

FIGURE 7
Management of Immune-Related Hepatic Toxicities^{1,4,5,7,8,11,13,14,23,31}

Background: Hepatotoxicity related to immune-therapy typically presents as elevated LFTs mainly AST, ALT, GGT and rarely bilirubin. The patient is usually asymptomatic and onset is variable with average 8-12 weeks after start of therapy. Rarely, patients present with fever, fatigue, nausea and abdominal pain. Monitoring LFTs are recommended at baseline and prior to each dose. Hepatic adverse events are usually grade 1-2 and occur in approximately 1-6% of patients on PD-1 inhibitors and more frequently in patients on CTLA-4 inhibitors but still <10%.

		MANAGEMENT (First rule out infectious causes and disease progression)				
		Description	Referral	Corticosteroids	Supportive Therapy	Immune Therapy
HEPATITIS	GRADE 1	AST/ALT up to 3 X ULN or total bilirubin up to 1.5 X ULN (or <2 X baseline). ^{*k}	Not required. Consider viral serology.	Not recommended.	Not required.	Monitor closely and continue immune therapy.
	GRADE 2	AST/ALT >3-5 X ULN or total bilirubin > 1.5-3 X ULN (or >2 baseline). ^{*k}	Consider hepatology/gastroenterology consult. Consider hepatitis serology.	Recheck liver function in 2-3 days & if no improvement, initiate prednisone 0.5-1 mg/kg/day PO or IV equivalent and increase if no improvement. Taper over 2-4 weeks for 0.5 mg/kg and ≥ 4 weeks for 1 mg/kg if liver function normalizes.	Not required.	Withhold therapy until resolution to grade 0-1 and prednisone ≤ 10 mg.
	GRADE 3	AST/ALT > 5-20 X ULN or total bilirubin > 3-10 X ULN. ^{*k}	Hepatology/gastroenterology consult. Consider liver biopsy to rule out other causes of hepatitis. [§]	High dose IV steroids, methylprednisolone 1-2 mg/kg/day followed by taper with prednisone 1-2 mg/kg/day PO over ≥ 4 weeks.	If transaminases do not decrease within 3 days after steroids, add mycophenolate mofetil (MM) 500-1000 mg PO q12h; discontinue once prednisone taper to 10 mg daily. If no improvement or worsening after 7 days: consult expert or switch to another immunosuppressant.*	Permanently discontinue therapy.
	GRADE 4	AST/ALT >20 X ULN or total bilirubin > 10 X ULN. ^{*k}				

§ Hepatitis A, C, CMV

* Tacrolimus 0.10-0.15 mg/kg/day; in the case of severe hepatotoxicity, the decision to use infliximab should be made after careful consideration of risk and benefit, and discussion with the patient.

⌘ For patients being treated with ICIs for hepatocellular carcinoma, these values may differ. Refer to the ICI product monograph.