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

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## Background

There is an ongoing medical need for predictive personalized allocation of disease modifying therapies (DMTs) in RRMS.

## Aims

Evaluation of the predictive value of the enzyme-linked immunospot technique (ELISPOT) brain reactive B-cell activity of peripheral blood cells to identify patients with relapsing-remitting multiple sclerosis (RRMS), who will clinically respond to glatiramer acetate (GA, Copaxone®) or interferon-ß 1a and 1b (IF-ß).

## Methods

RRMS patients of the NeuroTransData multiple sclerosis registry were retrospectively identified based on their treatment response or failure to GA vs. IF-ß, which were defined as more than 12 months without relapse activity after initiation of treatment or lack of treatment efficacy, respectively, as it had been documented by the treating physicians in the registry in time. The GA and the IF-ß group comprised n = 73/62 responding and n=35/37 non-responding patients, respectively. Exclusion criteria included other previous or current disease modifying therapie interfering with B-cell activity. Peripheral blood samples were investigated for brain reactive B-cell activity on ELISPOT plates after 96h in vitro polyclonal stimulation. B-cell activity spots were counted with an ImmunoSpot series 6 analyzer. Validity metrics of the ELISPOT testing results were calculated in relation to the documented clinical responsiveness in the two groups of injectables.

## Results

Positive test results indicate evidence of B-cell activity in ELISPOT testing, negative results no B-cell activity. The hypothesis of the study expected positive evidence of B-cell activity in GA responder and IF-ß non-responder and vice versa. Table 1 shows the proportions of patients in each strata which were correctly and falsly identified by ELISPOT testing as controlled by the individual clinical course of patients.

| | Test result | % | n | Test result | % | n | Total n |
|---|---|---|---|---|---|---|---|
| **Single strata** | correct test prediction | | | false test prediction | | | |
| **GA responder** | positive | 73.97 | 54 | negative | 26.03 | 19 | 73 |
| **GA non-responder** | negative | 80.00 | 28 | positive | 20.00 | 7 | 35 |
| **IF-ß responder** | negative | 74.19 | 46 | positive | 25.81 | 16 | 62 |
| **IF-ß non-responder** | positive | 72.97 | 27 | negative | 27.03 | 10 | 37 |
| **Combined strata** | | | | | | | |
| **GA responder & IF-ß non-responder** | positive & negative | 58.18 | 64 | negative & positive | 41.82 | 46 | 110 |
| **GA non-responder & IF-ß responder** | negative & positive | 54.64 | 53 | positive & negative | 45.36 | 44 | 97 |

**Table 1:** *Proportions of correct and false prediction of ELISPOT testing for single and combined strata of GA and IF-ß responder and non-responder*

| Metric | GA | IFN-ß | GA & IFN-ß |
|---|---|---|---|
| **Positive predictive value** | 0.89 | 0.63 | 0.78 |
| **Negative predictive value** | 0.40 | 0.82 | 0.28 |
| **Sensitivity** | 0.74 | 0.73 | 0.74 |
| **Specificity** | 0.80 | 0.74 | 0.76 |
| **False positive rate** | 0.20 | 0.26 | 0.24 |
| **False negative rate** | 0.26 | 0.27 | 0.26 |
| **Positive likelihood ratio** | 3.70 | 2.86 | 3.11 |
| **Negative likelihood ratio** | 0.33 | 0.36 | 0.35 |
| **Diagnostic odds ratio** | 11.37 | 7.76 | 8.99 |

**Table 2:** *ELISPOT test validity metrics*

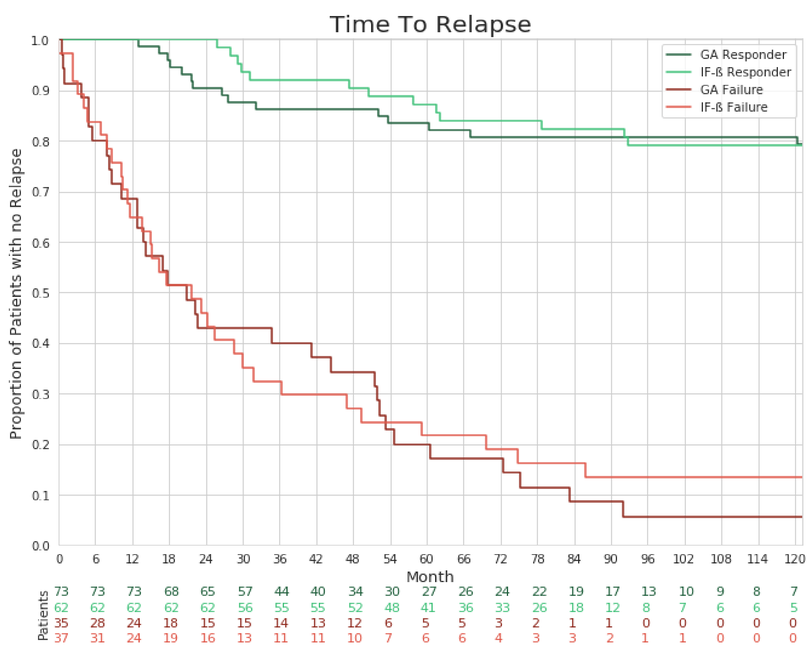


**Figure 1:** Time-to-relapse curves for GA and IF-ß responders and non-responders/failure

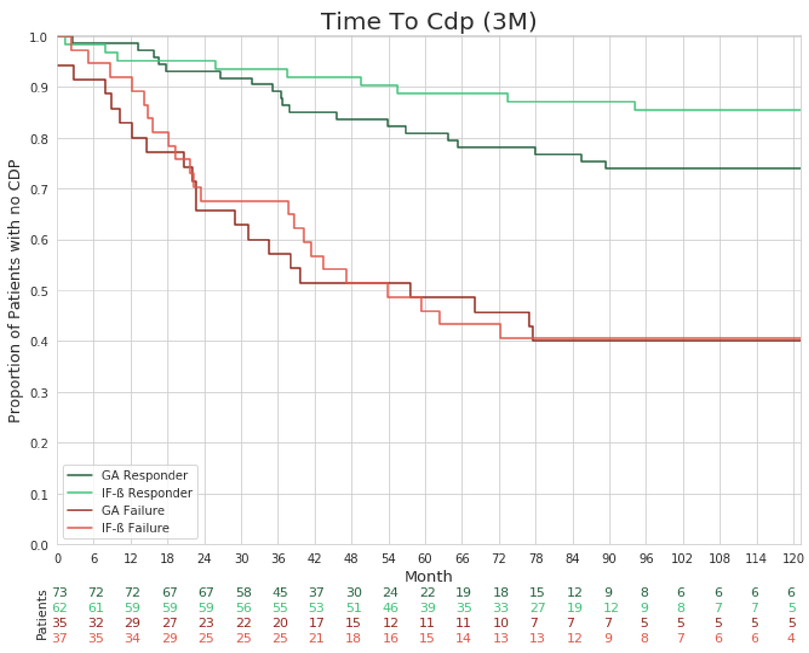


**Figure 2:** Time-to-3months-confirmed-EDSS-disability-progression (CDP 3M) curves for GA and IF-ß responders and non-responders/failure

## Conclusions

Measurement of brain-reactive B cells by ELISPOT was shown to provide clinically meaningful predictive probabilities of individual patients´ response to either GA or IF-ß. This assay can potentially improve individualized allocation of injectables in RRMS.

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ST nothing to disclose
DR nothing to disclose
TZ: honoraria for consulting, clinical studies, lecturing from Almirall, Bayer, Biogen, Celgene, Sanofi, Merck, Novartis, Roche, Teva
PVL: nothing to disclose
AB: consulting fees from and advisory board/speaker/other activities for NeuroTransData; project management/clinical studies for and travel expenses from Novartis and Servier.
SK: nothing to disclose