Anti-FcRn Treatment in Antibody-Associated Experimental Autoimmune Encephalomyelitis

Jana Remlinger, MSc - Department of Neurology, Inselspital, Bern University Hospital and Department for BioMedical Research (DBMR)

Questions & Answers from the Presentation

In your methods, you show that the anti-FcRn treatment is administered even before onset of the disease symptoms. Wouldn't this be a preventive treatment?

The timing of anti-FcRn application before the administration of MOG-IgG might indeed be a limitation in the translation to the human setting. However, it was applied after the active peptide immunization phase, creating an inflammatory CNS background. Thus, strictly speaking it is not a prophylactic treatment.

Have you seen any adverse treatment effects in your animals? What AE can be expected in patients?

We did not observe any adverse event in the animals. In the human setting, hypogammaglobulinemia can be expected due to the reduction of overall IgG by the anti-FcRn treatment. This leads to a reduced humoral immune response and therefore could harbor an increased risk for infections and have implications with vaccine responses. In the published phase 2 trials in myasthenia gravis and immune thrombocytopenia, the most common adverse event was headache and overall, the adverse events were reported to be mild to moderate.

Do you have any explanation why there was no treatment effect on the number of T and B cells in the evaluation of the spinal cord?

The main hallmarks of the used animal model are demyelination and macrophage infiltration, especially at the chronic disease stage as investigated here. Even though EAE is a mainly T cell driven model, the number of infiltrating T cells is relatively low compared to the absolute amount of macrophages that can be found in spinal cord lesions at the chronic disease stage (21 days post immunization). Therefore, differences in T cells might be less observable. B cell infiltration occurs mainly meningeal which presents some difficulties in the evaluation of the infiltrates. The spinal cord tissue has to be prepared carefully in order to get an insight into the meningeal infiltrations. Additionally, here again we have a relatively low number of B cells involved in the chronic lesions of EAE animals.

Striatech GmbH
Vor dem Kreuzberg 17
72070 Tübingen
Germany

Managing Directors:
Dr. Boris Benkner
Dr. Marion Mutter
Dr. Thomas Münch

Bank: Kreissparkasse Tübingen
IBAN: DE48 6415 0020 0004 1768 75
BIC/SWIFT: SOLADES1TUB
Ust.-ID: DE318011974

+49 7071 53 913 - 0
info@stria.tech
https://stria.tech
Amtsgericht Stuttgart HRB 764800

Do you know the reason why visual function is preserved while the treated animals still showed certain levels of clinical symptoms?

The anti-FcRn antibody treatment mainly affects the antibody-mediated part of the disease while the underlying demyelination and immune cell infiltration caused by the MOG peptide-immunization still remain. Therefore, spinal cord lesion formation and therefore motor symptoms cannot be prevented or reversed completely. The functional visual component might have a better treatment response because the visual system was overall less affected. Likewise, it might be hypothesized that the OMR measurement is not sensitive enough to detect very subtle changes. This might be evaluated with additional electrophysiological measurements.

Were the treated animals only the ones that had EAE symptoms or did you take all immunized animals?

This EAE model is a very consistent animal model in which we usually see an incidence of 80 to 100% after MOG-immunization and antibody administration. Still, some animals do not develop disease symptoms; consequently, we exclude them from the experiment and the analysis.

Is the FcRn receptor differently expressed in retina cells and optic nerve?

The treatment target FcRn is systematically uniformly distributed as it is expressed by endothelial cells as well as blood mononuclear cells. Therefore, we do not expect differences in FcRn expression between the optic nerve and the retina other than the different distribution of blood vessels in general. However, we have not investigated this in our experiments.

Does the dose of MOG affect the vision loss effect?

We have not investigated the effect of different MOG peptide or MOG-IgG concentrations on vision loss.

Slightly different MOG peptide-immunization protocols are used among the research groups but still leading to similar EAE symptomatology. However, a marked increase of the MOG peptide concentration leads to a stronger immune reaction and thus more severe disease symptoms.

Similarly, MOG-IgG administration aggravates the disease symptoms and higher concentrations would possibly lead to an increased effect.

Did you check for FcRn expression after treatment with FcRn antagonist to see if there is down regulation of the receptor?

We did not investigate the expression of FcRn in our experimental set-up.

Have you done any comparison of the pathologies/phenotypes you've investigated in animals without or less dramatic clinical symptoms/EAE?

In our experimental set-up, all animals in one treatment group were pooled for the analysis and not stratified by the severity of their disease symptoms. Moreover, animals that did not develop disease symptoms were excluded from the analysis.

In an earlier experiment, we did a correlation analysis of the disease severity independent of the treatment group or disease model (with and without administration of MOG-IgG) against visual acuity and observed an inverse correlation with a decrease of visual acuity in more severely affected animals.

Is this possible sensitivity of MOG difference depend on mice genetic background or strains? Have you been testing different strains of mice or rat?

In our paper, we used exclusively C57Bl/6J mice and have not compared to other mouse strains or rat models. This comparison would be hampered by the different effects of MOG-immunization in different mouse and rat strains. The disease course of EAE is known to vary between different mouse strains, age groups and peptide used for immunization (e.g. other CNS peptides like myelin basic protein or proteolipid protein induce EAE).