Que retenir de l'année 2004
1-Actualité thérapeutique

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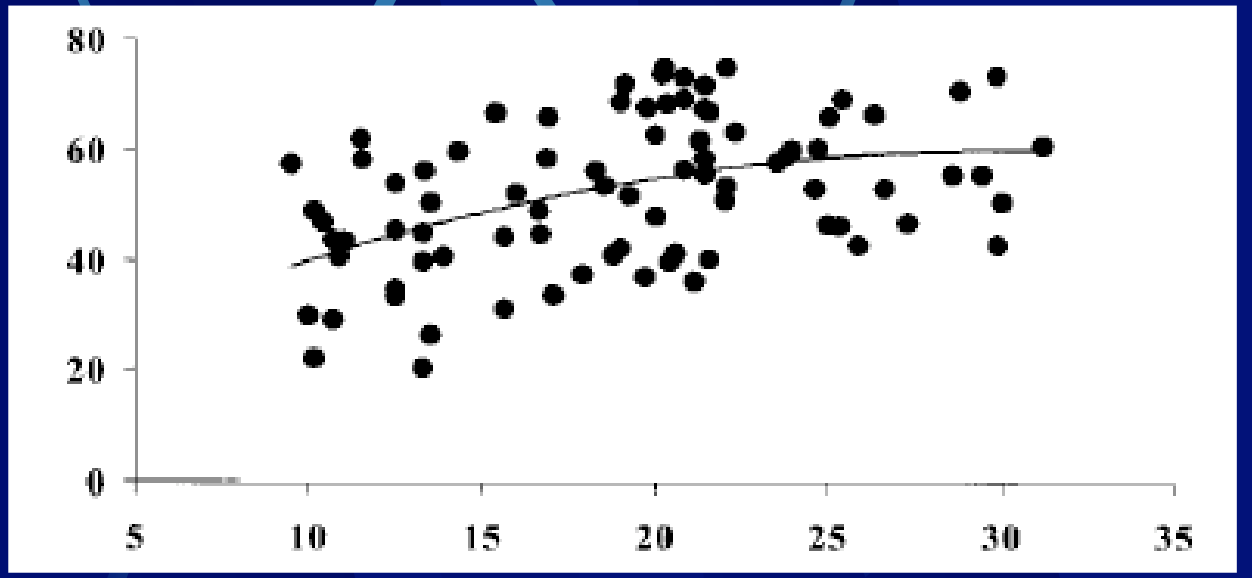
Cholangite sclérosante: Fortes doses d'AUDC (1)

10-13 mg/Kg n=18
14-17 mg/Kg n=14
18-21 mg/Kg n=34
22-25 mg/Kg n=12
26-32 mg/Kg n=8



Rost, Hepatology 2004

Cholangite sclérosante: Fortes doses d'AUDC (1)

Acides biliaires plasmatiques

Bile Acid	Before Treatment (n = 11)	UDCA Treatment mg/kg/d 10–13 (n = 18)	14–17 (n = 14)	18–21 (n = 34)	22–25 (n = 12)	26–32 (n = 8)
CA, mmol/L (%)	1.21 ± 0.10	0.88 ± 0.01	0.49 ± 0.01	0.67 ± 0.01	0.82 ± 0.12	0.53 ± 0.08
	(64.1 ± 5.1)	(24.1 ± 0.3)*	(27.0 ± 0.3)*	[18.8 ± 0.2]*	(16.7 ± 2.5)*	[21.8 ± 3.4)*
CDCA, mmol/L (%)	0.53 ± 0.07	0.79 ± 0.04	0.33 ± 0.03	0.65 ± 0.04	0.92 ± 0.08	0.43 ± 0.05
	(28.1 ± 3.8)	(21.7 ± 1.2)*	(18.2 ± 1.7)*	[18.2 ± 1.0]*	(18.8 ± 1.7)*	[17.5 ± 2.2)*
DCA, mmol/L (%)	0.12 ± 0.05	0.37 ± 0.07	0.13 ± 0.03	0.21 ± 0.03	0.25 ± 0.01	0.06 ± 0.03
	(6.4 ± 2.8)	(10.1 ± 1.9)	(7.0 ± 1.4)	[6.0 ± 0.9]	[5.2 ± 0.1)	[2.6 ± 1.2)
UDCA, mmol/L (%)	0.02 ± 0.01	1.56 ± 0.01	0.86 ± 0.01	1.99 ± 0.01	2.88 ± 0.11	1.41 ± 0.01
	(1.0 ± 0.7)	(43.1 ± 0.3)*	(46.9 ± 0.3)*	[56.0 ± 0.2]*†	(58.6 ± 2.3)*	[57.7 ± 0.4)*
LCA, mmol/L (%)	0.01 ± 0.01	0.04 ± 0.01	0.02 ± 0.01	0.03 ± 0.01	0.04 ± 0.02	0.01 ± 0.01
	(0.3 ± 0.1)	(1.0 ± 0.3)	(0.9 ± 0.3)	[1.0 ± 0.2]	[0.8 ± 0.4)	[0.4 ± 0.3)

Rost, Hepatology 2004

Prévalence de la stéatose

Contenu hépatique en TG par spectroscopie
N=2971

Ethnicity	n	Hepatic Triglyceride Content, %	Hepatic Steatosis, %
Hispanic			
Men	172	4.6 (2.7–11.9)	45
Women	229	4.6 (2.6–9.9)*	45*
All	401	4.6 (2.6–10.7)	45
White			
Men	375	4.4 (2.4–8.6)	42
Women	359	3.0 (1.9–5.3)	24
All	734	3.6 (2.1–7.3)	33
Black			
Men	499	3.2 (2.0–5.3)†	23†
Women	606	3.3 (1.9–5.3)	24
All	1105	3.2 (2.0–5.3)	24
All	2,287	3.6 (2.1–6.6)	31

Browning, Hepatology 2004

Stéatose et syndrome dysmétabolique

	Contenu hépatique en Triglycérides < 5,5%	>5,5%	p
n	1579	708	
Age (années)	45±9	46±10	0,03
BMI >30 (%)	33	67	<0,01
Glycémie > 1,1g/L (%)	11	18	<0,01
Insulino R (%)	23	58	<0,01
Triglycérides (%)	8	30	<0,01
Alcool (%)	6,3 ± 15,6	6,6 ± 15,3	ns

Browning, Hepatology 2004

Stéatose et transaminases

	Contenu hépatique en Triglycérides	
n	< 5,5% 1579	>5,5% 708
Alat > 40 UI/L Hommes >31 UI/L Femmes	3%	21% 79%*
Alat > 31 UI/L Hommes Alat > 19UI/L Femmes		54% 46%

* Alat normales

Browning, Hepatology 2004

Traitement de la stéato-hépatite non alcoolique par la pioglitazone

N=174

- Etude prospective 30 mg/J pioglitazone, 48 semaines
- Critères: ALA > 41 UI/L
  non diabétique
  Alcool < 70g/sem
  Stéatose>5% + inflammation (Brunt et al)
- 3 mois prétraitement
  - Réduction pondérale +vitamines

Objectif: réponse histologique (au moins 3 points)

Promrat, Hepatology 2004

Traitement de la stéato-hépatite non alcoolique par la pioglitazone

Parameter	Pre (n = 18)	Week 48 (n = 18)	P Value*
ALT (U/L)	99 ± 71	40 ± 25	<0.001
AST (U/L)	61 ± 36	34 ± 15	0.001
Alk P (U/L)	85 ± 21	69 ± 15	<0.001
Hct (%)	40.2 ± 3.7	41.2 ± 3.4	0.06
Glucose (mg/dL)	97.3 ± 11.7	95.2 ± 8.4	0.43
Insulin (μU/mL)	19.1 ± 14.2	13.6 ± 7.5	0.018
C-peptide (ng/mL)	5.8 ± 1.9	3.9 ± 1.1	<0.001
FFA_m (μEq/L)	768 ± 199	621 ± 229	0.03
Total cholesterol (mg/dL)	231 ± 64	244 ± 43	0.22
Triglycerides (mg/dL)	233 ± 207	215 ± 139	0.52
LDL cholesterol (mg/dL)	162 ± 50	161 ± 42	0.83
HDL cholesterol (mg/dL)	48 ± 13	50 ± 17	0.33

Promrat, Hepatology 2004

Traitement de la stéato-hépatite non alcoolique par la pioglitazone

Parameter (0–4)	Pre (n = 18)	Week 48 (n = 18)	*P* Value*
Presence of NASH (%)	17 (94)	6 (33)	<0.01
Steatosis	2.6 ± 1.2	1.0 ± 0.9	<0.001
Hepatocellular injury	2.2 ± 0.9	0.9 ± 0.8	<0.001
Parenchymal inflammation	3.3 ± 1.0	2.1 ± 1.2	<0.001
Portal inflammation	1.6 ± 1.1	1.4 ± 0.8	0.59
Mallory bodies	2.2 ± 1.5	1.4 ± 1.5	0.01
Fibrosis	2.0 ± 1.1	1.4 ± 1.1	0.04
NASH activity index (0–12)†	8.0 ± 2.1	4.0 ± 2.2	<0.001

Promrat, Hepatology 2004

Traitement de la stéato-hépatite non alcoolique par la pioglitazone

Parameter	Pre (n = 18)	Week 48 (n = 18)	P Value*
Weight (kg)	90.0 ± 13.9	93.5 ± 14.5	0.003
BMI (kg/m²)	32.4 ± 5.7	33.7 ± 6.3	0.004
Waist circumference (cm)	105.4 ± 10.8	104.1 ± 11.6	0.629
Waist/hip ratio	0.95 ± 0.06	0.91 ± 0.07	0.004
Total body fat (%)	35.8 ± 7.7	37.6 ± 8.2	<0.001
Fat mass (kg)	32.4 ± 8.0	35.5 ± 10.0	0.002
Lean mass (kg)	56.4 ± 12.1	56.6 ± 11.9	0.640
Liver fat by MRI (%)	47.5 ± 27.9	22.8 ± 22.6	0.001
Liver volume by MRI (cc)	2276 ± 537	1963 ± 261	0.02

Promrat, Hepatology 2004

Traitement de la stéato-hépatite non alcoolique par l'AUDC

N=174

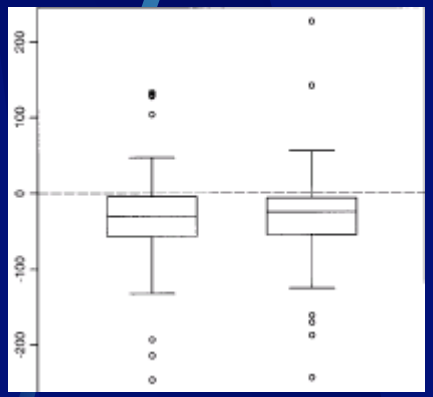
- Etude randomisée controlée AUDC 13-15mg/Kg/J vs placebo; 2 ans
  Critères: ALAT > 41 1,5 N, 3 mois
  Alcool < 40g/j
  Stéatose > 10% + inflammation (Brunt et al)

  Objectif: -25% ALAT

Lindor, Hepatology 2004

Traitement de la stéato-hépatite non alcoolique par l'AUDC

Alat



	AUDC	placebo	
n	80	86	
Dim. poids	56	65	ns
BMI	53	60	
Stéatose (-2)	2%	2%	ns
Inflammation (-2)	8%	5%	ns
Ballonisation (-2)	2%	2%	ns
Mallory (-2)	2%	2%	ns
Fibrose(-2)	6%	4%	ns

Lindor, Hepatology 2004

Traitement l'hépatite aigue alcoolique par anticorps monoclonal chimérique anti-TNFα (Infleximab)

- Etude randomisée controlée
  - Infleximab IV 10mg/Kg S0, S2, S4 + prednisolone 40 mg/j (28j)
  - placebo IV S0, S2, S4 + prednisolone 40 mg/j (28j)

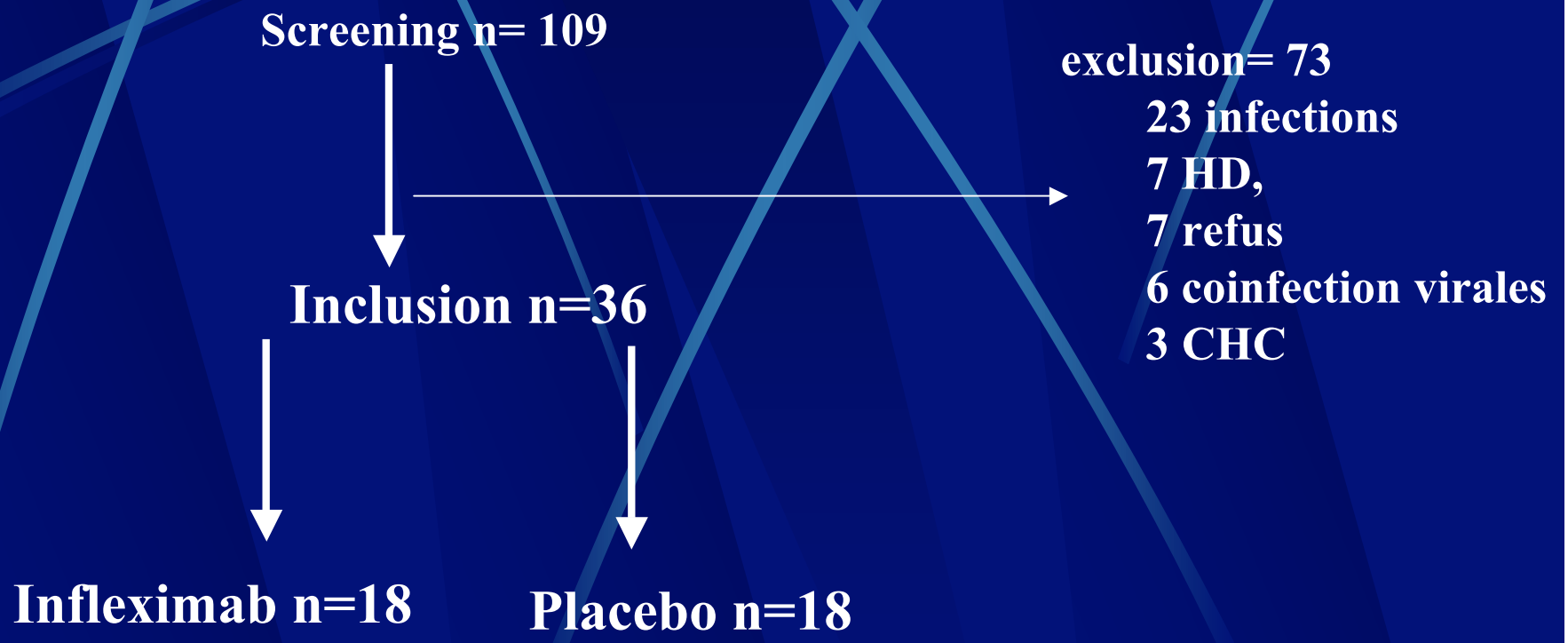
Critères:

ASAT >1,5 N
Alcool >50g/j
Maddrey >32 et PBH
Stéatose>10% + inflammation (Brunt et al)

Objectif: mortalité M2

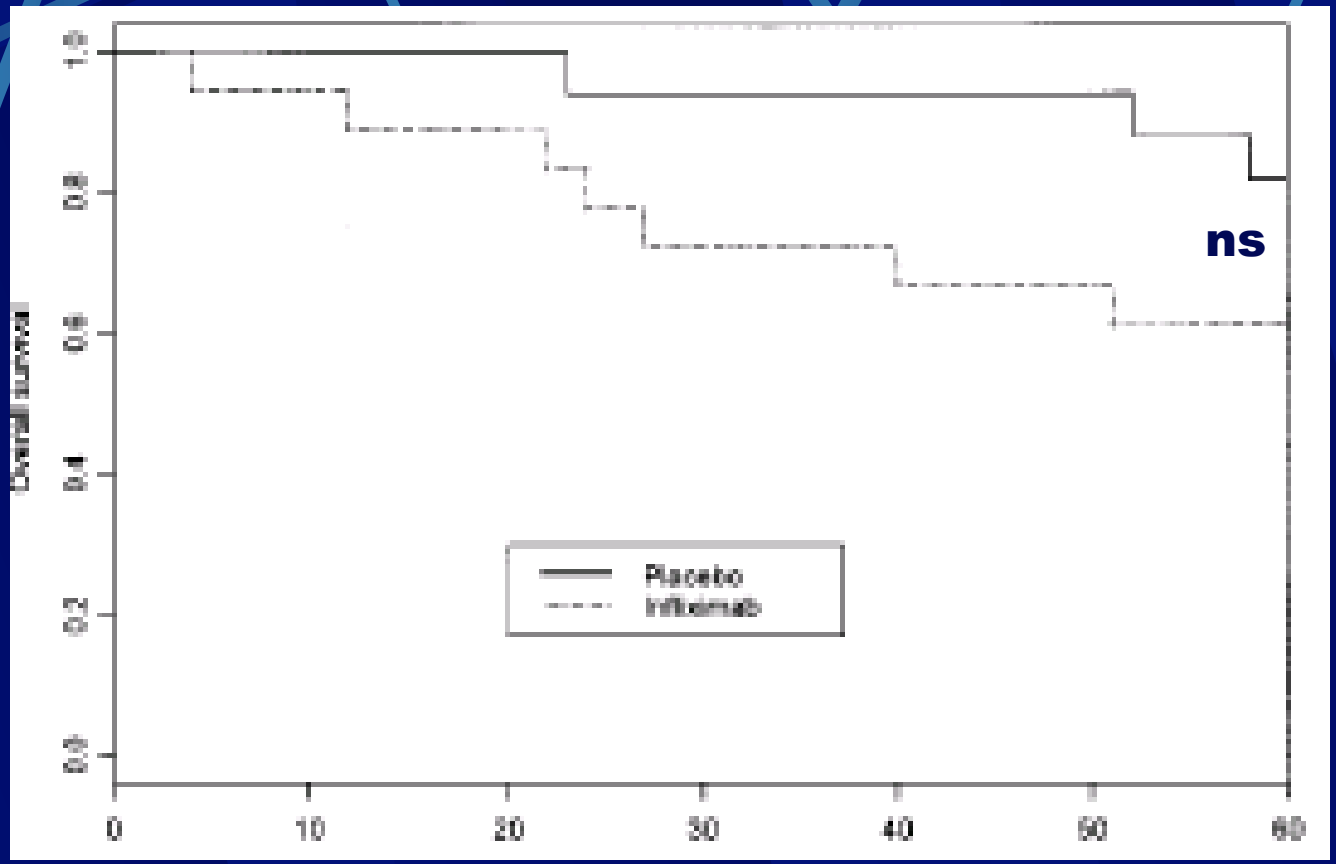
Naveau, Hepatology 2004

Traitement l'hépatite aigue alcoolique par anticorps monoclonal chimérique anti-TNFα (Infleximab)



Naveau, Hepatology 2004

Traitement l'hépatite aigue alcoolique par anticorps monoclonal chimérique anti-TNFα (Infleximab)



Naveau, Hepatology 2004

Traitement l'hépatite aigue alcoolique par anticorps monoclonal chimérique anti-TNFα (Infleximab)

	Inflexion	placebo	
infections	15/13 patients	5/3 patients	0,022
délais (jours)	20,4 ± 16	33± 14	ns
infec sévères	10/8 pts/4 décès	1/1 pt/1 décès	0,002

	Infections léthales	Autres	
Maddrey initial	70±5	57± 18	< 0.05

Naveau, Hepatology 2004

Hépatite autoimmune : fibrose et réponse aux corticoides

Etude rétrospective, n=73

- **Critères:**
  - **HAI (Alvarez, J hepatol 1999)**
  - **Exclusion initiale des cirrhose histologiques**
  - **Suivi histologique (score de Ishak)**

- **Traitement initial (Czaja, Hepatology 2002)**

combiné n=44 (74%)	monothérapie n=19 (26%)
S1: Prednisolone 30 mg/j + Imurel 50mg/j	Prednisolone 60mg/j
S2: Prednisolone 20mg/j + Imurel 50 mg/j	Prednisolone 40 mg/j
S3: Prednisolone 15 mg/j + Imurel 50mg/J	Prednisolone 30 mg/j
>S3: Prednisolone 10mg/j + Imurel 50mg/J	Prednisolone 20 mg/j

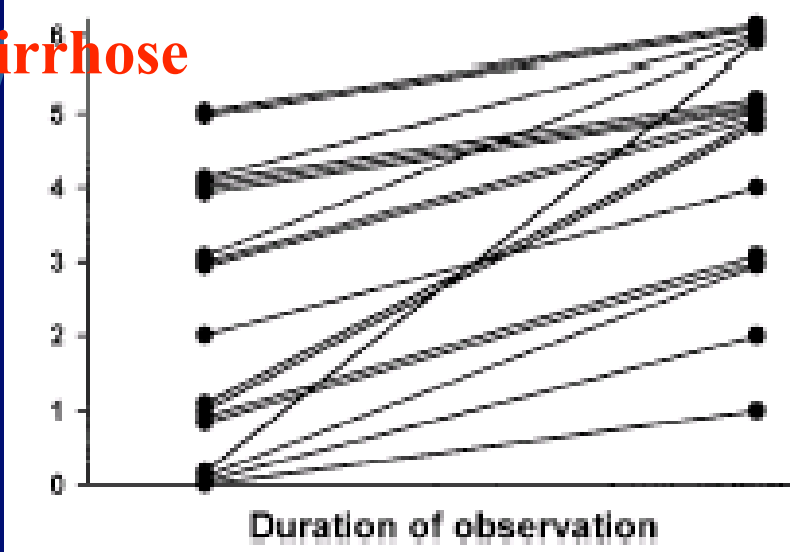
- **Echec**
  - **Prednisolone 60mg/j ou prednisolone 30mg/j + Imurel 150 mg/J**
- **Echappement ou rechute**
  - **Pred 0-20 mg/j + Imurel 25-150mg/j ou Pred 0-20 mg/j + Imurel 0-150mg/j**

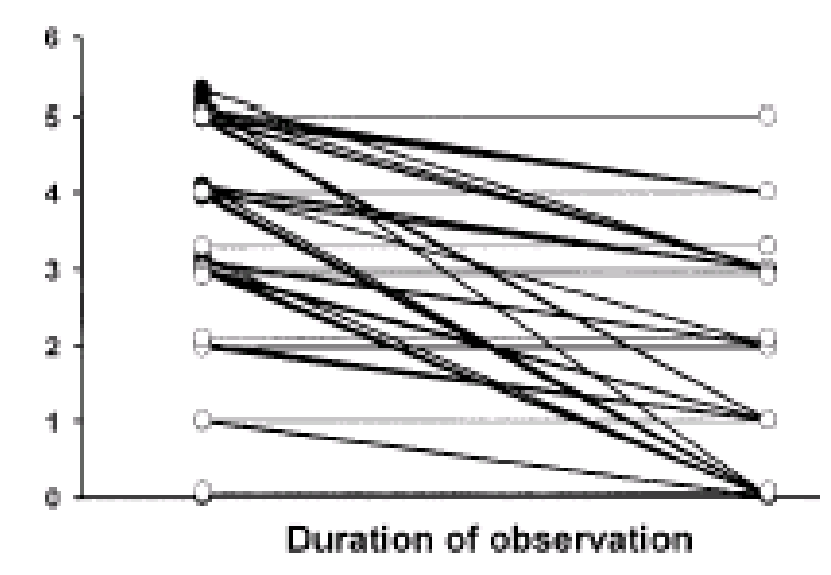
Czaja, Hepatology 2004

Hépatite autoimmune : fibrose et réponse aux corticoides

Score de fibrose	n	Initial	final	suivi
Progression	18(25%)	2,3/0,4	4,3/0,4	79/13
Stable	16(22%)	2,1/0,4	2,1/0,4	60/16
Diminution	39(53%)	3,6/0,2	1,4/0,2	58/8
Total	73(100%)	2,9/0,2	2,3/0,2	64/7

7% cirrhose





Czaja, Hepatology 2004

Hépatite autoimmune : fibrose et réponse aux corticoides

Initial	Progression (>2)	Stable/diminution	
Age	43/6	48/2	ns
femme	8(67%)	47(85%)	ns
Durée évolution	11/1	20/6	ns
Asat (UI/L)	589/115	592/51	ns
Bilirubine(mg/dl)	3,2/0,7	4/0,6	ns
G glob (g/L)	34/0,3	32/0,1	ns
IgG (g/L)	32,1/0,4	29/0,1	ns
HLA DR3+/DR4+	3/10(30%)	1/47 (2%)	0.01
HLA DR3+/DR3+	1/10(10%)	7/47 (15%)	ns
HLADR4+/DR4+	0/5(0%)	4/47 (8%)	ns

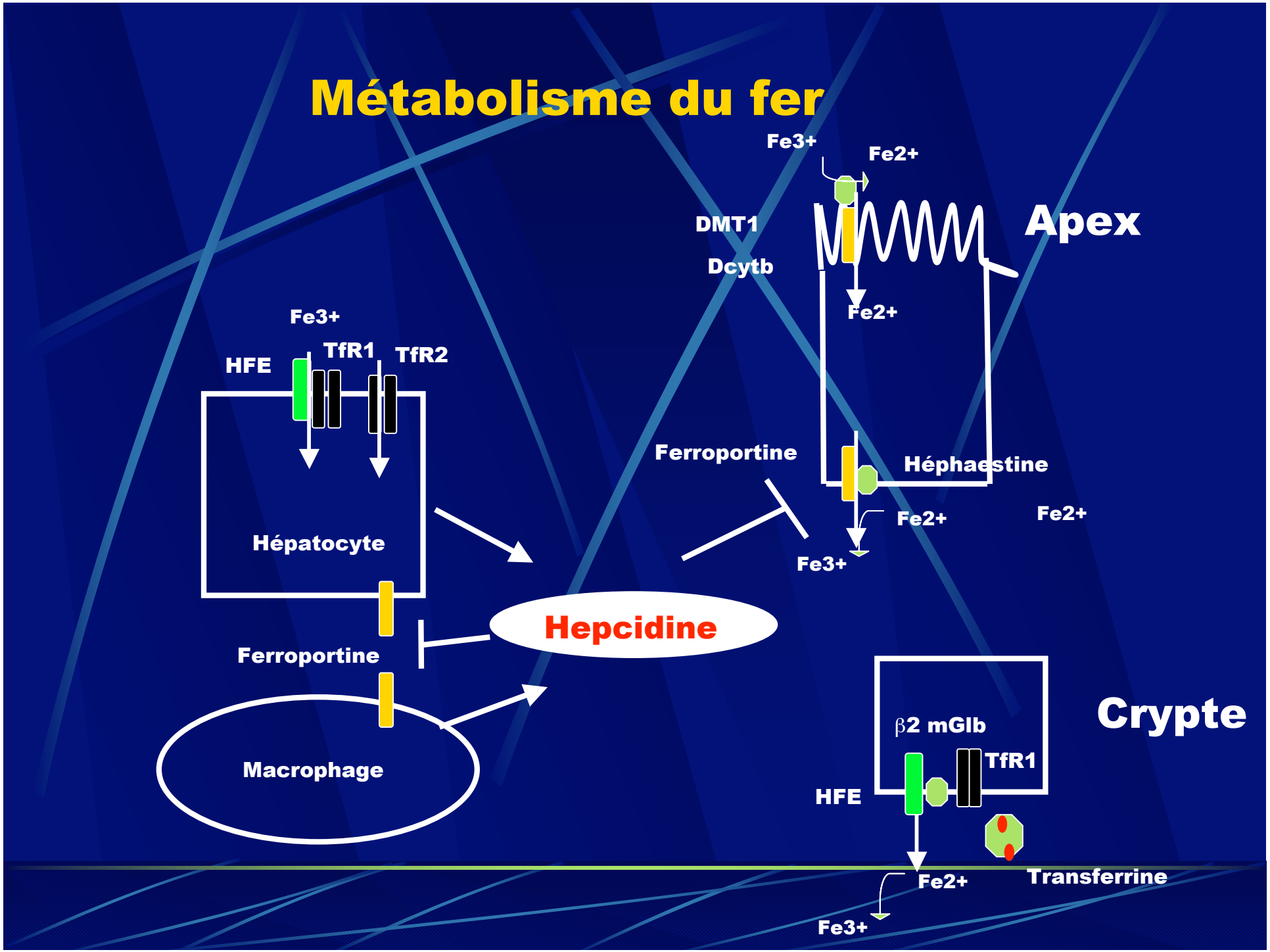
Czaja, Hepatology 2004

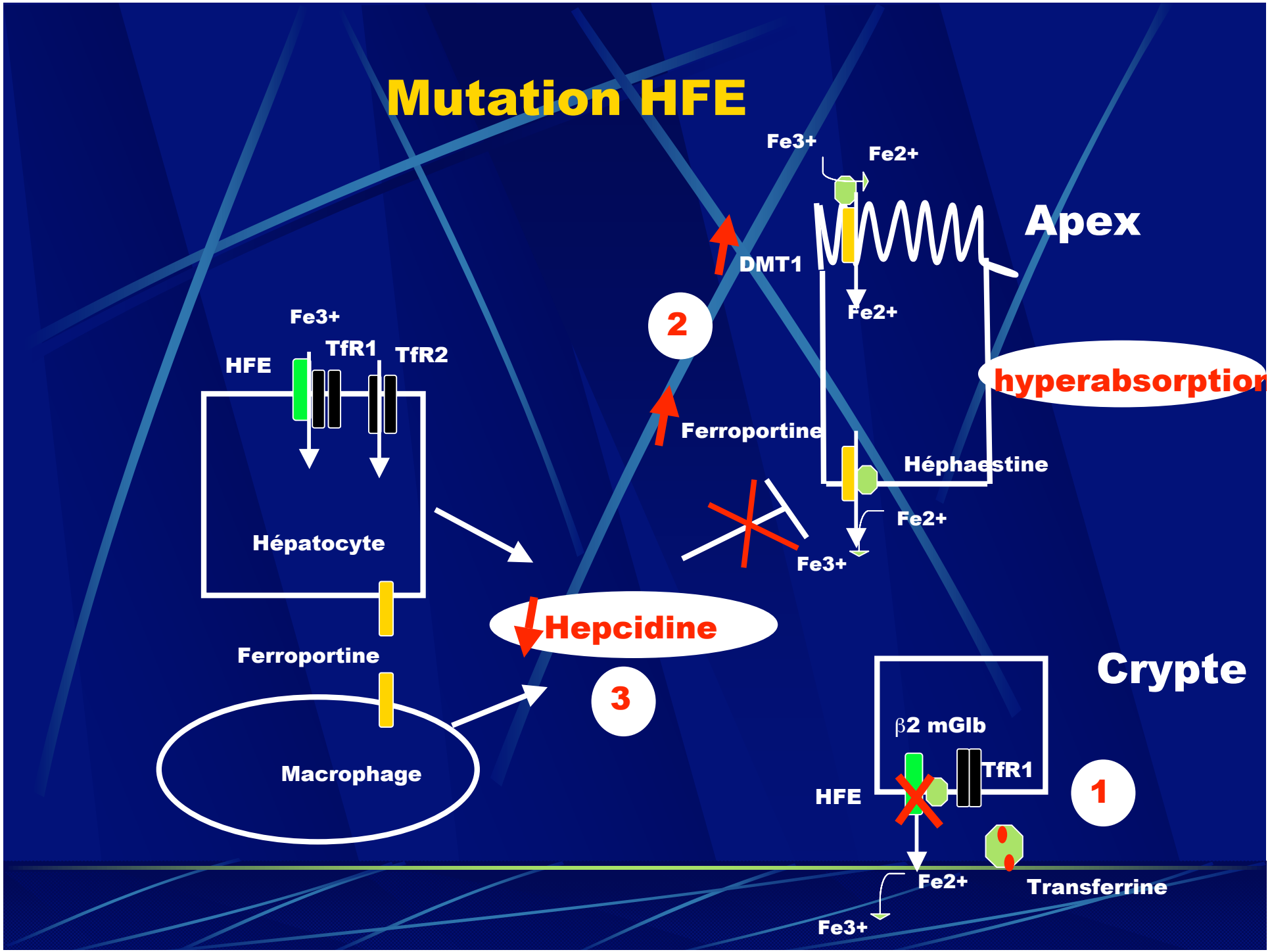
Hépatite autoimmune : fibrose et réponse aux corticoides

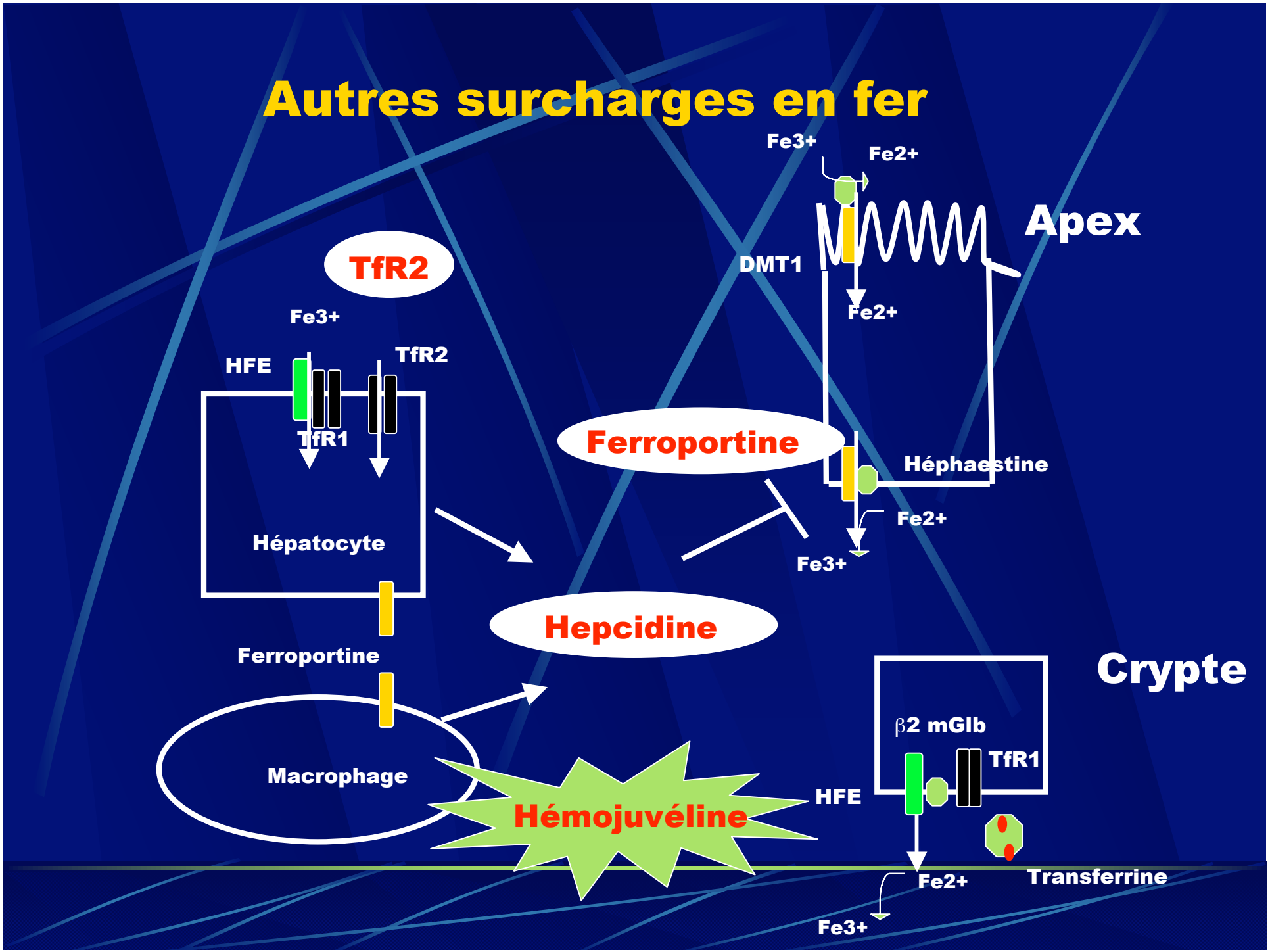
Treatment Outcomes Before Last Liver Biopsy Evaluation	Increased Fibrosis Scores		Stable or Decreased Fibrosis Scores (N = 55)
	Total (N = 18)	≥2 Points (N = 12)	
Remission	15 [83]	11 [92]	47 (85)
Relapse	13/15 [87]	10/11 [91]	36/47 (77)
Multiple relapses	12/15 [80]	9/11 [82]	26/47 (55)
Sustained remission	2/15 [13]	1/11 [9]	11/47 (23)
Incomplete response	1 [5]	0 [0]	1 (2)
Treatment failure	2 [11]	1 [8]	7 (13)
HAI at last tissue examination	3.2 ± 0.7*	3.1 ± 0.9†	1.7 ± 0.2*†
HAI resolution (HAI = 0)	0 [0]	0 [0]	7 (13)
HAI worse than ≥2 points	3 [17]‡	2 [17]	1 (2)‡
Active inflammation and continued treatment requirement	16 [89]	11 [92]	44 (80)
Duration of follow-up (mo)	79 ± 13	82 ± 16	57 ± 7

Czaja, Hepatology 2004

Que retenir de l'année 2004
2-Physiopathologie


Métabolisme du fer
Fe3+
Fe2+
DMT1
Dcytb
Apex
Fe2+
Fe3+
HFE
TfR1
TfR2
Hépatocyte
Ferroportine
Héphaestine
Fe2+
Fe2+
Fe3+
Hepcidine
Ferroportine
Macrophage
Crypte
β2 mGlb
TfR1
HFE
Fe2+
Transferrine
Fe3+


Mutation HFE
Fe3+
Fe2+
Apex
DMT1
Fe2+
2
hyperabsorption
Fe3+
TfR1
TfR2
HFE
Ferroportine
Héphaestine
Fe2+
Hépatocyte
Fe3+
Hepcidine
Ferroportine
Crypte
3
β2 mGlb
TfR1
Macrophage
HFE
1
Fe2+
Transferrine
Fe3+


Autres surcharges en fer
Fe3+
Fe2+
Apex
DMT1
Fe2+
TfR2
Fe3+
HFE
TfR2
TfR1
Ferroportine
Héphaestine
Fe2+
Hépatocyte
Fe3+
Hepcidine
Ferroportine
Crypte
β2 mGlb
TfR1
Macrophage
Hémojuvéline
HFE
Fe2+
Transferrine
Fe3+

Surcharges en fer

Individual	Origin	Number of affected individuals in family	Age at onset	Age at diagnosis	Serum ferritin ($\mu g\ l^{-1}$)	Transferrin saturation (%)	Hypo-gonadism	Arthro-pathy	Skin pigmentation	Glucose intolerance	Heart disease	Hepatic fibrosis	Mutation status	Effect on coding sequence
JH1-301	Canada	3	7	7	339	94	–	–	+	–	–	+	Compound heterozygous	I222N, G320V
JH3-201	Greece	1	21	25	2,283	100	+	+	+	–	–	+	Homozygous	G320V
JH4-203	Greece	1	39	49	4,127	90	+	+	+	–	–	+	Homozygous	I281T
JH5-201	Greece	2	32	39	3,553	100	+	+	+	+	+	+	Homozygous	G320V
JH6-205	Greece	2	25	32	2,500	100	+	+	+	+	+	+	Homozygous	G320V
JH7-201	Greece	3	20	21	NA	100	+	–	+	–	–	NA	Homozygous	G320V
JH8-202	Greece	1	26	33	5,900	98	+	–	+	–	–	+	Homozygous	C361fsX366
JH9-201	Greece	2	28	33	1,125	80	+	+	–	+	–	+	Homozygous	G99V
JH10-201	Greece	1	21	25	5,250	100	+	–	–	–	–	+	Homozygous	G320V
JH11-201	Greece	1	33	37	731	100	–	–	+	–	–	–	Compound heterozygous	G320V, R326X
JH12-201	Greece	1	29	31	2,254	100	+	–	–	–	–	NA	Homozygous	G320V
JH13-301	France	1	16	23	7,125	83	+	+	+	+	+	+	Homozygous	G320V

Papanikolaou, Nat Genet 2004

Surcharges en fer

	HFE1	HFE2 A	HFE2 B	HFE3	HFE4
Gène	HFE	Hémojuvéline	Hepcidine	Récepteur 2 Tf	Ferroportine
Chr.	6p21.3	1q21	19q13	7q22	2q32
Mutation	C282Y, H63D	G320V		E60X,Y250X,M172K	V163del
Rôle	Int. rTfR1	Reg hepcidine	Internal. Ferroportine	Captation hépatique	Captation Intestinale
Hepcidine	diminution	diminution	diminution	diminution	augmentation
Transm.	AR	AR	AR	AR	AD
Cible	foie, gl. Endoc, cœur	foie gl. Endoc, cœur	foie gl. Endoc, cœur	foie gl. Endoc, cœur	SRE
Age des symptômes	40-50	20-30	20-30	40-50	40-50