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Multiple Sclerosis Agents

Updated: July 1, 2015.

OVERVIEW

Multiple sclerosis is a chronic demyelinating disorder of the central nervous system of unknown etiology. It is most likely caused by a gradual, intermittent autoimmune destruction of myelin. The disorder is characterized by a relapsing-remitting course, but in a small proportion of paitents, it is unremittingly progressive even from the onset. The disease typically presents between the ages of 20 and 40 years and is more common in women than men. Rates of multiple sclerosis vary geographically, being highest in Northern parts of Europe and the United States and in Canada. Multiple sclerosis affects an estimated 400,000 persons in the United States and is the most common cause of neurologic disability in young adulthood.

Therapies of multiple sclerosis can be divided into disease modifying agents and symptomatic therapies. The disease modifying agents are largely immunomodulatory drugs including interferon beta-1a (Avonex, 1994 and Rebif, 2003), interferon beta-1b (Betaseron, 1993 and Extavia, 2008), peginterferon beta-1a (Plegridy, 2014), glatiramer acetate (Copaxone, 1996), alemtuzumab (Lemtrada, 2001), fingolimod (Gilenya, 2010), teriflunomide (Aubagio, 2012), and dimethyl fumarate (Tecfidera, 2013). Disease modifying agents that are used in resistant cases of multiple sclerosis some of which are not specifically approved for this use (off-label use) include methotrexate, cyclophosphamide, intravenous immunoglobulins, mitoxantrone (Novantrone), and natalizumab (Tysabri [now withdrawn]). The disease modifying agents are more effective in relapsing-remitting forms of disease than in the more severe and intractable progressive forms. Symptomatic therapies developed for multiple sclerosis include dalfampridine (4-aminopyrine, Ampyra: 2010), a potassium channel blocker that improves mobility and walking speed in patients with relapsing-remitting forms of multiple sclerosis.

While transient, asymptomatic and mild-to-moderate serum aminotransferase elevations occur not uncommonly with most of the drugs used to treat multiple sclerosis, clinically apparent hepatotoxicity is rare. Nevertheless, several convincing instances of acute liver injury have been reported for the various forms of interferon beta and glatiramer acetate. Importantly, clinically apparent liver injury was usually first attributed to these two agents several years after their introduction, and initially they were not believed to be hepatotoxic. Thus, the more recently introduced agents (fingolimod, teriflunomide and dimethyl fumarate) have not had wide enough general use to state that they do not cause clinically apparent liver injury, and all three have been associated occasionally with marked but transient increases in serum aminotransferase levels.

The following agents are discussed individually in LiverTox:

- Disease Modifying Agents
  - Alemtuzumab
  - Dimethyl Fumarate
  - Fingolimod
  - Glatiramer Acetate

ANNOTATED BIBLIOGRAPHY

References updated: 01 July 2015

Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Textbook of hepatotoxicity published in 1999, the drugs for multiple sclerosis are not discussed, the majority having been developed and introduced into clinical medicine since 1999).

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).

Interferon beta-1B for multiple sclerosis. Med Lett Drugs Ther 1993; 35 (900): 61-2. PubMed PMID: 8515719.

(Concise review of mechanism of action, efficacy, safety and costs of interferon beta-1b shortly after its approval for use in multiple sclerosis in the US, mentions that it is generally well tolerated; no mention of ALT elevations or hepatotoxicity).

Interferon beta-1A for relapsing multiple sclerosis. Med Lett Drugs Ther 1996; 38 (979): 63-4. PubMed PMID: 8692073.

(Concise review of efficacy and safety of interferon beta-1a [Avonex] shortly after its approval for multiple sclerosis in the US, mentions side effects of flu-like symptoms, injection site reactions, but does not mention ALT elevations or hepatotoxicity).

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").

Beta interferons for multiple sclerosis. Med Lett Drugs Ther 2002; 44 (1141): 88-9. PubMed PMID: 12381969.

(Concise review of efficacy, safety and costs of 3 forms of interferon beta for multiple sclerosis mentions that serum enzyme abnormalities were more frequent with Betaseron (beta-1b) and Avonex (beta-1a) than with Rebif (Beta-1a), but does not mention clinically apparent liver injury).

Natalizumab (Tysabri) for relapsing multiple sclerosis. Med Lett Drugs Ther 2005; 47 (1202): 13-5. PubMed PMID: 15711498.

(Concise review of mechanism of action, efficacy, safety and costs of natalizumab [humanized monoclonal antibody to integrin] shortly after its approval for this indication in the US, mentions hypersensitivity reactions and neutralizing antibody, but not ALT elevations or clinically apparent liver injury; this agent was withdrawn from the market one year later because of progressive multifocal leukoencephalopathy [PML]).

Alemtuzumab (Compath) off-label for relapsing multiple sclerosis. Med Lett Drugs Ther 2009; 51 (1307): 17-8. PubMed PMID: 19265776.

(Discussion of the off label use of alemtuzumab [humanized monoclonal antibody to CD52] for relapsing multiple sclerosis, mentions that side effects include infusion reactions, autoimmune thyroid disorders and thrombocytopenic purpura, but does not mention ALT elevations or clinically apparent hepatotoxicity).

Interferon beta-1b (Extavia) for multiple sclerosis. Med Lett Drugs Ther 2010; 52: 86-7. PubMed PMID: 21045760.

(Concise review of efficacy and safety of interferon beta-1b [Extavia] shortly after its approval in the US, mentions that hepatic enzyme elevations may occur).

Oral fingolimod (gilenya) for multiple sclerosis. Med Lett Drugs Ther 2010; 52 (1353-1354): 98-9. PubMed PMID: 21344782.

(Concise review of mechanism of action, efficacy, safety and costs of fingolimod shortly after is approval for use for multiple sclerosis in the US, mentions that common side effects are headache, cough, diarrhea, back pain and aminotransferase elevations; no mention of clinically apparent liver injury).

Dalfampridine (Ampyra) for MS. Med Lett Drugs Ther 2010; 52 (1347): 73-4. PubMed PMID: 20847716.

(Concise review of the mechanism of action, efficacy, safety and costs of dalfampridine shortly after its approval in the US, mentions common side effects were urinary tract infection, insomnia, dizziness, headache, nausea, fatigue, back pain and ataxia; no mention of ALT elevations or hepatotoxicity).

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 the mechanism of action, efficacy and safety of 5 new, oral therapies of multiple sclerosis, mentions serum enzyme elevations occurring in 8.5-12.5% of fingolimod treated vs 1.7% on placebo, and at an increased rate with teriflunomide).

Killestein J, Rudick RA, Polman CH. Oral treatment for multiple sclerosis. Lancet Neurol 2011; 10: 1026-34. PubMed PMID: 22014437.

(Review of the clinical usefulness and safety of 5 new oral therapies for relapsing multiple sclerosis, mentions that liver enzyme elevations can occur with teriflunomide and fingolimod therapy).

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).

Dimethyl fumarate (Tecfidera) for multiple sclerosis. Med Lett Drugs Ther 2013; 55 (1418): 45-7. PubMed PMID: 24662841.

(Concise review of mechanism of action, efficacy, safety and costs of dimethyl fumarate for multiple sclerosis shortly after its approval in the US mentions side effects of flushing, abdominal pain, nausea and lymphopenia, but not ALT elevations or hepatotoxicity).

Oh J, O'Connor PW. Safety, tolerability, and efficacy of oral therapies for relapsing-remitting multiple sclerosis. CNS Drugs 2013; 27: 591-609. PubMed PMID: 23801528.

(Review of new oral therapies for multiple sclerosis lists elevated serum enzymes as occurring with fingolimod, teriflunomide, dimethyl fumarate and laquinomod).

Peginterferon beta-1a (Plegridy) for multiple sclerosis. Med Lett Drugs Ther 2015; 57 (1468): 67-9. PubMed PMID: 25941954.

(Concise review of efficacy, safety and costs of peginterferon beta-1a shortly after its approval for use in multiple sclerosis in the US, mentions that injection site reactions and influenza-like symptoms are common adverse effects, but does not mention ALT elevations or 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).

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 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 newer disease modifying agents have little effect, stresses that 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 of medications).