Hepatic flares induced by disease-modifying treatments in patients with multiple sclerosis

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Abstract

Introduction
Multiple sclerosis is a chronic inflammatory disease of the central nervous system of autoimmune origin. During the last decades, several disease-modifying therapies have been licensed that ameliorate the course of the disease. The purpose of these DMT is to reduce inflammation, disease activity, as measured by MRI and relapse rate. However, DMT and interferons, in particular, are associated with a number of adverse reactions which include transient liver function abnormalities. The aim of this review was to discuss hepatic flares induced by disease-modifying treatments in patients with multiple sclerosis.

Conclusion
Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system of autoimmune origin. The onset of the disease is most frequently seen in young adults, between 20 and 40 years of age.

Although many aspects of MS pathogenesis have been elucidated, the exact causal mechanisms are still not fully understood. Interplay between environmental factors in genetically susceptible individuals is hypothesised. This concept is supported by a wealth of research findings. Once the disease has developed, it continues lifelong and there is still no cure. The course of the disease can be relapsing–remitting, which means that episodes with exacerbation of neurological symptoms alternate with periods of remission. Over time, these relapses often do not fully resolve, leading to a stepwise accumulation of disability. Moreover, after 10–15 years, one-half of patients with initial relapsing–remitting disease course will develop a secondary progressive disease that is characterised by a progressive increase of disability, independent of relapses and predominantly caused by deterioration of walking ability. Only about 10%–15% of patients exhibit a primary progressive disease course, which is defined by at least one year disease progression from the onset.

Although relapse rate and progression of the Expanded Disability Status Score (EDSS) are widespread parameters of disease activity, many patients with MS not only suffer from physical disability; but also suffer from neurocognitive decline, fatigue or depression. Hence, the diagnosis of MS is a life-changing event with a significant impact on family, society and the social welfare system. Fortunately, during the last decades, several disease-modifying therapies (DMT) have been licensed that ameliorate the course of the disease. The purpose of these DMT is to reduce inflammation, disease activity, as measured by MRI and relapse rate. However, DMT and interferons, in particular, are associated with a number of adverse reactions which include transient liver function abnormalities. The aim of this review is to discuss the following topics:

- The interplay between the liver and the role that immunological, environmental and pharmacological factors play in MS
- The role of interferons in inducing hepatic flares
- The role of GA in inducing hepatic flares
- The role of natalizumab in inducing hepatic flares
- The role of other treatments in inducing hepatic flares

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The disease-modifying treatments employed in MS are reported in Figure 1.

**Discussion**

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

**Multiple sclerosis and liver injury**

The liver is increasingly being thought as a site of immunological importance, containing CD4+, CD8+ and Natural Killer T cells. Liver test abnormalities in MS patients (without association with a specific drug treatment) have been reported as early as the 1950s, although the tests used in these early studies have been superseded. The possibility remains that MS itself or environmental factors associated with MS could set the MS patient to liver injury. As mentioned above, MS is recognised as an autoimmune disease. Other autoimmune diseases are associated with an increased risk of elevated liver tests. However, this association in MS has yet to be conclusively shown. Autoimmune liver diseases not related to drug treatment, have been reported in patients with MS, including cases of autoimmune hepatitis and primary biliary cirrhosis, although women in general are more likely to be affected by these diseases and a typical MS population is 60% female.

Several factors associated with the aetiology, immunology and treatment of MS could be thought as risk factors for liver injury in MS patients. In fact, MS has been associated with various viral infections (such as Epstein-Barr and herpes virus) and an increased prevalence of other diseases such as rheumatoid arthritis and inflammatory bowel disease, which are both associated with an increased risk of hepatic flares. Immunological processes in MS include elevations in numerous cytokines which have independently been associated with liver injury, including: IFN-gamma, IL-2 and TNF-alpha.

MS patients are high users of both prescribed and purchased medicines, herbal remedies and other complementary medicines. Polypharmacy, particularly with cytochrome P450 enzyme inducing or inhibiting agents, increases the risk of drug-induced hepatotoxicity. There are several reported cases of liver disturbances ranging from autoimmune hepatitis to fulminant liver failure and death in MS patients treated with specific drugs, other than the beta-interferons. Some of these drugs are independently associated with liver injury, such as pomepine, dantrolene, tizanidine, nitrofurantoin and azathioprine; while others have not been previously or have rarely been, associated with liver injury, such as potassium paminobenzoate, ranitidine, alkaloid contamination of herbal remedies (skullcap and pau d’arco). Theoretically, periods of active disease or exacerbation could increase the risk of liver injury. Multiple biological and environmental changes occur from trigger factors, such as viral infection, to in vivo cytokine modifications and the introduction of medications to treat relapse such as corticosteroids, but also glatiramer acetate and natalizumab.

**Figure 1:** Mechanisms of action of disease-modifying drugs in multiple sclerosis.

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β-1a treatment developed in the first six months after receiving interferon. In a study of more than 1,000 patients who received interferon β-1a treatment, 75% of liver function impairment developed within the first six months after starting therapy and regular liver function monitoring was suggested only during the first six months of treatment. Delayed liver function impairment is rare in the literature review. Only Christopher and coworkers and Liao and coworkers report a multiple sclerosis patient with delayed liver function impairment three years after interferon β treatment. Most multiple sclerosis patients on interferon treatment who had elevated liver function tests were usually asymptomatic and mild cases. Elevated liver function tests rarely led to interferon discontinuation. The liver enzymes usually return to normal ranges gradually after dose reduction or interruption of therapy. A high dose and high frequency of interferon β use may increase the risk of liver function impairment in patients with multiple sclerosis. Liver biopsies of these patients usually reveal portal inflammation with centrivenular haemorrhage and mononuclear cell infiltration, which is consistent with acute hepatitis.

The liver injury found in MS patients treated with Beta Interferon (IFNB) appears to be primarily hepatocellular rather than cholestatic. There are differences between the IFNBs in their association with elevated aminotransferases. The IFNBs also differ in their dose, route of administration, glycosylation, amino-acid sequencing, formulation pH, excipients, manufacturing and purifying process. The route of administration (subcutaneous (SC) versus intramuscular (IM)) is not thought to be of clinical significance and AST elevations are unlikely to occur after IM injections. None of the excipients (e.g. human albumin, sodium phosphate) used in the IFNB preparations appear likely to exacerbate or induce liver injury. Recombinant IFN-alpha and IFN-gamma cause dose-dependent hepatotoxicity. This also appears true with IFNB – the higher dose interferons given more frequently such as IFNB-1a (SC) and IFNB-1b (SC), being more likely to cause elevated aminotransferases than the lower-dose weekly IFNB-1a (IM). The importance of injection frequency is further highlighted by a study of hepatitis C patients treated with IFNB; increasing injection frequency, without increasing the total dose resulted in more patients developing elevated ALT. Increasing the time between injections might enable damaged hepatocytes to recover between injections. Increased patient weight increased the risk of developing elevated aminotransferases with IFNB. Indeed, a higher body mass index increases the risk of any person developing elevated aminotransferases. Propionic acid derivatives (naproxen, ibuprofen and indomethacin) increased the risk of elevated ALT in patients taking either placebo or IFNB, while paracetamol (acetaminophen) did not appear to increase the risk. Conversely, in other diseases treated with interferons, paracetamol use was associated with an increased risk of developing elevated aminotransferases. IFNB, in combination with i.v. methylprednisolone in an MS population resulted in more patients developing elevated aminotransferases than with IFNB alone. Disease duration, age and disability status (as measured by the EDSS) did not increase the risk.

Males are at a greater risk of elevated aminotransferases, both before and during IFNB treatment, possibly owing to laboratories not adjusting the upper normal range for males. All these factors mainly relate to the risk of developing dose-dependent aminotransferase elevations; there is not enough detailed cumulative information at present to know fully whether similar or different risk factors exist in serious cases of liver injury. To illustrate, in contrast to the male predominance in aminotransferase elevations (> UNL), the majority (26/30; 90%) of serious liver injury cases were in female patients.

The mechanism(s) of action of the IFNB-associated liver injury has yet to be elucidated. Evidence to date suggests that IFNBs cause both dose-dependent (Type A reactions) and idiosyncratic, unpredictable (Type B) reactions, such as acute liver failure. Several pathways may exist through which damage can occur and these may actually vary between patients, as is the case for other drugs. Further, the effect could be direct or indirect, through one of the many proteins or pathways affected by IFNB. Targets in the liver include the hepatocyte cell membrane, mitochondria or other cells such as Kupffer cells, which can activate cytokines and amplify injury.

One possible mechanism might be through the interferon-mediated decrease in mitochondrial mRNA expression, leading to impairment of mitochondrial function, reduced fatty acid oxidation and microvesicular steatosis. Interferons are known to affect cholesterol levels; IFNB has been associated with increased high density lipoproteins (HDL) in MS patients at two years although decreases in HDL were found in non-MS patients. Alterations in cholesterol could be another factor in the liver injury associated with IFNB treatment.

The role of glatiramer acetate in inducing hepatic flares

Glatiramer acetate (GA) is a mixture of random polymers of four amino acids which is antigenically similar to the myelin basic protein, a component of the myelin sheath of nerves with which it competes for presentation to T cells. The first
case of liver injury related to GA was firstly described by Neumann and coworkers. The patient previously experienced two episodes of severe necrotising hepatitis related to IFN-beta that was histologically and serologically proven autoimmune hepatitis (AIH) with the onset two months after the start of treatment. There was no increase of gammaglobulin, but the patient displayed a good response to steroid treatment. Subsequently, von Kalckreuth and coworkers reported another case of GA-related AIH; the patient previously experienced severe IFN-beta induced necrotising hepatitis, presented with histologically and serologically proven AIH developing two months after the start of the treatment and with an optimal response to steroidal treatment. After these two pivotal reports, other authors reported further examples of GA-related AIH, but also of GA-induced hepatic flare not resembling an AIH, as a direct drug-induced liver injury (DILI). The very recent report performed by Sinagra and coworkers describes two cases of hepatic flares induced by GA, the first one resembling a probable AIH, rather than a GA-induced liver injury, the second one a definite AIH. Both occurred in patients who had already experienced hepatitis exacerbations during previous beta-interferon treatment. In conclusion, GA is reported to be well-tolerated and, as mentioned above, very few cases of drug-induced liver disease have been reported. However, GA was suggested to induce autoimmune disease. It is believed that GA induces T helper type 2 cells that cross-react with myelin basic protein and may enhance the production of autoantibodies. Moreover, the commercial formula of Copaxone contains mannitol, recently identified as an immunoactive hapten, capable of provoking anaphylaxis. Therefore, it can be speculated that GA induces autoimmune side effects.

The role of natalizumab in inducing hepatic flares

Natalizumab is a monoclonal antibody initially approved in 2004 as DMT for MS.

DILI is a rare complication of natalizumab. Drugs, as natalizumab, that modulate T-cell activity and functions could induce liver injury and possible aetiopathogenetic theories involve a heightened sensitivity against self-antigens, induced by an immunomodulatory dysregulation (Th1 vs. Th2 and Th17), a spontaneous formation of autoantibodies (ANA, anti-dsDNA) and a direct imbalance of liver cytokine milieu. Natalizumab directly inhibits human leucocyte integrin; the drug does not undergo hepatic or renal metabolism and it is found unmodified in urine. To date, only two reports describe natalizumab-induced AIH.

In the case reported by Lisotti and coworkers, the presence of pre-existing AIH before natalizumab treatment could be suspected because of previous aminotransferase flare on IFN treatment and Anti Nucleus Antibodies (ANA) positivity, although as much as 22.5% of patients with MS show circulating ANA. Alternatively, immunomodulatory drugs previously administered to the patient might have masked the presence of an underlying AIH. Based on clinical presentation and biochemical parameters, the possibility of an idiosyncratic drug-induced liver injury could not be excluded. A liver biopsy would have been essential to achieve a clear diagnosis, but the procedure was refused by the patient.

Alternatively, in the report performed by Martinez-Lapiscina and coworkers, histopathological findings and optimal response to corticosteroids also argue for autoimmune hepatitis. However, we cannot distinguish if it was a type of hepatotoxicity that only implies autoimmune immunological effects or if natalizumab unmasked a genetic predisposition to autoimmune hepatitis because of its immunomodulatory properties.

The role of other treatments in inducing hepatic flares

Mitoxantrone is an immunosuppressant also used in cancer chemotherapy which was approved for MS in the year 2000. With regard to this drug, a case of drug rash with eosinophilia and systemic signs (DRESS) syndrome, characterised by very high eosinophilia and cholestatic hepatitis has been reported.

Fingolimod, a sphingosine-1-phosphate receptor modulator, became the first oral drug approved by the FDA, being followed in 2012 by teriflunomide, a drug that inhibits the synthesis of pyrimidine and disrupts the interaction of T cells with antigen presenting cell. Curiously, with regard to fingolimod, a case of Hepatitis E masquerading fingolimod-induced liver injury has been also reported. In contrast, up to now, no data are available on teriflunomide-induced liver injury.

Recommendations

Based on the aforementioned data, the authors would recommend the following:

- Patients should be aware of hepatic side effects such as malaise, febrile illness, weakness, lethargy, jaundice, anorexia, nausea, dark urine and pruritus, although some hepatic side effects will be difficult to distinguish from the side effects of IFNB or manifestations of MS itself. Regular testing of ALT, AST, AP and bilirubin, at least monthly for the first six months, then monthly thereafter probably can minimise Type A or dose-dependent reactions and a pre-treatment screen might be useful to eliminate other causes of liver test elevations (e.g. hepatitis, Wilsons disease). This recommendation for frequent testing is not evidence-based and
needs to be balanced against anxiety, pain, inconvenience and associated costs.

Conclusion
Liver enzyme monitoring should be undertaken in patients with MS during GA treatment, especially where there is a history of HF during previous treatment with IFN beta-1a. Furthermore, autoimmune disease, especially AIH, should be excluded and caution is advisable before prescribing GA in patients with concomitant liver disease.

With regard to natalizumab, autoantibody screening should be obtained before starting biological therapies, as well as on-treatment monitoring to detect early signs of immune-mediated diseases; positive autoantibodies represent a controversial issue for biological therapy and treatment should be considered on a case-by-case basis; finally, AIH or previous DILI should be considered as a contraindication to natalizumab treatment.

Up to now, no data are available to suggest a schedule in liver monitoring in patients treated with mitoxantrone, fingolimod or teriflunomide; however, regular monitoring of blood cell counts and liver enzymes is required.

Abbreviations list
AIH, autoimmune hepatitis; DILI, drug-induced liver injury; DMT, disease-modifying therapies; DRESS, drug rash with eosinophilia and systemic signs; EDSS, Expanded Disability Status Score; GA, glatiramer acetate; IFN-β, beta-interferons; IM, intramuscular; MS, multiple sclerosis; SC, subcutaneous.

References
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