Centre Hospitalier Régional Universitaire de Lille

Actualités sur le SHU atypique

Dr François Provôt, Lille

cnr-mat

SFTS 2021 XXXe CONGRÈS MARSEILLE 24-26 novembre 2021 PALAIS DU PHARO

Conflits d'intérêts

Orateurs

Sanofi

Boards

Sanofi

Alexion

Boehringer-Ingelheim

Astellas

« Sanofi ne recommande en aucun cas l'usage des produits en dehors de leurs indications approuvées. Merci de consulter le résumé des caractéristiques du produit avant de le prescrire. Les informations ci-après sont fournies pour un usage médical et scientifique uniquement, et sont destinées exclusivement aux participants de cette manifestation scientifique. »

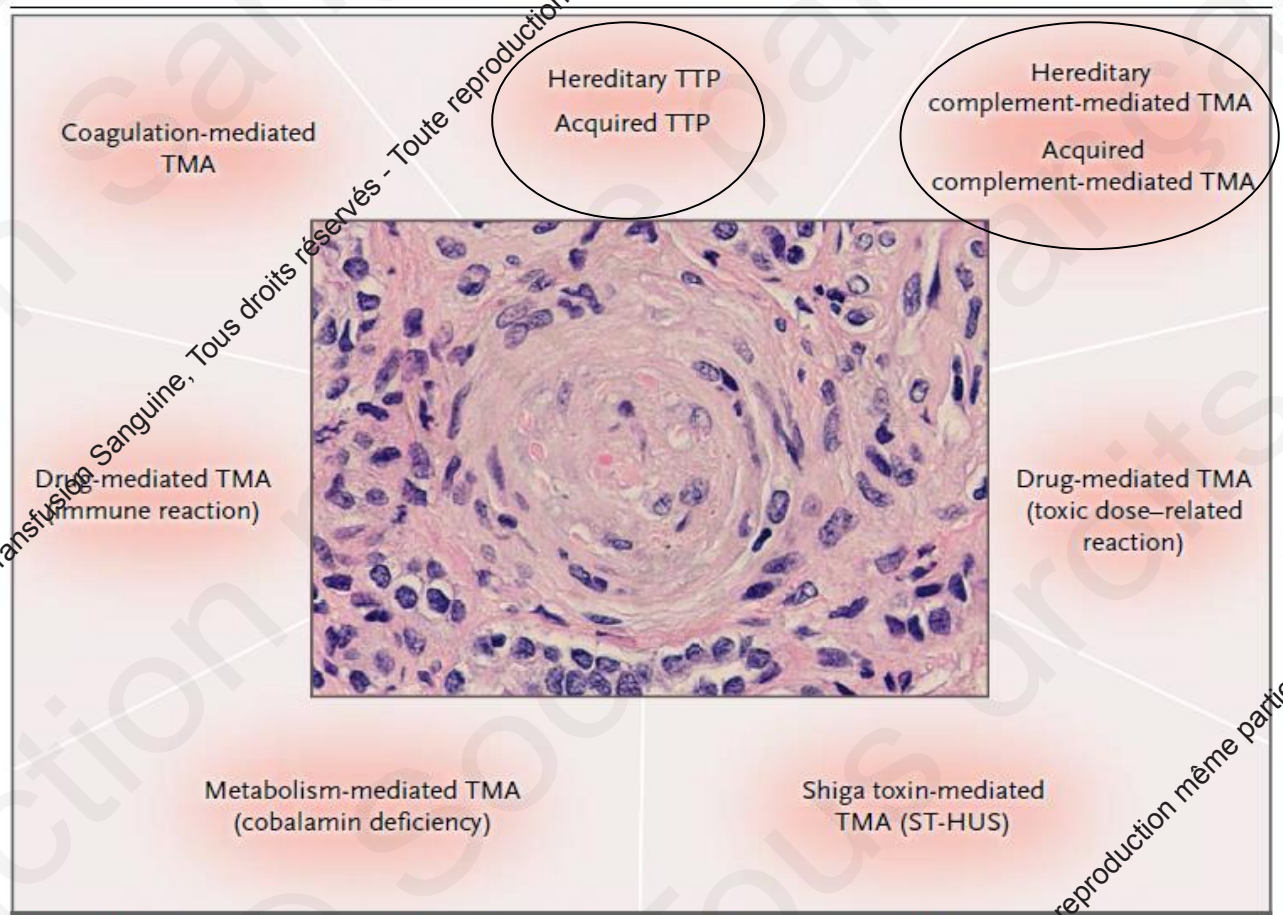
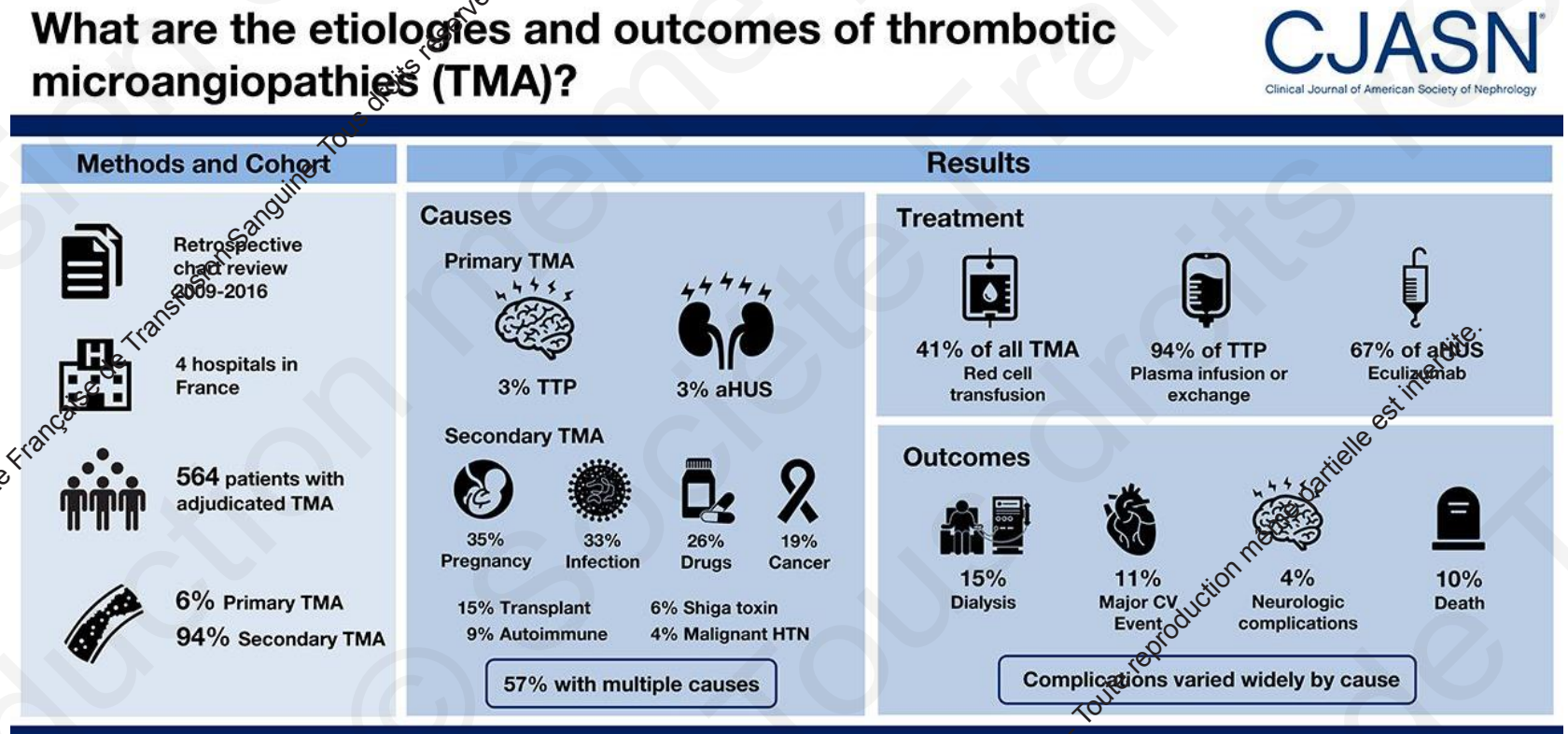


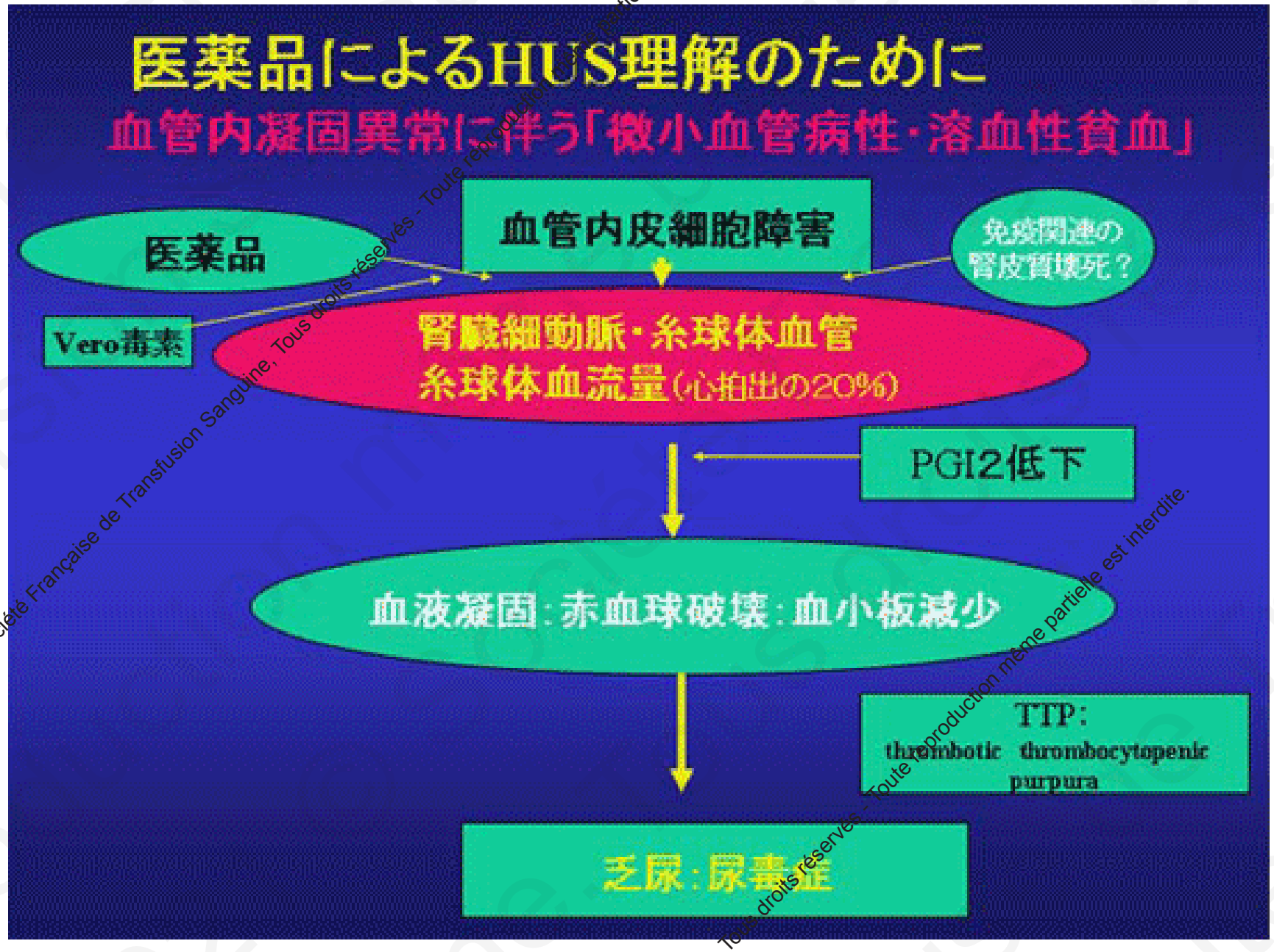
Figure 1. Pathological Features of the Nine Primary Thrombotic Microangiopathy (TMA) Syndromes.

For all primary TMA syndromes, the vascular pathological abnormalities that are observed in routine specimens are the same, as illustrated in the center of the figure by the renal arteriole occlusion with endotheliosis as well as lumen and vessel-wall fibrin. Proliferation in the myocyte layer ("onion skinning") is also present in this image. TTP denotes thrombotic thrombocytopenic purpura. (Courtesy of D.G. Holanda, Department of Pathology, University of Iowa.) Additional details are provided in an interactive graphic, available at NEJM.org.

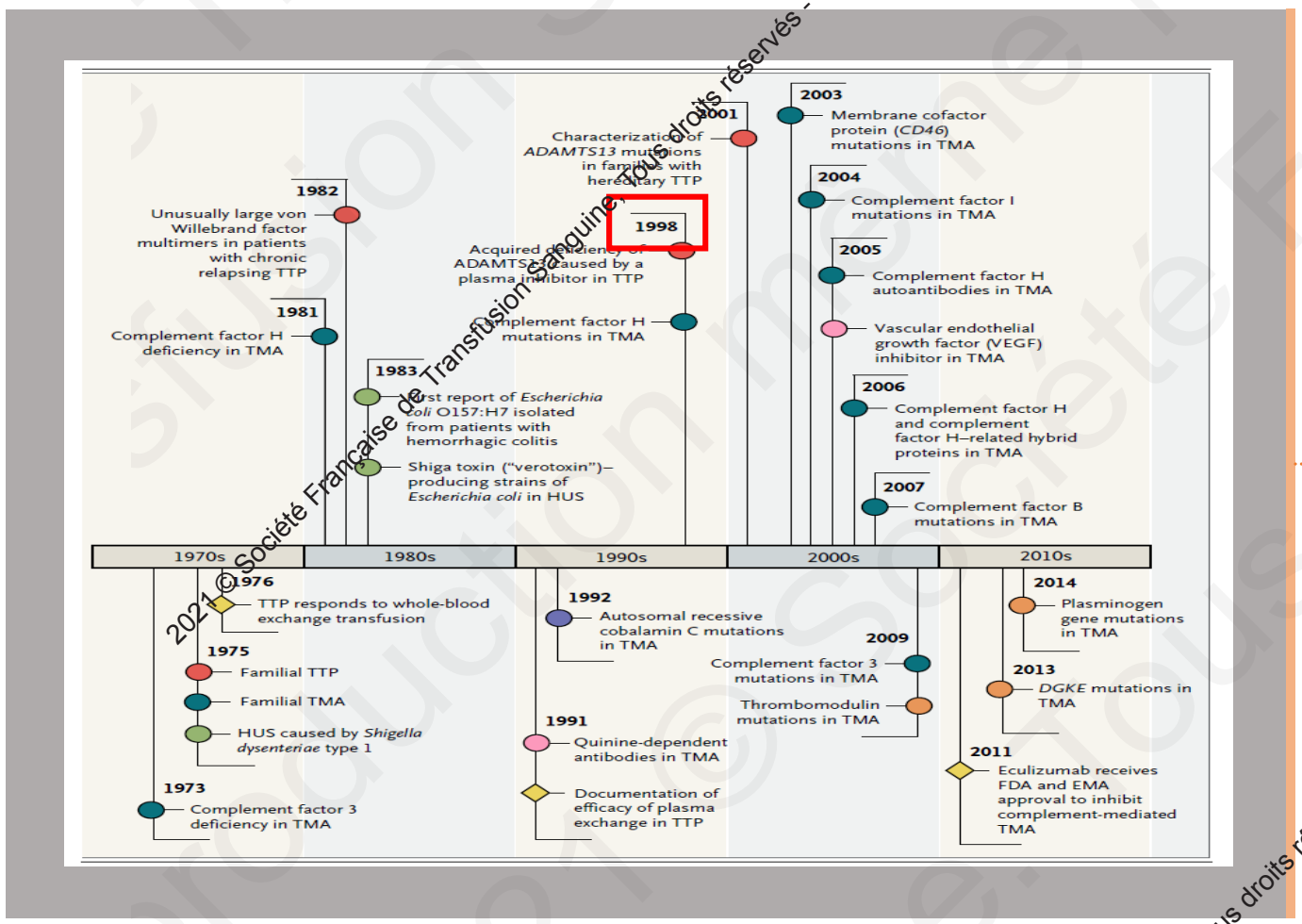
Etiologies des MAT



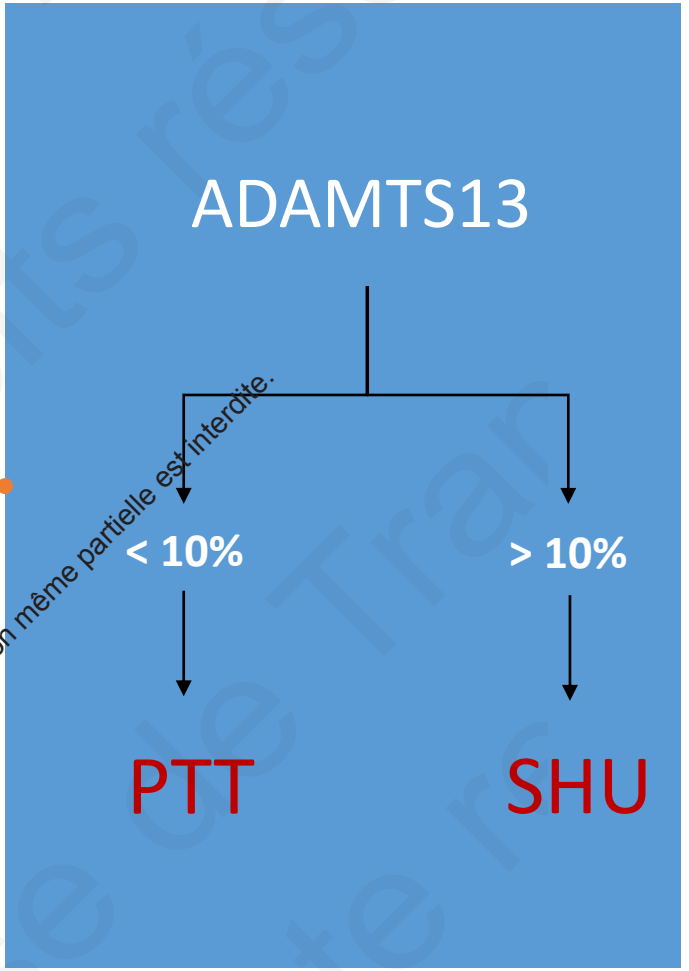
From Bayer G, et al. Clin J Am Soc Nephrol. 2019;14(4):557-566. ***Used with permission from The American Society of Nephrology.***
aHUS, atypical hemolytic and uremic syndrome; CV, cardiovascular; HTN, hypertension; TMA, thrombotic mictoangiopathy; TTP, thrombotic thrombocytopenic purpura.
Bayer G, et al. *Clin J Am Soc Nephrol.* 2019;14(4):557-566.



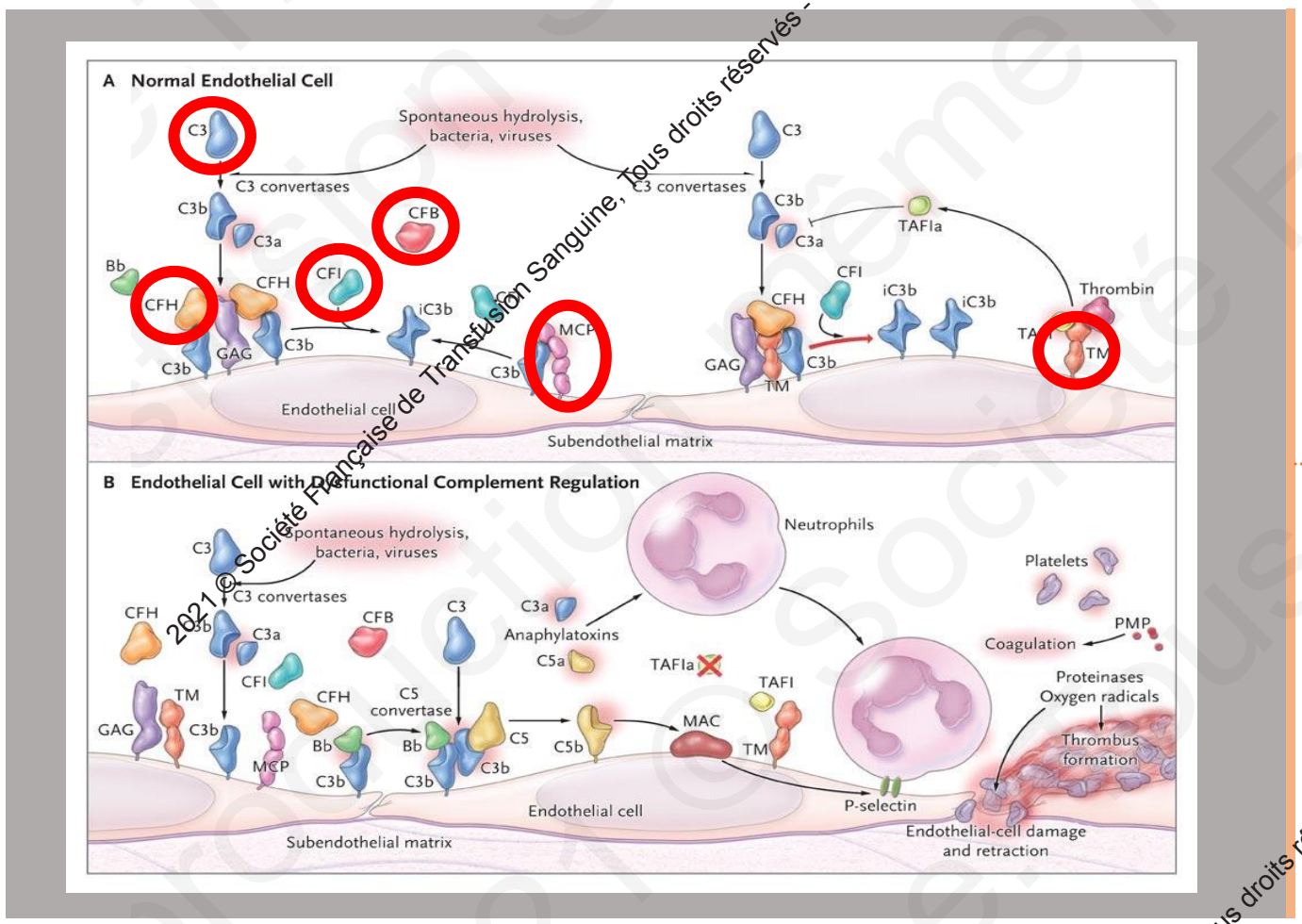
Découvertes Physiopathologiques dans les MAT

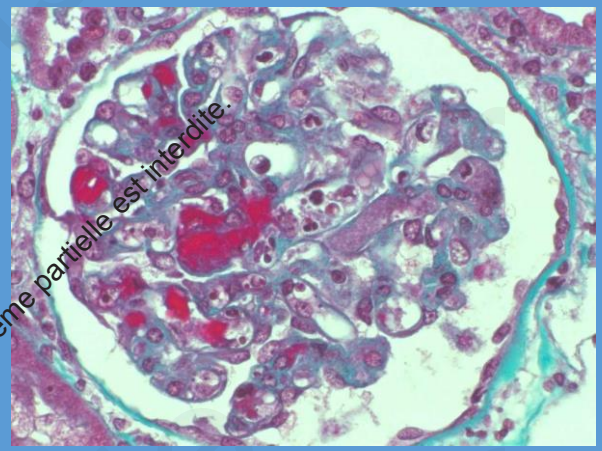


N ENGL J MED 371;7 NEJM.ORG AUGUST 14, 2014



Physiopathologiques du SHU atypique





Noris M, NEJM 2009

Registre Français SHU atypique

Table 1. Patients' characteristics at onset

Characteristic	Children	Adults	*P* Value
Patients (*n*)	89	125	
Female/male (*n*/*n*)	42/47	93/32	<0.001
Mean age at onset (yr)	1.5 (0 to <15)	31 (15–85)	
Familial HUS history, *n* (%)	24 (26.9)	18 (14.4)	0.02
Triggering events, *n* (%)	42 (47)	41 (33)	0.03
Diarrhea	35 (39)	19 (15)	<0.001
Respiratory infections	7 (8)	1 (1)	0.03
Pregnancy		18/93 females (19.3)	
Neurologic involvement, *n* (%)	14 (16)[a]	10 (8)	0.08
Mean serum creatinine (μmol/L)	257 (28–990) (*n*=82)	640 (111–2408) (*n*=113)	<0.001
Dialysis required, *n* (%)	48/81 (59)	93/115 (81)	<0.001
Platelets count, *n* (%)			
$> 150 \times 10^9$/L	12/81 (15)	15/93 (16)	0.78
$100–150 \times 10^9$/L	9/81 (11)	22/93 (24)	0.02
$50–99 \times 10^9$/L	26/81 (32)	31/93 (33)	0.84
$< 50 \times 10^9$/L	34/81 (42)	25/93 (27)	0.05
Mean hemoglobin (g/dl)	6.8 (3–12) (*n*=84)	7.2 (5–11.8) (*n*=93)	0.004
Hemoglobin > 10 g/dl, *n* (%)	5/84 (6)	10/93 (11)	0.16
Complete triad, *n* (%)[b]	60/81 (74)	77/93 (83)	0.11

Fakhouri F et al, Lancet 2017

Registre Français SHU atypique

Table 2. Genetic and acquired complement abnormalities in 200 families in which one member (sporadic form) or more than one member (familial form) met the criteria for atypical hemolytic uremic syndrome

aHUS	All Patients (n=214)	Familial Form[a] (n=28)	Sporadic Form (n=172)	P Value for Familial versus Sporadic Forms	Familial and Sporadic Forms (n=200)
Genetic/acquired abnormality					
CFH	59	10 (35.7)	45 (26.1)	0.27	54 (27.0)
MCP	20 (9.3)	4 (14.3)	15 (8.7)	0.36	20 (10.0)
CFI	18 (8.4)	0	18 (10.4)		18 (9.0)
C3	18 (8.4)	3 (10.7)	13 (7.6)	0.57	16 (8.0)
CFB	4 (1.9)	1 (3.6)	2 (1.2)	0.5	3 (1.5)
Anti-CFH antibodies	14 (6.5)	0	14 (8.1)		14 (7.0)
Combined	9 (42.)	2 (7.1)	6 (3.5)	0.27	8 (4.0)
THBD[b]	0	0	0		0
Complement-mediated disease	142 (66.3)	20 (71.4)	113 (65.7)	0.67	132 (66.0)
Undetermined/incomplete	72 (33.6)	8 (4/4) (28.6)	59 (34.3)	0.55	68 (34.0)

C3 diminué: 35,9%

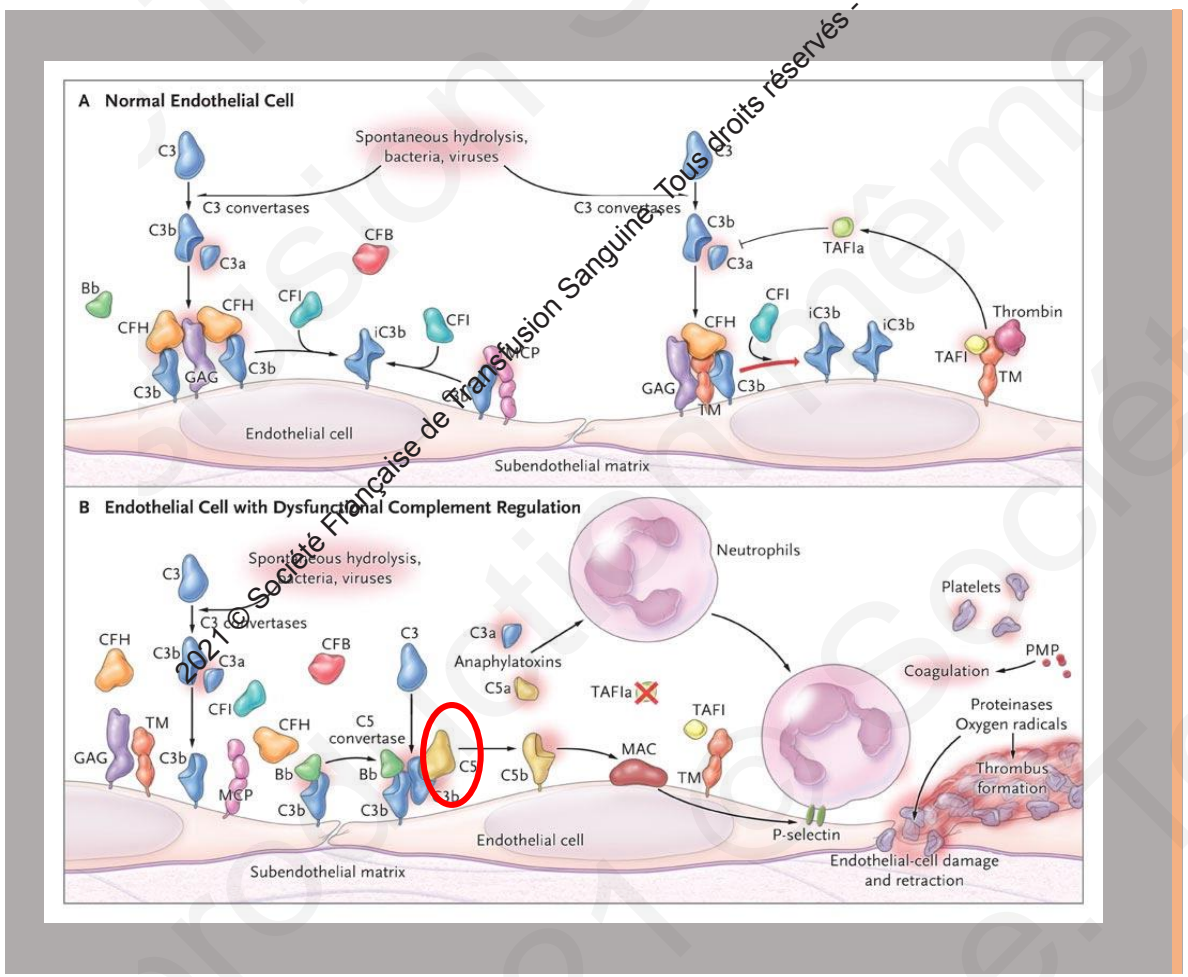
Fakhouri F et al, Lancet 2017

Registre Français SHU atypique

	ADULTES	ENFANTS
Suivi moyen (mois)	57	45
Rechute	35%	43%
Mortalité à 1 an	0,8%	6,8%
Dialyse en urgence	75%	
IRCT ou DC à 1 an	56%	29%
IRCT à 5 ans	64%	36%

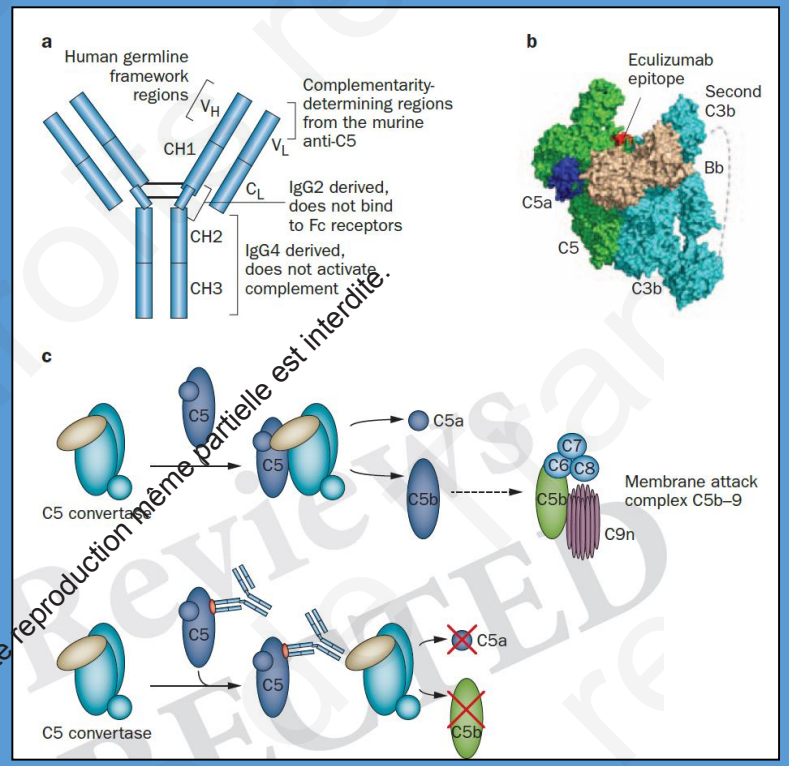
Fakhouri F et al, Lancet 2017

Traitement du SHU atypique



Noris M, NEJM 2009

ECULIZUMAB- Soliris®



Zuber J, Nat Rev Nephrol. 2012 Nov;8(11):643-57.

Protocole (AMM 2012)

- **Induction:**
  - **900 mg/sem pdt 4 semaines**
    - **Perfusion de 25-45 minutes**
- **Maintenance:**
  - **1200mg/15 jours**
- **Vaccinations (Menveo et Bexsero)**
- **En France: Oracilline**

The NEW ENGLAND JOURNAL of MEDICINE

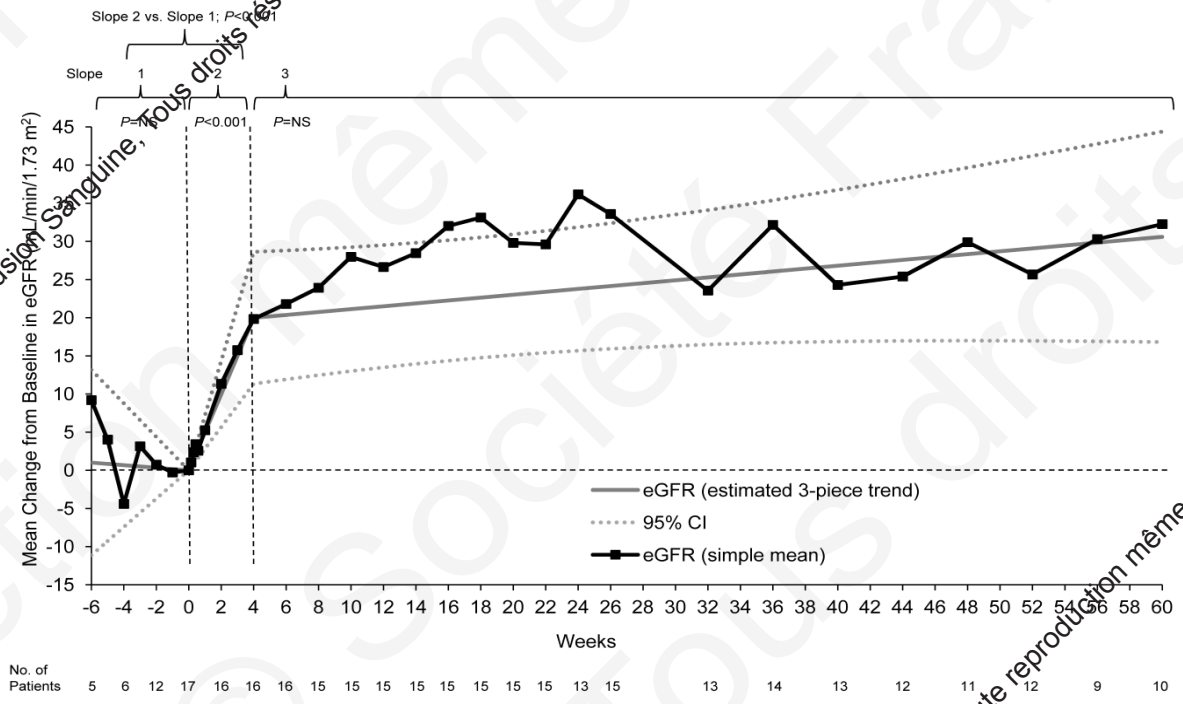
ORIGINAL ARTICLE

Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic–Uremic Syndrome

C.M. Legendre, C. Licht, P. Muus, L.A. Greenbaum, S. Babu, C. Bedrosian, C. Bingham, D.J. Cohen, Y. Delmas, K. Douglas, F. Eitner, T. Feldkamp, D. Fouque, R.R. Furman, O. Gaber, M. Herthelius, M. Hourmant, D. Karpman, Y. Lebranchu, C. Mariat, J. Menne, B. Moulin, J. Nürnberger, M. Ogawa, G. Remuzzi, T. Richard, R. Sberro-Soussan, B. Severino, N.S. Sheerin, A. Trivelli, L.B. Zimmerhackl,* T. Goodship, and C. Loirat

Essais Cliniques (C08.002- C08.003)

Figure S3. Three-Piece Linear Model—Change in eGFR: Trial 1.



Estimated glomerular filtration rate (eGFR) was calculated using the original Schwartz formula in adolescents[5] and the Modification of Diet in Renal Disease formula in adults.[6] For patients on dialysis, eGFR was calculated with the creatinine value immediately prior to dialysis or a fixed value of 10 mL/min/1.73 m^2.

+ 32 mL/min/1.73m^2 (17-45) through week 26 (P=0.001)
+ 32 mL/min/1.73m^2 (14-44) through week 60 (P<0.001)
Arrêt dialyse 4/5

Legendre C et al; NEJM 2013

ARRET DU SOLIRIS?

Alternatives AU SOLIRIS?

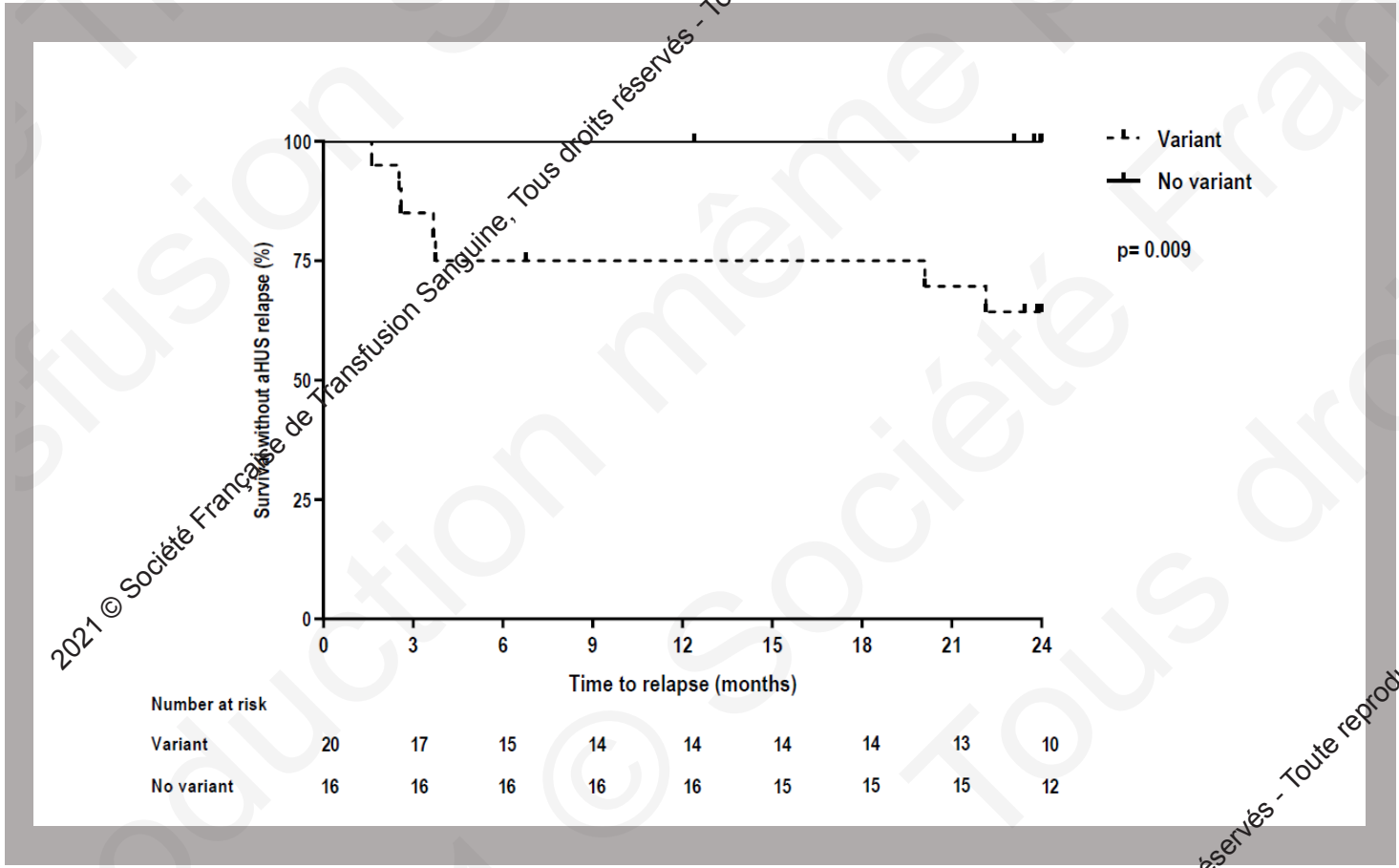
ARRET DU SOLIRIS?

PHRC STOP-ECU: Biologie à l'arrêt

	Age < 18 years (n=19)*	Age ≥ 18 years (n=36)	All (n=55)
At eculizumab discontinuation (inclusion)			
Duration of eculizumab treatment (months)	13.9 [0.95;57.4]	17.9 [4.2;59.3]	16.5 [0.95;59]
Serum creatinine (µmol/L)	50 [26;134]	124 [61;305]	97 [26;305]
Estimated glomerular filtration rate (ml/min/1.73m²)	112 [55;169]	62 [29;129]	80 [19 ;169]
Estimated glomerular filtration rate 30-60 ml/min/1.73m²	1 (5%)	16 (44%)	17 (30%)
Estimated glomerular filtration rate 15-29 ml/min/1.73m²	0	4 (11%)	4 (7%)
Urinary protein to creatinine ratio (g/mmol)	0.18 [0;3]	0.06 [0;0.38][c]	0.10 [0;3]

Fakhouri et al Blood 2021

PHRC STOP-ECU: Résultats



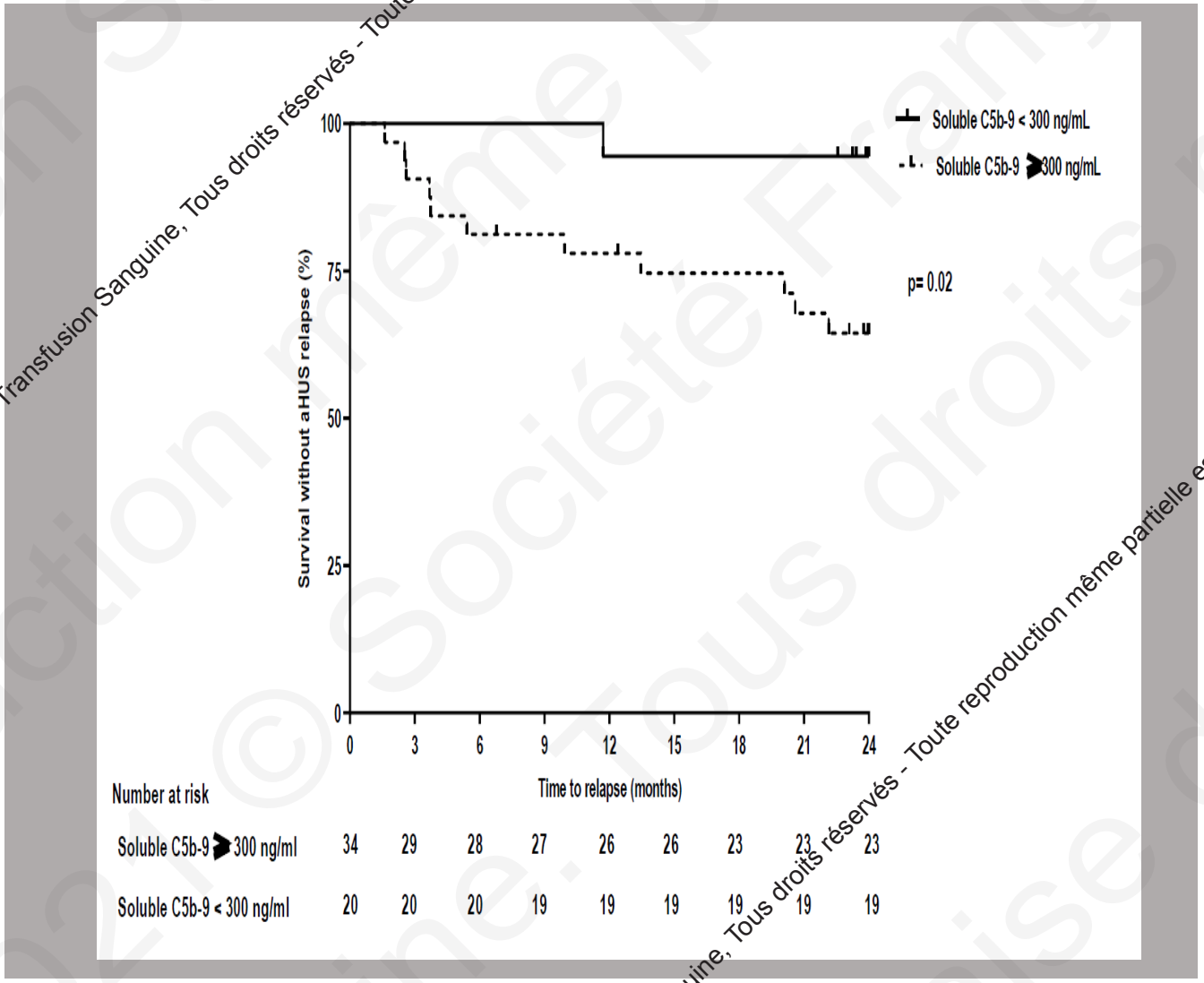
FH et MCP

=

50% de rechute

Fakhouri et al Blood 2021

PHRC STOP-ECU: intérêt du C5b9s



Fakhouri et al Blood 2021

PHRC STOP-ECU: Devenir si récidive?

- Rechute: 13/55 patients (23%)
- Dans la première année après l'arrêt
- Pas de difference entre enfants et adultes
- Trigger (79%)
- IRA (11/13) + MAT (12/13) et 1 EER
- Reprise Eculizumab = Récupération (11/13)

Surveillance

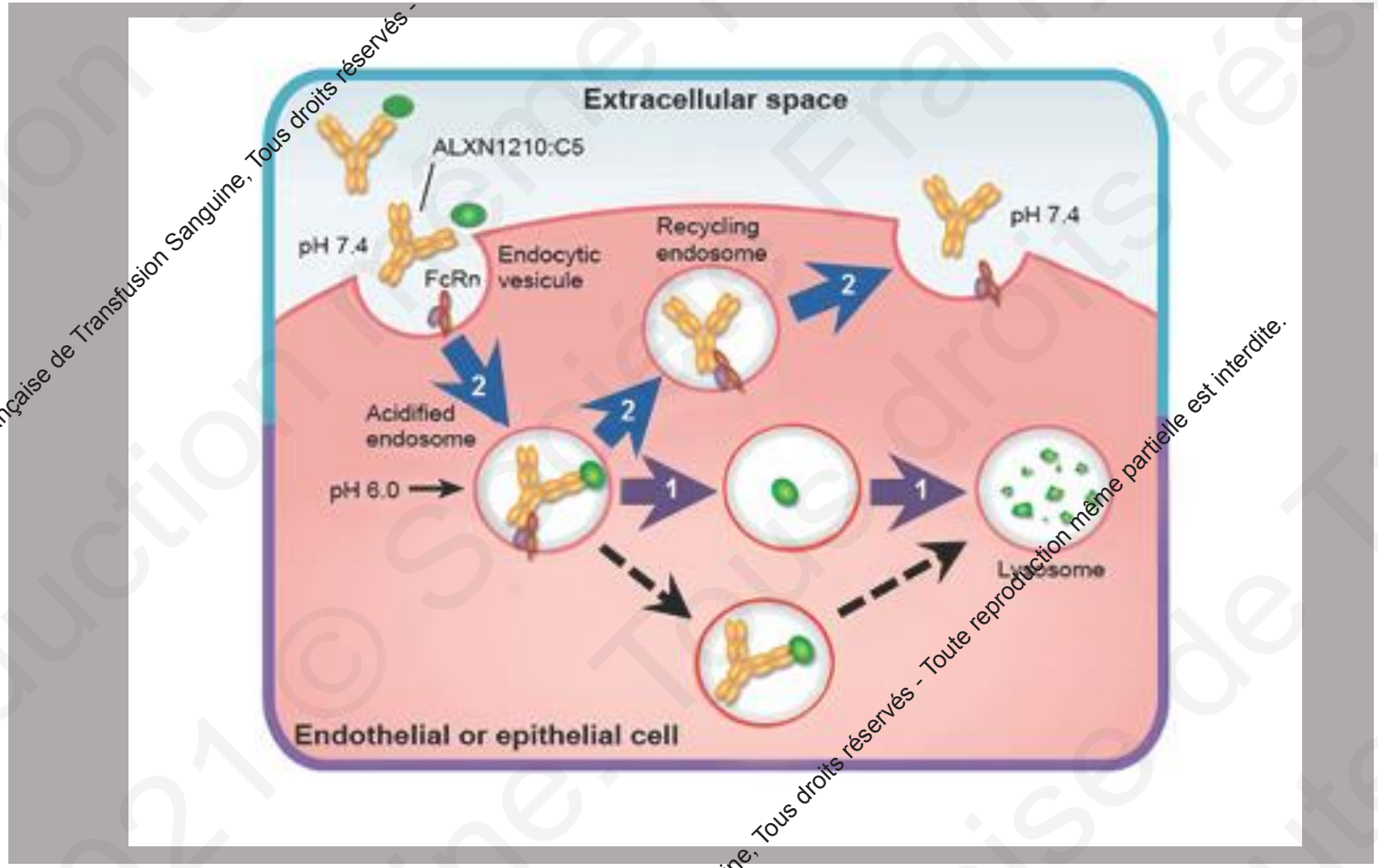
Creatinine
Protéinurie
Hémolyse

Education du patient

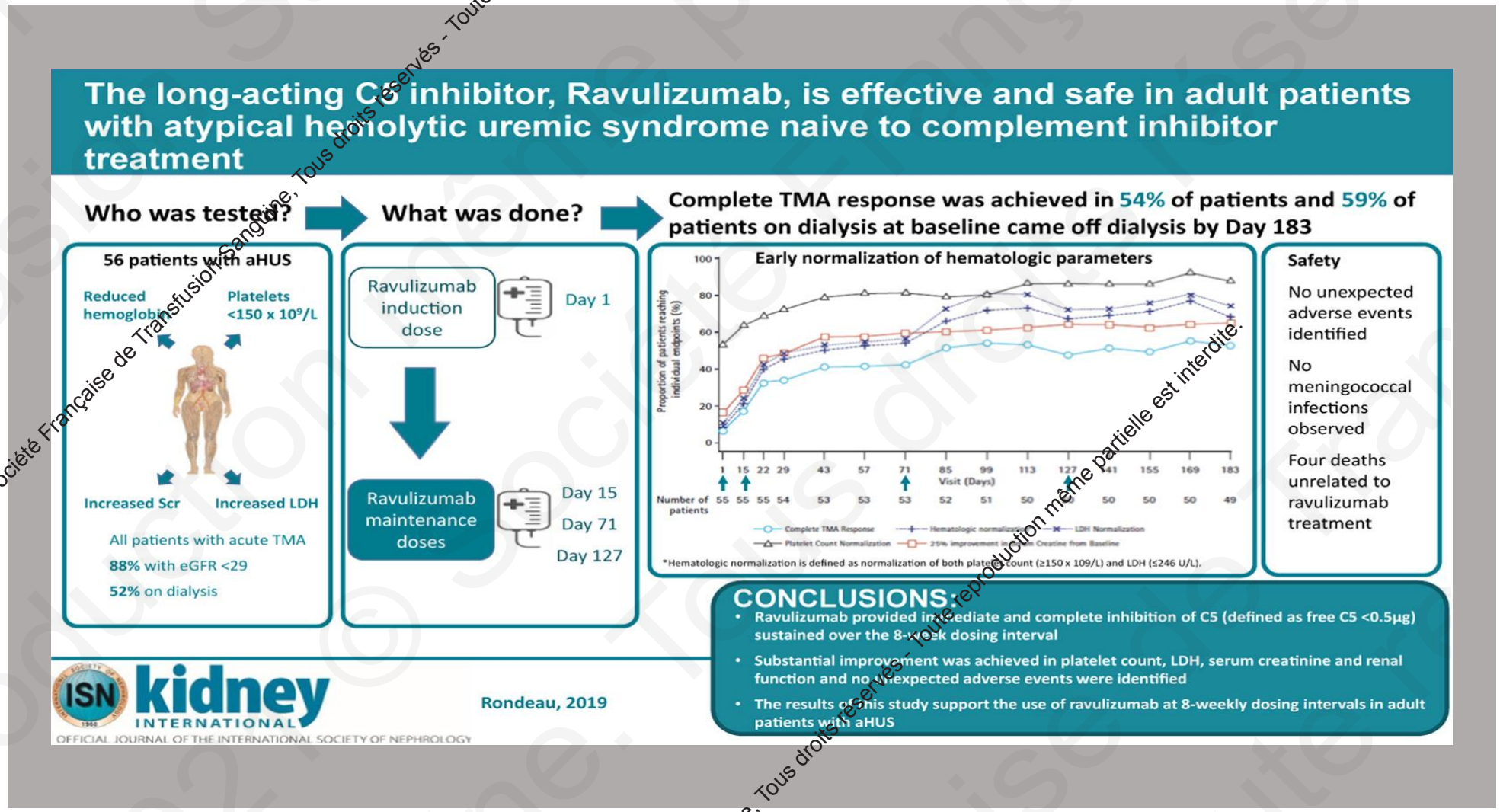
Fakhouri et al Blood 2021

Alternatives AU SOLIRIS?

RAVULIZUMAB

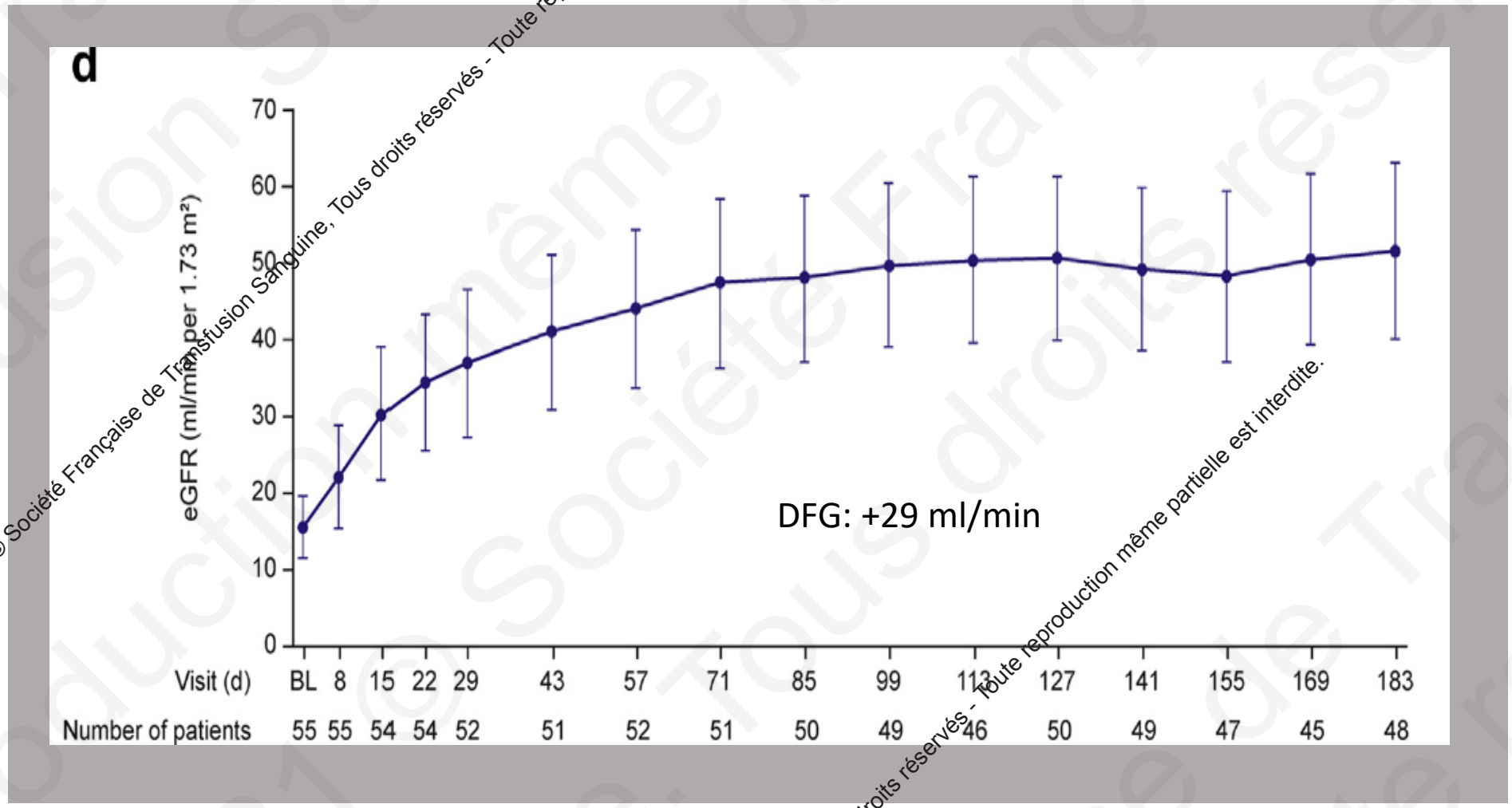


Ravulizumab dans le SHU atypique



Kidney International (2020) **97,** 1287–1296;

Ravulizumab dans le SHU atypique



Kidney International (2020) **97,** 1287–1296;

Protocole

- **Induction:**
  - **J 0 puis J15**
    - **Perfusion de 25-45 minutes**
- **Maintenance:**
  - **perfusion/8 semaines**
- **Vaccinations (Menveo et Bexsero)**
- **En France: Oracilline**

Conclusion

1998:

ADAMTS13

1998-2012

Mutations Voie alterne du cpt

AMM de l'ECULIZUMAB

2021:

- Switch de l'eculizumab vers le ravulizumab
- Discuter l'arrêt après 6 mois