X Workshop Nazionale

Innovazione e Ricerca per la Pratica Clinica

TERAPIE INNOVATIVE DELLE EPATITI CRONICHE VIRALI

Firenze, 13-14 gennaio 2020

Centro Congressi Hotel Londra

Problemi aperti nella terapia dell'epatite autoimmune

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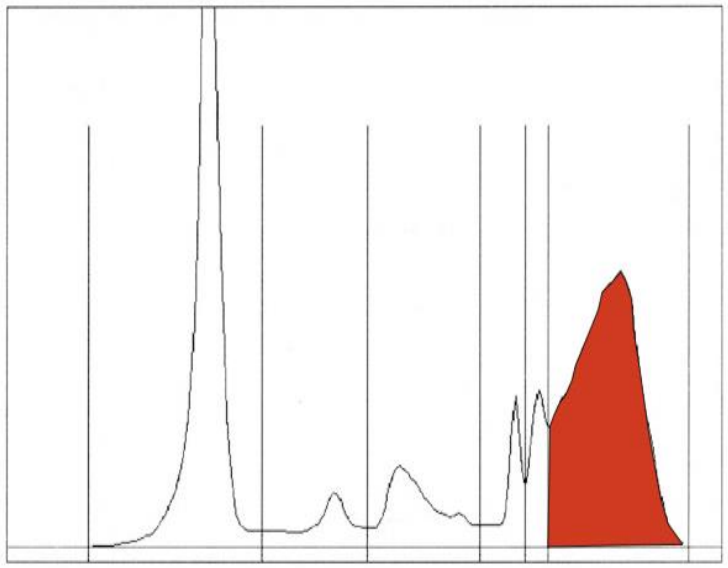
Autoimmune hepatitis

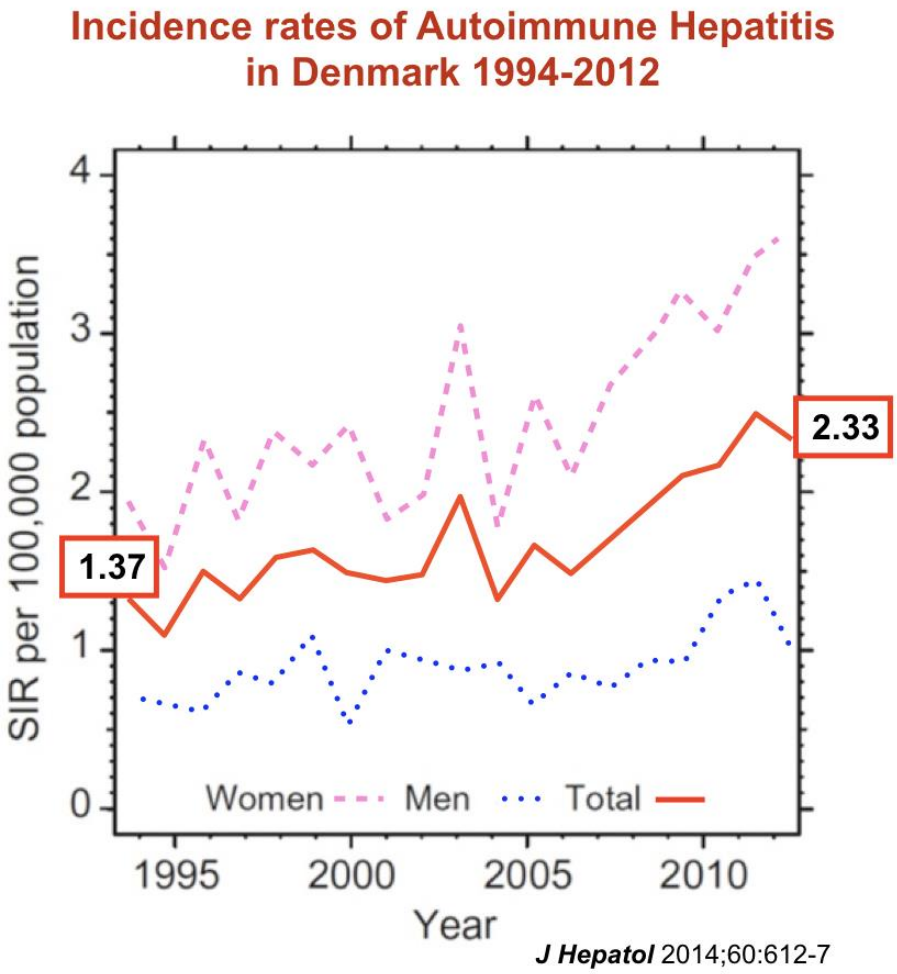
- High/very high ALT levels (>5x in 76%)
- Elevated IgG in 75%
- At least one or more of the following autoantibodies: ANA, SMA, anti-LKM1, anti-LC1, anti-SLA (95%)
- Histology:interface hepatitis



Total protein:100gr/L
Albumin:36.6%
Gammaglobulin:40.5%

IgG: 3513mg/dL
IgA: 687 mg/dL
IgM: 97 mg/dL

1721 AIH patients, 72% women, incidence peak 70 years. 77 OLT in 15 year follow-up
Incidence rate 1.68/100000/year ((**1994**), **2.33** (**2012**). 2.6 higher in women/man
Prevalence 23.9/100000 (34.6 for women, 13 for men)



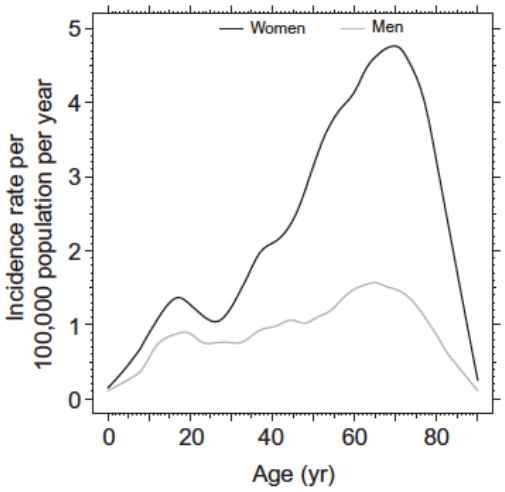
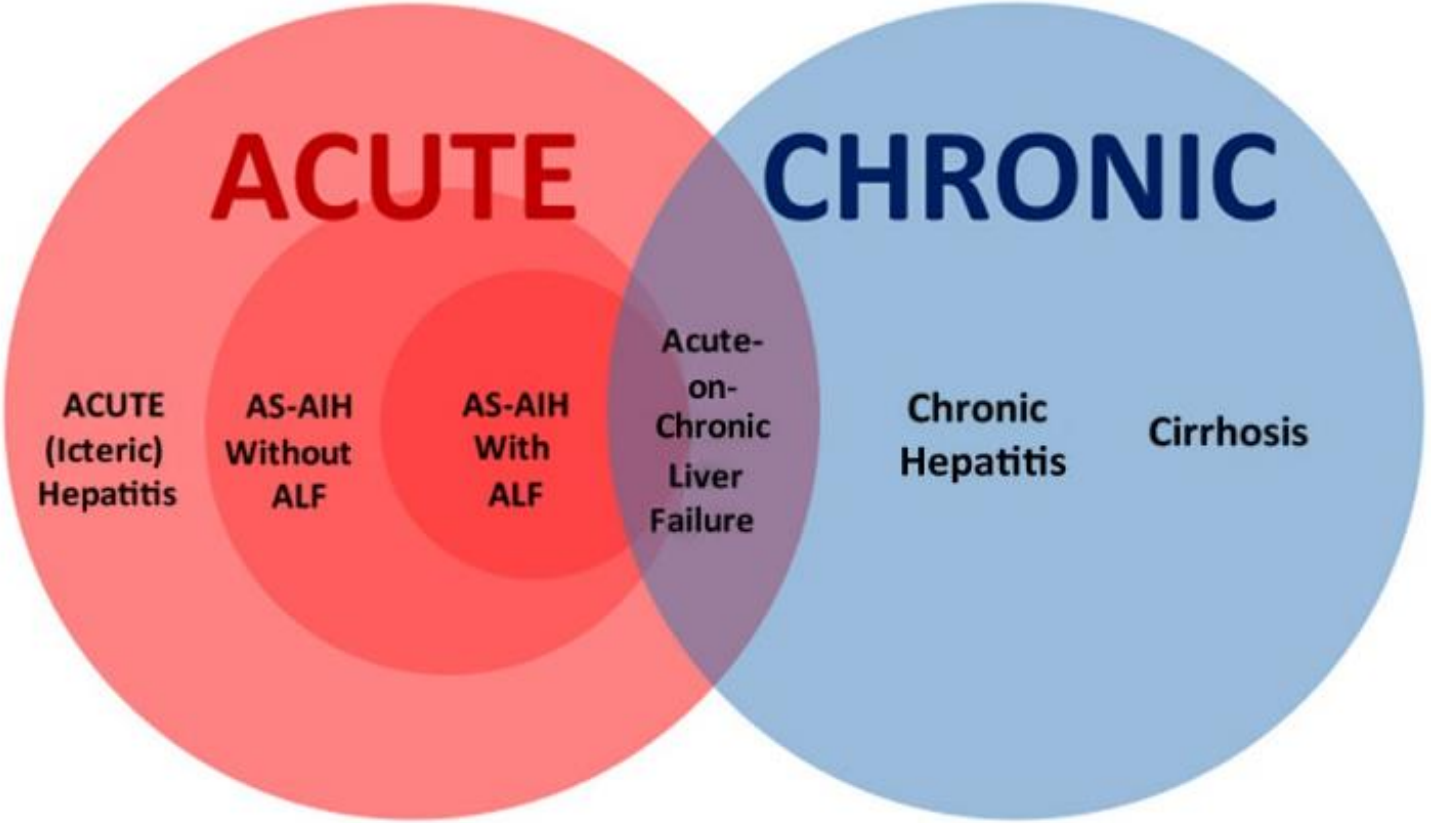


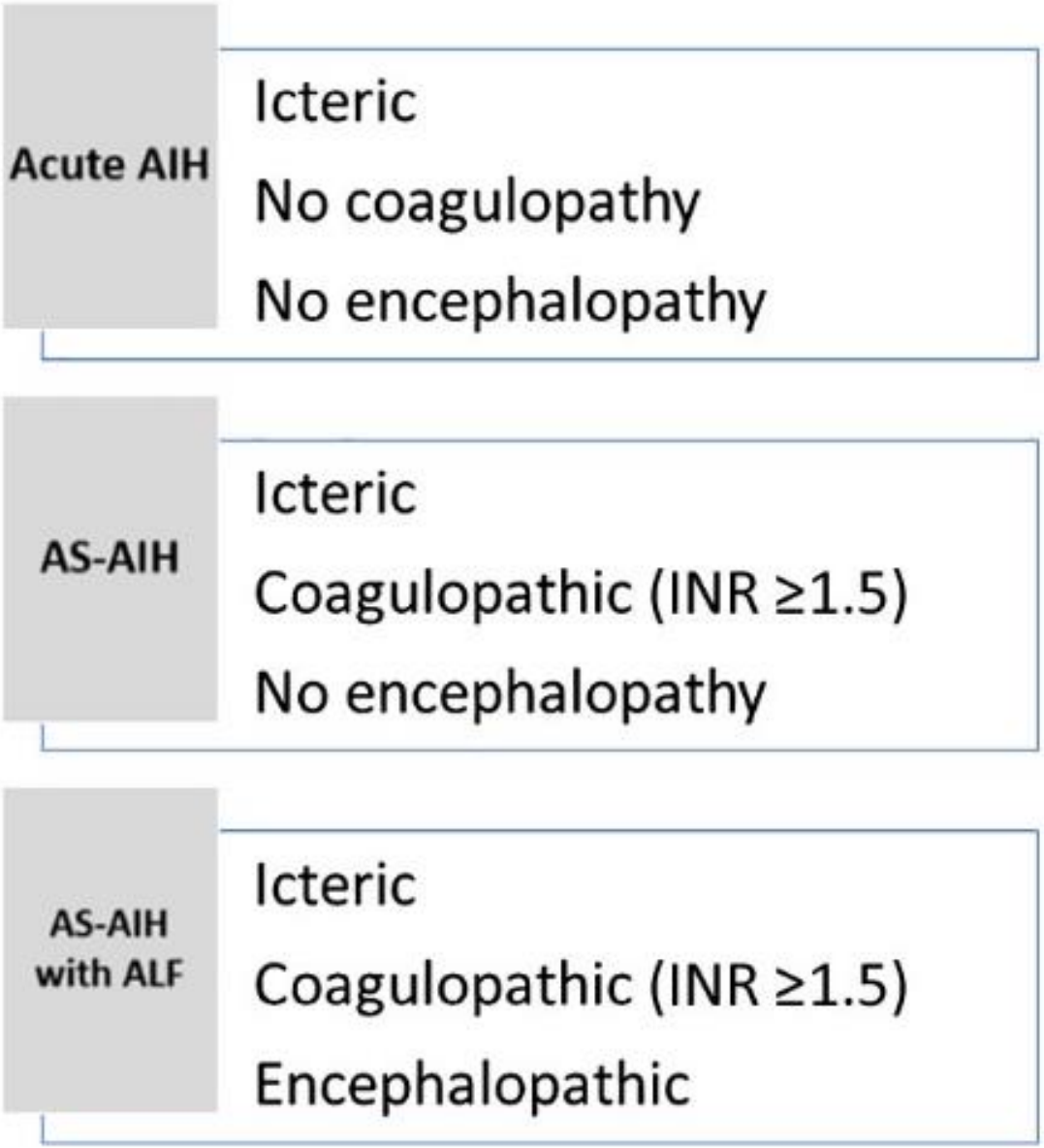
Fig. 1. Age- and sex-specific incidence rates of autoimmune hepatitis in Denmark, 1994–2012. We computed incidence rates in 1-year age groups and used a smoothing procedure to facilitate the visual interpretation of trends across age groups.

J Hepatol 2014;60:612-617

Clinical presentation of AIH

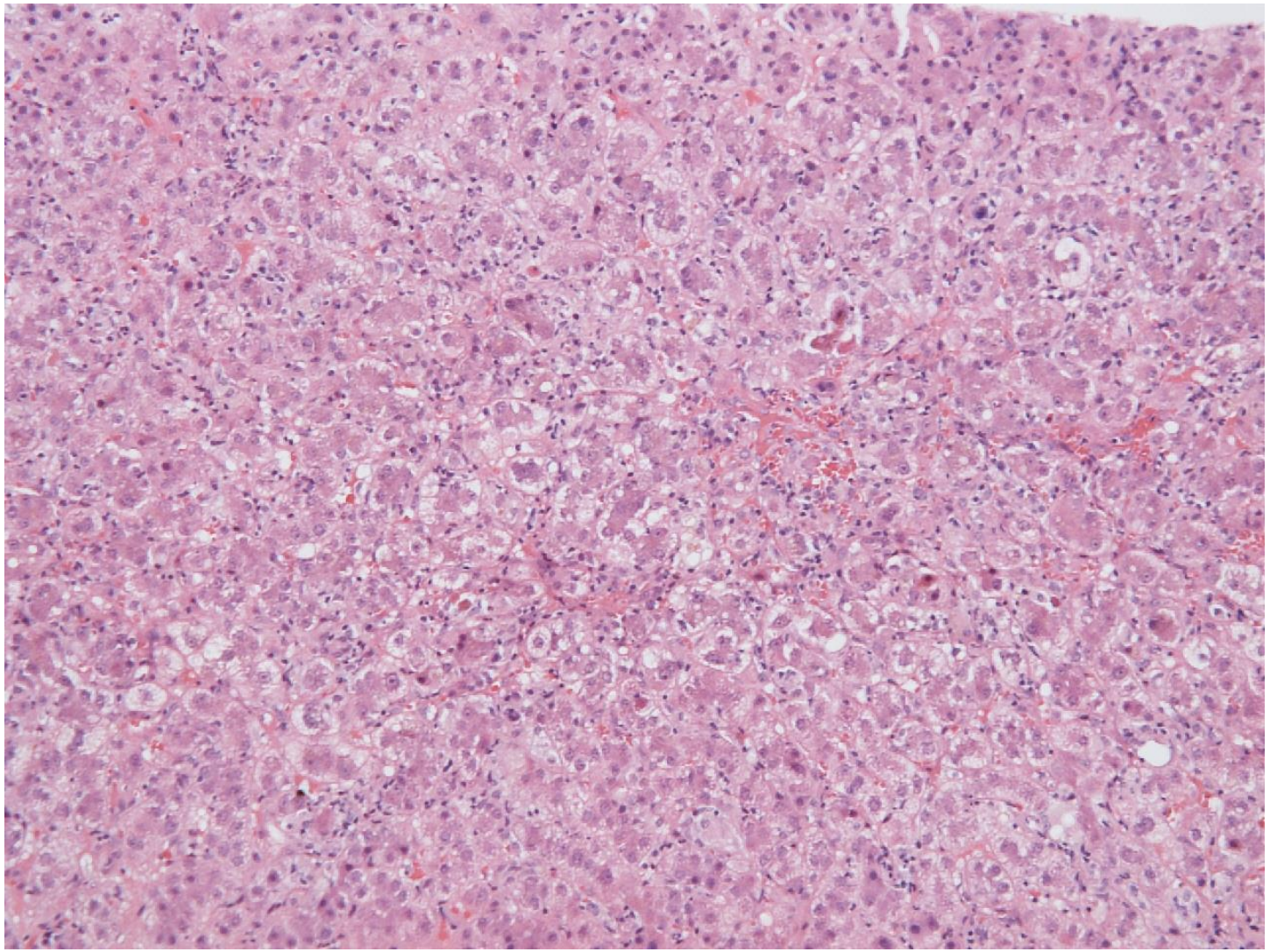


Liver Transplantation 2019,25:946-959



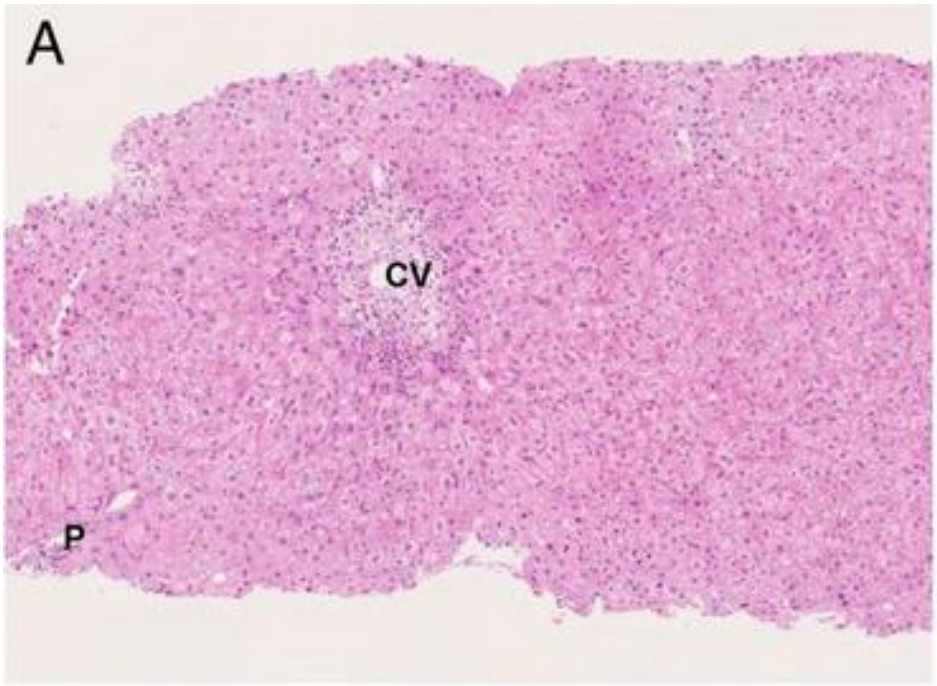
Liver Transplantation 2019,25:946-959

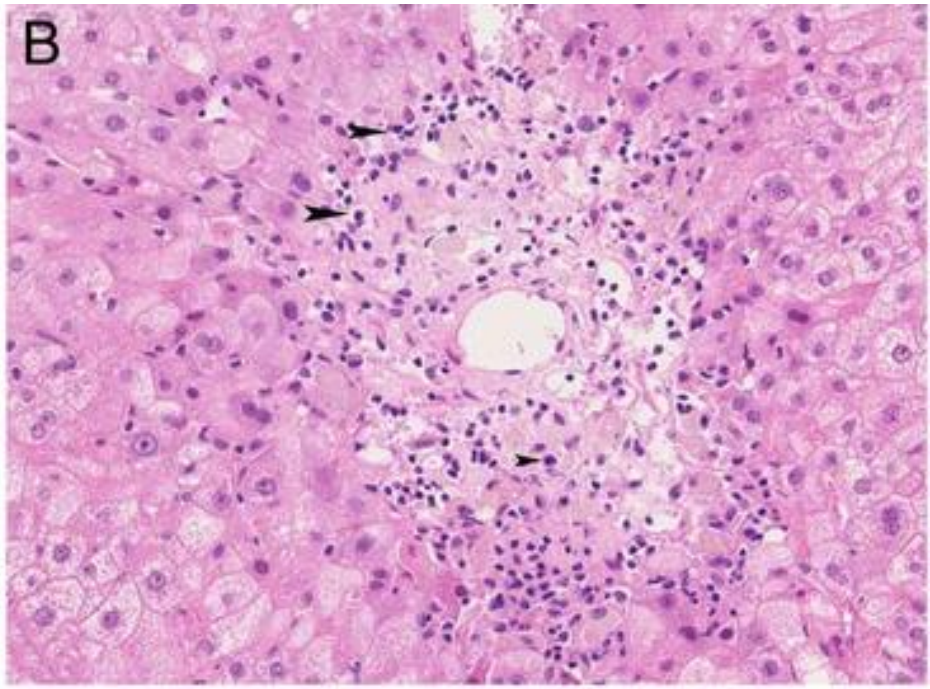
Acute Autoimmune Hepatitis



Diffuse lobular inflammation, ballooning, lobular disarray and spotty necrosis

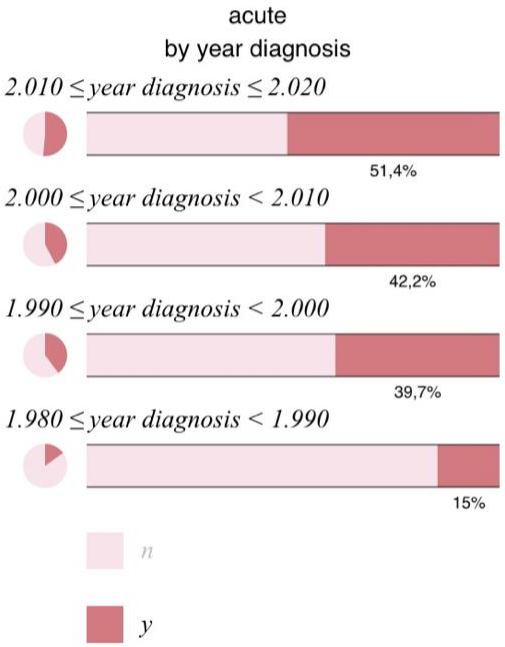
Centrilobular necrosis





- Centrilobular injury with prominent hepatocellular necrosis and lymphoplasmacytic infiltration has recently been recognized in the spectrum of AIH and may represent an early stage of the disease
- Centrilobular necrosis is the predominant finding in 29% of biopsies and the only finding in 2/3% of the cases (Hofer 2006, Miyak 2007)

Acute onset is become the predominant phenotype of AIH



Acute phenotype consistently increasing over the decades:

- **Increased awareness of the disease?**
- **Easy-to-use simplified diagnostic criteria?**
- **Standardised assays for autoantibody detection?**
- **Increased exposure to environmental/toxic trigger factor?**

Center of Autoimmune Diseases of the Liver and Biliary System, ***Bologna, Italy***

436 consecutive AIH patients
77% female sex
median age 42 yrs (2-82)

554 AIH patients	Acute Onset (40,8%)	Non Acute Onset (59,2%)	*p*
Age (mean ± SD)	40 ± 20	39 ± 19	ns
Female sex (%)	83	78	ns
ALT (x ULN)	30.4 ± 18	10.5 ± 11	< 0.001
Bilirubin (mg/dl)	10.4 ± 10	1.8 ± 2.5	< 0.001
Albumin (g/l)	37 ± 8	40 ± 7	p 0.004
INR	1.34 ± 0.4	1.15 ± 0.2	< 0.001
IgG (x ULN)	1.6 ± 0.7	1.5 ± 0.8	ns
ANA/SMA/LKM (%)	69/54/8	62/40/11	ns
Cirrhosis (%)	12.8	18.7	ns
Histological staging	2.4 ± 1.3	2.4 ± 1.3	ns
Histological grading	9.1 ± 3.3	6.9 ± 2.8	< 0.001
Extrahepatic Autoimmune Comorb (%)	26	38	ns

Dig and Liver disease 2018;50:698-702

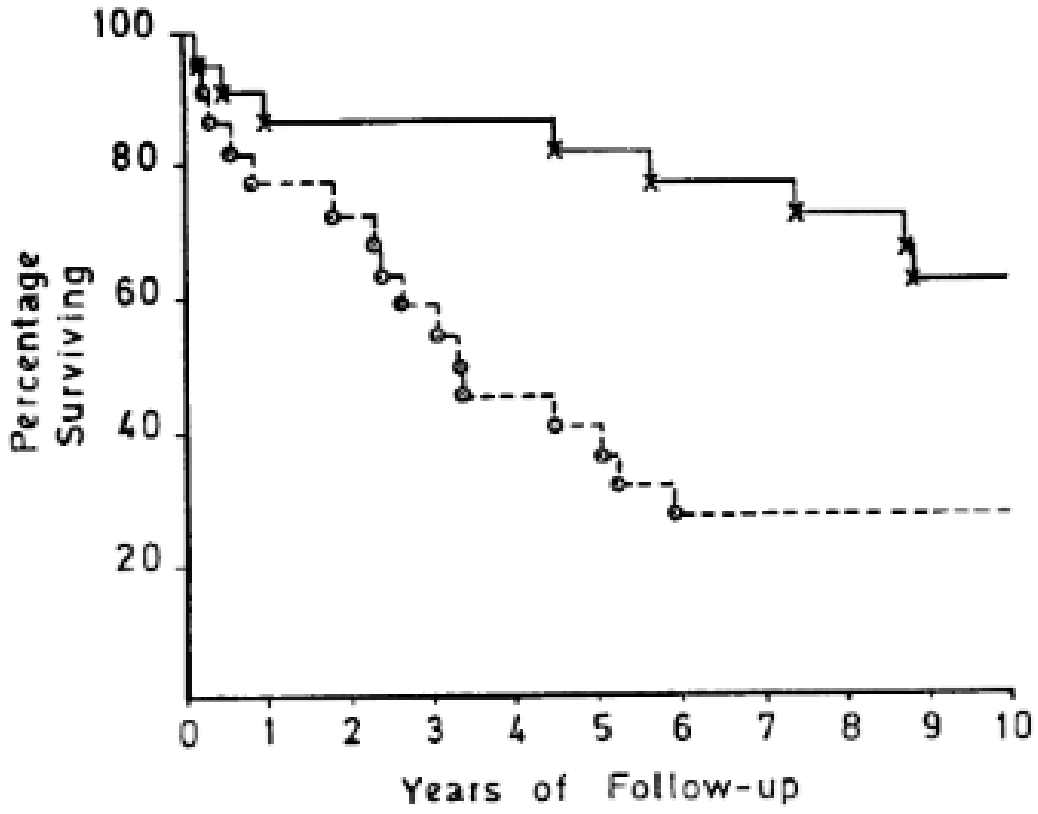
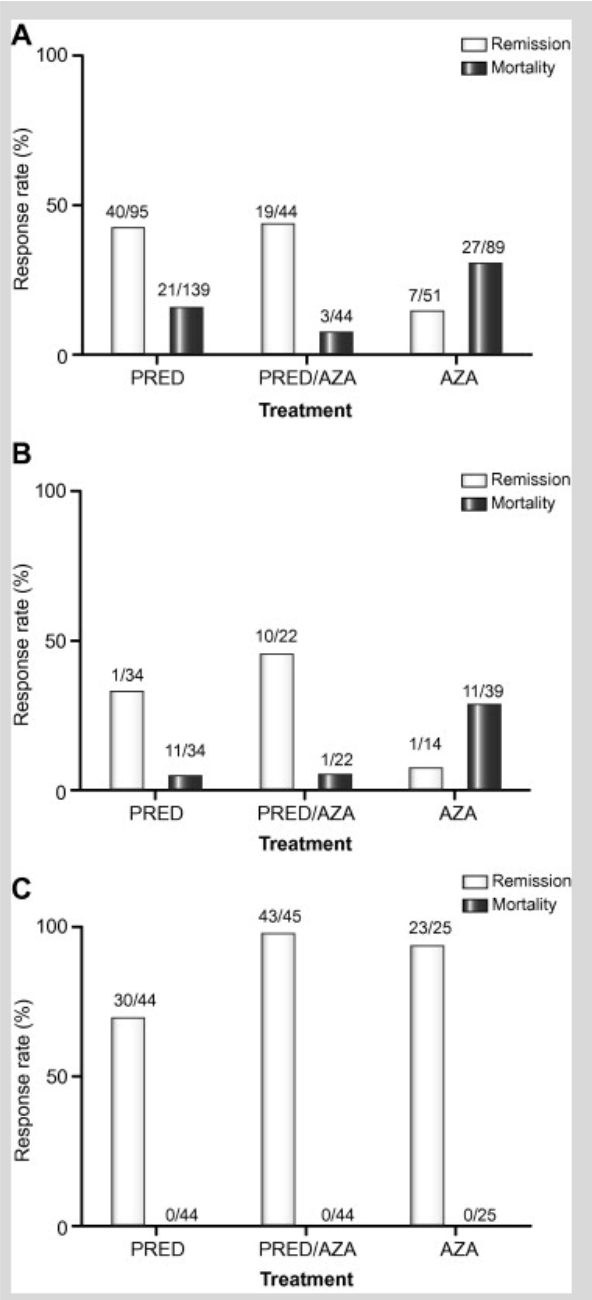


Fig. 3 *Life table survival curves of control and prednisolone treated patients.* ⊙– – –⊙ *Controls.* ×——× *Prednisolone.*

Kirk AP et al. Gut 1980;21:78-83



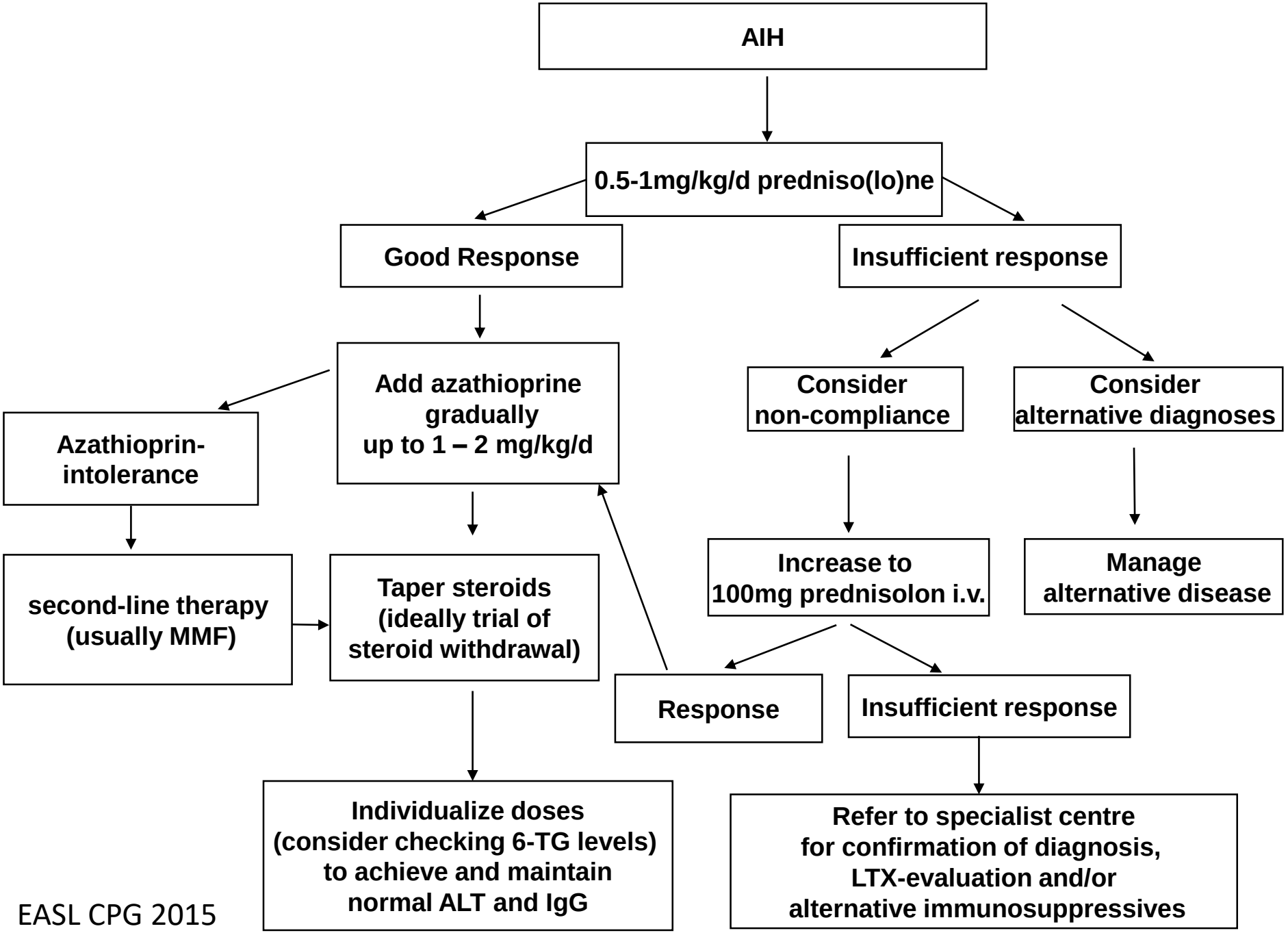
Effect of prednisone and azathioprine in autoimmune hepatitis treatment

A: induction therapy naive patients

B:induction therapy relapse AIH patients

C:maintenance therapy AIH patients

Lamers MMH 2010



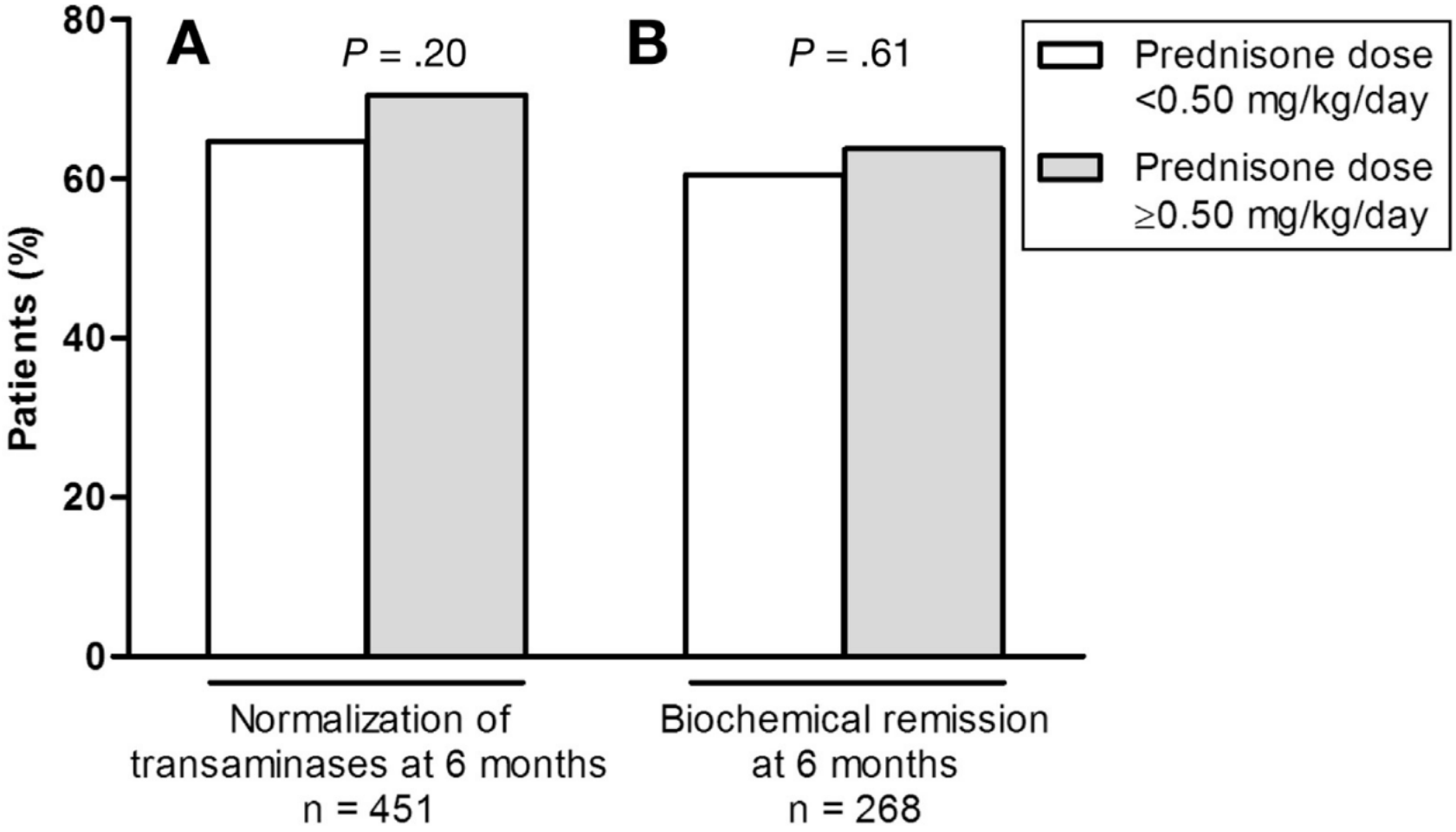
EASL CPG 2015

24. Predniso(lo)ne as initial therapy followed by the addition of azathioprine after two weeks is the first line treatment of AIH **(I)**
Initial dose of predniso(lo)ne should be between 0.5 and 1 mg/kg/day. Higher initial doses can induce remission more quickly albeit at the expense of steroid related side effects **(II-2)**

25. Azathioprine can be initiated whenever bilirubin levels are below 6 mg/dl (100 µmol/L) and ideally two weeks after the initiation of steroid treatment. The initial dosage should be 50 mg/day, and increased depending on toxicity and response up until a maintenance dose of 1-2 mg/kg **(II-2)**

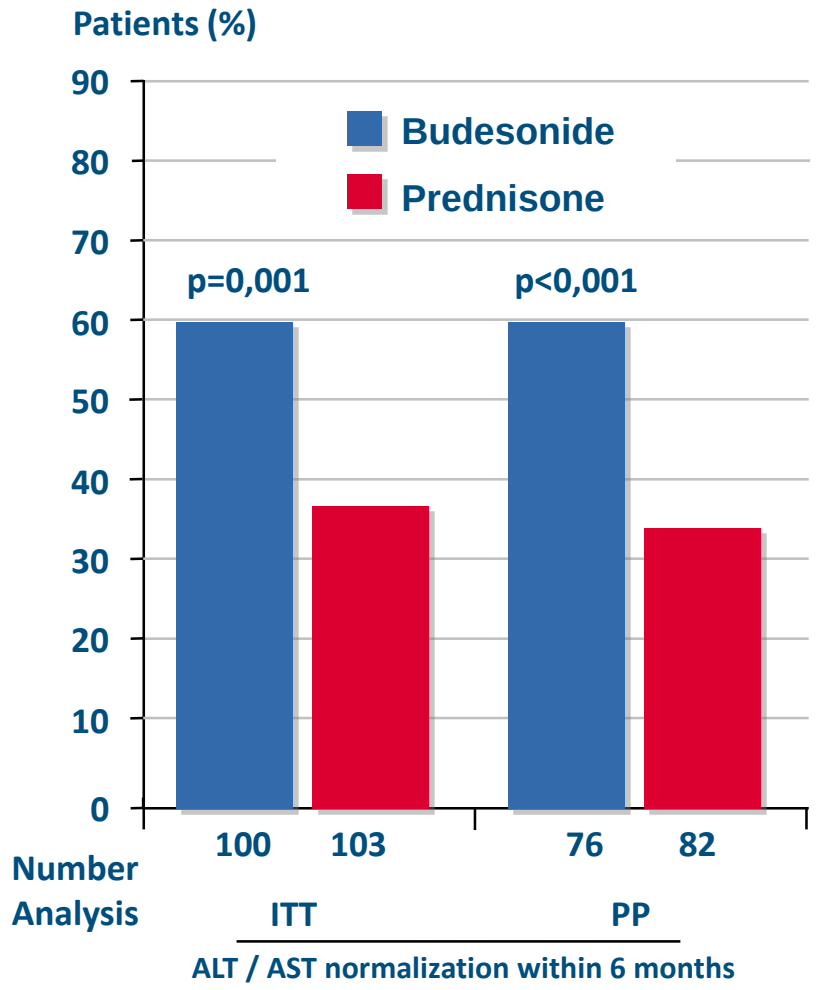
26. Treatment of AIH should be response guided and treatment regimens should be individualised **(III)**

EASL CPG 2015



Clinical Gastroenterology and Hepatology 2019;17:2068-2075

Budesonide



- n=203 Patients
- Double blind, multicentre trial
- Prednisone 40 mg tapering versus Budesonide 3 x 3 mg (both + Azathioprine)
- Complete biochemical remission and absence of predefined steroid specific side effects

(moon face, acne, buffalo hump, hirsutism, striae, diabetes, glaucoma, increased intraocular pressure)

- Unknown value in maintainig remission
- Unkown long term outcome of AIH patients receiving budesonide
- Unclear histologic effect
- Controindicated in cirrhosis

Manns et al. *Gastroenterology* 2010; 139:1198-206

CPG (Budesonide)

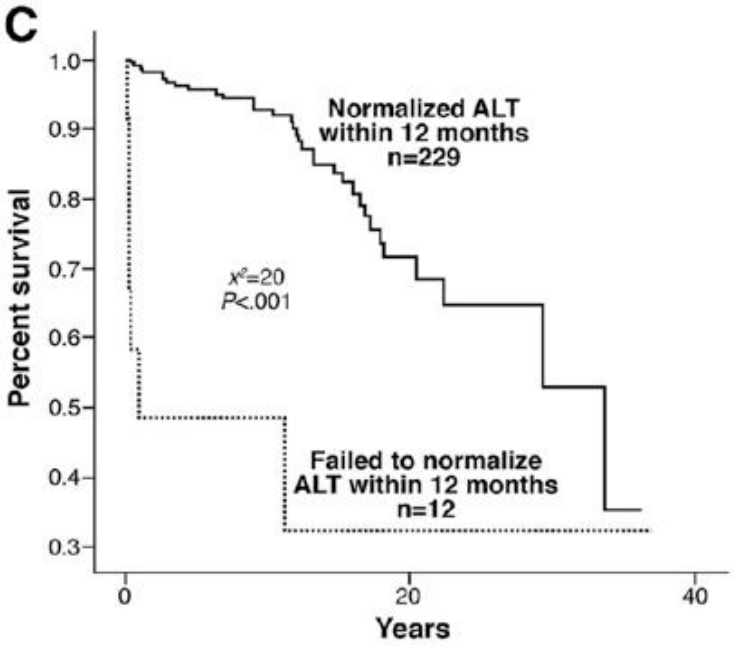
Budesonide (9 mg/day) plus azatioprine may therefore be considered in **treatment-naive non cirrhotic patients with early stage disease** and in whom untoward major steroid specific side effects are highly anticipated. However, we have **little information about the best approach to dose reduction** in budesonide treatment. Due to the short half-life of budesonide, it is not clear if reduction to twice daily (6 mg) and to once daily (3 mg) dosing is reasonable, or if the thrice daily dosing should be continued, reducing individual dose from 3mg to 2mg and 1 mg

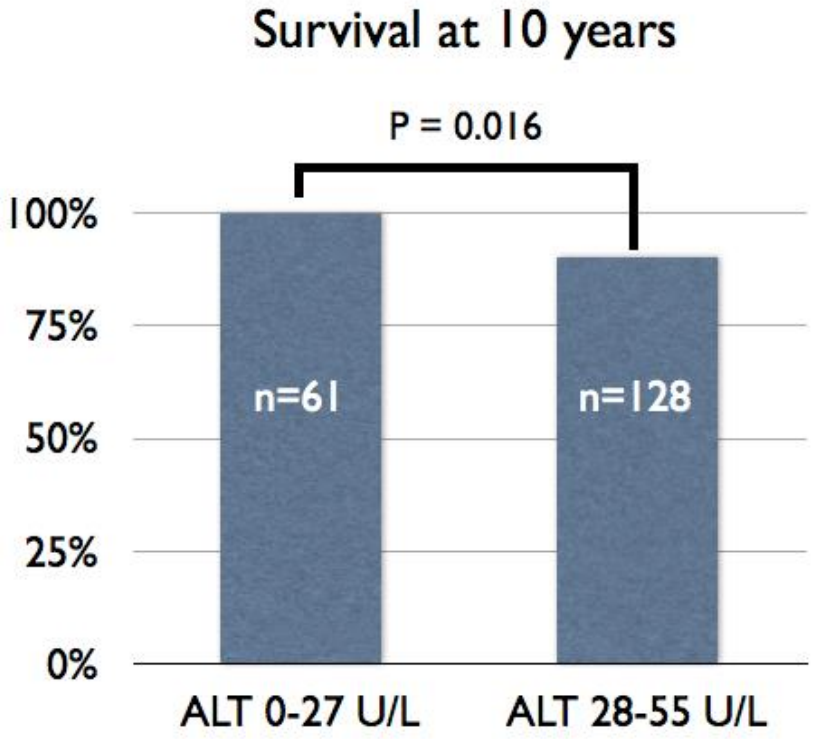
EASL CPG 2015

Remission


Inactive Liver Biopsy
Normal Immunoglobulins
Normal ALT/AST

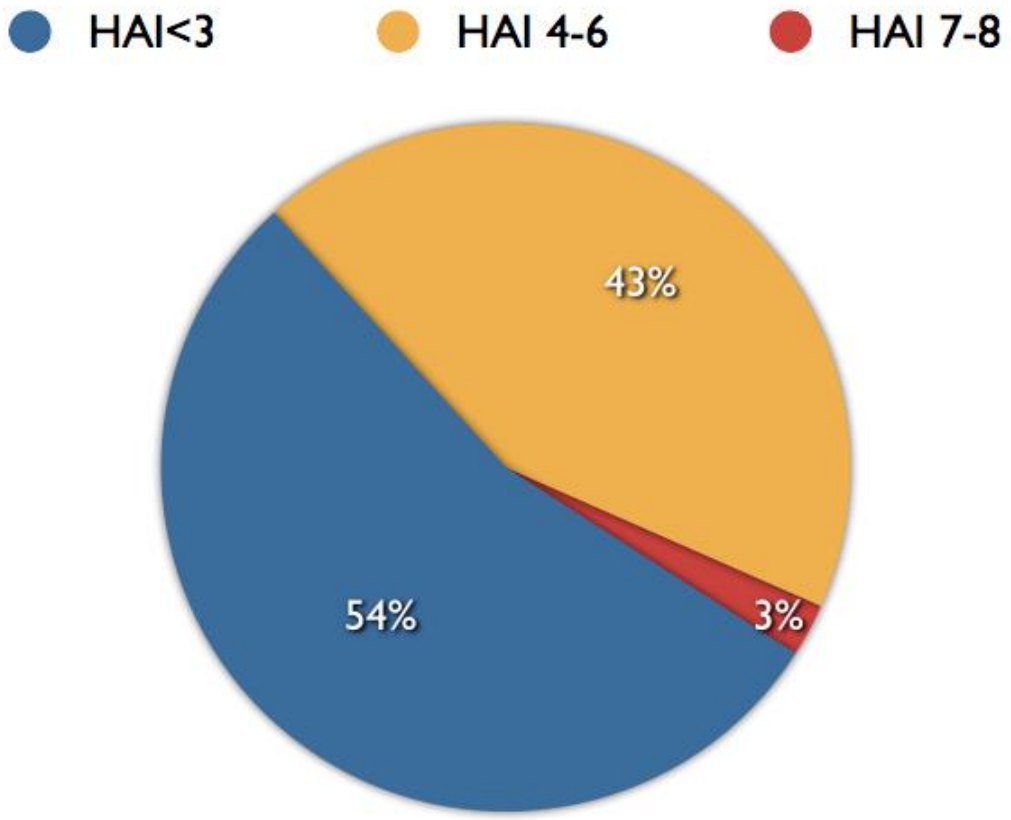
Survival according to ALT normalization





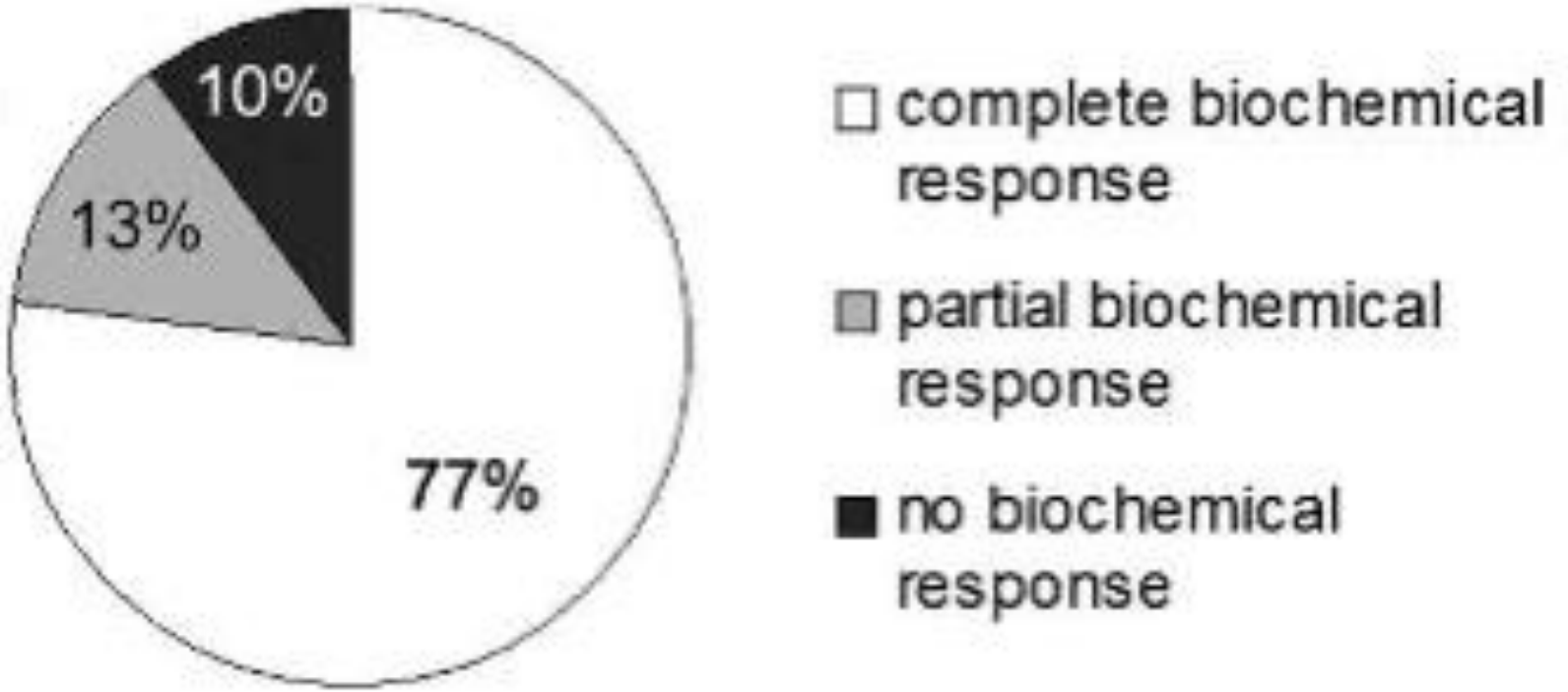
Hoeroldt B. et al Gastroenterology 2011;140:1980-1989

Histologic response to treatment after 24 months in maintained biochemical remission



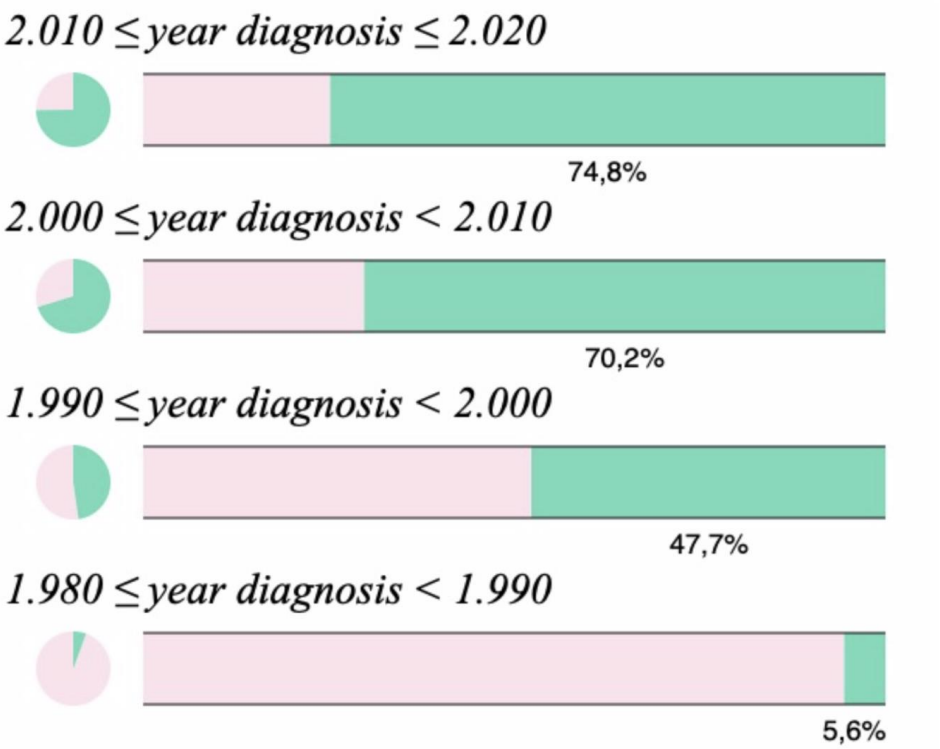
Dhaliwal H. et al. American J Gastroenterol 2015;110:993-999

Biochemical response to immunosuppression (after 6 months; 92 patients)



Schramm et al. Hepatology 2010;52:2247-48

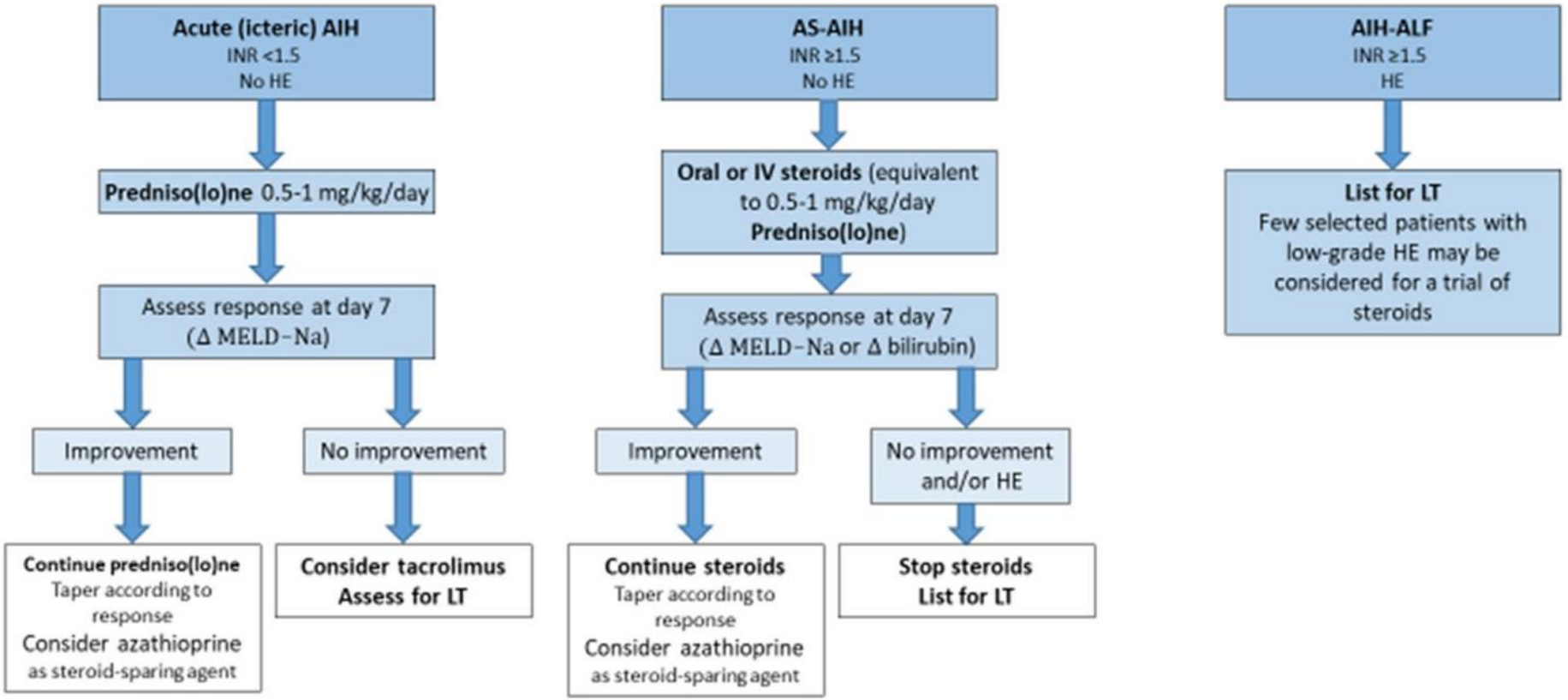
Responders



Incomplete responders

Complete responders

chi square, p < 0,001



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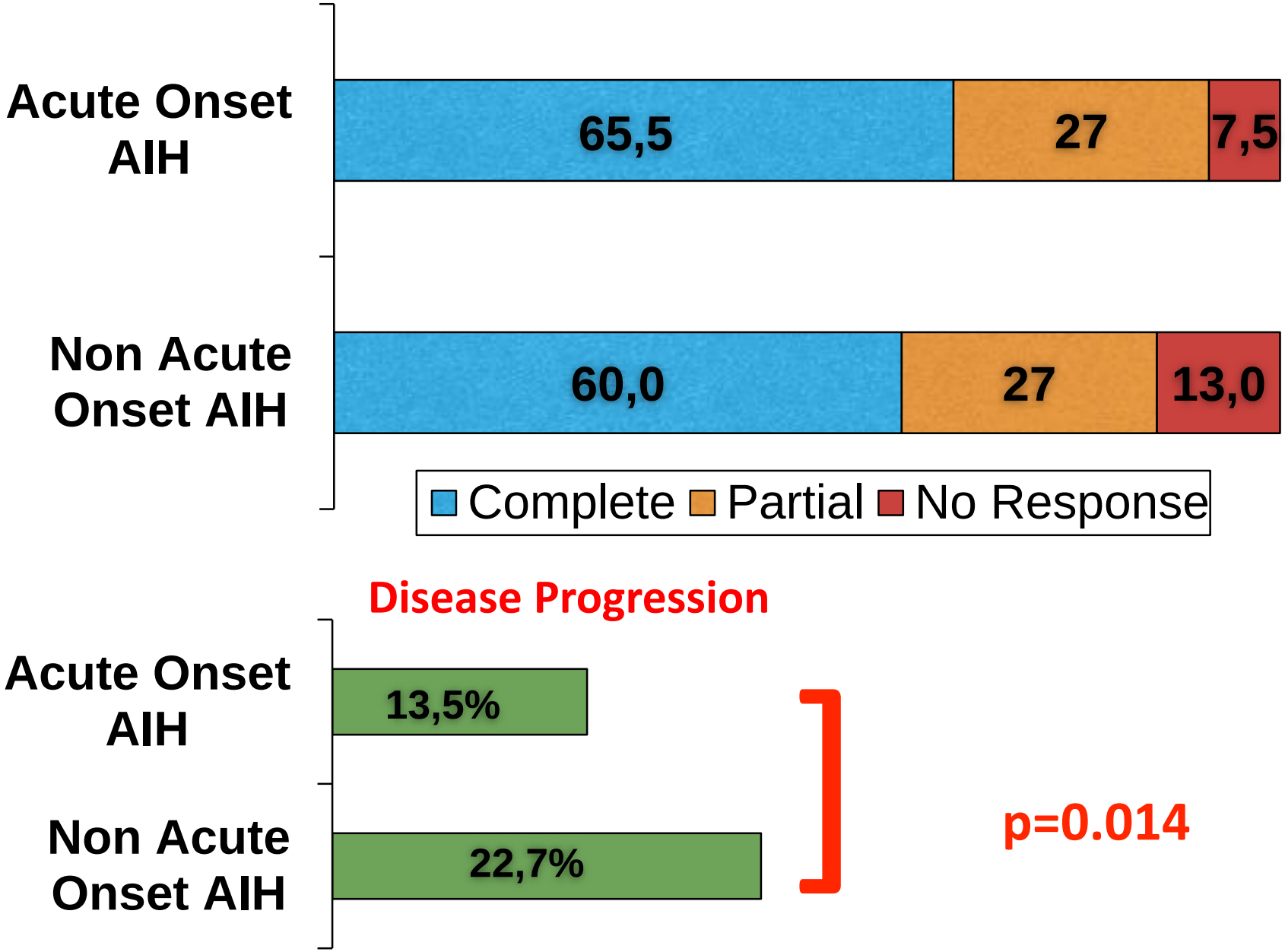
Acute Onset AIH
65,5
27
7,5
Non Acute Onset AIH
60,0
27
13,0
Complete
Partial
No Response
Disease Progression
Acute Onset AIH
13,5%
Non Acute Onset AIH
22,7%
p=0.014

Hepatology Research JSH

Original Article | Full Access

Prompt initiation of high-dose intravenous corticosteroids seems to prevent progression to liver failure in patients with original acute severe autoimmune hepatitis

Kalliopi Zachou, Pinelopi Arvaniti, Kalliopi Azariadis, Vasiliki Lygoura, Nikolaos K. Gatselis, Aggeliki Lyberopoulou, George K. Koukoulis, George N. Dalekos

First published: 24 September 2018 | https://doi.org/10.1111/hepr.13252

Conclusions

Prompt initiation of high-dose intravenous corticosteroids in original AS-AIH seems safe and efficient as it prevents disease deterioration and the need of liver transplantation. The long-term overall survival of these patients was high (97% for 5.3 years), while the long-term treatment response and corticosteroids withdrawal rates were higher compared to not-AS-AIH patients.

Fulminant presentation of autoimmune hepatitis: clinical features and early predictors of corticosteroid treatment failure

Manuel Mendizabal[a], Sebastián Marciano[c], María G. Videla[d], Margarita Anders[e], Alina Zerega[f], Domingo C. Balderramo[g], Matías R. Tisi Baña[b], Martín Barrabino[g], Octavio Gil[f], Ricardo Mastai[e], Silvina Yantorno[d], Adrián Gadano[c] and Marcelo O. Silva[a]

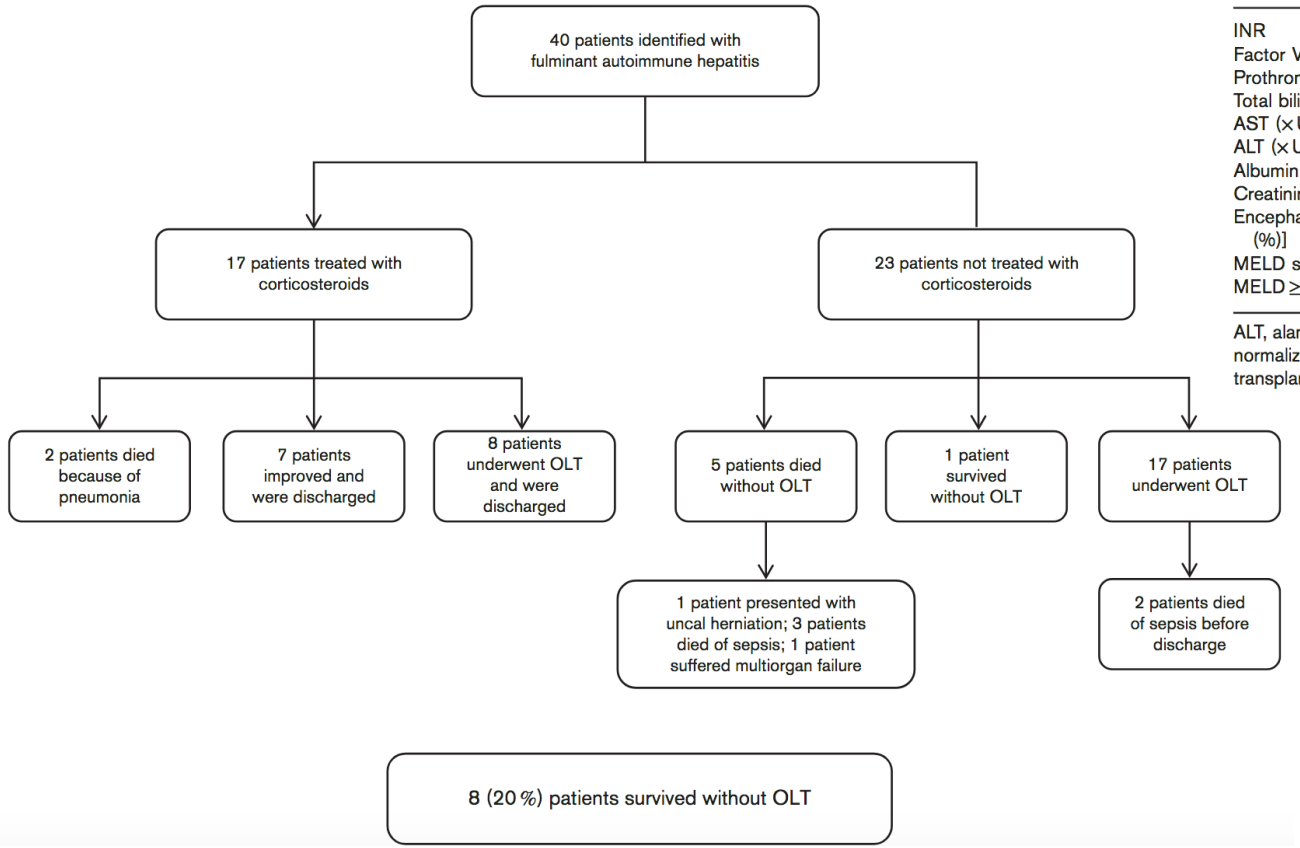

Table 3. Factors associated with steroid failure at initiation of therapy

Variables	Alive ($n=7$)	Death or OLT ($n=10$)	P
INR	1.9 ± 0.4	3.7 ± 2.1	0.02
Factor V (%)	53 ± 14	31 ± 12	0.007
Prothrombin time (%)	42 ± 9	23 ± 11	0.002
Total bilirubin (mg/dl)	16.6 ± 11.6	22.6 ± 8.3	0.2
AST (× ULN)	24 ± 23	24 ± 14	0.9
ALT (× ULN)	17 ± 15	19 ± 13	0.7
Albumin (mg/dl)	2.6 ± 0.7	2.8 ± 0.3	0.4
Creatinine (mg/dl)	0.6 ± 0.1	0.8 ± 0.3	0.2
Encephalopathy grade ≥ 3 [n (%)]	0 (0)	7 (70)	0.01
MELD score	23 ± 4	31 ± 7	0.008
MELD ≥ 27 [n (%)]	1 (14)	8 (80)	0.01

ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; OLT, orthotopic liver transplantation; ULN, upper limit of normal.

European Journal of Gastroenterology & Hepatology 2015, 27:644-648

Risk factors for an incomplete response to treatment and poor prognosis

- Cirrhosis
- Younger age or longer duration of disease before treatment
- Presence of anti-Ro52 and/or anti-SLA
- HLA B8-DR3 phenotype

Alternative options for insufficient response

Intolerance

- Measure aza metabolites
- Steroid monotherapy
- Budesonide
- 6-MP
- MMF

Insufficient response

- Concomitant diagnosis
- Check adherence
- Increase aza (up to 2,5 mg/kg)
- Add tacrolimus
- Add rituximab
- Add infliximab

Efficacy and Safety of Mycophenolate Mofetil and Tacrolimus as Second-line Therapy for Patients With Autoimmune Hepatitis

Cumali Efe,[*] Hannes Hagström,[‡] Henriette Ytting,[§] Rahima A. Bhanji,[‖] Niklas F. Müller,[¶] Qixia Wang,[#] Tugrul Purnak,[*] Luigi Muratori,[**] Mårten Werner,[‡‡] Hanns-Ulrich Marschall,[§§] Paolo Muratori,[**] Fulya Gunşar,[‖‖] Daniel Klintman,[¶¶,##] Albert Parés,[***] Alexandra Heurgué–Berlot,[‡‡‡] Thomas D. Schiano,[§§§] Mustafa Cengiz,[‖‖‖] Michele May-Sien Tana,[¶¶¶] Xiong Ma,[#] Aldo J. Montano-Loza,[‖] Thomas Berg,[¶] Sumita Verma,[###] Fin Stolze Larsen,[§] Ersan Ozaslan,[****] Michael A. Heneghan,[‡‡‡‡] Eric M. Yoshida,[##] and Staffan Wahlin[‡]

Table 3. Efficacy of MMF and Tacrolimus in Patients With Autoimmune Hepatitis

	MMF (n = 121)	Tacrolimus (n = 80)	*P* value
Response complete (all)	84 (69.4%)	58 (72.5%)	.639
Group 1 (n = 108)	n = 74	n = 34	
Complete response	68 (91.9%)	32 (94.1%)	.682
Group 2 (n = 93)	n = 47	n = 46	
Complete response	16 (34.0%)	26 (56.5%)	.029

MMF, mycophenolate mofetil.

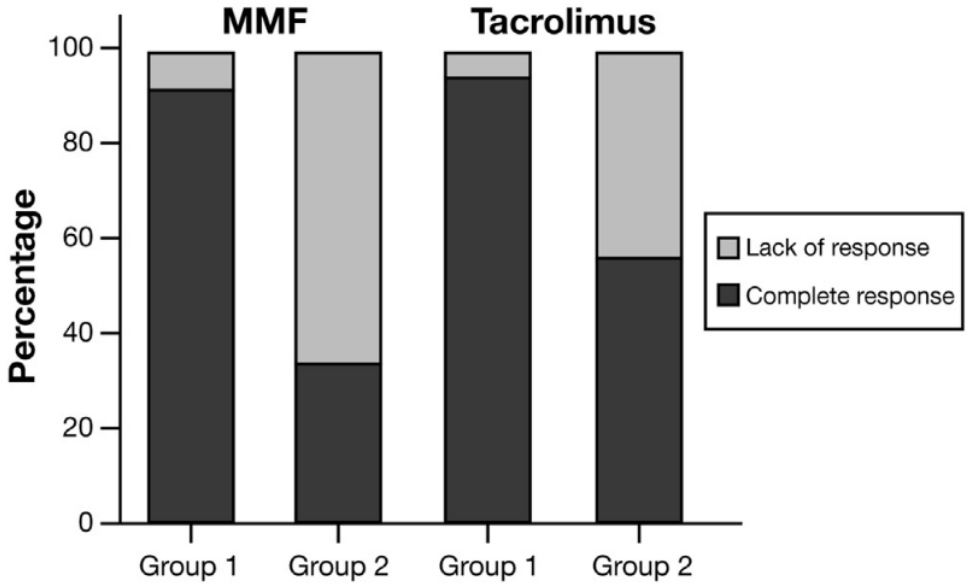

Figure 2. Therapy response rates for patients treated with MMF and tacrolimus. Complete response rates were decreased significantly through group 1 to group 2 ($P < .001$ for both).

Clinical Gastroenterology and Hepatology2017;15:1950-1956

Second and third-line treatment in AIH

- There are no controlled studies investigating second and third-line treatment options in patients with AIH
- Treatment recommandations are based on local expertise and published small case series
- The choise of treatment should be guided by the severity of disease, comorbidities, age and patient's preference

Open issues concerning the standard treatment

- Definition of the best induction protocol and definition of appropriate early response (6 months?)
- Is there a role for more aggressive, top down management at induction
- Low ALT and IgG values are adequate for defining biochemical remission?
- Should immunosuppression be intensified if elevated IgG but normal ALT?
- What is an acceptable maintenance steroid dose?
- When third–line therapy instituted

Thank you for your attention