Interferon beta in multiple sclerosis: experience in a British specialist multiple sclerosis centre

B D Dubois, E Keenan, B E Porter, R Kapoor, P Rudge, A J Thompson, D H Miller, G Giovannoni

SHORT REPORT

Background: The efficacy of interferon beta (IFN beta) is well established in relapsing-remitting multiple sclerosis (MS). However, the use of this drug in clinical practice is complex, especially because it is only partially effective, its long term efficacy and side effects are unknown, its efficacy may be abrogated by the development of neutralising antibodies, compliance is variable, and its cost effectiveness is controversial.

Objectives and Methods: Analysis of a prospectively followed up series of 101 MS patients treated with IFN beta was undertaken: (1) monitor the outcome of IFN beta treatment in clinical practice; (2) compare the immunogenicity of the three commercial IFN beta preparations available; (3) assess the proportion of patients fulfilling the current guidelines of the Association of British Neurologists for stopping IFN beta therapy.

Results: During a median treatment period of 26 months (range 2–85), the relapse rate decreased by 41%. Although the reduction in the relapse rate was similar for all three commercial products, none of the Avonex treated patients were relapse free, compared with 19% of the Betaseron treated and 27% of the Rebif treated patients (p=0.02). Neutralising antibodies were not detected in 19% of the Betaseron treated patients (0 of 18), compared with 12 of 32 (38%) Betaseron treated and 10 of 23 (44%) Rebif treated patients (p=0.02). Forty of 101 (40%) patients satisfied the current (2001) Association of British Neurologists criteria for stopping IFN beta treatment at some stage during their treatment.

Conclusion: IFN beta is effective in reducing the relapse rate in patients with relapsing-remitting MS in routine clinical practice. However, after a median treatment duration of 26 months, 40% of initially relapsing-remitting MS patients seem to have ongoing disease activity, presenting as disabling relapses or insidious progression.

Three large, multicentre, randomised, double blind, placebo controlled trials have demonstrated that interferon beta (IFN beta) reduces the relapse rate in patients with relapsing-remitting multiple sclerosis (MS)1–3 and in two of these studies IFN beta slowed the rate of accumulation of disability.4 One of the questions that has not been answered by these trials, is for how long IFN beta treatment should continue. This issue is important, not only to prevent unnecessary treatment, but to allow patients access to other potentially efficacious therapies and to enable health authorities to plan drug provision for MS.

This prospective audit describes the implementation of IFN beta therapy at a tertiary referral centre, the National Hospital for Neurology and Neurosurgery (NHNN) in London. The unblinded, observational concept carries a number of inherent limitations, such as drug selection criteria, potential unblinding effects, and patient selection criteria.

The aims of the audit were therefore (1) to evaluate the efficacy of IFN beta treatment in clinical practice; (2) to establish the immunogenicity of the different products and correlate the occurrence of neutralising antibodies (NABs) with clinical parameters; (3) to assess “failure of treatment” as defined by the recently published guidelines from the Association of British Neurologists (ABN).

METHODS Patients

An analysis was performed on all patients with relapsing-remitting MS who started IFN beta therapy before 1 January 2000 at the NHNN in London. Only patients who experienced at least two clinically significant relapses during the previous two years and had an Expanded Disability Status Scale (EDSS) score of less than 5.5 were given IFN beta. A minimum follow up period of at least 12 months at the NHNN was required to be included in the audit.

Demographic and efficacy parameters

The following parameters were assessed during the analysis: age at onset of disease, duration of disease, duration of treatment, and the IFN beta product. Disease course, relapse rate, time of relapse, corticosteroid use, and mobility were evaluated before treatment and at the end of the assessment period. Patients were classified as having secondary progressive disease only if there was a clear progression in at least the preceding six months without the interference of episodes. The annualised relapse rate and use of corticosteroids in the two years before treatment were compared with the respective rates on treatment. Relapses were defined as disabling if they required corticosteroid administration. Disability was not formally assessed with the EDSS but was prospectively scored using the following simple mobility scale: 0=asymptomatic; 1=able to walk unaided for more than 500 m; 2=able to walk unaided for less than 500 m; 3=walking with unilateral support; 4=walking with bilateral support; 5=needs wheelchair outdoors; 6=wheelchair bound.

The proportion of patients fulfilling the current guidelines of the ABN for stopping IFN beta therapy was also assessed. The ABN considers the following features as likely to indicate a lack of treatment efficacy:

1. two disabling relapses, as defined by the examining neurologist, within a 12 months period
2. development of secondary progressive MS
3. loss of ability to walk, with or without assistance, persistent for at least six months

Abbreviations: IFN beta; interferon beta; MS, multiple sclerosis; NAB, neutralising antibody; EDSS, Expanded Disability Status Scale; ABN, Association of British Neurologists
Neutralising anti-IFN beta antibodies

Neutralising anti-IFN beta-1a and beta-1b antibodies were tested for in serum of patients in whom blood samples were taken at baseline and one year after treatment onset using a standard cytopathic effect assay in an independent laboratory. Samples were coded and assayed blind.

Statistical analysis

Means and standard deviations of the mean were calculated for relapse rate, corticosteroid use, and mobility before and on treatment as well as on the absolute and relative differences of these parameters before treatment and at the end of the assessment period. The means of the duration of disease, the duration of treatment, and the age at onset of disease were also analysed. Statistical analysis on these mean values was performed using a paired sample or an independent samples t test. Fisher’s exact test was used to compare numbers of relapse free patients in various subgroups. Differences between products were assessed by one way analysis of variance. Influence of NABs on number of relapse free patients was assessed using the \( \chi^2 \) statistical method. Results were considered statistically significant if \( p<0.05 \).

RESULTS

The data concerning demographics, treatment efficacy, NABs, and stopping criteria are shown in table 1.

Patients

One hundred and one patients (67 women, 34 men) were started on IFN beta before 1 January 2000 and were followed up at the NHNN for at least 12 months. The median duration of treatment was 26 months (range 12–85). Five patients stopped treatment: two because of pregnancy and three (one taking Avonex, two taking Betaferon) because of lack of efficacy and persistent side effects. Five patients changed product during the assessment period. They were included in the general analysis, but not in the analyses that involved product comparisons.

Treatment efficacy

Relapse rate and corticosteroid use were significantly reduced after treatment with IFN beta. However, mobility worsened on the mobility scale (\( p<0.001 \)).

Twenty-three patients (22.8%, six taking Avonex, eight taking Betaferon, six taking Rebif, and three who changed products) developed secondary progressive disease by the end of the assessment period. No significant differences were found between the products in regard to their effect on relapse rate, corticosteroid use, and mobility. However, the number of relapse free patients differed significantly between the various products. None of the Avonex treated patients (0 of 22) was relapse free whereas seven of 37 (19%) Betaferon and 10 of 37 (27%) Rebif treated patients did not experience relapses during the treatment period (\( p=0.02 \)) (fig 1).

Neutralising anti-IFN beta antibodies

General analysis

NAB test results after one year of IFN beta therapy were available in 73 (48 female, 25 male) of the 101 relapsing-remitting patients. Anti-IFN beta antibodies were found in 22 (30%) of these 73 patients. In three (4%) patients (one taking Betaferon, two taking Rebif) the antibodies were not cross reactive between the IFN beta-1b and beta-1a preparations.

The means of the various demographic and clinical data were compared in antibody negative versus antibody positive patients. No significant differences were found for relapse rate, corticosteroid use, and mobility at baseline and at the end of

<table>
<thead>
<tr>
<th>Parameters</th>
<th>All products</th>
<th>Avonex n=24</th>
<th>Betaferon n=37</th>
<th>Rebif n=37</th>
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</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>n=101</td>
<td>n=24</td>
<td>n=37</td>
<td>n=37</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>age at onset of disease (y)</td>
<td>27.6 (7.0)</td>
<td>27.4 (6.9)*</td>
<td>26.6 (6.3)*</td>
<td>29.2 (8.0)*</td>
</tr>
<tr>
<td>duration of disease (y)</td>
<td>9.5 (6.3)</td>
<td>9.0 (6.8)*</td>
<td>9.5 (5.7)*</td>
<td>10.0 (7.8)*</td>
</tr>
<tr>
<td>duration of treatment (m)</td>
<td>29.4 (13.3)</td>
<td>29.8 (8.2)†</td>
<td>38.2 (12.6)†</td>
<td>19.2 (3.6)†</td>
</tr>
<tr>
<td>Efficacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>relapse rate at baseline</td>
<td>1.9 (0.9)†</td>
<td>2.2 (1.3)*</td>
<td>1.9 (0.7)*</td>
<td>1.9 (0.7)*</td>
</tr>
<tr>
<td>relapse rate at baseline</td>
<td>1.2 (1.2)†</td>
<td>1.3 (1.1)*</td>
<td>1.2 (1.4)*</td>
<td>1.1 (0.9)*</td>
</tr>
<tr>
<td>relapse free</td>
<td>16/96 (16.7%)</td>
<td>0/22†</td>
<td>7/37 (19%)‡</td>
<td>10/37 (27%)‡</td>
</tr>
<tr>
<td>corticosteroid use at baseline</td>
<td>0.9 (0.7)†</td>
<td>1.1 (0.8)*</td>
<td>0.9 (0.6)*</td>
<td>0.8 (0.7)*</td>
</tr>
<tr>
<td>corticosteroid use on treatment</td>
<td>0.6 (1.0)†</td>
<td>0.7 (1.2)*</td>
<td>0.6 (1.2)*</td>
<td>0.6 (0.8)*</td>
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<tr>
<td>mobility at baseline</td>
<td>1.4 (1.1)†</td>
<td>1.4 (0.9)*</td>
<td>1.4 (0.9)*</td>
<td>1.4 (1.0)*</td>
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<tr>
<td>mobility on treatment</td>
<td>2.1 (1.6)†</td>
<td>2.2 (1.7)*</td>
<td>2.1 (1.7)*</td>
<td>2.0 (1.6)*</td>
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<tr>
<td>SP on treatment</td>
<td>23/101 (22.8%)</td>
<td>7/24 (29.2%)</td>
<td>9/37 (23.3%)</td>
<td>6/37 (16.2%)</td>
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<tr>
<td>early discontinuation</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>0</td>
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<tr>
<td>Neutralising antibodies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>22/73 (30.1%)</td>
<td>0/18</td>
<td>12/32 (38%)</td>
<td>10/23 (44%)</td>
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<td>ABN stopping criteria</td>
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<tr>
<td>relapses or secondary progression</td>
<td>40/101 (39.6%)</td>
<td>10/24 (41.7%)</td>
<td>16/37 (43.2%)</td>
<td>13/37 (35.1%)</td>
</tr>
<tr>
<td>relapses</td>
<td>17/101 (16.8%)</td>
<td>3/24 (12.5%)</td>
<td>7/37 (18.9%)</td>
<td>7/37 (18.9%)</td>
</tr>
<tr>
<td>secondary progression</td>
<td>15/101 (14.9%)</td>
<td>4/24 (16.7%)</td>
<td>6/37 (16.2%)</td>
<td>4/37 (10.8%)</td>
</tr>
<tr>
<td>relapses and secondary progression</td>
<td>8/101 (7.9%)</td>
<td>3/24 (12.5%)</td>
<td>3/37 (8.1%)</td>
<td>2/37 (5.4%)</td>
</tr>
<tr>
<td>inability to walk</td>
<td>2/101 (2%)</td>
<td>1/24 (4.2%)</td>
<td>1/37 (2.7%)</td>
<td>0/24 (0%)</td>
</tr>
</tbody>
</table>

*p value not significant; †p<0.001; ‡p=0.02.
Finally, although IFN beta therapy was only stopped because of apparent lack of efficacy in 3% of patients, 40% of our patients would have fulfilled the current ABN criteria for stopping therapy. More than half of those (62.5%) had at least two disabling relapses in 12 months and 57.5% developed secondary progressive disease, with or without superimposed relapses. The time point at which the disabling relapse criterion was fulfilled demonstrates that the treatment response with regard to disabling relapses might be evaluated after as little as 18 months of IFN beta therapy. Analysis of the disease course of the 25 patients who fulfilled the ABN criteria on relapses for stopping therapy highlighted important features that should be taken into account. Of these 25 patients, 10 (40%) experienced a lower or equal number of relapses compared with baseline. On the other hand, five of 10 relapsing-remitting MS patients who had a higher relapse rate on treatment than at baseline, did not fulfill the ABN stopping criteria. These data question the current wisdom of defining a stopping criterion based solely on the number of disabling relapses. This will be difficult to implement on an individual patient basis particularly as IFN beta therapy is widely acknowledged to being only a partially effective therapy. It would be more appropriate to include both the baseline relapse rate and the severity of relapses in formulating a relapse based stopping criterion. In contrast, conversion to secondary progressive MS, which is more difficult to evaluate than relapses, may be a more practical stopping criterion to implement, particularly as IFN beta treatment does not show a robust effect in patients with secondary progressive disease.\footnote{The future evaluation of the appropriateness of stopping criteria may be assisted by using objective predefined markers of disease activity or progression, or both. Examples of these could include magnetic resonance imaging parameters or NABs.}

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**REFERENCES**


HISTORICAL NOTE

Sir James Crichton-Browne (1840–1938)

James Crichton-Browne was born in Edinburgh, the son of Dr WAF Browne, first superintendent of Crichton Royal, Dumfries. James was educated in Dumfries and began his medical studies at Edinburgh University in 1857, a pupil of Joseph Lister (1827–1912) and James Syme (1799–1879).

His interests in psychiatry were soon evident. As a medical student he read a paper to the Royal Medical Society, The psychical diseases of early life. Crichton-Browne graduated in 1861, and obtained the MD in 1862. He worked in asylums in Derby, Devon, and Newcastle. In 1866, at the early age of 26, he was appointed as Superintendent Medical Director of the West Riding Lunatic Asylum at Wakefield, and in nine years established the hospital as a leading centre of research and treatment. Though lacking Ferrier’s scientific ability, he was a skilled administrator and a flamboyant highly persuasive speaker. He inaugurated the Annual medical reports of the West Riding Asylum in 1871, which were published annually for six years, and 62 of these 79 articles came from Wakefield Asylum. And he appointed a pathologist, the first to occupy a post of this kind at a large asylum, with a view of giving the hospital a high reputation of their medical reports of the West Riding Asylum. In 1878, Crichton-Browne with Ferrier, Jackson, and a five-volume autobiography. He met Thomas Carlyle and his family in London and after Carlyle’s death he wrote extensively about him and his wife Jane Carlyle; he entered the seething controversy initiated by Froude, their biographer, about their personal lives and behaviour, which would now fill the tabloids for weeks.

Crichton-Browne assisted Charles Darwin with drawings and pictures when Darwin was writing his Expression of the emotions in man and animals. Such was Darwin’s regard for him that he proposed his election to the Royal Society in 1883. Queen Victoria bestowed a knighthood in 1886. He lived until 1937, publishing his last book in that, year. In 1865, he had married Emily, youngest daughter of Dr J Halliday, a surgeon in Seacombe, Cheshire. She died in 1903 leaving a son and a daughter. His second wife Emily, was daughter of General Sir E Bulwer, and a great-niece of Bulwer-Lytton (Edward Bulwer-Lytton, writer (1803–1875), who coined the memorable adage, “A good heart is better than all the heads in the world”). A portrait of Crichton-Browne by Hannah Gluckstein, 1928, is catalogued at the National Portrait Gallery. And you may not wish to learn that he was portrayed on a cigarette card in a series on Famous Scots published by Mitchell, Ardath in 1935.

Hodder and Stoughton, 1927. His recipe for longevity was—“work and plenty of it”.

References


4 Crichton Browne J. Stray leaves from a physician’s portfolio. London: Hodder and Stoughton, 1927.

5 Crichton-Browne J. The nemesis of Froude: a rejoinder to J A Froude’s “My Relations with Carlyle”. London and New York: John Lane, 1903.