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Case Report

Treatment of Refractory Checkpoint-Inhibitor-Induced Hepatitis with Tacrolimus: A Case and Review of the Literature

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Abstract: Immune-related hepatitis (irH) is a fairly frequent complication of immune checkpoint inhibitors (ICIs). Its management is generally based on withholding ICIs and on the rapid initiation of corticosteroids, which is successful in 63 to 96% of cases. Mycofenolate mofetil (MMF) is accepted as a second-line immunosuppressant in the case of the failure of corticosteroids. In rare cases, though, irH is also resistant to MMF and may lead to liver failure. There are no standard third-line treatments and current guidelines are based on a limited number of case reports. We present a case of a metastatic melanoma patient with an immune-related hepatitis refractory to corticosteroids and MMF, that was successfully reversed with tacrolimus. Unfortunately, this was complicated with a serious infection and progressive disease, which illustrates the complexity of treatment of steroid-refractory immunotherapy-related adverse events. Furthermore, we provided a literature review regarding the management of steroid-refractory hepatitis and proposed a strategy to circumvent the current uncertainties in the management of steroid-refractory irH.

Keywords: immune checkpoint inhibitor; immune-related adverse events; hepatitis; liver biopsy; tacrolimus; melanoma; review

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1. Introduction

Immune checkpoint inhibitors (ICIs) have dramatically changed the treatment paradigms for many tumor types in the last decade [1,2]. Today, the most commonly used ICIs in clinical practice are monoclonal antibodies (mAbs) directed: against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), such as ipilimumab or tremelimumab; against programmed cell death-1 (PD-1), such as nivolumab, pembrolizumab and cemiplimab; or against programmed cell death-ligand 1 (PD-L1), such as atezolizumab, avelumab or durvalumab. New classes of ICI targeting different checkpoints are under development, such as LAG3 (lymphocyte-activation gene 3) which has recently been targeted in melanoma by relatlimab, but also TIM3 (T-cell immunoglobulin and mucin domain 3), TIGIT (T-cell immunoreceptor with immunoglobulin and ITIM domains), IDO1 (indoleamine 2,3-dioxygenase 1) and OX40 [2–5].

However, the counterpart of the augmented immune response is a new range of autoimmune toxicities called immune-related adverse events (irAEs), potentially affecting every organ, including the liver [6]. International guidelines have proposed various terms for hepatotoxicity related to ICIs, and the terms of "immune checkpoint inhibitor-related hepatotoxicity" and "immune-related hepatitis" (irH) have been used interchangeably [7–11]. Severe irH, defined as grade 3 or higher (Table 1) is seen in 1 to 11% of patients treated with ICI [12]. The exact pathogenesis of irH is not fully understood but is likely to be multifactorial. There are several possible patterns of liver injury, mainly acute lobular hepatitis, sometimes confined to the centrilobular zone. Though, occasionally, a biliary injury

pattern is reported, as well as, rarely, steatohepatitis. In contrast to idiopathic autoimmune hepatitis, plasma cells are not usually present in large amounts [13].

Table 1. Severity of immunotherapy-related hepatitis (irH) according to the CTCAE version 5.0.

	AST or ALT	GGT or ALP	Bilirubin
Grade 1	1–3 × ULN	1–2.5 × ULN	1–1.5 × ULN
Grade 2	3–5 × ULN	2.5–5 × ULN	1.5–3 × ULN
Grade 3	5–20 × ULN	5–20 × ULN	3–10 × ULN
Grade 4	>20 × ULN	>20 × ULN	>10 × ULN
Grade 5	death		

CTCAE, common terminology criteria for adverse events; AST, aspartate aminotransferase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; ALP, alkine phosphatase; ULN, upper limit of normal (in the case that baseline value is normal—if not, numbers refer to baseline value).

The treatment of irH depends on the severity of the liver injury, as is categorized according to the most recent version of the Common Terminology Criteria for Adverse Events (CTCAE version 5.0; as shown in Table 1) [14]. The interruption of ICI is mandatory for grade 2 hepatitis or higher and steroids are the mainstay of treatment for severe cases. Retrospective data estimate that 4 to 37% of irH does not respond to steroids [15]. For these steroid-refractory cases, second-line treatment is recommended, with mycophenolate mofetil (MMF) and azathioprine being the most accepted treatment options [7,8]. For those patients who fail to respond to this second line treatment, different agents are being proposed [16,17]. There are few data but, based on a recent case series, about half of the steroid-refractory irH cases treated with MMF do not respond [18]. In this manuscript, we describe a case of steroid-refractory irH progressing to liver failure despite treatment with MMF, but then with a complete remission of hepatitis after the association of third-line treatment with tacrolimus.

2. Case Presentation

A 25-year-old male, with a history of pT1a cutaneous melanoma of the right neck 8 years earlier, was diagnosed with a nodal metastasis in the right parotid, for which he had a parotidectomy and selective neck dissection. A histopathologic examination revealed that two of the 28 lymph nodes were invaded by malignant melanoma, BRAF wild type. Positron emission tomography, combined with computer tomography (PET-CT), of the whole body did not show distant metastasis at this time. Adjuvant treatment with pembrolizumab 200 mg every three weeks was given. Unfortunately, after 18 weeks of treatment, he developed a locoregional relapse and liver metastasis on imaging (Figure 1). Magnetic resonance imaging (MRI) of the brain did not show any cerebral involvement. Pembrolizumab was stopped and nivolumab 1 mg/kg, together with ipilimumab 3 mg/kg, every three weeks was initiated.

After twelve weeks, however, he developed a grade IV hepatitis with elevation of transaminases and bilirubin (Figure 2). Clinical examination at this time was unremarkable; the body mass index was 20 kg/m^2. Only minor fatigue was reported by the patient. There was no history of potentially toxic ingestion of medication, drugs, alcohol or dietary agents. An ultrasound excluded vascular or biliary obstruction. Further lab results showed an international normalized ratio of 1.18 (normal value < 1.10), a normal albumin, and were negative for viral, metabolic and idiopathic autoimmune hepatitis (AIH). He was admitted and promptly treated with intravenous methylprednisolone 2 mg/kg daily. As there was no improvement after three days, MMF was associated (500 mg bid on day 5, escalated to 1000 mg bid on day 6). Liver biopsy (on day 7) showed an acute lobular hepatitis with a mixed inflammatory infiltrate, consisting predominantly of lymphocytes and macrophages, the latter frequently forming microgranulomas within the hepatic lobule (Figure 3A), with negative testing for Epstein–Barr virus (EBV) and cytomegalovirus (CMV), fitting the working diagnosis of irH.

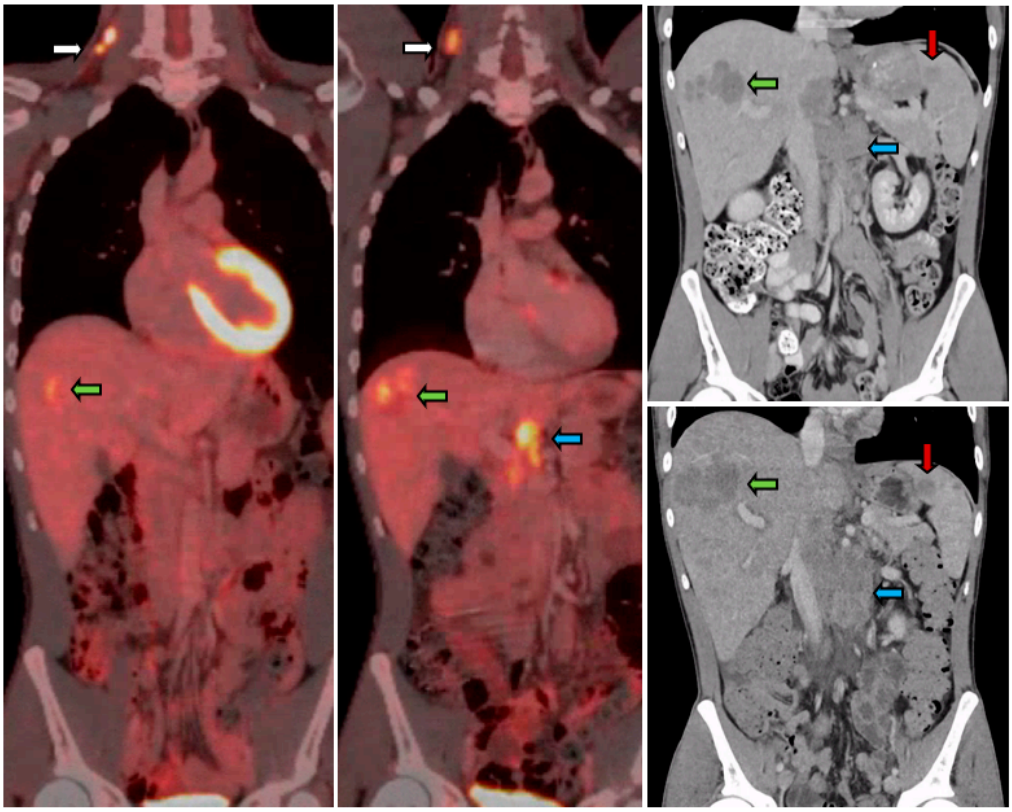

Figure 1. On the left, positron emission tomography combined with computer tomography (PET-CT) showed the initial diagnosis of local relapse in the neck (white arrow) and liver metastasis (green arrow). In the middle, PET-CT during the first admission showed slight progression of the liver metastasis (green arrow), stable disease in the neck (white arrow) and newly enlarged hilar lymph nodes (blue arrow). In the upper right, venous phase of the contrast-enhanced computer tomography (CE-CT) on final admission showed further progression of the known liver metastasis (green arrow) and hilar lymph nodes (blue arrow), as well as new spleen metastasis (red arrow). In the lower right, venous phase of the CE-CT, performed just before radiation therapy was started, showed in only two weeks fulminant progression of the hilar lymph nodes (blue arrow) with compression of the inferior vena cava, as well as progression of the liver (green arrow) and spleen metastasis (red arrow).

On day 10, the INR normalized, transaminases remained stable, but bilirubin levels steadily increased (Figure 2). There was no evidence of hemolysis, biliary tract obstruction or vascular impairment. After multidisciplinary consultation, tacrolimus was added (3 mg bid, target plasma level of 10–20 ng/mL) with gradual improvement in both transaminases and bilirubin. He was dismissed on day 17 under prophylactic co-trimoxazole (trimethoprim/sulfamethoxazole), dosed 160/800 mg three times per week. A repeat liver biopsy on day 27 showed reassuring results with a diminution of the lobular hepatitis (Figure 3B). But, on day 29, the patient developed a septic thrombophlebitis of the left cephalic vein with a *S. aureus* bacteremia, complicated by mediastinitis, requiring intravenous cefazolin (2000 mg tid for seven days) and, later, oral co-trimoxazole (160/800 mg bid for 35 days). Nevertheless, further dose reductions of first tacrolimus (to 2 mg bid), then steroids (to 32 mg) and later MMF (to 500 mg bid), were executed successfully. Afterwards, tacrolimus was reduced (to 1 mg bid), then stopped and eventually MMF was also stopped, still with an ongoing steady decline in liver tests (Figure 2). During this period, the patient could not participate in clinical trials because of the ongoing need for immunosuppression. Chemotherapy was not yet initiated because of the infectious complications. On day 79, however, the patient was admitted because of disease progression with massive growth of the retroperitoneal lymph nodes (Figure 1). Therefore, he was treated with escalation to intravenous steroids (Figure 2), from day 82 with oral temo-zolomide (daily 200 mg/m^2 for

five days as part of an intended 28-day cycle) and, on day 92–93, with radiotherapy (two of the five planned daily fractions of four Gray). Unfortunately, he died due to a refractory small bowel obstruction on day 97.

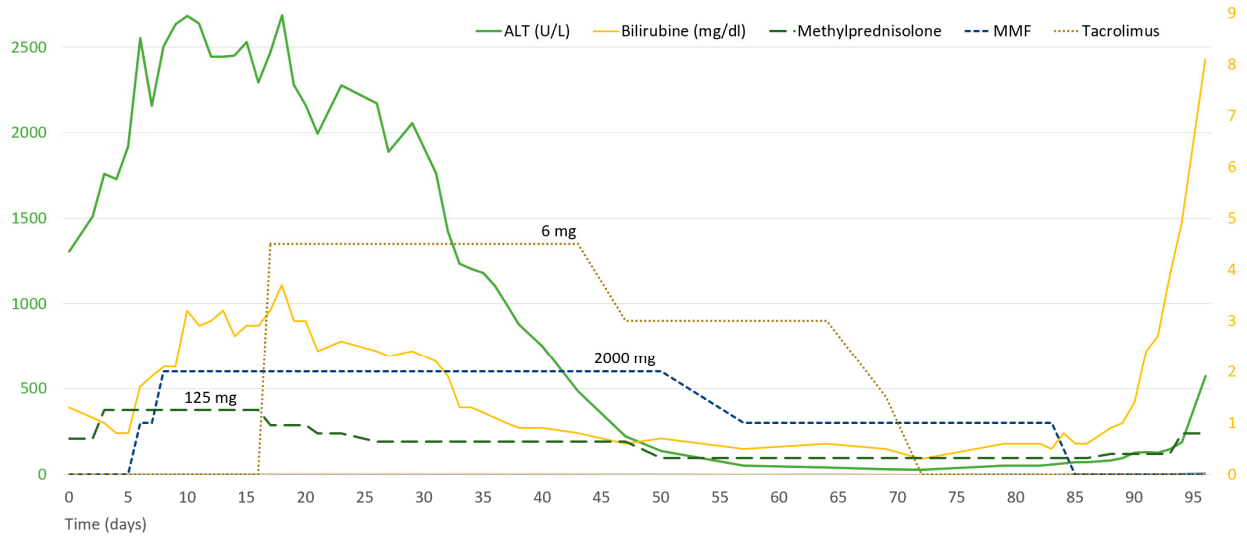

Figure 2. Chronological overview of the major liver-related lab values and medical interventions of the presented case. Day 0 is the day when the first elevation of liver tests is detected; this was exactly three weeks after the third administration of ipilimumab 3 mg/kg and nivolumab 1 mg/kg. For the depicted medications, the maximal daily dose was labeled to graph; the rest of the graph depicts the daily dose relative to this.

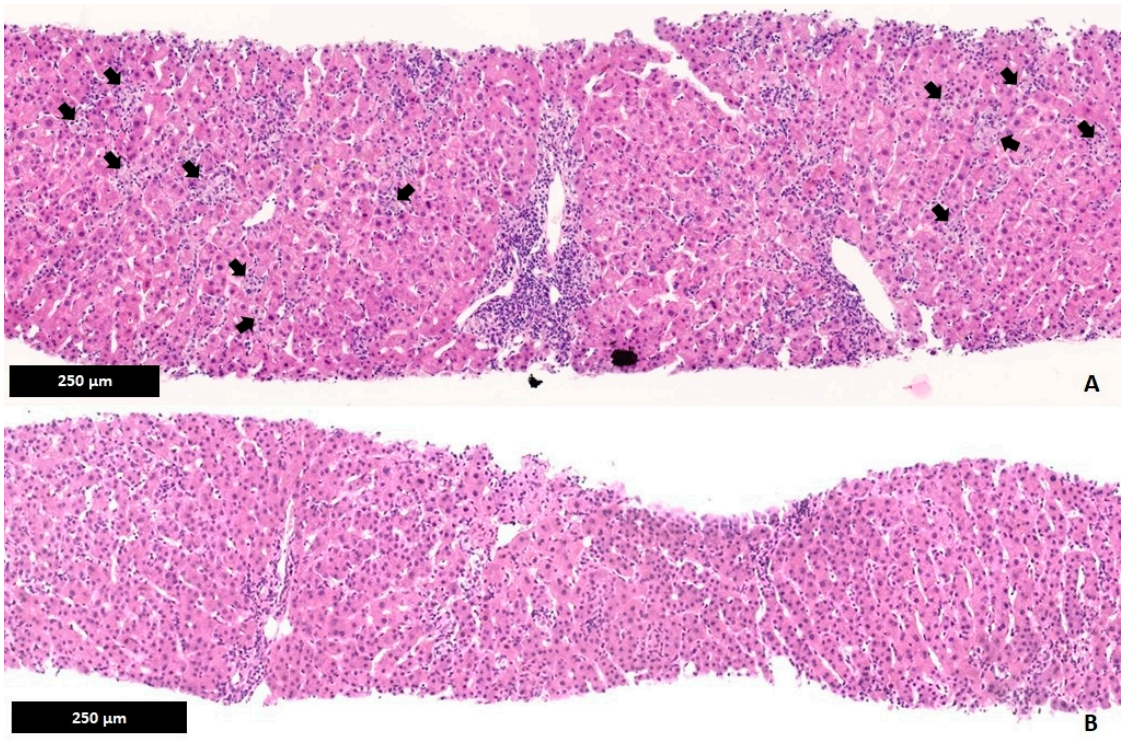

Figure 3. Histopathological findings of the liver biopsies. (**A**) On top, the first biopsy on day 7 showed an acute panlobular hepatitis with an inflammatory infiltrate consisting predominantly of lymphocytes as well as numerous macrophages frequently forming microgranulomas (arrows). (**B**) Below, the second biopsy on day 27 still showed a lobular hepatitis, but much less pronounced, with infiltration mainly of lymphocytes and few histiocytes.

3. Discussion

IrH is a severe and potentially life-threatening complication of ICIs. The timing of onset is different according to the setting but, globally, it is seen in the first six to twelve weeks of therapy [12]. The incidence of irH appears to be dose- and regimen-dependent. Table 2 summarizes the incidence as reported in some major phase II or III randomized controlled trials for melanoma. For anti-PD-1, anti-CTLA-4 and a combination of these two antibodies, grade 3 or 4 irH occurs in 1–2%, 3% and 10–15%, respectively [12,19,20]. The incidence of irH appears to be dose-dependent, especially for anti-CTLA-4 agents. Indeed, the initial trials with ipilimumab in metastatic melanoma patients used doses up to 10 mg/kg, which resulted in grade ≥ 3 hepatitis in 20.7% of patients [20–22]. Recently, the Checkmate-511 trial reported that the "flip dose" regimen of ipilimumab at 1 mg/kg + nivolumab 3 mg/kg had significant less toxicity compared to the "standard" ipilimumab 3 mg/kg + nivolumab 1 mg/kg [23].

Table 2. Incidence of irH in different regimens as reported in randomized trials for melanoma.

Author [Citation] + Median Follow-Up	Anti-CTLA-4 Monotherapy	Anti-PD-1 Monotherapy	Standard Combination Therapy	Flip Dose Regimen Combination Therapy	Relatlimab-Based Combination Therapy
Postow et al. [12] Not reported †	Any 2/46 (4%) G3≥ 0/46 (0%)	N/A	Any 21/96 (22%) G3≥ 10/96 (11%)	N/A	N/A
Larkin et al. [19] 12.3 months	Any 12/311 (3.9%) G3≥ 5/311 (1.6%)	Any 12/313 (3.8%) G3≥ 4/313 (1.3%)	Any 55/313 (17.6%) G3≥ 26/313 (8.3%)	N/A	N/A
Robert et al. [22] 7.9 months	Any 3/256 (1.2%) G3≥ 1/256 (0.4%)	Any 5/277 (1.8%) * G3≥ 5/277 (1.8%) *	N/A	N/A	N/A
Lebbé et al. [23] 18.7 months	N/A	N/A	Any 32/178 (18%) G3≥ 8/178 (4.5%)	Any 16/180 (8.9%) G3≥ 3/180 (1.7%)	N/A
Tawbi et al. [24] 13.2 months	N/A	Any 9/359 (2.5%) ° G3≥ 4/359 (1.1%) °	N/A	N/A	Any 20/355 (5.6%) G3≥ 14/355 (4.9%)

Postow et al. only reported the minimum follow-up time to be eleven months (†). Anti-CTLA-4 monotherapy was ipilimumab 3 mg/kg every three weeks for four cycles. Anti-PD-1 monotherapy used was nivolumab 3 mg/kg every two weeks or a fixed dose of 480 mg every four weeks (°) or pembrolizumab 10 mg/kg every three weeks (*). Standard combination therapy was ipilimumab 3 mg/kg with nivolumab 1 mg/kg every for four cycles and then further nivolumab 3 mg/kg every two weeks. The flip dose regimen was ipilimumab 1 mg/kg with nivolumab 3 mg/kg every three weeks and then further nivolumab 3 mg/kg every two weeks. Relatlimab was given at a fixed dose of 160 mg, in combination with nivolumab at a fixed dose of 480 mg, every three weeks. G3≥, grade 3 or higher (see Table 1); N/A, not applicable.

The treatment depends on the severity of liver Injury according to CTCAE (Table 1). Several international organizations have proposed guidelines for the management of irH (Table 3). As there are mostly no clinical signs or symptoms, routine lab tests before every cycle of immunotherapy are mandatory. In case of any rise in liver tests, work-up is mandatory, including a thorough clinical assessment with a review of medication (including alternative medicine and alcohol). For grade 1 IrH, ICI may be continued with caution and close follow-up. For grade 2 IrH, withholding ICI is always recommended [7–9]. Further diagnostic work-up should be initiated including lab investigations (for viral, metabolic and idiopathic AIH, as well as lipase and creatinine kinase) and imaging (to exclude progressive liver metastasis, biliary obstruction or thromboembolism). Liver biopsy is optional at this stage. Patients should be followed closely and lab tests should be repeated after a maximum of 3–4 days. The decision to start steroids, however, is debated; the SITC guidelines recommend the initiation of steroids in any grade 2 irH, whereas the ASCO, ESMO and NCCN guidelines propose close follow-up and initiation upon persistence or deterioration (Table 3) [7–9,15].

Table 3. Summary of international guidelines for irH supplied by different organizations.

Guidelines [Citations]	Grade 1	Grade 2	Grade 3	Grade 4
Consensus between the different guidelines	Continue ICI Clinical work-up (includ-ing review of medication, alcohol and food) No treatment for irH needed	Withhold until $\leq$ grade 1 FU once to twice weekly Add lab/imaging work-up if not yet added Rechallenge if grade $\leq$ 1 and prednisone $\leq$ 10 mg/day	Discontinue Promptly start steroids (at least 1 mg/kg/day) FU at least every 2 days Consider biopsy Taper over 4–6 weeks once $\leq$ grade 2	Permanently discontinue Promptly start steroids iv (at least 2 mg/kg/day) Daily labs (in hospital) Strongly consider biopsy Taper over $\geq$4–6 weeks once $\leq$ grade 2
SITC [9]	Monitor lab results weekly	Always start steroids at 0.5 mg/kg/day prednisone Taper over 1 month Biopsy is optional	If no improvement after 3 days start MMF	Same as grade 3
ASCO [7]	Monitor lab results weekly	Start steroids if irH persists for 3–5 days Further recommendations as SITC (but no biopsy)	Like STIC, but (if TMPT is normal) azathioprine can be considered	Same as grade 3
AGA [10]	Monitor lab results 1–2 times weekly Postponing therapy can be considered Consider MRCP or echo-endoscopy if negative US	Consider 0.5–1 mg/kg/day prednisone (if symptoms) If no resolution after 1–2 weeks start steroids Consider biopsy before starting steroids	If no improvement after 3–5 days consider MMF, azathioprine or tacrolimus Infliximab should only be considered with caution	In fulminant cases consider ATG

Table 3. *Cont.*

Guidelines [Citations]	Grade 1	Grade 2	Grade 3	Grade 4
NCCN [11]	Monitor lab results with increased frequency Consider MRCP if negative ultrasound	Consider 0.5–1 mg/kg/day prednisone (no time defined) Further recommendations as SITC (but no biopsy)	Like STIC Advise against infliximab	Same as grade 3
ESMO [8]	Work-up not strictly mandatory	If irH persist > 1 week or rises 0.5–1 mg/kg/day prednisone Taper over 2 weeks once grade ≤ 1	If AST or ALT > 400 U/L or in case of disturbed LF: iv 2 mg/kg/day prednisone If worsening on iv steroids add MMF and as needed tacrolimus	ATG can be considered in MMF-refractory cases as alternative to tacrolimus, cyclosporin, azathioprine or tocilizumab
BSMO [25]	Lab work-up (including lipase/creatinine kinase) and consider imaging Postpone 1 week if rising bilirubin or if any doubt	No steroids unless rising bilirubin	If AST and AST < 10 × ULN and bilirubin < 3 × ULN in anti-PD-(L)1: no steroids If worsening on iv steroids add MMF and as needed tacrolimus Rechallenge only after positive MDC	If bilirubin not rising (<3 × ULN) and normal INR and albumin and no hypoglycemia: 1 mg/kg/day po If MMF-refractory ATG is alternative to tacrolimus Rechallenge questionable

Grading according to CTCAE 5.0 (Table 1). SITC, Society for Immunotherapy of Cancer; ASCO, American Society of Clinical Oncology; AGA, American Gastroenterological Association; NCCN, National Comprehensive Cancer Network; ESMO, European Society of Medical Oncolgy; BSMO, Belgian Society of Medical Oncology; MRCP, magnetic resonance cholangiopancreatography; US, ultrasound; FU, follow-up; TPMT, thiopurine S-methyltransferase. LF, liver function; MDC, multidisciplinary consultation; ATG, anti-thymic globulin therapy.

For grade 3 and 4 irH, there is a broad consensus that ICI should be discontinued and steroids should be initiated immediately (1 to 2 mg methylprednisolone per kg daily). Liver biopsy should be considered in any grade 3 irH and is mandatory for steroid-refractory cases (i.e., no response after 3 to 5 days of optimal therapy), in cases of grade 4 irH or if another etiology is suspected [9]. Lab tests should be followed closely in collaboration with a hepatologist and hospitalization of patients should always be considered for intravenous steroid administration, careful monitoring of liver function tests and potential side effects of glucocorticoids. After a durable response has been achieved, steroids can be tapered over 4 to 6 weeks. In any other case, alternative explanations should be sought (e.g., metastasis, biliary tract obstruction or intercurrent infection). A liver biopsy should be performed, if not yet executed before steroid initiation, and additional immunosuppressants should be initiated after multidisciplinary consult. MMF is generally accepted as a second-line agent, although ASCO guidelines also suggest azathioprine after thiopurine methyltransferase (TPMT) deficiency is ruled out [7–9]. Evidence for third-line agents is scarce [8,10,26].

Given the lack of prospective trials, there are many unanswered questions regarding the optimal management of irH. Firstly, the timing and dose of initiation of corticosteroids is debated. International consensus guidelines generally advise initiating corticosteroids in persistent grade 2 irH, which is challenged by some case series of irH which resolved without corticosteroids. Nevertheless, these results must be interpreted with caution due to their retrospective character and small cohorts [27,28]. Also, the use of lower doses of steroids has been proposed, but the evidence supporting this is weak [29].

Secondly, there are no prospective data for the treatment of steroid-refractory irH. A minority of patients (4 to 37%) fail to respond on steroids and need secondary immunosuppressing agents [18,30]. Mycophenolate mofetil (MMF) is now the most accepted second-line therapy for irH (Table 3). MMF is a prodrug of mycophenolic acid, an inhibitor of inosine monophosphate dehydrogenase, and is used as an immunosuppressant in liver transplants and idiopathic AIH [18]. This enzyme is necessary for the production of purines during proliferation and is especially important in lymphocytes [21,31]. The recommended dose is between 1000 and 2000 mg daily in two oral gifts. The most important side effects include gastrointestinal toxicity and myelosuppression [9].

The use of azathioprine remains a possible alternative according to the American guidelines [7]. Azathioprine is a prodrug of 6-mercaptopurine (6-MP) and also works as a purine antagonist in lymphocytes. An important caveat is that about 5% of the Caucasian population is observed to carry genetic polymorphisms in the enzyme responsible for further degradation of 6-MP, called thiopurine S-methyltransferase (TPMT). This may lead to the accumulation of 6-MP with increased toxicity, especially myelosuppression [32]. TPMT-testing is therefore recommended, but waiting for this result might not be feasible in the acute setting of irH [7]. In idiopathic AIH, this agent is used more as a steroid-sparing compound, with its optimal efficacy being seen after some weeks to months [16].

Thirdly, a clinical challenge is posed by patients refractory to second-line immunosuppressants, as there are no prospective trials available and evidence is based on case reports or small case series. Recently, one Chinese article summarized a series of steroid-refractory irH in which 11 out of 23 patients treated with MMF needed a third-line immunosuppressant [18]. Calcineurin inhibitors, such as tacrolimus and cyclosporine, have been proposed (Table 3). Tacrolimus (also known as FK506) is an oral macrolide antibiotic with a powerful immunosuppressive activity (a 100 to 1000 times more potent calcineurin inhibitor than ciclosporin). Tacrolimus binds to intracellular proteins and this complex inhibits the enzyme calcineurin, which is needed for cytokine production. This loss-of-function results in a net inhibitory effect on both B and T cells, making tacrolimus a potential therapeutic option for any immune-mediated reaction [33]. Tacrolimus is used as an immunosuppressant in liver transplantation and steroid-refractory idiopathic AIH [34]. The dose can be titrated based on therapeutic drug monitoring, aiming at a plasma concentration between 5 and 20 ng/mL, thereby reducing the risk of major dose-dependent side effects,

e.g., nephrotoxicity and neurotoxicity [16,17]. Evidence of its use in irH is sparse thus far [21,29,35,36].

Other third-line immunosuppressants that have been proposed are anti-thymic globulin therapy (ATG) for fulminant hepatitis [37–40], plasma exchange in case of liver failure [40] and tocilizumab, a monoclonal antibody directed against IL6 [41,42]. Tocilizumab has been explored as a general strategy to mitigate ICI-related toxicity [43,44] and to permit a safe rechallenge after irH [45]. Infliximab is not recommended by most guidelines as it may exhibit additional drug-induced liver toxicity, although there are some case reports who do report successful treatment with infliximab [17,36].

Finally, international guidelines do not specify a treatment algorithm for steroid-refractory hepatitis and treatment decisions are made on a case-by-case basis, after thorough work-up and multidisciplinary consultation. As stated above, the current evidence is based on small retrospective studies, case reports and expert opinions. For now, we believe the choice of treatment depends on the severity of the hepatitis, the urgency of treatment, the performance state and comorbidities of the patient, as well as the availability of potential drugs and their expected adverse events. We consider the association of tacrolimus, in cases of irH not responding to MMF, depending on these factors.

Nevertheless, further insight is highly needed, through the collection of real-world data including patient characteristics, underlying malignancy, medication history and outcomes. Furthermore, we call for collaboration initiatives, gathering oncology practitioners and experts in the various domains of irAE to discuss individual cases, to aid clinicians in decision making and gaining expertise in these matters. In Belgium, the Belgian Society of Medical Oncology started the BiTOX initiative in 2021, with a two-weekly multidisciplinary virtual meeting. Any clinician can discuss a case of irAE with a multidisciplinary team, and receive advice from national experts in the field [25].

We want to underline that, besides the treatment of the irH, these patients under combined immunosuppression (IS) should be followed meticulously, as they are more prone to infectious complications or tumor progression, as was shown in our case here. We advocate the use of prophylactic cotrimoxazole to prevent *Pneumocystis jirovici pneumonia* for all patients with a protracted course of steroids (i.e., methylprednisolone $\geq$ 20 mg daily for $\geq$1 month), combined IS or protracted lymphopenia (<500/μL) [46]. Antifungal prophylaxis with oral fluconazole is common practice in hematologic malignancies, but in solid-organ malignancies this remains an area of debate [47–49]. The role of acyclovir for the prevention of herpes simplex and varicella zoster viral infections remains much less clear outside the context of hematologic stem cell transplantation [50].

Furthermore, despite the necessity of immunosuppressive agents to treat steroid-refractory irH, they might compromise the host's response against the tumor. Recently, a Dutch study reported that melanoma patients treated with secondary immunosuppressive agents had a shorter overall, progression-free and melanoma-specific survival, compared to patients who were treated with steroids alone [51]. However, the occurrence of irAE generally has not been associated with an impaired prognosis [52]. Further collection of real-world data is mandatory to provide further insight in this matter. Additionally, clinical trials focusing on "safer" regimens to mitigate the weakened host's antitumor response are needed.

To finish, we advocate for a multidisciplinary approach in the treatment and follow-up of steroid-refractory irH, with regular interdisciplinary discussion regarding choice of treatment, the clinical evolution, possible immunosuppressant weaning, complications from immunosuppressants and the extent of the disease.

4. Conclusions

Immunotherapy-induced hepatitis (irH) is a fairly common side effect of immune checkpoint inhibitors, that usually responds well to corticosteroids. Steroid-refractory irH is a clinical challenge and MMF is considered the standard second-line immunosuppressant. Up to 50% of MMF-treated patients may need a third-line immunosuppressant, but

evidence is scarce. Tacrolimus can be used as a third-line immunosuppressant, based on the current literature. Combined immunosuppressants should be used with caution, as they might dampen the antitumor response and impair prognosis. Furthermore, there is an increased risk of infectious complications. Multidisciplinary collaboration is mandatory, and we call for transmural networks to build expertise in managing complex irAEs. Furthermore, we call for the collection of real-world data to provide further insight in the clinical course and optimal management of steroid-refractory irH.

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