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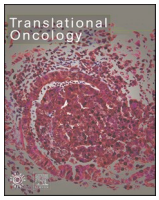

The Current status of steroid-refractory immune-checkpoint-inhibitor-related hepatotoxicity

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ABSTRACT

ICI-related hepatotoxicity (IRH) is becoming more and more common as immune checkpoint inhibitors (ICIs) have begun to be increasingly approved and used in combination with other anti-tumor drugs worldwide. Steroids are the first choice for the treatment of IRH, but the subsequent optimal treatment algorithm remains unclear if the disease progresses to steroid-refractory IRH. Therefore, in this paper we reviewed all the pertinent literature on steroid-refractory IRH to the greatest extent possible in an attempt to provide information on which to base an update of the treatment algorithm for steroid-refractory IRH.

Introduction

Immune checkpoints are important molecules that help to maintain the immune homeostasis of the body. Once bound to a ligand, this type of molecule down-regulates the function of immune cells such as T lymphocytes to prevent the body from damage caused by excessive activation of the immune system itself [1]. When immune checkpoint inhibitors (ICIs) combine with immune checkpoints to exert anti-tumor effects, some patients experience immune-related adverse events (irAEs), which can involve any organ of the body [2]. ICI-related hepatotoxicity (IRH) is a relatively common and lethal irAE [3–8] that can be divided into three modes: cholestatic liver injury, hepatocellular liver injury, and mixed hepatocellular and cholestatic liver injury [4]. Steroids are the first-line drugs used to treat IRH, but some patients either don't respond well to glucocorticoid therapy or relapse during drug withdrawal. Such patients can then progress to steroid-refractory IRH. Guidelines and consensus recommend that the drugs for the treatment of steroid-refractory IRH should be a variety of immunosuppressive agents [9–15] (Table 1), and some experts have also made attempts prescribe a specific treatment process for IRH [16–24]. However, there is still no broad consensus so far. Therefore, we have reviewed the current status of the treatment of steroid-refractory IRH in an attempt to make suggestions on the best treatment algorithm.

Prevalence of steroid-refractory IRH

At present, only retrospective data have been reported on the incidence of steroid-refractory IRH (Table 2). A study by Patrinely et al. analyzed patients from six centers in the United States and Australia and included all cancer patients who had received ICI monotherapy or combination therapy and developed immune hepatitis, regardless of the cancer type or the dosage used. The results showed that 92.1% of all 164 patients received glucocorticoid therapy, and 22.6% (37/164) required second-line immunosuppressive treatment (for example, mycophenolate, tacrolimus, or abatacept) due to steroid refractoriness [25]. In a study sponsored by Nicole A. Romanski et al. that focused on patients with metastatic melanoma who developed hepatotoxicity during treatment with ICIs, 31 of 43 patients with IRH (72.1%) received systemic steroid therapy, and 35.5% of the patients suffered a relapse of IRH during steroid tapering, though only two patients (4.7%) required the addition of second-line immunosuppressive drugs [26]. Similarly, Maaike Biewenga et al. conducted a study of 2,51 patients with advanced cutaneous melanoma who received ICI treatment. The patients received a total of 3111 treatments containing ICIs, and immune hepatitis occurred in 139 of these treatments. Additionally, 20% (25/124) of the 124 treatment periods with complete cases required the addition of second-line immunosuppressive drugs on the basis of glucocorticoids [27].

In a multicenter study initiated by Michael Li et al. that included 102

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Table 1
Recommendations for treatment of IRH from medical organizations worldwide.

Grade	Description	ESMO [23]	SITC [24]	ASCO [25]	MASCC [26]	AGA [27]	CSCO [28]	NCCN [29]
G1	AST/ALT<3 × ULN TBILI<1.5 × ULN ALKP*<2.5 × ULN	none	none	none	none	none	none	none
G2	AST/ALT 3~5 × ULN TBILI1.5~3 × ULN ALKP*2.5–5 × ULN	Prednisone 1 mg/kg/day	Prednison 0.5~1 mg/kg/day	Prednison 0.5~1 mg/kg/day	Prednison 0.5~1 mg/kg/day	Prednison 0.5~1 mg/kg/day	Prednison 0.5~1 mg/kg/day	Prednison 0.5~1 mg/kg/day
G3	AST/ALT 5~20 × ULN TBILI3~10 × ULN ALKP*>5 × ULN	ALT/AST<400 and normal bilirubin/clot time/ albumin:prednisolone 1 mg/kg/day;ALT/AST>400 or elevated bilirubin/ prolonged clotting time/ decreased albumin: (methyl)prednisolone, 2 mg/kg/day	prednisone 1~2 mg/kg/day	methylprednisolone 1~2 mg/kg/day	prednisone 0.5~2 mg/kg/day bid	methylprednisolone 1~2 mg/kg/day	methylprednisolone 0.5~1 mg/kg/day	Prednison/ methylprednisolone 1~2 mg/kg/day
G4	AST/ALT >20 × ULN TBILI>10 × ULN ALKP*>5 × ULN	Methylprednisolone 2 mg/kg/day	prednison 1~2 mg/kg/day	methylprednisolone 2 mg/kg/day	prednisone 0.5~2 mg/kg/day bid	methylprednisolone 1~2 mg/kg/day	Methylprednisolone 0.5~1 mg/kg/day	prednisone/methyl-prednisolone 1~2 mg/kg/day
Other immune-suppressants	-	Add mycophenolate mofetil after 2–3 days of ineffective intravenous injection of glucocorticoids; Consider adding tacrolimus if mycorcophenol ineffective; Antithymocyte globulin has been reported for glucocorticois-resistant and mycophanolate refractory IRH.	G3–4:Consider adding mycophenolate mofetil 3days after ineffective of glucocorticois	G3: Consider adding mycophenolate mofetil or acetazolamide 3days after ineffective of glucocorticois G4:Consider adding mycophenolate mofetil, instead of infliximab 3days after ineffective of glucocorticois G2~3 Other non-TNF-α immunosuppressants are optional	G2: If liver biopsy has not been performed after failure of first-line therapy, azathioprine, mycophenolate, or tacrolimus are considered. G3: Based on G2, the combination of the above three drugs was considered for drug resistance cases. G4: Based on G3, antithymoglobulin was considered for rapidly progressive hepatitis	G3–4: 3 days of glucocorticoids ineffective, consider mycophenolate, tacrolimus, azathioprine. If fulminant hepatitis, considering anti thymocyte globulin.	G3–4: If liver function does not improve after 3 days of glucocorticoids administration, consider adding mycophenolate, tacrolimus, budesonide, antithymic globulin, and plasmapheresis. Infliximab should not be used.	G3–4: If glucocorticoids is difficult to treat or does not improve after 1–2 days, consider adding mycophenolate/anti-thymocyte globulin(ATG)/ tacrolimus/ cyclosporine. Infliximab should not be used.

Abbreviation: European Society for Medical Oncology, ESMO; Society for Immunotherapy of Cancer, SITC; American Society of Clinical Oncology, ASCO; Multinational Association of Supportive Care in Cancer, MASCC; American Gastroenterological Association, AGA; Chinese Society of Clinical Oncology, CSCO; National Comprehensive Cancer Network, NCCN;.

* ALKP is added to MASCC grading.

melanoma patients with G3–4 IRH, the proportion of steroid-refractory IRH patients was 33.3% (34/102) [28]. However, in research on patients with melanoma initiated by Brandon M Huffman et al., only 11.8% (2/17) of patients needed to be treated with immunosuppressives in addition to steroids [29]. Another multicenter study initiated by Michael Li et al. included 215 patients with grade 3–4 IRH and analyzed the difference in efficacy of different initial corticosteroid doses (<1.5 mg/kg or ≥1.5 mg/kg methylprednisolone equivalents). Their study excluded patients with hepatocellular carcinoma and focused only on patients with hepatocellular injury. Grade 3 and 4 IRH were respectively defined as ALT > 200 U/L (5 times the upper limit of normal) and > 800 U/L (20 times the upper limit of normal). The results showed that among the 215 patients, 61 (28.4%) developed steroid-refractory IRH, including 29 (22.7%) patients in the <1.5 mg/kg group and 32 (36.8%) patients in the ≥ 1.5 mg/kg group ($P = 0.024$). Steroid-refractory IRH was more likely to occur in patients with inadequate initial steroid doses that later required higher doses [30]. In a study with Japanese patients reported by Imoto K et al., 3 of 56 (5.4%) patients with IRH suffered steroid resistance. Notably, the three patients were all grade 3 or 4 and accounted for 27.3% of all grade 3 or 4 patients [31]. However, the true incidence of steroid-refractory IRH, as well as the question of whether there are differences in outcomes by race, tumor type, number of lines of treatment, or treatment regimens still requires more prospective studies with large samples.

When should biopsy be performed?

To diagnose IRH the NCCN guidelines only recommend pathological biopsy for patients with abnormal G4 liver function without biopsy contraindications. Other patients can be diagnosed by asking their medical history, physical examination, hematological examination, and imaging examination [15]. Because patients with IRH may be asymptomatic and have no imaging abnormalities [32,33], a comprehensive hematologic examination is critical to exclude viral infections and autoimmune hepatitis, and to grade the severity. The CIOMS score (Council for International Organizations of Medical Sciences scale) [34, 35] or the RUCAM score (Roussel Uclaf Causality Assessment Method) [36–38] are both helpful for diagnosis. for steroid-refractory IRH, other etiologies, especially viral hepatitis, still need to be strictly excluded [39]. In addition, in order to avoid the wrong initiation of other immunosuppressive therapy due to other factors such as tumor liver metastasis, we still recommend that a biopsy be performed before diagnosis and treatment of steroid-refractory IRH if possible [40,23].

Which subgroup is the high-risk steroid-refractory IRH patients?

The relationship between pathological manifestations of IRH and sensitivity to immunosuppressive agents and prognosis has not been established [38]. Only few reports involve cholangitis pattern and cholangitis-and-hepatocellular pattern of IRH. A retrospective study reported an incidence of 4.2% (23/546) [41], However, because this type of patients have low sensitivity to glucocorticoids, patients with these patterns of IRH are still recommended to receive early multi-drug combination therapy and other more aggressive treatments to avoid persistent bile duct injury [42-46,35,23]. Thus, early identification of steroid-refractory individuals is crucial for effective control of IRH. Multi-drug resistance type 1 transporters (MDR1) may indicate resistance to steroids and early replacement regimens, such as ATG and cyclosporin A [44], and PD-L1-positive and PD-L2-negative may be biomarkers for predicting steroid-refractory IRH [47]. Increased levels of multiple cytokines (IFNγ, IL-1b, IL-6, IL-12p70, TNF α) may also indicate that steroids alone are not enough [48]. Even the same kind of infiltrating cells have different sensitivities to the same drug regimen [49,50], however, suggesting that the interval between changing regimens should be shorter to avoid the increased risk of adverse reactions caused by prolonged ineffective immunosuppression.

Steroid refractoriness or dose of steroid is not enough?

Current guidelines recommend methylprednisolone or equivalents up to 2.0 mg/kg for treating IRH. A retrospective study reported by Li et al. suggested that there was no difference in the progression to steroid-

Table 2
Incidence of steroid-refractory IRH.

Reference	Study type	Sample size	Nation	Cancer type	Frist-line glucocorticoids (%)	Second-line immunosuppression (%)	Outcome
J. Randall Patrinely Jr.et al. [25].	retrospective study	164	U.S.A., Australia	melanoma,lung cancer, Renal cell carcinoma, Squamous Cell carcinoma,Other	92.10%	22.60%	Five patients (3%) died of ICI hepatitis or complications of hepatitis treatment.
Nicole A. Romanski. et al. [26].	retrospective study	43	Denmark	melanoma	72.10%	4.70%	the hepatitis of all other patients resolved with or without intervention
Maaike Biewenga. et al. [27].	retrospective study	124*	Netherlands	melanoma	99%	20%	Three patients died due to the toxicity of which 2 patients had PD-1 inhibitor-induced colitis and ipilimumab induced nephritis as additional IRAEs.
ichael Li.et al. [28].	retrospective study	102	U.S.A.	melanoma	not available	33.30%	not available
Brandon M Huffman. et al. [29].	retrospective study	17	U.S.A.	melanoma	94%	11.80%	Two patients died from progression of either metastatic disease or fulminant liver failure while still on steroids.
Michael Li. et al. [30].	retrospective study	215	U.S.A.	melanoma,Non-small cell lung cancer,Renal cell carcinoma,Breast cancer,Urothelial cancer, Other	100%	28.40%	not available
Imoto K.et al. [31].	retrospective study	56	Japan	lung cancer,melanoma, head and neck cancers, renal cancer,stomach cancer,Others	9%	5.40%	Three patients died due to the underlying disease

* episodes.

refractory IRH between the initial >1.5 mg/kg corticosteroid dose group and the <1.5 mg/kg group, but patients with insufficient initial corticosteroid doses and who later increased the doses were more likely to develop steroid-refractory IRH. The patients also needed longer alanine transaminase (ALT) recovery time (HR 0.52, 95%CI 0.33–0.84, $P = 0.007$) and alkaline phosphatase (ALK) recovery time to ≤100 U/L (HR 0.40, 95%CI 0.25–0.64, $P < 0.001$) [30]. This seems to indicate that steroid-refractory IRH can still be diagnosed even if the initial corticosteroid dose of 1.5 mg/kg/day is still ineffective. However, in the case reported by Ooi R et al., after the initial 1 mg/kg/day PSL treatment, IRH recurred during steroid reduction, and AZA was ineffective, although in this case after three days of pulse treatment with 1000 mg mPSL, "So-called" steroid-refractory IRH was successfully treated. This patient remained free of recurrence of the primary disease one year after ICI withdrawal as well [51]. The above case suggests that it is necessary to consider the use of steroid pulse therapy before diagnosing steroid-refractory IRH, and the steroid pulse therapy may not affect the prognosis of patients with tumor treatment.

Treatment algorithms for steroid-refractory IRH

Currently, the exact mechanism of steroid-refractory IRH is still unclear, we made the following potential mechanism diagram (Fig. 1) based on the pathological findings reported in the literature and the sensitivity to immunosuppressive agents. the treatment algorithm for steroid-refractory IRH is due primarily to autoimmune hepatitis and the case reports of steroid-refractory IRH (Table 3).

Mycophenolate mofetil (MMF)

MMF is a prodrug of mycophenolic acid (MPA). The pharmacological actions of MPA are to suppress cell-mediated immunity and antibody production, induce apoptosis of T cells, suppress maturation of dendritic cells, decrease IL-1 expression, and increase antagonists of IL-1 receptors through binding with inosine monophosphate dehydrogenase (IMPDH) [69]. The adverse effects of MMF are primarily diarrhea, leukopenia, infection, and vomiting [71,72]. One case report indicated that the initial dose of MMF should be 2 g/day, and if symptoms become milder, the dose of glucocorticoid should be decreased gradually and monitored closely to prevent recurrence until all of the immunosuppressive treatments wear off [69].

Anti-themocyte globulin (ATG)

ATG is a type of antilymphocyte serum that is refined from the serum of rabbits or horses that have been sensitized by human thymocytes or T cells in advance. The functional target of ATG includes the antigens of T cells, B cells, NK cells, macrophages, dendritic cells, and adhesive and transport antigens, which are antigens that attend to many different pathways [73]. The adverse effects of MMF are primarily fever, chills, leukopenia, thrombocytopenia, and systemic infection [74,75]. for the treatment of autoimmune myocarditis, ATG is used to treat IRH without a recommended dose in the guidelines of the NCCN or ASCO in the United States, the ESMO in Europe, or the CSCO in China. Case reports have shown effective dosages that ATG has been applied in a base of glucocorticoid and MMF for a 2-dose interval of 24 h with a dosage of 1.5 mg/kg/day, or 100 mg for the first day and 50 mg for the second day [43,44].

Tacrolimus and cyclosporin

Both tacrolimus and cyclosporin are calcineurin inhibitors; they

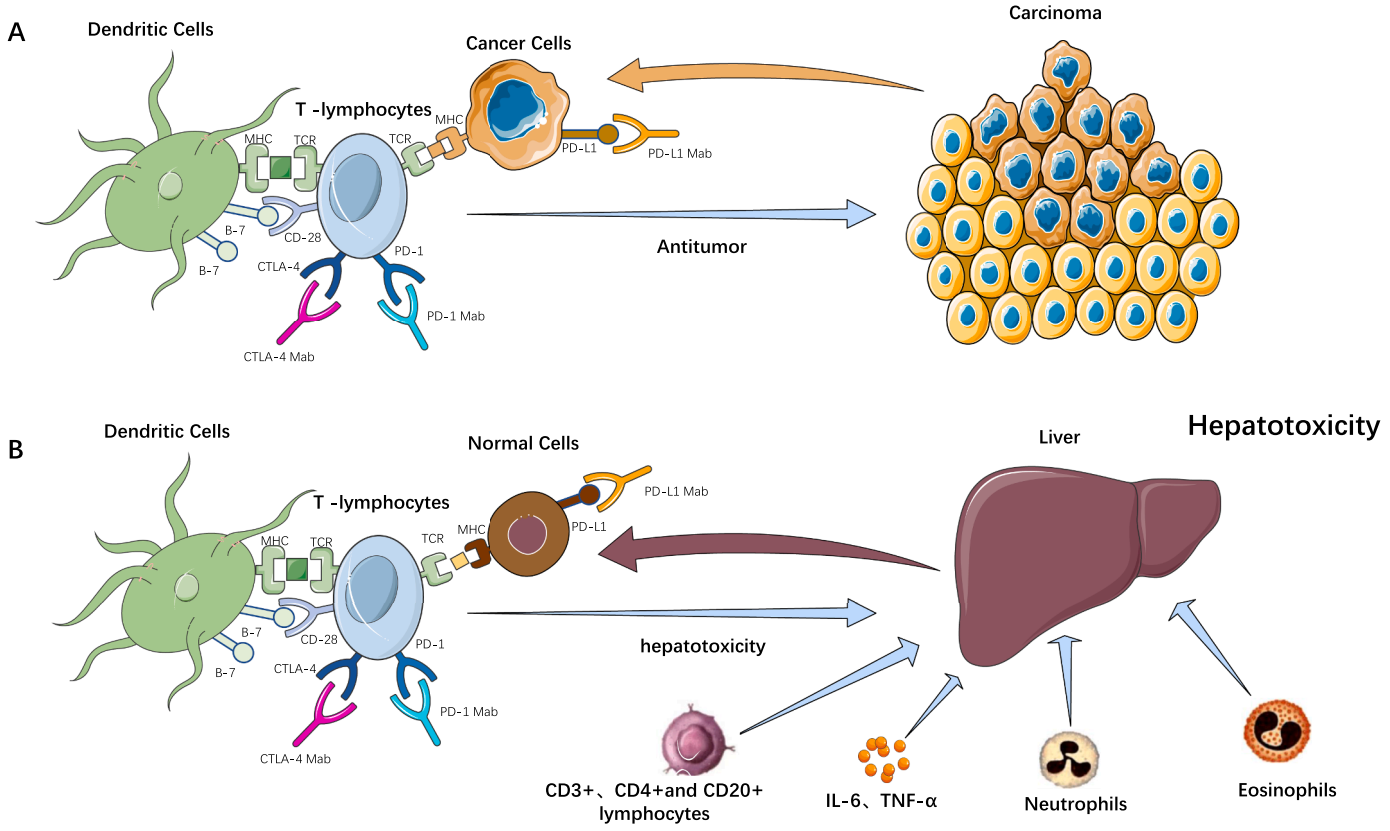

Fig. 1. Potential mechanisms of steroid-refractory IRH.
A. Main mechanism of antitumor action of immune cells.
B. Brief mechanism of T-cell-mediated hepatotoxicity, and CD3+, CD4+ and CD20+ lymphocytes, neutrophils, and eosinophils were also involved.

Table 3
Cases of steroid-refractory IRH.

Reference	Case	Disease	Cancer treatment	IRH Type	Biopsy	Immunohistochemistry	Cytokine	Initial treatment	subsequent treatment	Recovery	Retreatment With ICIs	Recurrent IRH
Ueno et al. [52]	1	Lung cancer	durvalumab	cholangitis and hepatitis	Y	CD8+ lymphocytes	/	PSL	MMF+PSL	Y	N/A	N/A
	2	Lung cancer	pembrolizumab	hepatitis	Y	CD8+ lymphocytes	/	PSL+UDCA	MMF+PSL+UDCA	Y	N/A	N/A
Kataoka et al. [47]	1	laryngeal cancer	nivolumab	cholangitis and hepatitis	Y	CD8+ and CD4+ lymphocytes	/	PSL	UDCA	Y	Y	N
Hori et al. [53]	1	Lung cancer	pembrolizumab	cholangitis	Y	CD8+ lymphocytes	/	mPSL followed by PSL	MMF	N	N	Death
Murayama et al. [50]	1	renal cell carcinoma	nivolumab and ipilimumab	cholangitis and hepatitis	Y	CD8+ and CD4+ lymphocytes	/	PSL+UDCA	mPSL; MMF	N	N	Death
	2	melanoma	pembrolizumab	cholangitis and hepatitis	Y	CD8+lymphocytes	/	PSL	MMF	Y	N/A	N/A
Tan et al. [46]	1	esophageal cancer	camrelizumab	cholangitis and hepatitis	Y	eosinophils and CD8+ lymphocytes	/	mPSL+UDCA	DPMAS and sequential PE	Y	N	N
Yoshikawa et al. [54]	1	Lung cancer	nivolumab	cholangitis and hepatitis	Y	CD8+, CD4+ and CD20+ lymphocytes	/	PSL+UDCA	PSL+MMF	N	N	Death
Hirasawa et al. [55]	1	Lung cancer	Nivolumab	cholangitis and hepatitis	Y	CD8+ and CD4+ lymphocytes	/	PSL	MMF; TAC	N	N	Death
Nakashima et al. [56]	1	Lung cancer	durvalumab	cholangitis and hepatitis	N	/	/	mPSL+ MMF	mPSL+AZA; mPSL+AZA+TAC; infliximab	Y	N/A	N/A
Sato et al. [57]	1	Lung cancer	pembrolizumab	cholangitis	Y	CD8+ lymphocytes	/	mPSL followed by PSL	PSL+UDCA	Y	N/A	N/A
Motomura et al. [58]	1	melanoma	ipilimumab and nivolumab	hepatitis (cholangitis is not clear)	Y	CD8+ lymphocytes	/	prednisone	mPSL+MMF; mPSL+MMF; NAC+ATG+mPSL+ MMF	Y	N/A	N/A
Kanaoka et al. [59]	1	Lung cancer	pembrolizumab	cholangitis and hepatitis	Y	CD8+,CD3+,CD4+and CD20+ lymphocytes. neutrophils and eosinophils (H&E)	/	PSL	AZA; AZA+PSL	Y	N/A	N/A
Ziogas et al. [23]	1	melanoma	ipilimumab	cholangitis and hepatitis	N	/	/	mPSL	MMF+mPSL+UDCA; MMF+mPSL+UDCA+TAC	Y	N	N
Liu et al. [60]	1	Lung cancer	pembrolizumab	cholangitis and hepatitis	N	/	IL-6 and TNF-α	mPSL	mPSL+bicyclol	Y	Y	N
Thorsteinsdottir et al. [61]	1	melanoma	pembrolizumab	cholangitis and hepatitis	Y	/	/	PSL	PSL+MMF; PE	N	N	Death
Nakano et al. [62]	1	laryngeal cancer	nivolumab	cholangitis and hepatitis	N	/	/	mPSL	mPSL+MMF	Y	N	Death
Hsu et al. [63]	1	hepatocellular carcinoma	nivolumab	cholangitis and hepatitis	N	/	/	prednisone	MMF +prednisone: MMF	Y	N/A	N/A
	1	Lung cancer	pembrolizumab		Y	CD8+ lymphocytes	/	PSL	AZA	Y	N	Death

(*continued on next page*)

Table 3 (*continued*)

Reference	Case	Disease	Cancer treatment	IRH Type	Biopsy	Immunohistochemistry	Cytokine	Initial treatment	subsequent treatment	Recovery	Retreatment With ICIs	Recurrent IRH
Tanaka et al. [64]				cholangitis and hepatitis								
Onishi et al. [45]	1	melanoma	nivolumab	cholangitis and hepatitis	Y	CD8+ lymphocytes	/	PSL	PSL+UDCA+bezafibrate	Y	N	Death
Riveiro-Barciela et al. [65]	1	melanoma	ipilimumab	cholangitis and hepatitis	N	/	/	steroids	MMF; PE	Y	N/A	N/A
Corrigan et al. [66]	1	melanoma	ipilimumab+nivolumab	cholangitis and hepatitis	Y	CD3+ and CD8+ lymphocytes	/	mPSL	mPSL+MMF; infliximab+mPSL tacrolimus	Y	N	N
Black et al. [49]	1	melanoma	ipilimumab+nivolumab	cholangitis and hepatitis	Y	T-lymphocytes (H&E) PD-L1-positive and PD-L2-negative	/	mPSL	MMF	Y (ALT normalisation was not reached until 105 U/L 6 weeks later)	N/A	N/A
McGuire et al. [44]	1	melanoma	pembrolizumab	cholangitis and hepatitis	Y	CD8+ and CD4+ lymphocytes	/	mPSL followed by dexamethasone	prednisone+MMF ATG	Y	N/A	N/A
Spänkuch et al. [67]	1	melanoma	ipilimumab+nivolumab	cholangitis and hepatitis	N	/	/	mPSL	mPSL+MMF; ATG+PSL	Y	Y	N
Iwamoto et al. [68]	1	melanoma	nivolumab	cholangitis and hepatitis	N	/	/	mPSL	mPSL+AZA	Y	N/A	N/A
Tanaka et al. [69]	1	melanoma	ipilimumab	cholangitis and hepatitis	N	/	/	mPSL	mPSL+MMF	Y	N	Death
Ahmed et al. [35]	1	melanoma	ipilimumab	cholangitis and hepatitis	N	/	/	mPSL	mPSL+MMF+ATG (ATGAM)	Y	N	N
Chmiel et al. [43]	1	melanoma	ipilimumab	cholangitis and hepatitis	N	/	/	mPSL	mPSL+MMF; mPSL+MMF+ATG (Thymoglobulin)	Y	N/A	N/A

abbreviation: PSL:prednisolone; MMF:mycophenolate mofetil; UDCA:ursodeoxycholic acid; mPSL:methylprednisolone; DPMAS:dual-molecule plasma adsorption system; PE:plasma exchange; TAC:tacrolimus; AZA: azathioprine; ATG:antithymocyte globulin. NA:Not hepatitis is defined: ALT and/or AST≥G2 when diagnosed as IRH, according to CTCAE 5.0. cholangitis is defined: ALP, GGT or TBIL≥G2 when diagnosed as IRH, according to CTCAE5.0.

exert their pharmacological actions through binding to calcineurin to inhibit the expression of IL-2 and as a result block the differentiation and maturation of T cells. Additionally, tacrolimus and cyclosporin can promote the expression of TGF-β and down-regulate the release of IFNγ in NK cells [70]. The adverse effects of tacrolimus include hypertension, fever, infection, tremor, headache, insomnia, and paresthesia [76], and the adverse effects of cyclosporin include renal dysfunction, tremor, hirsutism, hypertension, and gum hyperplasia [77]. for the treatment of IRH, there has been no recommended dosage of tacrolimus and cyclosporin. Beardslee (2019) suggested that the target concentration of tacrolimus should be 5–12 ng/ml to treat irAEs and that the initial dosage was commonly 0.01 to 0.06 mg/kg b.i.d. Moreover, Beardslee recommended that both of these should be considered in view of multiple factors such as concomitant other immunosuppressive agents, the patient's liver and kidney function, underlying diseases, and the drug delivery route. The agent of plasma concentration should be supervised twice for a week until reaching the target concentration, and afterwards the concentration should be supervised for 2 weeks or 1 month [78]. Gérard et al. reported that their treatment plan for irAEs with Cyclosporin, in a base of glucocorticoid, was 3 mg/kg for 3 days and afterwards oral 80 mg twice for 2 days. After alleviation of symptoms, they suggest first decreasing the dosage of glucocorticoid and monitoring the status of the patient closely to prevent recurrence. After this, they recommend decreasing the dosage of cyclosporin every 7 to 10 days until all of the immunosuppressive agents wear off [79].

Other immunosuppressive agents

Ziemer et al. have shared their treatment experience with severe autoimmune-like drug-induced liver injury that was induced by novoliumab and pembrolizumab with budesonide for 2–3 cycles. When increased grade 3 ALT of patients was diagnosed, novoliumab and pembrolizumab were stopped and methylprednisolone was applied. In order to minimize and decrease systemic glucocorticoid exposure, budesonide was given in combination with N-acetylcysteine and ursodeoxycholic acid. When the immunosuppressive treatment was restarted after three and a half weeks, budesonide and ursodeoxycholic acid were still used without consequent toxicity. However, the benefit of using budesonide to treat glucocorticoid-refractory IRH was not clear [80]. At present, budesonide is only recommended as a treatment for IRH by Chinese Guidelines (*Management of immune checkpoint inhibitor-related toxicity*, Guidelines of Chinese Society of Clinical Oncology, 2021).

Besides, other agents and blood purification are also candidates. Plasma exchange alone is ineffective for mixed steroid-refractory IRH, and DPMAS should be added to plasma exchange for cholangitis or mixed IRH [61,46]. AZA's sensitivity in treating IRH varies greatly, and this may be related to the dose or the different pathogenesis of IRH and AIH [56,59,64,68]. Tocilizumab (an interleukin (IL)−6 receptor neutralizing antibody) has been shown to be effective against cholangitis pattern steroid-refractory IRH, particularly in elevating anti-inflammatory regulatory cytokine levels [81]. Infliximab to treat IRH is not recommended by major guidelines either, but there have been some reports that have shown that infliximab was successfully used to rescue several cases of IRH after failures of other immunosuppressive agents [82,83]. Therefore, infliximab can be cautiously used under the condition that other immunosuppressive agents are valid. Based on the above and the characteristics of each immunosuppressive agents (Table 4), we propose a treatment algorithm for steroid-refractory IRH (Fig. 2).

Almost all current guidelines recommend permanent withdrawal of ICIs for G3–4 hepatotoxicity, except the NCCN guidelines, which recommend that for G3 hepatitis patients treated with CTLA-4 combined with PD-1/PD-L1, only PD-1/PD-L1 inhibitors should be used to restart treatment. The case reported by Spankuch et al. illustrates that it is safe to restart PD-1 monotherapy in patients initially treated with CTLA-4+PD-1 who develop G4 hepatitis and G3 cholangitis with steroid-refractory IRH [67] as well, and the case of Kataoka et al. also illustrates the safety of re-starting PD-1monotherapy in G3 cholangitis patients with steroid-refractory IRH [47]. Therefore, for patients with any pattern of G3 cholangitis steroid-refractory IRH, PD-1 monotherapy can be restarted. However, G4 patients still need to stop using the drug permanently until there is new evidence that may contravene this recommendation.

Table 4
Commonly used immunosuppressants: target, indication, and adverse reactions.

Category	Active ingredients	Indications (FDA)	Target	Adverse reactions (most frequently reported in system use)	Citation
Mycophenolic Acid	Mycophenolate mofetil	1 Kidney, Liver, and Heart Transplantation	1 T lymphocytes 2 B lymphocytes 3 Dendritic cell 4 Interleukin (IL)−1 and IL-1 receptor	Diarrhea,leukopenia, infection, vomiting	[37]
Anti-thymocyte globulin	Anti-thymocyte globulin [rabbit]	1 Kidney Transplantation 2 Use in conjunction with concomitant immunosuppression.	1 T lymphocytes	Urinary tract infection, abdominal pain, hypertension, nausea, shortness of breath, fever, headache, anxiety, chills, increased potassium levels in the blood, low counts of platelets and white blood cells	[41]
	Anti-thymocyte Globulin (Equine)	1 Kidney Transplantation 2 Aplastic Anemia	1 T lymphocytes	Fever, chills, leukopenia, thrombocytopenia, systemic infection, dermatologic reactions, such as rash, pruritus, urticaria, wheal, and flare.	[42]
Calcineurin Inhibitor	Tacrolimus	1 Liver, kidney, heart, or lung transplantation 2 Atopic dermatitis	1 T lymphocytes 2 B lymphocytes 3 Interleukin (IL)−1 beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, gamma interferon, tumor necrosis factor-alpha, and granulocyte macrophage colony-stimulating factor 4 IL-2 receptor	Abnormal renal function, hypertension, diabetes mellitus, fever, CMV infection, tremor, hyperglycemia, leukopenia, infection, anemia, bronchitis, pericardial effusion, urinary tract infection, constipation, diarrhea, headache, abdominal pain, insomnia, paresthesia, peripheral edema, nausea, hyperkalemia, hypomagnesemia, and hyperlipemia.	[46]
	Cyclosporin	1 Kidney, Liver, and Heart Transplantation 2 Rheumatoid Arthritis 3 Psoriasis 4 Keratoconjunctivitis sicca 5 Vernal keratoconjunctivitis	1 T lymphocytes 2 T-helper cell 3 T-suppressor cell 4 Interleukin-2	Renal dysfunction, tremor, hirsutism, hypertension, gum hyperplasia	[47]

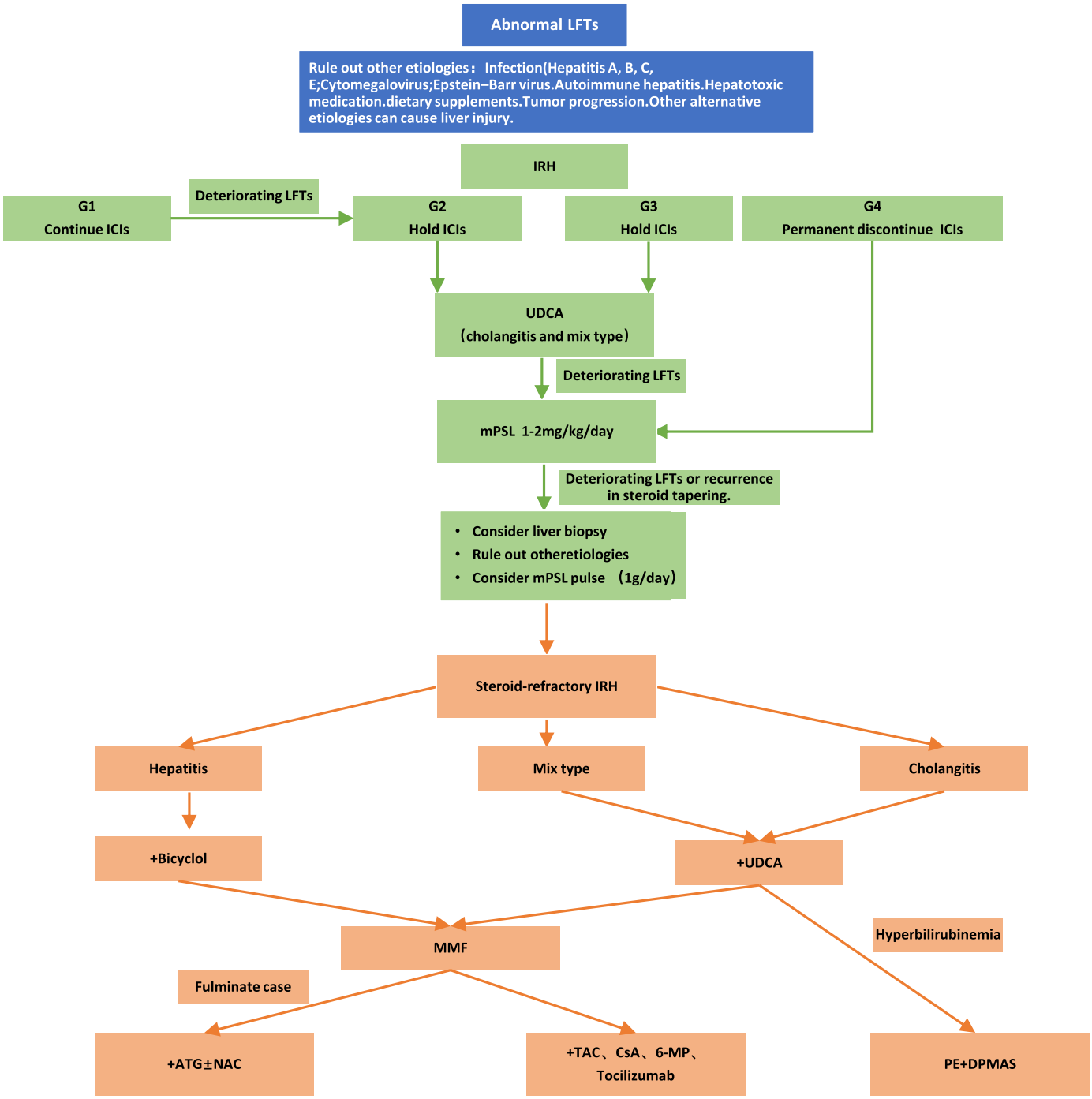

Fig. 2. Treatment algorithm for steroid-refractory IRH.

Conclusion

As more and more indications for ICIs have been approved, steroid-refractory IRH is set to become more and more common in clinical practice. There are many existing therapeutic drugs and treatment methods for IRH, and our current focus is on how to optimize the treatment algorithm. With a deeper understanding of steroid-refractory IRH from the perspective of pathogenesis, genotyping, and drug sensitivity, precise individualized treatment can become a reality.

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Ethic approval

Not applicable.

CRediT authorship contribution statement

Hui Xing: Validation, Formal analysis, Writing – original draft. **Yang Wang:** Methodology, Investigation, Writing – original draft. **Bo Qu:** Data curation, Writing – review & editing. **Qiang Wei:** Visualization. **Cuihua Li:** Visualization. **Chao Pan:** Visualization. **Hui Li:** Conceptualization, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Hui Li reports a relationship with MSD, Abbvie, Pfizer, Takeda, Janssen Pharmaceuticals, Dr. Falk Pharma. that includes: speaking and lecture fees.

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