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The heritage of glatiramer acetate and its use in multiple sclerosis

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Abstract

Multiple sclerosis (MS) is a chronic and progressively debilitating disease of the central nervous system. Treatment of MS involves disease-modifying therapies (DMTs) to reduce the incidence of relapses and prevent disease progression. Glatiramer acetate (Copaxone®) was the first of the currently approved DMTs to be tested in human subjects, and it is still considered a standard choice for first-line treatment. The mechanism of action of glatiramer acetate appears to be relatively complex and has not been completely elucidated, but it is likely that it involves both immunomodulating and neuroprotective properties. The efficacy of glatiramer acetate 20 mg/mL once daily as first-line treatment in relapsing-remitting MS is well established, with ample evidence of efficacy from both placebo-controlled and active-comparator controlled clinical trials as well as real-world studies. There is also a considerable body of evidence indicating that the efficacy of glatiramer acetate is maintained in the long term. Clinical trial and real-world data have also consistently shown glatiramer acetate to be safe and well tolerated. Notably, glatiramer acetate has a good safety profile in women planning a pregnancy, and is not associated with foetal toxicity. Until recently, glatiramer acetate was only approved as 20 mg/mL once daily, but a new formulation with less frequent administration, 40 mg/mL three times weekly, has been developed and is now approved in many countries, including Italy. This review examines the mechanism of action, clinical efficacy, safety and tolerability of glatiramer acetate to provide suggestions for optimizing the use of this drug in the current MS therapeutic scenario.

Keywords: Multiple sclerosis, Glatiramer acetate, Disease-modifying therapy, Pregnancy, Clinically isolated syndrome

Background

Multiple sclerosis (MS) is a chronic, progressively debilitating disease affecting the central nervous system (CNS). It is characterised by multifocal inflammation leading to demyelination, axonal damage and impaired nerve conduction; MS is usually thought to be an inflammatory, immune-mediated condition in the relapsing phase, but in the chronic progressive phase a neurodegenerative component is predominant [1]. The definition of clinically isolated syndrome (CIS) [2] is used to recognize the first clinical presentation of a disease that could be MS, but has yet to fulfil criteria of dissemination in time.

Several disease-modifying therapies (DMTs) are currently available to effectively treat MS, with the aim of abolishing/reducing the number of relapses and preventing disease progression [3]. Due to the chronic nature of the disease, when assessing/exploring the profile of a putative treatment both efficacy and safety have to be examined in the long term [4].

Glatiramer acetate (GA, Copaxone®) was the first of the currently approved drugs to be tested in human subjects with MS [5, 6]. However, the approval of GA by the European Medicines Agency (EMA), at the dose of 20 mg/mL once daily, subcutaneously administered, dates to 2001, when it joined interferon-beta (IFN-β) in the therapeutic armamentarium. The therapeutic indications are the following: first-line treatment of ambulatory patients with RRMS according to McDonald criteria and treatment of patients who have experienced a CIS and are considered

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at high risk of developing clinically definite multiple sclerosis (CDMS) [7].

Very recently, with the availability of a new GA formulation (40 mg/mL, injected three times weekly), that was demonstrated to be equally effective as the 20 mg/mL once daily dose in patients with RRMS [8] and was approved both by the EMA and the Food and Drug Administration (FDA), a substantial gain in patients' quality of life has been achieved. The aim of this review is examining the mechanism of action, clinical efficacy, safety and tolerability profiles of GA to provide suggestions for optimizing the use of this drug in the current MS therapeutic scenario.

Mechanism of action

The mechanism of action of GA in MS is complex, likely involving an interplay of immunomodulating and neuroprotective properties, with details still to be fully elucidated [9–13] (Fig. 1).

GA was originally designed by researchers at the Weizmann Institute in Israel as a synthetic analogue of myelin basic protein (MBP, an autoantigen implicated in the pathogenesis of MS), with the aim of using it as a molecular mimic of MBP to study the biology of experimental autoimmune encephalomyelitis (EAE), an animal model of MS [14]. GA is a standardised mixture of polypeptides randomly polymerized from four L-amino acids,

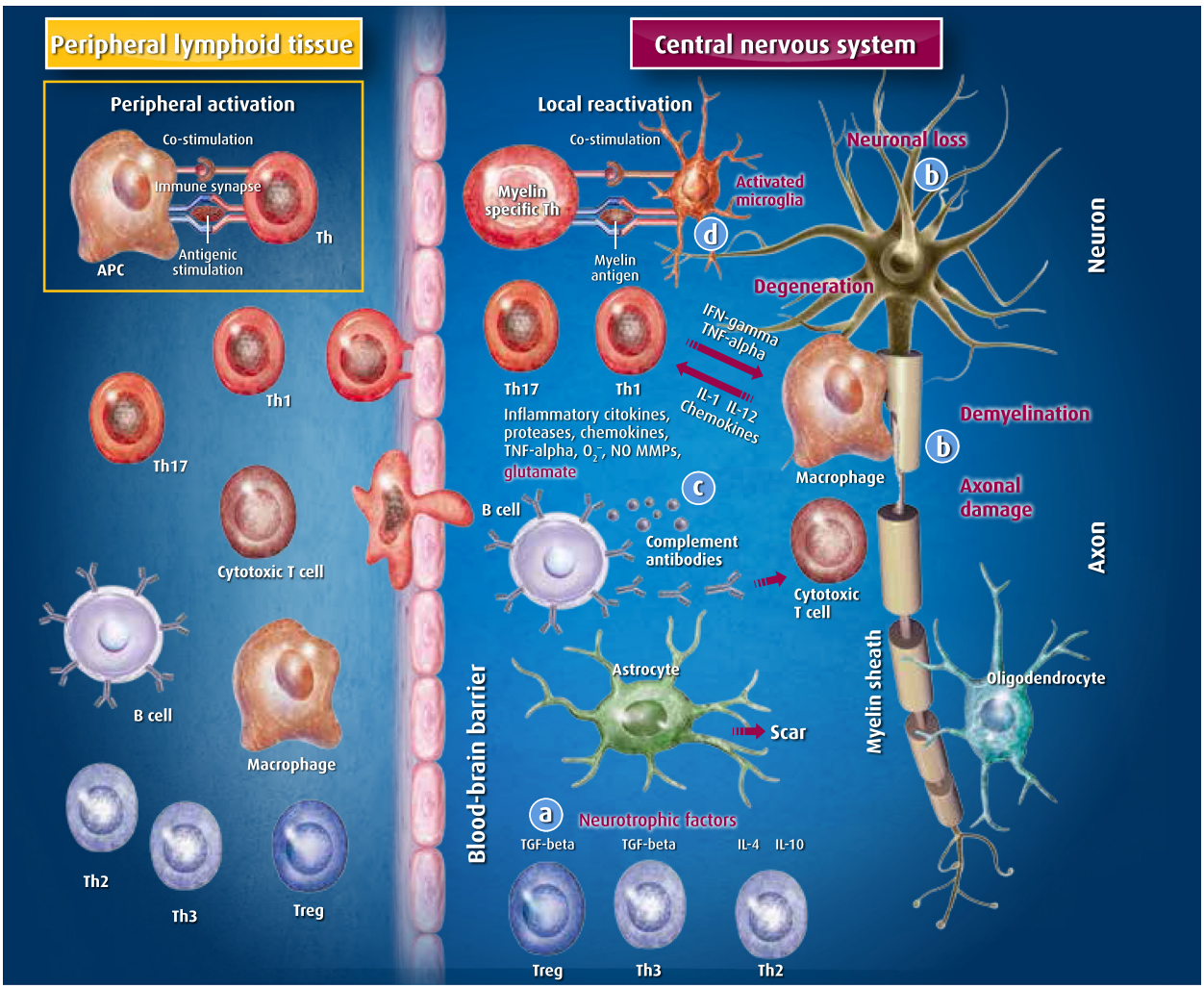

Fig. 1 Immune-mediated pathological and modulatory pathways in multiple sclerosis (MS) and possible neuroprotective actions of glatiramer acetate (GA). GA has been shown to increase levels of neurotrophic factors (**a**), which are reduced in the serum and the cerebrospinal fluid of MS patients and whose actions include protection of neurons against pathological insults. By inducing specific populations of Th2 cells in the periphery, GA may promote neural growth and inhibit inflammatory demyelination resulting in loss of axons, neurons and oligodendrocytes (**b**). GA has also been shown to oppose glutamate excitotoxicity by restoring normal kinetic properties of glutamate-mediated synaptic transmission in the striatum (**c**). GA may produce this effect by blocking synaptic alterations due to TNF-alpha released by activated microglia (**d**). APC, antigen presenting cell; IFN, interferon; IL, interleukin; MMP, matrix metalloproteinase; TGF, transforming growth factor; Th, T helper; TNF, tumor necrosis factor; Treg, regulatory T cell (Modified with permission from [11])

L-glutamic acid, L-lysine, L-alanine and L-tyrosine, in a defined molar residue ratio of 0.14:0.34:0.43:0.09. The same ratio is found in the amino acid sequence of MBP. The molecular mass of the constituent polypeptides of GA ranges from 4.7 to 11 KDa.

The researchers found that, surprisingly, the synthesised analogue did not induce EAE, but instead suppressed its development after exposure to crude myelin preparations [15]. This finding encouraged studies focussing on potential competition between GA and MBP in various immune cell-related events, especially in binding to major histocompatibility complex (MHC) molecules and T-cell antigen receptors [16, 17]. However, it should be noted that these results were mostly obtained using in vitro test systems, and their relevance to the mechanism of action of GA in vivo is uncertain. Aharoni and colleagues also reported that GA can block the proliferation of MBP-reactive T lymphocytes [18], but this finding was not reliably reproduced in subsequent studies. In fact, more recently, it has been shown that GA does not alter the proliferation of MBP-reactive T cells, but some GA-reactive T cells (specifically the Th2 cells) can respond to MBP by secreting protective cytokines [19]. GA-specific T cells, being able to cross the blood-brain barrier (while the drug itself is not) mediate the activity of GA in the central nervous system (CNS). Moreover GA-activated T cells are able to suppress EAE induced not only by MBP, but also by other encephalitogens, such as proteolipid protein (PLP) and myelin oligodendrocyte glycoprotein (MOG): this so-called "bystander suppression mechanism" is considered an essential component of the mechanism of action of GA [20].

An important immunomodulatory effect of GA – and possibly the primary mechanism behind its activity – is the induction of a shift in the phenotype of reactive T cells from a mostly pro-inflammatory Th1 pattern of cytokine secretion to a mostly anti-inflammatory Th2 pattern involving the production of IL-4, IL-5, IL-13, IL-10 and TGF-β [19, 21–27]. However, even if this is probably the most important mechanism of action of GA, other biological effects have been reported.

The role of Th17 cells (a subset of T cells that produce a distinct profile of proinflammatory cytokines, including interleukin [IL]-17, IL-6, IL-9, IL-21, IL-22, IL-23, IL-26 and tumour necrosis factor-α [TNF-α]) in the immunopathogenesis of MS and EAE has recently been elucidated [28–30]. GA was found to reduce Th-17-related neuroinflammation and levels of IL-17 and IL-6 in EAE mice [31, 32].

Studies have shown that, in addition to Th17 cells, GA acts on regulatory T (Treg) cells, whose role in suppressing autoimmunity is well recognized [33]. Patients with RRMS have an impaired CD4+ CD25+ Treg cells-related suppressive capacity [34], and functional alterations of Treg cells in RRMS may be associated with decreased expression of scurfin, a product of the transcription factor forkhead box P3 (Foxp3) [35]. GA can increase Foxp3 expression, and in vitro studies have shown that exposure of peripheral CD4+ T cells from healthy humans or GA-immunized mice to GA results in an increase in regulatory T cells, via activation of Foxp3 [36]. A similar finding was reported in a small study in RRMS patients, in which treatment with GA for up to 6 months increased total Treg numbers and reversed the Treg defect [37].

Additionally, it has been demonstrated that GA may act to cause a switch in the B cell phenotype of patients with MS, leading to the development of low but significant titres of GA-reactive IgG4 antibodies [38]. Because the isotype switch to IgG4 in B cells requires IL-4, an important anti-inflammatory cytokine, this finding further supports the anti-inflammatory action of GA in treated patients.

There is also evidence to suggest that GA, in addition to its action on the adaptive immune system, acts on the innate immune system by directly modulating the activity of myeloid cells, in particular monocytes and dendritic cells [39–42]. The properties of monocytes of RRMS patients undergoing treatment with GA have been compared with those of untreated patients and of healthy controls, showing that monocyte reactivity was inhibited in the treated patients. This study is important since it was the first to demonstrate this effect in human subjects treated with GA [43].

A number of studies have also addressed the question of the possible neuroprotective effects of GA. The results of in vitro and animal model studies have shed some light on the possible mechanisms of these effects. In addition to inducing an anti-inflammatory milieu in the CNS through the action of reactive T cells, GA has been shown to increase levels of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), the actions of which include protection of neurons against pathological insults [11, 44]. Another possible neuroprotective action of GA, against glutamate excitotoxicity, was recently reported in a mouse model of MS [45]: GA was found to restore normal kinetic properties of glutamate-mediated synaptic transmission in the striatum of treated animals, contrasting the excessive glutamate action on postsynaptic receptors. GA produces this effect (independently of its immunomodulatory action) possibly by blocking synaptic alterations induced by activated microglia-released TNF-α.

The induction of specific populations of Th2 cells in the periphery by GA may lead to an environment favouring axonal protection, neural growth and remyelination, as reported in an in vitro and in vivo study by Skihar and colleagues [46]. Exposure of mouse embryonic forebrain cells in culture to GA-reactive T cells resulted in increased levels of insulin-like growth factor-1 (IGF-1) and promoted

the formation of oligodendrocyte precursor cells (OPC). Subsequently, mice subjected to induced demyelination of the spinal cord were treated with GA; after 7 days, increased OPC generation and remyelination were observed, associated with higher levels of IGF-1 and BDNF in the spinal cord.

Some observations from clinical trials seem to support such effects. In a substudy of the PreCISe trial, patients treated with GA had increased brain concentrations of the neuronal integrity marker N-acetylaspartate, and an improvement in brain neuronaxonal integrity, whereas patients receiving placebo did not [47]. Also, magnetic resonance imaging (MRI) studies have demonstrated the ability of GA to reduce the proportion of new T1 hypointense lesions evolving into permanent black holes (markers of irreversible axonal loss), therefore supporting the neuroprotective scenario [48, 49].

Clinical efficacy

Subcutaneous GA has a long history of use for the treatment of RRMS. The initially approved dose, on the basis of animal studies, is 20 mg/mL once daily; still widely considered as standard, it was a keystone for all later drug development. Attempts to explore higher weekly doses (40 mg/mL once daily) showed no additive benefit [50, 51]. Recent results of the GALA study [8] indicate that maintaining a similar weekly dose, but with a different dosing regimen (40 mg/mL three times a week), provides advantages in clinical use without impacting on efficacy.

The feasibility of oral administration of GA was tested in the placebo-controlled CORAL trial [52]. Patients with RRMS received 50 mg or 5 mg of GA or placebo daily for 14 months. Neither dose of GA affected the primary endpoint (relapse rate) or any other clinical and MRI endpoint. Thus, further development of oral administration was discontinued. GA has been tested in progressive MS with negative results.

Once-daily formulation

In relapsing-remitting multiple sclerosis

The efficacy of GA 20 mg/mL once daily as first-line treatment in RRMS is well established in many phase II, III and IV studies.

Placebo-controlled trials The efficacy of GA on clinical and MRI-assessed outcomes has been demonstrated in two major pivotal placebo-controlled trials – the US Glatiramer Acetate trial [53] and the European/Canadian MRI study [54], and supported by an initial small study in 50 patients [55] (Table 1). This latter study provided the first clinical evidence supporting GA in RRMS, with 2 years of treatment with GA 20 mg/mL daily resulting in a significant difference in the proportion of patients experiencing no relapses versus placebo (56 % vs. 26 %; $p = 0.045$) [55]. The first pivotal trial, the US Glatiramer Acetate phase III study, provided clear evidence for the efficacy of GA, demonstrating a significant 29 % reduction favouring GA in annualised relapse rate (ARR) (0.59 vs. 0.84 for placebo; $p = 0.007$), supported by trends in the proportion of relapse-free patients (33.6 % vs. 27.0 %, respectively), and the median time to first relapse (287 vs. 198 days, respectively), after 2 years of treatment [53] (Table 1). In this study MRI measures were not used. A second study, the European/Canadian MRI trial, was planned in order to better define the profile of efficacy and safety of GA. It provided for the first time MRI evidence of the beneficial effect of GA; 9 months of therapy resulted in significant differences favouring GA versus placebo for most endpoints: mean total number of enhancing lesions on T1-weighted images (primary endpoint; 25.96 vs. 36.80; $p = 0.003$), number of new enhancing lesions (17.4 vs. 26.0; $p < 0.003$) and their change of volume ($p < 0.01$), number of new lesions detected on T2-weighted images (9.4 vs. 13.5, respectively; $p < 0.003$) and their change of volume ($p = 0.001$). Moreover, a significant reduction of the relapse rate was reported in the GA group versus placebo (33 %; $p = 0.012$) (Table 1). A later study that analysed MRI data from the European-Canadian trial using a fully automated, normalized method also showed a significant ($p = 0.037$ at 18 months) reduction in the development of brain atrophy in the GA group versus placebo [56]. A noteworthy finding of the European/Canadian MRI study was a reduction in severity of tissue disruption in newly-formed lesions with GA [48]: the percentage of new lesions evolving into permanent black holes was significantly lower in patients treated with GA than in those receiving placebo at 7 months (18.9 % vs. 26.3 %, respectively; $p = 0.04$) and at 8 months (15.6 % vs. 31.4 %, respectively; $p = 0.002$) after lesion appearance.

Active comparator-controlled trials GA has been compared head-to-head with high-dose subcutaneous IFN-β1a or -1b in two double blind trials in patients with RRMS: REGARD [57] and BECOME [58] (Table 1). Both showed comparable efficacy between GA and IFN-β1a or -1b. Moreover in the REGARD trial, GA was found to better protect against brain-volume loss (−1.07 % vs. −1.24 %; $p = 0.018$). These data were confirmed by two trials in which GA was used as reference comparator. In the BEYOND trial [59], two arms receiving IFN-β1b (250 μg and 500 μg) were included, along with a third arm receiving GA: no significant differences were found between groups either in the primary endpoint (ARR: 0.33 for IFN-β1b 500 μg, 0.36 for IFN-β1b 250 μg and 0.34 for GA; p = ns for all comparisons) and in all other clinical outcomes (Table 1). The CONFIRM trial [60] compared two doses of dimethyl fumarate versus placebo, again with a third

Table 1 Clinical trials

Study	Number of patients	Trial length	Key outcomes
Placebo-controlled trials			
Johnson et al. 1995 [53]	251 randomised 1:1 GA:PBO	2 years	Mean relapse rate: GA 1.19 versus PBO 1.68; $p = 0.007$ (29 % reduction) (ARR: GA 0.59 versus PBO 0.84)
Comi et al. 2001 [54]	239 randomised 1:1 GA:PBO	9 months	Mean reduction in total enhancing lesions GA vs PBO -10.8 (95 % CI -18.0 to -3.7; $p = 0.003$); 29 % reduction.
Bornstein et al. 1987 [55]	50 randomised 1:1 GA:PBO	2 years	Proportion of relapse-free patients GA 56 % vs 26 % PBO; $p = 0.045$
Active comparator-controlled trials			
Mikol et al. 2008 [57] (REGARD)	764 randomised 1:1 GA:IFNβ-1a	96 weeks	No between-group difference in time to first relapse (HR 0.94; 95 % CI 0.74–1.21; $p = 0.64$)
Cadavid et al. 2009 [58] (BECOME)	75 randomised 1:1 GA: INF-β1b	2 years	Similar median (75^{th} percentile) CAL count per scan in months 1–12, of 0.58 (2.45) vs 0.63 (2.76)
O'Connor et al. 2009 [59] (BEYOND)	2447 randomised 2:2:1 250 μg IFNβ-1b:500 μg IFNβ-1b:GA	3.5 years	No between-group differences in relapse risk or EDSS progression
Fox et al. 2012 [60] (CONFIRM)	Randomised 1:1:1:1 PBO: BG-12 twice daily:BG-12 three times daily:GA	96 weeks	ARR significantly lower with twice-daily BG-12 (0.22), three times-daily BG-12 (0.20), and GA (0.29) than PBO (0.40) (RR GA 29 %, $P = 0.01$).
Combination trials			
Goodman et al. 2009 [85] (GLANCE)	110 randomised 1:1 GA + NTZ versus GA alone	6 months	Mean rate of development of new active lesions over the 24-week study lower with combination therapy (0.03) vs GA alone (0.11; $p = 0.031$)
Lindsey et al. 2012 [116] (CombiRx)	1008 randomised 2:1:1 IFN + GA: IFN: GA	3 years	No difference in ARR between combination group and GA group (0.12 vs. 0.11). Both combination and GA alone superior to IFN group (0.16; $p = 0.022$ for combination group and $p = 0.027$ for GA group)
Clinically isolated syndrome			
Comi et al. 2009 [86] (PreCISe)	481 randomised 1:1 GA:PBO	36 months	GA reduced risk of CDMS by 45 % versus PBO (HR 0.55, 95 % CI 0.40–0.77; $p = 0.0005$)

95 % CI 95 % confidence interval, *ARR* Annualised relapse rate, *CAL* Combined active lesions, *CDMS* Clinically definite multiple sclerosis, *EDSS* Expanded disability status scale, *GA* Glatiramer acetate, *HR* Hazard ratio, *IFN* Interferon, *NTZ* natalizumab, *PBO* Placebo, *RR* Relative risk

arm with GA as a reference comparator. Even if the design of the trial did not allow a comparison between the two active treatments, both drugs proved to be significantly superior to placebo in all clinical and MRI outcomes (Table 1). In particular, GA significantly reduced the ARR versus placebo by 29 % ($p = 0.01$), thus confirming the results of the pivotal trials in a very large population sample (over 1400 patients). A post hoc subgroup analysis reported numerically similar relapse-related outcomes between the two dimethyl fumarate arms and the GA arm in most patient subgroups [61].

A systematic review summarising data from five randomised studies comparing IFN-β with GA in patients with RRMS confirmed a similar efficacy after 2 years of treatment [62].

Long-term and real-word data Even with all the limitations of long-term extension studies, due to potential selection bias, available data suggest that the efficacy of GA is maintained over time [63–71]. Moreover, there have been no reports of rebound effect or delayed disease reactivation after treatment discontinuation in extensions of clinical trials or post-marketing studies [63, 70, 72, 73].

The first follow-up of the US Glatiramer Acetate trial presented 15-year data [63]. Patients continuing in the study (100 of the initial 232) showed a reduced ARR (0.25 ± 0.34 per year vs. 1.12 ± 0.82 at baseline); 57 % had stable or improved Expanded Disability Status Scale (EDSS) scores (change ≤0.5 points) and 67 % showed stable disease, without transitioning to secondary progressive MS. The most frequently reported reasons for treatment discontinuation were patient perception of disease worsening ($n = 29$), a desire to switch or combine therapies ($n = 26$) and difficulty, inability, or unwillingness to adhere to the study protocol ($n = 32$). Twenty-year results are now available for the long-term extension of this study [64]. Of the initial 232 patients, 74 remain in the trial and have been continuously treated for a mean of 19.3 years. Very long-term use of GA appears to be associated with stable disease activity (cumulative ARR = 0.2; 24.3 % of patients remained free of relapse for the entire period) and low levels of accumulated disability (mean EDSS score 3.1 vs. 2.4 at baseline).

The extension of the European/Canadian MRI study offers serial long-term MRI data for a large cohort of patients treated with GA [70]. After the 9-month double-blind, placebo-controlled phase, all patients entered an open-label, active treatment phase in which they received GA 20 mg/mL once daily for a further 9 months, with a long-term follow-up visit (LTFU) scheduled at least five years after study entry. Overall, MRI results show that the effects of GA on MS activity are sustained (number of active lesions 0.9 at LTFU vs. 3.4 at baseline; percentage brain volume change −5.02 vs. baseline). Moreover, MRI results in the patients that were shifted from placebo to GA showed a significant reduction of MRI measures of disease activity, paralleling what was observed in the patients that received GA from the start. A notable finding is that the proportion of patients requiring walking aids at the LTFU was significantly lower ($p = 0.034$) in the group that received GA from the start of the study compared with delayed treatment, suggesting that early treatment may have a positive impact on long-term disease outcomes.

A 5-year brain MRI retrospective open study provides some evidence of the efficacy of GA in reducing brain volume loss [74]: smaller reductions in brain volume were observed in patients with RRMS treated with subcutaneous GA than with high-dose IFN-β regimens (percentage change in brain volume −2.27 % vs. −3.21 %; $p < 0.0001$).

Various studies report real-world data for GA treatment in RRMS [72, 73, 75, 76], confirming the efficacy profile of GA observed in the clinical studies. A significant impact of the treatment with GA on health-related quality of life has also been reported [77, 78], with beneficial effects including significant reductions in fatigue and in days of absence from work.

Controlled studies of MS treatments in children and adolescents are still lacking, but some published evidence, albeit retrospective, points to the efficacy of GA in this population. In an Italian cohort, 14 patients with a mean age of 13.1 years were treated for a mean of 5 years or more; these patients had a reduction in relapse rate, from about 3 per year before treatment initiation to 0.2–0.4 per year during the treatment period [79]. A small study of seven patients with RRMS who had disease onset at 9–16 years of age and began GA before 18 years of age showed that 24 months of treatment resulted in two of seven patients remaining relapse free over the study period, and three of seven patients having stable disability scores as measured by the EDSS [80].

Switching to glatiramer acetate Several trials have evaluated switching to GA from other MS therapies for safety and efficacy reasons [81–83]. For patients not responding to first line therapies GA can be offered as an alternative to so-called second line medications if there are concerns of tolerability/adverse events with the latter therapies. Most studies describe switches from IFNβ-1a or -1b to GA, reporting reductions in mean ARR after switching [81–83]. However, in those situations when the shift is due to failure of the previous treatment, results should be interpreted with caution because the regression to the mean phenomenon is a major concern. Therefore, randomised, controlled trials are needed to confirm these results.

Combination treatment trials Two important combination therapy trials are the CombiRx trial [84] and the GLANCE trial [85] (Table 1). In CombiRx, patients were randomised to GA 20 mg/mL once daily plus IFN-β1a 30 μg once weekly or to monotherapy with one of these medications plus placebo for 3 years. For the primary outcome of ARR, the combination therapy was significantly superior to IFN-β, reducing the relapse rate by 25 % ($p = 0.022$), while there was no significant difference between the combination therapy and GA. It should be noted that the study design allowed for the first time a comparison between intramuscular IFN-β and GA, with GA resulting superior (relapse rate reduction by 31 % compared with IFN-β; $p = 0.027$). The GLANCE study compared combination therapy with GA 20 mg/mL once daily plus intravenous natalizumab 300 mg every 4 weeks versus monotherapy with GA 20 mg/mL once daily plus placebo every 4 weeks. At 24 weeks, the combination therapy was superior on major MRI disease activity measures.

In clinically isolated syndrome

Early treatment with GA in patients with CIS has been shown to delay onset of CDMS in the placebo-controlled study PreCISe [86] (Table 1) and during its subsequent open-label extension period [87]. The study enrolled 481 patients with one unifocal neurological event and a positive MRI scan (defined as the presence of at least two cerebral lesions ≥6 mm in diameter on T2-weighted images). Patients were randomised to GA 20 mg/mL once daily or placebo for up to 36 months or until conversion to MS. GA was associated with a 45 % reduction in risk of conversion to MS (primary endpoint; $p = 0.0005$) and a delay in the time to conversion compared with placebo (336 days vs. 722 days, respectively). GA was associated with a 58 % reduction in number of new T2 lesions and a smaller volume of T2 lesions. During the extension phase (total 5 years' duration) the efficacy of GA was sustained, with a 41 % reduction in risk of conversion to MS in those treated with GA from the start compared with delayed treatment; in the GA group, there was a delay of 972 days before conversion to MS, a 42 % reduction in new T2 lesions per year ($p < 0.0001$) and a 22 % reduction in T2-

lesion volume (p = 0.0005). In the extension phase patients treated with GA from study entry showed a significant 28 % reduction (p = 0.0209) in brain volume loss compared with patients initially randomised to placebo, confirming the neuroprotective effects of GA. This is the first trial to demonstrate that early treatment with GA reduces brain atrophy versus delayed treatment in this setting.

In progressive forms of multiple sclerosis

GA was assessed in primary progressive forms of MS, with negative results. The PROMiSe study [88] was a randomised, double-blind, placebo-controlled, multicentre, international study that investigated the effect of GA on disability progression in 943 patients with progressive MS. After 3 years of treatment, the time to sustained accumulated disability was similar between GA- and placebo-treated patients (hazard ratio [HR] 0.87; 95 % CI 0.71 to 1.07; p = 0.1753). A post hoc analysis showed a possible effect in slowing clinical progression in male patients (HR 0.71; 95 % CI 0.53 to 0.95; p = 0.0193) [88], but a subsequent analysis of these results did not demonstrate an impact of gender on the efficacy of GA [89]. An additional study investigating metabolite ratios as determined by MRI in a subset of 58 patients from the PROMISe study showed no difference between the GA and placebo groups [90]. However, it should be noted that the PROMISe study was terminated early due to lack of effect, and that the low rate of disability progression and the high rate of premature discontinuations led to a decrease in power of the study, hampering the determination of a treatment effect [88].

Three times weekly formulation

The first trial to evaluate a high-dose regimen of GA was the phase III FORTE study [51] that compared the 40 mg/mL once daily dose with the standard 20 mg/mL once daily dose in patients with RRMS. Both doses showed similar effects on efficacy measures and no difference in the safety profile. Post-hoc analyses revealed potential benefits of the 40 mg/mL dose in some subgroups (for example, in the "frequent MRI cohort" patients treated with 40 mg/mL showed a slight numerical advantage in the reduction of the mean number of gadolinium-enhancing lesions at various timepoints vs. baseline). After this study the development of the high-dose once daily regimen was discontinued, but it provided a starting point for subsequent research on the high-dose, lower-frequency regimen (40 mg/mL three times weekly).

The efficacy of subcutaneous GA 40 mg/mL three times weekly in patients with RRMS was shown in the 1-year, double blind, placebo-controlled GALA study, involving about 1400 patients [8]. Significant reductions compared with placebo in relapse rate (34.0 %; $p < 0.0001$), cumulative number of gadolinium-enhancing T1 lesions (44.8 %; $p < 0.0001$) and new or enlarged T2 lesions (34.7 %; $p < 0.0001$) were reported; the numerical values of these parameters were very similar to those observed in the pivotal studies with the 20 mg/mL once daily dose. Three-year results of the open-label extension of the GALA study demonstrated sustained efficacy on ARR and MRI parameters of disease activity [91]. Patients switched from placebo to GA after the double blind phase reported significant gains in efficacy, but those treated with GA from study entry showed a significantly lower relapse rate (ARR 0.23 vs 0.30, respectively, p = 0.0052) and significantly fewer enhancing T1 lesions and new or enlarged T2 lesions (RR = 0.660, p = 0.0005 for T1; RR = 0.680, $p < 0.0001$ for T2) compared with patients with delayed treatment.

An important finding from a recent post hoc MRI analysis of data from the GALA study is that GA 40 mg/mL three times weekly (cumulative weekly dose of 120 mg) shares the ability of the standard formulation (cumulative weekly dose of 140 mg) to reduce conversion of new active lesions into black holes, markers of permanent damage and disability progression, with a significant 24 % reduction compared with placebo (p = 0.006) in the odds of conversion from new lesions at month 6 to black holes at month 12 [49].

In the absence of head-to-head studies comparing GA 20 mg/mL once daily and 40 mg/mL three times weekly, indirect comparisons have also shown very similar efficacy of the two doses [92, 93].

On the same lines, the GLACIER study, in which patients were asked to report the personal experience of shifting from the 20 mg/mL once daily dose to the 40 mg/mL three times weekly dose, demonstrated a favourable convenience profile and patient satisfaction when converting from the once-daily formulation [94].

Safety

After 20 years' continuous clinical use and more than 2 million patient-years' exposure, the safety profile of GA is well established. No evidence of any association of GA with immunosuppression or with malignant and autoimmune disease has been reported after 10 and 15 years follow-up [63, 65]. GA was not associated with psychiatric or mood disorders and in some studies a significant improvement in fatigue was observed, even in patients switching from other DMTs [78]. In a study of patients with RRMS and spasticity, switching from IFN-β to GA improved spasm frequency, muscle tone and pain after 3 months of treatment; these improvements were maintained over 6 months of treatment with GA [95]. A few cases of hepatotoxicity during treatment with GA have recently been reported [96–98], with no such cases reported in clinical trials, hence it is unclear at present if

liver function monitoring is warranted. It should be noted, though, that because some of the patients reporting this AE had concurrent autoimmune conditions, it is impossible to disentangle the potential contribution of GA treatment and the underlying condition to hepatotoxicity. IgE-mediated allergic reactions have also been described [99, 100].

Both formulations of GA appear equivalent from the safety standpoint [64, 91, 94]. In the GALA study AEs associated with administration of GA 40 mg/mL three times a week were found to be consistent with the known safety profile of GA 20 mg/mL once daily. Moreover, no new AEs emerged during treatment with high-dose GA [8, 91].

At present there are no controlled studies of DMTs in children and adolescents with MS, but published evidence, mostly retrospective studies, support a similar safety profile of GA in this population [79, 80]. GA, along with IFN-β, has been recommended as the standard treatment for paediatric RRMS in two position papers, one produced by European experts [101] and the other one by the International paediatric MS Study [102]. Since paediatric onset MS is characterized by high disease burden, early treatment, although off-label, should be promptly started after confirmation of the diagnosis. The favourable tolerability profile of GA should be considered when making a therapeutic choice [101, 102].

No limitations to concomitant administration of GA and other drugs have been identified; the medication is not linked to blood test abnormalities that require monitoring.

Pregnancy

Animal reproduction studies have failed to demonstrate a risk of GA treatment to the foetus, and post-marketing studies support the absence of foetal toxicity [103–108]. For these reasons GA has been classified as FDA Class B during pregnancy [109]. Most of the other drugs approved for the treatment of MS are categorized by the FDA as Class C, with the exception of mitoxantrone, classified as Class D (positive evidence of human foetal risk), and teriflunomide, classified as Class X (foetal toxicity) [104, 109]. GA can be continued right up until conception, unlike other DMTs for which a washout period is recommended prior to trying to conceive [104]. GA may also be used as bridging therapy in women planning a pregnancy who are receiving treatments requiring a washout period, if it exposes women to the risk of MS reactivation, and offers some advantages in women risking unplanned pregnancies.

While it is currently recommended that, as for any other DMT, GA should be discontinued after confirmed evidence of pregnancy and until childbirth, available evidence suggests GA could be continued at least throughout the first trimester, while further continuation of GA treatment may be assessed on a case-by-case basis [104]. An Italian retrospective study showed that the mother's exposure to GA when the drug was suspended within 4 weeks from conception was not associated with an increased frequency of spontaneous abortion nor with other negative pregnancy and foetal outcomes compared with women in whom the medication was suspended 4 weeks or more from conception, or who were untreated [107]. These findings confirm those of a previous observational study [106] suggesting that GA and the IFNs do not represent a significant risk for prenatal developmental toxicity. Relapse rate decreases during pregnancy, with a well-known increase in the first three months after childbirth [110] that sometimes requires second-line therapy to be controlled [103–105].

Tolerability

The tolerability of GA 20 mg/mL once daily has consistently been reported as good versus both placebo and active treatment in the previously mentioned clinical trials [54, 57, 59, 86], and the nature and frequency of treatment-related AEs were similar between short- and long-term treatment periods [63–65, 67]. The most common (>1/10) treatment-related AEs are transient injection-site reactions, occurring occasionally in about two thirds of patients [7]. These include injection site bruising, erythema, pain, pruritus and induration. Rarer cases of localized lipoatrophy and skin necrosis at injection sites have been reported during post-marketing [111, 112]. One peculiar injection-related tolerability issue with GA is the occurrence of immediate post-injection reactions (IPIR) that present immediately or a few minutes after the injection, consisting in flushing, chest tightness, palpitation, dyspnoea and intense anxiety. The crisis resolves spontaneously in a few minutes [53]. These reactions are unpredictable, affecting about 15 % of patients and seldom recurring more than once. The intensity of the reaction is not connected to any real risk to patients.

The tolerability of GA 40 mg/mL three times weekly has been shown to be similar to that of the 20 mg/mL once-daily formulation [8, 91]. Importantly, in the GLACIER study [94], three times weekly GA was found to be better tolerated than the once-daily formulation in terms of injection-related adverse events (IRAEs): the adjusted mean annualized rate of IRAEs was reduced by 50 % in patients receiving the new formulation (35.3 events per year vs. 70.4 events per year, respectively; $p = 0.0006$), while the rate of moderate/severe events was reduced by 60 % (0.9 events per year vs. 2.2 events per year, respectively; $p = 0.0021$). Furthermore, treatment convenience, as measured by the Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9) convenience subscale, was improved for patients switching from GA 20 mg/mL once daily to the three times weekly formulation

[94]. Recently, results from the extension phase of the GLACIER study confirm the safety profile of the 40 mg/mL three times weekly formulation, in terms of both IRAEs and convenience [113].

Conclusions

The availability of multiple drugs has totally changed the scenario of MS treatment. Treatment choices became much more complicated and decisions should be based on the combination of the efficacy and safety profiles. From this point of view GA associates a favourable efficacy profile, confirmed by more than 20 years of clinical use, with an excellent safety and tolerability profile. The burden of daily injections has been recently reduced by the availability of the new 40 mg/mL three times a week formulation, which has been shown to share the same efficacy of the 20 mg/mL once daily formulation, but with obvious advantages in terms of patient convenience.

GA has been classified as a first-line drug for the treatment of RRMS in Europe, with a clear indication both in naïve patients and in patients who discontinue other therapies for safety or tolerability issues. The recent evidence of the importance of personalized treatment implies that the assessment of the individual prognostic profile should drive treatment decisions, at the same time considering also patients' preference and convenience. Patients with a good prognostic profile as indicated by low disease activity – revealed by low brain lesion burden and few or absent active lesions at the time of treatment onset – may have a high probability of responding to first-line therapies, including GA. On the contrary, patients with very active disease in the early phases tend to require an induction approach to obtain a positive response to treatment.

Considering the choice among first-line therapies, GA offers an obvious advantage in young, potentially fertile women for the favourable safety profile in this population, as discussed above [107]. Patients with CIS are also expected to benefit from GA, given the evidence of efficacy in such patients, supported by extension studies showing clear protection from brain atrophy [86, 87]. Another possible use of GA is as maintenance treatment in patients who start with an induction approach because of a negative prognostic profile. Induction therapy has often the advantage of "reshaping" the immune system, which can then be maintained by GA [114, 115].

The classification of MS clinical courses [2] defines the importance of disease activity not only in RRMS, but also in patients with a progressive disease course. The presence of disease activity represents a clear target for DMTs. Among them, the use of GA should be considered because of the long-term safety and absence of negative impact on spasticity, a frequent AE of IFN-β treatment in this population. It should be noted, however, that conclusive data from clinical trials demonstrating the efficacy of GA in these patients are currently lacking.

We anticipate that the new 40 mg/mL three times weekly regimen might increase compliance and adherence. Therefore it is recommended that, in all consenting patients currently treated with the once daily formulation, the switch to the new formulation should be considered. An early start of GA treatment should be considered in the light of data on brain atrophy from the PreCISe study [87]: there was a significant (−28 %; $p = 0.0209$) difference when comparing early GA treatment versus delayed GA treatment.

In conclusion, clinical trials and real-life studies have consistently shown the efficacy and safety of both formulations of GA in the first-line treatment of patients with RRMS and for delaying the onset of clinically definite MS in patients with CIS. Overall, data suggest that while many types of patients can be expected to benefit from GA, the "ideal" subject would be one with RR disease or newly-diagnosed, young and active, wanting to lead a normal life. The use of GA for more than two decades shows a reassuring safety profile and optimal tolerability. The major concern may be the frequency of administration, an issue that the new formulation can be expected to minimize, contributing to the use of this drug. Besides patient convenience, the fact that no complex clinical monitoring is required during treatment clearly represents another strong point of the clinical use of GA.

Abbreviations

ARR: Annualized relapse rate; BDNF: Brain derived neurotrophic factor; CDMS: Clinically definite multiple sclerosis; CIS: Clinically isolated syndrome; CNS: Central nervous system; DMTs: Disease-modifying therapies; EDSS: Expanded disability status scale; GA: Glatiramer acetate; IFN: Interferon; IRAEs: Injection-related adverse events; LTFU: Long-term follow up; MBP: Myelin basic protein; MHC: Major histocompatibility complex; MRI: Magnetic resonance imaging; MS: Multiple sclerosis; RRMS: Relapsing-remitting multiple sclerosis; TNF: Tumour necrosis factor; TSQM-9: Treatment satisfaction questionnaire for medication-9.

Competing interests

GC has received honoraria as a consultant and for lecturing at scientific meetings from Novartis, Teva, Sanofi-Aventis, Genzyme, Merck Serono, Biogen, Bayer, Serono Symposia International Foundation, Excemed, Roche, Almirall, Chugai, Receptos and Forward Pharma.
AB has received honoraria for serving in the scientific advisory boards of Almirall, Bayer, Biogen, Genzyme, with approval by the Director of AOU San Luigi University Hospital, and has received speaker honoraria from Biogen, Genzyme, Novartis, Teva; his institution has received grant support from Bayer, Biogen, Merck, Novartis, Teva, from the Italian Multiple Sclerosis Society, Fondazione Ricerca Biomedica ONLUS and San Luigi ONLUS.
DC is an Advisory Board member of Almirall, Bayer Schering, Biogen, Genzyme, GW Pharmaceuticals, Merck Serono, Novartis, Teva and received honoraria for speaking or consultation fees from Almirall, Bayer Schering, Biogen Idec, Genzyme, GW Pharmaceuticals, Merck Serono, Novartis, Sanofi-Aventis, Teva. He is also an external expert consultant of the European Medicine Agency (EMA), and the principal investigator in clinical trials for Bayer Schering, Biogen Idec, Merck Serono, Mitsubishi, Novartis, Roche, Sanofi-Aventis, Teva. His preclinical and clinical research was supported by grants from Bayer, Biogen, Merck Serono, Novartis and Teva.

NDS has received honoraria or consultation fees from Novartis, Merck Serono, Biogen Idec, La Roche; has been member of Advisory Boards for Novartis, Merck Serono, Biogen Idec; has participated in company-sponsored speaker's bureau for Novartis, Merck Serono, Biogen Idec; has received travel reimbursements from Novartis, Merck Serono and Biogen Idec.
CF has received grants and personal fees from Teva, and grants from Merck Serono, Novartis and Fondazione Italiana Sclerosi Multipla.
AG serves on scientific advisory boards or as consultant for Merck Serono, Teva, Novartis, Biogen Idec; he has received honoraria for lecturing from Merck Serono, Biogen Idec, Novartis, Teva, Genzyme, Almirall.
PG is an Advisory Board member of Almirall, Biogen Italy, Sanofi-Genzyme, GW Pharmaceuticals, Merck Serono, Novartis, Teva and received honoraria for speaking or consultation fees from Almirall, Biogen Idec, Genzyme, GW Pharmaceuticals, Merck Serono, Novartis, Sanofi-Aventis, Teva. He is also an external expert consultant of the European Medicine Agency (EMA), and has been the principal investigator in clinical trials for Biogen Idec, Merck Serono, Novartis, Roche, Sanofi-Aventis, Teva, Almirall. His preclinical and clinical research was supported by grants from Bayer-Shering, Biogen-Idec, Merck-Serono, Novartis and Teva.
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MT has served on scientific Advisory Boards for Biogen Idec, Novartis, Almirall, Roche and Genzyme; has received speaker honoraria from Biogen Idec, Bayer-Schering, Sanofi Aventis, Merck Serono, Teva, Genzyme, Almirall and Novartis; has received research grants for her Institution from Biogen Idec, Merck Serono and Novartis.
The other Authors declare no conflicts of interest.

Authors' contributions
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