

# Autoimmune Hepatitis

## Part II



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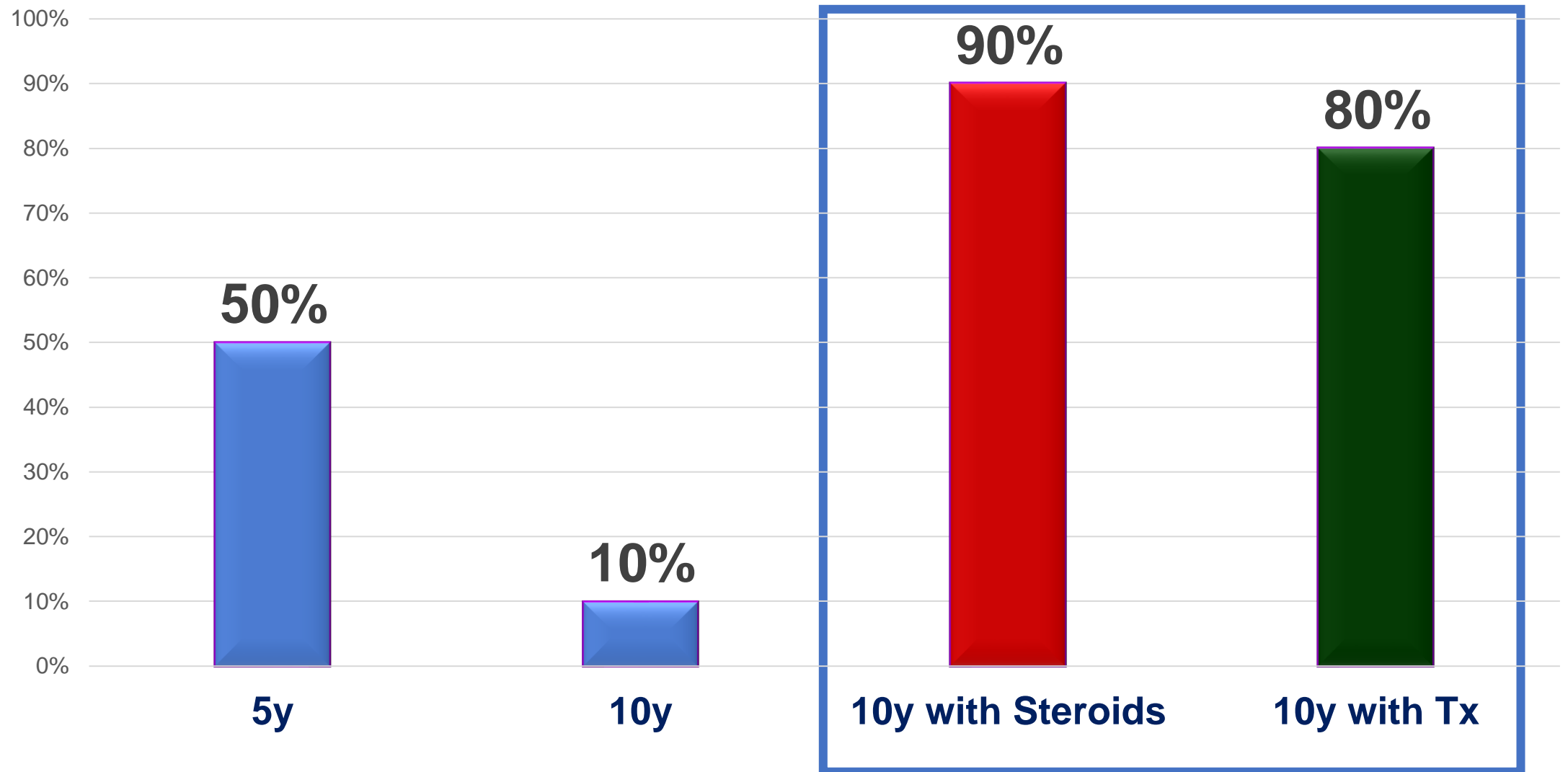
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عَذَابَ النَّارِ ﴿١﴾

# Natural History

## Survival





# AIH Treatment

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# Definitions



| Condition   | Definition  |
|---|---|
| <b>AIH</b>  | Characteristic histologic abnormalities (lymphoplasmacytic interface hepatitis), elevated AST, ALT, and total IgG and the presence of one or more characteristic autoantibodies |
| <b>Inactive cirrhosis</b>   | Absence of inflammatory infiltrates in both portal tracts and fibrous bands in cirrhosis  |
| <b>Acute severe AIH</b>   | Jaundice, INR $> 1.5 < 2$ , no encephalopathy; no previously recognized liver disease   |
| <b>ALF</b>  | INR $\geq 2$ ; hepatic encephalopathy within 26 weeks of onset of illness; no previously recognized liver disease   |
| <b>Biochemical remission</b>  | Normalization of serum AST, ALT, and IgG* levels  |
| <b>Histological remission</b>   | Absence of inflammation in liver tissue after treatment   |
| <b>Treatment failure</b>  | Worsening laboratory or histological findings despite compliance with standard therapy  |
| <b>Incomplete response</b>  | Improvement of laboratory and histological findings that are insufficient to satisfy criteria for remission   |
| <b>Relapse</b>  | Exacerbation of disease activity after induction of remission and drug withdrawal (or nonadherence)   |
| <b>Treatment intolerance</b>  | Inability to continue maintenance therapy due to drug-related side effects  |
| <b>* Patients with cirrhosis in biochemical remission may have persistent elevation of IgG.</b> |   |

# Aim of AIH treatment

- 1<sup>ry</sup> aim: complete histological remission.
- 2<sup>nd</sup> aim: minimal histological inflammation (HAI  $\leq 3$ ).



# Effects of response to treatment

- Untreated AIH ➡:
  - Liver fibrosis ➡ cirrhosis ➡ ESLD.
- AIH Treatment ➡:
  - Clinical, laboratory and histological improvement.
  - Regression or reversal of liver fibrosis.





# Pre Treatment Evaluation

## ■ TPMT activity:

- Test for **thiopurine methyltransferase activity** to detect patients with zero or near-zero TPMT activity (0.3-0.5%) to **avoid AZA severe myelosuppression**.

## ■ Vaccines:

- Use **recombinant** and **inactivated** vaccines.
- **AVOID live, attenuated vaccines** in persons on high doses of immunosuppression.
- Vaccines for **HAV and HBV** before treatment.
- **Response** to vaccines is relatively slow.

## ■ Reactivation of HBV Infection:

- +ve HBsAg;
  - Rituximab, High-dose corticosteroids, infliximab: **high risk**.
  - Moderate-dose corticosteroids: **moderate risk**.
  - low-dose prednisone, AZA: **low risk**.
- -ve HbsAg/+ve HBcIgG:
  - Rituximab: **high risk**.
  - High-dose corticosteroids, infliximab: **moderate risk**.
  - Moderate- and low-dose prednisone, AZA: **low risk**.
- Low risk -ve HbsAg/+ve HBcIgG ➡ monitoring and on demand treatment.
- Moderate/high risk ➡ preemptive antiviral therapy.



## ■ Bone Maintenance:

- Steroids and old age ➡ ↑ osteoporosis risk.
- **Baseline DEXA** scan and then every 2-3 years.
- Measure Vit D annually.
- **Steroids**: give 1-1.2g elemental calcium and 800 IU vitamin D.
- **Osteoporosis**: bisphosphonate.

## ■ Metabolic syndrome.

- Steroids ➡ ↑ DM and **cardiovascular diseases**.
- Assessment for all features of metabolic syndrome.

## ■ Depression:

- **Depression** is common in AIH and steroids ➡ ↑ risk.
- Screening and management for depression.

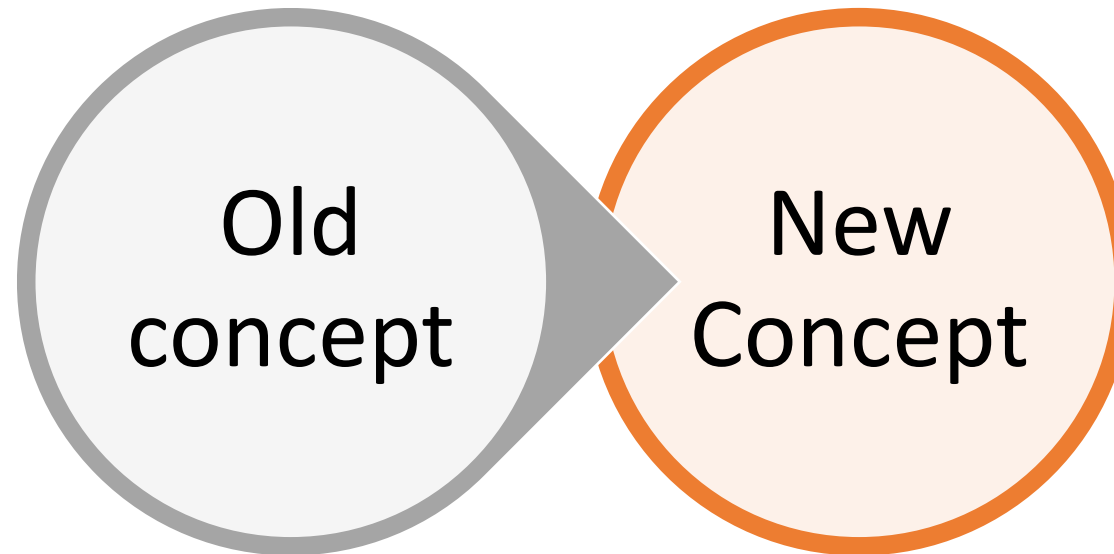
## ■ Pregnancy:

- Pregnancy may be planned 1 year after remission.
- **Patient education** is mandatory.
- **Continue** ➡ Maintenance doses of glucocorticoids and/or AZA.
- **AVOID**: MMF before and after pregnancy.
- **Varices** in a cirrhotic patients should be screened before and during 2<sup>nd</sup> trimester of pregnancy +/- EVL.
- **Surveillance** for flare in the 1<sup>st</sup> 6 months postpartum.



# Treatment Principles

# Indications of treatment



## OLD CONCEPT

- The presence of **histological activity** increases the response to steroids.
- **Asymptomatic inactive without cirrhosis**: 80% 10 year survival.
- **Spontaneous remission** may occur in asymptomatic mild disease.
- **Asymptomatic inactive cirrhosis**: 70-90% steroid free survival.
- **Burned out disease** or cirrhosis **does not benefit** from steroids.

## NEW CONCEPT

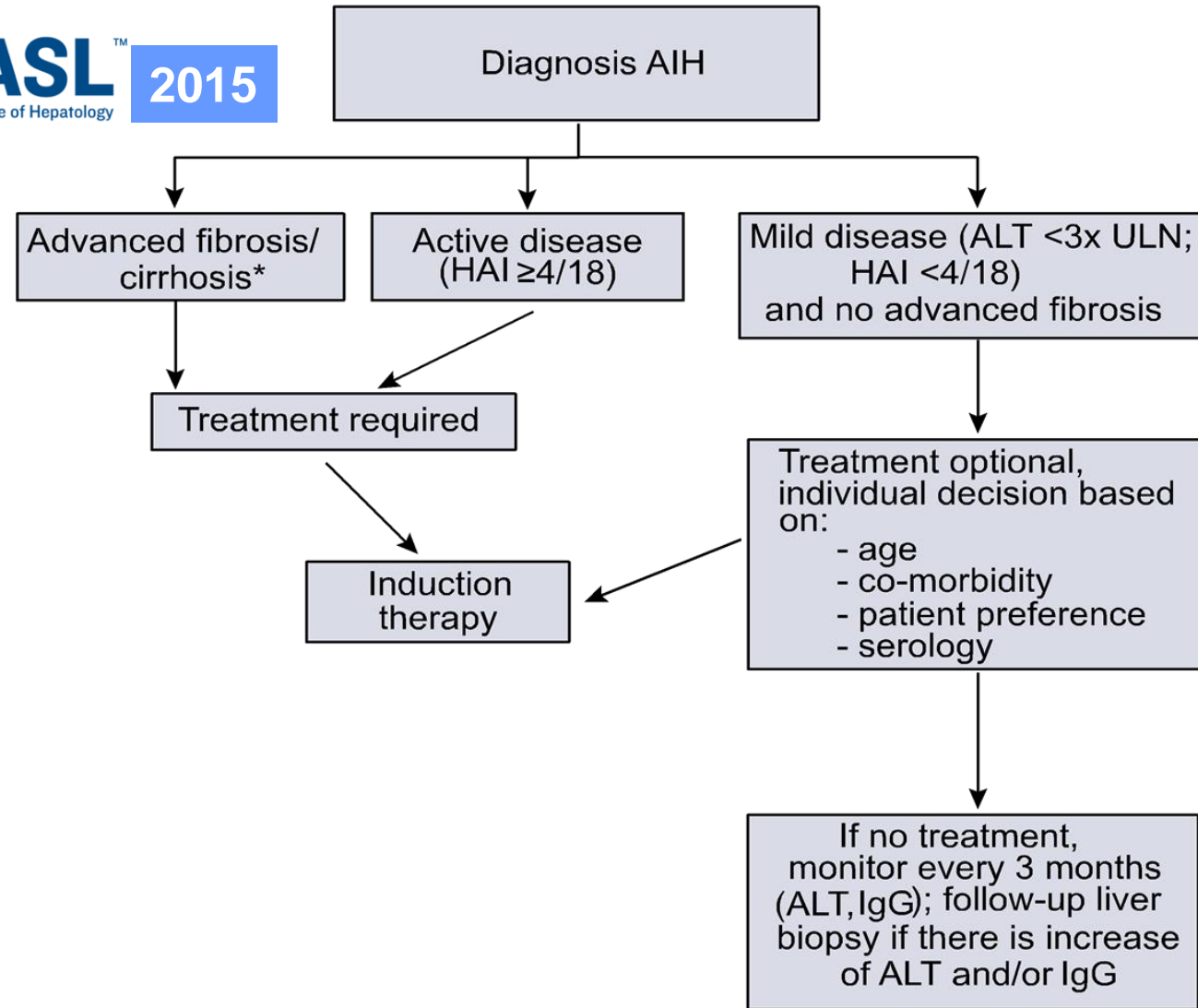
- Most studies included patients with moderate to severe disease.
- **AIH is a fluctuating disease** and patients with asymptomatic mild disease (25%) may **fluctuate to severe disease and cirrhosis**.
- Spontaneous **biochemical remission** may occur **despite** progressive histological activity.
- Italian study: asymptomatic mild disease have lower LFTs and mild HAI. It had **same percentage of development of cirrhosis, decompensation, HCC and listing to Tx or death**.
- **You may avoid treatment** in asymptomatic patients with mild disease of older age or with severe comorbidities.



## Indications for treatment of autoimmune hepatitis

|                   | ABSOLUTE   | RELATIVE   | NONE   |
|-------------------|--|--|--|
| <b>Clinical</b>   |  | ☯ Symptoms (fatigue, arthralgia, jaundice, abdominal pain)   | ☯ Asymptomatic   |
| <b>Laboratory</b> | ☯ AST $\geq 10$ ULN or AST $\geq 5$ ULN and IgG $\geq 2$ ULN | ☯ AST or IgG less than absolute criteria   | ☯ Normal or near normal AST and IgG  |
| <b>Histology</b>  | ☯ Bridging necrosis or multiacinar necrosis on histology     | ☯ Interface hepatitis<br>HAI $>4$  | ☯ Inactive cirrhosis or mild portal hepatitis  |
|                   | ☯ Incapacitating symptoms                                    | ☯ Osteopenia, emotional instability, hypertension, diabetes, or cytopenia (white blood cell counts $\leq 2.5 \times 10^9/L$ or platelet counts $\leq 50 \times 10^9/L$ ) | ☯ Severe cytopenia (WBCs $< 2.5 \times 10^9/L$ or platelet counts $< 50 \times 10^9/L$ ) or known complete deficiency of TPMT activity precludes treatment with azathioprine<br>☯ Vertebral compression, psychosis, brittle diabetes, uncontrolled hypertension, known intolerances to prednisone or azathioprine. |

## New Concept



All patients with AIH are candidates for therapy except individuals with inactive disease by clinical, laboratory, and histological assessment.

- Treatment in every AIH patient, unless there are compelling reasons not to treat.
- For example, a patient with active disease (elevated transaminases >3 normal values and hepatitis activity index (HAI) >4/18) requires treatment.
- Treatment probably no longer indicated in decompensated, burn-out cirrhosis, unless high inflammatory score on liver biopsy.

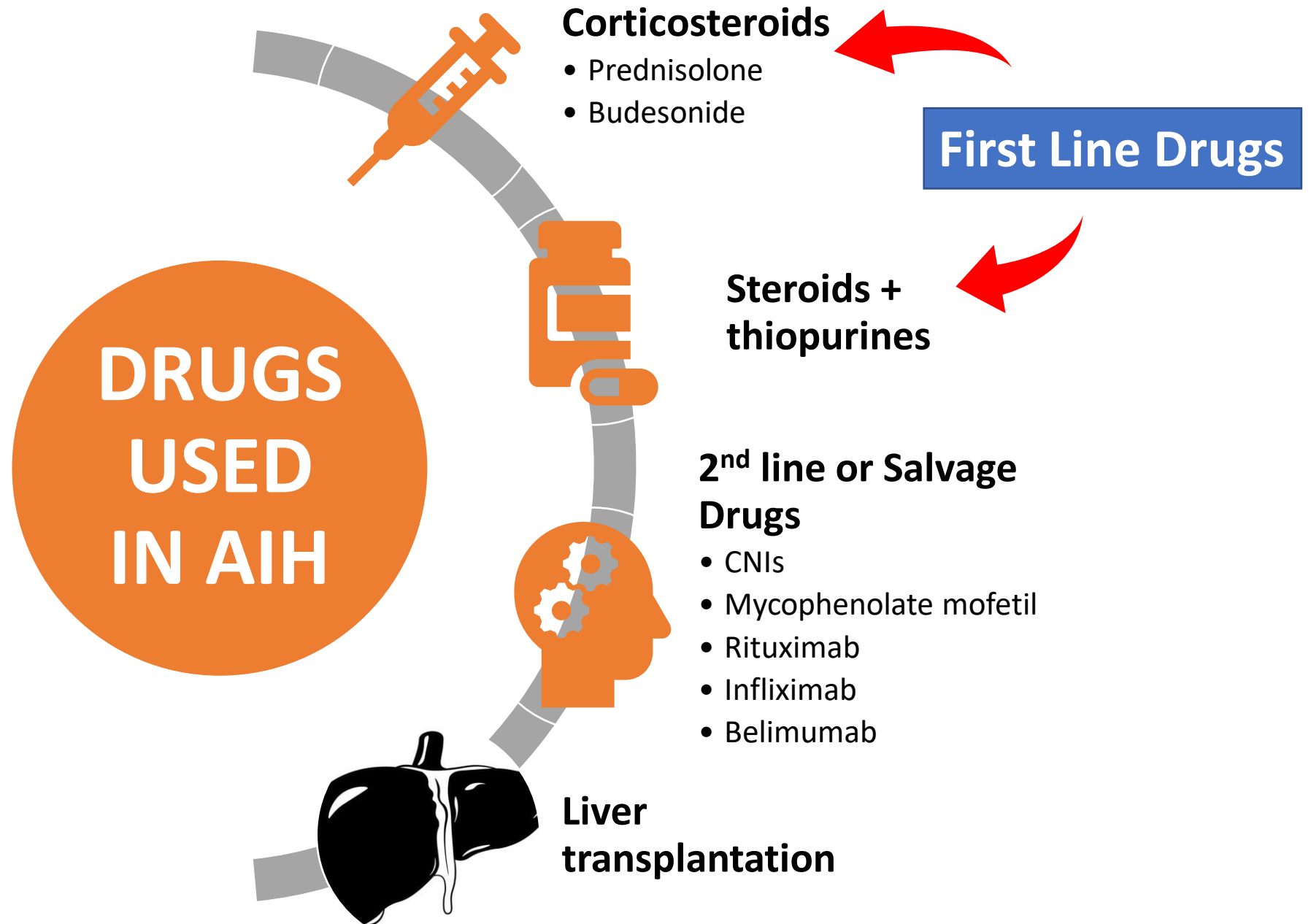
EASL. EASL Clinical Practice Guidelines: Autoimmune hepatitis. Journal of Hepatology 2015; 63:971-1004.





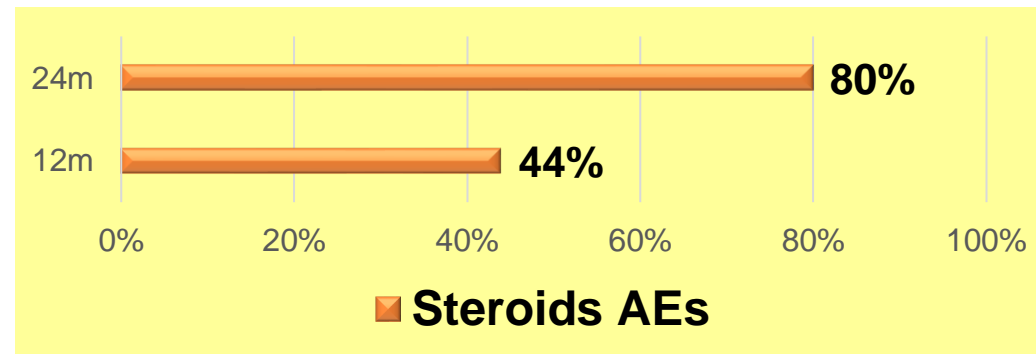
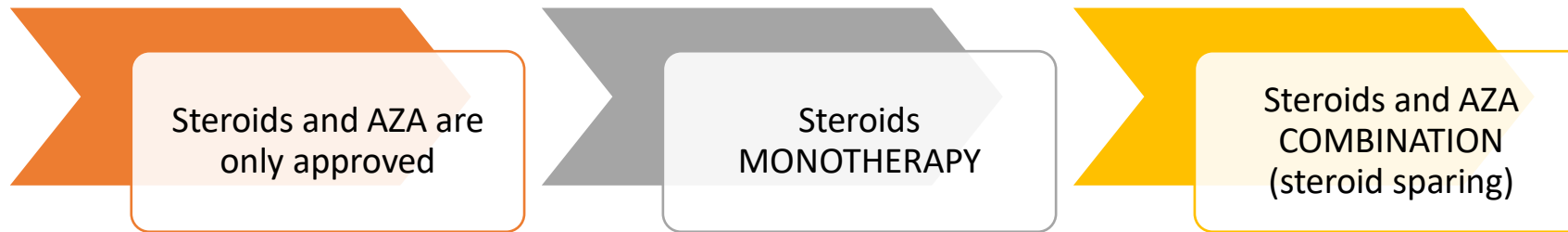
# Steps of AIH treatment







# Few armamentarium



# Steroids AEs

## SHORT-TERM

- Transient hyperglycemia.
- Infections.
- Viral replication..

## LONG-TERM

- Impaired wound healing
- **Cosmetic**: facial rounding, dorsal hump, acne, alopecia, hirsutism.
- Hypertension

- Weight gain and obesity
- Hyperglycemia and resistant DM
- Hyperlipidemia
- Osteoporosis
- Fluid retention
- Psychosis
- Myopathy
- Cataract and glaucoma.
- Pancreatitis



# Azathioprine AEs

- **Bone marrow:** myelosuppression ➡ leukopenia.
- **GI:** nausea, vomiting, villous atrophy with diarrhea.
- **Pancreas:** pancreatitis.
- **Liver:** cholestasis, nodular regenerative hyperplasia, sinusoidal obstruction syndrome.
- **Malignancy:** nonmelanoma skin cancer and non-Hodgkin lymphoma.



| Drug         | Side Effects   | Management Options  |
|--------------|--|---|
| Prednisolone | <ul style="list-style-type: none"> <li>• <b>Cosmetic:</b> Facial rounding, hirsutism, alopecia, dorsal hump, striae</li> <li>• <b>Systemic:</b> Weight gain, glucose intolerance/diabetes, hypertension, fatty liver, osteoporosis, vertebral compression, cataracts, glaucoma, opportunistic infections</li> <li>• <b>Quality of life:</b> Emotional instability, psychosis, depression, anxiety</li> </ul> | <ul style="list-style-type: none"> <li>• Actively taper to the lowest steroid dose needed for remission and attempt withdrawal after remission</li> <li>• Eye examinations for cataract and glaucoma</li> <li>• Lifestyle interventions for metabolic syndrome</li> <li>• Bone density monitoring</li> <li>• Vitamin D and calcium administration</li> <li>• Proactive screening and management for quality of life and mental health symptoms</li> </ul>                         |
| Budesonide   | <ul style="list-style-type: none"> <li>• Reduced intensity of the side effects from prednisone is possible despite first-pass metabolism</li> <li>• Unable to reach the liver with portal hypertensive shunts</li> <li>• Portal vein thrombosis in cirrhosis</li> </ul>  | <ul style="list-style-type: none"> <li>• Taper budesonide to the lowest effective dose and attempt withdrawal after remission</li> <li>• Do not prescribe in cirrhosis and acute severe AIH</li> </ul>  |
| AZA          | <ul style="list-style-type: none"> <li>• <b>Hematologic:</b> Mild cytopenia, severe leukopenia or bone marrow failure (rare)</li> <li>• <b>Gastrointestinal:</b> Nausea, emesis, pancreatitis</li> <li>• <b>Neoplastic:</b> Nonmelanoma skin cancer</li> <li>• <b>Cholestatic</b> liver damage (rare)</li> </ul>   | <ul style="list-style-type: none"> <li>• Check TPMT metabolizer status prior to prescribing</li> <li>• Monitor cell counts at least every 6 months</li> <li>• Reduce dose if mild cytopenia occurs</li> <li>• Discontinue in severe cytopenia</li> <li>• Discontinue in gastrointestinal intolerance</li> <li>• Avoid direct sunlight and have yearly dermatologic screening for skin cancer</li> <li>• Not recommended in decompensated cirrhosis or acute severe AIH</li> </ul> |





# Different Drug Protocols

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## Different Guideline Protocols

|              | AASLD 2010          |                     |                         | EASL 2015        |                      |                |
|--------------|---------------------|---------------------|-------------------------|------------------|----------------------|----------------|
|              | Monotherapy         | Combined Therapy    |                         | Combined Therapy |                      |                |
| Week         | Prednisolone mg/day | Prednisolone mg/day | AZA mg/day or mg/kg/day | Prednisolone     | or Budesonide mg/day | AZA mg/day     |
| 1            | 60                  | 30                  | 50 or 1-2               | 60 (1mg/kg)      | 9                    | 0              |
| 2            | 40                  | 20                  | 50 or 1-2               | 50               | 9                    | 0              |
| 3            | 30                  | 15                  | 50 or 1-2               | 40               | 6                    | 50             |
| 4            | 30                  | 15                  | 50 or 1-2               | 30               | 6                    | 50             |
| 5            | 20                  | 10                  | 50 or 1-2               | 25               | 6                    | 100 (1-2mg/kg) |
| 6            | 20                  | 10                  | 50 or 1-2               | 20               | 6                    | 100            |
| 7+8          | 20                  | 10                  | 50 or 1-2               | 15               | 6                    | 100            |
| 8+9          | 20                  | 10                  | 50 or 1-2               | 12.5             | 6                    | 100            |
| from week 10 | 20 and below        | 10                  | 50 or 1-2               | 10 and below     | 6 and below          | 100            |

For EASL if the patient is not 60kg use initial weight based formula Prednisolone 1mg/day and AZA 1-2mg/kg

- The response to the standard dose of 3 mg three times a day is slower than the response to prednisolone or prednisone starting at the equivalent dose (usually 1 mg per kg body weight); as a consequence, the prednisolone dose can be reduced more rapidly than the budesonide dose





- **Prednisolone monotherapy:**

- Start **high dose** and taper over 4 weeks.
- Fixed dose =weight based.
- In **cirrhosis** prednisolone=prednisone.
- **Preferred when** AZA is contraindicated.

- **Prednisolone + AZA:**

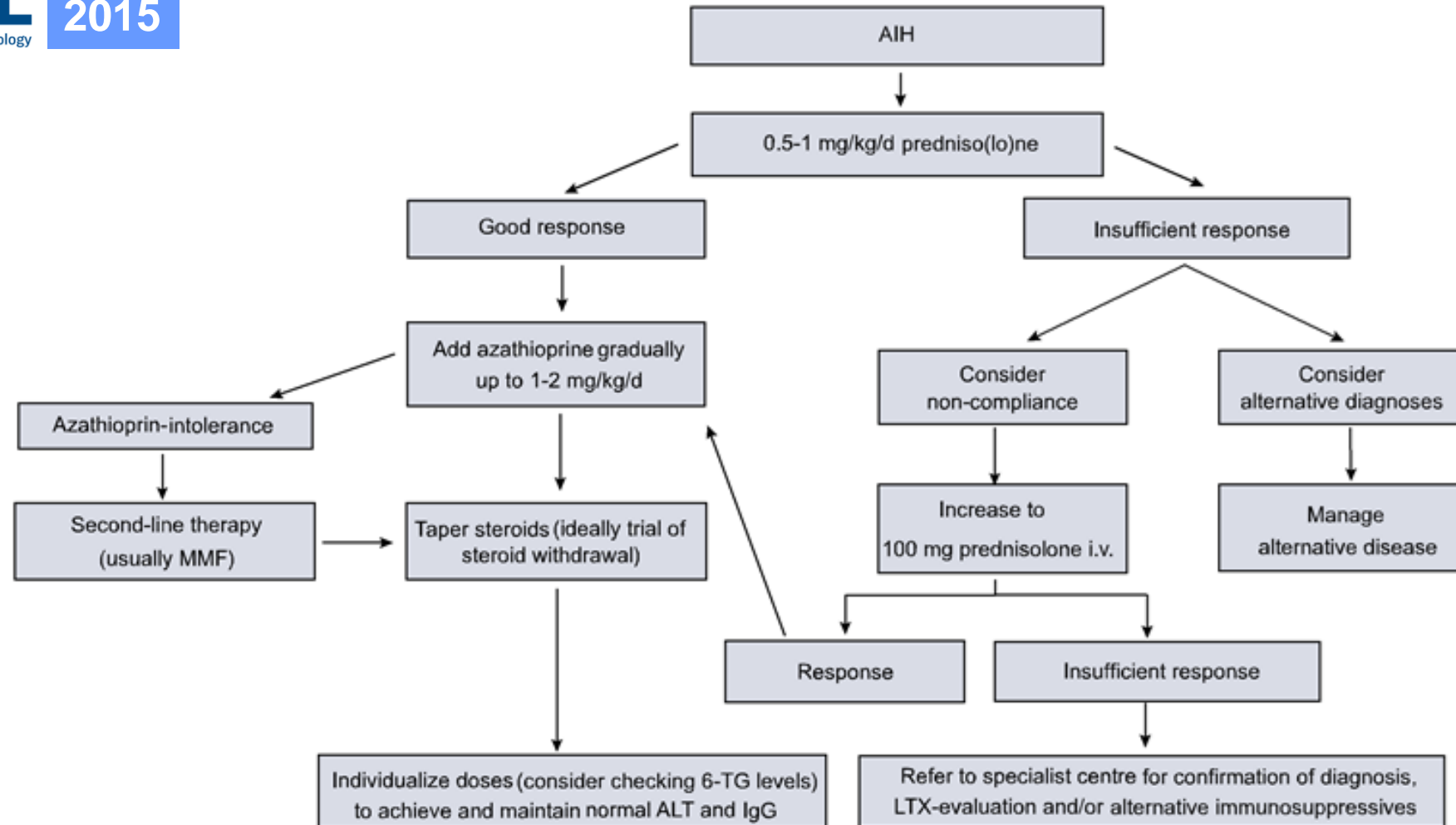
- Preferred to **avoid steroids AEs.**
- Measure TPMT

| Monotherapy  |                     | Combined Therapy    |                         |
|--------------|---------------------|---------------------|-------------------------|
| Week         | Prednisolone mg/day | Prednisolone mg/day | AZA mg/day or mg/kg/day |
| 1            | 60                  | 30                  | 50 or 1-2               |
| 2            | 40                  | 20                  | 50 or 1-2               |
| 3            | 30                  | 15                  | 50 or 1-2               |
| 4            | 30                  | 15                  | 50 or 1-2               |
| 5            | 20                  | 10                  | 50 or 1-2               |
| 6            | 20                  | 10                  | 50 or 1-2               |
| 7+8          | 20                  | 10                  | 50 or 1-2               |
| 8+9          | 20                  | 10                  | 50 or 1-2               |
| from week 10 | 20 and below        | 10                  | 50 or 1-2               |



- You use prednisolone or budesonide.
- Budesonide is contraindicated in cirrhosis, PHT and collaterals.
- Use combination therapy (steroids + AZA).
  - Start with high dose steroid for induction of remission (90% 6m remission).
  - Start AZA after 2 weeks of steroids.
- IV steroids can be used in fulminant liver failure.

| Combined Therapy  |              |                         |                |
|---|--------------|-------------------------|----------------|
| Week  | Prednisolone | or Budesonide<br>mg/day | AZA<br>mg/day  |
| 1   | 60 (1mg/kg)  | 9                       | 0              |
| 2   | 50           | 9                       | 0              |
| 3   | 40           | 6                       | 50             |
| 4   | 30           | 6                       | 50             |
| 5   | 25           | 6                       | 100 (1-2mg/kg) |
| 6   | 20           | 6                       | 100            |
| 7+8   | 15           | 6                       | 100            |
| 8+9   | 12.5         | 6                       | 100            |
| from wk 10  | 10 and below | 6 and below             | 100            |
| For EASL if the patient is not 60kg use initial weight based formula<br>Prednisolone 1mg/day and AZA 1-2mg/kg |              |                         |                |



## Therapeutic strategy in autoimmune hepatitis.

## MONOTHERAPY

- a) Prednisolone monotherapy: 40-60mg.
- Not preferred as first line.
  - Used only if AZA is contraindicated.

## DRUG COMBINATION:

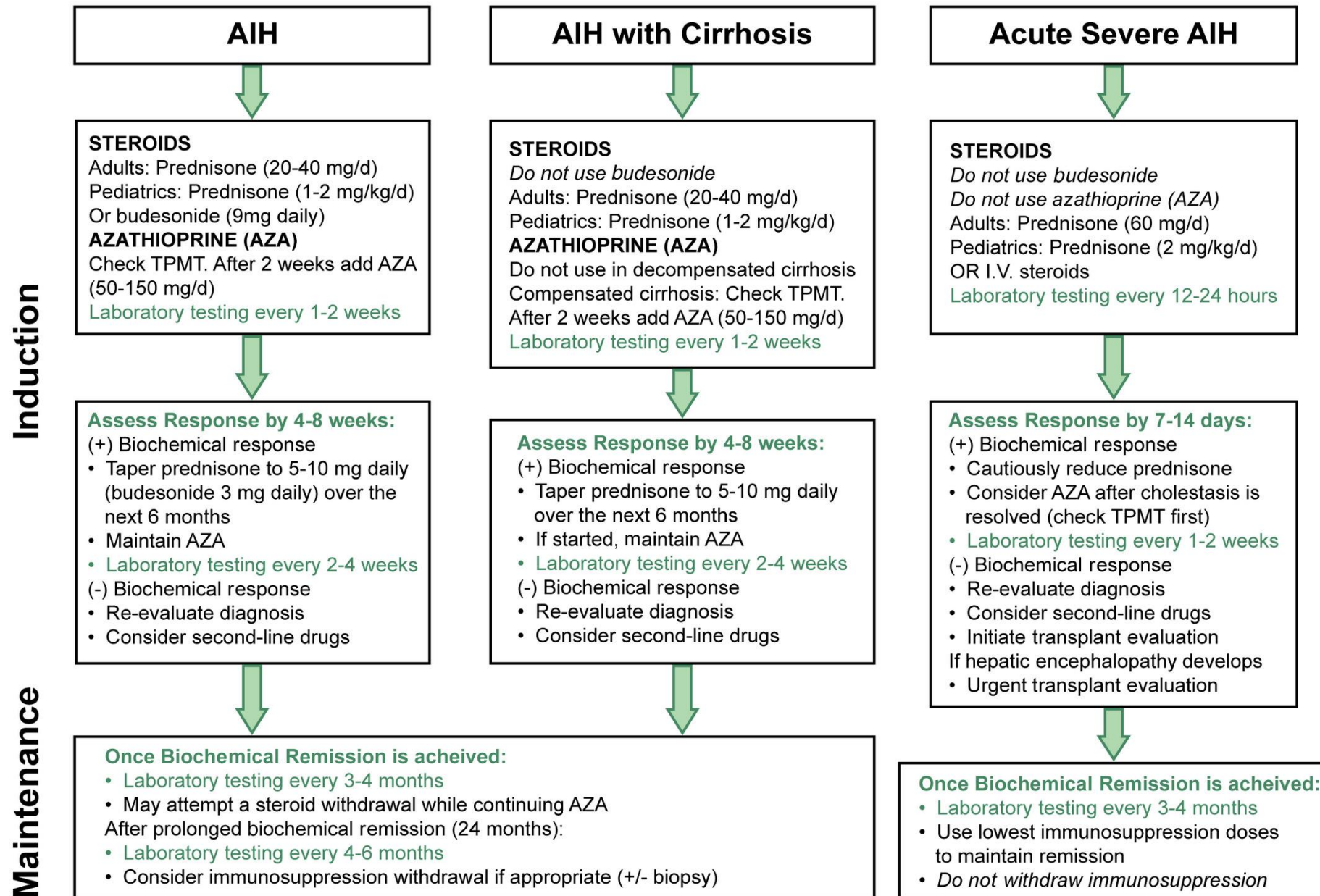
- 1) Budesonide 9mg/d + AZA 50-150mg/d.
  - Avoid in cirrhosis or acute severe AIH.
- 2) Prednisolone 20-40mg/d + AZA 50-150mg/d.
  - AZA can be started with steroids or delayed 2 weeks to assess TPMT and exclude AZA-hepatitis.
  - Stop AZA if cytopenia does not recover in 1-2 weeks.
  - 6-TGN level: 100 and 300 pmol/ $8 \times 10^8$  RBC should be done will loss of response.

## AFTER BIOCHEMICAL REMISSION:

- Reduce gradually prednisolone to 20mg/d (2.5-5 mg every 2-4 weeks) THEN LATER ON to prednisolone 5-10mg/d.
- Prednisolone may be stopped and continue on AZA only.



# First-Line Treatment of AIH



# Duration of therapy & drug withdrawal

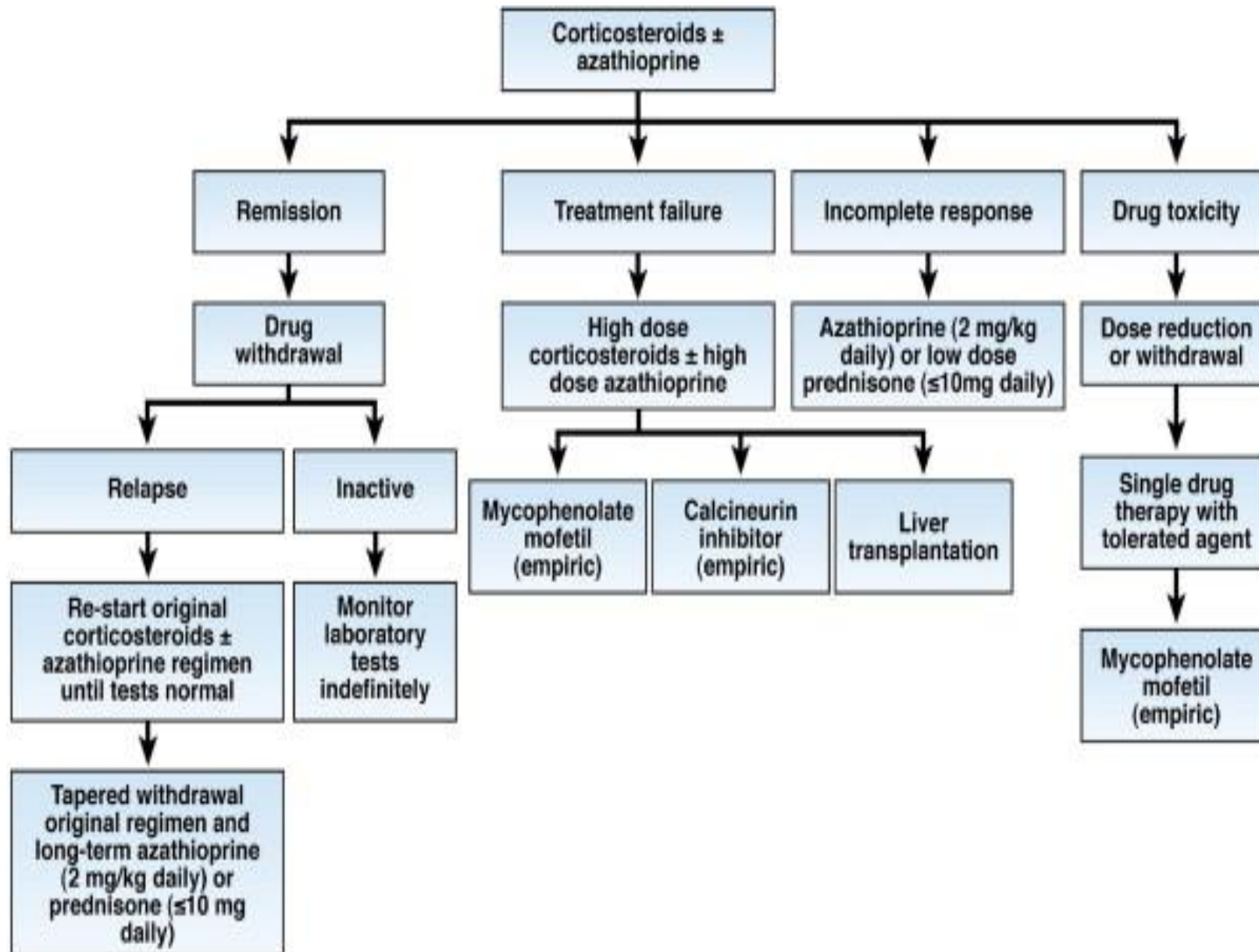
- **Aim:** sustained normal liver functions, IgG and liver histology.
  - LC ➡ chronic ↑ IgG levels
- **Histological lag:**
  - Histological improvement **lags ~8 months after lab improvement.**
  - **50%** of patients with **biochemical remission** have **histological activity.**
- **It is better to have prolonged consolidation treatment**
  - with either low-dose prednisone (2.5–10 mg/day) or 1.5–2 mg/kg AZA.
- **AASLD 2019:**
  - At least **2 years.**
  - Liver biopsy before drug withdrawal is **preferred but not mandatory** in adults.
- **EASL 2015:**
  - At least 3 years or
  - Or at least 24 months after complete normalization of serum transaminases and IgG levels (biochemical remission).
- **Never STOP treatment** except after confirmed histological improvement.
  - 30% 6m relapse after confirmed histological remission.



# Predictors of Treatment Response

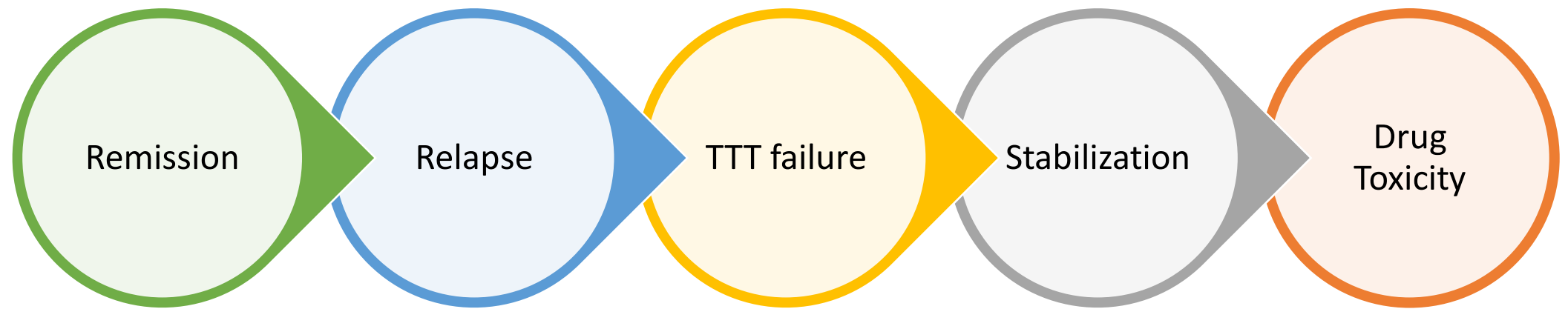
- AST and ALT improvement within 2 weeks.
  - Old patients  $\geq 60$ y and HLA DRB1\*04:01 are associated with rapid response.
- 6-months biochemical remission ➡ ↓ risk of progression to cirrhosis.
- Baseline predictors of biochemical remission:
  - ↑ Ferritin >2.1-fold ULN.
  - IgG <1.9-fold ULN.
- Baseline predictors of histological activity:
  - ↓ Vitamin D: histological severity, poor treatment response, progression to cirrhosis
  - ↑ Angiotensin-converting enzyme: correlates with fibrosis







# Pattern of treatment response



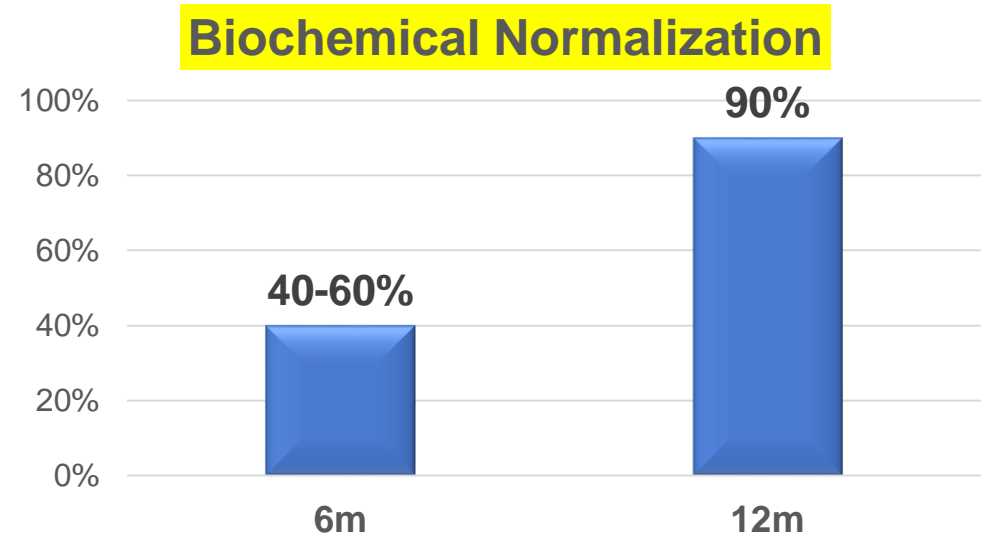
# Remission

## A. Old refuted concept:

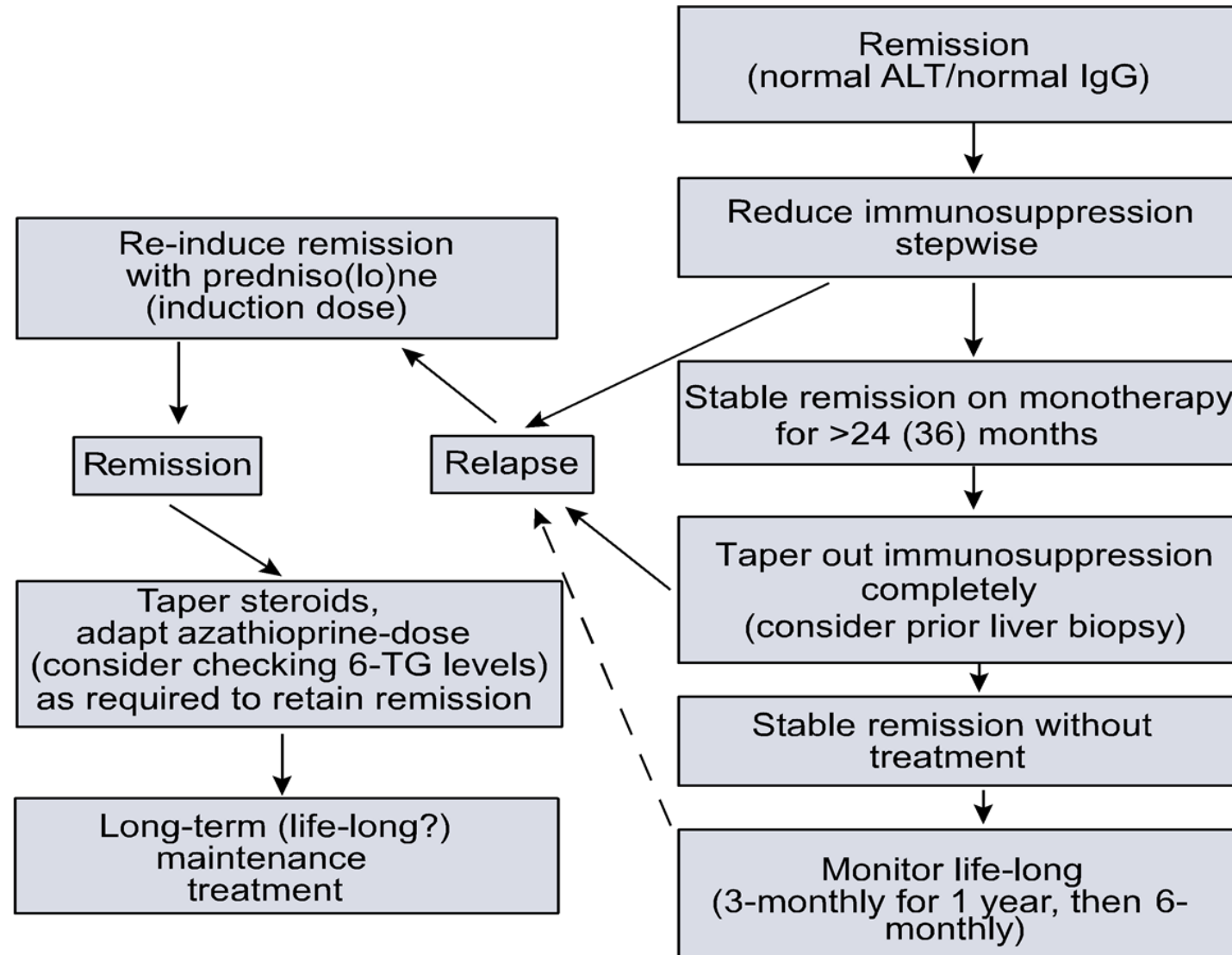
- AST <2ULN.
- 80% remission.

## B. New concept:

- **Biochemical and histological normalization.**
  - 80% of patients will achieve normalization of transaminases and IgG levels.
  - HAI score of <4/18 is used to define histological remission
- **20% remission.**
- **Remission is confirmed only after histological normalization.**
  - 50% of patients with biochemical remission have active histology.
  - Remission can be sustained with azathioprine monotherapy of 2 mg/kg bodyweight.
- **Strict follow up is needed to detect early relapse**



# Follow-up of autoimmune hepatitis patients who have achieved remission

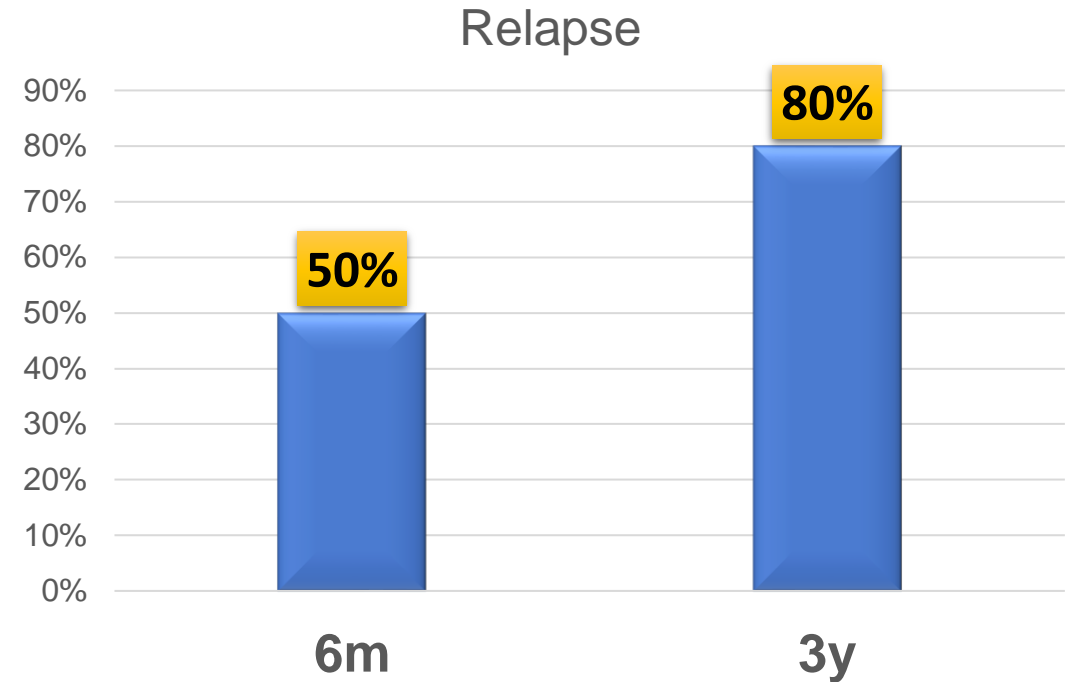


EASL. EASL Clinical Practice Guidelines: Autoimmune hepatitis. Journal of Hepatology 2015; 63:971-1004.



# Relapse

- It is **recurrence** of the clinical symptoms, biochemical and histological derangement.
- It is seen after steroid withdrawal or stoppage (50-90%).
  - **Adults**: 50-85%.
  - **Children**: 60-80%.
- **<20% of patients** can stop treatment successfully
- It is diagnosed by liver biopsy.
- Effect of relapse:
  - Progression to cirrhosis (30%) and liver failure (10%).
  - **Multiple relapses**: rapid cirrhosis and decompensation



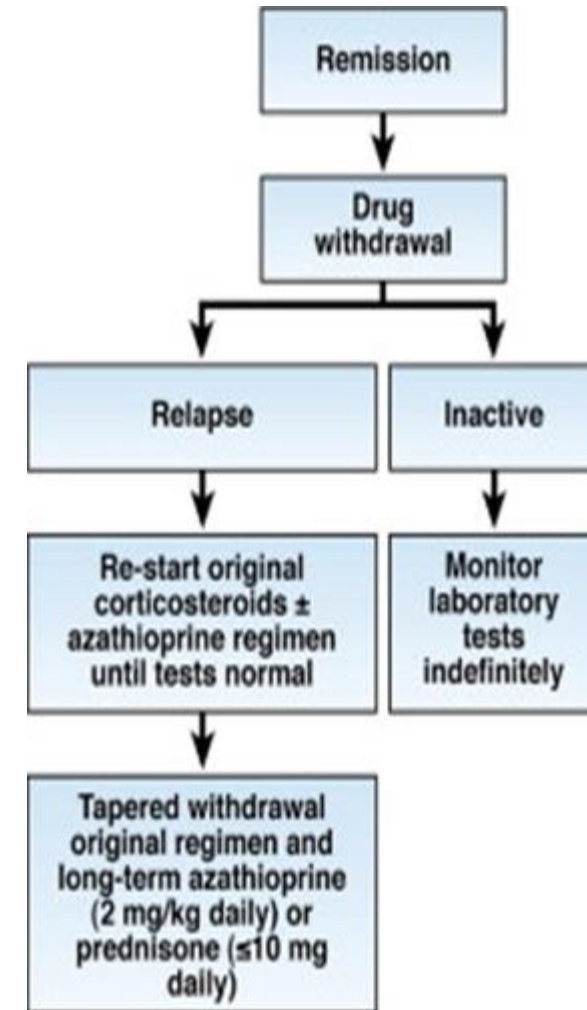
## PREDICTORS OF RELAPSE:

- Duration and completeness of inactive disease prior to treatment withdrawal.
- Psychological stress, concurrent autoimmune disease, treatment with multiple agents,
- Increased serum ALT and IgG levels at drug withdrawal, portal plasma cells in the liver tissue pre-withdrawal, delayed biochemical remission, and prednisolone monotherapy.



# Relapse management

- Reinduction of remission:
  - Use the regimen used for naïve patient.
  - After biochemical improvement, give AZA 2mg indefinitely to avoid multiple relapses.
  - Most relapsers have cirrhosis.
  - If AZA is contraindicated, give 7.5-10mg prednisolone.



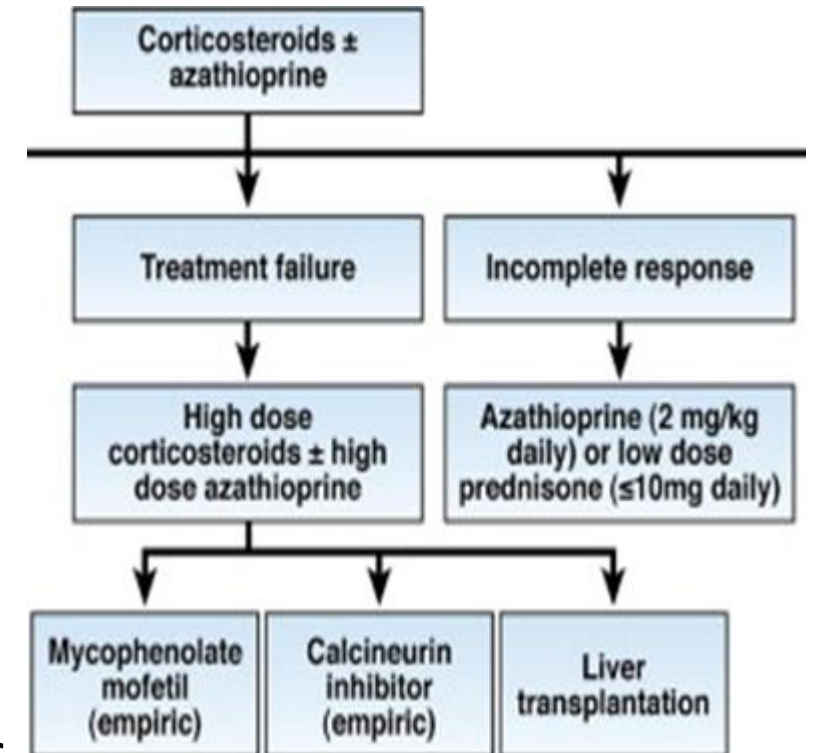
# Treatment Failure

- It is progression of the clinical, biochemical and histological parameters.
- 10% of patients had treatment failure.
- Recheck:
  - Diagnosis.
  - Patient compliance.
  - Co-diseases as viral.
  - AZA level: TGN concentrations  $>220$  pmol per  $8 \times 10^8$  red blood cells  
➡➡ remission.



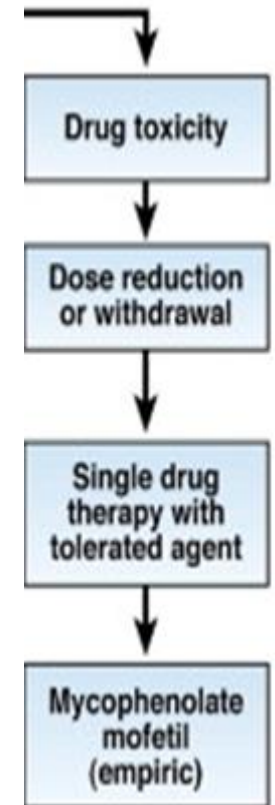
# Treatment Failure management

- **Regimens:**
  - **Pulse therapy** for acute severe cases.
  - **High-dose prednisone:** 60 mg daily.
  - **Drug combination:** prednisone 30 mg + AZA 150 mg daily.
  - **After improvement** reduce steroids by 10mg and AZA 50mg till the conventional maintenance doses.
- **Salvage therapy:**
  - 6-mercaptopurine 25–75 mg/day (few studies)
  - Mycophenolate mofetil (1-2 g/day).
  - Calcineurin inhibitors as tacrolimus.
  - Biologics (rituximab, infliximab).
  - Assess for liver transplantation.
- **AASLD 2019:** failed 1<sup>st</sup> line agents ➡ trial of MMF 1<sup>st</sup> or tacrolimus.



# Drug Toxicity

- Effect of drug toxicity: reduction of doses or withdrawal  
➡ ⬆ relapse or treatment failure.
- Steroids toxicity:
  - Add AZA to steroid regimen to spare steroids.
  - Switch to AZA monotherapy 2mg/kg.
- AZA toxicity:
  - Switch to steroids monotherapy.
  - Switch to other drug groups as tacrolimus.
- **AASLD 2019:** failed 1<sup>st</sup> line agents ➡ trial of MMF 1<sup>st</sup> or tacrolimus.





- **Infliximab 5mg/kg:**
  - It is anti-TNF.
  - It was effective as a rescue therapy.
- **Rituximab:**
  - It is anti CD 20.
  - Case reports: a good rescue drug.
- **Thioguanine** to AZA intolerant patients.
- **Belimumab:** anti BAFF.
- **AASLD 2019:**
  - Anti-TNF and anti-CD20 are possible alternative therapies after first-line and second-line regimens have failed, but the data supporting their use are limited.

# Incomplete response “stabilization”

- It is partial remission.
- Incidence: 15%
- Management:
  - Long term steroids.
  - Long term AZA.
  - MMF and calcineurin inhibitors.
  - Check for liver transplantation.
- **AASLD 2019:**
  - Failed 1<sup>st</sup> line agents ➡ trial of MMF 1<sup>st</sup> or tacrolimus.



|                            | Conventional treatments   |   | Possible empiric treatments  |   |
|----------------------------|---|---|--|---|
|                            | 1st choice  | 2nd choice  | 3rd choice   | 4th choice  |
| <b>Treatment failure</b>   | ☯ Prednisone (30 mg daily) and azathioprine (150 mg daily), or prednisone alone (60 mg daily)       | ☯ Prednisone (30 mg daily) plus mercaptopurine (1.5 mg/kg body weight daily)                        | ☯ Ciclosporin (5–6 mg/kg body weight daily) or prednisone (30 mg daily) plus mycophenolate mofetil (2 g daily) | ☯ Tacrolimus (4 mg twice daily)                         |
| <b>Drug toxicity</b>       | ☯ Azathioprine (2 mg/kg body weight daily) if prednisone intolerant                                 | ☯ Prednisone (20 mg daily) if azathioprine intolerant   | ☯ Budesonide (3 mg twice daily)  | ☯ UDCA (13–15 mg/kg body weight daily)                  |
| <b>Incomplete response</b> | ☯ Prednisone maintenance (10 mg daily) if serum AST level <three times normal value                 | ☯ Azathioprine maintenance (2 mg/kg body weight daily) if serum AST level <three times normal value | ☯ Budesonide maintenance (3 mg twice daily)  | ☯ UDCA maintenance (13–15 mg/kg body weight daily)      |
| <b>Relapse</b>             | ☯ Azathioprine maintenance (2 mg/kg body weight daily) if serum AST level <three times normal value | ☯ Prednisone maintenance reduced to (10 mg daily) if serum AST level <three times normal value      | ☯ Mycophenolate mofetil maintenance (2 g daily)  | ☯ Ciclosporin maintenance (5–6 mg/kg body weight daily) |



# Salvage Therapy

| Drug                             | Dose                                   | Actions  | Experience   |
|----------------------------------|--|--|--|
| <b>Ciclosporin</b>               | 3-5 mg/kg body weight daily            | Calcineurin inhibitor; impairs transcription of IL-2; prevents T-lymphocyte proliferation; increases hepatic TGF-        | Empiric first-line therapy in children and adults; empiric salvage therapy   |
| <b>Tacrolimus</b>                | 3-5mg twice daily                      | Calcineurin inhibitor; impairs transcription of IL-2; limits expression of IL-2 receptors; increases hepatic TGF-        | Beneficial in two small clinical experiences   |
| <b>Mycophenolate mofetil</b>     | 750-1000 mg twice daily                | Purine inhibitor; independent of thiopurine methyltransferase; impairs DNA synthesis; reduces T-lymphocyte proliferation | Beneficial as steroid-sparing agent in three small clinical experiences  |
| <b>Budesonide</b>                | 3 mg three times daily                 | Corticosteroid actions; high firstpass clearance by liver; metabolites devoid of glucocorticoid activity                 | Effective as frontline therapy of treatment-naive mild disease; not effective for treatment-dependent severe disease |
| <b>Anti-TNF mAb (Infliximab)</b> | 5 mg/kg body weight<br>Every 2-8 weeks | Active metabolites of azathioprine   | Infections<br>Induction of immune mediated liver injury  |
| <b>Rituximab</b>                 | 2x1000 mg infusions<br>Day 1 and 15    | Chimeric monoclonal anti-CD20 antibody that induces B-lymphocyte depletion   | Improvement in one patient   |



# New Treatment

**TABLE 2. APPLICATIONS OF IMMUNOPATHOGENESIS INSIGHTS TO PROPOSED NOVEL TREATMENTS IN AIH**

| Approach                 | Agent(s)   | Goal   |
|--------------------------|--|--|
| Treg adoptive transfer   | • <i>Ex vivo</i> generation and expansion of antigen-specific and -independent Tregs | Suppression of inflammation, long-term restoration of tolerance                                  |
| Treg expansion           | • Infusion of low-dose IL-2  | Expansion of suppressive Treg populations in the liver, long-term restoration of tolerance       |
| CD20 depletion           | • Anti-CD20  | Reduction in plasma cell activity and cross-presentation of self-antigen from B cells to T cells |
| BAFF receptor antagonism | • BAFF receptor antibody   | Reduction in B cell survival and cross-presentation of self-antigen from B cells to T cells      |

**Table 5.** Ongoing trials with new drugs in autoimmune hepatitis (AIH).

| Study name/NCT number | Study drug                | Treatment target                    | No. of patients | Primary endpoint                     |
|-----------------------|---------------------------|-------------------------------------|-----------------|--------------------------------------|
| AMBER/NCT03217422     | VAY736/ianalumab          | B-cell activating factor            | 80              | ALT normalization after 24 weeks     |
| NCT02556372           | JKB-122                   | Toll-like receptor 4                | 20              | Changes in ALT levels after 24 weeks |
| MERLIN/NCT02997878    | Mesenchymal stromal cells | Various immunomodulatory properties | 56              | Dose finding/safety                  |

- Assis DN. Immunopathogenesis of Autoimmune Hepatitis. Clinical Liver Disease 2020; 15:129-32.
- Pape et al. Clinical management of autoimmune hepatitis. United European Gastroenterology Journal 2019; 7:1156-63.



# AIH Special Conditions

# Acute Severe AIH or ALF due to AIH

|                  |   |
|------------------|---|
| Acute severe AIH | Jaundice, INR $> 1.5 < 2$ , no encephalopathy; no previously recognized liver disease                             |
| ALF              | INR $\geq 2$ ; hepatic encephalopathy within 26 weeks of onset of illness; no previously recognized liver disease |

- Acute severe AIH:
  - Prednisolone: 0.5-1 mg/kg/d.
  - If no response after 2 weeks ➡ LT evaluation.
- AIH and ALF:
  - Steroids do not increase survival.
  - MELD  $> 40$  ➡ poor survival.
  - Steroids may be deleterious in patients with severe decompensation.
  - Refer to LT center.



# DILI vs AIH

| Definite Association | Probable Association | Possible Association                  |
|----------------------|----------------------|---------------------------------------|
| ▪ Minocycline        | ▪ Propylthiouracil   | ▪ Ipilimumab (anti-CTLA-4)            |
| ▪ Nitrofurantoin     | ▪ Isoniazid          | ▪ Tremelimumab (anti-CTLA-4)          |
| ▪ Infliximab         | ▪ Diclofenac         | ▪ Nivolumab (anti-PD-1)               |
| ▪ Alpha-methyldopa   | ▪ Etanercept         | ▪ Pembroluzimab (anti-PD-1)           |
| ▪ Adalimumab         | ▪ Atorvastatin       | ▪ Atezolizumab (anti-PD-L1)           |
| ▪ Halothane          | ▪ Rosuvastatin       | ▪ Black cohosh (herbal medicine)      |
| ▪ Oxyphenisatin      | ▪ Clometacine        | ▪ Dai-saiko-to (herbal medicine)      |
| ▪ Dihydralazine      |                      | ▪ Germander (herbal medicine)         |
| ▪ Tienilic acid      |                      | ▪ Hydroxycut (nutritional supplement) |
|                      |                      | ▪ Trichloroethylene (toxin)           |
|                      |                      | ▪ Papaverine                          |
|                      |                      | ▪ Indomethacin                        |
|                      |                      | ▪ Imatinab                            |

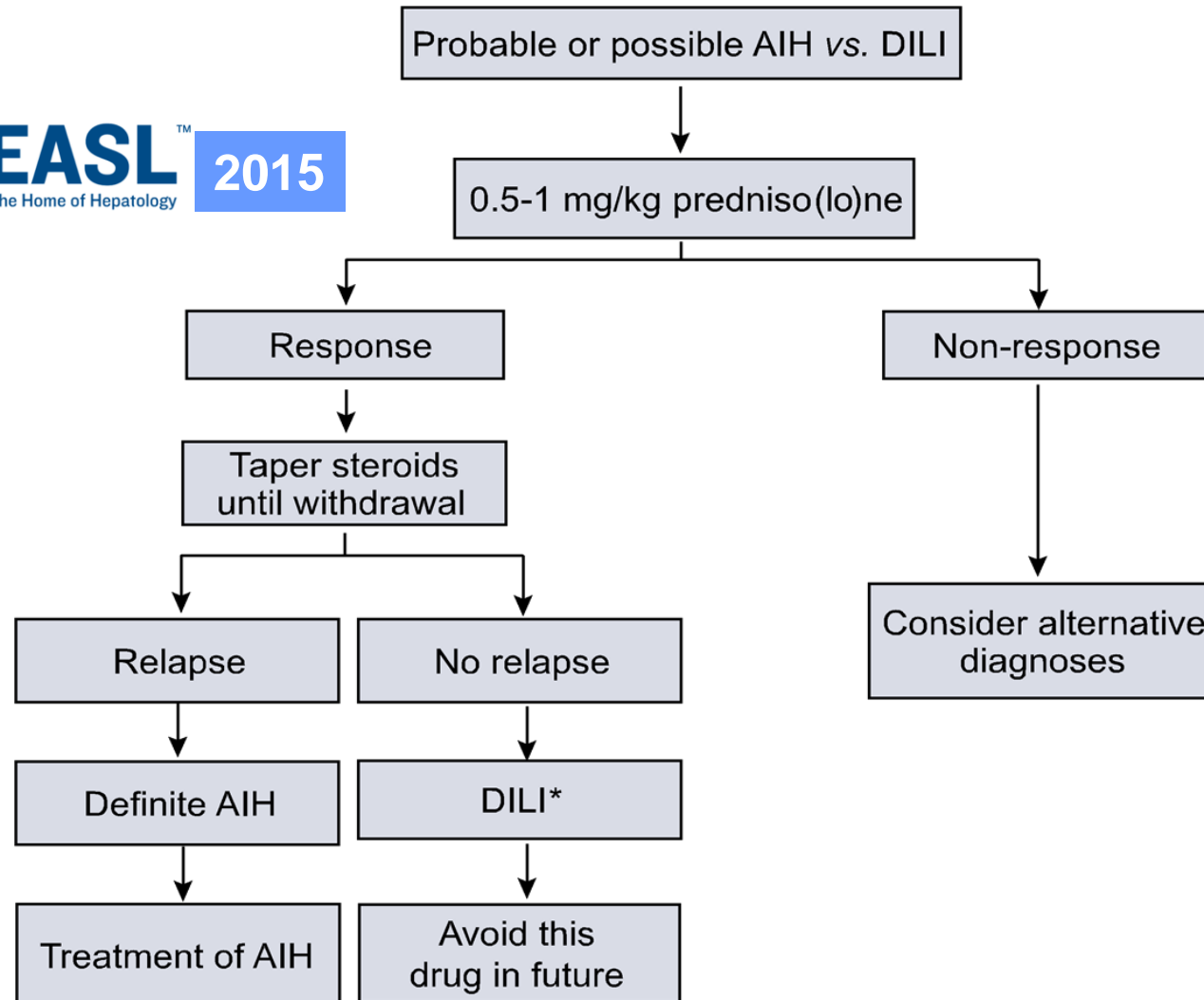
- DILI with a strong immunoallergic component mimicking AIH
- AIH mimicking as DILI due to drug exposure in recent weeks and spontaneous improvement after cessation of drug exposure
- AIH triggered by an offending drug (DILI-induced AIH)



# DILI vs AIH

| Clinical Features                            | Drug Induced AIH-Like Injury  | AIH  |
|--|---|--|
| Gender                                       | <ul style="list-style-type: none"> <li>Mainly women</li> </ul>                          | <ul style="list-style-type: none"> <li>Female predominance, but men also affected</li> </ul> |
| Acute onset                                  | <ul style="list-style-type: none"> <li>Majority (&gt;60%)</li> </ul>                    | <ul style="list-style-type: none"> <li>&lt;20%</li> </ul>                                    |
| Hypersensitivity (fever, rash, eosinophilia) | <ul style="list-style-type: none"> <li>Up to 30%</li> </ul>                             | <ul style="list-style-type: none"> <li>Unusua</li> </ul>                                     |
| Temporal relationship with drug              | <ul style="list-style-type: none"> <li>Positive</li> </ul>                              | <ul style="list-style-type: none"> <li>Negative</li> </ul>                                   |
| HLA DRB1*03:01 or DRB1*04:01 association     | <ul style="list-style-type: none"> <li>None</li> </ul>                                  | <ul style="list-style-type: none"> <li>Common</li> </ul>                                     |
| Concurrent autoimmune diseases               | <ul style="list-style-type: none"> <li>Unusual</li> </ul>                               | <ul style="list-style-type: none"> <li>Present in 14%-44%</li> </ul>                         |
| Cirrhosis at presentation                    | <ul style="list-style-type: none"> <li>Rare</li> </ul>                                  | <ul style="list-style-type: none"> <li>28%-33%</li> </ul>                                    |
| Management                                   | <ul style="list-style-type: none"> <li>Stop offending drug ± glucocorticoids</li> </ul> | <ul style="list-style-type: none"> <li>Glucocorticoids with AZA</li> </ul>                   |
| Relapse after drug withdrawal                | <ul style="list-style-type: none"> <li>Rare</li> </ul>                                  | <ul style="list-style-type: none"> <li>60%-87%</li> </ul>                                    |
| Progression to cirrhosis                     | <ul style="list-style-type: none"> <li>Rare</li> </ul>                                  | <ul style="list-style-type: none"> <li>7%-40%</li> </ul>                                     |
| Survival without transplantation             | <ul style="list-style-type: none"> <li>90%-100%</li> </ul>                              | <ul style="list-style-type: none"> <li>10-year survival, 89%-91%</li> </ul>                  |

# DILI vs AIH



- Stop offending drug and watch recovery within 1-3 months.
- Fulfilled Hy's criteria (>3fold ULN ATs and >2fold ULN bilirubin) or deterioration ➔ give steroids.
- Laboratory flare after steroid withdrawal suggest classic AIH



# Pregnancy in AIH

- Effect of AIH:
  - Amenorrhea.
  - Infertility.
  - Case reports of successful pregnancy.
- Effect of Pregnancy on AIH:
  - Pregnancy ➡ ↓ AIH activity  
➡ ↓ immunosuppressive drug doses.
  - Flare occurs postpartum with 1-6m ➡ strict monitoring + ↑ steroids dose.
- Drugs in Pregnancy:
  - **Steroids**: class C.
  - **Azathioprine**: class D. AASLD guidelines  
➡ continue AZA during pregnancy.
  - **MMF (CellCept)**: class ➡ class D to be avoided.

| Medication      | Safety Reports in Pregnancy                           |
|-----------------|---|
| Terlipressin    | Uterine ischemia                                      |
| Octreotide      | No harmful effects noted                              |
| Beta-blockers   | Fetal bradycardia, fetal growth retardation           |
| Lactulose       | No harmful effects noted                              |
| Rifaximin       | No harmful effects noted but limited data             |
| Corticosteroids | Inconsistent association with cleft abnormalities     |
| AZA             | Premature birth                                       |
| MMF             | Birth defects, spontaneous abortion                   |
| TAC             | Premature birth, transient neonatal renal dysfunction |

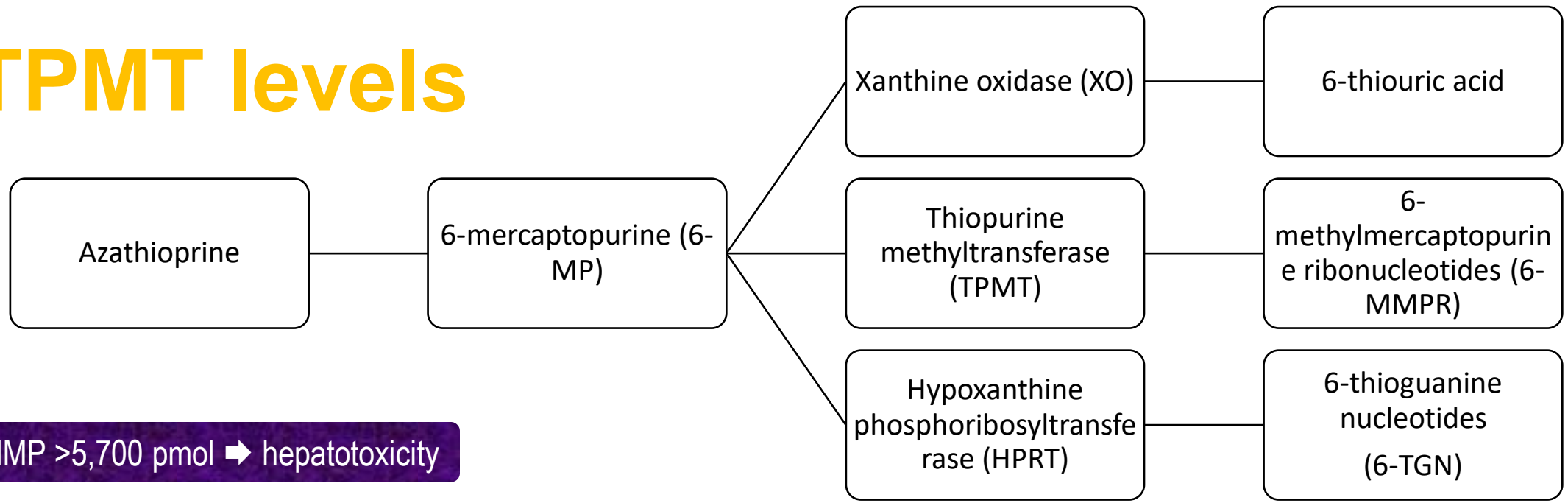


# Hepatocellular carcinoma and AIH

- AIH related cirrhosis ➡ ↑ incidence of HCC.
- **Risk Factors:** cirrhosis  $\geq 10$  years, portal hypertension, continuous inflammation, and immunosuppressive therapy  $\geq 3$  years.
- **Screening** protocols must be applied.
- **Problems:**
  - AIH causes macronodular cirrhosis that is difficult to be distinguished from HCC.
  - Biopsied may be needed.
- **Extrahepatic malignancy** is increased as screening is needed:
  - Cervix, lymphatic tissue, breast, bladder, soft tissue, and skin (non melanoma cancer).



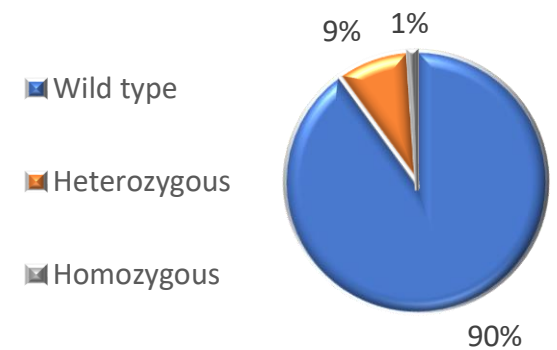
# TPMT levels



6-MMP >5,700 pmol ➔ hepatotoxicity

6TGN level: >220 pg/mL  
 TPMT level  
 TPMT gene mutation

- ↑TPMT function ➔ ↓ 6-TG levels ➔ loss of response
- ↓TPMT function ➔ ↑ 6-TG levels ➔ AZA toxicity
  - Gene mutation.



# Mood disorders

- Patients with AIH have commonly depressive symptoms and anxiety➡:
  - Non-adherence to treatment
  - ↓ health-related quality of life even when in biochemical remission.
- Physicians should actively ask patients about possible symptoms of depression and anxiety and refer them to mental healthcare providers if necessary.



# Liver Transplantation

- Indications:
  - Acute liver cell failure.
  - Decompensated liver cirrhosis.
- Post Tx survival: 80-90%.
- Post Tx events: ↑infections and ↑ rejection risk.
- Post Tx recurrence:
  - Incidence: 20% that increases with time (1y: 10%, 5y: 35-60%%).
  - Risk factors: pretransplant activity, discontinuation of steroids, Type I AIH
  - Controversy: weaning of steroids vs continuous glucocorticoid treatment.
  - AASLD 2019 preferred weaning but weak evidence.
- Treatment:
  - Add prednisolone ±AZA and optimize immunosuppressive levels.
  - Switch tacrolimus to cyclosporin.
  - mTors as salvage therapy.



# De novo or post-transplantation AIH

- Incidence: 3-5%.
- It is **unrelated** to the presence of Tx AIH.
- It is **similar** to classic AIH.
- It causes **graft dysfunction**.
- The Banff working group on liver allograft pathology:
  - “plasma cell–rich rejection” replace the terms “plasma cell hepatitis” and “de novo autoimmune hepatitis,” for graft dysfunction occurring >6 months after transplantation in association with severe lymphocytic cholangitis, plasma cell–rich central perivenulitis, and portal microvascular deposition of complement component 4d
  - This form of graft dysfunction has been described mainly in adult interferon-treated recipients with chronic hepatitis C and distinguishes adults from children with *de novo* AIH. It may be prudent to separate *de novo* AIH from plasma cell hepatitis/rejection.
- Management:
  - Add prednisolone  $\pm$ AZA to CNIs (tacrolimus or cyclosporine).
  - Mycophenolate mofetil.
  - Sirolimus.





| Categories                | Recurrent AIH   | De Novo AIH   |
|---------------------------|---|---|
| Clinical findings         | Graft dysfunction at 2 months-12 years                      | Indication for LT other than AIH  |
|                           | Asymptomatic to graft failure                               | Exclude plasma cell–rich rejection/plasma cell hepatitis  |
|                           | May be detected only by liver biopsy                        |   |
| Laboratory findings       | Increased serum AST, ALT, IgG levels                        | Increased serum AST, ALT, IgG levels  |
| Serological markers       | Same antibodies as pre-LT AIH                               | ANA, SMA, anti-LKM1   |
|                           | ANA, SMA common   |   |
|                           | Anti-LKM1 rare  |   |
| Histologic findings       | Lobular hepatitis, focal necrosis, pseudorosettes (early)   | Interface hepatitis   |
|                           | Interface hepatitis, lymphoplasmacytic infiltration (late)  | Lymphoplasmacytic infiltrates   |
|                           | Lobular collapse, confluent/bridging necrosis (severe)      |   |
| Treatment                 | Predniso(lo)ne, 30 mg daily, and AZA, 1-2 mg/kg daily       | Children <ul style="list-style-type: none"> <li>Predniso(lo)ne (1-2 mg/kg, &lt;60 mg daily) and AZA (1-2 mg/kg daily)</li> <li>Otherwise same as recurrent AIH adults</li> <li>Same as recurrent AIH</li> </ul> |
|                           | Predniso(lo)ne dose reduction to 5-10 mg daily in 4-8 weeks |   |
|                           | Predniso(lo)ne and AZA maintenance                          |   |
|                           | Continue calcineurin inhibitor                              |   |
| Rescue regimens (empiric) | MMF for AZA   | MMF for AZA   |
|                           | Switch calcineurin inhibitor                                | Rapamycin   |
|                           | Rapamycin   |   |
| Outcomes                  | 5-year patient survival, 86%-100%                           | Better in children than adults  |
|                           | Graft failure, 8%-50%                                       | Biochemical remission, 86%  |
|                           | Retransplantation, 33%-60%                                  | Retransplantation, 8%   |
|                           | Recurrent AIH in retransplanted liver, 33%-100%             | Patient survival, 95%   |

# AIH-Viral Hepatitis

- **Pre-DAA era:**

- It was difficult to differentiate AIH from HCV-hepatitis on liver biopsy and required expert hepatology pathologist.
- **Pegylated IFN** activates AIH as being immunomodulatory.
- **Steroids/AZA** activates HCV replication.
- **Steroids/AZA** activates HBV replication.
- It was a dilemma.

- **Post-DAA era.**

- HCV can be cured with 2-3month DAAs.
- **If AIH-Viral hepatitis:** first treat HCV with DAAs then begin steroids.
- The problem was solved.



# Overlap Syndrome and antibody negative hepatitis

- They will be discussed in a separate lecture.



| Goal   | Treatment  | Mechanism of Action   | Status of Development   |
|--|--|---|---|
| Decrease the numbers and/or functions of autoimmune effector cells and pathogenic autoantibodies | Immunosuppressive drugs: CNI, mTOR, antiproliferative agents | Inhibit proliferation of autoantigen-activated CD4 and CD8 T cells by reducing the amount and/or signaling of mitogenic IL-2 or block completion of T-cell division | SOC in multiple AI diseases. Combination therapies using subtoxic doses of two or more agents attractive. Ongoing research into prevention and management of toxicities |
|  | Anti-CD20  | B-cell depletion  |   |
|  | Anti-BAFF  | B-cell depletion followed by mobilization of memory B cells from lymphoid tissue. Potent inhibition of BAFF signaling in activated T cells                          | Off-label use as alternative therapy in AIH   |
|  | Anti-BAFF, followed by anti-CD20                             |   | SOC in SLE. Ongoing clinical trial in AIH   |
|  | Anti-CD40  | Depletion of memory B cells mobilized from lymphoid tissues by anti-BAFF  | Clinical trials planned in AI diseases  |
|  | Efgartigimod   | Block CD40-CD40L (CD154) costimulation of T cells and B cells   | POC. Clinical trial initiated in liver transplantation  |
|  | Inhibition of sphingosine-1-phosphate receptors              | First in class antibody fragment to block FcRn to increase IgG clearance and prevent IgG recycling  | POC to reduce pathogenic autoantibodies and Ig–autoantigen immune complexes   |
|  | Myeloid-derived suppressor cells                             | Prevent egress of activated T cells from lymph nodes into blood   | SOC in MS, new agents in development for other AI diseases  |
|  |  | Inhibit autoreactive T-cell activation and proliferation  | POC in preclinical models. Clinical trials planned in RA  |
| Decrease and/or inhibit proinflammatory cytokines  | Anti-TNF $\alpha$ or TNF $\alpha$ -receptor                  | Reduce TNF $\alpha$ -mediated tissue injury and proinflammatory signaling pathways  | SOC in multiple AI diseases. Studied as an alternative therapy in AIH   |
|  | Anti-IL-6 or anti-IL-6R                                      | Reduce pathogenic effects of proinflammatory IL-6 signaling in innate and adaptive immune responses   | SOC in RA, clinical trials ongoing in other AI diseases   |
|  | Anti-IL-12 (p40 subunit)                                     | Reduce pathogenic effects of proinflammatory IL-12 signaling in innate and adaptive immune responses  | SOC in psoriasis and Crohn's disease. Also blocks IL-23 signaling   |
|  | Anti-IL-17a or Anti-17R                                      | Reduce pathogenic effects of IL-17  | SOC for psoriasis and psoriatic arthritis. Clinical trials planned in other AI diseases   |
|  | Anti-IL-21   | Reduce multiple pathogenic effects of IL-21 in innate and adaptive immune responses   | Ongoing clinical trials in RA, T1DM, and Crohn's disease  |
|  | Anti-IL-23 (p19 or p40 subunits)                             | Reduce pathogenic effects of proinflammatory IL-23 stimulation of Th17 cells  | SOC in psoriasis and Crohn's disease  |
|  | Anti-Blys  | Reduce pathogenic B-cell selection, differentiation, and homeostasis  | SOC in SLE  |

| Goal   | Treatment  | Mechanism of Action  | Status of Development  |
|--|--|--|--|
| Inhibit signaling of proinflammatory cytokines                               | mTOR inhibition  | Decrease proliferation of activated CD4 and CD8 T cells by inhibiting signaling of IL-2  | SOC in solid organ transplantation and AI diseases. Alternative therapy in AIH   |
|  | Tofacitinib (JAK3 inhibitor of IL-2 signaling)                                 | Decrease proliferation of activated CD4 and CD8 T cells by inhibiting signaling of IL-2  | SOC in RA. Clinical trials planned   |
|  | Baricitinib (JAK1/2 inhibitor of IL-6 and IFN $\gamma$ signaling)              | Reduce pathogenic effects of proinflammatory IL-6 signaling through IL-6R in innate and adaptive immune responses and pathogenic effects of IFN $\gamma$ signaling in NK, NK T, CD4, and CD8 T cells                             | SOC in RA. Ongoing clinical trial in PBC   |
|  | Pacritinib (JAK2 inhibitor of IL-12/IL-23 signaling)                           | Reduce proinflammatory IL-12 and IL-23 signaling that polarizes increases CD4 Th1 polarization, secretion of IFN $\gamma$ and TNF $\alpha$ , cytotoxic activity of NK and CD8 CTLs, and differentiation of pathogenic Th17 cells | POC established. Ongoing clinical trials   |
|  | Filotinib (JAK1 inhibitor of IFN $\alpha$ /IFN $\beta$ signaling)              | Reduce immunopathogenic gene expression induced by type 1 IFNs   | POC established. Ongoing clinical trials   |
|  | Upadacitinib (selective JAK1 inhibitor of IFN $\alpha$ /IFN $\beta$ signaling) | Reduce immunopathogenic gene expression  | SOC for refractory RA  |
| Augment effects of immunosuppressant cytokines                               | rHuIL-10   | Reduce immunopathogenic effects of activated CD4 Th1 cells   | SOC to prevent pancreatitis post-ERCP<br>Trial in UC terminated for concern of Guillain-Barré syndrome   |
| Inhibit transendothelial migration of effector cells from blood into tissues | Inhibition of chemokine receptors or integrins                                 | Prevent tissue inflammation and injury by blocking transendothelial entry of effector cells from blood into target tissues   | SOC inhibition of $\alpha$ 4/ $\beta$ 7 integrin in UC. Clinical trial in PSC ineffective  |
|  |  | Prevent chemokine-induced terminal differentiation of effector cells   | Potential for clinical trials of other Food and Drug Administration–approved chemokine/integrin inhibitors   |
| Establish immunoregulatory control   | Low-dose IL-2 infusion to increase autoantigen-specific iTregs                 | Expansion of preexisting autoantigen-specific iTregs in vivo requires exposure to low concentrations of IL-2   | POC established<br>Clinical trials ongoing   |
|  | Infusion of autoantigen-specific iTregs generated ex vivo                      | Ex vivo generation of autologous autoantigen-specific iTregs followed by infusion to immunologically control autoantigen-specific CD4 Th-cell subset responses   | POC of iTreg generation ex vivo established. Future clinical trials planned in AIH. Viability, function, and distribution of iTregs after infusion unknown |
|  | Inhibition of bromodomain and extraterminal family of proteins                 | Inhibition of disease-specific epigenetic transcriptional enhancers, superenhancers, and enhancer RNA production to decrease autoimmune reactions  | POC established. Clinical trials ongoing   |
|  | Mesenchymal stem cells   | Inhibition of innate immune cells, effector T cells  | POC established. Clinical trials ongoing   |
|  |  | Induction of antigen-specific iTregs   |  |
|  |  | Reduction of TNF $\alpha$ secretion  |  |
| Establish physiologic immunoregulatory state of pregnancy                    | PIF  | Creation of immunosuppressive and immunomodulatory environment of pregnancy  | Phase 1b trial of synthetic PIF in AIH completed. Ongoing clinical trial   |



بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

..... رَبِّ إِنِّي لَمَّا أَنْزَلْتَ إِلَيَّ مِنْ خَيْرٍ فَقِيرٌ ﴿١﴾



A stylized sun graphic on the left side of the slide. It features a large, solid yellow circle representing the sun's disk, with several short, thick yellow dashes of varying lengths radiating from its top-left edge. The background is split: the top-left corner is orange, and the rest is white, separated by a large white arc that curves from the top right towards the bottom left.

# Thanks a lot