Autoimmune Hepatitis – Full clinical guideline

Reference no:CG-T/2023/192

Diagnosis: made on the basis of the clinical, laboratory and histological features and the exclusion of other causes of chronic hepatitis (consider drugs, Wilson's disease and viral infection).
Female:Male 3:1, Bimodal age pattern – peak in childhood/ teenage years then 4th-6th decade

Clinical features: Fatigue, general ill health, anorexia, wt loss, joint pains (swelling rare)
25% asymptomatic at Δ, 40% present as an acute hepatitis (autoantibodies may initially be negative) with jaundice
30-50% have another autoimmune disease
30% have cirrhosis at Δ

The International Hepatitis Group have drawn up criteria for the definition of Autoimmune Hepatitis for inclusion in clinical trials (Alvarez et al, J Hepatol 1999; 31:929-938) and have also proposed simplified criteria with – sens > 80% and spec > 90% at a cut off of ≥ 7 pts (See below).

Feature/parameter	Discriminator	Score
ANA or SMA+	≥1:40	+1*
ANA or SMA+	≥1:80	+2*
Or LKM+	≥1:40	
Or SLA+	Any titre	
IgG or immunoglobulin level	>Upper limit of normal	+1
	>1.1× Upper limit	+2
Liver histology	Compatible with AIH	+1
	Typical of AIH	+2
Absence of viral hepatitis	No	0
	Yes	+2

≥6 points: probable AIH; ≥7 points: definite AIH.
*Addition of points achieved for all antibodies (maximum 2 points).
ANA, antinuclear antibody; LKM, liver kidney microsomal antibody; SLA, soluble live antigen; SMA, smooth muscle antibody.

Adapted from Hennes et al. Hepatology 2008; 48:169-76

ANA is usually of a homgeneous or speckled pattern in AIH. 9-17% of patients will have negative liver autoantibodies. They are also not specific for AIH. 20-40% of patients with ALD have low ANA/ SMA titres. 25% of NAFLD patients are positive for ANA/ SMA and 20% meet IAIHG criteria for probable or definite AIH prior to biopsy

Causes: Post viral (Hepatitis A, EBV, Human Herpes 6, Measles)
Drugs* – e.g Nitrofurantoin, minocycline, interferon α, anti TNF
*Can be difficult to distinguish drug induced AIH from DILI. Consider treating with steroids until LFTs normal, then withdrawing steroids. Treat as AIH if initial response, then relapse.

Classification:

90% Type 1, 10% Type 2

Type 3 (Anti SLA) also described but similar to type1, though may be more severe.

Overlap syndromes (PBC:AIH and PSC:AIH)

Feature	Type 1 AIH	Type 2 AIH
Characteristic autoantibodies	ANA ASMA Anti-actin antibody Anti-SLA/LP antibodies 25% of patients negative ANA	Anti-LKM-1 antibody Anti-LC-1 antibody
Geographical variation	Worldwide	Worldwide
Age at presentation	All ages	Usually childhood and young adulthood
Sex (F:M)	3:1	10:1
Clinical phenotype	Variable	Generally severe
Histopathological features at presentation	Broad range: mild disease to cirrhosis	Generally advanced, ↑ inflammation/cirrhosis common
Treatment failure	Rare	Common
Relapse after drug withdrawal	Variable	Common
Need for long-term maintenance	Variable	Approximately 100%

Treatment

The majority of patients need treatment. A small number of patients (usually those with co-morbidities/ advancing age) with ALT < 3 x ULN, minimal activity (Ishak HAI < 4/18) and no advanced fibrosis on biopsy can be monitored with no treatment.

Initial Treatment:

- Start the patient on **Prednisolone 30mg/day** and reduce by 5mg per week to 20mg od, and then by 5mg every 2 weeks to 10mg daily
- AdCal D3 1 tab bd (bisphosphonate in steroid treated patients > 65yrs or with history of fragility #)
- If the patient has severe steroid side effects or there is good reason to wish to avoid the systemic effects of steroids (e.g diabetes) then **Budesonide 9mg/day** is an alternative in the absence of cirrhosis
- Check TPMT levels - 1:300 homozygous for deficiency allele (avoid Azathioprine), 10% heterozygous - intermediate activity
- When ALT <2 x normal add **Azathioprine 50mg or 1mg/kg**
  Mycophenolate Mofetil (MMF) 0.5-1g bd can be substituted in patients (10%) intolerant of Azathioprine. MMF is teratogenic. Both men and women require counselling on the risk of harm to the foetus. Patients must use effective contraception during and for 6 weeks (female)/ 12 weeks (male) after stopping treatment.

Treatment failure:

- 9% of patients have clinical, biochemical and histological worsening within 3-6 weeks
  Review diagnosis and if satisfied correct → Prednisolone 60mg for 4 weeks or Prednisolone 30mg + Azathioprine 150mg (70% improve with this strategy)

Azathioprine/ Mycophenolate monitoring:

- Initiation phase: FBC and LFTs weekly for four weeks then monthly for 3 months
- Maintenance phase: FBC, LFTs IgG levels every 3 months.
- A raised ALT on Azathioprine may indicate hepatotoxicity or disease relapse. Raised 6-MMPN levels may be associated with hepatoxicity

Maintainence therapy:

- Azathioprine 1-2mg/kg/day + Prednisolone 5-10mg/day or Azathioprine 2mg/kg monotherapy
- Treatment is aimed at achieving and maintaining a normal ALT and IgG
- Annual Fibroscan
- Consider repeat liver biopsy where Fibroscan fails to regress or shows progression.
  - Histological remission is usually 3-8 mths behind biochemical remission
- If persisting hepatitis on biopsy ↑ Azathioprine to 2mg/kg/day or switch to Tacrolimus
- DEXA scan every 1-5 years + advise annual optician review for cataracts/ glaucoma while on steroids
- Advise UV protection
- Ask GP to vaccinate for Hepatitis A and B and annually for influenza. Ensure up to date with COVID vaccination

Incomplete biochemical response:

- 13% of patients fail to enter remission by 36/12 – **Check compliance with therapy and consider testing for thiopurine metabolites. Low 6-TGN and 6-MMPN may indicate poor compliance while a disproportionately increased 6-MMPN may indicate preferential metabolism to the inactive 6-MMPN.**
- Consider - ↑ Pred by 2.5mg/d (<10mg/d) + (Azathioprine 2mg/kg/day or switch to Tacrolimus)

Treatment withdrawal:

- The vast majority of patients will require immunosuppressive therapy for life (>70% of patients will relapse within 12 months of stopping all therapy)
- Patients with advanced liver fibrosis should not be considered for treatment withdrawal
- Consider tapering out of steroids after biochemical remission for > 12mths - reinstitute steroids or increase Azathioprine to 2mg/kg/day if relapse

- Complete treatment withdrawal should only be considered in patients with complete biochemical remission for > 3 years on monotherapy – a liver biopsy to confirm complete histological remission prior to treatment withdrawal is recommended (relapse rate reduced to 30% in this group)
- Persistent hepatitis on liver biopsy or relapse on treatment withdrawal necessitates permanent immunosuppressive therapy

Further reading

EASL Clinical Practice Guidelines: Autoimmune hepatitis 2015
AASLD Practice guidelines. Diagnosis and management of Autoimmune Hepatitis. Updated 2019
BSG guidelines for management of autoimmune hepatitis. GUT 2011

Documentation Controls (these go at the end of the document but before any appendices)

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3</td><td>Status

Draft or Final</td><td>Final</td></tr>
<tr><td rowspan="3">Version / Amendment History</td><td>Version</td><td>Date</td><td>Author</td><td>Reason</td></tr>
<tr><td>3</td><td>2022</td><td>Liver Management Group</td><td>Previous version of guideline expired</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="5">Intended Recipients: All clinicians managing patients with liver disease</td></tr>
<tr><td colspan="5">Training and Dissemination: Forms part of liver handbook which is disseminated to all clinicians rotating through Hepatology</td></tr>
<tr><td colspan="5">Development of Guideline:
Job Title: Dr A Lawson (Consultant Hepatologist)</td></tr>
<tr><td colspan="5">Consultation with: Liver management group</td></tr>
<tr><td colspan="5">Linked Documents: State the name(s) of any other relevant documents</td></tr>
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