# Auto immune hepatitis

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21 t/m 23 juni a.s. zal de Dutch (Flamish) Liver Week plaatsvinden in Hampshire Hotel Fitland Leiden

Radboudumc

# Structure

- Case / clinical presentation
- Diagnosis
- Epidemiology
- Histology
- Genetics
- Natural course
- Treatment
  - When, how, what, stop
- Conclusion

- And of course……..Multiple choice questions

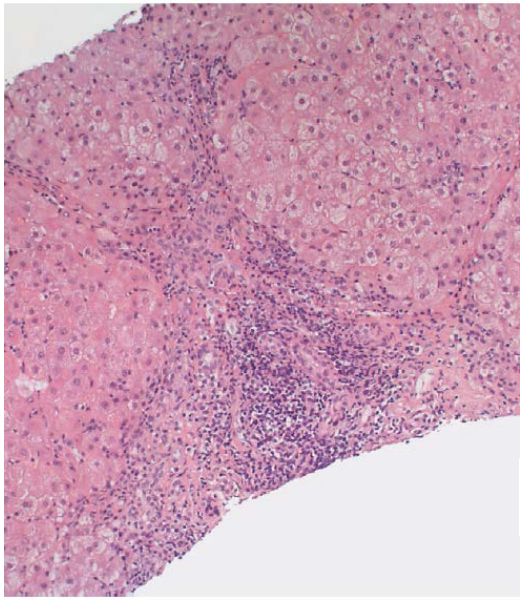
# 1

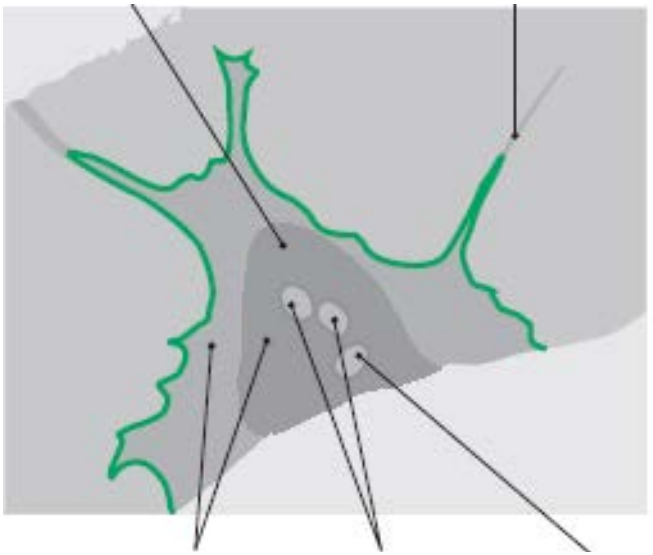
- A 18 yr-old female presents with malaise, fatigue, and myalgias. She mentions that her stools are lighter color than normal. Physical examination is remarkable for jaundice and a liver edge 2 finger breaths below the right costal margin. Her laboratory evaluation reveals a total bilirubin of 224 umol/L, ALAT of 3124 U/L, and an INR of 1.4. You think of autoimmune hepatitis. Which laboratory test is appropriate?

A. Antinuclear (ANA) and antismooth muscle antibodies (ASMA)
B. Antimitochondrial antibodies (AMA) and total lipid profile
C. Antibodies to soluble liver antigen (SLA)
D. Serum IgM
E. Anti liver-kidney-microsomal (LKM-1) antibodies

# Case

- 35-year-old female
- **History**
  - Fatigued, malaise, weight loss 2 kg / 2 months
- **Laboratory**
  - ESR 107 mm/1st hr IgG 50 g/L; ALP 734; IU/L, ALT 533 IU/L; AST 583 IU/L↑; Bil tot. 30 umol/L; GGT 385 IU/L
- **Auto immune serology**
  - ASM (1: 120) ANA (1: 360)
- **Histology**
  - Interface hepatitis
  - Piece meal necrosis





# Clinical Presentation of AIH

**Clinical picture**

- Histology
  - interface hepatitis with plasma cells / lymphocytes
  - Lobular or panacinar necrosis
- Laboratory
  - Predominant aminotransferase elevation
  - Autoantibodies
  - Hypergammaglobulinemia
- Exclusion of other chronic diseases (viral hepatitis)

- Diagnosis is based on four major criteria:
  elevated IgG levels (or total gamma globulins)
  characteristic autoantibodies
  histological features of hepatitis
  absence of viral hepatitis
- Response to immunosuppression is characteristic and supports the diagnosis

J Hepatol 2011 55 j 171–182

# AIH simplified diagnostic criteria

**Work-up (in context of elevated ALT**

- Autoantibodies
- IgG
- Liver biopsy
- Virus serology

| | | Points |
|---|---|---|
| Autoantibodies | ANA or SMA or LKM >1:40 | 1 |
| | ANA or SMA or LKM >1:80<br>SLA/LP Positive (>20 units) | 2 |
| IgG (or gamma-globulius) | Upper normal limit | 1 |
| | >1.10 times normal limit | 2 |
| Liver histology* | Compatible with AIH | 1 |
| | Typical for AIH | 2 |
| Absence of viral hepatitis | Yes | 2 |
| | No | 0 |

≥ 6 probable AIH; ≥7 definite AIH

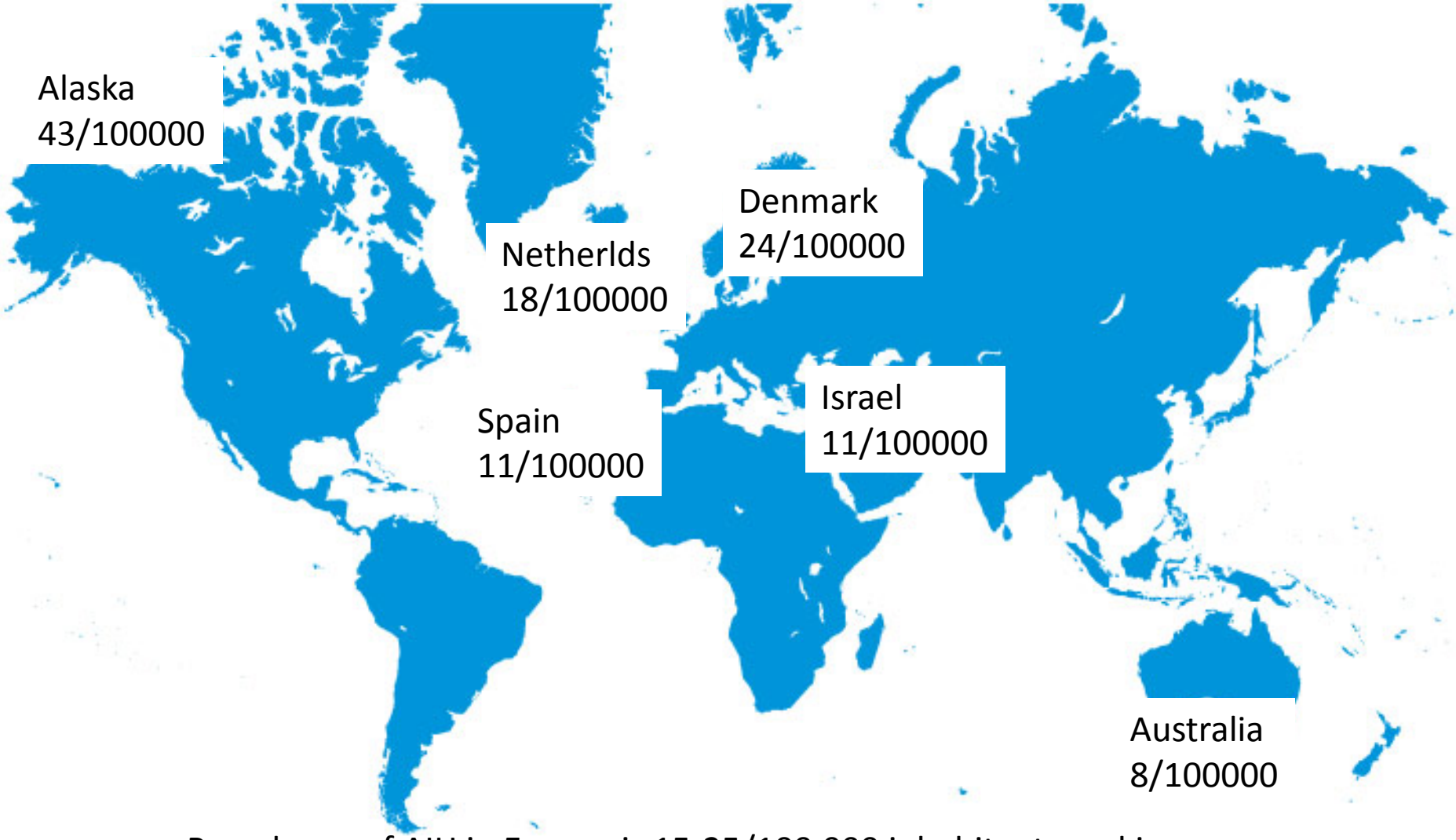
J Hepatol 2011 55, P 171–182

# AIH classification

## autoantibodies based

| AIH type | Autoantibodies | Specifics |
|---|---|---|
| 1 | ANA; SMA | -80% of cases<br>-adults<br>-slow onset |
| 2 | LKM1 LKM3; LC1 | -20% of cases<br>-pediatric<br>-fulminant cases |
| 3 | SLA/LP | similar to type 1<br>-more relapse<br>-more difficult to treat |

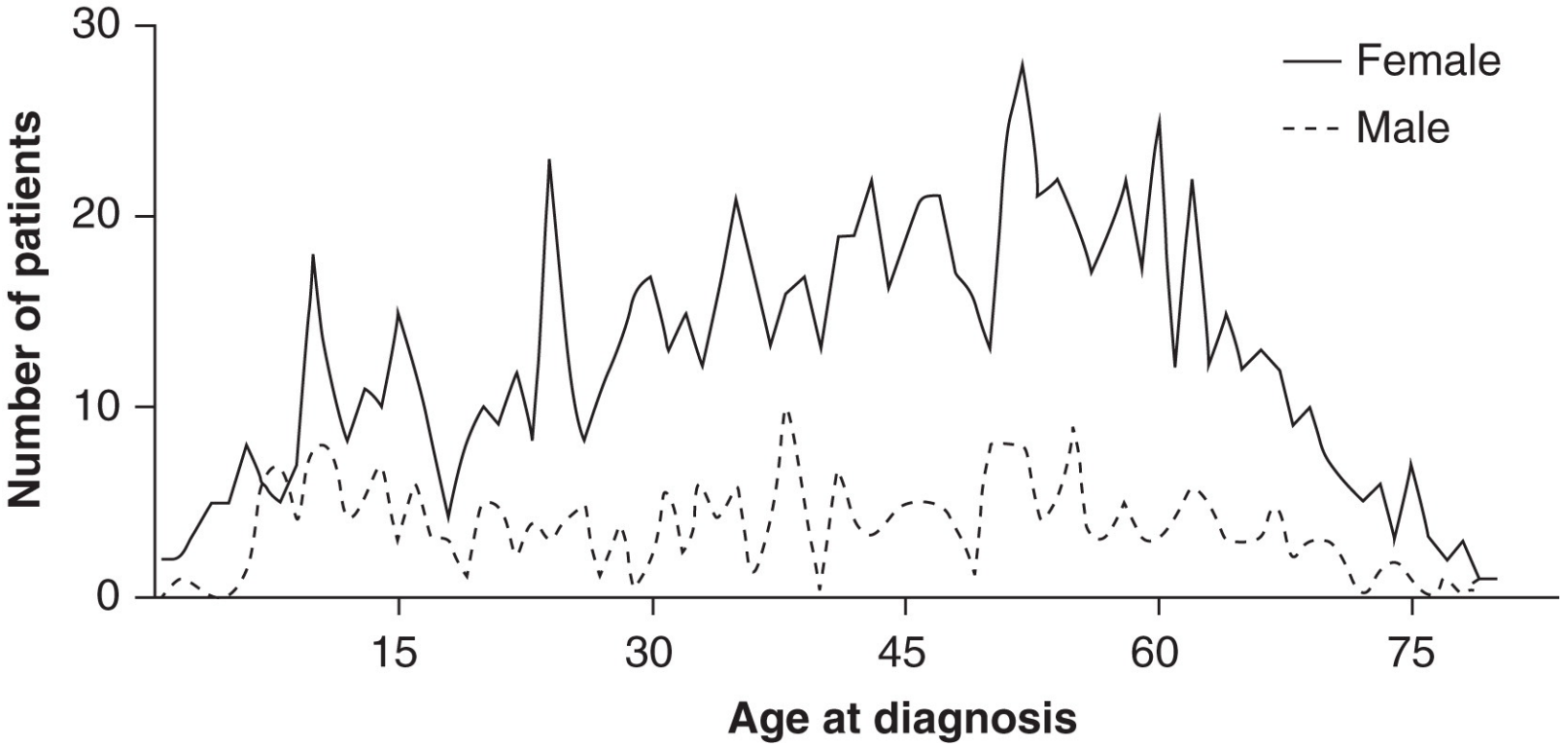
# Global AIH prevalence




Prevalence of AIH in Europe is 15-25/100.000 inhabitants and is increasing in both women and men

CPG AIH J Hep 2015

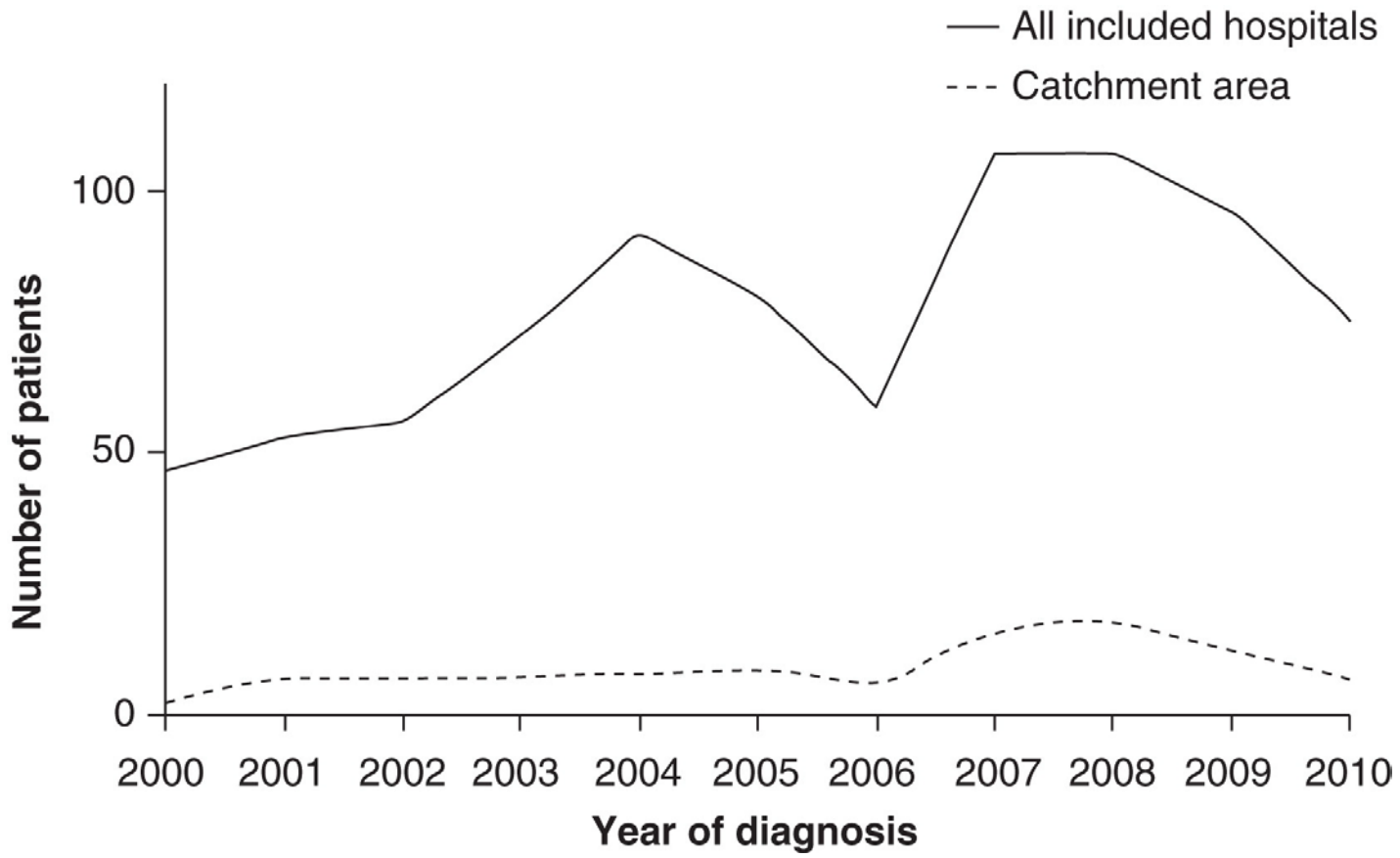
# Age at diagnosis of AIH




Scandinavian Journal of Gastroenterology 2014 ; 49 ;10; 1245

# AIH Incidence:

## Dutch nation wide study




1313 AIH patients (78% females)
Prevalence 18.3/100.000 (95% CI 17.3–19.4)
Annual incidence 1.1/100.000 (95% CI: 0.5–2)

Scandinavian Journal of Gastroenterology 2014 ; 49 ;10; 1245

# 2

- Which diagnostic procedure is a requirement to diagnose autoimmune hepatitis

1. Ultrasound
2. Liver biopsy
3. Magnetic cholangiopancreaticography
4. Fibroscan

# Role of Liver biopsy

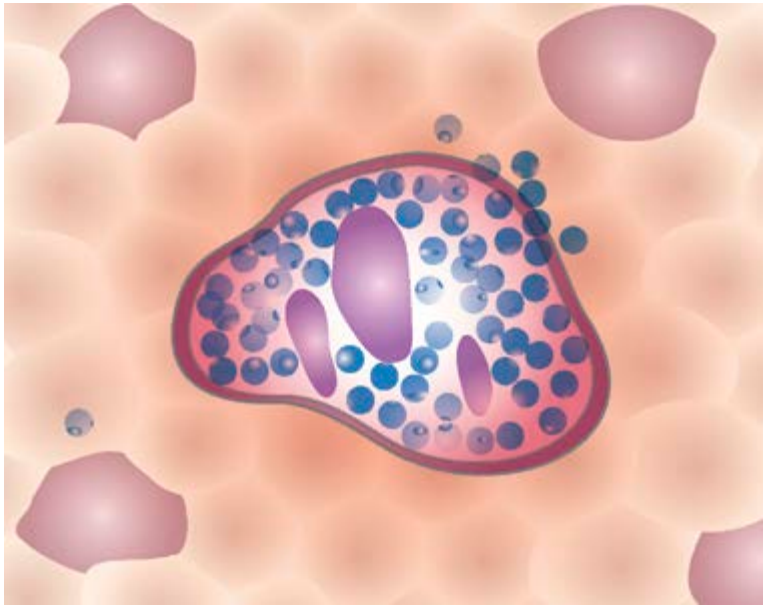
- **Liver biopsy is a prerequisite for the diagnosis of AIH**

- Essential to make or refute diagnosis
- Provides information on prognosis and management
- Excludes other liver diseases (NASH)
- Findings must be compatible rather than typical
- Best measure of disease activity
- Not necessary to confirm the relapse

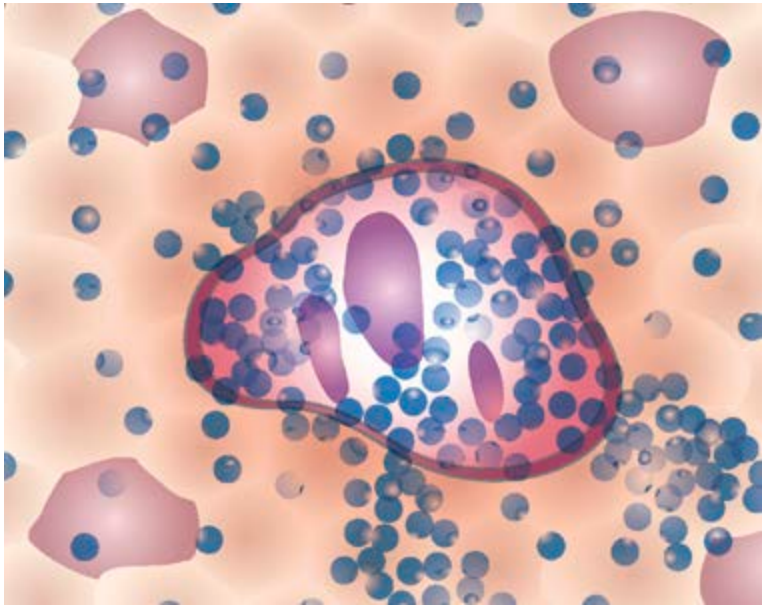
A definitive diagnosis of AIH cannot be established without a liver biopsy

# Portal triad

## Inflammation stages



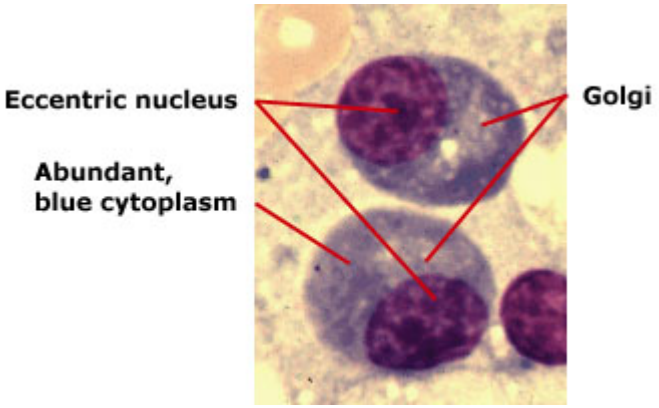
Portal inflammation

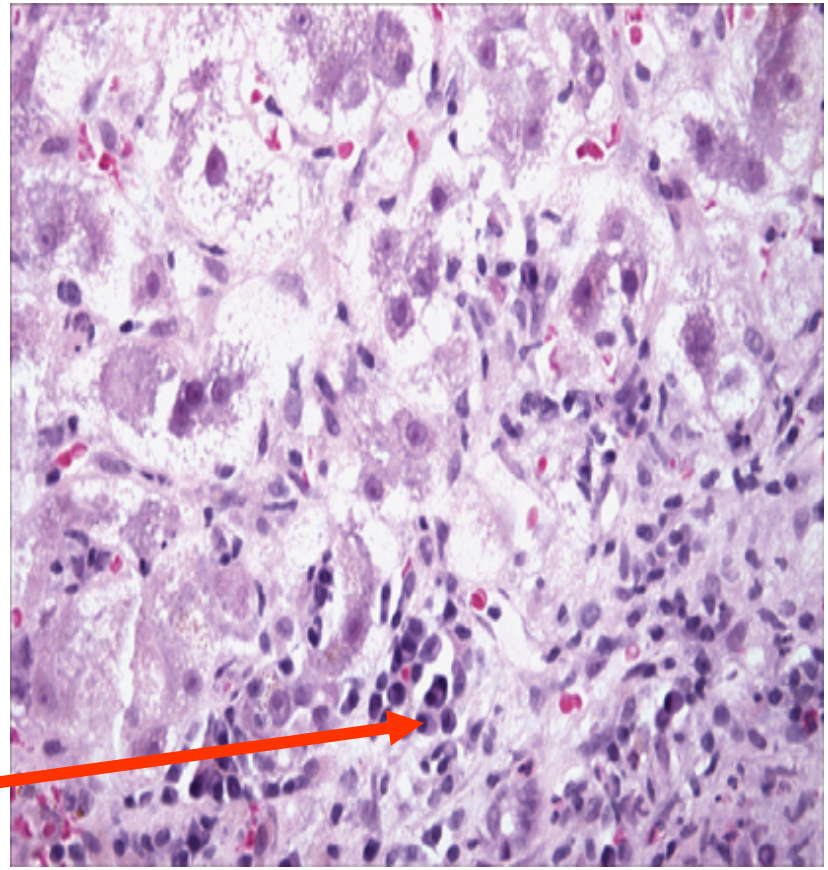


Interface hepatitis / piece meal necrosis

# Autoimmune Hepatitis
# Histology

- Prominent plasma cells



Plasma cells

# Ishak modification hepatic activity index (HAI)

| Item | Score |
|---|---|
| Periportal or periseptal interface hepatitis (piecemeal necrosis) | 0-4 |
| Confluent necrosis | 0-6 |
| Focal (spotty) lytic necrosis, apoptosis and focal inflammation | 0-4 |
| Portal inflammation | 0-4 |

**Clinical Relevance**

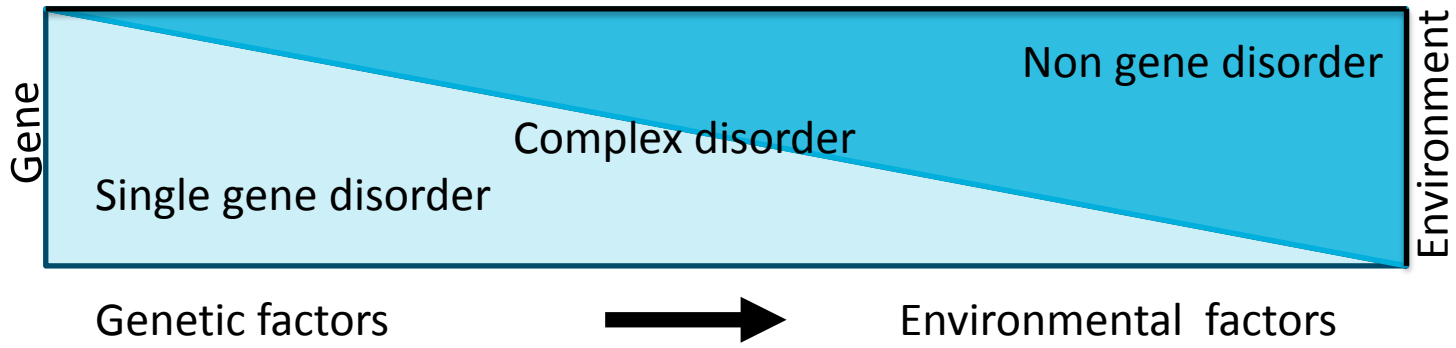
Decisions on start & stop therapy in AIH requires a liver biopsy

- Start therapy if HAI ≥ 4
- Stop therapy (if desired) HAI < 3

# AIH pathogenesis

# AIH & genetics

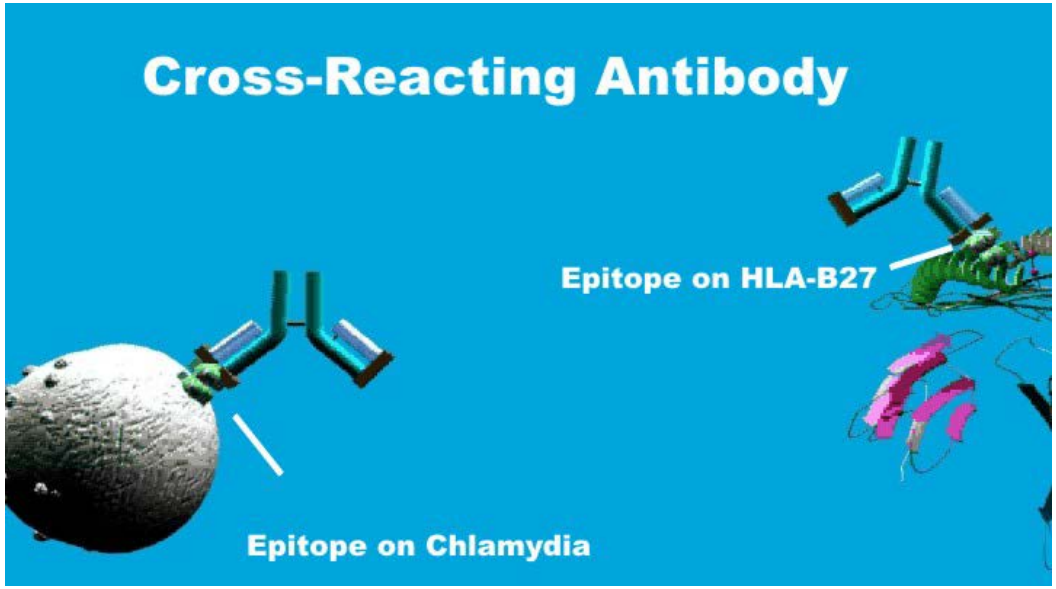
- **AIH: ‘complex trait’ disease**
  - Unknown mode of inheritance & involves one or more genes, operating alone or in concert, and interacts with (environmental) factors to affect risk of AIH




- **Association mapping**
  - Search for sequence variants that are shared among AIH patients

# AIH Pathogenesis

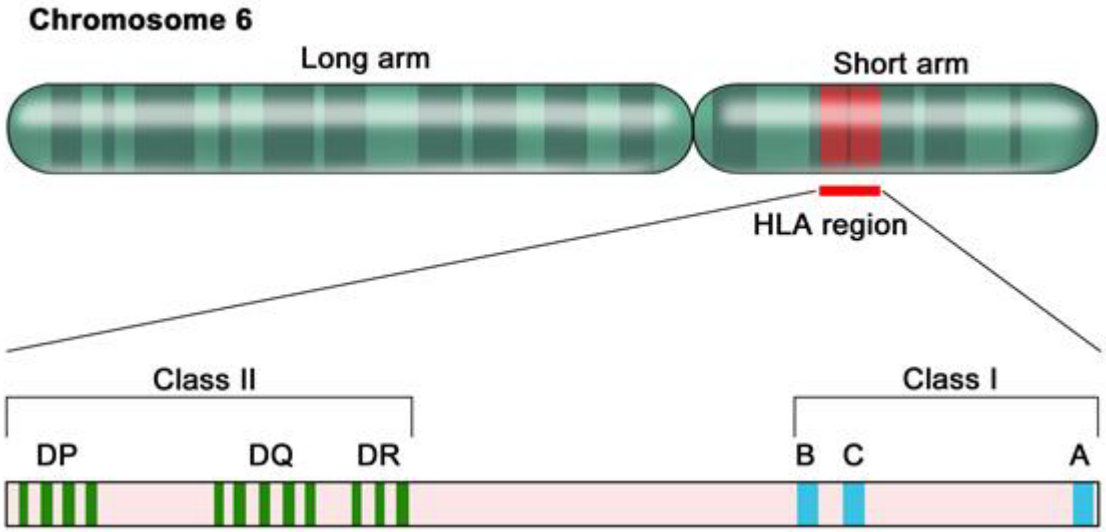
- Foreign antigens resemble self antigens : molecular mimicry
- Repeated or intense exposure to these antigens may override self tolerance and induce auto reactivity
- Apoptosis generates new antigens that perpetuate the inflammation and immune response




Hepatol Int. 2010 Jun; 4(2): 475–493

# The HLA system

- Human Leukocyte antigen (HLA) / major histocompatibility complex (MHC)
- Produces highly polymorphic glycoprotein complexes
- ~ 200 genes on chromosome 6
- 3 clusters
  - MHC class I: HLA-A, HLA-B, HLA-C
  - MHC class II: HLA-DR, HLA-DP, HLA-DQ
  - MHC class III: soluble components

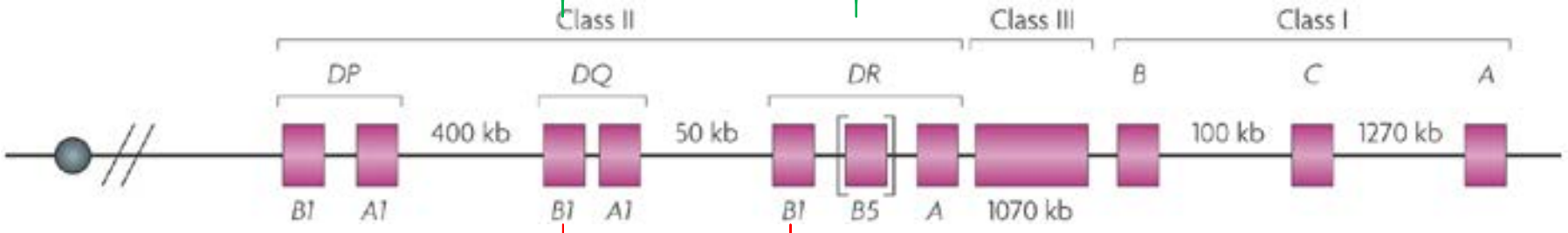


# Contribution of HLA class II to AIH

Protective

DQB1*04
DQB1*0301

DRB5*0101




DQA*0501
DQB*0201
DQB*06

DRB1*0301
DRB1*0401
DRB1*0404
DRB1*0405
DRB1*1301

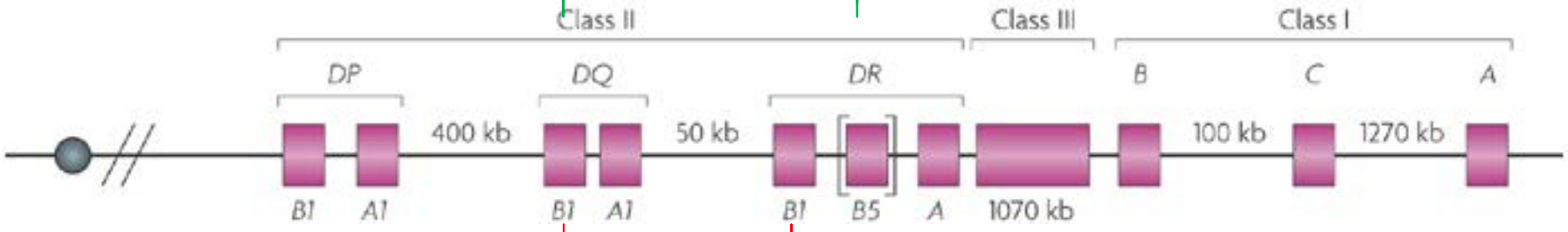
Risk

# Contribution of HLA class II to AIH

Protective

DQB1*04
DQB1*0301

DRB5*0101




DQA*0501
DQB*0201
DQB*06

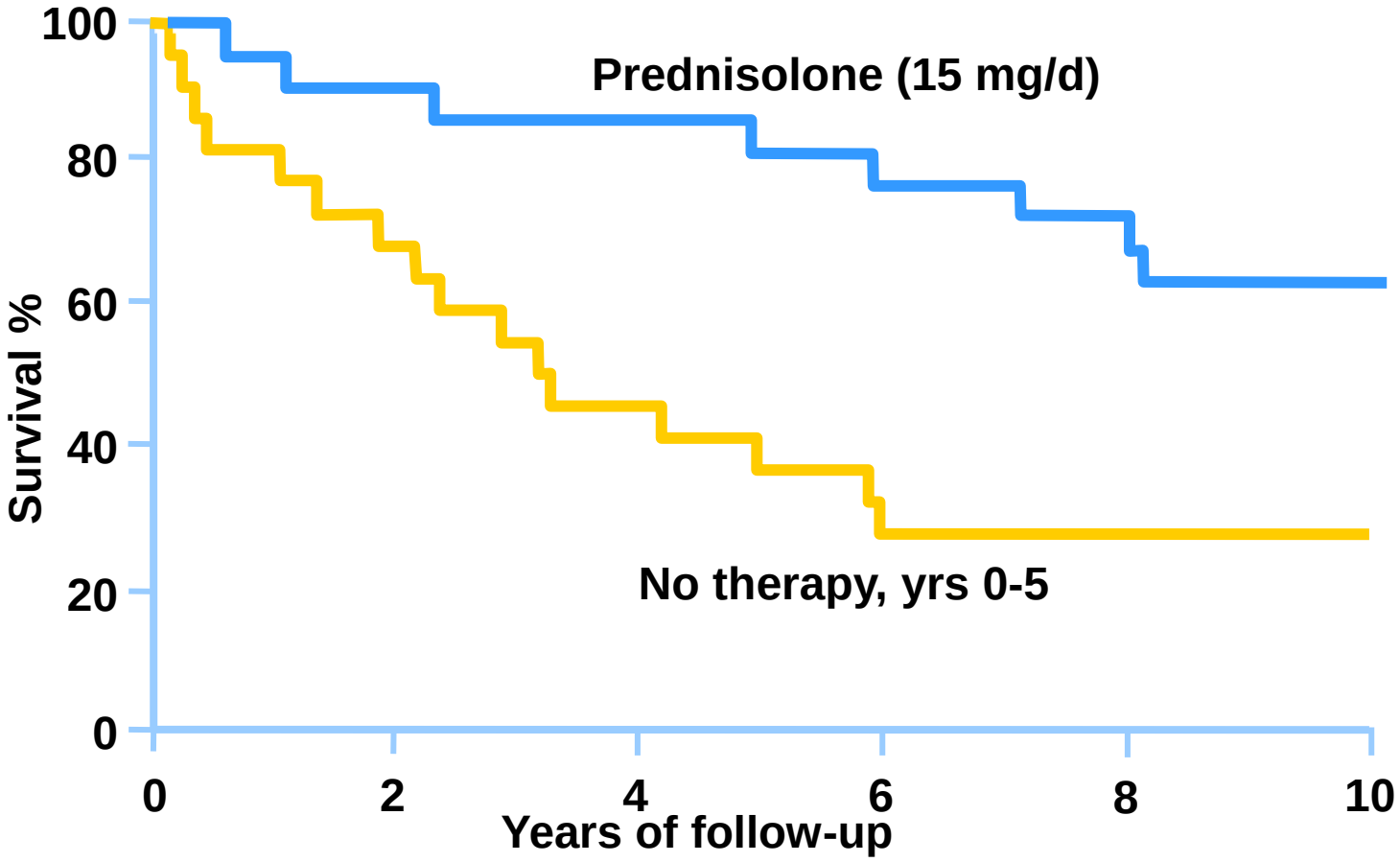
**DRB1*0301**
**DRB1*0401**
DRB1*0404
DRB1*0405
DRB1*1301

Dutch cohort
75%: HLA-DRB1*04:01 or *03:01 positive

Risk

# AIH : Natural course

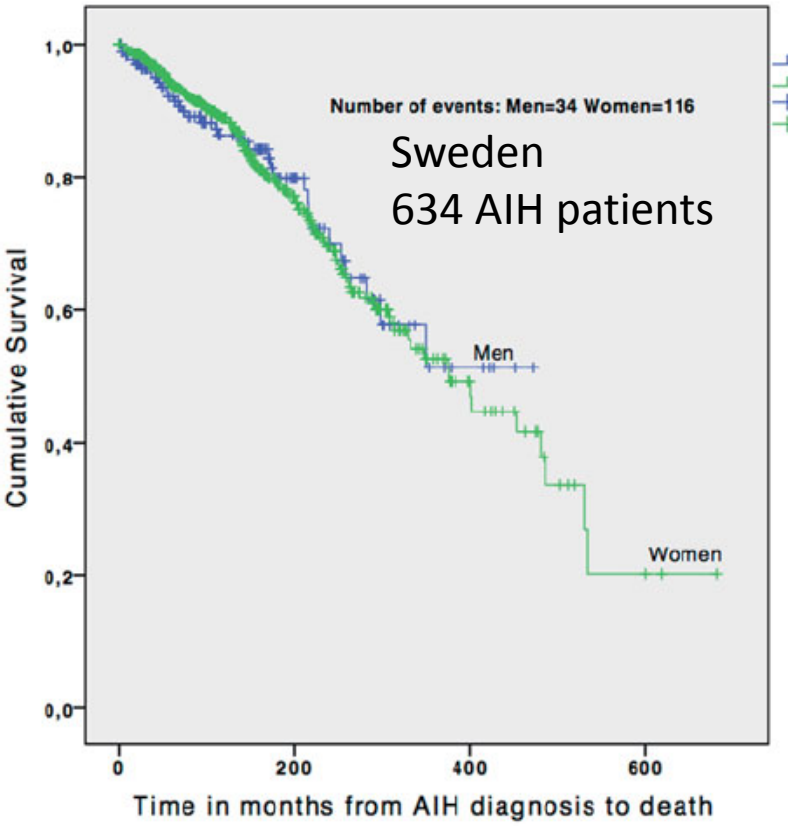
# Natural course of AIH




Cohort of 44 patients (1963-1967)
Untreated symptomatic AIH: 50% 3-5 year mortality rate
Untreated 3.3 yrs vs. Treated 12.2 yrs

Gut, 1980, 21:78

# AIH survival

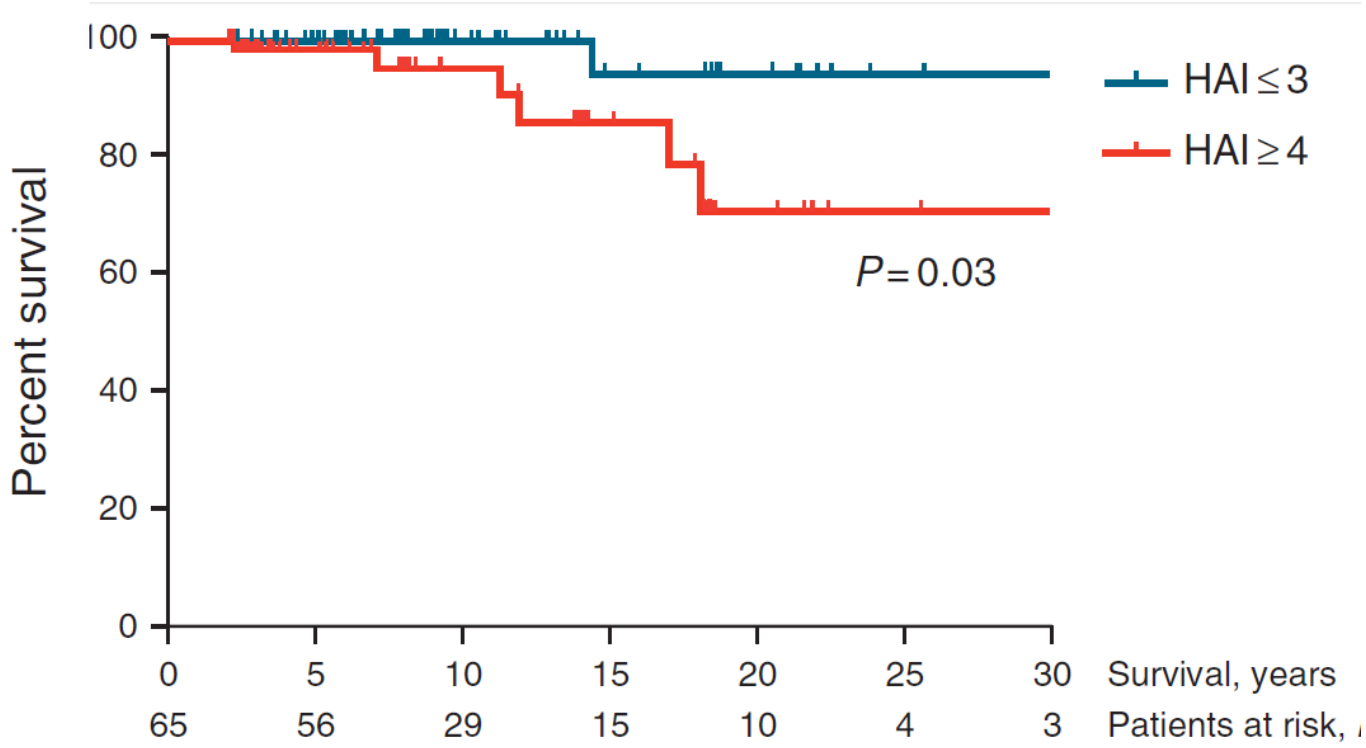



- Survival begins to diverge after 12 yrs (female) and 18 yrs (male)
- Cirrhosis at diagnosis: negative predictor for
  - overall (p=0.03) and transplant-free survival (p=0.002)
- No gender difference in survival

Scand J Gastroenterol. 2017 May 31:1-7.

# HAI score determines survival

Liver-related death or transplant




Persisting histological activity in patients with biochemical remission: independent risk factor for long-term (transplant-free) survival.

Am J Gastroenterol 2015; 110:993–999

# Cancer in AIH

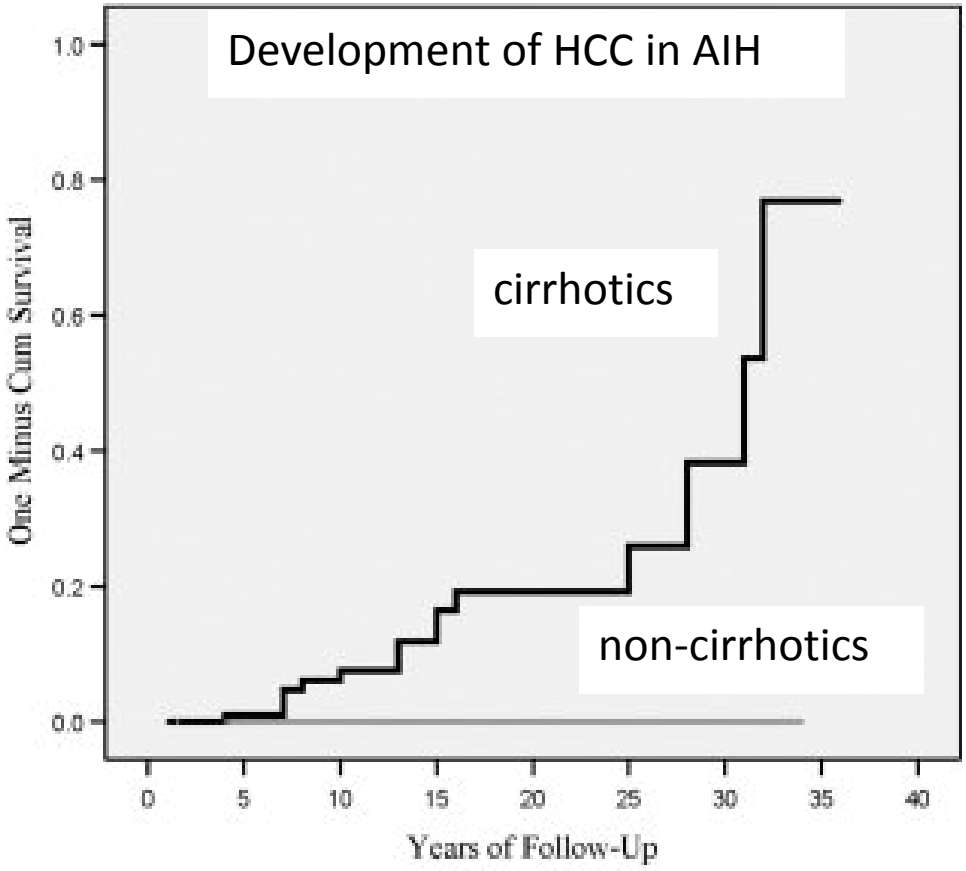
**Cancer**

Liver

- HCC only in cirrhotics
- Higher risk in males

Extrahepatic

- Relation to immunosuppression?
- Non melanoma skin cancer




Hepatology 2008 48, 863-870,

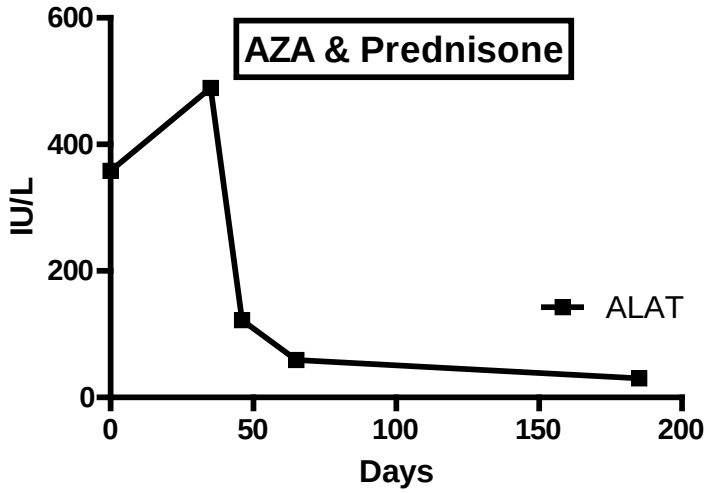
Radboudumc

# AIH & other autoimmune liver diseases

# Nitrofurantoin induced AIH

- **Medical history**
  - Hemithyreoidectomy
  - Recurrent cystitis
- **Drugs**
  - Nitrofurantoin 1 yr
- **Laboratory**
  - AP  171 IU/L , bili NL
  - ALT 489 IU/L, AST 414 IU/L
  - ANA, ASM negative
- **Radiology**
  - Right liver lobe atrophy
- **Histology**
  - Typical AIH
- **Treatment**
  - AZA 100 mg & Pred 5 mg
- **Follow-up**
  - Rapid remission

Confluent fibrosis & liver atrophy




Courtesy Karel van Erpecum UMCU

# Drug induced AIH

## Natural history & outcome

- Two recent AIH cohorts
- Search for drug-induced AIH cases

- USA series 24/261
- UK series 11/82
- Total 35/346 (~10%)

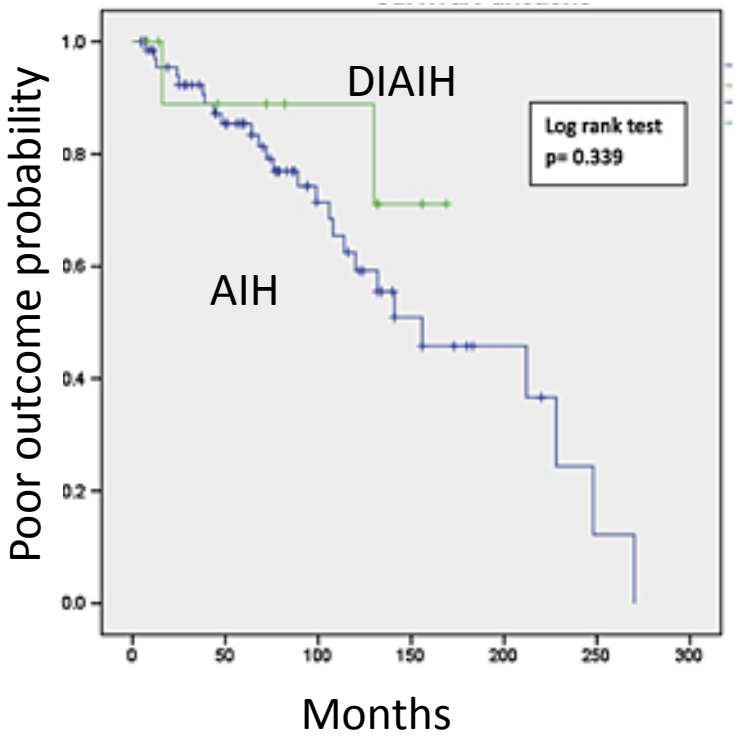
- Nitrofurantoin n=15/35
- Minocyclin, statins, herbal

Hepatology Research MAY 2015 DOI: 10.1111/hepr.12532
HEPATOLOGY 2010;51:2040-2048

# Drug induced AIH

## Natural history & outcome

- **Similar natural history**
- Autoantibodies
  - ANA (83% versus 70%)
  - SMA (50%  versus 45%)
- Histology
  - Grading & Staging
  - Cirrhosis is “absent” among DIAIH
- Radiology
  - Postnecrotic scarring: atrophy
- Treatment
  - Response to steroids
  - No relapse after discontinuation




Hepatology Research MAY 2015 DOI: 10.1111/hepr.12532
HEPATOLOGY 2010;51:2040-2048

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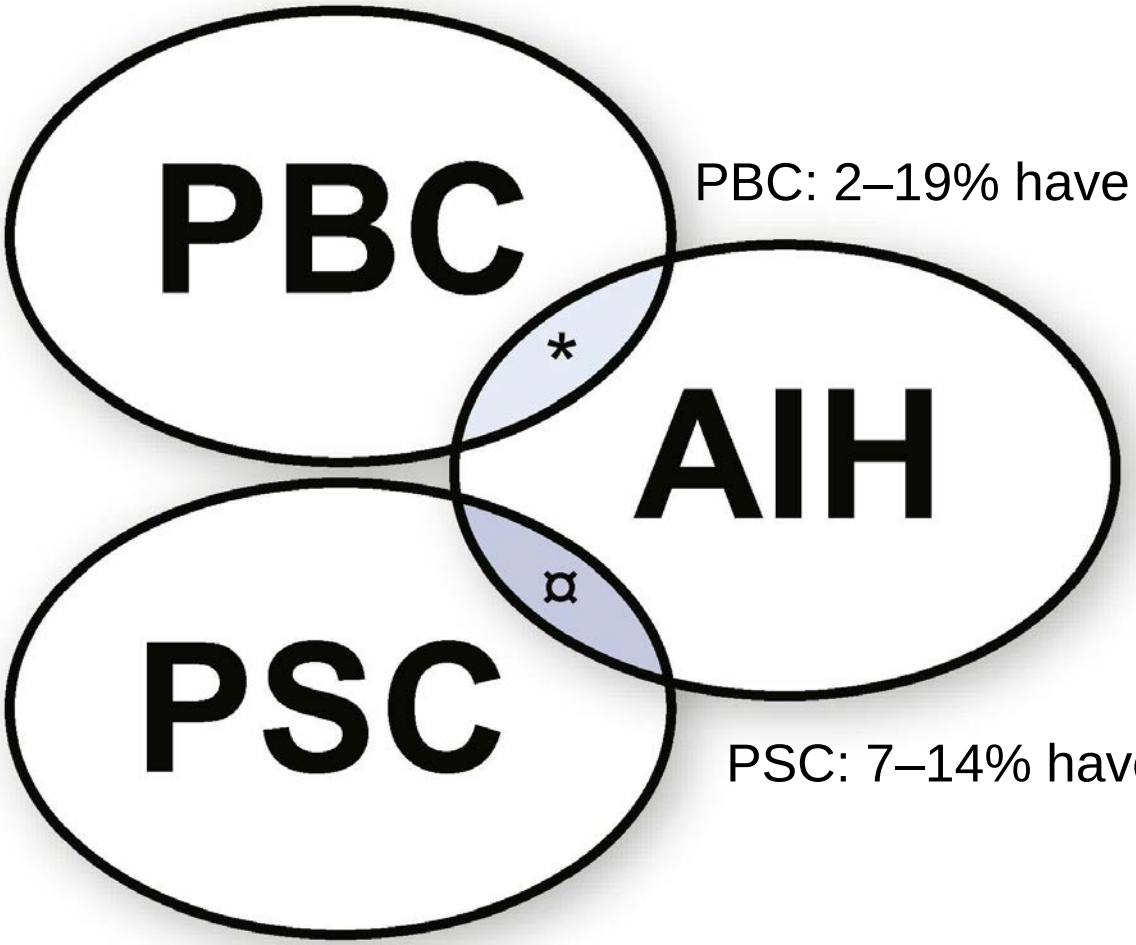
# Overlap syndromes with AIH



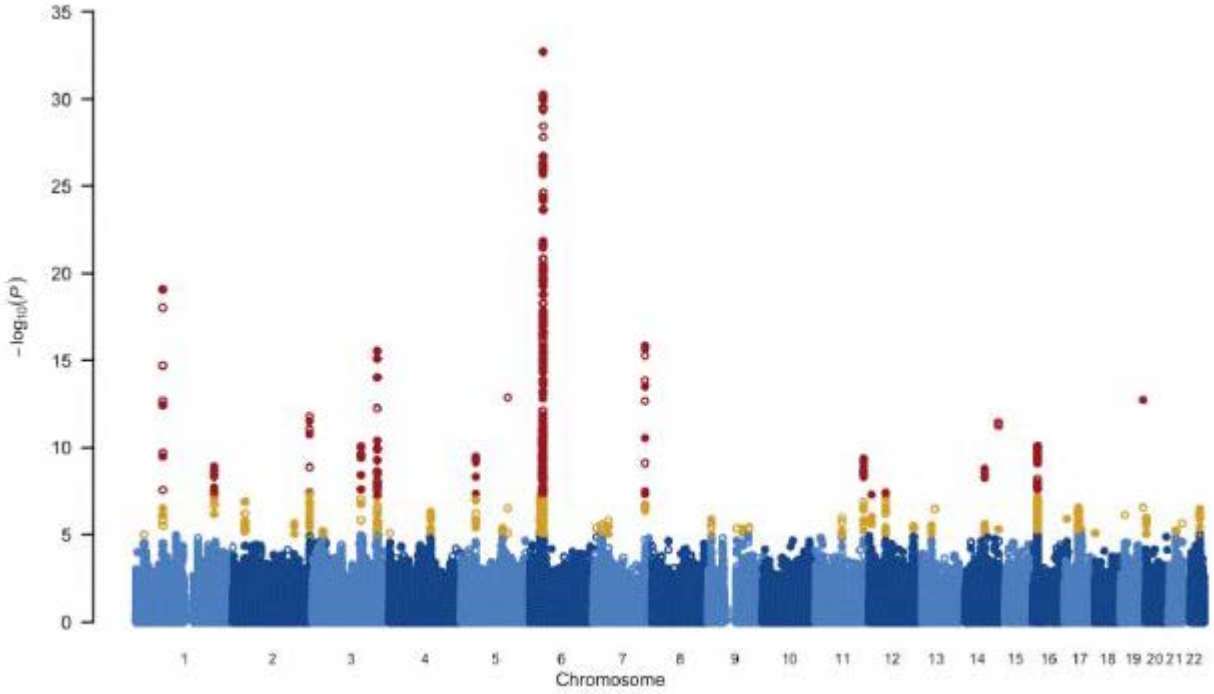

PBC: 2–19% have AIH features

PSC: 7–14% have AIH features

J Hep 2011 54, 374-385

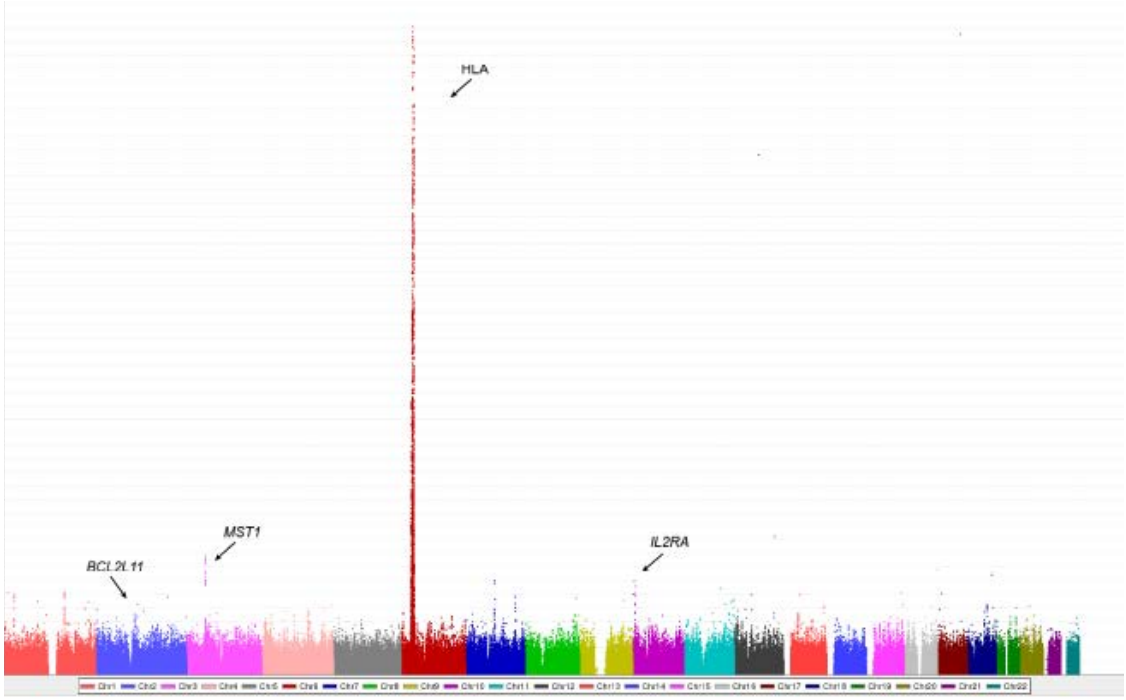
# HLA association

PBC



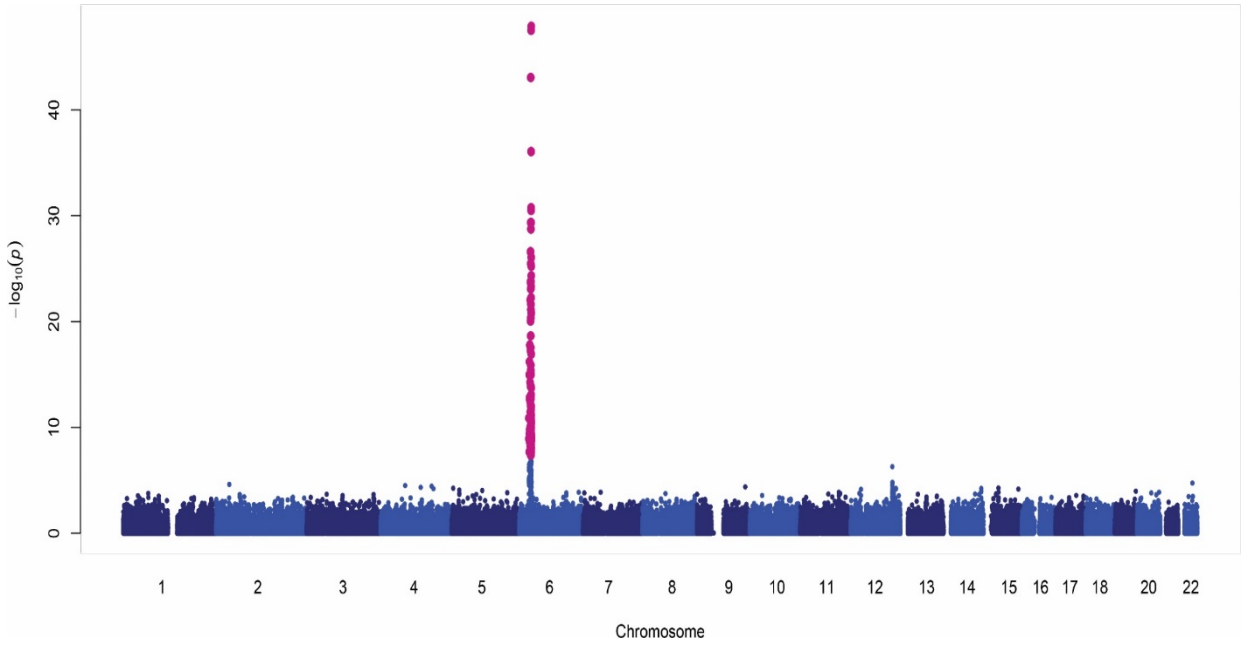
# HLA association

PSC

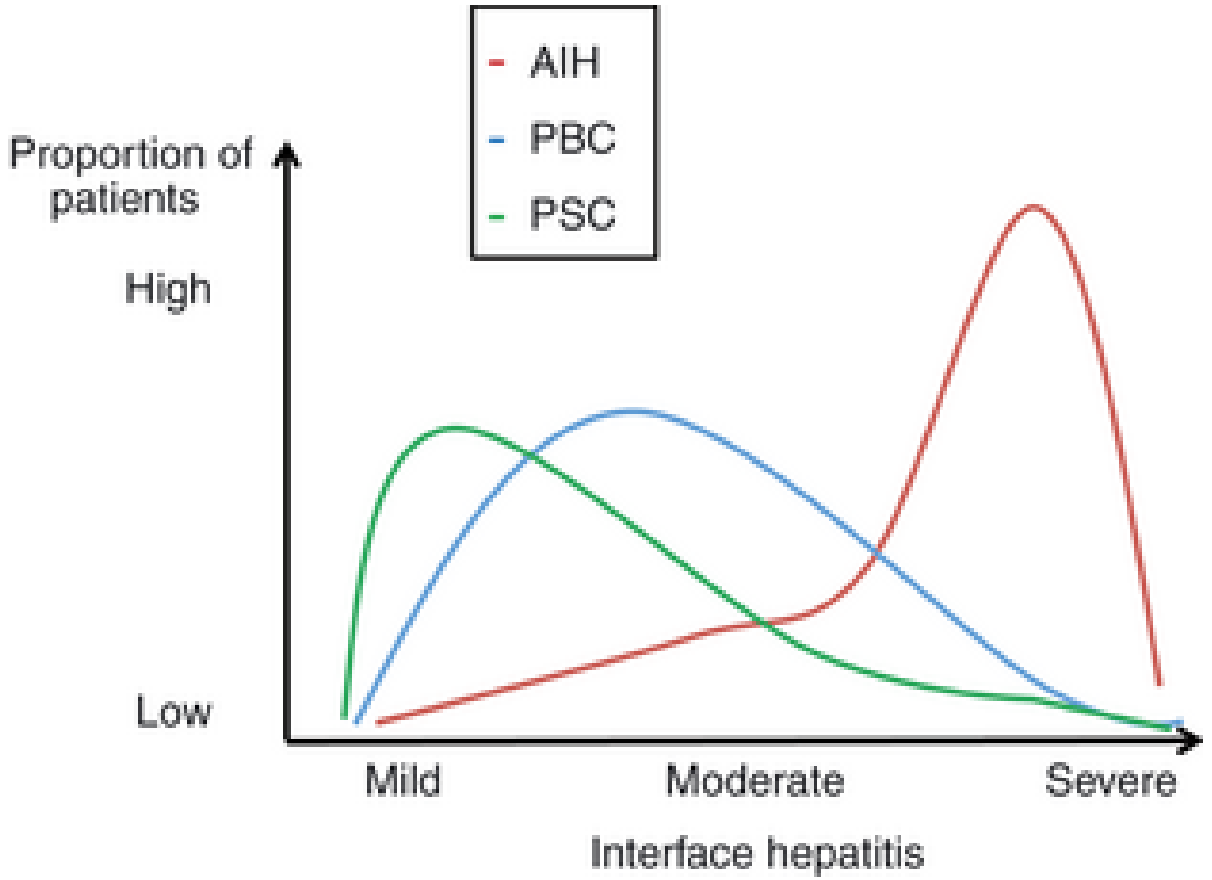


# HLA association

AIH



# Spectrum of autoimmune liver disease




Alimentary Pharmacology & Therapeutics 2012 36, pages 517-533,

# What to do with overlap syndromes

- **Diagnosis**
  - Predominant feature leads in diagnostic process
  - Overlaps are no  distinct diagnostic entities
  - Difficult to classify: PARIS criteria
  - PBC usually precedes AIH
  - Longitudinally collect data rather than at a single point (wait and see)

- **Pathogenesis**
  - Genetic factors of AIH, PSC & PBC overlap : HLA class II

- **Treatment**
  - Emperical / no evidence base
  - Dominant clinical feature should be treated first
  - Individualized therapy  and adjust according to response
  - Think twice before you start steroids

# AIH : Treatment

# Treatment

- Should I treat AIH, if so when?
- How should I treat?
- What should I give?
- Can I stop?

# 3

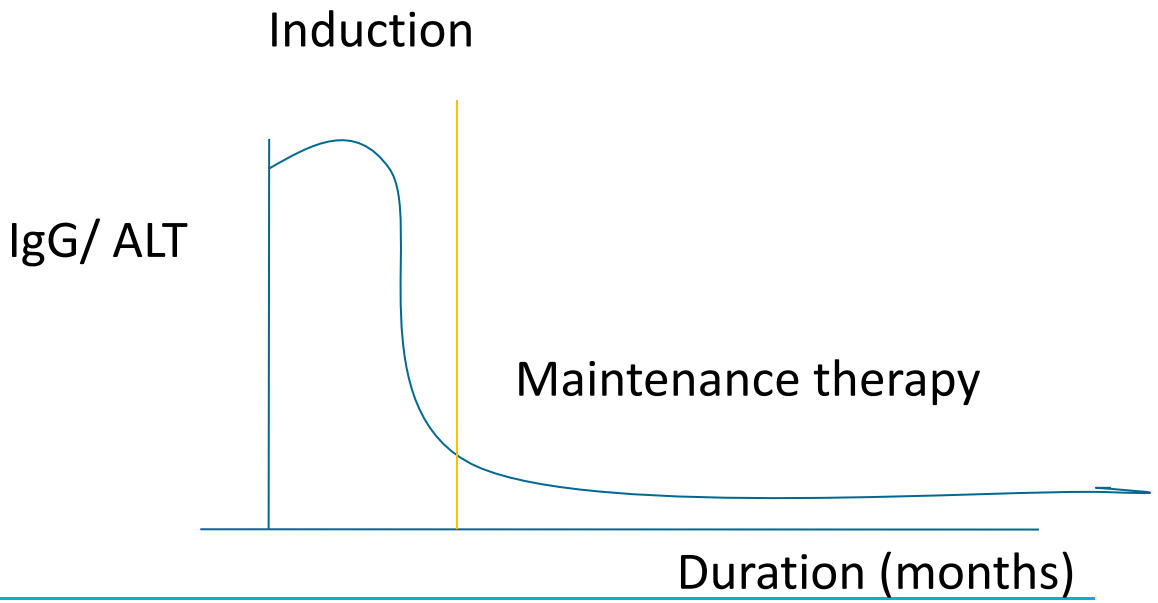
- You have diagnosed autoimmune hepatitis 12 months ago with a 64-year-old female and started treatment. She will visit your out-patient clinic. What is the best set of parameters to judge whether the autoimmune hepatitis is in remission?

1. Bilirubine & creatinine
2. ASAT & immunoglobulin M
3. Bilirubin & albumin
4. ALAT & immunoglobulin G

# Autoimmune Hepatitis

## Overall Goals of Treatment

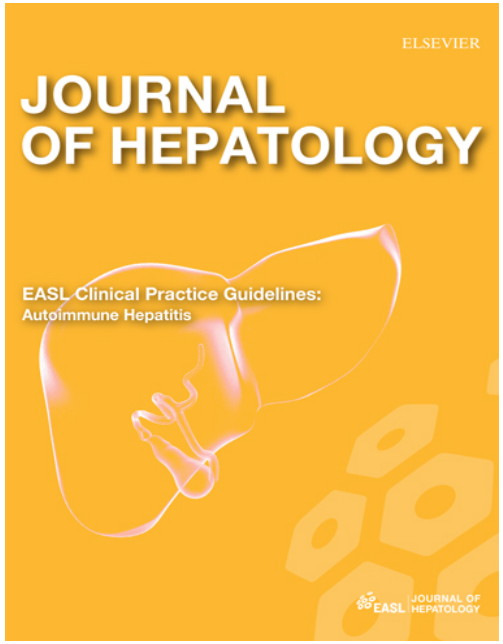
- Induce remission
- Prevent disease progression
- Minimize relapse of disease
- Improve survival
- Minimize medication side effects




Hepatology 2002;36:479; N Engl J Med 2006;354:54

# When to start treatment in AIH

1. Measure transaminases & IgG
   - ALT > 3 nl
   - IgG : elevated
2. Test for autoantibodies
   - ANA, ASM, SLA, LKM
3. Assess liver histology
   - Fibrosis stage
   - Hepatitis activity score (HAI)




**Start treatment***

- Active disease (HAI ≥ 4/18)
- Advanced fibrosis / cirrhosis
- Relapsers

***Exception:** mild disease: HAI < 4, no/ mild fibrosis, ALT < 3 nl
Balance treatment against co-morbidity and life expectancy

CPG AIH J Hep 2015

Radboudumc

# 4

- A 28 yr. old female presents for evaluation of abnormal liver-associated enzymes. Overall, she feels well and the physical exam is unremarkable. Labs reveal ASAT of 2124 U/L, ALAT of 2256 U/L, ANA and ASMA are positive. Liver biopsy shows severe panlobular necrosis. Which one of the following is the appropriate next step?

  A. Begin azathioprine as monotherapy of 50 mg daily until remission achieved.
  B. Begin cyclosporine 100 mg twice daily in combination with mycophenolate 500 mg twice daily.
  C. Refer patient for liver transplant evaluation
  D. Begin prednisone 30 mg daily
  E. Repeat liver associated enzymes in 3-4 weeks prior to making treatment decisions

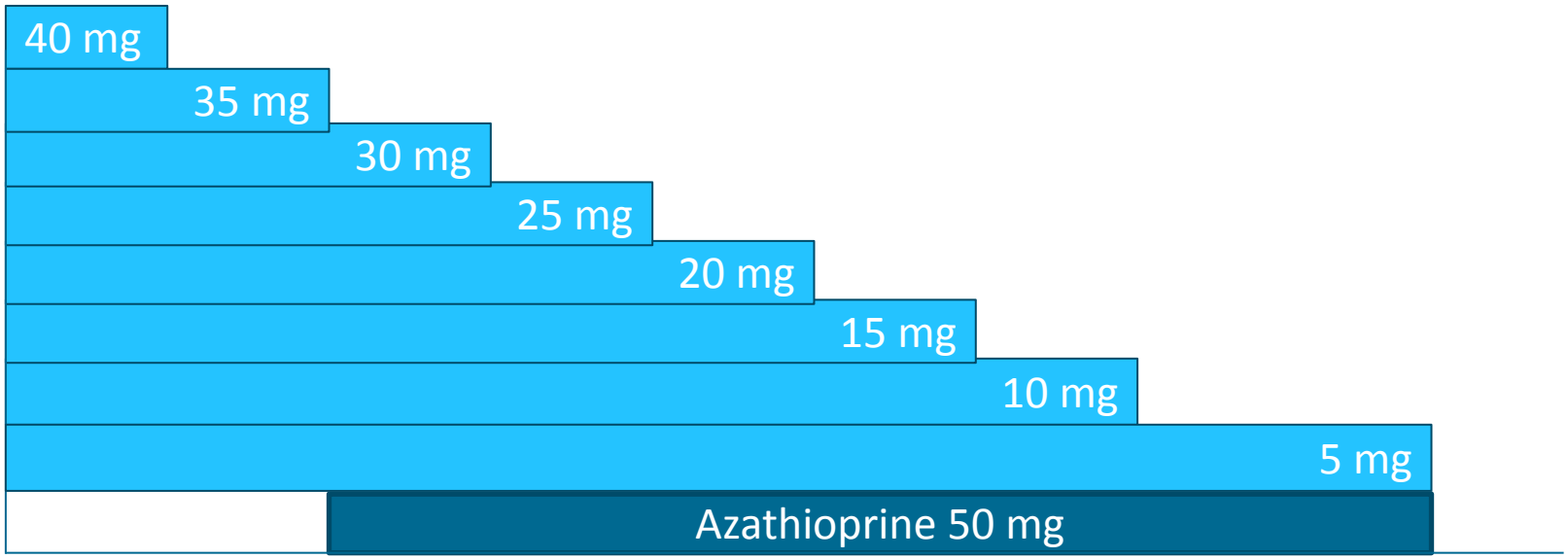
# How to start treatment in AIH

**EASL Clinical Practice Guidelines: Autoimmune hepatitis**☆

European Association for the Study of the Liver*

Example patient 75 kg

Prednisone: 0.5-1 mg/kg/day & Azathioprine 50 mg/day



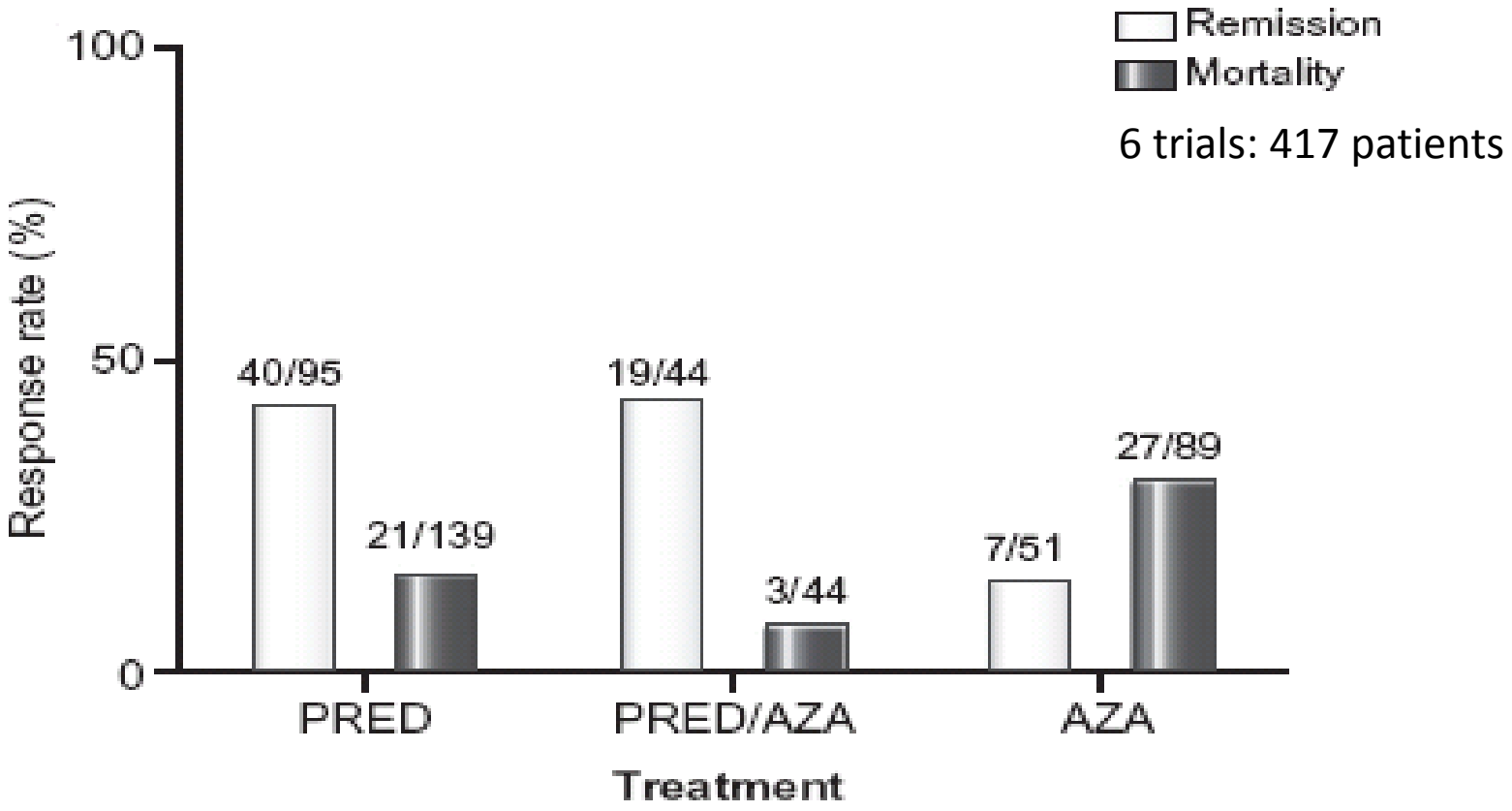

**Measure**

Efficacy: ALT & IgG as outcome measures

Safety: kreatinine, lipase, leukocytes

# AIH induction therapy

## naïve patients

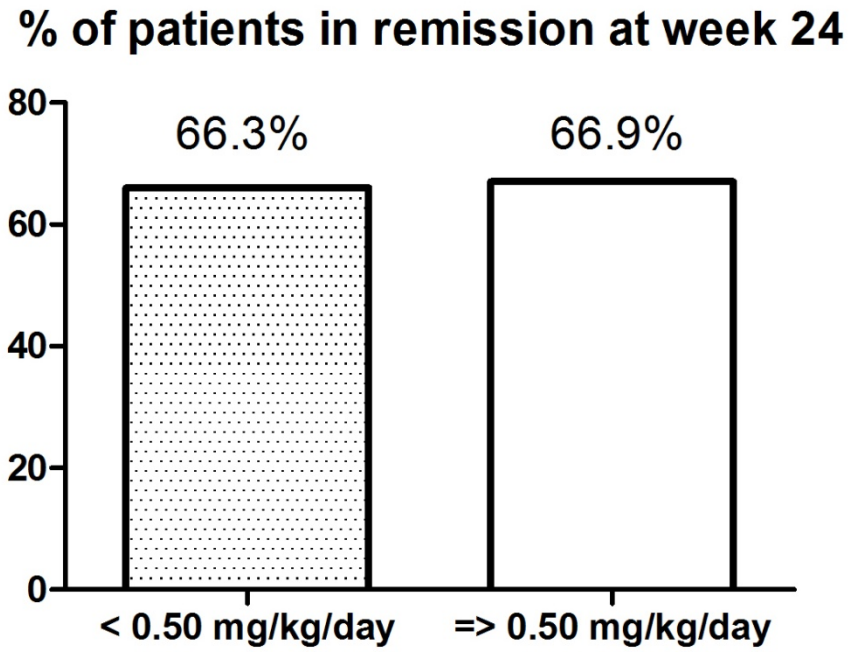



6 trials: 417 patients

PRED monotherapy & PRED + AZA are better in achieving AIH remission

J Hepatol. 2010 Jul;53(1):191-8

# Low or High Prednisone for induction

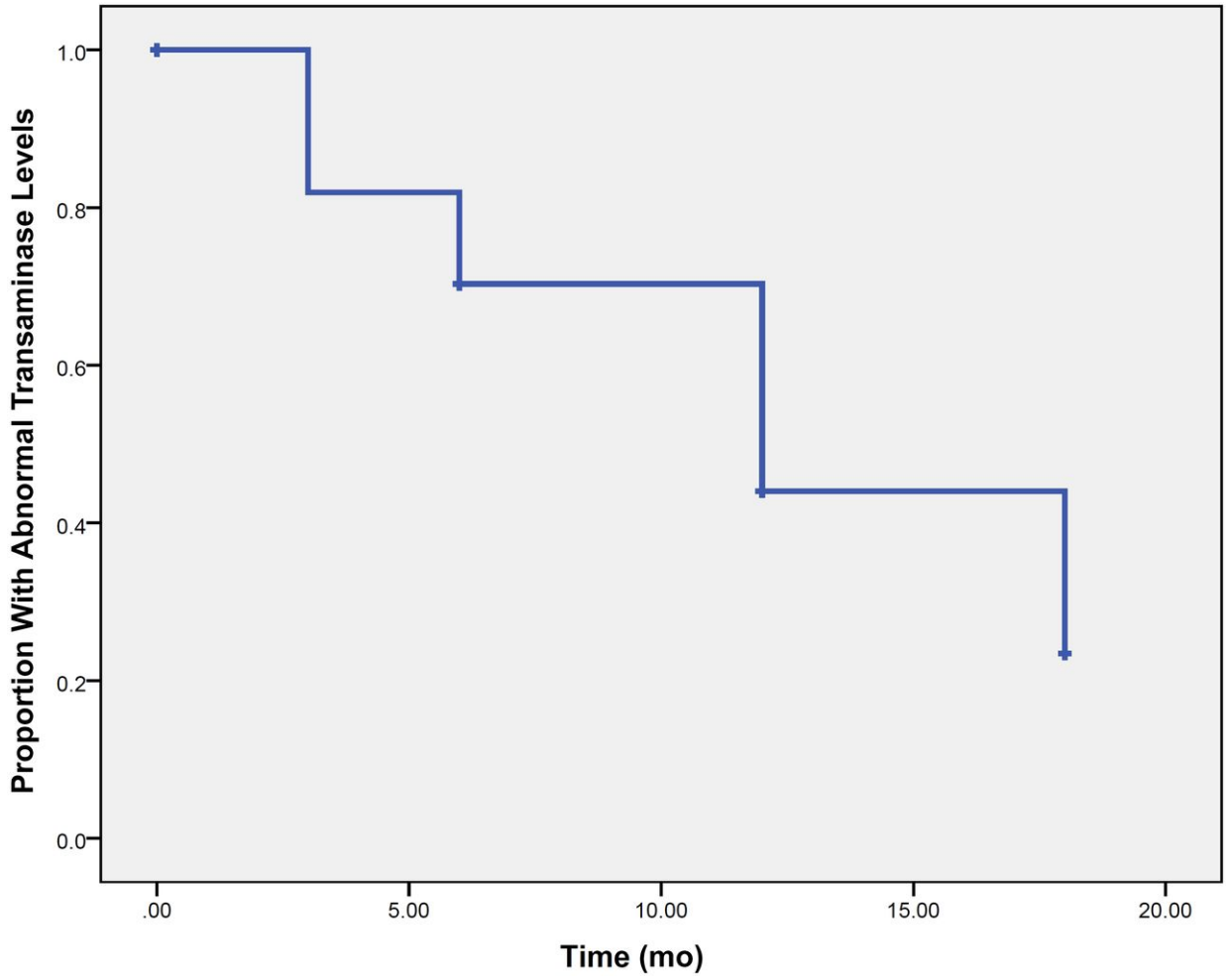



- Multicenter cohort study (Radboudumc, VUmc, Rijnstate, UKE Hamburg)
- 234 AIH patients analyzed for remission at week 24 (normal ALT)
- Remission of AIH defined as ALT < 45 IU/ml
- Remission is obtained regardless of Prednisone dosage

Pape et al. UEGW 2017 *Submitted*

# AIH: response to therapy

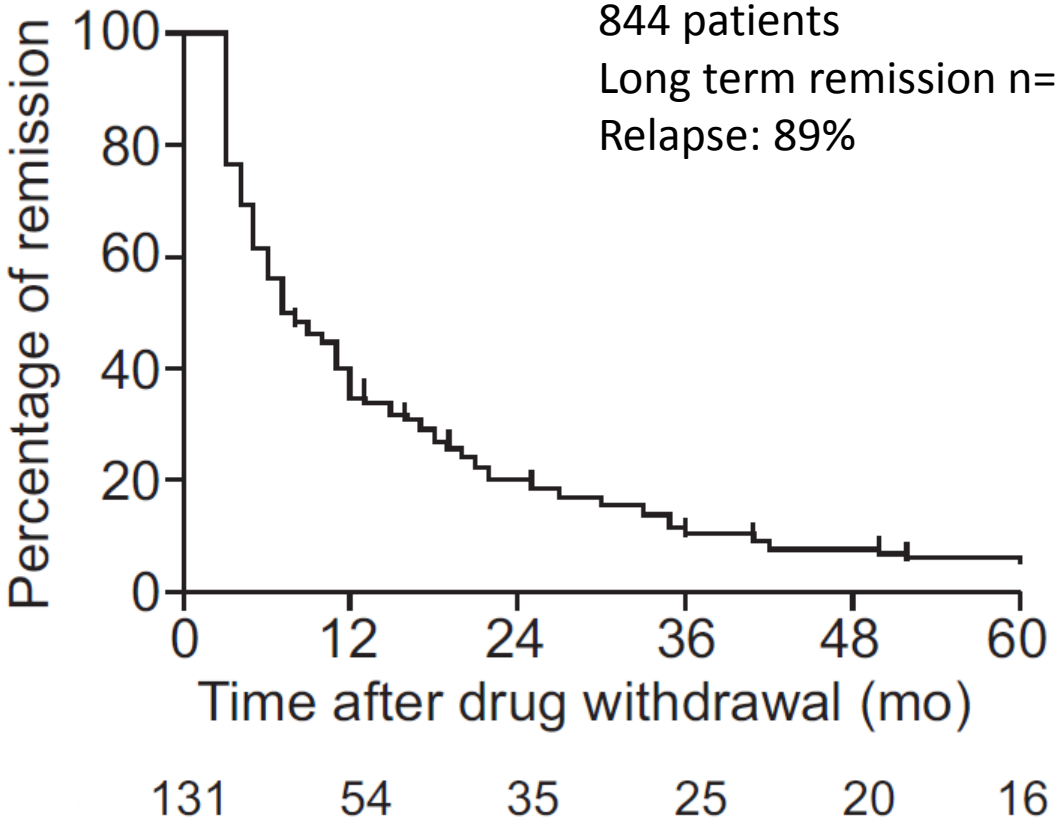
159 Canadian Pediatric AIH patients




Pediatrics November 2015, VOLUME 136 / ISSUE 5

Radboudumc

# Stopping AIH therapy




844 patients
Long term remission n=131 (nl ALT for 2 yrs)
Relapse: 89%

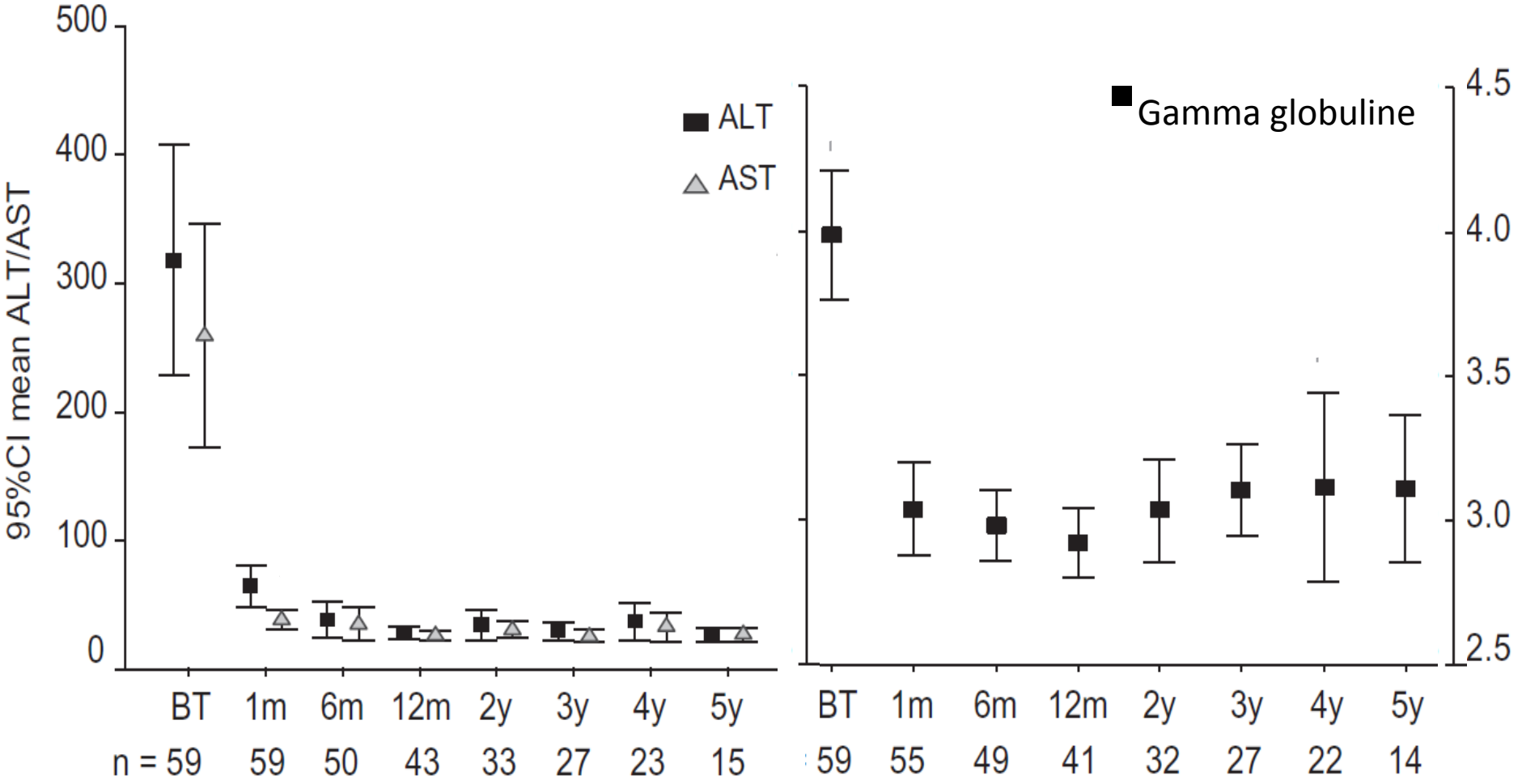
Relapse is universal in AIH: drug free remission is the exception

J Hepatol 2013 58 j 141–147

# Alternatives for Prednisone / Azathioprine?

# Mycophenolate induction therapy

## naïve patients




J Hepatol 2011;55 636–646

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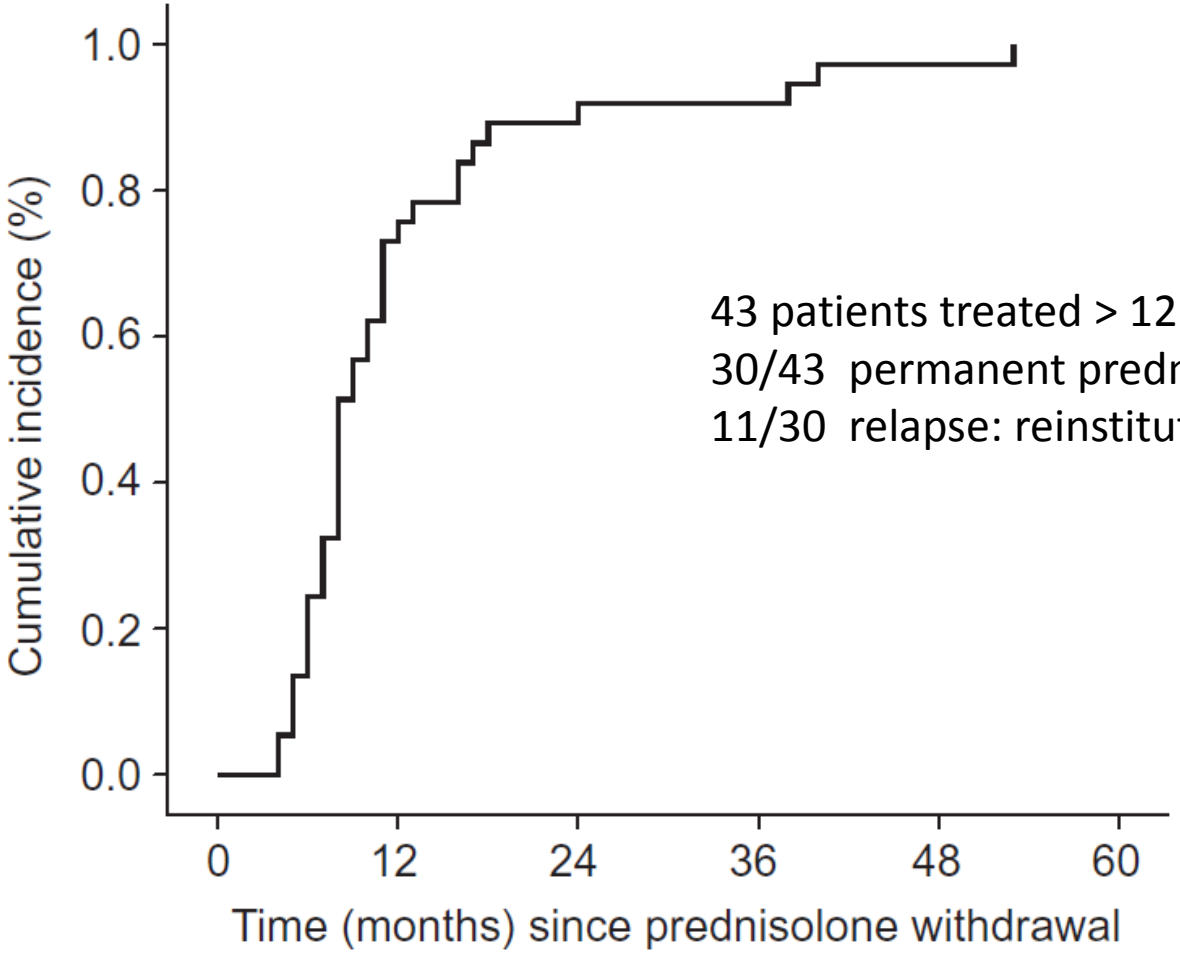
# Mycophenolate induction therapy

cumulative incidence of prednisolone withdrawal during MMF treatment




43 patients treated > 12 months
30/43 permanent prednisone withdrawal
11/30 relapse: reinstitute of prednisone

J Hepatol 2011;55 636–646

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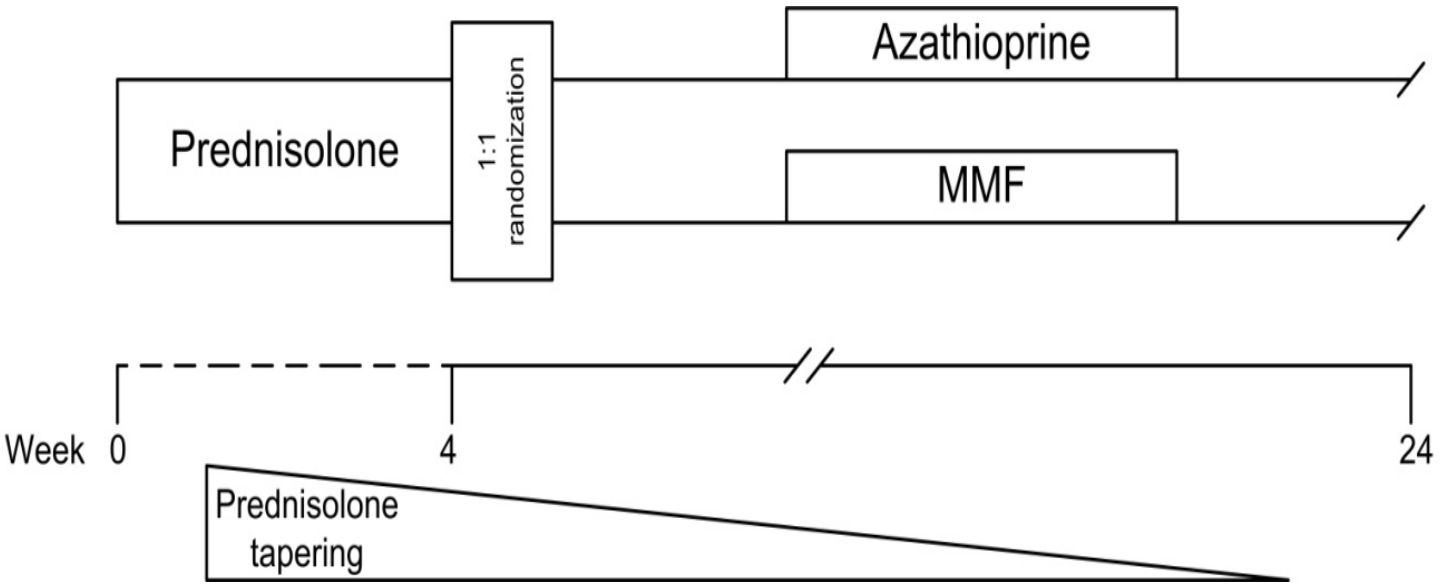
# DUTCH CAMARO trial

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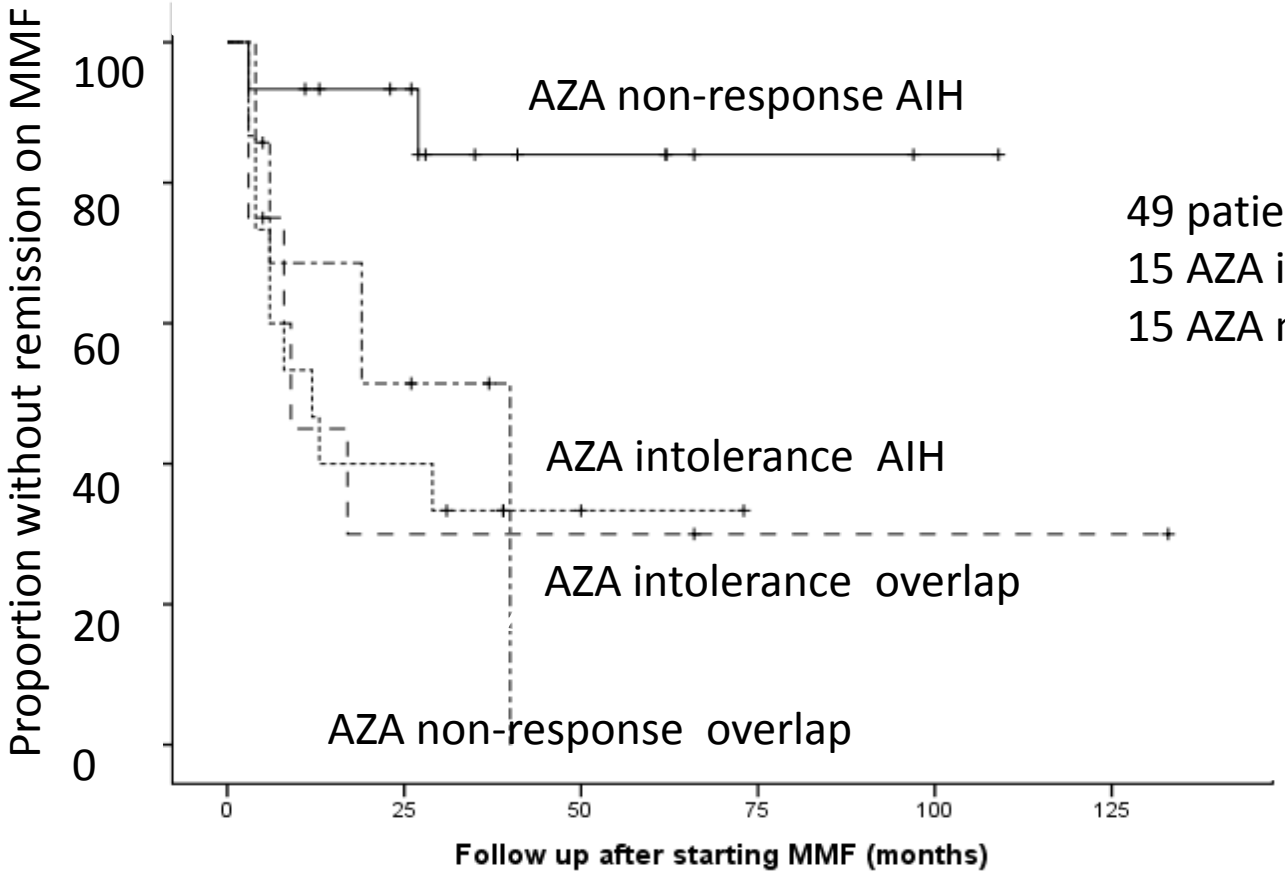
# Mycophenolate

## In AZA intolerance vs. nonresponse



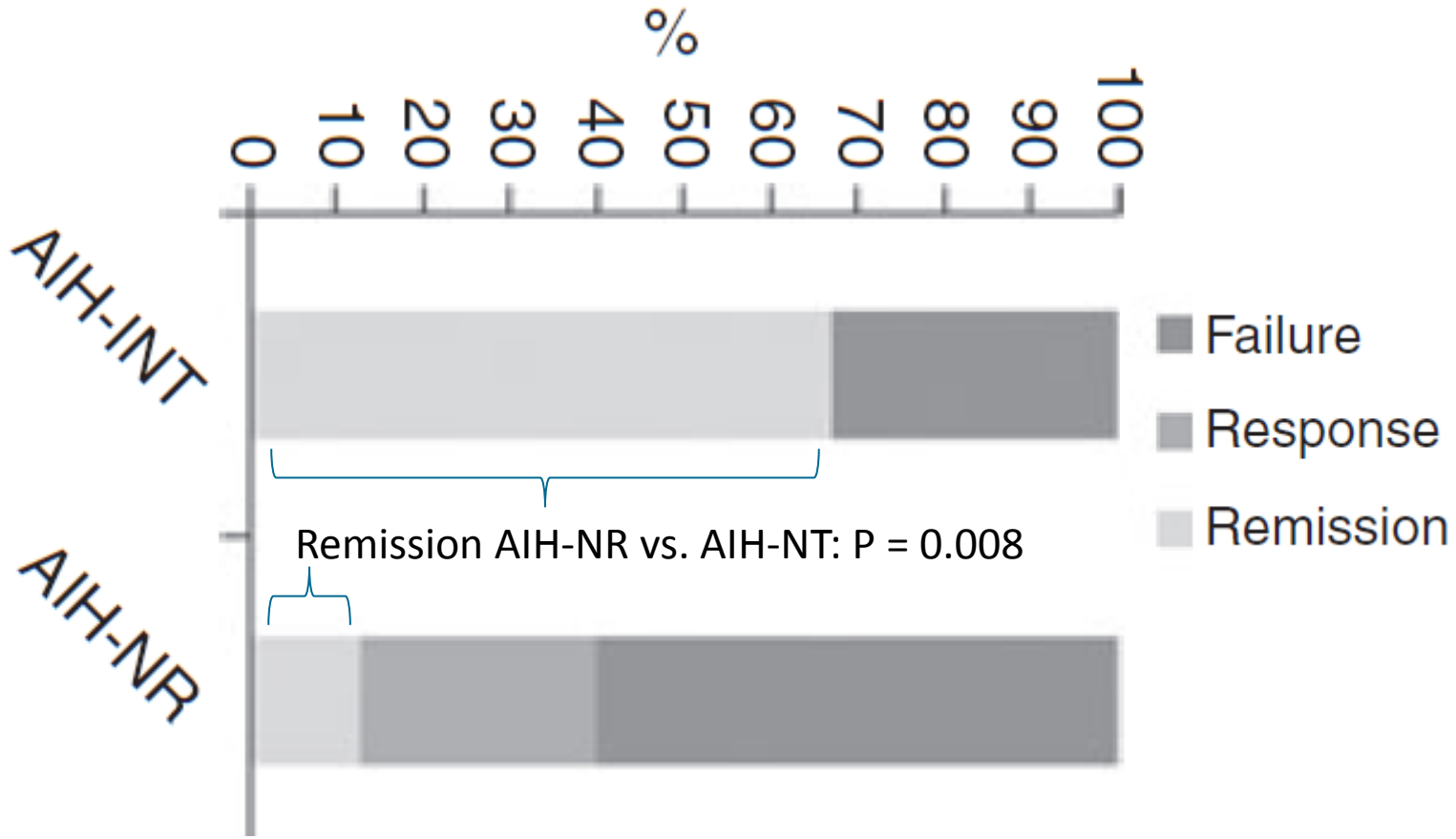

49 patients on MMF
15 AZA intolerant (AIH)
15 AZA non responders (AIH)

MMF induces response in AZA intolerance but less so in non responders

Aliment Pharmacol Ther 2011; 34: 335–343

# Mycophenolate

## In AZA intolerance vs. nonresponse

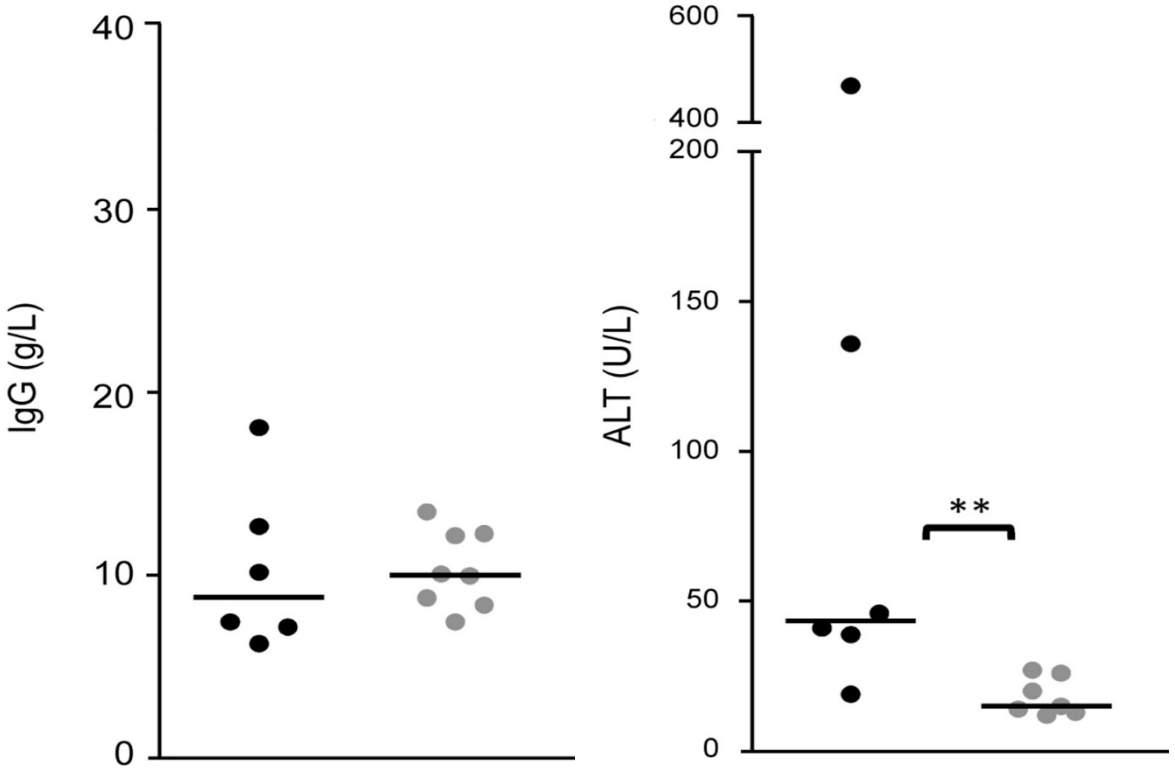



MMF induces remission in AZA intolerant > AZA nonresponders

Aliment Pharmacol Ther 2011; 34: 335–343

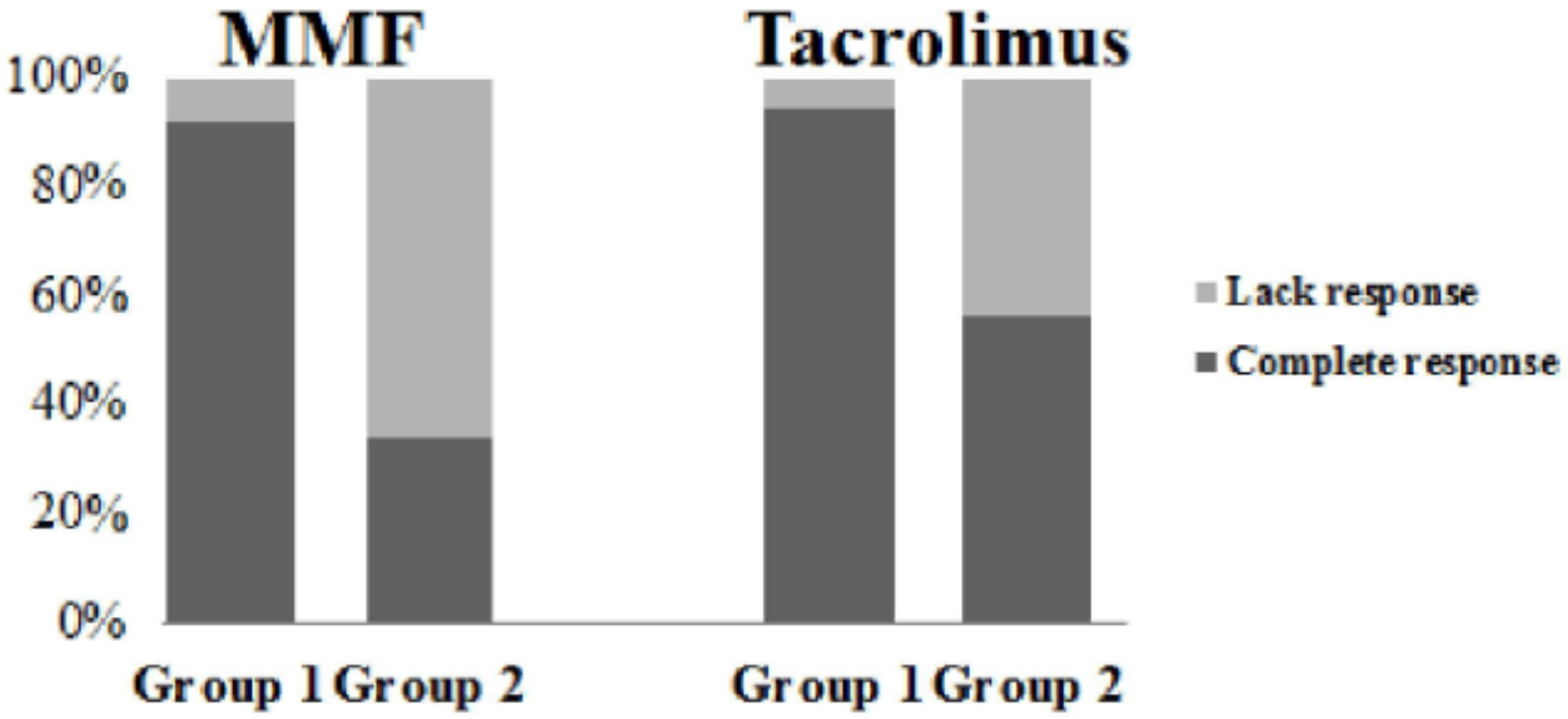
# Switching to 6MP in AZA intolerance

- Cohort of 22 AZA intolerant AIH patients
- After switch to 6-MP, 15/22 (68%)  biochemical response
- After 6 months 8/20 complete & 7/20 partial response




*Clinical Gastroenterology and Hepatology DOI: (10.1016/j.cgh.2015.09.037)*

# Second line after non response to AZA



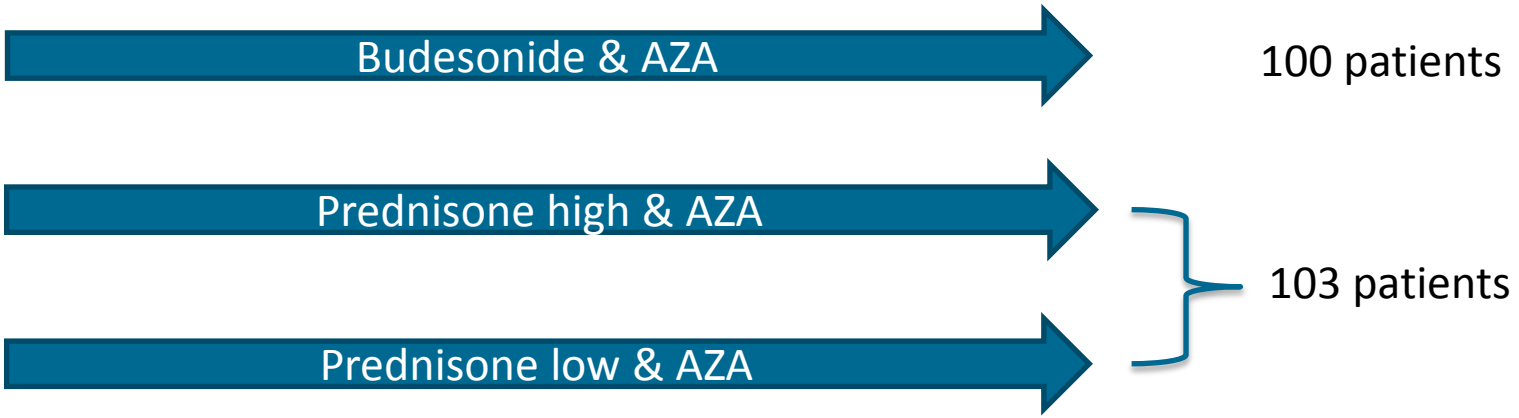

- Group 1: intolerant to AZA
- Group 2 non responders

Clin Gastroenterol Hepatol. 2017 Jun 8. pii: S1542-3565(17)30685-7.

# Budesonide

# Budesonide RCT in AIH

## 6 months




**Endpoints**

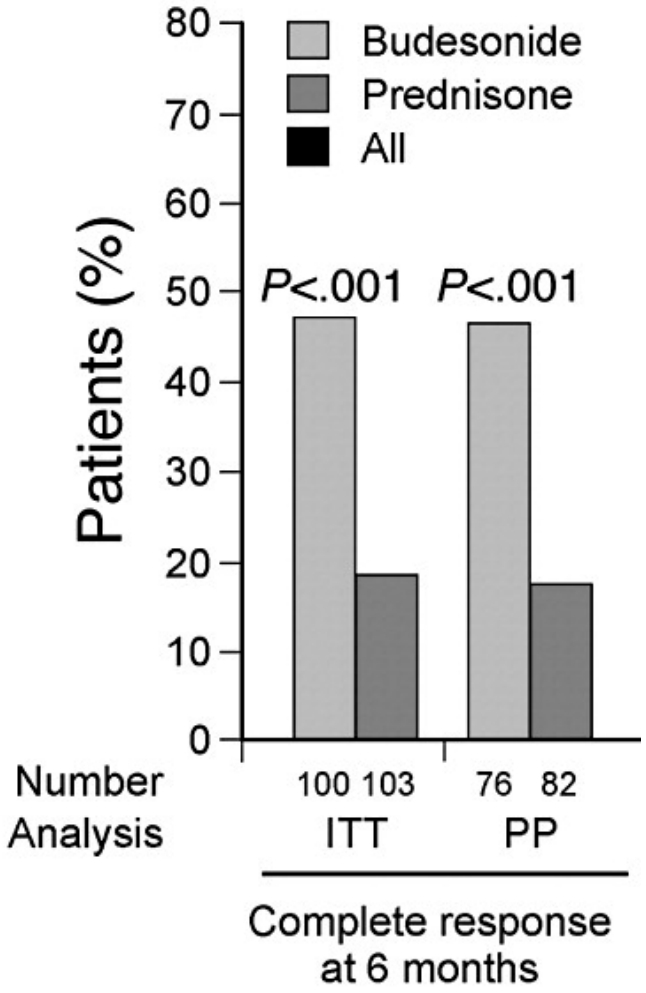
- At 6 months
- ALT & AST <NL w/o predefined steroid-specific side effects

**Dosage**

- Budesonide 9 mg/day
- AZA 1-2 mg/kg/day
- Prednisone high: week 1-8 cum 1820 mg , month 2-6: 10 mg/day
- Prednisone low: week 1-8 cum 1400 mg, month 2-6: 10 mg/day

# Treatment of AIH

## Induction

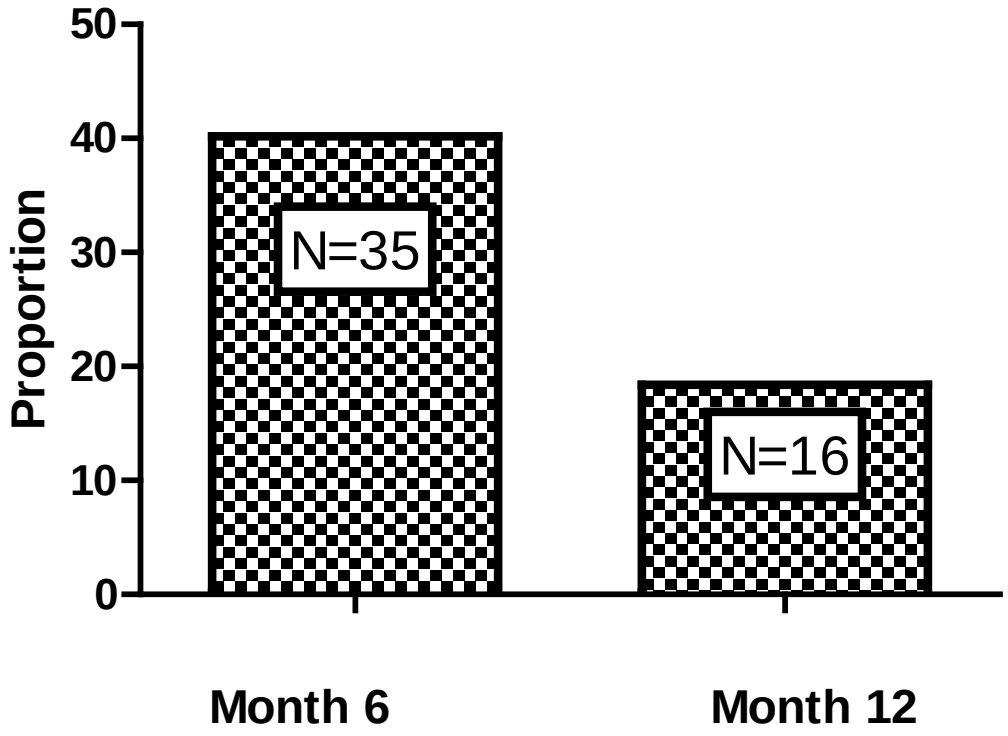



Budesonide & AZA induces and maintains remission in noncirrhotic AIH

Gastroenterology 2010 139, 1198-1206

# Budesonide in AIH

## Less adverse events in switchers

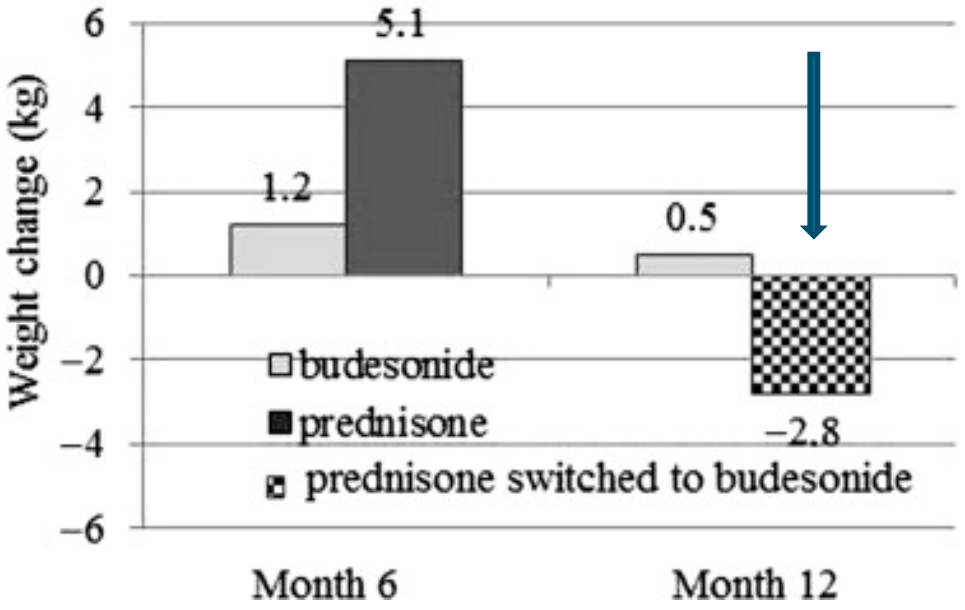



Decrease of Steroid Specific Side Effects in prednisone to budesonide switchers

# Budesonide in AIH

## Pediatric cohort

- 46  AIH patients (11 M; 35 F)
- Age 9-17 years
- RCT  6 months
- budesonide (n = 19)
- prednisone (n = 27)
- Follow-up
- 6 months of open-label budesonide



# Teaching points

- Clinical diagnosis, ALAT IgG , autoantibodies, histology
- Any age, Females . Males
- Do not treat without a liver biopsy result
- Cirrhosis matters
- Nitrofurantoin induced AIH
- Prednisone followed by azathioprine
- Stopping = Relapse, unless
- Azathioprine intolerance: MMF, 6-MP
- Azathioprine non response: oeps Tacrolimus?

# Multiple Choice  Questions

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# 1

- A 18 yr-old female presents with malaise, fatigue, and myalgias. She mentions that her stools are lighter color than normal. Physical examination is remarkable for jaundice and a liver edge 2 finger breaths below the right costal margin. Her laboratory evaluation reveals a total bilirubin of 224 umol/L, ALAT of 3124 U/L, and an INR of 1.4. You think of autoimmune hepatitis. Which laboratory test is appropriate?

A. **Antinuclear (ANA) and antismooth muscle antibodies (ASMA)**
B. Antimitochondrial antibodies (AMA) and total lipid profile
C. Antibodies to soluble liver antigen (SLA)
D. Serum IgM
E. Anti liver-kidney-microsomal (LKM-1) antibodies

# 2

- Which diagnostic procedure is a requirement to diagnose autoimmune hepatitis

1. Ultrasound
2. **Liver biopsy**
3. Magnetic cholangiopancreaticography
4. Fibroscan

# 3

- You have diagnosed autoimmune hepatitis 12 months ago with a 64-year-old female and started treatment. She will visit your out-patient clinic. What is the best set of parameters to judge whether the autoimmune hepatitis is in remission?

1. Bilirubine & creatinine
2. ASAT & immunoglobulin M
3. Bilirubin & albumin
4. **ALAT & immunoglobulin G**

# 4

- A 28 yr. old female presents for evaluation of abnormal liver-associated enzymes. Overall, she feels well and the physical exam is unremarkable. Labs reveal ASAT of 2124 U/L, ALAT of 2256 U/L, ANA and ASMA are positive. Liver biopsy shows severe panlobular necrosis. Which one of the following is the appropriate next step?

A. Begin azathioprine as monotherapy of 50 mg daily until remission achieved.
B. Begin cyclosporine 100 mg twice daily in combination with mycophenolate 500 mg twice daily.
C. Refer patient for liver transplant evaluation
**D. Begin prednisone 30 mg daily**
E. Repeat liver associated enzymes in 3-4 weeks prior to making treatment decisions

# Multiple Choice  Questions

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# Auto immune hepatitis

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21 t/m 23 juni a.s. zal de Dutch (Flamish) Liver Week plaatsvinden in Hampshire Hotel Fitland Leiden

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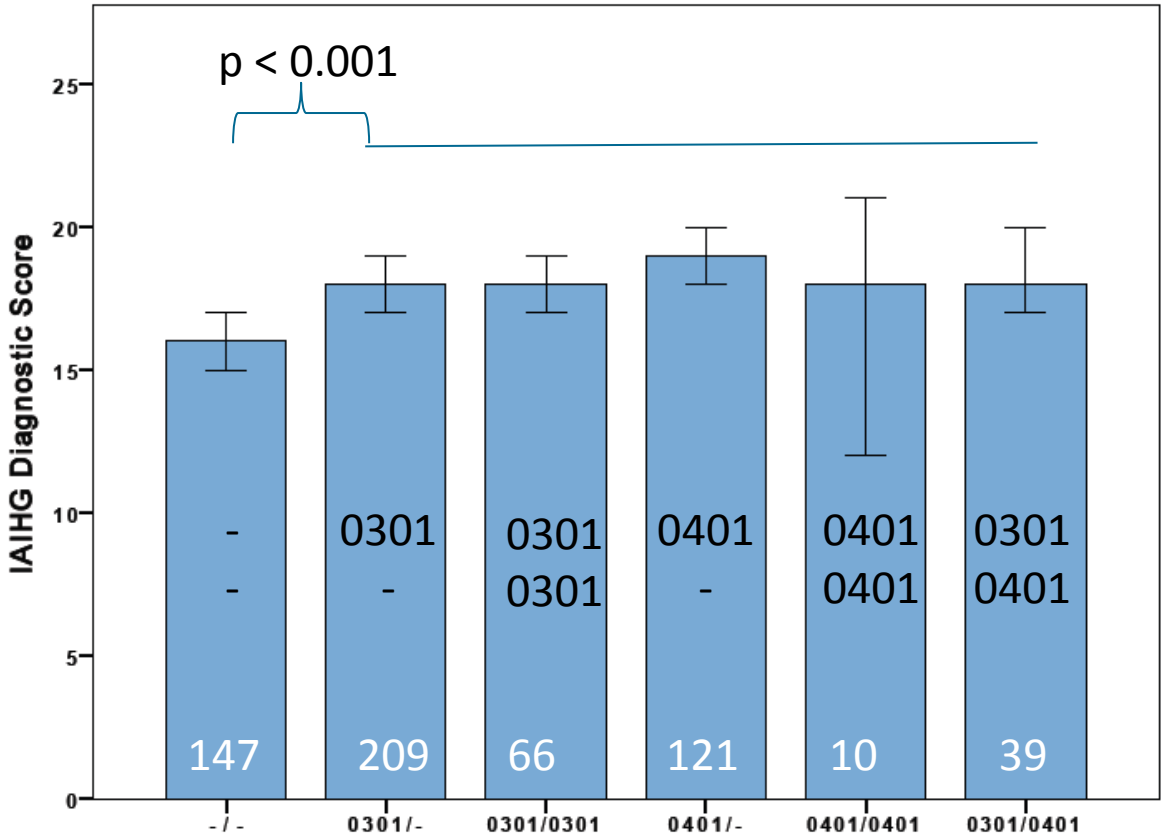
# Phenotypic effect of HLA DRB1



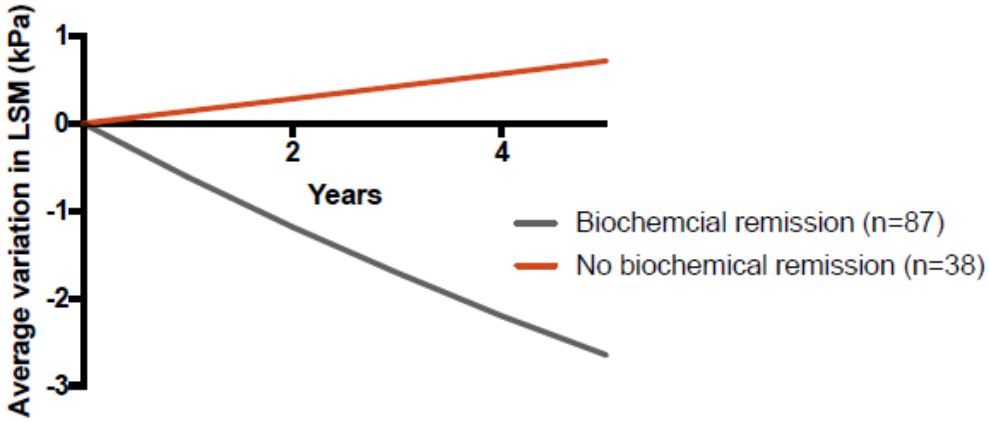

- 649 Dutch AIH type-1 patients;
- 75%: HLA-DRB1*04:01 or *03:01 positive
- Mutation positives have higher revised International Autoimmune Hepatitis Group (IAIHG) scores

Genes Immun. 2015 Jun;16(4):247-52
J Hepatol 1999;31:929-938.

# Conclusion

- AIH is a clinical diagnosis

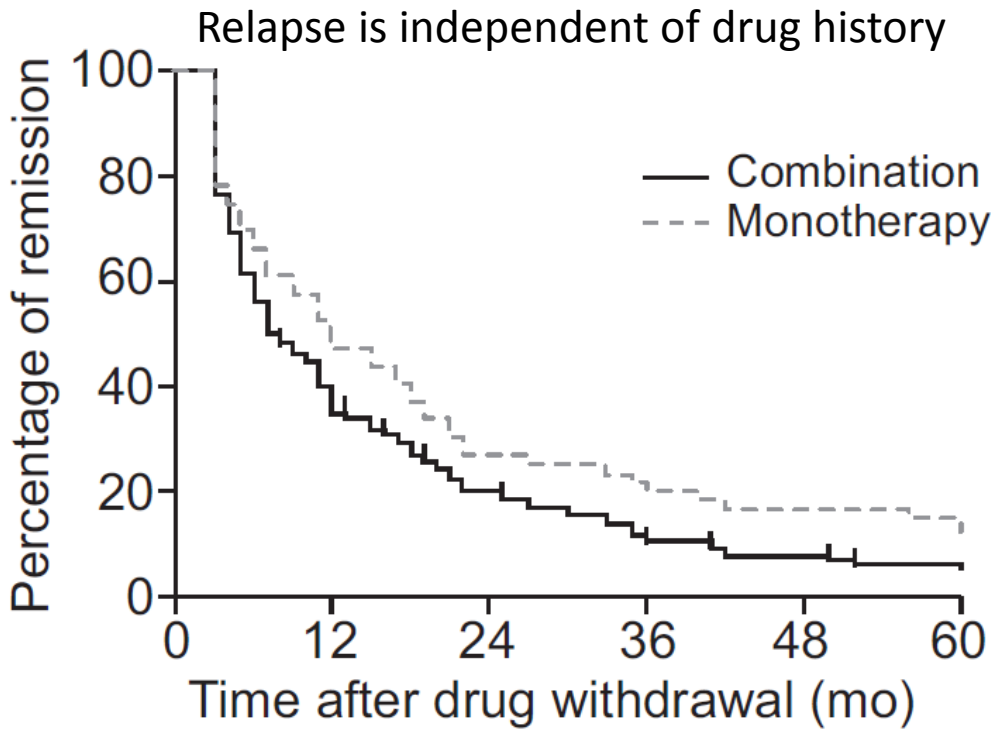
- The diagnosis of AIH relies particularly on presence of autoantibodies, hypergammaglobulinemia and typical or compatible histology **(II-2)**
- Prompt and timely diagnosis is crucial as untreated AIH has a high mortality rate **(I)**
- Histological demonstration of hepatitis is a prerequisite for the diagnosis of AIH and needs to be part of the initial diagnostic work-up **(II-2)**
- AIH is associated with a broad variety of other autoimmune diseases **(II-2)**
- Association with HLA-genes DR3 or DR4
- The simplified IAIHG scoring system is useful for clinical practice **(II-2)**
- All patients with active AIH should be treated **(I)**
- Dosage of therapy should be adapted to the activity of the disease **(III)**


Average variation in LSM (kPa)
1
0
-1
-2
-3
2
4
Years
Biochemcial remission (n=87)
No biochemical remission (n=38)

# Pregnancy & AIH

- Allow pregnancy in AIH
  - Cave AIH cirrhosis with portal hypertension
- Continue treatment
  - Azathioprine (can be detected in colostrum)
  - MMF is contraindicated in pregnancy
- Disease behavior
  - AIH goes into remission with pregnancy
  - Gestational flare unlikely (<5%)
  - Post partum flare occurs (~25%)
- Outcome
  - AIH cirrhosis: high fetal loss
  - Lower MELD scores : better outcome

# Risk factors for relapse




| Features | HR | 95% CI | P value |
|---|---|---|---|
| Concomitant autoimmune disease | 0.55 | 0.37-0.83 | 0.04 |
| Age <45 years at tapering of medication | 1.53 | 1.05-2.2 | 0.03 |

J Hepatol 2013 58 j 141–147

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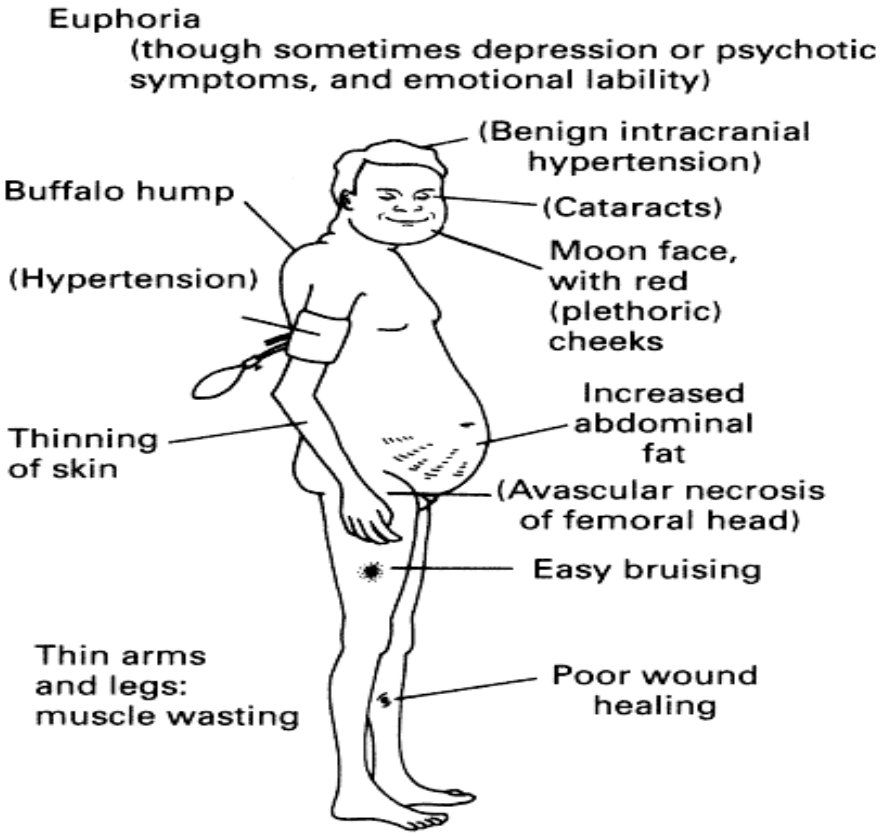
# Diagnostic features of the overlap syndromes of autoimmune hepatitis

| Overlap syndrome | Laboratory features | Serological features | Histological features | Cholangiographic findings |
|---|---|---|---|---|
| AIH-PBC | Consistent with Paris criteria*(19,30)<br>Mild forms may have AP ≤2×ULN (2,6) | AMA positive (2) | Interface hepatitis (30)<br>Destructive cholangitis (florid duct lesions) (30) | Normal (6) |
| AIH-PSC | AST/ALT>ULN (2)<br>γ-globulin and IgG >ULN (2)<br>AP or GGT>ULN (2) | AMA negative (2) | Interface hepatitis (34)<br>Ductopenia (34)<br>Portal edema or fibrous (34)<br>Obliterative fibrous cholangitis (rare) (34) | Bile duct strictures(2,18,20,72) |
| AIH-cholestatic syndrome | AST/ALT>ULN (2)<br>γ-globulin and IgG >ULN (2)<br>AP or GGT >ULN (2) | AMA negative (2) | Interface hepatitis (34)<br>Destructive cholangitis or bile duct loss (11,27) | Normal (2,11,27) |

# Side effects
# Prednisone / Azathioprine

# Steroid side effects

- **Mild but frequent (80%)**
  - Facial rounding, Weight gain
  - Dorsal hump striae
  - Hirsutism, Alopecia
  - Emotional Instability,
  - Glucose intolerance, Cataract
- **Severe but infrequent (13%)**
  - Osteopenia
  - Vertebral compression
  - Diabetes
  - Psychosis,
  - Hypertension




Arthritis Res Ther. 2014 Nov 13;16 Suppl 2:S2.

# Azathioprine side effects

- **Idiosyncratic reactions: 8%**
  - nausea
- **Hypersensitivity reactions: 5-10%**
  - fever, chills, arthralgias, myalgias, cutaneous eruptions
- **Infections: 7%**
  - opportunistic infections (OR: 3.1;  95% CI: 1.7–5.5)
- **Myelosuppression: 2-5%**
  - leukopenia (2–4%), anemia (0.9%) thrombocytopenia (0.2%)
- **Liver toxicity 0.5%**
  - Nodular regenerative hyperplasia
- **Pancreatitis 4%**
- **Malignancy**
  - Skin cancer, lymphoma

Expert Rev Gastroenterol Hepatol. 2014 Mar; 8(3): 223–240.

# Azathioprine side effects

| Age (years) | Annual incidence rate | | |
|---|---|---|---|
| | *Continuing* | *Discontinued* | *Never received* |
| <50 | 0.37 | 0 | 0 |
| 50–65 | 2.58 | 0.66 | 0.40 |
| >65 | 5.41 | 1.88 | 1.68 |

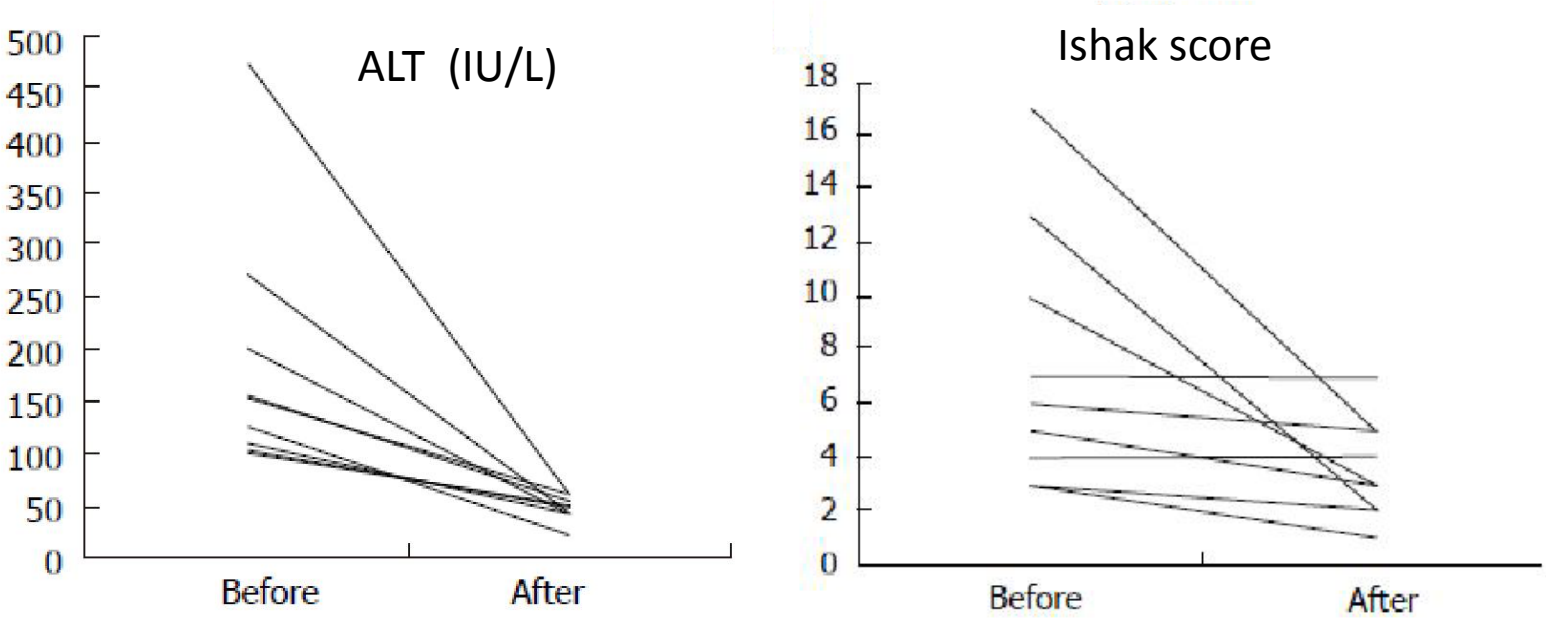
Risk of lymphoma

| Age (years) | Annual incidence rate | | |
|---|---|---|---|
| | *Continuing* | *Discontinued* | *Never received* |
| <50 | 0.66 | 0.38 | 0 |
| 50–65 | 2.59 | 1.96 | 0.60 |
| >65 | 4.04 | 5.70 | 0.84 |

Risk of non-melanoma skin cancer

Expert Rev Gastroenterol Hepatol. 2014 Mar; 8(3): 223–240.

# Tacrolimus




- 9 patients; follow up 18 months (12-37)
- tacrolimus in addition to prednisolone and azathioprin or mycophenolate mofetil.

World J Gastroenterol. 2007 June 21; 13(23): 3232-3236.

# Auto immune hepatitis

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