EFFICACY OF INTERFERON IN MULTIPLE SCLEROSIS

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ABSTRACT

Introduction of interferon b-1b in the therapeutic strategy against Multiple Sclerosis has resulted in a great amelioration of treatment in various terms. Relapse rates, delaying progression of the activity, improvement of imaging outcomes as well as reduction of disease activity itself consist great achievements against a pathological condition that challenged medical effectiveness throughout decades. Two recombinant human IFN-1a and an IFN-1b preparations have been proved effected and well tolerated. We reviewed the most important literature concerning pharmacodynamics, medical efficacy, tolerability and adverse effects of interferon-b usage. In parallel, despite the wide range of trials referring to INF-b treatment, we tried to categorize results of main trials in order to present our conclusions systematically.

Key words: interferon b-1b, Multiple Sclerosis, interferon-b usage

INTRODUCTION

Introduction of interferon b-1b in the therapeutic strategy against Multiple Sclerosis has resulted in a great amelioration of treatment in various terms. Relapse rates, delaying progression of the activity, improvement of imaging outcomes as well as reduction of disease activity itself consist great achievements against a pathological condition that challenged medical effectiveness throughout decades. The most remarkable benefits are related with the Relapsing-Remittable and Secondary Progressive forms of the disease, totally contributing to several hopeful conclusions concerning our therapeutic options.

Two recombinant human IFN-1a and an IFN-1b preparations have been proved effected and well tolerated [(1-4)]. Although their effectiveness is not doubted by our modern medical reality, there are still critical questions concerning specifically their optimal dosage and their relative efficacy and safety. Although this is inevitably an issue that preoccupies a series of recent publications, certainty of conclusions is still a chimera.

We reviewed the most important literature concerning pharmacodynamics, medical efficacy, tolerability and adverse effects of interferon-b usage. In parallel, despite the wide range of trials referring to INF-b treatment, we tried to categorize results of main trials in order to present our conclusions systematically.

MATERIALS AND METHODS

There are two main studies concerning Interferon optimal dosage that consist our main material: Evidence and benefit trial. Their results were combined with others originated by a wide variety of series, altogether being the material of our study. All trials studied have been published and characterized by a remarkable citation impact.

Concerning evidence trial, this was designed to assess both tolerability and efficacy of the 2 available IFN-b-1a preparations, examining their impact by clinical and imaging measures[5]. Patients received IFN-b-1a using different formulations by different routes (SC vs. IM), using different doses (44 vs. 30 ?g) and different dosing frequencies (TIW vs. QW).

Relatively, the benefit study aims to provide long-term data on the efficacy of high-dose (250 ?g), high-frequency IFN-b-1b in patients with an experience of a clinical event[6]. It is a Phase III Study which has a placebo-controlled, randomized, double-blind, parallel-group design finally achieving also to compare treatment initiated after the first event vs. just after the diagnosis of MS.

RESULTS

INF-b-1b has been proved to have a beneficial effect to therapy of relapse remitting multiple sclerosis. Trials have indicated that two doses, 8 million international units, MIU (250?g) or 1.6 MIU (50?g) given subcutaneously every other day, when compared to placebo, reduced significantly the number of relapse-free patients, the time to first relapse and ?RI activity, even though there were no significant effects on ?DSS. Furthermore, multicentre trials of INF-b-1b 8 MIU against placebo, demonstrated a significant reduction of clinical and imaging activity against Secondary Progressive Multiple Sclerosis, but no significant efficacy against the progression of this form.

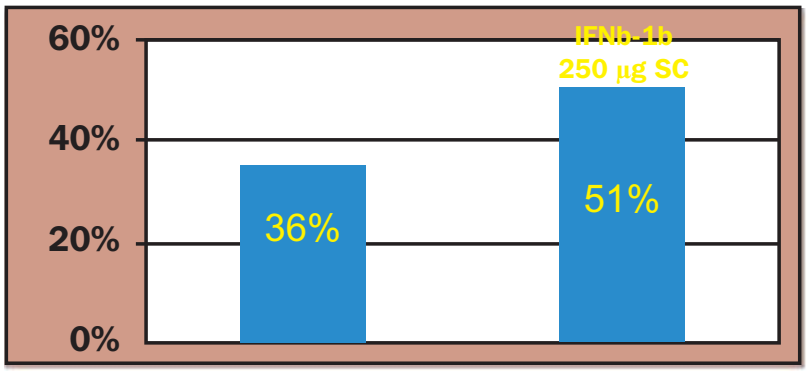
Relatively, IFN-b-1a (6 MIU) given intramuscularly, tested against placebo in a 2-year study, reduced significantly exacerbations of RRMS but did not improved significantly new T2 lesion creation. INF-b-1a doses of 22 or 44 ?g given subcutaneously three times a week, when compared to placebo,significantly increased time to first and second relapse, number of relapse-free patients and improved imaging parameters. However, IFN-b-1a once weekly 22mg subcutaneously in a secondary progressive MS has been proved not to effect significantly brain MRI measurement, clinical activity or brain atrophy progression.

Two great randomized trials have evaluated the comparative efficacy between intramuscular INF-b-1a vs. INF-b-1b (??COMIN trial) or subcutaneous INF-b-1a (EVIDENCE trial). INCOMIN trial showed that INF-b-1b was significantly better than intramuscular INF-b-1a in decreasing annual relapse rate and significantly ameliorated MRI measures and disability disorders. EVIDENCE trial proved as well that subcutaneous INF-b-1a 44 ?g ??W was significantly yet modestly more effective than intramuscular INF-b-1a 30?g QW treatment in clinical and imaging measures. Results of these two great trials have been as in diagrams.

INCOMIN trial results

OUTCOMES	SC IFN-B1a 44 µg TIW* (n = 339)	IM IFN-bla 30 µg QW (n = 338)	P p
Relapse free, no. (%)	191 (56)	163 (48)	0.023
Odds ratio (95% CI)	1.5 (1.1-2.0)		
Time to first relapse , 40th percentile, mos	13.5	6.7	0.002
Hazard ratio	0.70		
Annualized relapse rate	0.54	0.65.	0.033
Steroid courses per patient per year	0.19	0.28	0.009

EVIDENCE trial results (after 104 weeks)



However, other head to head open label studies did not show statistically significant difference in clinical efficacy between IFN beta products. The potential comparative superiority of IFN beta forms still remains controversial.

Efficacy of INF-beta is significantly affected by the development of Neutralizing antibodies (Nabs). Numerous studies indicate the formation of Nabs up to 35% of patients treated with interferon b-1b and up to 24% of patients receiving subcutaneous INF-b-1a. Main bioavailability factors include action of MxA protein which limits correspondence to therapy and expression levels of IFN response genes IFI127, TRIM69 and EPSTI1 [(7-9)].

Subcutaneous use of interferon may cause skin reactions and pain in the injection site. Menstrual cycle in women, liver function and white blood cell levels may also be affected [(10)]. Except all common side effects, there have been cases where the appearance of rare syndromes such as lupus, systemic sclerosis, dermatomyositis were reported. Besides, the potential correlation to breast cancer should be seriously considered.

DISCUSSION

Efficacy of interferon in other analysis IFN-b-1b was initially proved to be effective when examined in a double-blind versus placebo controlled trial involving 372 patients with RRMS in USA 1993. The primary outcome was the relapse rate as treatment with the higher dose reduces the relapse rate by approximately 30% and improved proportion of patients who were relapse free. It also reduced patients with relapses to the half1. Although there were no significant effects on EDSS, MRI activity was shown to be significantly decreased[1].

A second trial was performed in SPMS patients also concluding similar results. Significant reductions in time to becoming wheelchair bound, relapse rate and new and enhancing lesions for the 6 initial months of study[11].

When IFN-b-1a given intramuscularly was tested against placebo there were also remarkable outcomes. Patients treated with IFN-b-1a were significantly likely to reach the primary endpoint, length of time to progression of disability. Although no significant observation of T2 brain lesion load was observed, reduction of exacerbations reached 18%[12].

Finally, about INF-b-1a given subcutaneously, a large study included 560 patients with RRMS. Patients were randomized to receive treatment with INF-b-1a, 6 MIU or 12 MIU or placebo. In both treated groups, there was a decrease in the number of exacerbations of about 27% and 33% respectively while there was a significant decrease in their severity[4]. There was also a significant reduction of new and enlarging T2 lesions whereas a better response was shown to high doses in patients with higher disability[13].

Above results indicate the contributing effect of Interferon in treatment against MS. Combining these observations with those of INCOMIN and EVIDENCE trial, we could make firmer conclusions on the optimal dosing and efficacy. It seems that INF-b-1b is slightly superior to Inf-b-1a as well as the subcutaneous usage of INF-b-1a is modestly yet significantly preferable to the intramuscular one.

What remains uncertain?

There is a great issue concerning the development of Neutralizing Antibodies. Their appearance, even depended on dosage, remains uncertain about its clinical interest. What is more important is the ranged percentages of Nab that are mentioned by the various trials to be stimulated by Interferon-b usage.

Agent (Study)	Average Follow-Up	Dose	Frequency	NAB %
IFN-b-1a (PRISMS)	2 years	22 mg SC	3 times a week	23.8
IFN-b-1a (EVIDENCE)	48 weeks	30 μg IM	Once weekly	2
IFN-b-1b (NA-SPMS)	3 years	160 μg/m2 SC	Every other day	32
IFN-b-1b (BENEFIT)	2 years	250 μg SC	Every other day	29.9

Further, there are questions related to the exact definition of a treatment failure, evaluation criteria, MRI activity and patient selection. These are parameters that obviously create limitations to make firm conclusions. Probably, more specific criteria and consensus about treatment evaluation should be developed in order to determine a more objective evaluation of Interferon treatment.

CONCLUSION

The comparative advantage between interferon beta products still remains controversial but their significant contribution to therapy of MS is commonly accepted. Even if bioavailability and correspondence factors are accepted to be precise in a satisfying level, the appearance of new rare side effects indicates the essential research needed in order to increase tolerance. Large prospective studies comparing the efficacy and tolerability of various treatment strategies may offer the key to open the gate of full understanding of Interferon therapeutic prospective.

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