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Title

Treatment with the monoclonal antibody rituximab in Multiple Sclerosis
- a study based on an academic clinical trial

Abstract

Background: Multiple sclerosis (MS) is a chronic, inflammatory disease, affecting the central nervous system. A growing number of disease modifying treatment alternatives entails a need for an individualised risk-benefit-convenience analysis in the counselling of patients and methods to monitor the treatment effect, including markers for subclinical inflammation. Today, MRI and the biomarker neurofilament light chain (NFL) in cerebrospinal fluid (CSF-NFL) are commonly used. The development of new techniques for analysing NFL in very low concentrations in serum or plasma provides a promising opportunity for a less invasive method. Rituximab is a chimeric monoclonal antibody with B-cell depleting properties vastly used in rheumatological disease and certain haematological malignancies. Phase II studies have shown a beneficial effect on inflammation also in MS, the detailed mechanisms of action yet to be explained.

Aims: The aims of this thesis were to evaluate rituximab as a treatment alternative in relapsing remitting MS (RRMS) by describing the clinical effect and patient related outcome measures after a switch of therapy from first-line injectables to rituximab and to explore possible immunological mechanisms of B cell depletion as well as to evaluate the use of neurofilament in plasma (p-NFL) as an end-point in a clinical trial setting.

Methods: The thesis is based on the open-label phase II multicentre clinical trial Switch-To-RITUXimab in MS (STRIX-MS; EudraCT 2010-023021-38), in which 75 patients completed a therapy switch from first-line injectables to rituximab, and, to some part, the extended follow-up study, STRIX-MS extension (EudraCT 2013-002378-26). The disease modifying effect was evaluated by regular clinical evaluations, MRI and analyses of CSF-NFL. The clinical outcome was evaluated by the EDSS and SDMT scales. The questionnaires MSIS-29, FSMC and TSQM were used for the evaluation of patient related outcome measures. Immunological mechanisms of the B cell depletion were explored by the analysis of a broad panel of cyto- and chemokines in CSF by an electrochemiluminiscens method before and after therapy switch, and in comparison to healthy controls. The concentration of p-NFL was measured by an in-house NF-light assay on the Simoa platform with a Homebrew kit and explored for the use as a clinical trial end-point.

Results: During the follow-up, signs of inflammatory activity decreased. Both the mean number of Gd enhancing lesions (0.03 vs 0.36, $p=0.029$) and the number of new or enlarged T₂ lesions were reduced (0.01 vs 0.28, $p=0.01$). The mean concentration of CSF-NFL was reduced during the first year (491 vs 387, $p=0.01$). The corresponding reduction in plasma did not reach the level of statistical significance. The rating of overall treatment satisfaction improved significantly (6.3 vs 4.8, scale range 1-7, $p<0.001$). In the explorative immunological study, the immunological profile was altered after therapy switch with the most prominent reduction observed in the concentrations of IP-10 and IL-12/23p40.

Conclusions: The results indicate a disease modifying effect of rituximab in line with other studies and provide support for a superior treatment satisfaction with rituximab as compared with injectable therapies. However, the lack of control group hampers the possibility to draw definite conclusions on the therapy effect. The immunological effects of B cell depletion need to be further explored.

Keywords

Multiple sclerosis, Rituximab, Cytokines, Immunological profile, Neurofilament light, Treatment satisfaction

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