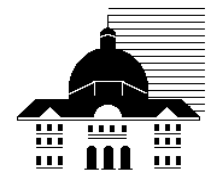


Hépatites auto-immunes

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Maladies Auto-Immunes Hépatiques

10-20 cas/100.000

HAI

Exclure les autres causes de maladies hépatiques

CBP

Cirrhose biliaire primitive

40-60 cas/100.000

CSP

Cholangite sclérosante primitive

10-30 cas/100.000

Diagnostic différentiel des hépatites

Maladies Auto-immunes
Hépatiques

Maladies Auto-immunes
/inflammatoires
Systémiques

Infections hépatotropes
e.g. VHA, VHB, VHC, VHE ...
Herpes virus

Toxicité médicamenteuse

Diagnostic différentiel des hépatites

Maladies Auto-immunes
Hépatiques

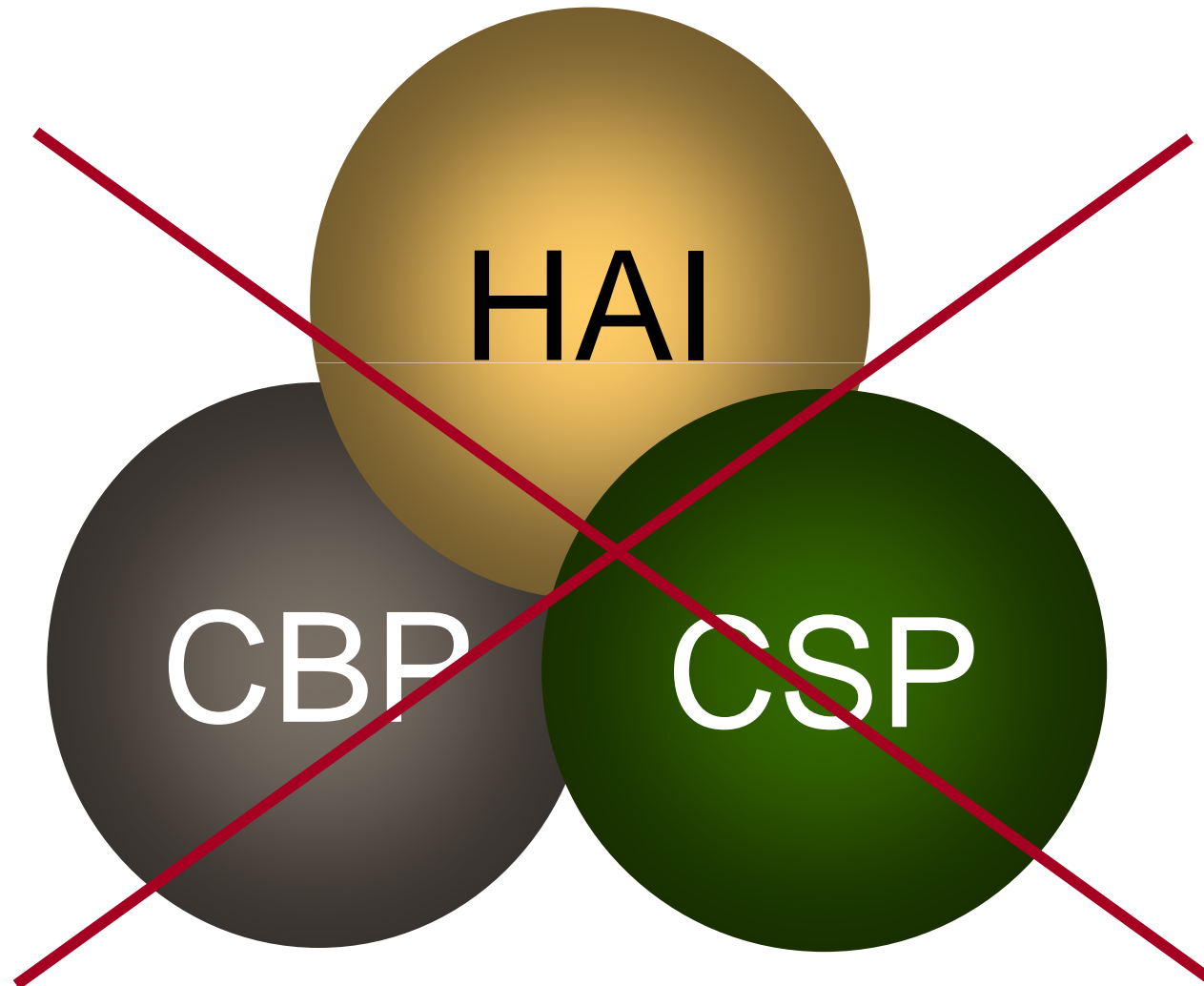
Maladies Auto-immunes
/inflammatoires
Systémiques

Infections hépatotropes
e.g. VHA, VHB, VHC, VHE ...
Herpes virus

Toxicité médicamenteuse

Maladies Auto-Immunes Hépatiques

Syndromes de chevauchement (... en 2001)



Maladies Auto-Immunes Hépatiques

Syndromes de chevauchement (... en 2014)

Les syndromes de chevauchement
peuvent apparaître dans le suivi !

CBP

CCP

Hépatites auto-immunes



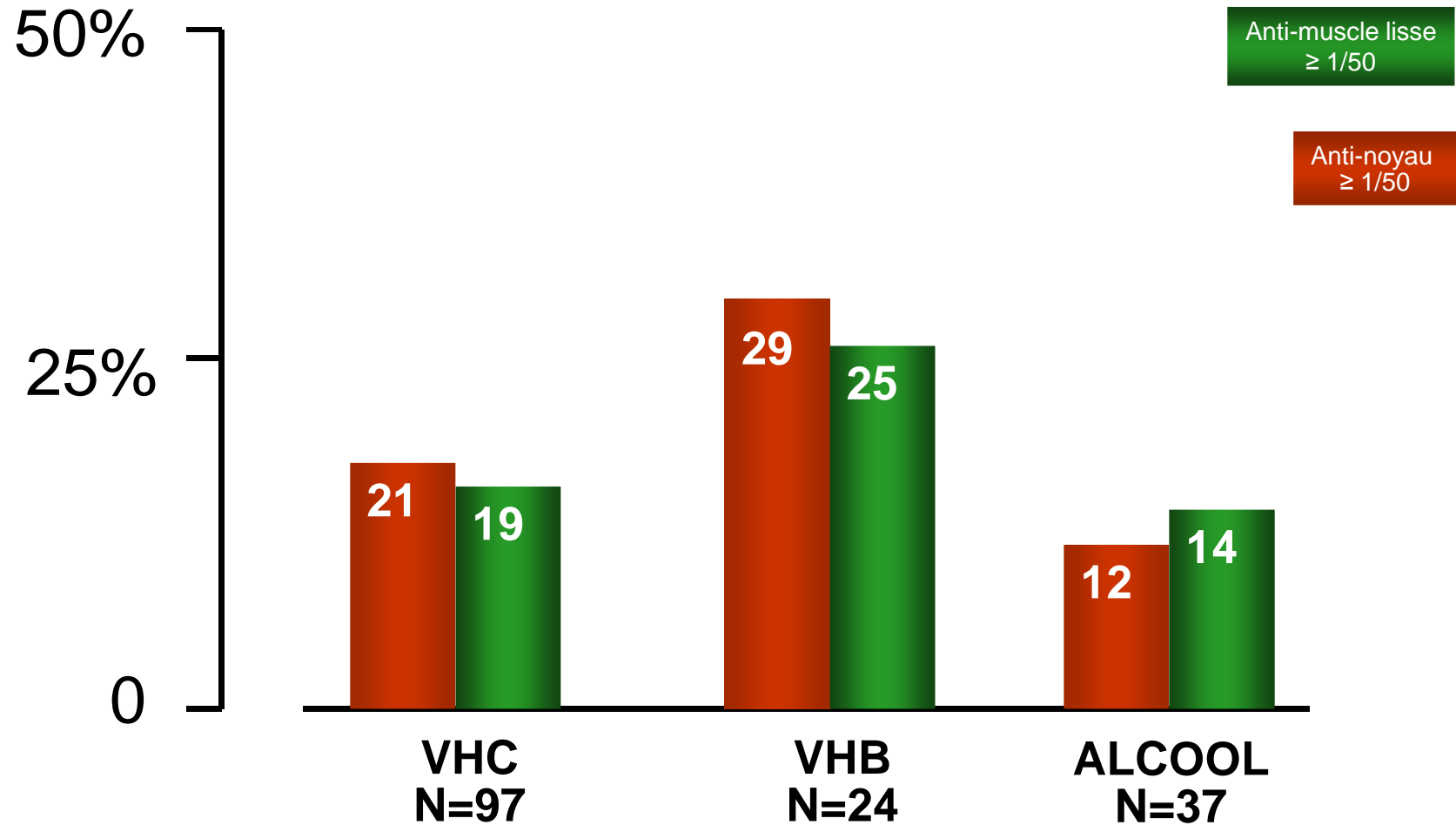
HAI

Commencer par exclure une hépatite virale!

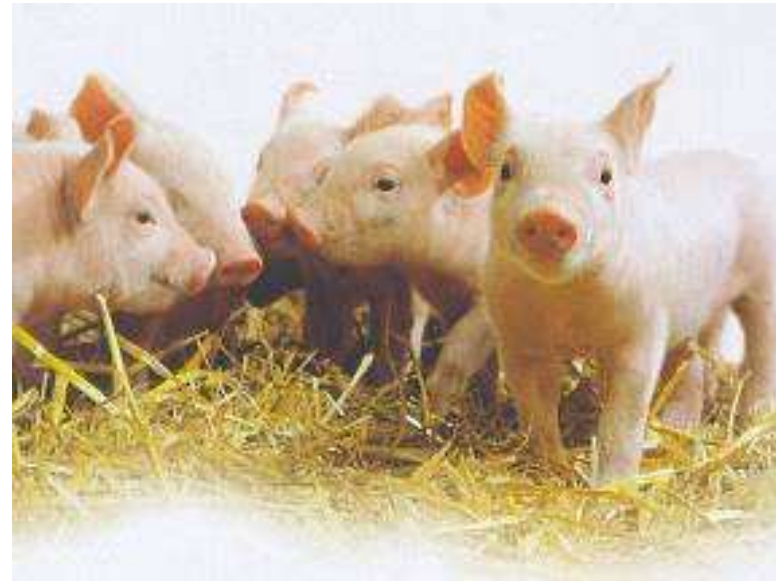
Hépatite C et auto-anticorps

• Ac anti-LKM-1	5%
• Anti-muscle lisse	10-20%
• Ac anti-nucléaire	20-35%
• Cryoglobuline de type 2	50-70%

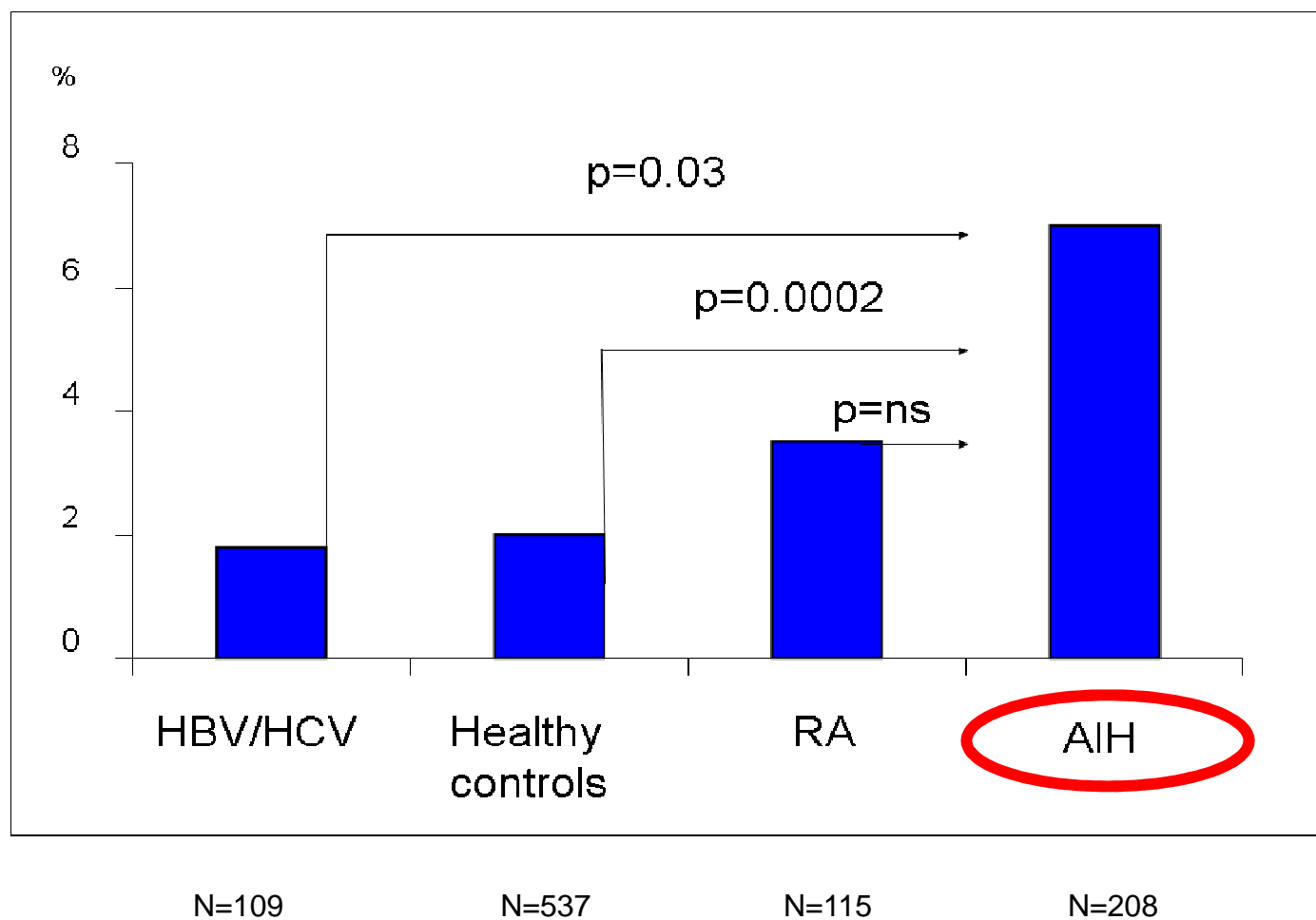
Hépatopathies et Auto-anticorps



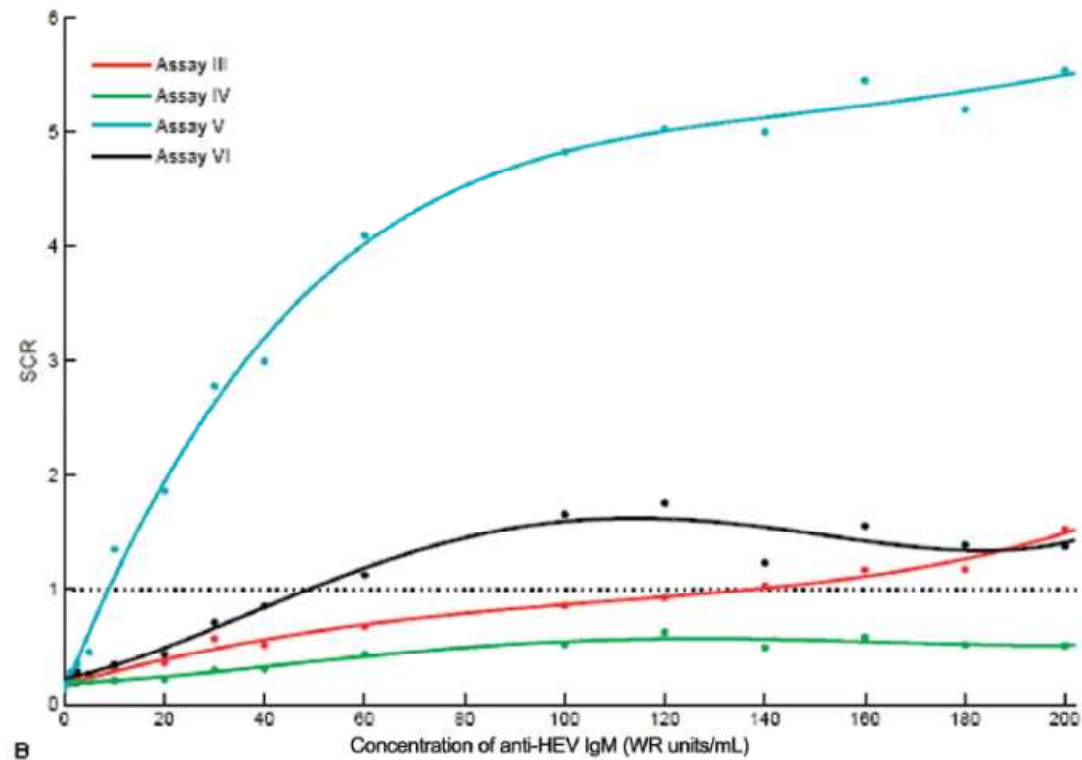
Hépatite E



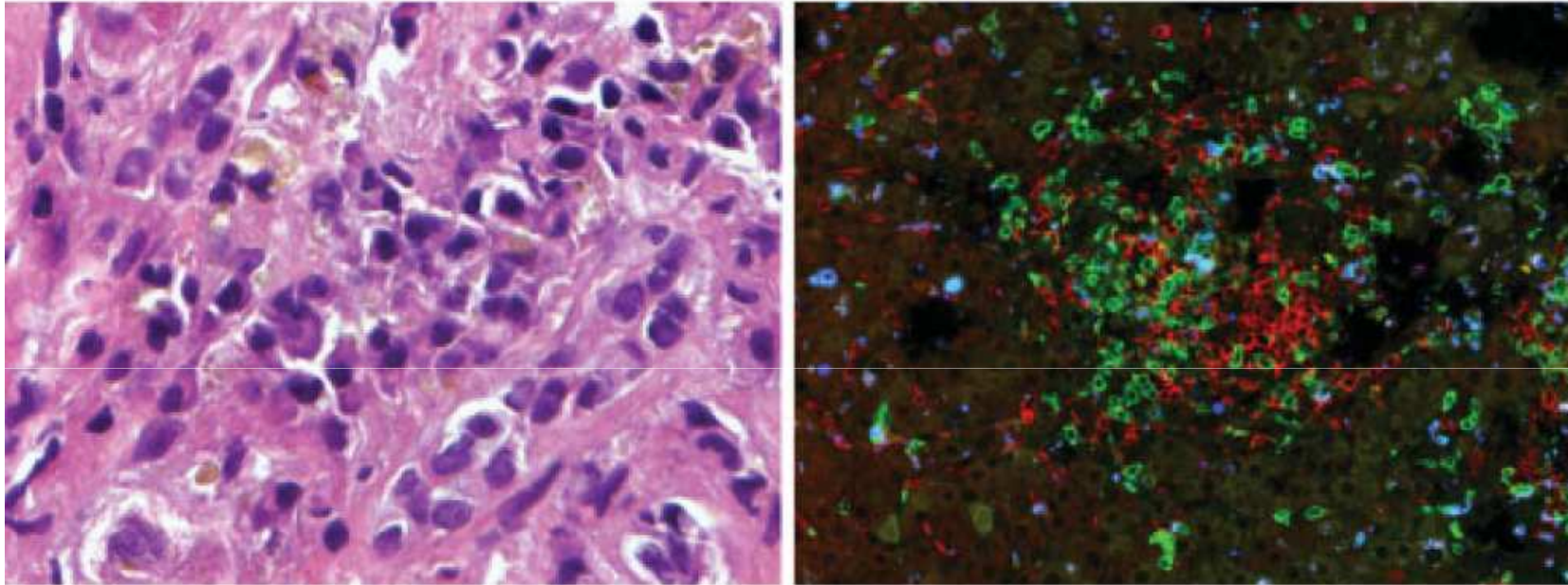
Prévalence élevée des anticorps anti-VHE au cours des HAI



Différences de seuils de sensibilité des tests IgM anti-VHE



Hépatite E - Histologie



CD8+ T -cells green; CD4+ T-cells red; FoxP3: blue

- absence d'aspect caractéristique du VHE
- diagnostic différentiel avec HAI peut être difficile

Stéatopathie non-alcoolique (NASH)

- Ac anti-nuclaire et anti-muscle lisse
- Scores d'HAI faussement positifs
- Biopsie hépatique indispensable

Table 1. Classification of Autoimmune Hepatitis.

Variable	Type 1 Autoimmune Hepatitis
Characteristic autoantibodies	Antinuclear antibody* Smooth-muscle antibody* Antiactin antibody†
Geographic variation	Worldwide
Age at presentation	Any age
Sex of patients	Female in approximately 75% of cases
Association with other autoimmune diseases	Common
Clinical severity	Broad range
Histopathologic features at presentation	Broad range
Treatment failure	Infrequent
Relapse after drug withdrawal	Variable
Need for long-term maintenance	Variable

* The conventional method of detection is immunofluorescence.

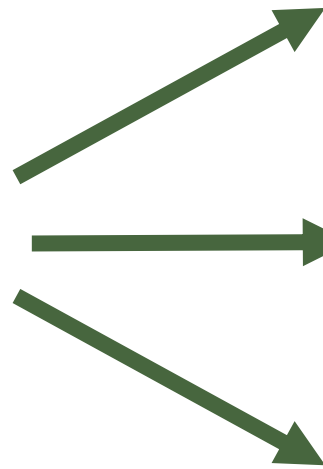
† Tests for this antibody are rarely available in commercial laboratories.

‡ This antibody is detected by enzyme-linked immunosorbent assay.

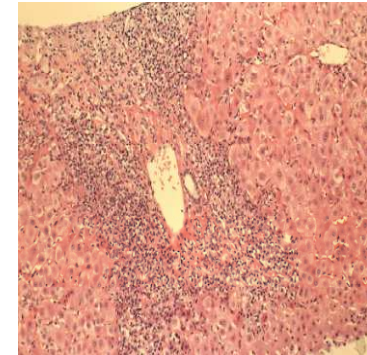
§ Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy is seen only in patients with type 2 disease.⁴⁷

HAI : Biopsie hépatique indispensable pour le diagnostic et la décision thérapeutique

**Biopsie
foie**



Diagnostic
Hépatite d'interface



Pathologies associées (CBP, CSP ?...)

Sévérité
Stade histo/ valeur pronostique

« Biopsie hépatique recommandée avant la fin du traitement »

Hépatites auto-immunes: au delà du foie

Vitiligo



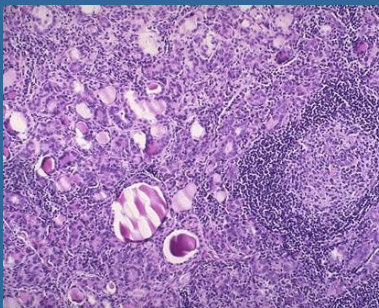
Diabete



Polyarthrite rhumatoïde



Thyroidite
Autoimmune



Lichen plan



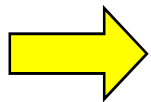
Iridocyclite



Diagnostic des hépatites auto-immunes

- **Aucun élément n'est spécifique** (biologique, immunologique, histologique) +++
- Un auto-anticorps isolé ne fait pas un diagnostic
- « The diagnosis of AIH is **a diagnosis of exclusion** »

(M. Manns, C. Strassburg, Gastroenterology 2001)



- Importance des critères diagnostiques négatifs
- Absence d'autres causes d'hépatopathie, sauf association (CBP, CSP)

Hépatites auto-immunes: score diagnostique

International AIH-Score

Table 1. Original Revised (1999) Criteria for the Diagnosis of AIH

Parameter/Discriminator	Score	Parameter/Discriminator	Score
Female sex	+2	Average alcohol intake	
ALP:AST (or ALT) ratio		<25 g/day	+2
<1.5	+2	>60 g/day	-2
1.5-3.0	0	Liver histology	
>3.0		Interface hepatitis	+3
Serum globulins or IgG above normal		Predominantly lymphoplasmacytic infiltrate	+2
>2.0			
1.5-2.0			
1.0-1.5			
<1.0	0	Optional additional parameters	
ANA, SMA, or LKM-1		Seropositivity for other defined antibodies	+2
>1:80	+3	HLA DR3 or DR4	+1
1:80	+2	Response to therapy	
1:40	+1	Remission alone	+2
<1:40	0	Remission with relapse	+3
AMA-positive	-4	Interpretation of aggregate scores	
Hepatitis viral markers		Pretreatment:	
Positive			>15
Negative			0-15
Drug history			
Positive			>17
Negative			2-17
Average alcohol intake			
<25 g/day	+2		
>60 g/day	-2		
Liver histology			

Avant traitement

Dg probable : 10 à 15; certain > 15

Après réponse au traitement

Dg probable : 12 à 17; certain > 17

Hépatites auto-immunes

Score diagnostique simplifié

Table 2. Simplified Diagnostic Criteria for Autoimmune Hepatitis

Variable	Cutoff	Points
ANA or SMA	$\geq 1:40$	1
ANA or SMA or LKM or SLA	$\geq 1:80$ $\geq 1:40$ Positive	2*
IgG	>Upper normal limit	1

≥ 6 : HAI probable, ≥ 7 : HAI certaine

of hepatitis is a necessary condition)	Typical AIH	2
Absence of viral hepatitis	Yes	2
		≥ 6 : probable AIH ≥ 7 : definite AIH

*Addition of points achieved for all autoantibodies (maximum, 2 points).

Score diagnostique simplifié des Hépatites Auto-Immunes

Meilleure spécificité... mais moindre sensibilité

Table 4. Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) of the Simplified and 1999 IAHG Criteria for the Diagnosis of AIH

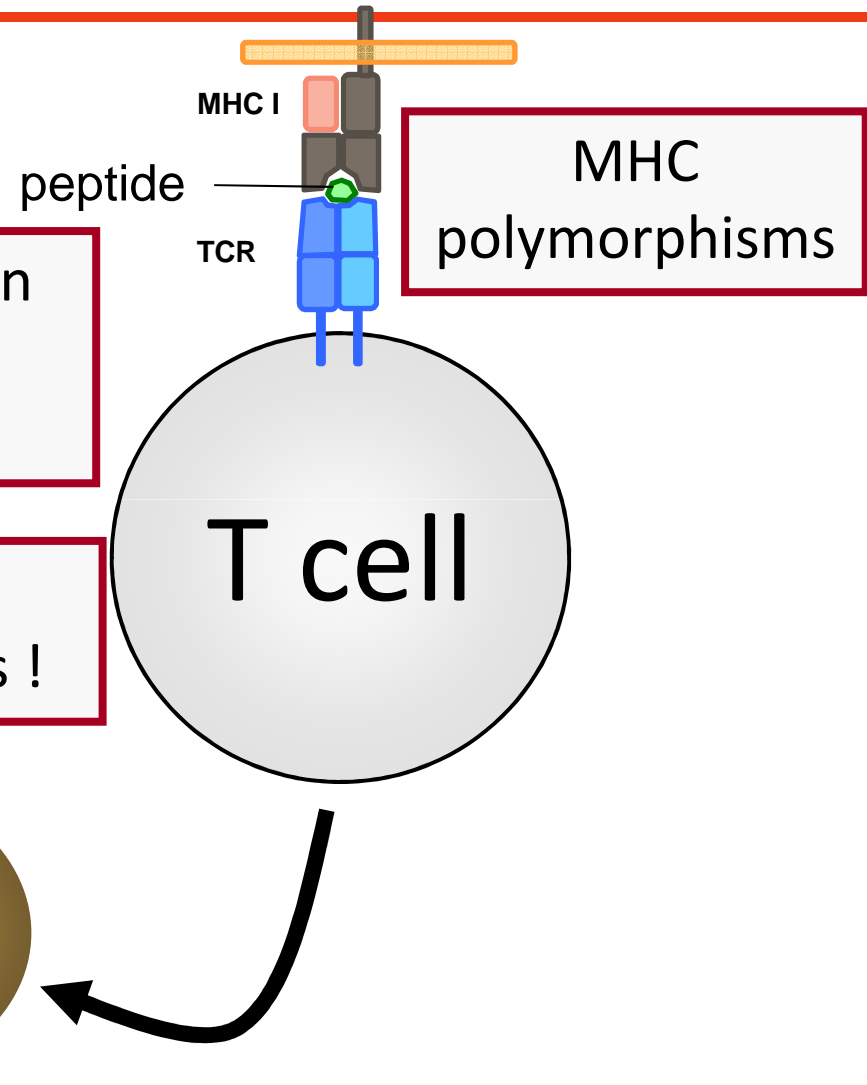
Criteria	Sensitivity	Specificity	PPV	NPV
Simplified Criteria				
Probable diagnosis AIH (6-7)	90%	98%	97%	92%
Definite diagnosis AIH (≥ 7)	70%	100%	100%	74%
Overall Diagnosis AIH (≥ 6)	90%	98%	97%	92%
1999 Criteria				
Probable diagnosis AIH (10-15)	100%	97%	96%	100%
Definite diagnosis AIH (≥ 15)	99%	98%	97%	99%
Overall Diagnosis AIH (≥ 10)	100%	97%	97%	99%

Hépatites auto-immunes: physiopathologie

Activation of T cells

Molecular mimicry between autoantigens and pathogens, drugs, etc.

1 T cell can recognize >1.000.000 different peptides !



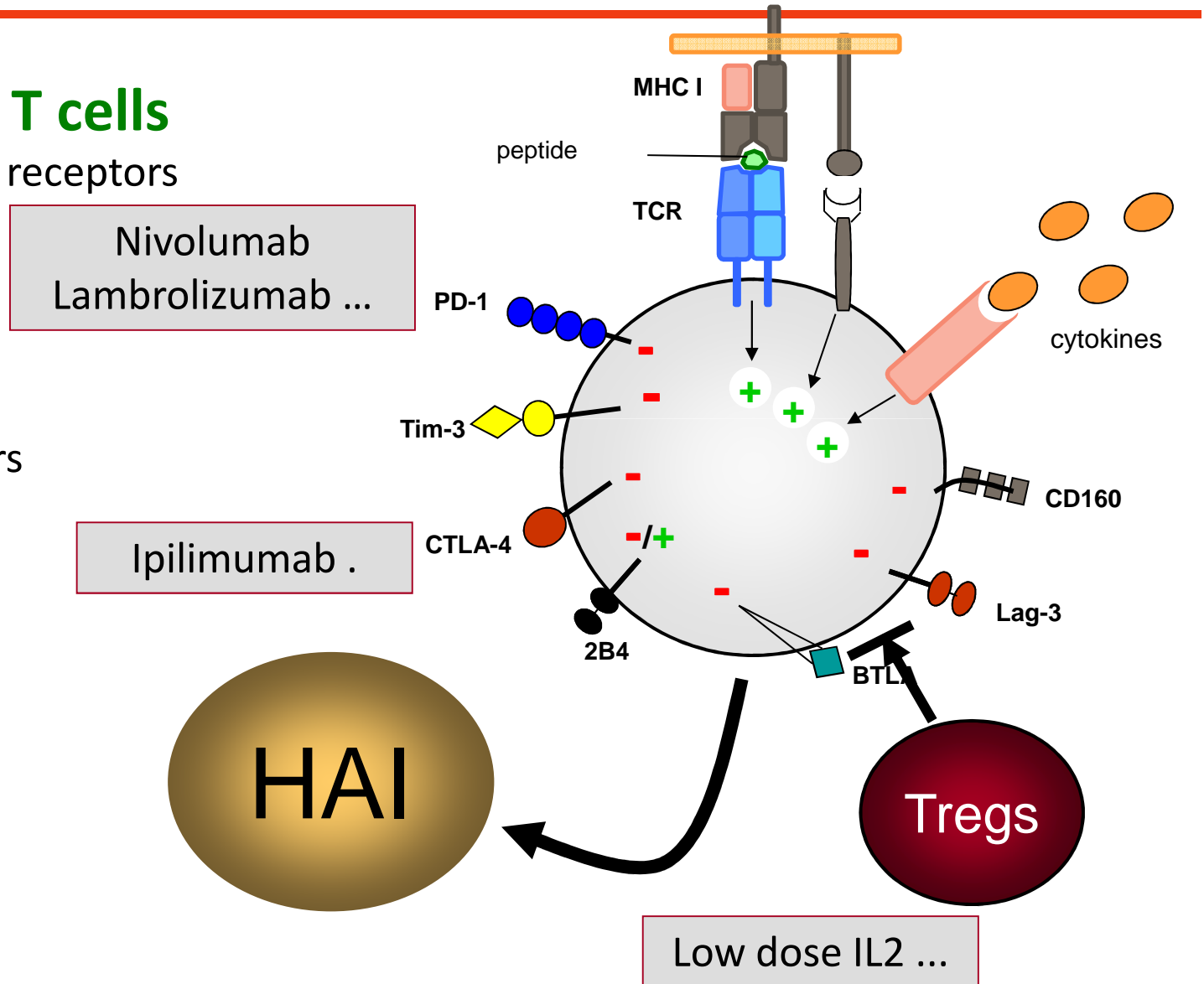
Hépatites auto-immunes: physiopathologie

Activation of T cells

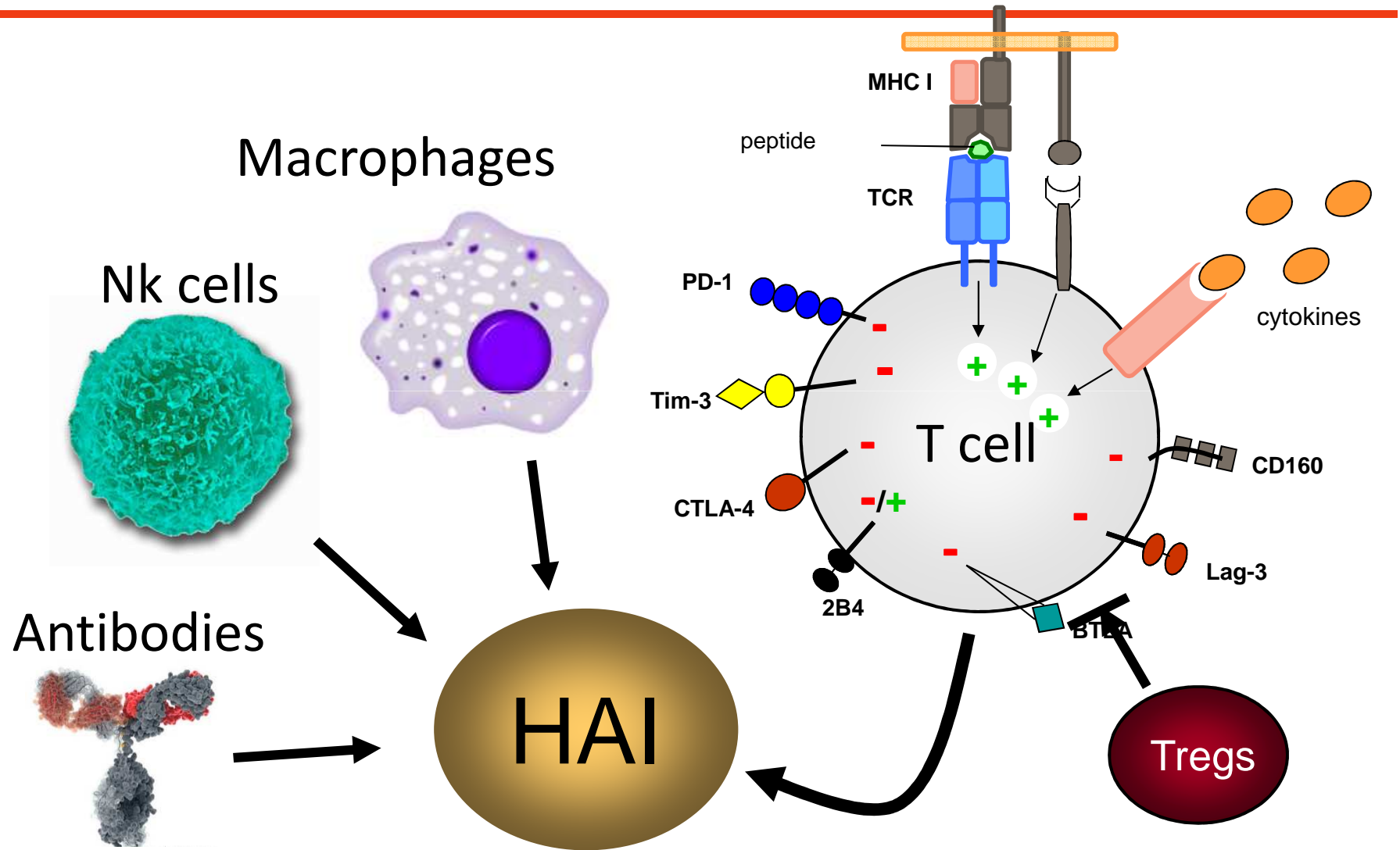
- Co-stimulatory receptors
- Cytokines

Regulatory mechanisms

Inhibitory receptors

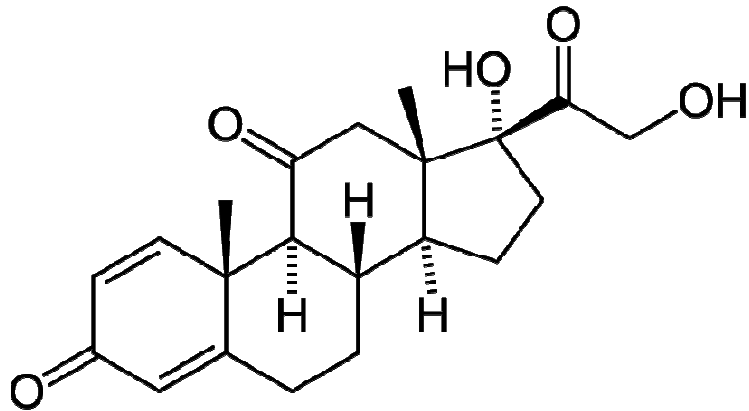


Hépatites auto-immunes: physiopathologie

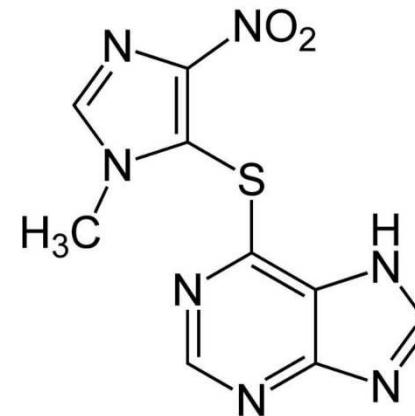


Hépatites auto-immunes: les traitements

Predniso(lo)ne

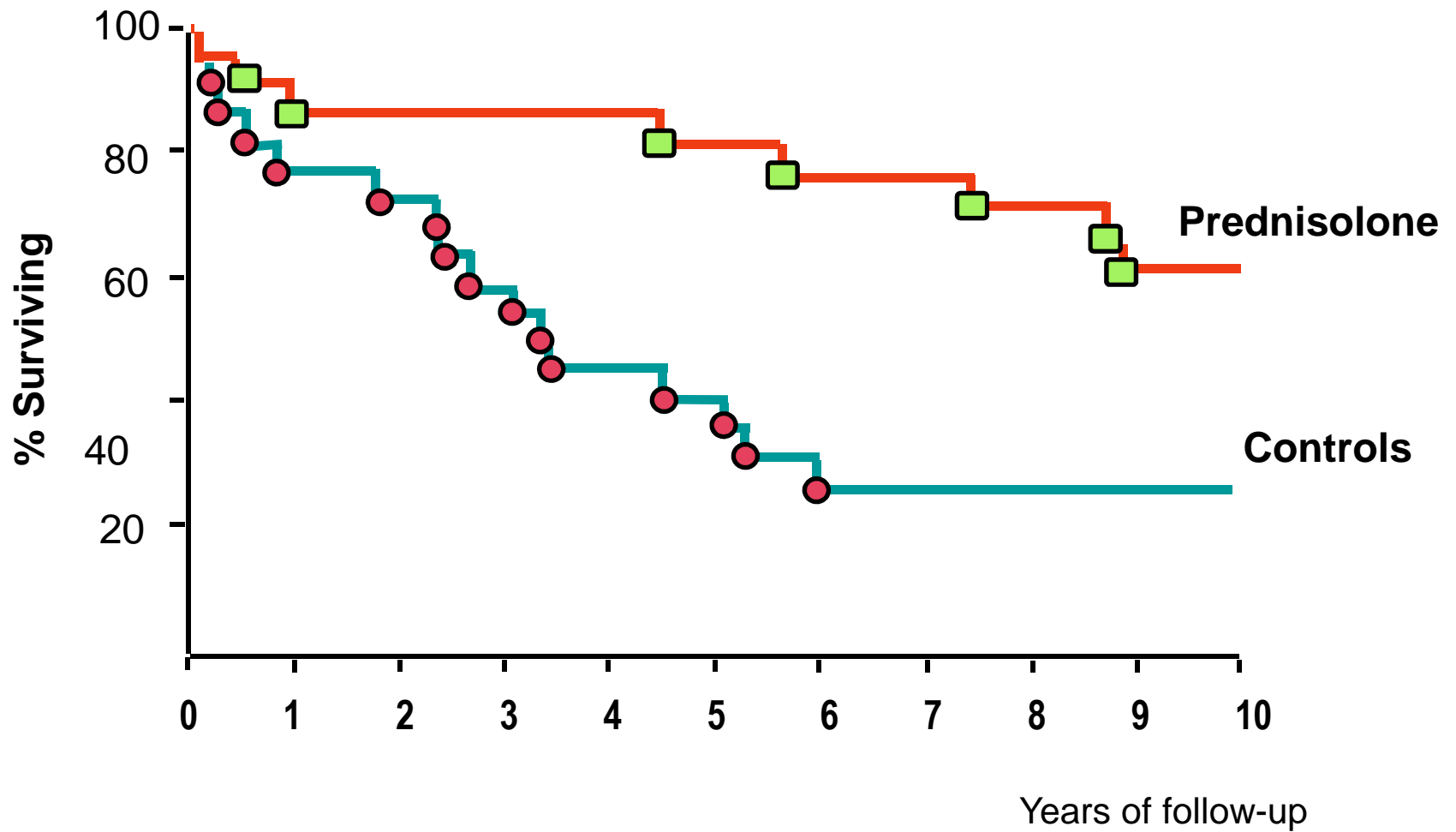


Azathioprine



Hépatites auto-immunes

Les corticoïdes améliorent la survie



Hépatites auto-immunes
Les objectifs du traitement

- 1. Induire une rémission**
- 2. Maintenir la rémission**

Hépatites auto-immunes

Les objectifs des traitements

Endpoints	Criteria	Recommendations
Remission	<ul style="list-style-type: none">• Disappearance of clinical symptoms,• Normalization of aminotransferases, bilirubin and γ-Globulins• Normal liver histology or inactive liver cirrhosis	<ul style="list-style-type: none">• Slow Reduction of steroids within 6 weeks• AST, ALT, total-bilirubin, and γ-Globulins in 3-week intervals during and 3 months after withdrawal• Then, every 6 months for 2 years, then every year

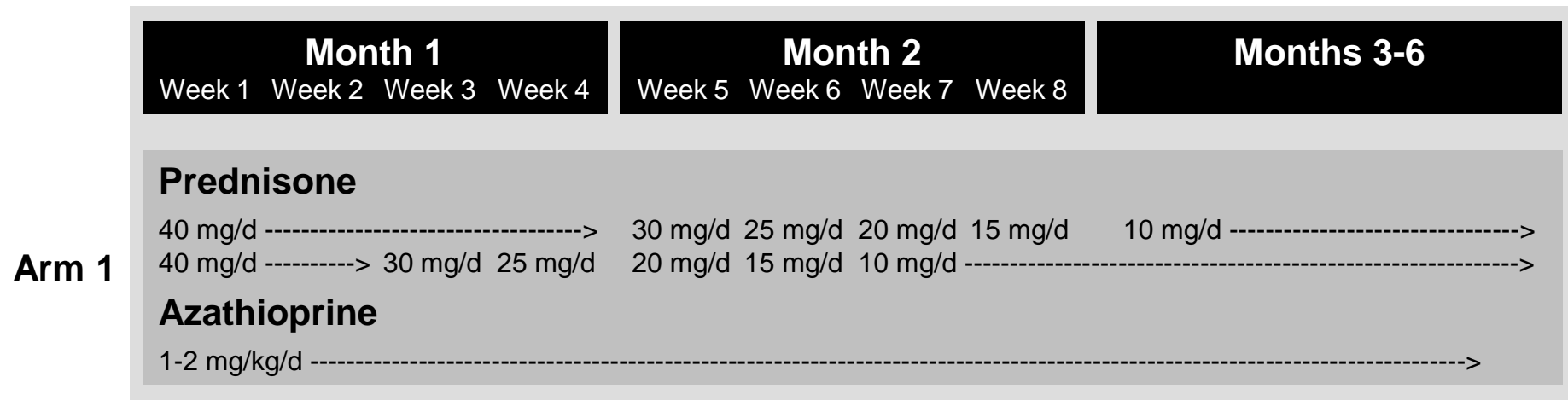
Hépatites auto-immunes: les traitements

Comment faire en pratique chez l'adulte ?

Monotherapy	
	Prednisone (mg/ d)
Week 1	60
Week 2	40
Week 3	30
Week 4	30
Maintenance -Therapy	20 and less

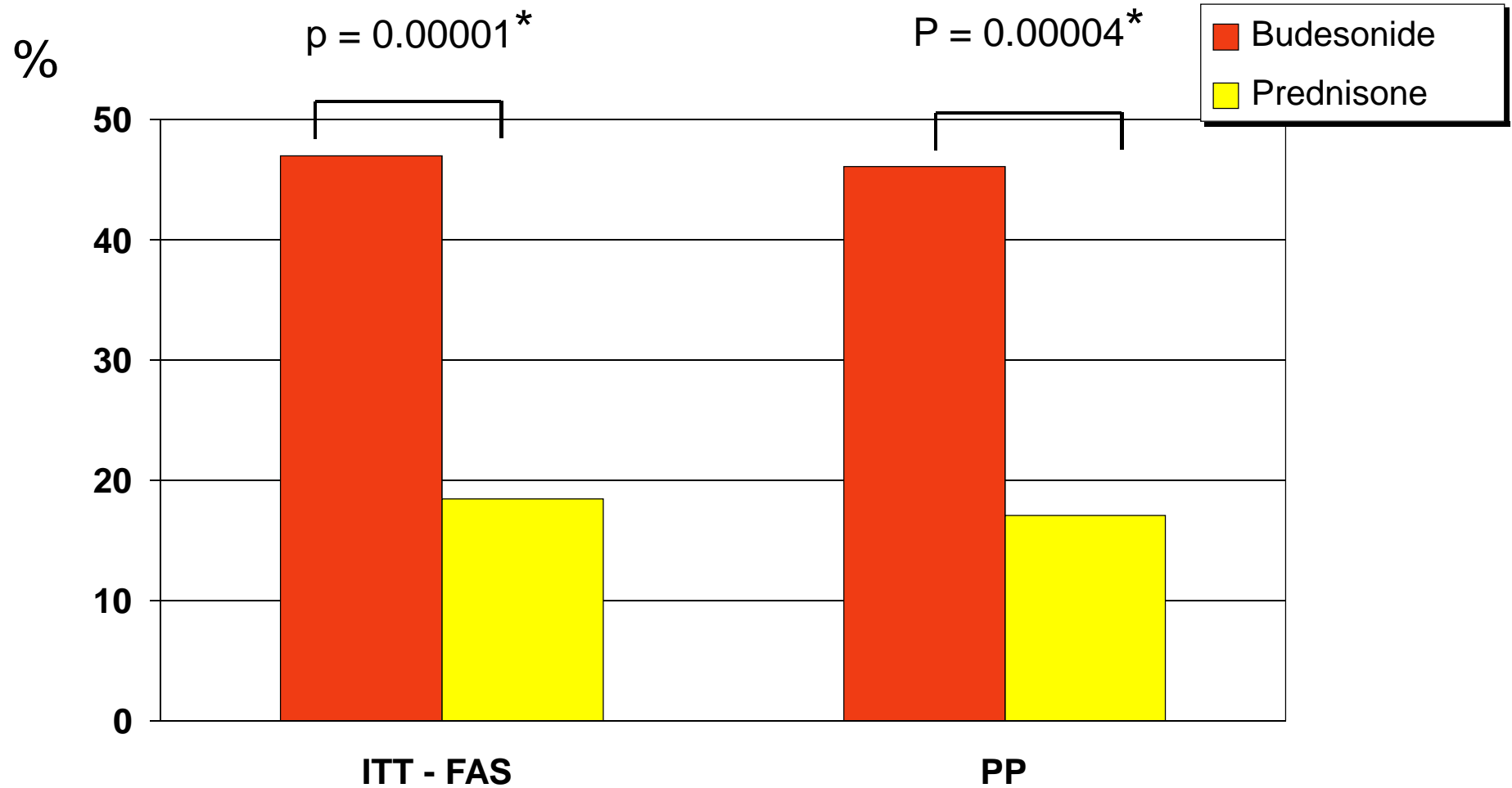
Hépatites auto-immunes

Le Budesonide diminue les effets secondaires de la corticothérapie



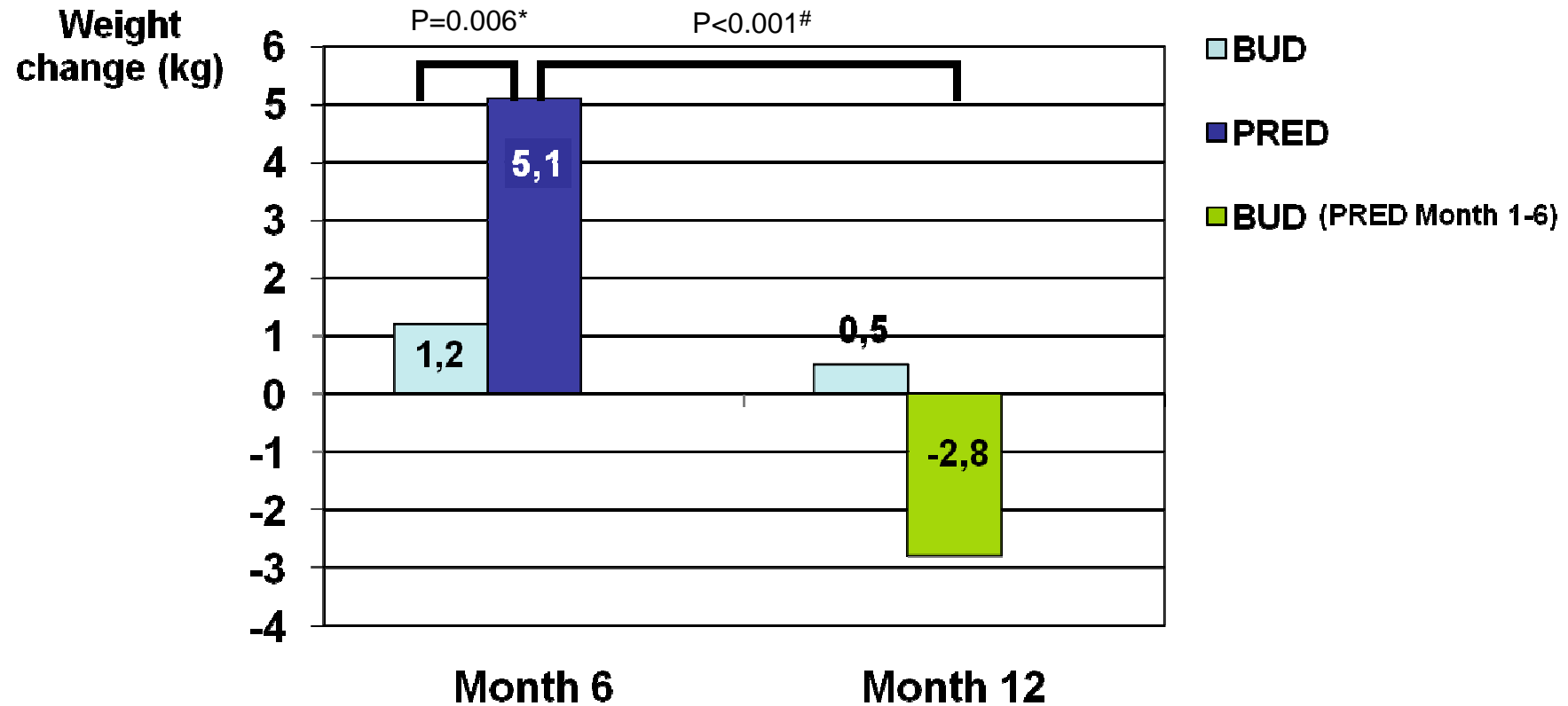
Budesonide au cours des HAI

Complete response (ALT normal & no steroid side effects)



European AIH-BUC Pediatric Subanalysis

Mean weight change at months 6 and 12



*Two sample t-test (two-sided)

paired t-test

Hépatites auto-immunes

Quand ne pas utiliser le budésonide?

Pas de Budésonide chez les patients cirrhotiques

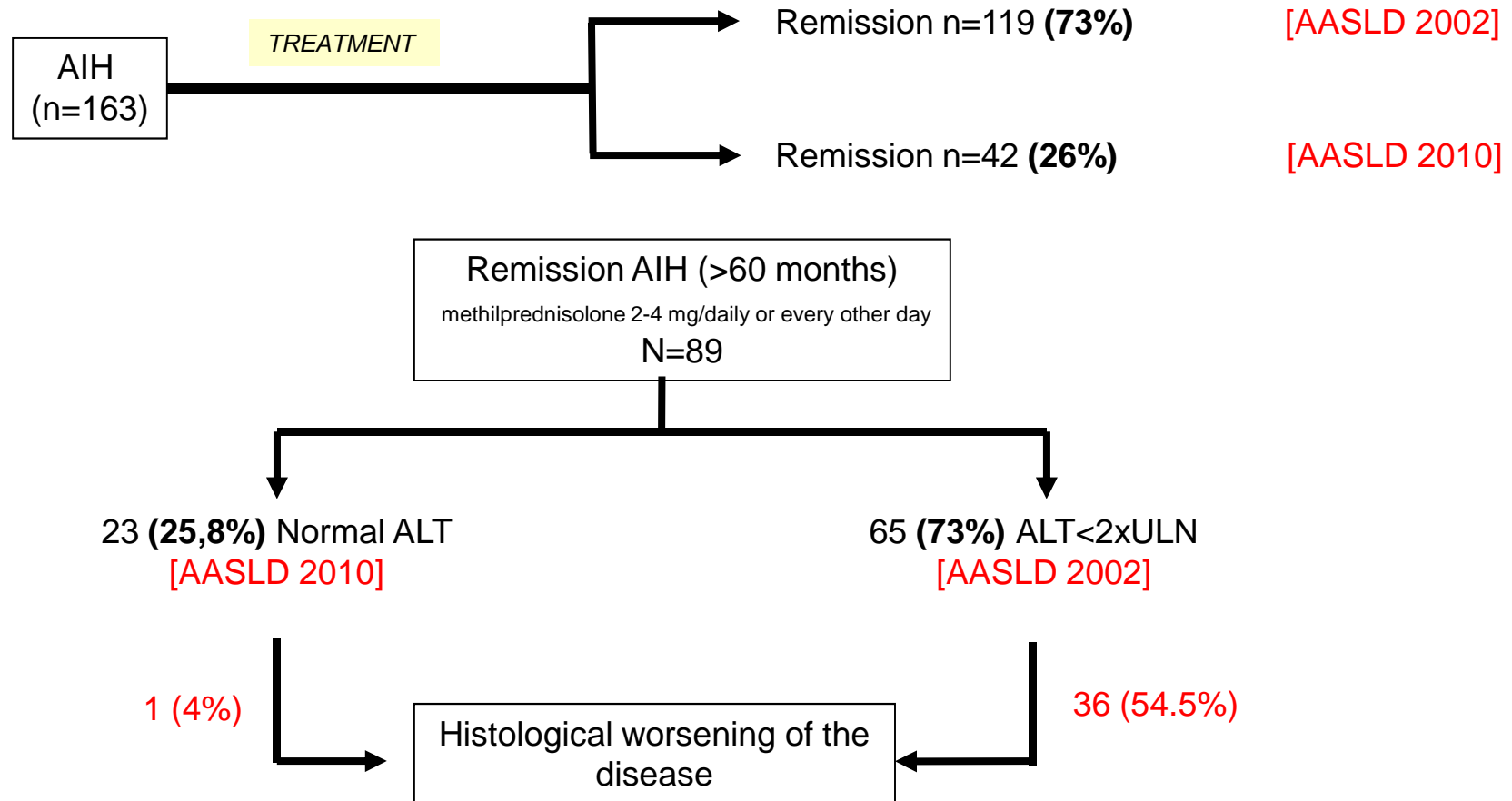
- Effets secondaires systémiques
- Risque de thrombose veineuse porte

Hempfling, Sauerbruch et al., Hepatology 2003

- Risque sd de Budd-Chiari

Mederacke et al., Ann Hepatol 2012

Critères de rémission AASLD 2002 vs. AASLD 2010 appliqués à une cohorte italienne de HAI



Hépatites auto-immunes: place du Mycophenolate ?

➤ **1ère ligne: MMF + prednisolone, 59 pts**

- 88% bonnes réponses précoces
- 37% arrêt des corticoïdes

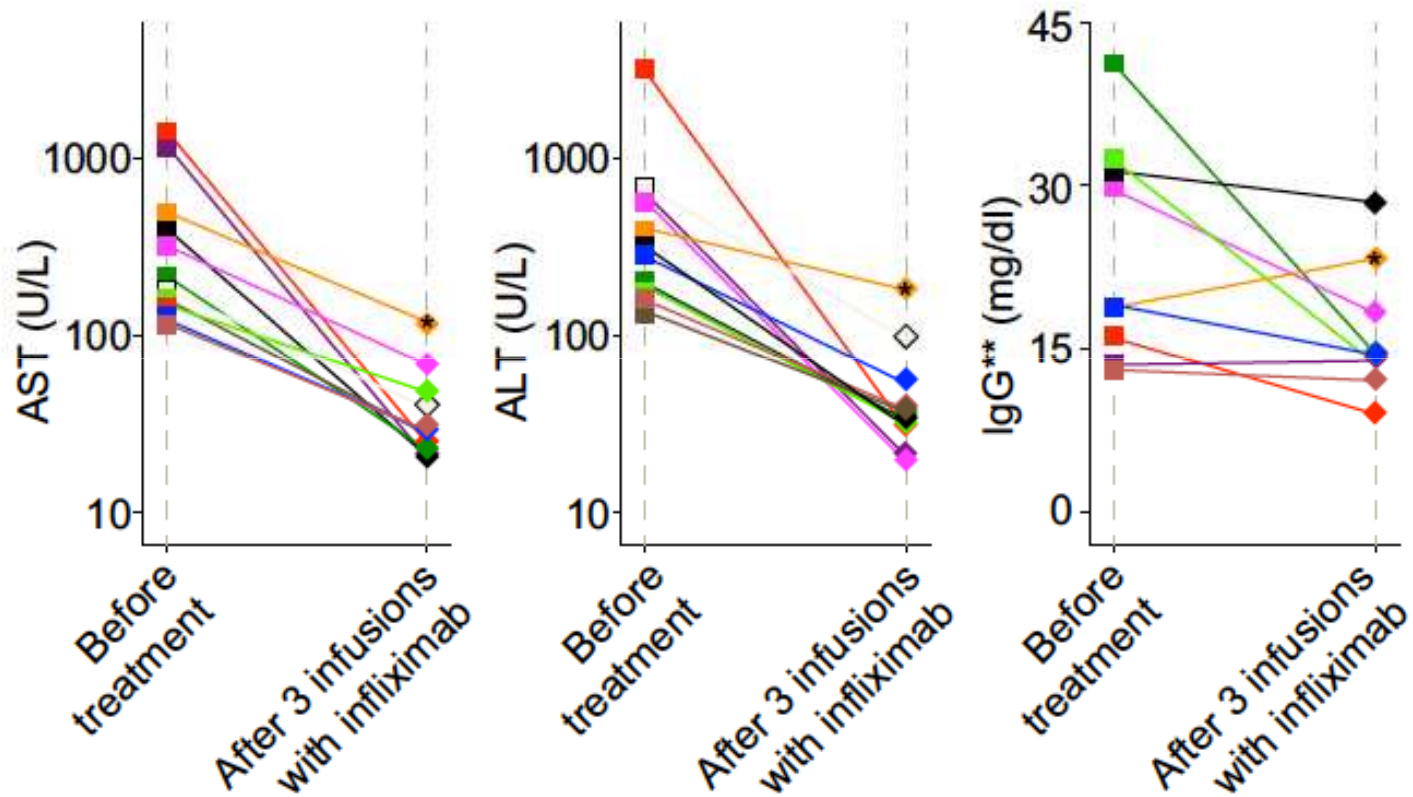
Zachou, Dalekos et al., J Hepatol 2011

➤ **2ème ligne: Aza intolérants/échec, 39 pts**

- 39% rémission complète

Hennes et al., Am J Gastroenterol 2008

Hépatites auto-immunes réfractaires: anti-TNF



HAI réfractaires et anti-TNF: trop d'effets secondaires

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 ongoing 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	Stopped after 8 mo due to full remission	6	Steroids tapered out
7	Steroid-induced diabetes, weight gain		Full remission	Treatment ongoing for 15 mo	14	10 mg/d
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

HAI réfractaires: et le Rituximab !

6 patients, HAI prouvée histo
Non répondeurs à prednisone + azathioprine



Rituximab

1000 mg i.v. à J1 et J15; 72 semaines FU



Semaine 24

- **AST** 90 +/- 23 vs. 31 +/- 4 U/L p = 0.03
- **IgG** 16.4 +/- 2.0 vs. 11.5 +/- 1.1 g/l p=0.056

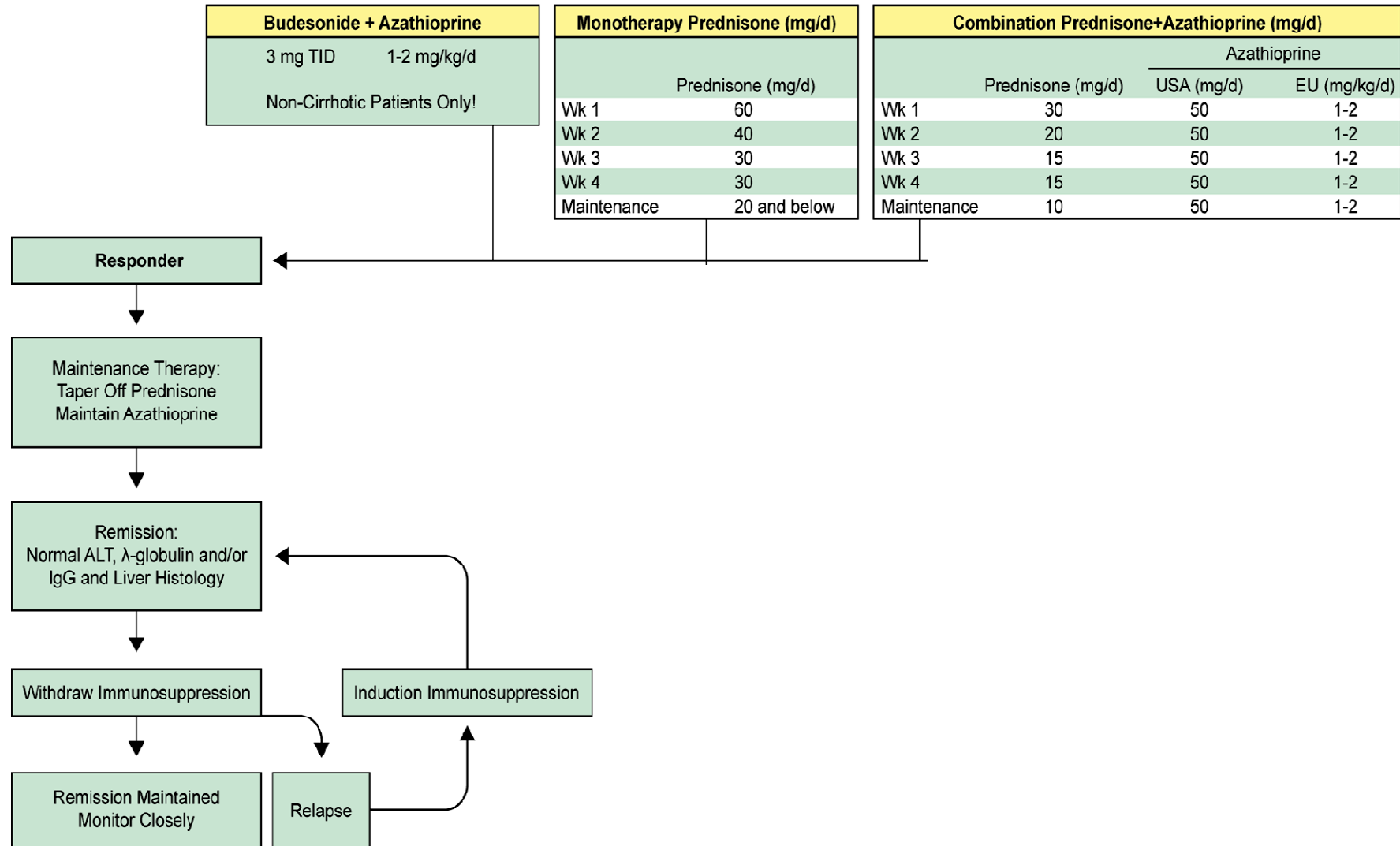
Traitement des hépatites auto-immunes

Budesonide + Azathioprine	
3 mg TID	1-2 mg/kg/d
Non-Cirrhotic Patients Only!	

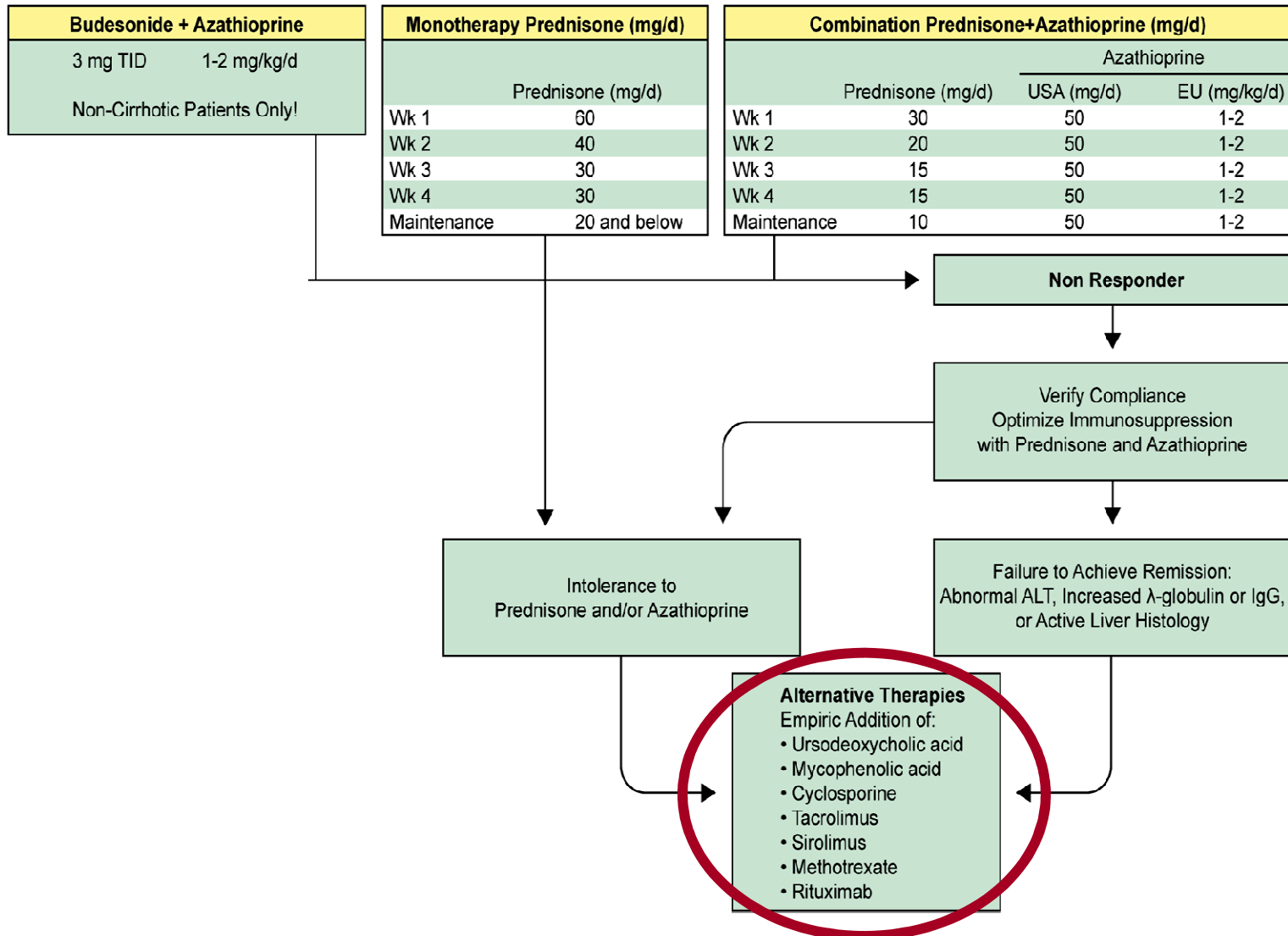
Monotherapy Prednisone (mg/d)	
	Prednisone (mg/d)
Wk 1	60
Wk 2	40
Wk 3	30
Wk 4	30
Maintenance	20 and below

Combination Prednisone+Azathioprine (mg/d)			
		Azathioprine	
	Prednisone (mg/d)	USA (mg/d)	EU (mg/kg/d)
Wk 1	30	50	1-2
Wk 2	20	50	1-2
Wk 3	15	50	1-2
Wk 4	15	50	1-2
Maintenance	10	50	1-2

Traitement des hépatites auto-immunes



Traitement des hépatites auto-immunes



Remerciements

Fanny Domont, Paris
Heiner Wedemeyer, Hannovre



Diagnostic différentiel des hépatites

Maladies Auto-immunes
Hépatiques

Maladies Auto-immunes
/inflammatoires
Systémiques

Infections hépatotropes
e.g. VHA, VHB, VHC, VHE ...
Herpes virus

Toxicité médicamenteuse

Table 1. Classification of Autoimmune Hepatitis.

Variable	Type 1 Autoimmune Hepatitis	Type 2 Autoimmune Hepatitis
Characteristic autoantibodies	Antinuclear antibody* Smooth-muscle antibody* Antiactin antibody† Autoantibodies against soluble liver antigen and liver–pancreas antigen‡ Atypical perinuclear antineutrophil cytoplasmic antibody	Antibody against liver–kidney microsome 1* Antibody against liver cytosol 1*
Geographic variation	Worldwide	Worldwide; rare in North America
Age at presentation	Any age	Predominantly childhood and young adulthood
Sex of patients	Female in approximately 75% of cases	Female in approximately 95% of cases
Association with other autoimmune diseases	Common	Common§
Clinical severity	Broad range	Generally severe
Histopathologic features at presentation	Broad range	Generally advanced
Treatment failure	Infrequent	Frequent
Relapse after drug withdrawal	Variable	Common
Need for long-term maintenance	Variable	Approximately 100%

* The conventional method of detection is immunofluorescence.

† Tests for this antibody are rarely available in commercial laboratories.

‡ This antibody is detected by enzyme-linked immunosorbent assay.

§ Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy is seen only in patients with type 2 disease.⁴⁷

Table 2. Histologic Differential Diagnosis of Chronic Hepatitis.

Disease	Distinguishing Features*
Autoimmune hepatitis	Conspicuous plasma-cell infiltrates
Primary biliary cirrhosis	Lymphocytic and granulomatous infiltrates of bile ducts; ductopenia
Primary sclerosing cholangitis	Fibrous obliterative cholangitis; ductopenia
Autoimmune cholangitis†	Lymphocytic and granulomatous infiltrates of bile ducts; ductopenia
Chronic viral hepatitis	Ground-glass hepatocytes; immunoperoxidase staining for hepatitis B surface and core antigens in patients with chronic hepatitis B; nodular-appearing infiltrates characteristic in patients with chronic hepatitis C; steatosis possible in patients infected with hepatitis C virus genotype 3
Chronic drug-induced hepatitis	No helpful distinguishing histologic features
Alpha ₁ -antitrypsin deficiency	Intracytoplasmic globules
Wilson's disease	Heavy copper deposition
Granulomatous hepatitis	Conspicuous and frequent granulomas
Graft-versus-host disease	Lymphocytic and granulomatous infiltrates of bile ducts; ductopenia
Alcoholic steatohepatitis	Steatosis; central inflammation and fibrosis; Mallory bodies
Nonalcoholic steatohepatitis	Glycogenated nuclei; steatosis; central inflammation and fibrosis; Mallory bodies

* These histologic features may be helpful in distinguishing among the causes of chronic hepatitis. Differences in histopathological findings among the diseases may be more apparent depending on the grade and stage of disease.⁵⁵

† There is still debate as to whether this entity is antimitochondrial-antibody-negative primary biliary cirrhosis.⁵⁶

Table 4. Drugs Used in the Treatment of Autoimmune Hepatitis in Adults and Children.

Drug	Initial Therapy	Maintenance Therapy	Comments
Prednisone or prednisolone	Used as monotherapy in adults (20–60 mg/day) and children (1–2 mg per kilogram of body weight/day); also used in combination therapy in adults (15–30 mg/day) and children (1–2 mg/kg/day) with azathioprine or mercaptopurine	Used as monotherapy in adults (5–15 mg/day) and children (1 mg/kg/day); also used in combination therapy in adults (5–10 mg/day) and children (0.5–1.0 mg/kg/day) with azathioprine or mercaptopurine	Relatively contraindicated in patients with osteoporosis, diabetes mellitus, glaucoma, cataracts, arterial hypertension, major depression, and femoral avascular necrosis; reduced doses may work; use of budesonide under investigation ⁷⁷
Azathioprine	Used in combination with prednisone or prednisolone in adults (50–100 mg/day) and children (1.5–2.0 mg/kg/day)	Used as monotherapy in adults (50–200 mg/day) and children (1.5–2.0 mg/kg/day); also used in combination therapy in adults (50–150 mg/day) and children (1.5–2.0 mg/kg/day)	Contraindicated in patients with homozygous thiopurine methyltransferase deficiency; relatively contraindicated in patients with heterozygous thiopurine methyltransferase deficiency, cancer, or cytopenia, and pregnant patients
6-Mercaptopurine	May be substituted for azathioprine in combination therapy in adults (25–100 mg/day) and children (0.75–1.0 mg/kg/day)	Used as monotherapy in adults (25–100 mg/day) and children (0.75–1.0 mg/kg/day); also used in combination therapy in adults (25–100 mg/day) and children (0.5–1.0 mg/kg/day)	Contraindicated in patients with homozygous thiopurine methyltransferase deficiency; relatively contraindicated in patients with heterozygous thiopurine methyltransferase deficiency, cancer, or cytopenia, and pregnant patients
Cyclosporine	Sometimes used as monotherapy in children ⁷⁸ ; sometimes used as an alternative drug in adults with treatment-refractory disease	Sometimes used as an alternative drug in adults with treatment-refractory disease	Once remission achieved in children, maintenance therapy initiated with a combination of prednisone and azathioprine ⁷⁸ ; role of tacrolimus in place of cyclosporine not established
Mycophenolate mofetil	Sometimes used in patients with treatment-refractory disease or in patients with adverse drug reactions to or intolerance of azathioprine, mercaptopurine, or both	Sometimes used in patients with treatment-refractory disease or in patients with adverse drug reactions to or intolerance of azathioprine, mercaptopurine, or both	Role of mycophenolate mofetil, methotrexate, and cyclophosphamide not established
Ursodiol	Sometimes used in combination with prednisone, azathioprine, or both	Sometimes used in combination with prednisone, azathioprine, or both	Role of ursodiol not established

Table 3. Characteristics of Autoimmune Hepatitis–Primary Biliary Cirrhosis Variant Syndromes.

Characteristic	Overlap Syndrome*	Autoimmune Cholangitis†
Antinuclear antibody	Absent	Generally present
Smooth-muscle antibody	Absent	Generally present
Antimitochondrial antibody	Present	Absent
Biochemical cholestasis†	Absent	Present
Histologic evidence of bile-duct abnormalities	Absent	Present
Cholangiographic abnormalities	Absent	Absent
Responsiveness to immunosuppression	Present	Variable

* This syndrome is also called antimitochondrial-antibody–positive autoimmune hepatitis.⁵⁸ There is debate as to whether autoimmune cholangitis and antimitochondrial-antibody–negative primary biliary cirrhosis represent different entities.^{56,63-66}

† This condition is characterized by elevated levels of serum alkaline phosphatase, γ -glutamyltransferase, or both.