drug information perspectives

Volume 29 (3) 2009

Contents

GLATIRAMER

SYNONYM: Copolymer 1

TRADE NAME: Copaxone

CLASSIFICATION: Immunomodulator; multiple sclerosis treatment; disease-modifier

ACTION:
Complex and not completely understood.

In multiple sclerosis, myelin sheath destruction and axonal loss may be due to inflammation caused by inflammatory cytokines produced by autoreactive T lymphocytes. Glatiramer does not enter the CNS, it acts peripherally. (1) It may reduce inflammation, by shifting pro-inflammatory Th1 responses to Th2 anti-inflammatory responses. Glatiramer-specific Th2 T cells are produced in the periphery, cross the blood brain barrier, are activated in the CNS by cross-reaction with myelin antigens, and then secrete anti-inflammatory cytokines such as IL-4, IL-5 and IL-10, which decrease inflammation (bystander suppression); (2) alters the activity of antigen-presenting cells such as monocytes and dendritic cells; (3) it may be neuroprotective: glatiramer-specific Th1 and Th2 T cells produce brain derived neurotrophic factor (BDNF), which mediates neuronal repair; (4) induces peripheral glatiramer-specific IgG4 antibodies that peak at 3 months then decrease to a low level; function unknown; (5) it may restore a low CD8+ response, and decrease free radicals.

Structurally resembles myelin basic protein (MBP) which can induce Experimental Allergic Encephalitis in animals, an animal model of multiple sclerosis; competes with the binding of MBP and other antigens to MHC-II on antigen-presenting cells. Preparations vary in their composition as a mixture of synthetic polypeptides (L-glutamic acid, L-lysine, L-alanine and L-tyrosine).

PHARMACOKINETICS:
Half-life: No data.
Absorption: This polypeptide mixture is rapidly hydrolysed at the injection site to free amino acids and short peptides, leaving 10% intact at the injection site after one hour.

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Distribution: Parent drug and hydrolysis products enter the lymphatic system and from there the systemic circulation. Highly polar and hydrophilic, therefore distribution is poor across the blood brain barrier. Not detected in plasma in humans.
Metabolism: See Absorption.
Elimination: Not detected in human urine or feces. In animals, major excretion is in urine with traces in feces.
Special populations:
- ***Elderly***: No data.
- ***Hepatic impairment***: No data.
- ***Renal impairment***: No data.
- ***Sex difference***: No data.
- ***Race***: No data.
- ***Pharmacogenetics***: No data.

USES AND EFFICACY:
Uses:
Effective symptomatic treatment of **Relapsing-Remitting Multiple Sclerosis**. The annualized relapse rate is reduced by 30% over 2 years. Benefit on sustained disease progression is less clear. Fewer patients show worsened disability in the short-term. Open-label longer term studies suggest that continued treatment may increase the likelihood that patients will remain ambulatory; more data are needed. MRI results show a decrease in T1 lesions and black holes.

Clinical course:
Response is slow, starting after 6-12 months, possibly related to the slow shift from Th1 to Th2 T cells around month 6 (see ACTION).

Major clinical trials
US Glatiramer Acetate Trial: In a randomized, double-blind placebo-controlled trial begun in 1991, 251 patients with relapsing-remitting multiple sclerosis and mean EDSS (disability) scores 2.4-2.8, with a mean prior 2-year relapse rate of 2.9, and average disease duration of 7 years were treated with glatiramer or placebo for 2 years. Patients with type 1 diabetes, Lyme disease or using NSAIDs were excluded. Glatiramer significantly reduced the 2-year relapse rate by 29% (0.59 versus 0.84 with placebo), with greatest benefit in those with lower initial disability scores. More patients improved and fewer deteriorated by 1 point on the mean EDSS when given glatiramer; however, there was no benefit on disease progression. Injection site irritation and post-injection reactions were common. [Neurology 1995;45:1268-1276.] After six years of followup, progression to disability was possibly less with treatment; 30% of patients using glatiramer had worsened EDSS compared with 77% in studies of the natural history of the disease. After 10 years of open-label treatment, 47% of the original active treatment group were continuing with the injections; 42% of these patients had worsened disability, and only 8% had an EDSS score of 6 (indicating that 92% could walk unaided), compared with this score in 28% of historical controls. Relapse rates were lower than baseline by about 80% after ten years without a major increase in disability. [Multiple Sclerosis 2006;12:309-320.] ***Study limitations***: Partly funded by the manufacturer. The initial placebo-controlled study was too short to show an effect on disease progression, especially with patients in the early stages of disease. Subsequent open trials suggest less disability but are hard to interpret without a proper control group. EDSS is not a sensitive or reliable measurement of disability; better disability scales e.g. MSFC, are preferred. Given the post-injection and injection site reactions with glatiramer, blinding may have been compromised. In the ten-year followup study, benefit may be overestimated since the 47% of patients who continued treatment were probably those who did well.

European/Canadian Glatiramer Acetate Study (2001): A randomized, placebo-controlled double-blind trial evaluated MRI results in 239 patients with relapsing-remitting MS, average age 34, mean disease duration 8 years, prior 2-year relapse rate 2.5-2.9, and mean number of enhancing lesions (indicative of local inflammation) 2.5-2.6. After 9 months, patients given glatiramer had significantly fewer enhancing lesions, fewer new T2 lesions (measure of disease burden), fewer relapses, significantly less change in EDSS and were significantly more likely to be progression-free.

Comparisons

Vs. Interferon beta

- Glatiramer has been equivalent to or better than interferon beta for short-term reduction of relapse rates. In an open randomized comparison of interferon beta-1a (Rebif) 44 mcg sc 3 times weekly versus glatiramer 20mg sc daily, there was no difference in annualized relapse rates after 96 weeks, no difference in T2 active lesions, but fewer gadolinium-enhancing lesions with interferon. Side effect profiles differ: flu-like symptoms and headache with interferon versus local and systemic injection reactions with glatiramer.

Advantages:

- While all patients develop IgG4 antibodies, there is no evidence that this reduces efficacy (unlike interferon beta)

Disadvantages:

- No data on prevention of longterm disability
- Daily injections

Place in therapy:

A first line therapy for maintenance treatment of relapsing-remitting MS. Degree of efficacy is controversial; an independent Cochrane review concluded that glatiramer does not prevent disease progression or substantially reduce relapse rates, while a meta-analysis that was partly company-sponsored and performed on the same studies found that it does reduce relapse rates. May be useful in patients who do not respond to interferon beta, or develop neutralizing antibodies to it.

Effect on disability and on relapse rates is controversial; short-term studies have difficulty showing an effect in a slowly progressive disease such as MS, but long-term placebo-controlled studies cannot be done for ethical reasons, and EDSS is not ideal for measuring disability.

Investigational/Unapproved Uses:

- ***Children***: In an open study with 7 children age 8-16 years, adverse events were similar to those seen in adults; efficacy was unclear but possibly useful in less severe disease. In a second study of 14 children, tolerance was good and relapse rates were low.
- ***Clinically Isolated Syndrome (CIS)***: The PreCISe study, evaluating the effect of glatiramer versus placebo over three years or until clinically definite MS occurs, was terminated early because of significant benefit, a 45% reduction in the development of MS.
- ***Combination therapy in Relapsing-Remitting MS***: Induction with mitoxantrone followed by glatiramer maintenance therapy has been effective in reducing MRI activity. Glatiramer plus interferon beta may be antagonistic; further research is needed. The combination of glatiramer and another drug for MS, natalizumab, has reduced MRI activity but not clinical outcomes, and is not recommended due to the risk of progressive multifocal leukoencephalopathy with natalizumab.
- ***Higher dosing***: A higher dose of 40mg daily has been investigated and may have greater efficacy, but it causes more frequent injection site reactions, urticaria, post-injection reactions, and affect lability.
- ***Neuromyelitis optica***: Reduced relapse rates in a few cases.
- ***Primary Progressive Multiple Sclerosis***: The PROMiSe trial failed to demonstrate benefit.

CONTRAINDICATIONS AND PRECAUTIONS:

Contraindications:

- ***Hypersensitivity***
- ***Intravenous injection*** (must be given subcutaneously).
- ***Children*** (no data).

Precautions:

- ***Patients with cardiovascular disease*** (risk unknown; trials excluded patients with cardiovascular disease; chest pain is a frequent adverse effect).
- ***COPD, asthma, anaphylaxis*** (risk unknown; not included in research trials).
- ***Immune function impairment*** (since this drug alters immune function, increased infection risk and altered immune response is possible).

- ***Injection site technique*** (risk of permanent lipoatrophy at the site of injection; follow proper technique).
- ***Report*** unexpected or serious reactions to Canada Vigilance, Canada's adverse drug reaction monitoring program.

PREGNANCY AND LACTATION:
Not teratogenic in animals. Two women who became pregnant discontinued therapy and delivered healthy babies. Among 31 pregnant women exposed in the first trimester, two babies were born with major malformations (club feet, cardiac defect); data are too few for any definite conclusion. MS relapse rates generally decrease during pregnancy. Assess risk:benefit.

No data on exposure through breast milk or effects on the infant. Unlikely to be excreted in breast milk due to the high molecular weight. MS relapse rates generally increase in the first three months postpartum. Caution.

SIDE EFFECTS:

Cardiovascular: Chest pain (26% vs. 10% with placebo; transient, onset after one month, may be part of a post-injection reaction (see Other)). Vasodilation (27% vs. 11% with placebo). Palpitations (11% vs. 5% with placebo). Peripheral edema (11% vs. 6% with placebo). Syncope (6% vs. 3% with placebo). Hypertension (frequent).

CNS: Migraine (7% vs. 4% with placebo). Abnormal dreams (frequent). Convulsions (case reports). Affect lability (at higher than recommended doses).

Dermatologic: Injection site reactions (90% versus 59% with placebo over 2 years; pain in 66%, redness in 58%, pruritus in 38%, induration in 20%; necrosis; mild reactions may respond to oral antihistamines or massage of injection site). Localized panniculitis (inflammation of subcutaneous fat, may precede lipoatrophy). Lipoatrophy at injection site (loss of subcutaneous fat, may be permanent; 1-2 cm deep depressions; asymptomatic; may progress even after discontinuing the drug; stop injecting in that site). Wart (2% vs. 0% with placebo).

Gastrointestinal: Nausea (23% vs. 18% with placebo). Vomiting (10% vs. 6% with placebo). Bowel urgency (frequent). Oral fungal infection (frequent).

Genitourinary: Vaginal fungal infection (13% vs. 7% with placebo). Impotence (2% vs. 0% with placebo). Amenorrhea, menorrhagia, urinary frequency.

Neuromuscular: Nystagmus (4% vs. 2% with placebo). Tremor (11% vs. 6% with placebo).

Ocular: Visual field defect (frequent). Eye disorder (6% vs. 1% with placebo).

Respiratory: Dyspnea (18% vs. 6% with placebo).

Other: Post-injection reaction (15-49% versus placebo 3-13%; just after injection: transient flushing, chest pain, chest tightness, tachycardia, palpitations, anxiety, dyspnea, urticaria, throat constriction; lasts 30 seconds to 30 minutes; resolves without treatment; can still occur after years of treatment). Glatiramer-specific antibodies are formed and IgG levels rise 3-fold (up to 100% of patients; clinical effect unknown). Life-threatening serum sickness (one case). Neck pain (12% vs. 7% with placebo). Facial edema (9% vs. 2% with placebo). Chills (4% vs. 1% with placebo). Lymphadenopathy (18% vs. 10% with placebo). Weight gain (6% vs. 0% with placebo). Carcinoma/neoplasm (case reports, causality unproven). Breast cancer (hazard ratio 3.1, not significant). Aggravated multiple sclerosis (case reports). Hyperthyroidism (case).

INTERACTIONS:

None known.

PARENTERAL ADMINISTRATION:
Subcutaneous injection ONLY: Single-use 20mg vials: Using a sterile syringe and adapter, transfer 1.1 mL of Sterile Water for Injection into the 20mg vial containing the powder. Gently swirl. Let stand at room temperature until solid material is completely dissolved. Withdraw 1.0 mL of the solution into a sterile syringe. Inject subcutaneously. Use within 8 hours. Discard unused solution.

DOSAGE:

Adults:
- Subcutaneous injection: 20mg once daily.

NURSING IMPLICATIONS:
For subcutaneous injection only.

Rotate sites: do not use the same injection area within 7 days. Do not inject into an area if it is sensitive or lumpy. Do not inject into an area if skin depression has occurred since that may make it worse.

Monitor the patient immediately after each injection for a post-injection reaction (flushing, chest pain, tachycardia, dyspnea, throat constriction). This usually resolves without treatment.

During therapy, assess injection sites for signs of local damage. Local redness and pain may respond to oral antihistamines or direct massage.

Encourage the patient to continue daily injections as prescribed. Results are slow and may not be apparent for months.

PATIENT INSTRUCTIONS:
Glatiramer (gla-TEE-ra-mer) is used for the treatment of relapsing-remitting multiple sclerosis.

Before using this medication, be sure to inform your physician if you are: pregnant or planning to become pregnant; breast-feeding; or have immunosuppression; cardiovascular disease, respiratory disease; allergies or history of adverse drug reactions.

Instructions for self-injection: Inject subcutaneously only. Use aseptic techniques as instructed. Inject into the back of the upper arms, abdomen, the upper buttocks and the front or outside of the thighs. Rotate sites: do not use the same injection area within 7 days. Do not inject into an area if it is sensitive or lumpy. Do not inject into an area if skin depression has occurred since that may make it worse.

Do not expose the drug product to light because it is sensitive to light. Do not reuse needles or syringes. Dispose of drug products safely.

Powder for injection: Store drug vials in refrigerator. If necessary, drug vials may be stored at room temperature for up to 14 days. Use within 8 hours of reconstitution. Discard unused portion.

Prefilled syringes: Store in refrigerator. If necessary, may be stored up to one month at room temperature. Remove the syringe for injection 20 minutes before you are going to use it to allow it to warm up to room temperature. Do not freeze it.

Irritation at the site of injection can occur. In some cases, a permanent indentation of the skin at the injection site has occurred. Do not inject into such areas again to avoid making them worse.

Some patients experience a reaction just after injecting this drug, with flushing, chest pain, palpitations, difficulty breathing, and hives. Such reactions usually go away within 15 minutes. However, if symptoms are severe, call for

medical aid immediately. If you experience this reaction or severe pain at the injection site, call your physician immediately. Do not take any more of this drug until your physician has told you to do so.

If you have experienced an unexpected or serious reaction to this drug, this can be reported to Health Canada's monitoring program (tollfree telephone 1-866-234-2345, tollfree fax 1-866-678-6789). Note that this is not an emergency number.

Store this drug in its original container, in the refrigerator (except as described above), away from heat, light and moisture. Store discarded needles and used syringes in a hard-walled plastic container with a secure lid, such as a coffee tin, and discard safely. Keep all drug products out of the reach of children.

PRESENTATION:
Injection: Powder for solution 20mg/vial. Prefilled syringes of solution 20mg/1mL.

References are available on request.

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