

Glatiramer Acetate (Copaxone®) in Multiple Sclerosis

Multiple sclerosis (MS) is the most common, non-traumatic, disabling neurological disorder in young adults. Although the aetiology of MS remains unknown, its pathogenesis includes an inflammatory demyelinating process with immune reactivity to antigens such as myelin components, and progressive neuronal and axonal damage.

The clinical course of relapsing remitting MS (RRMS) is punctuated by exacerbations or episodic neurological worsening. These attacks, or relapses, are followed within weeks to a few months by remissions, often with full recovery from clinical symptoms. However, recovery from some relapses can be incomplete, resulting in increased impairment and disability.¹ However, it is during the later progressive phase that the majority of the permanent disability is acquired. The impact of MS on the individual is variable but uncertainty is a constant feature which adds an extra psychological burden.

Management must be tailored to the individual patient in order to cope with the ongoing variability of the condition. In addition to treating acute relapses and managing clinical symptoms, disease modifying therapies (DMTs) are prescribed to decrease relapse frequency. This will have a direct effect on function but in addition there is the hope that reducing inflammation will lead over the longer-term to a reduction in subsequent neurodegeneration and disability.

Key aims of MS treatment currently include:

- Managing the wide and varied range of clinical symptoms and associated problems
- Treating active inflammatory disease i.e. acute relapses
- Disease modification: reducing/preventing future relapses and reducing disability
- Encouraging adherence to treatment in order to maximise the efficacy

The availability of disease modifying therapies (DMTs) for the treatment of MS in the 1990s represented a major step forward in the management of MS. These agents are currently considered to represent the best disease modifying therapeutic options for the treatment of RRMS.

Glatiramer acetate (Copaxone® – subcutaneous) and the other disease modifying drugs licensed for RRMS, interferon beta-1b (Betaferon® - subcutaneous) and interferon beta-1a (Avonex® - intramuscular; Rebif® - subcutaneous) have been shown to decrease relapse rate, increase the proportion of relapse-free individuals, decrease frequency of new enhancing lesions on magnetic resonance imaging (MRI) and decrease accumulating T2 MRI lesions burden.² This article will review the evidence and latest developments with glatiramer acetate (GA), one of the currently approved DMTs for RRMS.

What is glatiramer acetate?

Glatiramer acetate is a non-steroidal and non-interferon DMT. Its mode of action, which is based on its



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similarity to natural myelin, is different to that of interferon beta and other anti-inflammatory drugs used in MS. Previously referred to as copolymer-1 (Cop-1), it is made up of randomly assembled synthetic polypeptides composed of the four major amino acids found in the basic protein of myelin: L-alanine, L-glutamic acid, L-lysine and L-tyrosine.

The full mechanism of action of GA in humans still has some uncertainty attached. Possible processes include facilitating a shift to a less pro-inflammatory immune response, tolerance of a myelin response, or a broader neurotrophic effect.³

Clinical trials with glatiramer acetate

The first double-blind, randomised, placebo-controlled trial of GA in patients with RRMS was conducted in the US in the 1980s. Results showed the proportion of relapse-free patients was significantly higher in the GA-treated cohort compared to the placebo group (56% vs. 26%; $p=0.045$). The overall two-year relapse frequencies were 0.6 and 2.7 in the GA and placebo groups, respectively. The mean unconfirmed improvement on the Kurtzke Disability Status Scale (DSS) was 0.5 units with GA, whereas those taking placebo worsened by an average of 1.2 DSS units ($p=0.012$).⁴

A pivotal US multi-centre study of patients with RRMS, with two or more relapses in the two years before enrolment, showed a relapse rate at 24 months of $1.19 + 0.13$ for those treated with GA compared to $1.68 + 0.13$ for the placebo group, a 29% reduction in favour of GA ($p=0.007$); annualised rates were 0.59 and 0.84, respectively.⁵ The proportion of patients who improved, were unchanged or worsened by > 1 point on the expanded disability status scale (EDSS) at the end of two years, also favoured GA ($p=0.037$),⁵ although sustained disability was not reduced over the two years. At the end of a blinded extension phase (extended by a mean of 5.2 months in the GA and 5.9 months in the placebo arm) there was a 32% reduction in mean relapse rate with GA (1.34 for GA and 1.98 for placebo, $p=0.002$), with annualised relapse rates of 0.58 and 0.81, respectively. During the entire extended trial, 33.6% and 24.6% of GA -versus placebo-treated patients remained relapse-free, respectively ($p=0.035$).⁶

Continuous open label prospective follow-up of this study is ongoing.⁷ Of the original 251 patients, 208 chose to continue in the follow-up study and were all given GA. The annualised relapse rate of

patients treated from the beginning of the study dropped each year. Of the 152 patients followed at almost six years of continuous treatment with glatiramer acetate since trial entry, 25.7% remained relapse free.⁸ The mean annualised relapse rate of over six years for those who received GA from randomisation was 0.42 (95% CI=0.34-0.51), a 72% decrease compared with their pre-study rate.⁹ Of those treated with the agent from study inception, 69.3% were either neurologically unchanged (within 0.5 EDSS units of baseline) or had improved by at least one unit on the EDSS.⁸

At eight years, 56.6% of the original patients remained in the study.¹⁰ The annual relapse rate had declined to 0.2.¹⁰ The mean EDSS for the entire cohort was 3.14, which represents an increase of 0.55 units from randomisation.¹⁰ Patients treated with glatiramer acetate continuously for the entire ten-year study period showed better outcomes than those switched from placebo to GA which has led to the suggestion that earlier treatment may be more beneficial in the long-term.¹¹ However, it is difficult to draw conclusions from the extension phase due to factors such as regression towards the mean, the natural history of relapse rate reduction over time and patients continuing on treatment being unrepresentative of the total group.⁸ Indeed the GA from onset arm who entered the open label phase progressed in disability and relapsed less during the double blind phase than those who did not continue in the study. A similar bias in relapse frequency and in disability progression was seen in the placebo at onset group;⁸ for disability progression however the bias in this group was not statistically significant.⁸

Magnetic resonance imaging (MRI) studies provide a non-invasive estimate of some of the pathological changes in the central nervous system (CNS). MRI studies have shown that GA can reduce the number of new enhancing lesions,¹² decrease volume of enhancing lesions,¹² reduces the number of recently formed new lesions¹² and reduces the proportion of new lesions that develop into permanent black holes.¹³ Further data have shown an improvement in NAA:Creatinine ratios in patients treated with GA suggesting neuro-axonal recovery in MS patients.¹⁴

Combination therapy

Interferon beta and GA have different mechanisms of action, so it is reasonable to consider combination therapy. In vitro studies have shown both drugs have a greater effect on reducing the proliferation of myelin basic protein (MBP) -specific T cells than either drug alone.¹⁵ A small 12-month study of combination therapy with interferon beta -1a and GA showed that the combination was well tolerated and statistically significant improvements in the MSFC at six months and walking time at 12 months were demonstrated.¹⁶ A larger trial has been funded through the National Institute of Health to further explore these initial observations.

Tolerability

The long-term tolerability and safety of GA was investigated in patients with RRMS with over a

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decade of continuous use, with injection site reactions being the most common adverse effect.⁷ Immediate Post-Injection Reactions are described, which include one or more symptoms from vasodilatation, tachycardia, chest pain, dyspnoea or palpitations. These are short-lived, resolve spontaneously and do not persist over time.¹⁷ No time dependent adverse effects were observed and there was no evidence of haematological, hepatic or renal dysfunction, emergence of malignancy or development of other autoimmune diseases.⁷ Of 124 withdrawals from the ongoing, prospective study 23 were due to adverse events, 27 to patient perception of disease worsening and 22 to patient desire to switch or combine therapies. The remainder included reasons such as pregnancy or difficulty or unwillingness to adhere to the study protocol.⁷ The readiness of the 108 (46%) ongoing patients to continue the use of GA after ten years indicates the tolerability and safety of the drug.⁷ With long-term use, regular injections can result in skin changes, including lipoatrophy.¹⁷ These are usually mild¹⁷ and can be reduced and managed by good injection practice.

Glatiramer acetate in clinical practice

Glatiramer acetate is indicated for the reduction in frequency of relapses in ambulatory patients with RRMS characterised by at least two attacks of neurological dysfunction over the preceding two-year period.¹⁷ When the National Institute for Clinical Excellence (NICE) reviewed GA and interferon beta for use by the NHS the cost-effectiveness analyses obtained from the short-term data did not reach the required threshold. It was advised that DMTs be prescribed in a cost-effective manner to NHS patients and thus the 'risk sharing' agreement between the pharmaceutical companies and the Department of Health was set up. This scheme makes DMTs available to eligible patients on condition that the disability change is monitored in a cohort over ten years and that a target of £36,000 per QALY should be met over a twenty year projection - if necessary with price adjustment of the treatment.¹⁸

Under the risk sharing scheme, patients with RRMS who meet the 2001 criteria developed by the Association of British Neurologists, are eligible for NHS funded treatment.¹⁹ These guidelines state that patients can be offered GA provided that they have RRMS; can walk 100 metres or more without assistance; have had at least two clinically significant relapses in the past two years; are aged 18 years or older and do not have contraindications. The scheme recommends that any of the drugs should be stopped if patients suffer intolerable side-effects; become pregnant or are planning pregnancy; suffer two disabling relapses within a 12-month period; develop secondary progressive MS or lose the ability to walk, with or without assistance, for longer than six months.¹⁹

Interferon beta is associated with the development of neutralising antibodies (NABs) and the proportion of patients varies according to the specific formulation prescribed. Recently published guidelines from the European Federation of Neurological Societies (EFNS) on the use and relevance of NAB measurements, recommend that tests for the presence of NABs should be performed on

all patients treated with interferon beta at 12 and 24 months, positive tests should be reconfirmed after 3-6 months and patients who have persistently high levels of neutralising antibodies should have their interferon beta therapy discontinued.²⁰ Switching to GA is clearly still an option if these patients remain eligible. GA binding antibodies are common in patients on GA. Binding antibodies have not been shown to have an effect on disability or side-effects and there may even be a beneficial influence on relapses.²¹ It should be noted that because the efficacy of GA is likely to be related to its activation of immune mechanisms the production of antibodies may theoretically be beneficial.

A recent study demonstrated that prior treatment with interferon beta-1b does not reduce the efficacy or affect the tolerability of GA.³ The prospective, open-label study evaluated the efficacy of GA in a group of patients previously treated with interferon beta-1b (n=247) and a group of treatment-naïve patients (n=558). Results showed that annual relapse rates declined by about 75% in both cohorts.³ The researchers concluded that switching to GA could benefit patients who discontinue interferon beta therapy.

There is also growing interest in the use of DMTs in combination with short-term anti-inflammatory agents to treat patients with highly active forms of MS. Mitoxantrone (an immunosuppressant usually used to treat cancer, which has been approved for use in MS in the US) has previously been shown to reduce relapses in MS,²² but its long-term use is limited by its potential toxicity.²³ Previous attempts to extend its effectiveness with subsequent use of interferon beta have shown a deterioration in three out of ten patients.²⁴ In a recent observational study a combination of a limited course of mitoxantrone was overlapped with and followed by long-term GA in a consecutive series of 27 patients. The rapid reduction in relapse activity observed following the initiation of mitoxantrone was successfully maintained by the use of GA as a follow-up treatment. Results showed a sustained 90% reduction in annualised relapse rate (p<0.001), falling from 2.7 to 0.106 relapses per year, which has been maintained for a mean of 36 months in follow-up so far.²⁵ The combination therapy improved, or at least stabilised, existing levels of disability in the 27 patients taking part in the study, as measured by both clinical and MRI criteria. Thus the option of follow on therapy with GA appears to be promising.

Conclusion

MS is a chronic disabling disease. Although the immunopharmacology of GA is complex and not yet completely understood, it represents a useful and well-tolerated DMT for patients with RRMS. In addition, the lack of a requirement for routine blood test monitoring makes it a valuable option in practice. Glatiramer acetate offers an attractive first line therapy in the treatment of patients with RRMS and is the logical alternative for patients who are not responding adequately to interferon beta or who develop interferon beta NABs, and for those who suffer intolerable side-effects. The use of GA in combination with other immunosuppressive treatments looks promising for the future.

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