Les publications qui changent la vie de (d'un) interniste …

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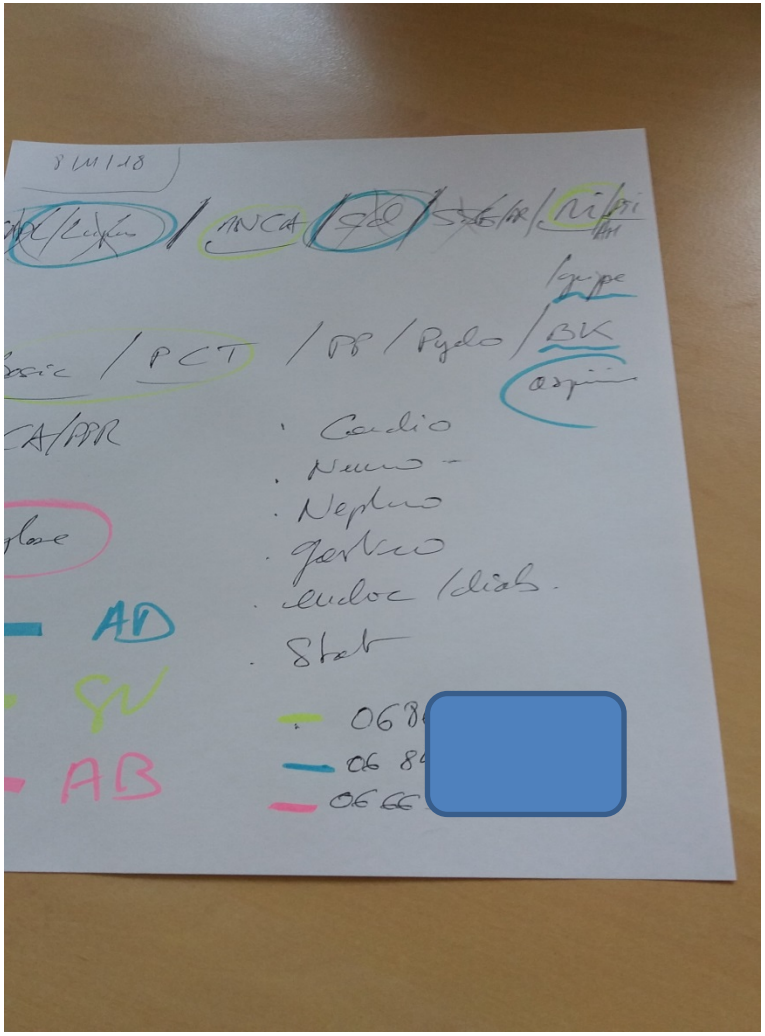
Doctor Who : on connait la date de lancement de la saison 11 ! — 5 sept. 2018

Très attendue par les fans, la nouvelle saison de "Doctor Who" portée par Jodie Whittaker sera diffusée sur la BBC à partir du 7 octobre.

Quid ?



Classification of primary antiphospholipid syndrome as systemic lupus erythematosus: Analysis of a cohort of 214 patients

Romain Paule[a,b], Nathalie Morel[b], Véronique Le Guern[b], Micaela Fredi[b], Laetitia Coutte[a], Meriem Belhocine[b], Luc Mouthon[a,b], Claire le Jeunne[a,b], Anthony Chauvin[f,g], Jean-Charles Piette[c,d], Nathalie Costedoat-Chalumeau[a,b,e,*]

Autoimmunity Reviews 17 (2018) 866–872

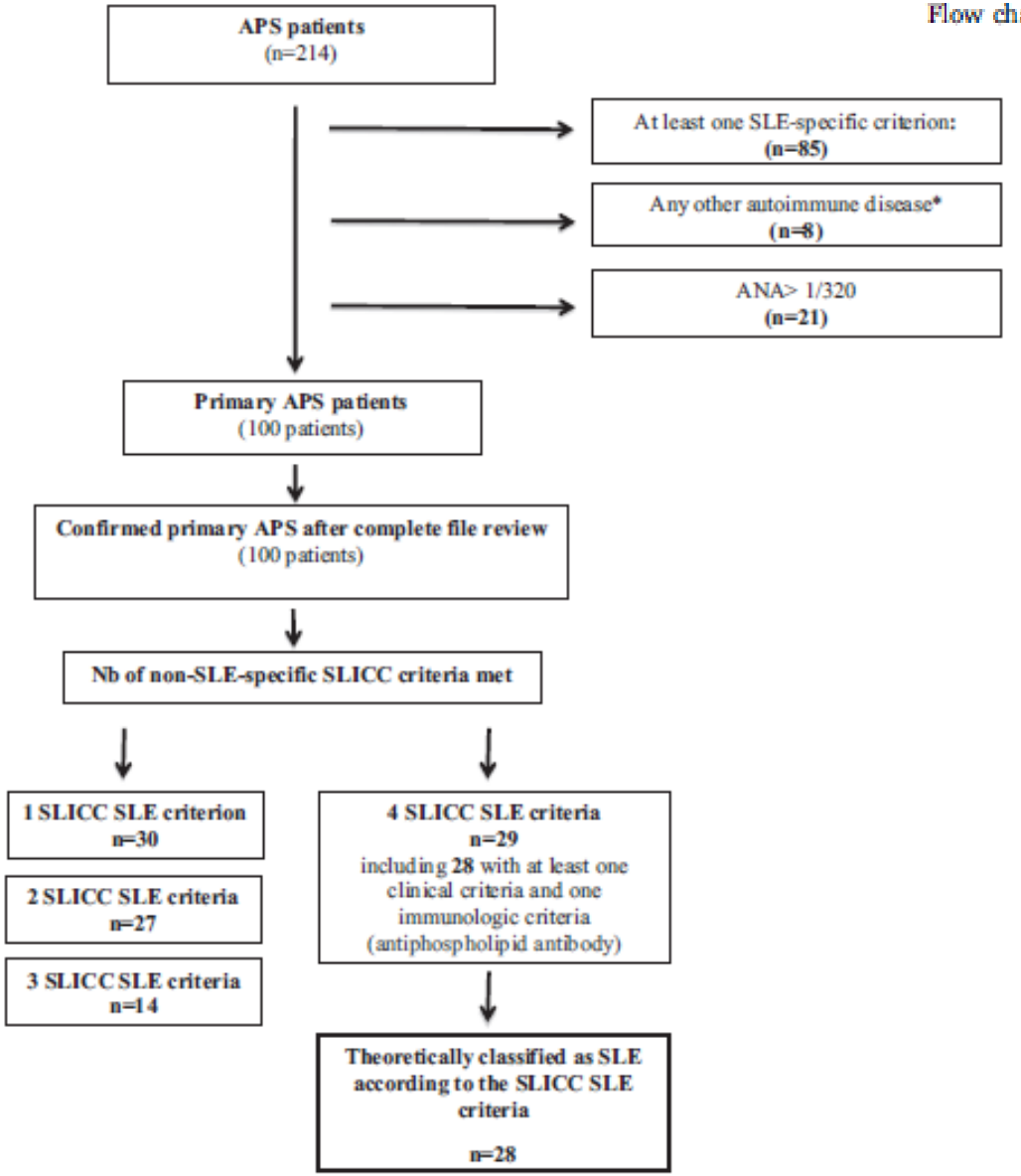
Le SAPL dans toutes ses formes…

- SAPL
  - Primaire : 35%
  - Secondaire : LES (50%), …
- SAPL
  - Obstétrical
  - Veineux
  - Artériel
  - …

	Critères de classification du LED	Détails
Critères cliniques	Lupus cutané aigu ou subaigu	Rash malaire Lupus bulleux Nécrolyse épidermique toxique Rash maculopapuleux Rash dans le cadre d'une photosensibilité Lésion psoriasiforme Lésion annulaire polycyclique
	Lupus cutané chronique	Rash discoïde Lésion verruqueuse Panniculite lupique Lupus tumidus Lupus engelure Lésion type lichen plan
	Lésion muqueuse orale ou nasale	Palais, bouche, langue ou nez
	Alopécie non cicatricielle	Lésion diffuse avec des cheveux cassés visibles
	Synovites ≥ 2 articulations Ou douleur ≥ 2 articulations + dérouillage matinal	
	Sérite	Pleurésie ≥ 1 jour Péricardite ≥ 1 jour
	Atteinte rénale	Protéinurie > 0,5 g/24 h Ou hématurie
	Atteinte neurologique	épilepsie, psychose, mononévrite, myélite, neuropathie périphérique, état confusionnel aigu
	Anémie hémolytique	
	Leucopénie	Leucocytes < 4 000/mm³ Ou lymphocytes < 1 000/mm³
	Thrombopénie	< 100 000/mm³
Critère immunologique	Autoanticorps ou anomalie de certaines fractions du complément	Anticorps anti-nucléaires > norme du laboratoire Anticorps anti-ADN double brin > norme du laboratoire Anti-Sm Anticorps antiphospholipides Complément abaissé Test de Coobs direct positif

Présence possible dans le SAPL primaire

Flow chart of the study.



SAPL primaire *pseudo-lupique*

Data	Study population of primary APS n = 100	Patients with at least 4 SLICC criteria n = 28 Group A	Patients with 3 or fewer SLICC criteria n = 72 Group B	A vs B p
Epidemiology				
Sex ratio (F/M)	82/18	22/6	60/12	0.79
Median age at diagnosis [Q1; Q3]*	34 [28–39]	31 [24–39]	35 [28–38]	0.27
Median follow-up since APS diagnosis (years) [Q1; Q3]*	9 [5–16]	12 [7–17]	8 [5–13]	**0.03**
Clinical data				
Obstetric phenotype (n, %)	26 (26)	3 (11)	23 (32)	**0.04**
Venous phenotype (n, %)	46 (46)	11 (39)	35 (49)	0.5
Arterial phenotype (n, %)	28 (28)	14 (50)	14 (19)	**0.005**
Valvulopathy (n, %)	16 (16)	10 (36)	6 (8)	**0.002**
Livedo (n, %)	14 (14)	8 (29)	6 (8)	**0.02**
CAPS (n, %)	11 (11)	9 (32)	2 (3)	**0.0001**
Laboratory data				
LA positivity (n = 99)	60 (61)	26 (93)	34/71 (48)	< **0.001**
ACL positivity	87 (87)	26 (93)	61 (85)	0.34
Anti-B2GPI positivity (n = 96)	48 (50)	19/26 (73)	29/70 (41)	< **0.001**
Simple-positive for APL biology	45 (45)	3 (11)	42 (58)	**0.09**
Double-positive for APL biology	15 (15)	7 (25)	8 (11)	0.12
Triple positive for APL biology	40 (40)	18 (64)	22 (31)	**0.003**
Clinical SLICC criteria				
Criterion 6: pleural effusions (in case of pulmonary embolism) (n = 96)	13 (12.5)	10/27 (37)	2/69 (3)	< **0.001**
Criterion 7: renal involvement (proteinuria representing 500 mg protein/24 h) (n = 81)	10 (12)	9/26 (35)	1/55 (2)	< **0.001**
Criterion 8: seizures (n = 96)	10 (10)	8/27 (30)	2/69 (3)	**0.0001**
Criterion 9: haemolytic anaemia (n = 95)	9 (9)	8 (29)	1/67 (1)	< **0.001**
Criterion 10: Leucopenia < 4000/mm^3 at least once OR Lymphopenia < 1000/mm^3 at least once (n = 95)	21 (22)	14 (50)	7/67 (10)	< **0.001**
Criterion 11: thrombocytopenia (< 100,000/mm^3) at least once (n = 99)	21 (21)	17 (61)	4/71 (6)	< **0.001**
Immunological SLICC criteria				
Criterion 1: ANA level > laboratory reference range	42 (42)	19 (68)	23 (32)	**0.002**
Criterion 5: low complement (C3, C4, CH50) (n = 81)	31 (38)	19/26 (73)	12/55 (22)	< **0.001**
Criterion 6: direct Coombs test in the absence of haemolytic anaemia (n = 60)	17 (28)	12/23 (52)	5/37 (14)	**0.003**

Quel(s) enseignement(s)

- Une forme particulière de SAPL se rapproche des critères SLICC du lupus :
  - Phénotype artériel
  - Peu d'atteinte obstétrical
  - Triple positifs
  - Contexte de CAPS

Attention à ne pas surtraiter ou ne pas étiqueter trop tôt ces patients *« pseudo-lupus »*

Manque une classification du SAPL primaire ou un critère « lupus-specific » en cas de SAPL associé…

CLINICAL TRIALS AND OBSERVATIONS

Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome

Vittorio Pengo,[1] Gentian Denas,[1] Giacomo Zoppellaro,[1] Seena Padayattil Jose,[1] Ariela Hoxha,[2] Amelia Ruffatti,[2] Laura Andreoli,[3] Angela Tincani,[3] Caterina Cenci,[4] Domenico Prisco,[4] Tiziana Fierro,[5] Paolo Gresele,[5] Arturo Cafolla,[6] Valeria De Micheli,[7] Angelo Ghirarduzzi,[8] Alberto Tosetto,[9] Anna Falanga,[10] Ida Martinelli,[11] Sophie Testa,[12] Doris Barcellona,[13] Maria Gerosa,[14] and Alessandra Banzato[1]

blood® 27 SEPTEMBER 2018 | VOLUME 132, NUMBER 13

ETUDE TRAPS

« Trial on Rivaroxaban in AntiPhospholipid Syndrome »

Méthode(s)

INCLUSION :

- Triple positifs
- Critère(s) clinique de SAPL

RANDOMISATION
(Multicentrique)

INR cible 2,5

Inclusion M1 M3 M9 M15 … M36

A chaque visite :

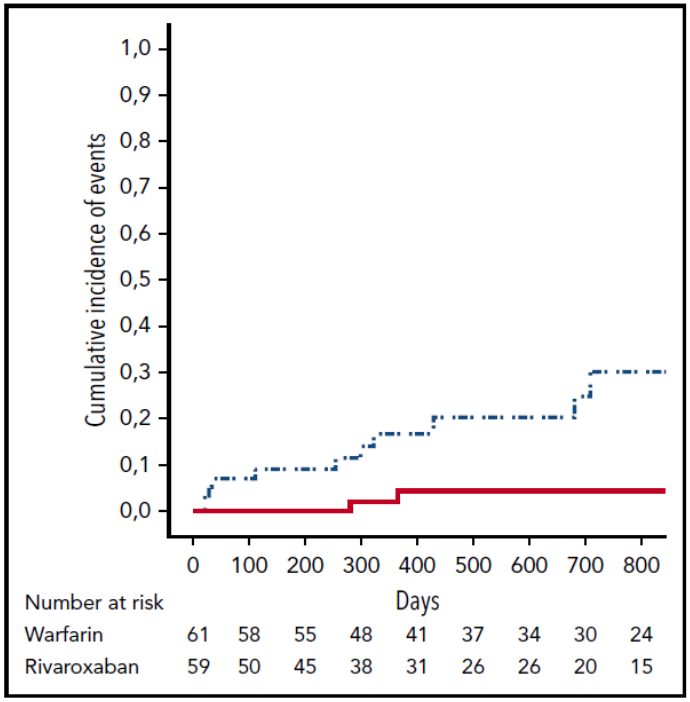
- Compte des comprimés
- Evènement(s) intercurrent(s)
- <u>Critère de jugement principal composite :</u>
  - **Incidence d'une MTEV**
  - **Hémorragie majeure**
  - **Décès de cause vasculaire**

Characteristic	Rivaroxaban (n = 59)	Warfarin (n = 61)
Females, n (%)	39 (66)	38 (62)
Age, y	46.5 ± 10.2*	46.1 ± 13.2*
Body mass index, kg/m²	26.1 ± 6.1*	25.5 ± 5.9*
CrCl, mL/min	117.0 ± 38.6*	109.3 ± 36.7*
Hemoglobin, g/L	131.7 ± 17.6*	135.9 ± 17.1*
Platelet count, ×10⁹/L	214.9 ± 73.8*	209.3 ± 63.5*
APS laboratory test positivity, n		
LA: dRVVT/aPTT/both	16/5/38	14/7/40
aCL: IgG or IgG + IgM/IgM only	57/2	52/9
aβ2GPI: IgG or IgG + IgM/IgM only	57/2	52/9
Autoimmune disease, n (%)	24 (41)	25 (41)
Systemic lupus erythematosus	10	15
Other autoimmune disease	14	10

Characteristic	Rivaroxaban (n = 59)	Warfarin (n = 61)
Previous thrombotic events, n (%)		
Arterial events	11 (19)	14 (23)
Stroke	8	8
Acute myocardial infarction	0	2
Other sites	3	4
Venous events	38 (64)	39 (64)
Deep vein thrombosis and/or pulmonary embolism	36	32
Other sites	2	7
Venous and arterial events	10 (17)	8 (13)
Pregnancy morbidity, n (%)†	16 (41)	12 (32)
Medications at time of randomization, n (%)		
Hydroxychloroquine	15 (25)	23 (38)
Corticosteroids	11 (19)	13 (21)
Other immunosuppressive drugs	17 (29)	21 (34)
Aspirin	11 (19)	10 (16)
Statins	7 (12)	10 (16)

Résultats : *arrêt prématuré !*

Outcome, n	"As treated" analysis			
	Rivaroxaban (n = 59)	Warfarin (n = 61)	HR (95% CI)	P
Thromboembolic events, major bleeding, and vascular death	11 (19)	2 (3)	6.7 (1.5-30.5)	.01
Arterial thrombosis Ischemic stroke Myocardial infarction	7 (12) 4 (7) 3 (5)	0 0 0	—	—
Venous thromboembolism	0	0		
Major bleeding	4 (7)	2 (3)	2.5 (0.5-13.6)	.3
Death	0	0	—	—



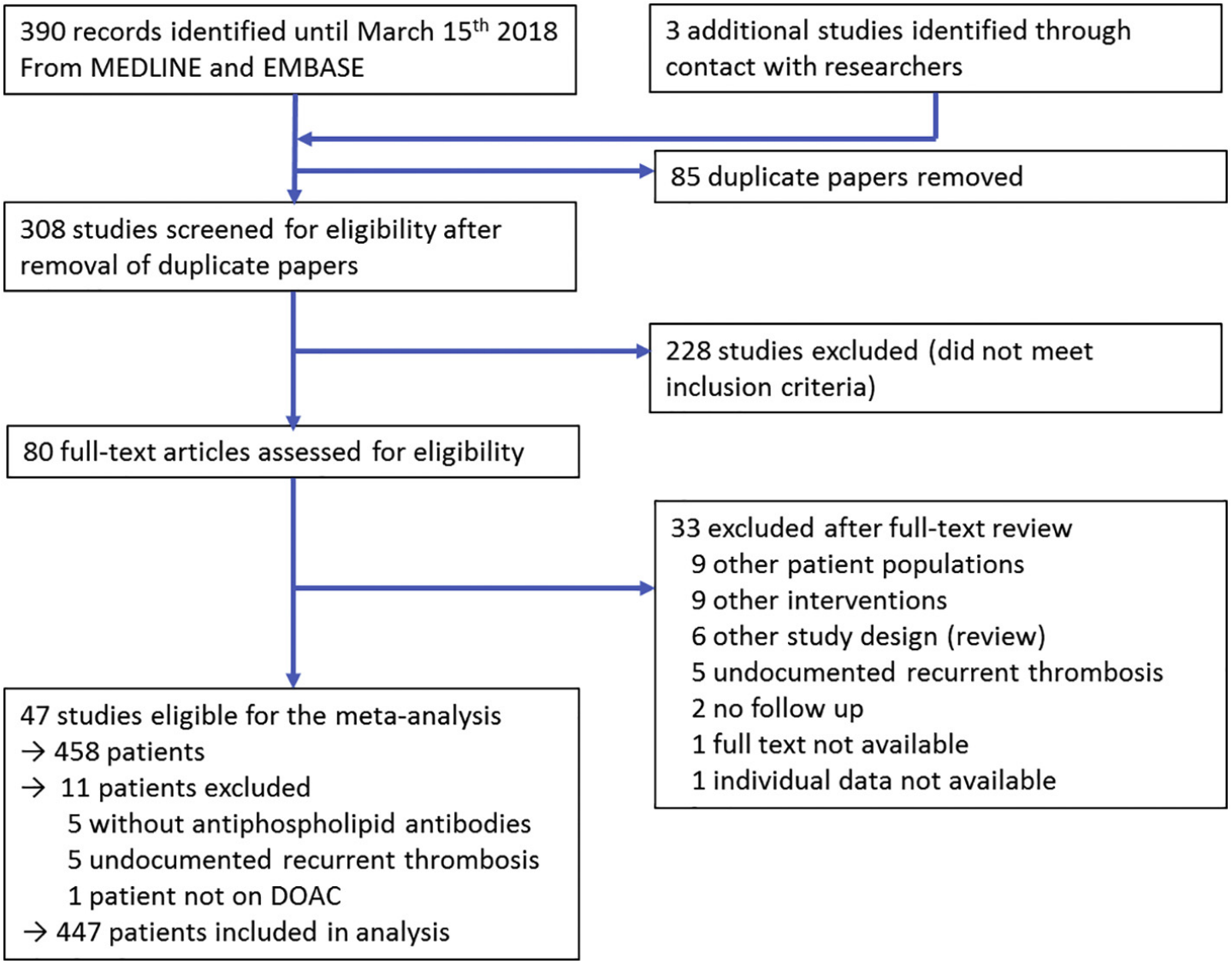
	Rivaroxaban	Warfarin
Discontinuation, n, (%)	9 (15)	3 (5)
Withdrawal of informed consent	2	1
Clinically relevant nonmajor bleeding	2	0
Planned pregnancy	3	1
Other	2	1

QUE FAIRE DES AOD dans le SAPL ?

Increased risk of thrombosis in antiphospholipid syndrome patients treated with direct oral anticoagulants. Results from an international patient-level data meta-analysis

Virginie Dufrost[a], Jessie Risse[a], Tatiana Reshetnyak[b], Maria Satybaldyeva[b], Yao Du[c], Xin-Xin Yan[c], Stella Salta[d,e], Grigorios Gerotziafas[d,e], Zhi-Cheng Jing[c], Ismaël Elalamy[d,e], Denis Wahl[a], Stéphane Zuily[a,*]

Autoimmunity Reviews 17 (2018) 1011–1021


390 records identified until March 15th 2018
From MEDLINE and EMBASE
3 additional studies identified through contact with researchers
85 duplicate papers removed
308 studies screened for eligibility after removal of duplicate papers
228 studies excluded (did not meet inclusion criteria)
80 full-text articles assessed for eligibility
33 excluded after full-text review
9 other patient populations
9 other interventions
6 other study design (review)
5 undocumented recurrent thrombosis
2 no follow up
1 full text not available
1 individual data not available
47 studies eligible for the meta-analysis
→ 458 patients
→ 11 patients excluded
5 without antiphospholipid antibodies
5 undocumented recurrent thrombosis
1 patient not on DOAC
→ 447 patients included in analysis

	Total population (n = 447)
Mean age, year ± SD	43.6 ± 10.9
Gender, n/N (%)	
Women	204/299 (68)
Male	95/299 (32)
Number of clinical criteria for APS classification, number ± SD	1.3 ± 0.5
History of clinical manifestations, n/N (%)	
Venous thrombosis	405/445 (91)
Arterial thrombosis	82/350 (23)
Small vessels thrombosis	11/174 (6)
Obstetrical morbidity	46/223 (21)
aPL profile	
LA	212/307 (69)
aCL	205/305 (67)
aβ_2-GPI	154/302 (51)
Double positivity	93/325 (29)
Triple positivity[a]	94/326 (29)
Underlying autoimmune disease, n/N (%)	
Primary APS	145/248 (58)
Secondary APS	103/248 (42)
SLE	92/247 (37)
Previous treatments, n/N (%)	
VKA	213/260 (82)
LMWH	7/260 (3)
Fondaparinux	2/260 (1)
None	36/260 (14)
Reason for switching, n/N (%)	
Simplification	6/242 (3)
Physician's choice	87/238 (37)
INR lability or poor adherence to INR monitoring	94/242 (39)
Bleeding during VKA	8/242 (3)
Recurrence during VKA	29/242 (12)
Patient's choice	13/238 (5)
DOAC, n/N (%)	
AntiXa	303/447 (68)
Rivaroxaban	290/447 (65)
Apixaban	13/447 (3)
Dabigatran	144/447 (32)
Duration of followed, month ± SD	16.2 ± 11.5

Table 2
Characteristics of all APS patients treated with DOACs.

Résultats vs épidémiologie …

Characteristics of all APS patients treated with DOACs.

	Total population (n = 447)	APS without recurrent thrombosis (n = 374)	APS with recurrent thrombosis (n = 73)

Characteristics of APS patients treated with anti-Xa.

	Total population (*n* = 303)	APS without recurrent thrombosis (*n* = 252)	APS with recurrent thrombosis (*n* = 51)

Characteristics of APS patients treated with dabigatran etexilate.

	Total population (n = 144)	APS without recurrent thrombosis (*n* = 122)	APS with recurrent thrombosis (*n* = 22)

- 16% récurrence de thrombose à 12 mois environ
  - 33% chez les « triple positifs »
- Données littéraires :
  - Récurrence de thrombose à 5 ans : 30 % chez les triples positifs…

Faut-il laisser de coté les AOD ?

- Surement pour les SAPL à haut risque
- Pas forcément pour les SAPL veineux et biologique peu sévère
- Pharmacocinétique :
  - Monitoring biologique de posologie ?
  - Génération de thrombine…
  - Observance …
- Intérêt de l'aspirine ?
- Quid de l'hydroxychloroquine ?

Review

HIBISCUS: Hydroxychloroquine for the secondary prevention of thrombotic and obstetrical events in primary antiphospholipid syndrome*

Autoimmunity Reviews 17 (2018) 1153–1168

Efficacité du traitement « classique »

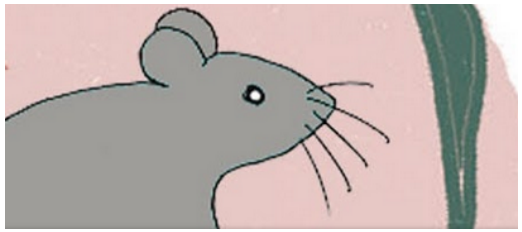
- SAPL :
  - 20 à 21% de récidive de MTEV à 5 ans
  - 30% en cas de « triple positifs »
  - Survie : 90,1% à 10 ans
- SAPL obstétrical :
  - 20-28% de récidive obstétricale

Cervera R, Khamashta MA, Shoenfeld Y, Camps MT, Jacobsen S, Kiss E, et al. Morbidity and mortality in the antiphospholipid syndrome during a 5-year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis 2009;68:1428–32.

Cervera R, Serrano R, Pons-Estel GJ, Ceberio-Hualde L, Shoenfeld Y, de Ramón E, et al. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis 2015;74:1011–8.

HCQ : le sauveur ?

- Immunomodulateur
- Efficacité cardiovasculaire et métabolique
  - Athérome
  - Hypocholestérolémiant
- Antithrombotique
- Antinéoplasique ?
- Survie, baisse des APL…



SAPL thrombotique

- ***Revue narrative***
- HCQ + AVK mieux que AVK seul dans les SAPL primaires (rechute de thrombose veineuse et artériel) et associés au LES
- HCQ : diminution du taux des APL
- Amélioration de la survie :
  - 68 % versus 95 % à 15 ans

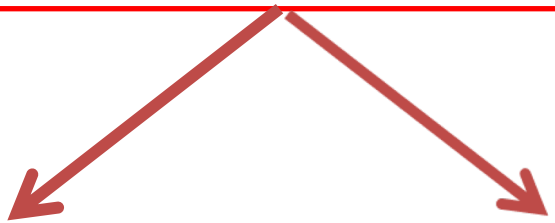
Thus, based on all these data dealing with the significant risk of thrombotic relapse, occurring under appropriate treatment, we propose the use of HCQ additionally to standard anticoagulant treatment for the prevention of thrombosis relapse in antiphospholipid syndrome.

SAPL obstétrical

- Bénéfice au cours de la grossesse :
  - Diminution mortalité néonatale, prématurité et RCIU (LES)
  - Augmente le taux de grossesse à terme
- Modalités de prescription :
  - Avant la grossesse (p 0,021)
  - Dose « normale » (400 vs 200mg, p 0,036)

Country	Methodology	Number of cases	Patients treated with HCQ
European The EUROAPS register led by the Europhospholipid group	Retrospective	247	3
European	Retrospective	30	14 including also asymptomatic aPL manifestations
Italy	Case report	1	1
USA	Case report	1	1
France	Prospective	14	14
Italy and England	retrospective	96	31
France	retrospective	118	41
International	retrospective	194	

However, the effect of HCQ was not adjusted for the use of other medications such as aspirin, heparins or steroids [10]. Selected experts agreed that adding HCQ could be considered in selected cases or after failure of standard treatment with aspirin and a heparin [10]. Specifically, most experts considered adding HCQ in specific situations: women with previous thrombosis, and/or with placenta-mediated complications, when a high risk aPL profile or concomitant cardiovascular risk factors are present or in case of allergy/intolerance to aspirin



HIBISCUS-O

HIBISCUS-T

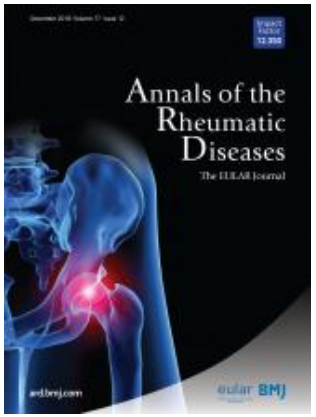
2 petits « apartés »

HYDROXYCHLOROQUINE : MYTHES ET RÉALITÉS

Cardiovascular effects of hydroxychloroquine: a systematic review and meta-analysis

Mathieu S, Pereira B, Tournadre A, Soubrier M

Annals of the Rheumatic Diseases 2018;77:e80



Characteristics	Studies (n)	HCQ users	HCQ non-users	Standardised mean difference (95% CI) Fixed or random effects	P value
Glycaemia, g/L	6	0.89±0.19	0.99±0.31	–0.28 [(–0.41 to –0.15)	<0.001
Total cholesterol, g/L	12	1.87±0.37	1.92±0.38	–0.57 (–0.97 to –0.18)	0.004
LDL cholesterol, g/L	12	1.06±0.36	1.11±0.35	–0.23 (–0.40 to –0.06)	0.009
HDL cholesterol, g/L	11	0.53±0.14	0.50±0.15	0.20 [(0.05 to 0.34)	0.007
Triglycerides, g/L	12	1.18±0.58	1.37±0.78	–0.32 (–0.50 to –0.14)	<0.001
Atherogenic index (TC/HDL)	6	3.46±1.25	3.99±1.40	–0.28 (–0.37 to –0.18)	<0.001

Table 1 Comparison of cardiovascular risk factors in case/control studies

33 references,
a total of 24 923 HCQ users and 36 327 non-users.
over a mean follow-up of 3 years

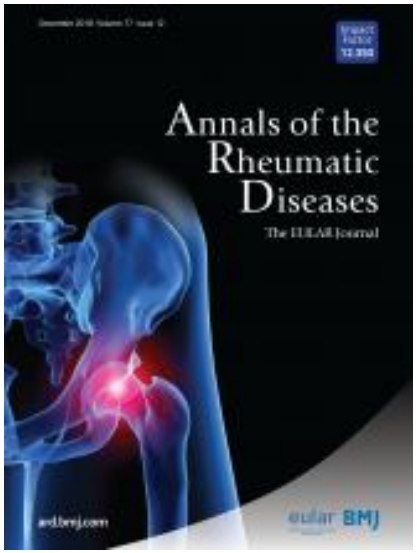
Table 2 Effects of 12 weeks of HCQ treatment on lipid and glycaemic parameters

Parameters	Studies (n)/ patients (n)	Standardised mean difference (95% CI) Fixed or random effect	P value	I^2 (%)
Total cholesterol	7/214	−0.32 (−0.52 to −0.13)	0.001	27
LDL cholesterol	6/193	−0.24 (−0.44 to −0.04)	0.019	0
HDL cholesterol	6/193	0.03 (−0.17 to 0.23)	0.750	0
Triglycerides	6/193	−0.20 (−0.40 to 0.002)	0.053	0
Glycaemia	4/160	−0.33 (−0.55 to −0.11)	0.004	43
Glycated haemoglobin	3/152	−0.34 (−0.57 to −0.12)	0.003	14

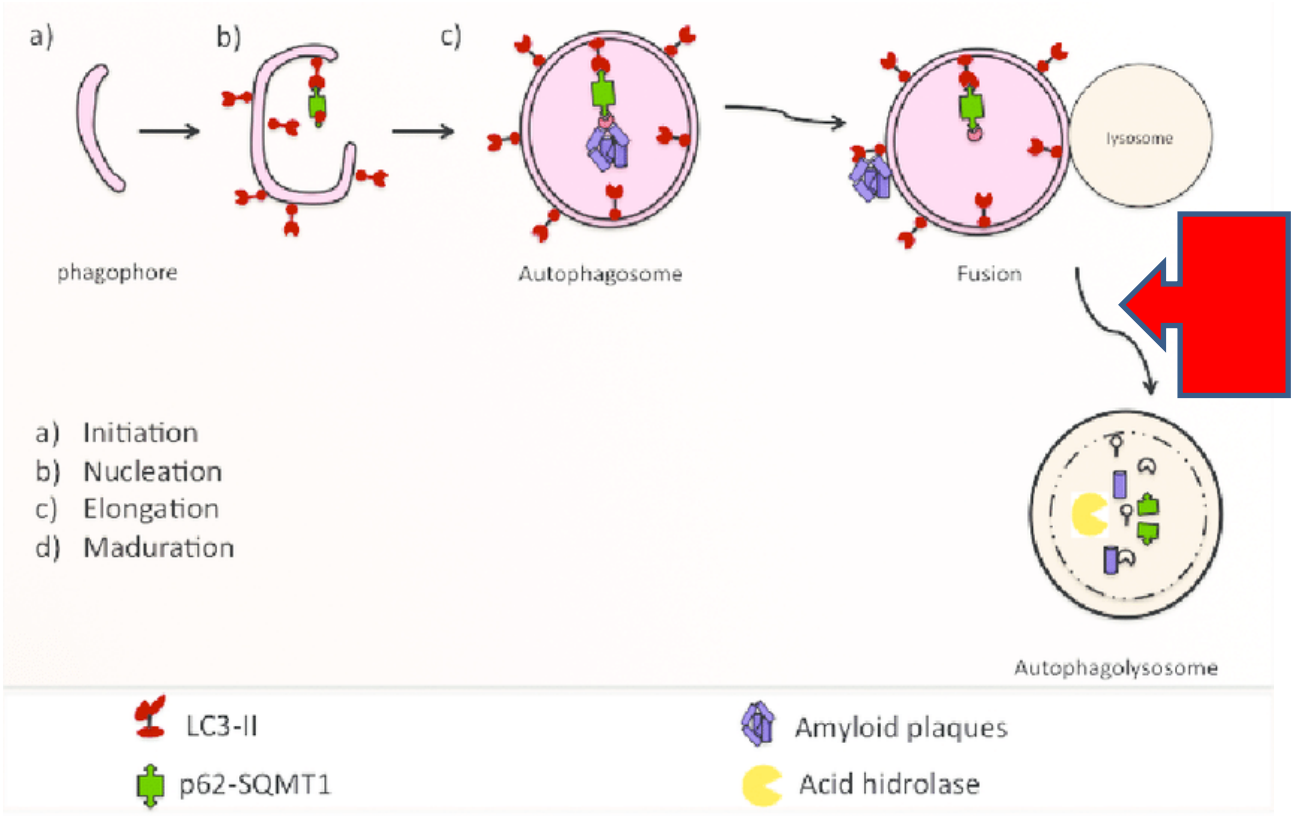
Chronic hydroxychloroquine/chloroquine exposure for connective tissue diseases and risk of Alzheimer's disease: a population-based cohort study

Laurence Fardet, Irwin Nazareth, Irene Petersen

Ann Rheum Dis. 2018 Sep 5. pii: annrheumdis-2018-214016.



Rationnel (éventuel !)



HCQ
Blocage de l'autophagie

Population

	Long-term exposed N=11 550	Short-term exposed N=4873	Unexposed N=30 930
Age (years)	56 (46–669)	57 (45–67)	57 (46–67)
Female, n (%)	8970 (77.7)	4023 (82.6)	23 251 (75.2)
Duration of follow-up after 'start date' (days)	1630 (935–2737)	1658 (923–2806)	1521 (1097–2377)
Dosage (mg/day)			
Hydroxychloroquine	261 (200–356)	391 (255–400)	–
Chloroquine	162 (102–224)	–	–
Underlying diseases, n (%)			
Rheumatoid arthritis	7866 (68.1)	3411 (70.0)	22 274 (72.0)
Lupus erythematosus	2.032 (17.6)	616 (12.6)	3105 (10.0)
Sjogren syndrome	781 (6.8)	412 (8.5)	2653 (8.6)
Other connective tissue diseases	782 (6.8)	401 (8.2)	2632 (8.5)
Light eruption	89 (0.7)	33 (0.7)	266 (0.9)

for ≥1 year, <1 year

Data from The Health Improvement Network (THIN) were used (January 1990–December 2016).

Résultats

	Long-term exposed (n=11 550) compared with short-term exposed (n=4873)		Long-term exposed (n=11 550) compared with unexposed (n=30 930)	
	Adjusted sHR	P values	Adjusted sHR	P values
Risk of dementia				
AD (AD medical codes)	1.03 (0.63–1.69)*	0.89	0.81 (0.58–1.12)*	0.20
AD (AD / 'senile dementia' medical codes)	0.97 (0.65–1.45)†	0.87	0.79 (0.60–1.04)†	0.09
AD (AD / 'senile dementia' medical codes or specific medications‡)	0.97 (0.67–1.39)†	0.85	0.78 (0.61–1.00)†	0.05
Vascular dementia§	1.05 (0.54–2.04)*	0.88	0.84 (0.55–1.28)*	0.41
Other or unspecified dementia§	0.83 (0.47–1.47)†	0.53	0.78 (0.53–1.14)¶	0.20
Symptoms	1.03 (0.81–1.31)**	0.82	1.14 (0.97–1.33)†	0.12
Risk of death	Adjusted HR	P values	Adjusted HR	P values
Overall population	0.93 (0.83–1.05)¶	0.25	0.79 (0.72–0.85)¶	<0.001
≤70 years old	0.84 (0.72–0.99)¶	0.04	0.66 (0.59–0.75) ¶	<0.001
>70 years old	1.05 (0.88–1.27)¶	0.57	0.94 (0.83–1.05)¶	0.28
Those diagnosed with AD	1.10 (0.44–2.74)††	0.84	1.08 (0.60–1.92)††	0.80

Toujours la MTEV

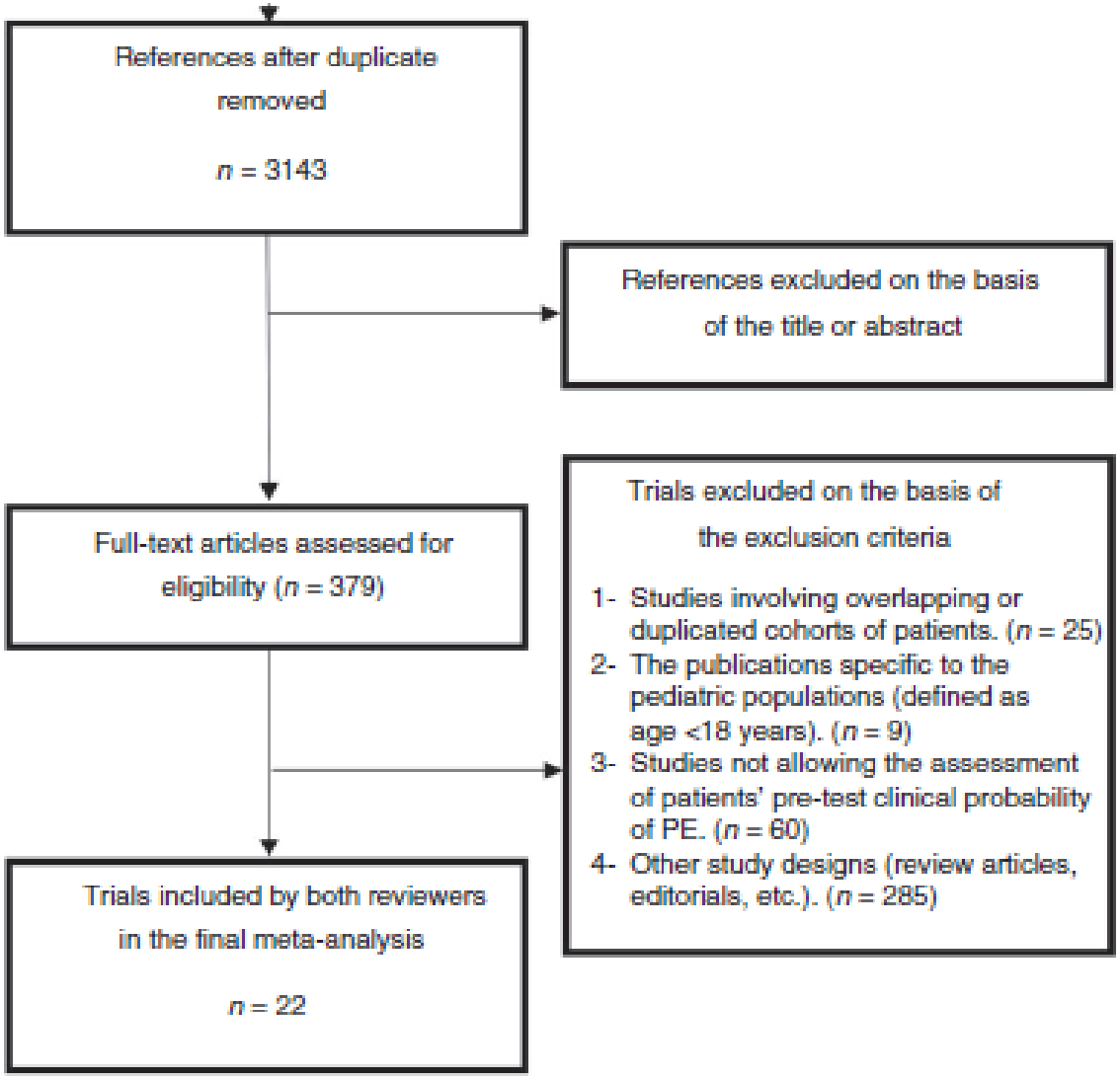
WHAT IS THE RISK OF A VENOUS THROMBOEMBOLIC EVENT AFTER A NEGATIVE COMPUTED TOMOGRAPHIC PULMONARY ANGIOGRAPHY RESULT?

Outcomes following a negative computed tomography pulmonary angiography according to pulmonary embolism prevalence: a meta-analysis of the management outcome studies

D. BELZILE,* S. JACQUET,* L. BERTOLETTI,†‡§ Y. LACASSE,*¶ C. LAMBERT,* J. C. LEGA**†† and S. PROVENCHER*¶

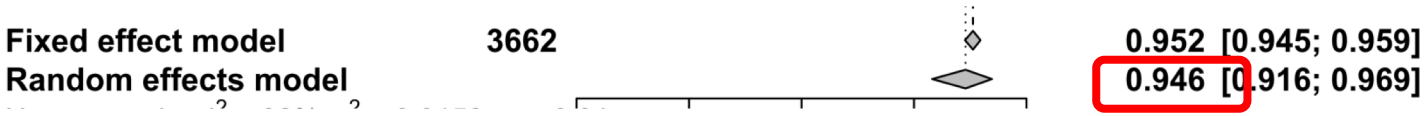
Journal of Thrombosis and Haemostasis, **16**: 1107–1120

jth
journal of
thrombosis and haemostasis™


References after duplicate removed
n = 3143
References excluded on the basis of the title or abstract
Full-text articles assessed for eligibility (n = 379)
Trials excluded on the basis of the exclusion criteria
1- Studies involving overlapping or duplicated cohorts of patients. (n = 25)
2- The publications specific to the pediatric populations (defined as age <18 years). (n = 9)
3- Studies not allowing the assessment of patients' pre-test clinical probability of PE. (n = 60)
4- Other study designs (review articles, editorials, etc.). (n = 285)
Trials included by both reviewers in the final meta-analysis
n = 22

Angio-TDM normale : 7863 patients

- 148 présentent une MTEV contemporaine
  - *ED : 113*
  - *Scintigraphie pulmonaire : 3*
  - *Artériographie : 4*
  - *NP : 28*
- *74 patients diagnostiqués MTEV au cours des 3 mois suivants*
  - *26 TVP*
  - *44 Embolie Pulmonaire*
  - *4 non précisés*



Sensibilité

Attention à la probabilité pré-test…

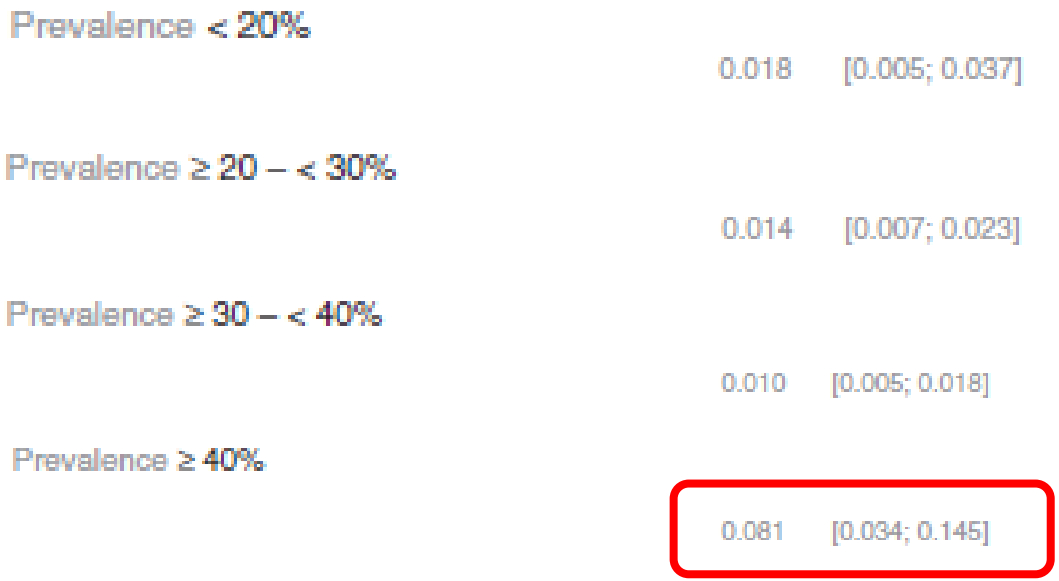


Fig. 4. Subgroup analysis according to the prevalence of pulmonary embolism (0–20%, 20–30%, 30–40% and > 40%). Confidence interval (CI) at 95%.

Faut-il « *jeter* » l'angio-TDM ?

- Problème de l'élément de comparaison ?
  - Les patients avaient-ils vraiment une EP?
  - Incidence de la MTEV « nosocomiale » ? (1/3)
  - Relecture des images ?
- Si la valeur pré-test est haute, traiter quand même ou faire ED systématique +++
- **Si la valeur pré-test est basse, VPN importante et suffisante !**

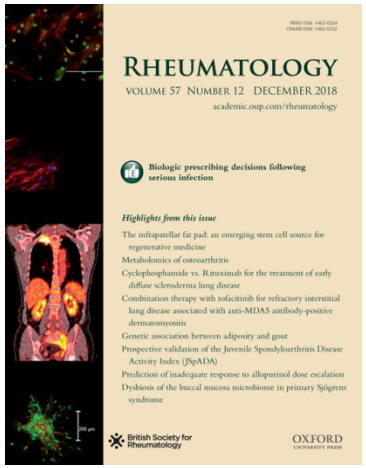
Pour changer de sujet…

LA SCLÉRODERMIE

Intravenous cyclophosphamide *vs* rituximab for the treatment of early diffuse scleroderma lung disease: open label, randomized, controlled trial

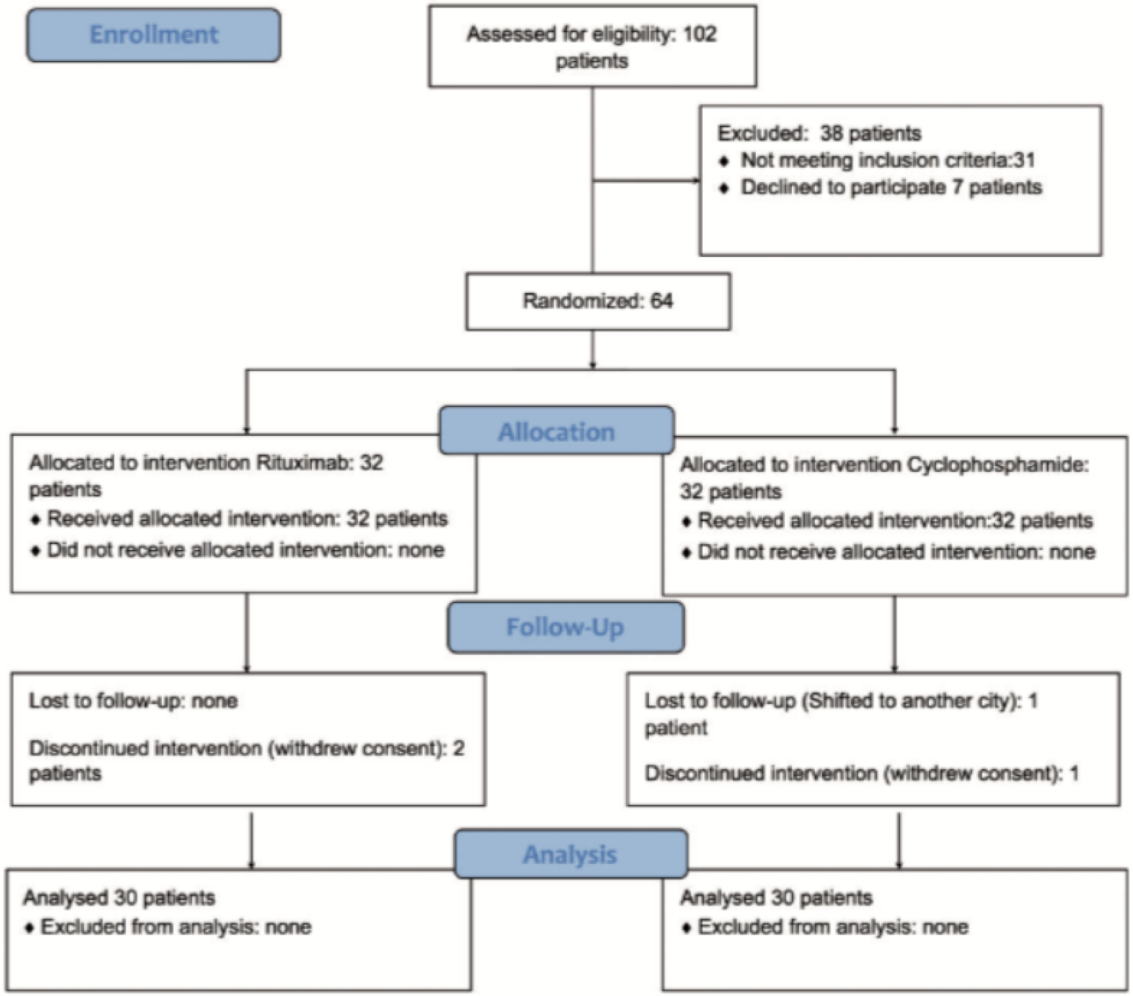
Geetabali Sircar, Rudra Prosad Goswami, Dipankar Sircar, Alakendu Ghosh, Parasar Ghosh

Rheumatology, Volume 57, Issue 12, 1 December 2018, Pages 2106–2113



Méthodologie « parfaite »

- Prospectif
- Contrôlé
- Randomisé
- *Ouvert…*
- Sur 2 ans en Inde
- Diagnostic : ACR 2013 avec atteinte pulmonaire modérée
  - NYHA II ou III
  - CVF 45-80%
  - TDM : PI



RTX 1g J0 J15
Puis maintenance RTX à 6 mois

CYC 0,5 g/m²/4 semaines
Puis maintenance MMF à 6 mois

Population

TABLE 1 Baseline characteristics of patients

Parameter	Rituximab group (30 patients)	Cyclophosphamide group (30 patients)	*P*-value
Age, years	34.67 (8.13)	36.50 (9.73)	0.43
Sex, females, *n* (%)	25 (83)	25 (83)	0.99
Duration of disease, months	21.57 (8.49)	23.0 (10.14)	0.56
Modified Rodnan skin score	21.77 (9.68)	23.83 (9.28)	0.41
6-min walking test, metres	359.63 (65.95)	335.9 (89.3)	0.25
Forced vital capacity, %	61.30 (11.28)	59.24 (12.96)	0.51
Forced vital capacity, l	1.51 (0.45)	1.42 (0.49)	0.45
Ejection fraction, %	62.65 (6.94)	60.30 (14.67)	0.78
Haemoglobin, g/dl	11.87 (1.01)	11.41 (1.98)	0.86
Medsger's score	8.33 (3.04)	9.60 (2.44)	0.08
Creatinine, mg/dl	0.75 (0.19)	0.75 (0.14)	0.99
>20% Lung involvement on CT, *n* (%)	25 (83)	25 (83)	1.00
Pulmonary arterial hypertension present, *n* (%)	4 (13)	5 (16)	0.74

Critère(s) de jugement :

- CVF
- score de Rodnan modifié
- TM6M
- Score de Medsger

Résultats

TABLE 2 Outcome measures at baseline and 6 months in each treatment group

Parameter	Rituximab ($n=30$)			CYC ($n=30$)		
	Baseline, mean (S.D.)	6 months, mean (S.D.)	*P*-value	Baseline, mean (S.D.)	6 months, mean (S.D.)	*P*-value
Forced vital capacity, %	61.30 (11.28)	67.52 (13.59)	0.002[a]	59.25 (12.96)	58.06 (11.23)	0.496[a]
Forced vital capacity, l	1.51 (0.45)	1.65 (0.47)	<0.001	1.42 (0.49)	1.42 (0.46)	0.356
Modified Rodnan skin score at baseline	21.77 (9.86)	12.10 (10.14)	<0.001	23.83 (9.28)	18.33 (7.69)	<0.001
Medsgers severity scale	8.33 (3.04)	4.67 (2.35)	<0.001	9.60 (2.44)	5.96 (2.81)	<0.001
6-min walking test, m	359.63 (65.95)	409.60 (69.29)	<0.001	335.90 (89.30)	349.14 (99.75)	0.428
Pulmonary hypertension present (%)	4 (13)	5 (16)		5 (16)	5 (16)	

Parameter	Difference at 6 months Mean (95% CI)	*P*-value
Forced vital capacity, %	9.46 (3.01 to 15.90)*	0.003[b]
Forced vital capacity, l	0.23 (−0.013 to 0.47)**	0.091[b]
Modified Rodnan skin score at baseline	−6.23 (−10.88, −1.58)***	0.001[b]
Medsgers severity scale	−1.30 (−2.64, 0.04)#	0.036[b]
6-min walking test, m	60.46 (16.07, 104.84)****	0.001[b]
Pulmonary hypertension present (%)	##	

Tolérance

TABLE 3 Adverse events in rituximab and CYC groups

Adverse event	Rituximab group (30 patients)	CYC group (30 patients)
Upper respiratory tract infections	2 (6.67)	2 (6.67)
Pneumonia	1 (3.34)	4 (13.4)
Urinary tract infections	1 (3.3)	2 (6.67)
Herpes zoster	1 (3.3)	3 (10)
Cholecystitis (requiring cholecystectomy)	1 (3.3)	0
Premature ovarian failure	0	2 (6.67)
Gangrene	0	1 (3.34)
Malignancy	0	1 (3.34)
Leukopenia	0	2 (6.67)
Vomiting	0	4 (13.4)
Transfusion reactions	3 (10)	0

Values are *n* (%) of the total patient population.

Conclusion

- RTX > CYC en terme d'efficacité
- RTX meilleur que le CYC en terme de tolérance
- Bémol(s) :
  - Formes peu sévères
  - Sclérodermies séropositives (anti-Scl70+)
  - Après 6 mois ?

Merci de votre attention !!