Cytopénies au cours du lupus

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Critères ACR 1997

- **1 -** Eruption malaire en ailes de papillon
- **2** -Eruption de lupus discoïde
- **3** -Photosensibilité
- **4** -Ulcérations orales ou nasopharyngées
- **5** -Polyarthrite non érosive
- **6** -Pleurésie ou péricardite
- **7** -Atteinte rénale:
  - protéinurie > 0.5g/24h

  ou - cylindres urinaires
- **8** -Attteinte neurologique
  - convulsions

  ou - psychose
- **9** -Anomalies hématologiques:
  - anémie hémolytique

  ou - leucopénie < 4000/mm3

  ou - lymphopénie < 4500/mm3

  ou - thrombopénie < 100 000/mm3
- **10** -Désordre immunologique
  - présence de cellules LE

  ou - anticorps anti-ADN natif

  ou - anticorps anti-Sm
  - fausse sérologie syphilitique
- **11** -Anticorps antinucléaires à taux anormal (en l'absence de médicaments inducteurs) :
  - titre anormal d'anticorps antinucléaires en immunofluorescence,

  ou - technique équivalente à n'importe quel moment de l'évolution, en l'absence de médicaments inducteur de lupus.

- Hemolytic anemia--with reticulocytosis

OR

- Leukopenia--< 4,000/mm^3 on ≥ 2 occasions

OR

- Lymphopenia--< 1,500/ mm^3 on ≥ 2 occasions

OR

- Thrombocytopenia--<100,000/ mm^3 in the absence of offending drugs

SLICC criteria

- **(9) Hemolytic anemia**
- **(10) Leukopenia (<4000/mm3) OR Lymphopenia (<1000/mm3)**
  - Leucopenia at least once: In the absence of other known causes such as Felty's syndrome, drugs, and portal hypertension.
  - Lymphopenia at least once: in the absence of other known causes such as corticosteroids, drugs, and infection
- **(11) Thrombocytopenia (<100,000/mm3)**
  - At least once in the absence of other known causes such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura

Prévalence

TABLE I. HAEMATOLOGICAL FINDINGS AT DIAGNOSIS AND FOLLOW-UP IN 624 SLE PATIENTS

Parameter	At diagnosis No (%) (n=624)	At the last follow-up No (%) (n=491)
Anaemia	393 (63.0)	254 (51.7)§
Thrombocytopenia	68 (10.9)	23 (4.8)§
Leukopenia	188 (30.0)	80 (16.8)§
Neutrophilia	103 (16.5)†	70 (26.9)†
Lymphopenia	141 (40.3)‡	86 (33.1)†
Raised ESR (>17)	495 (79.3)	300 (77.1)£
Low C3 (<0.83 g/l)	283 (45.4)	48 (34.5)Ψ
Low C4 (0.15 g/l)	263 (42.2)	49 (35.3)Ψ
AIHA	29 (4.6)	0 (0)
Coombs test (n=223)		
Direct +ve	80 (35.9)	13 (2.6)
Indirect +ve	6 (2.7)	
Direct & indirect +ve	13 (5.8)	
Negative	124 (55.6)	
APTT (n=408)		
Normal (<39)	256 (62.7)	
Prolonged (≥40)	152 (37.3)	
Positive ACA		
IgG	116 (49.7)¥	19 (38.8)¶
IgM	78 (33.5)¥	14 (28.6)¶
LAC (n=248)	67 (27.0)	

Table 1 – Clinical and serological profile of lupus patients.

	n	%
Photosensitivity	347/452	76.7
Oral ulcers	205/437	46.9
Malar rash	230/441	52. 1
Discoid lesions	57/441	15.1
Arthritis	281/458	61.3
Glomerulonephritis	183/457	40.0
Seizures	48/457	10.5
Psychosis	23/455	5.0
Serositis	81/457	17.7
Leukopenia	136/455	29.8
Lymphopenia	80/450	17.7
Hemolytic anemia	39/460	8.4
Thrombocytopenia	97/460	21.08
Anti Ro/SS-A	161/441	36.5
Anti La/SS-B	80/440	18.1
Anti RNP	110/421	26.1
Anti SM	87/434	20.0
Anti-dsDNA	150/444	33.7
Anticardiolipin IgG	54/443	12.1
Anticardiolipin IgM	53/443	11.9
Lupus anticoagulant	59/407	14.4
Rheumatoid factor	95/411	23.1
Antiphospholipid syndrome	33/439	7.5

80 % d'anomalies hématologiques

Aleem 2014
Skare 2015

Anémie

De multiples causes

Table 1 Causes of anaemia in patients with SLE

- Anaemia of chronic disease
- Blood loss
  - Gastrointestinal loss, menorrhagias
- Nutritional deficiencies
  - Iron, folate, B12
- Immune mediated
  - Haemolysis, red cell aplasia, haemophagocytosis, aplastic anaemia, pernicious anaemia
- Myelofibrosis
- Uraemia
- Treatment induced
- Microangiopathic haemolysis
  - Disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, drugs
- Hypersplenism
- Infection
- Myelodysplasia

Causes	N =132
ACD	49 **(37.1%)**
Iron DA	47 **(35.6 %)**
AIHA	19 (14.4%)
Others	17 (12.9%)

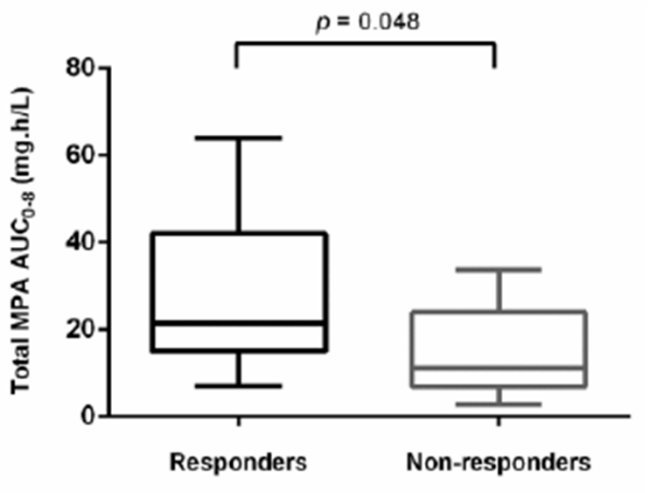
Même démarche qu'en dehors du lupus

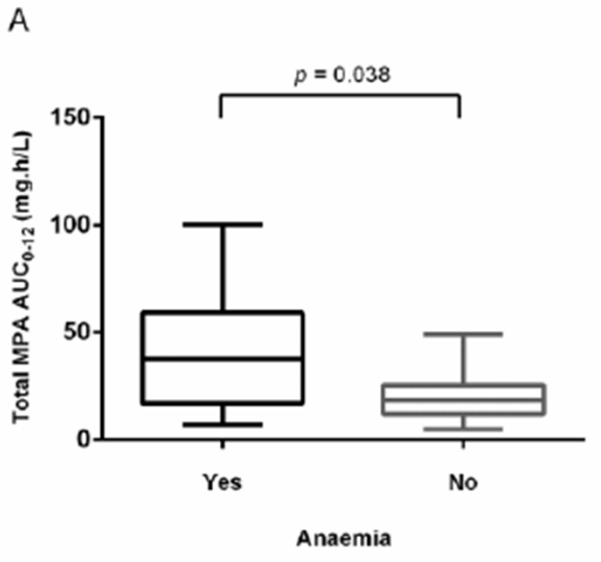
Prise en compte de l'activité du lupus

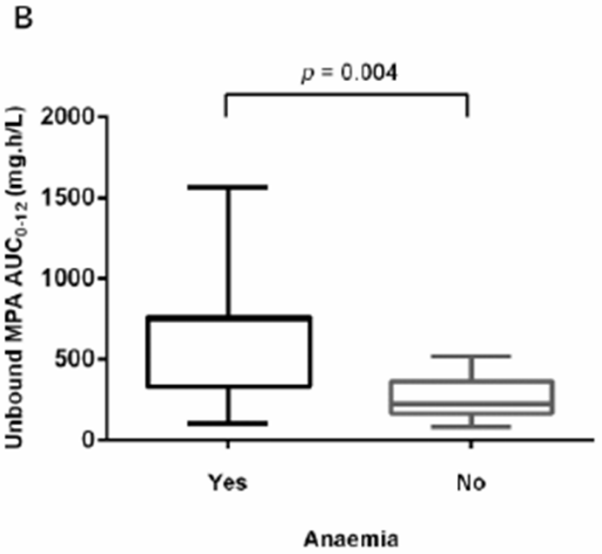
Voulgarelis 2000, Giannouli 2006

Anémie centrale: toxicité

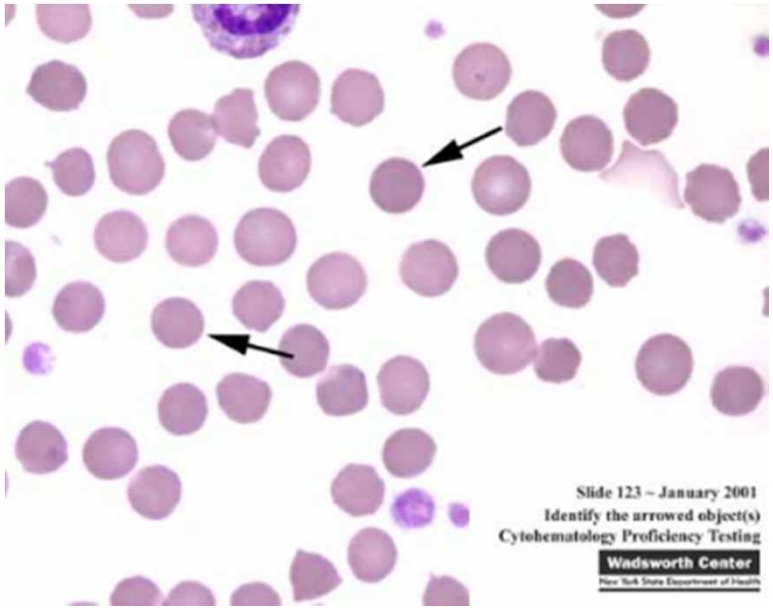
Rahman 2015

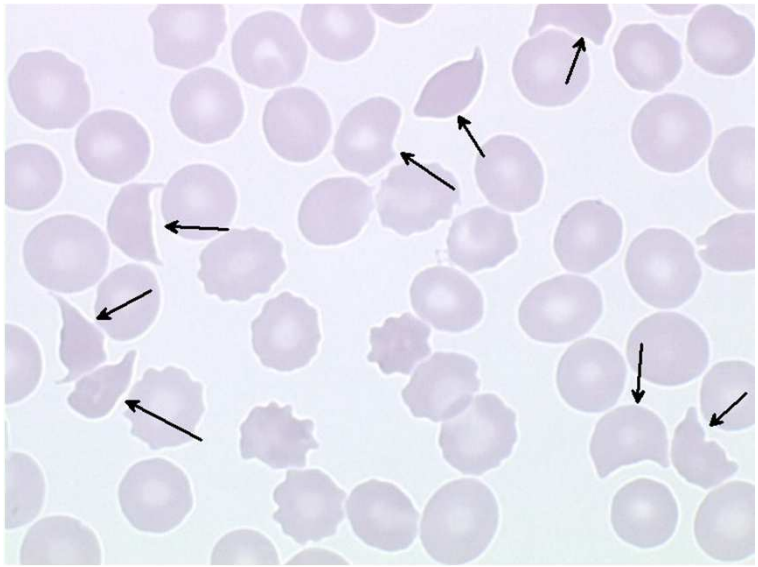






Anémie hémolytique





Coombs direct 35% des lupus au diagnostic

Sphérocytes = AHAI

Schizocytes = MAT

TABLE III. ASSOCIATION OF HAEMATOLOGICAL ABNORMALITIES WITH ORGAN INVOLVEMENT IN UNIVARIATE ANALYSIS

Haematological abnormality	Organ involvement	P-Values
Leukopenia	Oral ulcers	0.014
	Serositis	0.028
	Alopecia	0.044
Anaemia (all types)	Renal disease	<0.001
	Serositis	0.001
	Neurological disorder	0.045
Thrombocytopenia	Arthritis	0.004
	Serositis	0.029
	Neurological disorder	0.007
Coombs' positive haemolytic anaemia	Serositis	0.010
	Neurological disorder	0.002
C3 hypocomplimentemia	Serositis	<0.001
	Renal disease	0.008
Elevated IgG	Malar rash	0.030
	Renal disease	0.001
	Photosensitivity	0.045

Table 2 – Association studies of demographic, clinical and serological variables of lupus patients with hemolytic anemia.

	With hemolytic anemia n=39	Without hemolytic anemia n=421	p-Value	OR	95% CI
Age years – median (IQR)	35.0 (23.0–47.0)	40.0 (30.0–49.0)	0.06		
Leukopenia – n (%)	17/39 (43.5)	119/416 (28.6)	0.0506	1.9	0.9–3.7
Thrombocytopenia – n (%)	14/31 (35.8)	83/416 (19.9)	0.02	2.2	1.1–4.5
Anti-SM – n (%)	10/36 (27.7)	77/398 (19.3)	<0.0001	5.4	2.6–1.4
Anticardiolipin IgG – n (%)	10/38 (26.3)	44/405 (10.8)	<0.0001	5.8	3.0–11.2
Anticardiolipin IgM – n (%)	14/38 (36.8)	39/404 (9.6)	<0.0001	5.4	2.6–11.4
Lupus anticoagulant – n (%)	12/34 (35.2)	47/373 (12.6)	0.001	3.7	1.7–8.1

IQR: interquartile range; OR: odds ratio; 95% CI: 95% confidence interval.

ASSOCIATION SAPL ?

AHAI

Aleem, Skare

AHAI

Lupus évolutif

- TRAITER LE LUPUS

Lupus non évolutif n=26

- **Corticoïdes RC 96%**
- **PFS 73% à 180 mois**
- **Splénectomie 33% RC**

- **Rôle IS?**
- **Rôle Hydroxychloroquine?**

Gomard-Menesson 2006

AHAI- Lupus: rituximab

	Patients evaluable for outcome (n = 113), no. (%)	Variation in SELENA–SLEDAI score for different categories of responders for various organ involvements, mean ± SD (*P*)
Articular involvement	50	
Complete response	26 (52)	−8.2 ± 6.6 (<0.0001)
Partial response	10 (20)	−7.3 ± 4.0 (0.002)
No response	14 (28)	−3.8 ± 4.4 (0.02)
Cutaneous involvement	61	
Complete response	29 (48)	−12.1 ± 9.0 (<0.0001)
Partial response	14 (23)	−8.4 ± 6.7 (0.0002)
No response	18 (29)	−4.6 ± 4.0 (0.01)
Lupus nephritis	31	
Complete response	14 (45)	−14.9 ± 10.1 (0.0001)
Partial response	9 (29)	−9.4 ± 7.8 (0.004)
No response	8 (26)	0.25 ± 4.2 (0.88)
AIHA	13	
Complete response	9 (69)	−8.9 ± 8.6 (0.004)
Partial response	2 (16)	−9.0 ± 1.4 (NA)
No response	2 (15)	−1 (NA)
Autoimmune thrombocytopenic purpura	13	
Complete response	10 (77)	−4.9 ± 4.0 (0.004)
Partial response	2 (15)	−5.0 ± 4.2 (NA)
No response	1 (8)	0 (NA)

Terrier 2010

Microangiopathies thrombotiques

Autopsies

- 34/151 nécrops de MAT ont des signes de LES

  Levine 1964

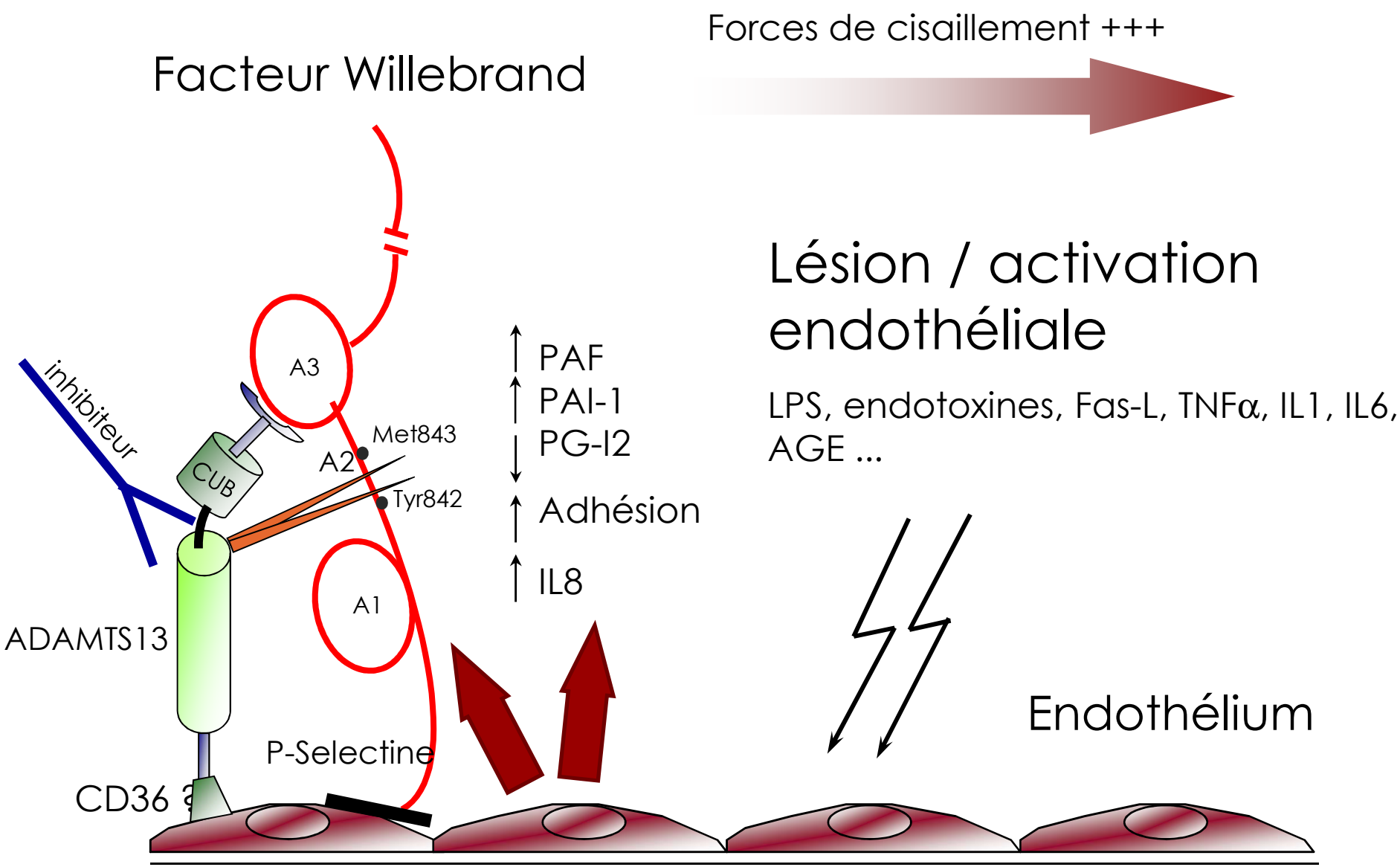
- 14/50 nécrops de lupus ont des signes de MAT

  Devinsky 1986

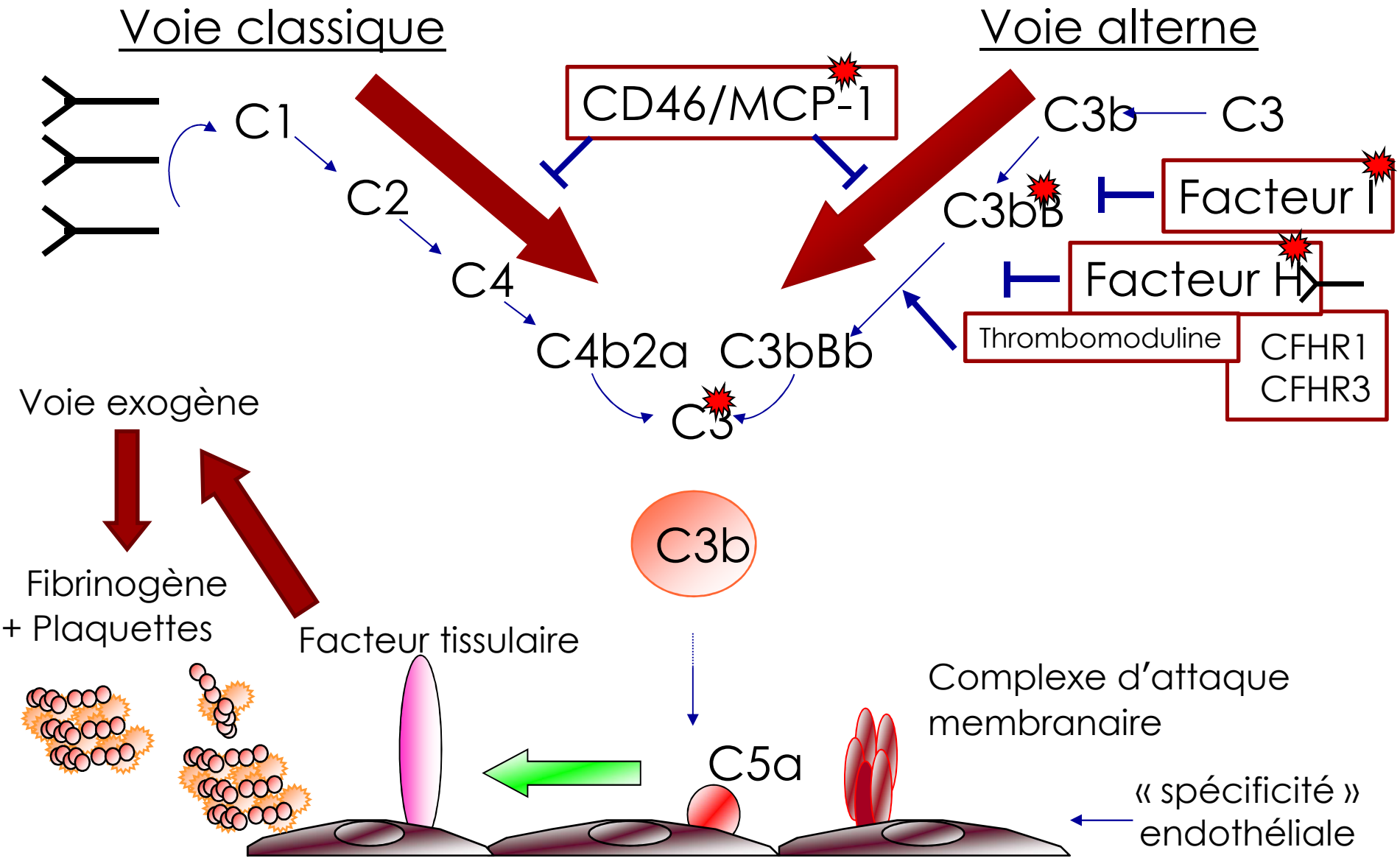
OVERLAP CAPS

Rodriguez-Pinto 2015

PTT et PROTEASE du FW



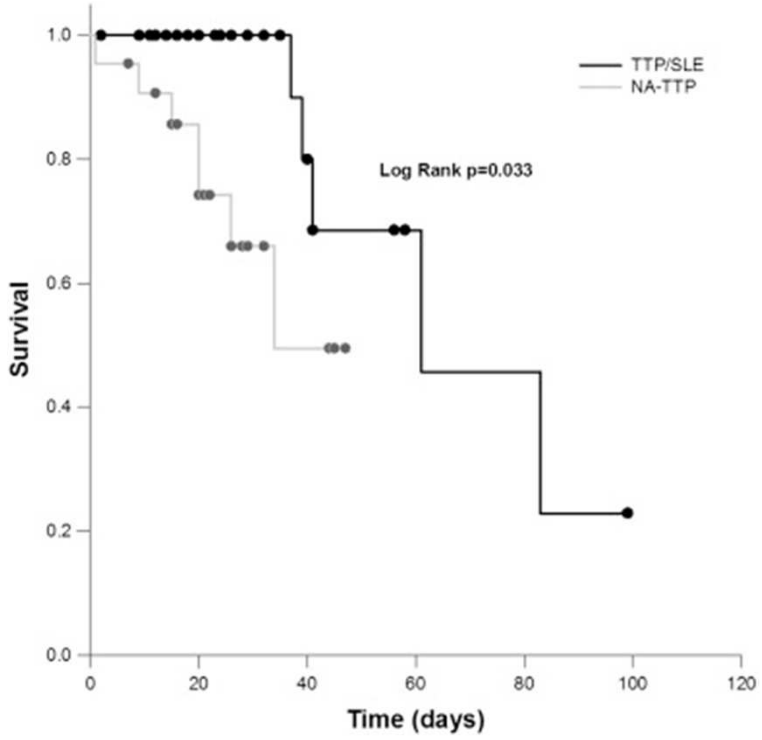
SHU et ANOMALIES du COMPLEMENT



Merayo-halico 2014

Clinical Feature	TTP/SLE n = 24 (%)	NA-TTP n = 22 (%)	p value (X^2)
Fever	10/24 (41)	9/22 (40)	0.95 (0.003)
Neurological symptoms	11/24 (45)	15/22 (68)	0.15 (2.33)
Cerebrovascular disease	4/24 (16)	6/22 (27)	0.48 (0.76)
Anaemic syndrome	13/24 (54)	7/22 (31)	0.22 (2.33)
Gastrointestinal symptoms	13/24 (54)	9/22 (40)	0.37 (0.80)
Cardiopulmonary symptoms	12/24 (50)	12/22 (54)	0.75 (0.09)
Purpura	10/24 (41)	13/22 (59)	0.36 (1.39)
Pentad	3/24 (12)	1/22 (4)	0.61 (0.91)
Laboratory Feature	**Mean ± SD[**]**	**Mean ± SD**	**p value**
Haemoglobin (g/dL)	**6.98 ± 0.4**	**8.72 ± 0.4**	**0.006**
Leukocytes (mm^3) ($x10^3$)	**7.4 ± 0.79**	**12.2 ± 1.75**	**0.013**
Total lymphocyte count (mm^3)	**829 ± 155**	**1639 ± 186**	**0.002**
Platelets (cel/µl) ($x10^3$)	36 ± 6.6	25 ± 5.1	0.18
Haemolysis Parameters			
Reticulocyte Index (%)	**3.7 ± 0.8**	**8.1 ± 1.1**	**0.003**
Haptoglobins (mg/dL)	91 ± 59	20 ± 0	0.43
Schistocytes (per field)	**5.11 ± 1.4**	**1.89 ± 0.26**	**0.046**
LDH[a] (UI/mL)	**746 ± 103**	**1383 ± 182**	**0.003**
Indirect bilirubin (mg/dL)	1.3 ± 0.26	2.82 ± 0.77	0.074
Renal Function			
Serum creatinine (mg/dL)	3.39 ± 1.05	1.88 ± 0.42	0.20
Creatinine clearance (mL/min)	56.3 ± 9.5	70.7 ± 8.03	0.26

Time (days)



TTP et lupus

- **Lymphopénie et peu de régénération**
- **ADAMTS 13 médian 41%**

Microangiopathies Thrombotiques

N= 105

Concomittant	45.7%
Après SLE	50.5%
Avant SLE	3.8%

Renal pathological damages	Total cases (n=52)	Death group (n=4)	Survival group (n=48)
IV	30	1	29
V	6	0	6
TMA[a]			1
II			2
III			2
VI	2	0	2
III and V	1	0	1
IV and V	1	0	1
V and TMA[a]	1	0	1
VI and TMA[a]	1	0	1
II and III	1	0	1
Normal	1	0	1

32/52 classe 4

Antibodies	Total	Death group	Survival group
Anti-ANA			5.5)
Anti-dsDN			0)
Anti-Sm			1.2)
Anti-phosp			9.3)
ADAMTS			7.9)
anti-ADAMTS13 antibody	22/24 (91.7)	2/2 (100)	20/22 (90.9)

ADAMTS13 <5% = 40%

A13 < 5% 66% des dcd

Various therapies	Total utilization rate (N=105) n (%)	Remission rate n (%)	Ref rate n			
PE alone[b]	6 (6.7)	3/6 (50)	3/			
ST and (or) cytotoxics without PE[c]	10 (9.5)	4/10 (40)	6/			
PE + ST[d]	35(33.3)	23/35 (65.7)	12			(multiple organ failure)
PE + cytotoxics	3 (2.9)	3/3 (100)	0	0	0	No
PE + ST + cytotoxics[e]	52 (49.5)	47/52 (90.4)	5/52 (9.6)	0	5/52 (9.6)	Refractory sTTP/ overwhelming infection
Rituximab + PE with or without ST (or cytotoxics)	11 (10.5)	10/11 (90.9)	1/11 (9.1)	1/11 (9.1)	0	No
Others	2 (2.9)	2/2 (100)	0	0	0	No

PEX + CT

+/-

Ritux et ou IS

+ CAPLACIZUMAB si tableau de PTT

JIANG 2005

TMA réfractaire

		Post–Eculizumab Treatment				
	1 mo Prior to Eculizumab	7 d	3 mo	6 mo	12 mo	Reference Range
Hemoglobin (g/dL)	6.4	8.3	9.6	10.6	11.4	11.2-15.7
Platelets ($\times 10^3/\mu L$)	25	78	178	188	216	155-369
Haptoglobin (mg/dL)	<10	21	40	142	136	40-219
LDH (U/L)	1,577	1,125	307	243	216	116-250
Creatinine (mg/dL)	3.9	2.4	2.1	1.9	1.6	0.7-1.1
SUN (mg/dL)	77	31	20	18	17	7-21
eGFR (mL/min/1.73 m^2)	19	29	34	37	47	>60
UPCR (mg/mg)	4.9	4.1	2.2	1.8	1.6	<0.2
C3 (g/L)	63	77	81	86	88	84-166
C4 (g/L)	12	15	20	24	20	13-36

Abbreviations: eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; SUN, serum urea nitrogen; UPCR, urinary protein-creatinine ratio.

El Husseini 2015

Lupus-atteinte médullaire

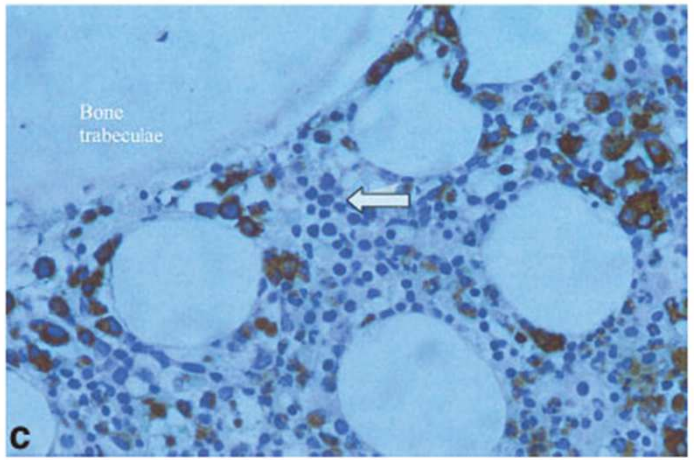
21 BM

cytopénies « périphériques »

- Hypocellulaire 47.6%
- Reticuline 76%
  - (MF 1/21)
- Nécrose 19%
- Plasmocytose 26%

Pereira 1998

	SLE (%)	MDS-RA (%)
Normal or increased bone marrow cellularity	17/40 (42.5)	10/10 (100)
ALIP+	27/40 (67.5)	10/10 (100)
BM necrosis	36/40 (90)	1/10 (10)
Dilatated sinuses	8/40 (20)	0
Dyserythropoiesis	40/40 (100)	10/10 (100)
Dysmegakaryopoiesis	40/40 (100)	10/10 (100)
CD34+ <3%	40/40 (100)	10/10 (100)



Voulgarelis 2006

Lupus-atteinte médullaire

DYSMYELOPOIESE / SMD like

Aspect SMD	Mais..Lupus
Hypocellularité	Niche conservée
Réticuline	Localisation anormale des précurseurs
Dysmyélopoièse	Nécrose

Dysérythropoièse

Lupus

Carences (biermer)

Myélodysplasie: étude cytogénétique

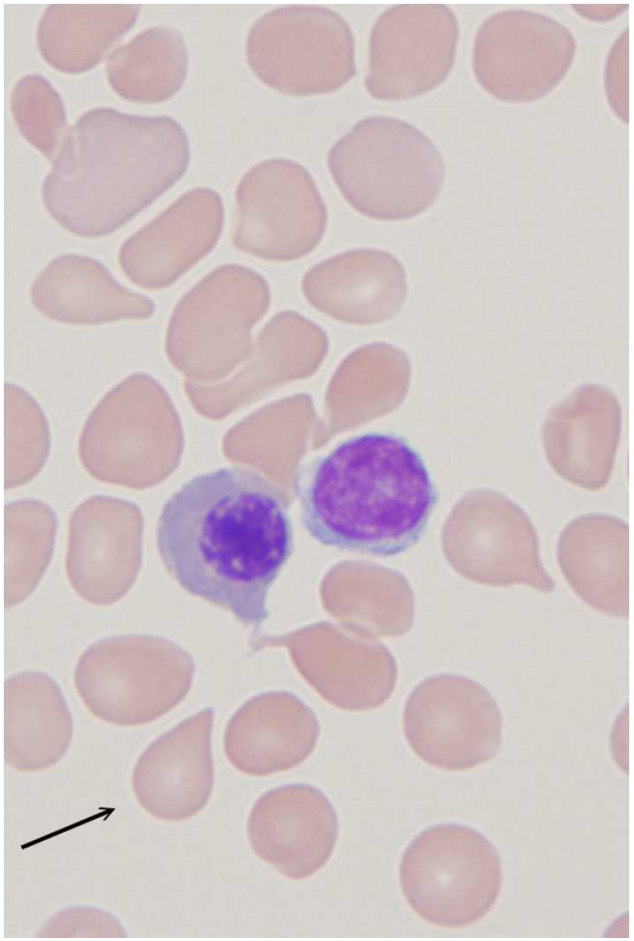


Table 4 Summary of the reported patients with systemic lupus erythematosus (SLE) with myelofibrosis[140 142–144 146 147 164–177]

	Average or number	Range or number evaluated
Age	35	12–70
Sex	23 women, 6 men	
Ethnicity	European White=8 Asians=4 Black Americans=2 Hispanic Americans=3 Middle Eastern=3	
White blood cell (units)	4265	1200–7700
Haemoglobin (g/dL)	7.9	2.7–13.9
Platelets (no/mm^3)	62 000	1000–341 000
Duration (weeks from SLE Dx)	124	0–572
Splenomegaly	12	29
Antinuclear antibody positivity	27	29
GC responsive	17	25
Improved cytopenias	23	29
Deaths	8	28

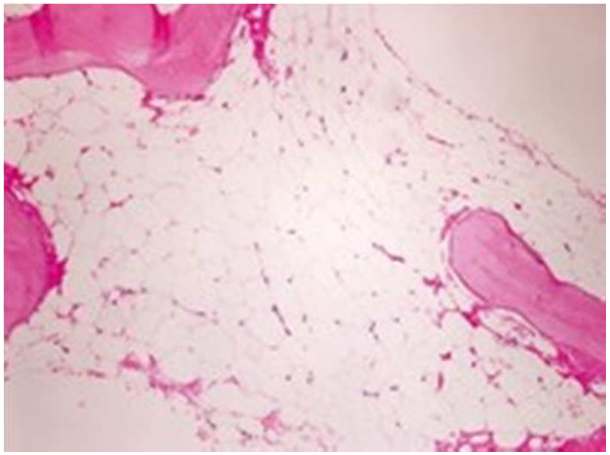
GC, glucocorticoid.

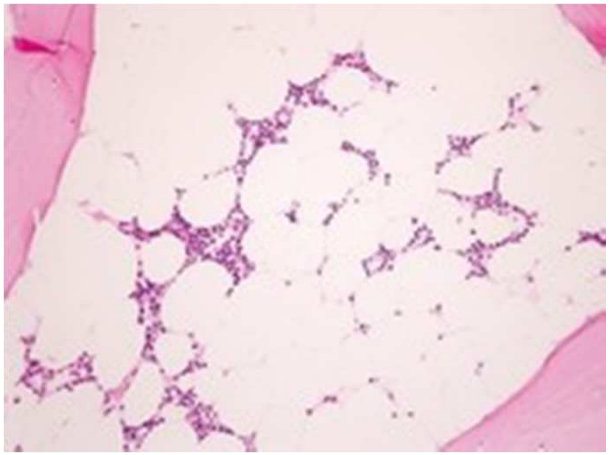
SplénoM 41%

CorticoS 60%

Fayyaz 2015

Myélofibrose





- 50 % après le diagnostic de LES, 50 % avec
- 15% de mortalité
- T et ou B médié

corticoides	17/26	
CYC	5/26	
PEX	5/26	
CYCLO	5/26	
HQ	4/26	
ATG	3/26	3 décès
AZA	2/26	
IgIV	2/26	
MTX	1/26	
Rituximab	1/26	

Aplasie médullaire

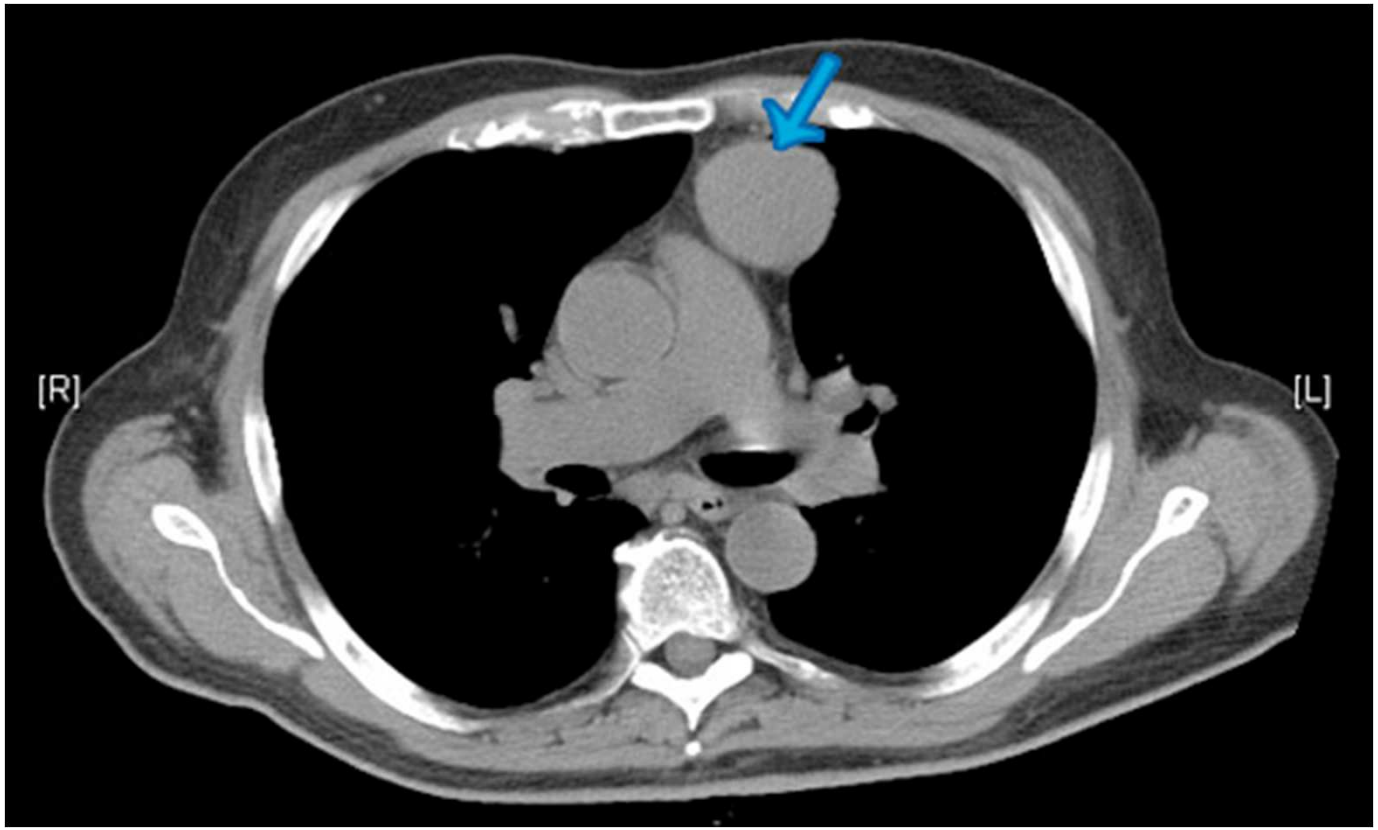
Chalayer 2015

Erythroblastopénie

- Environ 50 cas dans la littérature
- Se méfier Parvovirus B19 si immunodéprimé
- Anticorps anti EPO? T médié?
- Efficacité possible des IgIV
- Corticoides, hydroxychloroquine, Cyclosporine

Atzeni 2003,Zandman-Godard 2005, Fallahi 2014

Erythroblastopénie

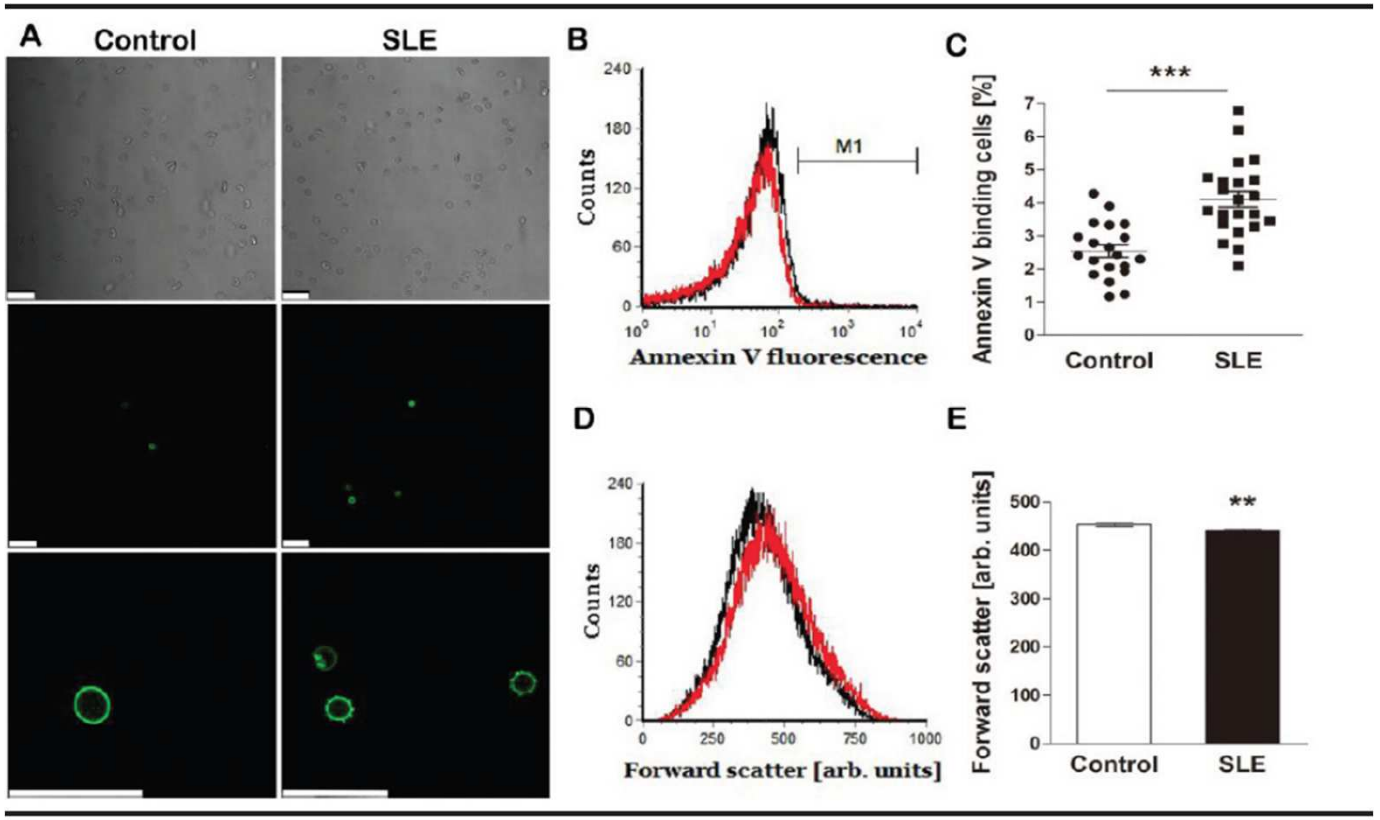


Mécanismes physiopathologiques

- « IgG of patients supress BM progenitor cells by direct binding to CD34+ cells »
- « T Cell mediated inhibition of haemopoiesis is the major cause of bone marrow failure in SLE »
- « Impaired EPO production in patient with SLE and ACD or AHA »

Brooks 1984, Liu 1995, Yamakasi 1984, Giannouli 2006

Eryptosis as a cause of anemia in SLE



JIANG 2016

Thrombopénie

- PTAI
- MAT
- Centrale

PTI/ SAPL

1000 SAPL: 29% P < 100 000

Table 1 Selected mechanisms of thrombocytopenia in antiphospholipid antibody (aPL)-positive patients

1. Increased platelet activation and destruction
   (a) Immune-mediated (aPL related, secondary ITP)
   (b) Thrombotic microangiopathy (CAPS, HELLP syndrome, aHUS, TTP)
   (c) Drug-induced (e.g., heparin)
2. Decreased platelet production
   (a) Hemophagocytic syndrome
   (b) Bone marrow necrosis
3. Increased platelet pooling
4. Pseudothrombocytopenia

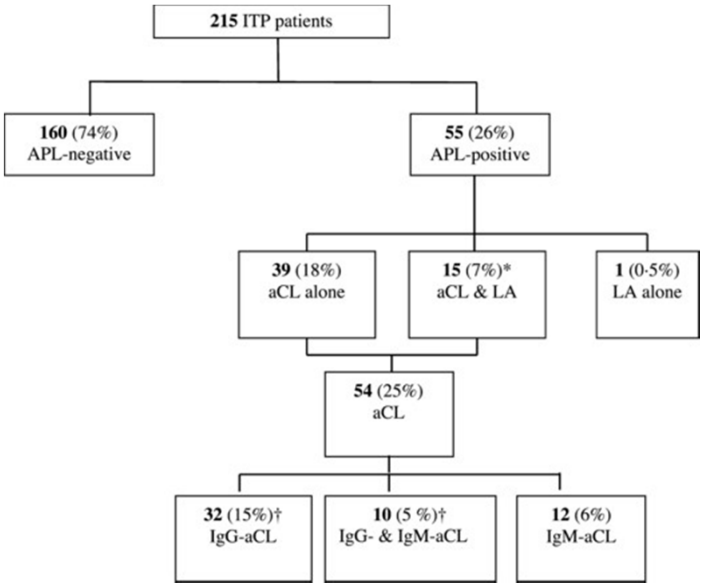


Table IV. Analysis of risk factors of thrombosis in the 215 ITP patients.

	Univariate analysis		Multivariate analysis	
Factor	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Male sex	2·2 (0·7–6·6)	0·16	1·1(0·3–3·7)	0·93
Age	1·4 (1·0–1·8)	0·02	1·6 (1·2– 2·4)	0·002
IgG-aCL ≥40 µg/dl	3·3 (1·0–10·9)	0·05	7·5 (1·8–31·5)	0·006
LA*	3·1 (1·0–10·4)	0·06	9·9 (2·3–43·4)	0·002
Danatrol	2·5 (0·8–7·5)	0·12	1·6 (0·5–5·1)	0·45
Splenectomy	3·4 (0·9–13·4)	0·08	2·2 (0·5–9·8)	0·31

Cervera 2002, Artim-Esen 2015,
Pierrot Deseilligny 2008

PTI - Lupus

Treatments	No. of Pts	Mean No. of ARA Criteria	No. of Pts with Incomplete SLE (%)	No. of Pts with Visceral Involvement Related to SLE (%)*	Median Duration of Thrombocytopenia Before Treatment (mo)	Mean Platelet Count Before Treatment (10^9/l)	No. of Longterm (PR or CR) Responders (%)	Percentage of Longterm Responders Among Pts with Incomplete SLE	Percentage of Longterm Responders Among Pts with Definite SLE	p Value‡
Oral prednisone alone	50	4.5 ± 1.5	11 (22%)	16 (32%)	0	17 ± 15	11/50 (22%)	9 %	25%	0.23
HDMP	10	5.8 ± 2.5	2 (20%)	8 (80%)	1	25 ± 14	0 (0%)	0 (0%)	0 (0%)	1
IVIG	31	4.6 ± 1.8	10 (32%)	11 (35%)	1	13 ± 12	0 (0%)	0 (0%)	0 (0%)	1
Danazol	18	4.8 ± 2.2	6 (33%)	7 (39%)	12	22 ± 17	9 (50%)	67%	41%	0.31
HCQ	11	4.3 ± 1	3 (27%)	2 (18%)	14	52 ± 43†	7 (64%)	33%	75%	0.28
IS	14	5.4 ± 2.3	3 (21%)	8 (57%)	18	21 ± 16	2 (14%)	33%	9%	0.38
Splenectomy	18	4.5 ± 1.5	5 (28%)	9 (50%)	17	19 ± 16	11 (61%)	60%	62%	0.68

Arnal 2002

PTI – Lupus Splenectomie n =25

- Suivi médian 9.5 ans post splenectomie
- Décès =9 (36%) 11.5 ans post splenectomie en médiane
- 1 OPSI
- Pas de poussée SLE dans cette étude

Réponse hématologique

- CR + PR = 16 (64%)
  - 8 sans traitement
  - 8 avec traitement complémentaire
- 9 rechutes

You 2004

	Patients evaluable for outcome (n = 113), no. (%)	Variation in SELENA–SLEDAI score for different categories of responders for various organ involvements, mean ± SD (*P*)
Articular involvement	50	
Complete response	26 (52)	−8.2 ± 6.6 (<0.0001)
Partial response	10 (20)	−7.3 ± 4.0 (0.002)
No response	14 (28)	−3.8 ± 4.4 (0.02)
Cutaneous involvement	61	
Complete response	29 (48)	−12.1 ± 9.0 (<0.0001)
Partial response	14 (23)	−8.4 ± 6.7 (0.0002)
No response	18 (29)	−4.6 ± 4.0 (0.01)
Lupus nephritis	31	
Complete response	14 (45)	−14.9 ± 10.1 (0.0001)
Partial response	9 (29)	−9.4 ± 7.8 (0.004)
No response	8 (26)	0.25 ± 4.2 (0.88)
AIHA	13	
Complete response	9 (69)	−8.9 ± 8.6 (0.004)
Partial response	2 (16)	−9.0 ± 1.4 (NA)
No response	2 (15)	−1 (NA)
Autoimmune thrombocytopenic purpura	13	
Complete response	10 (77)	−4.9 ± 4.0 (0.004)
Partial response	2 (15)	−5.0 ± 4.2 (NA)
No response	1 (8)	0 (NA)

Terrier 2010

PTI- Lupus: rituximab

PTI- Lupus: aTPO

Successful platelet count recovery in lupus-associated thrombocytopenia with the thrombopoietin agonist eltrombopag

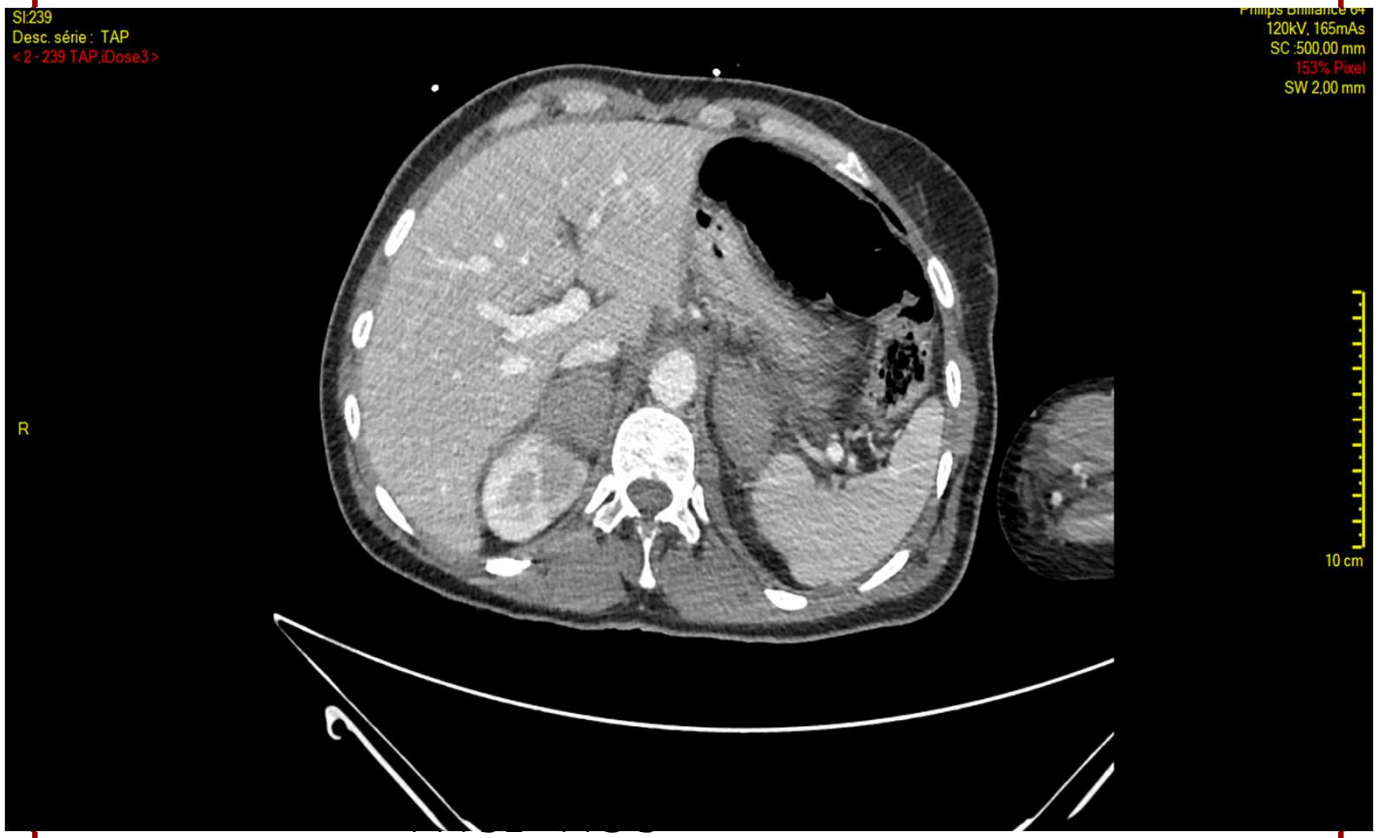
Phillip Scheinberg · Cristiane Carvalho Singulane · Luis Sergio Guedes Barbosa · Morton Scheinberg

Table 1. Characteristics of the patients with SLE-associated refractory immune thrombocytopenia who were treated with thrombopoietin-receptor agonists.

Case (ref)	Age, yrs	Sex	Previous Treatments	Thrombopoietin-receptor Agonist	Dose	Response	Time to Response	Adverse Events
#1 (PC)	69	F	CS, IVIG, splenectomy, RTX	Eltrombopag	25 mg/day	Yes	2 weeks	No
#2 (PC)	39	F	CS, IVIG, CYC, azathioprine, RTX	Romiplostim	2 mcg/kg/week, further increased to 7 μg/kg/week	Yes	2 weeks	No
#3 (6)	44	M	CS, IVIG, azathioprine, RTX, CYC	Romiplostim	2 mcg/kg/week	Yes	3 weeks	No
#4 (7)	34	F	CS, IVIG, RTX, CYC	Romiplostim (previously eltrombopag without response)	3 mcg/kg/week	Yes	6 days	No
#5 (8)	19	F	CS, IVIG, RTX	Romiplostim	NS	Yes	NS	Kidney-limited thrombotic microangiopathy
#6 (9)	55	F	CS, RTX, CSA	Eltrombopag	50 mg/day	Yes	2 weeks	No
#7 (10)	NS	NS	NS	NS	NS	No	NS	NS

Magnano 2014

Lupus a TPO



Guitton 2018

PTI- Lupus

- Intérêt de l'hydroxychloroquine
- Place du rituximab
- Peu d'étude prennent en compte l'activité lupique extra-hématologique
  - « Lupus hématologique »
  - Thrombopénie lors d'une poussée systémique
- Evaluation des agonistes TPO++ **Be Carefull !**

Neutropénie

- 17% des lupus < 1000 PN /mm3.
- <5% des lupus <500 PN/mm3
- < 50 cas rapportés d'infections sévère du neutropénique
- Réponse au GCSF

Fayyaz 2015

Neutropénie n=33 (vs 65)

	Prior to neutropenia			Episode of neutropenia		
	With neutropenia	Without neutropenia	*P*	With neutropenia	Without neutropenia	P
SLEDAI	5.2 ± 6.5	6.9 ± 5.6	0.27	5.8 ± 4.7	9.8 ± 6.7	0.001
Mex-SLEDAI	3.8 ± 4.9	5.4 ± 3.9	0.15	3.8 ± 3.4	6.4 ± 4.3	0.002
Infection (%)	–	–	–	75.7	49.2	0.012
Haemoglobin	11.6 ± 2.6	11.5 ± 2.3	0.87	8.9 ± 2.4	11.1 ± 2.4	<0.001
Leucocytes	5908 ± 3368	5925 ± 2942	0.98	1071 ± 654	8832 ± 4692	<0.001
Neutrophils	3793 ± 2627	4162 ± 2336	0.56	307 ± 253	7003 ± 4134	<0.001
Lymphocytes	948 ± 706	1143 ± 768	0.30	627 ± 616	1165 ± 979	<0.001
Platelets	224 ± 104	249 ± 142	0.44	138 ± 111	236 ± 145	0.001
MCV	89.1 ± 8.1	85.1 ± 7.2	0.04	89.18 ± 7.8	86.6 ± 7.1	0.12
MCH	30.4 ± 3	28.7 ± 3.1	0.04	30.5 ± 3.7	29.8 ± 3.1	0.33
SGOT	60.4 ± 145	45.1 ± 66.8	0.65	95.1 ± 151.3	42.7 ± 50.9	0.02
SGPT	53.8 ± 117	30.6 ± 40.8	0.38	83.3 ± 141.4	34.9 ± 46.5	0.02

TABLE 5. Variables associated with the development of neutropenia in SLE patients

Variables	OR (95% CI)	*P*
Use of immunosuppressive drugs	4.81 (1.1–20.8)	0.035
History of CNS involvement	5.04 (1.2–20.8)	0.025
History of thrombocytopenia	4.72 (1.8–12.6)	0.002
Use of concomitant medications	16.5 (2.9–94.4)	0.002

Durée moyenne 14 jours

Martinez Banos 2006

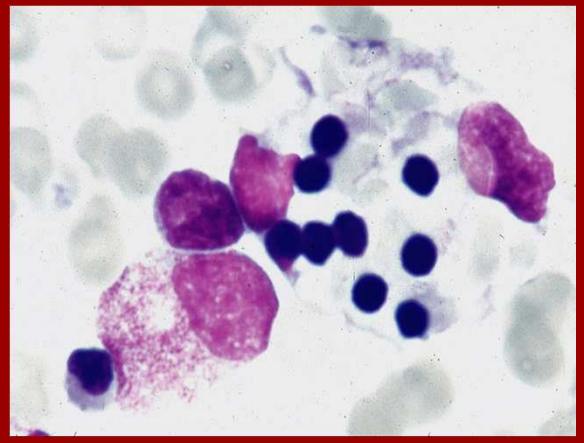
Neutropénie

- T médiée
- IgG médié
- TRAILs élevé

Association anti SSA

- **Anti SSA associé à la neutropénie**
- **Reconnaissance d'antigène Kd sur les PN et les précurseurs médullaires**

Kurrien 2000



Hemophagocytic Syndrome

Lionel GALICIER – lionel.galicier @sls.aphp.fr

10/24/2104

Diagnostic criterias - HLH 2004

- **Developed in a pediatric cohort with FHL**
- **May not be adapted to acquired HS**
- **Some tests are not routinely availables**
- **low specificity of Ferritinemia cut-off**
  - **Is 2000 µg/l better * ?**

Henter, 2007; Lehmberg K, 2014

Hscore estimate the risk of having HS

- Hscore < 90 risk of HS < 1%
- Hscore > 250 risk of HS > 99%

Free available at:
http://saintantoine.aphp.fr/score/

Fardet & Galicier 2014

Infection associated hemophagocytic syndrome

Robert J. Risdall, MD,* Robert W. McKenna, MD, Mark E. Nesbit, MD, William Krivit, MD, Henry H. Balfour, Jr, MD, Richard L. Simmons, MD, and Richard D. Brunning, MD

N = 19

Corticosteroids

Azathioprine n =14

6 deaths

Table 2. Group I Patients: Viral Infections

Patient	Virus implicated	Antibody titers*
1	None†	
2	None†	
3	Epstein Barr	2560 → < 10 (IgM IF)
4	None†	
5	Adenovirus	4 → 1024 (CF)

Table 4. Group II Patients with Herpes Group Viruses Other than Cytomegalovirus

		Viral infection confirmed by	
Patient	Virus implicated	Positive culture from	Antibody titer rise*
12	Herpes simplex	Bronchial washings	4 → 64 (CF)
14	Varicella-zoster†		<4 → 128 (CF)
17	Epstein Barr		<10 → 640 (IF)

Table 3. Group II Patients with Cytomegalovirus

	Cytomegalovirus infection confirmed by		
Patient	Isolation of CMV from	CF titer rise*	CMV inclusions
7			Lung, esophagus, lymph node (autopsy)
8			Liver, adrenal lymph node (autopsy)
9	Throat Urine		
10	Urine Sputum		Antemortem bone marrow biopsy liver, lung (autopsy)
11	Throat Urine	4 → 512	
13	Sputum Lung	16 → 128	Lung, lymph node (autopsy)
15	Urine	4 → 512	
16	Urine	8 → 256	
18	Urine	<4 → 128	
19	Blood Throat Urine	<4 → 512	

* Titers expressed as reciprocals of serum dilutions.

Table 1. Clinical characteristics of 26 patients with reactive hemophagocytic syndrome and systemic disease*

Patient no.	Age	Sex	Systemic disease	Clinical symptoms of RHS: Fever >38°C	Lymphadenopathy	Splenomegaly	Hepatomegaly	Skin lesions	Trigger factor of RHS†
1	72	F	RA	+	+	−	−	−	Both
2	46	F	SS	+	+	+	−	−	Infection alone
3	32	M	ASD	+	+	+	−	+	Onset alone
4	27	F	SLE	+	+	−	−	−	Onset alone
5	48	F	SLE	+	+	−	−	+	Both
6	63	F	ASD	+	−	+	−	−	Infection alone
7	48	F	MCTD	+	−	−	−	−	Infection alone
8	53	F	SLE	−	−	+	+	−	Infection alone
9	67	F	RA	−	−	−	−	−	Infection alone

TABLE 1. Prevalence of HPS and AAHS

Underlying diseases	SLE ($n=350$)	RA ($n=136$)	PM/DM ($n=98$)	Vasculitis ($n=91$)	SSc ($n=88$)	SS ($n=37$)	AOSD ($n=26$)	Others ($n=188$)	Total ($n=1014$)
Age (mean ± S.D.)	37 ± 14	62 ± 12	54 ± 14	55 ± 19	44 ± 15	54 ± 12	34 ± 16	44 ± 17	46 ± 18
Sex, female/male	293/57	104/32	72/26	62/29	78/10	36/1	20/6	142/46	807/207
HPS (%)	18 (5.1)	2 (1.5)	2 (2.0)	1 (1.1)	2 (2.3)	2 (5.4)	3 (11.5)	0 (0)	30 (3.0)
AAHS (%)	16 (4.6)	0 (0)	1 (1.0)	0 (0)	0 (0)	0 (0)	2 (7.7)	0 (0)	19 (1.9)

			+polymyositis						
18	62	F	SLE	+	−	−	−	−	Onset alone
			+myasthenia						
19	34	F	SLE	+	−	+	+	−	No
20	59	M	PAN	−	−	−	−	−	Both
21	34	F	SLE	+	+	−	−	−	Onset alone
22	37	F	SLE	+	+	−	−	−	Both
23	17	F	SLE	+	−	+	+	−	Onset alone
24	41	M	ASD	+	+	−	−	−	Onset alone
25	72	M	ASD	+	−	−	−	−	Onset alone
26	60	M	PAN	+	+	−	−	−	Infection alone

* RHS = reactive hemophagocytic syndrome; F = female; RA = rheumatoid arthritis; SS = primitive Sjögren's syndrome; M = male; ASD = adult Still's disease; SLE = systemic lupus erythematosus; MCTD = mixed connective tissue disease; PAN = polyarteritis nodosa.
† Trigger factors are onset of systemic disease, infection, both, or no circumstance.

SAM/Lupus revue 61 cas

	Total (n = 116)†	Underlying SLE (n = 61)
Treatment, no. (%)‡		
Corticosteroids	114 (98.3)	61 (100)
Prednisolone	79 (68.1)	50 (82.0)
IV MP	71 (61.2)	38 (62.3)
IVIG	28 (24.1)	12 (19.7)
Cyclosporine	24 (20.7)	13 (21.3)
IV CYC	17 (14.7)	11 (18.0)
G-CSF	8 (6.9)	2 (3.3)
Plasma exchange	5 (4.3)	3 (4.9)
Tacrolimus	5 (4.3)	2 (3.3)
Methotrexate	4 (3.4)	1 (1.6)
Etoposide	3 (2.6)	1 (1.6)
Vincristine	3 (2.6)	1 (1.6)
Splenectomy	2 (1.7)	1 (1.6)
Leukapheresis	1 (0.9)	0 (0)
CHOP	1 (0.9)	0 (0)
Biologic agents		
Infliximab	2 (1.7)	1 (1.6)
Etanercept	3 (2.6)	2 (3.3)
Rituximab	3 (2.6)	3 (4.9)
Tocilizumab	1 (0.9)	0 (0)
Effects of treatment, no. of responders/total no. (%)		
Initial therapy		
Corticosteroids	64/111 (57.7)	32/59 (54.2)
Corticosteroids alone	46/87 (52.9)	28/53 (52.8)
Corticosteroids + other agents§	18/24 (75)¶	4/6 (66.7)
IVIG	1/4 (25)	0/2 (0)
Cyclosporine	1/1 (100)	
Overall response to initial therapy	66/116 (56.9)	32/61 (52.4)
Therapy for corticosteroid-refractory disease#		
Cyclosporine	5/14 (35.7)	2/10 (20)
IV CYC	11/12 (91.6)**	5/6 (83.3)**
IVIG	1/12 (8.3)	0/7 (0)

Mortalité 10%

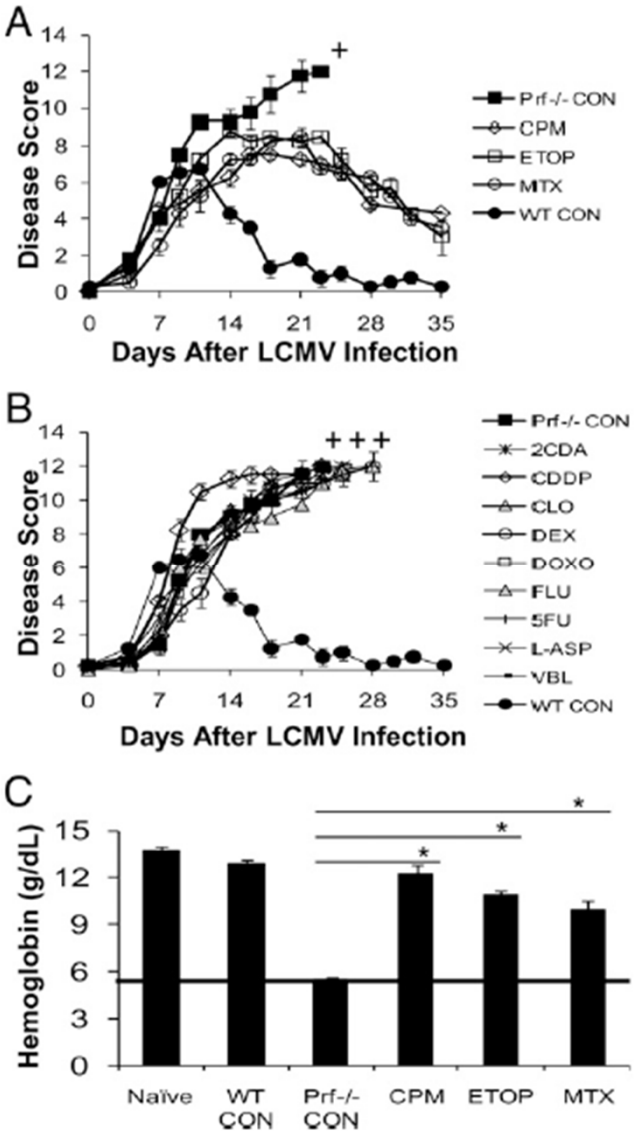
Kamakura 2014

SAM - CYC

- Modèle murin prf-/-
- Challenge LCMV

- Efficacité:
  - Etoposide
  - Cyclophosphamide
  - Methotrexate

- Innefficacité
  - Dexamethasone
  - Divers cytotoxique



Johnson 2013

SAM Lupus/ revue 93 cas

- 32 patients traités pas cyclosporine
  - 22 répondeurs (68%)
  - Réponse à la cyclo associée à
    - Neutropénie
    - Ferritine

Propose la cyclo en deuxième ligne après corticoides

Takahashia 2015

Cyclosporine - MAS

Table 5. Therapeutic interventions for patients with MAS associated with systemic JIA (n = 362)*

Intervention (no. of patients with data available if <362)	No. (%) of patients
Any corticosteroids (n = 349)	341 (97.7)
Intravenous corticosteroids (n = 349)	309 (88.5)
Oral corticosteroids (n = 335)	256 (76.4)
Cyclosporine (n = 348)	213 (61.2)
Intravenous immunoglobulin (n = 344)	125 (36.3)
Biologic medications (n = 341)	52 (15.2)
Anakinra	33 (9.7)
Etanercept	8 (2.3)
Rituximab	5 (1.5)
Tocilizumab	5 (1.5)
Infliximab	3 (0.9)
Canakinumab	3 (0.9)
Abatacept	1 (0.3)
Alemtuzumab	1 (0.3)
Etoposide (n = 339)	40 (11.8)
Other immunosuppressants (n = 336)	24 (7.1)
Methotrexate	12 (3.6)
Cyclophosphamide	3 (0.9)
Tacrolimus	2 (0.6)
Thalidomide	1 (0.3)
6-mercaptopurine	1 (0.3)
Vinblastine	1 (0.3)
Mycophenolate mofetil	1 (0.3)
Plasma exchange (n = 342)	14 (4.1)

Survie: 92%

Minoia: 2014

Lupus cytopénies

- Situation fréquente.
- Présentations variées. **Penser au lupus devant toutes cytopénies inexpliquées**
- EPO: oui, GCSF: Oui, **aTPO: Attention!**
- Penser maladie **active vs toxicité**
- Intérêt occasionnel de drogues peu utilisées (rituximab et cyclosporine)
- Penser au **SAM**