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Longitudinal assessment of immuno-metabolic parameters in multiple sclerosis patients during treatment with glatiramer acetate

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ABSTRACT

Objective. We investigated the effect of glatiramer acetate (GA) on the modulation of immune cell subpopulations and serum levels of multiple immune/metabolic markers in patients with relapsing–remitting multiple sclerosis (RRMS) to understand whether the treatment with GA could induce a specific change in the immunometabolic asset of patients with RRMS.

Material and methods. We performed an extensive peripheral blood immunophenotyping and measured serum levels of several parameters involved in the pathogenesis of RRMS and also relevant in the pathogenesis of metabolic syndrome and obesity such as leptin, soluble leptin-receptor (sLep-R), myeloperoxidase (MPO), soluble CD40 ligand (sCD40-L), soluble tumor necrosis factor-receptor (sTNF-R), monocyte chemoattractant protein 1 (MCP-1), soluble Inter-Cellular Adhesion Molecule-1 (sICAM-1) and osteoprotegerin (OPG), in

Abbreviations: GA, glatiramer acetate; RRMS, relapsing–remitting multiple sclerosis; sLep-R, soluble leptin-receptor; MPO, myeloperoxidase; sCD40-L, soluble CD40 ligand; sTNF-R, soluble tumor necrosis factor-receptor; MCP-1, monocyte chemoattractant protein 1; sICAM-1, soluble inter-cellular adhesion molecule 1; OPG, osteoprotegerin; CNS, central nervous system; IFN, interferon; APL, altered peptide ligand; MBP, myelin basic protein; TGF, transforming growth factor; Treg, regulatory T; EAE, autoimmune encephalomyelitis; CSF, cerebrospinal fluid.

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20 naïve-to-treatment RRMS patients and 20 healthy controls. We repeated these analyses over time at 6 and 12 months after starting GA treatment.

Results. Our analysis showed that naïve-to-treatment RRMS patients had a lower number of $CD16^+CD56^+$ NK cells, $CD19^+$ B cells, $CD4^+$ T cells co-expressing the MHC class II activation marker HLA-DR ($CD4^+DR^+$) and naïve $CD4^+CD45RA^+$ T cells in basal conditions. GA treatment induced a specific and significant decrease of circulating $CD19^+$ B cells. Naïve-to-treatment RRMS patients also showed a significantly higher number of $CD4^+$ T cells with a memory phenotype ($CD4^+CD45RO^+$) whose peripheral frequency was not affected by GA treatment. These changes over time associated with a higher serum concentration of leptin and lower levels of MPO. GA treatment also reduced significantly the circulating levels of sCD40-L and sTNF-R overtime.

Conclusions. Our data suggest that the clinical outcome of GA treatment is associated with changes in immune cell subpopulations and modulation of specific immunometabolic markers. These data add substantial evidence of the immune modulating effect of GA during RRMS and could be of relevance in understanding the pathogenesis of disease and its follow-up.

1. Introduction

Multiple sclerosis (MS) is an immune-mediated demyelinating disease of central nervous system (CNS) characterized by progressive neurodegeneration caused by an autoimmune response against self-antigens in individuals that are genetically susceptible [1]. Patients often display an initial clinically isolated syndrome, followed by a series of subacute clinical events that spontaneously decrease. In this case it refers to disease defined as relapsing remitting MS (RRMS) [2].

Glatiramer acetate (GA) represents, together with the family of beta-interferons (IFN)-β1α and 1β the first line agents for treatment of RRMS [3]. The mechanism of action of GA has been extensively investigated and it seems to be particularly related to its capacity to induce immune-deviation of the anti-myelin autoimmune response at different levels. It seems to act as an altered peptide ligand (APL) and inhibit activation of myelin basic protein (MBP)-specific T cells. Moreover, it has been described that treatment of RRMS patients with GA results in an induction of protective/regulatory cytokines such as interleukin (IL)-10, IL-4, and transforming growth factor-β (TGF-β) [4]. In addition, several studies have been reported that GA treatment increases the expression of the forkhead box P3 (FoxP3), the master gene of regulatory T (Treg) cells [4], a cellular subset involved in the control of immune responses and in the prevention of autoimmune diseases.

Previous analyses of Treg cells frequency in MS patients have provided conflicting results indicating no differences between MS patients and healthy controls [5,6], or a decreased level in MS patients [7,8]. Others have reported, that they find a disturbance in the development or function, or both, of Treg subpopulations [5,6,9]. Recent evidence indicates that metabolism controls T cell activation and loss of immune tolerance; in this context circulating factors at the interface between immunity and metabolism such as leptin, adiponectin, ghrelin and neuropeptide Y can alter susceptibility to experimental autoimmune encephalomyelitis (EAE) a mouse model of MS [10–12]. For example, the secretion of the adipocyte-derived leptin is generally increased in serum and cerebrospinal fluid (CSF) of naïve-to-treatment RRMS patients and correlates not only with the levels of peripheral blood Treg cells but also with disease severity and susceptibility [13]. In this context it has been shown that leptin controls both innate and adaptive immunity and, in particular, acts as a proinflammatory cytokine by inhibiting the proliferation of Treg cells and sustaining effector T cells activation and functions [14]; this evidence suggests its potential role in the pathogenesis of several autoimmune and inflammatory diseases. In agreement with these data, it is well accepted that the growing worldwide obesity epidemic has several damaging effect on public health, with regard not only to cardiovascular disease, diabetes mellitus type 2, sleep apnea, and osteoarthritis but also autoimmune diseases such as RRMS [15]. Indeed, a series of recent reports indicates that the excessive body weight is associated with increased risk of RRMS suggesting a very strong link between metabolic factors and immune system responses [16–18]. In particular, it is now well established that epidemic childhood obesity is likely to lead to increased incidence of RRMS, especially in adolescent girl [19] since it has been reported that there is a twofold increased risk of developing MS among subjects with a BMI ≥ 30 kg/m^2 at age 18–20 years, compared with normal weight subjects. In addition, it has been shown that the risk for MS is related to interactions between human leukocyte antigen (HLA) genotype and body mass index (BMI) status [17]. Indeed many genes have been identified for predisposition to MS, such as HLA-DRB1*15 allele conferring a threefold higher risk, while protective effect, with a twofold lower risk, was driven mainly by the HLA-A*02 [20]. It has been highlighted that there are a significant correlation between HLA-DRB1*15 and obesity, regardless of HLA-A*02 and at the same time a significant interaction between the absence of HLA-A*02 and obesity, regardless HLA-DRB1*15. Subjects with a BMI < 27 kg/m^2 and the two risk genotypes (carriage of DRB1*15 and absence of A*02) displayed an OR = 5.1–5.7 whereas the same genotype for subjects with BMI ≥ 27 kg/m^2 rendered an OR = 13.8–16.2 indicating the presence of interactions between BMI status and HLA genotype with regard to MS risk. This could be explained by assuming that the low-grade inflammatory state, correlated with obesity, synergizes with the adaptive, HLA molecule-restricted arm of the