CME

Mechanisms of action of glatiramer acetate in multiple sclerosis

Oliver Neuhaus, MD; Cinthia Farina, PhD; Hartmut Wekerle, MD; and Reinhard Hohlfeld, MD

Article abstract—Glatiramer acetate (GA, Copaxone [Teva Pharmaceuticals, Kansas City, MO], formerly known as copolymer-1) and interferon- (IFN)-β are both used for the immunomodulatory treatment of multiple sclerosis, but they act in different ways. Four major mechanisms of GA have been identified: 1) competition with myelin-basic protein (MBP) for binding to major histocompatibility complex (MHC) molecules; 2) competition of GA/MHC with MBP/MHC for binding to the T-cell receptor; 3) partial activation and tolerance induction of MBP-specific T cells (action as an altered peptide ligand); and 4) induction of GA-reactive T-helper 2- (TH2)-like regulatory cells. Of these four mechanisms, 1 and 2 presumably occur only in vitro and are therefore irrelevant for the in vivo effects of GA. In contrast, mechanisms 3 and 4 could occur in vivo and both could contribute to the clinical effects of GA.

NEUROLOGY 2001;56:702–708

Glatiramer acetate (GA, Copaxone [Teva Pharmaceuticals, Kansas City, MO], formerly known as copolymer-1) and interferon- (IFN)-β are now widely used for the immunomodulatory treatment of MS.[1-4] The mechanisms of action of these agents, although not completely understood, seem to be fundamentally different. Whereas IFN-β exerts its multiple immunomodulatory effects in an antigen-nonspecific way, GA seems to preferentially affect immune cells specific for myelin basic protein (MBP) and perhaps other myelin antigens.[5-7] This view rests mainly on evidence obtained in experimental autoimmune encephalomyelitis (EAE), an animal model of MS. Until recently the effects of GA on the human immune system were largely unknown. However, several new articles have shed light on the mechanisms of action of GA in MS. In this article, we briefly review these novel findings and put them into perspective with the previous observations in animal models.

Clinical effects of GA in EAE and MS. GA is a standardized, randomized mixture of synthetic polypeptides consisting of L-glutamic acid, L-lysine, L-alanine, and L-tyrosine with a defined molar residue ratio of 0.14 : 0.34 : 0.43 : 0.09 and an average molecular mass of 4.7 to 11.0 kDa, i.e., an average length of 45 to 100 amino acids. It has been known for a long time that GA has both suppressive and protective effects in EAE induced by various encephalitogenic antigens in different species.[5,8-13] With some exceptions (murine graft-versus-host disease [in doses higher than required to suppress EAE],[14] experimental uveoretinitis,[15] and inhibition of type II collagen-reactive T cells in vitro[16]), GA seems to be ineffective in other autoimmune models.[6] In addition to the subcutaneous (s.c.) route of administration, the oral form of GA has also been shown to be effective in EAE.[17,18] Daily s.c. administration of GA has beneficial effects on the clinical and MRI-defined course of patients with MS.[19-24]

Overview of the immunologic effects of GA in EAE. During the last three decades, the pioneering work of Michael Sela, Ruth Arnon, and their colleagues has laid the foundations for the approval of GA for use in the treatment of MS.[6,25] A large body of experimental evidence in numerous EAE models suggests that GA acts by several different mechanisms[7]:

Results of in vitro studies suggest that GA competes in some way with MBP.[26-28] Specifically, GA competes with MBP at the antigen-presenting cell (APC) level for binding to the major histocompatibility complex (MHC), and GA/MHC competes with MBP/MHC for binding to the T-cell receptor (TCR). GA binds to many different alleles of MHC class II molecules ("promiscuous binding").[29] Interestingly, the stereoisomer of GA, D-GA, which is composed of D-amino acids, binds as effectively to MHC class II[30] but fails to suppress EAE.[31] This suggests that competition for MHC binding alone is insufficient to explain the beneficial effects of GA.[5] At the TCR level,

From the Department of Neuroimmunology (Drs. Neuhaus, Farina, Wekerle, and Hohlfeld), Max-Planck Institute of Neurobiology, Martinsried; and the Institute for Clinical Neuroimmunology and the Department of Neurology (Dr. Hohlfeld), Ludwig Maximilians University, Munich, Germany.

Supported by a grant from TEVA. O.N. is a postdoctoral fellow supported by Deutsche Forschungsgemeinschaft and Max-Planck-Gesellschaft. The Institute for Clinical Neuroimmunology is supported by the Hermann and Lilly Schilling Foundation. R.H. is a consultant to TEVA.

Received September 29, 2000. Accepted in final form December 10, 2000.

Address correspondence and reprint requests to Dr. Reinhard Hohlfeld, Institute for Clinical Neuroimmunology, Klinikum Grosshadern, Ludwig Maximilians University, Marchioninistrasse 15, 81366 Munich, Germany; e-mail: hohlfeld@neuro.mpg.de

GA has been reported to act as an antagonist of the antigenic peptide MBP 82-100, but not MBP 1-11 and proteolipid protein (PLP) 139-151.[32]

Results of in vivo studies indicate that GA induces regulatory T cells of the T-helper 2- (TH2)-type in the peripheral immune system outside the CNS. When spleen cells from GA-treated mice were adoptively transferred into syngeneic animals, these cells protected from EAE induced by different CNS antigens.[33-35] Earlier researchers demonstrated a similar inhibitory effect with a "soluble factor" extracted from these cells,[36] which were later identified as anti-inflammatory TH2 cytokines.[34,35] Further support for the proposed protective role of GA-reactive regulatory T cells comes from the recent demonstration that GA-specific TH2 cells are present in the CNS of GA-treated mice.[37] GA-specific T cells also have a neuroprotective effect after adoptive transfer into rats with experimental crush lesions of the optic nerve.[38] This latter finding suggests the possibility that GA-specific TH2-like regulatory T cells not only provide protective cytokines such as interleukin-(IL)-4, IL-5, IL-13, and transforming growth factor-(TGF)-β, but also neurotrophic factors such as brain-derived neurotrophic factor (BDNF).[38,39]

Immunologic effects of GA in human subjects. The different effects of GA are listed and compared with the effects of IFN-β in the table.

High frequency of GA-reactive proliferating T cells in untreated subjects. In contrast to the lack of effect of GA on immune cells isolated from untreated animals, GA induces vigorous proliferation of peripheral blood lymphocytes (PBL) from untreated (unprimed) human subjects.[40-42] Phenotypic analyses revealed that the GA-responsive T-cell population in untreated subjects is polyclonal[43,44] and predominantly originates from the memory T-cell pool.[44] Recent findings indicate that the proliferative response to GA depends on both MHC class I- and MHC class II-restricted T cells.[45]

Reduced proliferative response in GA-treated patients. The proliferative response to GA decreases with time in GA-treated patients.[6,42,46-48] Recent results from our own group indicate that this decrease is specific to GA because it is not observed with recall antigens like tetanus toxoid and tuberculin.[49] Using limiting dilution assays, Schmied et al. observed that the constitutively high frequency of GA-reactive T cells in untreated patients initially tends to increase during the first months of GA therapy and only later decreases below baseline.[50] Theoretically, the observed decrease in GA-reactive T cells could be caused by anergy induction or activation-induced cell death of GA-specific T cells.[50]

Deviation from TH1 to TH2. TH cells can be divided into several types based on their characteristic cytokine secretion patterns and effector functions.[51-55] TH1 cells produce proinflammatory cytokines such as IL-2, IL-12, IFN-γ, and tumor necrosis factor- (TNF)-α. In contrast, TH2 cells produce downregulatory cytokines such as IL-4, IL-5, IL-6, IL-10, and IL-13. TH1 cells mediate proliferative and delayed hypersensitivity responses, whereas TH2 cells are involved in allergic pathways and support antibody production by B cells.[52]

Different lines of evidence suggest that GA treatment induces a shift from TH1 to TH2. GA treatment was shown to increase serum IL-10 levels and TGF-β and IL-4 mRNA in PBL, whereas it suppressed TNF-α mRNA.[55] Using intracellular double-immunofluorescence flow cytometry, we demonstrated that long-term GA-reactive T-cell lines (TCL) from patients with untreated MS and healthy controls predominantly produce IFN-γ and are to be classified as TH1 cells, whereas GA-reactive TCL from patients with GA-treated MS predominantly produce IL-4, i.e., behave like TH2-cells.[43] Recent observations on short-term[44,48] and long-term[56] GA-reactive TCL by other groups are consistent with these findings. In contrast to MBP-reactive TCL, GA-reactive TCL secrete IL-6, a TH2-related cytokine.[56] In addition, the IFN-γ : IL-5 ratio was biased toward IFN-γ in MBP-reactive TCL and toward IL-5 in GA-reactive TCL, in both treated and untreated patients.[42]

In contrast to the limiting dilution assay (which detects proliferation), results obtained with an automated ELISPOT assay (which detects cytokine production of individual cells) indicate that during GA therapy, there is an increase of GA-reactive T cells producing IL-4 or IFN-γ.[49] Specifically, the study by Farina et al.[49] demonstrated that patients with GA-treated MS show 1) a significant reduction of GA-induced proliferation of peripheral blood mononuclear cells; 2) a positive IL-4 ELISPOT response mediated predominantly by CD4+ T cells after in vitro stimulation with a wide range of GA concentrations; and 3) an elevated IFN-γ response partially mediated by CD8+ T cells after stimulation with high GA concentrations. All three effects were GA-specific because they were not observed with control antigens.[49] The GA-induced changes were stable over time and allowed the correct identification of GA-treated and untreated donors in most cases.[49] It therefore appears that during therapy, GA-reactive T cells are not physically deleted, but rather they are modified in such a way that they respond to in vitro challenge with GA by secreting cytokines but not by proliferating.

Effects on migratory potential of T cells. Using an in vitro model of lymphocyte migration, Prat et al. demonstrated that the migratory potential of lymphocytes freshly isolated from GA-treated patients was reduced compared with untreated patients.[57] In vitro treatment with IFN-β, but not GA, reduced lymphocyte migration rates, indicating that IFN-β acts directly on cell migration, whereas GA acts indirectly.[57] GA did not change the expression of adhesion molecules on human brain microvascular endothelial cells.[58] It is currently not known whether

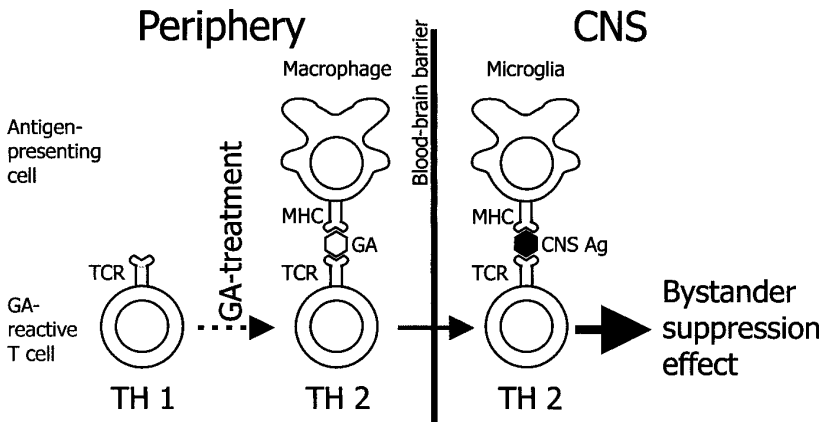

Figure. Schematic view of the putative mechanism of action of glatiramer acetate (GA). In the periphery, outside the CNS, GA initially stimulates a population of TH1-like T cells. During treatment, the properties of the GA-stimulated T cells change, and they become more TH2-like (dotted arrow). The activated GA-specific T cells enter the CNS, where they encounter CNS antigens like MBP bound to MHC class II and presented on the surface of microglia cells. The GA-reactive T cells are stimulated to secrete downmodulatory cytokines like IL-4, which exert a bystander suppressive effect on other T cells. TCR = T-cell receptor; MHC = major histocompatibility complex; Ag = antigen.

the reduced migratory potential is related to the TH1-to-TH2 shift observed with GA-specific TCL.[42-44,48,56]

Cross-stimulation with MBP and other antigens. GA was originally developed to *mimic* MBP for EAE induction.[6,8] Surprisingly, however, it turned out that GA *inhibits* MBP-induced EAE.[6] Ever since then, some form of partial cross-reaction or competition between MBP and GA has been considered crucial to the mechanism of GA. Most investigators of the human immune response to GA found that GA is not cross-reactive with MBP at the level of proliferation.[41,56] An exception was reported by Gran et al., who observed that a small number of GA-reactive TCL isolated from a patient treated with GA for more than 6 years proliferated in response to whole MBP and peptide MBP 83-99.[44]

Despite the lack of cross-stimulation at the proliferation level, there is clear evidence that GA and MBP may cross-stimulate T cells at the level of cytokine production. In our own study, about 10% of the tested GA-specific T cell lines could be cross-stimulated with MBP to produce low levels of cytokines.[43] In these experiments, TH1-type TCL preferentially produced IFN-γ, whereas TH2-type TCL produced IL-4.[43] Similar results were reported by others, using either MBP-specific TCL[42] for cross-stimulation with GA, or GA-reactive TCL[44] for cross-stimulation with MBP.

Interestingly, two of our GA-specific T-cell lines could be stimulated to produce IFN-γ with another myelin autoantigen, myelin-oligodendrocyte glycoprotein (MOG).[43] This indicates that the cross-stimulatory effect on cytokine production is not entirely restricted to MBP. It may also occur with other autoantigens. Indeed, one group of investigators found evidence that the immune response to GA in GA-treated patients becomes more "degenerate."[48] The authors reported that with increasing duration of treatment, the surviving GA-reactive T cells responded to an increasing number of components from a combinatorial peptide library.[48] These observations would add an interesting facet to the mechanism of GA action, implying that GA-reactive, TH2-like (protective) T cells might be activated not only by MBP, but also by other cross-reactive antigens. This might help to explain why GA had beneficial effects not only in EAE induced by MBP but also by MOG or PLP, and also in a few other experimental autoimmune diseases.[6,14,15]

Inhibition of MBP-specific T cells by GA. GA was found to inhibit the MBP-induced proliferation and IL-2 secretion of human MBP-specific TCL.[28] A trivial toxic effect of GA could be excluded because the inhibition was overcome by increasing the concentration of MBP.[28] A control antigen, tuberculin purified protein derivative (PPD), did not have any inhibitory effect.[28] GA also inhibited influenza virus hemagglutinin- and Borrelia burgdorferi-specific T-cell clones, although to a lesser extent than MBP-specific T cells.[44] In addition, GA was shown to inhibit the cytolytic ability of human MBP-specific TCL restricted to MS-associated HLA-DR types.[59] In a recent study, Gran et al. showed that GA inhibited IFN-γ production in MBP-reactive T cells in a dose-dependent manner and had a less pronounced effect on the secretion of IL-4 and IL-5.[44] In a subset of the analyzed T-cell clones, GA had a differential effect, i.e., it inhibited proliferation and IFN-γ production and induced IL-4 and IL-5 secretion. This indicates a differential influence of GA on the T-cell activation parameters.[44] Furthermore, GA was shown to induce a state of nonresponsiveness (anergy) in MBP-specific T-cell clones.[44] In principle, these inhibitory effects could occur at the level of binding of GA to the MHC or to the TCR.

Interaction with MHC. GA binds to purified HLA-DR molecules without antigen processing[29] and without any obvious preference for particular alleles.[60] Although distinct binding motifs of GA to MS-associated HLA-DR molecules could be defined, virtually all of the GA polypeptides seem to have a binding capacity to MHC class II, owing perhaps to their random composition.[61] In addition to MHC class II molecules, GA also seems to be able to inter-

Table *Comparison of major immunologic effects of glatiramer acetate (GA) and interferon (IFN)-β*

Effects	GA	IFN-β[71-73]
T-cell proliferation in vitro	Suppression of proliferation of MBP-reactive T cells in vitro[28]	Antigen-nonspecific suppression of T-cell proliferation[74,75]
Proliferation during treatment	Decreased proliferation of PBL to GA during treatment[6,42,47-49]	No known effect
Regulation of MHC expression	No known effect	Inhibition of IFN-γ-induced upregulation of MHC class II expression[76,77]
MHC binding	Direct and promiscuous binding of GA to different HLA-DR alleles[60,61]	No known effect
T-cell migration	Reduced migration of PBL from GA-treated patients (unknown mechanism)[57]; no effect on adhesion molecule expression on human brain microvascular endothelial cells[58]	Reduced T-cell migration caused by inhibition of matrix metalloproteinases (MMP),[78-80] increase of soluble adhesion molecules (sICAM-1, sVCAM-1),[80,81] and decrease of surface-expressed adhesion molecules (VLA-4)[82]
TH2 shift in PBL	Increased levels of IL-10 in serum and of mRNA for TGF-β and IL-4[55]; reduction of mRNA for TNF-α in PBL[55]	Induction of TH2 cytokines and reduction of TH1 cytokines in PBL[83-85]
TH2 shift in GA-specific T cells	Shift of GA-reactive T cells from TH1 towards TH2 during GA treatment[43,48]	No known effect
Cross-stimulation with MBP	Induction by GA of cytokine production in MBP-specific T cells and vice versa[42-44]	No known effect
Cross-inhibition of MBP-specific TCL	Inhibition of proliferation of T cells specific for MBP and some other antigens[28,44]	No known effect
TCR antagonism	TCR antagonism with MBP 82–100 (controversial findings)[32,44]	No known effect
APL effect on MBP-specific T cells	Induction of anergy in MBP-specific T-cell clones[44]	No known effect
Effects on antigen-presenting cells	Inhibition of TNF-α and cathepsin-B production in a monocytic cell line[62]	Several effects, e.g., inhibition of IFN-γ induction of FcγRI expression in monocytes[86]

Due to space limitations, only representative articles are cited for each mechanism.

APL = altered peptide ligand; HLA = human histocompatibility leukocyte antigen; IL = interleukin; MBP = myelin-basic protein; MHC = major histocompatibility complex; mRNA = messenger ribonucleic acid; PBL = peripheral blood lymphocytes; sICAM = soluble intercellular adhesion molecule; sVCAM = soluble vascular cell adhesion molecule; TCL = T-cell lines; TCR = T-cell receptor; TGF = transforming growth factor; TH = T-helper; TNF = tumor necrosis factor; VLA = very late antigen.

act with MHC class I.[45,49] It is therefore likely that part of the inhibitory effects described in the previous section occur by competition between GA and other antigens for MHC binding. Clearly, this type of competition could occur with any antigen and is therefore antigen-nonspecific. However, for reasons explained below, this mechanism is probably irrelevant for the in vivo effects of GA.

Interaction with TCR. In addition to competition at the MHC class II level, and consistent with animal data, GA was reported to act as a "TCR antagonist" against the MBP 82-100 peptide.[32] In contrast, in another study TCR-antagonistic effects were not observed.[44] However, when MBP-specific TCL were stimulated with different concentrations of GA, their subsequent response to the nominal antigen MBP was turned off, i.e., the T cells had been "anergized" by GA.[44] This suggests that a specific TCR engagement by GA does occur. This mechanism may be relevant to the in vivo effects of GA because it does not require the simultaneous presence of the nominal antigen (e.g., MBP).

Effect on monocytes. Although the vast majority of evidence suggests that GA acts primarily at the level of T cells, additional effects on other immune cells cannot be excluded. For example, GA was reported to inhibit a human monocytic cell line, THP-1.[62] In THP-1 cells stimulated with lipopolysaccharide or IFN-γ, GA reduced the percentage of cells expressing HLA-DR and DQ antigen and inhibited the production of TNF-α and cathepsin-B. In contrast, the production of IL-1β was increased.[62] The mechanism of these effects and their relevance to the overall mechanism of action of GA currently are unknown.

Conclusion: proposed mechanism of action of GA in multiple sclerosis. The results discussed in the previous sections suggest four major effects of GA on human T cells:

1. GA binds "promiscuously" to MHC class II and perhaps MHC class I molecules, thereby competing with the MHC binding of other antigens. This effect, which by its nature is antigen-nonspecific, is unlikely to play a role in vivo because after s.c. administration GA is quickly degraded to free amino acids and small oligopeptides.[63] Therefore it is not likely to reach the CNS where it could compete with the relevant auto-antigens for MHC binding.

2. GA/MHC competes with MBP for binding to the antigen-specific surface receptor of MBP-specific T cells ("TCR antagonism"). The experimental evidence supporting this effect is controversial. If it occurs, it is unlikely to be relevant in vivo because GA is unlikely to reach sites where it could compete with MBP.

3. GA/MHC binds to the TCR of T cells specific for MBP and, perhaps, other myelin antigens. In this view, GA acts like an "altered peptide ligand" (APL) relative to MBP. As a consequence, some of the myelin-specific, pathogenic T cells might become "anergic" or be otherwise changed in their properties, e.g., in their migratory potential. This effect would be relatively antigen-specific and presumably occur in the periphery at the injection sites or in their draining lymph nodes where the MBP-specific T cells might be confronted with GA. Although some in vitro findings support this mechanism, it is not yet known whether the functional properties of MBP-specific T cells are altered in GA-treated patients. It may be of relevance in this connection that we were unable to isolate MBP-specific TCL from GA-treated patients.[43]

4. GA treatment induces a TH1-to-TH2 shift in GA-reactive T cells in vivo. The GA-reactive T cells act as regulatory cells and have beneficial effects on the pathogenic autoimmune reaction. Compared with the other putative mechanisms, this currently has the strongest experimental support. We would like to propose the following scenario (figure): GA-reactive TH2-like T cells are able to cross the blood-brain barrier because they are activated by daily immunization.[64] During treatment, the properties of the GA-reactive T cells are changed in such a way that they increasingly become TH2-like.[43,48] Inside the CNS, the GA-reactive T cells are confronted with products of myelin turnover presented by local APC.[65] Some of the GA-reactive cells cross-react with MBP or MOG and are therefore stimulated to release anti-inflammatory cytokines such as IL-4, IL-6, IL-10, and even neurotrophic factors.[38,39,66] Subsequently, the production of pro-inflammatory cytokines such as IL-2 and IFN-γ by other inflammatory cells is reduced via a suppressive bystander effect.[34,35,67,68] Hypothetically, a similar process might occur in the periphery: Any viral or bacterial antigens that stimulate peripheral MBP-specific T cells by molecular mimicry[69,70] might also activate peripheral GA-specific, cross-reactive downregulatory T cells.

Acknowledgment

The authors thank Ms. Judy Benson for her helpful comments and careful reading of the manuscript.

References

1. Wolinsky JS. Copolymer 1: a most reasonable alternative therapy for early relapsing-remitting multiple sclerosis with mild disability. Neurology 1995;45:1245–1247.
2. Noseworthy JH. Progress in determining the causes and treatment of multiple sclerosis. Nature 1999;399(suppl):A40–A47.
3. Milo R, Panitch H. Glatiramer acetate or interferon-β for multiple sclerosis? A guide to drug choice. CNS Drugs 1999;11: 289–306.
4. Wolinsky JS. Glatiramer acetate. In: Hawkins CP, Wolinsky JS, eds. Principles of treatments in multiple sclerosis. Oxford, Woburn: Butterworth-Heinemann, 2000:71–94.
5. Arnon R, Sela M, Teitelbaum D. New insights into the mechanism of action of copolymer 1 in experimental allergic encephalomyelitis and multiple sclerosis. J Neurol 1996; 243(suppl 1):S8–S13.
6. Arnon R. The development of Cop-1 (Copaxone®), an innovative drug for the treatment of multiple sclerosis: personal reflections. Immunol Lett 1996;50:1–15.
7. Teitelbaum D, Arnon R, Sela M. Cop 1 as a candidate drug for multiple sclerosis. J Neural Transm 1997;49(suppl):85–91.
8. Teitelbaum D, Meshorer A, Hirshfeld T, Arnon R, Sela M. Suppression of experimental allergic encephalomyelitis by a synthetic polypeptide. Eur J Immunol 1971;1:242–248.
9. Teitelbaum D, Webb C, Meshorer A, Arnon R, Sela M. Suppression by several synthetic polypeptides of experimental allergic encephalomyelitis induced in guinea pigs and rabbits with bovine and human basic encephalitogen. Eur J Immunol 1973;3:273–279.
10. Teitelbaum D, Webb C, Bree M, Meshorer A, Arnon R, Sela M. Suppression of experimental allergic encephalomyelitis in rhesus monkeys by a synthetic basic copolymer. Clin Immunol Immunopathol 1974;3:256–262.
11. Lisak RP, Zweiman B, Blanchard N, Borke LB. Effect of treatment with copolymer 1 (Cop-1) on the in vivo and in vitro manifestations of experimental allergic encephalomyelitis (EAE). J Neurol Sci 1983;62:281–293.
12. Teitelbaum D, Fridkis-Hareli M, Arnon R, Sela M. Copolymer 1 inhibits chronic relapsing experimental allergic encephalomyelitis induced by proteolipid protein (PLP) peptides in mice and interferes with PLP-specific T cell responses. J Neuroimmunol 1996;64:209–217.
13. Ben-Nun A, Mendel I, Bakimer R, et al. The autoimmune reactivity to myelin oligodendrocyte glycoprotein (MOG) in multiple sclerosis is potentially pathogenic: effect of copolymer 1 on MOG-induced disease. J Neurol 1996;243(suppl 1):S14–S22.
14. Schlegel PG, Aharoni R, Chen Y, et al. A synthetic random basic copolymer with promiscuous binding to class II major histocompatibility complex molecules inhibits T-cell proliferative responses to major histocompatibility antigens in vitro and confers the capacity to prevent murine graft-versus-host disease in vivo. Proc Natl Acad Sci USA 1996;93:5061–5066.
15. Zhang M, Chan CC, Vistica B, Hung V, Wiggert B, Gery I. Copolymer 1 inhibits experimental autoimmune uveoretinitis. J Neuroimmunol 2000;103:189–194.
16. Fridkis-Hareli M, Rosloniec EF, Fugger L, Strominger JL. Synthetic amino acid copolymers that bind to HLA-DR proteins and inhibit type II collagen-reactive T cell clones. Proc Natl Acad Sci USA 1998;95:12528–12531.
17. Teitelbaum D, Arnon R, Sela M. Immunomodulation of experimental autoimmune encephalomyelitis by oral administration of copolymer 1. Proc Natl Acad Sci USA 1999;96: 3842–3847.
18. Weiner HL. Oral tolerance with copolymer 1 for the treatment of multiple sclerosis. Proc Natl Acad Sci USA 1999;96:3333–3335.
19. Bornstein MB, Miller A, Slagle S, et al. A pilot trial of Cop 1 in exacerbating–remitting multiple sclerosis. N Engl J Med 1987;317:408–414.
20. Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis. Results of a phase III multicenter, double-blind, placebo-controlled trial. Neurology 1995;45:1268–1276.
21. Johnson KP, Brooks BR, Cohen JA, et al. Extended use of glatiramer acetate (Copaxone) is well tolerated and maintains

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.