Journal of Neuroimmunology 235 (2011) 9–17

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Review article

Recent insights into the mechanism of action of glatiramer acetate

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ARTICLE INFO

Article history:
Received 1 July 2010
Received in revised form 20 January 2011
Accepted 24 January 2011

Keywords:
Multiple sclerosis
Glatiramer acetate
B cells

ABSTRACT

Glatiramer acetate (GA, Copaxone®, co-polymer 1) is an immunomodulatory therapy approved in 1996 by the United States Food and Drug Administration for treatment of relapsing–remitting multiple sclerosis. GA has a good safety profile, moderate efficacy, and a unique mode of action. Recent evidence in an animal model of MS, experimental autoimmune encephalomyelitis (EAE), suggests that GA effects on NK cells and B cells may contribute to therapeutic efficacy. We review the mechanism of action of GA, with particular focus on recent data suggesting a role for regulatory B cells.

Contents

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0165-5728/$ – see front matter
doi:10.1016/j.jneuroim.2011.01.009

1. Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS) characterized by a complex interplay between inflammation and neurodegeneration. Several attempts have been made to correlate clinico-pathological processes in MS patients. However, considering the observed heterogeneity of clinical, radiographic, morphological, and genetic features of the disease, it is likely that the immunological mechanisms involved in pathogenesis vary between individuals with MS and within an individual with MS over time. The pathological hallmark of MS is multifocal inflammatory attack on the white and gray matter with loss of oligodendrocytes in the chronic stages, damage to axons, significant neuronal loss, and gliosis with astrocyte proliferation and intensive glial fiber production. Complete or partial functional recovery (remission) seen in MS patients might be explained by a combination of resolution of inflammation, cortical remodeling/adaptation, and partial remyelination, which may be particularly active at early stages of the disease. Besides the profound axonal injury seen in active demyelinating lesions, there is substantial neuronal loss early in the disease process, characterized by a significant decrease in cortical volume and a decrease in N-acetylaspartate (NAA), a marker of neuronal integrity (Zivadinov et al., 2001). While functional consequences of inflammation and demyelination are at least in part reversible, deficits due to axonal and neuronal loss are irreversible.

Currently FDA-approved treatments for MS include immunomodulators (glatiramer acetate, interferon-β) and immunosuppressants (mitoxantrone, natalizumab). In the last 10 years, the treatment of MS has changed significantly, and further changes are expected in the near future. There are several new treatments including oral therapies that are in late phase clinical trials, and the oral agent, fingolimod, was recently approved by the FDA for treatment of relapsing–remitting MS (RRMS).

Glatiramer acetate (GA) is the generic name for the drug Copaxone® (also called Copolymer 1 or Cop 1). GA (average molecular mass 6.4 kDa) is composed of four amino acids (L-glutamic acid, L-alanine, L-lysine, and L-tyrosine) and was developed to mimic a major component of the myelin sheath, myelin basic protein (MBP), in order to induce experimental autoimmune encephalomyelitis (EAE), the animal model of MS. However, GA unexpectedly inhibited EAE in both rodents and monkeys (Sela and Teitelbaum, 2001). In patients with RRMS, GA reduced relapse rate and delayed progression of disability, leading to its approval in the US in 1996 (Johnson et al., 1995). GA is now licensed in much of the world for treatment of RRMS. GA is administered by subcutaneous injection at a dose of 20 mg per day. It is an immunomodulator with no immunosuppressive effect. The efficacy and safety of glatiramer acetate were demonstrated in three pivotal clinical trials: The first was a single center, double-blinded, placebo-controlled trial that included 50 patients with MS (Bornstein et al., 1987). The second was a 2-year, multicenter, randomized, double-blinded, placebo-controlled trial performed in 11 US centers that included 251 RRMS patients (Johnson et al., 1995). The third, a double-blinded, multicenter, multi-country MRI study, was conducted at 29 MS centers in six European countries and Canada, with participation of 239 patients (Comi et al., 2001).

Several studies in the murine EAE model and a few studies in humans have been conducted to better understand the mode of action of GA. However, the exact mechanism of GA activity remains elusive.

2. Immunology of MS/EAE and the mechanism of action of GA

Cells and molecules implicated in innate and adaptive immunity are known to be involved in the pathogenesis of EAE and MS. These primarily involve T cells, dendritic cells (DCs), B cells, and natural killer (NK) cells. Recent evidence indicates that each of these immune system components has an activating and inhibitory effect that promotes or inhibits, respectively, MS pathogenesis. The interdependence of T cells, antigen presenting cells (APCs), and cells of innate and adaptive immune systems necessary to elicit an immune response demonstrates the complexity of immune mechanisms implicated in disease pathogenesis.

Studies to date in MS patients and animal models indicate that GA mediates its suppression of MS/EAE by modulating the function of many different types of immune cells.

2.1. Role of T cells in MS pathogenesis and GA-mediated immune modulation of T cells

T lymphocytes are generally believed to play a central role in pathogenesis of MS (Zhang et al., 1992). Both $CD4^+$ and $CD8^+$ T cells are seen in MS lesions, with $CD4^+$ T cells predominating in acute lesions and $CD8^+$ T cells in chronic lesions (Raine, 1994). In addition, $CD8^+$ T cells are also found in "normal" appearing white matter (WM). *In vivo* studies indicate that axonal damage in active early MS lesions directly correlates with the presence of $CD8^+$ T cells (Bitsch et al., 2000). Although MS has been postulated to be a primarily T cell-mediated disease, it is unclear what triggers the development of neuroantigen-specific T cells and whether they are generated in the periphery or in the CNS. Autoreactive $CD4^+$ T cells are activated to a pro-inflammatory cytokine secreting T helper type 1 (Th1) phenotype by APCs (e.g., DCs, macrophages, and B cells); therefore, Th1 cells, DCs, macrophages, and B cells are extremely important in directing the immune pathology that is characteristic of MS.

A shift from Th1 responses to Th2 (anti-inflammatory cytokine secreting) type responses is protective in inflammatory conditions (Romagnani, 1999). Several studies have shown that GA skews T cell responses from a Th1 to Th2 phenotype, thereby promoting protective responses (Miller et al., 1998; Neuhaus et al., 2000; Qin et al., 2000; Duda et al., 2000; Chen et al., 2001; Franciotta et al., 2003; Weder et al., 2005; Sanna et al., 2006). A study by Aharoni et al. (1997) showed that T cell lines/clones induced by GA progressively polarized toward the Th2 phenotype, until GA-reactive T cell lines completely lost the ability to secrete Th1 cytokines. This study showed that transformation to the Th2 phenotype was not due to the immunization vehicle or to the growing conditions *in vitro*. Even though the GA-reactive T cells were not exposed to the autoantigen MBP, they cross-reacted with MBP. Adoptive transfer of the GA-reactive T cells *in vivo* suppressed EAE induced by whole mouse spinal cord homogenate (Aharoni et al., 1997). Although initial evidence for the Th2 shift induced by GA was primarily based on results of *in vitro* T cell studies, *in vivo* results in a murine model have also shown a GA-mediated Th2 shift by DC and monocytes, except in two studies, which showed that despite the absence of two prominent Th2 cytokines, interleukin (IL)-4 and IL-10, GA was still beneficial in suppressing EAE (Aharoni et al., 1997; Jee et al., 2006). Studies with MS patients confirm that daily injections of GA promotes the development of Th2 cells characterized by increased secretion of IL-5 and IL-13 (Duda et al., 2000; Chen et al., 2001; Sanna et al., 2006).

Taken together, most of these studies suggest that a primary activity by which GA mediates its protective effect is by inducing a shift to an anti-inflammatory Th2 type of T cell response.

Apart from activating $CD4^+$ T cells, GA also affects $CD8^+$ T cells. Studies by Karandikar et al. (2002) showed that while GA-induced $CD4^+$ T cell responses were comparable in healthy individuals and in MS patients, $CD8^+$ T cell responses were significantly lower in untreated MS patients. GA treatment resulted in up-regulation of $CD8^+$ T cells, with restoration to levels observed in healthy individuals. Later studies by the same group revealed that GA therapy enhanced the suppressor activity of $CD8^+$ T cells and that GA-induced cytotoxic $CD8^+$ T cells can directly kill $CD4^+$ T cells (Tennakoon et al., 2006).

The suppressive function of naturally occurring regulatory T cells (Tregs), which act against autoimmunity, is impaired in RRMS patients due to an age-inappropriate disproportion between the prevalence of