



Hot Topic Commentary

Immune Checkpoint Inhibitor–induced Liver Injury: A Critical Appraisal of Treatment and Rechallenge Controversies

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Absence of a standardized therapeutic consensus

The expanding use of immune checkpoint inhibitors (ICIs) in advanced malignancies, including hepatocellular carcinoma (HCC), has been accompanied by a rise in immune-related hepatotoxicity. Checkpoint inhibitor–induced liver injury (ChILI) is linked to significant diagnostic and therapeutic challenges, especially in patients with pre-existing liver disease. Despite the availability of major guidelines from the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), the Society for Immunotherapy of Cancer (SITC), and the American Gastroenterological Association (AGA), a standardized treatment consensus remains elusive.^{1–6} Key areas of divergence include thresholds for immunosuppression, the role of histological confirmation, second-line therapies, and re-exposure criteria. While corticosteroids remain first-line therapy, 20–30% of patients, particularly those with cholestatic or autoimmune-like injury, are steroid-refractory. Second-line agents such as mycophenolate mofetil (MMF) are commonly used, though data remain limited.^{1–6} Ursodeoxycholic acid (UDCA) has shown promise in cholestatic liver toxicity with recent retrospective data reporting good tolerance and favorable outcomes.¹ Rechallenge with ICIs remains controversial but is increasingly considered in selected patients. Recurrence rates vary from 22% to 31%, with most relapses being mild.^{1–6} Histological features, ANA titers, and autoimmune comorbidities may predict recurrence risk. In patients with HCC and cirrhosis, hepatotoxicity is harder to differentiate from tumor progression or other etiologies, underscoring the importance of biopsy and multidisciplinary evaluation.^{1,2,3,6} As evidence grows, re-evaluating current paradigms, especially permanent discontinuation of ICIs, may be warranted. Future studies must clarify therapeutic algorithms and rechallenge safety to optimize out-

comes in this complex population.

The increasing use of ICIs for the treatment of advanced malignancies, including HCC, has led to a parallel rise in immune-related adverse events. Among these, hepatotoxicity presents a unique clinical dilemma, particularly in patients with underlying liver disease. Despite a growing body of literature on ChILI, significant controversies persist regarding the indications for initiating therapy and the expected response rates, especially across different clinical guidelines.

Although the diagnostic criteria for drug-induced liver injury (DILI) are clearly established and are also relevant for ChILI (AST and/or ALT > 5 × ULN and ALP > 2 × ULN), discrepancies in grading systems, therapeutic thresholds, and response evaluation criteria remain in clinical practice.

Diagnostic criteria are inconsistent across studies, with over 50 liver-related terms used in pharmacovigilance databases. Real-world data often differ from clinical trial results due to diverse patient populations. Differentiating ChILI from tumor progression or drug interactions remains a key diagnostic challenge. Combination therapies with chemotherapy or targeted agents can increase hepatic susceptibility and make it more vulnerable to the impact of different types of liver damage.¹

ChILI is typically graded using the Common Terminology Criteria for Adverse Events (CTCAE), with most guidelines recommending corticosteroid therapy for grade 2 and 3 hepatitis. However, the exact thresholds for initiating immunosuppression, the choice of second-line agents, and recommendations for ChILI rechallenge differ notably between major societies such as ASCO,² ESMO,³ SITC,⁴ organ-specific bodies like AGA,⁵ and the National Comprehensive Cancer Network (NCCN).⁶

Oncology-driven guidelines generally adopt a more aggressive approach to the management of ChILI, recommending earlier initiation of corticosteroids and faster escalation to additional immunosuppressive therapies. For example, ASCO advises starting prednisone at 0.5–1 mg/kg/day as early as grade 2 toxicity without improvement within three to five days—escalating to 1–2 mg/kg for grade ≥3—and adding MMF if no improvement occurs.² Similarly, SITC guidance is in concordance with early corticosteroid initiation and rapid intensification but emphasizes obtaining histological confirmation before advancing to second-line treatment.⁴ ESMO and NCCN adopt a more conservative stance, allowing observation of some asymptomatic grade 2 cases with stable liver function and reserving corticosteroids for patients who develop elevations after ICI is held; however, it is not clear which of these

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Table 1. Comparison of the guidelines' recommendations for checkpoint inhibitor–induced liver injury (ChILI)

Guide-line	Indication for corticosteroids	Liver biopsy	Second-line therapy	ICI rechallenge
ASCO ²	Start at Grade 2 without improvement in 3–5 days (0.5–1 mg/kg/d)	For steroid-refractory patients or concerns about differential diagnosis	Consider adding azathioprine or mycophenolate	Allowed after complete resolution of Grade 2, without steroids or less than 10 mg/day. Consider permanently discontinuing ICI for Grades 3 and 4
ESMO ³	Start at Grade 2 if ALT/AST rise when rechecked	Selective use in more severe hepatitis (Grade 3 or more)	MMF (1,000 mg twice daily), tocilizumab (8 mg/kg), tacrolimus, azathioprine, cyclosporine, or anti-thymocyte globulin	ICI may be resumed after resolution grade 1 or 2, and CS tapering to below 10 mg/day. For grade 3 or 4, ICI should be permanently discontinued
SITC ⁴	Similar to ASCO, faster steroid escalation	Recommended in persistent or atypical cases	MMF	Permitted if resolved and no contraindications
AGA ⁵	Grade ≥2, but tailored in cirrhosis	Strongly encouraged, especially in cirrhosis	Consider alternative agents: MMF, tacrolimus, or azathioprine. Anti-thymocyte globulin in fulminant hepatitis	Generally discouraged after Grade ≥3 or second-line immunosuppression
AEEH ¹	Grade 3 or higher	Grade ≥ 3 not improving after ICI with-drawal	MMF 1,000 mg every 12 h and/or tacrolimus	Grade 3 or 4, rechallenge should be considered after appropriate risk-benefit assessment
NCCN ⁶	Start at Grade 2 without improvement or worsening after 3–7 days of holding ICI	Grade ≥ 3 if no contraindications	Consider adding MMF or tacrolimus; if refractory, consider tocilizumab or steroid-sparing immunosuppressive therapy	Following Grade 2, after ALT/AST return to normal, and steroids dose <10 mg/day. Permanently discontinuation in G4 liver dysfunction or permanent biliary stricture requiring ERCP

MMF, mycophenolate mofetil; ERCP, endoscopic retrograde cholangiopancreatography. AEEH, Asociación Española para el Estudio del Hígado; ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; SITC, Society for Immunotherapy of Cancer; AGA, American Gastroenterological Association; NCCN, National Comprehensive Cancer Network; ICI, Immune checkpoint Inhibitor.

patients develop grade 3 injury.^{3,6} Despite these slight differences, a common trend among oncology-based guidelines is a stringent stance toward rechallenge, with the exception of NCCN, which only considers permanent discontinuation for grade 4; all the other guidelines do not consider rechallenge beyond grade 2. In addition, they approve the use of second-line agents, often without solid evidence to support their safety or efficacy in immune-mediated hepatitis (Table 1).^{1,2–6}

One of the main sources of controversy is the variability in reported response rates to corticosteroid therapy. While most guidelines report that 70–80% of patients respond to corticosteroids, real-world data indicate that a substantial subset may be steroid-refractory or relapse after tapering.^{7,8} Steroid-refractory immune-related hepatotoxicity may arise through several mechanisms. In a subset of patients, the injury reflects more severe immune activation, with intense T-cell-mediated hepatocellular damage that exceeds the anti-inflammatory effect of corticosteroids. In other cases, the lack of response is associated with atypical histological patterns, particularly cholangitic or mixed patterns, including immune-mediated sclerosing cholangitis and small-duct ductopenia, which are characteristically less steroid-responsive than classical hepatocellular hepatitis. Delayed recognition of hepatotoxicity or late initiation of corticosteroid therapy may also allow prolonged uncontrolled inflammation, thereby reducing the likelihood of biochemical recovery. Furthermore, patients with underlying liver disease, such as cirrhosis, steatohepatitis, or chronic viral hepatitis, often show a blunted response to immunosuppression. Finally, in a proportion of cases, the injury may be driven by immune mechanisms independent of PD-1 or CTLA-4 blockade, involving alternative immune checkpoints or innate immune pathways, which limit the efficacy of corticosteroid therapy.

Liver biopsy can play an important role in diagnostic support. Histologically, ICI-induced hepatitis is characterized by predominantly centrilobular necrosis and an acute pattern of inflammation, rather than portal or periportal activity. Lobular hepatitis is indistinguishable from autoimmune hepatitis. The lobular infiltrate consists mainly of CD8+ T cells, with a relative absence of CD4+ T cells.⁹ Nevertheless, guidelines differ in how they incorporate histology into treatment decisions. ASCO and ESMO consider biopsy optional, whereas SITC and AGA increasingly advocate for histopathological assessment, particularly in cases of atypical or prolonged injury.^{2–5}

Interestingly, recommendations from the Spanish Association for the Study of the Liver¹ state that for patients who develop grade 3 or 4 hepatitis related to ChILI, the panel suggests discontinuing ICI therapy and initiating prednisone at a dose of 0.5–1 mg/kg/day. In selected patients with total bilirubin levels below 2.5 mg/dL, initiation of prednisone may be postponed, pending reassessment of liver function. In patients with grade 3 or 4 ChILI with bilirubin levels > 2.5 mg/dL and an INR > 1.5 (with or without hepatic encephalopathy), the panel recommends withholding treatment and starting prednisone (1–2 mg/kg/day) in combination with MMF or tacrolimus.¹

Beyond corticosteroids, the role of second-line agents remains uncertain. MMF is the most frequently recommended option, but response rates are inconsistent, and controlled trials are lacking. Infliximab is generally contraindicated due to concerns about exacerbating liver injury.^{2,3} However, in the most reported experience, infliximab treatment did not cause hepatotoxicity and resulted in sustained clinical response in nine of ten patients.¹⁰ These data challenge earlier concerns about TNF- α blockade in the setting of liver injury and support its consideration as a second-line therapy. The

evidence remains insufficient, underscoring the need for further prospective evaluation.

According to the DILI International Expert Working Group score, a potential role of plasma exchange in patients with severe DILI could be an interesting option.¹¹

Hountondji L *et al*.¹² conducted a multicenter retrospective study of 27 patients who received first-line UDCA monotherapy. Clinical data were collected from the time of diagnosis through week 52, with evaluation of liver enzyme normalization, recurrence, and clinical outcomes. Treatment with UDCA alone resulted in biochemical improvement in 81.5% of patients, with a mean time to response of 39.3 days. Most cases (77.8%) were classified as severe cholestatic hepatitis induced by ICIs (CTCAE grade ≥ 3). Macroscopic bile duct injury was identified in 37% of patients and was significantly associated with higher recurrence rates (75%, $p < 0.001$). All patients with recurrent DILI subsequently developed chronic liver disease. Rechallenge with ICIs was attempted in 52% of cases, with relapse occurring in 23% of them. These authors concluded that UDCA monotherapy may represent a suitable alternative to corticosteroid-based regimens in the management of cholestatic ChILI. However, this finding appears to be insufficient evidence, particularly when bile duct injury is present. The combination of UDCA and systemic corticosteroids rather than UDCA alone appears to be the safest option. A larger number of patients is needed to conclude that monotherapy with UDCA could benefit this group of patients.

Regarding the overall incidence of ChILI in HCC, it ranges from 5% to 20%, with higher-grade transaminase elevations occurring in approximately 3–9% of patients.^{13,14} The risk appears to be higher with combination regimens (e.g., atezolizumab plus bevacizumab or nivolumab plus ipilimumab) than with monotherapy, as observed in other tumor types.¹⁵ Importantly, in patients with underlying cirrhosis, distinguishing hepatotoxicity from tumor progression, viral hepatitis flare, or ischemic hepatitis remains diagnostically challenging. These findings contribute to delays in the initiation of immunosuppressive therapy and may worsen outcomes. These agents indicated in cirrhotic patients with concomitant HCC remain a critical and emerging area of investigation, largely due to the lack of well-documented evidence regarding the behavior and safety of these compounds in the context of underlying chronic liver disease. The rate of non-response to corticosteroid therapy is variable, ranging from 15% to 30%.^{16–24}

Clinical dilemmas in reintroducing immune checkpoint inhibitors

According to established guidelines, re-exposure to a drug following an episode of DILI should generally be avoided, particularly in cases characterized by immunoallergic features or severe hepatotoxicity, due to the high risk of triggering a more severe or even life-threatening recurrence. Consequently, international recommendations advocate for the permanent discontinuation of ICIs after grade 3 or 4 hepatotoxicity.^{2,11}

However, a point of divergence is the timing and safety of ChILI rechallenge following hepatotoxicity. ASCO and SITC permit reintroduction of immunotherapy after complete resolution of grade 2 hepatitis or lower, provided there is no alternative etiology and liver function has normalized.^{2,4} ESMO, however, recommends caution in rechallenge and suggests individualized decision-making, particularly in patients with a prior episode of grade 3 or higher toxicity.³ The AGA guideline expresses greater concern in patients with underlying cirrhosis or those who require second-line immunosuppression, in whom the risk-benefit ratio of re-treatment is less favorable.⁵

However, the association between the occurrence of

immune-related adverse events and improved oncological outcomes (objective response rate, progression-free survival, overall survival) is well documented in multiple systematic reviews and meta-analyses across tumor types and ICI classes.^{25,26}

We have to keep in mind that for many oncology patients, therapeutic alternatives may be extremely limited, rendering re-exposure to ChILI a potentially necessary strategy. With the rapid expansion in the use of these compounds and the accumulation of clinical experience, emerging data suggest that the traditional paradigm of permanent discontinuation may warrant reconsideration, at least within this specific context.

Recent evidence regarding hepatic outcomes following ChILI rechallenge after immune-related hepatitis indicates a lower recurrence rate than previously anticipated, with reported recurrence rates ranging between 23% and 35%.^{27–29} Figure 1 describes the steps of ChILI-induced liver damage, and Table 2 shows different studies assessing re-exposure after ChILI,^{21,28–30} analyzing the main variables on this topic, such as the pattern of liver damage, predictors, and severity of recurrence.

Across the available cohorts, rechallenge with ICIs after an initial episode of ChILI results in recurrent hepatitis in approximately 20–35% of patients, with remarkable consistency across heterogeneous study designs, cancer types, and ICI regimens. Most studies demonstrate that recurrent events are generally mild to moderate in severity and tend to resemble the index presentation rather than progress to fulminant liver failure. Importantly, fatal recurrences were not reported in any of the included cohorts, supporting the overall feasibility of re-exposure in selected patients.

The only prospective study to date focused on ICI reintroduction included 23 patients who had experienced prior grade 3 or 4 immune-mediated hepatitis (19 with grade 3 and 4 with grade 4, according to CTCAE v4). Upon re-exposure—predominantly to the same ICI agent—8 patients (35%) experienced recurrent hepatitis, which was generally manageable and did not result in excess mortality. All patients underwent thorough evaluation to exclude other causes of liver enzyme elevation. Except for one case, the severity of the recurrent hepatitis was comparable to the initial episode. Among those with recurrence, two patients developed concomitant colitis, and two developed hypophysitis as new immune-related adverse events. Notably, none of the patients with prior grade 4 hepatitis nor any of the four patients who had not received corticosteroids experienced relapse. Concomitant corticosteroid use was not associated with a reduced risk of recurrence. The only factors significantly associated with recurrence were elevated ANA titers and the presence of underlying autoimmune disease. Interestingly, patients who experienced recurrence also demonstrated improved oncologic outcomes.²⁷

In a multicenter, retrospective study, Patrinely *et al*.²⁹ described a cohort of 91 patients (58.6%) in which the patients did not resume ICI therapy after the initial episode of ChILI. Among the 66 individuals who were rechallenged, 40 with prior grade 1–2 injury and 26 with grade 3–4, recurrence occurred in only 25.8% ($n = 17$) (Table 2). Overall, this multi-institutional study demonstrates that ChILI is generally associated with favorable clinical outcomes, although management often necessitated treatment interruption, administration of high-dose corticosteroids, and, in some cases, escalation to second-line immunosuppression. Re-exposure to ICIs resulted in a relatively low but clinically meaningful rate of hepatitis recurrence.

Similarly, Hountondji *et al*.²⁸ reported a 23% recurrence

Mechanism- induced Checkpoint Inhibitor Hepatotoxicity

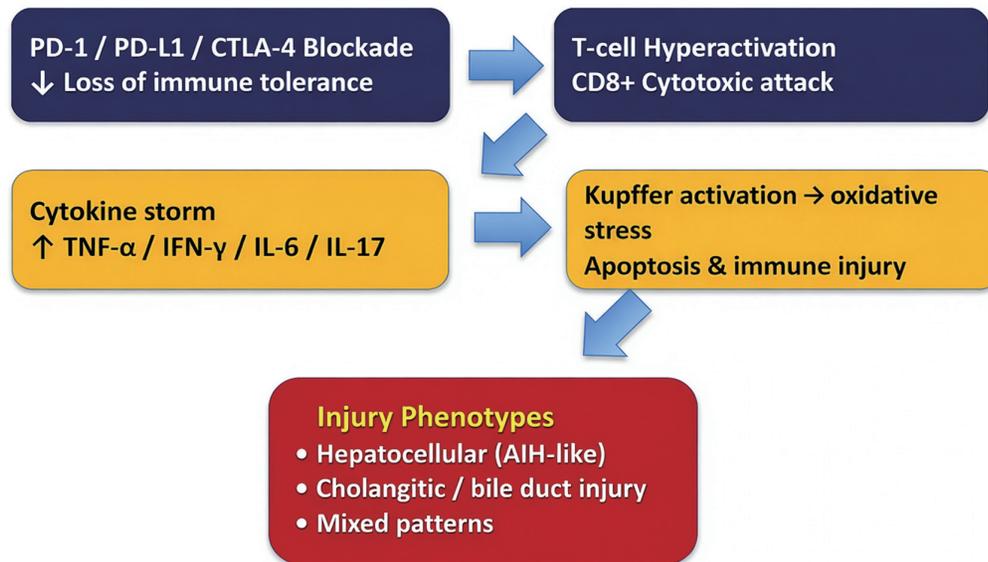


Fig. 1. Inhibition of programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) removes immune inhibitory checkpoints, thereby allowing expansion of effector T cells. The subsequent release of pro-inflammatory cytokines—tumor necrosis factor- α (TNF- α), interferon- γ (IFN- γ), and interleukin-6 (IL-6)—together with activation of Kupffer cells, promotes hepatocyte apoptosis and bile duct injury, accounting for the hepatocellular and cholangitic patterns observed in checkpoint inhibitor-induced liver injury (ChILI). ↓, decrease; ↑, increase.

rate of ChILI among 51 rechallenged patients (37 of whom had experienced grade ≥ 3 hepatitis). At the time of rechallenge, 35 patients remained under treatment for ChILI, 29 with corticosteroids (with or without UDCA), 5 with UDCA alone, and one with MMF. Neither the initial hepatitis pattern, type of ICI, nor presence of autoantibodies correlated with an increased risk of recurrence.

Collectively, this growing body of evidence supports the feasibility of ChILI rechallenge in selected patients, with relatively low recurrence rates and predominantly mild relapses. For patients with limited therapeutic options, this approach

offers a path to maintain potentially life-prolonging immunotherapy. However, the decision to reintroduce ICI therapy must be carefully balanced against the risk of recurrent hepatitis or new immune-related adverse events, especially in patients with a durable complete response, where the expected therapeutic benefit may be marginal. These decisions underscore the importance of multidisciplinary evaluation and individualized patient management.

In summary, we have to keep in mind that major clinical guidelines differ significantly in their criteria for initiating therapy, dependence on histological confirmation, expecta-

Table 2. Studies assessing re-exposure to checkpoint inhibitors after ChILI

Author/Year	Study design	N with initial ChILI	N rechallenged	Type of ICI reintroduced	Recurrent hepatitis (%)	Severity of recurrence	Predictors of recurrence	Notes
Patrinely et al., 2021 ²⁹	Multi-center retrospective	145	66	Same ICI as initial episode (PD-1, PD-L1, CTLA-4)	25.8% (17/66)	Similar to the index event	None identified	One of the largest cohorts; includes various cancers; standardized grading
Hountondji et al., 2024 ²⁸	Multi-center retrospective	51	51	PD-1 or PD-L1	23%	Mostly mild; no fatal cases	Cholestatic injury associated with recurrence	Focused on cholestatic ChILI; includes UDCA-first strategy
Peera-Phatdit et al., 2020 ³⁰	Retrospective	36	14	PD-1/PD-L1	28%	Similar to or milder than initial	None formally identified	Early key contribution; Clinical and epidemiological approach
Simonaggio et al., 2019 ²¹	Multi-center	93 (all irAEs; 22 hepatitis)	22	PD-1/PD-L1	17%	Mild	None identified	Not liver-specific; includes multiorgan irAEs

ChILI, checkpoint inhibitor-induced liver injury; PD-1, Programmed cell death protein 1; PD-L1, Programmed death-ligand 1; CTLA-4 Cytotoxic T-lymphocyte-associated protein 4; UDCA, Ursodeoxicolic acid; irAEs; immune-related Adverse Events.

tions regarding treatment response, and recommendations for ICI rechallenge. These discrepancies reflect both the scarcity of high-level evidence and the complex interactions between immune modulation, tumor biology, and underlying liver disease.

In patients with HCC and underlying cirrhosis, the use of ICIs poses a unique challenge. While ICIs offer critical therapeutic benefits in HCC, the risk of hepatotoxicity, particularly in cirrhotic patients, demands a rigorous risk-benefit assessment.

There remains a critical need for consensus on the optimal diagnostic and therapeutic approach in this population, especially concerning the role of liver biopsy, criteria for initiating immunosuppression, and the safety of ChILI rechallenge.

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Conflict of interest

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