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REVIEW ARTICLE

The Disease-Modifying Therapies of Relapsing-Remitting Multiple Sclerosis and Liver Injury: A Narrative Review

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Abstract

In this narrative review, we analyze pre-registration and post-marketing data concerning hepatotoxicity of all disease-modifying therapies (DMTs) available for the treatment of relapsing-remitting multiple sclerosis, including beta interferon, glatiramer acetate, fingolimod, teriflunomide, dimethyl fumarate, cladribine, natalizumab, alemtuzumab, and ocrelizumab. We review the proposed causal mechanisms described in the literature and we also address issues like use of DMTs in patients with viral hepatitis or liver cirrhosis. Most data emerged in the post-marketing phase by reports to national pharmacovigilance agencies and published case reports or case series. Serious liver adverse events are rare, but exact incidence is largely unknown, as are predictive factors. Unfortunately, none of the DMTs currently available for the treatment of multiple sclerosis is free of potential hepatic toxic effects. Cases of acute liver failure have been reported for beta-interferon, fingolimod, natalizumab, alemtuzumab, and ocrelizumab by different mechanisms (idiosyncratic reaction, autoimmune hepatitis, or viral reactivation). Patients with multiple sclerosis should be informed about possible hepatic side effects of their treatment. Most cases of liver injury are idiosyncratic and unpredictable. The specific monitoring schedule for each DMT has been reviewed and the clinician should be ready to recognize clinical symptoms suggestive for liver injury. Not all DMTs are indicated in cirrhotic patients. For some DMTs, screening for hepatitis B virus and hepatitis C virus is required before starting treatment and a monitoring or antiviral prophylaxis schedule has been established. Beta interferon, glatiramer acetate, natalizumab, and alemtuzumab are relatively contraindicated in autoimmune hepatitis due to the risk of disease exacerbation.

Plain Language Summary

Many disease-modifying therapies (DMTs) are approved for multiple sclerosis treatment, but liver injury is a concern. Patients can experience transaminase elevation during DMT treatment, and in rare cases, idiosyncratic and unpredictable acute liver failure. Currently, it is not possible to predict or prevent serious liver-related adverse events. Furthermore, autoimmune hepatitis and viral reactivation can also occur during DMT treatments. Since adverse events are greatly underreported, it is important to report cases of serious liver-related adverse events in the literature with adequate causality documentation to better understand the liver safety profiles of DMTs.

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Key Points

Patients with relapsing-remitting multiple sclerosis can experience transaminase elevation during treatment with disease-modifying therapies, and in rare cases, idiosyncratic and unpredictable acute liver failure.

Different mechanisms of liver injury, including idiosyncratic reaction, autoimmune hepatitis, and viral reactivation, have been reported.

Neurologists should know the monitoring schedule for each disease-modifying therapy and how to manage an alteration of liver function tests during treatment.

1 Introduction

In the past 20 years, the treatment scenario of relapsing-remitting multiple sclerosis (MS) has radically changed, with several disease-modifying therapies (DMTs) capable of reducing the frequency of relapses, disability accrual, and accumulation of irreversible damage by interfering with a variety of immunological mechanisms [1]. According to an escalation treatment strategy, we can classify DMTs into first-line treatments (beta interferon, glatiramer acetate, teriflunomide, dimethyl fumarate) and second-line treatments (natalizumab, fingolimod, alemtuzumab, cladribine, ocrelizumab), but treatment allocation is driven by an individualized evaluation of the risk–benefit profile, including the use of an induction strategy in certain patients [2].

Drug-induced liver injury (DILI) has received considerable attention by regulators, companies, researchers, and clinicians and currently represents the most common cause for stopping drug development or restricting indications after marketing authorization [3]. For example, in 2018 the European Medicines Agency (EMA) withdrew daclizumab, a monoclonal antibody initially approved for treatment of MS, due to serious and potentially fatal immune reactions (liver injury and encephalitis) [4].

In the pre-registration phase, Hy's law is the most specific predictor of a drug's potential to cause severe hepatotoxicity. Hy's law cases combine elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 times the upper limit of normal (ULN) with total bilirubin > 2 × ULN, and absence of a plausible alternative cause. Patients fulfilling Hy's law experience liver failure that is fatal or requires liver transplantation in at least 10% of cases [5]. The US Food and Drug Administration (FDA) has applied Hy's law since 1997 by blocking development of drugs with more than one Hy's law case in the clinical trial database [6]. The main limitation of Hy's law is that it depends on the size of the population exposed to the drug to detect idiosyncratic DILI cases when these cases have a rare incidence. If the incidence of severe liver injury is 1/10,000, at least 30,000 treated patient-years are required to have a 95% chance of detection [7]. None of the DMTs covered by this review had Hy's law cases in the pre-registration phase.

Every randomized controlled trial includes a detailed assessment of ALT and AST elevations (Table 1). Unfortunately, severity of liver injury is determined less accurately by ALT/AST elevations alone. Since 1983, the National Cancer Institute of the United States and National Institutes of Health published their Common Toxicity Criteria for Adverse Events (CTCAE), which set grades for elevations of serum transaminases. These have been updated periodically. Version 5.0 was published in 2017 and graded ALT/AST elevations as grade 1, mild (< 3 × ULN); grade 2, moderate (> 3 to <5 × ULN); grade 3, severe (> 5 to< 20 × ULN) and grade 4, life-threatening (> 20 × ULN) [8]. Grade 1 elevations are much less specific for DILI and can also be observed in placebo-treated patients or healthy individuals, often confounded by the effects of physical exercise or diets [9]. Moreover, grade 1 ALT/AST elevations were transient in most patients and often fell into the normal range even with continued treatment or with transient dose reduction or interruption. Directly translating the frequency of transaminase elevations during therapy into hepatotoxicity can be misleading.

For these reasons, the post-marketing phase is pivotal to monitor drug safety and gain insight into its real risk–benefit profile as it reflects actual clinical practice where comorbidities and poly-pharmacotherapy exist. There are two main sources for intercepting hepatotoxicity signals from drugs released on the market: reports to national pharmacovigilance agencies and published case reports or case series of toxic liver reactions. Both systems suffer from an underreporting problem, but case reports are more informative in determining causality. In general, the occurrence of a fatal case of liver injury defines the drug as a serious potential hepatotoxin, whereas a positive rechallenge represents the most convincing evidence for causality in DILI [10]. In the Livertox® database, drugs are classified into categories based on the number of published reports of convincingly documented, clinically apparent, idiosyncratic liver injury. Spontaneous reports to regulatory agencies or provided by the drug manufacturers are not included (Table 2).

As widely reported in recent literature [11, 12], extensive infectious disease screening is recommended at MS diagnosis and before starting a new DMT. The aim of infectious disease screening is to plan vaccinations or laboratory monitoring and start prophylaxis or treatment of latent or occult infections. This screening generally includes hepatitis

Table 1 Phase III liver safety results of disease-modifying therapies (DMTs)

Agent	Trial, year of publication	No. patients exposed	Years of exposure	ALT/AST elevation (Grade 1)[a]	ALT/AST elevation (Grade 3)[a]
Injective treatments					
Beta interferon	IFNB MS, 1993 [16]	226	2	9%[b]	1%
	MSCRG, 1996 [17]	158	2	< 10%[b]	n.r.
	PRISMS, 1998 [18]	373	2	4%[b]	< 1%
	SPECTRIMS, 2001 [22]	413	3	12%[b]	n.r.
	EVIDENCE, 2002 [19]	676	1.5	14%	2%
	Nordic SPMS, 2004 [23]	186	3	48%	n.r.
	SENTINEL, 2006 [148]	582	2	< 5%	< 1%
	BENEFIT, 2006 [24]	292	2	n.r.	17.8%
	OPERA I and II, 2017 [186]	826	2	< 10%	< 1%
	REGARD, 2008 [54]	381	3.5	10%	< 1%
	CAMMS223, 2008 [157]	107	3	15%	1%
	RNF, 2009 [20]	260	2	14%	4%
	BEYOND, 2009 [56]	1775	3.5	13%	n.r.
	TRANSFORMS, 2010 [80]	431	1	2%[b] (2% Grade 2)	< 1%
	REFLEX, 2012 [21]	344	2	10%	n.r.
	CARE MS I, 2012 [161]	187	2	17%	1%
	CARE MS II, 2012 [162]	187	2	17%	1%
	TENERE, 2014 [112]	101	2	57% (12% Grade 2)	4%
	ADVANCE, 2015 [25]	1332	2	35% (3% Grade 2)	1%
	ONWARD, 2016 [141]	57	2	6%	2%
	PARADIGMS, 2018 [83]	107	2	5%	< 1%
Glatiramer acetate	PROMISE, 2007 [203]	627	3	< 5%[b]	n.r.
	REGARD, 2008 [54]	375	2	4%[b]	<1%
	BEYOND, 2009 [56]	445	3.5	4%[b]	n.r.
	PRECISE, 2009 [55]	243	3	< 2%[b]	< 1%
	CONFIRM, 2012 [57]	351	2	37% (7% Grade 2)	3%
Oral treatments					
Fingolimod	FREEDOMS, 2010 [79]	854	2	17%[b] (10% Grade 2)	2%
	TRANSFORMS, 2010 [80]	849	1	7%[b] (8% Grade 2)	n.r.
	FREEDOMS II, 2014 [81]	728	2	9% (8% Grade 2)	2%
	INFORMS, 2016 [82]	483	4	12%	n.r.
	PARADIGMS, 2018 [83]	107	2	4%	1%
Teriflunomide	TEMSO, 2011 [109]	726	2	56% (6% Grade 2)	1%
	TOWER, 2014 [110]	780	2	12% (8% Grade 2)	3%
	TOPIC, 2014 [111]	423	2	18% (12% Grade 2)	5%
	TENERE, 2014 [112]	220	2	39% (6% Grade 2)	2%
Dimethyl fumarate	DEFINE, 2012 [123]	826	2	n.r. (6% Grade 2)	n.r.
	CONFIRM, 2012 [57]	703	2	51% (6% Grade 2)	2%
	APEX part 1, 2019 [124]	111	0.5	32% (5% Grade 2)	< 1%
Cladribine	CLARITY, 2010 [138]	884	2	< 10%	< 2%
	ORACLE MS, 2014 [140]	616	2	< 5%	< 1%
	ONWARD, 2018 (plus INFβ1a) [141]	172	2	2%	< 1%
Infusional treatments					
Natalizumab	AFFIRM, 2006 [147]	627	2	5%	< 1%
	SENTINEL, 2006 (plus INFβ1a) [148]	516	2	< 5%	< 1%
	ASCEND, 2018 part 1 [149]	439	2	< 10%	None
	ASCEND, 2018 part 2 [149]	566	2	< 10%	None

Table 1 (continued)

Agent	Trial, year of publication	No. patients exposed	Years of exposure	ALT/AST elevation (Grade 1)[a]	ALT/AST elevation (Grade 3)[a]
Alemtuzumab	CAMMS223, 2008 [157]	216	3	2%	< 1%
	CARE MS I, 2012 [161]	376	2	4%	0
	CARE MS II, 2012 [162]	596	2	4%	< 1%
Ocrelizumab	OPERA I and II, 2017 [186]	825	2	1%	None
	ORATORIO, 2017 [187]	482	2.5	2%	None

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *n.r.* not reported

[a]According to Common Terminology Criteria for Adverse Events, version 5.0

[b]When values of laboratory abnormalities were not reported in the paper, we report the data of adverse events by investigators' judgment, which means that an abnormal liver function test is considered an adverse event only when elevated liver function test levels were reported as adverse events by the investigators

Table 2 Disease-modifying therapies (DMTs) according to LiverTox categorization

Agent	Category	Last update
Injective treatments		
Beta interferon	A	May 4, 2018
Glatiramer acetate	B	March 14, 2018
Oral treatments		
Fingolimod	E*	February 6, 2018
Teriflunomide	D	January 15, 2017
Dimethyl fumarate	C	July 1, 2017
Cladribine	E	October 12, 2017
Infusional treatments		
Natalizumab	B	April 15, 2020
Alemtuzumab	C	April 14, 2020
Ocrelizumab	D	December 16, 2019

Drugs described on the website LiverTox (http://livertox.nih.gov) were classified into five categories based on the number of published cases:

Category A, ≥50 cases

Category B, 12-49 cases

Category C, 4-11 cases

Category D, 1-3 cases

Category E, none (*These agents have been suspected of having hepatotoxicity or were implicated in published cases that did not meet the criteria of possibly causality using the RUCAM method)

This listing is based on the published literature and **not** on spontaneous reports to regulatory agencies or the drug manufacturers

B virus (HBV) and hepatitis C virus (HCV). Screening tests should include HBsAg, HBcAb, HBsAb, and HCVAb. All patients positive for any of these markers should be referred to a specialist, with the exception of HBV-vaccinated patients with isolated HBsAb reactivity. MS patients with acute or chronic HBV or HCV infections should receive antiviral therapy and the timing for starting DMT therapy should be discussed with the hepatologist or the infectious disease specialist. MS patients with occult HBV infection should undergo periodic monitoring or prophylaxis, depending on the immunomodulatory treatment chosen. Patients negative for all HBV markers are candidates to start the vaccination course before receiving DMT therapy [13].

In this narrative review, we analyze pre-registration and post-marketing data of hepatotoxicity of DMTs for the treatment of relapsing-remitting MS (Table 3). We also address issues like use of DMTs in patients with HBV and HCV-related viral hepatitis or liver cirrhosis (Tables 4, 5). High-dose methylprednisolone is clearly hepatotoxic by direct toxicity (as opposed to idiosyncratic injury), but methylprednisolone-induced liver injury in MS is thoroughly discussed elsewhere [14]. Drugs approved for secondary progressive MS (e.g., mitoxantrone and siponimod) or symptomatic treatments (e.g., fampridine) are outside the scope of this review. Despite all efforts to carry out an exhaustive literature search, it is still possible that some relevant papers may have been omitted and this represents a potential limitation of this narrative review.

2 Methods

A.B. and M.L. performed a literature search on Medline with the terms 'multiple sclerosis' [MeSH] AND 'randomized controlled trial' [Publication Type], OR 'chemical and drug induced liver injury' [MeSH], OR 'liver diseases' [MeSH], OR 'retrospective studies' [MeSH] OR 'multicenter study' [Publication Type] OR 'multiple sclerosis/drug therapy' [MeSH] OR 'immunosuppressive agents/adverse effects' [MeSH] for each DMT. We retrieved articles published between January 1993 and December 2020. References of the identified articles were reviewed to retrieve additional relevant articles. Only papers published in English were

Table 3 Disease-modifying therapies (DMTs) and risk of liver injury

Agent	Phase III safety results		Year of FDA approval	Post-marketing data	Cases of acute liver failure
	Grade 1 ALT/AST elevation	Grade 3 ALT/AST elevation*			
Injective treatments					
Beta interferon	67%	1–2%	1993–2014	Drug discontinuation < 1% Some cases of DILI and autoimmune hepatitis	11 (autoimmune or DILI)
Glatiramer acetate	12%	2%	1996	Drug discontinuation < 1% Some cases of autoimmune hepatitis	None
Oral treatments					
Fingolimod	11%	2%	2010	Drug discontinuation < 1%	3 (DILI)
Teriflunomide	31%	2%	2012	Drug discontinuation 3–4%	None (but several cases reported for leflunomide)
Dimethyl fumarate	48%	2%	2013	Drug discontinuation < 1%	None
Cladribine	< 5%	< 2%	2019	No data	None
Infusional treatments					
Natalizumab	5%	< 1%	2004	Some cases of severe hepatitis (both DILI and autoimmune)	1 (HBV)
Alemtuzumab	4%	< 1%	2014	Autoimmune hepatitis (10.7/10,000 patients) 1 case of DILI with positive rechallenge	3 (Autoimmune)
Ocrelizumab	1–2%	None	2017	Rare cases of HBV reactivation	1 (Enterovirus)

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *DILI* drug-induced liver injury, *FDA* US Food and Drug Administration, *HBV* hepatitis B virus

*according to Common Terminology Criteria for Adverse Events, version 5.0

included in the review. The last search date was February 28, 2021.

Pre-registration data were extrapolated from randomized, controlled, phase III clinical trials. Supplementary appendices of each trial were also reviewed. In particular, for each trial we collected the acronym, the year of publication, the number of patients exposed to the study drug, the duration of exposure to the study drug, and the incidence of transaminases elevation of grade 1 and grade 3 according to CTCEA version 5.0. For studies that referred to different classifications of liver injury, these were converted to their equivalent CTCAE grade by the authors.

Post-marketing data were retrieved from all published reports available, including case reports, case series, and letters to the editor. The Livertox® database was accessed at http://livertox.nih.gov for each drug. Causality assessment was performed according to the Roussel UCLAF Causality Assessment Method (RUCAM) [15]; when RUCAM score was not reported in the paper, it was calculated by the authors on the basis of available data whenever possible.

During the literature search we selected 51 full-text papers for beta-interferon, 44 for glatiramer acetate, 37 for fingolimod, 22 for teriflunomide, 24 for dimethyl fumarate, 13 for cladribine, 16 for natalizumab, 32 for alemtuzumab, and 19 for ocrelizumab.

3 Disease-Modifying Therapies

3.1 Beta Interferon

Beta interferon is a cytokine with intracellular antiviral, antiproliferative, and immunomodulatory properties that has been approved for treatment of MS since 1993. Beta interferon is structurally distinct from alpha interferon, but they share the same cell surface receptors, although they activate separate signaling pathways. There are two types of beta interferon, IFNβ1a and IFNβ1b. All formulations are injections, either subcutaneous or intramuscular, and have different dosages and frequency of administration. Currently, five forms of beta interferon are available:

Betaseron/Betaferon©—interferon β1b, subcutaneous injection (250 µg) every other day. Approved 1993.

Extavia©—interferon β1b, subcutaneous injection (250 µg) every other day. Approved 1993.

Table 4 Disease-modifying therapies (DMTs) and viral hepatitis

Agent	Screening		Monitoring	Cases of HBV/HCV reactivation	Data on HBV/HCV patients	Other viral hepatitis
	HBV	HCV				
Injective treatments						
Beta interferon	No	No	No	None	Clearance of HCV in 1 patient	n.a.
Glatiramer acetate	No	No	No	None	n.a.	n.a.
Oral treatments						
Fingolimod	Yes	Yes	No	1 case of HCV reactivation	n.a.	Some cases of HEV hepatitis
Teriflunomide	Yes	Yes	No	None	n.a.	1 case of CMV hepatitis
Dimethyl fumarate	Yes	Yes	No	None	n.a.	1 case of HEV hepatitis
Cladribine	Yes	Yes	No[a]	1 case of new HBV infection	n.a.	n.a.
Infusional treatments						
Natalizumab	Yes	Yes	No	1 case of HBV ALF	n.a.	n.a.
Alemtuzumab	Yes (both HbsAg and HBcAb)	Yes	Yes[b]	None (reported only in hematological setting)	n.a.	Cases of HEV, CMV and adenovirus hepatitis
Ocrelizumab	Yes (both HbsAg and HBcAb)	Yes	Yes[c]	2 cases of HBV reactivation in HBsAg-negative/HBcAb-positive patients	1/300 HBV reactivation risk in HBsAg-negative/HBcAb-positive patients	1 case of ALF associated with enterovirus

ALF acute liver failure, *CMV* cytomegalovirus, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HEV* hepatitis E virus, *n.a.* not available

[a]Contraindicated in HBV or HCV active hepatitis

[b]Before every cycle. Prophylaxis in patients with positive HBV markers

[c]Every 3–6 months. Prophylaxis in patients with positive HBV markers

Table 5 Liver function tests screening and monitoring schedule for disease-modifying treatments (DMTs)

Agent	Liver function tests screening	ALT monitoring	Data in cirrhotic patients
Injective treatments			
Beta interferon	Yes	After 1, 3, 6 months and periodically thereafter	Not available
Glatiramer acetate	No (but suggested)	No	Not available
Oral treatments			
Fingolimod	Yes	After 1, 3, 6, 9, 12 months and bimonthly thereafter	Contraindicated in Child C patients
Teriflunomide	Yes	Every 2 weeks for 6 months, then bimonthly	Contraindicated in Child C patients Caution in fatty liver disease
Dimethyl fumarate	Yes	Yes (suggested every 6 months)	Not available
Cladribine	Yes	No	Contraindicated in Child B and C patients
Infusional treatments			
Natalizumab	Yes	Monthly for first 3 months, quarterly thereafter	Not available
Alemtuzumab	Yes	Monthly up to 48 months from last infusion	Not available
Ocrelizumab	Yes	No (but suggested semiannually)	Use only in Child A patients

ALT alanine aminotransferase

Avonex©—interferon β1a, intramuscular injection (30 µg) once weekly. Approved 1996.

Rebif©—interferon β1a, subcutaneous injection (8.8 µg, 22 µg, 44 µg) thrice weekly. Approved 2003.

Plegridy©—peginterferon β1a, subcutaneous injection (63 µg, 94 µg, 125 µg) every 14 days. Approved 2014.

All five forms of beta interferon have been shown to cause elevations in ALT levels (Table 1) [16–25]. The magnitude

of the effect initially reported in pre-registration clinical trials was significantly lower than that reported in a dedicated re-analysis of clinical trials data, which collected a prevalence of up to 67% of patients (grade 1) and these elevations were graded as severe in 1–2% of patients [26]. According to this paper, the incidence of symptomatic hepatotoxicity with interferon beta is 1/2300 treated patients or 1/4000 patient-years of use. Furthermore, a retrospective observational study confirmed a prevalence of ALT/AST elevations of 37% (grade 1), of 5% (grade 2), and of 1% (grade 3) in patients treated with beta interferon [27]. Transaminase elevations were more common in male sex [28], were dose related [28], and > 75% occurred during the first 6 months of treatment [28], although liver toxicity can occur even after years of exposure [29]. Most patients who achieved grade 1 and 2 ALT/AST elevations continued treatment with beta interferon despite this alteration and transaminases returned to normal values at subsequent controls [30]. In post-marketing experience, < 1% of patients discontinued beta interferon treatment because of hepatic adverse effects [30].

Beta interferon treatment requires screening of transaminase before starting the drug and periodic monitoring (after 1, 3, and 6 months, and periodically thereafter), with closer monitoring in case of elevation of transaminases > 3 × ULN (Table 5). If ALT/AST elevation is > 5 × ULN, the beta interferon dosage should be reduced from 50 to 25% (or administration delayed) and gradually increased when values return to normal, with careful laboratory monitoring. Therapy should be interrupted in case of persistent ALT/AST elevations or in case of onset of jaundice or other symptoms. Rechallenge should be avoided in cases with ALT/AST > 10 or bilirubin > 5 × ULN [31–33].

In the post-marketing phase, many cases of hepatotoxicity associated with beta interferon treatment have been reported, including cases of acute liver failure with fatal outcome, or requiring liver transplantation (Table 3). In some cases, the causality assessment was based on a positive rechallenge [34, 35]. The latency to onset is extremely variable and acute injury can arise after years of treatment [36, 37]. The Drug-Induced Liver Injury Network (DILIN) registry collected eight cases of beta interferon-induced liver injury, including a fatal case, that occurred in women and mostly had a hepatocellular pattern of liver damage; available liver histology demonstrated zone 3 necrosis and moderate chronic inflammatory infiltrates with lymphocytes, eosinophils, and plasma cells suggestive of an immune-mediated basis [38].

Several cases of beta interferon-induced autoimmune hepatitis have been reported. These cases were associated with detectable autoantibodies (anti-nuclear, anti-smooth muscle, anti-liver–kidney–microsomal antibodies) and hypergammaglobulinemia at presentation, had typical histological pattern at liver biopsy, and mostly responded to chronic immunosuppressive treatment (prednisone, azathioprine or mycophenolate mofetil) [39–42]. A case of primary biliary cirrhosis in a patient treated with beta interferon has been also reported [43]. Other autoimmune diseases have been associated with beta interferon treatment and include thyroiditis, myasthenia gravis, lupus erythematosus, rheumatoid arthritis, and Raynaud's phenomenon [33].

In literature, 11 case reports of acute liver failure associated with beta interferon have been published, seven of them with a final diagnosis of probable or definite autoimmune hepatitis and four with a diagnosis of DILI (but in three out of four cases, detectable autoantibodies were present). Two of them had a fatal outcome and seven underwent liver transplantation, while two recovered conservatively [41, 44–51].

Data on cirrhotic patients are not available and no cases of HBV or HCV reactivation under beta interferon have been reported (Tables 4, 5). There was a report of virological response after beta interferon treatment in a patient with both chronic HCV hepatitis and MS, but in the era of direct antiviral agents, this is anecdotal [52].

3.2 Glatiramer Acetate

Glatiramer acetate is a synthetic amino acid polymer antigenically similar to myelin basic protein and was approved for use in MS in 1996. Although different potential mechanisms have been considered, glatiramer acetate treatment induces a preferential Th2 deviation of T cells and promotes restoration of frequency and function of T regulatory cells in MS. Glatiramer acetate also exerts immunomodulatory effects on antigen presenting cells, such as monocytes [53]. The glatiramer acetate-recommended dosing regimen is 20 mg/mL day administered subcutaneously; in 2014 a new formulation of 40 mg/mL three times a week was introduced.

According to the phase III trials summarized in Table 1, transaminases elevation (any grade) was reported in about 12% of patients and graded as moderate in 7% of patients and as severe in 2% of patients [54–57]. Safety data, including extension studies, are available for up to 15 years of treatment [58, 59]. Real-world observational studies from Germany [60], Switzerland [61], and France [62, 63] confirmed a < 1% drug discontinuation rate due to hepatic adverse events.

No cases of liver toxicity according to Hy's Law were reported in the pre-registration trials of glatiramer acetate, so liver function test monitoring during glatiramer treatment is not required in the drug label (Table 5). In the post-marketing phase, > 50 cases of liver injury associated with glatiramer acetate treatment were reported to the FDA Adverse Event Reporting System (FAERS) database [64]. Fourteen cases of glatiramer-associated hepatitis have been published in the literature, 13 of which were histologically documented [65–68]. The onset has been within 1–8 months after starting therapy, with the typical presentation being a hepatocellular

pattern of liver injury, and all patients recovered completely within 1–5 months after drug withdrawal. Some cases have occurred in patients with prior transaminases elevation during beta interferon therapy or were temporally associated with methylprednisolone bolus therapy. Three of these cases were typical autoimmune hepatitis and required long-term immunosuppressive treatment (Table 3) [69–71]. Other autoimmune diseases have been associated with glatiramer acetate treatment and include myasthenia gravis and autoimmune thyroiditis. The exact mechanism of glatiramer acetate-induced autoimmune hepatitis is unknown. The hypothesis is that glatiramer acetate may induce Th2 cells, leading to the release of cytokines like interleukin-4, 6, and 10, and autoantibody production in predisposed patients. In five cases of glatiramer acetate-induced liver injury, a transient elevation of autoantibodies (anti-nucleus, anti-smooth muscle, or both) was reported, suggesting an immune-mediated basis for the liver injury [72–75]. Makhani and colleagues reported a well-documented case of glatiramer acetate-induced liver injury possibly related to mitochondrial damage, showing microvesicular steatosis, hepatocyte necrosis, and structural mitochondrial changes at liver biopsy [76]. No cases of acute liver failure in patients treated with glatiramer acetate have been reported, or any cases of HBV or HCV reactivation (Table 4). Data on cirrhotic patients are not available (Table 5).

3.3 Fingolimod

Fingolimod is a structural analog of sphingosine and acts as a sphingosine-1-phosphate receptor antagonist. By blocking this pathway, naive and central memory lymphocytes (but not effector memory T cells) become insensitive to signals necessary for egress from secondary lymphoid organs. Fingolimod was approved for treatment of MS in 2010 and the recommended dose is 0.5 mg orally once daily [77]. Peripheral B and T cell counts are reduced by approximately 75% from baseline after the first 1–2 weeks, an effect that persists for 4–6 weeks after withdrawal [77, 78].

According to the phase III trials summarized in Table 1, abnormal liver function tests (any grade) were reported in 11% of patients (pooling patients treated with fingolimod 0.5 mg and 1.25 mg daily) and were graded as severe in 2% of patients [79–83]. Liver function test levels returned to normal about 2 months after stopping treatment and can become elevated again in case of rechallenge. Safety data, including extension studies, are available for up to 14 years of treatment [84–86]. The hepatotoxicity signal emerging from phase III trials has had implications for the drug label. Since approval, fingolimod treatment required screening for transaminases and bilirubin before starting the drug, periodic monitoring (after 1, 3, 6, 9, 12 months, and bimonthly thereafter) and treatment interruption in case of persistent elevation of transaminases > 5 × ULN.

The mechanism by which fingolimod might cause liver injury is not known. It is extensively metabolized by the liver via the cytochrome P450 system, predominantly CYP-4F2 [87]. In patients with decompensated cirrhosis (Child C), the area under the curve (AUC) of fingolimod increased by 103%, the maximum concentration (C_{max}) of fingolimod phosphate decreased by 22%, and the apparent curve of elimination with half-life time increased by approximately 50% [88]. For these reasons, the use of fingolimod is contraindicated in patients with severe hepatic impairment. Caution is recommended when starting fingolimod treatment in cirrhotic patients with mild or moderate hepatic decompensation (Child A and B), although no dose adjustment is required (Table 5).

Real-world observational studies showed a heterogeneous pattern of liver function test elevation, ranging from 2% in Germany [89] to 4% in Spain [90, 91], 5% in Italy [92], 7–25% in the Middle East [93–95], 9% in Argentina [96], and 13% in Portugal [97]. Male and older patients were most frequently affected by transaminases elevation, maybe because of sex-dependent expression of cytochrome P450 [98]. Reducing the frequency of fingolimod administration to reverse moderately abnormal liver function tests is controversial [99]. According to the PARADIGM trial, liver adverse events seem lower in the pediatric population than in the adult population. One case of fingolimod-induced chronic liver injury has also been reported [100].

During subsequent post-marketing monitoring, three cases of acute liver failure requiring liver transplantation in patients treated with fingolimod were observed (Table 3). For this reason, in November 2020 the label of the drug was updated (Table 5), introducing further thresholds for treatment interruption (transaminases elevation > 3 × ULN and any bilirubin elevation, or symptomatic patient) [101, 102]. Fingolimod treatment should not be resumed unless a plausible alternative diagnosis for signs and symptoms of liver injury can be established.

Fingolimod has also been shown to attenuate the antiviral immune response in MS patients, so in patients with active viral hepatitis (HBV or HCV), fingolimod cannot be initiated until resolution of the active phase (Table 4). The risk of HBV reactivation in patients treated with fingolimod has not been well established but is likely low. In the TRANSFORMS trial, screening for viral hepatitis was not routinely performed but no cases of severe HBV infection were identified. In literature, a case of HCV reactivation in a patient with a 4-year sustained virological response after pegylated interferon/ribavirin antiviral therapy has been described, suggesting loss of immune control induced by fingolimod treatment [103]. Furthermore, some cases of acute hepatitis from hepatitis E virus (HEV) during fingolimod treatment

have been reported [104–106]. These cases are generally confused with DILI if anamnestic risk factor (consumption of raw or undercooked pork meat) is missed. Fingolimod was generally discontinued in these cases and resumed after normalization of liver enzymes and complete HEV viremia clearance.

3.4 Teriflunomide

Teriflunomide is the active metabolite of leflunomide, an immunomodulatory agent approved for the treatment of rheumatoid arthritis. Teriflunomide reversibly inhibits dihydro-orotate dehydrogenase, which is a key step in new pyrimidine synthesis for DNA replication. The activation and proliferation of lymphocytes are dependent upon pyrimidine synthesis and therefore are deeply sensitive to its inhibition. Teriflunomide was approved for use in MS in 2012 and the recommended dose is 14 mg orally once daily. During teriflunomide treatment lymphocyte and neutrophil counts are reduced by approximately 15% from baseline [103, 107, 108].

According to the phase III trials summarized in Table 1, serum aminotransferase elevations occurred in up to 50% of patients and were graded as moderate in 8% of patients, leading to drug discontinuation in 2–3% of patients [109–112]. Because of data from pre-registration trials and the known hepatotoxic potential of leflunomide, the Warnings and Precautions section of product labelling recommends ALT screening and monitoring every 2 weeks for 6 months, then bimonthly during treatment (Table 5). In case of ALT elevation > 2 × ULN, weekly monitoring is required, whereas in case of ALT elevation > 3 × ULN, interruption of treatment is mandatory. Due to the complexity of the monitoring schedule, patients treated with teriflunomide had the lowest adherence to liver functions test monitoring compared with those treated with fingolimod or dimethyl fumarate in a Canadian observational study [113]. In 2021, product labelling was revised: biweekly ALT monitoring is required only in patients with pre-existing hepatic disorders, taking concomitant hepatotoxic drugs, or with symptoms suggestive of liver damage, otherwise it is required monthly during the first 6 months of treatment [114].

In the extension studies, safety data are available for up to 9 years and confirmed a drug discontinuation rate due to hepatic adverse events in 3–4% of patients [115, 116]. Conversely, an observational study from Germany showed a < 1% drug discontinuation rate because of liver adverse events (Table 3) [117]. In 2020, the phase III trial of ofatumumab, which had teriflunomide treatment in the control arm, included 936 patients treated with teriflunomide for a median of 1.6 years and showed an incidence of hepatobiliary disorders < 2% [118].

In instances of suspected teriflunomide toxicity, elimination of the drug can be accelerated by cholestyramine or activated charcoal. Teriflunomide is eliminated slowly from the serum, probably due to enterohepatic recirculation. Without an accelerated elimination procedure using activated charcoal (50 g every 12 h for 11 days) or cholestyramine (8 g every 8 h for 11 days), drug levels can remain elevated for up to 8 months [118, 119].

Teriflunomide is contraindicated in cirrhotic patients with severe hepatic decompensation (Child C). A case of severe hypertriglyceridemia associated with teriflunomide treatment was reported, alongside another two cases with leflunomide, suggesting caution in the treatment of patients with fatty liver [120].

The risk of HBV reactivation in patients treated with teriflunomide has not been well assessed but is likely low (Table 4). In clinical trials, HBV screening was not universally performed, and no HBV cases were reported. Furthermore, leflunomide is not associated with high rates of HBV reactivation. No data on HCV patients treated with teriflunomide are available. In the TEMSO trial, a case of Cytomegalovirus hepatitis was reported in the teriflunomide arm, requiring drug interruption.

3.5 Dimethyl Fumarate

Dimethyl fumarate (BG-12) is a methylated, unsaturated dicarboxylic acid and was approved for treatment of MS in 2013. By activating the transcription factor nuclear-factor-E2-related factor 2, the drug induces expression of endogenous antioxidative factors in brain cells, which may protect from the detrimental effect of reactive oxygen intermediates released as part of the inflammatory process in MS [121]. The dimethyl fumarate recommended dose is 120 mg orally twice daily for 7 days, followed by a maintenance dose of 240 mg twice daily [122]. During dimethyl fumarate treatment, white cells and lymphocyte counts are reduced by approximately 10% and 30% from baseline.

According to the phase III trials summarized in Table 1, abnormal liver function tests were reported in up to 50% of patients and were graded as moderate in 6% of patients and severe in 2% of patients [57, 123, 124]. In the extension study, safety data are available for up to 5 years and confirmed a drug discontinuation rate due to hepatic adverse events in 1–2% of patients [125]. The hepatic adverse event profile was not different in patients previously treated with interferon beta [126].

Real-world observational studies from France [127], Spain [128], Germany [129], Denmark [130], and Italy [131–133] confirmed a discontinuation rate because of hepatic adverse events in <1% of patients. Furthermore, an oral formulation of fumaric acid is labelled in Germany for treatment of chronic plaque psoriasis; moderate liver

enzyme elevations were observed in 25% of patients in this setting [134].

In 2016, the first case report of severe acute liver injury associated with dimethyl fumarate was published [135]. An analysis of the FAERS database in the timeframe 2013–2016 collected 14 cases of clinically significant dimethyl fumarate-induced liver injury, 10 of which required hospitalization, and 7 fulfilled Hy's law criteria (Table 3). The most common presentation was a hepatocellular pattern with the majority of cases occurring within 1 month of treatment starting. Immunoallergic features and autoantibodies were not frequent, and all cases recovered after drug discontinuation [136]. The mechanism by which dimethyl fumarate causes liver injury is not known but is likely to be idiosyncratic. It is recommended to test serum levels of transaminases and total bilirubin before starting and during treatment with this medication (Table 5).

Patients with liver cirrhosis were excluded from dimethyl fumarate clinical trials. Dimethyl fumarate is extensively metabolized by serum and tissue esterases to monomethyl fumarate, further metabolized in the liver to fumarate which enters in the tricarboxylic acid cycle. Dimethyl fumarate metabolism is independent of the cytochrome P450 system. Therefore, in patients with liver cirrhosis, dimethyl fumarate therapy should be started with caution, without dose adjustments (Table 5).

Patients with active HBV or HCV infections were excluded from dimethyl fumarate clinical trials (but HBsAg-negative/anti-HBc-positive patients were not). The risk of HBV or HCV reactivation in patients treated with dimethyl fumarate has not been estimated but is likely low (Table 4). Recently, a peculiar case of HEV hepatitis in a patient treated with dimethyl fumarate has been reported in the literature [105].

3.6 Cladribine

Cladribine was approved in 2019 for the treatment of MS. Cladribine is a synthetic analog of adenosine, which is converted intracellularly to cladribine triphosphate, inhibiting DNA synthesis and repair, with subsequent induction of apoptosis. Cladribine preferentially affects lymphocytes because these cells are dependent on adenosine deaminase activity [137]. The cumulative recommended dose of cladribine is 3.5 mg/kg body weight over 2 years; it is administered orally for 2 weeks over 2 months as two annual courses. Each course consists of one or two 10-mg tablets (according to body weight) given once daily for 4 or 5 days. During cladribine treatment, lymphocyte count is reduced by approximately 50% from baseline.

According to the phase III trials, summarized in Table 1, abnormal liver function tests were uncommon and grade 3 transaminase elevation was reported in < 2% of patients [138–141]. In the extension study, safety data are available for up to 4 years [142–144].

Liver function test monitoring during cladribine treatment is not required according to the drug label (Table 5). Liver metabolism of cladribine is negligible. Pharmacokinetics and safety studies in patients with liver cirrhosis have not been conducted (Table 5), and cladribine is not recommended in patients with moderate or severe decompensation (Child B or C). A case of new HBV infection in the Clarity extension trial was reported. Another case of HBV reactivation in an HBsAg-negative/anti-HBc-positive patient was reported in the setting of intravenous cladribine administration for treatment of chronic lymphocytic leukemia [145]. Cladribine is contraindicated in active viral hepatitis (Table 4).

3.7 Natalizumab

Natalizumab is a humanized neutralizing IgG4κ monoclonal antibody against leukocyte α4 integrin that blocks leukocyte adhesion to vascular cell adhesion molecule 1 receptor on endothelial cells, thus inhibiting their migration into the central nervous system [146]. Natalizumab was approved for MS treatment in 2004 and is administered at a dose of 300 mg by intravenous infusion every 4 weeks [146].

According to the phase III trials summarized in Table 1, abnormal liver function tests were reported in 5% of patients and were graded as severe in < 1% of patients [147–149]. Safety data are available for up to 2 years of treatment in these trials; however, in extension studies up to 10 years, a rate of serious hepatobiliary adverse events was confirmed in < 1% of patients [150, 151].

Since 2010, six post-marketing cases of severe liver injury have been reported, prompting the addition of natalizumab-associated hepatic injury to the Warnings and Precautions section of product labelling [152]. The authors estimated the frequency of idiosyncratic clinically apparent liver injury from natalizumab to be 17 per 100,000 exposed patients. Hepatotoxicity can arise at any time during treatment, even after the first administration, and can show positive rechallenge.

Afterwards, severe cases of both natalizumab-induced liver injury and autoimmune hepatitis triggered by natalizumab have been reported, with many cases overlapping these two conditions and characterized by the presence of autoantibodies and a histological pattern of plasma cell infiltration, but without recurrence after steroid withdrawal [153–155]. No patient developed acute liver failure or progressed to chronic liver injury (Table 3). Currently, liver function test screening and monitoring are recommended, especially after the first three infusions, and quarterly thereafter (Table 5). Furthermore, patients should be instructed to

seek medical attention for signs and symptoms that suggest liver damage, such as jaundice and vomiting.

Pharmacokinetics and safety studies in patients with liver cirrhosis have not been conducted, although it should be considered that the drug does not undergo hepatic metabolism and is found unmodified in urine (Table 5).

Patients with HBV and HCV infections were excluded from clinical trials with natalizumab. In this regard, it should be emphasized that natalizumab has been associated with a slightly increased risk of viral infections, particularly from the herpes virus family. A fatal case of HBV-related acute liver failure has been reported (although it is unclear if it was an acute HBV infection during natalizumab treatment or reactivation from a chronic HBV carrier state) [156]. Therefore, HBV- or HCV-infected patients who are candidates for treatment with natalizumab should be evaluated by a hepatologist before starting treatment (Table 4).

3.8 Alemtuzumab

Alemtuzumab is a humanized monoclonal IgG1 antibody that selectively targets CD52, an antigen highly expressed on T and B lymphocytes. Binding of alemtuzumab to CD52 results in depletion of circulating T and B cells, following which a distinct pattern of T- and B-cell repopulation and a shift in cytokines toward a less inflammatory pattern occur [157]. Alemtuzumab was approved in 2014 for the treatment of relapsing MS and is also used in treatment of chronic lymphocytic leukemia. In the treatment of MS, the drug is administered intravenously over two courses: 12 mg/day for 5 consecutive days, followed by the same dose for 3 consecutive days 12 months later; additional courses may be considered. Despite a drug half-life of less than a week [158], treatment results in a rapid depletion of circulating lymphocytes that can persist for several years; median recovery of CD4+ cells took 35 months [159], whilst B cells returned within 7 months but continued to rise, reaching 124% of baseline 27 months post-treatment [160].

According to the phase III trials summarized in Table 1, abnormal liver function tests occurred in 4% of patients and were graded as severe in <1% of patients [161, 162]. Safety data are available for up to 12 years of treatment in these trials [163–166]. After alemtuzumab infusion, ALT and γ-glutamyl transferase peaked < 3 × ULN on day 5 and returned to normal in 30 days [167]. A case of severe DILI after alemtuzumab treatment with positive rechallenge was reported [168]. Data on cirrhotic patients are not available (Table 5).

Alemtuzumab treatment has been associated with onset of autoimmune disease, mainly through a mechanism of B-cell autoimmunity. More commonly, these conditions peak within 18–36 months after first infusion and include Graves' disease (reported in ~ 30% of patients treated with alemtuzumab) and, less commonly, autoimmune thrombocytopenia and Goodpasture syndrome [169, 170].

Interpreting lymphocyte reconstitution data from the pivotal phase III trials of alemtuzumab, Baker et al. have suggested that a more rapid CD19+ B-cell repopulation post-alemtuzumab, in the absence of T-cell regulatory mechanisms, might increase the risk of secondary autoimmunity [169]. According to the events reported post-marketing by the drug manufacturer, autoimmune hepatitis is a rare event, with an incidence of 10.7/10,000 patients treated with alemtuzumab [171, 172]. Two cases of alemtuzumab-induced acute liver failure have been reported in the literature; the first one was a patient with immune-mediated hepatitis requiring long-term immunosuppressive therapy, the other a patient with classic autoimmune hepatitis [173, 174]. Another case of fatal autoimmune hepatitis, probably alemtuzumab-related, was reported in the EudraVigilance database (Table 3) [175].

HBV and HCV reactivation have been described in patients with chronic lymphocytic leukemia treated with alemtuzumab, including some fatal cases of HBV reactivation [176]. As such patients were excluded from MS trials, the risk of these complications remains to be established in a neurological setting [177]. Extrapolating data from hematological patients, alemtuzumab therapy does have a high risk of HBV reactivation. In both HBsAg-positive/anti-HBc-positive patients and HBsAg-negative/anti-HBc-positive patients, antiviral prophylaxis is recommended for at least 6–12 months after the last dose [178, 179]. HCV exacerbation and possibly reactivation have also been described in patients receiving alemtuzumab therapy [180, 181]. Furthermore, cases of HEV-related acute hepatitis [182], cytomegalovirus-related hepatitis [183], and adenovirus hepatitis [184] after alemtuzumab therapy have been reported (Table 4).

3.9 Ocrelizumab

Ocrelizumab is a monoclonal IgG1 antibody that selectively targets CD20, depleting pre-B cells, mature B cells, and memory B cells without affecting lymphoid stem cells and plasma cells. Contrary to rituximab, ocrelizumab is a fully humanized antibody, designed to reduce immunogenicity [185]. Ocrelizumab was approved for treatment of MS in 2017 and is administered at a dose of 600 mg by intravenous infusion every 24 weeks. Treatment results in rapid decline in circulating B cells and decrease in immunoglobulin levels, effects that persist for 6–18 months after last dose [185].

According to the phase III trials summarized in Table 1, abnormal liver function tests occurred in 1–2% of patients. Safety data are available for up to 2.5 years of treatment in these trials. Only patients with mild hepatic impairment were included in clinical trials. Ocrelizumab is a monoclonal

antibody eliminated by catabolism (i.e., degradation into peptides and amino acids) rather than by hepatic metabolism [186, 187]. Liver function tests are recommended before starting ocrelizumab treatment. Liver function test monitoring is not required but is suggested before every infusion (Table 5).

Similarly to other anti-CD20 antibody therapies, the most important risk for the liver is represented by HBV reactivation, which may be complicated with fulminant hepatitis, acute liver failure and death or need for emergency liver transplantation [179]. This condition can occur in patients with chronic hepatitis B (HBsAg positive/anti-HBc positive) as well as in patients with resolved HBV infection (HBsAg negative/anti-HBc positive). It is appropriate here to summarize previous experience with rituximab, which was approved in 1997 and is used to treat non-Hodgkin lymphoma and chronic lymphocytic leukemia as well as rheumatoid arthritis, vasculitis, and essential mixed cryoglobulinemia. In an onco-hematological setting, rituximab (frequently associated with cyclophosphamide, doxorubicin, vincristine, and prednisone in the R-CHOP schedule) has been associated with a risk of HBV reactivation of 30%–60% in HBsAg-positive/anti-HBc-positive patients and 13%–22% in HBsAg-negative/anti-HBc-positive patients. Reactivation events may occur as late as 12 months after rituximab discontinuation, at a time when anti-HBs titers are waning [188]. In rheumatological patients, risk of HBV reactivation under rituximab therapy is less studied but is probably lower [189, 190]. Clinical guidelines suggest antiviral prophylaxis with entecavir or tenofovir (lamivudine only in HBsAg-negative/anti-HBc-positive patients), starting 7 days before the onset of rituximab and lasting 12–18 months after rituximab cessation. Liver function tests and HBV DNA should be tested every 3–6 months during prophylaxis and for at least 12 months after prophylaxis withdrawal as a large proportion of HBV reactivations develop after prophylaxis discontinuation [191, 192].

Data on ocrelizumab and risk of HBV reactivation are limited. In phase III trials, HBsAg-positive patients were excluded but HBsAg-negative/anti-HBc-positive patients with undetectable HBV DNA were allowed; no cases of HBV infection were reported in MS trials [193]. In phase III trials in rheumatoid arthritis, ocrelizumab, and methotrexate combined therapy was associated with a single case of HBV reactivation, establishing an incidence of 1/300 HBsAg-negative/HBcAb-positive patients (without prophylaxis) [194]. A single case report of HBV reactivation has been described in an HBsAg-negative/HBcAb-positive patient on ocrelizumab treatment for MS (without HBV prophylaxis); the patient later was demonstrated to carry immune-escape mutations involving production of a defective HBsAg [195]. A single case report of fulminant hepatitis requiring emergency liver transplantation during treatment with ocrelizumab for MS was published, but this was associated with echovirus 25, a member of the enterovirus family [196].

Consequently, HBV screening must be performed in all patients before starting treatment with ocrelizumab. Both HBsAg and HBcAb tests should be used. The presence of HBsAb does not prevent HBV reactivation, so the role for HBsAb screening before immunosuppressive therapy has not yet been established. For patients with positive HBV screening, hepatologist consultation is warranted. At present, chronic HBV hepatitis is considered a relative contraindication to the use of ocrelizumab in MS (Table 4).

4 Diagnostic Work-Up in the Event of Elevated Liver Function Tests

4.1 Neurologist Work-Up

How should a neurologist manage a patient with elevated liver function tests during treatment with DMTs? First, it is advisable to ask the patient about symptoms suggestive of liver damage: not only jaundice or dark urine, but it is also appropriate to interrogate the patient regarding nausea, vomiting, abdominal pain, fatigue, or anorexia. It is good clinical practice to instruct patients from the beginning of DMT treatment to inform the physician in case of onset of these symptoms. If the patient is symptomatic, treatment should be discontinued, and the patient referred to a hepatologist. If the patient is asymptomatic, the laboratory tests should be repeated after 1–2 weeks, depending on the extent of the elevation, to rule out an extrahepatic transient disease.

Confirmation or worsening of liver function test elevation should prompt physicians to request the first-level tests: viral serologies for HAV (IgM anti-HAV), HBV (HBsAg, IgM anti-HBc), HCV (anti-HCV), and HEV if available (IgM anti-HEV), autoantibodies (anti-nucleus, anti-mitochondria, anti-smooth muscle, anti-liver-kidney-microsomal antibodies), protein electrophoresis, and a hepatobiliary ultrasound. If a clear explanation for the elevation of liver function tests is found, the patient should be managed accordingly (e.g., infectious disease evaluation in case of acute hepatitis HAV, surgical evaluation in case of lithiasis of the biliary tract) and the possible interruption of DMT treatment should be discussed with the referring specialist [5]. A suggested algorithm to summarize the main steps of clinical management by the neurologist is presented in Table 6.

4.2 Hepatologist Work-Up

If first-level tests are negative, the patient must be referred to a hepatologist who will proceed with second-level tests to exclude alcoholic hepatitis (detailed history and dosage of desialylated transferrin), a metabolic condition (presence

Table 6 Clinical management of a patient with transaminase elevation during therapy with a disease-modifying treatment (DMT): algorithm for the neurologist

What to do in case of grade I transaminase elevation (ALT < 3 × ULN)?	Always rule out symptoms suggestive of liver damage. If asymptomatic, continue treatment and repeat transaminase biweekly. If alteration persists over 2–3 months, request the first-level tests and consult hepatologist
What to do in case of grade II transaminase elevation (ALT > 3 to < 5 × ULN)?	Always rule out symptoms suggestive of liver damage. If asymptomatic, continue treatment and repeat transaminase weekly. If alteration persists over 1 month, request the first-level tests and consult hepatologist
What to do in case of grade III transaminase elevation (> 5 to < 20 × ULN)?	Stop treatment, request the first-level tests and consult hepatologist
What to do if the patient is symptomatic?	Stop treatment, request the first-level tests and consult hepatologist
What to ask the patient and what to investigate before referring to the hepatologist?	Ask the patient about symptoms suggestive of liver damage (jaundice, dark urine, nausea, vomiting, abdominal pain, fatigue, anorexia) Ask the patient about other potential cause of liver damage (alcohol consumption, use of nonsteroidal anti-inflammatory drugs, acetaminophen or antibiotics, recent intake of seafood, mushrooms or undercooked pork meat, fever or rash)
What are the first-level viral serologies to request?	Hepatitis A virus (HAV): IgM anti-HAV antibodies Hepatitis B virus (HBV): HBsAg, IgM anti-HBc antibodies Hepatitis C virus (HCV): anti-HCV antibodies Hepatitis E virus (HEV): IgM anti-HEV antibodies
What are the other first-level tests to request?	Autoantibodies (anti-nucleus, anti-mitochondria, anti-smooth muscle, anti-liver-kidney-microsomal antibodies) Protein electrophoresis Hepatobiliary ultrasound
When to refer to hepatologist?	Grade III transaminase elevation (> 5 to < 20 × ULN) Persistent grade I–II transaminase elevation of unexplained origin Symptomatic patient It is suggested to refer the patient after performing first-level tests

ALT alanine aminotransferase, *ULN* upper limit of normal

of steatosis on ultrasound and associated conditions such as diabetes and obesity), herpetic viral hepatitis (serologies for cytomegalovirus, Epstein Barr virus, herpes simplex virus if associated extrahepatic manifestations such as rash, lymphadenopathy, and atypical lymphocytes are present), celiac disease (dosage of anti-transglutaminase antibodies), vascular causes (suggested by hepatic ultrasound Doppler, a history of cardiac comorbidity, or previous episodes of hypotension or syncope), or possibly genetic diseases (dosage of ferritin, ceruloplasmin, cupremia, alpha-1antitrypsin). The hepatologist will also collect a detailed drug history to identify any concomitant agent; in some cases, liver injury is associated with concomitant symptomatic medications, like non-steroidal anti-inflammatory agents [197], supplements [198], or even herbal medicines [199]. The hepatologist will also evaluate whether to submit the patient to a liver biopsy. In general, liver biopsy is not required for diagnosis, but can be necessary to distinguish DILI from autoimmune hepatitis (interface hepatitis with portal lymphocytic or lymphoplasmacytic cells extending into the lobule, emperipolesis, and rosettes are considered typical, unless not specific, for autoimmune hepatitis), in case of atypical presentation (ascites, chronic hepatitis, microvesicular steatosis) or in case of negative or incomplete de-challenge. Finally, the hepatologist will perform the causality assessment by RUCAM; RUCAM score indicates if a drug is a possible (3–5), probable (6–8) or highly probable (> 8) cause of the liver injury [15]. A RUCAM score > 5 consistently supports a diagnosis of DILI.

Some cases of DILI occur with autoimmune features, like autoantibody positivity and histological findings of interface hepatitis with portal and periportal infiltrates of lymphocytes, plasma cells, and eosinophils [200]. Furthermore, autoimmune hepatitis is not uncommon in patients with MS. According to a French observational study, the prevalence of autoimmune hepatitis is ten times higher in an MS cohort as compared with the general population (0.17 vs 0.02%) [201]. A recent literature review identified 40 reported cases of autoimmune hepatitis in patients with MS, but no patient was drug-naïve while autoimmune hepatitis occurred [202]. Differential diagnosis between drug-induced autoimmune hepatitis-like injury and true autoimmune hepatitis is challenging, and often the conclusive diagnostic confirmation comes only with the laboratory flare after glucocorticoid withdrawal, revealing autoimmune hepatitis [200].

Differentiation between these two conditions is extremely relevant to the neurologist. In the event of DILI, DMT treatment with the drug possibly or probably related to the liver injury must be permanently discontinued and never restarted. There is no cross-toxicity between DMTs, so previous hepatotoxicity does not influence the choice of subsequent treatments. In case of autoimmune hepatitis, the patient will need long-term treatment with immunosuppressants (e.g., prednisone and/or azathioprine), and this must be considered when choosing another treatment with DMTs. Beta-interferons, glatiramer acetate, natalizumab, and alemtuzumab are relatively contraindicated in autoimmune hepatitis due to the risk of disease exacerbation.

5 Conclusions

None of the DMTs currently available for the treatment of MS is free of potential hepatic toxic effects. Cases of acute liver failure have been reported for beta-interferon, fingolimod, natalizumab, alemtuzumab, and ocrelizumab by different mechanisms (idiosyncratic reaction, autoimmune hepatitis, or viral reactivation). Patients with MS should be informed about the possible hepatic complications of their treatment and should be educated to inform the physician about any onset of symptoms like jaundice, nausea, vomiting, abdominal pain, fatigue, or anorexia. Because most instances of DILI are idiosyncratic and independent of the dose and duration, it is not possible to predict or prevent them from occurring. The specific monitoring schedule for each DMT must be carefully observed, but unfortunately it is not proven that such strict monitoring prevents the rare occurrence of severe symptomatic cases. The clinician must pay particular attention to development, during DMT treatment, of clinical symptoms suggesting liver involvement. Some DMTs are contraindicated in cirrhotic patients or relatively contraindicated in autoimmune hepatitis, while hepatologist consultation is advisable before starting therapy in patients with chronic HBV or HCV hepatitis. Finally, since serious hepatic adverse events of medications are greatly underreported, it is important to report cases of serious liver-related adverse events in the literature with adequate causality documentation to better understand the liver safety profiles of DMTs.

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