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Glatiramer Acetate

A Review of its Use in Relapsing-Remitting Multiple Sclerosis

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Data Selection

Sources: Medical literature published in any language since 1980 on glatiramer acetate, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'glatiramer acetate' or 'copolymer-1' or 'COP-1'. EMBASE search terms were 'glatiramer acetate' or 'COP-1'. AdisBase search terms were 'glatiramer-acetate' or 'copolymer-1' or 'COP-1'. Searches were last updated 16 October 2002.

Selection: Studies in patients with relapsing-remitting multiple sclerosis who received glatiramer acetate. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: glatiramer acetate, relapsing-remitting multiple sclerosis, pharmacodynamics, pharmacokinetics, therapeutic use.

Contents

Summary

Abstract

Glatiramer acetate is a synthetic copolymer composed of a random mixture of four amino acids that modifies the immune response that results in the CNS inflammation, demyelination and axonal loss characteristic of relapsing-remitting multiple sclerosis (RRMS).

In three randomised, double-blind trials in patients with RRMS, subcutaneous glatiramer acetate 20 mg/day was significantly more effective than placebo for the primary outcome measure of each trial (mean relapse rate, proportion of relapse-free patients and number of gadolinium-enhancing lesions on magnetic resonance imaging [MRI] scans). The mean relapse rate was significantly reduced at endpoint (approximately one-third less) in the two larger trials (the US pivotal trial [primary endpoint] and the European/Canadian study [tertiary endpoint]) in patients receiving glatiramer acetate compared with those receiving placebo. The rate was 78% less for glatiramer acetate than placebo patients in the pilot trial that investigated a slightly different patient population. Glatiramer acetate significantly decreased disease activity and burden of disease, as assessed in the European/Canadian study using a range of MRI measures. Patients with RRMS treated with glatiramer acetate in the US trial were significantly more likely to experience improved disability (whereas placebo recipients were more likely to experience worsening disability) and their overall disability status was significantly improved compared with placebo recipients. Data from the active-treatment extension of the US trial suggest that glatiramer acetate has sustained clinical benefits up to 8 years.

Glatiramer acetate was generally well tolerated; the most commonly reported treatment-related adverse events were localised injection-site reactions and transient post-injection systemic reactions. Both reactions were generally mild and self limiting but were responsible for the majority of withdrawals from treatment (up to 6.5 and 3.5%, respectively). Glatiramer acetate is not associated with the influenza-like syndrome or neutralising antibodies that are reported in patients treated with interferon-β for RRMS.

The cost effectiveness of glatiramer acetate has yet to be definitively determined as assessment of available data is confounded by very different models, data sources and assumptions.

Conclusion. Glatiramer acetate has shown efficacy in well controlled clinical trials in patients with RRMS; it reduces relapse rate and decreases MRI-assessed disease activity and burden. It is generally well tolerated and is not associated with the influenza-like symptoms and formation of neutralising antibodies seen with the interferons-β. Based on available data and current management guidelines, glatiramer acetate is a valuable first-line treatment option for patients with RRMS.

Pharmacological Properties

The proposed mechanism of action of glatiramer acetate in modulating the autoimmune response in relapsing-remitting multiple sclerosis (RRMS) consists of two components. The first is the induction of glatiramer acetate-specific suppressor T cells (i.e. type 2 helper T lymphocytes [T_h2]) that are capable of directly and indirectly downregulating the inflammation in the CNS associated with multiple sclerosis (MS). Human studies have shown that these glatiramer acetate-reactive T cells are initially and predominantly T_h1 type (pro-inflammatory), but with exposure to glatiramer acetate there is a shift to a T_h2/T_h3-type response (anti-inflammatory). It is these glatiramer acetate-specific suppressor T cells, not glatiramer acetate itself, that may migrate into the CNS and downregulate the inflammation that is triggered by the antigenic products of demyelination (myelin basic protein [MBP] and other myelin antigens). In a small study involving patients with RRMS, this shift from T_h1- to T_h2-type T cells induced by glatiramer acetate was accompanied by clinical benefits.

The second feature of glatiramer acetate's mechanism of action is the inhibition of the autoreactive MBP- and other myelin antigen-specific T cells that would otherwise be stimulated to proliferate and release inflammatory cytokines. Current hypotheses include glatiramer acetate acting as an altered peptide ligand and engaging various T-cell receptor (TCR)s, and glatiramer acetate engaging the TCR and downregulating the MBP-specific T-cell response possibly by delivering a non-activating signal (anergy).

Recent research suggests that neuroprotection may be another mechanism of action accounting for the beneficial clinical effects of glatiramer acetate in RRMS.

Antibodies stimulated by glatiramer acetate treatment are non-neutralising and do not affect the clinical efficacy of the drug.

Few pharmacokinetic data are available for glatiramer acetate; following subcutaneous administration, the drug is rapidly degraded in the periphery, resulting in very low or undetectable serum concentrations. Glatiramer acetate is not required to be present in the serum to exert its anti-inflammatory action but absorption in proportion to the dose administered was rapid.

Therapeutic Efficacy

Glatiramer acetate has shown efficacy in treating patients with RRMS. In three randomised, double-blind trials (including a 2-year pilot trial and the larger US pivotal [2-year] and European/Canadian [9-month] studies) glatiramer acetate 20mg once daily, administered subcutaneously in patients with RRMS, was significantly more effective than placebo for the respective primary endpoint of each trial (proportion of relapse-free patients, relapse rate and number of enhancing lesions on magnetic resonance imaging [MRI] scans).

For patients receiving glatiramer acetate compared with those receiving placebo in the two larger comparative studies, the mean relapse rate (covariate adjusted) at study endpoint was 29% lower in the large US trial (where relapse rate was the primary endpoint) and 33% lower in the European/Canadian study (where relapse rate was the tertiary endpoint). In the pilot trial, glatiramer acetate recipients had a mean relapse rate 78% lower, and they were more than twice as likely to be relapse free, than placebo recipients. Relapse-related results in this pilot trial have not been reproduced in larger trials, possibly due to the patient population's having a shorter duration of disease and a higher baseline relapse rate than those in subsequent studies.

Glatiramer acetate decreased disease activity and burden of disease, as assessed by analysis of MRI scans, in patients enrolled in the European/Canadian study

where certain MRI measures were the primary and secondary endpoints. For the primary outcome measure, patients in the glatiramer acetate-treated group demonstrated 29% fewer gadolinium-enhancing CNS lesions (areas of acute inflammation representing disruption of the blood-brain barrier) than patients in the placebo group. For secondary MRI outcomes, glatiramer acetate showed significantly greater lesion reductions (ranging from 30 to 82.6%) than placebo. Although this 9-month trial period was considered too short to demonstrate a significant reduction in the volume of hypointense T1 lesions (representing areas of demyelination and axonal loss), further analysis of these scans has shown that, after 8 months, the proportion of new T2 lesions evolving into these hypointense T1 lesions ('black holes') in patients receiving glatiramer acetate was half that shown in patients receiving placebo.

Progression to sustained disability, as measured by the Kurtzke Expanded Disability Status Scale (EDSS), was a secondary endpoint in the two long-term trials. Patients with RRMS treated with glatiramer acetate in the pivotal US trial were significantly more likely to experience improved disability, and placebo recipients were more likely to experience worsening disability. The overall disability status was also significantly improved in this trial, although the change was modest. The pilot trial showed positive trends in delaying the onset or worsening of disability, although it did not have adequate statistical power to evaluate this outcome.

Preliminary results data from the active-treatment extension of the US trial suggest that glatiramer acetate has sustained clinical benefits up to 8 years.

Pharmacoeconomics

Two studies conducted in 2000 and 2001 investigating the cost effectiveness of glatiramer acetate in the treatment of RRMS are difficult to compare as they used different models and data sources and led to different conclusions.

According to a cost-utility analysis based on the clinical outcomes of a large placebo-controlled trial (the US pivotal trial) and its extensions, glatiramer acetate is cost effective compared with best supportive care alone for RRMS, from the perspective of the UK National Health Service. Cost-utility ratios improved with a longer duration of treatment for all three cost variables. At 8 years, cost per relapse avoided was £11 000, cost per disability unit avoided was £8 862 and cost per quality-adjusted life-year (QALY) gained was £22 586 (year 2000 costs).

An analysis conducted by the National Institute of Clinical Excellence used longer term modelling and concluded that neither glatiramer acetate nor the interferons-β were cost effective in the treatment of RRMS. The best mean cost per QALY gained (i.e. at 20 years of treatment and including MS Research Trust data on quality of life), expressed as a range covering all the agents under investigation, was between £35 000 and £104 000, which was more than the value considered favourable in the UK (£30 000).

Given the complexities of cost-effectiveness assessments in RRMS, a lifelong, disabling disease (for which clinical benefits of long-term treatment have only recently been published) and the limited amount of information available at present, it is impossible to draw a single definitive conclusion regarding the cost effectiveness of glatiramer acetate, and further data and evaluations in this field would be useful.

Tolerability

Subcutaneously administered glatiramer acetate 20mg is generally well tolerated. The most commonly reported treatment-related adverse events (data from three placebo-controlled clinical trials and pooled results from two of these and other

trials) are localised injection-site reactions and transient post-injection systemic reactions. The incidence of injection-site reactions (manifesting mainly as pain and erythema) was 64 and 73% with glatiramer acetate versus 37 and 38% with placebo (no p value reported).

Post-injection systemic reactions occurred with an incidence of 10–38% with glatiramer acetate versus <1–13% with placebo (no p value reported) and manifested as one or more symptoms (facial flushing, chest tightness, dyspnoea, palpitations, tachycardia, anxiety and/or sweating) occurring within minutes of an injection and lasting for 30 seconds to 30 minutes.

Both reactions were generally mild and self limiting but accounted for the majority of withdrawals from treatment. Overall withdrawal rates ranged from 6–8% with localised injection-site reactions accounting for up to 6.5% and post-injection systemic reactions for up to 3.5% (vs 0.8% with placebo, no p value stated).

Serious treatment-related events occurred in ≤2% of patients enrolled in clinical trials and, although no anaphylaxis was reported during the trials, three non-fatal cases of allergic reaction have since been recorded.

Glatiramer acetate is not associated with the influenza-like syndrome reported in patients treated with interferon-β.

Dosage and Administration

Glatiramer acetate is indicated for the long-term management of RRMS and is currently approved in numerous countries worldwide including the USA, Canada, the UK and many other European countries. Glatiramer acetate is administered once daily by subcutaneous injection at a standard dose of 20mg. Data on the use of glatiramer acetate in pregnant and nursing women, the elderly, patients younger than 18 years and those with impaired renal function are limited. Contraindications include intravenous administration and hypersensitivity to glatiramer acetate or mannitol (which is included in the injection formulation).

1. Introduction

Multiple sclerosis (MS) is a chronic, inflammatory disease of the CNS usually diagnosed in young adults (aged 20–40 years)[1] and affecting an estimated 2.5 million people worldwide.[2] It is an autoimmune condition,[3-5] possibly triggered in genetically susceptible individuals by one or more agents in the environment,[6,7] that results in unchecked inflammation causing demyelination of areas in the brain and spinal cord. Relapsing-remitting MS (RRMS) is the most common type of MS; approximately 85% of patients present with this type of MS.[1,7,8] It manifests as self-limited attacks of neurological dysfunction (relapses)[9] during which the patient experiences a sudden worsening of neurological symptoms such as numbness, tingling, muscle weakness, spasticity, visual disturbances, fatigue and dizziness.[10,11] These relapses are interspersed with periods of complete or partial remission. Although some patients continue on this course without becoming seriously disabled,[6,7,12,13] the majority (about 80%)[14] enter a phase within 5–15 years in which they experience an increase in overall disability with or without relapses (secondary progressive MS).[7,8,13,14] Within 10–15 years of a diagnosis of MS, 50% of patients are unable to walk unassisted,[6,15] and after 25 years 50% are wheelchair bound.[15]

Management of RRMS includes multidisciplinary rehabilitation, pharmacotherapy for symptoms and treatment of relapses and, more recently, pharmacotherapy for modifying the underlying disease in an attempt to prevent relapses and delay the progression to disability.[6,8,12]

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