Hepatic Immune-Related Adverse Event Management Algorithm

Grading of hepatitis	Action	Follow up
Grade 1 ALT/ AST >ULN but ≤3Xuln AND Bilirubin <1.5xULN	**Investigations** • Weekly LFT monitoring • Consider alternative causes **Management** • Continue ICI therapy with close monitoring	**If worsens:** • Treat as G2
Grade 2 ALT/AST >3xULN but ≤ 5x ULN AND / OR Bilirubin > 1.5x ULN but ≤ 3x ULN	**Investigations** • Twice weekly LFTs and INR • Review other medications • Review alcohol history • Liver screen [a] • Liver USS +/- portal vein doppler **Management** • Consider hepatology advice • Consider other causes e.g. metastases, biliary obstruction, pre-existing liver disease • Delay ICI therapy • Avoid hepatotoxic drugs • Commence oral prednisolone (1mg/kg, max 60mg OD**)** with PPI	**If LFTs improve back to <G1 limits:** • Taper steroids (see separate document) • Consider bone protection with AdCalD3 +/- bisphosphonates • Consider resuming ICI therapy if LFTs return to baseline and stable on Prednisolone ≤10mg OD **If no improvement or flare on steroid wean:** • Refer to hepatology • Increase prednisolone dose by 10mg (max 60mg OD) then slowly taper
Grade 3 ALT/AST > 5xULN AND / OR Bilirubin > 3x ULN OR symptomatic liver dysfunction	**Investigations** • Admit to hospital • Daily LFTs and INR • **Urgent hepatology referral** (including out of hours) • Other investigations and recommendations as above **Management** • Admit patient • Discontinue ICI therapy • Commence IV Methylprednisolone 1mg/kg/day OD + PPI (consider 2mg/kg/day if ALT/AST > 400) • Consider IV vitamin K 10mg for 3 days if raised INR • Monitor BMs • Consider liver biopsy if steroid refractory	**If LFTs improve to ≤G2 limits:** • Switch to PO prednisolone 1mg/kg OD (maximum 60mg OD) and taper as per standard regimen • Consider bone protection (with AdCalD3 +/- bisphosphonates), BM monitoring and PCP prophylaxis whilst on prolonged high-dose steroids **If no improvement after 3-5 days or rebounds:** • Continued discussion with hepatology • Consider adding 1g BD PO Mycophenolate mofetil [b] (under guidance of hepatology only) once infection excluded
Grade 4 ALT/AST > 20x ULN and/or Bilirubin > 10x ULN OR decompensated liver disease e.g. ascites, coagulopathy, hepatic encephalopathy	**Investigations** • As per G3 **Management** • Commence IV Methylprednisolone 2mg/kg/day OD + PPI	Recommendations otherwise as above.

[a] Liver screen: Hepatitis A, B, C and E), EBV, CMV, HIV, liver autoantibodies, iron studies

[b] Other options include tocilizumab, azathioprine or tacrolimus. If using azathioprine, test for thiopurine methyltransferase deficiency before commencing. Infliximab should not be used for patients with I-O induced hepatitis.

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