CAN WE AIM FOR A 'DISEASE-FREE STATUS' WITH CONTEMPORARY MS THERAPIES? –YES

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Traditionally, relapse rate and and disability progression using expanded disability status scale (EDSS) have been the primary outcome parameters of clinical trials, still required and accepted by regulatory agencies. Thus, IFN-beta preparations and glatiramer acetate (GA) have been shown to impact both parameters to different degrees. Over the past years we have seen a growing number of highly efficacious disease modifying therapies. High efficacy in conjunction with more sensitive radiologic outcome parameters has led to the concept of disease remission or “freedom from disease activity”. “Freedom from disease activity” or “disease activity free status” is currently defined by the absence of clinical activity (relapse, EDSS progression) and radiological (MRI) activity, typically gadolinium-enhancing lesions and new or enlarging T2-lesions. Initially described in a post hoc analysis of the pivotal natalizumab placebo-controlled trial, several clinical studies have meanwhile reported this combined clinical and radiological outcome parameter. Thus, phase III-trials using cladribine (CLARITY), fingolimod (FREEDOMS) and dimethylfumarate (DEFINE) have all shown a larger proportion (typically 2-3 fold) of patients being “free from disease activity” over placebo. Notably however, at least over the interval of the core studies of approximately 2 years, also a proportion of patients in the placebo arms remained free of disease activity. In addition to the observation intervals, these studies also highlight the relatively large contribution of the radiographic parameters to the composite outcome.

Also with longer existing immunotherapies such as IFN-beta and GA a sizeable proportion of patients will be “free from disease activity”. Thus, in the large, 3 year CombiRx trial roughly 20 percent of patients remained free from clinical and radiological disease activity with either intramuscular IFN-beta 1a or GA. The combination of IFN-beta 1a and GA proved to be superior to respective monotherapies, driven by radiological, but not clinical stability outcome. As with all new “surrogate” outcome parameters, we will have to learn if these observed differences will lead to clinically meaningful alterations in long term (comparative) effectiveness. It will also remain to be demonstrated if relevant clinical symptoms such as neuropsychological or neurocognitive dysfunction are sufficiently covered by the current definition of disease activity free status. Also, future definitions may come up with more refined parameters (e.g. brain atrophy, T1 “black holes”). Still, current data suggests that already with existing immunotherapy we can achieve the goal of “freedom from disease activity” for a considerable proportion of patients at least in early stages of the disease. More than a modern “marketing” for newer substances, the concept of disease remission can have benefits for all stakeholders. Thus, being “disease activity free” may foster adherence in patients and affect psychosocial aspects. For physicians the goal to achieve a remission state will lead to constant reassessment of the current treatment and its benefit risk profile. For translational science the notion that a proportion of patients will respond particularly well highlights the need for individualized biomarkers to predict treatment outcome. Finally, raising treatment goals will also have an impact on new therapeutic developments and clinical studies. In turn, feasibility of the “freedom from disease activity” outcome parameter in smaller proof of concept trials may lead to faster clinical development programs and ultimately lower the barriers for novel MS-therapies.