

Symptom Grade

GRADE 1

ALT or AST > ULN - 3x ULN

GRADE 2

ALT or AST 3 - 5x ULN

GRADE 3

ALT or AST 5 - 20x ULN

GRADE 4

ALT or AST > 20x ULN

Management escalation pathway

Continue treatment

If both ALT & AST are Grade 1:
postpone 1 week

Withhold ICPI treatment

If rising ALT/AST when re-checked
start oral prednisolone 1 mg/kg

Cease treatment

ALT/AST < 10 x ULN and normal bilirubin/INR/albumin: oral prednisolone 1 mg/kg

ALT/AST > 10 x ULN or raised bilirubin/INR/low albumin: i.v. (methyl)prednisolone 2 mg/kg

i.v. (methyl)prednisolone 2 mg/kg

Permanently discontinue treatment

Assessment and Investigations

If > ULN - 3x ULN repeat in 1 week

Control until normalisation

Re-check LFTs/INR/albumin every 3 days

Review medications, e.g. statins, antibiotics and alcohol history

Perform liver screen:
- Hepatitis A/B/C serology
- Hepatitis E PCR
- Anti-ANA/SMA/LKM/SLA/LP/LCI
- Iron studie

Consider imaging for metastases/portal trombosis

As above; daily LFTs/INR/albumin

Perform US with Doppler

Low threshold to admit if clinical concern

If refractory after 3 days consult hepatologist

As above; hepatology consult
Consider liver biopsy

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Review medications:
e.g. statins, antibiotics, alcohol history and alternative medicines (herbs)

Perform liver screen:
- Hepatitis A/B/C serology
- Hepatitis E PCR
- Anti-ANA/SMA/LKM/SLA/LP/LCI - Iron studies

Consider imaging for metastases/portal trombosis

Abbreviations:

ICPI = immune checkpoint inhibitor
ALT = Alanine transaminase
AST = Aspartate transaminase
ANA = anti nuclear antibodies
ULN = Upper limit of normal
LFT = liver function test
SMA = smooth muscle antibody
LKM = liver/kidney microsome type 1
SLA = soluble liver antigen
LP = liver/pancreas
LCI = liver cytosolic antigen
US = ultrasound

Steroid wean:

-G2: once G1, wean over 2 weeks; re-escalate if worsening; treatment may be resumed once prednisolone < 10 mg
-G3/4: once improved to G2, can change to oral prednisolone and wean over 4 weeks; for G3, rechallenge only at consultant discretion

Worsening despite steroids:

- If on oral change to i.v. (methyl)prednisolone
- If on i.v. add MMF 500-1000 mg b.d.
- If worse on MMF, consider addition of tacrolimus
- A case report has described the use of anti-thymocyte globulin in steroid + MMF-refractory fulminant hepatitis

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