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Commentary on Standard Dose Weekly Intramuscular Beta Interferon-1a May Be Inadequate for Some Patients with Multiple Sclerosis: A 19-Year Clinical Experience Using Twice a Week Dosage

Robert W Baumhefner

Neurology Service, Veterans Administration West, Los Angeles Healthcare Center, Los Angeles, CA, USA

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***Correspondence:**
*Dr. Robert W Baumhefner, Neurology Service, Veterans Administration West, Los Angeles Healthcare Center, Los Angeles, CA, USA; Email: jaguar60@g.ucla.edu

When beta interferon was more widely used to treat relapsing multiple sclerosis (MS), the results from a number of studies showed that its efficacy was related to both dose and frequency of administration[1-3]. When we were treating relapsing MS patients with weekly IM beta interferon-1a at the VA West Los Angeles Medical Center in the early 1990s, we noted a large proportion of patients had breakthrough disease activity. Rather than switch these patients to higher dose subcutaneous preparations of beta interferon, which would subject these patients to new cutaneous side effects and the risk of a higher prevalence of developing neutralizing antibodies to beta interferon[2,4], we began to increase the dose of IM beta interferon-1a to twice a week. Our objective was to confirm the results of others that a higher dose and frequency of administration of beta interferon was more efficacious for some MS patients, and that this could be done with IM beta interferon -1a. Also, to our knowledge, it was the first study where the dose of beta interferon was increased in patients with breakthrough disease on a lower dose. This was not a designed clinical trial, but was permitted by the VA pharmacy service in the interest of patient care.

The study was submitted for Human Research Protection Program (HRPP) determination of whether internal review board (IRB) approval was required. The administrator of the VA Greater Los Angeles Healthcare System IRB #1 judged the study as being a review of a clinical undertaking to treat MS and drive MS into remission by increasing the administration of an Federal Drug Administration (FDA)-approved medication in patients and analyzing the clinical data in a systematic aggregate manner to determine whether the successful outcome in these patients was more than anecdotal and warranted the undertaking of more systematic research. The HRPP agreed that the endeavors up to this point were clinically driven, endorsed this work as a write-up of clinical experiences suggesting the feasibility of future research, and is not human subject research per se. In light of this, it was also determined that participant consent was not required.

Many of these patients subsequently had disease stability for extended periods of time. The retrospective analysis of our experience with this treatment was reported in this article[5].

We reported on a cohort of 92 patients with relapsing-remitting and relapsing secondarily progressive MS disease treated with weekly IM interferon beta-1a. 19 patients were either lost to follow-up or had their treatment discontinued due to side effects or other reasons. Of the remaining 73 patients, 15 remained stable on this treatment

and 58 patients (79%) had breakthrough disease. 53 of these patients were subsequently treated with twice per week IM beta interferon-1a. There was adequate follow-up for at least 2 years on 44 of these patients. 23 of these patients (52%) had no further breakthrough disease for 24 months or more defined as the primary outcome measure. 10 of these patients were stable for 60 months or more. 17 patients had breakthrough disease within 24 months, and 4 patients could not tolerate the increase in dose of beta interferon. Breakthrough disease was defined as any clinical relapses, new T2 or gadolinium enhanced lesions on brain MRI, or significant worsening of baseline Extended Disability Status Score (EDSS) or the graded neurological exam confirmed on the next clinic visit. An intent to treat analysis of the 53 patients administered at least one dose of twice per week IM beta interferon-1a was conducted. One patient was lost to follow-up before any data could be collected. A linear regression model was performed, with the dependent variable being any breakthrough disease activity and the independent variable being episodes of time over a 3-year period: every month, every half year, or quarter year. It showed a significant decrease in mean percentage of disease activity over all time points[5]. The only characteristic that significantly differentiated those patients who did not respond to the increase in frequency of interferon beta administration was a higher number of relapses in the 2-year period prior to any interferon beta-1a treatment.

This study was unique in many respects, it was a real-world experience of using IM beta interferon-1a to treat MS at one VA center where access to MS medications was not limited by third party payers. Patients were followed for extended periods of time, up to 20 years. It included all patients without any restriction or entry criteria. It is the first reported study of increasing the dose of IM beta interferon-1a to twice per week dosing in MS patients who had breakthrough disease on the standard dose of once per week.

The present study is deficient in many respects. It is retrospective, non-randomized, open-label, and selective in being VA-based with a much higher number of male patients than other studies. The intent-to-treat analysis lacks a comparison group of patients with breakthrough disease who were not switched to twice per week IM beta interferon-1a.

Despite the multiple deficiencies, it suggests that a higher weekly dose of more frequently administered IM beta interferon-1a is beneficial for MS patients with breakthrough disease on the standard weekly dose[5]. The results of our study are also consistent with previous studies that have shown a dose response relationship for beta interferon treatment of clinically active relapsing-remitting MS[2,3]. Treatment with IM beta interferon-1a has the advantages of a lack of significant cutaneous side effects of subcutaneous formulations and a low incidence of the development of neutralizing antibodies[4]. While we do not advocate the off-label use of IM beta interferon-1a twice a week, the more recent FDA approval of a subcutaneous preparation of peginterferon beta-1a for MS, which gives a higher dose of beta interferon-1a over a 2-week period and significantly increases the half-life of the drug over time, would be a viable option[6]. While it is still a subcutaneous injection, not an IM injection as was stated in our paper, the number of injections is significantly reduced, minimizing the incidence of skin reactions and possibly the incidence of developing neutralizing antibodies. This drug has more recently been shown to have high patient satisfaction, convenience, and high overall adherence rates in real world practice settings[7].

What is the relevance of the results of our study for the current realm of disease modifying treatment (DMT) in relapsing MS? Since the first Federal Drug Administration (FDA) approval of subcutaneous beta interferon-1b for relapsing MS in 1993, the DMT of MS has gone through several stages. There are now more than 18 FDA approved agents for DMT of MS. They can be divided into so called first line DMTs, generally older agents of mild to moderate efficacy, better tolerated, with mild side effects, and a long track record of safety.

These include beta interferon-1a and b, glatiramer acetate, dimethyl fumarate, and teriflunomide. The so called second line agents were more recently approved, have higher efficacy but more serious side effects and suppress the immune system to a greater degree, which can lead to more frequent infections and sometimes serious opportunistic infections, such as PML. These include fingolimod, siponimod, cladribine, natalizumab, alemtuzumab, ocrelizumab, and ofatumumab[8].

Traditionally, treatment of MS is started with a first line agent with close monitoring for breakthrough disease and switching to more efficacious second line agent if and when this occurs. However, there is a growing opinion among MS specialists that more efficacious agents should be the initial treatment of relapsing MS, even in its earliest stages[8,9]. This is predicated on the facts that there is currently no reliable indicator of the prognosis of a patient with MS, clinical monitoring of MS disease activity is not sensitive enough and does not detect a substantial amount of subclinical CNS damage that occurs early in the disease, and treatment of MS patients with agents of mild to moderate efficacy, only to later find breakthrough disease allows for years of CNS damage to accumulate, which could be minimized by treatment with higher efficacious agents earlier in the disease. Also, some newer high efficacy agents have much less serious side effects that can be adequately managed in early MS[9].

There is, however, the entity of clinically isolated syndrome (CIS), where a patient has an acute attack of symptoms consistent with MS and an MRI with lesions suggestive of demyelinating disease. Follow-up of these patients indicate that 60-90% of these patients go on to have MS. Treatment of these patients with interferon beta-1a or b, or gadolinium acetate have been shown to significantly reduce the percentage of patients progressing to clinically definite MS over a 2-3 year period, prolong the time to conversion to MS and reduce the number of new T2 lesions and gadolinium enhanced lesions on brain MRI[10]. When two dosing frequencies of subcutaneous interferon beta-1a were compared, 44 micrograms 3 times per week showed a hazard ratio of 0.49 versus placebo for the conversion of CIS to clinically definite MS over a 2-year period, while the hazard ration for 44 micrograms once per week was 0.69[11]. Both regimens were significant, but there was a suggestion of dose response relationship. There is a growing consensus that patients with CIS should be treated. If IM beta interferon-1a is contemplated for treatment of CIS, the results of our study should be taken into account.

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