Long-term Experience of Glatiramer Acetate (Copaxone®) in the Treatment of Clinically Isolated Syndrome and Relapsing–Remitting Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is a chronic, disabling condition with severe clinical and social consequences. Glatiramer acetate (GA) has been widely used for more than 15 years as a first-line disease-modifying agent in the treatment of relapsing–remitting MS (RRMS). It appears to have multiple modes of action, including the induction of GA-reactive T-helper 2 (Th2) immunoregulatory cells and the stimulation of neurotrophin secretion in the central nervous system, which may promote neuronal repair. Clinical trial data show that GA reduces the relapse rate in RRMS, can delay or halt disability progression, and brings about improvement in magnetic resonance imaging (MRI) measures of disease activity, including reduction of brain atrophy. Early treatment with GA can reduce the risk of developing clinically definite MS in patients with clinically isolated syndrome. Furthermore, it has an excellent safety and tolerability profile. Recent data from patients treated for 15 years have indicated that more than half of the patients on long-term GA therapy have stable or improved disability scores.

As a chronic disease of the central nervous system (CNS), multiple sclerosis (MS) is characterized by a complex interplay between inflammation, demyelination, remyelination, gliosis, and neuronal injury.[1] It continues to be a major cause of acquired neurologic disability in young adults worldwide, particularly in people of northern European origin.[2] It affects women with twice the frequency of men and the average age of diagnosis is 37 years.[3] The worldwide total estimated prevalence for the past three decades is 83 cases/100,000 population.[4]

The clinical course of MS is heterogeneous, with variability both between and within patients, and has been categorized as clinically isolated syndrome (CIS), relapsing–remitting MS (RRMS, which accounts for 85 % of MS patients in the initial disease course), primary progressive MS (PPMS), and secondary progressive MS (SPMS).[5,6] RRMS is characterized by relapses, symptoms of which include numbness, blurred vision, difficulty walking, fatigue, and pain. Symptoms are usually temporary and are followed by periods of remission.[6]

The immunopathogenesis of MS is thought to be heterogeneous; however, the inflammatory demyelinating plaque is characteristic of all forms of MS.[7] Immune-mediated injury to myelin and oligodendrocytes may occur when peptides in myelin attach to the cleft of major histocompatibility complex (MHC) class II molecules on antigen-presenting cells (APCs) including macrophages, monocytes, and dendritic cells.[8] Activation of APCs can trigger an immune response against the bound antigen and leads to secretion of pro-inflammatory cytokines and the differentiation of naïve CD4+ T cells into T-helper 1 (Th1) and T-helper 17 (Th17) cells, resulting in inflammation and autoimmunity. Th1 and Th17 cells are capable of migration into the CNS and have been identified in active lesions.[9,10] Th1 cells undergo continued proliferation and secretion of pro-inflammatory cytokines, leading to myelin damage and neuronal loss. Further activation of resident microglia can lead to cross-reactivity, which maintains inflammation and further damage to the myelin sheath.[11] Impaired function of regulatory T cells (Tregs), which act against autoimmunity, allows further pathologic activation of autoreactive T cells and exacerbates the feedback loop that causes continual damage to the CNS.[12] Additionally, activated B cells appear to be participants in the creation of myelin lesions by producing antibodies that mediate and promote demyelination.[13]

MS represents a considerable therapeutic challenge, because of its significant heterogeneity and unpredictable clinical course. Glatiramer

acetate (GA; Copaxone®, co-polymer 1) was first tested in clinical trials in the mid-1980s and approved by the US Food and Drug Administration (FDA) for the treatment of RRMS in 1996; previously, therapies had been limited. GA is a mixture of synthetic peptides composed of random sequences of four amino acids (tyrosine, glutamate, alanine, and lysine) in a defined molar ratio with a length of 40–100 residues, and is structurally similar to myelin basic protein (MBP), a major component of myelin.[14] It is administered as a daily subcutaneous (sc) injection (20 mg).

Since its introduction, GA has been widely used as a first-line disease-modifying agent in RRMS. Extensive experience on its efficacy and safety has been gained in regular clinical use. A number of clinical studies and analyses have identified the short- and long-term benefits of GA (and other first-line disease-modifying agents such as interferon beta-1a [IFNβ-1a] and interferon beta-1b [IFNβ-1b]) in reducing relapses, disability progression, and the development of new magnetic resonance imaging (MRI) lesions. This article will review the long-term efficacy and safety data of GA.

Glatiramer Acetate Mechanism of Action

The mechanism of action of GA differs from other available treatments for MS. It is thought to produce anti-inflammatory effects mainly by functional inhibition of MBP-reactive T lymphocytes and induction of T-helper 2 (Th2) lymphocytes in the CNS. The clinical immunomodulatory effect of GA was originally believed to result from a change in T-cell differentiation, cytokine secretion in CD4+ cells, and an increase in regulatory B-cell properties.[15–17] Subsequent findings from clinical studies and animal models indicated that GA has more widespread immunomodulatory actions on cells of both the innate and adaptive immune systems.

GA has been demonstrated to downregulate the expression of interleukin (IL)-17 and IL-6 in animal models of MS and in peripheral blood mononuclear cells from patients with MS, modulating the inflammatory response from Th1 and Th17 cells.[17–19] Furthermore, GA therapy has been found to induce CD8+ T-cell responses in patients with MS.[20]

Recent evidence suggests multiple mechanisms of action for GA that include possible neuroprotective and/or neuroregenerative effects.[21,22] The secretion of neurotrophic factors, including brain-derived neurotrophic factor (BDNF) and insulin growth factor (IGF), may promote neuronal repair.[23,24]

Multiple Sclerosis Therapy with Glatiramer Acetate
Clinical Trial Data

The first clinical study of GA was a double-blind, randomized, placebo-controlled Phase II trial of patients (n=50) with RRMS receiving either daily injections of 20 mg GA or placebo for two years. Two-year average relapse rates were 0.6 and 2.7 per patient in the GA and placebo groups, respectively.[14]

In the first Phase III multicenter, double-blind, placebo-controlled trial (n=251) of GA, patients were randomized to receive GA (n=125) or placebo (n=126) for two years. The primary endpoint was a difference in the MS relapse rate. The final two-year relapse rate was 1.19 ± 0.13 for patients receiving GA and 1.68 ± 0.13 for those receiving placebo,

a 29 % reduction in favor of GA (p=0.007) (annualized rates [ARR] = 0.59 for GA and 0.84 for placebo). Furthermore, 33.6 % of patients receiving GA and 24.6 % receiving placebo were relapse-free. In an evaluation of disability as measured by the expanded disability status scale (EDSS), significantly more patients receiving GA showed improvement and more receiving placebo worsened (p=0.037).[25] A blinded extension of this study from one to 11 months (mean: 5.4 months GA group, 5.9 months placebo group) confirmed the sustained efficacy in terms of relapse rate and disability progression, high tolerance, and safety profile of GA.[26]

The trial was further extended as an open-label study,[27] as discussed below in the section entitled 'Long-term Studies.' This trial and its extension now constitute the longest continuous evaluation of a disease-modifying drug (DMD) in MS and show continued benefits in terms of decreased relapse rates, decreased disability progression, and decreased transition to SPMS.

Magnetic Resonance Imaging Studies

MRI provides a useful measure of inflammation and neurodegeneration in MS. MRI studies indicated that GA has a favorable effect on tissue disruption in MS lesions once they are formed.[28]
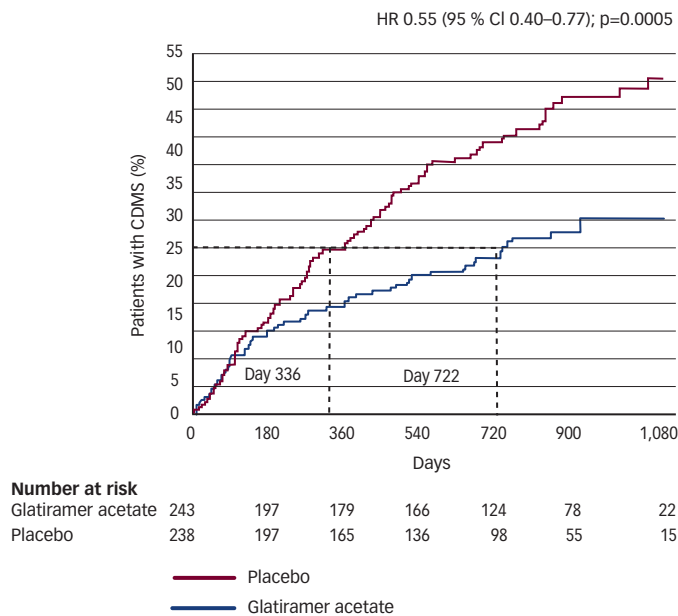
A large study in Europe and Canada randomized 239 patients with RRMS to either GA or placebo and obtained monthly brain MRI scans for nine months, followed by an open-label extension for nine months. The primary outcome measure, the mean number of gadolinium (Gd)-enhancing lesions, showed a 29 % reduction at nine months in the GA-treated group compared with placebo (p=0.003). Secondary outcomes, including the number of new enhancing lesions, the volume of enhancing lesions, and the changes in the volume and number of T2-weighted images, were also significantly reduced by treatment with GA.[29] Compared with placebo, GA reduced by 50 % the proportion of new MS lesions evolving into chronic black holes over an eight-month period (p=0.002).[28]

MRI lesion reduction is only a robust measure of treatment efficacy if the effect is homogeneous across patients. In an analysis of the European/Canadian trial data,[29] lesion reduction owing to treatment was estimated to range between 20 and 54 % in 95 % of the patients, indicating that GA has a homogeneous effect on MRI-measured disease activity in RRMS.[30]

The assessment of brain volume changes on MRI scans can provide a measure of progressive atrophy reflecting the neurodegenerative aspects of MS pathology. This was first demonstrated by use of the structural Image evaluation, using normalization, of atrophy (SIENA) technique to show less brain volume loss in GA-treated patients compared with placebo in the GA European/Canadian trial.[31] Recent five-year data indicated that GA (20 mg sc daily), low-dose IFNβ (Avonex®, 30 μg intramuscular [im] weekly), and high-dose IFNβ (Betaseron®, 250 μg sc every other day) significantly reduced the loss of brain volume in MS compared with no treatment (p<0.0001). The GA-treated group experienced a smaller loss in brain volume over five years, compared with the IFNβ-treated groups.[32] In the Rebif versus glatiramer acetate in relapsing MS disease (REGARD) trial, GA significantly reduced brain atrophy compared with IFNβ-1a.[33]

Although no significant difference in percentage brain volume change was found during the nine-month double-blind phase of the European/Canadian

Figure 1: Graph Depicting the Risk of Progressing to Clinically Definite Multiple Sclerosis with Glatiramer Acetate versus Placebo

HR 0.55 (95 % CI 0.40–0.77); p=0.0005

Number at risk

Glatiramer acetate	243	197	179	166	124	78	22
Placebo	238	197	165	136	98	55	15

— Placebo
— Glatiramer acetate

Kaplan–Meier curves with Cox's proportional hazard ratio were used to model the amount of time for conversion to clinically definite multiple sclerosis (CDMS) for patients assigned to glatiramer acetate (GA) and placebo. There was a delay of 386 days (115 %) in conversion to CDMS for first-quartile patients receiving GA compared with those receiving placebo. CI = confidence interval; HR = hazard ratio. Source: Comi et al., 2009.[35]

trial, there was a significantly lower mean percentage brain volume change in GA patients during the open-label extension.[29] Similarly, recent five-year data from the study to evaluate early GA treatment in delaying conversion to clinically definite MS (CDMS) of subjects Presenting with CIS (PRECISE) trial have shown a reduction in brain atrophy after five years, although this was not observed in the initial randomized phase.[34]

Effect of Early Treatment with Glatiramer Acetate

Early treatment with GA has been found to reduce the risk of developing CDMS compared with placebo. In the randomized, double-blind PRECISE trial (n=481), patients presenting with CIS with unifocal manifestation, a first event suggestive of MS, and two or more T2-weighted brain lesions measuring 6 mm or more, were randomly assigned to receive either GA (n=243) or placebo (n=238) for up to 36 months, unless they converted to CDMS. The primary endpoint was time to CDMS, based on a second clinical attack. GA was found to reduce the risk of developing CDMS by 45 % compared with placebo (hazard ratio 0.55, 95 % confidence interval [CI] 0.40–0.77, p=0.0005). The time for 25 % of GA-treated patients to convert to CDMS was prolonged by 115 % compared with placebo, from 336 to 722 days (see *Figure 1*).[35]

Recently, five-year data from the PRECISE trial have been reported. Most of the patients from the randomized trial (85 %), entered the open-label phase of the study and 60 % completed an average of 4.3 years of follow-up. GA reduced the risk of conversion from CIS to CDMS by 41 % compared with placebo (hazard ratio 0.59, p=0.0005). The percentage of brain volume change during the entire observation period was significantly lower in patients treated early, an effect that was not seen in the earlier phase of the study.[34] These findings have led to suggestions

that GA should be increasingly used for CIS patients with MRI results showing multifocal lesions.

Comparison of Glatiramer Acetate and Interferon Beta Treatments

Head-to-head comparison trials have so far shown largely similar efficacy between IFNβ treatments and GA. In the first multicenter, randomized parallel open-label trial to directly compare GA and IFNβ-1a in RRMS (n=764, REGARD trial), no significant differences were observed between the two drugs in the study endpoints, which included time to first relapse and change in the volume of T2 and contrast-enhancing MRI lesions.[33]

Similar clinical effects between GA and IFNβ-1b were also observed in the Betaferon efficacy yielding outcomes of a new dose (BEYOND) trial (n=2,244), in which outcome measures included relapse risk, the proportion of relapse-free patients, time to first relapse, disability accumulation, and most MRI parameters.[36] A further head-to-head trial (Betaseron versus copaxone in multiple sclerosis with triple-dose gadolinium and 3 Tesla MRI endpoints [BECOME] study, n=75) comparing IFNβ-1b and GA identified similar MRI clinical activity between the treatments.[37]

Switching from Other Therapeutic Agents to Glatiramer Acetate

Switching to GA may be beneficial in patients with RRMS who have an inadequate response to other first-line immunomodulatory therapy (IFNβ-1a or IFNβ-1b). A prospective, open-label study found that prior IFNβ-1b treatment does not negatively influence the efficacy, safety, or tolerability of subsequent GA therapy.[38] In another study, patients were switched from IFNβ-1a to GA because of persistent clinical disease activity or persistently unacceptable toxicity as determined by the treating neurologist. Switching from IFNβ-1a to GA reduced the mean ARR from 1.23 to 0.53 (p=0.0001).[39] In a further study, in a patient cohort three years after switching from IFNβ-1b to GA, the ARR fell by 57–78 %.[40]

The Coptimize study is a longitudinal study assessing disease course, characteristics, and reason for switching and has recruited RRMS patients switching from any MS drug to GA. To date, 144 clinics in 19 countries have contributed data from 637 patients. After 12 months of switching there was a 65 % reduction in ARR after switching to GA (n=155, p<0.0001) and EDSS was stable during the whole period.[41]

Some investigators have recently reported the successful switching to GA of MS patients who were receiving natalizumab and tested positive for John Cunningham (JC) virus antibodies.[42] Changing therapy maintained efficacy and no progressive multifocal leukoencephalopathy (PML) cases were reported following the switch. Further studies on a group of 35 patients switching from natalizumab to GA are in progress.

In an Italian study, 23 patients with RRMS who discontinued natalizumab after 12–18 months' treatment were switched to GA 20 mg/day, which they received for at least six months to a maximum of 12 months.[43] The low ARR established during the natalizumab treatment was maintained during GA treatment (0.42 ± 0.7/year) and EDSS was stable in all patients. On MRI scanning, patients showed some evidence of disease

reactivation, but not of disease evidence of rebound (four or five new lesions maximum). Overall, GA was considered to be an effective and safe option for MS patients who are discontinuing natalizumab therapy.

Adherence, Safety, and Tolerability of Glatiramer Acetate Treatment

Studies have indicated that GA has a favorable safety profile compared with the other DMDs for MS. Unlike IFNβ, GA does not cause liver function abnormalities, leukopenia, or thyroid disease and is not associated with depression. The influenza-like symptoms characteristic of IFNβ treatment do not occur with GA.[33]

GA is the only therapy to be given a category B pregnancy classification, meaning that although no adverse effects have been found in animal studies, no adequate studies have been carried out in pregnant women to demonstrate its safety in humans. Other MS treatments are at least category C or D. A recent prospective study showed that 13 of 14 pregnancies resulted in live births, with GA treatment throughout pregnancy for nine of the women.[44]

Long-term safety data indicate that adverse effects known to be related to GA therapy are consistent with known side effects of GA administration. These include local injection-site reactions, such as erythema, pain, and lipoatrophy,[45,46] and symptoms associated with a rare self-limited post-injection reaction, which include vasodilatation, chest pain, tachycardia, palpitation, or dyspnea. However, these systemic reactions are transient and self-limited.[45,46] There have been no reported incidents of hematologic, hepatic, or renal dysfunction, immunosuppression, malignancy, or other autoimmune disorders.[27] GA is also the only therapy that does not require any continued laboratory monitoring or further specialist studies. IFNβ administration still requires blood counts, liver functions, and antibody detection.

A recent study in the US aimed to determine the predictors of adherence to GA treatment among 146 patients with MS who were treatment-naive (TN) and 88 who were treatment-experienced (TE).[47] During a 12-week treatment period there was no difference between the groups in adherence (86 % in both groups). The predictors of adherence, however, were different. For TN patients these factors were greater functional self-efficacy, higher self-injection competence at baseline, and improvement in self-injection competence over the first month of therapy. For TE patients, the predictors were lower body mass index and longer duration of MS predicted adherence. It was concluded that measures to improve self-efficacy should be taken with TN patients but the predictors for TE patients need more investigation.

The Correlative analyses of adherence in relapsing–remitting MS (CAIR) study is a prospective, web-based, patient-centered, cohort study in the Netherlands. Its primary objective is to investigate whether GA adherence is associated with specific disciplines of care or quantities of specific care. The secondary objective is to investigate whether specific aspects of the socioeconomic situation, healthcare and caregivers, disease, treatment, or patient characteristics impact GA adherence.[48] This study is ongoing, with recruitment planned to complete in July 2011 and assessments planned to take place over a 12-month duration.

Figure 2: Expanded Disability Status Scale Scores in the 15-year Long-term Study of Glatiramer Acetate Therapy
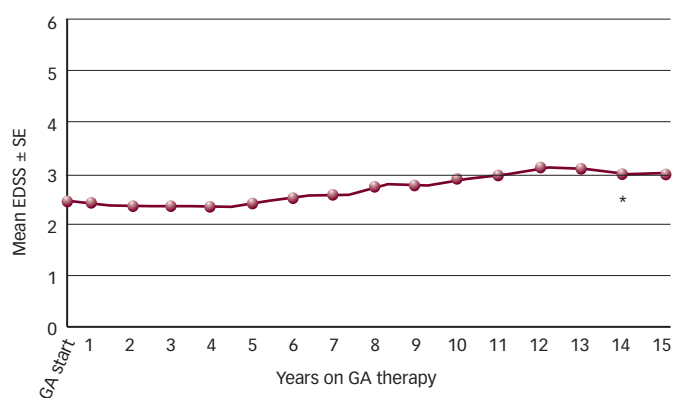
Yearly mean expanded disability status scale (EDSS) scores for ongoing patients (n=100) in the glatiramer acetate (GA) study at the 15-year analysis. The asterisk (*) indicates that the yearly mean EDSS scores for years 14 and 15 are derived from the scores of patients who were originally randomized to GA in the placebo-controlled phase of the study (n=90). SE = standard error. Source: Ford et al., 2010.[27]
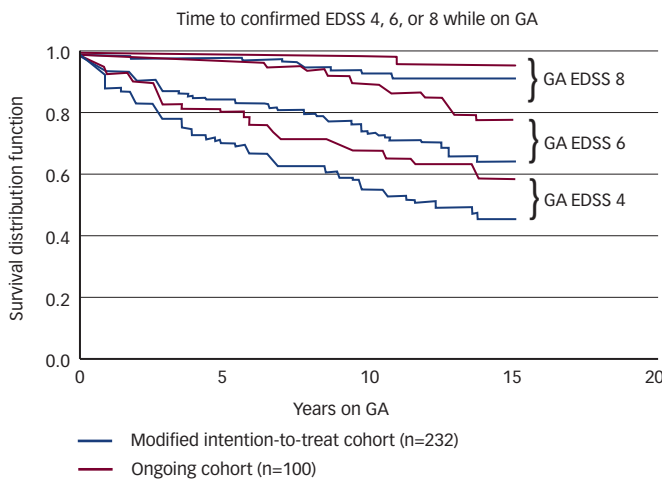
In a recent retrospective claims analysis comparing adherence and persistence among MS patients treated with disease-modifying therapies (DMTs) including GA, patients taking IFNβ-1a had significantly higher adherence compared with other DMTs, possibly owing to the less frequent dosing schedule for IFNβ-1a.[49] Economic studies have shown that improved adherence in MS patients treated with GA compared with other MS drugs results in better outcomes leading to improved cost-effectiveness.[50] Analyses of data from large populations of MS patients in the US drawn from the Data Mart database has shown that, compared with IFNβ-1a (sc or im) and IFNβ-1b, GA provides improved relapse rate reductions and consequently lower medical costs.[51–53] An analysis of records of a population of 284 patients with MS in the US showed that, during treatment with GA, IFNβ-1a, or IFNβ-1b, only GA was associated with significantly fewer days missed from work due to short-term disability (18.24 fewer days, p<0.03), worker's compensation (29.50 fewer days, p<0.04), or any reason (53.70 fewer days, p<0.003).[54]

A study in Europe and the US on a planned population of 1,350 patients with RRMS that aims to evaluate the efficacy of GA given as three weekly 40 mg doses (rather than daily 20 mg doses) versus placebo is currently in progress (A study in subjects with relapsing–remitting multiple sclerosis to assess the efficacy, safety and tolerability of glatiramer acetate injection 40 mg administered three times a week compared to placebo [Glatiramer acetate low-frequency administration; GALA] trial).[55] Randomized treatment will last for 12 months followed by an open-label extension. Recruitment has recently completed and the primary completion date is November 2012. If shown to be effective and safe, three-times-weekly dosing of GA may be a more convenient and tolerable regimen for patients with MS and may consequently improve treatment adherence.

Long-term Studies

The US GA trial has been ongoing since 1991. A total of 232 patients started randomized treatment and received at least one dose of GA. As of February 2008,[27] 100 patients remained in the open-label extension of this study. Patients enrolled in the extension study have a mean GA

Figure 3: Kaplan–Meier Curve with Time to Confirmed Disability

Time to confirmed EDSS 4, 6, or 8 while on GA

} GA EDSS 8

} GA EDSS 6

} GA EDSS 4

Years on GA

Survival distribution function

— Modified intention-to-treat cohort (n=232)
— Ongoing cohort (n=100)

EDSS = expanded disability status scale; GA = glatiramer acetate.
Source: Ford et al., 2010.[27]

treatment duration of 13.6 years. For ongoing patients, the ARR maintained a decline from 1.12 ± 0.82 at baseline to 0.25 ± 0.34 per year. Fifty-seven per cent had stable/improved EDSS scores, 65 % had not transitioned to SPMS, and 82 % remained ambulatory without mobility aids. For all patients on GA therapy (i.e. all those who received at least one dose of GA since study initiation), the ARR declined from 1.18 ± 0.82 to 0.43 ± 0.58, 54 % had stable or improved EDSS scores, and 75 % had not transitioned to SPMS (see *Figures 2* and *3*). There were no long-term safety issues and the commitment of patients to take daily sc injections for 15 years emphasizes the long-term tolerability and patient acceptance of GA.[27] This trial remains the only prospectively designed study to examine long-term improvements in disability among any of the approved therapies.

Three observational studies have investigated long-term GA use in MS and have provided evidence of inhibition of disability progression.[56–59] A French study involved 205 patients with RRMS who received GA as part of a compassionate-use program. The patients were followed up for 3.5 to eight years, during which time the mean EDSS scores were largely unchanged and only 5.7 % of the patients showed disability progression after five years (defined as an increase of one point in EDSS score after five years).[57] An Argentinian study[56] used information drawn from a national registry which gathers information on patients who receive DMDs. Among 174 GA-treated patients, during a six-month duration, approximately 22 % improved by ≥1 EDSS point, 2.5 % were unchanged, and 15 % showed EDSS progression by ≥1 point. The median time from diagnosis to an EDSS score of 6.0 was 15 years for patients receiving GA versus nine years for an untreated cohort of 360 patients. A study in the

US on a smaller group of patients with RRMS (n=46) also included the use of GA on a compassionate-use basis but for much longer durations (up to 22 years).[58] A majority of patients (57 %) showed either unchanged or improved EDSS scores. Only 10 of 28 (36 %) patients who had baseline EDSS scores <4.0 showed a last observed value of ≥4 and only eight of 34 (24 %) with a baseline EDSS score <6.0 worsened to a score of ≥6.0. These observational studies therefore appear to indicate that in patients receiving long-term treatment at MS treatment centers in different countries, GA had a beneficial inhibitory effect on disability progression compared with concurrent MS patients who were not receiving treatment.

Concluding Remarks

Currently, a new generation of MS therapies is emerging, with novel mechanisms of action and new delivery modalities, that include several oral and monoclonal antibody treatments. Although one of the oral medications has recently been approved, it remains unclear whether such therapies will provide patients with a higher standard of long-term efficacy and safety than is provided by the current selection of injectable DMDs. GA is an established DMD with a substantial number of clinical studies, analyses, and experience in the clinic that provide evidence to support its continued use in RRMS. Long-term studies of continuous GA administration up to 15 years show that the medication decreases relapse rates and decreases or stabilizes disability progression. There is also evidence to suggest that early GA therapy can reduce the risk of developing CDMS when given to patients with early-stage disease. In addition, the efficacy of GA in reducing relapse rates has been shown in several studies to contribute to improved adherence, better cost-effectiveness, and greater ability to remain in employment compared with the IFNβ treatments. GA, therefore, is at least as effective as the IFNβs in the early years of treatment, but long-term data suggest that it is more effective if treatment is started earlier in the disease course rather than delaying it. In addition, in several studies GA therapy has proven to be beneficial for patients with MS who switch from IFNβ, or from natalizumab, where patients test positive for JC virus and are at risk of PML. Furthermore, GA has the most favorable safety and tolerability profile of all agents available for the treatment of MS; it is not associated with the influenza-like symptoms characteristic of the IFNβs and is consequently an attractive option for many patients with MS.

GA is therefore likely to continue as a first-line therapy for use in RRMS for the foreseeable future. GA has a complex mechanism of action that is known to modulate immune and inflammatory pathways at several different levels. Although new oral and monoclonal antibody treatments are now emerging for MS treatment, the multiple modes of action that GA exerts on the pathological processes of MS confer substantial efficacy. This efficacy and tolerability in long-term use are factors that are likely to continue to make GA valuable as a mainstay of MS therapy for some years to come. ■

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