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Glatiramer Acetate Treatment of Multiple Sclerosis: An Immunological Perspective

Michael K. Racke^{*,†} and Amy E. Lovett-Racke[‡]

Glatiramer acetate (GA) has been used as an immunomodulatory agent for the treatment of relapsing-remitting multiple sclerosis (MS) in the United States since 1996. It is currently one of two first-line agents for use in the treatment of relapsing-remitting MS. GA was the first agent to be used in the treatment of MS that was developed using the animal model of MS called experimental autoimmune encephalomyelitis. In this commentary, we examine the development of GA as a treatment for MS and discuss its mechanism of action as suggested by recent studies using modern immunologic methods. *The Journal of Immunology*, 2011, 186: 1887–1890.

In the United States, >350,000 people have been diagnosed with multiple sclerosis (MS), an inflammatory, demyelinating disease of the CNS. MS is characterized by perivascular, mononuclear cell infiltrates and hypothesized to be an autoimmune attack against CNS myelin; these features are also characteristic of experimental autoimmune encephalomyelitis (EAE), an animal model used to study MS that is induced by an immune response to myelin Ags (1). Whereas both MS patients and healthy controls have been shown to have immune responses to a number of myelin Ags, myelin-reactive T cells in MS have been shown to have a memory phenotype, unlike the naive phenotype seen in healthy individuals (2). The majority of patients with the disease are women, and because most patients are diagnosed during their third and fourth decades, the majority of patients have to deal with the effects of the disease for most of their adult life. IFN- β -1b and -1a were the first drugs approved by the Food and Drug Administration (FDA) for use in the treatment of patients with relapsing-remitting MS (RRMS), and glatiramer acetate (GA) soon followed suit in 1996 (3–5) (Table I). GA (Copaxone, previously known as Copolymer 1, or Cop-1; Teva Pharmaceuticals) was the first drug approved for the treatment of MS that was developed as a result of its ability to inhibit the signs of EAE, and it continues to be studied by immunologists in terms of how it mediates its therapeutic effects (6) (Fig. 1).

Early studies

GA, a random polymer of glutamic acid, lysine, alanine, and tyrosine, was initially examined by Michael Sela, Ruth Arnon, and colleagues (5, 7, 8) at the Weizman Institute for its ability to cause EAE and to determine whether it could replace myelin basic protein (MBP) as an encephalitogen. Despite having an amino acid composition similar to MBP, GA did not cause EAE. Interestingly, these studies were initiated at a time when MHC and TCRs had not been discovered, and Ag recognition was a poorly understood process. The investigators at the Weizman Institute were never able to cause EAE with GA, but discovered that animals given this compound were resistant to the development of EAE (7). This observation has led many immunologists to examine how administration of a random polymer can alter expression of an autoimmune process like that observed in EAE or MS. Lando and colleagues (9) hypothesized that GA's effects were mediated by suppressor cells, because protection could be adoptively transferred from GA-treated mice to normal syngeneic recipients. This would be the first of several studies to suggest that GA could influence EAE through a regulatory population of immune cells.

GA inhibited the ability of lymphocytes to respond to MBP *in vitro* (10). Studies we performed 20 y ago showed that GA could inhibit not only a response to MBP, but also several Ag-specific murine T cell hybridomas (11). Because it had only recently been determined that T cells recognized peptide Ags in the context of MHC molecules, it was clear that a random polymer like GA would be able to bind many MHC molecules. This suggested that GA could inhibit responses of T cells with many different Ag specificities and not just those T cells specific for myelin Ags. Although most immunologists would not find this hard to believe today, 20 y ago there were those who maintained that GA had some specificity for MBP, based on its ability to inhibit EAE, but not other autoimmune disorders (12).

Immune deviation

The studies that demonstrated GA was effective in ameliorating EAE led to studies in humans with MS. GA treatment of MS patients led to an increase in serum IL-10, suppression of TNF- α mRNA, and an increase in IL-4 and TGF- β mRNA

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Abbreviations used in this article: APL, altered peptide ligand; EAE, experimental autoimmune encephalomyelitis; FDA, Food and Drug Administration; GA, glatiramer acetate; MBP, myelin basic protein; MRI, magnetic resonance imaging; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; Treg, regulatory T cells.

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Table I. Major placebo-controlled clinical trials using GA

	Year Published	No. of Patients	Primary Outcome	Significance (p Value)	Reference
First GA trial in RRMS	1987	50	Number of relapses	0.045	8
First GA trial in CPMS	1991	106	Confirmed progression	NS	40
Pivotal GA trial in RRMS	1995	251	Relapse rate	0.007	5
European/Canadian trial in RRMS	2001	239	Total number of enhancing lesions on MRI	0.003	17
Oral trial of GA in RRMS	2006	1912	Total number of confirmed relapses	NS	32
GA trial in PPMS	2007	943	Time to change in EDSS	NS	41
GA trial in CIS	2009	481	Progression to CDMS	0.0005	36

CDMS, clinically definite MS; CIS, clinically isolated syndrome; CPMS, chronic progressive MS; EDSS, expanded disability status score; PPMS, primary progressive MS.

in PBLs (13). The immune cells responsible for these changes were not identified in these early studies, but this study and others suggested GA altered the cytokine environment to one that was less inflammatory (13).

As immunologists better understood T cell recognition, GA was thought to act as an altered peptide ligand (APL) and inhibit activation of MBP-specific T cell clones in vitro (14). An APL is a peptide that has had its amino acid sequence changed so that a T cell that responded to the original peptide might now have a different response, such as secreting a different set of cytokines. By acting as an APL, GA could alter pathogenic T cell responses such that anti-inflammatory cytokines predominated. When an APL therapy of the immunodominant peptide of MBP in a MS clinical trial resulted in increased magnetic resonance imaging (MRI) activity and relapses in several patients (15), it was hypothesized that a random polymer such as GA might be a safer way to antagonize autoreactive T cells like those encountered in MS.

Interestingly, the initial phase III clinical trials that used GA for the treatment of RRMS did not use MRI as an outcome measure, and this led to criticism regarding the efficacy of the drug (5, 8). Because attacks occur infrequently over the course of a clinical trial, MRI is often used as a surrogate marker to measure disease activity in MS clinical trials. IFN- β had shown excellent results in inhibiting MRI activity (16), and the Canadian-European study of GA that used MRI suggested that it took several months on GA therapy to observe a sig-

nificant effect on MRI parameters (17) (Table I). To combat these perceived shortfalls, another potential mechanism for the drug was hypothesized: GA-reactive T cells would home to the CNS, recognize myelin Ags as an APL, and secrete anti-inflammatory rather than proinflammatory cytokines (18). In addition, neurotrophic factors were also detected in the CNS of mice that received GA (19). Thus, GA-reactive T cells were delivering neuroprotective cytokines to the site of inflammation in MS patients. Because the GA-reactive T cells were required to enter the CNS to provide this neuroprotective benefit, it provided a reason for why GA did not need to reduce gadolinium-enhancing lesions and inflammation in the same way as shown for IFN- β and natalizumab to elicit similar therapeutic benefit.

Because GA is a random polymer, it was logical that there would be numerous peptides that could be recognized by myelin-reactive T cells in patients with MS. Not only was GA shown to antagonize T cell clones specific for epitopes of MBP, other studies demonstrated that GA could induce apoptosis of myelin-reactive T cells, induce production of regulatory cytokines like those produced by CD4⁺ regulatory T cells (Treg), or by eliminating immune cell populations targeted by a regulatory cytotoxic T cell response (20, 21).

Soon, several studies examined the cytokine production of myelin-reactive T cells directly ex vivo from GA-treated patients (13). Because myelin-reactive T cells appeared to be of a Th2 phenotype, this suggested GA could alter the pathogenic potential of myelin-reactive T cells and participate in bystander suppression. Importantly for the MS patients, the Th2 response observed correlated with the clinical benefit (22).

Treg

Several studies have shown that GA increases the expression of Foxp3, a transcription factor that has been used to identify CD4⁺ Treg. In MS patients in whom Foxp3 expression was reduced in CD4⁺ T cells, GA appeared to reverse that deficiency (23). Of interest is the observation that almost all activated human T cells express Foxp3 at some point during differentiation (24). It still needs to be clarified whether the CD4⁺ T cells that respond to GA are the typical differentiated Treg, or whether they are just activated T cells transiently expressing Foxp3 in response to GA.

CD8⁺ T cells and their potential as Treg

Work from Hohlfeld's group (25) had observed that CD8⁺ T cells responded to GA by producing IFN- γ . Using a novel flow cytometric approach, Karandikar et al. (26) showed that both CD4⁺ and CD8⁺ T cells responded to GA. Sur-

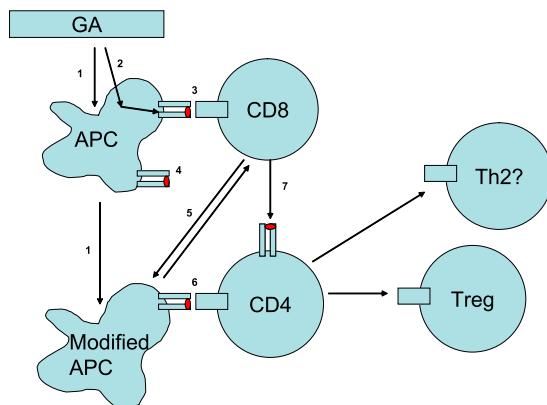


FIGURE 1. Possible mechanisms of action of GA. GA acts directly on APC to modify them into noninflammatory type II cells (1). GA is processed by APC (2) through class I (cross-presentation; 3) and class II (4) presentation pathways and is presented to CD8⁺ and CD4⁺ T cells, respectively. A robust CD8⁺ T cell response is either enhanced by or results in killing/modification of APC subsets (5). Presentation by modified APC results in generation of CD4⁺ Treg (6). Direct killing of Th1 CD4⁺ T cells results in deviation toward Th2 responses (7).

Table II. Major prospective active comparator trials with GA

	Year Published	No. of Patients	Primary Outcome	Reference
REGARD: IFN- β 1a versus GA in RRMS	2008	460	Time to first relapse	32
BECOME: IFN- β 1b versus GA by monthly MRI	2009	75	Combined active lesions/MRI scan	35
BEYOND: IFN- β 1b versus GA in RRMS	2009	2244	Relapse risk	33

In these trials, there were no significant differences in the primary outcome measures.

prisingly, MS patients who had not been treated with GA had an impairment of their CD8⁺ T cell response to GA (26). With GA treatment, MS patients demonstrated an expansion of the CD8⁺ T cell response while showing a reduction in the CD4⁺ T cell response, as had been observed by others (27). These CD8⁺ T cells that responded to GA demonstrated superior regulatory function when compared with CD8⁺ T cells from MS patients not on GA therapy (28). The CD8⁺ T cell regulatory function that was impaired in untreated MS patients improved dramatically after several months of GA treatment. Thus, GA corrects a deficit in a regulatory CD8⁺ T cell function in MS patients that returns to that observed in healthy individuals (28).

Although these CD8⁺ T cells that respond to GA have several characteristics of Treg that have been observed in animal models, one question still unanswered is whether this CD8⁺ T cell population that expands in response to GA treatment in MS patients is predictive of a therapeutic response. Prospective studies will need to address this important question in a larger MS patient cohort.

APCs

Another area in which GA may affect the immune response is at the level of APCs. The observations previously mentioned regarding immune deviation may have resulted by altering the ability of APC to promote pathogenic T cell differentiation. Monocytes from GA-treated MS patients produced less TNF- α compared with those from untreated patients when exposed to LPS (29). In another study, more IL-10 and less IL-12 were secreted from monocytes from GA-treated MS patients (30). A recent study by Weber and colleagues (31) showed GA could induce type II monocytes in the EAE model. These type II monocytes induced by GA were able to transfer protection in EAE. These observations also need to be observed in larger patient cohorts to see whether they predict a therapeutic response.

Clinical studies

The effectiveness of GA in patients with RRMS has been shown in several clinical trials (Table I). Unfortunately, similar efficacy was not observed in patients with progressive forms of the disease, thus GA is currently FDA-approved only for RRMS. In addition, oral administration of GA was ineffective in treating RRMS (32) (Table I). Because GA did not have the same robust and early effect on MRI disease activity that was observed with IFN- β , head-to-head trials were conducted to determine whether one agent had a more rapid benefit on reducing the time to the next clinical relapse, relapse risk, and MRI activity on 3T MRI (33–35) (Table II). Surprisingly, GA showed similar effectiveness in preventing all of these parameters when compared with high-dose IFNs, suggesting that MRI may not be the best surrogate marker for disease activity. Because of studies such as those described above, GA

and IFN- β are considered first-line agents for the treatment of RRMS. In addition, because GA has been shown to be beneficial in patients with clinically isolated syndromes who are at high risk to convert to clinically definite MS, GA is also FDA-approved for these patients (36).

Future prospects

The effectiveness of GA in the treatment of MS patients and its lack of toxicity have resulted in the consideration of GA for other autoimmune disorders. Interestingly, although GA was protective in EAE and MS, it exacerbated disease in collagen-induced arthritis (37). Binding motifs within GA have been determined for various HLA-DR molecules associated with both MS and rheumatoid arthritis (38). Work has also focused on determining whether other copolymers may have enhanced efficacy compared with GA. For example, whereas GA did show efficacy in a model of autoimmune uveitis, a novel copolymer of FYAK showed even greater efficacy in EAE and experimental autoimmune uveitis (39). Thus, work on understanding the mechanism of how these random polymers ameliorate autoimmune disease may ultimately result in even better treatments for a number of autoimmune disorders.

Summary

GA was the first treatment used in MS that was developed through the use of the EAE model. It received FDA approval based more on its clinical effects and the fact that there appeared to be evidence to suggest that GA modulated the immune response in a beneficial way. There are now >100,000 MS patients in the United States who inject themselves with this random polymer. Because of its long history of tolerability and safety, it will likely remain an important option for the treatment of MS patients for years to come.

Disclosures

The authors have no financial conflicts of interest

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