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## Reconsidering the Concept of First-Line, High-Efficacy Treatment

Dr. Hartung:

My name is Hans-Peter Hartung. I am Chairman of the Department of Neurology and Director of the Center of Neurology and Neuropsychiatry at Heinrich-Heine University in Dusseldorf, Germany.

Well, in MS, we can basically take 2 different approaches, using initially, early on, high-efficacy treatment, which comes with certain risks, and then switch to less efficacious, potentially less risky treatments or no treatment at all. By contrast, we can pursue the approach of escalation, which means we start off with a less efficacious treatment and then, considering the response, the extent of disease control would escalate to a second, more effective drug and maybe cycle further, escalate to a third drug. Well, first of all, we have gratifyingly a very broadened therapeutic arsenal, and the question is which of the different options to choose.

Now, I think there is evidence that has been accumulated along several lines to suggest that short of

curing the disease, we need to initiate treatment very early on. Now, the question arises: Should I embark on a highly effective treatment? We would all agree that in patients with highly active disease, defined either on clinical or MRI grounds, it is appropriate to start with high-efficacy treatments even if that may carry a higher risk in terms of side effects, either short term or long term. Most of the long-term side effects we don't even know right now.

There are clear prognosticators, if one looks at the group level, who will be in need of a more aggressive approach. Those are patients with severe disease, high number of relapses, relapses in strategic locations of the central nervous system. Think about brain stem or spinal cord. Other features that we know are conveying a higher risk for faster disease progression—in these you would, of course, and can nowadays, also, in most countries resort to high-efficacy treatment early on.

There are regulatory limits in some countries where to stipulate it that you need to start with a more modestly effective drug and then, as dictated by the clinical response, have to switch to a higher efficacy drug. But if one looks at clinical trial data, if one looks at the natural history of multiple sclerosis, you would think that one loses precious time—one gets out of this window of therapeutic opportunities with such an escalating approach. We know from large epidemiological studies, while we may not absolutely translate this 1:1 if we face an individual patient, but that older age at onset, shorter interval between relapses, severe relapses, time to reach a critical level of disability—EDSS 4—strategic location of lesions, number of lesions on baseline MRI scan, all dictate the rate of progression and, consequently, the need for more active and effective intervention in a given patient.

So, a comprehensive analysis of all these factors that prognosticate a poorer outcome, a faster progression, more quicker attainment of severe disability will help us to make the choice between highly effective treatment and the more conventional escalation approach.

Those which have a regulatory approval for use in highly active patients are fingolimod, and then on a probably more active scale and more effective scale, cladribine, natalizumab, alemtuzumab, ocrelizumab. I think this is true given the concerns that arose initially in terms of serious adverse events. I think with more and more experience, the safety profile has been firmly established, and some of the initial concerns really could be alleviated, which means physicians, neurologists, have become more comfortable using the drugs even if they are associated with some serious adverse effects. With high efficacy initial treatment, you upload the risks associated with treatment of multiple sclerosis. With the escalating approach, you sort of encounter adverse events along the treatment.

Furthermore, I think the paradigm of the mode of action has changed and allowed to group treatments into sort of continuous immunomodulating or immunosuppressant therapies and those that are now termed immune reconstitution therapies. I think we probably need to differentiate the impact of science

and our better understanding and experience with these treatments and limitations imposed upon us by regulatory agencies and also resource availability in various countries.

So, I think with better long-term experience, a better way to judge the risk-benefit ratio, one would feel more comfortable and use more readily these highly active treatments. I think all... As I mentioned and I'd just like to repeat and emphasize, all evidence suggests that trying to impact the disease as early as possible will better the long-term outcome. So, my personal feeling and hope is that we will leave the escalation approach and really adopt more rigorously the high-efficacy early treatment interventional approach.