aHUS
To stop or not to stop eculizumab?

Proposals issuing from the

April 26, 2013 meeting of the French Study Group for aHUS and C3G

F. Fakhouri, C.Loirat and V.Fremeaux-Bacchi, February 1, 2014

Reason to question life-long eculizumab treament

Nobody knows the new natural history of patients who have preserved renal function under eculizumab : what will be their course following eculizumab withdrawal?

Current proposals take into account

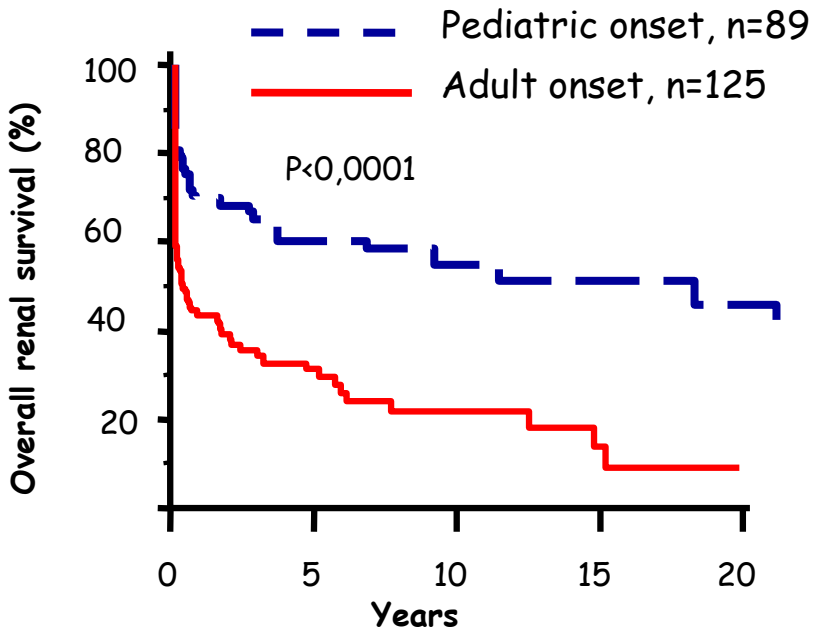
- Prognosis according to age at onset
- Phenotype-genotype correlations
- The risk of relapses according to age at onset, genetic background and time since onset
- The role of infections as triggers of relapses in children
- The risk of meningococcal infection under eculizumab

Prognosis of aHUS according to age at onset and genotype

French Cohort, Pre-eculizumab era

Renal outcome is better but mortality higher in children than in adults

French cohort, pre-eculizumab era, 214 patients



Number of aHUS patients at risk

Pediatric onset	89	34	17	13	6
Adult onset	125	18	7	2	0

Mortality: 8% in children, 2% in adults

End stage renal failure or death

	Children	Adults
First episode	16%	46%
1 yr f-up	29%	56%
5 yrs f-up	36%	64%

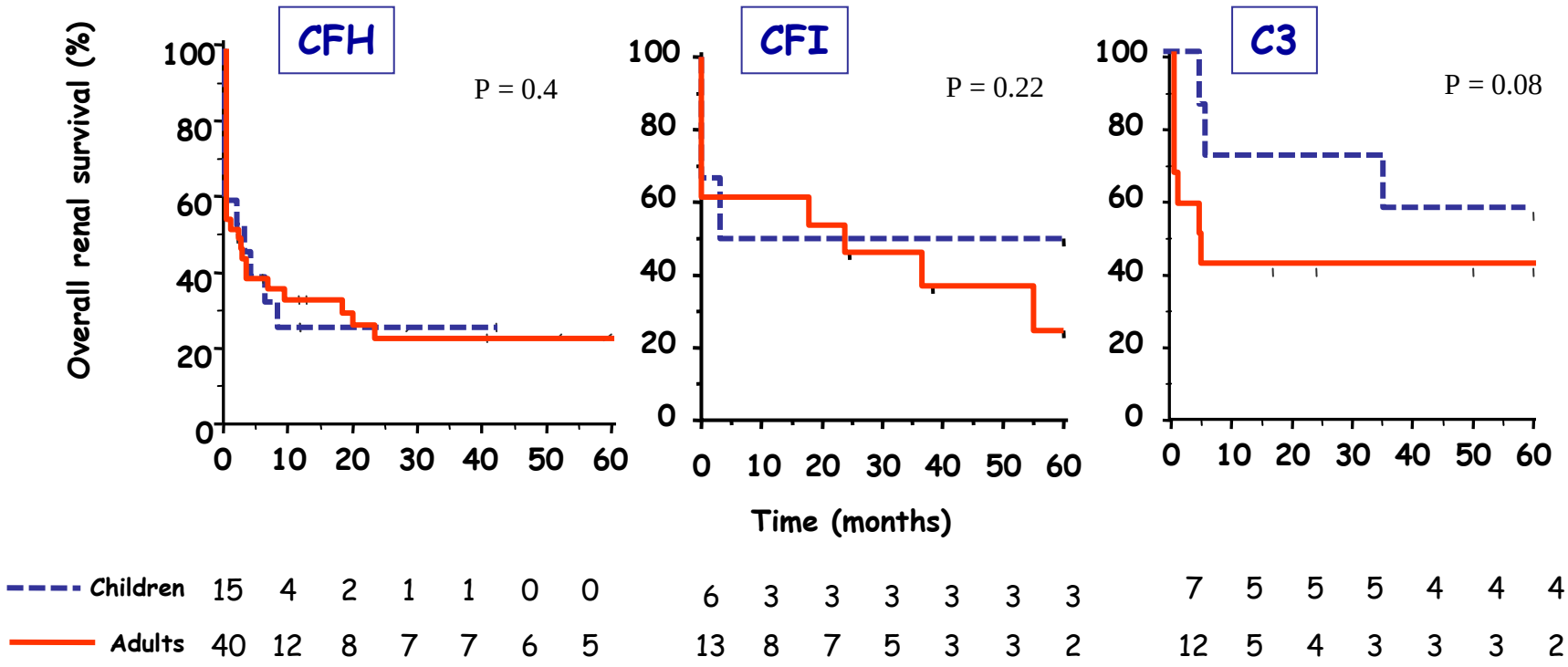
39% of children and 80% of adults received plasma exchanges (PE)/ plasma infusions (PI) at first episode

Fremeaux-Bacchi *et al, CJASN 2013*

Prognosis according to age at onset and genotype

French cohort, pre-eculizumab

- **Whatever the age at onset, CFH-HUS have a catastrophic prognosis**
- **Prognosis of CFI-HUS and C3-HUS is slightly less severe, without significant differences between adults and children**

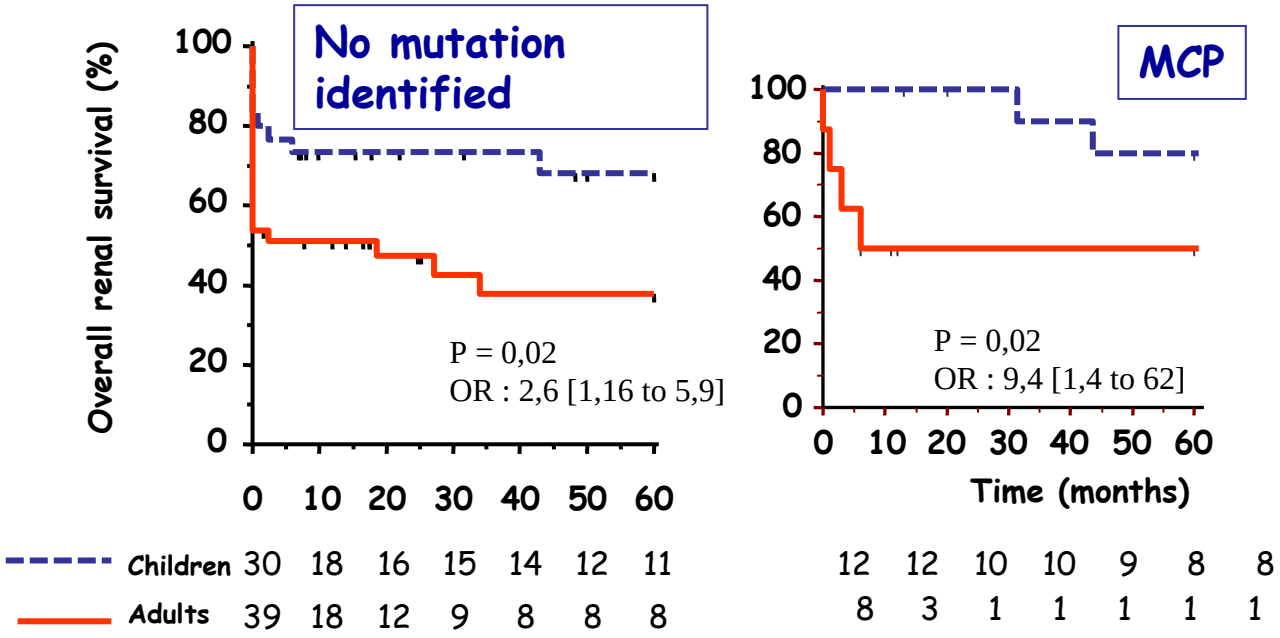


Fremeaux-Bacchi et al, CJASN 2013

Prognosis according to age at onset and genotype

French cohort, pre-eculizumab

- **In adults, prognosis of MCP-HUS and HUS with no mutation identified is as poor as that of CFH/CFI/C3-HUS**
- **In children, HUS with no mutation identified has a more favourable prognosis**
- **MCP-HUS with pediatric onset has the best prognosis (25% of ESRD at median follow-up 17.8 years)**



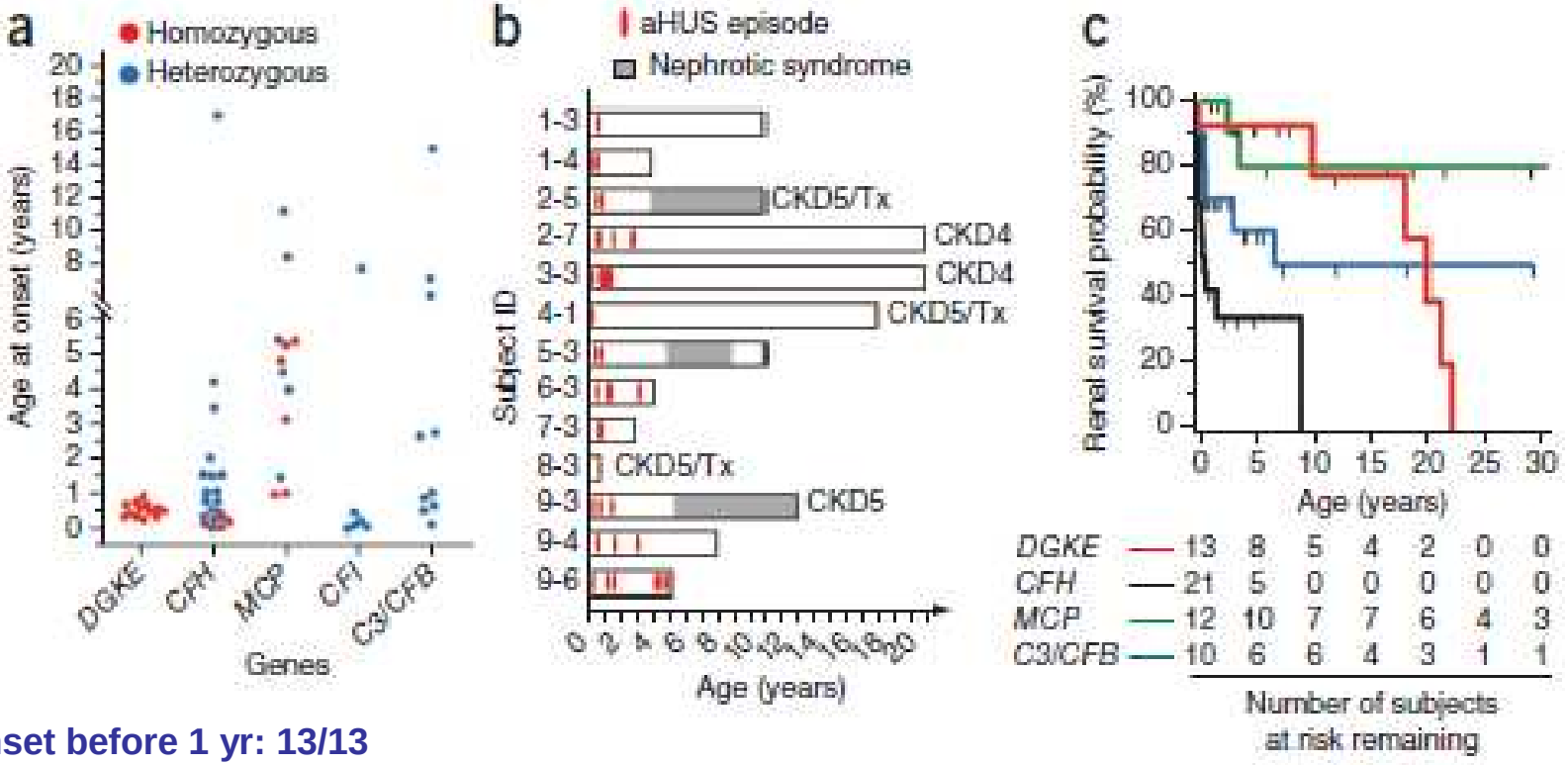
Fremeaux-Bacchi et al, CJASN 2013

But all HUS are not complement-dependent…

The new gene: recessive *DGKE* mutations cause aHUS and appear to have a low risk of post-transplant recurrence

DGKE encodes diacylglycerol kinase ε (lipid kinases family) expressed in endothelium, platelets and podocytes

13 children with sporadic (6 pedigrees) or familial (3 pedigrees, 2–3 siblings) aHUS



- **Onset before 1 yr: 13/13**
- DGKE mutations explain 27% (13/49) of aHUS presenting in the first year of life
- Relapses during the 5 1st years
- HT, proteinuria ± NS, hematuria → CKD grade 4/5 between 20 and 25 yrs
- **Uncertain efficacy of eculizumab (7 cases)**
- **No post-transplant recurrence (3 cases)**

Lemaire, Fremeaux-Bacchi *et al*. *Nature Genetics* 2013

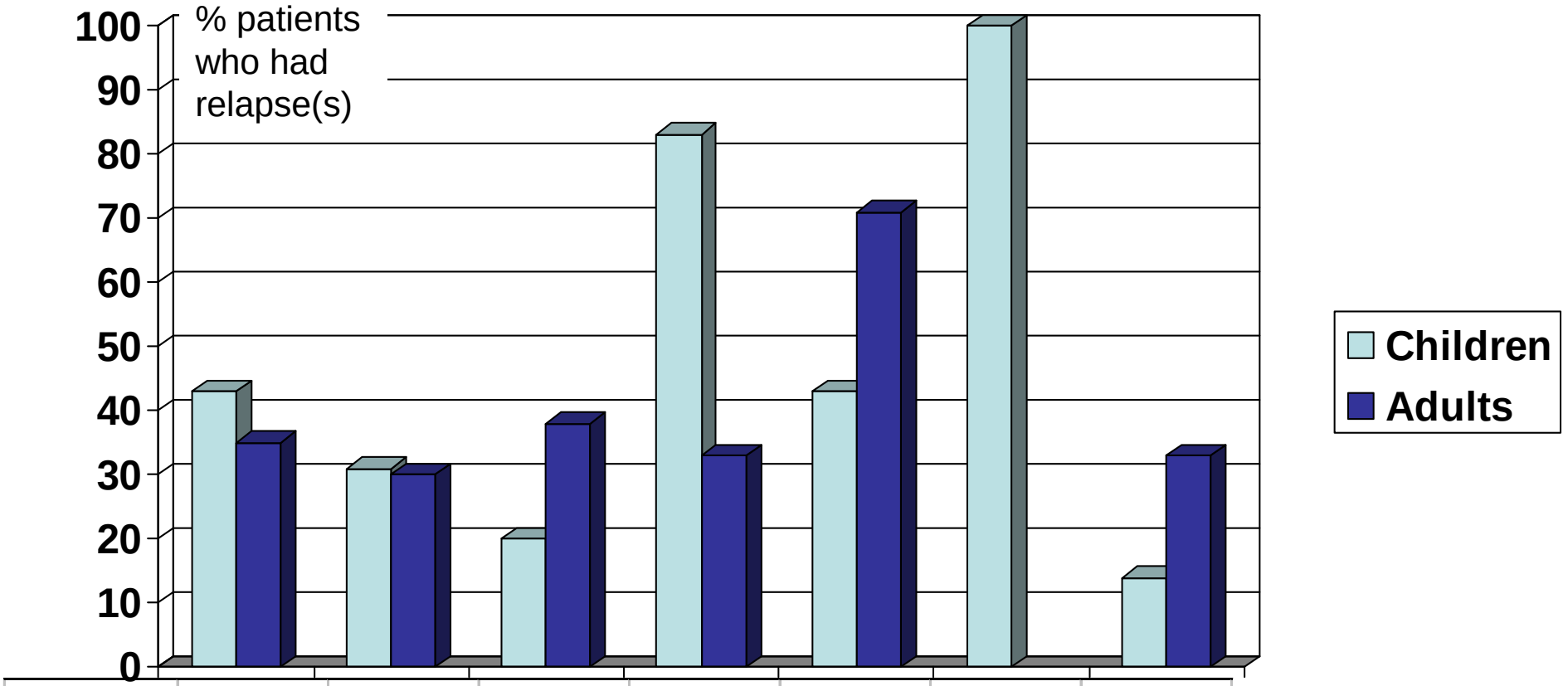
The risk of relapses in patients surviving the first episode without ESRD

French cohort, pre-eculizumab
214 patients (89 children, 125 adults)

V.Fremeaux-Bacchi et al, CJASN 2013, modified : 5 children classified in the article as « no mutation identified » and 1 child as CFB mutation are now known to have DGKe mutation. Therefore the risk of relapses has been re-analysed to take into account this new group.

aHUS is a relapsing disease

Among patients who had not died or reached ESRD at 1st episode, 43% (28/65) of children and 35% (23/66) of adults had relapses



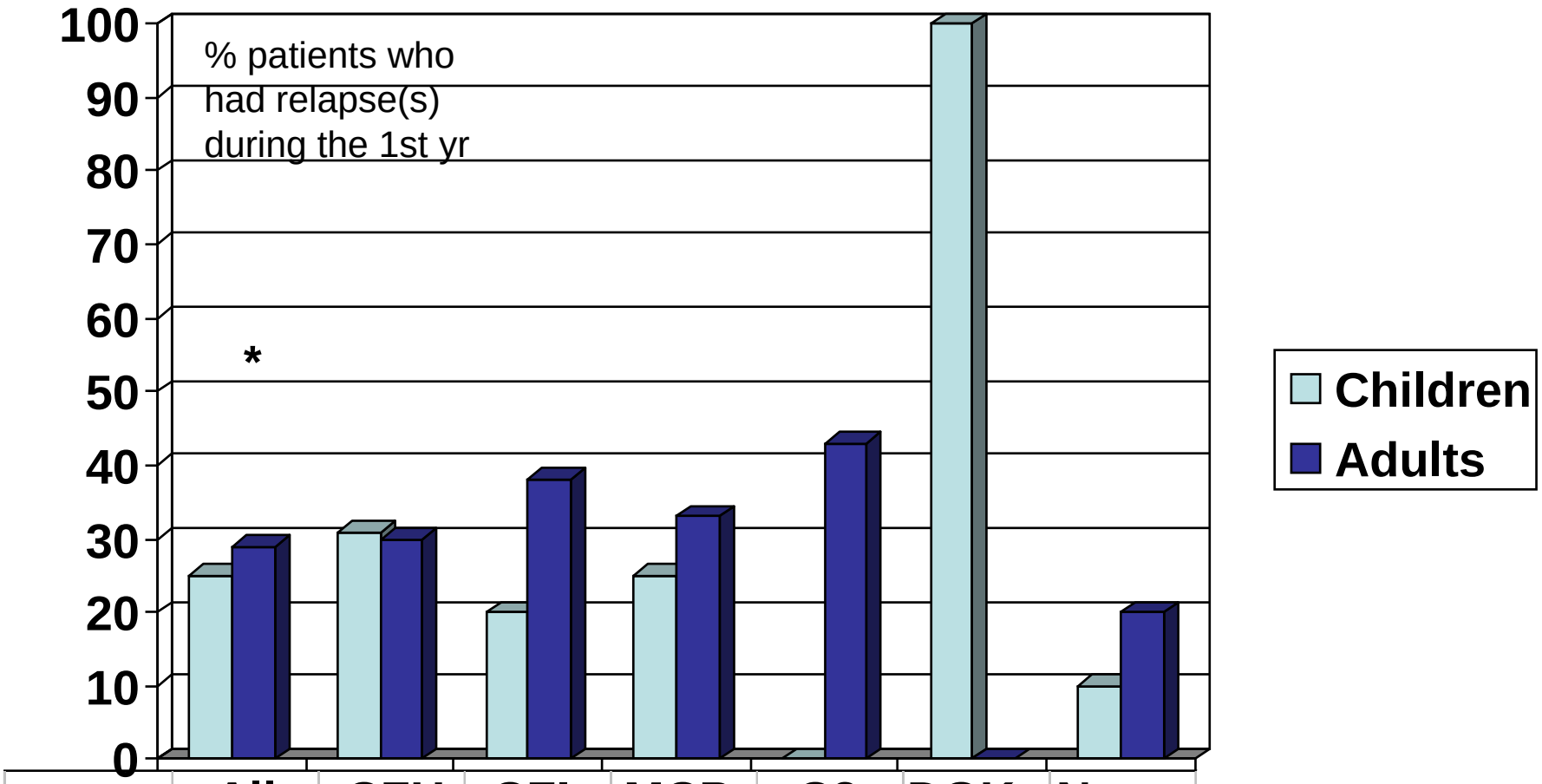
n	All	CFH	CFI	MCP*	C3	DGKe	None
Children	65	13	5	12	7	5	21
Adults	66	19	8	11	7	0	21

* Relapses in MCP-HUS:83% in children vs 33% in adults, p=0.03

Fremeaux-Bacchi et al, CJASN 2013; modified

The risk of relapse during the first year

Among patients who had not died or reached ESRD at 1st episode, 25% (16/65) of children and 29% (19/65 documented) of adults had relapses the 1st year

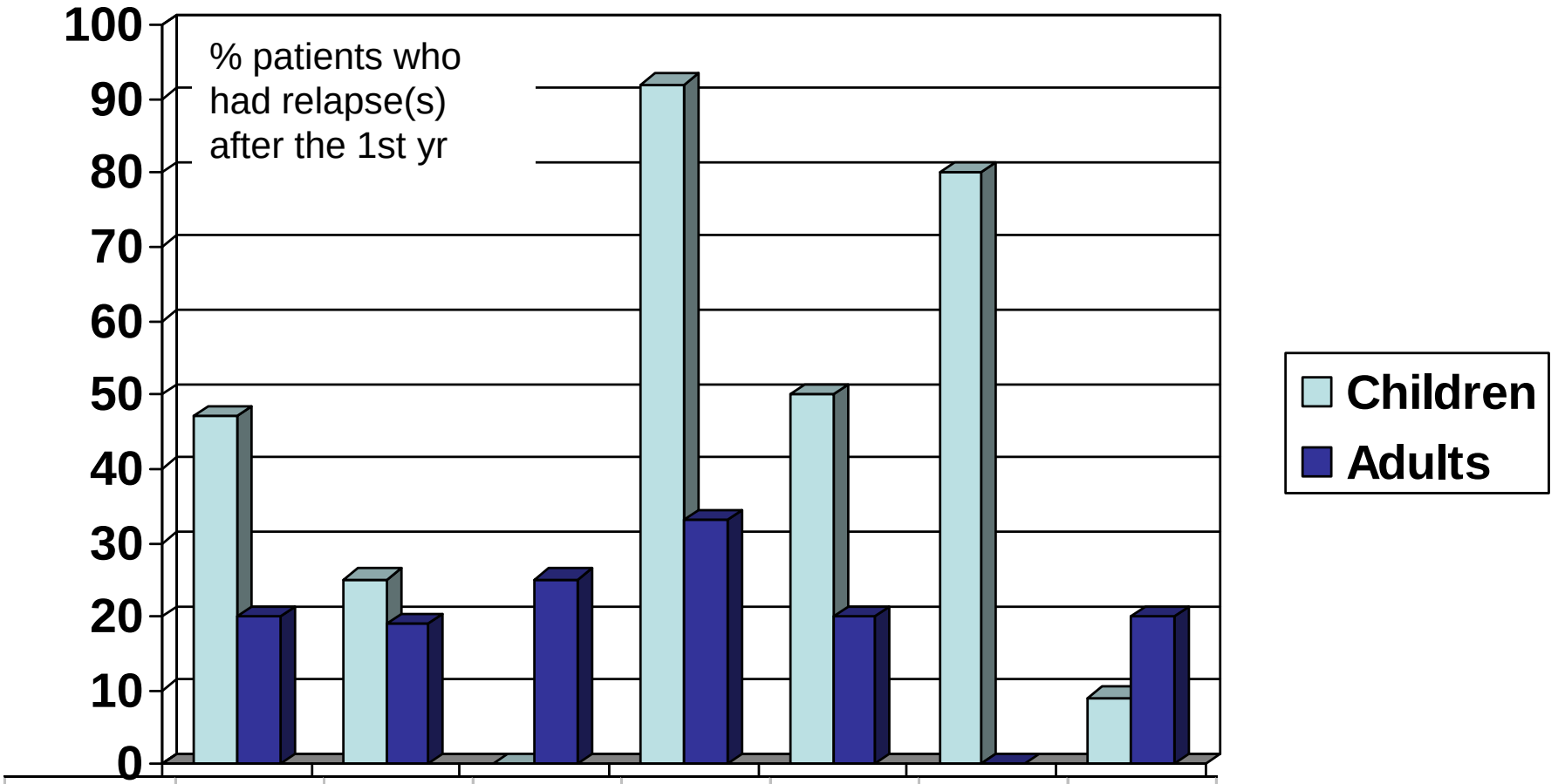


n	All	CFH	CFI	MCP	C3	DGKe	None
Children	65	13	5	12	7	5	21
Adults	66	19	8	11	7	0	21

Fremeaux-Bacchi et al, CJASN 2013, modified

The risk of relapse after the first year

Among patients who had not died or reached ESRD at 1st episode, 47% (25/53) of children and 20% (11/55) of adults had relapses after the 1st year, p= 0.002

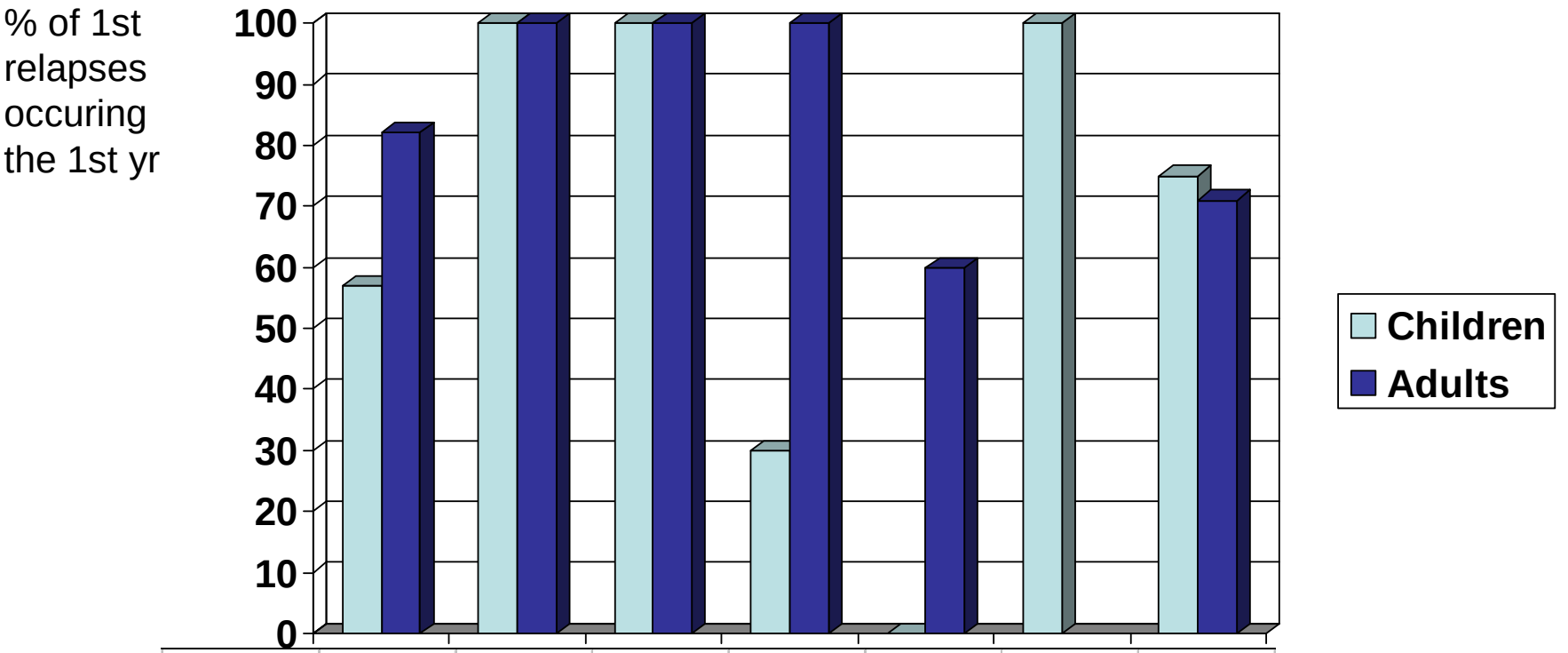


n	All	CFH	CFI	MCP	C3	DGKe	None
Children	53	8	3	12	4	5	18
Adults	55	16	8	3	5	0	20

Fremeaux-Bacchi et al, CJASN 2013, modified

Among relapsers, the high risk period for relapse is mostly the first year

82% (19/23) of 1st relapses in adults and 57%(16/28) in children occured during the 1st year, a high risk period except for MCP-HUS and C3-HUS in children

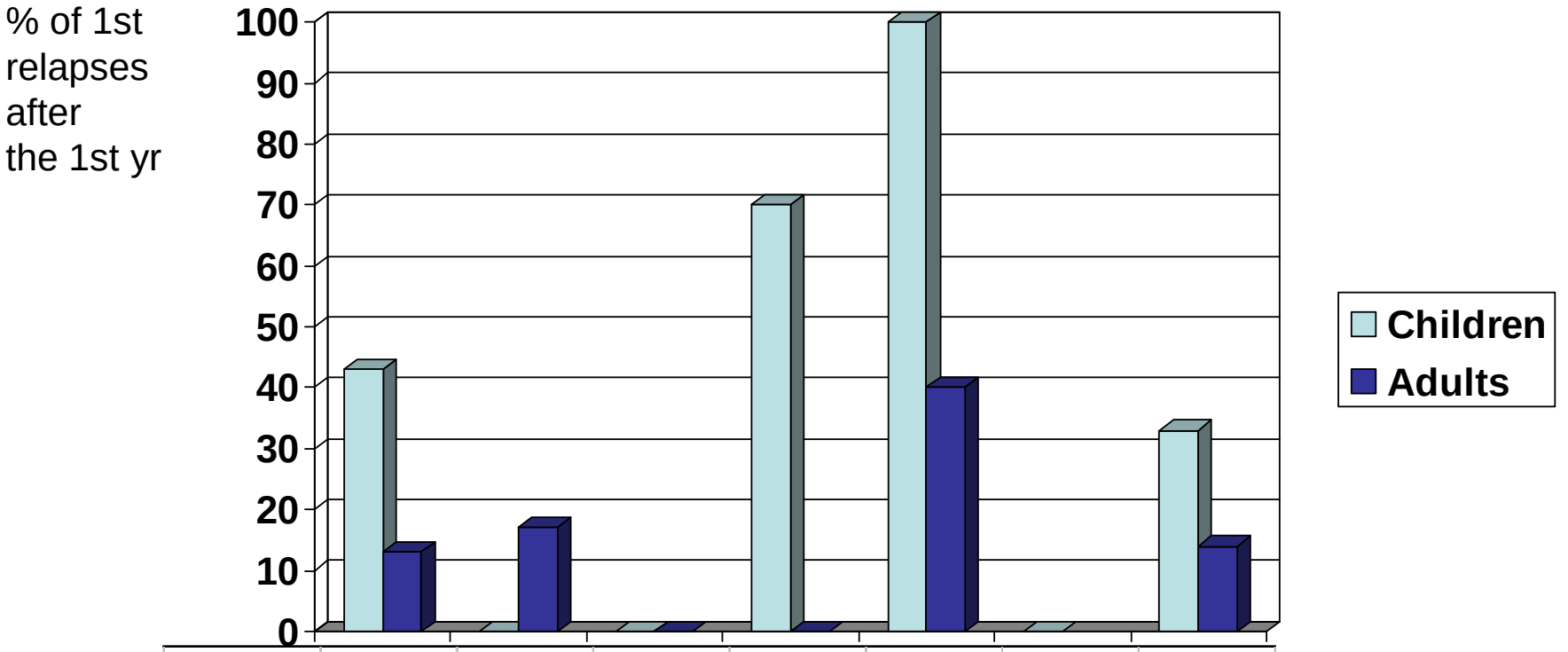


n	All	CFH	CFI	MCP	C3	DGKe	None
Children	28	4	1	10	3	5	3
Adults	23	6	3	2	5	0	7

Fremeaux-Bacchi et al, CJASN 2013, modified

Among relapsers, the risk of 1st relapse after the 1st year is < 20%, except in children with MCP/C3/no mutation-HUS and adults with C3-HUS

13% (3/23) of first relapses in adults and 43% (12/28) in children occured after the 1st yr



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Children	28	4	1	10	3	5	3
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Fremeaux-Bacchi et al, CJASN 2013, modified

The risk of invasive meningococcal infection is one of the reasons to question life-long maintenance of eculizumab

Invasive meningococcal infections (meningitis) in aHUS patients treated with eculizumab

Invasive meningococcal infection reported in

-**Two patients** (transplanted; CFH mutation;17 and 19 y; vaccinated; no antibioprophylaxis) **treated outside of protocoles (out of approximately 65)** (Davin, *AJKD 2010* and *Bouts, Pediatr Nephrol 2011*; Struijik, *AJT 2013*)

-**Two patients in trial C10-004 (out of 100 patients treated within trials)** (Fakhouri *et al, ASN, FR-OR057, Nov 8, 2013)*

-**First case in France**, April 2013, Pau-Bordeaux: young woman;HUS on native kidneys; CFH mutation; vaccinated and on prophylactic methyl-penicilline (penicilline resistant meningococcus)

→ Favourable outcome in all

Obligatory anti-meningococcal vaccine

- Conjugate tetravalent vaccines against serogroups A, C, W135 and Y
- **Anti-B vaccine (Bexsero) available in France since Dec 11, 2013 must now be associated**

Continuous antibioprophylaxis obligatory in France

- Oral methyl penicillin (full dose, twice daily) (resistance not exceptionnal)

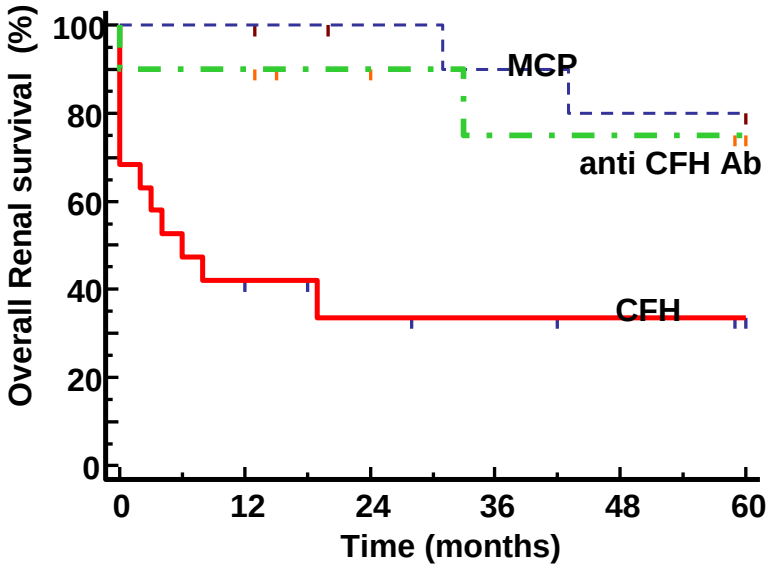
- **Repeated information** to the patient, his family and family doctor
- **Information card**

Proposals for children (< 18years)

The specific problem of anti-CFH antibody-associated HUS

aHUS with anti-CFH Ab

Favorable outcome if treated early (PE+steroids+immunosuppressive trt) French pediatric cases



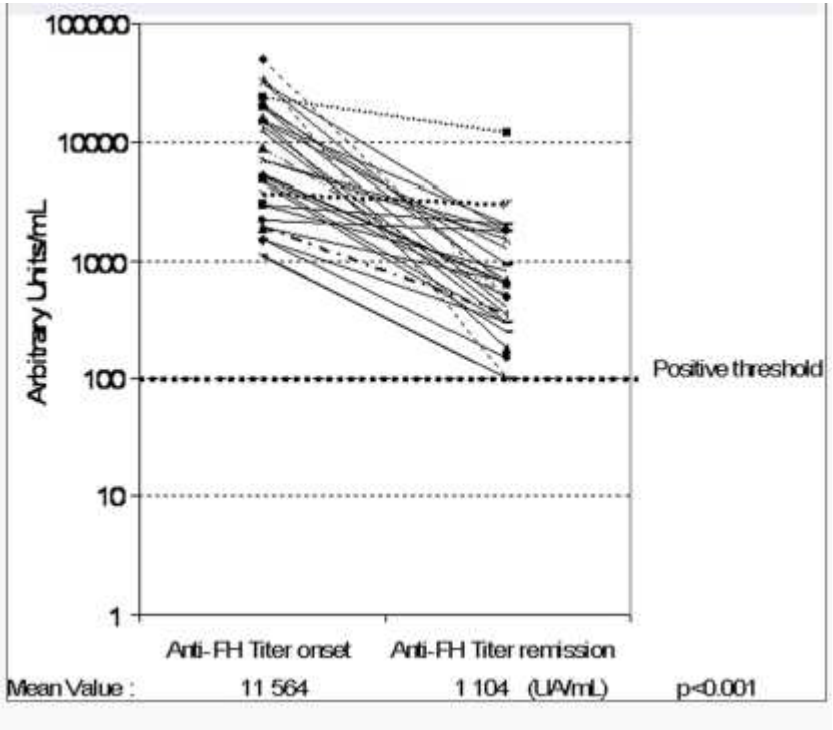
Number of aHUS patients

CFH	19	6	4	3	2	1
MCP	12	12	10	9	8	8
Anti CFH Ab	10	9	6	5	5	4

MCP vs anti CFH Ab (p=0.6)
CFH vs anti CFH Ab (p=0.02; OR : 3.7 [1.2 -11])
CFH vs MCP (p=0.002; OR : 5.8 [1.8 -18])

Fremeaux-Bacchi *et al, CJASN 2013*

Monitoring of anti-CFH Ab should guide treatment tapering



Dragon-Durey *et al, JASN 2010*

Anti-CFH antibody-associated HUS
Benefit from early PE+ immunosuppression with subsequent maintenance immunosuppression

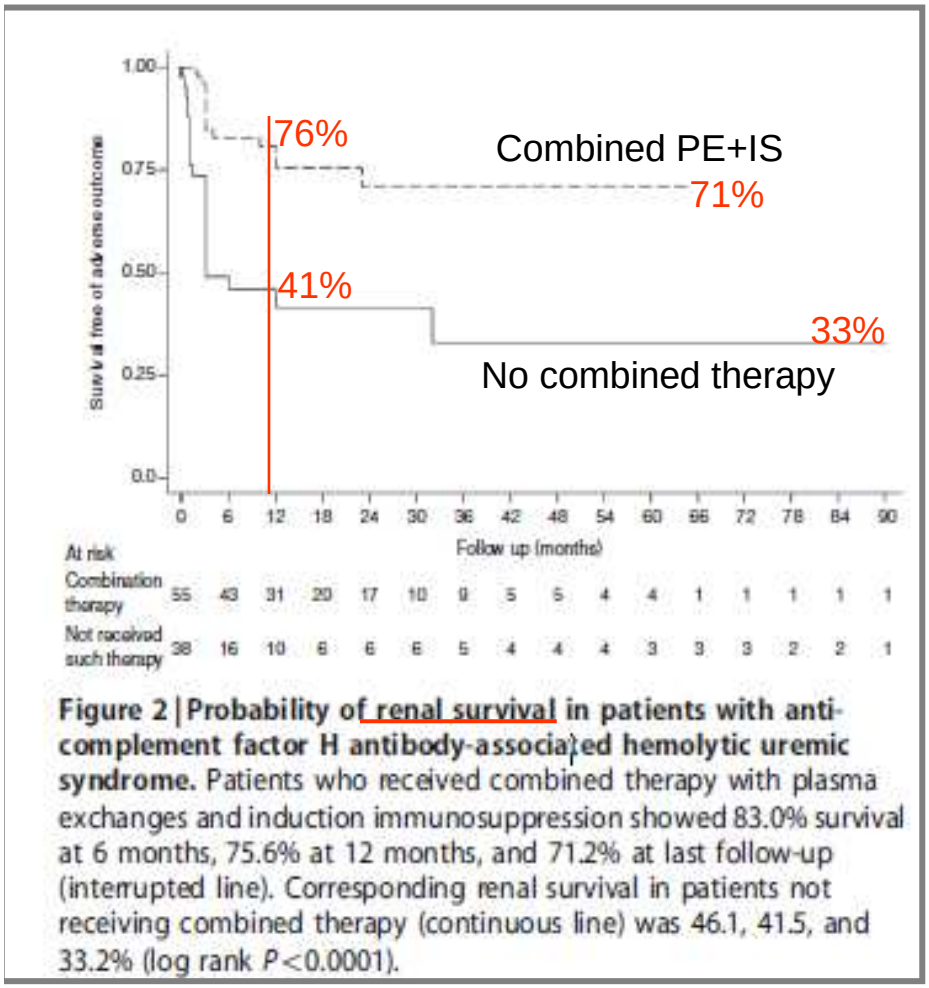


Figure 2 | Probability of renal survival in patients with anti-complement factor H antibody-associated hemolytic uremic syndrome. Patients who received combined therapy with plasma exchanges and induction immunosuppression showed 83.0% survival at 6 months, 75.6% at 12 months, and 71.2% at last follow-up (interrupted line). Corresponding renal survival in patients not receiving combined therapy (continuous line) was 46.1, 41.5, and 33.2% (log rank $P<0.0001$).

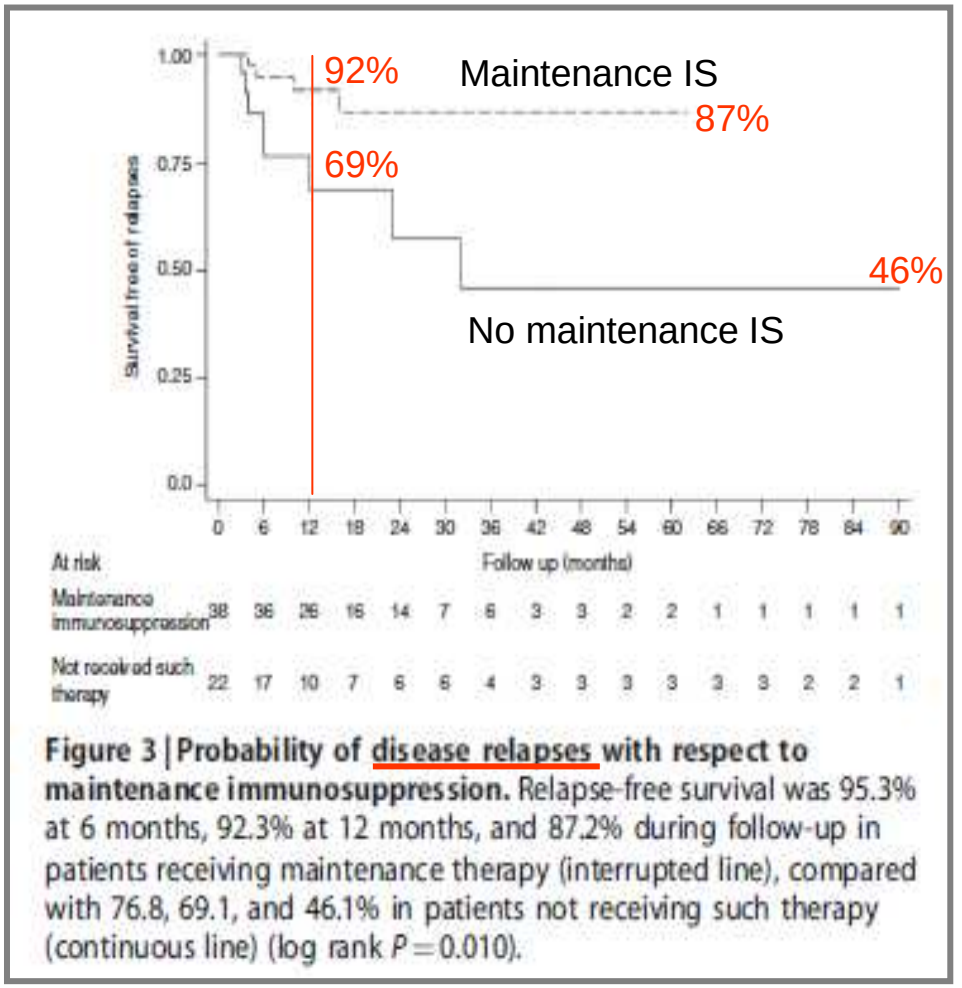
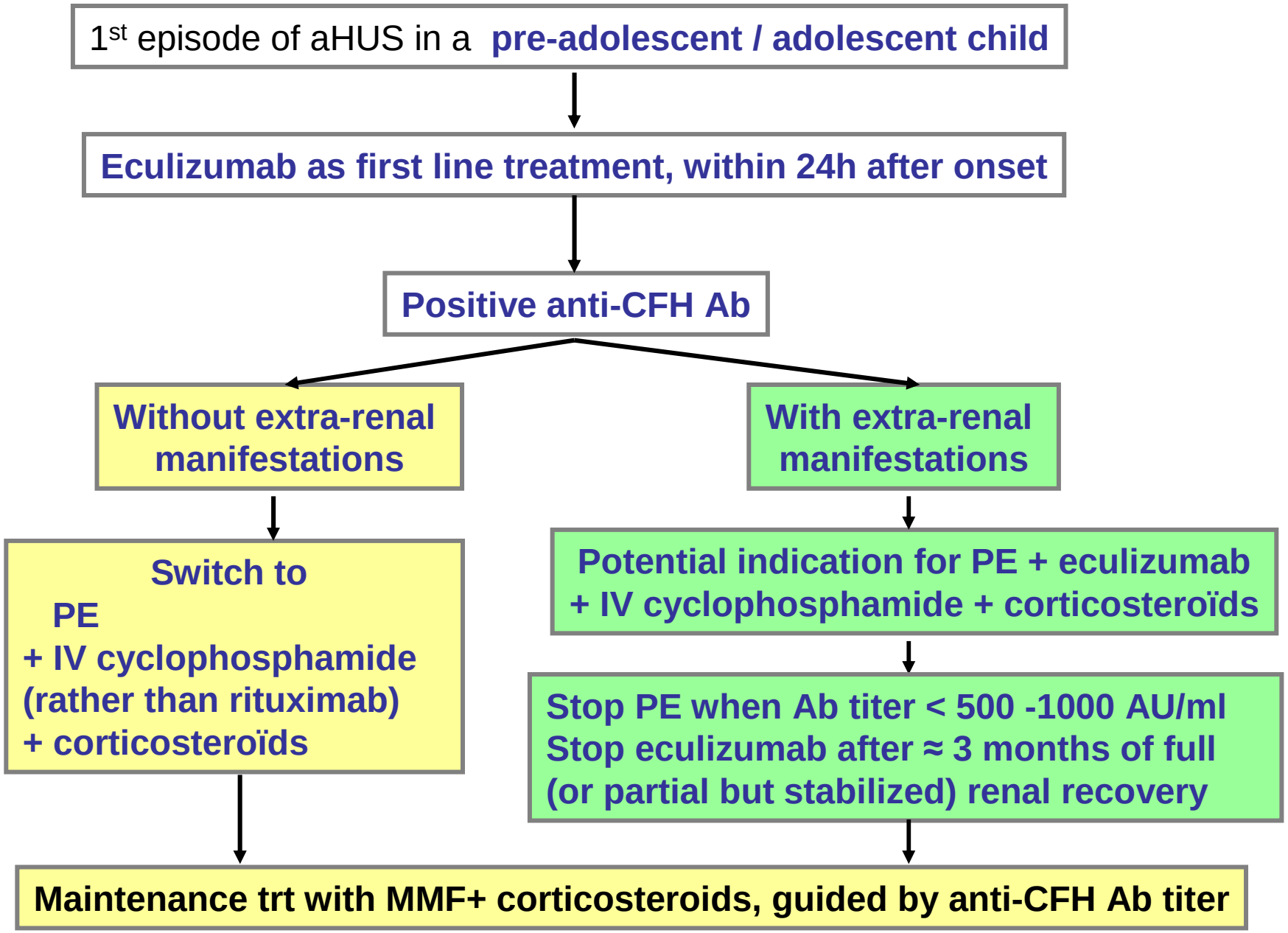


Figure 3 | Probability of disease relapses with respect to maintenance immunosuppression. Relapse-free survival was 95.3% at 6 months, 92.3% at 12 months, and 87.2% during follow-up in patients receiving maintenance therapy (interrupted line), compared with 76.8, 69.1, and 46.1% in patients not receiving such therapy (continuous line) (log rank $P=0.010$).

Sinha *et al, KI 2013*

Which treatment for aHUS with anti-CFH antibodies?



Criteria required for considering withdrawal of eculizumab in children

(anti-CFH antibody-HUS excluded)

Principle: Eculizumab withdrawal will not be consider in children who have not recovered normal GFR under eculizumab, to avoid any additional loss of GFR in case of relapse

Criteria required for considering eculizumab withdrawal in children

➢ **Clinical remission: no** manifestations of micro or macro-vascular TMA, such as
- cerebro-vascular events or other neurologic manitfestations
- ischemic cardiac events or cardiomyopathy
- peripheric/distal ischemic manifestations
- pulmonary arterial hypertension
- pancreatitis…

AND

➢ **Full hematologic remission:**
- Hemoglobin ≥ 11g/dl
- LDH ≤ ULN
- Schizocytes< 1%
- Haptoglobin ≥ LLN
- Plaquettes ≥150 000/mm3

AND

➢ **FULL renal recovery:**
- eGFR ≥ 90 ml/min/1.73 m2
- Normal U prot/creat (≤ 0.02 g/mmol ou 0.20 g/g) or at least negative urine stick
- Normal BP under ≤1 anti-HT drug
- No microscopic hematuria (< 10 000 RBC/ml)

Genetics is essential for the decision of eculizumab withdrawal in children

Timing for eculizumab withdrawal in children treated for a first episode of aHUS on native kidneys

1. Isolated MCP mutation associated - HUS

First episode
Evolution generally favourable after each episode and low risk of ESRD despite relapses

→ **Stop eculizumab after 3 months of full remission + full renal recovery under eculizumab**

•Immediate reinitiation of eculizumab (delay < 24h),
•Investigate for immune deficiency

Early relapse (≤ 1 year after eculizumab withdrawal)

→ **Stop eculizumab after 6 months of full remission +full renal recovery under eculizumab**

•Immediate reinitiation of eculizumab (delay < 24h)

Late relapse (>1 year after eculizumab withdrawal)

→ **Stop eculizumab after 3 months of full remission + full renal recovery under eculizumab**

Timing for eculizumab withdrawal in children treated for the first episode of aHUS on native kidneys

2. HUS other than MCP-HUS

Mutation with high risk of ESRD in case of relapse

- CFH mutation, CFH/CFHR1 recombination/hybrid CFH
- C3 or CFB gain of function mutation
- Combined mutations
- CFI mutation

→ **Stop eculizumab**

- **Not before the end of 3rd year of life (3rd birthday)**

AND

- **After 2 years of full remission and full renal recovery under eculizumab**

Other situations

- Rare variant
- No mutation identified

→ **Stop eculizumab**

- **After 1 year of full remission and full renal recovery under eculizumab**

Eculizumab withdrawal in adults

Timing for eculizumab withdrawal in adults treated for the first episode of aHUS on native kidneys

Stop eculizumab

- **After 1 year of full remission and full renal recovery under eculizumab or partial recovery with no TMA biological features and/or lesions on renal biopsy**

Points common to adults and children

Biological monitoring after eculizumab withdrawal

Which biological monitoring

BCC, schizocytes, haptoglobin, LDH, creatinine

Education of the patient for urine dipstick for protein and hemoglobin (or urinary protein/creatinine ratio and RBC count on urine sample

Frequency after eculizumab withdrawal

-1/ week during the first month (+ urine dipstick 2/week)

-1/ 2weeks from M2 to M6 (+ urine dipstick 2/week)

-1/month after M6 (+ weekly urine dipstick)

Intensified monitoring in case of infection, vaccination,surgery, traumatism :

2/week 1st week, then 1/week x 3 weeks

NB: monitoring schedule to be potentially modified according to additional information about the delay of occurrence of relapses in patients who stopped treatment

Reasons to re-initiate eculizumab

- Complete triad of HUS
- Incomplete triad of HUS

→ Reinitiation within 12-24 h

- Signs of sub clinical TMA:

  Normal Hb, platelet count and creatinine level but

  - LDH >ULN
  - Haptoglobin < LLN
  - Isolated proteinuria / hematuria / HT → renal biopsy to confirm TMA lesions and eculizumab reinitiation
- Any extra-renal manifestation of TMA

  → Reinitiation after confirmation

Another circumstance for eculizumab withdrawal: resistance to treatment

Definition of resistance = Symptoms/signs of ongoing TMA despite complement blockade

- **Despite doses/intervals allowing complete and permanent complement blockade** (monthly controls) as suggested by
  - Trough CH50 < 10% (according to technique)
  - Trough free eculizumab level >150ug/ml

- **Ongoing TMA defined by**
  - Persistance or relapse of hemolysis (LDH>ULN, Hb<10g/dl, hapto < LLN, ±schizo>1%)
  - and /or persistance or relapse of thrombocytopenia < 150.000/mm3
  - and/or persistance or appearance of proteinuria (U protein/creat >0.02-0.20 g/mm (mild-moderate) or ≥0.20 g/mm (important)) and /or hematuria >200 000 RBC/ml, and/or no improvement of GFR with active TMA lesions at renal biopsy (double contours ± arteriolar thrombi arteriolaires

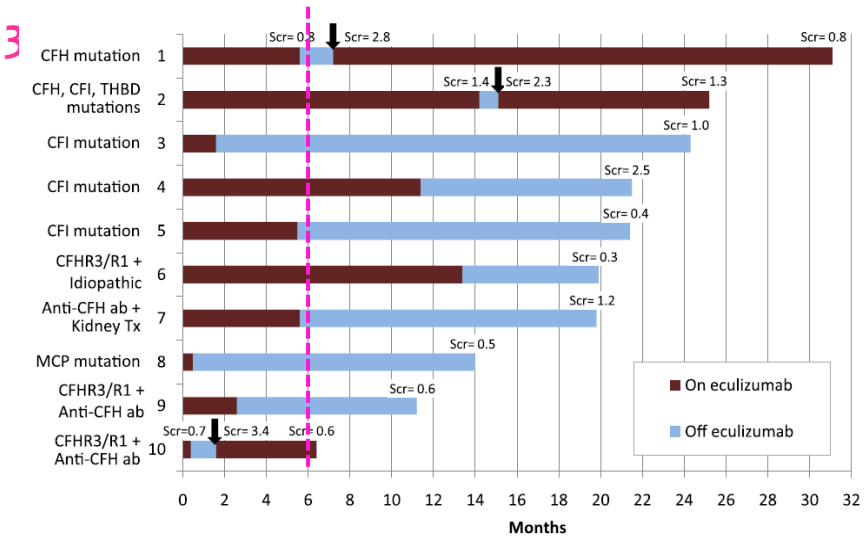
- **A fortiori if DGKe mutation identified**

Discontinuation of Eculizumab Maintenance Treatment for Atypical Hemolytic Uremic Syndrome: A Report of 10 Cases

Ardissino, AJKD 2013

Table 1. Patients' Baseline Characteristics and Biomarkers of TMA Activity Before Eculizumab Discontinuation and at Last Available Observation

Patient No.	Age at aHUS Onset (y)	Sex	Complement Abnormality[a]	Relapse	Time Since Start of Eculizumab (mo)	Duration of Eculizumab Discontinuation (mo)	Scr (eGFR[b])		Platelet Count (10^3/μL)		LDH (IU/L)		Haptoglobin (mg/dL)		UPCR (mg/mg)	
							T1	T2	T1	T2	T1	T2	T1	T2	T1	T2
1	4.3	M	CFH (p.Ser1191Leu)	Yes	31.0	1.5	0.92 (49)	0.80 (58)	334	290	367	206	97	103	0.67	0.17
2	37.7	F	CFH (p.Arg1210Cys) + CFI (p.Asp519Asn) + THBD (p.Ala43Thr)	Yes	25.2	0.9	1.41 (44)	1.25 (51)	244	227	482	219	117	94	1.53	0.96
3	52.7	M	CFI (p.Ile140Thr)	No	24.3	22.7	1.03 (97)	1.00 (100)	180	256	467	371	312	292	NA	0.08
4	34.8	F	CFI (p.Gly269Ser)	No	21.5	10.1	2.72 (29)	2.54 (22)	281	286	406	403	98	88	1.38	0.70
5	2.6	M	CFI (p.Asp519Asn)	No	21.4	15.9	0.38 (132)	0.44 (117)	261	299	517	426	68	105	0.35	0.24
6	1.3	F	Homozygous deletion at *CFHR3/R1* locus	No	19.9	6.5	0.29 (128)	0.27 (138)	447	390	688	654	91	60	3.46	2.32
7[c]	19.1	M	Anti-CFH antibody (titer, 27 IU)	No	19.8	14.2	1.33 (72)	1.20 (79)	245	167	390	325	236	178	0.14	0.08
8	5.4	F	MCP (p.Phe175Val)	No	14.0	13.5	1.28 (36)	0.52 (89)	300	420	682	423	46	78	3.21	0.20
9	13.3	M	Anti-CFH antibody (titer, 100 IU) + homozygous deletion at *CFHR3/R1* locus	No	11.2	8.6	0.64 (110)	0.58 (122)	268	298	435	371	108	106	0.22	0.19
10	10.9	F	CFH (p.Gln950His) + homozygous deletion at *CFHR3/R1* locus + anti-CFH antibody (titer 230 IU)	Yes	6.4	1.2	0.95 (73)	0.66 (105)	180	239	466	221	88	88	0.45	0.12



En France…

34 pts (E + Ad) : arrêt Ecu

5 rechutes (14%)

4 FH et 1 MCP