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Predictors of clinical response to interferon β1b therapy in patients with multiple sclerosis

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Background and Objective: Multiple sclerosis (MS) is a chronic and progressive inflammatory immune-mediated demyelinating disease. Interferon-β1b (IFN-β1b) treatment is effective in ameliorating relapsing-remitting MS[1], and the efficacy of IFN-β1b is potentially attributable to the immune regulatory properties of the drugs. However, some patients show a poor response to this drug. The proportion of patients who do not respond to therapy and whether particular clinical factors can predict the response to treatment are unknown. The aim of this study was to identify clinical, MRI, and biological markers predictive of clinical response to IFN-β1b therapy and to evaluate the following long-term effect of IFN-β1b treatment on chemokine receptor expression in MS patients.

Methods:
Patients: Ten patients (all women; 49 ± 11 years) included in this study had definite MS, according to McDonald criteria and were treated with IFN-β1b 8 MIU given subcutaneously every other day for at least 2 years. We compared clinical and laboratory data, including anti-aquaporin-4 (AQP4) antibody, longitudinally extensive spinal cord lesions extending over three vertebral segments, in two groups of patients - 5 of whom had relapses and the other 5 were relapse-free.
Flow cytometry: We investigated the expression of Th1-related CXCR3 and CCR5 chemokine receptors and Th2-related CCR4 chemokine receptors on T cells derived from patients undergoing IFN-β1b therapy. Venous blood was collected in heparinized tubes and analyzed within 2 h. Whole blood was labeled with directly conjugated monoclonal antibodies, according to the manufacturer's instructions, using anti-CD3 PerCP, anti-CD4 FITC, anti-CD8 FITC, anti-CXCR3 PE, anti-CCR5 PE, and anti-CCR4 PE[2]. Flow cytometric data were processed using CellQuest software.

Results: Conventional MS was more common in the no-relapse than in the relapse group and the no-relapse patients did not show longitudinally extensive spinal cord lesions from MRI. In addition, the no-relapse patients showed lower Kurtzke's expanded disability status scale (EDSS) scores, shorter disease duration, a greater number of relapses in the year prior to IFN-β1b treatment, and a markedly lower frequency of auto-immune antibodies, including anti-AQP4 antibody (Table 1). Before IFN-β1b treatment, no difference was observed in the percentage of CD4+CXCR3+ cells, CD8+CXCR3+ cells, CD4+CCR5+ cells, CD8+CCR5+ cells, CD4+CCR4+ cells, or CD8+CCR4+ cells between these groups. The percentages of CD4+CXCR3+ cells were significantly decreased after 6-24 months IFN-β1b treatment compared with the pretreatment level, while no changes for those percentages were observed in the untreated MS patients group (Figure 1A). Treatment with IFN-β1b reduced the percentage of CXCR3-expressing CD4 T cells in both relapse and non-relapse groups during the first 12 months. At 24th months after the treatment, the CXCR3 expression for non-relapse patients was still reduced. However, CXCR3 expression for relapse patients returned to the baseline level (Figure 1B). No significant changes were observed in the percentage of CCR5 or CCR4-expressing CD4 T cells between the relapse patients and the non-relapse patients.

Conclusions: Clinical findings preceding the therapy, spinal cord MRI findings or frequency of auto-immune antibodies may be the predictors of response to IFN-β1b therapy, and continuation of the decreased percentages of CD4+CXCR3+ cells may implicate long-term effectiveness to IFN-β1b treatment.

Table 1: Clinical, MRI, and biological markers in non-relapse patients and relapse patients.

	Non-relapse (n = 5)	Relapse (n = 5)	p value
Type of MS (CMS : OSMS)	4 : 1	1 : 4	0.058
Disease duration	2.4 ± 2.2	13.8 ± 11.0	0.032
EDSS score	3.0 ± 1.1	5.1 ± 1.7	0.032
Relapse rate during 1 years before IFN-β	2.8 ± 1.0	1.6 ± 0.9	0.048
ANA titer (20×2^{X})	0.25 ± 0.50	3.40 ± 2.97	0.06
Serum antoantibodies	1 / 5 (0%)	4 / 5 (80%)	0.058
Anti-AQP4 antibody	1 / 5 (20%)	3 / 5 (60%)	0.20
Longitudinally extensive spinal cord lesion	0 / 5 (0%)	3 / 5 (60%)	0.038

MS; multiple sclerosis, CMS; conventional MS, OSMS; optic-spinal MS, EDSS score; Kurtzke's expanded disability status scale score, IFN-β; interferon-β, ANA; antinuclear antibody, AQP4; aquaporin 4.

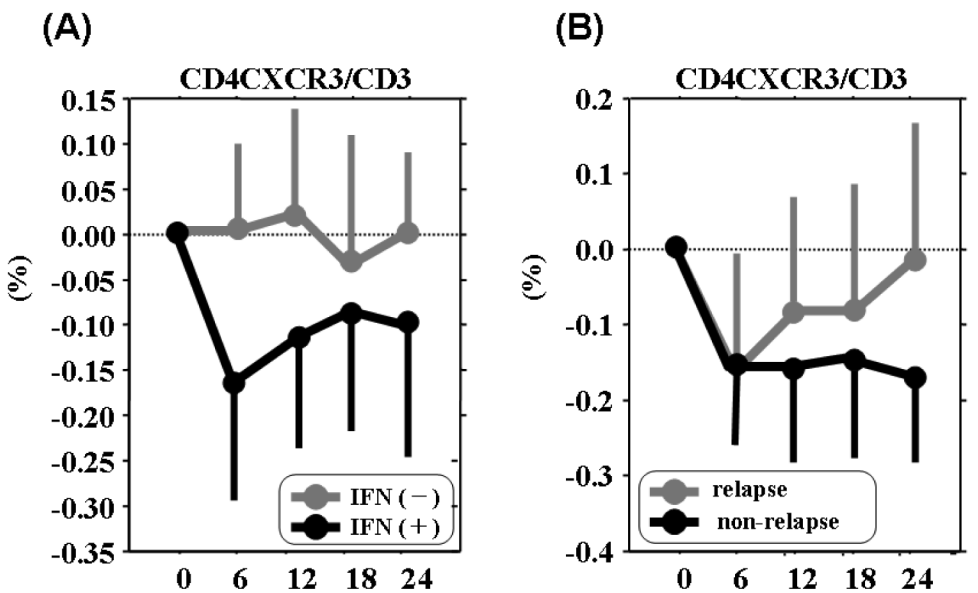

Figure 1. Changes in the percentages of CXCR3-expressing CD4 T cells during IFN-β1b treatment. (A) Comparisons between IFN-β1b treated and untreated patients. (B) Comparisons between non-relapse and relapse patients.

References

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