Multiple Sclerosis Therapies and Drug-Induced Liver Injury

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Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system and the association with other autoimmune diseases is well-documented. There are many therapeutic options for the treatment of MS. Most of the available drugs cause drug-induced liver injury (DILI) to variable extents with heterogeneous clinical and biological manifestations, including liver injury with or without signs of hypersensitivity and autoimmunity. The different disease-modifying therapies (DMTs) and immunomodulating treatments used in the management of MS include interferon beta (IFN-β), glatiramer acetate (GA), natalizumab, fingolimod, mitoxantrone, teriflunomide, dimethyl fumarate, alemtuzumab, daclizumab, and ocrelizumab. These drugs are largely available in the USA and Europe, but with some differences in indications.

multiple sclerosis liver injury drug-induced liver injury

1. Interferon Beta (IFN-β)

IFN-β is a cytokine and belongs to a group of naturally occurring proteins which interact with cell surface receptors to produce immunomodulatory effects. There are two types of IFN-β used in the treatment of MS, IFN-β 1a and IFN-β 1b, which are manufactured under five market forms and administered subcutaneously at different dosages with various periodicities:

- Recombinant IFN-β 1b is found under three market forms: Betaseron, Betaferon, and Extavia. Recombinant IFN-β 1b is administered subcutaneously every day at the dose of 250 µg. Extavia is also approved for weekly administration.

- Rebif is a recombinant IFN-β 1a that is administered subcutaneously at different doses: 8.8 µg, 22 µg, or 44 µg thrice weekly.

- Plegridy is a recombinant peginterferon-β1 that is administered subcutaneously at the doses of 63 µg, 94 µg, or 125 µg every two weeks.

IFN-β is frequently used to prevent relapse of MS. All forms of IFN-β are well known to cause mild liver injury that can occasionally lead to severe liver injury with jaundice. Post-marketing studies suggest that 30–60% of MS patients exposed to an IFN-β have elevations in liver function tests, justifying monitoring of liver function tests during IFN- β treatment. Although fulminant liver failure requiring liver transplantation has been reported in MS

patients, only around 1–2% of IFN-β-exposed MS patients experience severe elevations of liver function tests [1][2][3]. The usual delay for elevations in liver function tests is 2–12 months after starting therapy. The clinical pattern is usually hepatocellular. Fever, rash, and eosinophilia are not common. Autoimmune features are somewhat common, but may relate more to the underlying MS rather than DILI. Most reported cases have occurred in females [1][2][3]. The mechanisms of IFN-β hepatotoxicity are only partially documented [1][2][3] with the asymptomatic elevations in transaminases reported as potentially dose dependent. The cases with acute jaundice occasionally associated with autoimmune features may represent the triggering of an underlying autoimmune mechanism [1][2][3].

2. Methylprednisolone Pulse Therapy

Intravenous (IV) corticosteroid therapy with methylprednisolone (MPDN) is indicated for the treatment of relapse of MS. A recent study by Kimura H et al. investigated the development of liver injury after MPDN pulse therapy. From 2005 to 2016, eight patients (/120, 6.7%) with MS developed liver injury after MPDN pulse therapy. Liver injury usually develops beyond two weeks after MPDN treatment. The clinical profile evoked idiosyncratic acute hepatocellular liver injury; in one case, pathological findings AIH [4]. Assessment of the French pharmacovigilance database allowed the collection of 97 cases of liver injury associated with MPDN from 1985 to 2016 [5]. The prevalence of female sex was 58.8% with a median age of 46 years. MS was the indication for MPDN pulse therapy for 26 cases. MPDN had been administered intravenously in 79.4% of cases. The pattern was predominantly mild/moderate hepatocellular liver injury followed by recovery. A positive rechallenge was observed in 10/13 patients re-exposed to IV administration [5]. Among the cases collected in a Spanish registry, three female cases were reported with acute hepatocellular liver injury at 2–6 weeks after the IV exposure. Rechallenge was positive in two cases [6]. The frequency of liver injury induced by IV MPDN has been addressed by Nociti et al. [7]. They performed a prospective observational study on the risk of liver injury in patients with MS treated with IV MPDN (1000 mg/day for 5 days). The authors collected liver data on a total of 251 cycles of treatment for 175 patients over one year. An increase in transaminases above the ULN (>45 U/L) was observed among 8.6% of patients. The liver injury was significant in 2.5% of the patients, meeting Hy's law criteria. An extensive diagnostic work-up led to the identification of DILI in three cases and AIH in three other cases. More recently, another prospective study investigating potentially hepatotoxic drugs revealed 13 cases with various neurologic autoimmune diseases occurring with a median latency of 5 weeks after MPDN pulse therapy. Liver injury developed after repeated pulses and was typically hepatocellular with marked severity, leading to liver transplantation in six cases. Histological features showed interface hepatitis and portal fibrosis with mixed inflammatory cells; features suggestive of AIH. Liver injury rapidly responded to prednisone administration [8].

The detailed mechanisms of liver injury caused by MPDN pulse therapy have not been studied. The cases collected in the studies described above show heterogeneity in the clinical and histological findings, sometimes arguing for an idiosyncratic drug reaction, or conversely autoimmune liver injury in some cases. Several hypotheses are proposed as Davidov et al. who propose a direct hepatotoxicity [9], whereas Caçao et al. attribute the development of AIH to MPDN-induced liver injury [10]. In addition, the role of excipients associated with

corticosteroids, such as saccharin, can also be evoked as previously described [11][12]. Indeed, whereas MPDN pulse therapy can cause acute liver injury, it is also well-known that oral corticosteroid therapy is currently used to treat liver injuries with autoimmune and allergic components [13][14]. Importantly, liver injury rapidly improved following oral prednisone administration in a German series of cases of DILI associated with MPDN pulse therapy [8].

3. Glatiramer Acetate (GA)

GA is a drug made of synthetic polypeptides mimicking myelin proteins. GA acts through an immunomodulating activity of converting pro-inflammatory Th1 cells into regulatory Th2 cells. Thereby, GA decreases inflammation, which leads to a reduced risk of relapse of MS [5].

GA induces the release of cytokines, like IL-4, IL-6, and IL-10, and also enhances the production of autoantibodies. Therefore, one may speculate that GA induces autoimmune side effects. At large, randomized controlled trials of GA in patients with MS, serum ALT elevations were >3× ULN in 7% of GA-treated patients compared to 3% of placebo recipients [15][16]. It is noteworthy that over a dozen cases of clinically apparent liver injury with jaundice have been reported since the approval and the more widespread use of GA [16][17][18][19][20][21][22][23][24][25][26][27][28][29][30].

This low number of DILI cases may indeed explain the absence of a GA-associated risk of DILI in the Antonazzo et al. pharmacovigilance study [31]. The clinical characteristics of the reported cases of GA-associated liver injury are presented in **Table 1**. Interestingly, six patients that had previously been treated with interferon switched to GA due to abnormal liver assessments, potentially suggesting a predisposition to an autoimmune reaction [19][24][25][26]. The majority of cases involved females with a mean age of 35 years. The delay in symptom onset varied from 7 days to 8 months, and mostly within 1–3 months after starting therapy. The typical presentation was a hepatocellular pattern with serum liver enzyme elevations [16][17][18][19][20][21][22][23][24][25][26][27][28][29][30]. There are arguments in some patients for an autoimmune hepatotoxicity: presence of autoantibodies (including anti-nuclear (A-NA) and anti-smooth muscle (A-SMA) antibodies), liver biopsy showing characteristic histopathological lesions, response to corticosteroid therapy [4].

Table 1. Cases of glatiramer acetete (GA)-associated liver injury.

Case	Sex	Age (Years)	Profile (Hep: Hepatocellular; Cho: Cholestatic)	Antibodies	Liver Biopsy	Previous Treatment before GA	Recovery (Days)	Treatment for Recovery
Deltenre et al. (2009) [17]	F	52	Hep	ANA: 1/320 ASMA: 1/80	Centrilobular damage Lymphocyte Macrophage Eosinophil	MPDN	90	No

Case	Sex	Age (Years)	Profile (Hep: Hepatocellular; Cho: Cholestatic)	Antibodies	Liver Biopsy	Previous Treatment before GA	Recovery (Days)	Treatment for Recovery
Onmez et al. (2013) [18]	F	36	Hep	Negative	Polymorphonuclear-rich mixed-type inflammatory cell reaction	GA + MPDN	36	No
Neuman et al. (2007) [19]	H	71	Hep	ANA: 1/1280	Drug-induced liver-injury without fibrotic changes of the liver	IFN (switch due to elevation in liver function test)	30	Budesonide and mycophenolate mofetil
Antezan et al. (2014) [20]	F	28	Hep	Negative	Hepatocellular necrosis, portal bridging, and portal lymphocytic inflammation		30	No
Subramaniam et al. (2012) [21]	F	31	Hep	ASMA: 1/320	Centrilobular hepatocyte necrosis with portal-venous bridging, along with mild portal and interface hepatitis			
Flaire et al. (2015) [22]	F	56	Hep	Negative	Centrilobular hepatocyte necrosis with inflammatory infiltrates composed of lymphocytes and eosinophils	MPDN	45	No
La Gioia et al. (2014) [23]	F	25	Hep	Negative	Inflammatory infiltration: lymphocytes, histiocytes, plasma cells, and a few eosinophil granulocytes		56	
Makhani et al. (2013) [24]	F	15	Hep	Negative	Lymphocytic inflammatory infiltration with mild portal fibrosis, no plasma cells, and	IFN (switch due to elevation in liver	54	No

Case	Sex	Age (Years)	Profile (Hep: Hepatocellular; Cho: Cholestatic)	Antibodies	Liver Biopsy	Previous Treatment before GA	Recovery (Days)	Treatment for Recovery
					no signs of chronic liver disease	function test)		
Fernandez et al. (2015)	F	42	Hep	ANA: 1/640	No biopsy	IFN (switch due to elevation in liver function test)	30	
Sinagra et al. (2013) [26]	F	41	Hep	ANA: 1/320	Moderate interface hepatitis with eosinophilic infiltration and porto-portal fibrosis	IFN (switch due to elevation in liver function test)	30	
Sinagra et al. (2013) [26]	F	29	Hep	ANA: 1/160	Lymphoplasmacytic infiltration with porto-portal fibrosis and slight ductal proliferation	IFN (switch due to elevation in liver function test)		CTC + azathioprine
Almeida et al. (2016) [27]	F	65	Hep	ANA: 1/40 ASMA 1/40	No biopsy	MPDN	147	
Arruti et al. (2012) [28]	F	46	Hep	Negative	No biopsy			CTC
Von Kalckreuth et al. (2008) [29]	F	42	Cho	ANA and ASMA positive	Severe portal and periportal lymphocytic inflammation with necrosis	IFN (switch due to elevation in liver function test)		CTC + azathioprine
Michels F et al. (2020) [30]	F	23	Hep	Negative	Hepatocyte necrosis CD38-positive lymphocytes			CTC

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moderate–severe for eight cases and mild for six. Ten patients required hospitalization but there were no cases leading to liver transplantation or death. Possible mechanisms for DILI associated with DMF include hypersensitivity, AIH, or infection [32][33][34].

5. Teriflunomide

ANA: anti-nuclear antibodies, CTC: corticosteroids, IFN: interferon, MP: Methylprednisolone, ASMA: anti smooth muscle antibodies.

Teriflunomide is an immunomodulatory drug indicated for the prevention of relapse of MS. Teriflunomide is the active metabolite of leflunomide, used to treat rheumatoid poly arthritis, which has shown to cause liver injury with immunoallergic features. Indeed, the effect of teriflunomide on the liver has been carefully evaluated [22]. The oral administration of teriflunomide is frequently associated with an asymptomatic increase in transaminases among 13–15% of patients included in clinical trials. An asymptomatic increase in ALT levels >3× ULN occurred in 6% of teriflunomide-treated patients compared to in 4% of patients receiving placebo [22][23][24][25]. Elevation in transaminases was within the first 6 months of administration. Recovery rapidly followed after withdrawal of teriflunomide, and even among half of the patients with continued administration suggesting an adaptation of the liver to this drug [22][23][24][25]. Very rare cases of symptomatic hepatitis without liver failure have been reported [22][26]. The mechanism of elevation in transaminases is unknown. There is no sign of allergic or autoimmune reaction [22][23][24][25][26].

6. Alemtuzumab

Alemtuzumab is a recombinant humanized monoclonal antibody against CD52, which is present on B and T cells, monocytes, and natural killer cells. Binding to CD52 produces a depletion of B and T cells. The subsequent cell repopulation is made of B and T cells with a different pattern and a modification in cytokine production towards a less inflammatory profile. Alemtuzumab is indicated in relapsing and remitting MS. Infusion of alemtuzumab is frequently followed by a mild and transient increase of transaminases. A case of liver failure has been observed after several episodes of liver injury with signs of autoimmunity following rechallenge [29]. Alemtuzumab can cause autoimmune diseases. This is likely due to a more rapid CD19+ B cell repopulation in the absence of T cell regulatory mechanisms. An example is Graves' disease, which develops in approximately 30% of patients up to 3 years after the onset of alemtuzumab treatment [35]. Alemtuzumab can also cause reactivation of hepatitis B virus infection, not only in HBsAg carriers, but also in patients with isolated anti-HBc antibodies with severe liver injury. The reactivation of hepatitis C virus (HCV) has also been observed [22]. In a patient with positive HCV serology, the distinction between HCV reactivation and DILI is provided by the detection of serum HCV RNA by polymerase chain reaction (PCR) and evaluation of alemtuzumab causality. Assessment of the latter is by using the DILIN expert method or the RUCAM.

7. Natalizumab

Natalizumab is a humanized neutralizing IgG4k antibody against α-4 integrin that blocks the migration of leukocytes into the brain. Natalizumab exhibits a potent immunosuppressive activity and is an approved therapy in patients with active relapsing and remitting MS. In phase III studies, the asymptomatic increase of transaminases was similar in the natalizumab-treated patients to the placebo group (5% vs. 3%) [22]. Since marketing of natalizumab, a few cases of liver injury have been reported over a period of more than 10 years [22][30][33][34][36]. In a small series of six cases, liver injury occurred with a very variable delay in onset; after the first administration of natalizumab or much later. Liver injury was associated with the presence of autoantibodies in three patients. Corticosteroid therapy was associated with recovery [34][36].

8. Ocrelizumab

Ocrelizumab is a fully humanized monoclonal IgG1 antibody against CD20. Ocrelizumab allows the depletion of pre-B cells, mature B cells, and memory B cells, without the modification of plasma cells or lymphoid stem cells, leading to a reduction in immunogenicity. Ocrelizumab is indicated for the treatment of adult patients with active relapsing forms of MS. Mild-to-moderate serum aminotransferase elevations were reported among 1–2% of patients under ocrelizumab therapy. Similar to rituximab, ocrelizumab may cause HBV or echovirus reactivation [37][38][39]. In case of acute liver injury, reactivation of HBV may be distinguished from DILI by the detection of HBV DNA in serum in addition to the evaluation of ocrelizumab causality; the latter performed by using the DILIN expert method or the RUCAM.

9. Cladribine

Cladribine is a synthetic analog of adenosine which induces apoptosis by inhibiting DNA synthesis and repair. Apoptosis is mainly induced in lymphocytes as they are dependent on adenosine deaminase activity, thus decreasing lymphocyte count. In phase III clinical trials, liver enzyme abnormalities were not common and elevated transaminases >5x ULN occurred in less than 2% of patients. The post-marketing experience of cladribine use does not reveal a high risk of hepatotoxicity. However, very rare cases of HBV reactivation have been recorded [40][41][42][43][44].

References

1. Francis, G.S.; Grumser, Y.; Alteri, E.; Micaleff, A.; O'Brien, F.; Alsop, J.; Stam Moraga, M.; Kaplowitz, N. Hepatic Reactions during Treatment of Multiple Sclerosis with Interferon-Beta-1a: Incidence and Clinical Significance. Drug Saf. 2003, 26, 815–827.
2. Tremlett, H.L.; Yoshida, E.M.; Oger, J. Liver Injury Associated with the Beta-Interferons for MS: A Comparison between the Three Products. Neurology 2004, 62, 628–631.
3. Fontana, R.J.; Hayashi, P.; Bonkovsky, H.L.; Kleiner, D.E.; Kochhar, S.; Gu, J.; Ghabril, M. Presentation and Outcomes with Clinically Apparent Interferon Beta Hepatotoxicity. Dig. Dis. Sci. 2013, 58, 1766–1775.
4. Kimura, H.; Takeda, A.; Kikukawa, T.; Hasegawa, I.; Mino, T.; Uchida-Kobayashi, S.; Ohsawa, M.; Itoh, Y. Liver Injury after Methylprednisolone Pulse Therapy in Multiple Sclerosis Is Usually Due to Idiosyncratic Drug-Induced Toxicity Rather than Autoimmune Hepatitis. Mult. Scler. Relat. Disord. 2020, 42, 102065.
5. Cottin, J.; Pierre, S.; Pizzoglio, V.; Simon, C.; Durrieu, G.; Bleyzac, N.; Gouraud, A.; Dumortier, J. Methylprednisolone-Related Liver Injury: A Descriptive Study Using the French Pharmacovigilance Database. Clin. Res. Hepatol. Gastroenterol. 2020, 44, 662–673.

6. Zoubek, M.E.; Pinazo-Bandera, J.; Ortega-Alonso, A.; Hernández, N.; Crespo, J.; Contreras, F.; Medina-Cáliz, I.; Sanabria-Cabrera, J.; Sanjuan-Jiménez, R.; González-Jiménez, A.; et al. Liver Injury after Methylprednisolone Pulses: A Disputable Cause of Hepatotoxicity. A Case Series and Literature Review. United Eur. Gastroenterol. J. 2019, 7, 825–837.
7. Nociti, V.; Biolato, M.; De Fino, C.; Bianco, A.; Losavio, F.A.; Lucchini, M.; Marrone, G.; Grieco, A.; Mirabella, M. Liver Injury after Pulsed Methylprednisolone Therapy in Multiple Sclerosis Patients. Brain Behav. 2018, 8, e00968.
8. Allgeier, J.; Weber, S.; Todorova, R.; Neumann, J.; Gerbes, A. Acute Liver Injury Following Methylprednisolone Pulse Therapy: 13 Cases from a Prospectively Collected Cohort. Eur. J. Gastroenterol. Hepatol. 2022, 34, 457–461.
9. Davidov, Y.; Har-Noy, O.; Pappo, O.; Achiron, A.; Dolev, M.; Ben-Ari, Z. Methylprednisolone-Induced Liver Injury: Case Report and Literature Review. J. Dig. Dis. 2016, 17, 55–62.
10. Cação, G.; Santos, E.; Martins Silva, A. Concurrent Autoimmune Hepatitis in Multiple Sclerosis. Mult. Scler. Houndmills Basingstoke Engl. 2018, 24, 350–353.
11. Negro, F.; Mondardini, A.; Palmas, F. Hepatotoxicity of Saccharin. N. Engl. J. Med. 1994, 331, 134–135.
12. Larrey, D. Drug-Induced Liver Diseases. J. Hepatol. 2000, 32, 77–88.
13. Björnsson, E.S.; Vucic, V.; Stirnimann, G.; Robles-Díaz, M. Role of Corticosteroids in Drug-Induced Liver Injury. A Systematic Review. Front. Pharmacol. 2022, 13, 820724.
14. Hu, P.F.; Xie, W.F. Corticosteroid Therapy in Drug-Induced Liver Injury: Pros and Cons. J. Dig. Dis. 2019, 20, 122–126.
15. Zimmerman, H.J. Oncotherapeutic and Immunosuppressive Agents. In Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver, 2nd ed.; Zimmerman, H.J., Ed.; Lippincott: Philadelphia, PA, USA, 1999; pp. 673–708.
16. Ziemssen, T.; Ashtamker, N.; Rubinchick, S.; Knappertz, V.; Comi, G. Long-Term Safety and Tolerability of Glatiramer Acetate 20 Mg/Ml in the Treatment of Relapsing Forms of Multiple Sclerosis. Expert Opin. Drug Saf. 2017, 16, 247–255.
17. Deltenre, P.; Peny, M.-O.; Dufour, A.; Nady, M.E.; Henrion, J. Acute Hepatitis Induced by Glatiramer Acetate. BMJ Case Rep. 2009, 2009, bcr0920080913.
18. Onmez, A.; Eminler, A.T.; Ergenç, H.; Baykara, M.; Uslan, I.; Tamer, A. Drug-Induced Liver Injury by Glatiramer Acetate Used for Treatment of Multiple Sclerosis: A Case Report. J. Investig. Med. High Impact Case Rep. 2013, 1, 2324709613517493.
19. Neumann, H.; Csepregi, A.; Sailer, M.; Malfertheiner, P. Glatiramer Acetate Induced Acute Exacerbation of Autoimmune Hepatitis in a Patient with Multiple Sclerosis. J. Neurol. 2007, 254,

816–817.

20. Antezana, A.; Herbert, J.; Park, J.; Kister, I. Glatiramer Acetate-Induced Acute Hepatotoxicity in an Adolescent with MS. Neurology 2014, 82, 1846–1847.
21. Subramaniam, K.; Pavli, P.; Llewellyn, H.; Chitturi, S. Glatiramer Acetate Induced Hepatotoxicity. Curr. Drug Saf. 2012, 7, 186–188.
22. Flaire, A.; Carra-Dalliere, C.; Ayrignac, X.; Blanc, P.; Labauge, P. Glatiramer Acetate-Induced Hepatitis in a Patient with Multiple Sclerosis. Acta Neurol. Belg. 2016, 116, 99–100.
23. La Gioia, S.; Bacis, G.; Sonzogni, A.; Frigeni, B.; Conti, M.Z.; Vedovello, M.; Rottoli, M. Glatiramer Acetate-Induced Hepatitis in a Young Female Patient with Multiple Sclerosis. Mult. Scler. Relat. Disord. 2014, 3, 732–734.
24. Makhani, N.; Ngan, B.; Kamath, B.M.; Yeh, E.A. Glatiramer Acetate-Induced Acute Hepatotoxicity in an Adolescent with MS. Neurology 2013, 81, 850–852.
25. Fernández Fernández, N.; Joao Matias, D.; Pisabarros Blanco, C.; Rodríguez Martín, L.; Aparicio Cabezudo, M.; Linares Torres, P.; Hernando Martín, M.; Olcoz Goñi, J.L. Hepatitis induced by glatiramer acetate. Gastroenterol. Hepatol. 2015, 38, 280–281.
26. Sinagra, E.; Raimondo, D.; Cottone, S.; Guddo, F.; Gabriele Rizzo, A.; Amvrosiadis, G.; Perricone, G.; Cottone, M.; Madonia, S. Does Glatiramer Acetate Provoke Hepatitis in Multiple Sclerosis? Mult. Scler. Relat. Disord. 2014, 3, 266–268.
27. Almeida, J.; Solà-Valls, N.; Pose, E.; Blanco, Y.; Sepúlveda, M.; Llufriu, S.; Gines, P.; Saiz, A. Liver Injury and Glatiramer Acetate, an Uncommon Association: Case Report and Literature Review. Ther. Adv. Neurol. Disord. 2017, 10, 367–372.
28. Arruti, M.; Castillo-Triviño, T.; de la Riva, P.; Martí-Massó, J.F.; López de Munain, A.; Olascoaga, J. Autoimmune hepatitis in a patient with multiple sclerosis under treatment with glatiramer acetate. Rev. Neurol. 2012, 55, 190–192.
29. von Kalckreuth, V.; Lohse, A.W.; Schramm, C. Unmasking Autoimmune Hepatitis under Immunomodulatory Treatment of Multiple Sclerosis—Not only Beta Interferon. Am. J. Gastroenterol. 2008, 103, 2147–2148.
30. Michels, S.; Zizer, E.; Barth, T.F.; Wassner, A.; Fangerau, T.; Taranu, D.; Bachhuber, F.; Tumani, H.; Senel, M. Drug-Induced Liver Injury Associated with the Biosimilar Glatiramer Acetate (Clift®). Mult. Scler. Relat. Disord. 2020, 40, 101948.
31. Antonazzo, I.C.; Poluzzi, E.; Forcesi, E.; Riise, T.; Bjornevik, K.; Baldin, E.; Muratori, L.; De Ponti, F.; Raschi, E. Liver Injury with Drugs Used for Multiple Sclerosis: A Contemporary Analysis of the FDA Adverse Event Reporting System. Mult. Scler. Houndmills Basingstoke Engl. 2019, 25, 1633–1640.

32. Biolato, M.; Bianco, A.; Lucchini, M.; Gasbarrini, A.; Mirabella, M.; Grieco, A. The Disease-Modifying Therapies of Relapsing-Remitting Multiple Sclerosis and Liver Injury: A Narrative Review. CNS Drugs 2021, 35, 861–880.
33. Muñoz, M.A.; Kulick, C.G.; Kortepeter, C.M.; Levin, R.L.; Avigan, M.I. Liver Injury Associated with Dimethyl Fumarate in Multiple Sclerosis Patients. Mult. Scler. Houndmills Basingstoke Engl. 2017, 23, 1947–1949.
34. Uetrecht, J. Mechanistic Studies of Idiosyncratic DILI: Clinical Implications. Front. Pharmacol. 2019, 10, 837.
35. Baker, D.; Herrod, S.S.; Alvarez-Gonzalez, C.; Giovannoni, G.; Schmierer, K. Interpreting Lymphocyte Reconstitution Data from the Pivotal Phase 3 Trials of Alemtuzumab. JAMA Neurol. 2017, 74, 961–969.
36. O'Connor, P.W.; Li, D.; Freedman, M.S.; Bar-Or, A.; Rice, G.P.A.; Confavreux, C.; Paty, D.W.; Stewart, J.A.; Scheyer, R.; Teriflunomide Multiple Sclerosis Trial Group; et al. A Phase II Study of the Safety and Efficacy of Teriflunomide in Multiple Sclerosis with Relapses. Neurology 2006, 66, 894–900.
37. LiverTox. Available online: http://livertox.nlm.nih.gov (accessed on 10 September 2022).
38. Ciardi, M.R.; Iannetta, M.; Zingaropoli, M.A.; Salpini, R.; Aragri, M.; Annecca, R.; Pontecorvo, S.; Altieri, M.; Russo, G.; Svicher, V.; et al. Reactivation of Hepatitis B Virus with Immune-Escape Mutations after Ocrelizumab Treatment for Multiple Sclerosis. Open Forum Infect. Dis. 2019, 6, ofy356.
39. Nicolini, L.A.; Canepa, P.; Caligiuri, P.; Mikulska, M.; Novi, G.; Viscoli, C.; Uccelli, A. Fulminant Hepatitis Associated with Echovirus 25 during Treatment with Ocrelizumab for Multiple Sclerosis. JAMA Neurol. 2019, 76, 866–867.
40. Giovannoni, G.; Comi, G.; Cook, S.; Rammohan, K.; Rieckmann, P.; Soelberg Sørensen, P.; Vermersch, P.; Chang, P.; Hamlett, A.; Musch, B.; et al. A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis. N. Engl. J. Med. 2010, 362, 416–426.
41. Cook, S.; Vermersch, P.; Comi, G.; Giovannoni, G.; Rammohan, K.; Rieckmann, P.; Sørensen, P.S.; Hamlett, A.; Miret, M.; Weiner, J.; et al. Safety and Tolerability of Cladribine Tablets in Multiple Sclerosis: The CLARITY (CLAdRIbine Tablets Treating Multiple Sclerosis OrallY) Study. Mult. Scler. Houndmills Basingstoke Engl. 2011, 17, 578–593.
42. Leist, T.P.; Comi, G.; Cree, B.A.C.; Coyle, P.K.; Freedman, M.S.; Hartung, H.-P.; Vermersch, P.; Casset-Semanaz, F.; Scaramozza, M.; Oral Cladribine for Early MS (ORACLE MS) Study Group. Effect of Oral Cladribine on Time to Conversion to Clinically Definite Multiple Sclerosis in Patients with a First Demyelinating Event (ORACLE MS): A Phase 3 Randomised Trial. Lancet Neurol. 2014, 13, 257–267.

43. Leist, T.; Cook, S.; Comi, G.; Montalban, X.; Giovannoni, G.; Nolting, A.; Damian, D.; Syed, S.; Galazka, A. Long-Term Safety Data from the Cladribine Tablets Clinical Development Program in Multiple Sclerosis. Mult. Scler. Relat. Disord. 2020, 46, 102572.
44. Busuttil, D.P.; Chasty, R.C.; Fraser, M.; Copplestone, J.A.; Prentice, A.G. Delayed Reactivation of Hepatitis B Infection after Cladribine. Lancet 1996, 348, 129.