Updates in Autoimmune Hepatitis

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Genes, environment and their interactions alter the risk of developing AIH.
Determining activity, severity and chronicity of disease

- Current guidelines recommend liver biopsy at the time of first presentation.
- Liver biopsy is a critical tool for
  - Identifying features that are supportive of diagnosis
  - Determining disease severity (inflammatory activity and fibrosis stage)
  - Discriminating acute vs. chronic presentations

- Classical histological findings
  - Chronic AIH include lymphoplasmacytic infiltration in portal tracts Plasma-cell enrichment.
  - Varying degrees of interface hepatitis
  - Rosette formation
  - Development of periportal fibrosis, bridging fibrosis and cirrhosis
  - Lobular inflammation predominates in acute presentation
  - Hepatocyte ballooning, lobular disarray and spotty hepatocyte apoptosis/necrosis.
  - Extensive hepatocyte necrosis, ranging from confluent necrosis through bridging necrosis to panacinar or multiacinar necrosis
Treatment goals

• Resolution of liver biochemistry
  • ~75% of patients, of whom ~80% also attain normal serum immunoglobulin values.

• Normal ALT 39% to 65% of patients within 6 months of starting treatment (93% at 1 year).

• Complete biochemical and immunological remission (serum aminotransferases, bilirubin and IgG values all ≤ULN) associated with:
  • Reduced histological disease activity
  • Regression of liver stiffness as assessed by TE, and histological fibrosis regression after a median of 5.5 years (range 1.0–9.7 years; relative risk [RR] 3.66).

• However histological improvement lags behind normalisation of laboratory values by at least 6–12 months

Hartl, J. J Hepatol. 2018; 68: 754–763
Parameters associated with long-term mortality

- Presence of cirrhosis or liver decompensation
- Repeated relapses
- Age, because older age is predictive of all-cause death/transplant
- Younger age may be associated with liver-related death/transplant.
- Failure to attain normal serum transaminases within 6–12 months of presentation is associated with a >5-fold increased risk of liver-related death or transplantation.
Presence of cirrhosis is associated with a treatment failure and dismal prognosis

- De novo cirrhosis develops despite treatment in 14% (range 6%-40%) of patients with AIH
- 15% to 20% of patients do not achieve normal serum transaminases.
- Predictors of cirrhosis development
  - Delay or failure in achieving initial normalization of transaminases
  - Repeated relapses
- Weak correlations between transaminases and NIS.
  - Follow-up biopsy in treated patients, 40% to 55% have persistent interface hepatitis or an Ishak necroinflammatory score (NIS) greater than 3.
  - Serum immunoglobulin G (IgG) has been proposed as an additional predictor of histological remission

Gleeson. Clinical Liver Disease, 2019 7:24-29
Inducing and maintaining remission

- Corticosteroids, either prednisolone or budesonide, are the mainstay of treatment for AIH, inducing remission.
  - Budesonide has a higher affinity for the glucocorticoid receptor and undergoes over 90% hepatic first pass metabolism.
  - The labelled indication excludes individuals with cirrhosis.
- Corticosteroids alone or in combination with azathioprine are considered equally effective
  - Combination therapy can be instituted either at diagnosis, or with a slight delay of 2–4 weeks before starting azathioprine.
- Phased introduction of azathioprine for managing and traversing the side effects of treatment
- Biochemical remission can be maintained in the majority of patients with prednisolone (gradually tapered to $\sim 7.5–12.5$ mg/day), + azathioprine $1–2$ mg/kg/day.
Management algorithm

Rapid Response to Treatment of AIH Associated with Remission at 6 and 12 Months

- Retrospective cohort study, AIH from 12 centers in 7 countries in Europe with prednisolone.
- A decrease of more than 80% of AST after 8 weeks of treatment was significantly associated with normalization of transaminase levels at 26 and 52 weeks ($P<.001$)
- Rapid responders
  - ($\geq 80\%$ decrease in level of AST after 8 weeks) more likely to achieve normalization of transaminases at 26 and 52 weeks.
  - Lower risk of liver-related death or transplantation (adjusted hazard ratio 0.18; 95% CI 0.05–0.63; $P=.007$).

Pape et al Clinical Gastroenterology and Hepatology, November 2019, In Press
Factors to be considered for assessing corticosteroid responsiveness

• Corticosteroid treatment is by itself a cause for obesity, diabetes and fatty liver, and worsening liver tests during treatment may not be a call for more corticosteroids.

• Non-adherence to therapy should be considered as cause of treatment failure, and this must be excluded before treatment escalation.
Risk factors for treatment failure

- Poor adherence
- Disease onset at an early age (≤40 years)
- Acute severe (fulminant) presentation
- Jaundice or high serum bilirubin level at diagnosis
- MELD score ≥12 points at presentation
- Lack of improvement in laboratory indices within 1–2 weeks of corticosteroid treatment
- Inability to improve the MELD, MELD-Na, within 7 days of corticosteroid treatment
- Antibodies to soluble liver antigen (anti-SLA) are associated with more severe histological changes, longer duration of treatment, higher risk of relapse
- Anti-SLA are associated with HLA DRB1*03 and antibodies to ribonucleoprotein/Sjogren's syndrome A antigen (anti-Ro/SSA)
Autoimmune hepatitis differential diagnosis or overlaps

• Corticosteroid responsiveness: failure of the disease to improve suggests an alternative diagnosis.

• These conditions may be underrecognized
  • Wilson disease
  • Chronic hepatitis C
  • Non-alcoholic fatty liver disease
  • Celiac disease
  • Drug toxicity

• AIH may undergo transitions to emerging cholestatic diseases during its course, such as PBC or PSC.
  • Consequently, all patients with treatment failure warrant histological evaluation and endoscopic or magnetic resonance cholangiography
Histology remains the cornerstone in therapeutic decision making. TE is useful for course monitoring.

- Liver stiffness strongly correlated with histological fibrosis.
- The performance of TE was impaired when transient elastography was performed within 3 months from start of treatment.
- Liver stiffness correlated with histological grading ($p = 0.558$, $p = 0.001$), but not with staging.
- Accuracy for diagnosing cirrhosis was excellent in patients treated for 6 months or longer.

Hartl et al. October 2016, Pages 769-775
Transient elastography in monitoring disease course in autoimmune hepatitis

Changes of liver stiffness measurement (LSM) in dependence of complete biochemical remission and fibrosis stage

Hartl et al, Journal of Hepatology Volume 68, 2018, Pages 754-763
Histologic significance of biologic parameters

Histological disease activity in dependence of biochemical remission in autoimmune hepatitis

Complete biochemical remission (normal ALT- and IgG-levels) (n = 22)

Normal ALT-levels (n = 28)

Normal IgG-levels (n = 35)

No biochemical remission (elevated ALT-or/and IgG-levels) (n = 38)
Long-term prognostic significance of persisting histological activity despite biochemical remission in autoimmune hepatitis

(A) all-cause death or transplant
(B) liver-related death or transplant.

Relapse is more likely to occur at treatment withdrawal in the event persistent histological inflammatory activity is present (HAI >3). Thus it has been advised that biopsy be performed routinely for all patients prior to trying cessation of therapy.

Dhaliwal HK, Am J Gastroenterol 2015;110:993-999.
Managing incomplete treatment response or treatment failure

- First line treatment: combination of prednisolone and azathioprine
  - Approximately 15% of patients experience insufficient response or
- Mycophenolate mofetil (MMF)
- Calcineurin inhibitors, such as tacrolimus
- Infliximab.
- Anti-B cell therapy with rituximab.
Calcineurin inhibitors

- Tacrolimus and cyclosporine are options for third-line therapy in AIH.
- Tacrolimus is a more than cyclosporine.
- Calcineurin inhibitors can have considerable side effects with nephrotoxicity and hypertension.
- Transaminase levels, albumin, bilirubin and prothrombin time significantly improve.
- Target trough level is related to the relative indication.
  - If tacrolimus is used as an adjunct to existing dual therapy advised trough levels = 3–5 ng/ml
  - If tacrolimus is the mainstay of immunosuppression, trough levels = 5–7 ng/ml.

Journal of Hepatology 2019 70, 773-784
Efficacy and safety of mycophenolate mofetil and tacrolimus as second-line therapy for patients with autoimmune hepatitis

<table>
<thead>
<tr>
<th></th>
<th>MMF <em>(n=121)</em></th>
<th>Tacrolimus <em>(n=80)</em></th>
<th>P value</th>
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<tbody>
<tr>
<td>Response Complete (all)</td>
<td>84 (69.4%)</td>
<td>58 (72.5%)</td>
<td>0.639</td>
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<tr>
<td>Group I steroid or AZA side effects <em>(n=108)</em></td>
<td>n=74</td>
<td>n=34</td>
<td></td>
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<tr>
<td>Complete Response</td>
<td>68 (91.9%)</td>
<td>32 (94.1%)</td>
<td>0.682</td>
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<tr>
<td>Group II no response to standard therapy <em>(n=93)</em></td>
<td>n=47</td>
<td>n=46</td>
<td></td>
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<tr>
<td>Complete Response</td>
<td>16 (34.0%)</td>
<td>26 (56.5%)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

- Median initial and follow up doses for MMF were 1500 (500-2000) and 1000 (0-2000) mg/day,
- Tacrolimus 4 (1-8) and 3 (0-6) mg/day
- After initiation of MMF, the median steroid dose was decreased from 10 (2.5-22.5) to 5 (0-10) mg/day, and after initiation of tacrolimus from 10 (5-50) to 5 (0-10) mg/day
- Significant side effects / drug withdrawal in 10% of patients

Long-term follow-up of patients with difficult to treat type 1 autoimmune hepatitis on Tacrolimus therapy

- 16 AIH patients treated with Tacrolimus between 2003 and 2014 were analyzed from two tertiary referral liver centers.
- Median duration of treatment: 24 months, follow-up of 60 months.
- Median Tacrolimus dosage was 2 mg/day
- Significant improvement in immunoglobulin G and Aspartate transaminase level.
- 9/17 (52%) compliant and definite AIH patients remained on Tacrolimus at end of follow-up and prednisolone dose reduction was achieved from 10 to 5 mg.
- All patients are alive, one patient underwent liver transplantation.
- 4/17 (24%) patients developed overlap with primary sclerosing cholangitis over follow-up period.

Biologics in the treatment of AIH
Anti-TNF in the treatment of AIH

• One retrospective series has reported success in using infliximab
• Reduction of inflammation,
• Decrease in transaminases (pretreatment AST 475 U/L ± 466 → 43 U/L ± 32)
• Decrease in IgG (pretreatment 24.8 mg/dl ± 10.1 → 17.38 mg/dl ± 6).
• Infectious complications 7/11 patients
• Anti-TNF also associated with hepatotoxicity in a number of case series with Anti-TNF induced autoimmune hepatitis

Efficacy of rituximab in difficult-to-manage Autoimmune Hepatitis: International Autoimmune Hepatitis Group

- For each course of treatment, patients received two doses of rituximab (1000 mg in each dose) via intravenous infusion, administered two weeks apart
- Premedication, consisting of acetaminophen 1000 mg and diphenhydramine 50 mg, PO 60 min before each infusion.
- Patients remained on stable doses of AZA for at least three months before rituximab and throughout the follow-up period. Prednisone was continued at stable doses for at least three months before and for three months following rituximab

Than et al, J Hepatol, Nov 2019
Changes in liver enzymes aspartate transaminase (AST), alanine transaminase (ALT), bilirubin, albumin after rituximab treatment

Significant improvements in ALT, AST

Significant change in bilirubin, with median levels declining from 17 to 11 umol/L by six months post-treatment (p = 0.007).

Than et al, J Hepatol, Nov 2019
Changes in immunoglobulin G concentration after rituximab treatment

- MELD scores were recorded at both pre-treatment and 12 months post-treatment in 18 patients, and were not found to change significantly, with medians of 8 (interquartile range 6–9) and 7 (6–12), respectively ($p = 0.821$).

IgG levels significantly dropped

Than et al, J Hepatol, Nov 2019
Rituximab therapy leads to a lower burden of corticosteroid use.

- Changes in prednisolone doses between 3 months pre- and 12 months post-rituximab therapy
- Significant reduction in prednisolone doses were detected, from a median of 15 mg to 10 mg ($p = 0.003$), with a total of 13 (62%) patients having a dose reduction.

Than et al, J Hepatol, Nov 2019
Rituximab treatment significantly reduces AIH flares.

- A total of 5 patients (23%) developed flares of AIH during the follow up period. The earliest flare occurred 135 days (4 months) after the first dose of rituximab, with the other four cases occurring at 21, 22, 23 and 24 months.

- Kaplan–Meier analysis estimated the rates of freedom from flare to be 95% and 71% at one and two years, respectively, after the first dose of rituximab.

- Of the five patients who developed AIH flares, four (80%) were treated with a second dose of rituximab. Two of these four patients subsequently developed recurrence of AIH activity at 236 days (8 months) and 471 days (15 months) after their second rituximab infusions.
### Holistic care of the patient with autoimmune hepatitis.

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| **Timely and individualized therapy** | • Treatment regimens tailored to inflammatory activity, disease severity and patient tolerability  
• Elderly patients: lower low dosages of corticosteroids (10–20 mg prednisolone, or equivalent).  
• Pregnancy: spontaneous disease remission common, but disease relapse often in the post-partum  
• Acute onset, fulminant presentations: less favorable response to corticosteroids (≈50%) (60% needing transplantation; 20% mortality).  
• Failure to induce remission loss of prior response must prompt investigation for sclerosing cholangitis. |
| **Maintaining adherence to treatment** | • Stratified, personalized approach.  
• Optimized care provision through evaluating, monitoring and education  
• Monitoring of thiopurine metabolites facilitates tailoring of therapy and monitoring drug compliance. |
| **Symptomatology and extrahepatic manifestations** | • Consider budesonide as first line in non-cirrhotic patients with features of metabolic syndrome and/or diabetes mellitus.  
• Side effects of thiopurines. Improved tolerability by starting with lower dosages and titration.  
• Fatigue and arthralgia correlate with underlying disease activity.  
• Pruritus in chronic cholestatic liver diseases, but may herald an ‘evolving’ sclerosing cholangitis. |
| **Surveillance of complications** | • Bone density measurements at the onset of corticosteroid therapy.  
• Hepatocellular carcinoma screening for patients with established liver cirrhosis.  
• Check for gastroesophageal varices according to Baveno guidelines. |
| **Side effects of therapy** | • HbA1c monitored 6–12-monthly, and BMD 3–5-yearly if prednisolone continues >10 mg/day.  
• Monitoring strategy under thiopurine therapy  
• Checking full blood count and renal function. |
Take Home Messages

• Autoimmune hepatitis is a chronic, frequently relapsing immune-mediated liver injury.
• The goal of treatment is to prevent the development of end-stage liver disease and reduce the risk of patients needing liver transplantation.
• The risk vs. benefit of immunosuppression in patients with decompensated cirrhosis is less clear. Treatment of acute - severe presentations is advised to be done in close liaison with a liver transplant unit.
• Corticosteroids, either prednisolone or budesonide, are the mainstay of inducing remission in patients with AIH.
• Biopsy to be performed prior to treatment withdrawal,
• All patients who stop therapy are monitored closely for relapse.
• Mycophenolate mofetil, tacrolimus and biologics, have been considered for cases of relapse or intolerability to first-line treatments.
Take Home Messages

• Long-term management strategies for AIH should include:
  • Selective use of maintenance of immunosuppressive therapy
  • Lifelong monitoring for relapse and for fibrosis progression
  • HCC surveillance in patients with cirrhosis
  • Advice and monitoring to minimize cancer risk
  • Maintenance of bone health
  • Attention to cardiovascular risk factors, especially when high steroid burden