Pro-inflammatory biomarkers predictive of poor response to Interferon beta1a in multiple sclerosis

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Background:

Interferons are immunomodulators with incomplete efficacy and several adverse effects. Recently oral drugs have become available, with different mechanisms of actions and safety profile. Therefore, the development of biomarkers helping to predict the response to already available drugs is very much expected.

Aim

We aimed to identify possible immunometabolic biomarkers able to predict the response to IFN beta 1-a in MS patients followed prospectively.

Patients & Methods

This is a 12 month longitudinal prospective study on RRMS patients, all treated with available IFN beta 1a formulations and followed-up according to clinical practice every 3 months with EDSS and clinical relapses recording .
We performed every 6 months fluorescent bead-based immunoassay to evaluate the serum levels of sCD40L, sICAM-1, monocyte chemotactic protein 1 (MCP1), Myeloperoxidase (MPO), IL-6, resistin, leptin and sTNF-R and brain enhanced MRI. General linear model with negative binomial distribution and log link was used for statistical analysis.

Results

We included in the study 45 patients. Twenty-two patients were naïve (48.9)% and 23 were already on IFN beta 1a therapy since 4.1±3.4 years. Clinical and demographic features are summarized in table 1. At baseline, in the subset of naive patients (n=22, disease duration, 6.4 ±7.1yrs), the presence of enhancing lesions on MRI was associated with lower values of MCP-1 (p<0.001) while EDSS score positively correlated with IL-6 and leptin values (p=0.006 and 0.041 respectively). After removing the effect of several covariates (gender, BMI, age at onset, duration of illness, treatment naïvete, number of relapse in the previous two years and presence of MRI enhancing lesion at baseline) by using a general linear model with negative binomial distribution and log link, sCD40L emerged as a significant predictor of relapse number (ARR 2.45, 95% CI; 1.69–3.57; P<0.001). The same was true for IL-6 (ARR 1.33, 95% CI; 1.01–1.76; P =0.019) and for Leptin (ARR 1.02, 95% CI; 1.01–1.03; P <0.001) (Table 2). When considering all the three markers in the same model, the independent effect of each of them was confirmed. In modeling the overall enhancing lesions count in the year of follow up, sTNF-R emerged as a significant predictor causing almost a doubling of the lesion count ratio for every unit (ng/ml) (ARR 1.97, 95% C.I. 1.22; 3.17, p=0.005), and Leptin role was confirmed (ARR 1.04, 95% C.I. 1.02 ; 1.07, p=0.001) (Table 3). These effects were confirmed when both predictors were added in the same model.

Table 1
Clinical and demographic features of MS patients

Baseline demographic and clinical characteristic	
Female, n (%)	31 (68.9)
Age, mean ± SD, year	26.4 ± 7.6
Age at onset, mean ± SD, year	33.18 ± 7.9
BMI, mean ± SD, kg/m2	24.5 ± 3.6
Disease duration, mean ± SD, year	13.2 ± 6.4
Naive to treatment, n (%)	22 (48.9)
IFNbeta-1a treated, n (%)	23 (51.1)
IFN treatment duration, mean ± SD, year	4.12 ± 3.44
Annualized Relapse Rate (ARR) in the previous two years, mean ± SD	0.8 ± 0.5
EDSS at baseline, median [min ; max]	2.5 [1.5 ; 4.5]
Patients experiencing at least one relapse in the previous trimester, n (%)	27 (60.0)

Table 2
Adjusted rate ratio (ARR) for relapse rate in IFNbeta-1a treated RRMS patients.

	ARR [95% CI]	P
s-CD40L	2.45 [1.69-3.57]	<0.001
s-TNFR	1.49 [0.99-2.23]	0.053
MCP-1	0.85 [0.24-2.97]	0.793
MPO	1.00 [1.00-1.01]	0.246
s-ICAM1	0.99 [0.99-1.00]	0.355
IL-6	1.39 [1.10-1.76]	0.006
Resistin	1.13 [1-1.27]	0.057
Leptin	1.02 [1.01-1.03]	<0.001

Table 3
Adjusted rate ratio (ARR) for new gadolinium-enhancing lesions on MRI in IFNbeta-1a treated RRMS patients at 12 months follow-up.

	ARR [95% CI]	p value
s-CD40L	1.07 [0.62-1.85]	0.815
s-TNFR	1.97 [1.22-3.17]	0.005
MCP-1	0.54 [0.13-2.23]	0.397
MPO	1.00 [0.99-1.00]	0.187
s-ICAM1	1.00 [1.00-1.01]	0.063
IL-6	0.74 [0.39-1.4]	0.355
Resistin	0.9 [0.78-1.04]	0.155
Leptin	1.04 [1.02-1.07]	0.001

Conclusion

We found a negative correlation between MCP-1 and MRI disease activity at baseline in naïve MS patients, maybe due to the regulation of T-cell polarization (1),while IL-6 and leptin levels were related to EDSS at baseline (2,3).
Levels of sCD40L (4), IL-6 and leptin at baseline were predictive of poor clinical response (relapses) while TNF-R (5) and leptin levels predicted radiological activity on IFN-beta 1a treatment 12 months follow-up.
Baseline pro-inflammatory profile seems related to a poor response to IFN beta-1a, suggesting utility of immunometabolic profiling for treatment decision, in the light of the actual wider therapeutical spectrum. These analysis, however, should be repeated and confirmed also in other treatment groups.

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