, EDSS, clinical, diagnostic data and the major outcome measures. Twenty-five patients (89.3%) were Saudis and 3 patients (10.7%) were non-Saudis. Twenty patients (71.4%) were women, and 8 patients (28.6%) were men with female:male ratio of 2.5:1. The mean age was 32 years (range 19-43 years), and the mean age of onset was 25 years (range 11-38 years). The longest duration of follow-up was 54 months and the shortest was 24 months, the mean duration of follow up was 2.54 years. The lesion sites at initial presentation, as evident by the clinical symptomatology was supratentorial[1] in 22 patients (78.6%), brainstem in 6 (21.4%), cerebellum in 14 (50%), optic nerve in 8 (28.6%), and spinal cord in 8 (28.6%). The most common combination was supratentorial and cerebellar, and the least common combination was optic nerve and spinal cord.

The evoked potentials were abnormal. Pattern-shift visual evoked potentials were abnormal with unilateral or bilateral prolongation of P100 in 21 patients (75%).

Brainstem auditory evoked potentials were abnormal in 5 patients (17.9%) with unilateral or bilateral loss of Waves IV and V. Somatosensory evoked potentials were abnormal in 19 patients (67.9%) with prolongation of central conduction or asymmetric cortical potential amplitudes. In 17 patients (60.1%), more than one evoked potential study was abnormal.

Magnetic resonance imaging of the brain showed typical multiple hyper-intense lesions on T2-weighted images in all patients. Cerebrospinal fluid immunological analyses for either, high IgG or oligoclonal bands were performed in only 19 patients (67.9%). The other CSF parameters, cells, protein and sugar were normal in all patients.

We analyzed the outcome measures, relapse rate, proportion of patients who are free of relapses, the mean time to the first relapse and EDSS in all patients up to 2-years' duration of treatment. Thirteen patients (32.5%) had no relapse, while the other 15 patients (37.5%) had reduction in their annual relapses. The mean number of annual relapses after treatment was 0.96 ± 1.17 compared to before treatment of 2.89 ± 1.17 (P<0.0001). There were no statistically significant differences in the mean EDSS scores in patients receiving IFN beta 1b before treatment (2.11) and after treatment (1.71). The mean difference in EDSS before and after treatment was 0.39 ± 0.88 (P=0.024). The scores during acute relapses were excluded.

The most common adverse effect was mainly influenza-like illness, which was seen in 16 patients (57%), most of these reactions were in the form of fatigue, malaise and high temperature, which occurs 6-8 hours after injection. Most of these reactions occurred in the first 3 months of treatment. The other major reactions were injection site reactions which occurred in 9 patients (32%) in the form of pain, erythema and hyperpigmentation at the site of injection. Only one patient had skin nodules at the site of injection, and none had skin necrosis or necessitated drug withdrawal. Only one patient had mildly elevated transaminases (<5 time's normal value) with normal bilirubin and alkaline phosphatase. There was no effect on psychological status, except in 2 patients (7.1%) with mood alteration and insomnia, which responded to tricyclic anti-depressant or paroxetine. There were no suicidal attempts in our series. Four patients (14.3%) had menstrual disturbances in the form of irregular cycles but none had infertility. However, 25% of patients did not have any reaction and no withdrawal as a result of side effects.

The reason and timing of withdrawal, relapse rate and EDSS after withdrawal in the 4 drop-outs patients were analyzed. The mean duration of treatment on withdrawal was 8.5 months, and only one patient had relapse after one and half years from withdrawal, with no acute relapses and no change in their disability scales in the other patients. The most likely cause of withdrawal was due to inconvenience to every other day injections.

Discussion. Multiple sclerosis behaves in different ways among different ethnic groups, our study shows that the disease behaves in a way similar to that seen in patients from Europe and North America (especially the age of onset between 11-38 years, which is similar to patients of Kurtzke and Alpine et al).[18,19] Also, the most common anatomical locations of the lesions seen in our Saudi patients were in the cerebrum and cerebellum, as compared to a predilection to the optic nerves and spinal cord that was reported in the Asian and Japanese series.[20,21] In our study, the reduction in relapse rate was seen in 37.5%, while no relapses in 32.5%, which is similar to that shown in the previous studies for IFN B1b, IFN B1a and copolymer-1.[1,6-8,12,16] The mean time to first relapse was increased from 1.9 attacks in 12 months to 1.0 attacks in 13.6 months. Magnetic resonance imaging findings support the clinical impression of acute relapses.[17] Weinshenker and his colleagues showed that a high relapse frequency early in MS correlated with a 10 year disability outcome that becomes stronger with time.[22] In other series, there was no consistent evidence to this relationship.[23,24] The previous studies failed to demonstrate an effect of B1b on disability, however, in our study, the time to sustained progression in disability was increased at this dose. The EDSS allows us to quantify the transient and permanent disability by choosing the 1-point progression and confirming the scores after 3 months, also the exclusion of the disability scores during acute relapses, reduces the bias, and the treatment effect remained significant. Our limitation in this study was the short-term follow-up, and disabilities are at the lower end. So probably, long-term follow-up and higher scores may reflect the true effect. Also the use of confirmed 1-point progression was suitable as a measure of disability, despite the difficulties in assessing some variables in EDSS, lack of precision in some grade, and probably not very sensitive to worsening in the patient's clinical status.[10,23,25,26] So whether treatment-related decrease in relapses leads to a decrease in long-term disability remains to be shown.

In previous studies, T2 lesion load was roughly correlated with the clinical disability and could be used as a useful marker for the possible effect of IFN B1b on the disease burden.[27] However, these MRI parameters were not studied in our current trial.

In the Arab peninsula, a milder form of the disease was reported.[2] We looked at the follow-up in drop-outs, and the absence of acute relapses except in one out of 4 patients and stability of the EDSS scores, may probably reflect that we are dealing with a milder form of the disease.[2] This will be examined further as our patients' database expands.

However, interferon treatment showed a statistically significant benefit in reducing relapse rate, probably delaying time to progression in disability but no significant change in EDSS, and its safety profile was reassuring. Our findings were better than the previous studies for IFN B1b particularly in terms of local

injection-site reaction. This can be explained by the time spent in educating the patients and revising their doses, needle size, techniques, also the use of ice before and after the injection and rotating the injection sites.[3,6,7] With regard to influenza-like illness, we have a better profile, probably due to the use of paracetamol, and taking injections at bedtime.[7,28] None of our patients required non steroidal anti-inflammatories or oral prednisolone.[29,30] Although the adverse effects were definite and uncomfortable for few weeks, they gradually diminished over few months. We identified asymptomatic slightly raised liver transaminase values, but none had serious toxic effects. Menstrual disturbance occurred in 10%, which is low compared with the previous studies of 28%. The true effect probably is masked by the use of oral contraceptives and no effect on fertility was shown in our patients.[31] None of our patients showed treatment failure necessitating detection of neutralizing antibodies at this level.[32]

In conclusion, compared to previous studies, our current data showed significant reduction in annual exacerbation rate in patient's with frequent relapses, low disability, safety and tolerance. There was a trend to the slow progression of disability in our patients, but we failed to demonstrate a significant effect at this stage, longer follow-up periods are required. Secondly, our drop-out patients did not show any progression, which suggests that we may be dealing with a milder form of the disease. So, despite a clear and significant effect of IFN B1b on exacerbation rate, a reduction in disability remains unsolved, and the question is, is IFN 1b worthwhile in patients with R-R MS?[33]

The successful management of adverse effects and thorough patient education on the natural history of the disease, absence of curative treatment, and possible side effects of the medication critically determine whether the patient will adhere to the treatment and explains our low drop-out number. Further separate studies are needed to determine the appropriate doses of IFN and the length of the treatment.

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References

1. Kurtzke JF. Geographic distribution of multiple sclerosis. An update with special reference to Europe and Mediterranean region. ***Acta Neurol Scand*** 1980; 62: 65-80.
2. Yaqub B, Daif A. Multiple sclerosis in Saudi Arabia. ***Neurology*** 1988; 38: 621-623.
3. Prism's Study Group. Randomized double-blind placebo-controlled study of Interferon-B1a in relapsing-remitting multiple sclerosis. ***Lancet*** 1998; 352: 1498-1504.
4. Weinshenker BG, Rice GP, Noseworthy JH, Carriere W, Baskerville J, Ebers GC. The natural history of multiple sclerosis: geographically based study. 4. Applications to planning and interpretation of clinical therapeutic trials. ***Brain*** 1991; 114: 1057-1067.
5. Eber GG, Paty DW. Natural history studies and applications to clinical trials. In: Paty DW, Ebers GC, editors. Multiple Sclerosis. Philadelphia (PA): F.A. Davis Co; 1997. p. 192-228.
6. IFNB Multiple Sclerosis Study Group. Interferon Beta-1b is effective in relapsing-remitting multiple sclerosis 1. Clinical results of multicentre randomized double blind, placebo-controlled trial. ***Neurology*** 1993; 43: 655-661.
7. IFNB-Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. Interferon Beta-1b in the treatment of multiple sclerosis. Final outcome of the randomized controlled trial. ***Neurology*** 1995; 45: 1277-1285.
8. Paty DW, Li DK. Interferon Beta-1b is effective in relapsing-remitting multiple sclerosis. II: MRI analysis results of a multicentre randomized double blind, placebo-controlled trial. ***Neurology*** 1993; 43: 662-667.
9. Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. ***Ann Neurol*** 1983; 13: 227-231.
10. Kurtzke JF. Rating neurological impairment in multiple sclerosis: an expanded disability status scale (EDSS). ***Neurology*** 1983; 33: 1444-1452.
11. Schumacher GA, Beebe G, Kibler RF. Problems of experimental trials of therapy in multiple sclerosis: Report by the panel on the evaluation of experimental trials of therapy in multiple sclerosis. ***Ann N Y Acad Sci*** 1965; 122: 552-568.
12. Paty DW. Trial measures in multiple sclerosis: The use of magnetic resonance imaging in the evaluation of clinical trials. ***Neurology*** 1988; 38: 82-83.
13. Paty DW, Oger JT, Kastrukoft LF, Hashimoto SA, Hooge JP, Eisen KA et al. MRI in the diagnosis of MS: A prospective study with comparison of clinical evaluation, evoked potentials, oligoclonal bands, and CT. ***Neurology*** 1988; 38: 180-185.
14. Liu C, Blumhardt LD. Assessing relapses in treatment trials of relapsing-remitting multiple sclerosis: Can we do better? ***Mult Scler*** 1999; 5: 22-28.
15. Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM et al. IFN-Beta 1a for disease progression in relapsing-remitting multiple sclerosis. ***Ann Neurol*** 1996; 39: 285-294.
16. Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP et al. Copolymer I reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: Results of Phase III multicentre, double blind, placebo-controlled trial. ***Neurology*** 1995; 45: 1268-1276.
17. Lukes SA, Crooks LE, Aminoff MJ, Kaufman L, Panitch HS, Mills C et al. Nuclear magnetic resonance imaging in multiple sclerosis. ***Ann Neurol*** 1983; 13: 592-601.
18. Kurtzke JF. Clinical manifestations of multiple sclerosis. In: Vinken PT, Bruyn GW, editors. Handbook of Clinical Neurology. Amsterdam: North Holland Publishing Company; 1970. p. 161-201.
19. McAlpine D, Lumsden CE, Acheson ED. Multiple sclerosis. A reappraisal. 2nd ed. London (UK): Churchill Livingstone Publishers; 1972. p. 83-307.
20. Kuroiwa Y, Igata A, Hahara K, Koshijima S, Tsubaki T, Toyokura Y et al. National wide survey of multiple sclerosis in Japan: Clinical analysis of 1,084 cases. ***Neurology*** 1975; 25: 845-851.
21. Kuroiwa Y, Hung TP, Landsborough D, Suhpark C, Singha lBS, Soemargo S et al. Multiple sclerosis in Asia. ***Neurology*** 1977; 27: 188-192.
22. Weinshenker BG, Bass B, Rice GPA, Noseworthy J, Carriere W, Baskerville J et al. The natural history of multiple sclerosis: A geographically based study. 2. Predictive value of the early clinical course. ***Brain*** 1989; 112: 1419-1428.
23. Willoughby EW, Paty DW. Scales for rating impairment in multiple sclerosis: A critique. ***Neurology*** 1988; 38: 1793-1798.
24. Fillippi M, Paty DW, Kappos L, Barkhot F, Compston DAS, Thompson AJ, et al. Correlations between changes in disability and T2-weighted brain MRI activity in multiple sclerosis: a follow-up study. ***Neurology*** 1995; 45: 255-260.

25. Scharrack B, Hughes RAC. Clinical scales for multiple sclerosis. ***J Neurol Sci*** 1996; 135: 1-9.
26. Francis DA, Bain P, Swan AV, Hughes RAC. An assessment of disability rating scales used in multiple sclerosis. ***Arch Neurol*** 1991; 48: 299-301.
27. Khoury ST, Guttmann CRG, Orav EJ, Hohol MJ, Ahn SS, Hsu L et al. Longitudinal MRI in multiple sclerosis: Correlation between disability and lesion burden. ***Neurology*** 1994; 44: 2120-2124.
28. Lublin FD, Whitaker JN, Eidelman BH, Miller AE, Arnason BGW, Burks JS. Management of patients receiving Interferon Beta-1b for multiple sclerosis: Report of a consensus conference. ***Neurology*** 1996; 46: 12-18.
29. Munschauer FE III, Kinkel RP. Managing side effects of Interferon Beta in patients with relapsing-remitting multiple sclerosis. ***Clin Ther*** 1997; 19: 883-893.
30. Rio J, Nos C, Mazo ME, Tintore M, Montalban X. Low dose steroids reduce flu-like symptoms at the initiation of IFN-Beta 1b in relapsing-remitting multiple sclerosis. ***Neurology*** 1998; 50: 1910-1912.
31. Vial T, Descotes J. Clinical Toxicity of the interferons. ***Drug Saf*** 1994; 10: 115-150.
32. Paty DW, Goodkin D, Thompson A, Rice G. Guidelines for physicians with patients on IFN B1b (the use of an assay for neutralizing antibodies NAB). ***Neurology*** 1996; 47: 865-866.
33. Compston A. Beta Interferon and multiple sclerosis: not a final solution for the problem. ***Br J Hosp Med*** 1995; 53: 547-552.