

CONGRESS NEWS

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Every cloud has a silver lining: This year's Bayer Schering Pharma International Scientific symposium in Stockholm, Sweden, had exactly such a lining at the Stadshuset (© Y.C.Z.).

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MS – consolidating recent lessons learned

Battlefield CNS

Neurologists from all over the globe gathered in Stockholm, Sweden, to discuss the most effective ways to win the "battle" against multiple sclerosis (MS). The diversity of the topics covered by international speakers in numerous lectures was as varied as the 14 islands of Stockholm, ranging from the advantages of early treatment with interferon beta-1b (IFNB-1b, Betaferon®), new insights into MS management and aspects for improvement, cognitive deficits in early MS, sexual dysfunction – still a taboo for many MS patients and their partners – to possible new therapeutic approaches. The fact that Betaferon® is the only therapy that to date has proven to effectively delay disability progression in patients with a first clinical event suggestive of MS and that its optimal dose is 250 µg was underlined by scientific data. Chairmen David Bates, London, UK, and Jan Hillert, Stockholm, Sweden, welcomed the audience and led through the interactive scientific symposium.

The importance of early treatment

"We learned a lot about CNS vulnerability during the different phases of MS," Heinz Wiendl, Würzburg, Germany, said in his introductory remarks. Development and progression of MS are associated with axonal loss which begins early in the disease and so does brain atrophy. Permanent axonal loss even sets in before MS is diagnosed, finally leading to irreversible neurological disability. He showed an impressive video clip titled "Neuronal killing: 'the kiss of death' in real time," showing migrating cytotoxic T-cells contacting neurons (Meuth et al., in preparation). "CD8+ T-cells can kill neurons fast and efficiently, inducing lethal hits by calcium influx within ten minutes upon encounter," he explained.

Collateral damage and friendly fire

He compared the central nervous system (CNS) of MS patients to a battlefield with T-cells passing the blood-brain barrier, entering the CNS and attacking dendrocytes and myelin sheets.

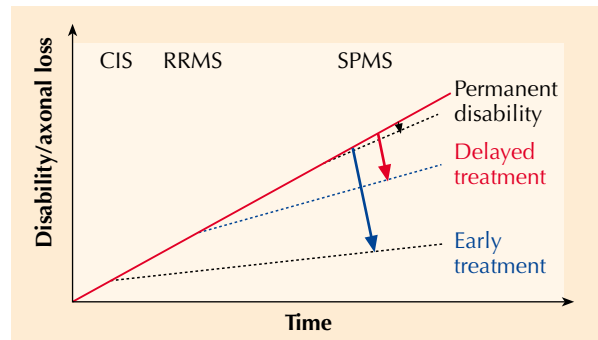


Figure 1: Schematic model of MS: Potential impact of treatment on disability progression. Importance of early initiation of treatment in MS (slide: Wiendl).

He added: "We have a lot of collateral damage indicating that the structure of the CNS – mostly neurons – is also degenerating. We also have friendly fire which means that there are also protective elements in the immune system."

The importance of early treatment – the BENEFIT study

BENEFIT (BEtaferon® in Newly Emerging multiple sclerosis For Initial Treatment) is the first study in CIS patients prospectively designed to examine longer-term impacts of early versus delayed treatment on disease progression. In this multicenter, double-blind, placebo-controlled trial, the importance of early high-dose/high-frequency IFNB treatment initiation was thoroughly investigated. Patients with a first clinical demyelinating event suggestive of MS and MRI scans indicative of the disease, were treated within 60 days after the first episode either with 250 µg IFNB-1b s.c. (n = 292) or placebo (n = 176) every other day for a period of up to two years or until the diagnosis of MS was confirmed. After completion of the 2-year study period, patients could opt to participate in the prospectively planned follow-up phase and 89% of both the former IFNB-1b (n = 261) and the placebo group (n = 157) did so.

Over a 3 year observation period, 51% of the patients switching onto IFNB-1b after initially receiving placebo (the so-called delayed treatment group) developed CDMS. In contrast only 37% of patients who received IFNB right after the first episode developed CDMS over the same period, resulting in a highly significant relative risk reduction of 41% over 3 years (figure 2). Moreover, for the first time in such an early study population the pre-planned analysis of the 3-year-data revealed a 40% risk reduction for disability progression (figure 4). Relapse rates were also positively influenced by IFNB-1b therapy. Most importantly, patients whose therapy was delayed did not catch up with the early treatment group.

Cognition

The 3-year-analysis revealed better PASAT (Paced Auditory Serial Addition Test) scores for patients in the early treatment arm receiving IFNB-1b (figure 3).

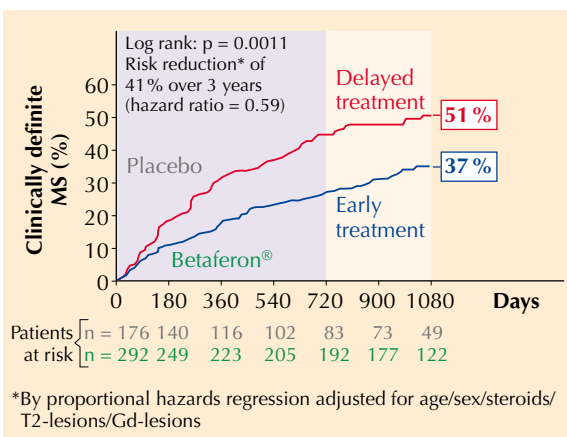


Figure 2: Time to CDMS. 3-year results of the integrated data set (slide: Wiendl).

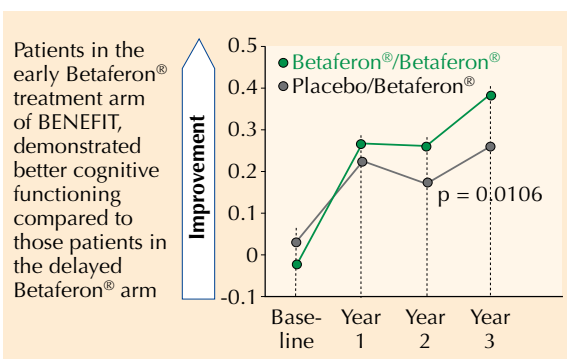


Figure 3: BENEFIT: Cognition – PASAT scores in early and delayed treatment (slide: Langdon).

Thus Wiendl favors early treatment to counterbalance inflammation and to prevent degeneration and further damage (figure 1). This is best done as early as possible, he said. Patients, too, want to delay the onset of disability as long as possible. "What is lost by delaying treatment cannot be regained at a later stage", he said. Wiendl considered the fact that degeneration starts in the early phases of the disease a key argument for early treatment initiation. Yet, irreversible damage only allows for a narrow time frame for intervention – the so-called window of opportunity in which treatment may most successfully delay disease and disability progression. Wiendl argued that treatment is more effective in the inflammatory stage of the disease when there are still more intact axons to protect.

Wiendl further mentioned the results of the BENEFIT trial (see box for more details) and the positive impact of IFNB-1b on the development of MS. Referring to the data, he pointed out that early therapy with this disease-modifying agent after the first demyelinating event delays and reduces the risk for recurrent disease activity (clinical or MRI) leading to the diagnosis of MS compared to delayed treatment. Betaferon® was the first and only disease-modifying drug (DMD) proven to reduce the risk for EDSS progression by 40% in patients with a first event suggestive of MS (figure 4) and leads to a greater relapse rate reduction over three years compared to delayed therapy. Wiendl concluded that these findings support the value of early treatment with IFNB-1b even after the very first clinical presentation of the disease.

Translating early treatment into clinical practice

Lou Brundin, Stockholm, Sweden, gave tips on how to convey recent scientific findings to the newly diagnosed and make sure they receive proper and early treatment. She pointed out that it may be helpful to communicate the importance of early treatment and its long-term benefits as revealed, for example, by the BENEFIT trial (see above). The study demonstrated that more than half of all patients with a clinically isolated syndrome (CIS), if left untreated, developed MS according to the McDonald criteria within six months, rising to an even higher percentage (85%) within two years. Early treatment significantly reduced conversion to clinically definite MS (CDMS). According to the speaker, neurobiology renders further arguments in favor of early treatment: Nitric oxide (NO) metabolites in the cerebrospinal fluid (CSF) of MS patients correlate to disease activity. There is a dose-dependent reduction of neurons after NO exposure. Other experimental results showed that subjecting stem cells to MS-equivalent NO levels reduced formation of neurons.

Don't wait and see!

Brundin said that unfortunately, some physicians still prefer to wait and see. Therefore, she presented case reports of young

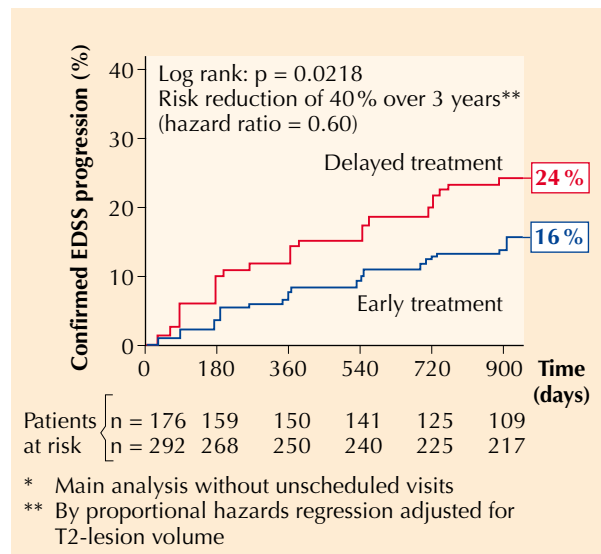


Figure 4: Time to confirmed EDSS progression* (slide: Wiendl).

MS patients to point out why one should not "wait and see", suggesting to those who do not wish to treat their patients immediately to at least monitor the patients closely with the aid of MRI scans until treatment can begin.

Being told that one has MS is indeed difficult to accept and can lead to denial and depression and some patients, too, may want to postpone treatment until they have come to terms with the diagnosis. These facts have to be considered when facing treatment initiation at very early stages of the disease. Thus it is even more important to have arguments ready, so patients will agree with early treatment. Nonetheless, in patients with a first event suggestive of MS, other diagnoses initially have to be ruled out, leaving the patient at high risk of developing CDMS before treatment initiation.

Do we see cognitive deficits early in MS?

Dawn Langdon, London, UK, talked about cognitive impairment in MS, affecting 45%-65% of the patients. Cognitive dysfunction has a dramatic impact on social functions, mood, quality of life and employment, she said. Yet it has not been routinely assessed in MS trials and little is known about the severity in advanced disease.

EDSS and MRI – predictors of cognitive status

In the 16-year-LTF, 179 patients (67% female), average age 51.4 years, completed several cognitive tests, evaluating attention, verbal memory and executive functions. It was shown that memory and complex attention declined most. Significant cognitive problems in at least one area of information process-

ing was reported by 38% of the patients. Current cognitive test scores correlated significantly with both current and baseline EDSS (Expanded Disability Status Scale) and BOD (burden of disease) as detected on T2-weighted MRI (magnetic resonance imaging) scans. Apart from pre-morbid intellectual level, EDSS at baseline and MRI T2 BOD at baseline were the best predictors of cognition at 16 year follow up. This suggests that the disease course is set early on.

CogniCIS and CogniMS

Two new international, prospective, multicenter observational studies (CogniCIS and CogniMS) aim at assessing cognitive deficits over a 2-year period in CIS patients and in patients newly diagnosed with CDMS. Their goals are to show whether cognitive function may predict conversion to MS and to investigate interactions between impaired cognitive function, depression, fatigue and quality of life in the short term and in the long run. Langdon presented baseline data of both trials. They were comparable in all 40 participating countries in Europe, Asia, the Americas and the Middle East.

Evidence of a dose-response curve

The response to IFNB depends on the dose, **Giancarlo Comi, Milan, Italy**, said. Clinical data from the INCOMIN (INdependent COMparison of INTERferon) and EVIDENCE (EVIDence of Interferon Dose response: European North American Comparative Efficacy) trials, both showed that higher dose and more frequent administrations of IFNB (250 µg IFNB-1b, 44 µg IFNB-1a s.c.) were more effective than lower and less frequent doses (30 µg IFNB-1a i.m.). Yet, tolerability was not sacrificed for greater efficacy.

Higher IFNB-1b doses

The optimal dose for treatment of patients with RRMS is 250 µg IFNB-1b, Comi said, referring to the recent findings of the BEYOND (Betaferon® Efficacy Yielding Outcomes of a New Dose) trial in which all three therapeutic options significantly lowered relapse rates compared to the year before treatment initiation (figure 5). Neither the percentage of patients with confirmed EDSS progression nor the percentage of patients without major relapses revealed significant differences. Changes in T1 black hole volume were not significantly different in the three treatment arms which may lead to the conclusion that not only glatiramer acetate (GA), but also IFNB-1b therapy has a neuro-protective potential. IFNB-1b was superior to GA in regard to MRI T2 lesion volume change and gadolinium-enhancing lesion volume.

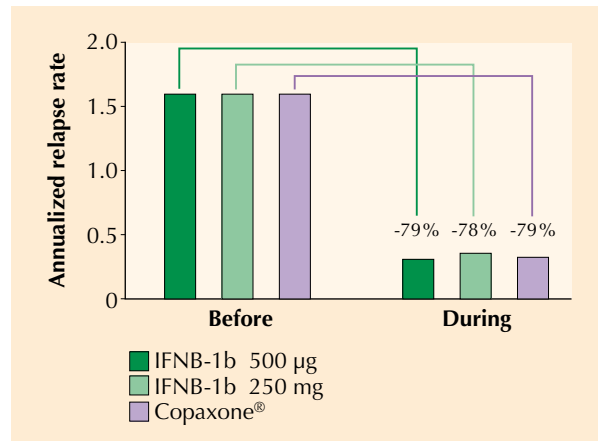


Figure 5: Annualized relapse rates one year before and during treatment (BEYOND data) (slide: Comi).

Putting new clinical data into perspective

Patricia Coyle, New York, NY, USA, also talked about the BEYOND data (table 1) and compared the baseline data of the BEYOND study (n = 2244; mean duration of disease: 5.3 years; average number of relapses in both years prior to study enrollment: 2.1; EDSS < 2.0: 31% of the patients) with those of the IFNB-1b pivotal trial (n = 372, mean duration of disease: 8.0 years, average number of relapses in both years before enrollment: 3.4, EDSS < 2.0: 18% of the patients). She concluded: When comparing data from historical studies to the results of contemporary trials, treatment outcomes are better when therapy is initiated earlier. She pointed out that T2 burden in early disease seems to correlate with long-term clinical outcomes, including disability, cognition and progression to SPMS.

16 LTF

The 16 LTF (16-year long-term follow-up study) also showed that baseline T2 BOD predicts long-term disability and cogni-

Table 1: Comparison of baseline data with the pivotal trial (slide: Rieckmann).

	BEYOND (n=2244)	Betaferon® pivotal (n=372)
Study started in	2003	1988
Age (mean)	35.7	35.5
Mean duration of disease (years)	5.3	8.0
Number of relapses in prior year (mean)	1.6	n.a.
Number of relapses in prior 2 years (mean)	2.1	3.4
EDSS < 2.0 (% patients)	31%	18%
EDSS (mean)	2.3	2.9
Gd-enhancement (%)	47%	n.a.
Number of Gd+ lesions (mean)	2.2	n.a.

tive performance. Coyle further emphasized that in early RRMS there is a linear relationship between T2 BOD and EDSS over time.

Recent lessons from clinical trials on tolerability and adherence

Clinical experience with IFNB-1b dates almost back two decades to the start of the pivotal trial. Since then, much progress has been made in maximizing tolerability of IFNB-1b, Peter Rieckmann, Vancouver, Canada, said. Titration at therapy initiation to improve tolerability should be considered standard clinical practice, he said. Rieckmann's advice: "Titrate medication stepwise, gradually increase to higher doses!" Moreover, flu-like symptoms should be reduced by concomitant prophylactic administration of NSAIDs. In addition, an optimal injection technique may reduce injection site reactions and pain. It was demonstrated that specialized nurses are vital to ensure adherence to treatment. They teach new patients how to self inject, review their injection techniques and help them to stay motivated.

High value of smaller needle size and autoinjectors

In the BEYOND trial which revealed a lower drop-out rate in the 250 IFNB-1b treatment arm compared to the GA group (13% versus 17%) injection-site reactions and injection-site pain were seen more often in the GA group (figure 6). In the prospective, observational BRIGHT (Betaferon® versus Rebif® Investigating Higher Tolerability) study with 445 RRMS patients, frequency and severity of injection site pain up to one hour after the injections were considerably lower in the IFNB-1b s.c. than in the IFNB-1a s.c. group. The proportion of pain-free injections was also higher among patients receiving IFNB-1b. A further subgroup analysis (n = 226) revealed that using the 30 gauge (G) needle instead of a 27 G needle resulted in less injection site pain.

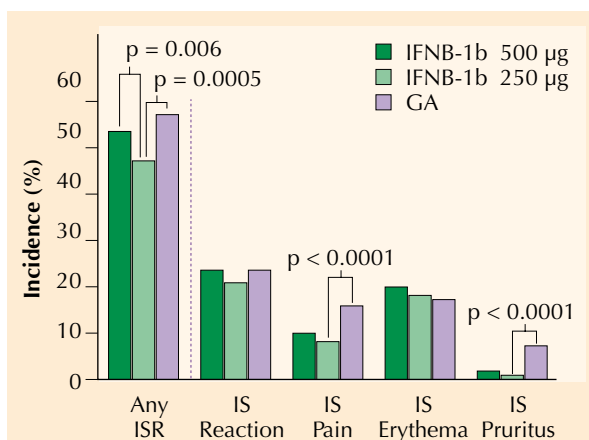


Figure 6: Injection-site reactions, occurring in at least 5% of one group. The adverse event "lipoatrophy" only occurred in the GA group 2.2% (BEYOND study) (slide: Rieckmann).

Practical aspects to improve MS patient management

The most efficacious treatment is of no use, if the patients do not adhere to it. Carlo Pozzilli, Rome, Italy, emphasized that adherence to treatment is of utmost importance and may be a major obstacle in long-term treatment of patients with chronic illnesses. In MS, every third patient discontinues IFNB treatment within three to five years, thereof 10-20% drop out within the first three to six months. The top seven reasons for lack of adherence are perceived lack of efficacy, injections site reactions, flu-like symptoms, mood changes, headaches, liver test abnormalities and fatigue. Nonetheless, the physician has to assess further factors such as MS-related cognitive impairment, depression and anxiety complicating decision-making by the patient, Pozzilli said.

Due to the unpredictability of the disease course it is difficult for the patient to develop realistic expectations. Therefore, Pozzilli suggested explaining that early treatment is effective and may be more successful than therapy later on, involving patients in decisions about their treatment.

If patients want to give up due to side effects, he suggested referring them to a support program. Nurse contacts may enhance compliance, particularly in the first year of therapy. Moreover, the MS nurse plays a central role for the patient in long-term treatment, providing information, advice, care and crisis intervention. Continued support by the BETA Nurse system, the use of autoinjection as well as the www.ms-gateway.com website support adherence.

BEACON

The influence of selected factors on adherence to IFNB-1b, for example, the role of frequent nurse contacts, will be investigated in detail in CIS and early RRMS patients in a prospective, multicenter, international, observational trial (BEACON = BEtaferon® prospective study on Adherence, COping and Nurse support). Patients' ways of coping with treatment adherence will be analyzed and drop-out rates will be documented. The results will also show whether the newly developed "Risk of Drop-out Questionnaire" (RODQ), which will be completed by the nurses, is a useful tool to estimate the patients' risk of stopping therapy.

How to convey data into daily clinical practice

"The rationale for early treatment is not based solely on the severity of the clinical disease, but on preventing cumulative axonal damage, cerebral atrophy and eventual irreversible disability."
Hurwitz

Knowing that inflammation predominates early in the disease, diminishes over time, and may be responsible for axonal damage, and that anti-inflammatory therapy is best started in the early phase, we have to convey this knowledge into daily routine. **Barrie Hurwitz, Durham, North Carolina, USA**, was amazed when in his interactive lecture 7% of his listeners still stated that they would not treat CIS patients. "This is a concern I have. Why do some not want to treat early on?" Thus he reminded the audience of the positive results of the BENEFIT trial thanks to early treatment and of the differences in conversion rates if patients were left untreated. Cognitive function was also less affected in patients receiving early IFNB-1b treatment (figure 3) (also see box). These beneficial effects of IFNB-1b on cognition were also shown in the 3-year preplanned secondary analysis of the EUSPMS study.

"Early treatment with an efficacious and well tolerated DMD is desirable and slows disability progression. Treat all stages of MS – CIS, RRMS and SPMS – as all are likely to worsen," he said. "Tolerable DMD's produce better adherence," he added.

Treating MS today – committed to developing a better future

Hillert talked about possible future treatment options in MS, saying that a range of new promising compounds are currently in clinical development. Most of these agents aim at better convenience. There are oral agents and intravenous drugs such as alemtuzumab, which is given in yearly cycles. Nonetheless, Hillert pointed out that in the near future the therapeutic landscape is unlikely to change a lot. New therapeutic options won't be available before 2010. The focus will remain on early treatment and ensuring maximum therapeutic benefits by optimizing adherence to and tolerability of the existing DMDs.

MS and sexuality

Livia Sousa, Coimbra, Portugal, led through one of the afternoon sessions about "MS and sexuality", explaining that in MS, sexual dysfunction is a frequent, disease-related finding in men (75%) as well as in women (50%) and has a significant impact on the quality of life of the afflicted and their partners even early on. Yet, sexual problems and their consequences in MS were long overlooked and thought to be only affecting quality of life in the long run. In addition, many patients with MS do not link their problems to their disease. A common response to sexual dysfunction within the MS population is to reduce sexual activity and be quiet rather than speak up or discuss the problems with the partner or physician. Thus this issue should be addressed by neurologists early on during the course of the disease, **Sven Schippling, Hamburg, Germany**, advised. Sexual problems in MS can be directly related to physical changes in the CNS, particularly lesions in the spinal cord.

In 2–7% of the patients, bladder and sexual dysfunction can be the primary manifestation of MS. In 10–18%, both problems occur along with other clinical symptoms early in the course of the disease. In women with MS, impaired genital sensation (40–60%), decreased sexual interest (30–60%), lower orgasmic capacity (30–40%) and vaginal lubrication (30–40%) or dyspareunia (20–30%) are common. In men with MS, erectile (40–70%), orgasmic (15–40%) and libido disorders (30–60%) have been reported.

Andreas Hill, Hamburg, Germany, pointed out that neurological symptoms such as fatigue, weakness and spasms may indirectly contribute to sexual problems. For example, fatigue may suppress sexual desire and spasticity may cause pain. Secondary sexual dysfunctions include bladder and bowel dysfunction, incoordination, cognitive impairment, altered genital sensations and discomfort in non-genital areas. Tertiary sexual dysfunctions include psychological, emotional, social and cultural aspects such as fear of being sexually rejected, feeling less attractive, depression or anger, which may also interfere with sexual response and aggravate dysfunction. Nonetheless, some MS patients report positive changes such as an increased sexual desire and sensitivity, increased intimacy in their relationship and a tendency of growing closer together.

Coping strategies

According to Hill, open communication by patient, partner and physician is the key for adaptation and treatment. As for symptom management, Hill suggested emptying the bladder before sexual activities, controlling fluid intake, shape up the muscles of the pelvic floor by simple exercises and adjusting medication. (SSRIs, for example, are known to increase sexual dysfunction.) Finally, PDE-5-inhibitors may be tried for treatment in men. Yet, future trials will have to address diagnosis and therapeutic options of sexual dysfunction, both in men and women with MS in more detail and will have to show whether hormone treatment, PDE-5-inhibitors or further novel drugs may be of help in female sexual dysfunction.

NABs and MS therapy

Neutralizing antibodies (NABs) to IFNB preparations occur in a proportion of patients, as with other protein-based therapeutic biologicals. In recent years, researchers dedicated considerable effort trying to understand persistence and effect of NABs to IFNB preparations. Yet, clinical consequences of NABs are not clearly understood, even though the hypothesis has been put forward that persistent high titers adversely affect patient outcomes. But what exactly are persistent high titers and which assay should be used for assessment? So far, no consensus on clinically relevant threshold values for NAB titers has been reached. Comparing NAB rates from different studies is difficult, because different assays are used and criteria for antibody positivity vary. Thus in an afternoon session

current evidence-based knowledge was presented and clearly distinguished from assumptions regarding NABs and MS. **Gavin Giovannoni, London, UK**, moderator of this parallel session, said that assays for detection of antibodies are not standardized and that different assays do exist. Moreover, the correlation between NAB titers and clinical outcomes are not consistent in multiple studies or different types of IFNB.

Potential consequences

Key characteristics of NABs to therapeutic proteins are the epitope, affinity (determining whether antibodies will be mostly, partly or minimally bound), concentration and persistence, Giovannoni explained. Clinical consequences of antibody formation are highly variable, ranging from little treatment response, loss of efficacy as seen after injections of insulin, factor VIII concentrates and HCG or enhancement of efficacy as observed when using growth hormones, allergic and anaphylactic reactions or serious cross-neutralization of endogenous proteins noted in some patients receiving erythropoietin (EPO).

Hillert summarized current evidence on NABs in MS, including his own research results with IFNB. He admitted that NABs to GA are poorly understood: Therapy induces binding antibodies (BAb) in virtually all patients and more BAb are present in relapse-free MS patients than in those suffering from relapses. For IFNB there are conflicting data as distinct properties of all three available products affect the overall impact of the NABs. For example, NAB titers due to treatment with subcutaneous IFNB-1a tend to be higher than with IFNB-1b [1, 2], seroprevalence is higher with IFNB-1b than with subcutaneous IFNB-1a, but IFNB-1b is less immunogenic [3]. In the latter, titers are often low and low titers have little effect on the drug's bioactivity. Moreover, there is a probability of reverting to NAB-negative status for NAB-positive patients [4]. Patients treated with IFNB-1b are more likely to revert to a NAB-negative status, i.e. NABs tend to disappear more quickly than during IFNB-1a s.c. therapy, Hillert said. Transience of NABs to IFNB-1b may be due to lower titers. Over eight years NABs to IFNB-1b (88%) largely disappear [5]. Hillert concluded that one cannot clinically predict the NAB status and that the incidence of therapeutically relevant NAB titers appear to be similar for IFNB-1a s.c. and IFNB-1b [6].

Giovannoni explored the correlation between NAB titers, NAB persistence and in-vivo/ex-vitro bioactivity. An important part of his presentation was dedicated to review the correlation of NAB titers and zero-conversion. Patients with high NAB titers seem less likely to zero-convert regardless if IFNB-1a or 1b. However, it's not yet clear what's a high titre for IFNB-1b. Furthermore, he explored whether in-vivo/ex-vitro bioactivity does predict the clinical outcome. There is currently no firm answer to this question. MxA, often used as a marker for IFNB, correlates well with NAB status, but does not take into account the

large number of gene and cellular networks induced by IFNB-1b.

Last, but not least, Hurwitz, talked about fears and concerns, the evidence, solutions and options, outlining clinical findings to date in patients NAB positive to IFNB-1b. After discussing the findings, he presented four options: 1) Avoiding high-dose/high-frequency IFNB, because there is a chance for NABs during IFNB-1b treatment. But since a high-dose/high-frequency regimen is superior to low-dose/low-frequency, he concluded that sacrificing better efficacy to prevent a possible lack of effect in a minority of patients is not a good option. Option 2 would be to measure NABs routinely to identify patients potentially at risk and switch them in case they become Nab positive: However, NABs to IFNB-1b frequently disappear. So why switch to a lesser potent agent if the patient is doing well, he said. According to Hurwitz, routine testing and switching in case NAB titers are positive is not a good option. A reasonable option to help decide to switch therapy, however, would be option 3, measuring NABs only in suboptimal responders to identify patients doing poorly due to NABs. Nonetheless, suboptimal responders, irrespective of their consistency NAB status, should always routinely be offered other therapeutic regimens, Hurwitz added. The last option (# 4) he offered was to ignore the Nab issue, because the data are inconclusive, NABs to IFNB-1b disappear over time and it won't affect the way non-responders are treated. Yet, some suboptimal responders – possibly due to NABs – may be missed and thus Hurwitz considered this another reasonable option.

He concluded that it is likely that NABs play little or no role in inducing a poor clinical response to IFNB-1b in MS and that these results do not suggest that routine testing for NABs is of clinical value. So far, 3-year analyses of the BENEFIT trial show that NAB positivity, regardless of the titer did neither affect IFNB-1b efficacy in delaying conversion to CDMS nor disability progression. Confirmation in another comparably large independent trial is definitely needed [7].

New therapeutic approaches

From a long list of challenges in research and development, the complexity and heterogeneity of MS and the lack of ideal experimental animal models are the most prominent. Nonetheless, several experimental agents, focussing on the immune system (figure 7) and aiming at reduction of inflammation are currently being investigated in MS. **Hans-Peter Hartung, Düsseldorf, Germany**, listed the most promising therapeutic agents currently under clinical investigation. One of these promising agents is Alemtuzumab which has been used in chronic B-cell lymphocytic leukemia and was approved in 2001 for this indication. Alemtuzumab is directed at membrane antigens (CD52) which are expressed on the surface of T- and B-cells.

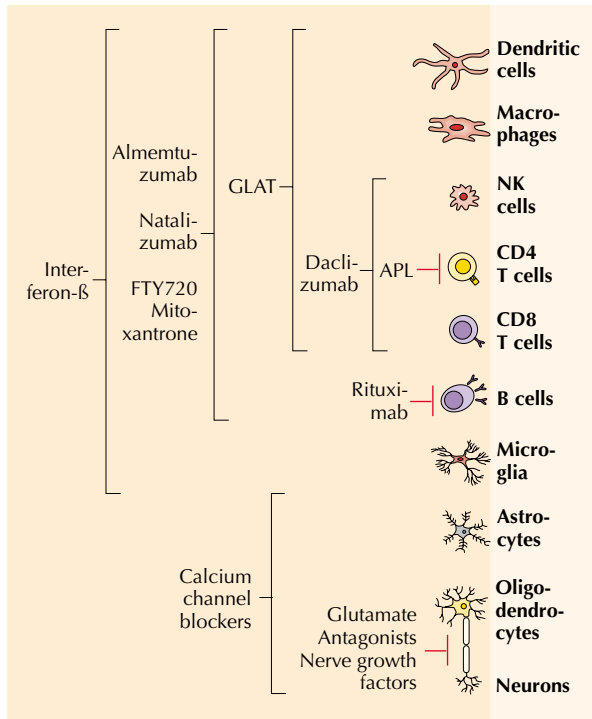


Figure 7: Targets of current and possible future MS therapies (slide: Hartung) [10].

The humanized monoclonal antibody revealed potential benefits especially in patients with relapsing-remitting MS. In the early course of the disease Alemtuzumab seems to protect neurons and axons in toxic inflammatory surroundings, preventing demyelination and leading to preservation of axons in the long run. This hypothesis is based on early experiences with Alemtuzumab in Cambridge. This cohort included 36 SPMS and 22 drug-naïve RRMS patients. Whereas in both RRMS and SPMS the relapse rate was highly reduced, disability was affected differently depending on the course of the disease. SPMS patients continued to accumulate disability progression, RRMS patient showed an impressive reduction in disability explained Alastair Compston, Cambridge, UK.

In CAMMS 223, a randomized, rater-blinded, multicenter phase II clinical trial, low- and high-dose alemtuzumab (given in

yearly cycles) was compared to 44 µg IFNB-1a (three times per week) in a total of 334 treatment-naïve patients with early active RRMS. Interim analyses showed a clear treatment effect in favor of alemtuzumab on relapse rate and on accumulation of disability. However, dosing had to be suspended and a safety monitoring plan to be implemented after six patients treated with alemtuzumab developed immune-mediated thrombocytopenia (ITP). After two years, alemtuzumab reduced the risk for sustained accumulation of disability by $\geq 65\%$ ($p < 0.01194$) and for relapses $\geq 75\%$ ($p < 0.00328$) in comparison high-dose, high-frequency IFNB-1a. Compston presented the final results from the CAMMS 223 trial.

Moderator of this afternoon session, Eva Havrdová, Prague, Czech Republic, rendered details on CARE-MS (Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis), a phase III trial development program for alemtuzumab in patients with RRMS, to date consisting of two randomized, open-label, multicenter, rater-blinded phase III studies, CARE MS I and II. While CARE-MS I focuses on alemtuzumab administration in early active, treatment-naïve RRMS patients, CARE-MS II targets at clinically active RRMS patients with breakthrough disease during currently approved disease-modifying therapy. Both studies have started recruitment at participating centers in Australia, Europe and Northern and Latin America.

Y. C. Zwick, Munich, Germany

References

1. Deisenhammer F et al.ECTRIMS 2005; Poster #605.
2. Gneiss C et al. Mult Scler 2006; 12(6): 731-737.
3. International Scientific Symposium. Abstracts. Stockholm 2008.
4. Sorensen PS et al. Neurology 2005; 65(1): 33-39.
5. Rice GPA et al. Neurology 1999; 52(6): 1277-1279.
6. Sominanda A et al. Mult Scler 2007; 13(2): 208-214.
7. Goodin DS et al. J Int Med Res 2007; 35(2): 173-187.
8. Hohlfeld R et al. Nt Clin Pract Neurol 2005; 1: 34-44.
9. Coles AJ et al. J Neurol 2006; 253(1): 98-108.
10. Hemmer B et al. Ann Neurol 2007; 62(4): 314-326.
11. Kappos L et al. Neurology 2006; 67(7): 1242-1249.
12. Baum K et al. Mult Scler 2007; 13(9): 1153-1160.
13. Brochet B et al. Rev Neurol (Paris) 2006; 162(6-7): 735-740.

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