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# CCL2 (MCP-1) and CCL5 (RANTES) levels in the peripheral blood of multiple sclerosis patients treated with Glatiramer Acetate (Copaxone)

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**Abstract**

*The MCP-1 and RANTES levels were measured in 20 multiple sclerosis patients before and after 1 year daily treatment with 20 mg of subcutaneously applied glatiramer acetate. The level of MCP-1 in serum from multiple sclerosis patients was lower than in control subjects. After one year of therapy with glatiramer acetate, the level of MCP-1 was almost identical with that at the starting point. The concentration of RANTES in MS, both before and after therapy, did not differ from the control subjects. The results emphasise the marked difference between the influence of glatiramer acetate and IFNβ-1a on the expression of the studied cytokine. Glatiramer acetate therapy in multiple sclerosis is not so much an effective as a protective factor of antiinflammatory cytokines, it should be regarded as a down-regulator of proinflammatory agents.*

***Key words:*** *MCP-1, RANTES, multiple sclerosis, Copaxone*

## Introduction

Glatiramer acetate (GA, Copaxone) is one of the most effective immunomodulatory drugs in the therapy of multiple sclerosis (MS), an autoimmune disease of the central nervous system [9]. The key point in the mechanism of action seems to be the effect of GA on lymphocytes of both types Th1 and Th2/Th3 and subsequently on the cytokine network [7].

In our previous studies on this subject, we have established that the expression in the peripheral blood of interleukin 18 (interferon gamma inducing factor) is significantly down-regulated after 6 months therapy of MS by GA [4]. In subsequent studies we have found that interleukin 12 and interleukin 10 are affected differently by the treatment of MS patients with GA [5]. It is important to point out a significant decrease of Il 12, a proinflammatory cytokine after 3 and 6 months of therapy. The changes in Il 10, the antiinflammatory cytokine expression, were insignificant.

To elucidate the effect of therapy on other cytokines essential in the pathogenesis of autoimmune diseases of the nervous system, we have undertaken a study on the expression of the following chemokines: the monocyte chemoattractant protein -

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1 (CCL2 – MCP-1) and CCL5-RANTES (Regulated upon Activation Normal T -cell Expression and Secreted).

MCP-1 affects the differentiation of Th0 lymphocytes into Th2 cells and this happens to up-regulate the production of antiinflammatory interleukin 4 (Il4). The action of RANTES on Th1 response causes an enhancement of the expression of proinflammatory cytokines Il-1, TNFα and of IFNγ.

## Material and methods

Peripheral blood samples were taken from 20 patients (12 females and 8 males) with relapsing-remitting multiple sclerosis that was diagnosed according to the Poser et al [8] and Mc Donald et al. [6] diagnostic criteria. The mean duration of the disease was 8.25±4.9 years and the EDSS disability scale of MS was 3.0±1.18.

The patients were treated daily with 20 mg of subcutaneously applied glatiramer acetate (GA-Copaxone) and laboratory tests were performed before and after one year of treatment. The investigations were approved by the Regional Ethics Committee of The Medical University in Poznań. The control group consisted of 20 healthy blood donors matched according to age and sex to the study group.

The MCP-1 levels and RANTES in the blood serum were measured in duplicate by the ELISA immunoassay test using Quantikine human MCP-1 or RANTES kits (R&D Systems, USA). For statistical comparison of differences between MS and control subjects, the nonparametric U Mann-Whitney test was used and data from the MS group before and after therapy were evaluated by means of the Wilcoxon test.

## Results

The level of MCP-1 in the serum from MS patients was found to be significantly lower than that in sera from control subjects. After one year of therapy with GA, the level of MCP-1 was almost identical with that found at the starting point, and of course, lower than that established in the control subjects (Table I). The concentration of RANTES in MS patients, both before and after therapy, did not differ from levels in the serum of the control subjects (Table II).

**Table I.** MCP-1 serum level (pg/ml) in MS patients treated with Glatiramer

| | Before therapy | 12 months of therapy |
|---|---|---|
| MS patients | 0.454±0.150* | 0.452±0.152 |
| control group | 0.652±0.204 | |

*> *differences statistically significant at the probability level of p<0.05*

**Table II.** RANTES serum level (pg/ml) in MS patients treated with Glatiramer acetate

| | Before therapy | 12 months of therapy |
|---|---|---|
| MS patients | 0.641±0.150 | 0.663±0.196 |
| control group | 0.688±0.247 | |

## Discussion

Glatiramer acetate, a mixture of synthetic peptides, is an immunomodulatory drug effective in the treatment of MS. After therapy, a significant decrease of the relapse rates, of development of new lesions visible in MRI and slowing of disability progression have been documented [9]. Hence, a possible immunological mechanism of GA action, a modulation of the cytokine signalling system may be considered.

Summarising the results of studies concerning the MCP-1 expression in multiple sclerosis, it is possible to assume that the low and medium expression of this chemokine controls the immunological response and is down-regulated in relapses, thus limiting the progression of focal lesions in the central nervous system [1,10]. However, the GA therapy applied in our study, did not affect significantly the decreased level of circulating MCP-1 in MS, in contrast to Interferon β-1a which happened to raise the MCP-1 serum concentration.

In some studies, an increased expression of RANTES during MS relapses has been reported, and this increase was more evident in CSF than in the peripheral blood [2,11]. In our study we could not confirm the findings concerning the increased concentration of RANTES in the blood serum of MS patients. The results pertaining to the effect of MS treatment with GA differ from those obtained in studies tracing the effect of treatment with Interferon β-1b, another immunomodulatory drug used in therapy of MS, which was shown to cause a marked decrease of RANTES levels [2].

The results of our study, despite the negative findings concerning the effect of one year GA therapy on MCP-1 and RANTES expression allow some interesting remarks to be made. The first one is to stress the marked difference between the influence of GA and IFNβ-1a on the expression of the studied cytokines. The second one is that GA therapy in MS is not so much an effective as a protective, factor of antiinflammatory chemokines, it should rather be regarded as a down-regulator of proinflammatory cytokines.

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