



Auto-immune liver diseases: treatment of difficult patients

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**International Conference
on the Management of
Liver Diseases**

Organised by: **Pr Patrick MARCELLIN**
Association for the Promotion of Hepatologic Care
(APHC)



CONFLICT OF INTEREST

None

Case 1

Madam LG, 57 year old

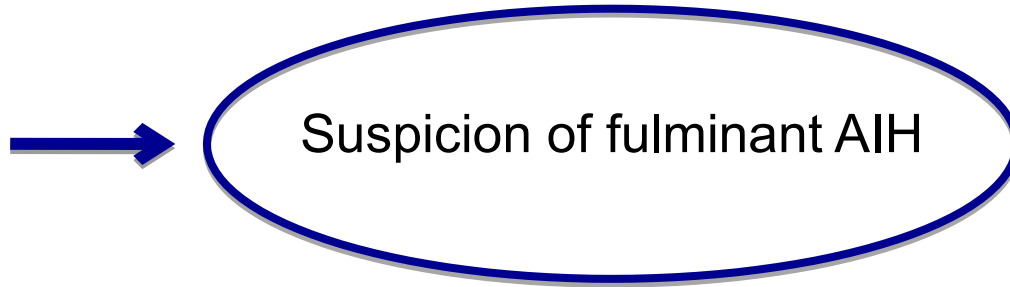
June 2008: Liver Transplantation for fulminant hepatitis

- **Family history** → autoimmunity (SLE, rheumatoid arthritis)
- **Past medical history** → uneventful
- **Virus/Bacteria** → negatives
- **Immunology** Anti-tissue Ab: ANA + 1:80 homogeneous and speckled, AMA, ASMA, anti-LKM1, anti-LC1 → negatives; IgG 14.9 (N<12.5)
- **Toxic (drugs/medications)** → negatives

Madam LG, 57 year old

Explant liver histology : massive, confluent necrosis, high lymphocytic infiltrates, few plasma cells

The pathologist conclusion: no signs for etiological orientation



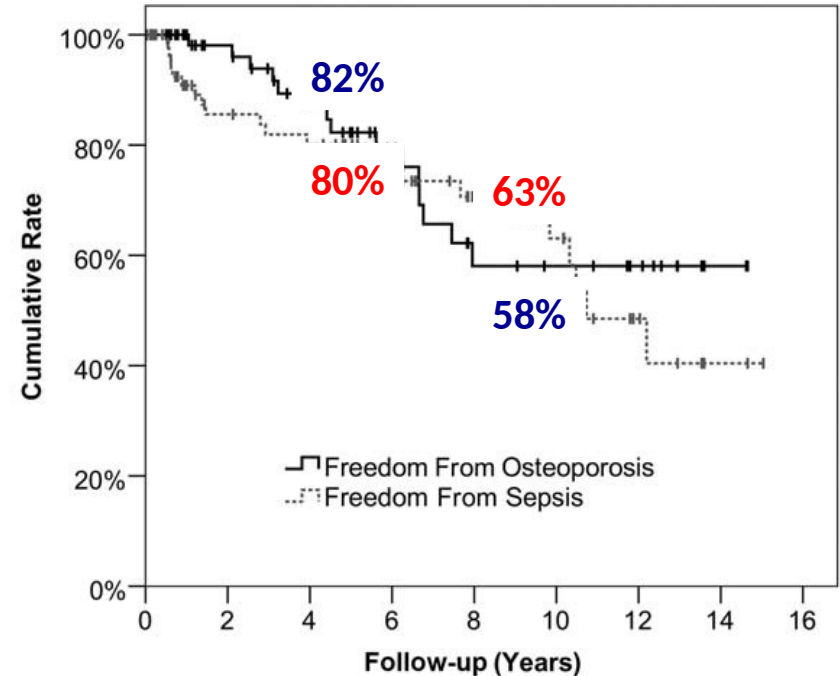
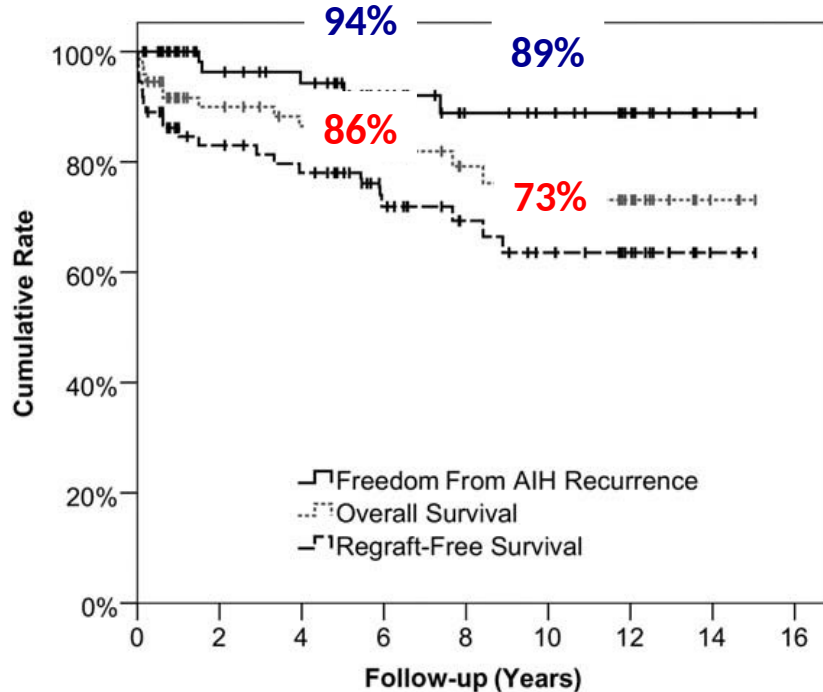
Would you keep low dose of steroids ?

A. YES

B. NO

Long-term use of steroids after LT in AIH recipients is safe

Single center study : 73 patients, 86% maintained on prednisolone



Survival of AIH recipients after LT

Comparison of survival outcomes with the existing literature

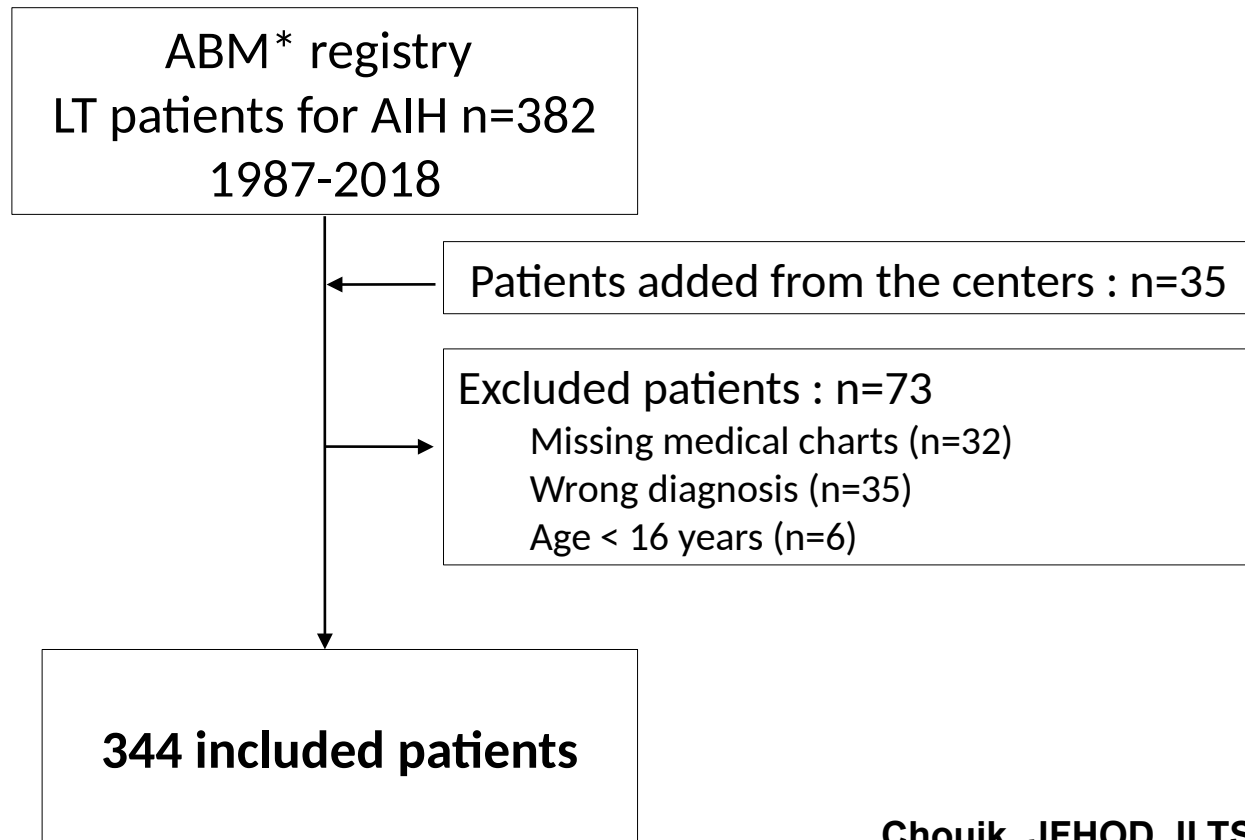
Publication	1 Year	3 Year	5 Year	10 Year
Overall Survival				
Our data	92	90	86	73
Schramm et al. ²¹ (2010; ELTR)	—	—	73	—
Kashyap et al. ²² (2010; UNOS)	89	84	80	—
Montano-Loza et al. ¹² (2009)	—	—	81	77
Campsen et al. ¹³ (2008)	—	—	91	—
Aberg et al. ²³ (2011)	90	—	82	72
Regraft-free survival				
Our data	86	81	78	64
Schramm et al. ²¹ (2010; ELTR)	—	—	66	—
Kashyap et al. ²² (2010; UNOS)	85	78	75	—
Montano-Loza et al. ¹² (2009)	—	—	—	—
Campsen et al. ¹³ (2008)	—	—	—	—
Aberg et al. ²³ (2011)	86	—	76	65

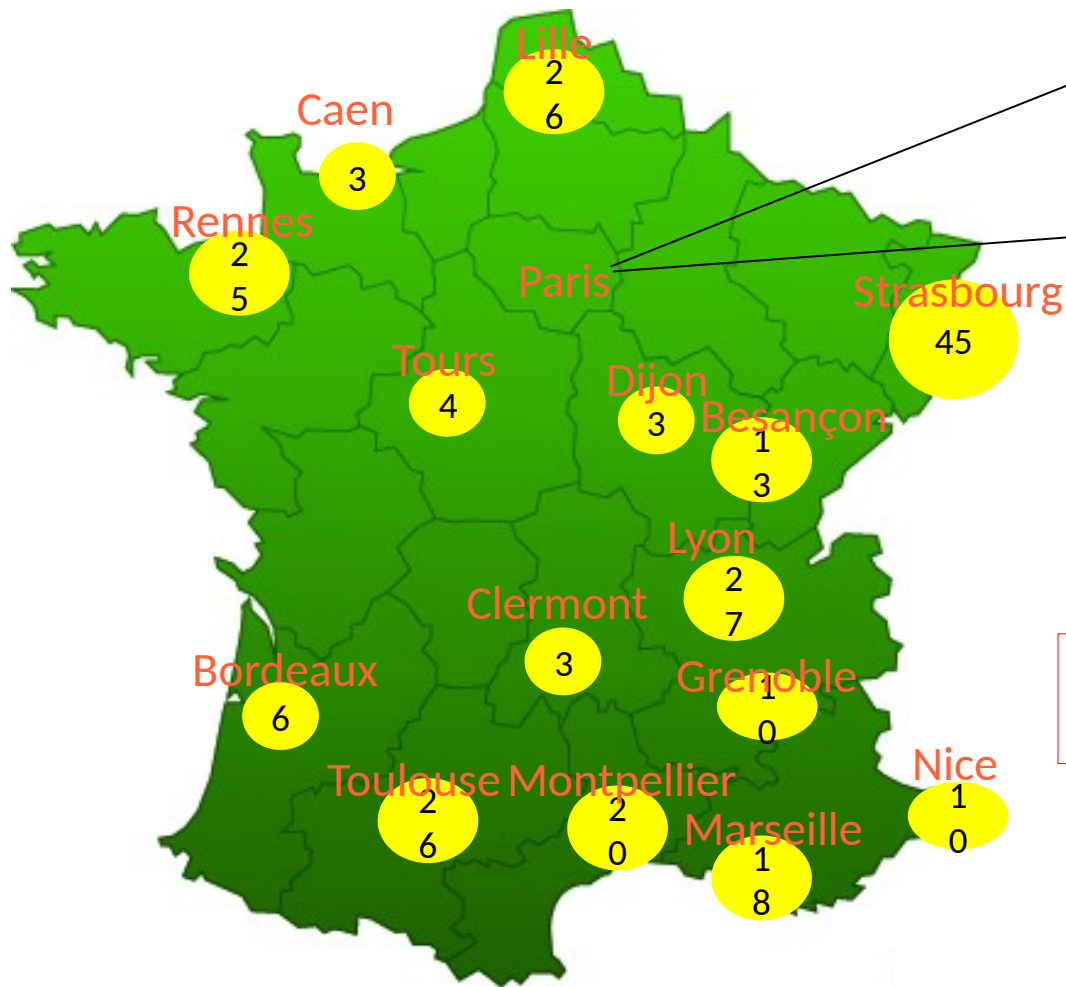
NOTE: Data are given as %.

Risk factors for AIH recurrence after LT

Risk Factors for Recurrence	Statistical Method Applied	Reference
Discontinuation of steroid therapy	Observational study*	Milkiewicz et al. ⁽²⁵⁾ (1999)
HLA mismatching between donor and recipient for HLA-DR3 or DR4	Observational study	Duclos-Vallée et al. ⁽²⁸⁾ (2003); Neuberger et al. ⁽⁵⁴⁾ (1984)
	Multivariate Cox analysis	Balan et al. ⁽⁵³⁾ (2008)
Tacrolimus-based immunosuppressive regimens	Univariate analysis (Fisher's exact test)	Ayata et al. ⁽⁴⁵⁾ (2000)
HLA-DR3 or HLA-DR4 incidence in the transplant recipient	Univariate analysis (Fisher's exact test)	González-Koch et al. ⁽²⁷⁾ (2001)
Abnormal pre-LT AST, ALT, IgG	Multivariate Cox analysis	Montano-Loza et al. ⁽⁵⁾ (2009)
Retransplantation for recurrent AIH	Observational study	Reich et al. ⁽²⁶⁾ (2000)
Transplantation for chronic AIH (patients transplanted for fulminant AIH seem to be protected from recurrence)	Observational study	Reich et al. ⁽²⁶⁾ (2000)
Concomitant autoimmune disease	Multivariate Cox analysis	Montano-Loza et al. ⁽⁵⁾ (2009)
Moderate to severe inflammatory activity or plasma cell penetration in the liver explants	Multivariate Cox analysis	Montano-Loza et al. ⁽⁵⁾ (2009)
High-grade inflammation in the native liver at LT	Univariate analysis (Fisher's exact test)	Ayata et al. ⁽⁴⁵⁾ (2000)

French Multicenter study on AIH LT recipients





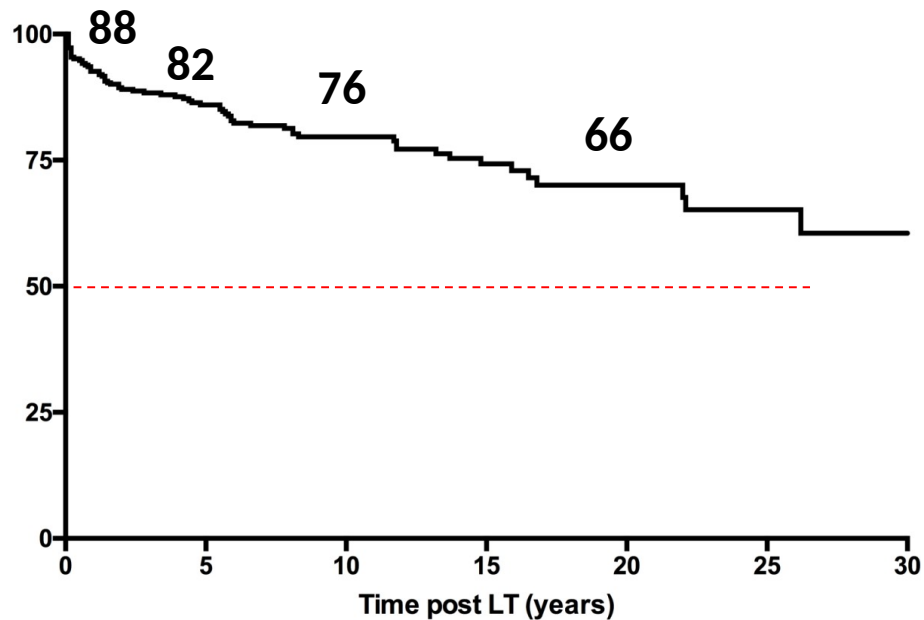
Beaujon : 48
Paul Brousse : 46
Saint-Antoine : 5
Créteil : 6

344 patients

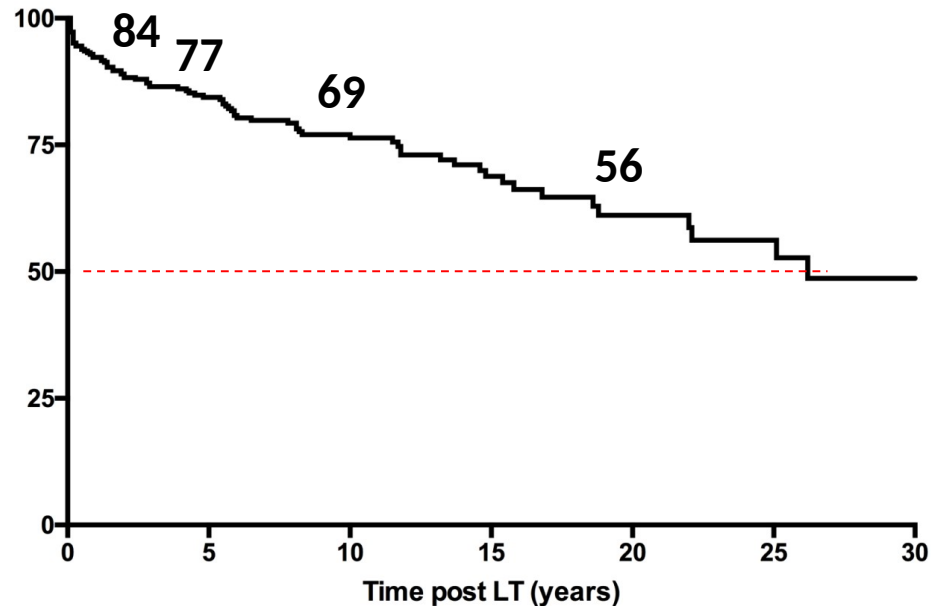
Median follow-up **74**
(IQR, 28-152) months

Patient and graft survival

Patient survival



Graft survival



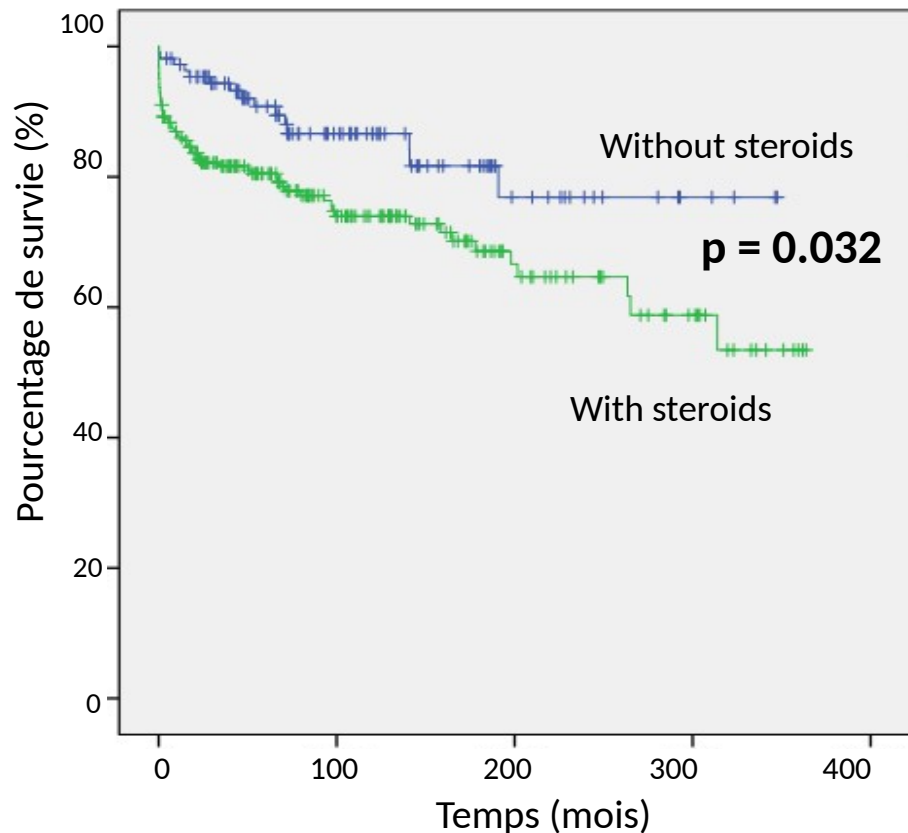
number at risk

344 206 123 68 35 20 3

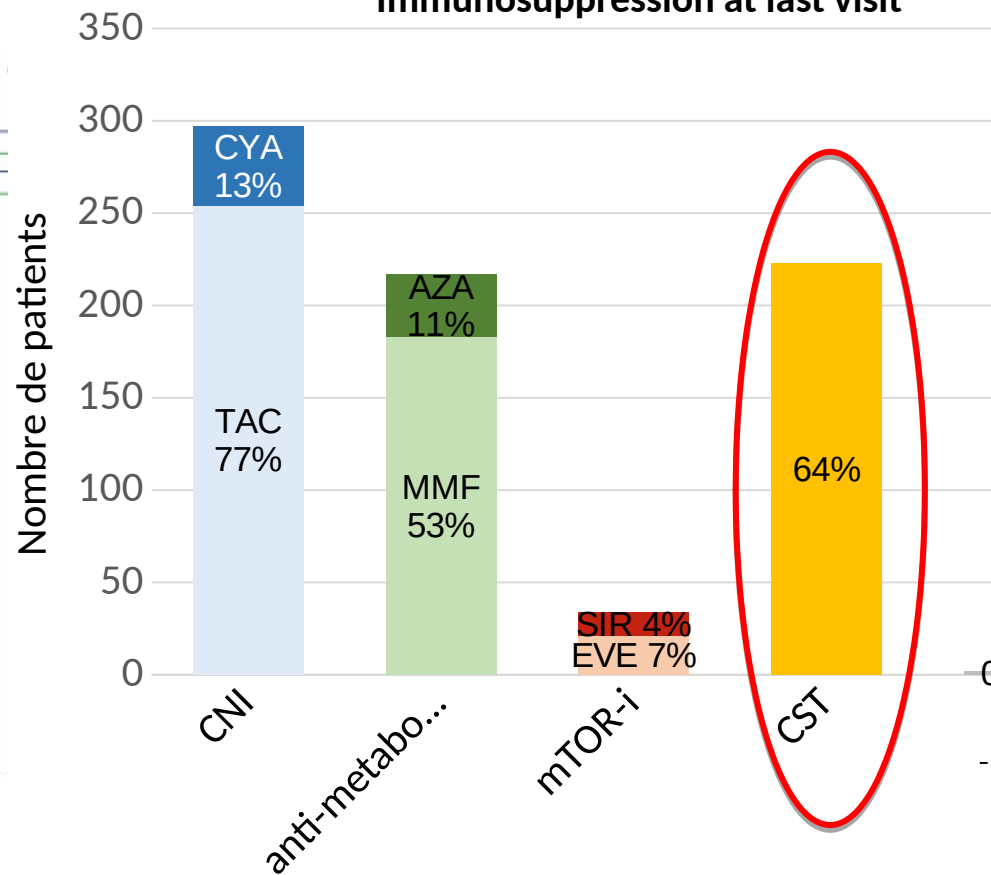
344 199 115 59 30 17 3

Long term use of corticosteroids after LT

Survival according to steroids use



Immunosuppression at last visit



Pro: Steroids Can Be Withdrawn Posttransplant in Recipients With Autoimmune Hepatitis

Avash Kalra, James R. Burton Jr., and Lisa M. Forman

Liver Transpl 2018

Steroids

- Are associated with a lot of side effects
- Do not prevent AIH recurrence
- Do not increase the risk of acute cellular rejection
- Do not increase the risk of graft loss or death

Con: Steroids Should Not Be Withdrawn in Transplant Recipients With Autoimmune Hepatitis

Eleni Theocharidou and Michael A. Heneghan

Liver Transpl 2018

Steroids

- Do not increase the risk of sepsis or osteoporosis
- May reduce AIH recurrence
- May reduce acute cellular rejection

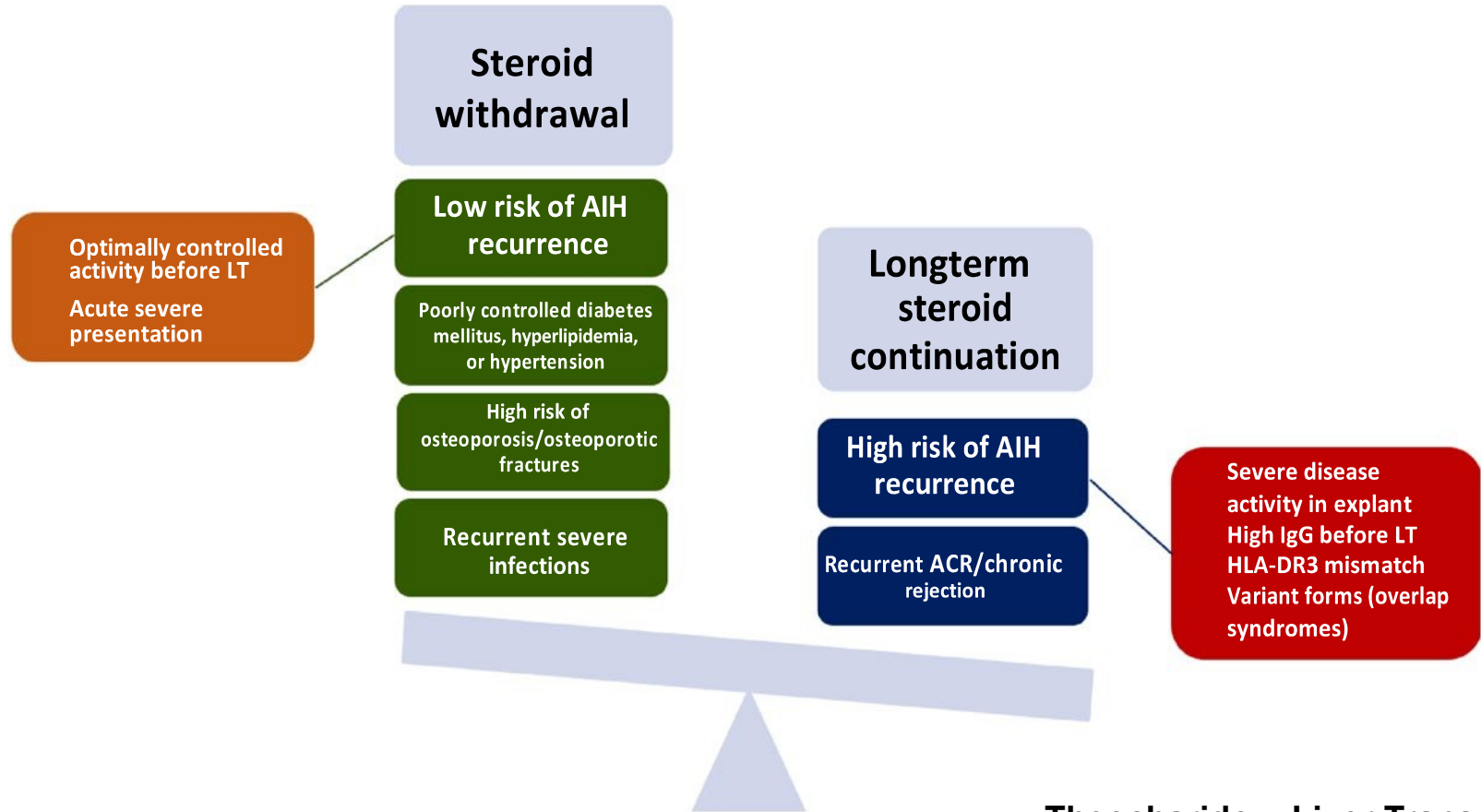
Continuation vs discontinuation of steroids after LT

OUTCOME	RESULTS	GRADE OF EVIDENCE QUALITY
Recurrent autoimmune hepatitis	<p>Two retrospective studies^{1,2} and one RCT³ reported no significant difference in recurrence of autoimmune hepatitis after LT</p> <p>¹ Campsen J, et al. Liver Transplantation 2008;14:1281</p> <p>² Heffron TG, et al. Transplant Proc 2002;34:3311</p> <p>³ Junge G, et al. Transplant Proc 2005;17:1695</p>	LOW
Acute cellular rejection	No studies reported frequencies of acute cellular rejection	
Graft loss	No studies reported frequencies of graft loss	
Death	<p>One RCT³ reported no significant difference between the two groups</p> <p>³ Junge G, et al. Transplant Proc 2005;17:1695</p>	VERY LOW
Re-transplantation	No studies reported re-transplantation	

Continuation vs discontinuation of steroids after LT

Glucocorticoids can be discontinued after LT, and patients monitored for recurrence of AIH

Continuation vs discontinuation of steroids after LT



Would you keep low dose of steroids ?

A. YES

B. NO

At 5 years after LT

Immunosuppression :

- Tacrolimus 3 mg twice/day Trough level : 5-7 ng/mL
- MMF 1g twice/day
- Corticosteroids 5 mg / day

At 5 years after LT

Comorbidities developed in the past 5 years: diabetes, HTA, overweight

Laboratory tests:

AST IU/L	25	Tot bili $\mu\text{mol/L}$	12	GB G/L	7.45
ALT IU/L	27	PT %	100	Hb g/L	13.5
GGT IU/L	43	INR	0.9	Plts G/L	275
PAL IU/L	45	FV %	105	Creatinine	85

Immunology :

- Normal IgG and ANA + 1:160

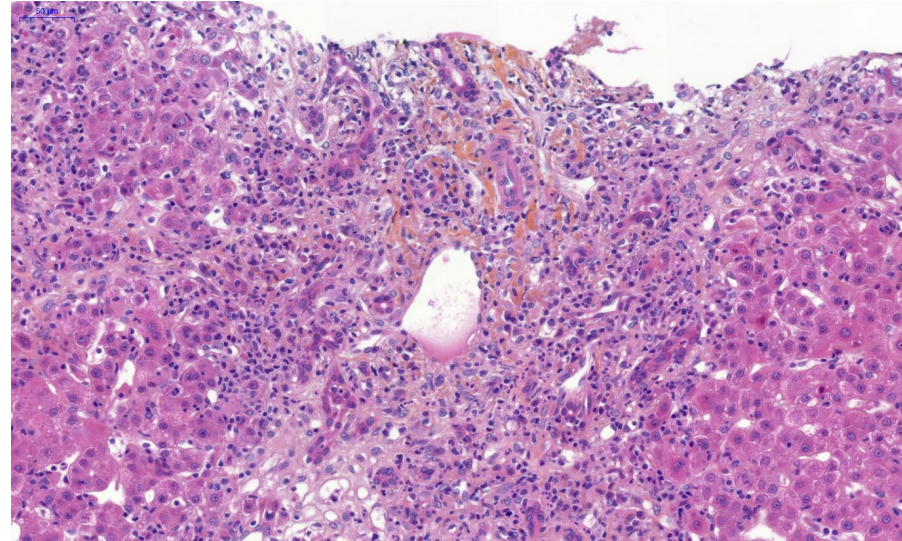
Would you perform a liver biopsy ?

A. YES

B. NO

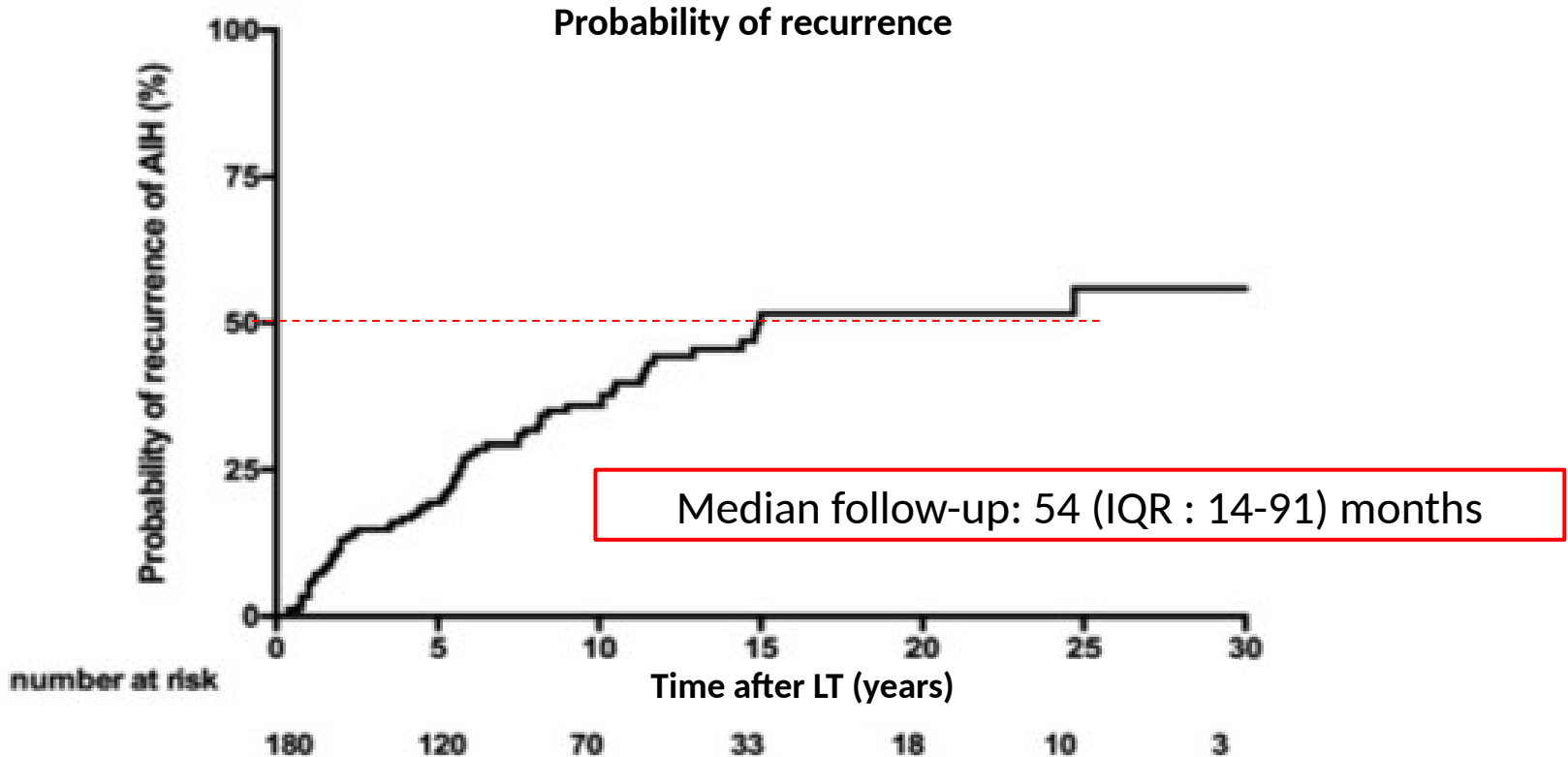
Definition of histological AIH recurrence

- Interface hepatitis
- Perivenular lymphoplasmocytic infiltration
- Lobular activity
- Pseudo-rosetting of the hepatocytes



AIH recurrence post-LT

Analysis performed on 180 patients with ≥ 1 biopsy
76/180 (42%) patients had recurrent AIH



Histological AIH recurrence precedes biochemical recurrence

Single center study, 17 AIH LT recipients
Follow-up > 10 years

- 7 (41%) patients developed AIH recurrence
- 4 patients had histological abnormalities by protocol biopsies

Table 4 Clinical recurrence and outcome in the four patients in whom histological recurrence was diagnosed in protocol biopsies

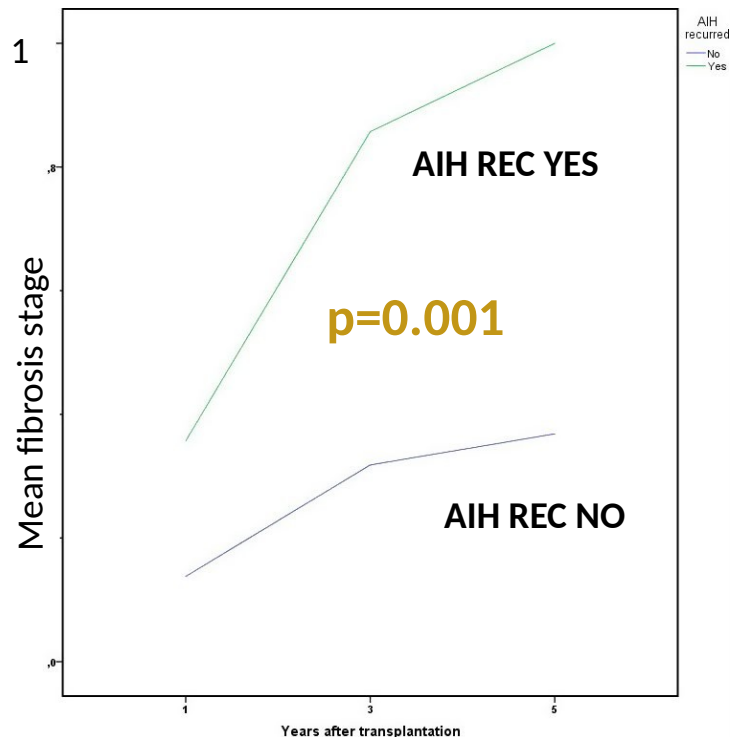
Patient (OLT)	Delay post- OLT (y)	Liver enzyme titre (ALT (IU/l)) (N<43)	Autoantibody titre	Histological features	Treatment
51	15	1000	ANA=1:640, anti- SMA=1:160, anti-SLA-	Substantial portal inflammatory plasmocyte infiltration, moderate septal fibrosis	Switch to FK*
155	10	80	SMA=1:640, anti-SLA+	Substantial plasmocyte infiltration in portal tract	Higher dose resumption of steroid therapy
205	11	182	SMA=1:640, anti-SLA-	Moderate plasmocyte infiltration in portal tract	Higher dose resumption of steroid therapy
421	10	680	SMA=1:320, anti-SLA-	Substantial portal inflammatory plasmocyte infiltration, scant areas of lobular necrosis	Switch to FK* and retransplantation

FK, tacrolimus; OLT, orthotopic liver transplantation; ALT, alanine aminotransferase; ANA, antinuclear antibodies; SMA, smooth muscle antibodies; SLA, soluble liver antigen.

AIH recurrence after LT survival

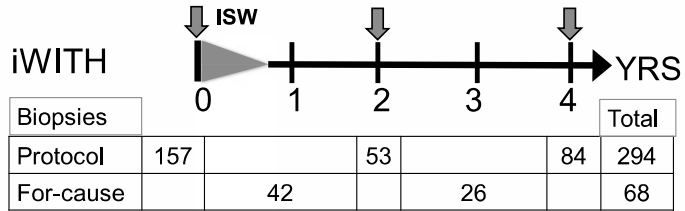
Single center study (Finland) : 42 LT AIH recipients with ≥ 1 biopsy

- AIH histological recurrence : 15 (36%) pts
- Normal LFTs in 3 (20%) pts
- Immunosuppression without AZA/MMF increased the risk of AIH recurrence (OR 1.47, $p=0.018$)
- Significant association between AIH recurrence and fibrosis progression ($p=0.003$)



Protocol liver biopsy is safe after LT

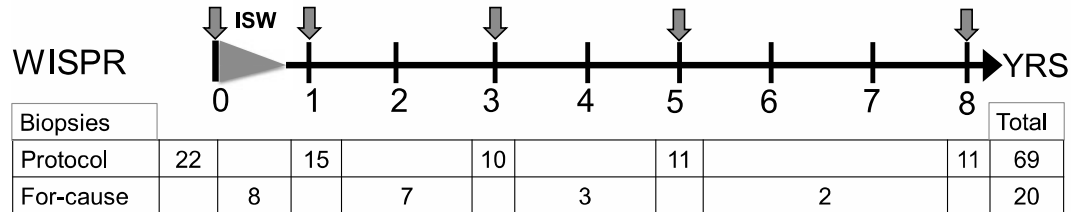
Data from 2 clinical trials on immunosuppression withdrawal in paediatric liver transplant recipients



All biopsies	
Protocol	363
For-cause	88
Total	451

- **Complications : 5.5% of LB**

- Mild : 1.8%
- Moderate : 1.8%
- Severe : 2%



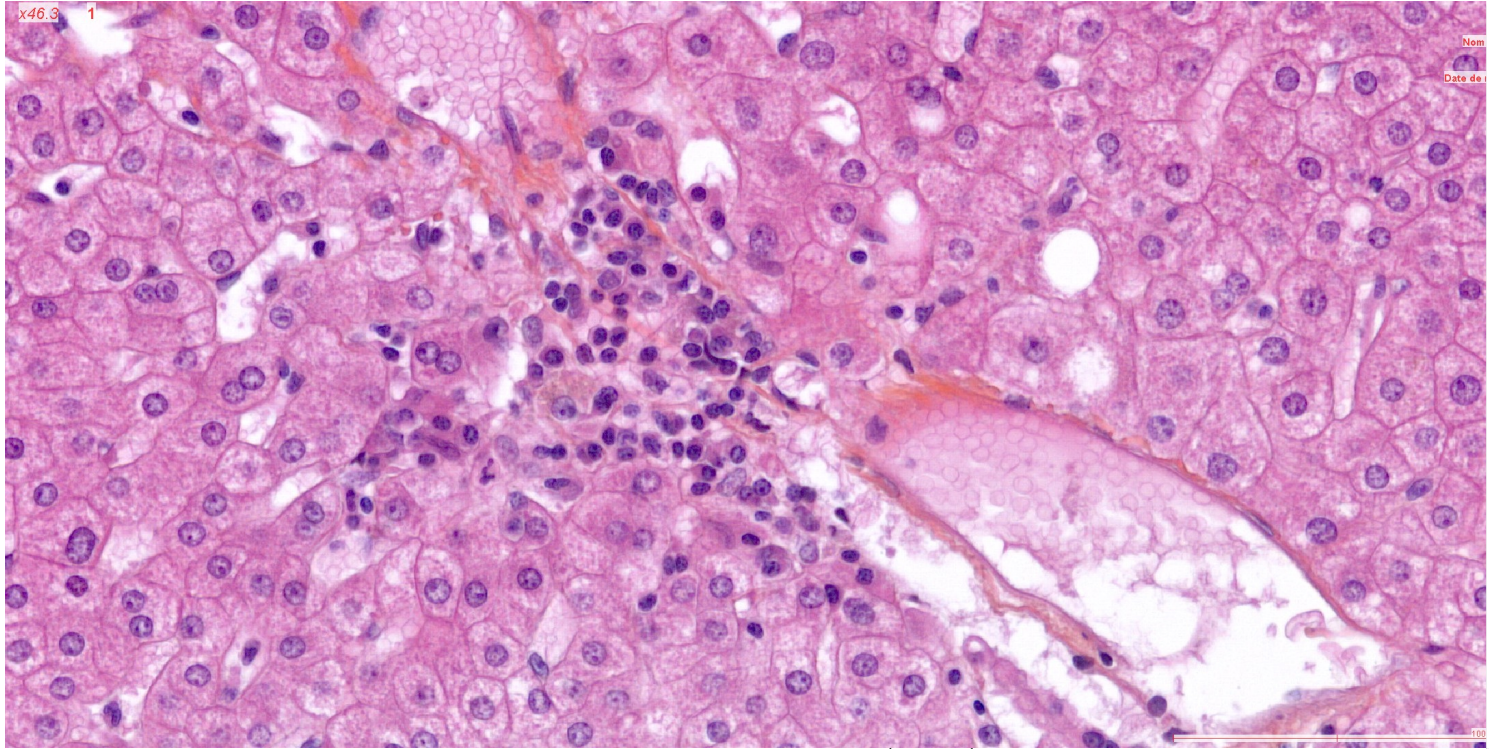
- 89% resolved within 1 week

Would you perform a liver biopsy ?

A. YES

B. NO

Liver biopsy at 5 years post-LT



Chronic hepatitis with mild activity (A1) highly heterogeneous and portal fibrosis (F1)

Courtesy of Prof Guettier

At 10 years after LT

Immunosuppression :

- Tacrolimus 3.5 mg /day Trough level : 3-4 ng/mL
- MMF 1g twice/day
- Corticosteroids 5 mg / day

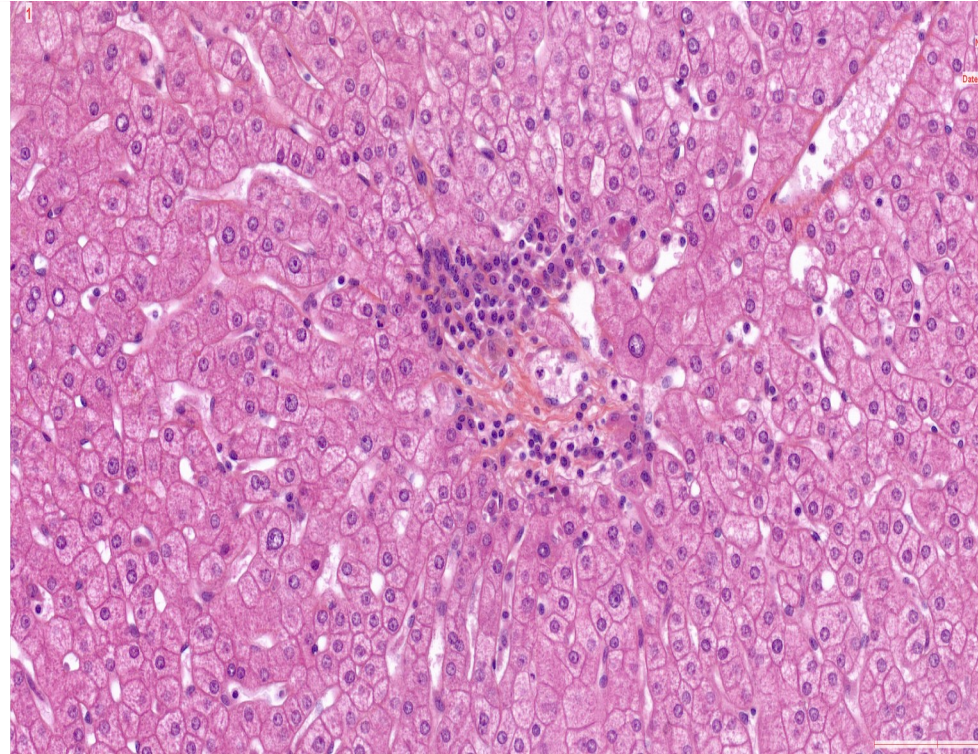
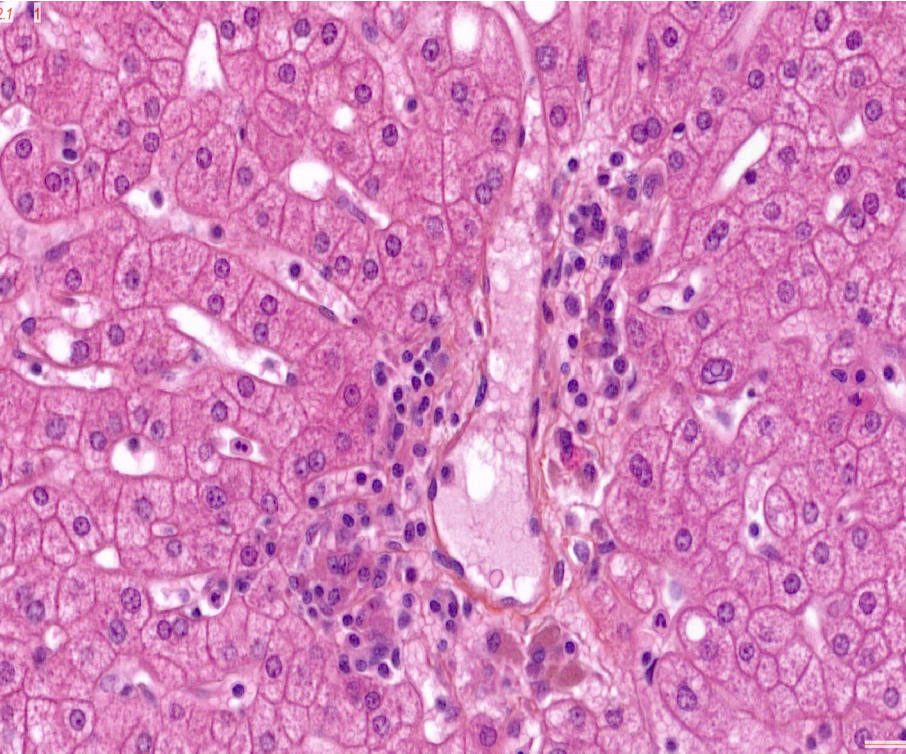
Biology :

- Normal LFTs

Immunology :

- Normal IgG and ANA + 1:80

Liver biopsy at 10 years post-LT



Centrilobular hepatitis with plasma cells infiltrates compatible with mild AIH recurrence. F1

Courtesy of Prof Guettier

Case 2

Mister WG, 18 year old

November 2015: hospital admission for acute severe hepatitis

Past medical history : uneventful

Laboratory test:

AST IU/L	1950	Tot bili $\mu\text{mol/L}$	131	GB G/L	4.95
ALT IU/L	2295	PT %	39	Hb g/L	11.2
GGT IU/L	153	INR	2.19	Plts G/L	82
PAL IU/L	149	FV %	43	MELD	24

Definite AIH

Simplified criteria of the IAIHG

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
	>1.1x upper limit	+2
Liver histology (evidence of hepatitis is a necessary condition)	Compatible with AIH	+1
	Typical of AIH	+2
	Atypical	0
Absence of viral hepatitis	No	0
	Yes	+2

ANA + 1:1280

homogeneous pattern

ASMA + 1:1280

anti-actine

IgG :48 g/dL

Typical histology

Fibrosis F3

Therapy and evolution

Corticosteroids at 1 mg/kg/day



Rapid improvement



Add of Azathioprine when bilirubin was normal



Disease control

3 years later...

At outpatient clinic the patient complained of fatigue and appeared jaundice

Laboratory tests

AST IU/L	1660	Tot bili $\mu\text{mol/L}$	138	GB G/L	3.28
ALT IU/L	2100	PT %	66	Hb g/L	15
GGT IU/L	139	INR	1.33	Plts G/L	82
Creatinin $\mu\text{mol/L}$	79	FV %	82	MELD	19

3 years later...

Immunology

- IgG 43
- ANA 1:1280
- ASMA 1:640

Treatment

AZA 2mg/kg/day

What the most probable diagnosis?

- A. Non-compliance
- B. AZA hepatotoxicity
- C. Loss of response

Drug adherence and psychological factors

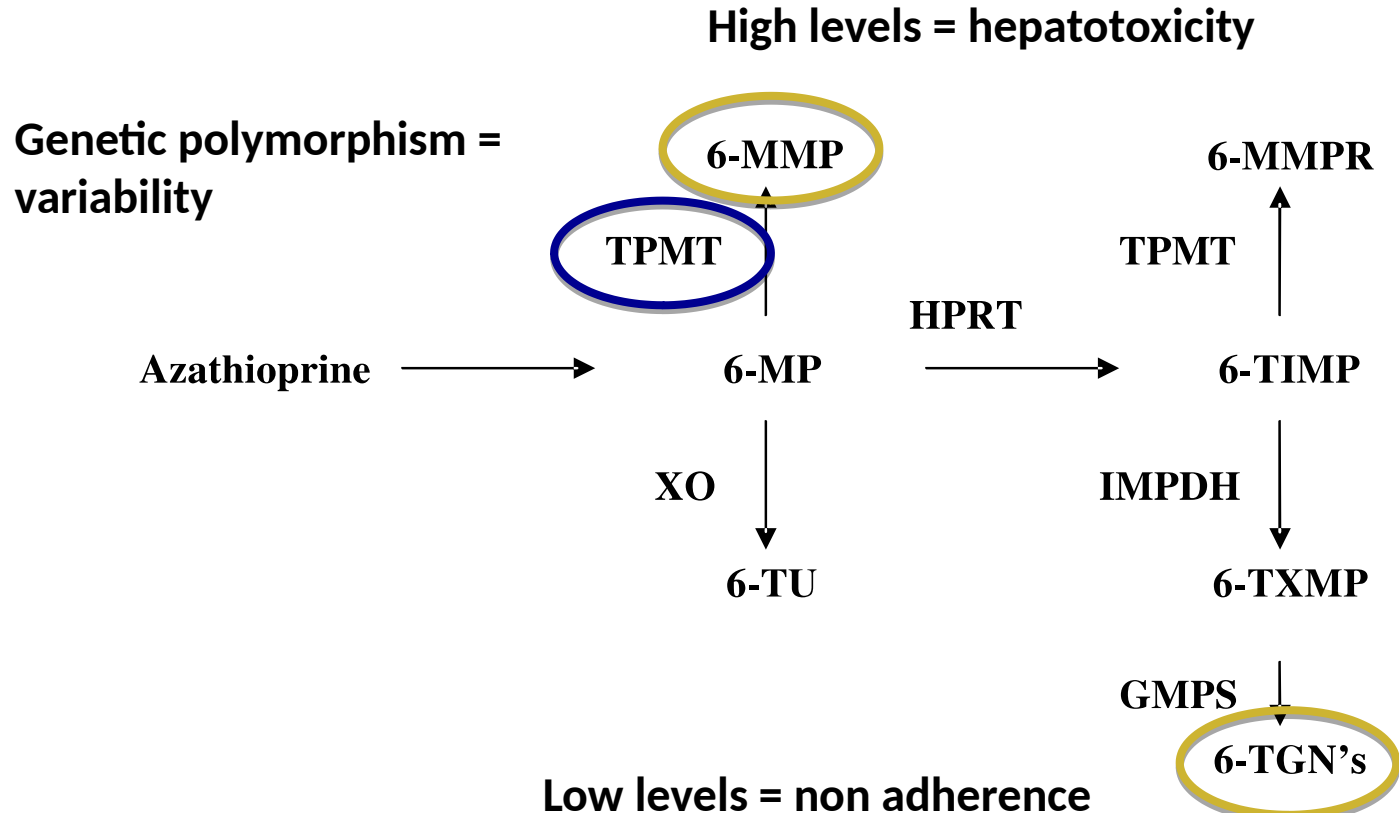
52 AIH patients assessed with :
Patient Health Questionnaire-9 (PHQ9)
Generalized Anxiety Disorder-7 (GAD7)
Experiences in Close Relationship Scale (ECR)

Psychological factors based on AIH treatment response

	AIH treatment	
	Responders (n = 28)	Non-responders (n = 24)
Depressive symptoms		
PHQ9 total score	4.8 ± 4.8	6.8 ± 5.6
PHQ9 ≥10	3 (11%)	5 (21%)
Anxiety symptoms		
GAD7 total score	2.5 ± 4.0**	5.1 ± 5.1**
GAD7 ≥10	1 (14%)	5 (21%)
Relationship style scores		
ECR-avoid score	20.3 ± 10.0**	25.8 ± 7.5**
ECR-anxiety score	19.7 ± 9.9	24.0 ± 11.1

**Wilcoxon rank sum test statistically significant ($p < 0.05$).

AZA metabolites in AIH

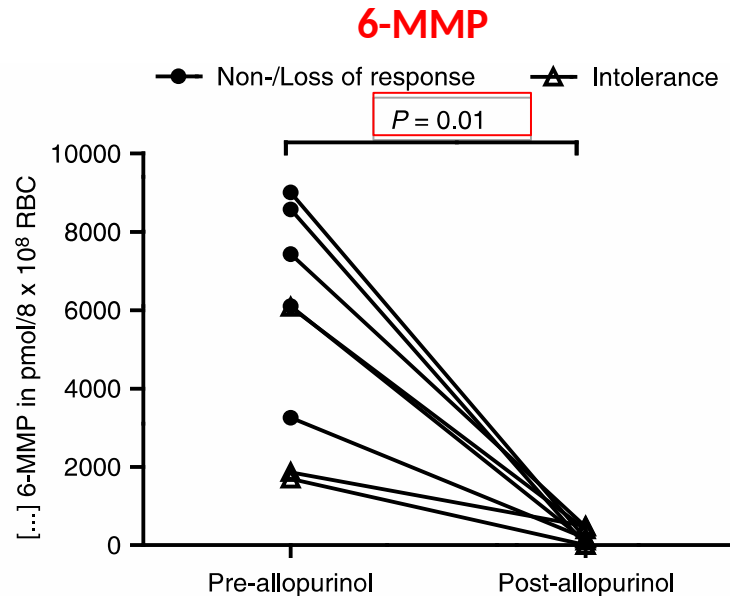
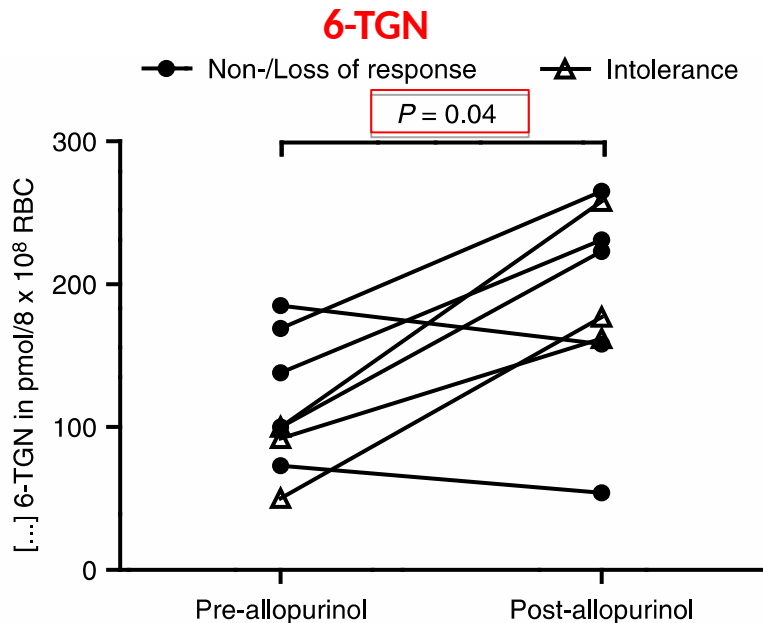


Thiopurine methyltransferase and AZA metabolites in AIH

- Advanced fibrosis but not TPMT genotype or activity predicts AZA toxicity
- There is a high variability in 6-TG and 6-MMP levels, no consensus on a cut off level for remission
- 6-TG and 6-MMP metabolite levels can differentiate **azathioprine-induced hepatotoxicity (HIGH 6-MMP)** from **non-adherence (LOW 6-TGN)**

Thiopurine metabolites & Allopurinol

Add of Allopurinol 100 mg to thiopurine in 8 patients because of intolerance, nonresponse or loss of response



Significant improvement of transaminases

What the most probable diagnosis?

- A. Non-compliance**
- B. AZA hepatotoxicity
- C. Loss of response

Would you perform a liver biopsy?

A. Yes

B. No

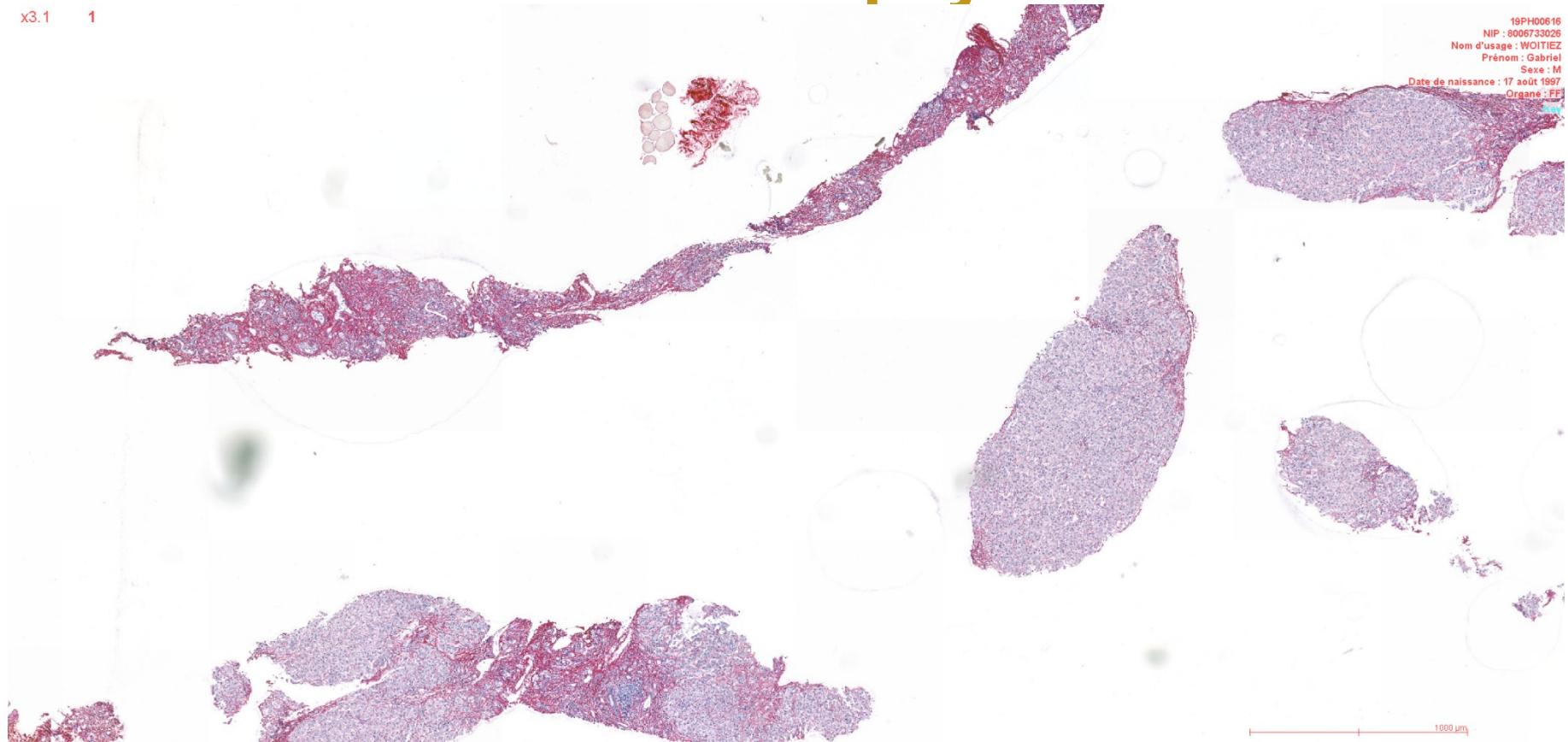
Would you perform a liver biopsy?

A. Yes

B. No

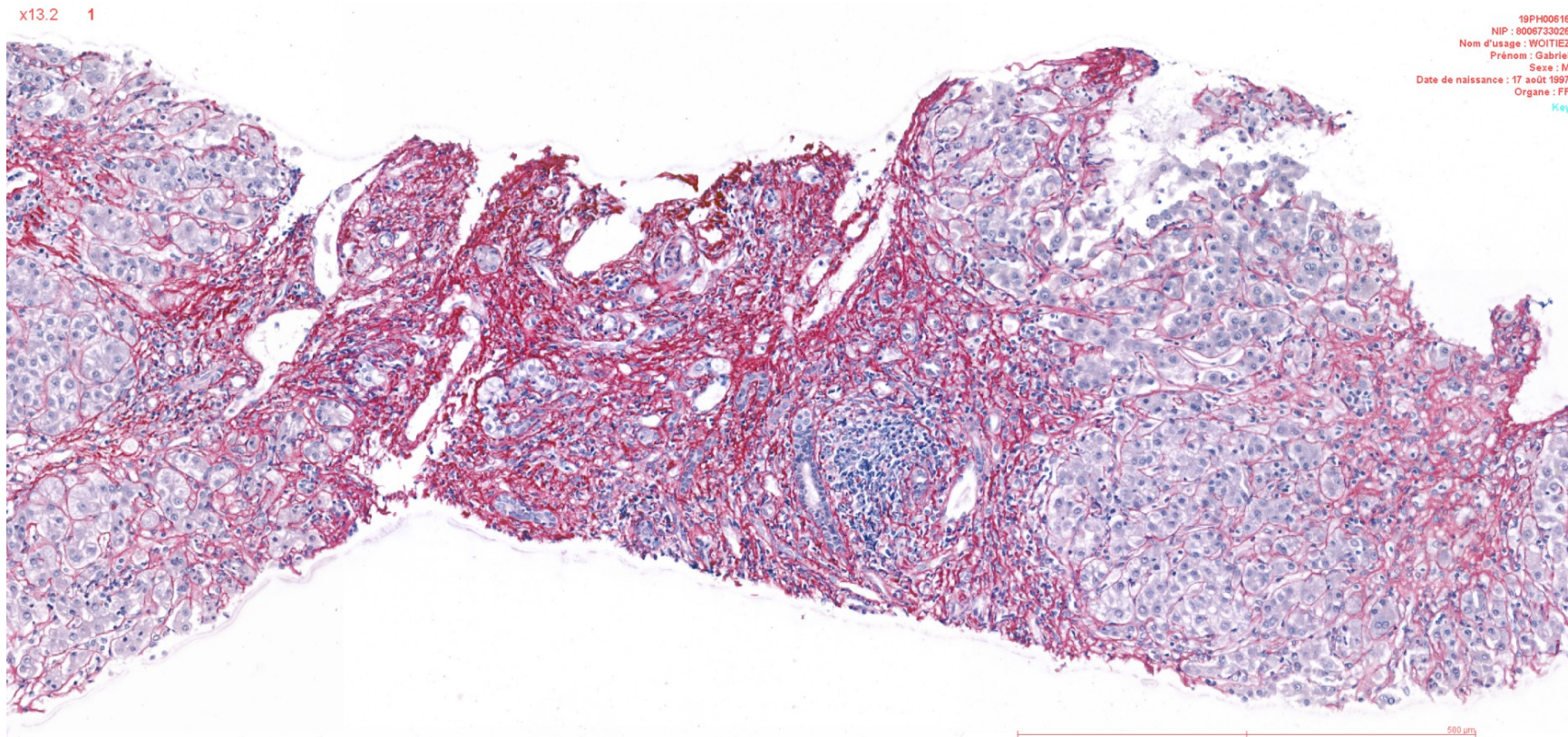
Liver biopsy

x3.1 1



Liver biopsy

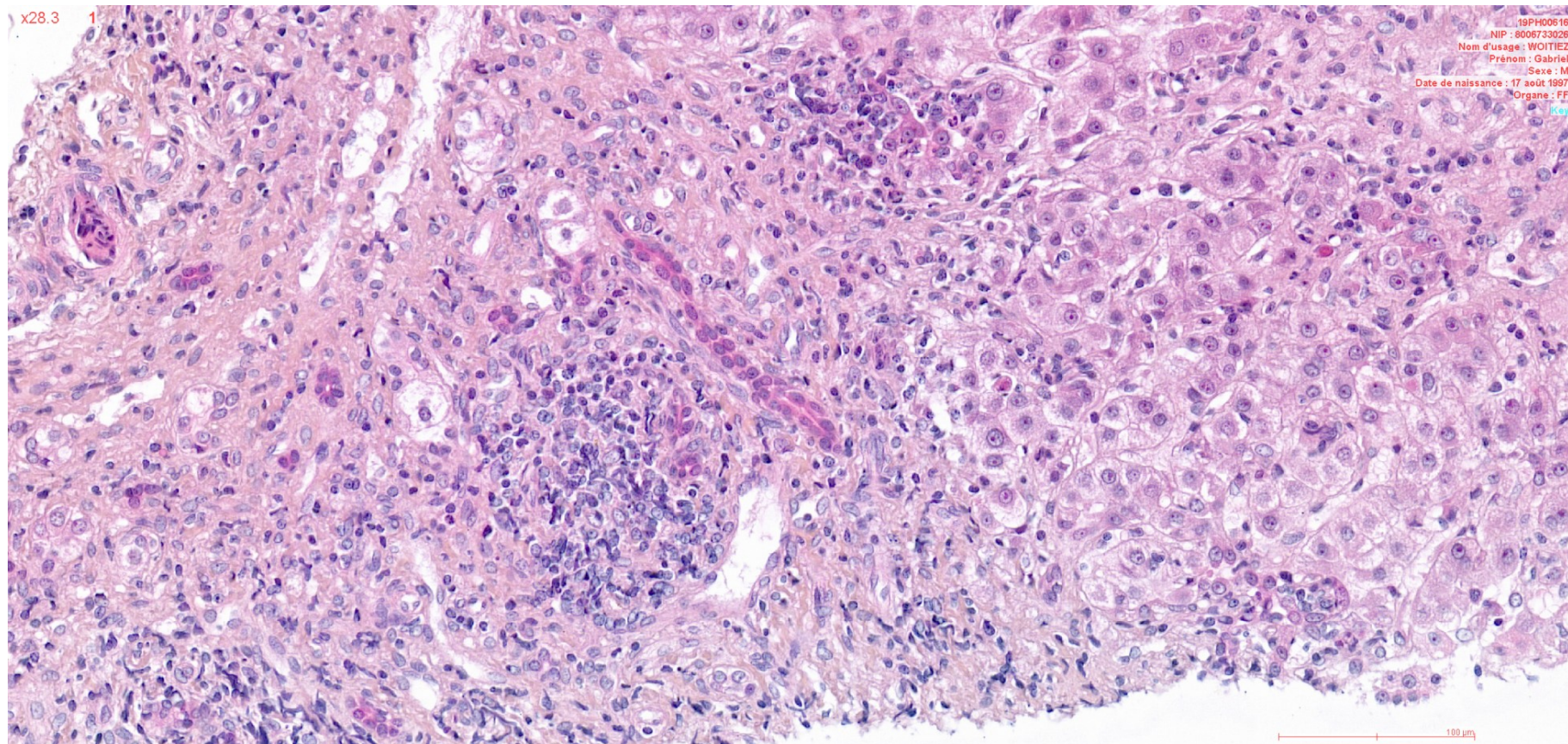
x13.2 1



19PH00516
NIP : 8006733026
Nom d'usage : WOITIEZ
Prénom : Gabriel
Sexe : M
Date de naissance : 17 août 1997
Organe : FF

Key

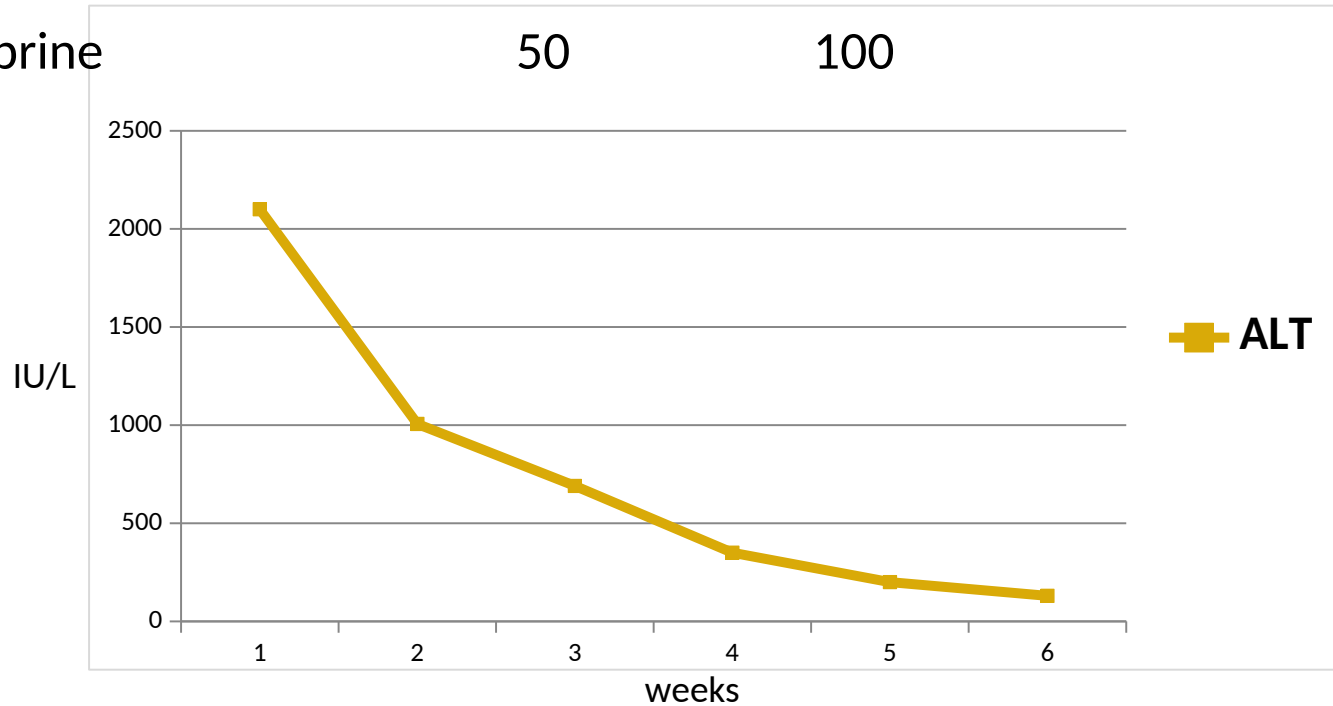
Liver biopsy



Therapy and evolution

Corticosteroids 65 55 45 35 25 20
mg/day

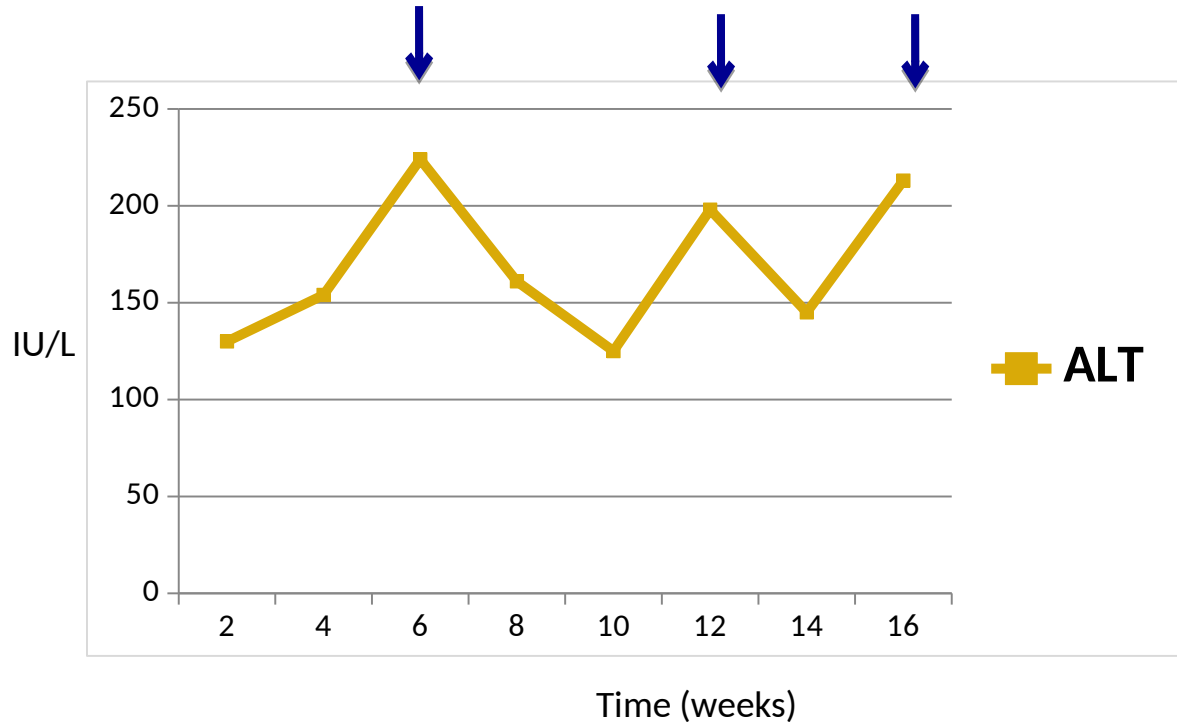
Azathioprine
mg/day



During the follow-up

Azathioprine 150 mg/day

Corticosteroids decrease below 20 mg followed by increase



What is the more suitable treatment ?

A. Budesonide

B. MMF

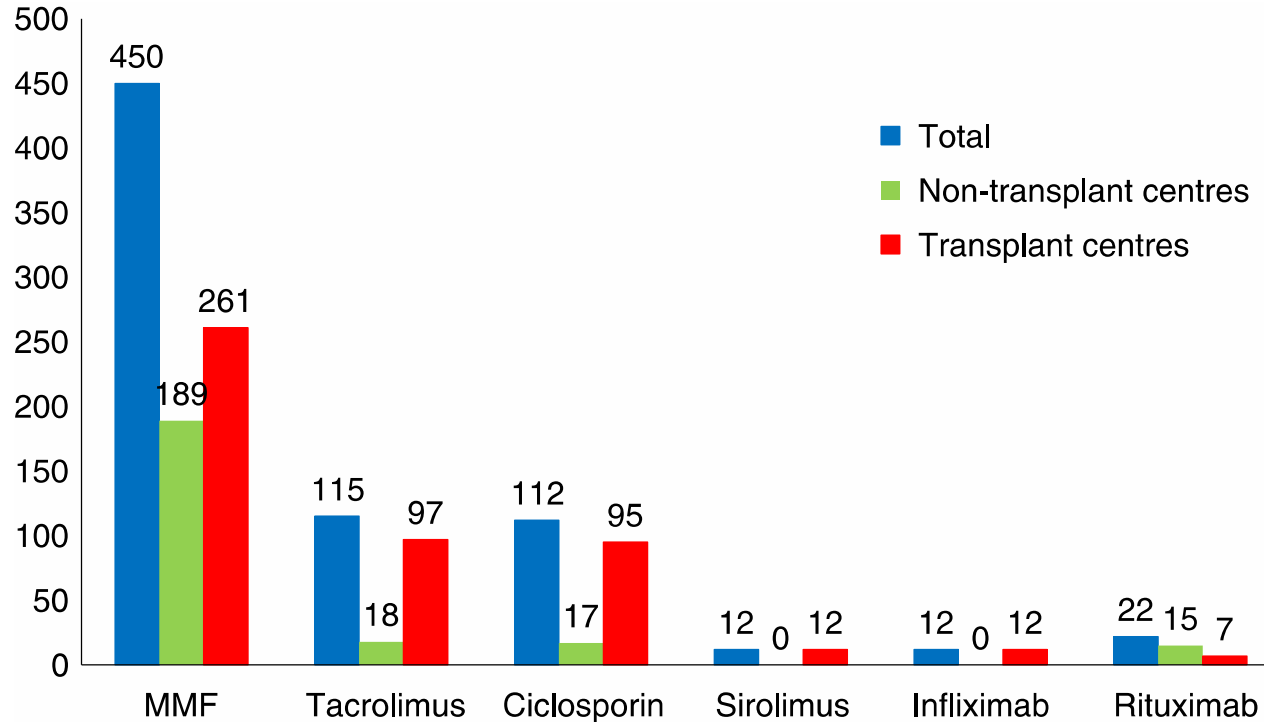
C. Tacrolimus / Cyclosporine

D. Anti-TNF

E. Rituximab

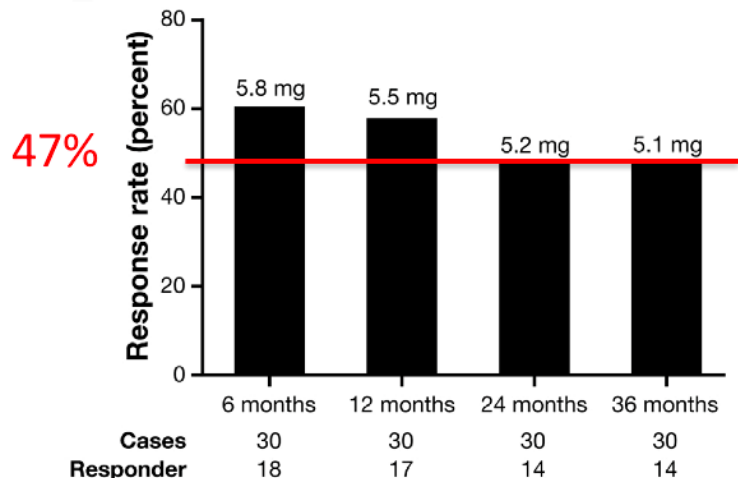
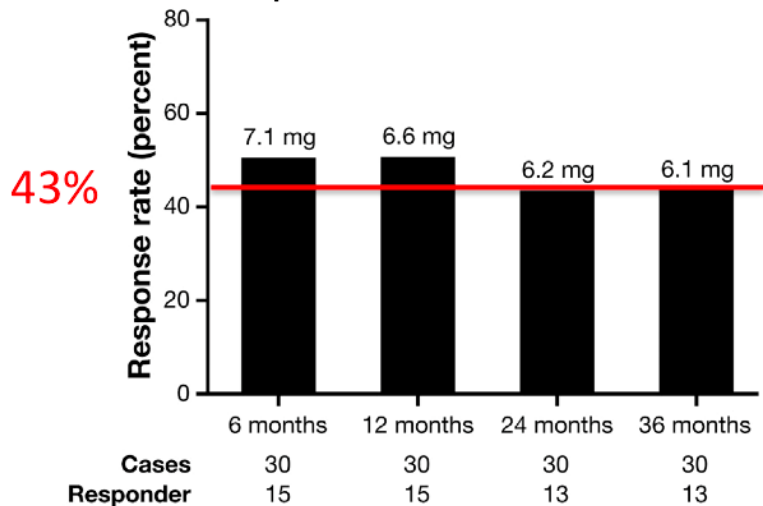
Rescue therapy in AIH

Reported use of second-line therapy in AIH patients - Multicenter (37) survey



Budesonide second-line therapy in AIH

Retrospective analysis – 60 patients switched
30 prednisolone side effects vs 30 prednisolone dependency



At last f/u only 38% of patients on budesonide with a response rate of 78%

MMF second-line therapy in AIH

Twelve studies – 397 patients

- Pooled response rate 0.58 (95% CI 0.54-0.63)
- Pooled adverse events rate 0.14 (95% CI 0.11-0.17)

Five studies – 309 patients

Pooled response rate



Intolerance to standard therapy :
0.82 (95% CI 0.77-0.87)

Non responders to standard therapy :
0.32 (95% CI 0.24-0.39)

Tacrolimus second-line therapy in AIH

Efficacy of MMF and tacrolimus in patients with AIH

Group 1 : side effects
to standard therapy

Group 2: non
responders to
standard therapy

	MMF (n = 121)	Tacrolimus (n = 80)	<i>P</i> 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.

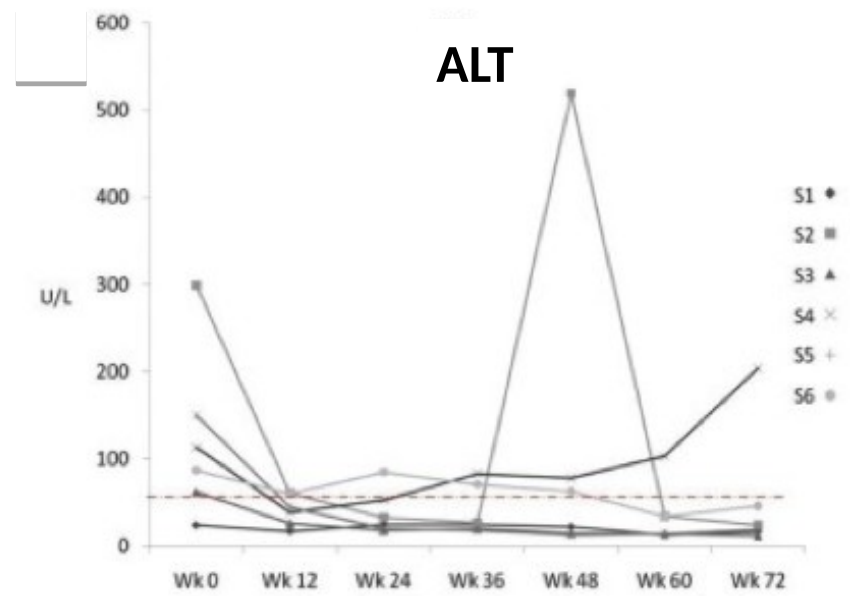
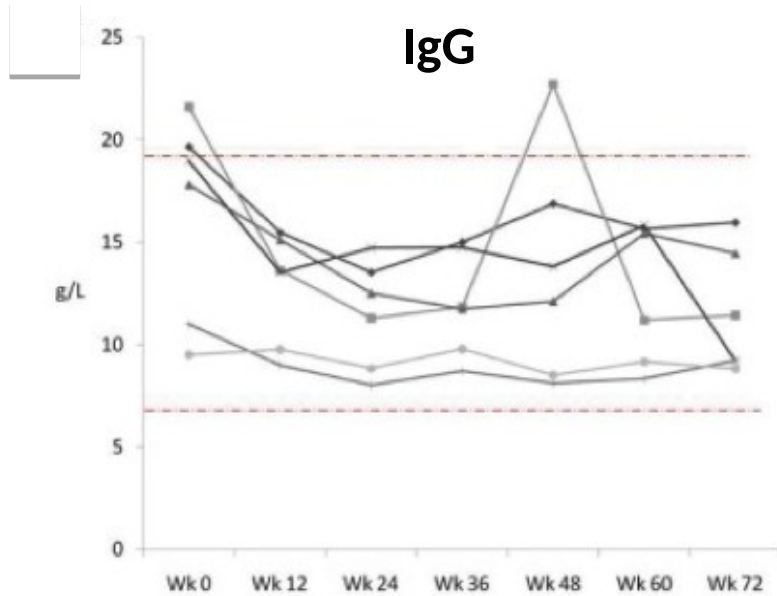
Infliximab rescue treatment in AIH

Patient	Cause of infliximab treatment	Complications of treatment	Response to treatment	Duration of treatment	Number of infusions	Prednisolone dose
1*	Cirrhosis, cyclophosphamide hepatitis, flare under ongoing standard treatment	Multiple infectious complications	Repeated prompt full remission	Treatment ongoing (on/off) since 2001	>>40 infusions	20 mg/d
2	Azathioprine intolerance, MMF intolerance, aggravated depression under steroids	Shingels	Initial remission, flare under on-going treatment	Treatment stopped after 18 mo due to flare under treatment	14	5 mg/d
3	Azathioprine intolerance, MMF intolerance, cyclophosphamide cumulative dose reached	Pneumonia, recurrent urinary tract infections	Full remission	Treatment ongoing for 31 mo	22	5 mg/d
4	Steroid-induced diabetes and weight gain, uncontrolled disease with cirrhosis	Pneumonia	Incomplete remission with elevated IgG	Treatment stopped after 8 mo after pneumonia	9	10 mg/d
5	Steroid-aggravated depression, weight gain	Recurrent herpes labialis	Repeated full remission	Treatment ongoing (on/off) for 24 mo	10	10 mg/d
6	Steroid-refractory flare under treatment		Full remission	Sto to 1		
7	Steroid-induced diabetes, weight gain		Full remission	Tre 15 mo		
8	Azathioprine intolerance		Full remission	Treatment ongoing for 12 mo	7	10 mg/d
9	Azathioprine intolerance		Full remission	Treatment ongoing for 15 mo	10	10 mg/d
10	Azathioprine induced pancreatitis	Ocular <i>herpes simplex</i> infection, recurrent urinary tract infections	Partial response	Treatment stopped after 6 mo due to allergic reaction and incomplete response	6	15 mg/d
11	Azathioprine intolerance		Full remission	Treatment ongoing for 13 mo	10	10 mg/d

7 / 11 (64%) Full remission

Rituximab rescue therapy in AIH

Single center pilot study. Six patients **intolerant or refractory** to prednisone +/- AZA treatment - Rituximab 1000mg i.v. day 1 and 15



No severe side effects

Burak, Can J Gastroenterol 2013

What is the more suitable treatment ?

A. Budesonide

B. MMF

C. Tacrolimus / Cyclosporine

D. Anti-TNF

E. Rituximab



Coordinated by Prof. A. Lohse

Prospective and retrospective registries