In-vivo B-cell activity predicts response to treatment with glatiramer acetate and interferons in patients with relapsing-remitting multiple sclerosis (RRMS)

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OBJECTIVE
Investigation of the enzyme-linked immunospot (ELISPOT) assay for the ex-vivo detection of brain-reactive B cells as a predictive marker for individual responses to glatiramer acetate (GA) versus interferon-ß (IF-ß) in RRMS patients.

BACKGROUND
There is an ongoing medical need for an effective predictive personalized allocation of disease modifying therapies (DMTs) in RRMS. Pilot studies with small sample sizes showed predictive potential of ELISPOT to identify RRMS patients responding to GA by in-vivo immunological response (1), correlating with clinical response (2,3).

POPULATION & METHODS
Inclusion criteria:
RRMS patients of the German doctor´s owned NeuroTransData MS registry
GA responders on GA >= 12m without relapses: n= 68
GA treatment failures: n= 35
IF-ß responders on IF-ß >=12m without relapses: n=55
IF-ß treatment failures: n= 37
Exclusion criteria: previous or current DMT interfering with B-cell activity.
Relapses, EDSS, DMTs have been captured in-time with 3.5 visits/year.

ELISPOT
After overnight resting of blood samples peripheral blood mononuclear cells (PBMCs) were isolated using Biocoll density gradient centrifugation. For polyclonal stimulation of B cells, PBMCs were cultured in RPMI-1640 supplemented with IL-2 and R848 for 96 h. 1 x 10^6 cells were plated on whole normal human brain tissue lysate-coated wells and incubated for 26 h. Afterwards, spots were developed using the Vector Blue AP-kit and counted with an ImmunoSpot Series 6 Analyzer.

RESULTS
ELISPOT achieved a clinically useful robustness to predict clinical efficacy of GA and IF-ß with a sensitivity of 0.73, specificity of 0.76, positive predictive value 0.78, negative predictive value 0.29 and a diagnostic odds ratio of 8.50.

CONCLUSIONS
Testing of the brain-reactive B-cell response with ELISPOT enables a true personalized prediction of clinical response to GA and IF-ß in about 3 out of 4 RRMS patients. This ELISPOT assay shows the potential to improve individual allocation of injectables in RRMS.

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2.Farina C, Wagenpfeil S, Hohlfeld R (2002) Immunological assay for assessing the efficacy of glatiramer acetate (Copaxone) in multiple sclerosis. A pilot study. Neurol 249: 1587–1592

3. Rovituso DM, Duffy CE, Schroeter M, Kaiser CC, Kleinschnitz C, Bayas A, Elsner R, Kuerten S. (2015) The brain antigen-specific B cell response correlates with glatiramer acetate responsiveness in relapsing-remitting multiple sclerosis patients. Sci Rep 5:14265