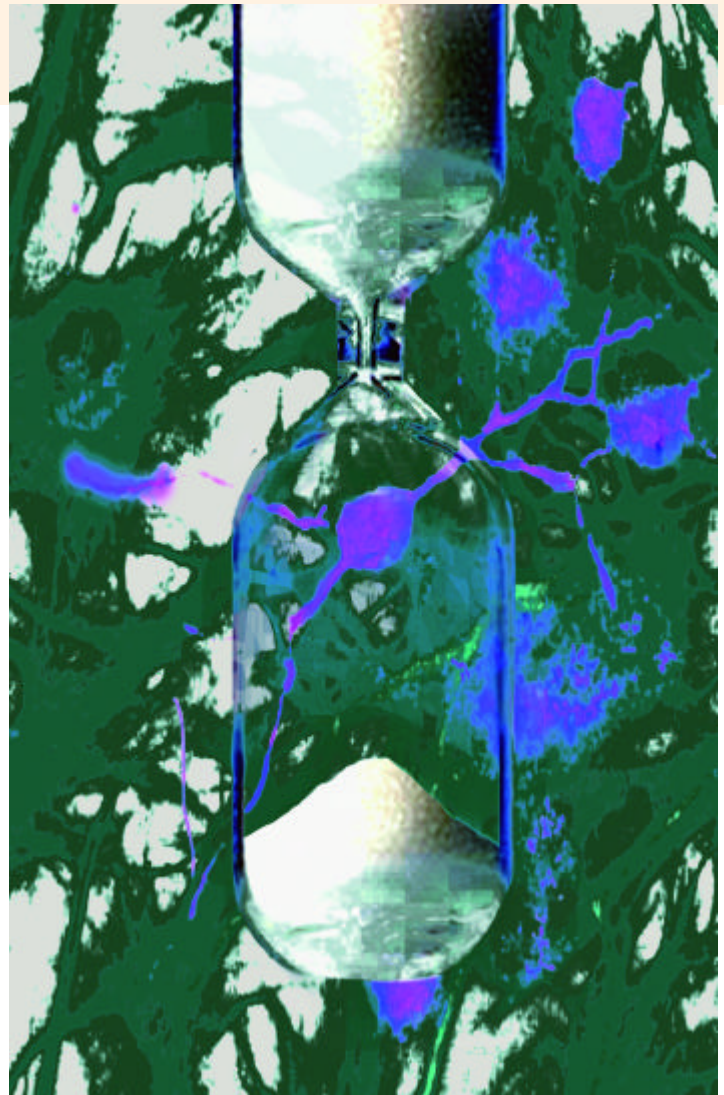


MS-NEWS

Benefit from Time:
Results from the Three-Year
BENEFIT Study



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Multiple Sclerosis (MS) is a progressive, chronic disease that can cause irreversible damage in its early stages, even before any permanent symptoms or disabilities are apparent (1). The availability of disease-modifying therapies raises the question of how early treatment should be started. Pathological and radiological evidence indicates that aspects of permanent injury, including axonal loss, occurs from very early on in the course of the disease process of MS and are even apparent before the diagnosis can be confirmed in patients with a first demyelinating event suggestive of MS (2-5). Studies have shown that early diagnosis and treatment can positively impact patient outcomes (6, 7).

The BENEFIT (Betaferon® in Newly Emerging MS For Initial Treatment) study was conducted to provide a clearer rationale to support early intervention in patients with the first symptoms highly suggestive of multiple sclerosis. Results were recently published from the three-year integrated analysis of the BENEFIT study in *The Lancet* (8). Just prior to the publication, four of the BENEFIT Study key investigators were interviewed on the outcomes and implications for patients and physicians. Nancy Sumner reports on the highlights of these interviews.

Can you tell us a little about multiple sclerosis (MS) and its symptoms?

Dr. Montalban: Multiple sclerosis is a demyelinating, inflammatory, and sometimes degenerative disease that is the second leading cause of disability in young adults. MS is called the "chameleon of neurology" because there are a variety of different symptoms that are different from one person to another, including inflammation of the spinal cord, brain stem syndrome, and diplopia or double vision.

Why should MS be treated early?

Dr. Montalban: Multiple sclerosis should be treated early because we know that there is irreversible brain tissue loss at the very earliest stage of the disease, and this is correlated to inflammation that can be reduced through early treatment.

Dr. Freedman: The damage in MS occurs very early in the disease, so by the time many patients present, they have already accumulated significant amounts of irreversible damage to the nervous system. One can argue that even at that point, it is too late. Once the disease has been identified, given the fact that we have medications that address the early phase of the disease, you can't start early enough.

"Multiple sclerosis should be treated early because we know that there is irreversible brain tissue loss at the very earliest stage of the disease, and this is correlated to inflammation that can be reduced through early treatment."

Dr. Montalban

Dr. Comi: I am a very strong supporter of early treatment for two simple reasons. First, we know that each new lesion destroys a part of the brain, the spinal cord or the optic nerves, so if we eliminate or reduce the risk of a lesion, we protect against this damage. Second, we know now that

even in the secondary progressive phase of the disease, most if not all of the damage is related to what happened weeks, months and years before. We know that if the axons remain demyelinated, even if they survived the first attack, they will die sooner or

later. We have only one opportunity to prevent the damage. When the damage is done, we cannot prevent further deterioration of nerve function and further deterioration of the neurological condition as a consequence.

What exactly is meant by “early treatment”?

Dr. Montalban: Early treatment means that the patient has had one episode that is suggestive of multiple sclerosis. From an academic point of view, they don't yet have multiple sclerosis, but you can be pretty sure that they will develop multiple sclerosis based on the results of the MRI and other tests. That is the point at which we have to start treatment.

What was the main question addressed in the study?

Dr. Kappos: The burning question for everyone in this phase of the disease is whether early intervention makes a difference in the development of later disability, that is, the long-term burden of impairment and disability for the patient.

Dr. Freedman: The primary endpoint of the BENEFIT study was to determine whether implementing a potent anti-inflammatory therapy like Betaferon® at the earliest identifiable stage of MS could delay the next event. To make this result meaningful, we also wanted to see an effect on long-term progression. We suspected that if this medication is started as early as possible, it might be able to delay or prevent long-term progression of the disease, but nobody had really looked at that. BENEFIT was the first study to address it.

Dr. Comi: The trial provided two opportunities. The first was to see whether the patients who moved from no treatment to treatment would receive the same benefit as those who received treatment

throughout the two-year study. The second was to explore the impact of early treatment on disability, which is in any case the most important outcome. There was evidence that there was a strong effect on accumulated disability—of course, disability in this very early phase is a modest disability, but this is only the beginning.

What was the main result of the BENEFIT 3 year analysis?

Dr. Kappos: The main result of the study is that early treatment really does make a difference. People who start later with treatment have a disadvantage that can be measured on the EDSS neurological scale. They have more impairment or perhaps even disability, even in this very early phase of the disease.

“The information from the three-year analysis is quite startling: implementing Betaferon® therapy after the first event alone led to a 40% risk reduction in progression, seen as early as three years after initiation of therapy.”

Dr. Mark Freedman

Dr. Freedman: The information from the interim three-year analysis is quite startling: implementing Betaferon® therapy after the first event alone led to a 40% risk reduction in progression, seen as early as three years after initiation of therapy.

Dr. Comi: The main result of the BENEFIT trial in this extended three-year period is the evidence, for the first time, that if we target the disease very early with Betaferon®, we can modify the accumulation of disease and disability. I think this is a milestone in the treatment of MS.

How did you define disability progression in the study?

Dr. Kappos: EDSS is a ten-step scale that describes the progression of disability in MS over the whole course of the disease, which will usually last 30 or 40 years. Ten means death due to MS, and zero means there is no disability that the patient feels or that a neurologist can find in a neurological examination. Disability progression in the BENEFIT

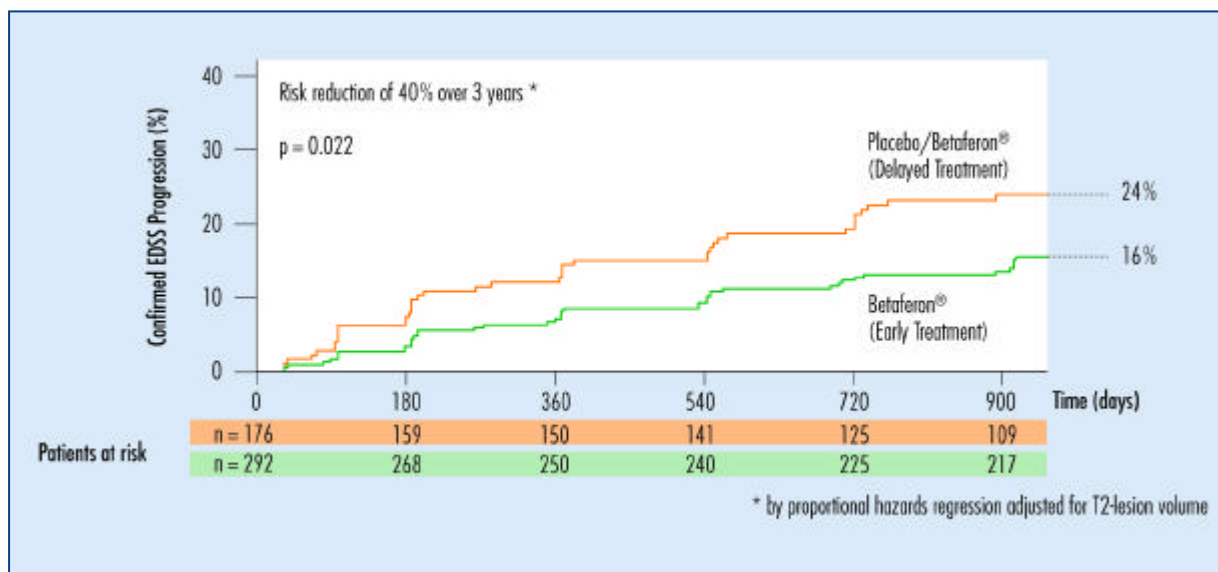


Fig. 1 Time to Confirmed Disability Progression: Kaplan Meier estimates for the probability of progression of disabilities measured by EDSS (8)

trial is defined as a change by one full step in the EDSS scale that is confirmed six months later. It is not related to a relapse, but has to be something that lasts and has a permanent impact on the life of the patient.

Would you say that very early in the course of the disease is the real window of opportunity for treatment?

Dr. Montalban: There is a very good window of therapeutic opportunity at the very earliest stage. We have observed from the results of clinical trials that the outcomes of treatment during the later stages of the disease are not very good; in the medium stage they are fair, but the best results have been found with treatment at the very earliest stages of the disease. That's very clear.

"The main result of the BENEFIT trial in this extended three-year period is the evidence, for the first time, that if we target the disease very early with interferon beta 1b, we can modify the accumulation of disease and disability. I think this is a milestone in the treatment of MS."
Dr. Comi

Dr. Freedman: There was a concept held by many physicians that some patients who have had a first attack, even though they are high risk, may not develop MS. Maybe some of them are going to have a very benign course, so maybe we should wait and see what comes up on their MRI or after a year or two of follow-up. It was thought that there was nothing to lose by waiting. This study changes that whole concept. BENEFIT has created a paradigm shift in our thinking about treatment, because it has shown us that 85% of the placebo patients who have evidence of silent disease on their MRI will in fact be diagnosed with Mc Donald MS within a year or two years. Would you wait until that occurs? BENEFIT also tells us that waiting leads to more irreversible damage, and those patients who delay therapy are 40% more likely to have a progression than those who get the early start. These are two very important messages.

Did you expect the impact on disability at three years?

Dr. Freedman: When we set up this study, the primary endpoint was to delay the next event, that was the important thing to be looking at, at least in first event individuals. These are patients in the very, very earliest identifiable phase of the disease. Progression is something we associate with accumulated disease activity, so seeing it very early in a first event population would not have been expected at all. Nonetheless, we wanted to look at disease progression, so we built in a second phase to do that.

BENEFIT was really two studies in one: the two-year initial phase of the study, and then an extension phase. Everyone from the first phase was rolled into the second extension phase so that we could address some important topics such as disease progression. We did not expect to see anything until probably five years, when most progression starts to become decipherable, but when we did an interim analysis at three years, there it was: a significant progression in the placebo-switched patients. The group that had been receiving placebo for a period of time and then switched to Betaferon was at three years significantly worse than the patients who got the early start on therapy. This was totally unexpected. Just that short period of time they spent without Betaferon cost them dearly, because once you have accumulated damage, it is very unlikely that you can undo it. What is lost is not regained. The delay in therapy — meaning sometimes just thinking about the disease for a year to a year and a half — made all the difference in the world to these patients, because they are now worse after three years. What they lost by not going on therapy during that first year and a half, they will now carry with them for probably the life of the disease.

“Once we know that the patient has multiple sclerosis, I believe there is absolutely no reason to wait... Combined with the observation that if we prevent early, we have long-term benefits, the decision is quite easy to make. If we inform the patient about the risks of future disability and then explain that we have the opportunity to prevent this, I cannot believe that the patient will not be in agreement with this decision. It’s a matter of informed opinion.”

Dr. Comi

Have other studies of immunomodulatory drugs found the same effect?

Dr. Kappos: These results are novel because we were able for the first time to show an impact in this very early phase of the disease, and also to separate this impact from an immediate effect on relapses. At the time point when disability was measured, the number of relapses was equal in both groups because they were both on the same treatment, and therefore the effect on disability cannot be due to an immediate effect on relapses. I think that with these results, we have stronger arguments for early treatment and more people in this situation will decide to take this opportunity.

Dr. Freedman: It is conceivable that some of the other therapies that have shown an effect in established relapsing disease might be able to show an effect on progression even at this first attack stage, but that has not been proven. Why would you play guesswork with your disease? Why wouldn't you go with something that has been proven?

Based on the study findings, what are the implications for clinical practice?

Dr. Montalban: The first clear implication is that we have to promote early detection of multiple sclerosis. The second is to teach neurologists that they should treat patients early in the course of multiple sclerosis because we have very safe and powerful drugs nowadays.

Dr. Comi: Once we know that the patient has multiple sclerosis, I believe there is absolutely no reason to wait. This is a preventive treatment, and prevention is best when used as early as possible. Combined with the observation that if we

prevent early, we have long-term benefits, the decision is quite easy to make. It's a matter of informed opinion.

Dr. Freedman: Some patients are worried about taking high dose, high frequency medication right from the start, but as I've told you, the damage is already done. Already these patients are showing irreversible changes even after the first event. Given the fact that you're dealing with irreversible

damage, why would you play guesswork with your disease?

"These results are novel because we were able for the first time to show an impact in this very early phase of the disease, and also to separate this impact from an immediate effect on relapses... With these results, we have stronger arguments for early treatment and more people in this situation will decide to take this opportunity."
Dr. Kappos

Dr. Comi: What I will recommend to a neurologist is, first, pay a lot of attention to the diagnosis because we must be absolutely certain that this is the right diagnosis, and second, start the treatment as soon as you are sure this is a MS patient. There is absolutely no reason to wait to treat.

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The views expressed by the participants in this discussion are not reflective nor endorsed by Bayer Schering Pharma AG.

Betaferon® Composition: Recombinant interferon β -1b 250 μ g (8.0 MIU) per ml when reconstituted. Betaferon contains 300 μ g (9.6 million IU) of recombinant IFN β -1b per vial. **Indications:** Betaferon is indicated for the treatment of patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite MS. Patients with relapsing-remitting MS and two or more relapses within the last two years, patients with secondary progressive MS with active disease, evidenced by relapses. **Contraindications:** Initiation of treatment in pregnancy. Patients with a history of hypersensitivity to natural or recombinant interferon β , human albumin or to any excipients. Patients with current severe depression and/or suicidal ideation. Patients with decompensated liver disease. **Precautions:** ♦ The administration of cytokines to patients with a pre-existing monoclonal gammopathy has been associated with the development of systemic capillary leak syndrome with shock-like symptoms and fatal outcome. ♦ In rare cases, pancreatitis was observed with Betaferon use, often associated with hypertriglyceridaemia. ♦ Betaferon should be administered with caution to patients with previous or current depressive disorders, in particular to those with antecedents of suicidal ideation. Depression and suicidal ideation are known to occur in increased frequency in the MS population and in association with interferon use. Patients treated with Betaferon should be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physician. Patients exhibiting depression should be monitored closely during therapy with Betaferon and treated appropriately. Cessation of therapy with Betaferon should be considered. Betaferon should be administered with caution to patients with a history of seizures, to those receiving treatment with anti-epileptics, particularly if their epilepsy is not adequately controlled with anti-epileptics. ♦ Thyroid function tests are recommended regularly in patients with a history of thyroid dysfunction or as clinically indicated. In addition to those laboratory tests normally required for monitoring patients with MS. Complete blood and differential white blood cell counts, platelet counts, and blood chemistries, including liver function tests (e.g. AST (SGOT), ALT (SGPT) and γ -GT), are recommended prior to initiation and at regular intervals following introduction of Betaferon therapy, and then periodically thereafter in the absence of clinical symptoms. ♦ As for other beta interferons, severe hepatic injury, including cases of hepatic failure, has been reported rarely in patients taking Betaferon. The most serious events often occurred in patients exposed to other drugs or substances known to be associated with hepatotoxicity or in the presence of co-morbid medical conditions (e.g. metastasising malignant disease, severe infection and sepsis, alcohol abuse). Patients should be monitored for signs of hepatic injury. Withdrawal of Betaferon should be considered if the levels of serum transaminases significantly increase or if they are associated with clinical symptoms such as jaundice. In the absence of clinical evidence for liver damage and

after normalisation of liver enzymes a reintroduction of therapy could be considered with appropriate follow-up of hepatic functions. ♦ Caution should be used and close monitoring considered when administering interferon β to patients with severe renal failure. ♦ It should also be used with caution in patients who suffer from pre-existing cardiac disorders. Patients with pre-existing significant cardiac disease, such as congestive heart failure, coronary artery disease or arrhythmia, should be monitored for worsening of their cardiac condition, particularly during initiation of treatment with Betaferon. Rare cases of cardio-myopathy have been reported: If this occurs and a relationship to Betaferon is suspected, treatment should be discontinued. ♦ Serious hypersensitivity reactions may occur. If reactions are severe, Betaferon should be discontinued and appropriate medical intervention instituted. ♦ Injection site necrosis has been reported in patients using Betaferon. It can be extensive and may result in scar formation. If the patient experiences any break in the skin, which may be associated with swelling or drainage of fluid from the injection site, the patient should be advised to consult with his/her physician before continuing injections with Betaferon. If the patient has multiple lesions Betaferon should be discontinued until healing has occurred. Patients with single lesions may continue on Betaferon provided the necrosis is not too extensive, as some patients have experienced healing of injection site necrosis whilst on Betaferon. ♦ Neutralising activity was observed in patients in the different clinical trials. Between 23% and 41% of the patients developed serum interferon β -1b neutralising activity; between 43% and 55% of these patients converted to a stable antibody negative status during the subsequent observational period of the respective study. The development of neutralising activity is associated with a reduction in clinical efficacy only with regard to relapse activity. The decision to continue or discontinue treatment should be based on clinical disease activity rather than on neutralising activity status. **Side effects:** At the beginning of treatment adverse reactions are common but in general they subside with further treatment. The most frequently observed adverse reactions are a flu-like symptom complex and injection site reactions, which are mainly due to the pharmacological effects of the medicinal product. Injection site reactions occurred frequently after administration of Betaferon. The following side effect listing is based on reports from post marketing surveillance: Very common: Flu-like symptoms, chills, fever, injection site reaction, injection site inflammation, injection site pain; common: Injection site necrosis, uncommon: anemia, thrombocytopenia, leukopenia, depression, hypertension, vomiting, nausea, alanin aminotransferase increased, aspartate aminotransferase increased, urticaria, rash, pruritus, alopecia, myalgia, hypertonia; rare: skin discoloration, menstrual disorder, chest pain, malaise, sweating, weight decrease. **Marketing Authorisation Holder and Numbers:** Bayer Schering Pharma AG, D-13342 Berlin, Germany, EU/1/95/003/003, -004, -005, -006 **Preparation Date:** 06/06, Please refer to the Summary of Product Characteristics for further information.

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