

CONGRESS NEWS

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The Scientific
Bayer Schering Symposium
was held in Rome, Italy
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Early intervention for long-lasting benefit

Multiple sclerosis – a worldwide affair

Research about initial events in multiple sclerosis (MS) demonstrated how devastating even early pathological changes may be, clearly supporting early treatment. Axonal transection starts early in the course of the disease and is related to the degree of inflammatory activity which sets in even before clinical symptoms are present, generally continues during remission and is not at all restricted to episodes of clinical impairment. Therefore, MS experts agreed that successful therapy of MS should start as soon as possible to reduce inflammation and axonal damage, let alone disability. Guidelines about treatment initiation have been developed based on data from clinical trials with patients with a first clinical event suggestive of MS. Data have shown that early intervention can indeed lead to long-lasting benefit. Based on the convincing results of the BENEFIT trial (Betaferon® in Newly Emerging MS For Initial Treatment) in patients with clinical isolated syndromes (CIS) receiving early interferon beta-1b treatment, EMEA extended the indications for this long- and well-known drug with its excellent long-term safety and tolerability profile. Thus interferon beta-1b now is not only approved for therapy of patients who already suffer from relapsing remitting MS (RRMS) or secondary progressive MS (SPMS), but also for patients with a first clinical event suggestive of MS (CIS), before the diagnosis of clinically definite MS (CDMS) can be established.

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- MS in children and adolescents

Rationale for early treatment

Giancarlo Comi, Milan, Italy, listed a wide range of arguments for early treatment of MS. For instance, he reviewed the immunopathological aspects of MS and reminded the audience that the early irreversible nerve damage is at least partially related to inflammation and that longitudinal immunopathology changes occur. While degeneration and disability increase over time, inflammation and treatment response decline. Moreover, he pointed out that recovery mechanisms become less effective over time. The fact that the immune-modulated activity underlying MS gets more difficult to control as the disease progresses and that immunomodulating drugs are targeting inflammation which is predominant in the early phases of MS, all support the arguments in favor of early treatment.

Further support for early treatment was provided by clinical trials – BENEFIT [8], CHAMPS (Controlled High-Risk Subjects Avonex® Multiple Sclerosis Prevention Study [7]) and ETOMS (Early Treatment of Multiple Sclerosis [4]). First of all, there were lessons learned from the placebo groups of these trials, Comi said, presenting the bad news first. The BENEFIT data, for example, revealed that patients with a first event suggestive of MS and abnormal MRI scans were at high risk of developing MS. If left untreated, 45% of the patients developed CDMS and within two years 85% of the placebo patients developed “McDonald MS” Comi further pointed out that brain atrophy is already present in CIS patients (figure 1).

Early intervention can make a major difference

The good news is that recent study results clearly demonstrated that early intervention in patients with a first demyelinating event suggestive of MS delays the rate of conversion to CDMS. Comi emphasized that interferon beta-1b (Betaferon®) significantly reduces the risk for “McDonald MS” as well as progression to CDMS (in ETOMS by 35%, $p = 0.045$, $n = 309$; in BENEFIT by 50%, $p < 0.0001$, $n = 468$), prolonged the time span to CDMS

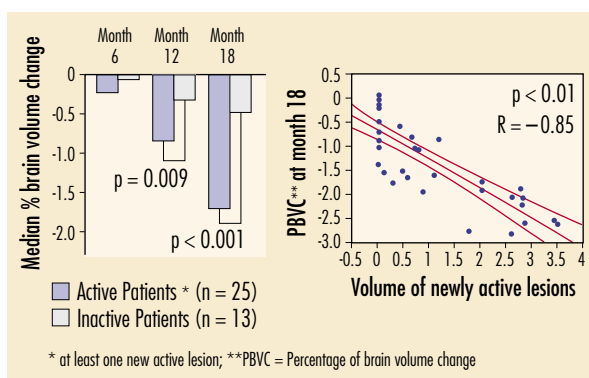


Figure 1: Left: Median brain volume change in CIS patients – according to MRI activity during their first MRI scans. Right: Correlation of MRI activity and the development of brain atrophy in CIS patients over 18 months (slide: Comi) [15].

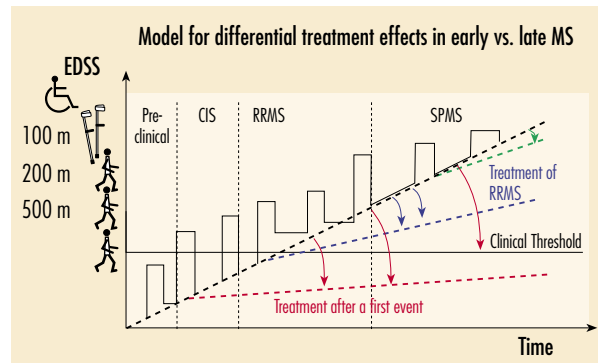


Figure 2: Window of therapeutic opportunity: Treatment initiated at various stages of MS can affect outcomes: The black line demonstrates the natural course of the disease, the red, green and blue lines different possible treatment effects (slide: Comi).

and reduced MRI activity. For patients with a monofocal onset – i.e. in a less disseminated onset of disease in which clinical symptoms can be explained by one single CNS lesion – risk reduction for progression to CDMS was even more pronounced (in CHAMPS: 44%, $p = 0.002$, $n = 383$; BENEFIT: 55%, $p < 0.0001$, $n = 246$), Comi summed up the findings in CIS populations.

Critical window of opportunity

Treatment results, however, may differ depending on when treatment is initiated and there is evidence of a better response to interferon beta early in the course of disease (figure 2). Because inflammation predominates in the early phases of the disease and diminishes over time, therapy directed at reducing inflammatory activity is best started early. Comi referred to this as the “window of therapeutic opportunity in MS”. Therefore, treatment initiation immediately after the first event should be strongly considered. Moreover, he wondered if starting therapy at this time would delay disability progression from reaching the clinical threshold in the long run.

Thus in spite of a lack of long-term data, more and more convincing arguments have accumulated that support a paradigm shift towards earlier MS treatment.

Prognostic factors at disease onset

Implications for treatment initiation

At disease onset, high lesion load in initial cranial MRI (magnetic resonance imaging) is associated with poor prognosis. Patients who started out with more T2 lesions show greater disability. Interferon beta-1b is currently one out of two interferon beta preparations which are approved for treatment of patients with a first demyelinating event suggestive of MS (clinically isolated syndrome = CIS) and at high risk of developing CDMS.

But when is it the best time to start treatment in CIS patients? Ralf Gold, Bochum, Germany, pointed out that the German speaking MS Therapy Consensus Group (MSTCG) [14] proposed treatment initiation in CIS patients, if subclinical dissemination is present in MRI scans and a functionally relevant symptom does not sufficiently regress within two months after high-dose corticosteroid treatment or if there is a high lesion load (more than six lesions on a cranial MRI) or new inflammatory lesions (gadolinium enhancement or increase of T2 lesions) in a follow-up MRI scan two to three months later. Of course, other illnesses mimicking MS have to be ruled out first before any disease-modifying therapy is initiated. The presence of an intrathecal IgG synthesis in the cerebrospinal fluid (CSF) is yet another prerequisite, Gold added.

In addition, Mar Tintoré, Barcelona, Spain, summed up a number of clinical features, MRI parameters and biological markers which have been associated with a higher risk of a second attack and development of disability. Research in CIS patients revealed that the presence of even a very small number of baseline MRI lesions is associated with an increased risk of developing MS and that the increase in lesions seen in the first five years correlates with the degree of disability in the long run. In the Barcelona CIS cohort, patients were classified at the onset of symptoms according to the Barkhof criteria. Patients without any Barkhof criteria at baseline had a low relapse risk while patients with one and two Barkhof criteria had an intermediate risk and patients with three or four Barkhof criteria had a very high risk for another attack within a very short period of time. EDSS at five years correlated with the baseline number of Barkhof criteria and patients fulfilling three to four criteria had a higher risk of developing disability. Tintoré concluded that these results highlight the importance of MRI in patients with a first attack. MRI serves as a reliable prognostic marker and at this early stage remains the best tool for classifying patients according to their risk of conversion to CDMS or development of disability and thus for selecting candidates for treatment, she said. Furthermore, Tintoré concluded that the presence of oligoclonal bands is an independent risk factor for conversion to CDMS, but not for development of disability.

Lack of association between anti-myelin antibodies and progression to MS

Moreover, Tintoré observed that anti-myelin antibodies did not predict a second attack in her CIS cohort. This was confirmed by the data of the BENEFIT trial in which the prognostic relevance of antibodies – anti-myelin basic protein (anti-MBP) and anti-myelin oligodendrocyte glycoprotein antibodies (anti-MOG) – was also investigated. Baseline sera of 462 patients were analyzed and 94% were followed for 24 months. Yet, there was a lack of association between these antibodies and progression to MS [9]. These negative results were in line with most other smaller studies [10, 13] and the Barcelona CIS cohort with a

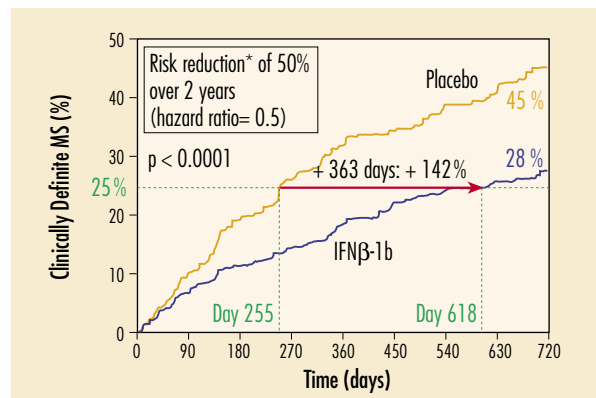


Figure 3: BENEFIT 2-years data: Interferon beta-1b delayed the onset of a CDMS by one year: $p < 0.0001$, hazard ratio 0.50 (0.36-0.70), 95% confidence interval (CI) (slide: Kappos). *by adjusted proportional hazards regression

mean follow-up of 46.5 months [11], Ludwig Kappos, Basel, Switzerland, said.

BENEFIT – the earlier, the better

The BENEFIT trial aimed to demonstrate efficacy, safety and tolerability of subcutaneous high-dose, high-frequency interferon beta-1b injections in patients with a first clinical demyelinating event suggestive of MS, including patients with mono- or multifocal presentation. In this multicenter, randomized, double-blind, placebo-controlled trial, 468 CIS patients with at least two clinically silent brain MRI lesions either received 250 µg interferon beta-1b every other day ($n = 292$) or placebo ($n = 176$) until CDMS was diagnosed or they had been followed for 24 months. Primary outcome measures were "time to CDMS" and "time to McDonald MS (2001)". After two years, 45% of the placebo patients (versus only 28% of the interferon beta-1b

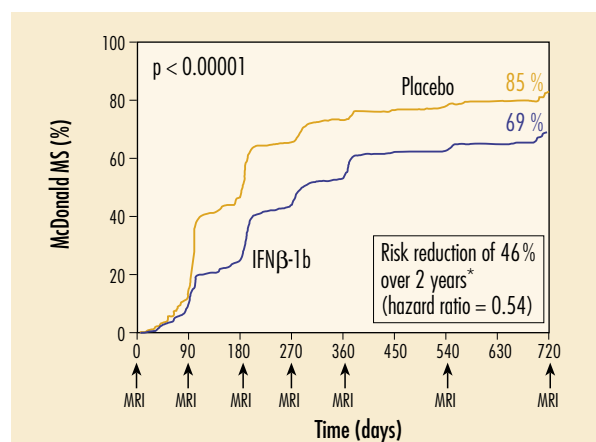


Figure 4: Within two years, interferon beta-1b reduced the risk of MS according to the McDonald criteria by 46%: $p < 0.00001$, hazard ratio 0.54 (0.43-0.67), 95% CI (slide: Kappos). *by adjusted proportional hazards regression

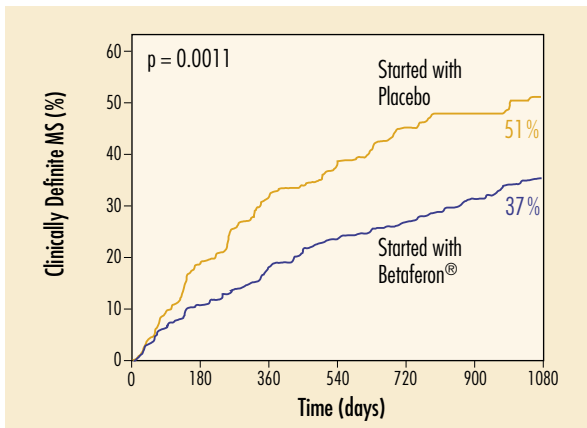


Figure 5: Time to CDMS (3-year integrated analysis) (slide: Kappos).

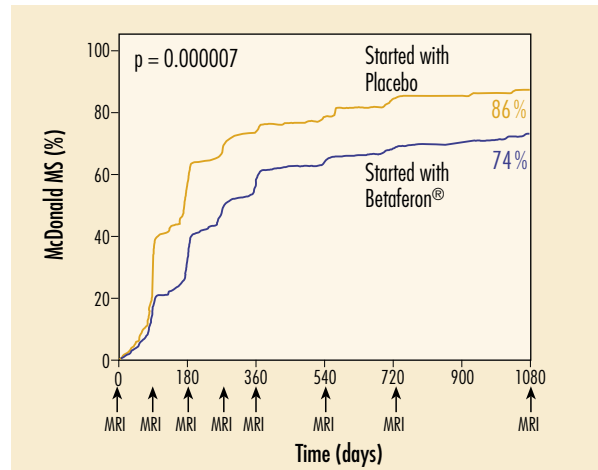


Figure 6: Time to MS according to the McDonald criteria - 3-year integrated analysis (slide: Kappos).

BENEFIT follow-up study: 3-year data

At the AAN's 59th Annual Meeting in Boston, Massachusetts, United States, Freedman presented new data confirming that early - compared to delayed - initiation of interferon beta-1b therapy in patients with a first demyelinating event, suggestive of MS, can reduce the risk of permanent neurological impairment by 40% over three years (hazard ratio 0.60, 95% CI 0.44-0.80; p=0.0011). "This is a truly novel finding that has not yet been demonstrated for any other immunomodulatory MS treatment and underscores the urgent need to treat patients early rather than waiting for further signs of MS to develop. Physicians and patients should consider these unprecedented findings when making treatment decisions," Freedman said.

Interferon beta-1b postpones disability

He concluded: Early interferon beta-1b therapy delays and reduces the risk for recurrent disease activity (clinical or MRI) leading to the diagnosis of MS. Patients treated early were less likely to progress to clinically definite MS compared to those who delayed treatment up to 24 months. The risk of sustained EDSS (Expanded Disability Status Scale) progression was reduced by 40% over three years. This clinically important and statistically significant effect of interferon beta-1b therapy may be even more pronounced than shown in the data since the majority of patients in whom treatment was postponed received at least one year of interferon beta-1b treatment. These findings support the value of early treatment with interferon beta-1b immediately after the first clinical presentation of the disease.

patients) had converted to CDMS and 85% fulfilled the McDonald criteria. Treatment with interferon beta-1b, however, delayed the overall risk of developing CDMS (risk reduction: 50%) (figure 3) and "McDonald MS" (risk reduction: 46%) (figure 4). Treatment showed a good safety and tolerability profile. Kappos added that 96% of the study participants who completed the trial wished to participate in the open-label follow-up study and most of the former placebo patients switched to interferon beta-1b treatment in the follow-up period.

Early versus late treatment effect

Finally, Kappos, a member of the BENEFIT steering committee, showed 3-year-data, revealing that only 37% of the patients who started interferon beta-1b right from the beginning, but 51% of the patients initially not receiving any treatment but placebo, developed CDMS. Former placebo patients receiving late treatment could not catch up with the advantages initial therapy with interferon beta-1b showed for those patients receiving interferon beta-1b from the start (figure 5). Similar effects were seen when looking at the McDonald criteria. After two years, 69% of the interferon beta-1b, but 85% of the placebo patients progressed to "McDonald MS". After three years there was still quite a difference: 74% (interferon beta-1b patients) versus 86% (former placebo patients) (figure 6). Kappos concluded: The advantage gained by treatment with interferon beta-1b immediately after the first clinical event suggestive of MS is maintained three years after treatment initiation, although former placebo patients were also on active therapy by then.

However, another question remains: How does early versus later interferon beta-1b treatment affect disability later in the course of disease? This question was discussed on the Meeting of the American Academy of Neurology (AAN) in Boston, in May 2007. The outcome of this meeting is summarized in the box on the left.

Recognizing a sub-optimal treatment response

Realistic treatment expectations

Therapeutic options in MS have advanced considerably in recent years. Effective drugs emerged and current disease-modifying agents offer – to varying extent – the opportunity to control MS. But there are pitfalls such as poor adherence to treatment, an important factor in not achieving long-lasting benefits, a sub-optimal treatment response or an unbalanced risk-benefit ratio.

According to **Carlo Pozzilli, Rome, Italy**, it is striking that poor adherence is a major issue in MS with more than one third of MS patients discontinuing interferon beta treatment within five years, the highest discontinuation rate taking place within the first six months of therapy. Long periods of non-visible disease progression and the fact that the disease is treated with prophylactic agents, make it even more challenging for the clinician to motivate the patient to stick to a prescribed treatment. Therefore, he quoted Cochrane reviewer RB Haynes [6]:

"An effective intervention to enhance compliance would be as important a development as any new drug."

He then listed general factors influencing adherence to therapy such as self-reliance in the ability to overcome challenges, coping strategies, cognitive impairment, depression and the degree of support by the physician, family and the healthcare team. An important aspect of patient motivation is to avoid false expectations, demotivation or premature treatment discontinuation. According to Pozzilli, realistic expectations in MS are: Less frequent and less severe relapses, better recovery after relapses, prevention or postponement of disability progression, reduction of brain lesion activity and of accumulation of burden of disease, better quality of life, improved cognitive functioning and less fatigue. However, one has to distinguish between patients' expectations and expectations of physicians. Prompt and effective help when problems occur is also essential. Common emotional reactions to MS diagnosis are shock, anxiety or sometimes even relief, when patients finally know what's happening to them, Pozzilli said. Thus when communicating the diagnosis, he advised emphasizing positive aspects, explaining current research efforts and discussing available therapies. Another relevant aspect is to determine how actively a patient wants to be involved in the decision-making process. Generally, knowledge and information help to empower the patient with respect to disease management. He added that most MS patients prefer an active role in treatment but there might be some cultural differences. Furthermore, caregivers also need to be taken into consideration when aiming for long-lasting benefits. In the majority of cases, the partners (65%) of the patients or other family members (15%) take over as caregivers. Therefore, the speaker even referred to the caregiver as the "second patient". Ideally, however, a coordinated healthcare

team and a MS nurse are available to support the patient. Although the role of a MS nurse is crucial, the neurologist should also be available for the patient, because more frequent visits to a neurologist may help to increase patient motivation and adherence.

Depression & anxiety

Further factors influencing adherence and decisions are cognitive impairment or depression and anxiety. And it is amazing that anxiety and depression in recently diagnosed MS patients and their partners is similar. This shows that at least in the early phase of the disease, depression is a result of the accumulated burden of adverse stressful experience, Pozzilli said. Moreover, emotional disturbances, frequently observed in CIS patients, show a tendency towards normalization in relapse-free patients. Therefore, a more stable clinical course should trigger less emotional distress, he added.

Defining treatment response

Recognizing when a patient is obtaining or is not obtaining the expected benefit from a disease-modifying agent and discussing alternative therapy options was the topic of a lecture by **Mark S. Freedman, Ottawa, Canada**. He said that a prerequisite is to have a preconceived notion of a treatment response in order to know when a "sub-optimal" response is being achieved. Various schemes for judging treatment responses have been proposed, but evidence validating the various approaches is lacking. One approach is to weigh the treatment experience in terms of relapse, progression or MRI change and to compare some of these results to the pre-treatment period or baseline characteristics, Freedman explained. This approach was taken by the Canadian MS Working group. Another approach examines various clinical criteria, based on number of relapses, disability progression or a combination of both.

3-gauge optimization model

Freedman explained the model of the Canadian MS Working group. This 3-gauge optimization model [5]. allows to judge

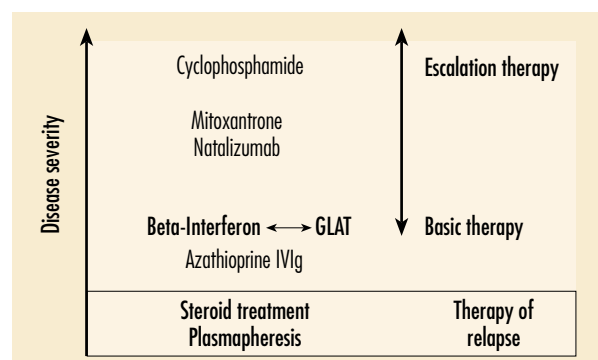


Figure 7: Update 2006: Recommendations from German speaking countries for treatment of patients with relapsing remitting MS (slide: Coyle, Gold, Freedman) [mod. 14]

What the future may bring

Alastair Compston, Cambridge, UK, talked about the potential role of alemtuzumab – a humanized monoclonal antibody directed at membrane antigens (CD52) which are expressed at high levels on T- and B-lymphocytes and to a lesser extent on monocytes and eosinophils [2] – in MS and presented early open-label and phase II experience. Alemtuzumab – which was approved for treatment of B-cell chronic lymphocytic leukemia in 2001 – kills lymphocytes by antibody-dependent cytotoxicity and complement-mediated lysis, acting on mature lymphocytes and not hematological progenitors [3]. Compston explained that the sustained depletion of T-lymphocytes allows annual (or even longer) treatment cycles.

Early experience with alemtuzumab in MS was gathered in the UK in 36 patients with SPMS and increasing disability and in 22 drug-naïve patients with RRMS and a high relapse rate early on as well as in patients in whom licensed treatment had failed. Annual relapse rate in both RRMS (-94%) and SPMS patients (-97%) was reduced [3] and so was new lesion formation during treatment with alemtuzumab. But although annual relapse rate dropped in RRMS and SPMS alike, disability was affected differently, dependent on the phase of the disease. While RRMS patients showed an impressive reduction in disability at six months, SPMS patients continued to accumulate disability. This might represent an early rescue of neurons and axons from a toxic inflammatory environment, indicating

that early prevention of demyelination might prevent long-term axonal degeneration.

CAMMS223 – long lasting effect on disability

In 334 treatment-naïve patients with early RRMS, efficacy and safety of alemtuzumab (12 mg/day or 24 mg/day for five days) versus interferon beta-1a (44 µg, three times per week) are currently (December 2004 – September 2007) being compared in a randomized, controlled, phase II-study (CAMMS223). An interim analysis after one year showed a clear treatment effect in favor of alemtuzumab on relapse rate and on accumulation of disability. However, six patients treated with alemtuzumab developed immune-mediated thrombocytopenia (ITP). The first patient with premonitory symptoms did not seek medical attention until the onset of a cerebral hemorrhage that proved fatal. Subsequently, alemtuzumab was suspended, a comprehensive risk management plan and enhanced monitoring were immediately implemented to identify risk factors for ITP. These efforts have been effective and all subsequent cases were identified shortly after onset and responded well to treatment. Current status: Alemtuzumab patients will be followed for three years after their last dose for safety. Re-dosing is currently under discussion with the regulatory authorities. The three-year analysis from the phase II-study will be reported atECTRIMS in October 2007.

the level of breakthrough disease by "level of concern" that the chosen drug is not producing an optimal response. Each gauge represents a continuum from "no" to "high" level of concern. And three "low", any two "medium" ratings or any one "high" concern are indications that might warrant a change in management. However, once a treatment will be stopped in favor of a different agent, further data is needed to decide what to switch to. A first option – in case the patient already receives interferon beta – might be to increase the dose and frequency of interferon beta therapy. This concept is supported by available studies indicating that there is a dose-response, suggesting that higher and more frequent doses offer greater therapeutic benefits.

"Escalating" immunotherapy in RRMS

Furthermore, Freedman presented recommendations from German speaking countries for treatment of patients with RRMS in which interferon beta and glatiramer acetate are listed for basic therapy. Escalating treatment options are more potent, but associated with higher risks of major adverse events. They include natalizumab and mitoxantrone as an escalation level above the basic disease-modifying treatments and subsequently suggest other immunosuppressants such as

cyclophosphamide. Plasmapheresis is proposed as an option for severe relapses not responding to steroid treatment (figure 7).

Have we reached maximum efficacy yet?

Treatment of patients suffering from RRMS with interferon beta is an established method to modify the course of the disease. However, preliminary data suggest that the interferon beta-1b efficacy ceiling has not yet been reached, Hans-Peter Hartung, Düsseldorf, Germany, explained. Therefore, this question is currently being further explored. Efficacy of an interferon beta dosage higher than currently administered was investigated in BEYOND (Betaferon® Efficacy Yielding Outcomes of a New Dose), a randomized, multicenter phase III-trial, still continuing to examine efficacy, safety and tolerability of 500 µg versus 250 µg interferon beta-1b versus 20 mg glatiramer acetate once daily over a period of at least two years in 2,220 treatment-naïve patients. Is there a maximum efficacy of interferon beta-1b? The BEYOND data which are expected by the end of this year will provide further insights into the topic of dose-efficacy relationship and also compare efficacy of interferon beta-1b with glatiramer acetate. Study outcomes include relapse rate, percentage of relapse-free patients, time to first re-

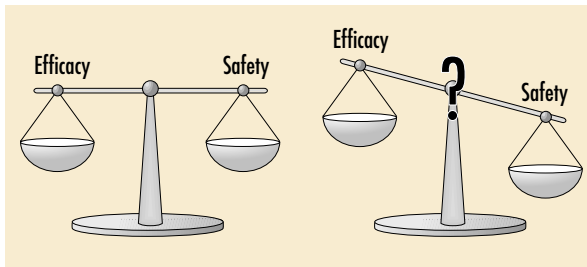


Figure 8: Treatment with first-line agents versus second-line agents in MS: Balanced risk benefit ratio of first-line agents (left): Current first-line disease-modifying drugs – interferon beta and glatiramer acetate – have a favorable risk-benefit ratio in short and long-term therapy. Unbalanced efficacy and safety ratio of second-line agents? (right) (slides: Coyle).

lapse, time to confirmed EDSS progression, black holes, changes in MSFC, burden of disease, atrophy and quality of life.

Risk-benefit ratio

Which factors motivate doctors to prescribe certain treatments, Patricia Coyle, New York, NY, USA, asked. Her answer: Physicians are guided by disease, drug and patient factors, available evidence, published guidelines and their personal experience. And then there is the risk-benefit ratio which also influences the choice of treatment. Currently, Coyle said, high-dose, high-frequency interferon beta therapy offers the best risk-benefit ratio among available drugs for RRMS (figure 8).

Interferon beta has the most abundant evidence for efficacy and also provides the opportunity to limit long-term disability. Due to its efficacy in both early and later stages of MS, as well as its balanced benefit-risk ratio, it is widely indicated for use in MS. Coyle said that early high-dose treatment had the best impact (PRISMS, 4 year data). In addition, there are further indications that there is a dose-response curve, and that higher doses given more often offer the greatest therapeutic benefits. Studies such as INCOMIN and EVIDENCE have shown that high-dose and high-frequency regimens are more potent than a low-dose and low-frequency administration. In particular, higher and more frequent dosing of interferon beta increases the possibility of a better outcome. Moreover, maintaining a high-dose, high-frequency treatment is crucial even in well-responding patients as demonstrated by the interferon beta dose-reduction study, Coyle added. And to achieve the best possible outcome, continuous drug administration is mandatory. Data from long-term follow-up studies with disease-modifying drugs confirm that treatment with interferon beta and glatiramer acetate showed a good safety and tolerability profile in the long run and that therapeutic effects are long lasting. Taken together, sustained long-term benefits in patients with RRMS can be achieved by promptly initiating effective treatment right after a first event and by continuous drug administration.

Interferon beta-1b: Good safety and tolerability profile over many years

Today, knowledge about interferon beta-1b, the first disease-modifying therapy to be approved for the treatment of MS patients, is based on more than 600,000 patient years which have been acquired from numerous controlled studies including CIS, RRMS and SPMS patients. Douglas S. Goodin, San Francisco, California, USA, stressed the importance of long-term studies in a chronic disease like MS that evolves over decades and talked about the implications of the 16-year long-term follow-up (16-year LTF) for long-term patient management. The 16-year LTF, which included most RRMS patients who had participated in the pivotal trial that started in 1988, is the longest and most complete follow-up of any interferon beta therapy in MS. Its data revealed that interferon beta-1b continues to demonstrate a highly favorable risk-benefit profile even over many years. Longer exposure to interferon beta-1b over 16 years correlated inversely with relapse rate and directly with prolonged time to both EDSS 6 and development of SPMS. Interferon beta therapy was also associated with an excellent safety profile. Goodin's conclusion: Disease-modifying therapy favorably affects the long-term course of MS and categorical changes in EDSS are valid predictors of long-term function.

Diagnostic criteria & drugs in a pediatric population

MS in children and adolescents

MS is increasingly diagnosed during childhood (< 10 years) and adolescence (10-16 years). About 10-20% of these young patients have a close relative with MS. Although juvenile MS is very similar to MS in adults, in some cases there may be an additional spectrum of MS phenotypes, making it tougher to diagnose the disease. In a pediatric population, clinical and MRI overlaps with acute disseminated encephalomyelitis (ADEM) are possible. In addition, many other illnesses have to be ruled out such as subacute sclerosing panencephalitis, neuroborreliosis, neoplasms, mitochondrial disease, Devic's neuromyelitis optica, Schilder's myelinoclastic diffuse sclerosis, relapsing myelitis, optic neuropathy, leucodystrophy and collagen vascular disease. In addition, only limited literature on treatment of MS in children is available.

Mefkure Eraksoy, Istanbul, Turkey, shared her MS experience in children and adolescents in Turkey.

Do CSF and MRI findings differ?

Eraksoy emphasized that oligoclonal IgG bands in CSF are present in most children with MS who experienced a first or second demyelinating event before the age of 16 (> 90%) [12]. However, children may have fewer T2 hyperintense areas in the

Atlas of MS

Since there is limited information available about resources to tackle the huge medical, social and economic burden caused by MS in every country, an international survey was conducted by the MSIF (Multiple Sclerosis International Federation) in cooperation with the WHO (World Health Organization). For the first time, information and data on epidemiology of MS, the availability and accessibility of resources to diagnose, inform, treat, support, manage and rehabilitate people with MS worldwide will be available in one database for analysis and comparison at country, regional and global levels. In addition, the Atlas of MS confirms that diagnosis, treatment, care and support of MS patients vary considerably in different countries. Alan Thompson, London, UK, presented some of the data on

prevalence, access to MRI, number of neurologists and MS nurses as well as the diagnostic criteria most commonly used globally. Thompson stressed the importance of clinical expertise in interpreting the history and evaluation of clinical signs to determine if relapse criteria are fulfilled and if there is evidence for dissemination in time and space. And he expressed his hope that the atlas – being updated as new information is received – will motivate governments and healthcare providers to improve MS treatment worldwide. The availability of valid criteria on which a reliable diagnosis can be based was essential for the database of the atlas. Therefore, Thompson gave a brief overlook on key changes in the diagnostic criteria over the years (Internet: www.atlasofms.org).

early stage of the disease, hence not meeting the MRI diagnostic criteria established for adults. She further explained that in children, a monosymptomatic onset of disease is frequent and that the most common symptoms include brain-stem, sensory, motor involvement and optic neuropathy. In childhood onset of MS, typical lesions detected in MRI scans are Dawson's fingers, confluent demyelination, posterior fossa lesions, spinal cord and optic nerve lesions. According to Eraksoy, the McDonald criteria apply to all patients between 10 and 59 years of age. However, special care must be taken when diagnosing MS in children who are not yet ten years old. She emphasized that in the young, meticulous clinical, radiological and cerebrospinal fluid follow up is essential.

Can current drugs be used without concern?

The European Agency for the Evaluation of Medicinal Products (EMA) recently asked drug companies to change their labels, reducing the minimum age of treatment initiation with interferon beta to 12 years. Indeed, Eraksoy concluded that accumulated data and observations suggest that the safety profile in adolescents from 12 to 16 years of age receiving disease-modifying treatments is similar to that seen in adults. The speaker also mentioned that safety and tolerability of interferon beta-1b in children was investigated by Banwell B et al. last year [1]

and no serious side effects and no unexpected adverse events were reported, but there were flu-like symptoms, injection site reactions and elevations in liver function tests. Thus interferon beta use in children should include regular monitoring, especially of liver enzymes.

Yvette Corinne Zwick, Denver, CO, USA

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