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**The Art and  
Science of Multiple  
Sclerosis Care**

Timely issues involving MS patient care were the focus for discussion at this year's Annual Meeting of the Consortium for Multiple Sclerosis Centers (CMSC) in Toronto, Canada.

With a theme of *The Art and Science of Multiple Sclerosis Care*, the meeting had its largest ever attendance, with over 1000 healthcare professionals and others specialising in the care of people with MS taking part. The CMSC promotes a team approach to MS care and this was evident in the diversity of the programme: presentations reflected the views of the patient, the healthcare professional and the researcher.

This issue of *Medical Express Reports* discusses highlights from the CMSC meeting, including the CME-accredited 2<sup>nd</sup> Annual Symposium, *Evidence-based Healthcare: A Framework for Care of the Multiple Sclerosis Patient*. In addition, new comparative data on the tolerability of some current treatments for MS are presented, and future treatment strategies are discussed that may be used to increase the clinical benefits for patients.



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Toronto, Canada, venue for the Annual Meeting of the Consortium for Multiple Sclerosis Centers.

## Increasing adherence with education and support

The management of side-effects is essential for adherence to immunomodulatory treatments for MS, and it is clear that patients will not benefit from treatments with proven efficacy if they do not take them correctly.

Amy Perrin Ross of the Loyola University Medical Center, Chicago, USA presented an overview of the current treatment support available for patients with MS. Methods such as dose escalation and prophylactic treatment with non-steroidal anti-inflammatory drugs can limit flu-like symptoms, whilst autoinjector devices and skin

cooling can reduce skin reactions. Furthermore, patient support schemes, such as the BETA (Betaseron® Education, Training and Assistance) Nurse Program are proactive in helping patients and can increase retention rates.

Further details of this discussion are reported on page 2. ■

# Effective management of flu-like symptoms and skin reactions

Non-adherence to therapy is a major issue for patients with MS, with an estimated average of over 50% of patients taking their medication incorrectly, reported Amy Perrin Ross, of the Loyola University Medical Center, Chicago, USA.

The NARCOMS (North American Research Consortium in MS) registry of patients found that the main reasons quoted by patients for non-adherence to immunomodulatory therapy were:

- an increase of MS symptoms (21%)
- lack of obvious benefit (15%)
- flu-like symptoms (14%)
- skin reactions (<10%).

**... dose escalation plus concomitant ibuprofen treatment significantly reduced the occurrence of flu-like symptoms**

Simple measures, such as dose escalation and concomitant treatment with non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, can almost prevent the incidence of flu-like symptoms. In an open-label study, with gradual dose escalation, 6/15 (40%) of patients experienced flu-like symptoms in the first 10 weeks of treatment with Betaseron®, and prophylactic treatment with ibuprofen reduced the incidence to 3/18 (17%). A combination of dose escalation plus concomitant ibuprofen treatment significantly reduced the occurrence of flu-like symptoms further to 1/16 (6%). Thus, dose escalation and more liberal use of NSAIDs could have a substantial impact on long-term tolerability and, therefore, encourage adherence.

Data have also shown that flu-like symptoms largely disappear with time. An extension of the original pivotal relapsing-remitting (RR) MS Betaseron® trial to 12 years found that the frequency of flu-like symptoms was just 5% in Year 12, compared with 65% in Year 1 (with

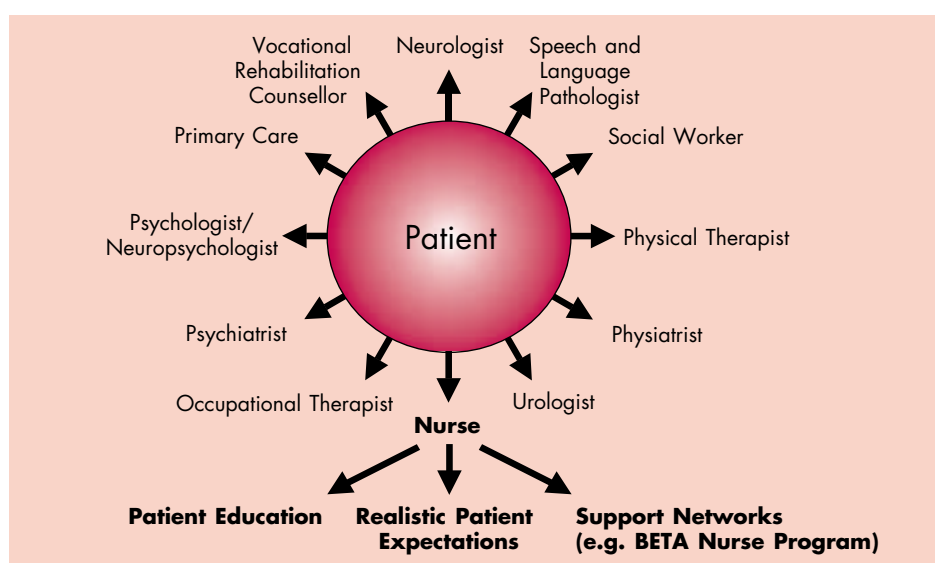


Figure 1: Patient-centred care and good nursing strategies can promote patient adherence.

most of the cases of flu-like symptoms disappearing after 3 months).

Skin reactions can be managed successfully through effective injection technique. Straightforward measures such as the use of autoinjectors, rotating the injection site, using a dry needle, allowing the drug to come to room temperature, and ice pre- and post-injection can all successfully reduce patient discomfort.

The Autoject® 2 study in 12 patients with RRMS receiving Betaseron® demonstrated a 54% decrease in the incidence of skin reactions with the introduction of the Autoject® device into

**54% decrease in the incidence of skin reactions with the introduction of the Autoject® device**

**Good support plays a key role in encouraging patients to stay on therapy**

the injection routine, reported Amy Perrin Ross.

Supportive literature has also been used successfully in many chronic illnesses to increase patient adherence, and patient education and empowerment are crucial. Nursing strategies can promote adherence by ensuring that patients have realistic expectations and can foster a strong nurse-patient relationship, as well as promoting the idea of a support network (Figure 1).

The BETA (Betaseron® Education, Training and Assistance) Nurse Program gives patients dedicated specialist MS and telephone nurses who offer education in MS treatment-related issues, training, and assistance with

**Managing side-effects ... eliminates the possibility that a drug will be chosen for convenience over efficacy**

support programmes such as BETA Friends and MS Pathways. For patients receiving Betaseron® therapy, the BETA

Nurse Program has successfully increased retention rates to 88% over a 13-month period, compared with 63% for historical controls. Proactive strategies like these help patients to help themselves receive the maximum efficacy available from immunomodulatory treatments for their condition.

Patients deserve to have the highest possible benefit from their MS treatment, thus reducing the number, severity and frequency of relapses. This can only be

achieved if patients adhere to their therapy. Focusing on the management of flu-like symptoms with gradual dose escalation and NSAIDs, and skin reactions with autoinjectors and other simple techniques, as well as encouraging patients to enrol in support programmes, will increase the efficacy of a patient's therapy. Managing side-effects will improve a patient's overall satisfaction and quality of life, and thus eliminates the possibility that a drug will be chosen for convenience over efficacy. ■

## Comparable tolerability for approved and higher dose Betaseron®



Increasing the dose of Betaseron® beyond the currently approved dose of 250 µg does not result in significantly more adverse events, despite the possible increased systemic biological activity of the 500 µg dose, reported the BEYOND first phase study group (Poster S06 CMSC 2004). The benefits of high-dose, high-frequency interferon beta treatment are clear (see page 6), and it is reasonable to expect that increasing the dose further will offer even greater therapeutic benefit for people with MS.

The 12-week, first phase of the BEYOND (Betaseron® Efficacy Yielding Outcomes of a New Dose) programme randomised patients with relapsing-remitting MS to 250 µg (38 patients) and 500 µg (33 patients) Betaseron®. The dose titration schedule was equally effective in both treatment groups, with over 90% of patients in each arm attaining the target dose during the study.

The two doses of Betaseron® were well tolerated with no new or unexpected adverse events arising from either dose. Some observed adverse events tended to be more frequent with the 500 µg ('BEYOND') dose, but the incidence of injection site pain was low and comparable to that with the 250 µg dose, and there were fewer injection site reactions in the 'BEYOND' dose group (Figure 2).

The goal of the BEYOND programme is to establish whether 500 µg Betaseron® is a well-tolerated and more efficacious

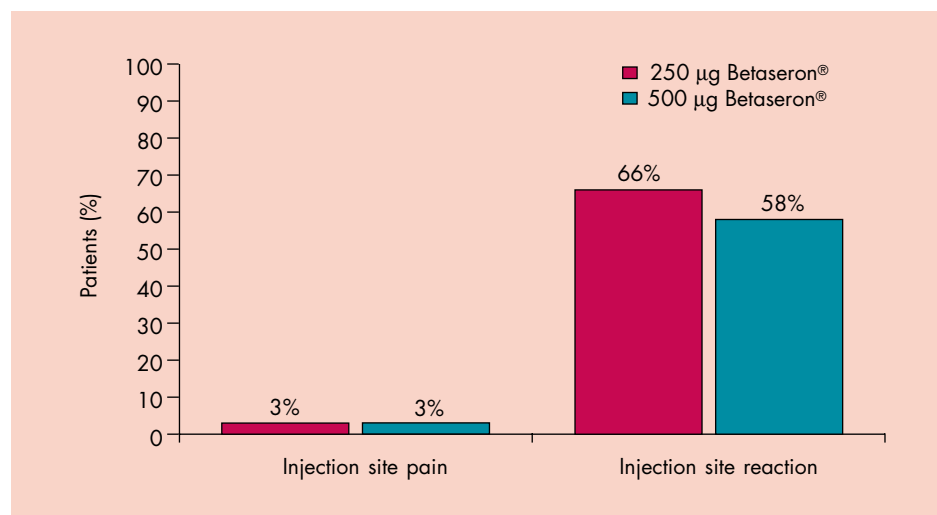


Figure 2: Incidence of injection site pain and reaction, with 250 µg versus 500 µg Betaseron®.

MS treatment than any currently available. These first-phase data support the now-recruiting second phase of BEYOND. This large, multicentre, randomised, double-blind study will compare the safety, tolerability and efficacy of Betaseron® at the 'BEYOND'

500 µg dose with the currently approved 250 µg dose, and will be the first study to explore the question of the relative effectiveness and tolerability of Betaseron® and glatiramer acetate. ■

# Injection pain dependent on treatment choice

For patients taking chronic therapies for control of their MS, tolerability and comfort of injection are just as important as the effectiveness of their therapy. This was evident from three reports during the Annual Meeting of the CMSC, which drew attention to differences between the tolerability of the two high-dose, high-frequency therapies: Betaseron® and Rebif® (Table 1).

Study	Patients	Treatments	Findings or objectives
COMFORT (complete)	64 healthy male volunteers	<ul style="list-style-type: none"> <li>Betaseron® sc 250 µg eod for 4 weeks</li> <li>or</li> <li>Rebif® sc 44 µg 3×/week for 4 weeks</li> </ul>	<ul style="list-style-type: none"> <li>Rebif® injections are consistently more painful at 5-minutes and 30-minutes post-injection</li> <li>The pain caused by Rebif® injections is more severe</li> <li>Injection site reactions are more frequent and more severe with Rebif®</li> </ul>
CRISP (complete)	20 patients with MS recently starting therapy with either Betaseron® or Rebif®	<ul style="list-style-type: none"> <li>10 consecutive injections of Betaseron® sc 250 µg eod or</li> <li>10 consecutive injections of Rebif® sc 44 µg 3×/week</li> </ul>	<ul style="list-style-type: none"> <li>Rebif® injections are consistently more painful immediately after injection, and at 10-minutes and 1-hour post-injection</li> <li>The pain caused by Rebif® injections is more severe</li> </ul>
BRIGHT (recruiting)	>600 patients with MS recently starting therapy with either Betaseron® or Rebif®	<ul style="list-style-type: none"> <li>15 consecutive injections of Betaseron® sc 250 µg eod or</li> <li>15 consecutive injections of Rebif® sc 44 µg 3×/week</li> </ul>	<ul style="list-style-type: none"> <li>To assess the severity and quality of injection site pain</li> <li>To assess the frequency and severity of injection site reactions</li> <li>To determine the influence on injection site pain on patient satisfaction with therapy</li> </ul>

sc: subcutaneous; eod: every other day; COMFORT: COMparative study FOR Two high-dose interferons in MS. CRISP: Canadian Betaseron® versus Rebif® study on Injection Site Pain. BRIGHT: Betaseron® versus Rebif® InvestigatinG Higher Tolerability.

Table 1: Comparison of three studies with Betaseron® and Rebif®.

The COMFORT study examined tolerability in terms of injection site pain and injection site reactions in healthy volunteers. Whilst there is no reason to believe that the results would be any

different in patients with MS, the CRISP study in 10 patients with MS was, nevertheless, performed and supports the view that Rebif® injections are more painful than Betaseron®

injections. Now, a large multicentre study (BRIGHT) is underway to confirm these results. The data from the BETA Nurse Program discussed on page 8 also concur with these findings. ■

## A brighter future for patient tolerability

Evidence from COMFORT (COMparative study FOR Two high-dose interferons in MS) and CRISP (Canadian Betaseron® versus Rebif® study on Injection Site Pain) show that injection site pain experienced by patients with MS may be dependent on the therapy selected. To explore this further, a multicentre, non-randomised, prospective, observational study of patients with relapsing-remitting MS is now underway, as detailed at the Annual Meeting of the CMSC in Toronto by Dr Karl Baum of the Henningsdorf Hospital, Germany (Poster W05 CMSC 2004).

As in COMFORT and CRISP, the BRIGHT (Betaseron® versus Rebif® InvestigatinG Higher Tolerability) study will compare the two high-dose, high-frequency interferon beta subcutaneous treatments (250 µg Betaseron® every other day or 44 µg Rebif®

three times weekly). The study will run in at least 100 centres and is anticipated to recruit at least 300 patients to each arm.

The outcome of BRIGHT is expected to determine the influence of injection site

pain on patient satisfaction with therapy and will provide physicians with data on patient comfort and convenience during treatment using one of the two high-dose, high-frequency interferon beta therapies. ■

# Patient 'COMFORT' drives choice of therapy

The COMFORT (COMparative study FOR Two high-dose interferons in MS) provides clear evidence that Betaseron® causes less injection site pain and fewer injection-site reactions than Rebif®. Both therapies are otherwise well tolerated and have been shown to offer comparable efficacy.

Nurses and physicians need to be able to make informed decisions about the most appropriate management of their MS patients, reported Dr Sam Hunter of the Advanced Neurosciences Institute in Nashville, USA (Poster S13 CMSC 2004). This applies not only to the effectiveness of the available therapeutic options, but also how well they are tolerated by patients.

Both of the available high-dose, high-frequency interferon beta subcutaneous treatments (Betaseron® and Rebif®) are effective for the treatment of MS, and have similar efficacy, but questions remain regarding their relative tolerabilities. Until recently, there have been no direct comparative studies of these two high-dose treatments, although anecdotal evidence has suggested that Rebif® is associated with more injection site pain than Betaseron®.

The COMFORT study examined the tolerability of Betaseron® compared with Rebif® as measured by injection site pain and injection site reactions. In total, 64 healthy male volunteers were randomised to receive subcutaneously either 250 µg Betaseron® every other day ( $n=32$ ) or 44 µg Rebif® three times weekly ( $n=32$ ) over a 4-week period. After every injection, volunteers assessed the injection site pain at 5-minutes and 30-minutes post-injection using a visual analogue scale (VAS), which ranged from 0 mm (no pain) to 100 mm (worst pain imaginable). Two days after each injection, an investigator blinded to treatment allocation also assessed the severity of the injection site reaction using a 4-point categorical rating scale. During the course of the study, 434 Betaseron® and 384 Rebif® injections were administered.

Results from COMFORT demonstrate that the overall incidence of injection site pain was significantly greater with Rebif®

injection compared with Betaseron® (Figure 3C).

The findings from COMFORT suggest that treatment with Betaseron® rather than Rebif® will help minimise the pain burden on patients with MS. It seems reasonable to infer that patients are, therefore, more likely to adhere to their Betaseron® treatment regimen and, thus, derive the intended clinical benefit. ■

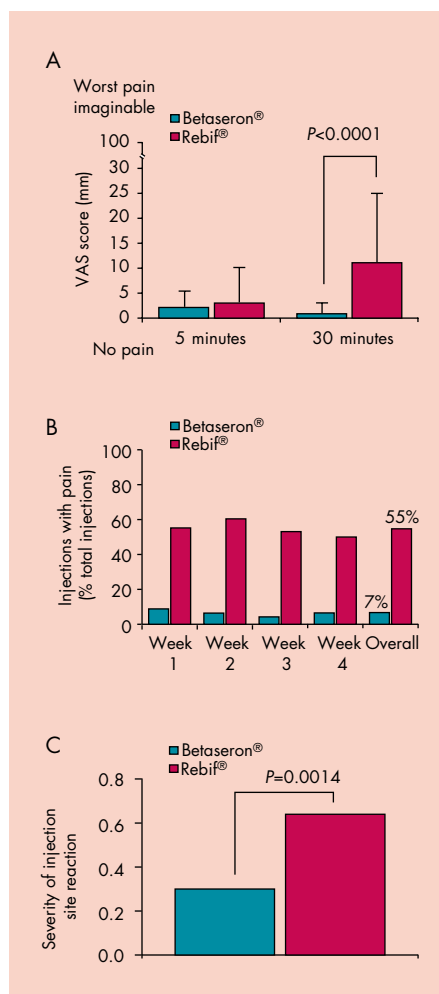


Figure 3: Injection site pain and reactions: Betaseron® versus Rebif®.

than with Betaseron®. At 30 minutes, the injection site pain after Rebif® injection was greater than at 5 minutes, whereas with Betaseron® the pain decreased over time (Figure 3A). Overall, only 7% of Betaseron® injections were painful after 30 minutes compared with 55% of Rebif® injections (Figure 3B). This was consistent over the 4 weeks of the study. Furthermore, Rebif® was also associated with a significantly greater overall severity of injection site reactions per

## CRISP results support Betaseron®

CRISP (Canadian Betaseron® versus Rebif® study on Injection Site Pain) confirmed that Rebif® injections are consistently more painful than Betaseron® injections in patients with MS, concluded Colleen Harris of the University of Calgary MS Clinic in Canada at the recent CMSC meeting in Toronto (Poster S27 CMSC 2004).

This single centre, open label, comparative Phase IV pilot study assessed the injection site pain associated with 10 consecutive subcutaneous injections of either 250 µg Betaseron® every other day or 44 µg Rebif® three times weekly in patients with MS. Ten patients were enrolled in each treatment arm.

The results of CRISP showed that, in patients with MS, injections of Rebif® were more frequently painful when compared with Betaseron® injections. Furthermore, the pain felt upon injection with Rebif® was more severe than for Betaseron®. The burden of pain in MS patients is often under-estimated and is an important feature of their disease. Any methods by which pain can be reduced should be welcomed. These results may, in part, be due to the Rebif® drug formulation which is more acidic than that of Betaseron®, or may be because of differences in drug concentration or structure. ■

# Benefits of high-dose, high-frequency interferon beta treatment supported

The results of comparative trials of interferon beta treatments support the benefits of higher and more frequent dosing on clinical and magnetic resonance imaging (MRI) parameters of disease activity, said Dr George Kraft of the Western Multiple Sclerosis Center at the University of Washington in Seattle, USA.

Whilst the pivotal trials produced data that may have seemed comparable, studies such as INCOMIN (INdependent COMparison of INterferon) and EVIDENCE (EVIDence for Interferon Dose Effect: European North American Comparative Efficacy) show that there are significant differences among the interferon beta therapies.

INCOMIN was an independent, multicentre, randomised comparison of Betaseron® and Avonex® with blinded evaluation of MRI scans and an open-label clinical evaluation in patients with relapsing-remitting MS. The results demonstrated the superior efficacy of Betaseron® in terms of the proportion of

**Doses of interferon beta higher than those currently approved may improve on clinical benefits**

relapse-free patients and Expanded Disability Status Scale progression, as well as the proportion of patients with no new T<sub>2</sub> lesions and T<sub>2</sub> burden of disease. EVIDENCE was a similar comparison of Rebif® and Avonex® with a blinded evaluation of the primary clinical outcome. This also demonstrated

the superiority of the high-dose, high-frequency regimen.

It is now reasonable to consider that doses of interferon beta higher than those currently approved may improve on the available clinical benefits. Results from a pilot study investigating the safety and tolerability of a 500 µg ('BEYOND') dose of Betaseron® are reported on page 3. The BEYOND programme is examining the safety, tolerability and efficacy of 500 µg Betaseron® subcutaneously every other day, in comparison with the currently approved 250 µg dose and glatiramer acetate, and will be the largest MS population study to date with an estimated 2200 patients. ■

# NAb are not a major cause of sub-optimal response to Betaseron® therapy

Causes other than the presence of neutralising antibodies (NAb) must be considered for sub-optimal response to therapy, advocated Dr Pat Coyle of SUNY at Stony Brook, New York, USA (Poster S07 CMSC 2004); and, as a result of uncertainty over the clinical relevance of NAb, treatment decisions should be based on an individual's clinical response to therapy and not their NAb status.

This conclusion was drawn after review of the data from MS patients tested for NAb in North America, Europe and Australasia. Schering AG and Berlex

**Treatment decisions should be based on an individual's clinical response to therapy and not their NAb status**

offered a free testing service to physicians who were interested in the NAb status of patients whom they perceived as sub-optimal responders to Betaseron®, although in Australia NAb status was a requirement for reimbursement.

Of the 6000 patients tested, the majority were NAb negative with only a few patients having NAb titres that were considered high (7% in the North American cohort and 8% in the European and Australasian cohort). Indeed, the frequency of high NAb

titres observed was no higher than had been previously reported in clinical trials. Yet this population was likely to have been enriched for patients who were not responding fully to Betaseron® treatment. Recent research suggests that any effect on relapse-related outcomes during treatment is more likely with high NAb titres. Other causes must, therefore, be considered for the sub-optimal response, for example, inadequate dosing or poor adherence to therapy, concluded Dr Coyle. ■

# Early treatment is essential

Treating MS early on in the disease course may be critical in shutting down or slowing the abnormal immune process, said Dr Pat Coyle of SUNY at Stony Brook, New York, USA at the CMSC Meeting 2004.

In brain tissue examined from 39 patients with MS, acute axonal injury, as measured by increased amyloid precursor protein, was significantly greater in those patients with disease duration of less than 1 year. Furthermore, inflammatory cell numbers are also highest in early MS. Axon protective treatments, said Dr Coyle, should be started as early as possible and continued for some years.

CHAMPS (Controlled High-risk subjects Avonex® MS Prevention Study) and ETOMS (Early Treatment of MS Study) demonstrated improved outcomes in clinically isolated syndrome patients treated with interferon beta compared with results obtained in relapsing-remitting (RR) MS patients. Furthermore, long-term studies suggest that immunomodulatory therapies for MS have changed the natural history of the disease, supporting the therapeutic rationale for early intervention. For example, from the Vancouver COSTAR database, which followed 63 RRMS patients taking disease-modifying therapy, only 6.9% developed secondary-progressive MS in greater than 11 years.

This is significantly different from the expected value of 67.3% ( $P < 0.0001$ ).

The Betaseron® 5-year extension study in patients with RRMS also demonstrated continued suppression in terms of exacerbations and T<sub>2</sub> lesion burden (Figure 4 A, B), whilst the 12-year data showed a positive effect on T<sub>2</sub> lesion burden (Figure 4 C).

At the first attack of MS, evidence of multiple sequestered antigens to myelin components (such as anti-MOG and anti-MBP) is an indication of more severe disease and predicts an early conversion to clinically definite MS. This provides a strong argument for early immunomodulatory treatment to delay this event.

‘A proactive approach to disease therapy has been adopted in other diseases such as rheumatoid arthritis and systemic lupus erythematosus, indicating a change in treatment paradigms for chronic conditions. The first few years of disease are the critical time to intervene,’ concluded Dr Coyle. ■

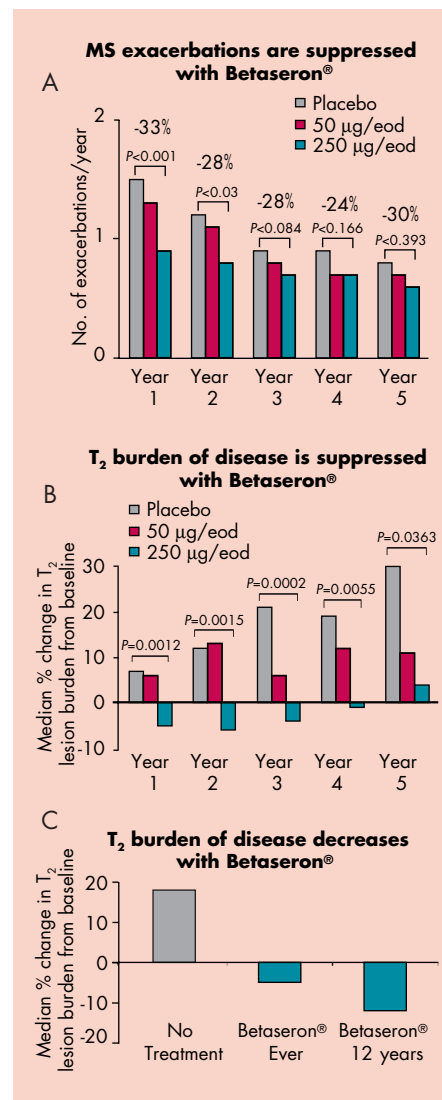


Figure 4: Betaseron® – 5-year extension study in patients with RRMS.

# Patient care needs to be evidence based

The importance of assembling the evidence regarding MS treatment so that informed choices regarding best available efficacy can be made was acknowledged at the CMSC meeting 2004 by Kathleen Costello of the Maryland Center for MS, Baltimore, USA.

Reports, such as the *Disease modifying therapies in multiple sclerosis*<sup>1</sup> paper published by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, were highlighted as an essential aid in medical decision-making. ‘Reports such as these critically evaluate the literature to better understand the true value of

different therapeutic interventions,’ said Kathleen Costello.

This report considered the clinical usefulness of the currently available disease-modifying therapies, and classified them according to evidence from clinical trials, producing final recommendations for physicians treating

patients with MS. A synopsis of conclusions and recommendations of the subcommittee was then published.

This evidence-based approach assists physicians by providing an important and rigorous guide to the quality of the available medical literature. ‘This is the best attempt to utilise the best information to give the best treatment,’ concluded Kathleen Costello.

1. Goodin DS *et al.* *Neurology* 2002;58:169–178. ■

# Patients switch to Betaseron® for greater efficacy, greater comfort

Lack of efficacy using other treatments, and injection site reactions and injection pain, are key drivers for patients to change to Betaseron® therapy from other products, reported Randall Schapiro of the University of Minnesota, USA (Poster S04 CMSC 2004).

In the BETA (Betaseron® Education, Training and Assistance) Nurse Program in the USA, a substantial number of patients switching to Betaseron® from Avonex® (675 patients in one 12-month period) and glatiramer acetate (422 patients) did so because of a perceived lack of efficacy (75% and 61%, respectively), either by the patient or the physician (Figure 5 A, B). And, of those switching from Rebif® to Betaseron®

(177 patients), 59% did so because of painful injections, injection site reactions or other injection reactions (Figure 5 C).

By providing consistent individualised care, BETA nurses help patients start, adjust to and maintain Betaseron® treatment. Whilst greater efficacy is an important driver for patient satisfaction from therapy, this should not be at the expense of tolerability. When

considering the data from over 6000 patients enrolled in the Program, almost 90% were still on Betaseron® 13 months after beginning therapy.

Clearly, ensuring that patients remain on therapy and gain the most from their treatment requires creative and long-term support, such as that provided by the BETA Nurse Program in the USA and similar initiatives throughout the world. ■

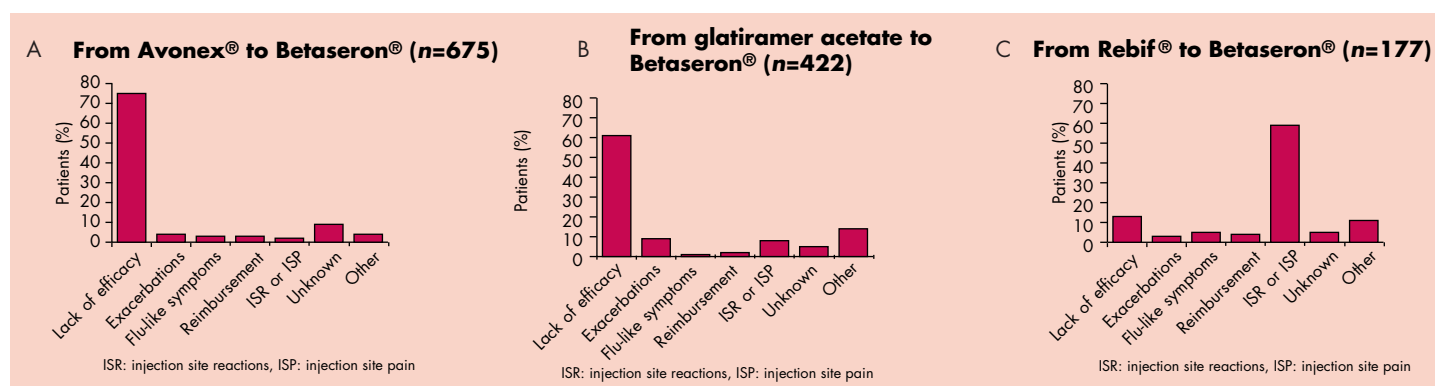


Figure 5: Reasons why patients switch therapy to Betaseron®.



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