Efficacy, safety, and cost-effectiveness of glatiramer acetate in the treatment of relapsing–remitting multiple sclerosis

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Abstract: The current Multiple Sclerosis (MS) therapeutic landscape is rapidly growing. Glatiramer acetate (GA) remains unique given its non-immunosuppressive mechanism of action as well as its superior long-term safety and sustained efficacy data. In this review, we discuss proposed mechanisms of action of GA. Then we review efficacy data for reduction of relapses and slowing disability as well as long term safety data. Finally we discuss possible future directions of this unique polymer in the treatment of MS.

Keywords: multiple sclerosis, glatiramer acetate, copaxone[®], disease modifying therapies

Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) that affects an estimated two million people worldwide and is one of the most common causes of neurological dysfunction among young adults [Noseworthy *et al.* 2000]. Pathologically, MS is characterized by perivascular, mononuclear cell infiltrates, and demyelination [Frohman *et al.* 2006; Martin *et al.* 1992; Olsson, 1992; Dhib-Jalbut and McFarlin, 1990; McFarland and Dhibjalbut, 1989; Hafler and Weiner, 1987]. Although incompletely understood, several lines of evidence suggest that MS pathogenesis involves a T-cell-mediated inflammatory injury to myelin and axons. Epidemiologic and genetic studies point to probable exposure of specific antigens in a genetically susceptible individual, that induce helper T cells to inappropriately target myelin proteins such as MBP. Interactions with adhesion molecules assist these autoreactive T cells in migration across the blood–brain barrier into the CNS. They can then reactivate upon encountering CNS myelin antigens on antigen-presenting cells (APCs), causing them to differentiate into a pro-inflammatory phenotype that produces several cytokines that disrupt the blood–brain barrier and recruit humoral and cellular inflammatory mediators such as cytotoxic T cells, activated B cells and

macrophages [Owens *et al.* 2003; Qin *et al.* 1998]. The cumulative effects of these inflammatory mediators results in demyelination and axonal destruction [Trapp *et al.* 1998].

Whereas MS was largely considered untreatable for more than a century, eight disease-modifying therapies (DMT) have been Food and Drug Administration (FDA) approved in the United States between 1993 and 2010. Four interferon beta (IFNB) products (Betaseron[®], Avonex[®], Rebif[®] and most recently Extavia[®]), and glatiramer acetate (GA; Copaxone[®]) are broadly considered first-line immunomodulatory agents. Mitoxantrone (Novantrone[®]), an immunosuppressant and natalizumab (NTZ; Tysabri[®]), a monoclonal antibody against selective adhesion molecules, are both commonly considered as second-line agents. Fingolimod (FTY; Gilenya[®]), an S1P receptor modulator, is the more recent addition to the MS armamentarium and the first oral agent approved in the United States.

Amongst these DMTs, GA stands out with its unique mechanism of action and excellent long-term safety data. It was the first therapy derived from studying the animal model of MS, experimental autoimmune encephalomyelitis (EAE), albeit serendipitously. Originally called Copolymer-1, GA is a random polymer of glutamic acid, lysine,

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alanine, and tyrosine that was intended to be encephalitogenic and induce EAE in mice. In fact, Cop-1 treated mice were found to be resistant to developing EAE, suggesting that the polypeptide was immunogenic but not encephalitogenic [Teitelbaum *et al.* 1971]. This early discovery led to the compound's development in treating MS patients, culminating in its FDA approval in 1996. Now, 15 years later, a large body of evidence from immunologic studies and clinical trials has established that GA is a safe and effective long-term therapy for the treatment of Multiple Sclerosis. There has been greater than one million patient years exposure to GA [Teva Pharmaceutical Industries Ltd, 2010], and the drug is currently the most prescribed DMT in the US MS market. In this review, we discuss proposed mechanisms of action of GA. Then we review efficacy data for reducing relapses and slowing disability as well as long-term safety data. Finally we discuss possible future directions of this unique polymer in the treatment of MS.

Proposed mechanisms of action

Our understanding of the mechanism of action of GA has evolved with our understanding of the immune response. Over the past 40 years there have been several different mechanisms attributed to GA as a means of altering disease expression in MS (Table 1). These include (1) immune deviation by inducing a shift in the cytokine production of responding T cells, (2) generation of bystander suppressor cells, (3) expanding regulatory T-cell function, (4) altering APCs, (5) providing neurotrophic support mediated by brain-derived neurotrophic factor (BDNF) production, and (6) possibly modulating the functional properties of regulatory B cells.

Evidence to support the role of GA in inducing peripheral tolerance stems from its ability *in vitro* to act as an altered peptide ligand that antagonizes T-cell clones specific for MBP 82-100 [Aharoni *et al.* 1999]. Indeed, GA treatment in MS patients leads to an increase in serum interleukin 10 (IL-10), suppression of tumor necrosis factor alpha (TNF- α) mRNA, and an increase in IL-4 and transforming growth factor beta (TGF- β) mRNA in peripheral blood lymphocytes, representing a GA-induced shift in the cytokine environment to one that is less inflammatory [Miller *et al.* 1998]. A second possible mechanism of action of GA involves generating bystander suppressor cells. It has been hypothesized

that T cells would become activated to various peptides present in GA. Then later, when these GA-reactive T cells home to the CNS, they would recognize some myelin antigens as an altered peptide ligand and secrete anti-inflammatory, rather than pro-inflammatory cytokines [Aharoni *et al.* 1997]. A third possible mechanism of action for GA involves expanding regulatory T-cell function. Several studies demonstrated that GA increased Foxp3 expression, a transcription factor that has been used to identify CD4+ regulatory T cells (Treg) [Hong *et al.* 2005]. However, given that almost all activated human T cells express Foxp3 at some point during differentiation [Pillai *et al.* 2007], further work is needed to clarify whether GA responsive CD4+ T cells are the typical differentiated Treg. CD8+ T cells may be another candidate for T regulatory function. GA-naïve MS patients have been shown to have an impaired CD8+ T-cell response to GA [Karandikar *et al.* 2002]. Following GA treatment, MS patients demonstrate an expansion of CD8+ T-cell responses. These CD8+ T cells that responded to GA demonstrate a superior regulatory function when compared with those of GA-naïve MS patients. Thus, it appears that GA corrects a deficit in regulatory CD8+ T-cell function in MS patients that returns to that observed in healthy individuals [Tennakoon *et al.* 2006]. Another possible GA mechanism of action involves altering the ability of APCs to promote pathogenic T-cell differentiation. Monocytes from GA-treated patients, for example, produce lower levels of TNF- α following exposure to lipopolysaccharide (LPS), as compared with monocytes from untreated patients [Weber *et al.* 2004]. Similarly, another investigation showed that GA-treated monocytes produced more IL-10 and less IL-12 compared with monocytes from untreated patients [Kim *et al.* 2004]. Weber and coworkers demonstrated that GA could induce activated monocytes that transfer protection in the EAE mouse model of MS [Weber *et al.* 2007]. A fifth potential mechanism of action currently being explored involves neuroprotection mediated through BDNF. BDNF provides support for survival and differentiation of neurons and glial cells as well as facilitating synaptic plasticity [De Santi *et al.* 2011]. Ziemssen and coworkers demonstrated that *in vitro*, GA has the potential to increase BDNF by human Th1 and Th2 cells [Ziemssen *et al.* 2002]. In the EAE mouse model of MS, transferred GA-reactive T cells migrate to the brain and produce BDNF locally [Aharoni *et al.*

Table 1. Proposed mechanism of action for glatiramer acetate.

	Proposed mechanism of action	References
1	Immune deviation by inducing peripheral immune tolerance	[Aharoni <i>et al.</i> 1999; Miller <i>et al.</i> 1998]
2	Generation of bystander suppressor cells	[Aharoni <i>et al.</i> 1997]
3	Expanding regulatory T-cell function	[Hong <i>et al.</i> 2005; Karandikar <i>et al.</i> 2002; Tennakoon <i>et al.</i> 2006]
4	Altering APC ability to promote pathogenic T-cell differentiation	[Kim <i>et al.</i> 2004; Weber <i>et al.</i> 2004, 2007]
5	Providing neurotrophic support mediated by BDNF production	[Aharoni <i>et al.</i> 2005; Azoulay <i>et al.</i> 2005; Ziemssen <i>et al.</i> 2002]
6	Modulating functional properties of regulatory B cells	[Kala <i>et al.</i> 2010]

APC, antigen-presenting cell; BDNF, brain-derived neurotrophic factor.

2005]. Linker and coworkers recently demonstrated that EAE mice deficient for CNS BDNF manifest a more aggressive disease course and an overall increased axonal loss. Injecting these mice with BDNF led to a less severe disease course and direct axonal protection, implying that BDNF appears to play a functional role in mediating axon protection [Linker *et al.* 2010]. Human GA-treated T cells also have been shown to produce BDNF, possibly providing neurotrophic support to the CNS [Azoulay *et al.* 2005]. Several lines of emerging evidence suggests that B cells have a role in the immunopathogenesis of MS [Boster *et al.* 2010]. Whereas prior studies have focused largely on GAs immunoregulatory functions related to T cells, recent work by Kala and coworkers suggest that GA may also have protective effects in the EAE model of MS through its effects on regulatory B cells [Kala *et al.* 2010]. B cells from GA-treated mice increased production of IL-10, reduced expression of costimulatory molecules and diminished proliferation of myelin oligodendrocyte glycoprotein specific T cells. B cells transferred from GA-treated mice suppressed EAE severity in recipient mice, as well as increasing IL-10 production, inhibiting the proliferation of autoreactive T cells of both Th1 and Th17 phenotypes, and peripheral CD11b(+) macrophages. The number of dendritic cells and regulatory T cells in recipient mice, however, remained unaltered. These results suggest that B cells may be important to the protective effects of GA in EAE and deserve further investigation in both EAE and MS.

Over the last four decades, several possible immunomodulatory mechanisms of action for

GA have been considered. Many of these mechanisms were formulated through EAE, and more recently through sophisticated immunologic investigations. Future studies such as the NIH funded CombiRx trial, which includes genomic and proteomic sub-studies, will hopefully clarify which of these mechanisms is predictive of improved therapeutic outcomes in GA treated MS patients.

Clinical efficacy: relapses

Pivotal trial

Several early GA investigations in MS patients [Bornstein *et al.* 1991; Bornstein *et al.* 1987; Bornstein *et al.* 1982; Abramsky *et al.* 1977] suggested excellent patient tolerability and potential benefit, thereby paving the way for the first large phase III clinical trial. Johnson and coworkers conducted a 2-year, randomized, double-blind, placebo-controlled multicenter trial in 251 patients [Johnson *et al.* 1995]. The mean relapse rate (the study's primary end point) in GA-treated MS patients was reduced by 29% compared with the placebo arm (annualized relapse rate [ARR] GA 0.59 *versus* placebo 0.84; $p=0.007$). Amongst secondary end points, a higher proportion of GA-treated patients remained relapse free (33.6% GA compared with 27% in placebo; $p=0.03$) and time to first relapse while on study trended to favor the treatment arm (287 days for GA, 198 days in placebo, $p=0.097$). (Table 2)

Contemporary clinical trials

Recently, several head-to-head clinical trials examined the efficacy and safety of two different high-dose, high-frequency interferon DMTs

compared with GA. Mikol and coworkers conducted a 96-week randomized, multicenter, parallel-group, open-label study comparing GA ($n=378$) and 40 μg IFNB-1a sq tiw ($n=386$) in relapsing–remitting MS (RRMS) patients diagnosed using the McDonald criteria. There was no significant difference between-groups in time to first relapse, the studies primary end point (hazard ratio [HR] 0.94; 95% confidence interval [CI] = 0.74–1.21; $p=0.64$). It is important to note, however, that relapse rates were lower than expected in both treatment arms [Mikol *et al.* 2008].

O’Conner and coworkers compared two doses of IFNB-1b and GA in 2447 McDonald criteria RRMS patients in a randomized (2:2:1 block design 250 μg IFNB-1b:500 μg IFNB-1b:20 mg GA), prospective multicenter clinical trial (BEYOND trial). No differences between treatment groups were found in the primary end point of relapse risk or in Expanded Disability Status Scale (EDSS) progression. The authors concluded that both doses of IFNB-1b had similar clinical effects as GA despite different adverse event profiles, the tolerability of both GA and IFNB-1b was similar [O’Connor *et al.* 2009].

In an MRI focused comparison, Cadavid and coworkers examined 75 RRMS or clinically isolated syndrome (CIS) patients randomized to either IFNB-1b or GA and imaged monthly for 2 years. They found no between-group differences in the median combined active lesions (CALs) per patient per MRI scan for months 1–12 (IFNB-1b 0.63 *versus* GA 0.58, $p=0.58$), nor were there differences in new lesions or clinical relapses for 2 years. The authors concluded that patients in both groups showed similar MRI and clinical activity [Cadavid *et al.* 2009].

Comi and coworkers examined two different doses of GA (40 mg *versus* 20 mg) in 1155 RRMS patients during a 12-month, double-blind, prospective, parallel-group trial. Using an intent-to-treat analysis, the authors concluded there was no gain in efficacy at the higher dose. Mean ARR (the primary end point) was 0.35 ± 0.99 and 0.33 ± 0.81 in the 40 mg and 20 mg arms, respectively (relative risk [RR] 1.07; 95% CI = 0.88–1.31; $p=0.486$). A total of 77% of patients in both arms remained relapse free. Similarly, both groups demonstrated a reduction in the mean number of gadolinium-enhanced (Gd+) T1 lesions (70% in both) and

new T2 lesions, with a non-statistically significant trend favoring the high-dose arm. Patients tolerated both GA doses well with similar safety profiles [Comi *et al.* 2011].

The ability of early GA treatment to delay onset of clinically definite multiple sclerosis (CDMS) was studied in a 36-month, placebo-controlled, prospective, randomized, double-blind, multicenter trial (Precise trial). A total of 481 patients with CIS (monofocal presentation) and screening MRI scans with ≥ 2 T2 brain lesions (≥ 6 mm diameter) were enrolled. Using an intent-to-treat analysis, GA reduced the risk of developing CDMS (defined as a second clinical attack) by 45% compared with placebo (HR 0.55; 95% CI = 0.40–0.77; $p=0.0005$). The time for 25% of trial patients to convert to CDMS was prolonged 115% (336 days in placebo arm *versus* 722 days in GA arm) [Comi *et al.* 2009].

Combination trials

Glatiramer acetate may represent an ideal candidate for combination therapy to achieve synergistic effects with other DMTs. The combination of IFNB-1a to GA is attractive as their mechanisms may be complementary, a claim that was supported by both early work *in vitro* [Milo and Panitch, 1995] and a pilot study of 33 RRMS patients [Lublin *et al.* 2001]. These encouraging results have led to an ongoing NIH-funded, multicenter, prospective, randomized trial comparing the use of combination IFNB-1a IM and GA *versus* either agent alone in RRMS patients. Another promising combination involves sequential use of mitoxantrone followed by GA ‘maintenance’. Vollmer and coworkers compared 40 RRMS patients with an active screening MRI scan randomized to either three monthly mitoxantrone infusions followed by 12 months of daily GA therapy *versus* 15 months of GA monotherapy. Compared with monotherapy, the sequential combination produced an 89% greater reduction (RR = 0.11; 95% CI = 0.04–0.36; $p=0.0001$) in Gd+ T1 lesions at months 6 and 9 and a 70% reduction (RR = 0.30; 95% CI = 0.11–0.86; $p=0.0147$) at months 12 and 15. Moreover, mean relapse rates were 0.16 in the combination group, compared with 0.32 with GA monotherapy. Both treatment arms were well tolerated [Vollmer *et al.* 2008; Ramtahal *et al.* 2006]. Another combination study demonstrated the safety of GA with monthly NTZ in 110 RRMS patients over a period of 6 months (GLANCE trial) [Goodman *et al.* 2009]. Metz and

Table 2. Multiple sclerosis clinical trials with glatiramer acetate: relapse rate.

Trial	Design	N	MS type	Key outcome measures	References
Pivotal	2 year, DB, PC, MC	251 GA:PCBO	Posner RRMS	ARR: GA 0.59 <i>versus</i> PCBO 0.84; $p = 0.007$ (29% reduction)	[Johnson <i>et al.</i> 1995]
REGARD	96-week, OL, PG, MC	764 randomized 1:1 GA:IFNB-1a sq tiw	McDonald RRMS	No between-group differences in ARR [HR 0.94; 95% CI 0.74–1.21; $p = 0.64$] Note: ARR lower than expected in both arms	[Mikol <i>et al.</i> 2008]
BEYOND	MC	2447 randomized 2:2:1 250 µg IFNB-1b:500 µg IFNB-1b:GA	McDonald RRMS	No between-group differences in relapse risk or EDSS progression	[O'Connor <i>et al.</i> 2009]
FORTE	1 year, DB, PG	1155 Randomized 1:1 GA 20 mg: GA 40 mg	McDonald RRMS	ARR: 0.35 ± 0.99 for 40 mg <i>versus</i> 0.33 ± 0.81 for 20 mg (RR 1.07; 95% CI 0.88–1.31; $p = 0.486$)	[Comi <i>et al.</i> 2011]
PRECISE	36 month, DB, PC, MC	481 Randomized 1:1 GA <i>versus</i> PCBO	Monofocal CIS with +MRI scans	GA reduced risk of CDMS by 45% <i>versus</i> PCBO (HR 0.55, 95% CI 0.40–0.77; $p = 0.0005$)	[Comi <i>et al.</i> 2009].
GA after induction with Mitoxantrone	15 month, OL	40 Randomized 1:1 mitoxantrone IV q month x 3 then GA x 12 months <i>versus</i> GA alone x 15 months	McDonald RRMS with active MRI	89% greater reduction in Gd+ lesions at months 6 and 9 (RR 0.11, 95% CI 0.04–0.36; $p = 0.0001$) 70% reduction at months 12 and 15 (RR 0.30, 95% CI 0.11–0.86; $p = 0.0147$) ARR: combo group 0.16 <i>versus</i> GA monotherapy 0.32	[Ramtahal <i>et al.</i> 2006; Vollmer <i>et al.</i> 2008].
					(continued)

Table 2. Continued.

Trial	Design	N	MS type	Key outcome measures	References
GLANCE	6 month, phase II, DB, PC	110 randomized 1:1 GA + NTZ versus GA alone	RRMS	Combo resulted in less MRI activity (new active, new Gd+, new/enlarging T2) Combination was safe	[Goodman <i>et al.</i> 2009]
GA in combination with minocycline	9 month, DB, PC, MC	44 randomized 1:1 GA + minocycline versus GA alone	RRMS	Combo improved MRI Trend favoring combo to decreased risk of relapse	[Metz <i>et al.</i> 2009]
DB, double blind; PC, placebo controlled; MC, multicenter; OL, open label; PG, parallel group; ARR, annualized relapse rate; PCBO, placebo; HR, hazard ratio; RR, relative risk; CI, confidence interval; GA, glatiramer acetate; Combo, combination therapy group; Gd+, gadolinium-enhanced T1 MRI lesion; RRMS, relapsing–remitting multiple sclerosis; NTZ, natalizumab; IFNB, interferon beta; CIS, clinically isolated syndrome; EDSS, Expanded Disability Status Scale; CDMS, clinically definite multiple sclerosis.					

coworkers studied the addition of minocycline, an antibiotic with immunomodulatory properties, plus GA compared with GA alone in a double-blind, placebo controlled study of 44 RRMS patients. The combination resulted in significantly lower number of MRI lesions and demonstrated a nonsignificant trend favoring decreased risk of relapse, as compared with GA alone [Metz *et al.* 2009]. It is reassuring that GA is well tolerated and appears synergistic in these early investigations.

Clinical efficacy: progression of disability

The clinical investigations reviewed above demonstrate that GA is moderately effective in reducing inflammatory disease activity, as measured by reductions in relapse rates, T2 and Gd+ T1 MRI lesions. The evidence for GA to delay long-term disability, however, is less clear. A meta-analysis of three randomized, double-blind, placebo-controlled trials (*n* = 540) concluded that GA decreased pooled adjusted ARR as well as decreased accumulated disability (RR 0.6; 95% CI = 0.4–0.9; *p* = 0.02) [Martinelli Boneschi *et al.* 2003].

A more recent Cochran meta-analysis, however, concluded that GA had no effect on MS disease progression [Munari *et al.* 2004]. Their conclusion was consistent with results from a prospective, randomized, placebo-controlled trial of 943 primary progressive MS (PPMS) patients (PROMiSe Trial) that failed to show a treatment effect of GA to slow disease progression (HR 0.87; 95% CI = 0.71–1.07; *p* = 0.175). This result must be interpreted cautiously, however, given that both low event rates and premature study-termination limited the study’s power to find such an effect. Also of note, a *post hoc* analysis suggested GA slowed clinical progression in men with PPMS (HR 0.71; 95% CI = 0.53–0.95; *p* = 0.0193) [Wolinsky *et al.* 2007].

Given the long-term nature of MS, brief (often 2 years long) clinical trials may be inadequate to capture the effect of GA on long-term disability, explaining the variable results described above. As such, we may need to turn to open-label extensions of phase III trials (long-term follow up [LTFU]) and population-based studies to assess the ability of GA to delay disease progression. Recently, Ford and coworkers published a 15-year follow up to the pivotal phase III GA trial by Johnson and coworkers, creating the longest

continuous evaluation of a DMT in MS. They defined the modified intent-to-treat group (mITT) as the 232 patients who received at least one GA injection during the pivotal trial. The ongoing cohort represents the 100 (43%) patients in the mITT group that were prospectively followed with bi-annual EDSS evaluations from 1991 until February of 2008. Annualized relapse rates in the ongoing cohort declined from 1.12 ± 0.02 the year before starting GA to 0.2 ± 0.34 at the 15-year analysis. EDSS only changed by 0.6 ± 2.0 points over 15 years in the ongoing cohort, including 57% of ongoing patients whose EDSS remained stable or improved (change ≤ 0.5 points). The proportion of the ongoing cohort to reach EDSS of 4, 6, and 8 was 38%, 18%, and 3%, respectively. Moreover, 75% of the ongoing patients had not transitioned to secondary progressive (SPMS). The authors conclude that MS patients with mean disease duration of 22 years who received GA for up to 15 years had reduced relapse rates, decreased disability progression, and fewer transitions to SPMS [Ford *et al.* 2010]. Several limitations necessitate careful interpretation of Ford's results however. These limitations include the open-label design, lack of a control group, possible selection bias favoring 'GA super-responders' in the ongoing cohort, a large percentage of drop outs, and unblinded assessments. Limitations notwithstanding, this long-term data suggests that GA may slow MS disease progression as compared with natural history data [Weinshenker *et al.* 1989].

Miller and coworkers reported on 46 RRMS patients treated with GA for up to 22 years (median 12 years) in a prospective, open-label, compassionate-use study where EDSS was measured every 6 months. Mean EDSS increased 0.9 ± 1.9 from a pretreatment score of 3.0 ± 1.8 ($p = 0.076$). Only 36% (10/28) of patients had a baseline EDSS of <4.0 increased to ≥ 4.0 at last observation. Similarly, only 24% (8/34) patients with baseline EDSS of <6.0 increased to ≥ 6.0 at last observation. A total of 57% of patients had unchanged or improved EDSS scores. Of the 18 remaining patients at the time of publication, 17% with baseline EDSS <4.0 reached EDSS ≥ 4.0 and 28% with baseline <6.0 reached EDSS ≥ 6.0 . The authors readily point out that the trial design precludes definite conclusions about efficacy. Beyond the open-label design, limitations that must be considered include the small number of patients, possible selection bias

for 'GA super-responders', unblinded evaluations and a GA formula change during the course of the investigation. Nonetheless, the study suggests a low disability progression for these GA patients over a 22-year period of prospective observation [Miller *et al.* 2008].

Recently, Veugelers and coworkers reported on 1752 MS patients followed from 1980 to 2004 at a regional MS clinic serving the entire population of Nova Scotia, Canada. Using survival methods, they observed a significant reduction in EDSS progression following the introduction of DMTs in July 1998. Prior to this date, estimated median progression time from MS symptom onset to EDSS 6 was 14.4 (95% CI = 12–17.4) years. After this date, the estimated time was 18.6 (95% CI = 5.9–21.9) years. A Cox proportional hazard analysis, after adjusting for confounders, revealed a relative HR of 0.44 (95% CI = 0.35–0.55), supporting the claim that patients in this population progressed faster in the epoch prior to initiation of DMTs. Further analysis examined the posttreatment annual EDSS progression rates (relative to pretreatment progression) among 742 RRMS patients in the clinic, including 162 who were treated with GA. Compared with pretreatment rates, the relative progression was significantly lower after starting GA (relative progression: 0.89; 95% CI = 0.81–0.97). Again, several limitations of this investigation necessitate careful interpretation of its results, including the open-label and uncontrolled design, the lack of randomization and unblinded evaluations. The authors suggest that evaluations of 'real-world' clinic settings may help complement brief randomized controlled trials in establishing the efficacy of DMTs to slow disease progression [Veugelers *et al.* 2009].

Surrogate MRI markers that correlate with disability may also shed light on the ability of GA to influence disease progression. These markers include T1 hypo-intensities, brain atrophy, diffusion weighted imaging, and MR spectroscopy. Chronic T1 hypo-intensities or 'black holes' represent axonal loss and extracellular matrix destruction [van Waesberghe *et al.* 1999] and correlate with changes in long-term disability [Tam *et al.* 2011]. Fillipi, Comi and coworkers examined the effect of GA on black hole development in a *post hoc* analysis of 239 MS patients who participated in the placebo-controlled clinical trial [Comi *et al.* 2001] involving monthly

MRI scans. GA-treated patients had a lower percentage of new lesions that evolved into T1 'black holes' as compared with placebo patients on MRI scans performed at 7 months (18.9% *versus* 26.3%; $p=0.04$) and 8 months (15.6% *versus* 31.4%; $p=0.002$) following lesion appearance [Filippi *et al.* 2001]. More recently, Cadavid and coworkers studied conversion rates of acute black holes (ABHs) to chronic black holes (CBHs) in 75 patients who received monthly MRI scans for up to 2 years while randomized to either IFNB-1b or GA in the BECOME study. The conversion from ABHs to CBHs was 15.2% with IFNB-1b and 21.4% with GA ($p=0.06$). The authors concluded that only a minority of new brain lesions in MS patients taking GA or IFNB-1b convert to CBHs [Cadavid *et al.* 2009].

Brain atrophy, which is accelerated in MS, has also been shown to correlate with MS disease progression [Fisher *et al.* 2000]. As eloquently reviewed by Rovaris and colleagues elsewhere [Rovaris *et al.* 2005], data supporting the effect of GA on preventing MS-related brain atrophy are conflicted and dedicated studies of adequate duration are likely required.

Khan and coworkers studied the effects of GA on brain proton magnetic resonance spectroscopy (^1H -MRS), a nonconventional MRI technique that allows examination of axonal integrity *in vivo* by quantifying the neuronal marker N-acetylaspartate (NAA). At 2 years, GA-treated patients had a 10.7% increase in NAA/Cr in the voxel of interest (VOI; $p=0.03$) and a 71% increase in the normal appearing white matter (NAWM; $p=0.04$). This was compared with an untreated group of patients, where NAA/Cr decreased by 8.9% in the VOI ($p=0.03$) and by 8.2% in the NAWM ($p=0.03$) [Khan *et al.* 2005]. At year four, they found that compared with baseline, GA-treated patients had a 12.7% increase in the NAA/Cr ratio ($p=0.03$) [Khan *et al.* 2008].

Although there is no class I evidence that GA slows progression, this may be in part because those trials were not constructed in a way to determine such an effect. A review of the LTFU and population-based data, as well as MRI correlates to disability progression, which may be more sensitive to detect such an effect, provides some support for this claim. At present, the question remains unsettled in the medical

literature and there is a clear need for better designed clinical trials.

Safety and tolerability

Glatiramer acetate received FDA approval in 1996 and has been used for over two decades in some countries. The test of time has proven its significant safety and tolerability profile (Table 3). The most common side effect, occurring in 80% of patients, is local injection site reaction experienced as erythema and pruritus. Around 10–15% of GA-treated patients experience a generally isolated postinjection reaction (IPIR) experienced as chest tightness, shortness of breath, palpitations, anxiety and flushing lasting 15–30 minutes. These frightening reactions have not been associated with any cardiovascular or other systemic consequences in the more than 20 years since its first description [PDR Network, 2010]. They are not considered dangerous but require that the clinician provide proper patient education and reassurance. No drug–drug interactions have been reported with GA therapy. Unlike IFNs, NTZ, and FTY, GA does not cause liver function abnormalities, leukopenia, or thyroid disease [Kieseier and Stuve, 2011; Plosker, 2011; Cohen *et al.* 2010; Polman *et al.* 2006]. An increase in spasticity, depression, and fatigue, which may be seen with IFNB use, has not been associated with GA [Meca-Lallana *et al.* 2010; Simone *et al.* 2006]. Neutralizing antibody development (NAB), which has been associated with treatment failure in patients treated with IFNB and NTZ, does not appear to be a concern with GA therapy [Karussis *et al.* 2010]. Perhaps most importantly, GA is unique in its nonimmunosuppressant mechanism of action. This is unlike IFNB injections (which induce systemic and intrathecal immunosuppressive cytokines) [Rudick *et al.* 1998], NTZ (which functions as a compartmental immunosuppressant) [Rudick and Sandrock, 2004], or FTY (which may function as a reversible functional immunosuppressant) [Cohen *et al.* 2010]. It is also significant that there have been no reported deaths associated with use of GA [Ford *et al.* 2010].

Pregnancy

The FDA assigns categories to drugs based on risk of use during pregnancy. Of the currently approved therapies, mitoxantrone, NTZ, FTY and IFNB are all considered pregnancy category C, defined as 'no human studies are available and adverse fetal effects have been shown in animals' [PDR Network, 2002]. Only GA is considered

Table 3. DMT side effects.

DMT/indications	Usual dose	Main adverse effects	References
IFNB-1a (Avonex [®]) CIS, RRMS, SPMS IFNB-1a (Rebif [®]) CIS, RRMS, SPMS IFNB-1b (Betaseron) CIS, RRMS, SPMS	30 µg IM once weekly 44 µg SC 3 times per week [22 or 44 µg doses available] 250 µg SC every other day	IFN class: – Flu-like symptoms – Injection-site reactions (SC administration) – Laboratory abnormalities (liver enzymes, white blood cell count, red blood cell count, platelets, thyroid function); – Depression – Neutralizing antibodies – Pregnancy category C – Injection-site reactions – Systemic reactions/IPIR (chest tightness tachycardia, flushing, dyspnea) – Pregnancy category B – Infusion reactions – PML – Hepatotoxicity – Neutralizing antibodies – Pregnancy category C – Bradycardia, heart block – Increased intraocular pressure – Infection – Neoplasms – Hepatotoxicity – Leukopenia, lymphopenia – Dyspnea – Pregnancy category C – Cardiomyopathy – Treatment related leukemia – Infection risk – Alopecia – Amenorrhea – Maximum lifetime dose - pregnancy category D	[The IFNB Multiple Sclerosis Study Group, 1993; PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group, 1998]
Glatiramer acetate (Copaxone [®]) CIS, RRMS	20 mg SC/day		[Comi et al. 2001; Johnson et al. 1995]
Natalizumab (Tysabri [®])	200 mg IV q4wks		[Polman et al. 2006; Rudick et al. 2006]
Fingolimod (Gilenya [®])	0.5 mg po qd		[Cohen et al. 2010; Kappos et al. 2010]
Mitoxantrone (Novantrone [®])	Variable per protocol IV		[Hartung et al. 2002]

DMT, disease-modifying therapy; IFN, interferon; PML, progressive multifocal leukoencephalopathy; IPIR, immediate postinjection reaction.

category B, defined as ‘no controlled human studies are available but animal studies show either no risk or minimal risk to the fetus’. Whereas GA use is not generally endorsed during pregnancy, it is reassuring that several recent observations report no negative effects to mother or fetus [Fragoso *et al.* 2010]. It is also relevant that GA may be preferred over IFNB by women in the postpartum period with any history or predisposition to depression.

Cost

The introduction of immunomodulatory biologic agents for MS has helped to change the course of the disease. Under budgetary constraints, health services payers are challenged to differentiate the economic value of these agents for formulary selection and/or placement in determining consumption options for subscribers. This is a complex task and available medical literature is incomplete. One analysis by Goldberg and coworkers examined the 2-year cost-effectiveness of four first-line RRMS DMTs (GA, IFNB-1a IM injection, IFNB-1a SC injection, and IFNB-1b SC injection), finding 2-year reductions in disability progression steps to be 0.05, 0.15, 0.12, and 0.11, respectively. GA was among the top three baseline therapies, having the most favorable costs per relapse avoided. Relapses avoided and prevention in disability progression steps were used to calculate the medical savings, assuming a cost per relapse of US\$4682 and a cost per progression of disability step of US\$1788, with the primary end point cost per relapse avoided [Goldberg *et al.* 2009]. Becker and Dembeck recently reanalyzed Goldberg and colleagues’ data, challenging the data selection criteria used. In their reanalysis they concluded that IFNB-a1 IM was more cost-effective than originally analyzed, while the other DMTs (GA included) remained stable [Becker and Dembek, 2011]. Rajagopalan and coworkers examined direct and indirect costs, absences, medical costs, and utilization by place of service in 153 employees with RRMS from a healthcare claims database. The authors concluded that IFNB-1a and IFNB-1b users had significantly greater reductions in sick leave costs after therapy initiation compared with GA and IFNB-1a SC [Rajagopalan *et al.* 2011]. Shadow costs incurred in association with therapies, such as additional treatment for associated side effects as well as compulsory laboratory monitoring must also be considered, weigh favorably with GA. Using evidence from long-term published studies,

Earnshaw and coworkers derived the cost-effectiveness from the US healthcare and societal perspectives of GA and NTZ relative to symptomatic management alone in RRMS patients. They determined the lifetime direct medical costs of GA, NTZ and symptomatic management US\$408,000, US\$422,208, and US\$341,436, respectively. Patients on DMTs had more years in EDSS 0.0–5.5 (GA 1.18 and NTZ 1.09, respectively), more years relapse free (GA 1.30 and NTZ 1.18), and more quality adjusted life years (QALYs; GA 0.1341 and NTZ 0.1332). Compared with symptomatic management, the incremental cost per QALY was US\$496,222 for GA or US\$606,228 for NTZ. The authors concluded that both DMTs are associated with increased benefits compared with exclusive symptomatic management and that GA was associated with a cost saving compared with NTZ [Earnshaw *et al.* 2009]. Although findings differ in determining which therapy is the most cost-effective, studies do support that medical costs are reduced overall in treatment adherent MS patients.

Summary

The current MS therapeutic landscape is rapidly growing. The eight currently FDA-approved therapies (GA, four IFNB products, NTZ, mitoxantrone, and FTY) will soon be joined by up to three novel oral agents that all had positive phase III clinical trials in the past year. These include teriflunimide [Sanofi-Aventis, 2010], laquinimod [Teva Pharmaceutical Industries Ltd, 2011] and BG-12 [BiogenIdec, 2011]. Several promising monoclonal antibodies are soon to complete phase III trials as well, such as alemtuzumab, dacluzimab, and ocrelizumab. Whereas more choices are a boon for MS patients, clearly diagnostic algorithms and prognostic indicators must evolve as we learn how to best position each one of these products for optimal treatment of MS.

Glatiramer acetate remains unique among this growing list of MS therapeutics given its unique and nonimmunosuppressive mechanism of action as well as its superior long-term safety data and sustained efficacy data. For these reasons GA will likely remain a viable first-line option for RRMS patients. The LTFU data suggests that some patients are ‘GA super-responders’ and we expect that in the not-so-distant future proteomic and genomic data will help identify these ‘super-responders’ *a priori*. Given

encouraging results from early forays into GA in combination, it will likely also find a position in conjunction with other drugs as add on therapy. Lastly, as treatment algorithms shift from an 'escalation model' to an 'induction and maintenance model' as commonly applied in oncology, GA will be a viable 'maintenance' therapy following treatments such as cyclophosphamide, mitoxantrone, and alemtuzumab.

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Conflict of interest statement

Dr. Boster has received honoraria from TEVA Neuroscience for speaking and consulting.

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