Glatiramer Acetate Therapy: The Plot Thickens

GLATIRAMER ACETATE (COPAXONE; TEVA Pharmaceuticals, North Wales, Pa) is a random polymer of glutamic acid, lysine, alanine, and tyrosine, and is of considerable interest for its ability to reduce the frequency of relapses in relapsing-remitting multiple sclerosis (MS).[1] Several mechanisms have been proposed to explain these findings. Lando et al[2] suggested that inhibition of clinical disease in an animal model of MS, experimental autoimmune encephalomyelitis, was due to suppressor cells because protection could be adoptively transferred from glatiramer acetate–treated mice. Early studies suggested that glatiramer acetate could inhibit antigen-specific responses through competition for major histocompatibility complex molecules.[3] More recent work suggests that glatiramer acetate treatment of MS patients and mice with experimental autoimmune encephalitis has several potential mechanisms, although the favored one seems to be of inducing a shift in the balance of Th1 and Th2 cells.[4,5] However, the exact T-cell populations responsible for these shifts were not characterized immunophenotypically in most of these studies. Glatiramer acetate has been shown to act as an altered peptide ligand and antagonize T-cell clones specific for myelin basic protein 82-100 in vitro.[6] In addition, recent studies also propose an effect on antigen-presenting cells, suggesting that the mechanism of action is more complex than mere immune deviation.[7,8] It

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is thus unclear whether glatiramer acetate acts by altering the cytokine phenotype of myelin-reactive T cells, deletes these cells, or induces a regulatory T-cell population which mediates its effects through regulatory cytokines or direct suppression/elimination of target immune populations.

With regard to the 2 major immunomodulatory drugs presently used in relapsing-remitting MS, the mechanism of action of neither interferon beta nor glatiramer acetate is well understood. This has become a major issue with the recent withdrawal of natalizumab (Tysabri; Biogen Idec, Cambridge, Mass), which blocks the adhesion molecule VLA-4 on activated lymphocytes.[9] Since the combination of both natalizumab and interferon beta resulted in the appearance of progressive multifocal leukoencephalopathy in 2 MS patients, aggressive blockade of inflammation at the blood-brain barrier appears to have significant consequences. Use of interferon beta may also have effects that counter some of the proposed actions of glatiramer acetate, such as bystander suppression and neuroprotection. Thus, understanding how MS therapies, including glatiramer acetate, regulate lymphocyte trafficking and alter the function of immune cells is of significant interest to neurologists caring for MS patients.

Recently, using a novel flow cytometric assay, we provided the first direct evidence that glatiramer acetate therapy induces not only CD4+, but also CD8+ T-cell responses.[10] In fact, treatment of MS patients with glatiramer acetate results in the differential expansion of these glatiramer acetate–reactive CD8+ T cells, while the glatiramer acetate–reactive CD4+ T-cell response diminishes over time, suggesting that these T cells may exert a regulatory function and mediate the therapeutic effect of glatiramer acetate. Other investigators have also suggested the involvement of CD8+ T cells in the response to glatiramer acetate. In this context, the mechanisms regulating the trafficking of glatiramer acetate–reactive T cells becomes an important issue.

In this issue of the ARCHIVES, Allie et al[11] examine the chemokine receptor expression on both glatiramer acetate–reactive and myelin-reactive T cells from MS patients treated with GA. As previously shown, these authors have observed a shift in the cytokine secretion of both glatiramer acetate–reactive and myelin-reactive T cells from a Th1 to Th2 phenotype. In agreement with our findings and those of others, these authors have also observed a decrease in CD4+ glatiramer acetate–reactive T cells over time and an increase in CD8+ glatiramer acetate–reactive T cells.

However, the most intriguing observations are related to the chemokine expression of the glatiramer acetate–reactive and myelin-reactive T cells. The authors observed that prior to glatiramer acetate therapy, myelin basic protein–reactive, tetanus toxin, and glatiramer acetate–reactive T cells expressed high levels of the Th1-associated chemokine receptors CXCR3, CXCR6, and CCR5. However, after 12 months of therapy, these molecules were significantly down-regulated with a concomitant increase in the chemokine receptor CCR7. This was only significant on CD4+ glatiramer acetate–reactive T cells, not CD8+ glatiramer acetate–reactive T cells.

These shifts in chemokine receptor expression may have significant effects on the trafficking of these T-cell populations. Allie et al show that as these shifts in chemokine expression occur, the glatiramer acetate–reactive T cells that lose expression of CXCR3 no longer migrate well in response to interferon-inducible protein

10, while these T cells now migrate better to the chemokine MIP3β, a ligand for CCR7. These findings may have implications for the concept of bystander suppression and the notion that glatiramer acetate–reactive T cells exert their effect in the central nervous system. During the inflammation that occurs during MS, interferon-inducible protein 10 is expressed in brain tissue along with an increase in CXCR3-expressing lymphocytes.[12] If one of glatiramer acetate's major effects is to alter the expression of these chemokine receptors, then it is possible that glatiramer acetate–reactive CD4+ T cells may not be preferentially recruited to the central nervous system as previously hypothesized. On the other hand, recruitment of CCR7-expressing T cells to the lymphoid tissue may allow for regulatory effects to occur in the immune compartment. Interestingly, since the changes from a CXCR3- to CCR7-expressing cell population are not observed on CD8+ T cells, it is also possible that glatiramer acetate–reactive CD8+ T cells may be able to exert a regulatory effect in an interferon-inducible protein 10–expressing inflammatory environment such as the inflamed central nervous system in MS.

Our group has also recently observed that there are a significant number of CD8+ myelin-reactive T cells in patients with MS.[13] While it is not known whether these T cells are pathogenic, we have recently observed that many of these CD8+ myelin-reactive T cells have downregulated the costimulatory molecule CD28 and upregulated the CD57 surface marker, which is characteristic of chronically stimulated lymphocytes. In terms of MBP-reactive T cells, Allie et al observed that CXCR3 expression was reduced on CD4+ myelin basic protein–reactive T cells, but not CD8+ myelin basic protein–reactive T cells. This would imply that glatiramer acetate therapy might reduce recruitment of CD4+ T cells to the central nervous system, but not affect the recruitment of CD8+ T cells to that site. Further work will be required to determine whether CD8+ myelin-reactive T cells have pathogenic activity, as has been suggested in some experimental autoimmune encephalomyelitis models.

Overall, the observation that glatiramer acetate therapy alters chemokine receptor expression of both glatiramer acetate–reactive T cells and myelin-reactive T cells would suggest that by inference, lymphocyte traffic will also be altered. In addition to glatiramer acetate, with the introduction of nataluzimab to the mix and the known effects of interferon beta on adhesion molecule expression, it is clear that a better understanding of lymphocyte trafficking will be important to our understanding of the pathogenesis of MS and its manipulation as a means of therapeutic intervention. We will eagerly await the next chapter of this saga to know whether alteration of lymphocyte trafficking will lead to successful management of MS.

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Funding/Support: Drs Karandikar and Racke are supported by National Institutes of Health grants NS37513, NS44250, and AI 53439. Dr Karandikar is a Harry Weaver Neuroscience Scholar of the National Multiple Sclerosis Society.

REFERENCES

1. Johnson KP, Brooks BR, Cohen JA; Copolymer 1 Multiple Sclerosis Study Group. 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.
2. Lando Z, Teitelbaum D, Arnon R. Effect of cyclophosphamide on suppressor cell activity in mice unresponsive to EAE. *J Immunol*. 1979;123:2156-2160.
3. Racke MK, Martin R, McFarland HF, Fritz RB. Copolymer-1-induced inhibition of antigen-specific T cell activation: interference with antigen presentation. *J Neuroimmunol*. 1992;37:75-84.
4. Gran B, Tranquill LR, Chen M, et al. Mechanisms of immunomodulation by glatiramer acetate. *Neurology*. 2000;55:1704-1714.
5. Neuhaus O, Frina C, Wekerle H, Hohlfeld R. Mechanisms of action of glatiramer acetate in multiple sclerosis. *Neurology*. 2001;56:702-708.
6. Aharoni R, Teitelbaum D, Arnon R, Sela M. Copolymer 1 acts against the immunodominant epitope of 82-100 of myelin basic protein by T cell receptor antagonism in addition to major histocompatibility blocking. *Proc Natl Acad Sci U S A*. 1999;96:634-639.
7. Weber MS, Starck M, Wagenpfeil S, Meinl E, Hohlfeld R, Farina C. Multiple sclerosis: Glatiramer acetate inhibits monocyte reactivity in vitro and in vivo. *Brain*. 2004;127:1370-1378.
8. Kim HJ, Ifergan I, Antel JP, et al. Type 2 monocyte and microglia differentiation mediated by glatiramer acetate therapy in patients with multiple sclerosis. *J Immunol*. 2004;172:7144-7153.
9. Miller DH, Khan OA, Sheremata WA, et al; International Natalizumab Multiple Sclerosis Trial Group. A controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med*. 2003;348:15-23.
10. Karandikar NJ, Crawford MP, Ratts RB, et al. Glatiramer acetate (Copaxone) therapy induces CD8+ T cell responses in patients with multiple sclerosis. *J Clin Invest*. 2002;109:641-649.
11. Allie R, Hu L, Mullen KM, Dhib-Jalbut S, Calabresi PA. Bystander modulation of chemokine receptor expression on peripheral blood T lymphocytes mediated by glatiramer therapy. *Arch Neurol*. 2005;62:889-894.
12. Balashov KE, Rottman JB, Weiner HL, Hancock WW. CCR5+ and CXCR3+ T cells are increased in multiple sclerosi sand their ligands MIP-1-alpha and IP-10 are expressed in demyelinating brain lesions. *Proc Natl Acad Sci U S A*. 1999; 96:6873-6878.
13. Crawford MP, Yan X, Ortega S, et al. High prevalence of autoreactive neuroantigen-specific CD8+ T cells in multiple sclerosis revealed by novel flow cytometric assay. *Blood*. 2004;103:4222-4231.