A Case of Decompensated Cirrhosis

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Clinical Case (1)

- A 63 year old woman
- No history of diseases
- Caucasian
- With a depressive syndrom
- Treated for a AIH type 1 since the age of 62
- No extra hepatic manifestations
- At the time of diagnosis:
  - PT: 72% ,
  - ALT: 10 X ULN; AST: 5 X ULN
  - Total Bilirubin: 20 μmol/L
  - IgG: 22 g/dL
  - ANA: 1/640; SMA: 1/320; anti SLA/LP- ; AMA-
  - Liver biopsy: F4 with a moderate activity in the portal tract + Pericentral necrosis
  - HLADRB1*04:01

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Clinical Case (2)

Table 6. Simplified diagnostic criteria of the International Autoimmune Hepatitis Group [28].

Feature/parameter	Discriminator	Score
ANA or SMA+	≥1:40	+1*
ANA or SMA+	≥1:80	+2*
or LKM+	≥1:40	+2*
or SLA/LP+	Any titer	+2*
IgG or γ-globulins level	>upper limit of normal >1.1x upper limit	+1 +2
Liver histology (evidence of hepatitis is a necessary condition)	Compatible with AIH Typical of AIH Atypical	+1 +2 0
Absence of viral hepatitis	No Yes	0 +2

Definite autoimmune hepatitis: ≥7; Probable autoimmune hepatitis: ≥6. *Addition of points achieved for all autoantibodies (maximum, two points). Typical liver histology for autoimmune hepatitis = each of the following features had to be present namely, interface hepatitis, lymphocytic/lymphoplasmacytic infiltrates in portal tracts and extending into the lobule, emperipolesis (active penetration by one cell into and through a larger cell), and hepatic rosette formation. Compatible liver histology for autoimmune hepatitis = chronic hepatitis with lymphocytic infiltration without all the features considered typical. Atypical = showing signs of another diagnosis, like steatohepatitis.

AIH simplified score = 8
⇒ Definite AIH

Clinical Case (3)

- An induction of therapy was performed by 1mg/Kg prednisolone therapy then Azathioprine (1mg/kg) was introduced

    – A complete remission (normalisation of ALT and Ig G: 12 g/dL) was obtained after 3 months of combination of therapy

  – At 1 year because of normalisation of ALT, prednisolone was stopped and azathioprine was maintained at a dosage of 50 mg/day

  – At 2 years after diagnosis, azathioprine was stopped because of maintenance of normalisation of ALT and a marked decrease level of IgG 14.5 g/dL   (N < 12.0 g/dL)

Clinical Case (4)

In November 2017:

- Jaundice
- Ascites and Encephalopathy= 0
- Total Bilirubin: 60 μmol/L, conj: 35 μmol/L
- ALT: 10 X ULN
- PT: 58%, V factor: 68%
- IgG: 25 g/dL
- US: heterogeneous parenchyma, no biliary tract abnormalities, viral tests (HBV, HCV, HEV) are negative

Questions (1)

The diagnosis of a severe relapse of an autoimmune hepatitis with an icteric decompensation is assessed
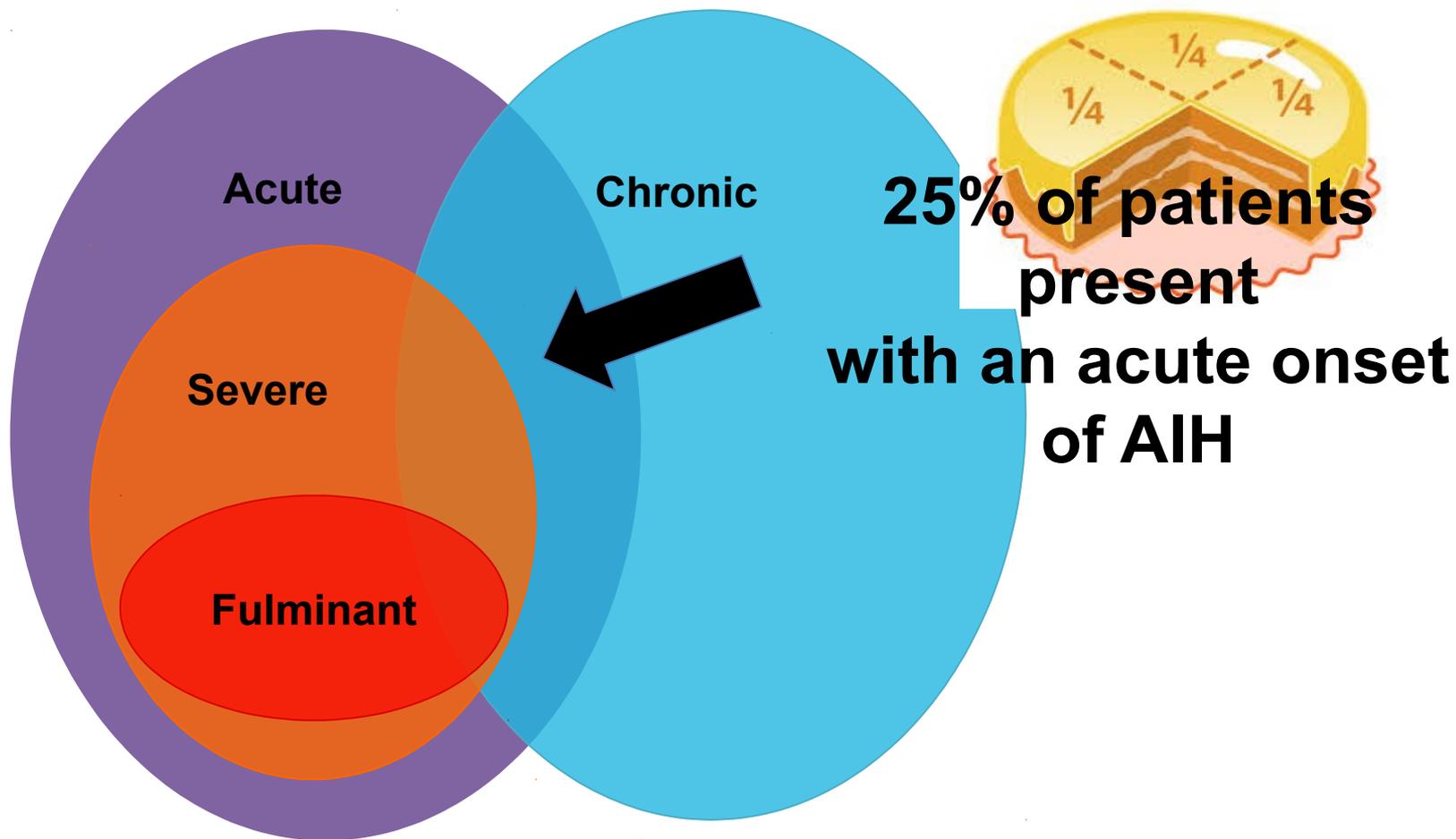
- Are there any explanations for this complication ?
  - Are the age and the clinical presentation at the onset of the disease anusual ?
  - Presence of cirrhosis ?
  - Other pathological characteristics ?
  - An immunoserological test ?
  - A genetic factor ?
  - Insufficient initial therapy ?
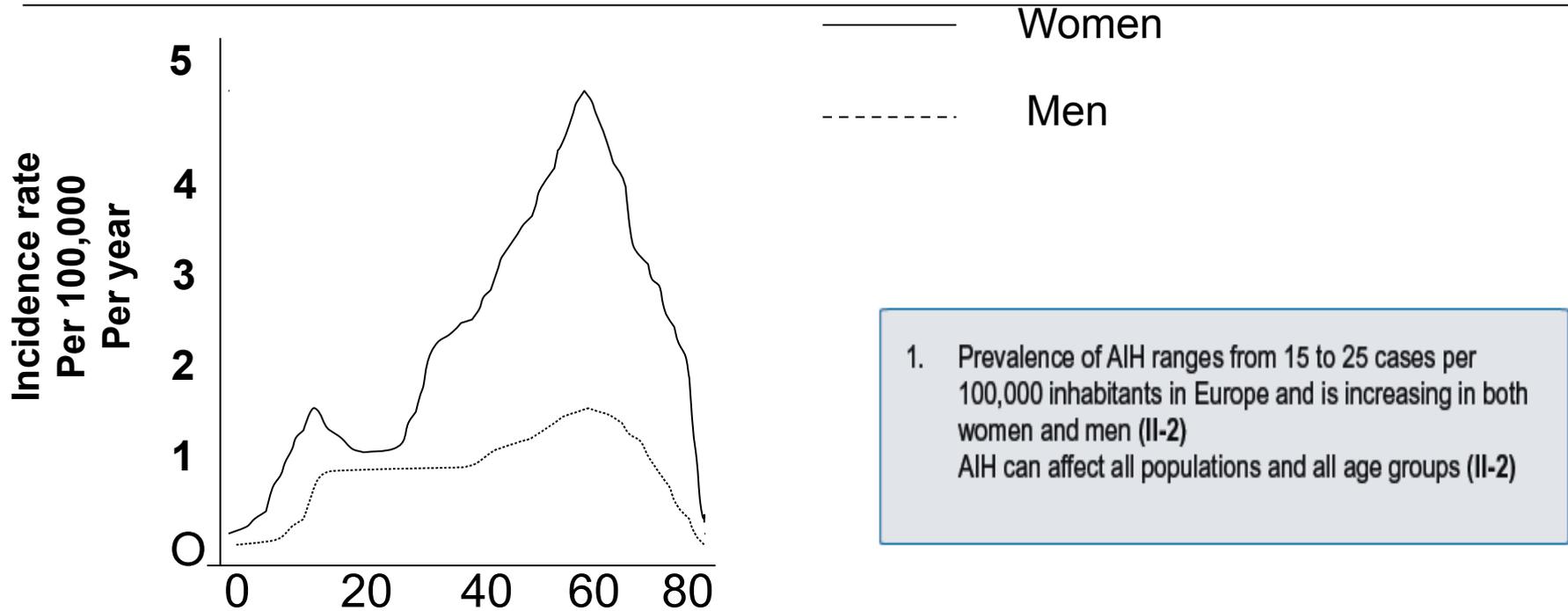 - Was therapy stopped too soon ?

Questions (1)

The diagnosis of a severe relapse of an autoimmune hepatitis with an icteric decompensation is assessed

- Are there any reasons explaining this complication ?
  - Are the age and the clinical presentation at the onset of the disease unusual ?
  - Presence of cirrhosis ?
  - Characteristics of liver biopsy ?
  - An immunoserological test ?
  - A genetic factor ?
  - Insufficient initial therapy ?
  - A too rapid stopping therapy ?

Clinical Presentation of Autoimmune Hepatitis: A Large Spectrum

Acute

Chronic

Severe

Fulminant

25% of patients present with an acute onset of AIH

Age and sex-specific incidence rates of autoimmune hepatitis in Denmark, 1994-2012

1. Prevalence of AIH ranges from 15 to 25 cases per 100,000 inhabitants in Europe and is increasing in both women and men (II-2)
AIH can affect all populations and all age groups (II-2)

Characteristic	
Patients affected	• Any age (with a bimodal distribution usually with peaks around puberty and between 4th and 6th decade although a significant proportion of patients are even older (above 65 years of age))
	• Both sexes (♀: ♂ ≈ 3:1)
	• All ethnic groups

Gronbaek et al. J Hepatol 2014
EASL Clinical Practice Guidelines: Autoimmune Hepatitis J Hepatol 2015

Baseline factors associated with Cirrhosis at AIH at diagnosis

Table 2. Baseline Factors Associated With Cirrhosis at AIH Diagnosis

Factors (at Diagnosis)	No. Cases with Cirrhosis (%)	OR	95% CI	P-value
Gender				
Male	18 (51%)	2.78	1.23-6.18	0.01
Female	27 (28%)	1		
Age at presentation				<0.01
Group 1 (0-20yrs)	5 (42%)	0.61	0.17-2.27	NS
Group 2 (21-40yrs)	3 (11%)	0.10	0.03-0.40	<0.01
Group 3 (41-60yrs)	16 (30%)	0.36	0.15-0.85	0.02
Group 4 (>60yrs)	21 (54%)	1		
Anti-SMA (titer ≥1:80)	26 (32%)	0.78	0.38-1.63	NS
ANA (titer ≥1:80)	24 (31%)	0.76	0.37-1.56	NS
IgG (>14g/L)	41 (35%)	2.00	0.53-7.60	NS
Bilirubin (>50µmol/L)	44 (34%)	2.00	0.93-4.28	NS
ALP (>150U/L)	27 (34%)	1.03	0.50-2.10	NS
Albumin (<36g/L)	25 (51%)	3.33	1.57-7.07	<0.01
Platelet (<150U/L)	18 (75%)	9.11	3.28-25.30	<0.01
INR (>1.2)	20 (59%)	4.23	1.86-9.60	<0.01
ALT				NS
Group A (<3x ULN)	10 (40%)	1.25	0.49-3.20	NS
Group B (3-5x ULN)	4 (29%)	0.75	0.21-2.64	NS
Group C (5-10x ULN)	6 (27%)	0.71	0.25-2.03	NS
Group D (>10x ULN)	25 (35%)	1		

Analyses were performed with binary logistic regression.

Table 3. Baseline Factors Associated With Advanced Liver Fibrosis at AIH Diagnosis

Factors (at Diagnosis)	No. Cases with Advanced Fibrosis (%)	OR	95% CI	P-value
Gender				
Male	24 (69%)	1.71	0.75-3.86	NS
Female	55 (56%)	1		
Age at presentation				0.02
Group 1 (0-20yrs)	11 (92%)	4.32	0.50-37.57	NS
Group 2 (21-40yrs)	13 (46%)	0.34	0.12-0.94	0.04
Group 3 (41-60yrs)	27 (50%)	0.40	0.16-0.95	0.04
Group 4 (>60yrs)	28 (72%)	1		
Anti-SMA (titer ≥1:80)	51 (62%)	1.35	0.67-2.75	NS
ANA (titer ≥1:80)	41 (53%)	0.54	0.26-1.11	NS
IgG (>14g/L)	71 (61%)	2.10	0.69-6.46	NS
Bilirubin (>50µmol/L)	49 (65%)	1.89	0.93-3.82	NS
ALP (>150U/L)	47 (60%)	1.03	0.50-2.10	NS
Albumin (<36g/L)	42 (86%)	7.62	3.07-18.91	<0.01
Platelet (<150U/L)	23 (96%)	21.77	2.84-166.91	<0.01
INR (>1.2)	29 (85%)	5.68	2.03-15.88	<0.01
ALT				NS
Group A (<3x ULN)	13 (52%)	0.65	0.26-1.63	NS
Group B (3-5x ULN)	12 (86%)	3.6	0.75-17.32	NS
Group C (5-10x ULN)	9 (41%)	0.42	0.16-1.10	NS
Group D (>10x ULN)	45 (63%)	1		

Analyses were performed with binary logistic regression.

Ngu et al. Hepatology 2013

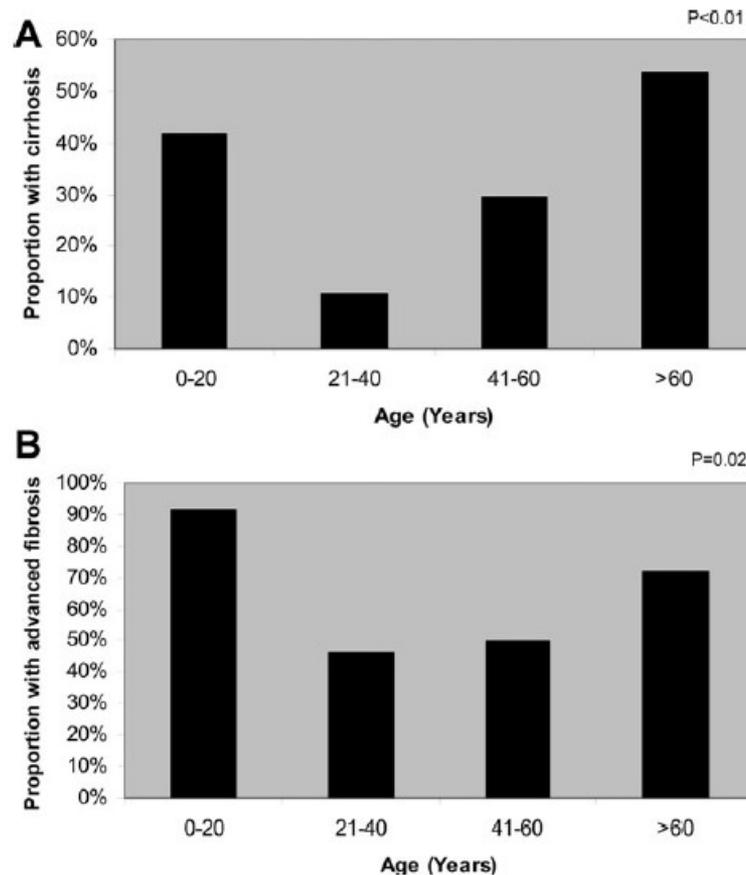# Baseline factors associated with Cirrhosis at AIH at diagnosis

Fig. 1. (A) Proportion of patients with cirrhosis at AIH diagnosis in different age groups. (B) Proportion of patients with advanced liver fibrosis at AIH diagnosis in different age groups.

Ngu et al. Hepatology 2013

Prediction of Short-and Long-Term Outcome in Patients with Autoimmune Hepatitis

Table 4. Factors Associated With Death and Requirement for Liver Transplantation

Factors		P Value	HR	95% CI
Association with death				
Gender	Males	n.s.	0.62	0.09-4.26
	Females		1	
Age	≥18 years	n.s.	1.91	0.25-14.86
	<18 years		1	
SLA/LP	Positive	0.037	6.93	1.12-42.79
	Negative		1	
DRB1*03:01	Positive	n.s.	1.14	0.16-8.02
	Negative		1	
DRB1*04:01	Positive	n.s.	6.44	0.97-42.76
	Negative		1	
Cirrhosis	Yes	0.003	21.25	2.80-164.62
	No		1	
Association with death or LT				
Gender	Males	n.s.	0.39	0.88-1.74
	Females		1	
Age	≥18 years	n.s.	0.96	0.22-4.12
	<18 years		1	
SLA/LP	Positive	0.021	4.25	1.24-14.56
	Negative		1	
DRB1*03:01	Positive	n.s.	3.29	0.68-15.90
	Negative		1	
DRB1*04:01	Positive	n.s.	3.04	0.69-13.35
	Negative		1	
Cirrhosis	Yes	0.009	5.39	1.52-19.13
	No		1	

Analyses were performed with Cox's proportional regression. Subjects were censored at death or death and LT.
Abbreviations: HR, hazard ratio; CI, confidence interval; n.s., not significant.

Kirstein et al. Hepatology 2015

Predictors of Poor outcome in patients with AIH: A population-based study

Table 5. Factors Associated With Liver-Related Death or Requirement for Liver Transplantation

Factors	HR	95% CI	P-value
Gender			
Male	0.97	0.29-3.19	NS
Female	1		
Age at presentation			0.02
Group 1 (0-20yrs)	1.24	0.25-6.09	NS
Group 2 (21-40yrs)	0.10	0.01-0.85	0.04
Group 3 (41-60yrs)	0.15	0.04-0.62	0.01
Group 4 (>60yrs)	1		
Anti-SMA (titer ≥1:80)	0.89	0.29-2.72	NS
ANA (titer ≥1:80)	1.03	0.35-3.08	NS
IgG (>14g/L)	0.43	0.09-1.98	NS
Bilirubin (>50μmol/L)	1.75	0.47-6.44	NS
ALP (>150U/L)	2.12	0.58-7.72	NS
Albumin (<36g/L)	5.47	1.50-19.93	0.01
Platelet (<150U/L)	3.37	0.97-11.67	NS
INR (>1.2)	1.53	0.50-4.71	NS
ALT	0.72	0.48-1.11	NS
Abnormal ALT at 6 months	4.82	1.48-15.72	<0.01
Histological stage ≥ 3	4.03	0.89-18.19	NS
Cirrhosis	2.81	0.91-8.63	NS

Analyses were performed with univariate Cox proportional hazards regression.
Subjects were censored at liver-related death or liver transplantation.

Table 6. Factors Associated With Liver-Related Death or Requirement for Liver Transplantation

Factors	HR	95% CI	P-value
Age at presentation			0.01
Group 1 (0-20yrs)	0.414	0.08-2.12	NS
Group 2 (21-40yrs)	0.08	0.01-0.78	0.03
Group 3 (41-60yrs)	0.08	0.02-0.40	<0.01
Group 4 (>60yrs)	1		
Albumin (<36g/L)	6.30	1.61-24.68	<0.01
Abnormal ALT at 6 months	7.79	2.12-28.68	<0.01

Ngu et al. Hepatology 2013

Long term Outcome of Japanese With type 1 AIH

Table 3. Comparison of Factors Between AIH Patients with and Without Liver-Related Death and Survival Analysis

	Liver-Related Death				Cox Proportional Hazard Model	
Factors	**− (n = 196)**	**+ (n = 7)**	**P**	**Kaplan-Meier Log-Rank Test**	**HR (95% CI)**	**P**
Background						
Sex, women/men	172/24	6/1	1	0.469		
HLA-DR4+/HLA-DR4−/ND	116/49/31	5/0/2	0.273	0.187		
Anti-HBc+/anti-HBc−/ND	24/163/9	2/5/0	0.398	0.524		
At diagnosis						
Age, years, median (range)	57 (12-86)	49 (33-58)	0.069	0.705†		
Acute onset	138	4	0.431	0.842		
Severe symptom*	68	2	1	0.243		
Liver cirrhosis	25	0	0.600	0.205		
Histology at diagnosis						
F3-F4/F1-F2/ND	83/108/5	5/2/0	0.305	0.587		
A2-A3/A0-A1/ND	162/29/5	5/2/0	0.571	0.542		
Treatment and response						
Relapse	42	6	0.001	0.016		
Relapse two or more times	21	6	<0.001	0.003	12.8 (1.5-109.9)	0.02

Abbreviations: HR, hazard ratio; ND, not determined.
Data are presented as no. of patients unless noted otherwise.
*Severe symptom: total bilirubin >5.0 mg/dL and/or prothrombin time <40%.
†Age >58 years.

Yoshizawa et al. Hepatology 2012

Long term Outcome of Japanese With type 1 AIH

Table 5. Comparison of Factors Between AIH Patients With and Without Occurrence of HCC and Survival Analysis

	HCC				Cox Proportional Hazard Model	
Factors	− (n = 195)	+ (n = 8)	P	Kaplan-Meier Log-Rank Test	HR (95% CI)	P
Background						
Sex, women/men	171/24	7/1	1	0.982		
HLA-DR4+/ HLA-DR4−/ND	115/49/31	6/0/2	0.255	0.220		
Anti-HBc+/anti-HBc−/ND	23/163/9	3/5/0	0.093	0.021		
At diagnosis						
Age, years, median (range)	57 (12-86)	53 (33-58)	0.136	0.306†		
Acute onset	136	6	1	0.545		
Severe symptom*	67	3	1	0.710		
Liver cirrhosis	24	1	1	0.640		
Histology at diagnosis						
F3-F4/F1-F2/ND	82/108/5	6/2/0	0.179	0.270		
A2-A3/A0-A1/ND	161/29/5	6/2/0	0.679	0.615		
Treatment and response						
Relapse	42	7	<0.001	0.002		
Relapse two or more times	21	6	<0.001	0.001	9.1 (1.8-45.5)	0.007

Abbreviations: HR, hazard ratio; ND, not determined.
Data are presented as number of patients unless noted otherwise.
*Severe symptom: total bilirubin >5.0 mg/dL and/or prothrombin time <40%.
†Age >58 years.

Yoshizawa et al. Hepatology 2012

Autoimmune Hepatitis in the Elderly

Table 1. Characteristics of Patients at Presentation

	Older Patients	Younger Patients
Female/male	18/2	14/6
Age (yr)	69 (65–77)	24 (14–32)
Observation time (mo)	40 (4–164)	76 (13–189)
Alanine aminotransferase (U/L)*	223 (12–1692)	195 (51–1660)
γ-Globulin (g/L)*	24 (11–73)	26 (9–50)
Acute icteric hepatitis (n)*	9	8
Definite histological cirrhosis (n)*	3	3
ANA (n, median titer)*	14 (160)	17 (160)
SMA (n, median titer)*	12 (80)	14 (80)
SLA/LP (n)*	3	6
LKM-1 (n)*	0	2
Only SLA/LP (n)*	1	1
HLA A1 (n)†	4	15
HLA B8 (n)‡	5	14
HLA A1-B8 (n)§	4	14
HLA DR3 (n)*	7	9
HLA DR4 (n)*	7	2

All patients were tested for autoantibodies. ANA = antinuclear antibody; SMA = smooth muscle antibody; LKM-1 = liver-kidney microsomal antibodies type 1.
* Difference statistically not significant.
† $p = 0.002$.
‡ $p = 0.015$.
§ $p = 0.005$; 15 of the older and 18 of the younger patients were HLA class I haplotyped (14 and 13, respectively, for class II).

Table 2. Outcome Variables

	Older Patients	Younger Patients
Time to diagnosis (mo)*	8.5 (0–348)	3.5 (0–58)
Complete remission (n)†	18	17
Patients with relapse (n)†	6	10
Number of relapses (n)†	9	17

* $p = 0.048$.
† Difference statistically not significant.

Schramm C et al. Am J Gastroenterol 2001

IMMUNITY & AGEING

The effect of ageing on human lymphocyte subsets: comparison of males and females

Jun Yan[1], Judith M Greer[1], Renee Hull[3], John D O'Sullivan[1,3], Robert D Henderson[1,3], Stephen J Read[3],
Pamela A McCombe[1,2,3*]

Questions (1)

The diagnosis of a severe relapse of an autoimmune hepatitis with an icteric decompensation is assessed

- Are there any reasons explaining this complication ?
  - Are the age and the clinical presentation at the onset of the disease unusual ?
  - Presence of cirrhosis ?
  - Characteristics of liver biopsy ?
  - An immunoserological test ?
  - A genetic factor ?
  - Insufficient initial therapy ?
  - A too rapid stopping therapy ?

Clinical and demographic factors associated with a poor outcome

Presence of cirrhosis at presentation:

Yes:

- Feld JJ *et al*. Hepatology 2005
- Werner M *et al*. Scand J Gastroenterol 2010
    - Verma S *et al*. Am J Gastroenterol 2004
    - Al-Chalabi T *et al*. Clin Gastroenterol Hepatol 2008
    - Kirstein M *et al.* Hepatology 2015

No:

- Roberts SK *et al.* Gastroenterology 1996
- Radhakristhnan SR *et al.* Dig Liver Dis 2010
- Ngu JH *et al.* Hepatology 2013
- Yoshizawa K *et al*. Hepatology 2012

Effects of symptoms and cirrhosis on natural history and outcome

Table 4. Outcome of Patients With AIH by Subgroup

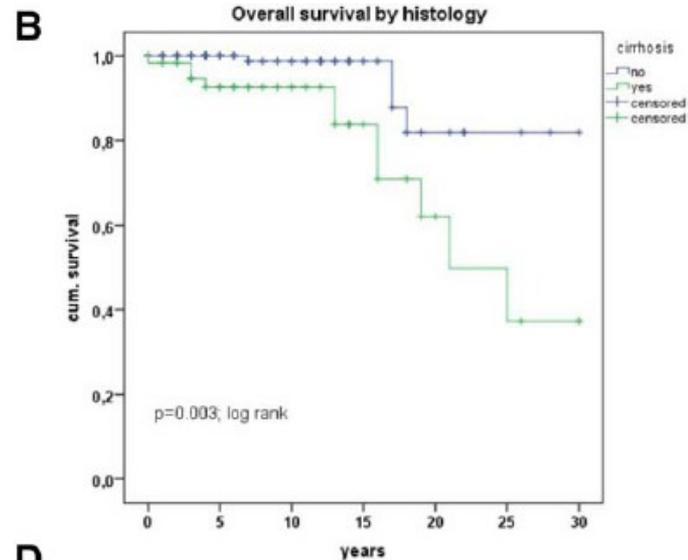|	Asymptomatic at Presentation (n = 31)	Symptomatic at Presentation (n = 94)	P	Cirrhosis at Presentation (n = 42)	No Cirrhosis at Presentation (n = 83)	P	All Patients (n = 125)
Endpoints	5 (16.1%)	15 (16.0%)	NS	16* (38.1%)	4* (4.8%)	<.0001	20 (16.0%)
Transplant	2 (6.5%)	8 (8.5%)	NS	9* (14.2%)	1* (1.2%)	<.0001	10 (8.3%)
Liver death	1 (3.2%)	7 (7.4%)	NS	5 (11.9%)	3 (3.6%)		8 (6.4%)
All death	3 (9.7%)	7 (7.4%)	NS	7* (16.7%)	3* (3.6%)	.02	10 (8.3%)
5-Year survival	87.2% (CI 73.7–100%)	90.2% (CI 83.8–96.7%)	NS	76.3%* (CI 62.8–89.8%)	96.7%* (CI 92.3–100%)	<.05	89.6% (CI 83.7–95.4%)
10-Year survival	80.0% (CI 62.5–97.5%)	83.8% (CI 75.1–92.6%)	.80	61.9%* (CI 44.9–78.9%)	94.0%* (CI 87.4–100%)	.003	83.0% (CI 75.1–90.8%)
5-Year liver-related survival†	91.3% (CI 79.8–100%)	90.2% (CI 83.8–96.7%)	NS	78.7%* (CI 65.6–91.8%)	96.7%* (CI 92.3–100%)	< .05	90.5% (CI 84.9–96.1%)
10-Year liver-related survival†	89.5% (CI 75.7–100%)	83.8% (CI 75.1–92.6%)	.22	67.2%* (CI 50.6–83.9%)	94.0%* (CI 87.4–100%)	.003	85.1% (CI 77.6–92.5%)

**10 –year survival: 61.9 %
(CI 44.9%-78.9%)
vs
94%
(CI 87.4%-100%)**

Feld JJ et al. Hepatology 2005

Cumulative Survival vs Years of follow-up

Cirrhosis
□ Present
□ Absent

Present (n=42) (n=38) (n=36) (n=34) (n=29) (n=25) (n=22) (n=17) (n=14) (n=10) (n=9)
Absent (n=75) (n=68) (n=61) (n=54) (n=51) (n=45) (n=40) (n=36) (n=33) (n=26) (n=22)

Prediction of Short-and Long-Term Outcome in Patients with Autoimmune Hepatitis

Kirstein et al. Hepatology 2015

Predictors of Poor outcome in patients with AIH: A population-based study

Table 5. Factors Associated With Liver-Related Death or Requirement for Liver Transplantation

Factors	HR	95% CI	P-value
Gender			
Male	0.97	0.29-3.19	NS
Female	1		
Age at presentation			0.02
Group 1 (0-20yrs)	1.24	0.25-6.09	NS
Group 2 (21-40yrs)	0.10	0.01-0.85	0.04
Group 3 (41-60yrs)	0.15	0.04-0.62	0.01
Group 4 (>60yrs)	1		
Anti-SMA (titer ≥1:80)	0.89	0.29-2.72	NS
ANA (titer ≥1:80)	1.03	0.35-3.08	NS
IgG (>14g/L)	0.43	0.09-1.98	NS
Bilirubin (>50μmol/L)	1.75	0.47-6.44	NS
ALP (>150U/L)	2.12	0.58-7.72	NS
Albumin (<36g/L)	5.47	1.50-19.93	0.01
Platelet (<150U/L)	3.37	0.97-11.67	NS
INR (>1.2)	1.53	0.50-4.71	NS
ALT	0.72	0.48-1.11	NS
Abnormal ALT at 6 months	4.82	1.48-15.72	<0.01
Histological stage ≥ 3	4.03	0.89-18.19	NS
Cirrhosis	2.81	0.91-8.63	NS

Analyses were performed with univariate Cox proportional hazards regression. Subjects were censored at liver-related death or liver transplantation.

Table 6. Factors Associated With Liver-Related Death or Requirement for Liver Transplantation

Factors	HR	95% CI	P-value
Age at presentation			0.01
Group 1 (0-20yrs)	0.414	0.08-2.12	NS
Group 2 (21-40yrs)	0.08	0.01-0.78	0.03
Group 3 (41-60yrs)	0.08	0.02-0.40	<0.01
Group 4 (>60yrs)	1		
Albumin (<36g/L)	6.30	1.61-24.68	<0.01
Abnormal ALT at 6 months	7.79	2.12-28.68	<0.01

Ngu et al. Hepatology 2013

Long term Outcome of Japanese patients With type 1 AIH

Yoshizawa et al. Hepatology 2012
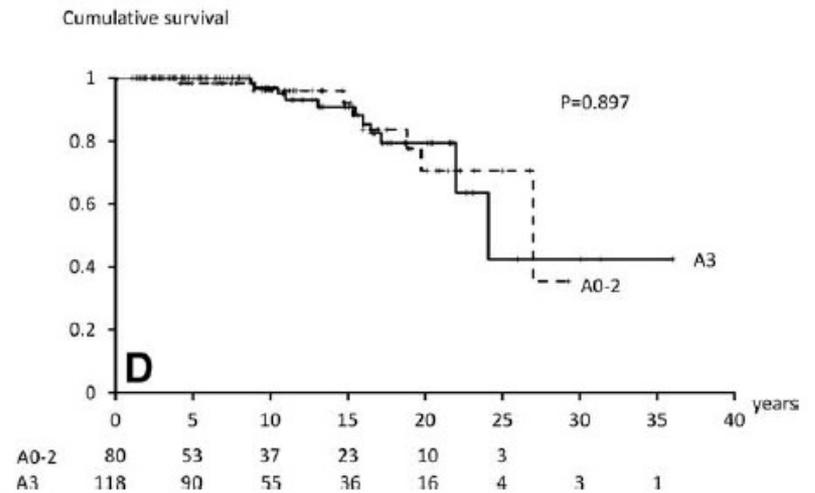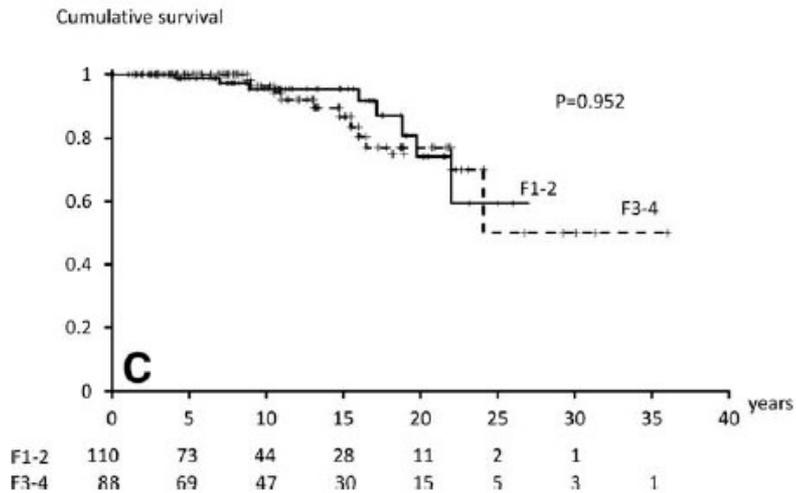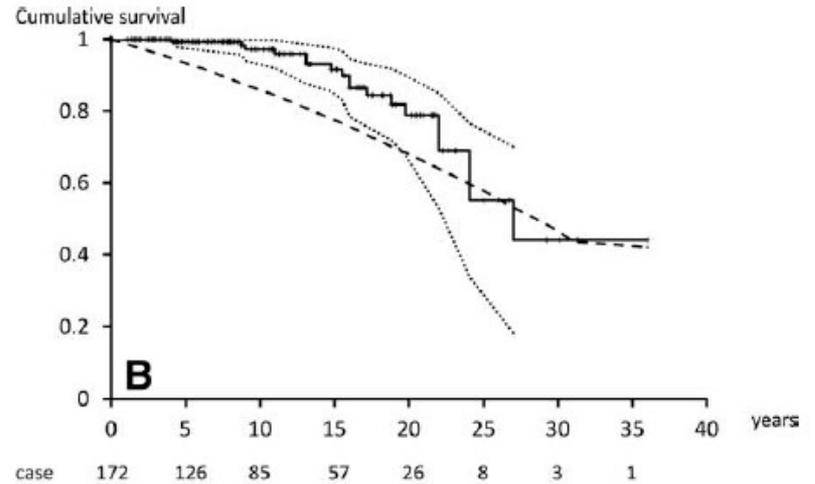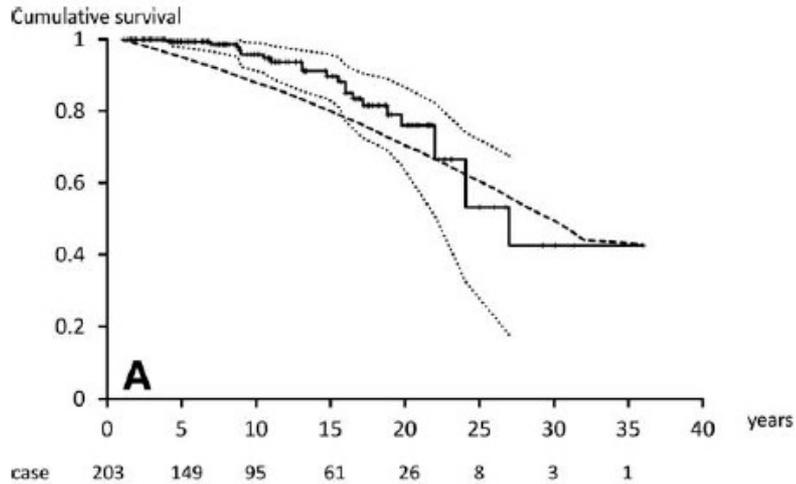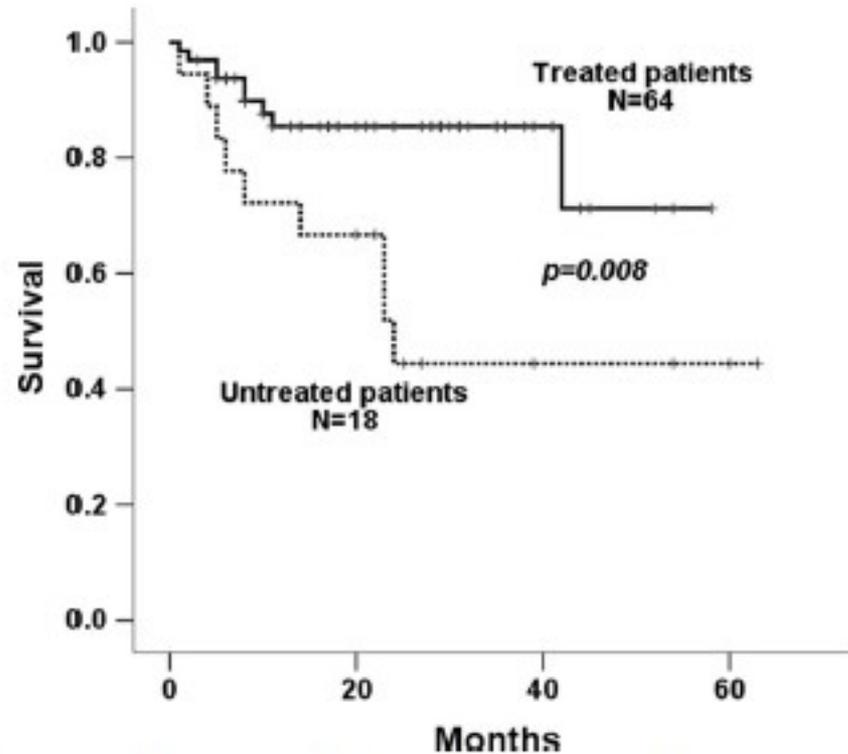
Management of cirrhosis

Fig. 1 Overall survival of patients treated or untreated with corticosteroids. The liver-related death or transplantation free probability was significantly lower in untreated patients ($p = 0.008$)
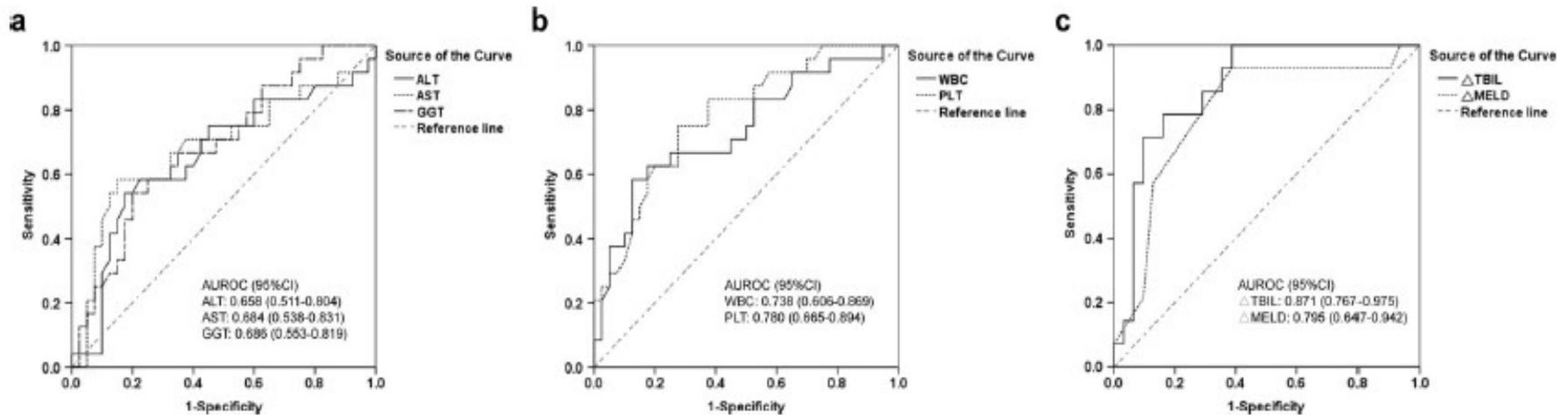
Wang et al. Clinic Rev Allerg Immunol 2017

Management of cirrhosis

Fig. 2 ROC curves depicting the prognostic value for treatment outcomes of selected parameters which were significantly different between reversal and non-reversal groups. a ROC curves of ALT, AST, and GGT. b ROC curves of WBC and PLT. c ROC curves of ΔTBIL and ΔMELD

Wang et al. Clinic Rev Allerg Immunol 2017

The conflicting data concerning cirrhosis suggest that patients with cirrhosis should be offered prompt treatment to avoid hepatic decompensation.

Questions (1)

The diagnosis of a severe relapse of an autoimmune hepatitis with an icteric decompensation is assessed

- Are there any explanations for this complication ?
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  - Presence of cirrhosis ?
  - **Other pathological characteristics ?**
  - An immunoserological test ?
  - A genetic factor ?
 - Insufficient initial therapy ?
  - Was therapy stopped too soon ?

Clinical Case (1)

- A 63 year old woman
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  - PT: 72% ,
  - ALT: 10 X ULN; AST: 5 X ULN
  - Total Bilirubin: 20 μmol/L
  - IgG: 22 g/dL
  - ANA: 1/640; SMA: 1/320; anti SLA/LP- ; AMA-
  - **Liver biopsy: F4 with a moderate activity in the portal tract + Pericentral necrosis**
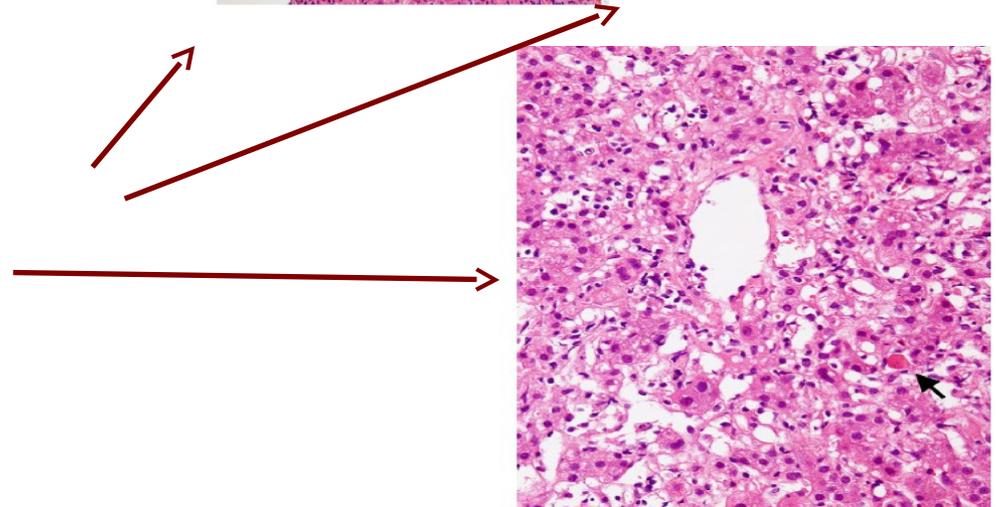 - HLADRB1*04:01

The different pattern of histological lesions of AIH

In the portal tract:
Interface hepatitis
Rosetting of hepatocytes
Predominant Lymphocytic/
Plasmacytic infiltration
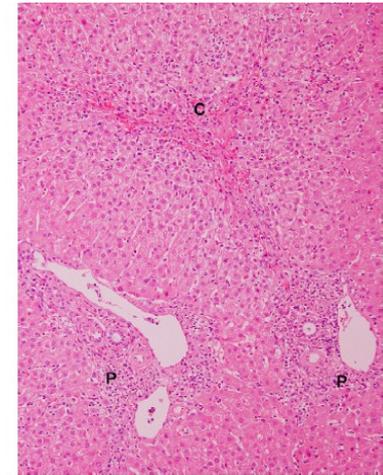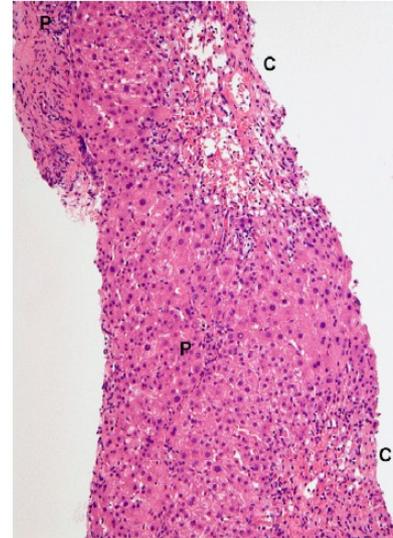
In the centrilobular zone:

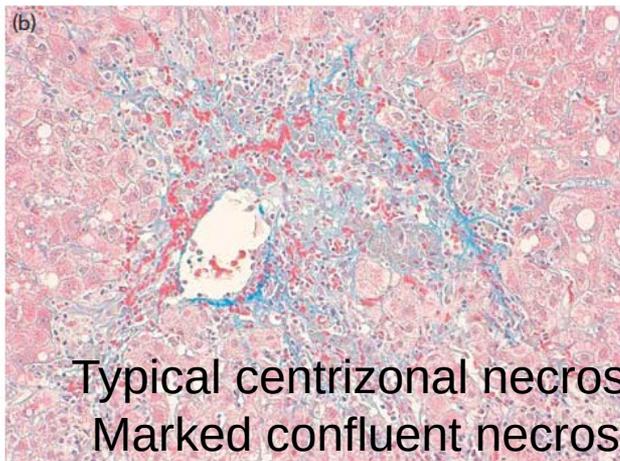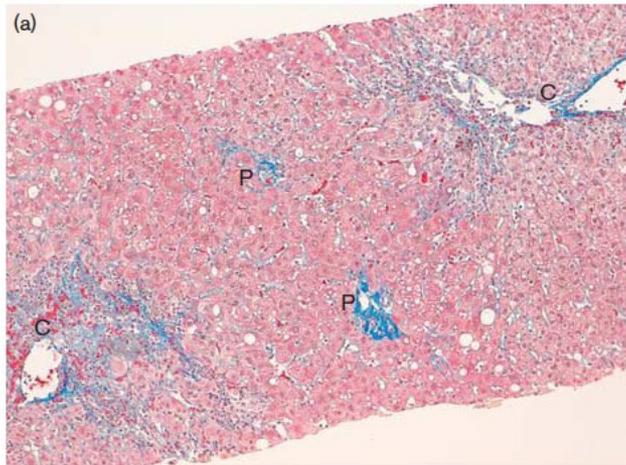*Pratt DS et al. Gastroenterology 1997*

Te HS et al. Gut 1997

Singh R et al. Am J Gastroenterol 2002

Zen Y et al. Hum Pathol 2007
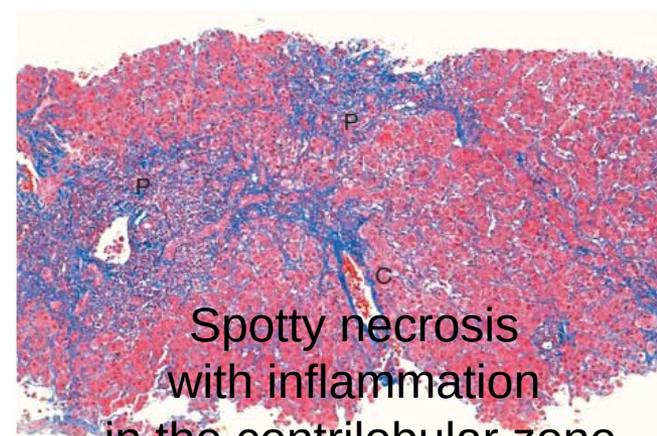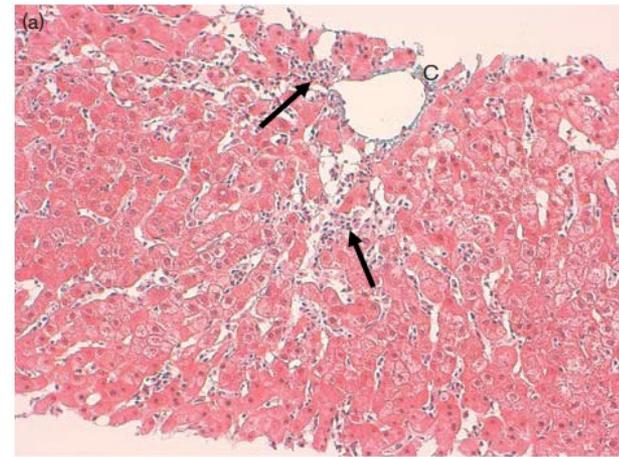
Histological lesions of AIH:
Centrilobular zonal necrosis as a hall mark of a distinctive subtype of AIH
Aizawa Y et al. Eur J Gastroenterol Hepatol 2016

Typical centrizonal necrosis:
Marked confluent necrosis
in the centrilobular zone

≠

Spotty necrosis
with inflammation
in the centrilobular zone

Histological lesions of AIH:
Centrilobular zonal necrosis as a hall mark of a distinctive subtype of AIH
Aizawa Y et al. Eur J Gastroenterol Hepatol 2016

Table 1. Comparisons of demographic and clinical characteristics between AIH patients with and without histologic evidence of CZN

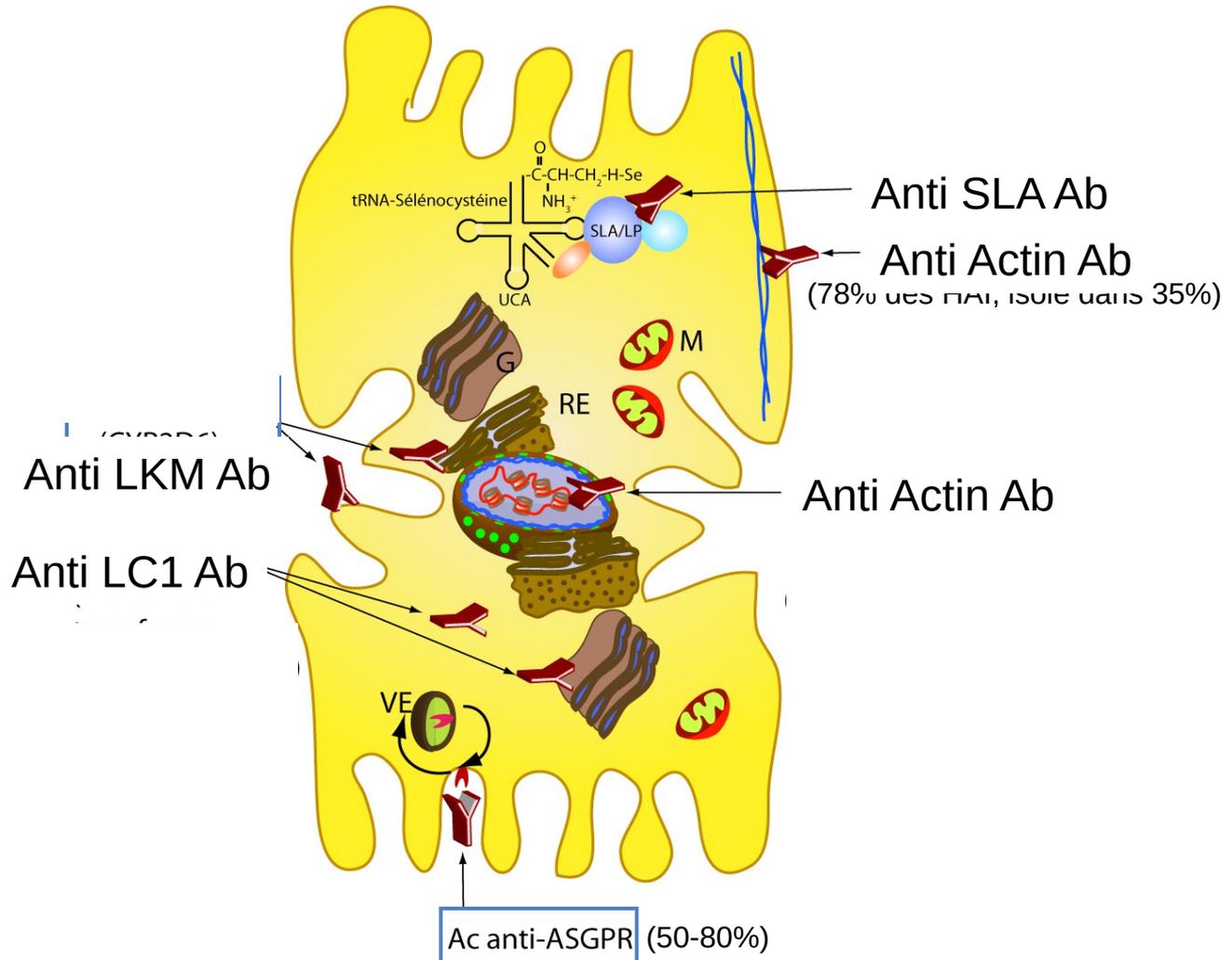|	CZN group (N=15)	Non-CZN group (N=98)	P-value
Age (years)	68 (46–76)	57 (49–68)	0.173
Female sex	14 (93.3)	88 (89.8)	0.395
Acute onset	12 (80.0)	43 (43.9)	0.012
Other autoimmune disease	4 (26.7)	13 (13.3)	0.237
ANA-positive: ≥ 40	8 (53.3)	89 (90.8)	0.006
ANA-high titer positive: ≥ 160	1 (6.7)	59 (60.2)	<0.001
AST (IU/l)	356 (180–614)	221 (109.5–485)	0.133
ALT (IU/l)	563 (284–683)	284.5 (126–555.5)	0.036
ALP (IU/l)	462 (378–496)	459 (315–575)	0.633
GGT (IU/l)	122 (73–186)	172.5 (83.5–279.5)	0.365
Total bilirubin (mg/dl)	1.0 (0.9–1.6)	1.1 (0.8–3.5)	0.654
Albumin (g/dl)	4.0 (3.8–4.1)	3.8 (33–4.1)	0.050
Serum IgG (mg/dl)	1816 (1482–2141)	2455 (1917.5–3063)	<0.001
Serum IgM (mg/dl)	93 (57–115)	160 (97.5–260.5)	0.001
Platelet count (10^4/µl)	19.0 (14.7–19.9)	18.0 (13.5–23.1)	0.923
Prothrombin time (%)	82.0 (68.0–90.5)	85.5 (76.4–99.8)	0.472
Histology			
F0–F1	8 (53.3)	27 (27.6)	0.069
F2–F4	7 (46.7)	71 (72.4)	
Interface hepatitis (moderate to severe)	8 (53.3)	89 (90.8)	0.001
Lymphoplasmacytic infiltrate	10 (66.7)	89 (90.8)	0.021
Rosetting	11 (73.3)	80 (81.6)	0.487
Pretreatment AIH score	15 (12–17)	18 (16–20)	<0.001

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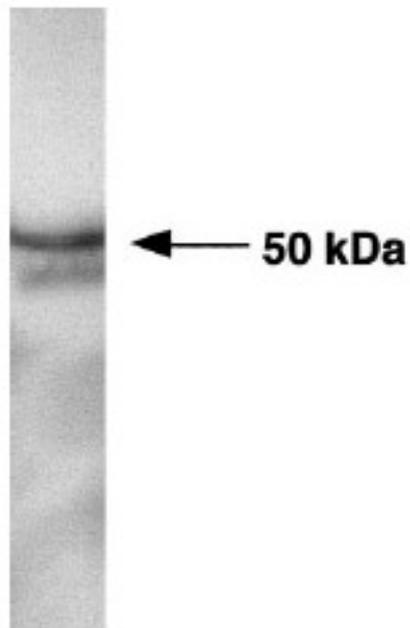# Antigen-Antibody Relation in Autoimmune Hepatitis

Anti SLA Ab

Anti Actin Ab
(78% des HAI, isolé dans 35%)

Anti LKM Ab

Anti Actin Ab

Anti LC1 Ab

Ac anti-ASGPR (50-80%)

Thanks to Eric Ballot
Immunology Saint Antoine
UMR – S 1193

Type 2

Type 1

Antibodies to Conformational Epitopes
of Soluble Antigen Define a Severe
Form of Autoimmune Liver Disease

← 50 kDa

Fig. 1. Immunoprecipitation of *in vitro* translated tRNP$^{(Ser)Sec}$/SLA. Immunoprecipitation with a serum containing high titer of anti-tRNP$^{(Ser)Sec}$/SLA antibody (cpm 3575) from a patient with type 1 AIH. The protein (band pointed by an **arrow**) translated from the tRNP$^{(Ser)Sec}$ cDNA has the predicted size of 50 kd.

4 patients positive for anti-tRNP$^{(Ser)Sec}$/SLA on at least ...n, 10 died or required liver transplantation compared ...he 37 persistently seronegative patients ($P < .01$). The ...n survival/requirement for transplantation remains sig- ...the 2 children who died of liver-unrelated conditions ...lymphoma) are removed ($P = .02$).
...the 203 controls, only 3 were positive including 1 pa- ...iliary atresia and 2 with SLE (Table 1).

Ma et al. Hepatology 2002

Prediction of Short-and Long-Term Outcome in Patients with Autoimmune Hepatitis

A Total patient population

Legend:
- Males (black)
- Females (white)
- >=18 years
- <18 years
- 1
- 2
- Anti-SLA/LP

X-axis: Gender, Age, Type
Y-axis: n= (0 to 400)

Table 4. Factors Associated With Death and Requirement for Liver Transplantation

Factors		P Value	HR	95% CI
Association with death				
Gender	Males	n.s.	0.62	0.09-4.26
	Females		1	
Age	≥18 years	n.s.	1.91	0.25-14.86
	<18 years		1	
SLA/LP	Positive	0.037	6.93	1.12-42.79
	Negative		1	
DRB1*03:01	Positive	n.s.	1.14	0.16-8.02
	Negative		1	
DRB1*04:01	Positive	n.s.	6.44	0.97-42.76
	Negative		1	
Cirrhosis	Yes	0.003	21.25	2.80-164.62
	No		1	
Association with death or LT				
Gender	Males	n.s.	0.39	0.88-1.74
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	No		1	

Analyses were performed with Cox's proportional regression. Subjects were censored at death or death and LT.
Abbreviations: HR, hazard ratio; CI, confidence interval; n.s., not significant.

Kirstein et al. Hepatology 2015

Prediction of Short-and Long-Term Outcome in Patients with Autoimmune Hepatitis

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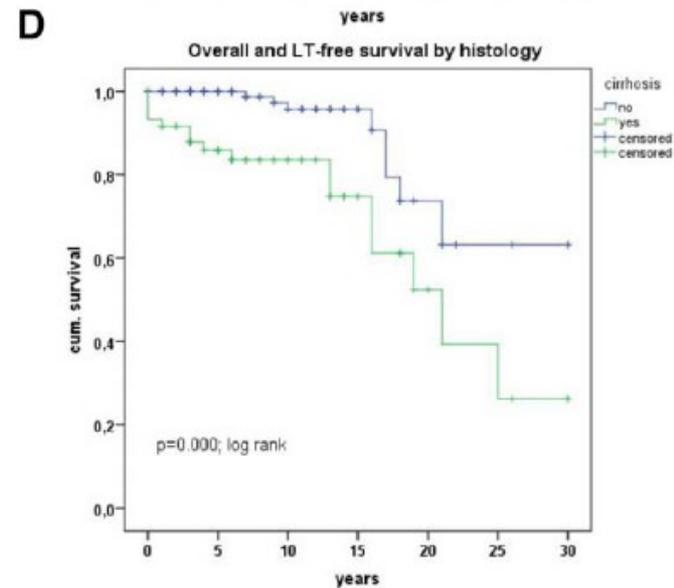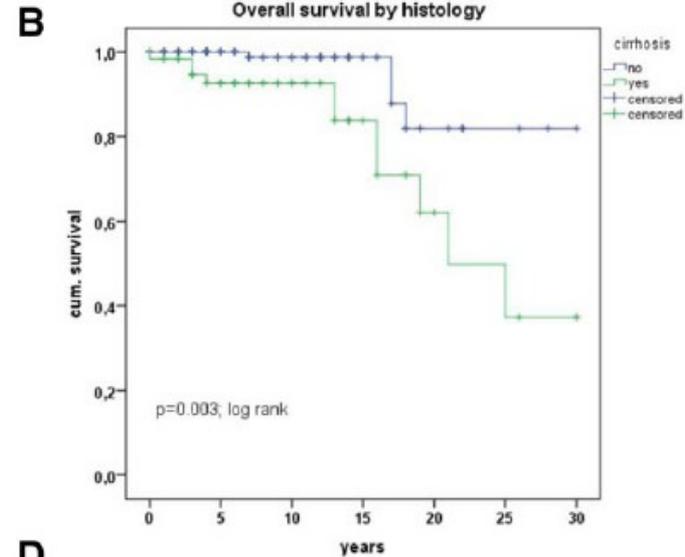
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Kirstein et al. Hepatology 2015

Prediction of Short-and Long-Term Outcome in Patients with Autoimmune Hepatitis

Kirstein et al. Hepatology 2015

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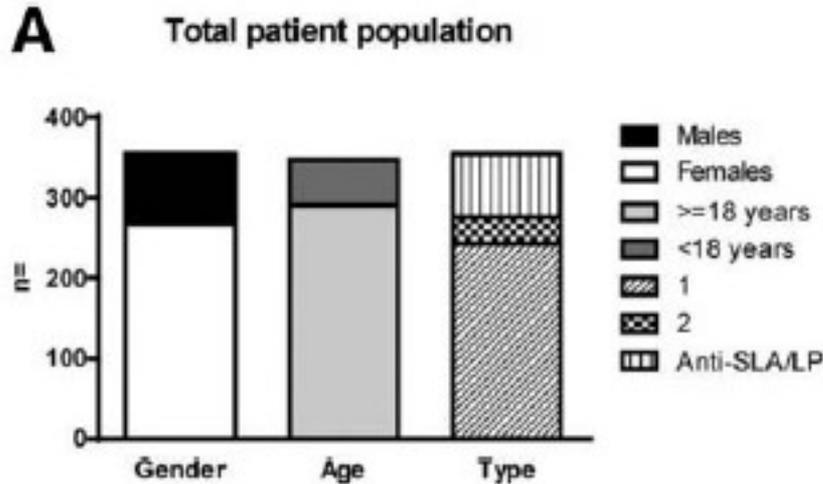# Prediction of Short-and Long-Term Outcome in Patients with Autoimmune Hepatitis

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Kirstein et al. Hepatology 2015

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  – At 1 year because of normalisation of ALT, prednisolone was stopped and azathioprine was maintained at a dosage of 50 mg/day

  – At 2 years after diagnosis, azathioprine was stopped because of maintenance of normalisation of ALT and a marked decrease level of IgG 14.5 g/dL   (N < 12.0 g/dL)

Therapy

Table 7. Treatment proposal for adult patients with AIH (e.g. 60 kg).

Week	Prednisolone (mg/day)	Azathioprine (mg/day)
1	60 (= 1 mg/kg body weight)	-
2	50	-
3	40	50
4	30	50
5	25	100*
6	20	100*
7 + 8	15	100*
8 + 9	12.5	100*
From week 10	10	100*

Reduction of prednisolone to 7.5 mg/day if aminotransferases reach normal levels and after three-months to 5 mg/day, tapering out at three-four months intervals depending on patient's risk factors and response. *Azathioprine dose of 1–2 mg/kg according to body weight.

Treatment Response in Patients with Autoimmune Hepatitis

No Cirrhosis:

Initial dose of prednisolone of 1 mg/kg of body weight
Tapered to within the next 3 months
to a maintenance dose to 5 to 10 mg/day
+
From the beginning, combination with Azathioprine
at a dose of 1 to 1.5 mg/kg of body weight

10%
13%
77%

□ complete biochemical response

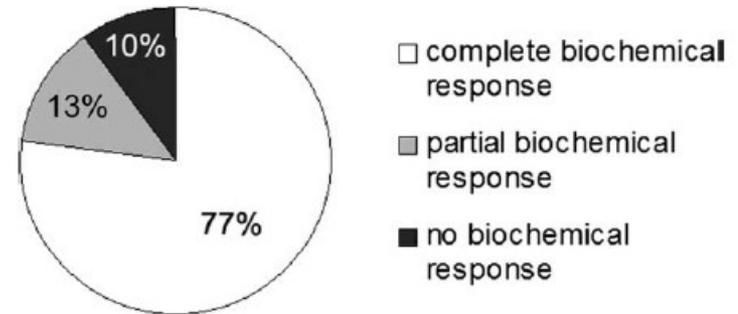▦ partial biochemical response

■ no biochemical response

Fig. 1. Biochemical response after 6 months of treatment in 92 patients with noncirrhotic AIH. Complete response is defined as normalization of aminotransferases and IgG/gamma-globulins, partial response is defined as a reduction of aminotransferases and IgG/gamma-globulins to less than 2 times the upper limit of normal, and no response is defined as none of the above.

Schramm C et al. Hepatology 2010
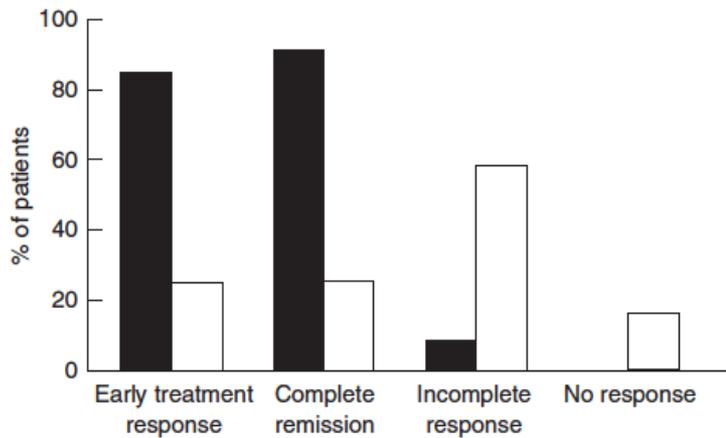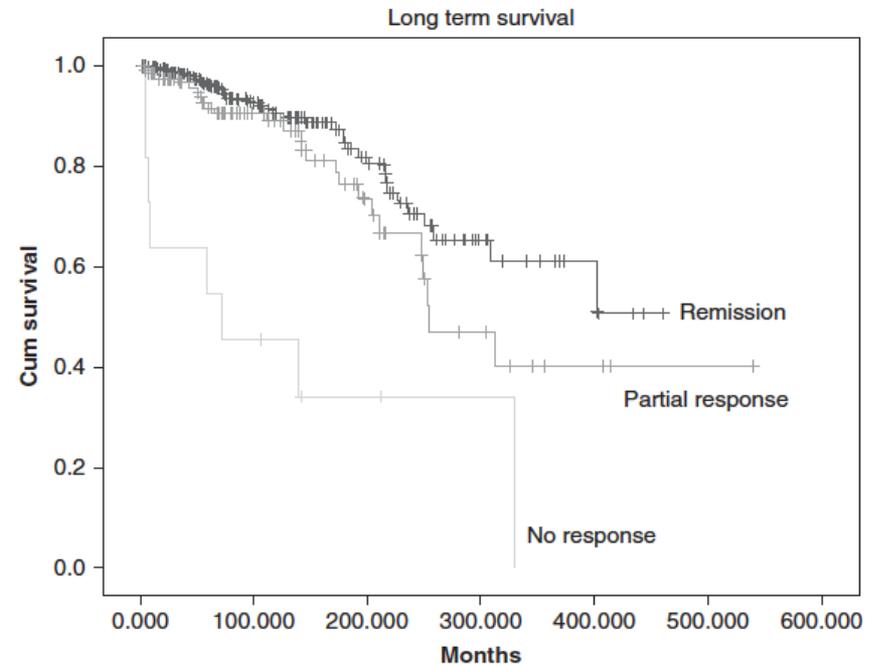
The importance of the initial response

Fig. 1. A comparison of response to immunosuppressive therapy between transplant patients (□) and non-transplant patients (■). Treatment response was statistically different for all paired comparisons ($P < 0.05$).

Tan P et al. Liver Int 2005
Werner M et al. Scand J Gastroentrol 2010

Baseline factors associated with Liver-Related Death or Requirement for Liver transplantation

Table 5. Factors Associated With Liver-Related Death or Requirement for Liver Transplantation

Factors	HR	95% CI	P-value
Gender			
Male	0.97	0.29-3.19	NS
Female	1		
Age at presentation			0.02
Group 1 (0-20yrs)	1.24	0.25-6.09	NS
Group 2 (21-40yrs)	0.10	0.01-0.85	0.04
Group 3 (41-60yrs)	0.15	0.04-0.62	0.01
Group 4 (>60yrs)	1		
Anti-SMA (titer ≥1:80)	0.89	0.29-2.72	NS
ANA (titer ≥1:80)	1.03	0.35-3.08	NS
IgG (>14g/L)	0.43	0.09-1.98	NS
Bilirubin (>50μmol/L)	1.75	0.47-6.44	NS
ALP (>150U/L)	2.12	0.58-7.72	NS
Albumin (<36g/L)	5.47	1.50-19.93	0.01
Platelet (<150U/L)	3.37	0.97-11.67	NS
INR (>1.2)	1.53	0.50-4.71	NS
ALT	0.72	0.48-1.11	NS
Abnormal ALT at 6 months	4.82	1.48-15.72	<0.01
Histological stage ≥ 3	4.03	0.89-18.19	NS
Cirrhosis	2.81	0.91-8.63	NS

Analyses were performed with univariate Cox proportional hazards regression. Subjects were censored at liver-related death or liver transplantation.

Table 6. Factors Associated With Liver-Related Death or Requirement for Liver Transplantation

Factors	HR	95% CI	P-value
Age at presentation			0.01
Group 1 (0-20yrs)	0.414	0.08-2.12	NS
Group 2 (21-40yrs)	0.08	0.01-0.78	0.03
Group 3 (41-60yrs)	0.08	0.02-0.40	<0.01
Group 4 (>60yrs)	1		
Albumin (<36g/L)	6.30	1.61-24.68	<0.01
Abnormal ALT at 6 months	7.79	2.12-28.68	<0.01

Analyses were performed with multivariate Cox proportional hazards regression and included candidate factors that were significant (P < 0.05) from the univariate associations.
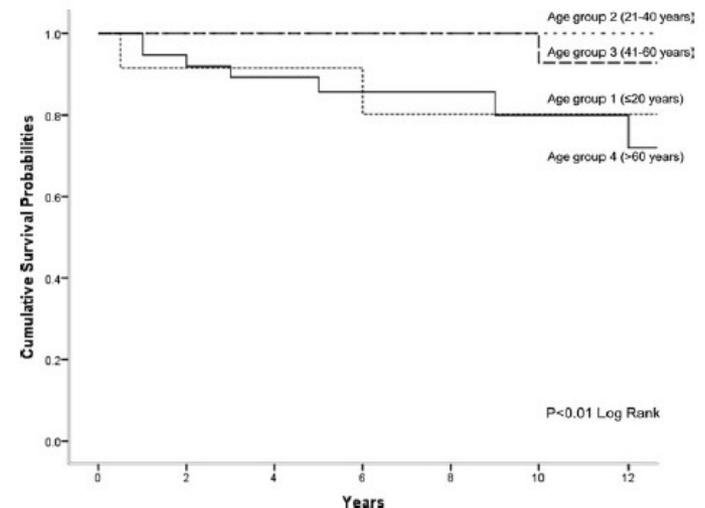

Fig. 2. Cumulative survival estimates to liver-related death or requirement for liver transplantation in different age groups.

Ngu et al. Hepatology 2013

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Long term outcome of patients with AIH

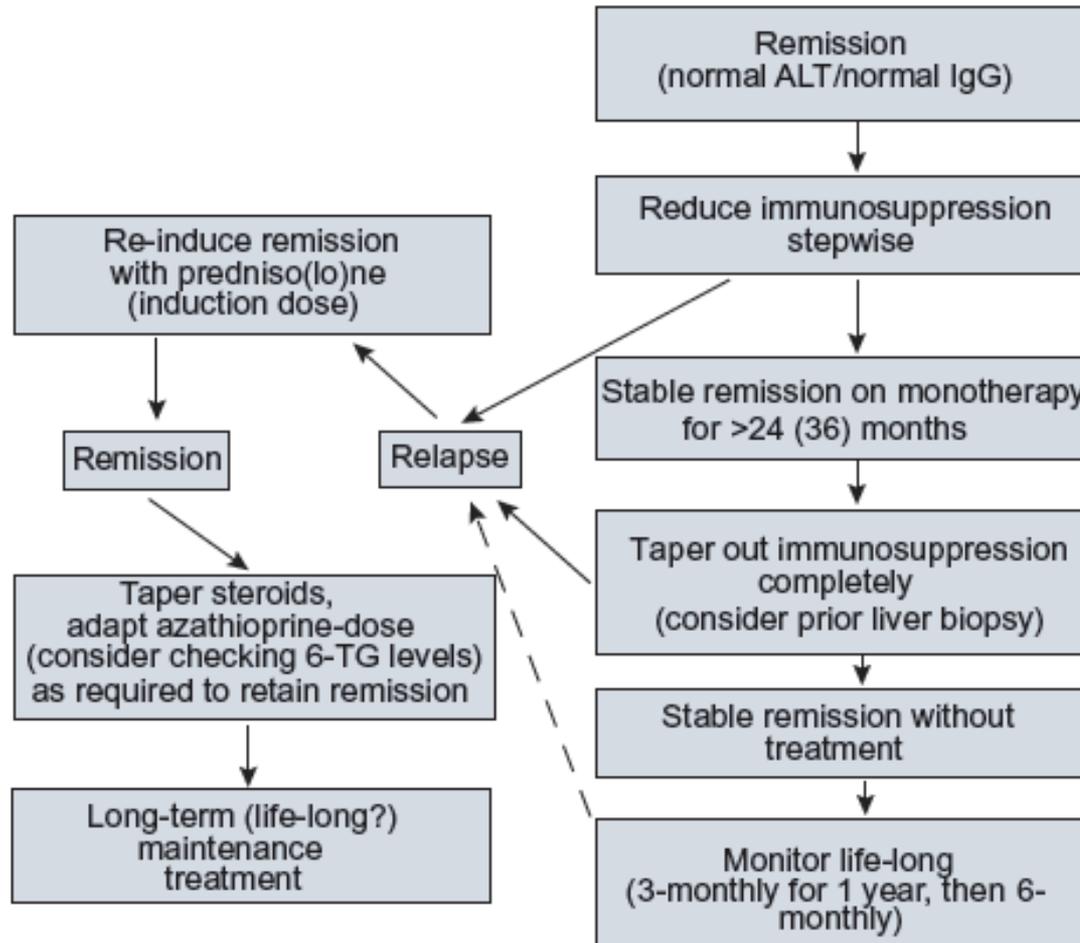- *Are there any stopping rules ?*

  - Yes ?
  - No ?

Follow-up

Fig. 5. Follow-up of autoimmune hepatitis patients who have achieved remission. Note that drug-free remission of autoimmune hepatitis is infrequent and cannot be achieved in the majority of patients.

EASL Clinical Practice Guidelines: Autoimmune Hepatitis J Hepatol 2015

Biological Criteria of Remission in patients with AIH

Elevated levels of aminotranferases +
IgG/gamma-globulins, or both
indicate
histological activity

Luth S et al. J Clin Gastroenterol 2008
Montano-Loza AJ et al. Am J Gastreonterol 2007
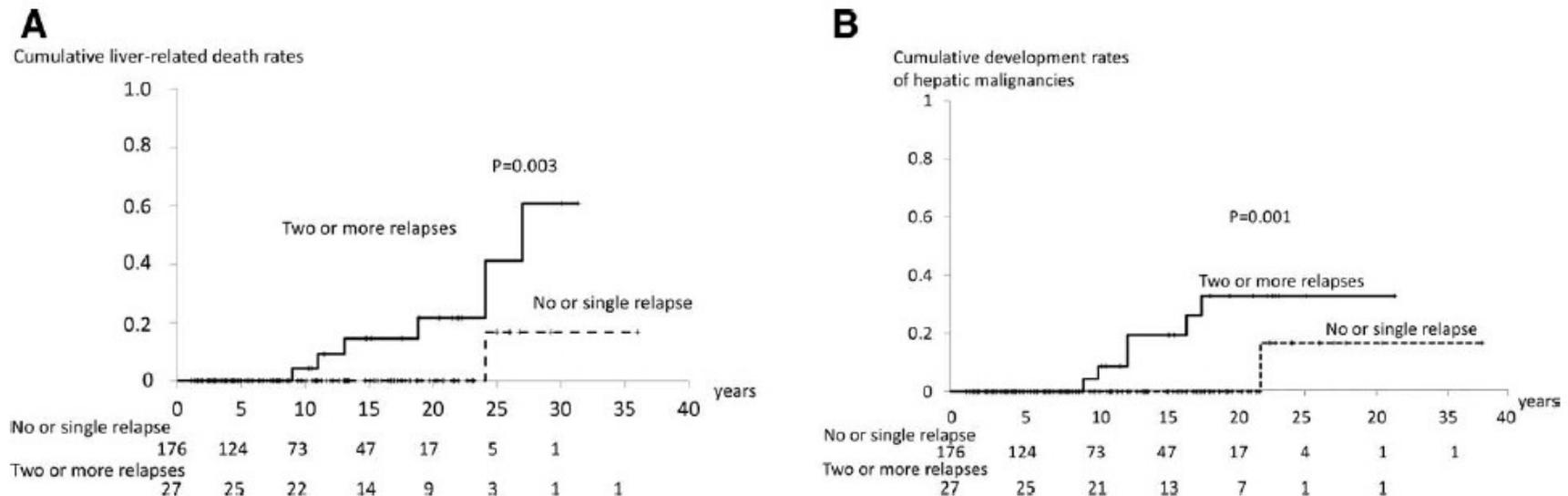
Long term Outcome of Japanese With type 1 AIH

Fig. 3. (A) Cumulative liver-related death rates of patients who experienced no or a single relapse (broken line) and those with two or more relapses (solid line). The prognosis of patients with repeated relapses was poorer than those with remission or a single relapse ($P = 0.003$). (B) Cumulative hepatic malignancy rates of patients who experienced no or a single relapse (broken line) and those with two or more relapses (solid line). The development rate of hepatic malignancies was higher in patients with repeated relapses than in those with remission or a single relapse ($P = 0.001$).

Yoshizawa et al. Hepatology 2012

Long term Outcome of Japanese With type 1 AIH

Withdrawal of therapy
was considered if remission
was achieved and maintained
for at least 2 years
and the patient agree to cessation

Yoshizawa et al. Hepatology 2012

Table 1. Characteristics of the Long-term Follow-up AIH Cohort (n = 203)

Characteristics	Values
Age at diagnosis, years	55.5 (12-86)
Sex, women/men	177/26
Mean observation period, months	131 (13-432)
IAIHG score before treatment	17.4 (10-22)
Definite AIH	172 (84.7)
Acute onset	142 (70.0)
Chronic onset	61 (30.0)
Severe symptom at diagnosis*	72 (35.5)
Cirrhosis at diagnosis	26 (12.8)
Stage F3 or F4 at diagnosis (n = 198)	88 (44.4)
HLA-DR4 (n = 169)	121 (71.6)
Overlap with primary biliary cirrhosis	8 (3.9)
Achieved remission	203 (100)
Treatment withdrawal	13 (6.4)
Relapse	48 (23.6)
Relapse two or more times	27 (13.3)
Death	22 (10.8)
Liver-related death	7 (3.4)
ANA $\times 40$ or more	194 (95.6)
AMA or M2-positive	11 (5.4)
Platelet count, $\times 10^4/mm^3$	17.3 (3.9-33.6)
Bilirubin level, mg/dL†	5.7 (0.3-30.4)
ALT level, U/L‡	622.1 (47-5,586)
ALP level, U/L§	498.1 (101-1,984)
IgG level, mg/dL§§	2,981.2 (1,110-7,600)
Anti-HBc (n = 193)	26 (13.5)

Long term Outcome of Japanese With type 1 AIH

Table 3. Comparison of Factors Between AIH Patients with and Without Liver-Related Death and Survival Analysis

Factors	Liver-Related Death			Kaplan-Meier Log-Rank Test	Cox Proportional Hazard Model	
	− (n = 196)	+ (n = 7)	P		HR (95% CI)	P
Background						
Sex, women/men	172/24	6/1	1	0.469		
HLA-DR4+/HLA-DR4−/ND	116/49/31	5/0/2	0.273	0.187		
Anti-HBc+/anti-HBc−/ND	24/163/9	2/5/0	0.398	0.524		
At diagnosis						
Age, years, median (range)	57 (12-86)	49 (33-58)	0.069	0.705†		
Acute onset	138	4	0.431	0.842		
Severe symptom*	68	2	1	0.243		
Liver cirrhosis	25	0	0.600	0.205		
Histology at diagnosis						
F3-F4/F1-F2/ND	83/108/5	5/2/0	0.305	0.587		
A2-A3/A0-A1/ND	162/29/5	5/2/0	0.571	0.542		
Treatment and response						
Relapse	42	6	0.001	0.016		
Relapse two or more times	21	6	<0.001	0.003	12.8 (1.5-109.9)	0.02

Abbreviations: HR, hazard ratio; ND, not determined.
Data are presented as no. of patients unless noted otherwise.
*Severe symptom: total bilirubin >5.0 mg/dL and/or prothrombin time <40%.
†Age >58 years.

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Clinical Case (4)

In November 2017:

- Jaundice
- Ascites and Encephalopathy= 0
- Total Bilirubin: 60 μmol/L, conj: 35 μmol/L
- ALT: 10 X ULN
- PT: 58%, V factor: 68%
- IgG: 25 g/dL
- US: heterogeneous parenchyma, no biliary tract abnormalities, viral tests (HBV, HCV, HEV) are negative

Questions (2)

The diagnosis of a severe relapse with an icte
decompensation is assessed

How do you treat this decompensation ?

Answers

1. The same regimen as the initial one

2. A regimen with lower dosage of steroids and azathioprine

3. An inscription on the waiting list of liver transplantation

4. An other regimen of therapy

Clinical Case (5)

- An induction of therapy was performed by 1mg/Kg prednisolone therapy then Azathioprine (1mg/kg) was introduced

    – A complete remission (normalisation of ALT and Ig G: 12 g/dL) was obtained after 1 month of combination of therapy

Therapy of Relapse

33. Only a small minority of patients stay in remission without maintenance therapy. A trial of treatment withdrawal requires close cooperation between patient and physician. A relapse occurs most commonly within 12 months after treatment withdrawal. However, relapse may even occur many years later. Patients should therefore be closely monitored after treatment withdrawal, and surveillance continued lifelong. An increase in IgG can precede the rise of transaminases in a relapse (II-2)

34. Treatment of the relapse or flare may require steroid doses similar to the induction regimen. Earlier detection of relapse allows lower doses of immunosuppressants to re-induce full remission (II-2)

35. Patients who have received adequate immunosuppression and have relapsed during drug withdrawal, or who experienced a flare during adequate maintenance therapy should be kept on immunosuppression permanently (II-2)
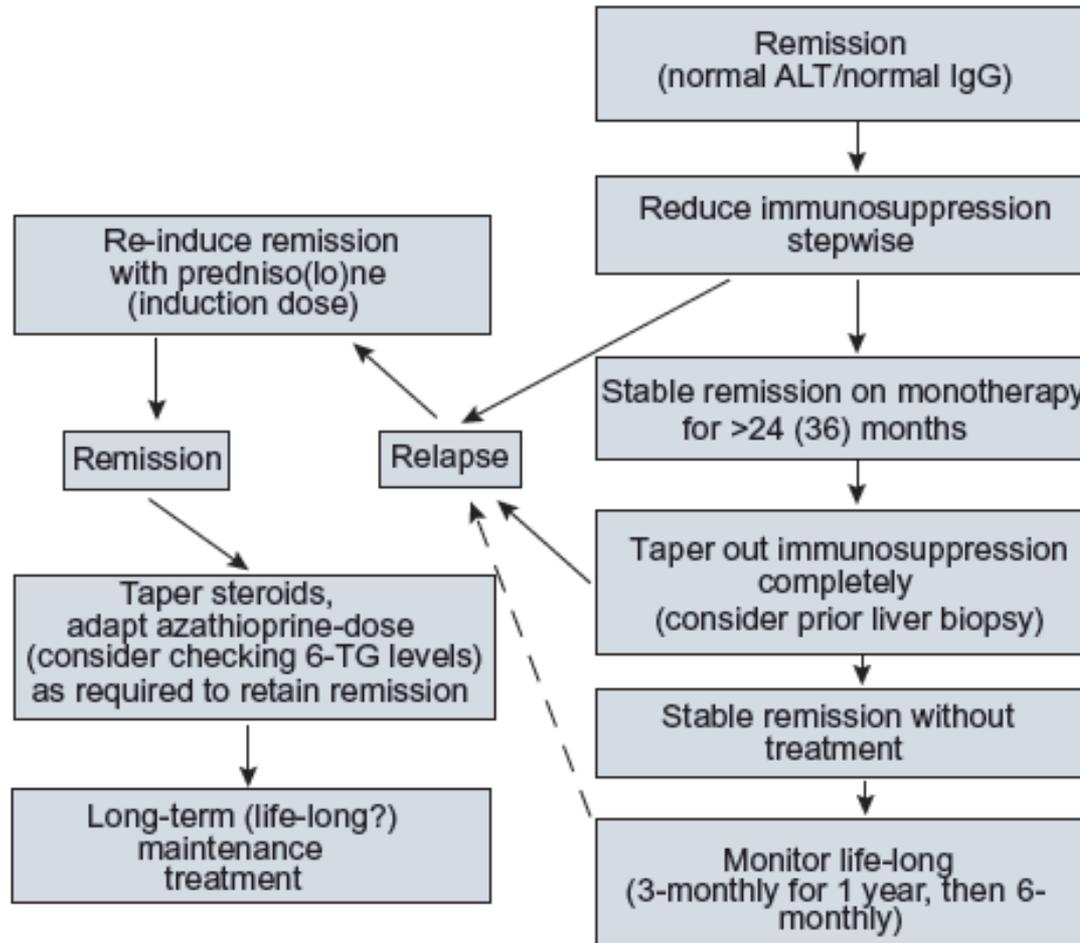
Follow-up

Fig. 5. Follow-up of autoimmune hepatitis patients who have achieved remission. Note that drug-free remission of autoimmune hepatitis is infrequent and cannot be achieved in the majority of patients.

EASL Clinical Practice Guidelines: Autoimmune Hepatitis J Hepatol 2015

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n=203

Adverse effects of long-term immunosuppressive therapy:

	N (%)
Osteoporosis	25 (12.5%)
Diabetes mellitus	20 (10.3%)
Fatty liver change	19 (9.4%)
Cataract	5 (2.5%)
Compression fracture of spine	1
Cerebral bleeding	1
Gastric ulcer	1
Psychiatric problem	1

Yoshizawa et al. Hepatology 2012

Latest News

At the begining of January, the patient is in good health and has normal liver tests