

CONGRESS NEWS

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Scientific symposium
„MS management today.
Striving for long-term success“
in Malta 2005
(Photo: Y. C. Zwick)

Early treatment and more than 16 years of clinical experience
with interferon beta-1b

Striving for long-term success

"MS is a treatable disease in the year 2005. This wasn't always so, but it is very treatable now, especially if we get to it early before the damage occurs. If we wait too long, we can't retrieve what we've lost," Randall Schapiro¹, Minneapolis, Minnesota, USA, said in Malta. Since MS is a chronic illness, it necessitates life-long therapy aiming at altering or halting the course of the disease and preventing or postponing long-term disability. At an interactive scientific symposium on MS in Malta, chairmen Anthony Galea Debono¹, Guardamangia, Malta, and David Bates¹, Newcastle upon Tyne, UK, welcomed nearly 700 international neurologists to share their experience. The scientific program was devoted to close examination of available long-term data on immunomodulating therapies. First results of a novel approach chosen for long-term follow-up of interferon beta-1b patients, who once participated in the North American pivotal trial, dating back to 1988, were presented. Further topics of discussion were interferon beta, early intervention, dose optimization, personalized MS management and new compounds under development.

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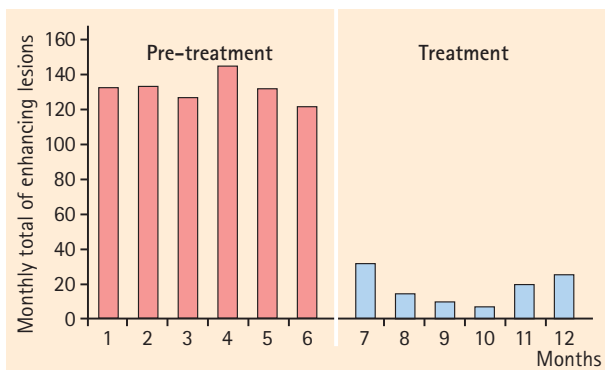


Figure 1: Rapid onset of action on MRI activity in RRMS: Mean number of total monthly enhancing lesions before and after initiation of interferon beta-1b therapy (n = 27) (7) (slide: Rieckmann).

While prevalence of MS is low in Malta – 5 in 100,000 Maltese in 1978 and 13.2 in 100,000 in 1999 – it still is a major problem in other European countries, affecting young adults and their families. Even in nearby Sicily, the prevalence rate of 120 in 100,000 people is a lot higher than on the Maltese islands, Debono¹ noted.

Like the catacombs beneath Malta, much is also hidden below the surface in MS. There is subclinical disease activity such as inflammation, demyelination and axonal/neuronal loss. If left untreated, MS leads to disability and decline in quality of life in about half of the patients within 15 years of diagnosis, Peter Rieckmann¹, Würzburg, Germany, emphasized. Yet substantial improvement in MS management has been possible thanks to advanced diagnostic techniques along with the McDonald criteria (McDonald et al. Annual Neurol 2001; 50: 121-7), a better understanding of MS pathology, greater emphasis on early diagnosis and effective treatment options.

Reduce the damage – enhance repair

According to Rieckmann¹, this life-long neurological disease requires a multimodal approach including physical and acute relapse therapy and on top of it all, disease-modifying drugs. Since immunomodulating drugs became available, frequency and severity of relapses, development of lesions within the CNS as well as disability can be effectively reduced. Interferon beta-1b was the first beta interferon to be introduced and to date efficacy and safety data are based on more than 550,000 patient years. In the pivotal trial, interferon beta-1b revealed not only positive effects on annual relapse rate (34% reduction) and median time to the first relapse, but also on the number of hospital admissions due to MS. In addition, the 5-year-data showed a continued reduction in MRI lesions over time. Today, the drug still offers an unsurpassed risk-benefit ratio.

Interferon beta-1b is thought to interfere with T-cell activation, cytokine production and cellular activity, underlying inflammation and destruction within the central nervous system, the speaker said. Moreover, interferon beta-1b may also help maintain the integrity of the blood-brain barrier and reduce the number of activated autoimmune T-cells reaching the CNS. A reduction in new lesions is an early sign of an effective interferon treatment; MRI scans revealing its rapid onset of action (figure 1).

What about dose and frequency?

When it comes to dose and frequency of interferon beta, it is not advisable to switch to a lower total weekly dose even in patients free from clinical and MRI disease activity for many years. This was revealed by a small study of 27 patients (1) clearly favoring a high-dose/high-frequency regimen of interferon beta-1b over interferon beta-1a i.m. (figure 2). All in all, various studies such as INCOMIN and EVIDENCE have shown that high-dose and high-frequency is more potent than low-dose and low-frequency of administration.

And even though an argument in favor of a once-weekly interferon beta treatment might be that less frequent injections should provoke less frequent adverse events and promote compliance, closer examination of the safety data of the INCOMIN and the EVIDENCE studies did not show a significant advantage in terms of compliance with the different therapeutic regimens, Barrie Hurwitz¹, Durham, North Carolina, USA, added. These findings were recently endorsed by a retrospective survey by O'Rourke et al. (6). Thus, there are conclusive data – based on analyses of pivotal as well as head-to-head trials – that show that more frequent and higher doses of interferon beta are more effective than a once-a-week low-dose.

Beyond the standard dose

Furthermore, preliminary studies suggest that the interferon beta ceiling for efficacy using eod administration regimes has not yet been reached. Will there be an additional benefit if the dose of interferon beta is increased above any currently

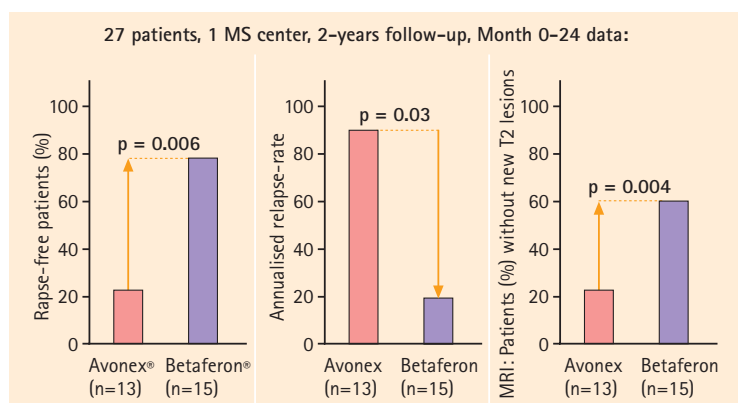


Figure 2: The dose-reduction study: Dose and frequency do make a difference (1) (slide: Rieckmann).

Table 1: Best (optimal) treatment response to date (slide: Hurwitz¹).

clinically isolated syndrome (CIS)	interferon beta
early relapsing–remitting MS (RRMS)	high-dose/high-frequency interferon beta
relapsing–remitting MS (EDSS - 5.5)	high-dose/high-frequency interferon beta
secondary progressive MS (SPMS)	high-dose/high-frequency interferon beta, mitoxantrone
primary progressive MS (PPMS)	nil to date (phase II results of high-dose/high-frequency interferon beta)

available high-dose, high-frequency interferon beta regimen? And will this dose still be safe and well tolerated?

Currently, the effects of an even higher than the currently approved dose of interferon beta-1b are being examined: The findings of the first 12-week-phase of the BEYOND (Betaferon®, Efficacy Yielding Outcomes of a New Dose) trial, investigating tolerability as well as safety and evaluating dose escalation in 71 treatment-naïve patients either receiving regular (250 µg) or high doses (500 µg) of interferon beta-1b, were tantalizing. In this pilot study, the BEYOND dose was well tolerated – injection site reaction and injection pain not being different for the two doses – and a marked reduction of gadolinium-enhancing lesions and volume was seen for both doses of interferon beta-1b. However, the effect had a greater magnitude with the higher dose.

The results of the larger, 2-year, randomized, double-blind, multicenter BEYOND dose flexibility study, currently ongoing, will potentially confirm these findings with final results expected in 2007. Since only a head-to-head comparative trial can provide reliable evidence to answer the question of differences in efficacy among beta interferon preparations and glatiramer acetate, the results of this controlled study investigating two different doses of interferon beta-1b (250 and 500 µg s.c. every other day) and of glatiramer acetate (20 mg every day) in approximately 2,100 RRMS patients, will also provide a comparison of a non-interferon drug versus interferon beta.

Optimal treatment

Hurwitz¹ advise how to avoid a suboptimal treatment response is to start treatment early, use more effective drugs first (high-dose, more frequent interferon beta) for which robust long-term data are now starting to become available, induce remission with cytotoxics which is potentially risky, however, or use combination therapy from the start. "So what is the best you can do? If you apply evidence-based medicine and look at the currently available studies in CIS (clinically isolated syndrome), it's low-dose beta interferon trials that have shown benefits up until now. In early RRMS, on the basis of Durelli's INCOMIN trial, it's clearly interferon beta-1b over interferon beta-1a i.m. and in RRMS to an EDSS to 5.5, it's again the high-dose/high-frequency beta interferons that have the best outcome measures. In SPMS it is high-dose/high-frequency interferon beta and mitoxantrone. Unfortunately, we have nothing yet for PPMS," Hurwitz¹ said (table 1).

"Starting before too much damage is done"

Anticipating the benefit: Interferon beta-1b in early MS

Inflammatory activity in RRMS is not confined to episodes of clinical impairment, but starts prior to the first attack and usually continues even during remission. And progressive disability seems to reflect cumulative and irreversible axonal loss. In addition, the immune-mediated activity underlying MS may become more difficult to control as the disease progresses and as time passes. This supports an early treatment strategy.

But what do we know now about early treatment and patients with a CIS? If CIS patients have MRI abnormalities, the likelihood that they will develop clinically definite MS (CDMS) is very high, Chris Polman¹, Amsterdam, The Netherlands, explained. The presence of lesions predisposes to MS, whereas the number of lesions determines when disability will develop. Data by Brex et al. (2) suggest that patients with more T2 lesions at the time of CIS show greater disability after 14 years than people with fewer abnormalities in their CNS. Furthermore, it was demonstrated that early intervention with intramuscular interferon beta-1a after a first clinical demyelinating attack delays the second event and hence the shift in diagnosis from CIS to CDMS.

Polman¹ stated that considerable evidence supports early treatment and that allowing patients to start with a high-efficacy product such as interferon beta-1b (Betaferon) very early may alter the natural course of the disease and may yield an even greater effect on limiting disease progression, but long-term benefits remain to be demonstrated.

Polman¹ then discussed various studies investigating beta interferon treatment in CIS patients. When comparing the BENEFIT (487 CIS patients, full results available later in 2005), ETOMS (309 CIS patients) and CHAMPS (383 CIS patients) trials, beta interferon dosages differed markedly. Moreover, patients in the last study had fewer MRI lesions and fewer enhancing lesions at baseline to begin with. Patients with a multifocal presentation were excluded by protocol. While in ETOMS, 89% of the patients and in BENEFIT, 69% had nine T2 lesions or more, in CHAMPS, only 29% of the patients revealed eight T2 lesions or more and 70% had no enhancing lesions at all (versus 41% in ETOMS and 57% in BENEFIT). Nonetheless, the BENEFIT trial, so far had the lowest drop-out rate, indicating that interferon beta-1b despite

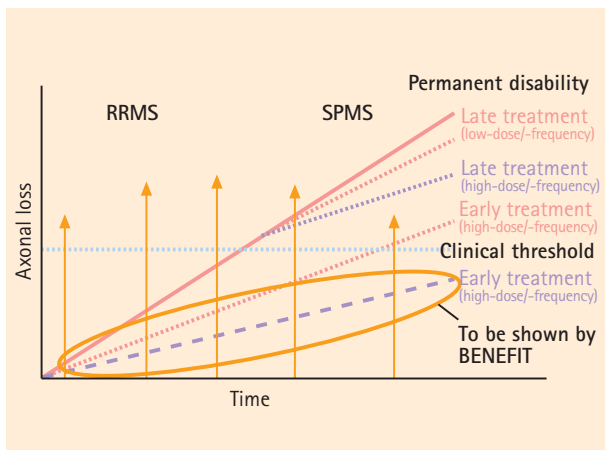


Figure 3: Early/Late treatment and dose/frequency. Model: Different effects of high- versus low-dose interferon beta treatment in early versus late MS (slide: Polman¹).

a more frequent dosing regimen is well accepted by CIS patients. In addition, it is the only study with a prospective follow-up and the five-year extension serves to evaluate longer-term benefits of early intervention.

BENEFIT (BEtaferon in Newly Emerging multiple sclerosis For Initial Treatment), a multicenter, double-blind, placebo-controlled trial, aims at assessing the importance of an early onset of a high-dose/high-frequency interferon beta administration. Therefore, patients with a first clinical demyelinating event suggestive of MS and an MRI screening scan indicative of the disease were treated within 60 days after the first episode with 250 µg interferon beta-1b s.c. or placebo every other day for a period of up to two years or until the diagnosis of MS was confirmed. Polman¹ pointed out that a standardized scheme was developed and some lesions originally considered to lead to a "monosymptomatic" presentation were re-classified and then documented to lead to a "polysymptomatic" presentation or vice versa. Rather than using the terms "monosymptomatic" and "polysymptomatic", however, they were renamed and are now referred to as "monofocal" or "multifocal" presentations. Patients were then monitored to assess treatment effects prior to a second attack and long-term effects of an early versus a delayed treatment on disease progression were documented. Moreover, MRI and molecular prognostic markers are being investigated. BENEFIT will be the first study that also incorporates a longer observation period. Final results will be presented later this year at theECTRIMS 2005, and are expected to provide answers for patients with a first attack and a CIS as well as data on the effects of a high-dose/high-frequency interferon beta-1b dosing regimen on conversion to definite MS. If BENEFIT can show that permanent disease disability and the onset of impairment can be delayed, then this perhaps may offer a clearer rationale for early intervention (figure 3).

"We have come a long way"

Randall Schapiro¹, Minneapolis, Minnesota, USA, emphasized that times have changed in MS treatment. Back in the '60s, MS treatment consisted of fever therapy and ACTH administration. Moreover, vitamins were given intravenously, EEGs were done on everybody and patients had to take a hot bath, he remembered: "If the patients looked bad, we knew they had MS." In 1965 the workup for MS did not yet include evoked potentials and diagnosis was clinical. In the '70s the diagnosis was still clinical and so it was in the '80s and '90s despite the use of MRI scans and spinal taps. In the '90s - the era of clinical studies - "approved" therapy for MS included interferon beta-1b, starting a new treatment era. Schapiro¹ referred to the new millennium as the treatment era of evidence-based medicine. Today, immunomodulating drugs provide ways to control the disease. Still, comprehensive symptom management is necessary to limit disability and delay impairment in the activities of daily living. MS patients are confronted with the task of integrating their disease and its consequences into their lives in a way that, in spite of the illness, they may still live as normally as possible.

Shared decision making

He then presented case reports, pointing out that MS is a disease with a wide-ranging impact on physical and emotional functioning. Among the most common problems are bladder dysfunction and fatigue. However, MS is as varied as each individual it affects. Thus, an ideal strategy would be a multidisciplinary approach combining medication, rehabilitation, patient education and psychological support: Neurologists, nurses, social workers, psychologists and physical therapists join forces. This team principle has been pursued for more than 25 years in the clinic Schapiro is working for, where they try to help people with MS maximize their independence and quality of life. Schapiro¹ also mentioned that 79% of patients prefer an active role in treatment decisions which should be considered when treating MS patients.

More experience necessary

Novel approach to long-term follow-up

"We need to get long-term data and look at long-term disability," Randall Schapiro¹¹, Minneapolis, Minnesota, USA, announced. Therefore, a novel approach on long-term follow-up of MS patients who started treatment 16 to 18 years ago was initiated in January 2005. In Malta preliminary findings were presented.

Nowadays, the scientific community in collaboration with drug companies is trying to figure out what happened to the patients originally included in the pivotal trials. Did they stay on the medication? How is their walking ability today? When asked

what the first results are and whether they indicate improvement, Schapiro¹¹ said: "There is a clear difference in walking skills, there's a clear difference in activities of daily living among the people who take the medicine. It does work!" He also recited a personal experience: "I run a huge MS center in the United States in Minneapolis. I follow 3,000 patients with MS on a regular basis, I had my own floor in the hospital for most of the past 28 years and until the advent of Betaferon, I used to have 16 hospitalized patients every week having problems with their MS. Now I have four. It is clearly different."

16-year LTF - May 2005 data

Georg Ebers¹, Oxford, UK, then presented preliminary data (also see box) of the 16-year long-term follow-up (16-year LTF) of interferon beta-1b treatment in RRMS which employed cross-sectional data from pivotal trial patients, allowing comparisons with well-characterized natural history data and a control cohort of untreated patients. It is planned to perform two analyses: Patients will be stratified by original dose groups (250 µg, 50 µg, placebo) and by overall length of exposure to interferon

beta-1b. ("Betaferon always" group, "Betaferon ever" group and "Betaferon never" group). Data on survival, disease status, relapse rate, MSFC, EDSS scores, MRI outcome, side effects, antibody titers, cognitive function and quality of life are being assessed.

Ebers¹ pointed out that after all these years, it was possible to locate 72% of all patients from the original cohort within five months. As of May 19, 2005, the majority of identified patients was still alive (89%). These latest interim results showed that - compared with the patients once in the placebo group - more patients initially treated with interferon beta-1b were still walking either unaided or with aids (classified as "ambulatory") (figure 4). The data suggest that long-term treatment with interferon beta-1b is safe and well tolerated.

Furthermore, the preliminary findings are consistent with the widespread concept that early treatment initiation might have a lasting impact on outcome, but does not yet establish it. Yet,

16-year LTF - April 2005 data (3)

Interferon beta-1b was the first immunomodulatory therapy approved for treatment of RRMS patients, based on the double-blind, placebo-controlled, randomized North American interferon beta-1b pivotal trial which confirmed that 250 µg interferon beta-1b, administered subcutaneously every other day, is effective and well tolerated in these patients. In this 372-patient study with three treatment arms (placebo, 50 µg and 250 µg interferon beta-1b), enrollment took place between June 1988 and May 1990.

Now, a 16-year long-term follow-up of interferon beta-1b treatment in RRMS is being performed to evaluate the impact of this drug on long-term success and to generate hypotheses about the relationship of clinical and imaging parameters and outcomes in these patients. This observational study is the longest follow-up for any MS treatment and will provide valuable information on patients who once entered the pivotal trial. By now, median time spans of 20.5 years since diagnosis and about 23.5 years since the onset of MS symptoms have passed. All seven centers in the USA and all four Canadian sites involved in the original trial agreed to participate in the follow-up study. Patients who participated in the North American interferon beta-1b pivotal study were and still are being contacted and asked to also take part to form "the North American cohort". The primary analysis examines the outcome of patients treated with interferon beta-1b, and patients will be stratified by original dose group and by overall length of exposure to interferon beta-1b. The secondary analysis includes comparisons with two natural history cohorts for which untreated RRMS patients will be recruited in the United Kingdom according to the pivotal trial

protocol selection criteria. They will form "the UK cohort" and will be matched to patients in the North American cohort for age, gender, duration of disease, relapse rate, level of disability and disease status. In addition, a well-characterized natural history control group derived from the London, Ontario, Canada, database comprises a population-based group of MS patients who received virtually no disease-modifying treatments.

Preliminary findings

Recruitment began in January 2005 and as of April 7, 2005, 63% of all patients from the original trial had been identified with 89% of these patients still alive and 11% deceased. 94% of the patients who initially received 250 µg interferon beta-1b were still alive, compared to 92% assigned to low dose (50 µg) interferon beta-1b and 82% originally assigned to placebo. 42% of all patients identified in April 2005 reported that they are walking unaided or with aids and 19% said they require a wheelchair or are bedridden.

Benefit may increase with IFN exposure

So far, patients who were originally treated with 250 µg interferon beta-1b in the pivotal trial are more likely to report continued ability to walk than those patients who received placebo. So the preliminary differences between the original treatment groups may indicate that delaying interferon beta-1b treatment has an adverse effect on long-term outcomes and that early treatment initiation has a long-lasting beneficial impact. Confidence in these preliminary findings, however, may increase as additional patients are located.

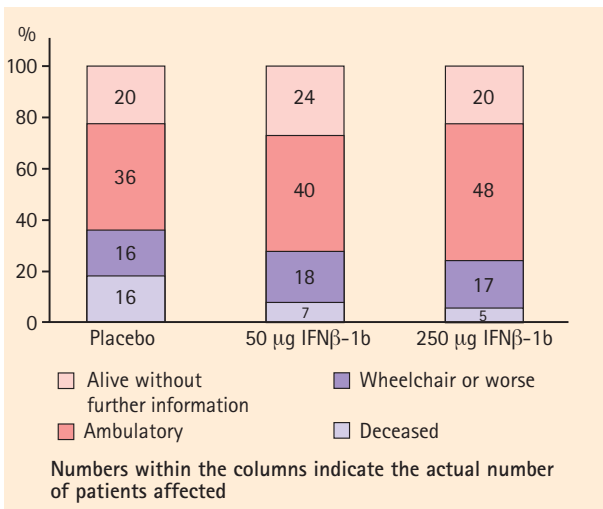


Figure 4: 16-year follow-up with interferon beta-1b in RRMS patients: Patient status according to original treatment allocation as of May 19, 2005 (n = 267/identified patients only) (slide: Ebers¹).

scheduling of identified patients is still going on, Ebers¹ emphasized, and more detailed analyses will be available later in 2005.

Once completed, this study will provide a unique source of information due to the length of observation, the high rate of ascertainment and the variety of parameters investigated. It may generate hypotheses about variables of importance for MS patients not yet fully considered in controlled studies, for example, cognitive parameters (5). Because the follow-up covers a period of 16 years, it can be anticipated that cognitive deficits, another major problem in MS, will have occurred in many patients and cognitive evaluation may also serve to assess treatment efficacy in the long run.

Pitfalls of long-term studies

Ludwig Kappos¹, Basel, Switzerland, talked about pitfalls of long-term studies. Prospective controlled clinical trials usually do not last for more than two to three years. In addition, results stemming from short-term studies cannot be extrapolated reliably to obtain estimates of long-term efficacy. Because until now, long-term follow-up investigations on efficacy and safety are lacking, other studies and approaches are necessary to obtain valuable long-term data. He explained that two types of studies - comprehensive patient registries with a systemic follow-up on a regular basis and long-term follow-up of patients participating in controlled clinical studies - may help to obtain valuable long-term data. But even though patient registries have the advantage of being really comprehensive, often not enough data can be obtained and observation quality may not be optimal. Moreover, therapeutic decisions are not standardized and may depend on unknown factors. On the other hand, a long-term follow-up of patients in controlled studies provides data of MS patients who are well characterized at baseline and demonstrate more than average compliance. However, are these patients really representative of the total population?

According to Kappos¹, long-term follow-up is helpful to assess tolerability, adherence and maybe prognostic indicators, but not to evaluate efficacy, since conditions are no longer standardized and internal control groups are lacking, as they can only be set up for a maximum of two years. External controls are possible, however. Being aware of the importance of a long-term follow-up as well as the methodological pitfalls, researchers have initiated several studies and developed comprehensive external control groups, as currently done by the Sylvia Lawry Center for MS Research, he said.

Kappos¹ conclusion: Even though better studies are certainly necessary, some conclusions about long-term effects of immunomodulatory drugs are possible:

- reproducible benefit across studies
- long-lasting effect, no indication of rebound
- good long-term tolerability
- potential to define responder/non responder profile not yet fully explored

Personalized approach to patient care

Fostering adherence

"We know drugs don't work in patients who don't take them", Carmel Higgins¹, Newcastle upon Tyne, UK, said, speaking about influences on adherence and the role of specialized MS nurses.

Being an MS specialist nurse herself, she explained that providing information, comprehensive initial training, support and advocacy are of utmost importance for patients with MS. "What chances do MS patients have if they don't understand what MS is going to do? So what chance do they have to understand what therapy is going to do for them," she asked.

Today, MS patients are looking for reliable and valid information about their disease and available treatments, an active role in disease management and a better communication with healthcare professionals. Understanding the illness is a prerequisite to acceptance and also provides strength to cope with the disease, since for many of the afflicted, the uncertainty of what comes next and the inescapable consequences that might be encountered in the future are difficult to endure. According to Higgins¹, members of the health care team should provide in-depth information including demonstration of how to optimize life. A multidisciplinary team is therefore elementary and is ideally composed of a neurologist, a specialized MS nurse, a family doctor, a psychologist, a social worker, a physiotherapist and an occupational therapist.

The role of an MS nurse

Specialized MS nurses, for example, may spend a lot more time with the patients than doctors do, therefore encountering and hopefully alleviating many of their fears. They may identify potential areas of concern and difficulties and "may act as a

patient's advocate", Higgins¹ said. Moreover, the increased use of nurses has shown positive effects on compliance both in hospitals and primary care settings.

Compliance and adherence

The extent to which a patient takes her/his medicine, follows a diet and adapts her/his lifestyle to the recommendations of the healthcare provider used to be called "compliance", but less subserviently should be referred to as "adherence" implying voluntary actions rather than strict obedience. In Higgins¹ experience, factors with a negative influence on adherence are higher EDSS scores and a secondary progressive course of the disease. Also, patients are usually at higher risk of failing to adhere in the initial six months of therapy. Non-adherence often is a result of unrealistic expectations and lack of information concerning management of side effects and their appropriate treatments. Thus, Higgins¹ is convinced that if "we can manage side effects more efficiently, we can increase adherence." Easy tips such as the use of a dry needle, gel packs prior as well as after injection and an autoinjector, injection site rotation and gentle massage have resulted, in her experience, in minimizing injection site reactions. Tolerability may be improved by gradual dose escalation, co-medication with ibuprofen or paracetamol, evening administration, extra support and constant reassurance that symptoms in general diminish within a few months, she added. Therefore, her advise is: Injection supervision and training, more frequent nurse visits, direct clinic/telephone access, reinforcement of physician support for therapy and enrollment in patient support programs.

Furthermore, injection site pain may depend on the drug as demonstrated in the CRISP study (Canadian Rebif, versus Betaferon Study on Injection Site Pain) (figure 5). The BRIGHT study (Betaferon versus Rebif® Investigating Higher Tolerability) is a larger trial investigating similar questions, but the results still have to be awaited.

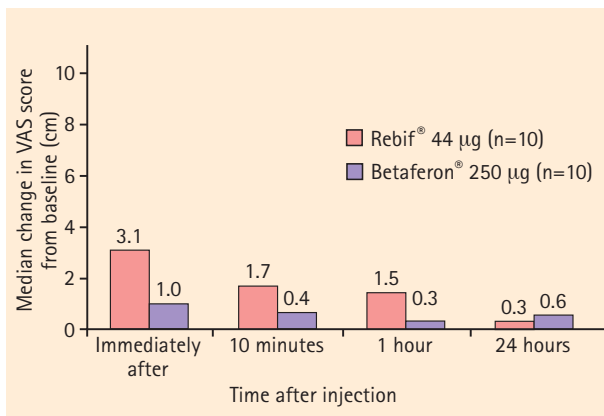


Figure 5: The CRISP study: Evaluation of injection site pain in MS patients (carried out in a Canadian pilot phase IV trial with 20 MS-patients and 10 consecutive injections): Less pain immediately after injection as well as ten minutes and an hour thereafter in interferon beta-1b users (4) (slide: Higgins¹).

Table 2: Treatment benefit – NNT (slide: Rieckmann¹).

therapy/indication	number needed to treat (NNT)
oral triptan/ migraine, pain-free	3
interferon beta-1b/ MS, relapse-free	6
carotid-endarterectomy/ stroke or cardiovascular death	12
insulin/diabetes, prevent neuropathy	15
pravastatin/ heart attack prevention	33
hormone replacement/ hip fracture in osteoporosis	121
aspirin/heart attack prevention	208
ACE inhibitor/survival rate after myocardial infarction	210

How to convey study results to patients?

But how can treatment benefits be translated to the patients? Peter Rieckmann¹, Würzburg, Germany, proposed explaining the effect of interferon beta by comparing the number needed to treat with other drugs for other illnesses such as diabetes or migraine (table 2). Then it becomes obvious that in MS interferon beta is quite effective, since only small numbers of patients have to be treated before a beneficial effect can be seen. When taking aspirin, in contrast, to prevent myocardial infarction, 208 patients need to be treated before one heart attack may be prevented.

Outlook

Long-term commitment to neurology

Joachim-Friedrich Kapp¹, New Jersey, USA, said that "breakthrough treatment does not come in short intervals." Nonetheless, he reminded the audience that in 1993, the era of MS as a treatable disease began, and currently several therapeutic novelties are under development in the company's drug discovery unit.

He explained that MS strategies may be improved by exploring and maximizing further potentials of interferon beta-1b, by searching for new treatment approaches and by advancing the concept of personalized therapy. Therapy must control the disease, change its course and come up with better prognosis in the long run for the sake of the patients.

Somatic cell therapy

Schering's commitment to neurology not only covers MS but extends to other incurable neurological disorders such as Parkinson's disease in which implantation of Spheramine (dopamine-producing human retinal pigmented epithelial cells on gelatin microcarriers) may soon be a promising therapeutic option. Results of a pilot study revealed improvement in UPDRS (Unified Parkinson's Disease Rating Scale) motor scores in off-phases, total UPDRS and activities of daily living. No serious adverse events and no dyskinesias in off-phases were attributed to this innovative therapeutic approach, Kapp explained. In a placebo-controlled phase IIb trial (STEPS) safety, tolerability and efficacy are now being investigated in 68 patients with advanced Parkinson's disease. To date, 66 patients have been enrolled, 34 treated and so far no treatment-related adverse events have been reported.

Currently in MS, the results of two phase III trials are being awaited to establish high-dose/high-frequency therapy in CIS patients and early MS (BENEFIT) and to establish interferon beta-1b double dose and provide a comparison of interferon beta with glatiramer acetate (BEYOND). Referring to the BENEFIT trial, Kapp¹ said: "So I hope to show that those data demonstrate that interferon beta-1b alters the long-term prognosis of MS. And we also hope to see that the data strongly support interferon beta-1b as the drug of choice for first time treatment because of the much improved prognosis."

Aiming at fewer injections

New compounds under development in MS are leukotrien A4 hydrolase inhibitors, microglia downregulators and urokinase

plasminogen activator inhibitors in MS, but they are still preclinical and have not yet reached the stage of clinical development. Moreover, pegylated interferon beta-1b is being investigated.

Furthermore, alemtuzumab (Campath®), a (lymphocyte-depleting, humanized) monoclonal antibody which so far has been used in chronic B-cell lymphocytic leukemia, may have a potential therapeutic effect in MS. Preliminary results of a phase II study in RRMS are encouraging and two interim analyses exist, which revealed no clinically symptomatic cases of Grave's disease to date. Early treatment of naive RRMS patients with this drug may result in a favorable treatment effect. In addition, a once-a-year infusion has a high appeal. The Cambridge cohort including 36 SPMS and 22 RRMS patients revealed a 94% reduction of annualized relapse rate in the latter. "It almost wiped out relapses," Kapp¹ said. However, SPMS patients continued to accumulate disability.

Gene therapy for more comfort and convenience?

Interferon beta-1b gene therapy may be another future option for treatment of MS, its goal being a single injection of the IFN-beta gene every three to six months and a controlled dosage through regulated gene expression by administration of an inducer. "Actually we inject two plasmids. Plasmid number one will code for an initially inactive regulator protein, a receptor, and we use a steroid to activate that receptor," Kapp¹ explained: "It will then activate the production of the interferon beta protein. If that works that will be quite a progress in terms of coming up with something much more convenient for the patients."

Yvette Corinne Zwick, DVM

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Impressum

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