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Optimal management of auto-immune

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Inserm – Institut national de la santé et de la recherche médicale

Mister F, 32 year old

October 2014 : admitted to the hospital for acute severe hepatitis

Since 1 month: jaundice, fatigue

Laboratory tests at admission

AST IU/L	498	Tot bili µmol/L	334	GB G/L	9
ALT IU/L	602	PT %	20	Hb g/L	15
GGT IU/L	80	INR	5.22	Plts G/L	125
Creatinine	86	FV %	21	MELD	37

Who is Mister F ?

Lifestyle:

- lives in a camping car
- wife, 1 child
- Unemployed
- Alcohol consumption > 150 g/d
- Tobacco 1 p/d
- Regular cannabis consumption

Past medical or surgical history:

Uneventful

No recent travel, no IV drugs, no medications

Diagnostic work-up

Virology

Ab HAV, Ag HBs, Ab HBs, Ab HBc, Ab HCV, HIV, HTLV 1-2, PCR CMV, EBV, HSV, HHV6, HHV8, HEV → Negatives

Immunology

Anti-tissue Ab: ANA + 1:80 homogeneous and speckled, AMA, ASMA, anti-LKM1, anti-LC1 → negatives

IgG 13.90 (N<12.5), IgA 5.32 (N<3.07), IgM 2.31 (N<1.53)

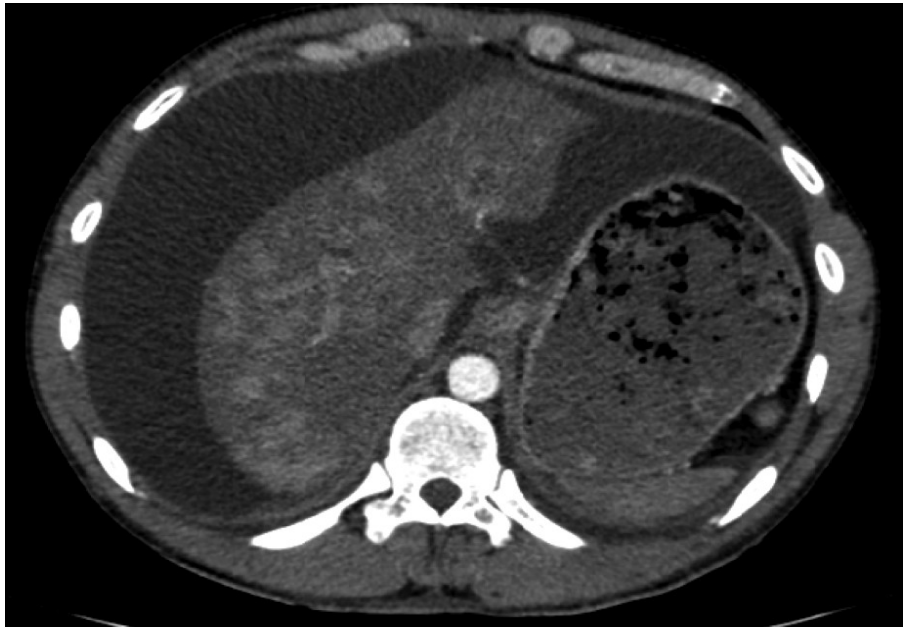
Infection

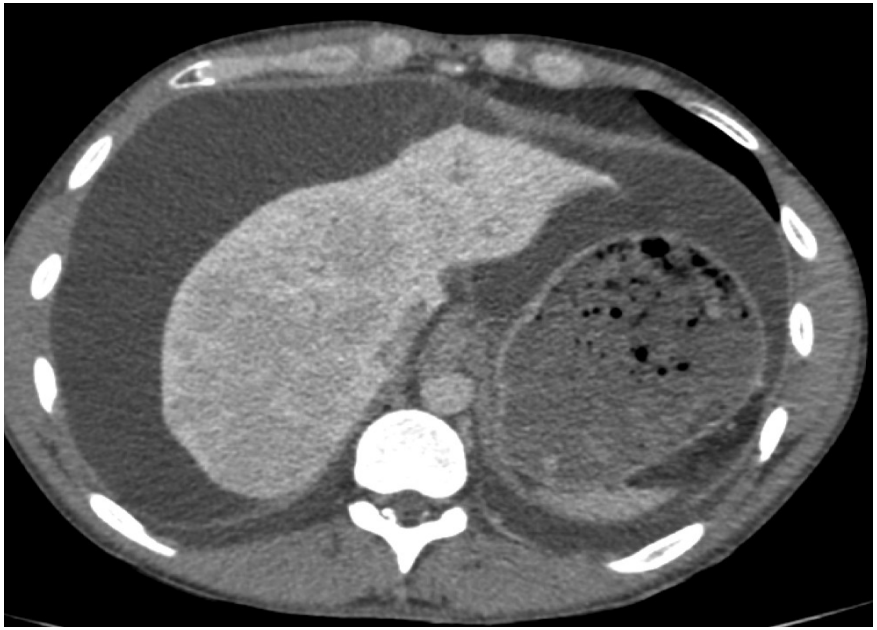
Urinary test - , blood test -, ascites -

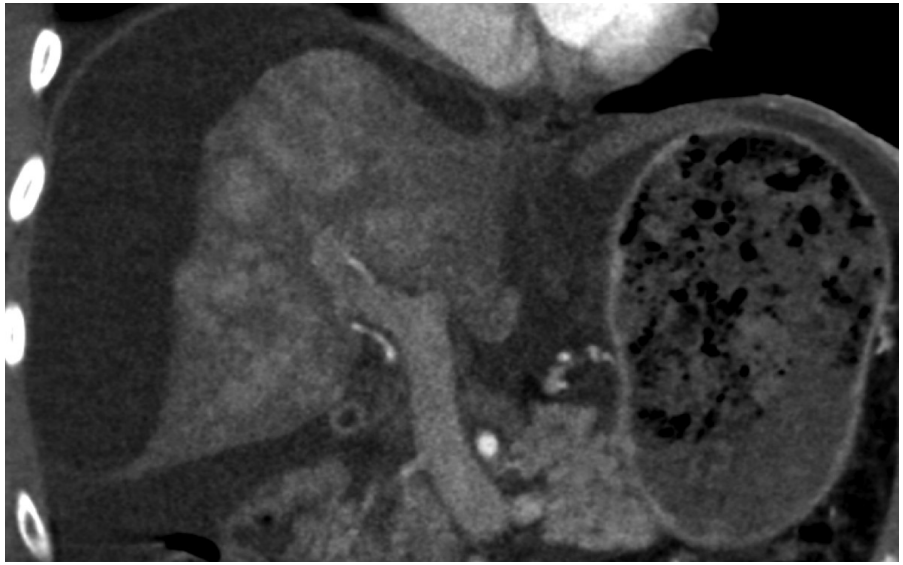
Toxic

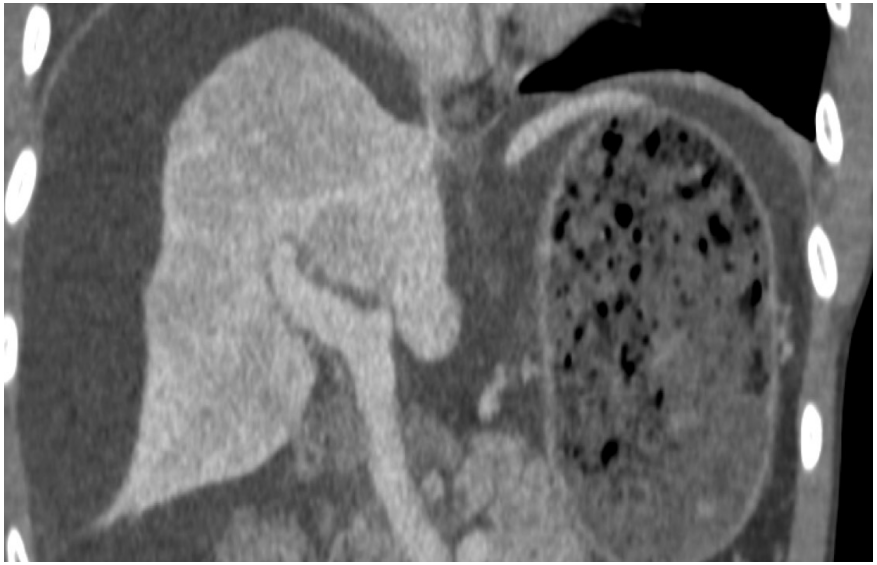
Plasma and urine : THC +

At CT scan









How would you manage this patient ?

A. Perform a transjugular liver biopsy

B. Administer corticosteroids

C. List the patient for liver transplantation

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Simplified diagnostic criteria of the International Autoimmune Hepatitis Group

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

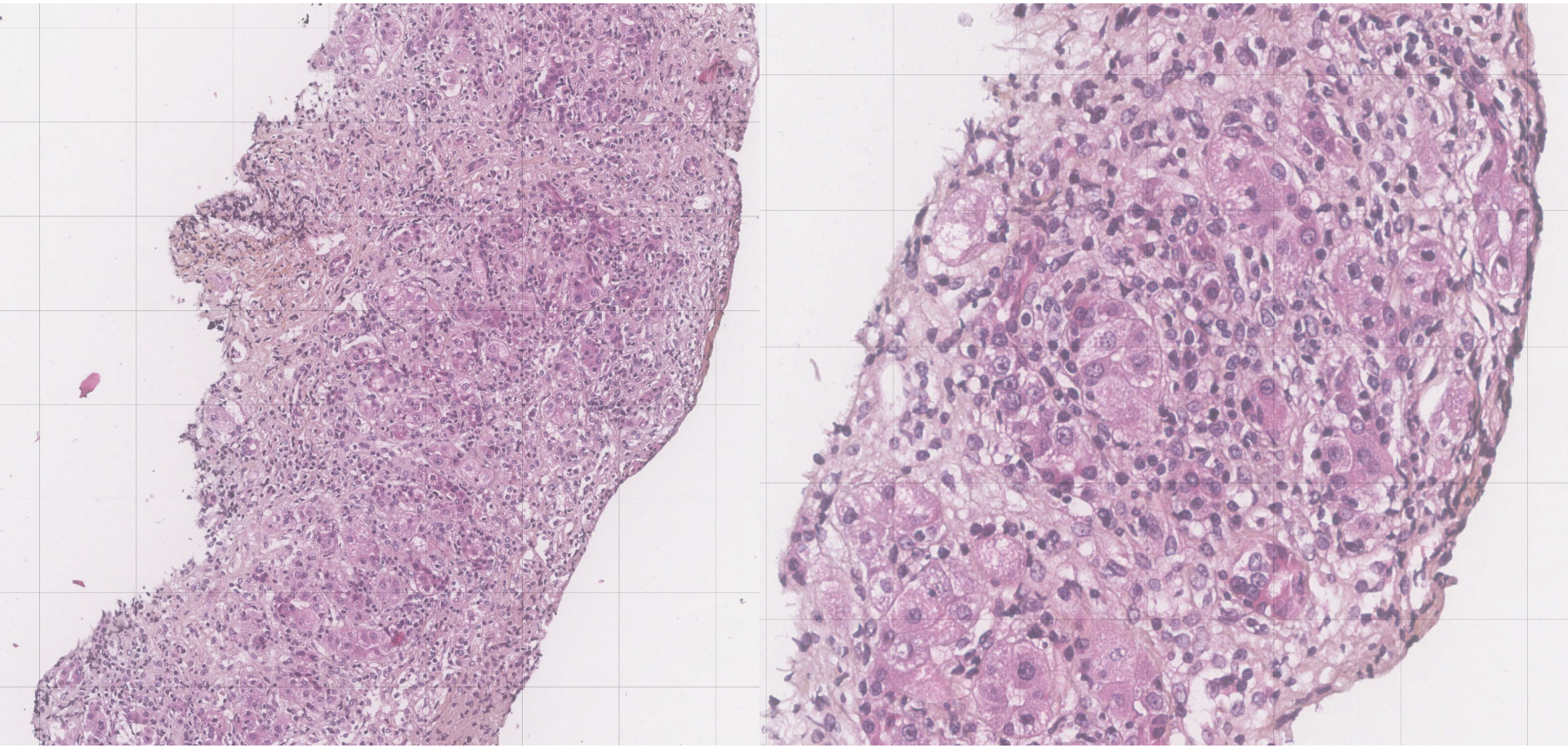
?

= 6

Definite AIH ≥ 7 and Probable AIH ≥ 6

Hennes, Hepatol 2008

At histology



Pour courtoisie du Dr M Sebagh

« Hepatitis with sub acute evolution, sub-massive necrosis. The presence of plasma cells is evocative of AIH»

AIH histological features

Typical

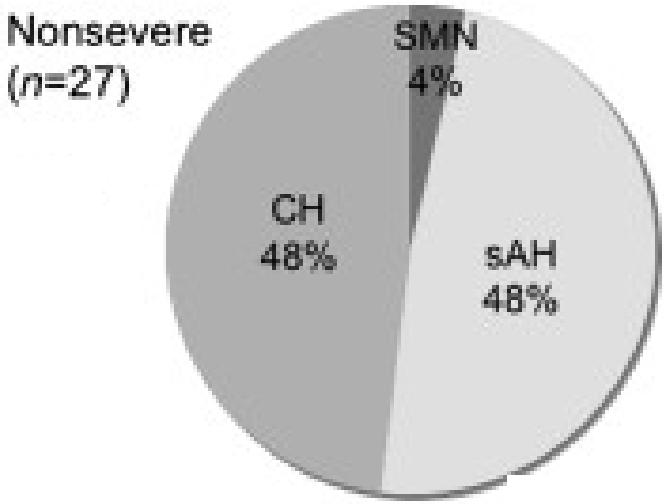
- Interface hepatitis
- Lymphocytic/lymphoplasmacytic infiltrates in portal tracts and extending into the lobule
- Emperipolesis
- Hepatic rosette

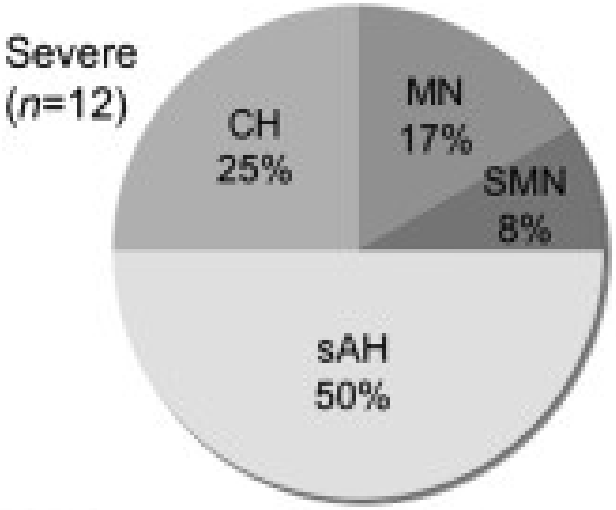
Compatible

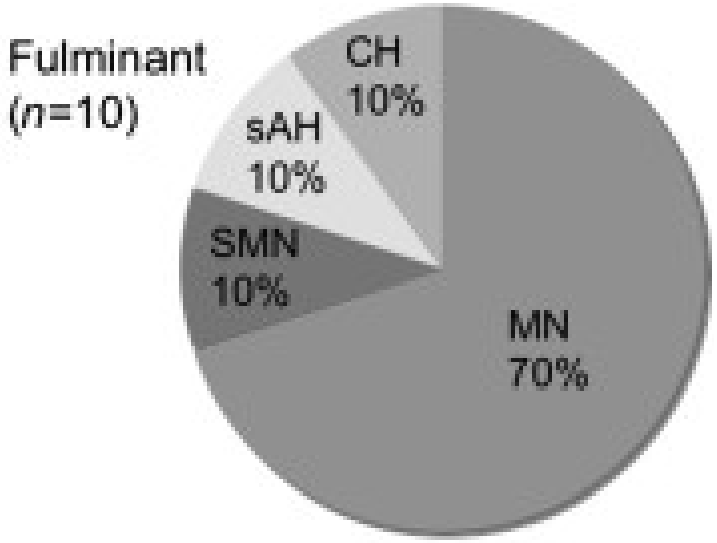
- Chronic hepatitis with lymphocytic infiltration without all the features considered typical

EASL Guidelines, Journal of Hepatol 2015

Histology in acute onset of AIH: challenging







CH: chronic hepatitis
MN: massive necrosis
SMN: submassive necrosis
sAH: severe acute hepatitis

Fujiwara, Liver International 20

Centrilobular inflammatory infiltration

Infiltration of Plasma Cells into Liver Tissue

	Portal areas (frequency per portal area)[a]				Central areas (no. of specimens containing plasma cells)
	<1%	1%–5%	5%–10%	>10%	
Acute AIH (n = 15)	1	6	5	3	5 (33%)
AH-HAV (n = 15)	13	2	0	0	0
AH-HBV (n = 25)	22	3	0	0	0
AH-HCV (n = 15)	12	2	1	0	0
AH-drug (n = 10)	9	1	0	0	0

Abe, Clinical Gstroenterol and Hepatol 2007

Characteristic histological features in AIH-ALF

72 patients from the ALF Study.
The diagnosis of probable AIH-ALF was based on 4 features:

1. Massive hepatic necrosis
2. Lymphoid follicles
3. Plasma-cell infiltration
4. Central perivenulitis

Histological features of AIH-ALF predominate in the centrilobular zone

Stravitz, Hepatology

Simplified diagnostic criteria of the International Autoimmune Hepatitis Group

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
		= 8

Definite AIH ≥ 7 and Probable AIH ≥ 6

Hennes, Hepatol 2008

Mister F, 32 year old

October 2014 : admitted to the hospital for acute severe hepatitis

Clinical exam: jaundice, no hepatic encephalopathy

Laboratory tests at admission and 3 days later

AST IU/L	498 > 400	**Tot bili µmol/L**	**334 > 349**
ALT IU/L	602 > 559	**PT %**	**20 > 14**
GGT IU/L	80 > 97	**INR**	**5.22 > 5.9**
Creatinine	96	**FV %**	**21 > 19**

Would you treat this patient ?

A. No. The patient is too severe. List the patient for liver transplantation

B. Yes. Treat with 1mg/kg/day of corticosteroids

C. Yes. Treat with 0.5mg/kg/day + azathioprine

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Management of AS-AIH

29. Patients with acute severe AIH should be treated with high doses of intravenous corticosteroids (≥1 mg/kg) as early as possible. Lack of improvement within seven days should lead to listing for emergency liver transplantation **(III)**

EASL Guidelines, J Hepatol 2

Management of Acute Liver Failure

King's College criteria

ALF not due to paracetamol

- INR >6.5 or
- 3 out of 5 following criteria:
  - Aetiology: indeterminate aetiology hepatitis, drug-induced hepatitis
  - Age <10 years or >40 years
  - Interval jaundice-encephalopathy >7 days
  - Bilirubin >300 µmol/L
  - INR >3.5

Beaujon-Paul Brousse criteria (Clichy)

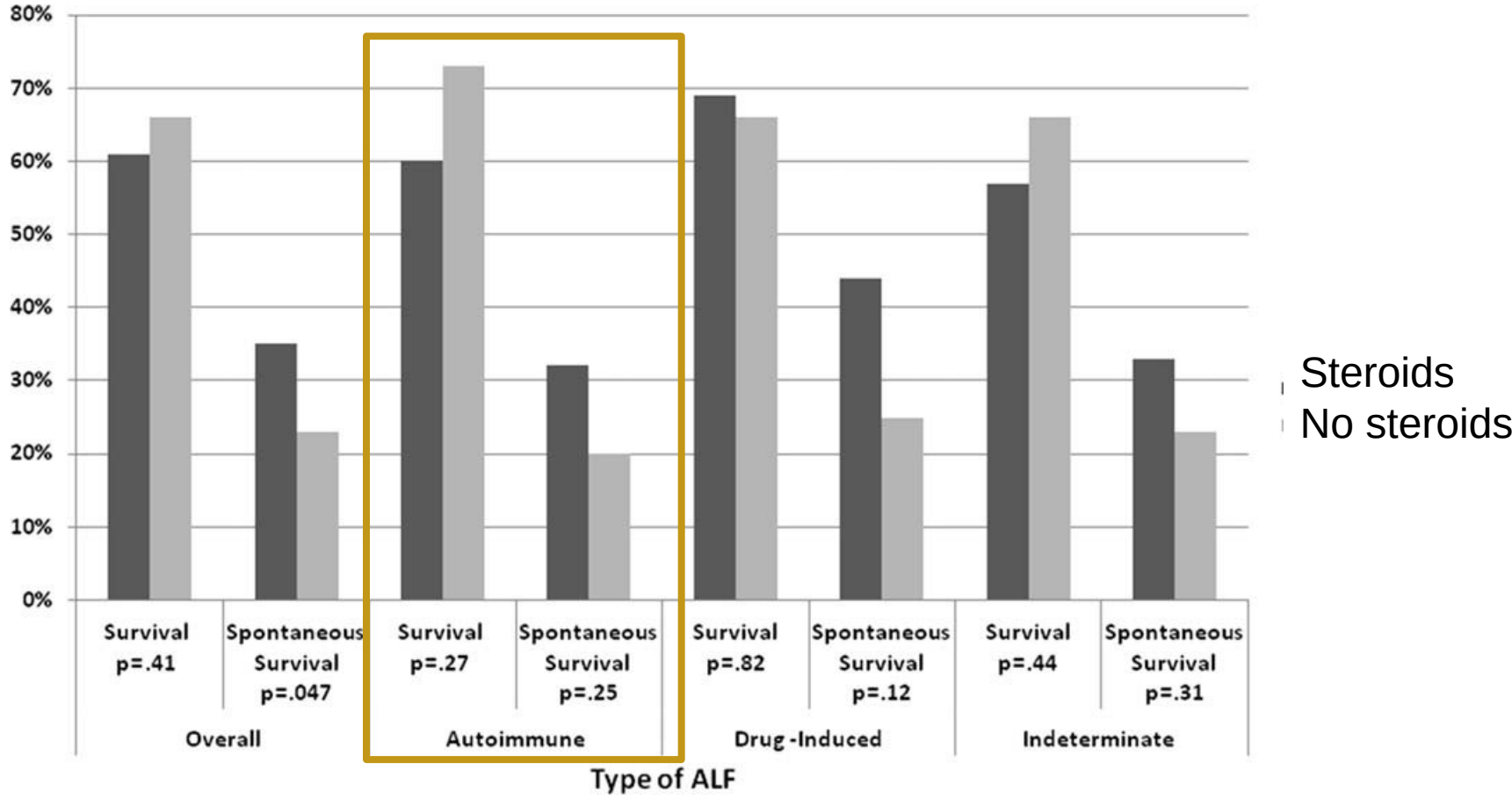
- Confusion or coma (hepatic encephalopathy stage 3 or 4)
- Factor V <20% of normal if age <30 year

  or
- Factor V <30% if age >30 year

EASL Guidelines, J Hepatol 2

Steroid Use in Acute Liver Failure

Overall and spontaneous survival among different aetiologies of ALF



Mean INR 3.33

Karkhanis, Hepatology 2014

The role of corticosteroids is still highly debatable in acute severe autoimmune hepatitis

Uselessness of corticosteroids in severe and fulminant forms

Ichai, Liver Transpl 2007

12/16 (75%) treated patients

↓

10/12 (83%) liver transplantation

The role of corticosteroids in modifying outcome

Yeoman, J Hepatol 2015

23/32 (75%) treated patients

↓

10/23 (43%) liver transplantation

De Martin, J Hepatol 2015

Prognostic factors in AS-AIH patients treated with corticosteroids

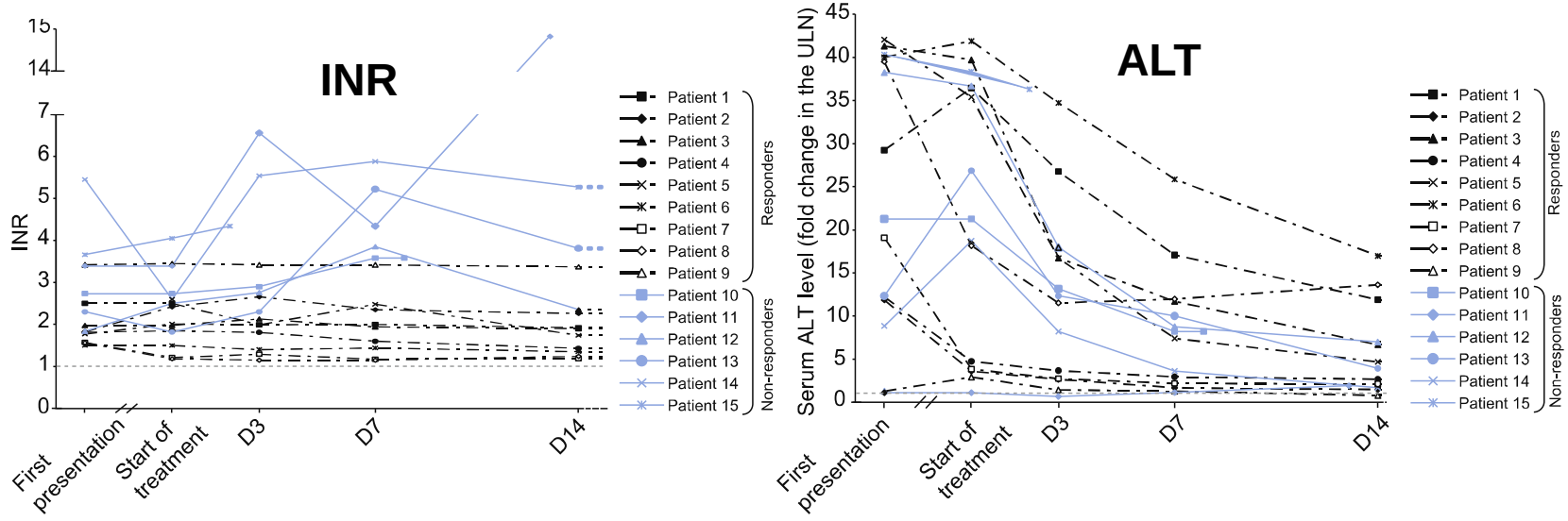
15/17 (88%) treated patients

↓

9/15 (60%) liver transplantation

Prognostic factors :

- Massive Hepatic Necrosis type 5
- INR at presentation : cut off 2.46
- MELD at presentation : cut off 28.5



Moenne-Loccoz, J Hepatol 2016

Early predictors of treatment failure in icteric AIH..

At diagnosis

- Median bilirubin

(451 lmol/L vs 262 lmol/L, P

5 0.02)

- INR (1.62 vs 1.33, P 5

  0.005),

- MELD score (26 vs 20, P

  5 0.02)

Analysis of area under the AUROC values at day 7

- Delta bilirubin

  (AUROC 0.68)

- Delta creatinine

  (0.69)

- Delta MELD (0.79)

Heterogeneous population including pediatric patients, severe and not severe AIH

Yeoman, Hepatology 2011

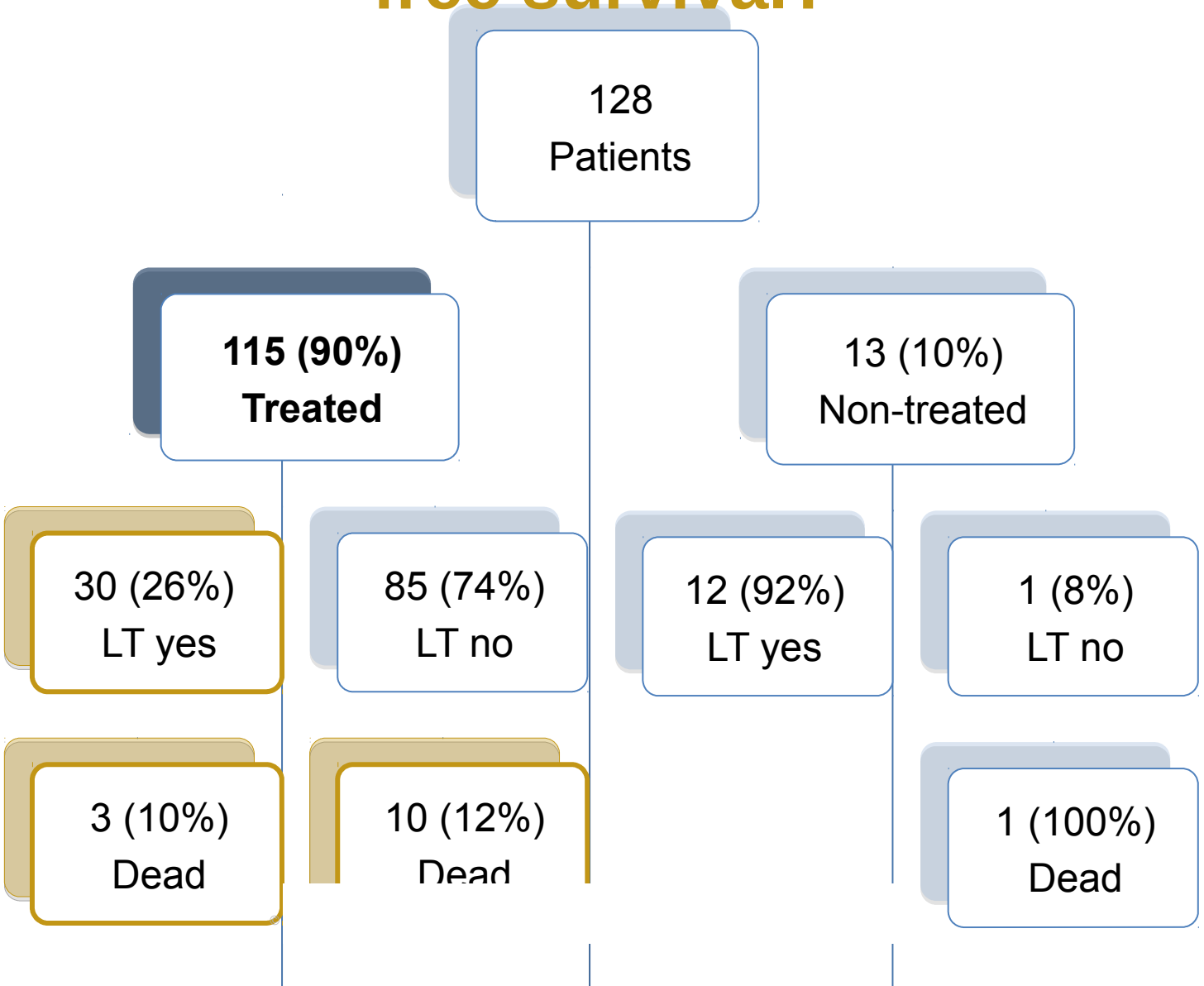
Multicenter French study

FILFOIE
FILIÈRE DE SANTÉ MALADIES RARES DU FOIE DE L'ADULTE ET DE L'ENFANT

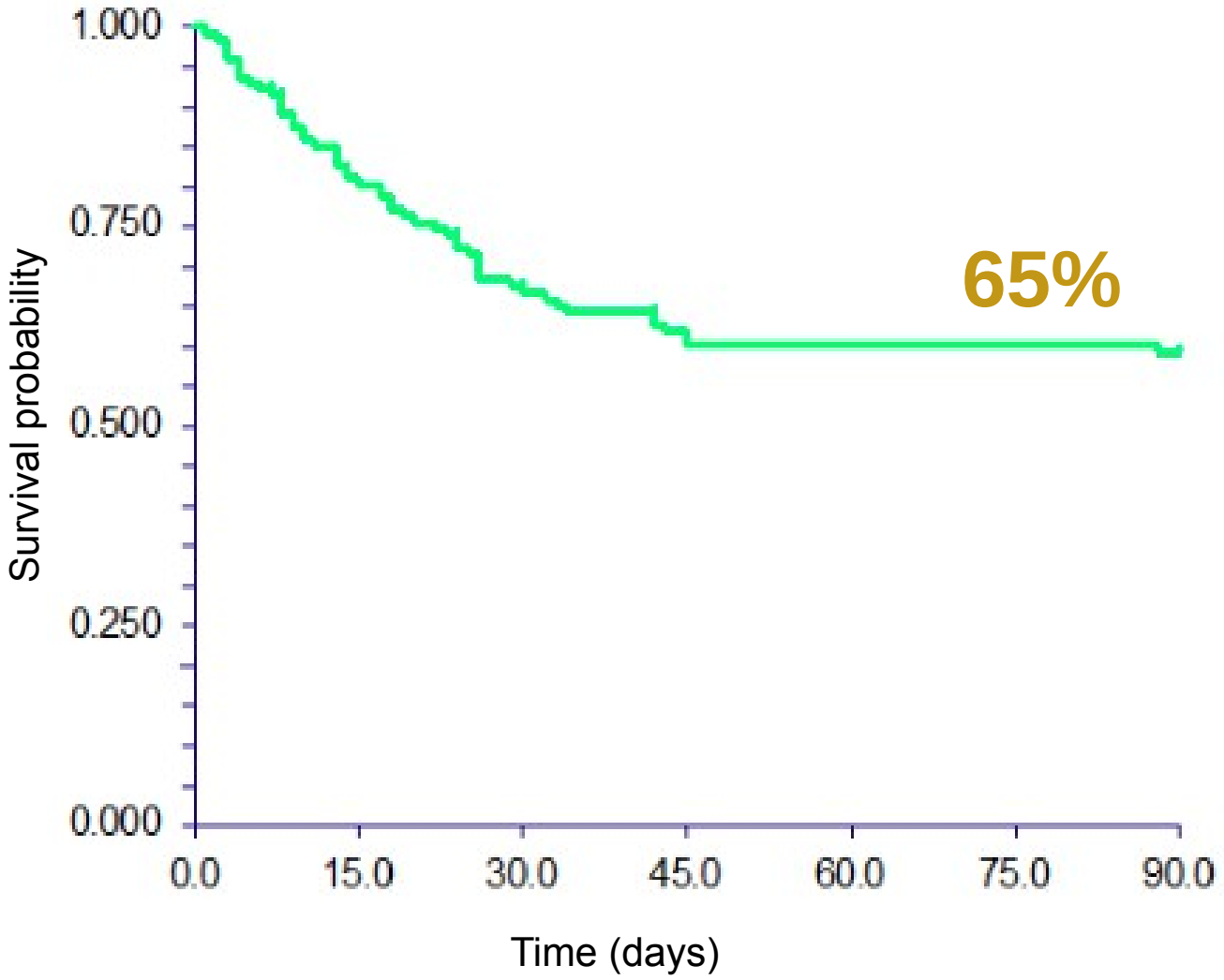
Hépatinov

HOPITAL PAUL BROUSSE
Centre Hépato-Biliaire

Which are the predictive factors for corticosteroid response defined by the LT-free survival?



Corticosteroid response at 90 days



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Predictive factors of corticosteroid response

	Responders N= 75	Non Responders* N= 38	p
Age, years	52 [39-63]	54 [41-61]	0.9803
Gender, female	58 (75)	24 (67)	0.3365
HE	**1 (1)**	**5 (14)**	**0.0185**
ALT, IU/L	784 [407-1120]	699 [408-1124]	0.9067
Total bilirubin, µmol/L	272 [207-386]	346 [265-414]	0.0803
INR	**1.6 [1.4-2]**	**2.7 [2-3.6]**	**<.0001**
Creatinine, µmol/L	59 [52-72]	63 [50-71]	0.9374
MELD	**22 [21-24]**	**28 [26-32]**	**<.0001**
Platelets, G/L	**202 [145-275]**	**130 [81-196]**	**0.0007**
Infection	**13 (19)**	**13 (36)**	**0.0468**
Admission corticosteroids, days	7 [3-10]	4 [2-9]	0.4058
Fibrosis stage 0-1/ 2-3/ 4	**29(43)/27(40)/12(18)**	**14(56)/3(12)/8(32)**	**0.0333**

2 patients were excluded, 1 dead and 1 LT before day 3 of corticosteroid therapy

The continuous variables are expressed using median [range IQR 1st and 3rd]. The qualitative variables are expressed using number (%).

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Creatinine, µmol/L	59 [52-72]	63 [50-71]	0.9374			
MELD	**22 [21-24]**	**28 [26-32]**	**<.0001**			
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Predictive factors of corticosteroid response

	Responders N=75	Non Responders* N=38	p
Delta ALT d3-d0	-132 [-391/-45]	-89 [-317/-13]	0.3573
Delta Total bilirubin d3-d0	**-51 [-85/-14]**	**17 [-19/64]**	**<.0001**
Delta INR d3-d0	**0 [-0.16/0.0]**	**0 [0.0/0.2]**	**0.0162**
Delta MELD d3-d0	**-0.9 [-2.2/0.07]**	**0.3 [-0.43-1.5]**	**0.0015**
Delta ALT d7-d0	-278 [-577/-88]	-186[-482/-18]	0.3841
Delta Total bilirubin d7-d0	**-98 [-140/-22]**	**6.5 [-90/117]**	**0.0072**
Delta INR d7-d0	**-0.2 [-0.3/0.0]**	**0.2 [-0.2/0.4]**	**0.0004**
Delta MELD d7-d0	**-2.8 [-4.13/-1]**	**0.0 [-1.0/2.8]**	**0.0004**

2 patients were excluded, 1 dead and 1 LT before day 3 of corticosteroid therapy

The continuous variables are expressed using median [range IQR 1st and 3rd]. The qualitative variables are expressed using number (%).

Predictive factors of corticosteroid response

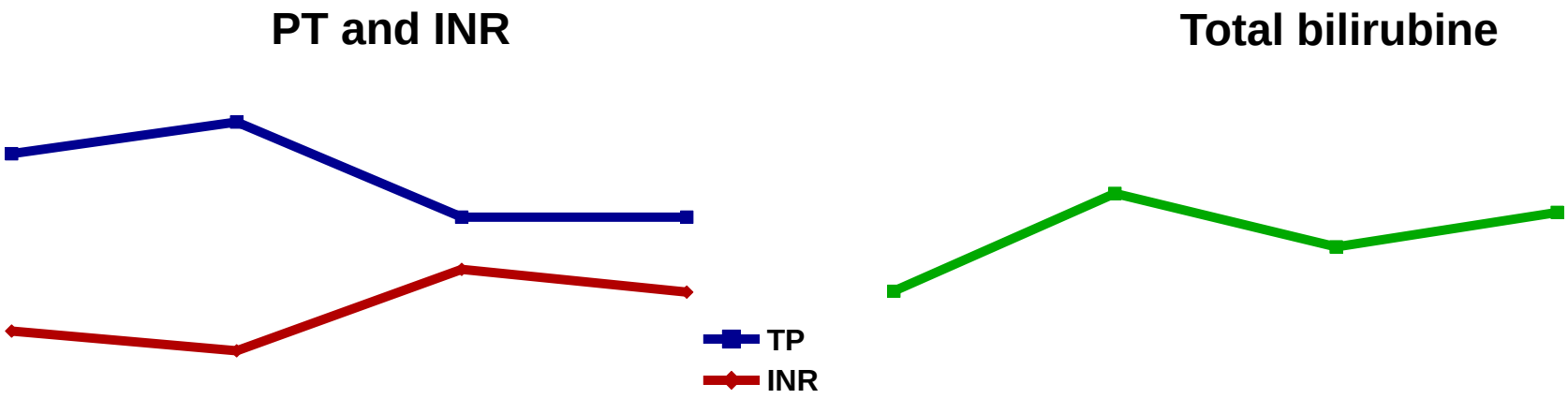
	Responders N=75	Non Responders* N=38	p	OR	95% CI	p
Delta ALT d3-d0	-132 [-391/-45]	-89 [-317/-13]	0.3573			
Delta Total bilirubin d3-d0	**-51 [-85/-14]**	**17 [-19/64]**	**<.0001**	**1.017**	**1.001-1.034**	**0.0365**
Delta INR d3-d0	**0 [-0.16/0.0]**	**0 [0.0/0.2]**	**0.0162**			
Delta MELD d3-d0	**-0.9 [-2.2/0.07]**	**0.3 [-0.43-1.5]**	**0.0015**			
Delta ALT d7-d0	-278 [-577/-88]	-186[-482/-18]	0.3841			
Delta Total bilirubin d7-d0	**-98 [-140/-22]**	**6.5 [-90/117]**	**0.0072**	**1.004**	**1.000-1.008**	**0.0485**
Delta INR d7-d0	**-0.2 [-0.3/0.0]**	**0.2 [-0.2/0.4]**	**0.0004**			
Delta MELD d7-d0	**-2.8 [-4.13/-1]**	**0.0 [-1.0/2.8]**	**0.0004**			

2 patients were excluded, 1 dead and 1 LT before day 3 of corticosteroid therapy

The continuous variables are expressed using median [range IQR 1st and 3rd]. The qualitative variables are expressed using number (%).

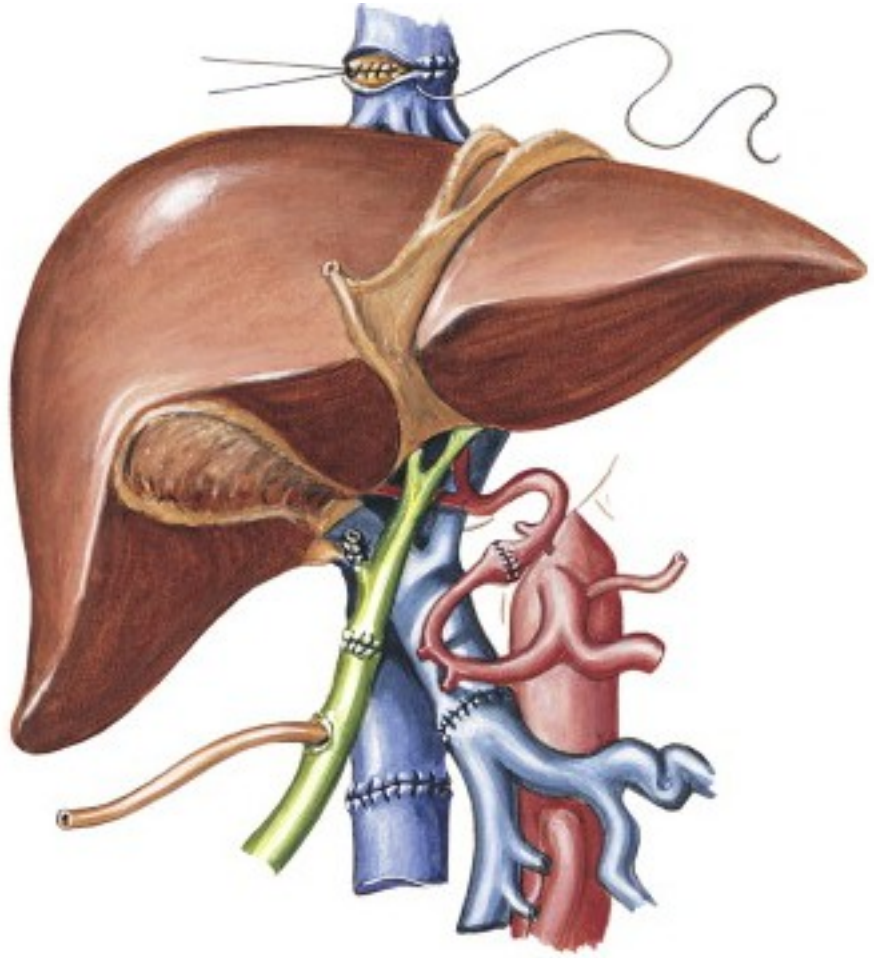
Evolution of Mister F on corticosteroids

Corticosteroid initiation the 9th October (1mg/kg/day)



At day 7 since corticosteroid administration MELD = 40 + grade 3 hepatic encephalopathy

16.10.2014 Liver transplantation



Miss K, 31 year old

October 2014 : outpatient clinic for cutaneous rash with no pruritus

Laboratory tests

AST IU/L	**75**	Tot bili µmol/L	17	GB G/L	5.2
ALT IU/L	**140**	PT %	83	PNN	3
GGT IU/L	28	INR	1	Hb g/L	13
ALP IU/L	60	FV %	92	Plts G/L	340

Who is Miss K ?

Lifestyle:

- Psychologist
- Not married
- No alcohol consumption
- No tobacco
- No IV drug, transfusion, recent travel, tattoo

Past medical or surgical history:

- Juvenile epilepsy treated with depakin stopped at 15y
- Herpes zoster during infancy
- Depressive sdr

Treatment:

Valdoxan (agomelatine) since March 2014

Diagnosis and Evolution

Conclusion: hepatic toxicity of agomelatine (anti-depressent) → Stop Valdoxane

Laboratory tests 2 months later

AST IU/L	**75 > 1052**	**Tot bili µmol/L**	17 > **212**	GB G/L	5.2
ALT IU/L	**140 > 1684**	PT %	83 > 69	PNN	3
GGT IU/L	28 > **137**	INR	1 > 1.32	Hb g/L	13
ALP IU/L	60 > 117	FV %	92 > 87	Plts G/L	340

Diagnostic work-up

Virology

Ab HAV, Ag HBs, Ab HBs, Ab HBc, Ab HCV, HIV, HTLV 1-2,
PCR CMV, EBV, HSV, HHV6, HHV8, HEV → Negatives

Metabolic liver disease

Ferritin, serum iron and transferrin saturation: normal
Ceruleoplasmin : normal

Immunology

IgG : 17.33 (7 - 16) / IgA : 2.56 (0.7 – 4) / IgM : 1.27 (0.4 – 2.3)
ANA 1:320 speckled, ASMA, Anti LKM1 and LC1 : negatives

CT scan Normal

Histology

“Sub-acute hepatitis with punctual, confluent and bridging necrosis. Portal and septal fibrosis. Inflammatory infiltrate contains plasma cells and lymphocytes. Moderate regenerative activity.

Features compatible with toxic and autoimmune hepatitis diagnosis.”

What is your final diagnosis ?

A. Drug induced liver injury

B. Autoimmune hepatitis

C.Drug-induced AIH

D. Immune-mediated DILI

What is your final diagnosis ?

A. Drug induced liver injury

B. Autoimmune hepatitis

C.DILI/AIH

D.Immune-mediated DILI

No clear answer

RUCAM: Roussel-UCLAF Causality Assessment Method

RUCAM Causality Assessment

Drug: _____ Initial ALT: _____ Initial Alk P: _____ R ratio = [ALT/ULN] ÷ [Alk P/ULN] = _____ ÷ _____ = _____

The R ratio determines whether the injury is hepatocellular (R > 5.0), cholestatic (R < 2.0), or mixed (R = 2.0 – 5.0)

	Hepatocellular Type		Cholestatic or Mixed Type		Assessment
1. Time to onset					
	Initial Treatment	**Subsequent Treatment**	**Initial Treatment**	**Subsequent Treatment**	**Score** (check one only)
○ From the beginning of the drug:					
• Suggestive	5 – 90 days	1 – 15 days	5 – 90 days	1 – 90 days	☐ +2
• Compatible	< 5 or > 90 days	> 15 days	< 5 or > 90 days	> 90 days	☐ +1
○ From cessation of the drug:					
• Compatible	≤ 15 days	≤ 15 days	≤ 30 days	≤ 30 days	☐ +1
Note: If reaction begins before starting the medication or >15 days after stopping (hepatocellular), or >30 days after stopping (cholestatic), the injury shou be considered unrelated and the RUCAM cannot be calculated.					
2. Course	**Change in ALT between peak value and ULN**		**Change in Alk P (or total bilirubin) between peak value and ULN**		**Score** (check one only)
After stopping the drug:					
• Highly suggestive	Decrease ≥ 50% within 8 days		Not applicable		☐ +3
• Suggestive	Decrease ≥ 50% within 30 days		Decrease ≥ 50% within 180 days		☐ +2
• Compatible	Not applicable		Decrease < 50% within 180 days		☐ +1
• Inconclusive	No information or decrease ≥ 50% after 30 days		Persistence or increase or no information		☐ 0
• Against the role of the drug	Decrease < 50% after 30 days **OR** Recurrent increase		Not applicable		☐ -2
○ **If the drug is continued:**					
• Inconclusive	All situations		All situations		☐ 0
3. Risk Factors:	**Ethanol**		**Ethanol or Pregnancy (either)**		**Score** (check one for each)
○ Alcohol or Pregnancy	Presence		Presence		☐ +1
	Absence		Absence		☐ 0
○ Age	Age of the patient ≥ 55 years		Age of the patient ≥ 55 years		☐ +1
	Age of the patient < 55 years		Age of the patient < 55 years		☐ 0

4. Concomitant drug(s):	Score (check one only)
○ None or no information or concomitant drug with incompatible time to onset	☐ 0
○ Concomitant drug with suggestive or compatible time to onset	☐ -1
○ Concomitant drug known to be hepatoxic with a suggestive time to onset	☐ -2
○ Concomitant drug with clear evidence for its role (positive rechallenge or clear link to injury and typical signature)	☐ -3

5. Exclusion of other causes of liver injury:		Score (check one only)
Group I (6 causes): ○ **Acute viral hepatitis** due to **HAV** (IgM anti-HAV), or ○ **HBV** (HBsAg and/or IgM anti-HBc), or ○ **HCV** (anti HCV and/or HCV RNA with appropriate clinical history) ○ **Biliary obstruction** (By imaging) ○ **Alcoholism** (History of excessive intake and AST/ALT ≥ 2) ○ **Recent history of hypotension, shock or ischemia** (within 2 weeks of onset) **Group II (2 categories of causes):** ○ Complications of underlying disease(s) such as autoimmune hepatitis, sepsis, chronic hepatitis B or C, primary biliary cirrhosis or sclerosing cholangitis; or ○ Clinical features or serologic and virologic tests indicating acute CMV, EBV, or HSV.	○ All causes in Group I and II ruled out	☐ +2
	○ The 6 causes of Group I ruled out	☐ +1
	○ Five or 4 causes of Group I ruled out	☐ 0
	○ Less than 4 causes of Group 1 ruled out	☐ -2
	○ Non drug cause highly probable	☐ -3

6. Previous information on hepatotoxicity of the drug:	Score (check one only)
○ Reaction labeled in the product characteristics	☐ +2
○ Reaction published but unlabeled	☐ +1
○ Reaction unknown	☐ 0

7. Response to readministration:			Score (check one only)
○ Positive	Doubling of ALT with drug alone	Doubling of Alk P (or bilirubin) with drug alone	☐ +3
○ Compatible	Doubling of the ALT with the suspect drug combined with another drug which had been given at the time of onset of the initial injury	Doubling of the Alk P (or bilirubin) with the suspect drug combined with another drug which had been given at the time of onset of the initial injury	☐ +1
○ Negative	Increase of ALT but less than ULN with drug alone	Increase of Alk P (or bilirubin) but less than ULN with drug alone	☐ -2
○ Not done or not interpretable	Other situations	Other situations	☐ 0
		TOTAL (add the checked figures)	

Abbreviations used: ALT, alanine aminotransferase; Alk P, alkaline phosphatase; ULN, upper limit of the normal range of values
Modified from: Danan G and Benichou C. J Clin Epidemiol 1993; 46: 1323-30.

4. Concomitant drug(s):		Score (check one only)
○ None or no information or concomitant drug with incompatible time to onset		☐ 0
○ Concomitant drug with suggestive or compatible time to onset		☐ -1
○ Concomitant drug known to be hepatoxic with a suggestive time to onset		☐ -2
○ Concomitant drug with clear evidence for its role (positive rechallenge or clear link to injury and typical signature)		☐ -3

5. Exclusion of other causes of liver injury:		Score (check one only)
Group I (6 causes): ○ **Acute viral hepatitis** due to **HAV** (IgM anti-HAV), or ○ **HBV** (HBsAg and/or IgM anti-HBc), or ○ **HCV** (anti HCV and/or HCV RNA ○ **Biliary obstruction** (By imaging) ○ **Alcoholism** (History of excessive ○ **Recent history of hypotension,** **Group II (2 categories of causes):** ○ Complications of underlying dise B or C, primary biliary cirrhosis o ○ Clinical features or serologic and	○ All causes in Group I and II ruled out ○ The 6 causes of Group I ruled out oup I ruled out Group 1 ruled out y probable	☐ +2 ☐ +1 ☐ 0 ☐ -2 ☐ -3

6. Previous information on hepatoto		Score (check one only)
○ Reaction labeled in the product		☐ +2
○ Reaction published but unlabele		☐ +1
○ Reaction unknown		☐ 0

7. Response to readministration:			Score (check one only)
○ Positive		n) with drug alone	☐ +3
○ Compatible		ubin) with the suspect drug which had been the initial injury	☐ +1
○ Negative		) but less than ULN with	☐ -2
○ Not done or not interpretable	Other situations	Other situations	☐ 0

TOTAL (add the checked figures)

0 or less = drug is excluded

1 to 2 = unlikely

3 to 5 = possible

6 to 8 = probable

>8 = highly probable

Abbreviations used: ALT, alanine aminotransferase; Alk P, alkaline phosphatase; ULN, upper limit of the normal range of values
Modified from: Danan G and Benichou C. J Clin Epidemiol 1993; 46: 1323-30.

Valdoxan = Agomelatine

- Literature

- Agomelatine and hepatotoxicity: implications of cumulated data derived from spontaneous reports of adverse drug reactions
  Gahr M et al. Pharmacopsychiatry 2013

- Antidepressant-induced liver injury: a review for clinicians
  Voican CS et al. Am J Psychiatry 2014

- Hepatotoxicity related to agomelatine and other new antidepressants: a case/noncase approach with information from the Portuguese, French, Spanish, and Italian pharmacovigilance systems
  Montastruc F et al. J Clin Psychopharmacol. 2014

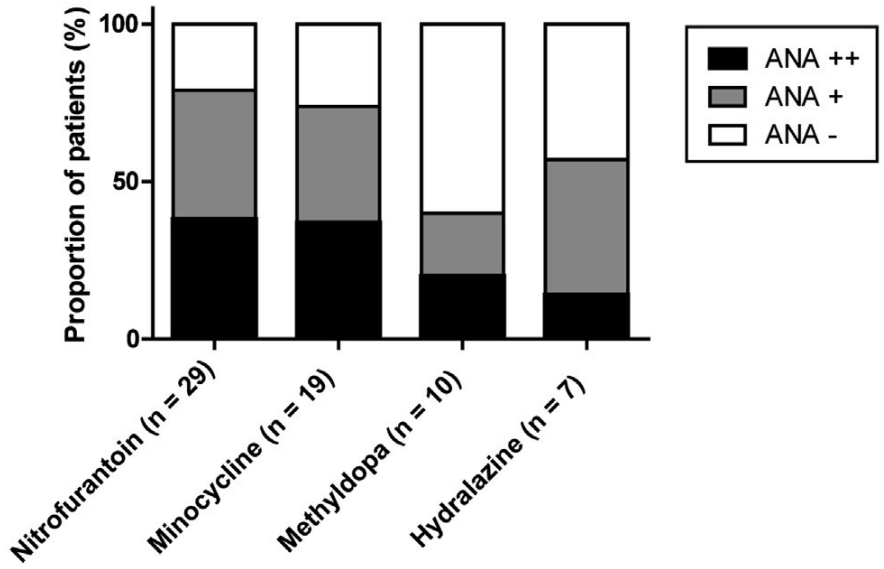
- A systematic review of agomelatine-induced liver injury
  Freiesleben et al. J Mol Psychiatry 2015

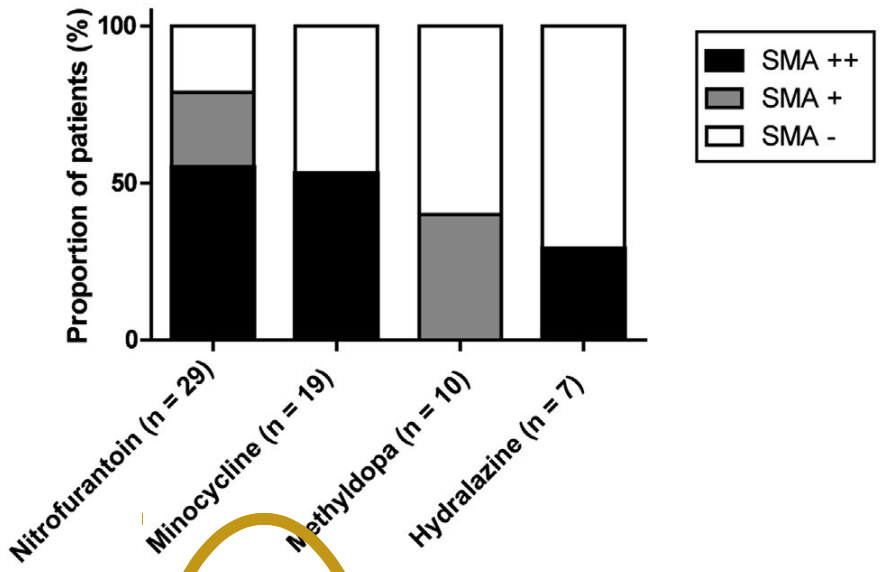
Drug-induced Autoimmune-like Hepatitis

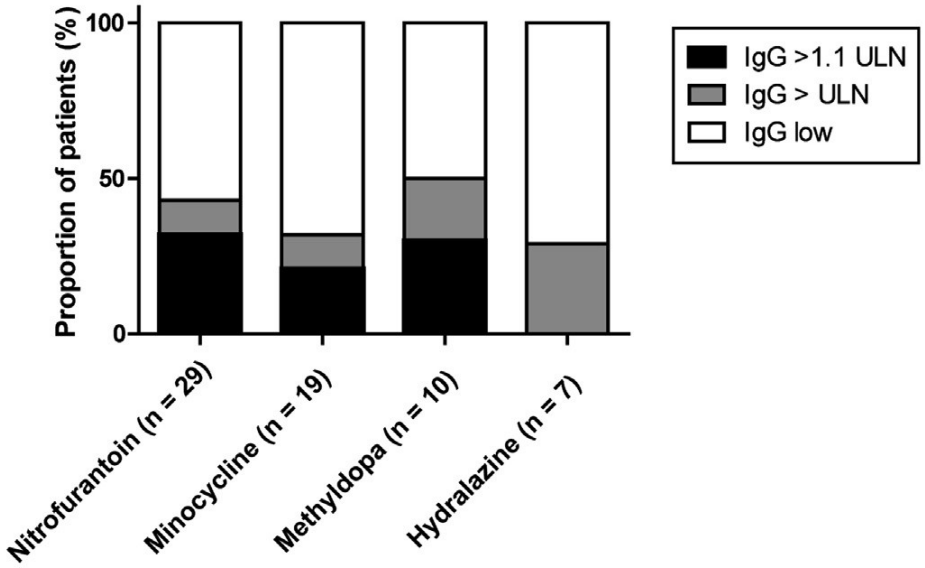
- Accounts for up to 10% of acute hepatitis and 25-50% of patients with acute liver failure
- Incidence 1.3/100.000 in rural England to 2.4/100.000 in Spain and Sweden
- 80-90% of female
- Rare: 9% of DILI

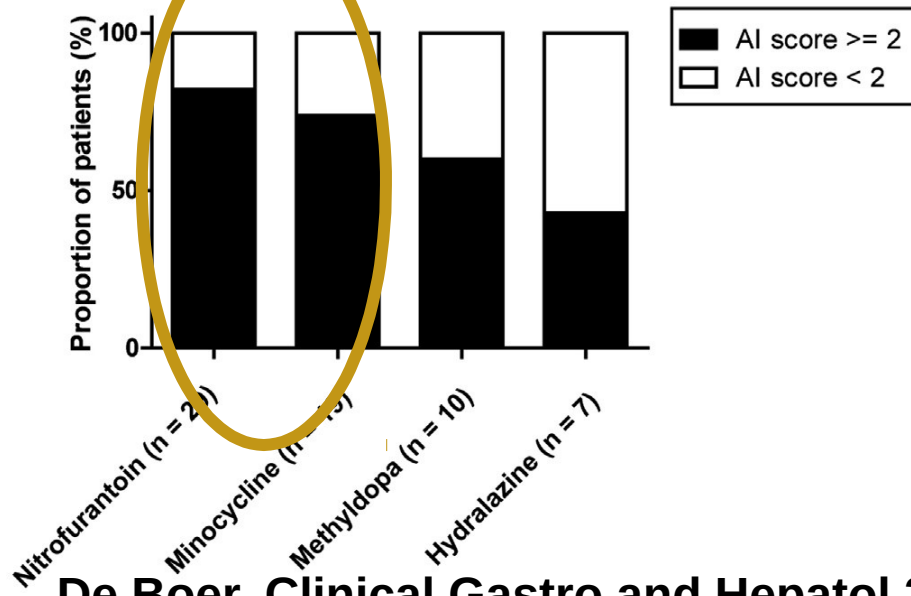
Czaja, Dig Dis Sci 20

Drug-induced Autoimmune-like Hepatitis









De Boer, Clinical Gastro and Hepatol 2

DILI and AIH: suggested diagnosis and clinical characteristics

	Characteristics
AIH with DILI	Patients with known AIH; probably chance association; often advanced fibrosis on histology
Drug-induced AIH	Patients with unrecognized AIH or predisposition to AIH, in whom AIH is unmasked or induced by DILI; good response to steroids; relapse after withdrawal of immunosuppression with the need for continued immunosuppressive treatment; chance association of drug intake in a patient with first presentation of AIH cannot be ruled out
Immune-mediated DILI	Clinical, biochemical, and histological signs similar to AIH; eosinophilia and rash may be present; usually no advanced fibrosis; good response to steroids; remission is maintained after successful withdrawal of steroids

Weiler-Normann, J Hepatol 20

DILI and AIH: clinical and biological characteristics

Comparison of the demographic, seropositivity, AIH score and liver tests, between DILI/AIH and AIH alone

	AIH Patients (n = 237)	DIAIH (n = 24)	P Value
Age	52 (37-62)	53 (24-61)	NS
Sex, females (%)	184 (78%)	20 (92%)	NS
ANA positive (%)	165/237 (70%)	20 (83%)	NS
SMA positive (%)	106/237 (45%)	12/24 (50%)	NS
Both ANA and SMA (%)	69/237 (29%)	9/24 (38%)	NS
Seronegative (%)	29/237 (12%)	1/24 (4%)	NS
Simplified AIH score: Probable or definite (%)	181/237 (76%)	19/21 (90.5%)	NS
AST (<48 U/L)	392 (154-1031)	679 (291-956)	NS
ALT (<55 U/L)	480 (185-1141)	728 (255-1141)	NS
ALP (115 U/L)	241 (138-350)	376 (229-514)	0.0166
TB (<1.0 mg/dL)	2.0 (1.0-8.0)	4.0 (1.0-12.0)	NS
Albumin (>3.5 g/dL)	3.4 (2.95-3.7)	3.1 (2.6-3.6)	NS
INR (<1.2)	1.1 (1.0-1.3)	1.1 (1.0-1.3)	NS
IgG (<1500 g/dL)	2020 (1618-2702)	1905 (1600-2455)	NS
Gamma globulins (<1.7 g/dL)	2.5 (2.0-3.2)	2.55 (2.2-3.1)	NS
Jaundice at presentation	110/237 (46%)	12/24 (50%)	NS

Björnsson, Hepatology 2

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Björnsson, Hepatology 2

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Jaundice at presentation	110/237 (46%)	12/24 (50%)	NS

Björnsson, Hepatology 2

DILI and AIH: histological characteristics

Comparison between DILI/AIH and AIH alone

	DIAIH	AIH	P Value
Grade (Batts and Ludwig)	3 (2-3)	3 (2-3)	NS
Portal inflammation	2 (2-3)	2 (2-3)	NS
Lymphoplasmacytic (absent/present)	19/23 (83%)	22/23 (96%)	NS
Interface hepatitis	2.5 (1.5-3.0)	2.0 (1.0-3.0)	NS
Lobular hepatitis	2.0 (1.0-3.0)	2.0 (1.0-3.0)	NS
Zone 3 necrosis	15/23 (65%)	12/22 (55%)	NS
Confluent necrosis	7/23 (30.4%)	2/22 (9%)	NS
Rosette formation	7/22 (31.8%)	5/22 (22.7%)	NS
Stage	0 (0-2)	1 (0-3)	0.06
Compatible	8/24 (33%)	8/24 (33%)	NS
Typical	16/24 (66%)	15/24 (63%)	
Atypical	0	1/24 (4%)	

Björnsson, Hepatology 2

How would you manage this patient ?

A.Wait and see

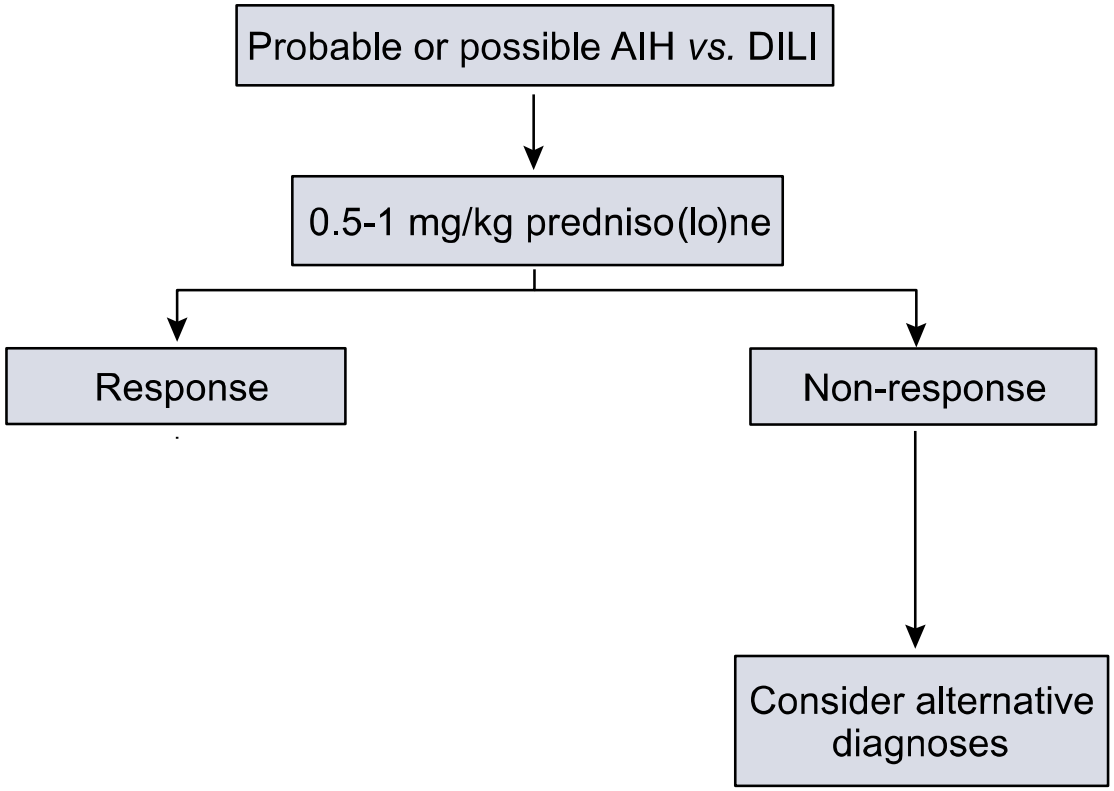
B. Administer corticosteroids

How would you manage this patient ?

A.Wait and see

B. Administer corticosteroids

AIH vs DILI



EASL Guidelines, J Hepatol 2

Drug-induced AIH: improvement with drug discontinuation and relapse

Characteristics of 7 patients with DI-AIH at presentation and at time of relapse

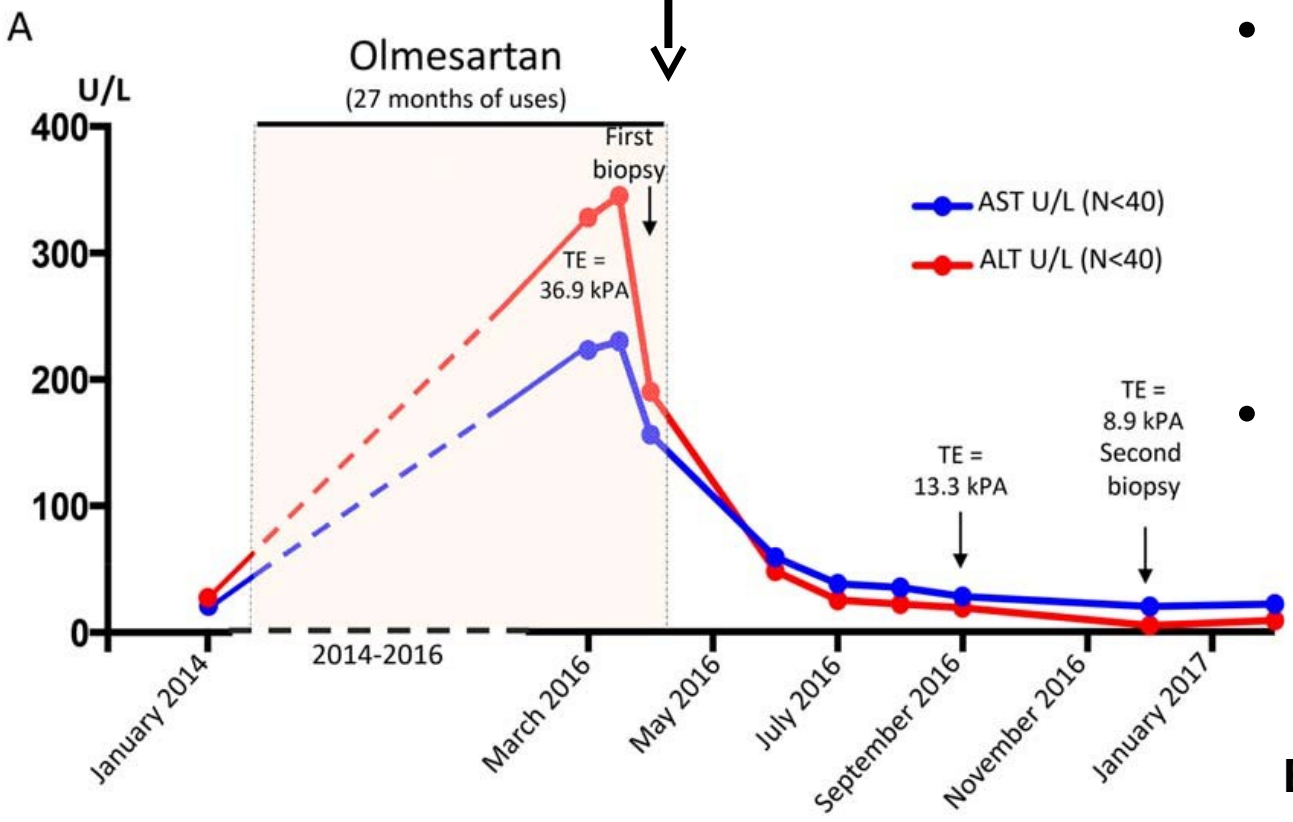
Patient (Age/Sex)	ALT at First Onset (IU/l)	IgG at First Onset (mg/dL)	ANA titer at First Onset	Time to Relapse (Days)	ALT at Relapse (IU/L)	IgG at Relapse (mg/dL)	ANA Titer at Relapse	Causative Drug
56 F	1617	1570	<40	300	95	2751	80	Ofloxacin
20 M	1018	1170	80	30	280	1720	160	Diclofenac sodium
67 F	992	1370	320	500	715	1670	2560	Herbal medicine
31 F	567	1480	<40	40	149	1770	160	Cefaclor
52 F	1170	1863	<40	100	230	2580	320	Loxoprofen sodium hydrate
68 F	418	1698	<40	20	218	2237	80	Herbal medicine
66 F	808	1460	<40	50	622	2320	40	Benzbromarone

All patients improved on corticosteroid therapy

Sugimoto, Hepatology 20

Autoimmune-like chronic hepatitis induced by Olmesartan: case report

Stop of olmesartan without introduction of corticosteroids



First liver biopsy

- Extensive fibrosis with formation of early nodules.
- Portal lymphocytic inflammation and marked interface hepatitis.

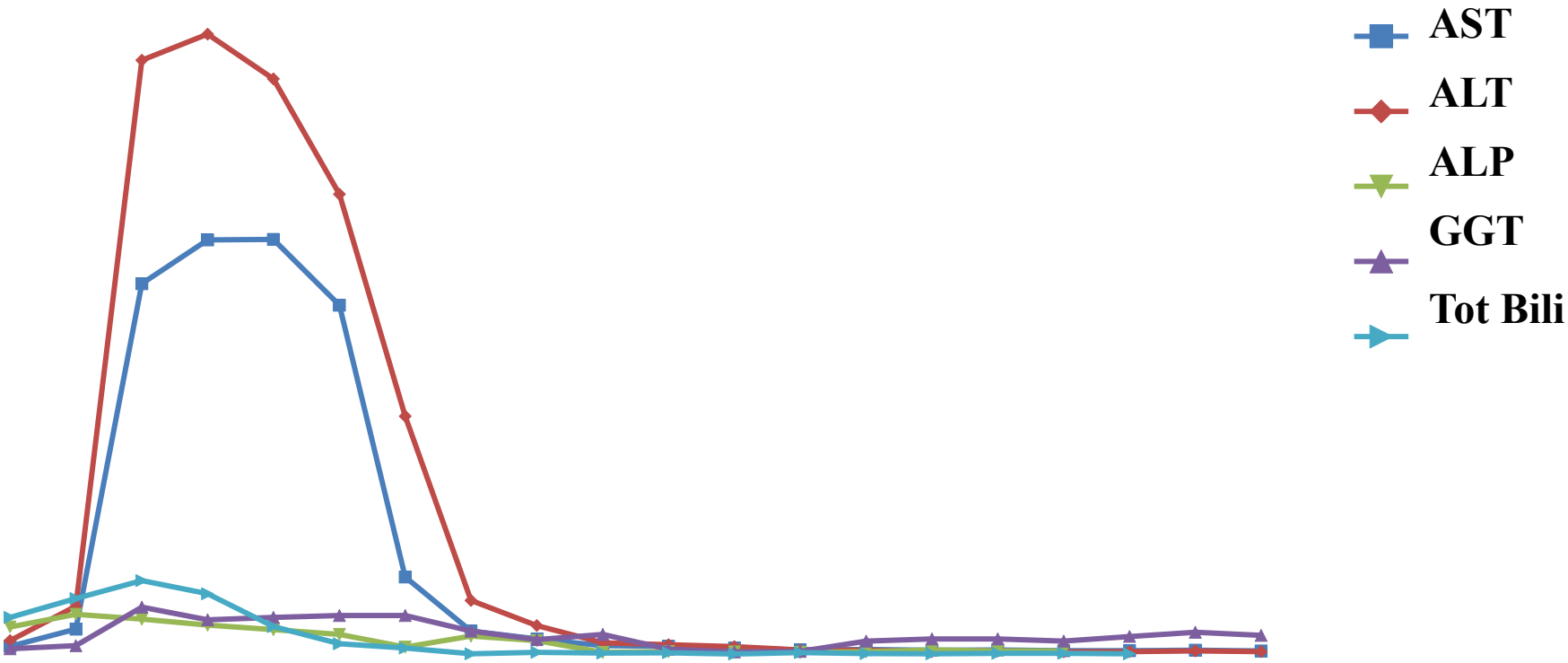
Barge, Hepatology 201

Evolution of liver tests of Miss K

Introduction of corticosteroids

Introduction of azathioprine

IgG Control : 8.33
ANA and ASMA : 1:80



2 years later how would you manage this patient?

A. Perform liver biopsy

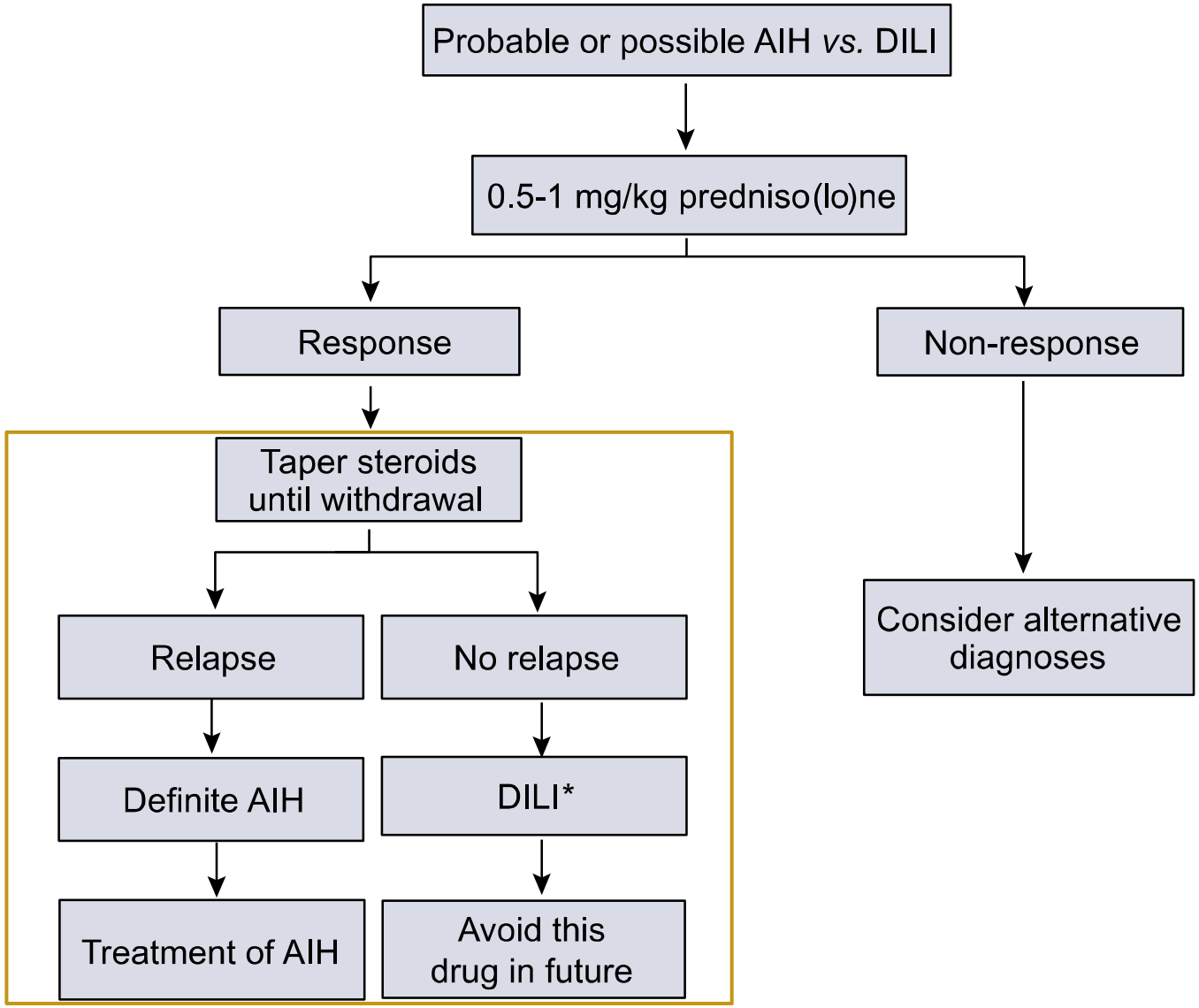
B. Stop corticosteroids

2 years later how would you manage this patient?

A. Perform liver biopsy

B. Stop corticosteroids

AIH vs DILI



EASL Guidelines, J Hepatol 2

AIH-DILI: corticosteroid discontinuation

Comparison of therapy and outcome between AIH-DILI and AIH alone

	AIH Patients (n=237)	DIAIH (n=24)	p
Immunosuppressive therapy (%)	222/237 (94%)	21/24 (88%)	NS
Steroids and azathioprine (%)	191/222 (86%)	12/21 (57%)	0.0024
Steroids alone (%)	31/222 (14%)	9 (43%)	0.0024
Trial of discontinuation successful (%)	18/52 (35%)	14/14 (100%)	<0.0001

No relapse occurred after corticosteroid discontinuation in all DIAIH during a median follow-up of 36 months

Björnsson, Hepatology 2

Recurrent DILI with different drugs (Spanish Registry)

- 9 (1.2%) patients with 2 DILI episodes caused by two different drugs
- Mean age 67 years [34-84]
- Time to liver injury onset and duration of therapy ranged between 2 days and 3 years
- In all cases the pattern of liver injury was hepatocellular
- In 4 patients the diagnosis of AIH-DILI was made
- All patients with AIH-DILI improved on corticosteroids
- Steroids withdrawal was successfully attempted in 2 pts

Lucena, J Hepatol 201

And Miss K?

- Miss K is on 50 mg/d of azathioprine
- 3 years after the DIAIH episode
- Tolerance is excellent
- She does not want to stop treatment taking the risk of a possible AIH reactivation..