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Glatiramer acetate for the treatment of multiple sclerosis

Jerry S Wolinsky
University of Texas Health Science Center at Houston, 6431 Fannin Street, Houston, TX 77030, USA

Glatiramer acetate (Copaxone®, Teva Pharmaceuticals Ltd) is a collection of immunomodulatory, synthetic polypeptides indicated for the treatment of relapsing-remitting multiple sclerosis (RR MS). Preclinical and clinical studies provide an evolving understanding of the mechanisms by which glatiramer acetate exerts both immunological and potential neuroprotective effects that account for its clinical efficacy. The results of pivotal controlled clinical trials and long-term data, derived from organised extension studies, are evaluated in detail and supportive data from open-label comparison, combination treatment and therapeutic switch studies are considered in order to determine the place of glatiramer acetate among other approved therapies for RR MS. The efficacy of glatiramer acetate is stable or may increase over time and the drug has a favourable side effect profile. Glatiramer acetate is an appropriate first-line immunomodulatory therapy for RR MS.

Keywords: Copaxone, glatiramer acetate, immunomodulatory therapy, magnetic resonance imaging, multiple sclerosis

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1. Introduction

Multiple sclerosis (MS) is an inflammatory disease of the CNS that leads to myelin destruction and axonal loss. It is the most common, non-traumatic, disabling neurological disorder in young adults [1]. Although the aetiology of MS remains unknown, its pathogenesis is believed to include autoimmune reactivity to myelin components, placing it among the organ-specific autoimmune diseases. In relapsing-remitting (RR) MS, the clinical course is punctuated by exacerbations or episodic neurological worsening. These attacks or relapses, are followed within weeks to a few months by remissions, often with full recovery from clinical symptoms. However, recovery from up to 40% of all relapses is incomplete, leaving measurable neurological deficits or disability [2]. Progressive forms of MS are characterised by a gradual downhill course over many months to years without remissions, so that the patient acquires increasing clinical deficits, either beginning at presentation (primary-progressive [PP] MS) or after a period of RR disease (secondary-progressive [SP] MS).

Currently approved immunomodulator therapies for RR MS include glatiramer acetate (GA) and the recombinant IFNs, (IFN-β_{1a}, Avonex®, Biogen, Inc.; IFN-β_{1a}, Rebif®, Serono, Inc.; IFN-β_{1b}, Betaseron®, Berlex Laboratories), all of which modify the course of this progressively disabling neurological disease. Immunomodulatory treatments reduce disease activity and the accumulation of disability in RR MS. The National Multiple Sclerosis Society recommends initiation of therapy with an immunomodulator as soon as possible following diagnosis of RR MS [201]. Results of magnetic resonance spectroscopy (MRS) and pathology studies show that inflammatory activity can cause irreversible axonal damage in the early phases of the disease, reinforcing the need for early and aggressive treatment [3,4]. Mitoxantrone (Novantrone™), an antineoplastic agent, is also approved for the treatment of relapsing MS, but is generally reserved for secondary progressive and severe RR forms of the disease [5].

GA (formerly known as copolymer 1 or Cop 1) is indicated for the reduction of the frequency of relapses in RR MS. The drug is approved in 42 countries

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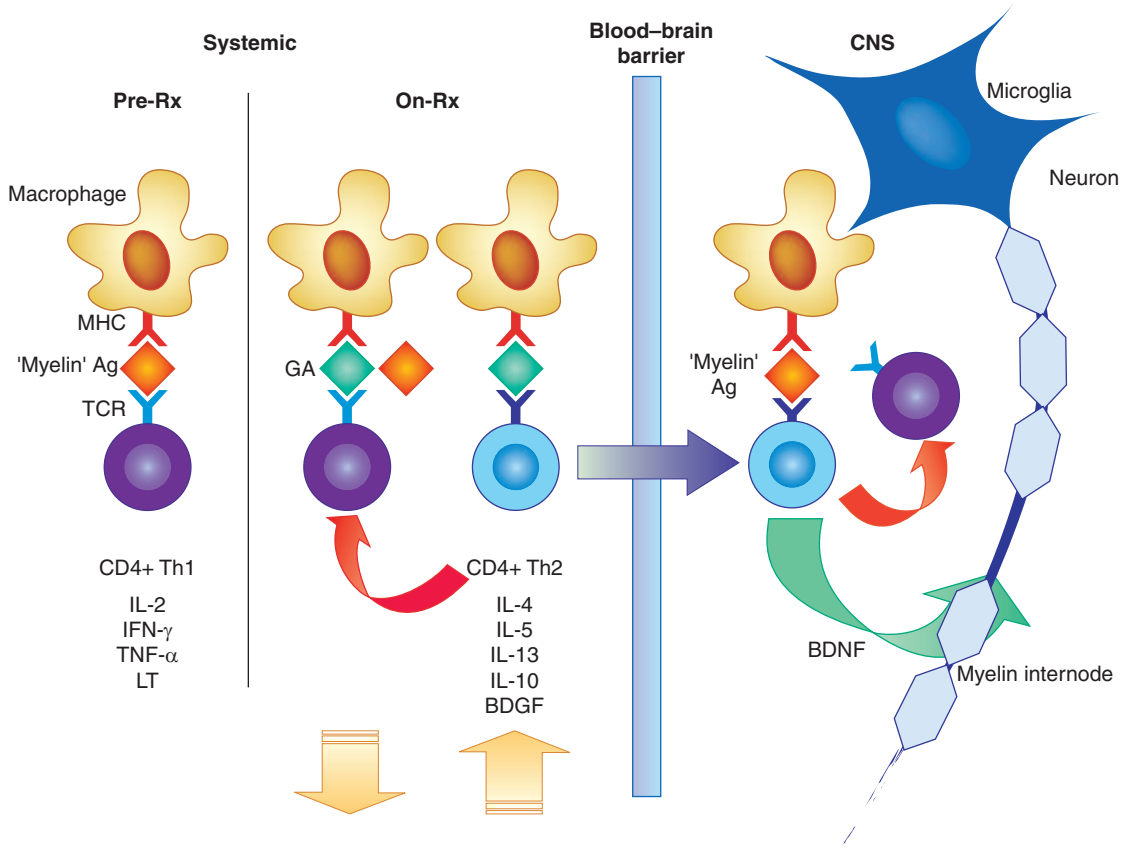

Figure 1. A simplified diagrammatic representation of the immunopharmacology of GA in MS therapeutics. The Pre-Rx portion of the panel emphasises the baseline state in MS with CD4+ Th1 myelin antigen-reactive cells being activated by systemic antigen processing cells, including macrophages, that present foreign antigens that are myelin-like ('myelin' Ag) in the context of surface MHC to the TCR; invoking the concept of molecular mimicry. Stimulated CD4+ Th1 'myelin' Ag-reactive cells secrete a number of pro-inflammatory cytokines (IL-2, IFN-γ, TNF-α and LT). With GA therapy, GA may displace some 'myelin' Ag. More importantly, on presentation and stimulation of GA and 'myelin' Ag-reactive CD4+ Th1 cells, GA silences crossreacting CD4+ Th1 'myelin' Ag-reactive cells through anergy, apoptosis or antigen-specific mechanisms. Concomitantly, GA stimulates and expands a population of GA-reactive CD4+ Th2 cells that secrete anti-inflammatory cytokines (IL-4, -5, -13 and -10) to systemically inhibit 'myelin' Ag-reactive CD4+ Th1 cells (red arrow). With continued therapy the net result is a reduced proportion of CD4+ Th1 and an increased proportion of GA and 'myelin' crossreactive CD4+ Th2 cells. When these GA and 'myelin' crossreactive CD4+ Th2 cells gain access to the CNS by trafficking across the blood–brain barrier, they are restimulated by true myelin Ags processed and presented by microglia, a brain-resident macrophage. On restimulation, the GA-reactive CD4+ Th2 cells secrete anti-inflammatory cytokines to inhibit 'myelin' Ag reactive CD4+ Th1 cells within the CNS and also secrete tropic factors, such as BDNF that may facilitate neuronal survival (green arrow). Modified from Neuhaus [14] and other sources.

Ag: Antibody; BDNF: Brain-derived neurotrophic factor; BDGF: Brain-derived growth factor; GA: Glatiramer acetate; LT: Leukotriene; MHC: Major histocompatibility complex; MS: Multiple sclerosis; Rx: Treatment; TCR: T cell receptor.

worldwide, including the US, Canada, Australia, Europe and Israel. A comprehensive review of GA was published in this journal in 2001 [6]. New data on the long-term clinical experience with GA, comparative studies, therapy switching studies and magnetic resonance imaging (MRI) findings have since become available.

GA is the acetate salt of a synthetic mixture of polypeptides that consists of random sequences of four naturally-occurring amino acids: L-glutamic acid, L-lysine, L-alanine and L-tyrosine in racemeric form at a defined molar ratio of 1.4:3.4:4.2:1.0, respectively. The copolymer was first synthesised in 1967 by Arnon *et al.* at the Weizmann Institute of Science [7] in an attempt to simulate some of the then known physicochemical properties of myelin basic protein (MBP) to induce and then dissect experimental allergic encephalomyelitis (EAE). EAE is a laboratory animal model of organ-specific autoimmune CNS inflammatory disease with some similarities to MS. Even though GA proved incapable of inducing EAE, it did demonstrate a marked effect in suppressing EAE when animals were subsequently challenged with MBP [8,9].

2. Immunopharmacology

The mechanisms of action of GA in humans remain uncertain but substantial preclinical data support both immunomodulatory and neuroprotective effects of the drug. At least five

interdependent processes are thought to contribute to the effects of GA (Figure 1):

- High affinity binding to the major histocompatibility complex (MHC) within the antigen binding pocket.
- Competition with MBP at the antigen-presenting cell (APC) level for binding to MHC and subsequent inhibition of MBP-specific T cell activation through competition with MBP–MHC complexes for the T cell receptor.
- Induction of a shift in GA-reactive T cells from a T helper Type 1 (Th1) to a T helper Type 2 (Th2) phenotype.
- Migration of GA-specific T cells into the CNS.
- Neuroprotection induced via promotion of neurotrophic factors.

As would be expected of repeated injection of any foreign protein, immunisation with GA consistently induces GA antibodies; whether these may contribute or detract from the clinical effects of the drug are also considered in this section.

2.1 High-affinity binding to major histocompatibility complex

Fundamental to the development of an antigen-specific, T-cell-dependent immune response is the processing and presentation of a fragment of the antigen by an APC to a T cell precursor. This occurs when an appropriately processed antigen is bound by physicochemical interactions within the antigen-binding cleft of the MHC of an APC. The resulting unique structure is presented on the cell surface of the APC where it can interact with the complementary hypervariable portions of the T-cell receptors of appropriate T cells. Formation of this trimolecular complex is a critical, although not necessarily sufficient, prerequisite to stimulating signals that activate and condition the behaviour of the T cell.

Intact GA binds directly to MHC displayed on fixed APCs [10]. This binding can be blocked by anti-DR, but not anti-DQ, or anti-Class I antibodies, and GA binding to Class II must occur at, or very near to, the peptide-binding cleft. Isolated DR molecules exposed to GA form covalently linked complexes [10] and this interaction is not easily blocked by the staphylococcal B antigen. Staphylococcal B antigen has a known binding site to the Class II antigen that resides outside of the antigen-binding cleft. The binding of GA to a Class II antigen is of high avidity and has been demonstrated for all common MS-associated DR haplotypes. Based on the crystallographic structure of the immunodominant peptide of MBP and DR2 [11], it appears that the repeated alanines and tyrosines in GA may facilitate the anchoring of GA within binding pockets of the Class II binding cleft. Further, variation in amino acid sequence inherent to GA could account for its ability to efficiently bind to a wide array of different Class II haplotypes. However, the high-affinity interaction between GA and Class II antigen alone is not sufficient to explain the mechanism of action of the drug, as the immunobiologically inert dextrorotatory form of GA binds with similar avidity to DR.

2.2 Competition with myelin basic protein

In vitro studies have shown that GA competes with MBP at the level of APC for binding to the MHC [12]. GA appears to have greater MHC-binding affinity than MBP and other myelin-associated proteins (e.g., proteolipid protein [PLP] and myelin oligodendrocyte glycoprotein [MOG]). Thus, GA efficiently displaces MBP-, PLP- and MOG-derived peptides from the MHC binding site, but is not displaced by these antigens once it is bound to the MHC [6]. GA isomers have the same effect on MHC but do not suppress EAE [13]. After binding to MHC, the GA–MHC complex competes with available MBP/MHC molecules for binding to T-cell receptors. As a consequence, some of the myelin-specific, pathogenic T cells may become anergic or otherwise altered [14].

2.3 Induction of shift from T helper Type 1 to T helper Type 2 lymphocytes

Data from animal models and *ex vivo* studies of human lymphocytes show that exposure to GA induces a relative anti-inflammatory state by causing a shift in the GA-reactive lymphocyte population from a dominant Th1 state to a Th2 dominant state [14,15]. Th1 cells produce IL-2, IL-12, IFN-γ and TNF-α, which generally behave as pro-inflammatory cytokines, whereas Th2 cells produce IL-4, -5, -6, -10 and -13, which generally exert anti-inflammatory effects. GA-reactive peripheral blood lymphocytes from untreated MS patients mostly express TNF-α mRNA, whereas those harvested from GA-treated patients mainly express IL-10, transforming growth factor (TGF)-β and IL-4 mRNA [16]. The shift towards Th2 bias is also demonstrated by the diminished ratio of IFN-γ/IL-5 secretion of GA-reactive T cell lines isolated from MS patients both before and during GA therapy [15,17]. The GA-reactive Th2 cells are believed to act as regulatory cells to modulate the pathogenic immune reaction. Many T cell lines reactive to a number of potentially encephalitogenic myelin proteins, when stimulated *in vitro* with GA, do not proliferate but do secrete cytokines with a predominant IL-5 pattern [18].

It is important to realise that two phenomena are occurring in concert as patients begin therapy with GA. Both naive and memory GA-reactive $CD4^+$ T cells are part of the resident T cell repertory of mice and men [19]. With initiation of therapy, the numbers of GA-reactive T cells that can be found using proliferation assays progressively falls after a transient increase within the first month of therapy. The reduced response is evident within 3 – 6 months, substantial at 12 months and is decreased by 75% from baseline at 24 months after initiating treatment [20]. The proportion of patients with a negative *in vitro* proliferative response to GA increased from 5% at baseline to 40% at 2 years. Moreover, treatment with GA results in increased apoptosis of a substantial percentage of activated ($CD69^+$) $CD4^+$ T cells [21]. Thus, as the shift from a Th1 to a Th2 state is being established, the numbers of Th1 GA-reactive cells is also falling. Many of the above effects are likely to occur systemically, resulting in reduced availability of autoaggressive cells for entry into the CNS over time.

The Th2-biased immunological response seen with GA is sustained over long-term treatment. Chen *et al.* [22] isolated 48 GA-reactive T cell lines from 10 RR MS patients who had taken GA for 6 – 9 years. Proliferative responses, cytokine production and crossreactivity with whole MBP and the MBP immunodominant peptide 83-99 were compared with responses obtained from 10 MS patients tested before GA treatment and after shorter treatment periods (1 – 10 months). Long-term treatment with GA resulted in a 2.9-fold decrease in the estimated precursor frequency of GA-reactive T cells. Nevertheless, the sustained response to GA remained Th2-biased and, in part, crossreactive with MBP and MBP (83-99), as measured by proliferation and cytokine-release assays [22].

2.4 Migration of activated T cells into the central nervous system

Areas of active CNS demyelination and axonal loss in MS white matter lesions contain substantial numbers of inflammatory cells. GA does not appear to directly inhibit the transmigration of these inflammatory cells into the CNS. Rather, repeated systemic activation by daily GA treatment stimulates GA-reactive T cells, which increasingly become Th2-like [23]. *In vitro* models demonstrate that Th2 cells can penetrate the CNS [24]. Adoptively transferred GA-reactive T cells administered systemically to recipient mice are detectable in the animals' CNS [23,25]. GA-reactive Th2 cells in the CNS are postulated to decrease local inflammation through 'bystander suppression'. It is thought that GA-specific Th2 cells within the CNS are restimulated by-products of myelin turnover presented by local APCs. The antigen presented within the CNS cannot be GA, as the drug is rapidly metabolised in subcutaneous tissue at the administration site. Local reactivation of GA-specific T cells stimulates the release of anti-inflammatory cytokines such as IL-4, -6, -10, TGF-β and brain-derived neurotrophic factor (BDNF), but not IFN-γ [25,26]. The production of pro-inflammatory cytokines, including IL-2 and IFN-γ, is inhibited through this bystander effect. The mechanism of bystander suppression may make GA useful in other autoimmune diseases of the CNS where Th1 cells predominate [27].

2.5 Neuroprotection

A recently identified mechanism of action of GA is related to a potential neuroprotective effect of some autoreactive Th1 and Th2 cells. This possibility was first raised after unexpected findings were reported in a rodent optic nerve crush injury model, which typically results in a predictable loss of retinal-ganglion neurons. In early experiments, animals injected with MBP-reactive T cells immediately after the crush injury exhibited attenuated subsequent loss of retinal ganglion neurons, but also suffered adoptive transfer EAE [28]. In subsequent experiments, rats subjected to optic nerve crush injury and then injected with GA-specific T cells showed increased retinal ganglion neuron survival, compared with injured controls, and did not develop EAE [29]. Moreover, in a murine model in which intraocular injection of glutamate destroys retinal ganglion neurons, glutamate toxicity was reduced in mice immunised with GA, but not in those immunised with either MBP or MOG [30]. The neuroprotective effects of GA have since been demonstrated in several animal models. Compared with untreated controls, GA treatment reduced axonal damage in C57/bl mice with chronic EAE [31], and increased survival time and improved motor function in a murine model of amyotrophic lateral sclerosis (ALS) [32].

A variety of mechanisms underpinning the neuroprotective effects of GA are currently under investigation. Kayhan *et al.* [33] demonstrated that in mice, induction of EAE leads to fourfold elevation in nitric oxide (NO) secretion. NO is an inflammatory mediator thought to affect regulation of the immune response, permeability of the blood–brain barrier, trafficking of cells to the CNS and immunosuppression. NO has been implicated in primary demyelination via nonspecific damage to the myelin sheath of axons, as well as promoting direct oligodendrocyte death [34]. Treatment of EAE mice with GA leads to a significant decrease in NO secretion by the splenocytes in response to the encephalitogen [33].

Another neuroprotective mechanism may involve GA-stimulated secretion of BDNF, a neurotrophic factor that plays an important role in plasticity and development of the nervous system [27,35]. Ziemssen *et al.* [36] determined that GA-specific Th2 and Th1 peripheral blood mononuclear cells produce BDNF. Using three GA-specific long-term T cell lines with phenotypes Th1, Th1/0 and Th0 derived from a healthy subject and one T cell line with a Th2 phenotype derived from a GA-treated MS patient, they demonstrated that all four T cell lines could be stimulated to produce BDNF [36]. Similarly, Chen *et al.* [26] studied BDNF production in 73 GA-reactive, 13 MBP-reactive and two tetanus toxoid (TT)-reactive T cell lines isolated from 12 MS patients treated with GA. BDNF levels produced by GA-specific T cells generated during treatment were higher than those generated pretreatment. Among the 73 GA T cell lines generated, 14% secreted levels of BDNF two standard deviations above the GA T cell line mean. All GA-reactive T cells that secreted high levels of BDNF were Th2 biased. A total of 26, 14 and 13 GA-, MBP- and TT T cell lines, respectively, originated from the same 4 MS patients and could be compared directly. The mean BDNF level for the GA-reactive T cell lines was significantly higher than that for the MBP- and TT-reactive T cell lines.

The signal transducing receptor for BDNF, the full-length 145 tyrosine kinase receptor (trk) B, is expressed in neurons and astrocytes in MS lesions [37]. Therefore, BDNF secreted by GA-reactive Th1 and Th2 cells in the CNS could exert neurotrophic effects directly in the MS target tissue. GA-reactive T cells also appear to have a reduced ability to transform bipolar microglia into a morphologically activated ameboid form [38].

2.6 Glatiramer acetate antibodies

Immunisation of mice and other laboratory animals with GA results in the development of polyclonal GA antibodies.

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