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Dimethyl Fumarate

Updated: July 1, 2017.

OVERVIEW

Introduction

Dimethyl fumarate is an antiinflammatory and immunomodulatory agent that is used to treat relapsing multiple sclerosis. Dimethyl fumarate is associated with a low rate of transient serum enzyme elevations during treatment, but has not been linked to instances of clinically apparent liver injury with jaundice.

Background

Dimethyl fumarate (dye meth' il fue' ma rate) is a methylated, unsaturated dicarboxylic acid which has distinctive antiinflammatory and immunomodulatory activities, both in vitro and in vivo. Its mechanism of action is believed to be via activation of the nuclear factor E2-related factor (Nrf2) pathway, which is important in modulating inflammatory cytokines and inducing antioxidant responses. Dimethyl fumarate and other fumarate esters have been used with promising results in psoriasis, sarcoidosis, alopecia areata and multiple sclerosis. In several large, randomized controlled trials, methyl fumarate (BG-12) was shown to reduce relapse rates and improve neuroradiologic outcomes in adult patients with relapsing-remitting multiple sclerosis. Methyl fumarate was approved for use in relapsing multiple sclerosis in the United States in 2013 and is now available in delayed release capsules of 120 and 240 mg under the brand name Tecfidera. The recommended dose is 120 mg twice daily for 7 days, followed by a maintenance dose of 240 mg twice daily. Common side effects are flushing (25% to 50%), gastrointestinal symptoms of nausea, diarrhea or abdominal pain (10% to 60%), dizziness, erythema (5%) and skin rash (9%).

Hepatotoxicity

In large randomized controlled trials of dimethyl fumarate in patients with psoriasis and multiple sclerosis, serum ALT elevations were frequent, occurring in up to 25% of patients. The elevations, however, were generally mild-to-moderate and resolved rapidly even without dose modification. Elevations above 3 times ULN were reported in 6% of dimethyl fumarate compared to 3% to 6% 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 methyl fumarate. Despite this, several cases of clinically apparent liver injury with jaundice were reported within 2-3 years of its approval and more wide scale use. Most cases occurred within 2 to 3 months of starting dimethyl fumarate but instances with more prolonged latency were reported. The typical case presented with acute hepatitis like features, marked increases in serum aminotransferase levels, and only modest alkaline phosphatase elevations. Immunoallergic features and autoantibodies were not frequent and all patients recovered upon stopping the medication with no reported instances of chronic injury or hepatic failure.

Likelihood score: C (probable rare cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which dimethyl fumarate causes liver injury is not known but is likely to be idiosyncratic. It is extensively metabolized by serum and tissue esterases to monomethyl fumarate, which is further metabolized in the liver to fumarate which enters the tricarboxylic acid (TCA) cycle. Dimethyl fumarate metabolism is independent of the cytochrome P450 system.

Outcome and Management

While chronic therapy with dimethyl fumarate can be associated with mild-to-moderate serum aminotransferase elevations, it has been linked only rarely to cases of clinically apparent liver injury. There is no reason to suspect that there is cross sensitivity of the hepatic injury from dimethyl fumarate with other agents used to treat multiple sclerosis.

Drug Class: Multiple Sclerosis Agents

CASE REPORT

Case 1. Acute hepatitis arising after 4 weeks of dimethyl fumarate therapy.

[Modified from: Jüngst C, Kim YJ, Lammert F. Severe drug-induced liver injury related to therapy with dimethyl fumarate. Hepatology 2016; 64: 1367-9. PubMed Citation]

A 26 year old woman with multiple sclerosis was found to have de novo elevations in serum aminotransferase levels (ALT 284 U/L) 4 weeks after starting dimethyl fumarate (120 mg twice daily). The drug was stopped, but over the next 4 weeks she developed fatigue, nausea, abdominal pain and dark urine followed by jaundice. She had no history of liver disease, alcohol abuse or risk factors for viral hepatitis and was not taking other medications. On examination, she was jaundiced, but had no rash, fever or signs of hepatic failure. Serum bilirubin was 9.0 mg/dL, ALT 1256 U/L, alkaline phosphatase 133 U/L and INR 1.58. Other causes of acute liver injury were excluded. Tests for hepatitis A, B, C and E were negative as were autoantibodies. Imaging of the liver showed no evidence of biliary obstruction. A liver biopsy showed acute hepatitis with bridging necrosis. There was bile duct injury but no duct loss, hepatic steatosis or fibrosis. During the next month, symptoms resolved and liver tests decreased towards the normal range. When seen a year later all blood tests were normal and she was being managed on glatiramer acetate.

Key Points

Medication:	Dimethyl fumarate (120 mg twice daily)
Pattern:	Hepatocellular (R=36)
Severity:	3+ (jaundice, hospitalization)
Latency:	4 weeks to ALT elevations, 7-8 weeks to jaundice
Recovery:	Within 1 to 2 months
Other medications:	None reported

Laboratory Values

Days After Starting	Days After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Dimethyl fumarate started (120 mg twice daily					

Table continued from previous page.

4 weeks	0	284			Drug stopped
8 weeks	4 weeks	1256	133	9.0	Jaundice & symptoms
	4.5 weeks	941	123	11.6	Liver biopsy
9 weeks	5 weeks	729	129	15.4	
10 weeks	6 weeks	342	137	1.6	
15 weeks	9 weeks	48	74	0.4	Asymptomatic
> 1 year	> 1 year	Normal	Normal	Normal	On glatiramer
Normal Values		**<35**	**<104**	**<1.2**	

Comment

This patient was found to have serum enzyme elevations four weeks after starting dimethyl fumarate. The aminotransferase were approximately 8 times the upper limit of normal and had been normal when tested before starting the multiple sclerosis agent. The drug was promptly discontinued, but the patient went on to develop clinical symptoms and jaundice and four weeks later had biochemical and histological features of an acute hepatitis. She was symptomatic for several weeks, but ultimately recovered without specific therapy. This was the initial report of clinically apparent liver injury due to dimethyl fumarate which had been associated with a modest rate of serum enzyme elevations during registration trials. This patient was fortunate to have had the drug stopped promptly; a delay may have led to a more severe and consequential course. Most instances of liver injury associated with dimethyl fumarate have arisen during the first 1 to 2 months of therapy and routine monitoring, as was done for this patient, is not unreasonable.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Dimethyl Fumarate – Generic, Tecfidera®

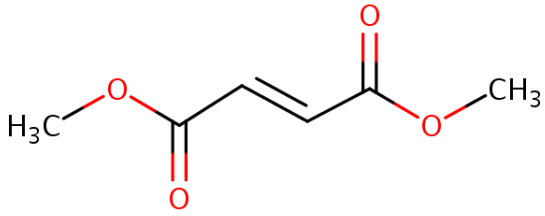
DRUG CLASS

Multiple Sclerosis Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Dimethyl Fumarate	624-49-7	C6-H8-O4	

ANNOTATED BIBLIOGRAPHY

References updated: 01 July 2017

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; dimethyl fumarate is not discussed).

Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013.

(Multi-authored textbook of hepatotoxicity published in 2013 does not discuss the drugs for multiple sclerosis).

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).

Mrowietz U, Christophers E, Altmeyer P. Treatment of psoriasis with fumaric acid esters: results of a prospective multicentre study. German Multicentre Study. Br J Dermatol 1998; 138: 456-60. PubMed PMID: 9580799.

(Open label trial of fumarate esters in 101 patients with psoriasis; major side effects were gastrointestinal complaints [56%] and flushing [31%]; biochemical laboratory results were reported to have not changed).

Hoefnagel JJ, Thio HB, Willemze R, Bouwes Bavinck JN. Long-term safety aspects of systemic therapy with fumaric acid esters in severe psoriasis. Br J Dermatol 2003; 149: 363-9. PubMed PMID: 12932244.

(Retrospective review of tolerance of fumarate ester therapy of psoriasis in 66 patients treated for up to 14 years; side effects included flushing [55%], diarrhea [42%], and decrease in lymphocyte counts; ALT elevations occurred in 2 and GGT in 14 patients, but were transient, not associated with jaundice and led to discontinuation in only 2 patients).

Harries MJ, Chalmers RJ, Griffiths CE. Fumaric acid esters for severe psoriasis: a retrospective review of 58 cases. Br J Dermatol 2005; 153: 549-51. PubMed PMID: 16120141.

(Retrospective analysis of 58 patients with psoriasis who were treated with fumarate esters; side effects of flushing, diarrhea and abdominal discomfort were common; 4 patients developed liver enzyme abnormalities, prompting discontinuation in 3, but no details provided).

Schimrigk S, Brune N, Hellwig K, Lukas C, Bellenberg B, Rieks M, Hoffmann V, et al. Oral fumaric acid esters for the treatment of active multiple sclerosis: an open-label, baseline-controlled pilot study. Eur J Neurol 2006; 13: 604-10. PubMed PMID: 16796584.

(Open label study of fumarate esters in 10 patients with multiple sclerosis; 4 patients developed ALT elevations [less than twice ULN], but all resolved without modification of dose).

Kappos L, Gold R, Miller DH, Macmanus DG, Havrdova E, Limmroth V, Polman CH, et al.; BG-12 Phase IIb Study Investigators. Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. Lancet 2008; 372(9648): 1463-72. PubMed PMID: 18970976.

(Controlled trial of 3 doses of dimethyl fumarate vs placebo for 24 weeks in 257 adults with relapsing-remitting multiple sclerosis; elevations in serum aminotransferase levels above 3 times the ULN were more common in patients on the highest doses of dimethyl fumarate, but were not accompanied by symptoms or increases in serum bilirubin and all resolved upon discontinuation; no specific details provided).

Gold R. Oral therapies for multiple sclerosis: a review of agents in phase III development or recently approved. CNS Drugs 2011; 25: 37-52. PubMed PMID: 21128693.

(Review of oral medications for multiple sclerosis under development including dimethyl fumarate [BG-12], fingolimod, teriflunomide, laquinimod and cladribine; no discussion 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, and no patient developed jaundice or clinically apparent liver injury).

Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, Tornatore C, et al.; DEFINE Study Investigators. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med 2012; 367: 1098-107. PubMed PMID: 22992073.

(Controlled trial of 2 doses of dimethyl fumarate vs placebo for up to 2 years in 1234 patients with relapsing multiple sclerosis; transient ALT elevations above 3 times ULN occurred in 6% of dimethyl fumarate vs 3% of placebo recipients, but no patient developed jaundice or clinically apparent liver injury).

Oh J, O'Connor PW. Safety, tolerability, and efficacy of oral therapies for relapsing-remitting multiple sclerosis. CNS Drugs 2013; 27: 591-09. PubMed PMID: 23801528.

(Review of efficacy and safety or oral agents for multiple sclerosis, including fingolimod, teriflunomide, dimethyl fumarate, laquinimod and cladribine, none of which have raised major issues of hepatotoxicity).

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).

Dubey D, Kieseier BC, Hartung HP, Hemmer B, Warnke C, Menge T, Miller-Little WA, et al. Dimethyl fumarate in relapsing-remitting multiple sclerosis: rationale, mechanisms of action, pharmacokinetics, efficacy and safety. Expert Rev Neurother 2015; 15: 339-46. PubMed PMID: 25800129.

(Review of the mechanism of action, pharmacology, efficacy and safety of dimethyl fumarate in multiple sclerosis, mentions that aminotransferase elevations occurred in 25% of patients, but these abnormalities generally resolved and discontinuation was required in <1% of patients; no mention of clinically apparent liver injury).

Sheremata W, Brown AD, Rammohan KW. Dimethyl fumarate for treating relapsing multiple sclerosis. Expert Opin Drug Saf 2015; 14: 161-70. PubMed PMID: 25382392.

(Review of the structure, mechanism of action, clinical efficacy and safety of dimethyl fumarate, mentions that the most common side effects are flushing and gastrointestinal complaints [pain, diarrhea and nausea] and that laboratory abnormalities include increase in aminotransferase levels and decrease in lymphocytes; no mention of clinically apparent hepatotoxicity).

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 dimethyl fumarate or other drugs used for multiple sclerosis).

Jüngst C, Kim YJ, Lammert F. Severe drug-induced liver injury related to therapy with dimethyl fumarate. Hepatology 2016; 64: 1367-9. PubMed PMID: 27228386.

(26 year old woman developed abnormal liver tests 4 weeks after starting dimethyl fumarate for multiple sclerosis, subsequently developing jaundice despite prompt discontinuation [bilirubin 9.0 mg/dL, ALT 1256 U/L, Alk P 133 U/L, INR 1.6], resolving within 2 months).

Muñoz MA, Kulick CG, Kortepeter CM, Levin RL, Avigan MI. Liver injury associated with dimethyl fumarate in multiple sclerosis patients. Mult Scler 2017 Jan 1. [Epub ahead of print] PubMed PMID: 28086032.

(Among 14 cases of liver injury attributed to dimethyl fumarate reported to the FDA during the first 3 years after its approval, 12 were women, 2 men, ages 25 to 56 years, jaundice in 8, average latency 101 days [4 to 302], mostly hepatocellular, improving with discontinuation, none fatal).