# Evidence-based Medicine Analysis of Immunomodulatory Treatment for Multiple Sclerosis

*a report by*

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## Evidence-based Medicine and Trial Results

Evidence-based medicine (EBM) is the judicious and conscientious use of current best evidence in making decisions about the care of individual patients. It teaches physicians how to draw clinically meaningful conclusions from clinical trials and how to compare results of different trials. In most trials, the active drug is compared with placebo and the results of different trials are not immediately comparable. EBM compares disease event (or bad outcome) rate. Disease event rate in the study population is compared with the expected disease event rate in the overall affected population, which is assumed to be similar to that of the group of patients treated with a placebo drug. The placebo reproduces all the psychological and even biological effects of taking a drug, being carefully followed up without taking the active drug.

Disease event rate is usually called the risk of the disease and the risk ratio (RR) is how many times the risk of the disease event is greater (or smaller) in the actively-treated group in comparison with the control or reference group. If the risk of the disease in the treated group is equal to the expected risk (the risk in the placebo group), this means that the drug was not effective and the RR is 1. If the disease risk was reduced by the active drug, the RR will be below 1, and to know if the reduction is significant the confidence interval (CI) is examined. CI is a measure of the uncertainty of study results, and is based on the idea that the same study, repeated on different samples, would not yield always the same result, but results spreading around the true unknown result. All these results are assumed to have a Gaussian distribution, and 95% CI includes most of the possible values of the Gaussian curve. If this range does not contain 1, this indicates that all risk ratios in this range have a less than 5% probability of being equal to 1; that is they are significantly different from 1 at a probability level below 0.05. This is usually assumed as a satisfactory level of significance. EBM also calculates the risk reduction – that is to what extent the active drug reduces the probability of the disease event compared with the placebo group (always representing expected disease event rate in the population). The most informative figure is the absolute risk reduction (ARR). To be significant, ARR 95% CI should not include 0 (i.e. no risk reduction), nor any negative number (a negative risk reduction is a risk increase, i.e. in the group under study, disease event rate increased instead of decreased). Another informative figure is the number of patients needed to treat (NNT) to prevent the bad outcome of the disease event. NNT CI should not include 0 or a negative number or, on the other hand, infinity. If the NNT is 0 or a negative number, this means that you must not treat patients to prevent the bad outcome. If it is infinite, this means that you have to treat an infinite number of patients to prevent the bad outcome, i.e. you will never be able to prevent the bad outcome.

Finally, since all EBM measures are calculated from RR, the event rate should always be used in the control group as a reference. They are therefore normalised to the respective control group and can be compared from one trial to another.

## The Major Clinical Trials in Relapsing-remitting Multiple Sclerosis

### Interferon Beta

In 1993, the first randomised clinical trial (RCT) of interferon-beta (IFNβ) in relapsing-remitting multiple sclerosis (RRMS) was published. It included 372 patients randomised to receive placebo or IFNβ-1b for two years. IFNβ-1b at a dose of 250μg subcutaneously every other day, when compared with placebo, reduced the clinical relapse rate (-34%; p<0.0001) – the primary end-point of the study. It also reduced the median number of T2 active lesions (-83%; p<0.009) and the median volume of T2 disease burden (-17.3%; p=0.001) on magnetic resonance imaging (MRI) scans. Risk ratios, absolute risk reductions and NNTs were all statistically significant for the primary clinical end-point (occurrence of relapses) and for MRI activity (see *Table 1*).

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*Table 1: Risk Ratios (RR) and Absolute Risk Reductions (ARR) of Adverse Outcomes (Relapse, Progression, or MRI Activity) and Numbers Needed to Treat (NNT) to Prevent the Adverse Outcomes Calculated for the Published Multicenter Randomised Controlled Trials (References Indicated Between Parentheses in Table Second Row) with Disease Modifying Drugs (Interferon Beta, Glatiramer Acetate) in Relapsing-remitting Multiple Sclerosis*

| | IFNB MS, 1993(2) | | MSCRG, 1996(4) | | PRISMS, 1998 (8) | | INCOMIN, 2002 (10) | | Glat, 1995 (25) | | Glat, 2001(26)* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | IFN beta-1b (SC 250µg EOD) | Pl | IFN beta-1a (IM 30µg OW) | Pl | IFN beta-1a (SC 44µg TIW) | Pl | IFN beta-1b (SC 250µg EOD) | IFN beta-1a (IM 30µg OW) | Glatiramer (SC 20mg D) | Pl | Glatiramer (SC 20 mg D) | Pl |
| Patients w/h relapses (n/n at risk) | 97/124 | 116/123 | 126/158 | 120/143 | 130/184 | 167/187 | 47/96 | 59/92 | 83/125 | 92/126 | 53/119 | 61/120 |
| RR (95% CI) | 0.83 (0.75–0.92) | | 0.95 (0.85–1.06) | | 0.79 (0.71–0.88) | | 0.76 (0.59–0.99) | | 0.91(0.77–1.07) | | 0.88 (0.67–1.15) | |
| RRA (95% CI) | 16.1% (7.7–24.4) | | 4.2% (-4.5–12.9) | | 18.7% (10.7–26.6) | | 15.0% (1.2–29.2) | | 6.6% (-4.7–17.9) | | 6.3% (-6.3–18.9) | |
| NNT (95% CI) | 7 (5–14) | | 24 (8 – ∞) | | 6 (4–10) | | 7 (3–85) | | 16 (6 – ∞) | | 16 (6 – ∞) | |
| Patients w/h progression (n/n at risk) | 34/124 | 45/123 | 121/158 | 115/143 | 54/184 | 77/187 | 13/96 | 28/92 | 42/125 | 44/126 | n.a. | n.a. |
| RR (95% CI) | 0.75 (0.52–1.08) | | 0.95 (0.85–1.07) | | 0.71 (0.54–0.95) | | 0.44 (0.25–0.80) | | 0.96 (0.68–1.36) | | | |
| RRA (95% CI) | 9.2% (-2.4–20.7) | | 3.8% (-5.4–13.1) | | 11.8 (2.2–21.5) | | 16.9% (5.3–28.5) | | 1.3% (-10.4–13.1) | | | |
| NNT (95% CI) | 11 (5 – ∞) | | 27 (8 – ∞) | | 9 (5–46) | | 6 (4–19) | | 76 (8 – ∞) | | | |
| Patients w/h MRI activity (n/n at risk) | 84/111 | 103/115 | 83/120 | 78/113 | 128/184 | 173/187 | 34/76 | 54/73 | n.a. | n.a. | 98/119 | 98/120 |
| | **,° | | • | | ° | | ° | | | | • | |
| RR (95% CI) | 0.84 (0.75–0.96) | | 1.00 (0.84–1.19) | | 0.75 (0.68–0.84) | | 0.60 (0.46–0.80) | | | | 1.01 (0.90–1.14) | |
| RRA (95% CI | 14% (4–24) | | 0.0% (-12–12) | | 22.9% (15.3–30.6) | | 29.2% (14.2–44.3) | | | | -0.7% (-10.4–9.1) | |
| NNT (95% CI) | 8 (5–25) | | -714 (-∞ – 8.32) | | 5 (4–7) | | 3 (2–7) | | | | -146 (-∞ – 11) | |

*All data calculated according to the intention to treat analysis principles (patients lost to follow-up taken as adverse outcomes, if not differently reported; patients who stopped treatment but remain in follow-up considered with their final response at the end of follow-up) on two year results except when indicated.*

*\*Study duration: 9 months; \*\*5 year data; •Gadolinium-enhancing MRI activity; °PD-T2 MRI activity; IFN=interferon; SC = subcutaneous; EOD=every other day; IM=imtramuscular; OW=once weekly; TIW=three in week; D=daily; n.a.=not applicable. RR is statistically significant if its 95% CI does not include 1; ARR if it does not vary between negative and positive percentages; NNT if its does not vary from negative to positive, including the infinite (positive or negative).*

The MSCRG (Multiple Sclerosis Collaborative Research Group) trial included 301 patients randomised to receive placebo or IFNβ-1a (30µg intramuscularly once weekly) for two years. After two years, IFNβ-1a, when compared with placebo, reduced the confirmed 1.0 point expanded disability status scale (EDSS)6 progression rate (-37%; p=0.02) – the primary end-point of the trial. It also reduced the relapse rate (-18%; p=0.04) and the median number of active (gadolinium-enhancing) MRI lesions (-33%; p=0.05). Median volume of T2 disease burden seen on MRI was also reduced, but this was not significant (-6.7%; p=0.36). The MSRCG trial was stopped earlier than originally intended without pre-planned stopping rules and the reason for stopping is difficult to understand (not being related to severe adverse events occurrence or to early confirmation of efficacy; the usual reasons for stopping a trial). The reliability of the definition of confirmed progression (the primary outcome in MSRCG study) in patients with shorter than two-year follow-up is questionable. In this study, several patients who worsened in the first year of the study actually improved in the second year. Later improvement would suggest that patients were experiencing prolonged exacerbations, rather than unremitting disease progression. Intention to treat analysis is stated but not correctly applied, since only 57% of patients (172/301) completed the full two years on medication. It is of interest that the reduction of relapse rate in the first year of therapy (-9.6%, not significant) was less than that observed in the subgroup completing two years' treatment (-32%; p=0.002), suggesting that the full clinical benefits of once-weekly 30µg IFNβ-1a might be delayed for a year or more after starting treatment. In addition, the annualised relapse rate of the patients who did not complete the two-year study (a subset of patients who completed at least one year of treatment) was higher in IFN_β-1a (1.03) than in placebo-treated patients (0.80), indicating either that two-year completers were biased towards a better treatment response or, again, that once-weekly 30µg IFNβ-1a needs over one year to yield full clinical benefit. Risk ratios, absolute risk reductions and NNTs failed to reach statistical significance for all outcome measures (including the occurrence of disease progression, the primary end-point of the trial) (see *Table 1*).

The Prevention of Relapses and Disability by IFNβ-1a Subcutaneously in Multiple Sclerosis (PRISMS) study enrolled 560 patients randomised to two-year treatment with placebo or IFNβ-1a (22 or 44µg subcutaneously three times weekly).

IFNβ-1a at a dose of 44μg, three times weekly, reduced relapse rate (-32%; p<0.005), the primary end-point of the trial. It also reduced the confirmed 1.0 point EDSS progression rate (-30%; p<0.05), the median number of T2 active lesions (-78%; p<0.0001) and the median volume of T2 disease burden seen on MRI (-14.7%; p<0.0001) when compared with placebo. Risk ratios, absolute risk reductions, and NNTs were all statistically significant both for clinical end-points and for MRI activity (see *Table 1*).

### Randomised Comparative Trials of Different IFNβ Treatment Protocols

The issue of the relative efficacy of IFNβ-1b and -1a has been recently addressed in the Independent Comparison of Interferon (INCOMIN) trial. This study directly compared the clinical and MRI efficacy of IFNβ-1b (250μg every other day subcutaneously) to once-weekly IFNβ-1a (30μg intramuscularly). INCOMIN was a controlled study where 188 patients, with an EDSS score between 1.0 and 3.5 and at least two relapses in the preceding two years, were randomised, with allocation concealment, to treatment with either drug for two years. INCOMIN is the only multicentre trial examining IFNβ for the treatment of MS not sponsored by drug companies, with funding coming via institutional sources instead (the Italian Ministry of Health and the Italian MS Society).

Over the two years, every-other-day IFNβ-1b increased the proportion of patients without relapses (primary clinical end-point) (+42%; p=0.03); without new T2 lesions at MRI (primary MRI end-point) (+112%; p<0.0003); and without confirmed 1.0 score EDSS progression (+25%; p<0.005); and slowed time to confirmed disability progression (p<0.01) when compared with once-weekly IFNβ-1a. Risk ratios and absolute risk reductions with every-other-day IFNβ-1b compared with once-weekly IFNβ-1a were all statistically significant (see *Table 1*) and were similar to those observed for multiple-weekly injection IFNβ formulations compared with placebo in the pivotal trials. NNT values are low (see *Table 1*), statistically significant and fall within the range of those calculated from published data from all previous controlled trials of type I IFNs in MS.

Another recent trial, published by Panitch et al. in 2002, compared IFNβ-1a, 44μg subcutaneously, three times weekly (n=339) and IFNβ-1a, 30μg intramuscularly once-weekly (n=338). The Evidence for Interferon Dose Effect: European–North American Comparative Efficacy (EVIDENCE) trial was a multicentre, prospective,

randomised, assessor-blinded study. The initial phase of the study was 24 weeks, with patients having the option to remain on study medication for up to 48 weeks. At 24 weeks, IFNβ-1a given at 44μg three times weekly had a significantly greater effect than 30μg once-weekly on several relapse-related outcomes. Significantly more patients were relapse-free with the three times weekly dosing schedule at 44μg (74.9%) than with once-weekly dosing at 30μg (63.3%; p=0.022). In addition, 44μg of IFNβ-1a reduced the risk of suffering a first relapse by 30% and increased the number of patients free from new T2 lesions by 30%. At 48 weeks, clinical and MRI effects still favoured the high-dose, three times weekly IFNβ-1a, although the difference between the two groups became less pronounced. Risk ratios and absolute risk reductions with 44μg three times weekly IFNβ-1a compared with 30μg once-weekly IFNβ-1a were all statistically significant (see *Table 1*).

Two major studies, INCOMIN and EVIDENCE, therefore support the hypothesis that the dose and dosing schedule have a major impact on the clinical efficacy of IFNβ, indicating the need for frequent high-dose administration of IFNβ in order to optimise efficacy in patients with RRMS.

### Side Effects

The majority of the side effects associated with IFNβ use are most likely during first three to six months of treatment and decline in frequency thereafter. The frequency of side effects is similar with IFNβ-1a or IFNβ-1b with two exceptions. There is a higher incidence of both local skin reactions and positive titers for neutralising antibodies (NAb) against IFNβ in IFNβ-1b-treated patients. Local skin reactions to IFNβ tend to decline with improved injection technique. NAb have been associated with reduced levels of IFN-induced biological markers. NAb may also affect IFNβ clinical and MRI efficacy. While some studies found a detrimental effect of NAb on treatment response, others did not. In general, a negative association between NAb occurrence and IFNβ efficacy was demonstrated by long-term studies. Long-term evaluations show that the impact of NAb on clinical outcomes may be delayed for between three and four years. It is worth noting that NAb frequency is lower for intramuscular IFNβ-1a (which has been associated with the lowest NAb frequency, 2–6%) compared with subcutaneous IFNβ-1a and IFNβ-1b (22–38%). Different frequencies of occurrence are probably related to a different immunogenicity of IFNβ preparations but also to the different doses and frequency of administration used in the various IFNβ protocols.

Strategies to reduce the occurrence of NAb have been studied. The addition of 1g ethylprednisolone each month to IFNβ therapy was well tolerated and reduced the development of NAb by over 50%. Another approach is to increase the IFNβ dose. The PRISMS study, which compared the efficacy of 22 or 44μg IFNβ-1a subcutaneously three times a week in patients with RRMS, showed that NAb frequency was significantly lower in patients treated with the higher dose. The Optimization of Interferon for MS (OPTIMS) study, a multicentre prospective trial investigating outcomes with two IFNβ-1b doses, 250μg or 375μg, administered subcutaneously every other day, showed that NAb-positive patients treated with 375μg IFNβ-1b had a significantly greater probability of NAb disappearance (hazard ratio: 1.5; 95% CI: 1.04-2.15; p=0.02), and an over five-fold lower risk of having persistent MRI activity during treatment compared with patients treated with the currently approved 250μg dose (RR=5.41; 95% CI:1.67–17.84; p=0.001).

### Treatment Protocol

In conclusion, a single weekly administration of IFNβ, while more attractive for patients, may be less effective, or its effects might be delayed by at least one year from the start of treatment. It is important for patients to receive the best treatment with the quickest onset of beneficial effect, which in this case is most likely IFNβ given in multiple weekly injections. Arguments that NAb against IFNβ-1b deleteriously affect the eventual course of MS must be evaluated in long-term comparisons.

### Glatiramer Acetate

The first large RCT of glatiramer acetate (GA) in RRMS included 251 patients randomised to receive either placebo or 20mg GA subcutaneous daily for up to three years. GA reduced relapse rate (-29%; p=0.007), the primary end-point; and slowed unconfirmed 1.5 point EDSS progression (-28%; p=0.037), compared with placebo. No MRI outcome measures were assessed as part of this trial. Risk ratios, absolute risk reductions and NNTs failed to reach statistical significance for all outcome measures (see Table 1).

A second short-duration European/Canadian trial was undertaken to look specifically at MRI measures. It involved 249 patients randomised to receive either placebo or 20mg GA for nine months. GA reduced the total number of enhancing lesions (the primary end-point) (-35%; p=0.001), relapse rate (-33%; p=0.012) and the median change in T2 disease burden (-8.3%; p=0.0011). The

reliability of results is certainly biased by the short duration of the trial. Risk ratios, absolute risk reductions and NNTs failed to reach statistical significance for all outcome measures (see Table 1).

### Side Effects

GA is well tolerated. Only minor, short-lived local skin reactions are common. Localised lipoatrophy at the site of injection has been reported in as many as 45% patients, mostly women. In some cases, lipoatrophy occurred within months of therapy initiation. Once in every 1000 injections, a systemic reaction may occur, such as dyspnea, flushing, chest tightness or palpitations, resolving in seconds or minutes without sequelae. This rare event seems benign, even though its cause is unknown.

### Treatment Protocol

The only protocol used for GA is 20mg subcutaneously per day.

### Conclusions

Conclusions come from two recently published Cochrane reviews. For IFNβ no clear evidence of the persistence of the efficacy over the long-term came out from a systematic analysis of published trials with type I IFN in RRMS. This Cochrane review concluded, in fact, that IFN has a certain effect in RRMS in reducing relapses and disability during the first year of treatment, but the clinical effect beyond the first year of treatment is not clear. For GA, Munari et al. assessed efficacy by pooling together data from four published individual trials. Authors used intention-to-treat analysis and calculated the risk ratio with the fixed effect model for most outcomes (disability progression at two years, EDSS change at two years and proportion of patients with relapses), using a random model only in case of outcomes with a significant heterogeneity (mean number of relapses at one and two years). GA did not seem better than placebo either in preventing clinical progression or in reducing the number of relapse-free patients at two years. For the mean number of relapses, the weighted mean difference showed no significant decrease of relapse at one and two years.

IFNβ has some effect in reducing relapses and disability progression, although some doubts about its long-term efficacy still remain. GA does not seem better than placebo from a systematic review of published trials. ■

*A version of this article containing references can be found in the Reference Section on the website supporting this briefing (www.touchneurology.com).*