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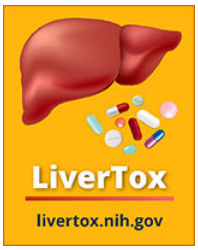

Glatiramer Acetate

Updated: March 14, 2018.

OVERVIEW

Introduction

Glatiramer acetate is a mixture of synthetic polypeptides that has unique antiinflammatory and immunomodulatory activities and that is used to treat relapsing-remitting multiple sclerosis. Glatiramer therapy is associated with a low rate of transient serum enzyme elevations during therapy and has been linked to rare instances of clinically apparent liver injury with jaundice.

Background

Glatiramer (gla tir' a mer) acetate is a mixture of synthetic polypeptides containing 4 amino acids: glutamic acid, alanine, tyrosine and lysine. The amino acid polymers have distinctive immunomodulatory activities in multiple sclerosis which are believed to be due to inhibition of binding of myelin proteins to major histocompatibility complex (MHC) molecules, which interrupts T cell activation directed at basic myelin. In several large, randomized controlled trials, glatiramer was shown to reduce relapse rates and improve neuroradiologic outcomes in adult patients with relapsing-remitting multiple sclerosis. Glatiramer was approved for use for multiple sclerosis in the United States in 1996 and is available in prefilled syringes of 20 mg and 40 mg generically and under the brand names Copaxone and Glatopa. The recommended dose is 20 mg subcutaneously once daily or 40 mg three times weekly. Common side effects are injection site reactions (pain, erythema, pruritus, induration), as well as mild and transient hypersensitivity reactions of flushing, chest tightness, dyspnea and anxiety occurring within minutes of the injection in about 10% of patients.

Hepatotoxicity

In large randomized controlled trials of glatiramer acetate in patients with multiple sclerosis, serum ALT elevations above 3 times ULN were reported in 7% of glatiramer compared to 3% of placebo recipients. The enzyme elevations were usually transient and not associated with symptoms or jaundice, requiring drug discontinuation in less than 1% of patients. No cases of acute hepatitis or clinically apparent liver injury were reported in the preregistration trials of glatiramer. Subsequent to the approval and more wide spread use of glatiramer, however, more than a dozen instances of clinically apparent liver injury with jaundice have been reported. The onset has been within 1 to 3 months of starting therapy, and the typical presentation has been with a hepatocellular pattern of serum enzyme elevations sometimes with autoantibodies (ANA, SMA), but without hyperglobulinemia or histologic features of autoimmune hepatitis. Reported cases have been self-limited with recovery within 1 to 3 months of stopping treatment. Autoantibodies also resolve with resolution of the liver injury. Some patients have later presented with spontaneous autoimmune hepatitis, which has been described in patients with multiple sclerosis not on disease modifying agents.

Likelihood score: B (likely cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which glatiramer might cause liver injury is not known, but is likely due to a triggering of an underlying predisposition to autoimmune hepatitis. The synthetic polypeptides are metabolized in multiple cells and the amino acids are probably reused in protein synthesis. Thus, the polypeptides are more likely to trigger an autoimmune reaction rather than cause direct hepatic injury or provide an immunogenic metabolic break-down product.

Outcome and Management

While chronic therapy with glatiramer acetate can be associated with mild-to-moderate serum aminotransferase elevations, these elevations are usually transient and asymptomatic and rarely require dose interruption. Rare instances of acute liver injury with jaundice have resolved with discontinuation. Corticosteroid therapy should be considered in instances with severe or persistent liver injury, but the dose and duration of therapy should be kept to a minimum. There is little evidence for cross sensitivity to liver injury among the various disease modifying drugs for multiple sclerosis such as methyl fumarate, fingolimod, teriflunomide and interferon beta. However, in several instances, the pattern of injury is similar and autoimmunity a likely mechanism.

Drug Class: Multiple Sclerosis Agents

CASE REPORT

Case 1. Acute self-limited hepatitis attributed to glatiramer acetate therapy.

[Modified from: Subramaniam K, Pavli P, Llewellyn H, Chitturi S. Glatiramer acetate induced hepatotoxicity. Curr Drug Saf 2012; 7: 186-8. PubMed Citation].

A 31 year old woman with relapsing multiple sclerosis developed fatigue, anorexia and jaundice five weeks after starting glatiramer acetate (20 mg subcutaneously once daily). Her multiple sclerosis had been recently diagnosed and she had not received previous disease modifying therapy. She had no history of liver disease, drank alcohol sparingly and denied having risk factors for viral hepatitis. She had a melanoma removed surgically 5 years previously, but did not receive systemic chemotherapy and had no evidence of recurrence. Her only other medication was thyroxine for hypothyroidism. She had a history of depression, but was not receiving antidepressants. She had no history of drug allergies and was not taking over-the-counter or herbal medications. Examination revealed jaundice, but no other evidence for acute or chronic liver disease. Laboratory testing showed a serum bilirubin of 6.4 mg/dL, ALT 1056 U/L, AST 276 U/L, alkaline phosphatase 143 U/L and GGT 341 U/L. Values had been normal when tested before glatiramer therapy (Table). Serum albumin was 3.7 g/dL, globulins 2.9 g/dL and prothrombin time 21 seconds. Tests for hepatitis A, B and C and for EBV and CMV infections were negative. While antinuclear and liver-kidney membrane antibodies were negative, smooth muscle antibodies (SMA) were present (1:320). Ultrasonography showed increased echogenicity of the liver without evidence of biliary obstruction or masses. A liver biopsy showed acute hepatitis with bridging hepatic necrosis, which was considered more likely due to a toxic than autoimmune process. Glatiramer was stopped, and she began to improve rapidly. Two months and eight months later her symptoms had resolved, SMA was no longer positive and all liver tests were normal.

Key Points

Medication:	Glatiramer acetate (20 mg subcutaneously once daily)

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Pattern:	Hepatocellular (R=~20)
Severity:	3+ (jaundice, hospitalization)
Latency:	5 weeks
Recovery:	Within two months
Other medications:	Thyroxine

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Pre	0	18	56	0.5	Routine
5 weeks	0	1056	143	6.4	Jaundice, admission
13 weeks	8 weeks	40	79	1.2	Follow-up
1 year	8 months	Normal	Normal	Normal	SMA negative
Normal Values		**<55**	**<110**	**<1.2**	

Comment

A young woman with new onset multiple sclerosis developed jaundice within 5 weeks of starting subcutaneous injections of glatiramer acetate. She had no other risk factors for liver disease and laboratory testing and hepatic imaging excluded other common causes of jaundice. The disease resolved rapidly once glatiramer was stopped. This case is fairly typical of the clinically apparent acute liver injury reported with glatiramer, with onset between 1 and 3 months of starting, a hepatocellular pattern of liver injury, occasional autoantibody formation (which can also accompany multiple sclerosis), and rapid improvement upon stopping. The cause of the injury is unclear as it is unlikely that small polypeptides could be hepatotoxic. Thus, a more likely possibility is that the liver injury is due to autoimmune response induced by the therapy, perhaps as a part of the autoimmune predisposition that accompanies multiple sclerosis. The liver injury typically resolves even without immunosuppressive therapy. Glatiramer acetate therapy has been associated with activation of other autoimmune conditions during treatment including myasthenia gravis and autoimmune thyroiditis.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Glatiramer Acetate – Generic, Copaxone®, Glatopa®

DRUG CLASS

Multiple Sclerosis Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Glatiramer Acetate	147245-92-9	Protein	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 14 March 2018

Zimmerman HJ. Oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 697-8.

(Expert review of hepatotoxicity published in 1999; glatiramer is not discussed).

Krensky AM, Bennett WM, Vincenti F. A case study: immunotherapy for multiple sclerosis. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1025-7.

(Textbook of pharmacology and therapeutics).

De Keyser J. Autoimmunity in multiple sclerosis. Neurology 1988; 38: 371-4. PubMed PMID: 3347339.

(Among 828 patients with multiple sclerosis seen at a single referral center in the UK, 4.8% had a history of another autoimmune disease [most frequently hyper- or hypothyroidism, rheumatoid arthritis or diabetes] and serologic testing showed autoantibodies in 41% of 105 multiple sclerosis patients [without known autoimmune disease] compared to 23% of neurologic disease controls, most frequently ANA and parietal cell antibodies).

Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, Myers LW, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology 1995; 45: 1268-76. PubMed PMID: 7617181.

(Among 250 patients with multiple sclerosis treated with glatiramer or placebo by daily injection for 2 years, relapse rates were 29% lower with glatiramer and side effects were similar except for injection site reactions and immediate post-injection systemic reactions [15% vs 3%]; there were no differences in laboratory test results between the two groups).

Glatiramer acetate for relapsing multiple sclerosis. Med Lett Drugs Ther 1997; 39 (1004): 61-2. PubMed PMID: 9217693.

(Concise review of mechanism of action, efficacy, safety and costs of glatiramer acetate for relapsing multiple sclerosis shortly after its approval in the US, mentions injection reactions [local and systemic], but that "no hematological or hepatic toxicity has been detected").

Frese A, Bethke F, Lün P, Stöuer F. Development of myasthenia gravis in a patient with multiple sclerosis during treatment with glatiramer acetate. J Neurol 2000; 247: 713. PubMed PMID: 11081814.

(35 year old woman with relapsing multiple sclerosis developed ptosis due to myasthenia gravis 18 months after starting glatiramer [Anti-AChR positive], glatiramer was stopped and she was treated with thymectomy, azathioprine and corticosteroids; mentions that myasthenia has been described in patients with multiple sclerosis on no specific therapy and with interferon-beta).

Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging--measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group. Ann Neurol 2001; 49: 290-7. PubMed PMID: 11261502.

(Among 239 patients with multiple sclerosis who were treated with glatiramer or placebo for 9 months, relapse rates were 33% lower in the glatiramer treated patients and side effects were similar except for injection site reactions [71% vs 28%] and immediate systemic reactions [38% vs 13%]; there were no differences in laboratory results between groups).

Heesen C, Gbadamosi J, Schoser BG, Pöu D. Autoimmune hyperthyroidism in multiple sclerosis under treatment with glatiramer acetate--a case report. Eur J Neurol 2001; 8: 199. PubMed PMID: 11285002.

(30 year old woman with relapsing multiple sclerosis developed clinically apparent hyperthyroidism 3 years after starting glatiramer therapy; no mention of autoantibody titers or liver tests).

de Seze J, Canva-Delcambre V, Fajardy I, Delalande S, Stojkovic T, Godet E, Vermersch P. Autoimmune hepatitis and multiple sclerosis: a coincidental association? Mult Scler 2005; 11: 691-3. 16320729. PubMed PMID: 16320729.

(Among 1800 patients with multiple sclerosis followed at regular 6 month intervals at a single French referral center, 5 [0.3%] developed a sustained increase in serum enzymes, 2 of whom had fatty liver disease and 3 autoimmune hepatitis [ANA negative] that eventually required long-term corticosteroid therapy).

Neumann H, Csepregi A, Sailer M, Malfertheiner P. Glatiramer acetate induced acute exacerbation of autoimmune hepatitis in a patient with multiple sclerosis. J Neurol 2007; 254: 816-7. PubMed PMID: 17351724.

(71 year old man with multiple sclerosis developed ALT elevations during interferon beta therapy and, when switched to glatiramer, developed jaundice [bilirubin 7.5 mg/dL, ALT 317 U/L, Alk P 138 U/L, ANA 1:1280], resolving within 4 weeks of stopping, but then presented one year later with spontaneous autoimmune hepatitis responding to budesonide).

von Kalckreuth V, Lohse AW, Schramm C. Unmasking autoimmune hepatitis under immunomodulatory treatment of multiple sclerosis--not only beta interferon. Am J Gastroenterol 2008; 103: 2147-8; author reply 2148. PubMed PMID: 18796115.

(42 year old woman with relapsing multiple sclerosis developed hepatitis and jaundice while on interferon beta, resolving upon stopping, but recurring within 2 weeks of starting glatiramer [bilirubin 14.7 mg/dL, INR 1.6], responding to corticosteroid therapy but developing ANA and SMA reactivity).

Deltenre P, Peny MO, Dufour A, Nady ME, Henrion J. Acute hepatitis induced by glatiramer acetate. BMJ Case Rep. 2009; 2009. PubMed PMID: 21686565.

(52 year old woman with multiple sclerosis was found to have elevated ALT levels 3 months after starting glatiramer and one month after a 5 day course of high dose methylprednisone [bilirubin normal, ALT 8 times ULN, Alk P normal, ANA 1:320], resolving rapidly only once glatiramer was stopped).

Carter NJ, Keating GM. Glatiramer acetate: a review of its use in relapsing-remitting multiple sclerosis and in delaying the onset of clinically definite multiple sclerosis. Drugs 2010; 70: 1545-77. PubMed PMID: 20687620.

(Systematic review of the mechanism of action, pharmacology, efficacy and safety of glatiramer acetate in multiple sclerosis mentions that ALT elevations are less common with glatiramer than interferon beta; no mention of hepatotoxicity).

Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, Yang M, et al.; CONFIRM Study Investigators. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med 2012; 367: 1087-97. PubMed PMID: 22992072.

(Controlled trial of dimethyl fumarate vs glatiramer vs placebo in 1417 patients with relapsing multiple sclerosis; ALT elevations above 3 times ULN occurred in 6% of dimethyl fumarate, 7% of glatiramer and 6% of placebo recipients, but no patient developed jaundice or clinically apparent liver injury).

Arruti M, Castillo-Triviñ, de la Riva P, Martíassó, Ló de Munain A, Olascoaga J. [Autoimmune hepatitis in a patient with multiple sclerosis under treatment with glatiramer acetate]. Rev Neurol 2012; 55: 190-2. Spanish. PubMed PMID: 22825980.

(46 year old woman developed fatigue 2 months after starting glatiramer acetate [bilirubin 1.8 mg/dL, ALT 579 rising to 1055 U/L, Alk P normal, INR 1.6], biopsy suggesting autoimmune hepatitis despite ANA and SMA negativity, liver tests becoming normal after corticosteroid therapy that was later switched to azathioprine alone).

Subramaniam K, Pavli P, Llewellyn H, Chitturi S. Glatiramer acetate induced hepatotoxicity. Curr Drug Saf 2012; 7: 186-8. PubMed PMID: 22873505.

(31 year old woman with relapsing multiple sclerosis developed jaundice 5 weeks after starting glatiramer acetate [bilirubin 6.4 mg/dL, ALT 1056 U/L, Alk P 143 U/L], resolving within 8 weeks of stopping: Case 1).

New drugs for relapsing multiple sclerosis. Med Lett Drugs Ther 2012; 54 (1403): 89-91. PubMed PMID: 23183318.

(Concise review of efficacy, safety and costs of new disease modifying drugs for multiple sclerosis lists side effects in a table including "transaminase elevations" for interferon beta, fingolimod and teriflunomide, and "hepatotoxicity" for natalizumab, but not for glatiramer or mitoxantrone).

Makhani N, Ngan BY, Kamath BM, Yeh EA. Glatiramer acetate-induced acute hepatotoxicity in an adolescent with MS. Neurology 2013; 81: 850-2. PubMed PMID: 23884038.

(15 year old girl with relapsing multiple sclerosis developed ALT elevations 6 months after starting interferon beta therapy and again 2 months after starting glatiramer [bilirubin normal, ALT 253 U/L, ANA & SMA negative], resolving within 2 months of stopping).

Onmez A, Eminler AT, Ergenç H, Baykara M, Uslan I, Tamer A. Drug-induced liver injury by glatiramer acetate used for treatment of multiple sclerosis: a case report. J Investig Med High Impact Case Rep 2013; 1: 2324709613517493. PubMed PMID: 26425591.

(36 year old woman with multiple sclerosis developed jaundice a month after starting glatiramer [bilirubin 24.4 mg/dL, ALT 1475 U/L, Alk P 231 U/L, ANA negative], liver tests returning to normal within 6 weeks of stopping).

Antezana A, Herbert J, Park J, Kister I. Glatiramer acetate-induced acute hepatotoxicity in an adolescent with MS. Neurology 2014; 82: 1846-7. PubMed PMID: 24843037.

(28 year old woman with multiple sclerosis developed jaundice 6 months after starting glatiramer [bilirubin 8 mg/dL, ALT 1103 U/L], resolving within 1 month of stopping and not recurring on natalizumab; mentions that FDA has received 95 reports of liver injury attributed to glatiramer).

Sinagra E, Raimondo D, Cottone S, Guddo F, Gabriele Rizzo A, Amvrosiadis G, Perricone G, et al. Does glatiramer acetate provoke hepatitis in multiple sclerosis? Mult Scler Relat Disord 2014; 3: 266-8. PubMed PMID: 25878015.

(Two women with relapsing multiple sclerosis, ages 29 and 41 years, developed jaundice one month after starting glatiramer, having had serum enzyme elevations without jaundice on interferon beta [bilirubin 4 and 5 mg/dL, ALT 1260 and 4410 U/L, Alk P 342 and 383 U/L, ANA 1:160 and 1:320], resolving with stopping in one patient, but requiring long term corticosteroid therapy in the second).

La Gioia S, Bacis G, Sonzogni A, Frigeni B, Conti MZ, Vedovello M, Rottoli M. Glatiramer acetate-induced hepatitis in a young female patient with multiple sclerosis. Mult Scler Relat Disord 2014; 3: 732-4. PubMed PMID: 25891553.

(25 year old woman with relapsing multiple sclerosis developed ALT elevations 7-8 months after starting glatiramer [ALT 106 rising to 1433 U/L, bilirubin 1.5 mg/dL, Alk P 113 U/L, ANA & SMA negative], resolving within 2 months of stopping).

Pawate S, Bagnato F. Newer agents in the treatment of multiple sclerosis. Neurologist 2015; 19: 104-17. PubMed PMID: 25888198.

(Summary of the efficacy and safety of new drugs for multiple sclerosis mentions that fingolimod, laquinimod and teriflunomide have been associated with serum enzyme elevations during treatment, but no specifics given).

English C, Aloi JJ. New FDA-Approved Disease-Modifying Therapies for Multiple Sclerosis. Clin Ther 2015; 37: 691-715. PubMed PMID: 25846320.

(Systematic review of efficacy and safety of the newer disease modifying therapies of multiple sclerosis lists ALT elevations as adverse events associated with fingolimod, teriflunomide and dimethyl fumarate, but not peginterferon beta or alemtuzumab).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 7 [0.8%] were attributed to interferon beta, but none were linked to glatiramer or other drugs used for multiple sclerosis).

Feinstein A, Freeman J, Lo AC. Treatment of progressive multiple sclerosis: what works, what does not, and what is needed. Lancet Neurol 2015; 14: 194-207. PubMed PMID: 25772898.

(Commentary on management of progressive multiple sclerosis in which most of the new, disease modifying agents have little effect, and major attention should be paid to management and relief of symptoms such as fatigue, bladder dysfunction, spasticity, pain, depression and cognitive dysfunction; no discussion of liver related adverse effects).

Fernández Fernández N, Joao Matias D, Pisabarros Blanco C, Rodríguez Martín L, Aparicio Cabezudo M, Linares Torres P, Hernando Martín M, et al. [Hepatitis induced by glatiramer acetate]. Gastroenterol Hepatol 2015; 38: 280-1. PubMed PMID: 25042243.

(42 year old woman with multiple sclerosis on glatiramer for 6 months was found to have ALT elevations [bilirubin 2.2 mg/dL, ALT 602 U/L, Alk P normal] which fell into the near normal range within one month of stopping, although ANA became positive [1:640]).

Almeida J, Solà-Valls N, Pose E, Blanco Y, Sepúlveda M, Llufriu S, Gines P, et al. Liver injury and glatiramer acetate, an uncommon association: case report and literature review. Ther Adv Neurol Disord 2017; 10: 367-372. PubMed PMID: 29090021.

(65 year old woman with multiple sclerosis developed abnormal liver tests one week after starting glatiramer acetate [bilirubin normal, ALT 481 rising to 667 U/L, Alk P normal], resolving 5 months after stopping).