CMR
CENTRE MALADIES RARES
VASCULARITES | SCLÉRODERMIES
GOUGEROT-SJÖGREN | LUPUS

Lupus érythémateux systémique : Actualités traitement

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European Reference Network
for rare or low prevalence complex diseases

Network
Connective Tissue and Musculoskeletal Diseases (ERN ReCONNET)

Classification Lupus

ACR SLE classification criteria

1. Vespertilio
2. Lupus discoïde
3. Photosensibilité
4. Ulcérations buccales ou nasopharyngées
5. Polyarthrite non érosive
6. Pleurésie ou péricardite
7. Convulsions ou psychose
8. Protéinurie > 0,5 g/24h ou cylindres urinaires
9. Anémie hémolytique ou cytopénie (leucopénie < 4000/µL ou lymphopénie < 1500/µL ou thrombopénie < 100 000 /µL)
10. Anticorps anti-ADN natif ou anti-Sm ou sérologie syphilitique faussement positive ou titre anormal d'anticorps anti-cardiolipine ou présence d'un anti-coagulant circulant
11. Présence d'un titre anormal d'anticorps anti-nucléaires

Arthritis Rheum. 1997;40(9):1725

ARTHRITIS & RHEUMATISM
Vol. 64, No. 8, August 2012, pp 2677–2686
DOI 10.1002/art.34473

Derivation and Validation of the Systemic Lupus International Collaborating Clinics Classification Criteria for Systemic Lupus Erythematosus

Michelle Petri,[1] Ana-Maria Orbai,[1] Graciela S. Alarcón,[2] Caroline Gordon,[3] Joan T. Merrill,[4] Paul R. Fortin,[5] Ian N. Bruce,[6] David Isenberg,[7] Daniel J. Wallace,[8] Ola Nived,[9] Gunnar Sturfelt,[9] Rosalind Ramsey-Goldman,[10] Sang-Cheol Bae,[11] John G. Hanly,[12] Jorge Sánchez-Guerrero,[13] Ann Clarke,[14] Cynthia Aranow,[15] Susan Manzi,[16] Murray Urowitz,[17] Dafna Gladman,[17] Kenneth Kalunian,[18] Melissa Costner,[19] Victoria P. Werth,[20] Asad Zoma,[21] Sasha Bernatsky,[14] Guillermo Ruiz-Irastorza,[22] Munther A. Khamashta,[23] Soren Jacobsen,[24] Jill P. Buyon,[25] Peter Maddison,[26] Mary Anne Dooley,[27] Ronald F. van Vollenhoven,[28] Ellen Ginzler,[29] Thomas Stoll,[30] Christine Peschken,[31] Joseph L. Jorizzo,[32] Jeffrey P. Callen,[33] S. Sam Lim,[34] Barri J. Fessler,[2] Murat Inanc,[35] Diane L. Kamen,[36] Anisur Rahman,[7] Kristjan Steinsson,[37] Andrew G. Franks Jr.,[25] Lisa Sigler,[1] Suhail Hameed,[1] Hong Fang,[1] Ngoc Pham,[1] Robin Brey,[38] Michael H. Weisman,[39] Gerald McGwin Jr.,[2] and Laurence S. Magder[40]

SLICC ACR SLE classification criteria

11 criteria => 17 criteria (11 clinical + 6 immunological)

Lupus if :

- 4 **criteria** including 1 clinical AND 1 immunological
- OR renal involvement with histological proof (IRSNP 2003) with ANA (antinuclear antibodies) ot anti-AND antibodies

Petri M et al., Ann Rheum Dis.2012;64:2677-2686

Nouvelle classification (ACR/EULAR)

Critère d'entrée — *Critères pondérés*

AAN 1/80 →

Renal	Proteinuria	4
	Class II/V	8
	Class III/IV	10
SLE-specific Ab	**Anti-Sm**	6
	Anti-dsDNA	6

Aringer M, Eular 2018

<u>Nouvelles « règles »</u>

- **21 critères, 7 cliniques et 3 sérologiques**
- **Classés et pondérés hiérarchiquement**

Figure 2. Classification criteria for systemic lupus erythematosus

Entry criterion
Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria
Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score.

Clinical domains and criteria	Weight	Serological domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serositis			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Arthritis	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

TRAITEMENT DU LUPUS

Grands principes

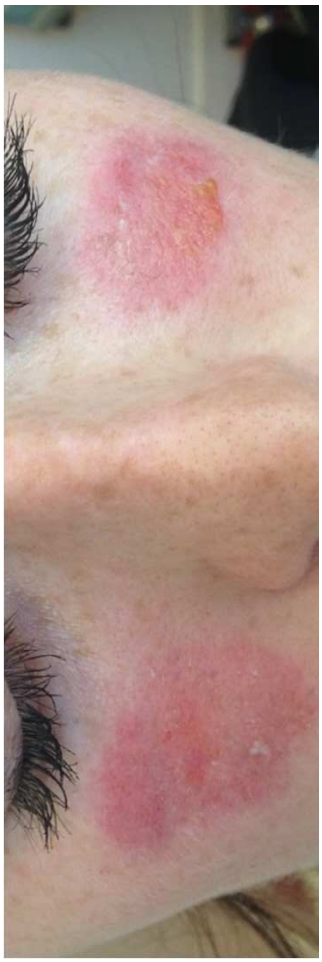
Treat-to-target in systemic lupus erythematosus: recommendations from an international task force

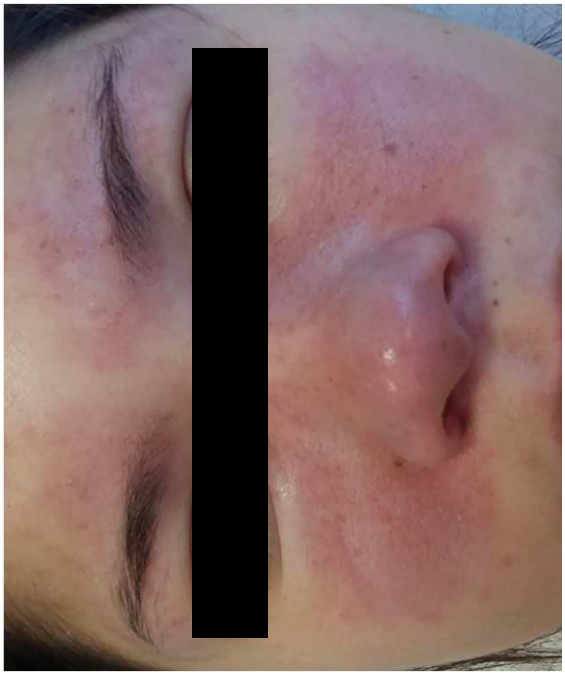
Ronald F van Vollenhoven,[1] Marta Mosca,[2] George Bertsias,[3] David Isenberg,[4] Annegret Kuhn,[5] Kirsten Lerstrøm,[6] Martin Aringer,[7] Hendrika Bootsma,[8] Dimitrios Boumpas,[9] Ian N Bruce,[10] Ricard Cervera,[11] Ann Clarke,[12] Nathalie Costedoat-Chalumeau,[13] László Czirják,[14] Ronald Derksen,[15] Thomas Dörner,[16] Caroline Gordon,[17] Winfried Graninger,[18] Frédéric Houssiau,[19] Murat Inanc,[20] Søren Jacobsen,[21] David Jayne,[22] Anna Jedryka-Goral,[23] Adrian Levitsky,[1] Roger Levy,[24] Xavier Mariette,[25] Eric Morand,[26] Sandra Navarra,[27] Irmgard Neumann,[28] Anisur Rahman,[29] Jozef Rovenský,[30] Josef Smolen,[31] Carlos Vasconcelos,[32] Alexandre Voskuyl,[33] Anne Voss,[34] Helena Zakharova,[35] Asad Zoma,[36] Matthias Schneider[37]

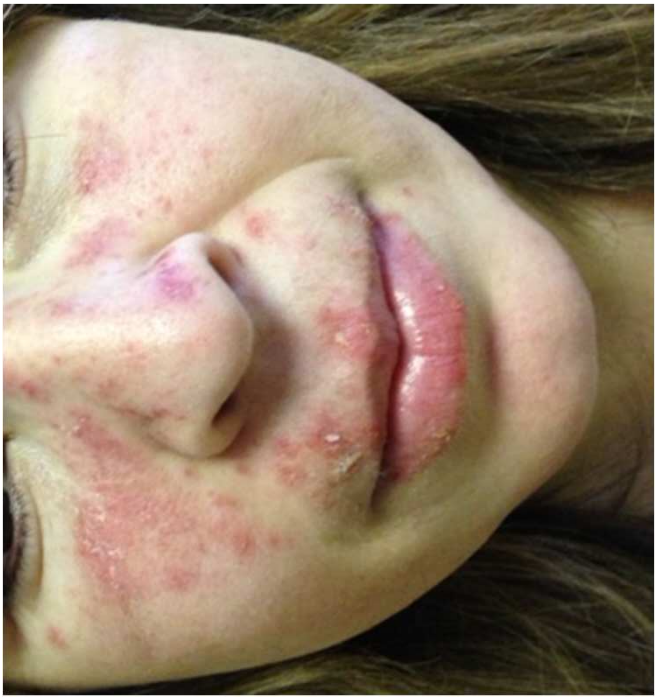
van Vollenhoven RF, *et al*. *Ann Rheum Dis* 2014

Recommendations:

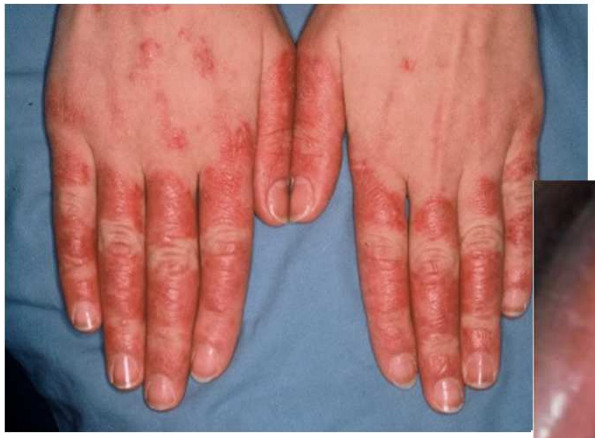
1. The treatment target of SLE should be remission of systemic symptoms and organ manifestations or, where remission cannot be reached, the lowest possible disease activity, measured by a validated lupus activity index and/or by organ-specific markers.
2. Prevention of flares (especially severe flares) is a realistic target in SLE and should be a therapeutic goal.
3. It is not recommended that the treatment in clinically asymptomatic patients be escalated based solely on stable or persistent serological activity.
4. Since damage predicts subsequent damage and death, prevention of damage accrual should be a major therapeutic goal in SLE.
5. Factors negatively influencing health-related quality of life (HRQOL), such as fatigue, pain and depression should be addressed, in addition to control of disease activity and prevention of damage.
6. Early recognition and treatment of renal involvement in lupus patients is strongly recommended.
7. For lupus nephritis, following induction therapy, at least 3 years of immunosuppressive maintenance treatment is recommended to optimise outcomes.
8. Lupus maintenance treatment should aim for the lowest glucocorticoid dosage needed to control disease, and if possible, glucocorticoids should be withdrawn completely.
9. Prevention and treatment of antiphospholipid syndrome (APS)-related morbidity should be a therapeutic goal in SLE; therapeutic recommendations do not differ from those in primary APS.
10. Irrespective of the use of other treatments, serious consideration should be given to the use of antimalarials.
11. Relevant therapies adjunctive to any immunomodulation should be considered to control comorbidity in SLE patients.

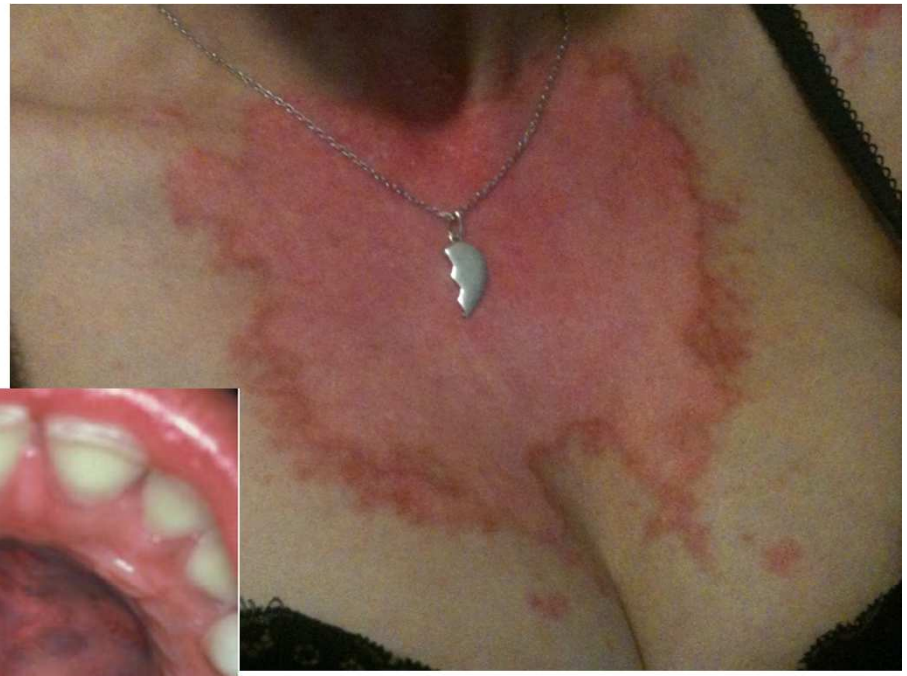


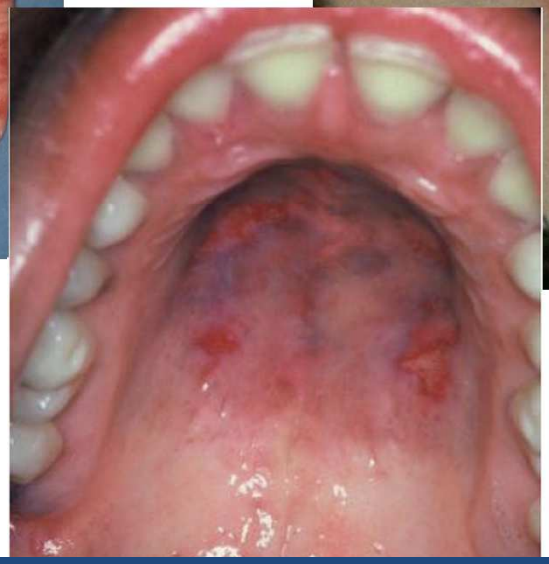




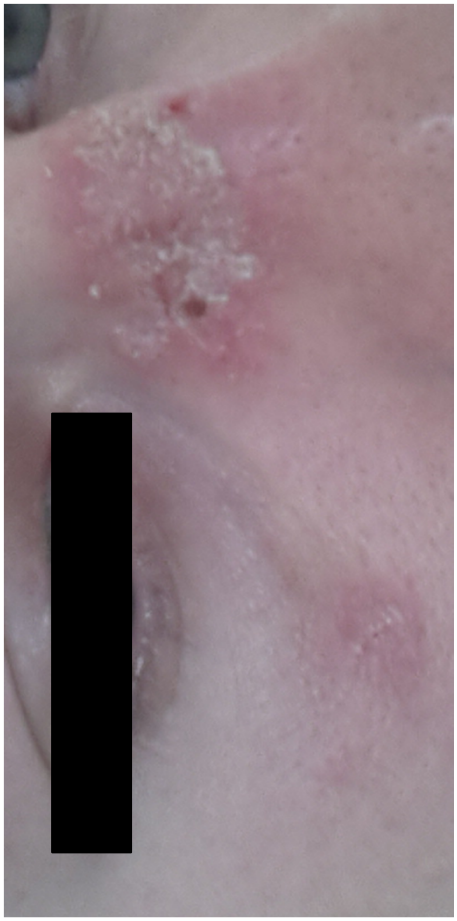
Lupus cutané aigu

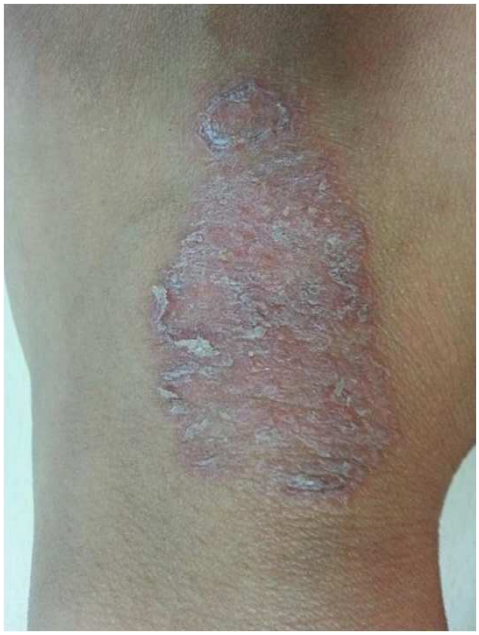


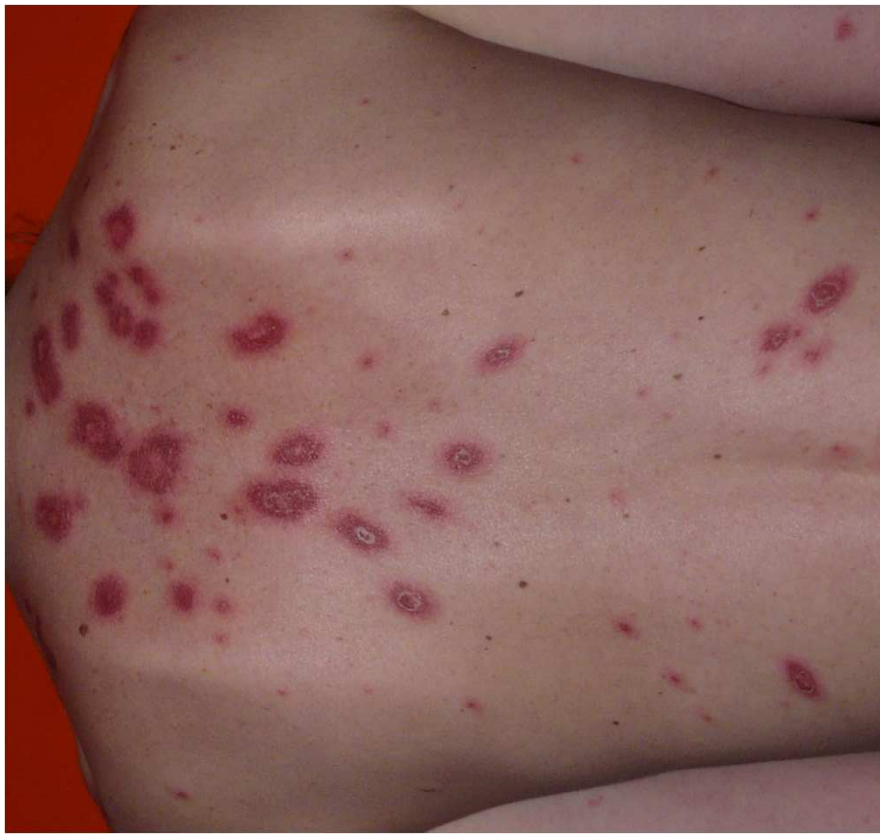




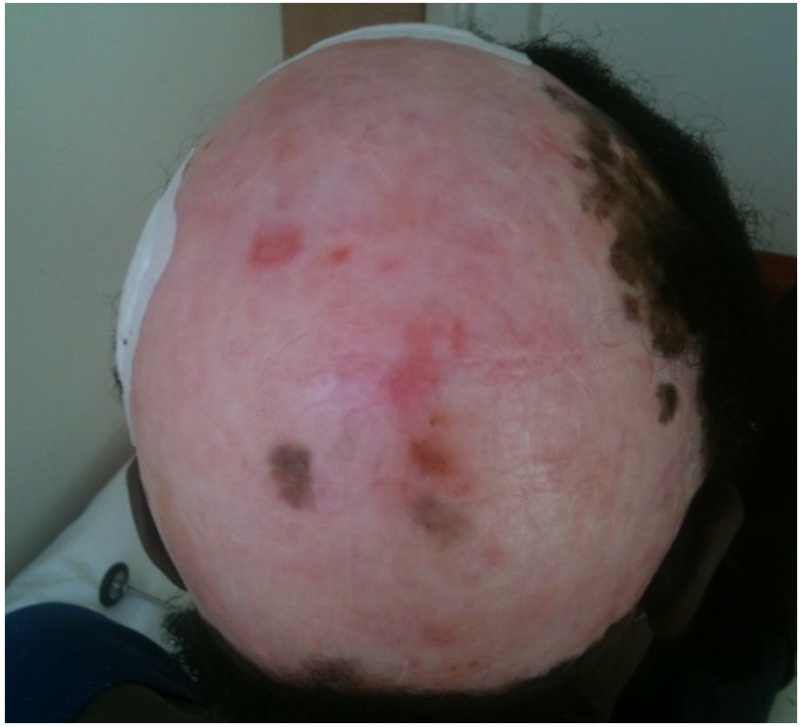
Traitement de la poussée systémique
HCQ, MTX, traitements locaux

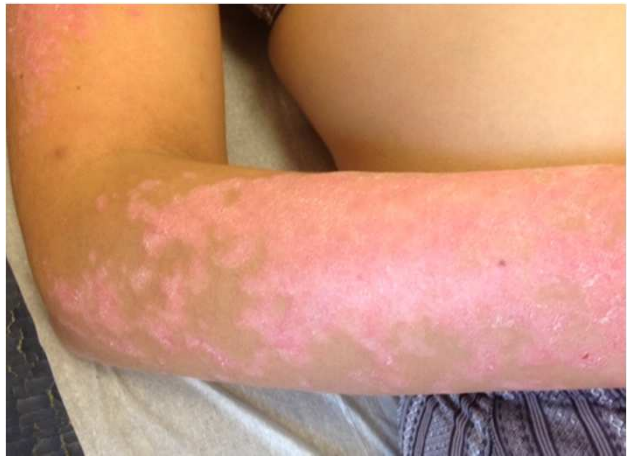






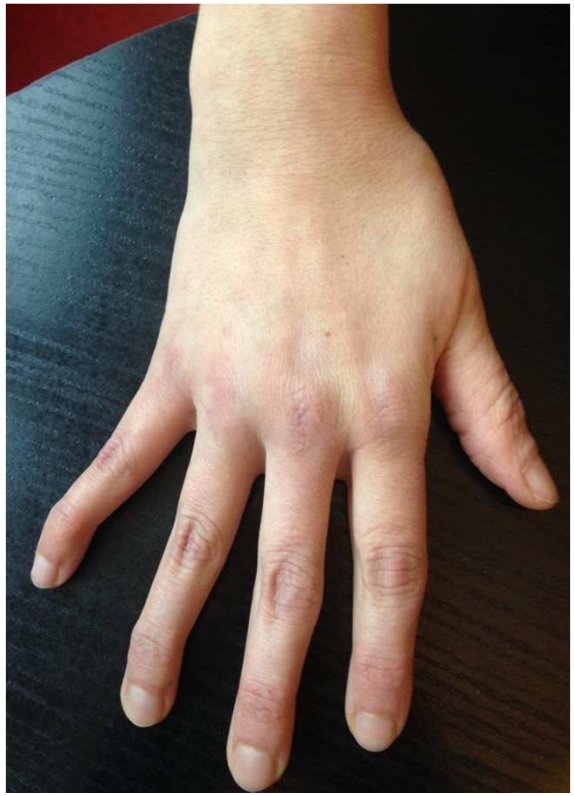
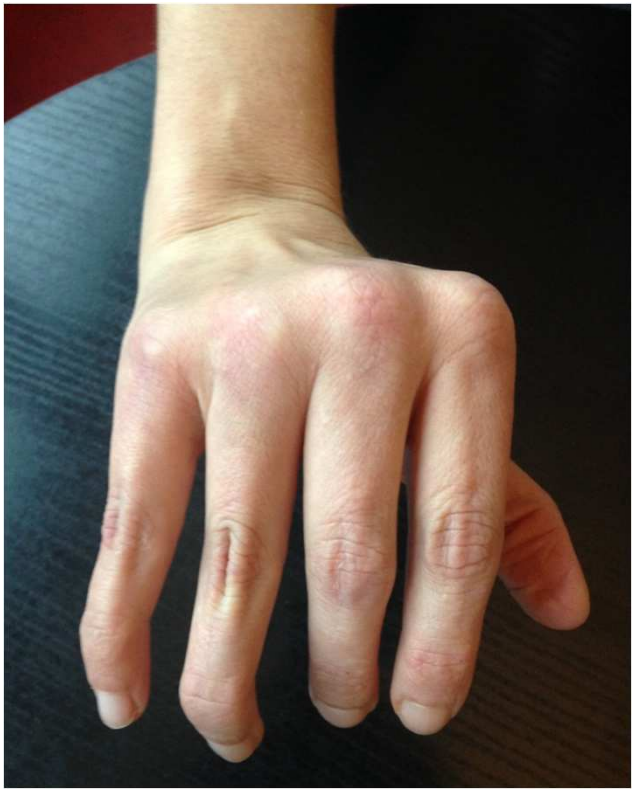
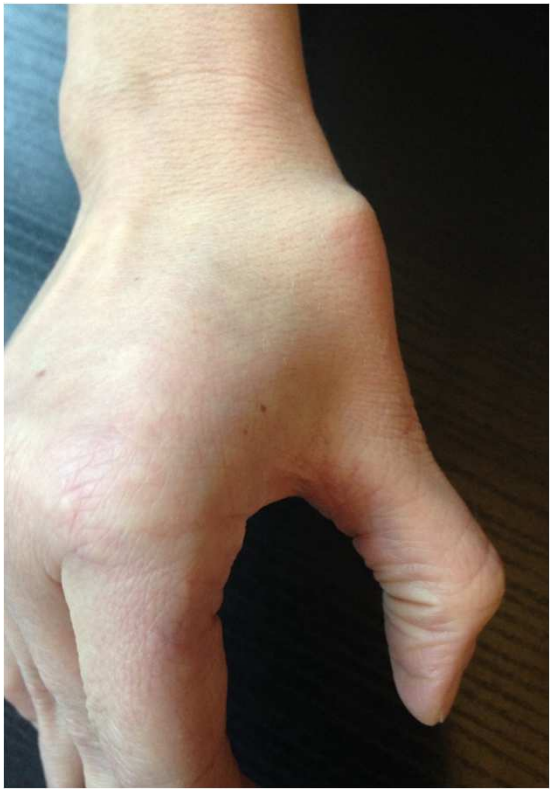
Lupus cutané subaigu et discoïde





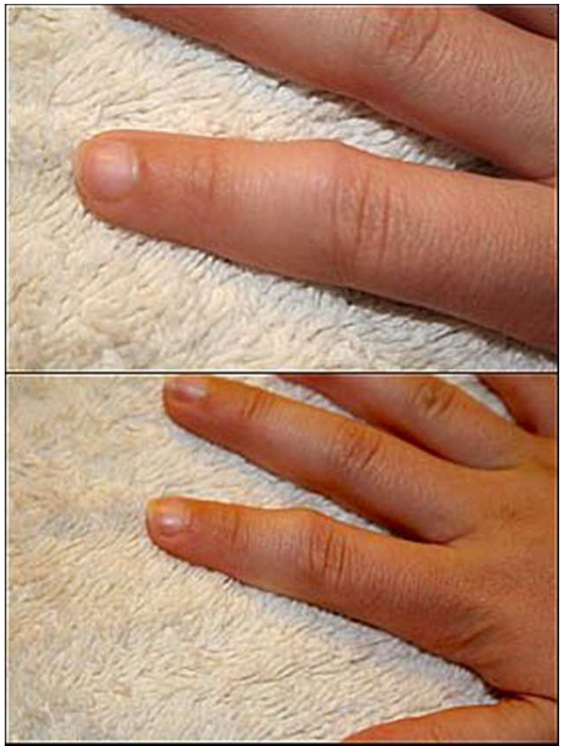
Plaquénil (AMM), dermocorticoides,
MTX puis thalidomide…

Articulations

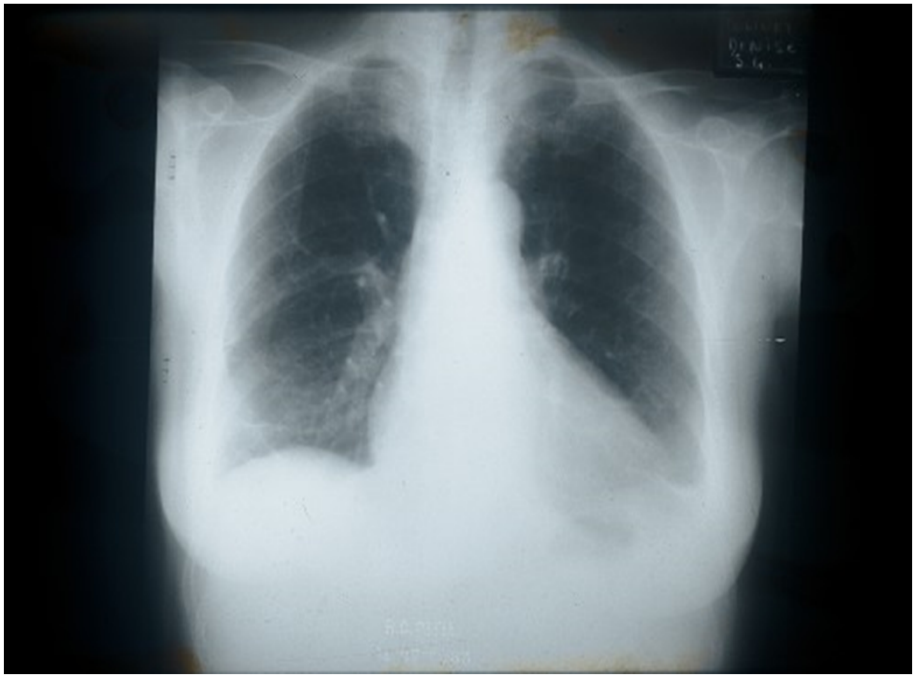
Rhumatisme de Jaccoud
Rééducation fonctionnelle (+ traitement si activité)

Articulations



HCQ ± CT (± BSM) ± MTX

Sérites



CT 0,5 mg/kg/j ou beaucoup moins
(+ HCQ) + Colchicine

Lupus (2015) 24, 1479–1485
http://lup.sagepub.com

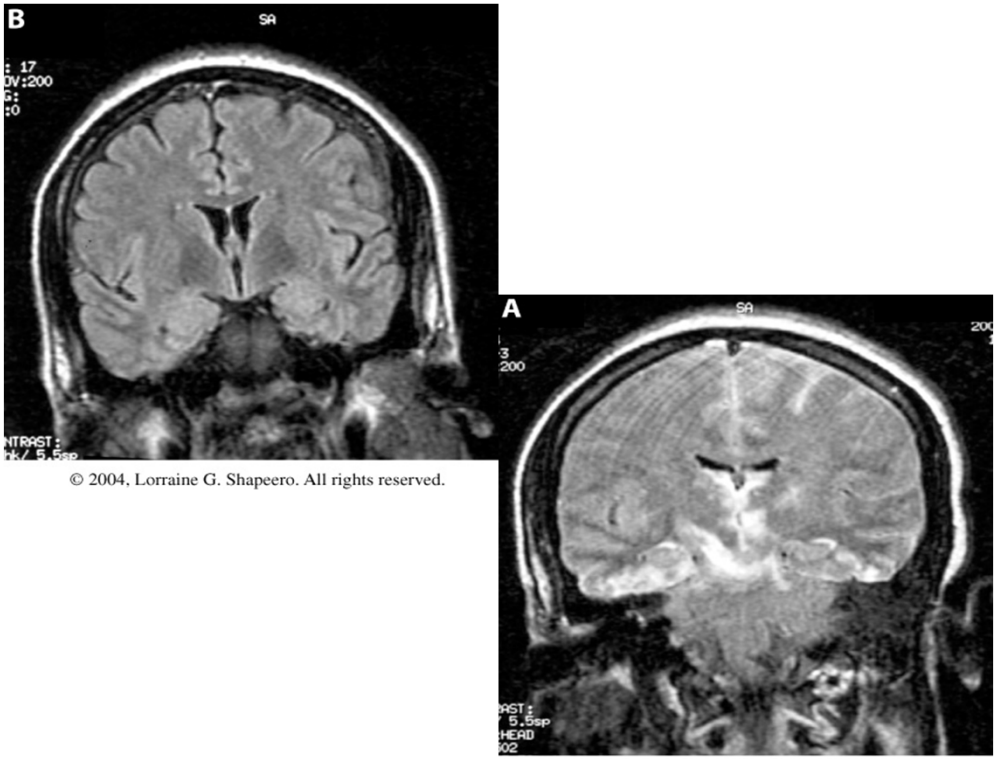
PAPER

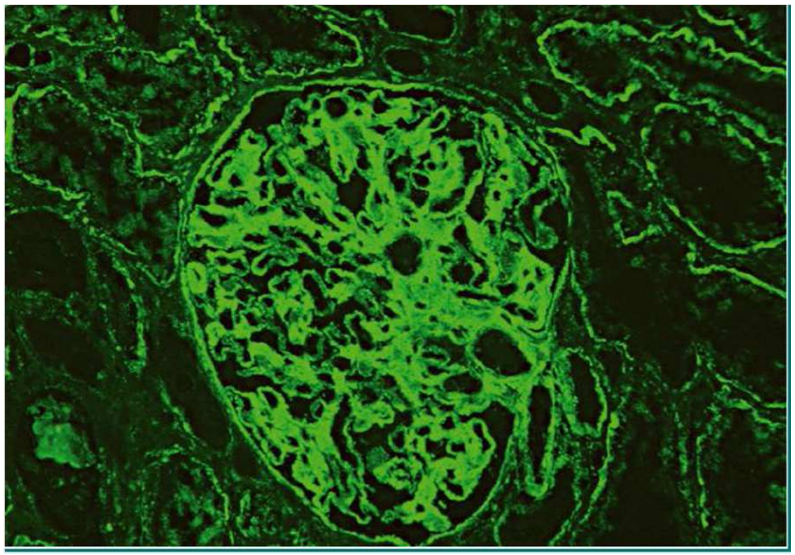
Colchicine: a simple and effective treatment for pericarditis in systemic lupus erythematosus? A report of 10 cases

N Morel[1], M Bonjour[1], V Le Guern[1], C Le Jeunne[1], L Mouthon[1], J-C Piette[2] and N Costedoat-Chalumeau[1]

Si péricardite : Colchicine (+ HCQ)

Rein, SNC





BSM puis CT 1 mg/kg => 0,5 + IS (+ Plaquénil)

Echanges plasmatiques

Traitement du lupus

Biothérapies

Belimumab

- Nouveau traitement intéressant (épargne cortisonique), mais « cher pour du Plaquénil », effet lent, pour les formes non sévères, plus efficace si activité

- Commercialisé aux U-S depuis 2011, en Europe depuis 2012 (lupus actif extra-rénal)
- En France, difficulté d'utilisation
  - Car dans le GHS, à la charge de l'établissement de soin
  - Administration IV
  - Cout annuel : en baisse

- Forme sous-cutanée (/semaine, 1000 Euros/mois)

Les anti-B : RITUXIMAB

- Plus de 800 lupus sévères traités en ouvert
  - Formes réfractaires
  - Efficacité dans 80 % des cas, mais association fréquente à EDX
  - Bonne tolérance, quelques maladies sériques
- Méta-Analyse: 188 lupus
  - Grande efficacité (91%)
  - Analyse difficile +++
- Nombreuses études ouvertes
- Les registres : AIR
  - 136 patients, lupus le plus souvent réfractaires

Mais echec des 2 essais randomisés (Explorer et Lunar)

Rituxilup

Prospective observational single-centre cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids

Marie B Condon,[1] Damien Ashby,[1] Ruth J Pepper,[1] H Terence Cook,[1,2] Jeremy B Levy,[1] Megan Griffith,[1] Tom D Cairns,[1] Liz Lightstone[1,2,3]

Ann Rheum Dis 2013;**72**:1280–1286.

A venir ..

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

The 2018 pipeline of targeted therapies under clinical development for Systemic Lupus Erythematosus: a systematic review of trials

Renaud Felten[a], Elida Dervovic[b], François Chasset[c], Jacques-Eric Gottenberg[a], Jean Sibilia[d], Florence Scher[b], Laurent Arnaud[d,*]

Name of the database	Number of SLE trials identified
ClinicalTrials.gov	623
EU Clinical Trials Register (EU-CTR)	160
ISRCTN (International Standard Randomised Controlled Trial Number)	159
German Clinical Trials Register	50
Cuban Public Registry of Clinical Trials	40
Chinese Clinical Trial Registry	31
Japan Primary Registries Network	29
Clinical Trials Registry - India	19
Australian New Zealand Clinical Trials Registry	11
Clinical Research Information Service - Republic of Korea	4
The Netherlands National Trial Register	4
Sri Lanka Clinical Trials Registry	3
Thai Clinical Trials Register	3
Brazilian Clinical Trials Registry (ReBec)	1
Iranian Registry of Clinical Trials	0
Pan African Clinical Trial Registry	0
Peruvian Clinical Trials Registry	0

Plusieurs axes thérapeutiques

Lymphocyte B

Molecules	Mechanisms of action	Pharmaceutical company	Current development phase
B cells			
AMG 570	Anti-BAFF and B7RP-1 (ICOSLs) bispecific antibody-peptide conjugate	Amgen	Phase I
TRU-015	Anti-CD20	Pfizer	Phase I
SM03	Anti-CD22 human-murine chimeric monoclonal antibody		Phase I
Milatuzumab	Anti-CD74	Immunomedics, Inc.	Phase I/phase II
XmAb5871	Anti-CD19 (cible FcγRIIb)	Xencor, Inc.|PPD|ICON plc	Phase II
Obinutuzumab	Anti-CD20	Hoffmann-La Roche	Phase II
RC18	Anti-BAFF/APRIL	RemeGen	Phase II
Atacicept	Anti-BAFF/APRIL	EMD Serono|ZymoGenetics	Phase II/Phase III
Epratuzumab	Anti-CD22 humanized antibody	UCB Pharma	Phase III
Abetimus Sodium	Synthetic toleragen molecule targeting B cells	La Jolla Pharmaceutical Company	Phase III
Tabalumab	Anti-BAFF	Eli Lilly and Company	Phase III
Rituximab	Anti-CD20	Genentech, Inc.	Phase III
Ocrelizumab	Anti-CD20	Genentech, Inc.|Roche Pharma AG	Phase III
Blisibimod	BAFF antagonist "peptibody"	Anthera Pharmaceuticals	Phase III
Belimumab	anti-BAFF humanized monoclonal antibody	GlaxoSmithKline	Phase IIII
Plasma cells			
Ixazomib	Second-generation boronate proteasome inhibitor	Takeda	Phase I
Bortezomib	Proteasome inhibitor	Millennium Pharmaceuticals	Phase IIII

Lymphocyte T

Molecules	Mechanisms of action	Pharmaceutical company	Current development phase
B/T cell costimulation			
AMG 557	Anti-ICOSL	Amgen	Phase I
MEDI-570	Anti-ICOS	MedImmune LLC|AstraZeneca	Phase I
RG2077	CTLA4-Ig	Repligen	Phase I/phase II
Dapirolizumab	Anti-CD40L	UCB Biopharma S.P.R.L.|UCB Pharma	Phase II
BI 655064	Anti-CD40	Boehringer Ingelheim	Phase II
Theralizumab	Anti-CD28	Theramab LLC	Phase II
Lulizumab pegol	Anti-CD28	Bristol-Myers Squibb	Phase II
Abatacept	CTLA4-Ig	Bristol-Myers Squibb	Phase II/Phase III
pDC			
Venetoclax (ABT-199)	Anti-BCL-2	AbbVie	Phase I
Talacotuzumab	Anti-CD123	Janssen Research & Development, LLC	Phase I
BIIB059	Anti-BDCA2	Biogen	Phase II

Cytokines

Molecules	Mechanisms of action	Pharmaceutical company	Current development phase
Chemokines and their receptors			
SAR113244	Anti-CXCR5	Sanofi	Phase I
Imalumab	Anti-MIF/macrophage migration inhibitory factor inhibitors	Baxalta now part of Shire|Shire	Phase I
Emapticap	CCL2 inhibitor	Noxxon Pharma AG	Phase I
PF-06835375	Chemokine inhibitor	Pfizer	Phase I
Cytokines and their receptors			
MRA 003 US	Anti-IL-6R		Phase I
NNC0114-0006	Anti-IL-21	Novo Nordisk A/S	Phase I
BOS161721	IL-21 modulators	Boston Pharmaceuticals	Phase I/phase II
Ustekinumab	Anti-IL12/23	Janssen Research & Development, LLC	Phase II
BT063	IL 10 inhibitor	Biotest	Phase II
Vobarilizumab	Anti-IL-6R	Ablynx	Phase II
Interleukin 2	Low dose of IL-2	Iltoo Pharma	Phase II
PF-04236921	IL-6 inhibitors	Pfizer	Phase II
Sirukumab	IL-6 inhibitor	Janssen Research & Development, LLC	Phase II
Etanercept	Anti-TNF		Phase II
BIIB023	Anti-TWEAK	Biogen	Phase II
Infliximab	Anti-TNF		Phase III
Brentuximab	Anti-CD30	Seattle Genetics, Inc.	Phase II

Petites molécules

Molecules	Mechanisms of action	Pharmaceutical company	Current development phase
Interferons			
AGS-009	Anti-interferon α	Argos Therapeutics	Phase I
AMG 811	Anti-interferon γ	Amgen	Phase I
JNJ-55920839	Anti-interferon type 1	Janssen Research & Development, LLC	Phase I
IFN-Kinoid	Therapeutic vaccine composed of IFNα2b coupled to a carrier protein	Neovacs	Phase II
Rontalizumab	Anti-interferon α	Genentech, Inc.	Phase II
Sifalimumab	Anti-interferon α	MedImmune LLC	Phase II
Anifrolumab	Anti–interferon-α receptor monoclonal antibody (IFNAR1)	AstraZeneca|MedImmune LLC	Phase III
Kinases of the intracellular machinery			
Tofacitinib	Selective JAK1 and JAK3 inhibitor	Pfizer	Phase I/phase II
Baricitinib	Selective JAK1 and JAK2 inhibitor	Eli Lilly and Company	Phase II
Filgotinib	Highly selective JAK1 inhibitor	Gilead Sciences	Phase II
Evobrutinib	Bruton's tyrosine kinase (BTK) inhibitor	EMD Serono Research & Development Institute, Inc.|Merck KGaA|EMD Serono	Phase II
BMS-986165	Tyk2 inhibitor	Bristol-Myers Squibb	Phase II
Solcitinib	Janus kinase 1 (JAK1) inhibitor	GlaxoSmithKline	Phase II
Fostamatinib	Inhibitor of the spleen tyrosine kinase (Syk)	Rigel Pharmaceuticals	Phase II
Sphingosine-1-phosphate			
Amiselimod	Sphingosine 1-phosphate (S1P) receptor modulator	Mitsubishi Tanabe Pharma Corporation	Phase I
Cenerimod	S1P receptor 1 agonist	Actelion	Phase II
KRP203	S1P receptor 1 agonist	Novartis Pharmaceuticals	Phase II

Anifrolumab : anti-récepteur IFN

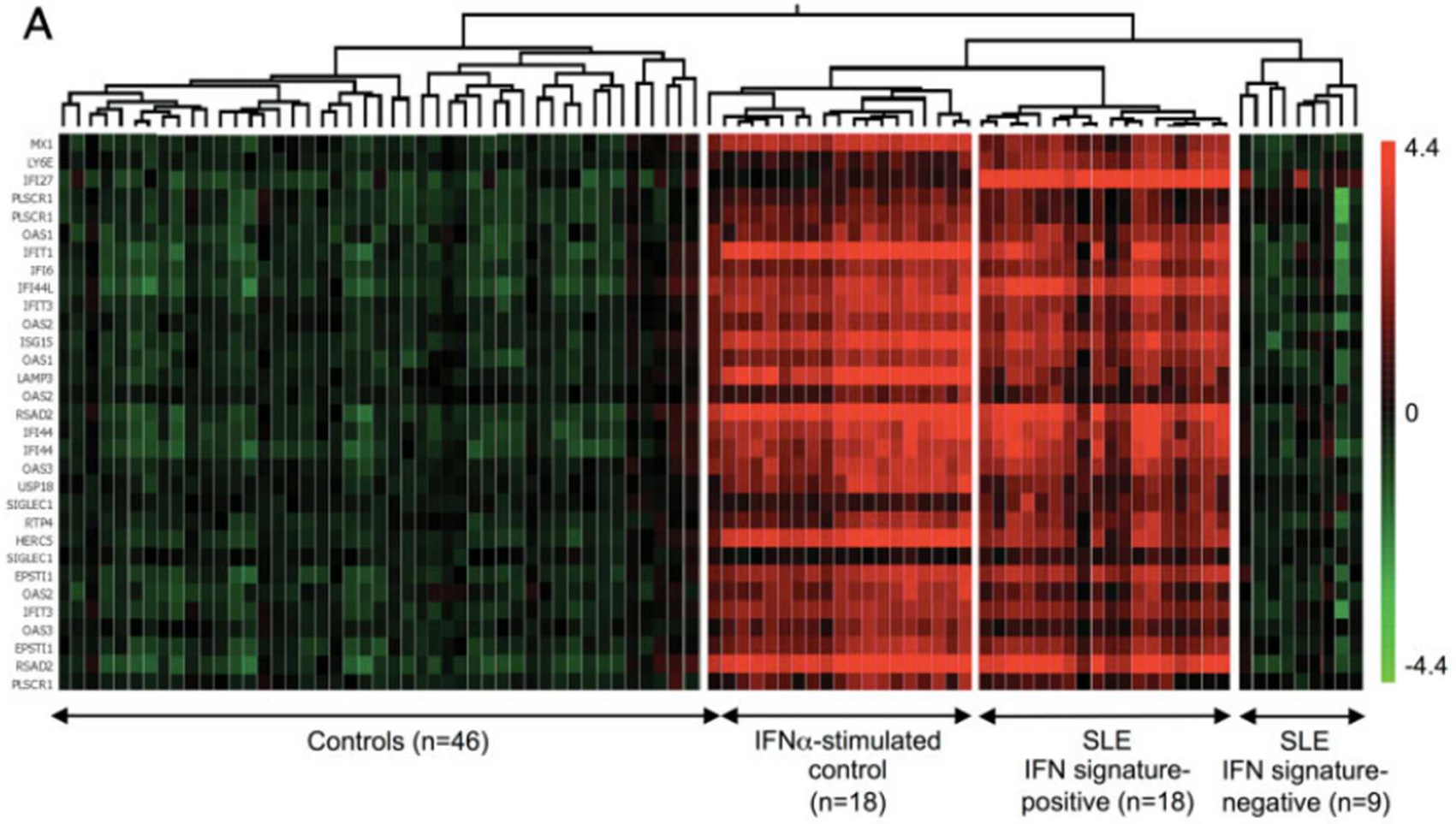
Anti-IFNAR, Phase II, 305 patients
PBO, 300mg q4w, 1,000 mg q4w
1ry: SRI-4 at D169 with sustained reduction of OCS (<10 mg/d and ≤D1 dose between D85 and 169)

SRI-4/OCS taper D169	PBO %	300 mg %	1,000 mg %
ALL	17.6	34.3*	28.8
IFN^{high}	13.2	35.0*	28.2*
IFN^{low}	30.8	29.2	30.8

*: FAH educated guess (Jan, 2016)

Furie R *et al.*, ACR 2015 Annual Meeting

Signatures moléculaires => traitement individualisé



Lauwerys B *et al*. Arthritis Rheum 2013; 65: 447

Traitements prometteurs … (phase 2)

- *Rituximab (anti-CD20)*
- Epratuzumab (anti-CD22)
- Blisibimod (anti-BAFF)
- Abatacept (anti-CTLA4 Ig)
- Anifrolumab (anti type 1 IFN receptor)
- Lupuzor (peptid)

- Atacicept (anti-BAFF/APRIL)
- Baricitinib (JAK1 et JAK2 inhibiteur; Lancet 2018)
- Ustekinumab (Anti Il12/23; Lancet 2018)

Mais en phase 3…

- *Rituximab (anti-CD20)* → *échec* (Lunar, Exp.)
- Epratuzumab (anti-CD22) → *échec (Embody)*
- Blisibimod (anti-BAFF) → *échec*
- Abatacept (anti-CTLA4 Ig) → *échec (BMS)*
- Anifrolumab (anti type 1 IFN receptor) → *échec (Tulip 1)*
- Lupuzor (peptid) → *échec*

- Atacicept (anti-BAFF/APRIL)
- Baricitinib (JAK1 et JAK2 inhibiteur; Lancet 2018)
- Ustekinumab (Anti Il12/23; Lancet 2018)

Pourquoi ?

Lupus: complexe, hétérogène

Echelles d'activité compliquées

Critères de jugement mal définis

Trop de CT, d'immunosuppresseurs

Ethnie mal prise en compte

Traitement du lupus

La base

Traitement du lupus

- Plus d'HYDROXYCHLOROQUINE

HYDROXYCHLOROQUINE

Hydroxychloroquine

- Prevention des poussées de lupus
- Réduction des infections (dont fièvre Q, Whipple), *antimalarial*
- Hypoglycémiant
- Antithrombotique
- Hypolipémiant
- « Séquelles, dommages »

=> Améliore la survie

Costedoat-chalumeau. Antimalarials and SLE. In: Lahita, et al. Systemic lupus erythematosus. Elsevier. 5th éd. 2010;1061-81.

Ruiz-Irastorza, et al, Ann Rheum Dis 2010;69: 20-28

Research

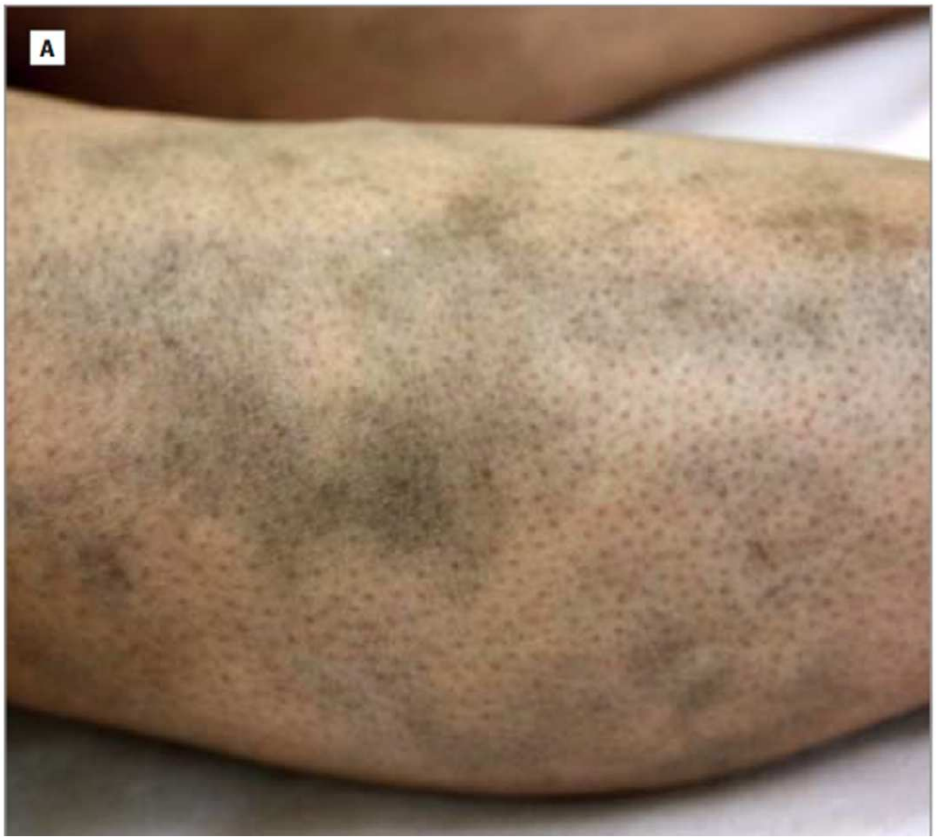
Original Investigation

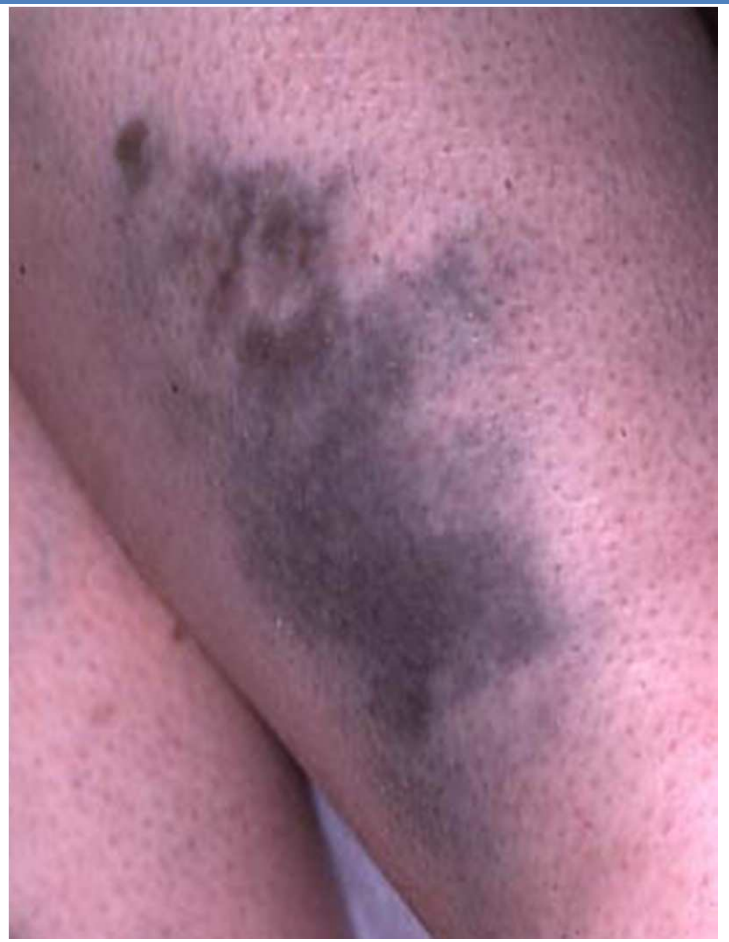
Hydroxychloroquine-Induced Pigmentation in Patients With Systemic Lupus Erythematosus
A Case-Control Study

Moez Jallouli, MD; Camille Francès, MD; Jean-Charles Piette, MD; Du Le Thi Huong, MD; Philippe Moguelet, MD; Cecile Factor, PhD; Noël Zahr, PhD; Makoto Miyara, MD, PhD; David Saadoun, MD, PhD; Alexis Mathian, MD, PhD; Julien Haroche, MD, PhD; Christian De Gennes, MD; Gaelle Leroux, MD; Catherine Chapelon, MD; Bertrand Wechsler, MD; Patrice Cacoub, MD; Zahir Amoura, MD; Nathalie Costedoat-Chalumeau, MD, PhD; for the PLUS (Plaquenil LUpus Systemic) Study Group

JAMA Dermatol. doi:10.1001/jamadermatol.2013.709
Published online July 3, 2013.

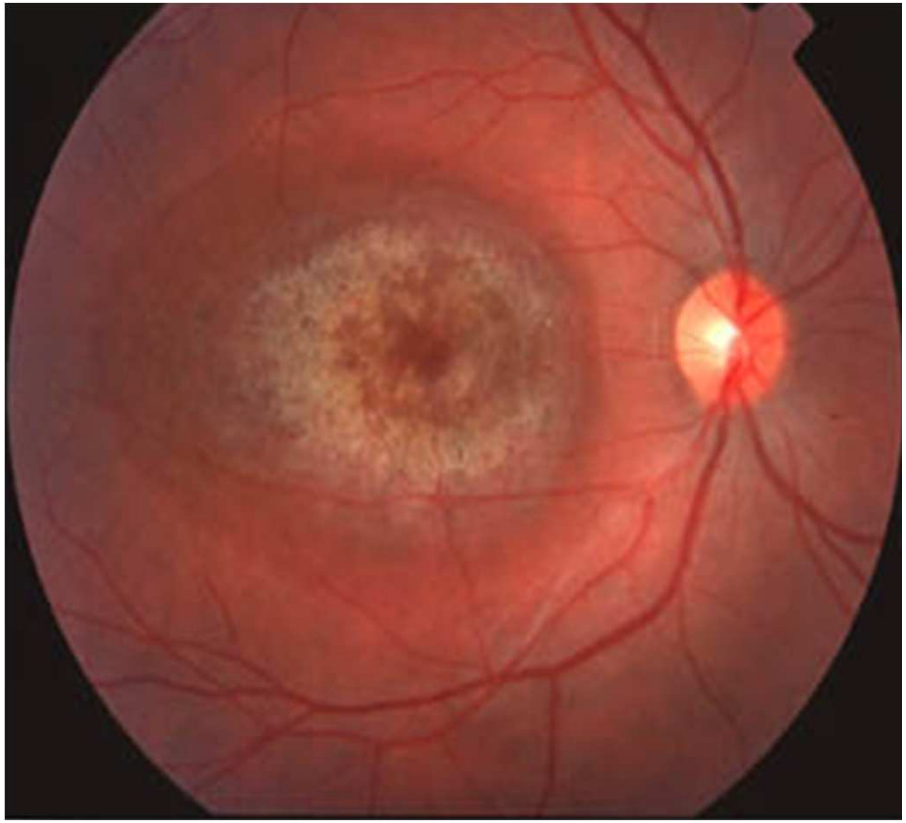
Figure 1. Patient Photographs





A, Bluish-green pigmentation on the legs in a patient with systemic lupus erythematosus without lupus lesions at the time of the skin biopsy. B, Brown pigmentation on the legs in another patient who had systemic lupus erythematosus associated with diffuse discoid lupus. The skin biopsy was performed on the brown area distant from discoid lesions.

Effets secondaires ophtalmologiques



AMERICAN ACADEMY™
OF OPHTHALMOLOGY

American Academy of Ophthalmology Statement

Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision)

Michael F. Marmor, MD,[1] Ulrich Kellner, MD,[2] Timothy Y.Y. Lai, MD, FRCOphth,[3] Ronald B. Melles, MD,[4] William F. Mieler, MD,[5] for the American Academy of Ophthalmology

Marmor et al. Ophthalmology. 2016;123:1386-94

Rétinopathie infra-clinique

Dépend de la dose journalière et de la durée d'exposition

- <1% à 5 ans
- <2% à 10 ans
- 20% à 20 ans

Dose quotidienne sans risque : 5 mg/kg/j d'HCQ pris en pharmacie.

Marmor et al. Ophthalmology. 2016;123:1386-94

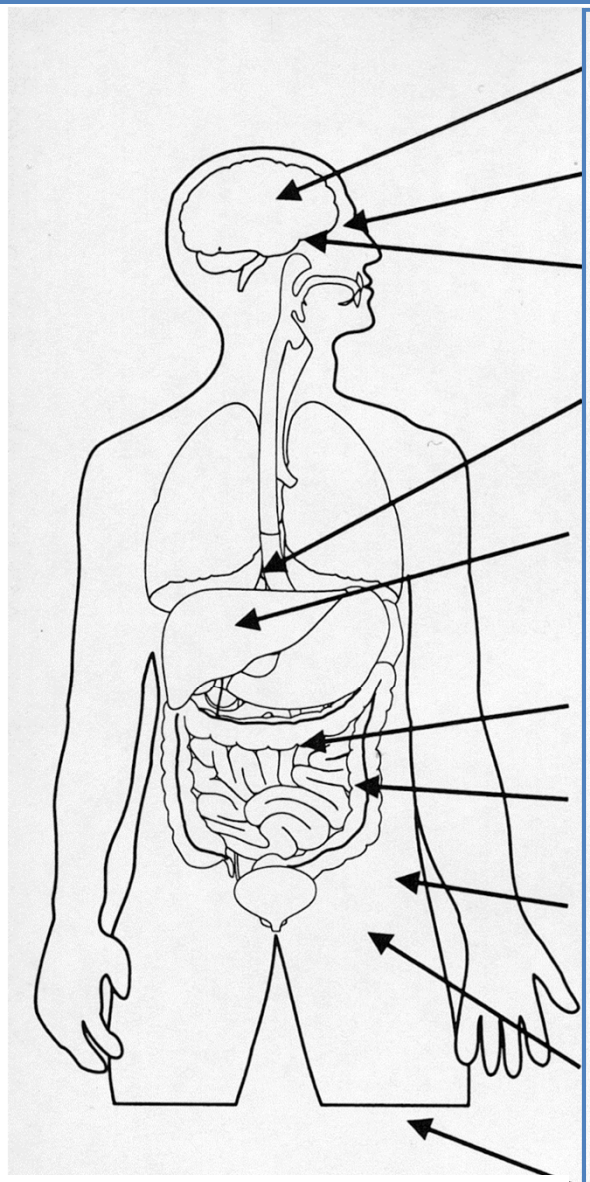
Timeline	Baseline examination within first year of use Annual screening after 5 yrs of use
Recommended Screening Procedures	
Ocular examination	Dilated retinal examinations are important for detection of associated retinal disorders, but should *not* be relied on for screening (low sensitivity).
Automated visual field	White 10-2 threshold testing. Interpret with a low threshold for abnormality, and retest if abnormalities appear.
In addition, if available, perform one or more of the following objective tests	
SD-OCT	Rapid test that can be done routinely; can show abnormalities very early, even before field loss
mfERG	Valuable for evaluation of suspicious or unreliable visual field loss; may show damage earlier than visual field testing
FAF	May validate other measures of toxicity; can show abnormalities earlier than field loss
Not Recommended for Screening	
Fundus photography	Recommended for documentation, especially at baseline, but not sensitive for screening
Time-domain OCT	Insufficient resolution for screening
Fluorescein angiography	Use only if corroboration of pigmentary changes is needed
Full-field ERG	Important for evaluation of established toxicity, but not for screening
Amsler grid	Use only as adjunct test
Color testing	Use only as adjunct test
EOG	Questionable sensitivity

EOG = electro-oculogram; FAF = fundus autofluorescence; mfERG = multifocal electroretinogram; SD-OCT = spectral domain optical coherence tomography.

Traitement du lupus

- Plus d'HYDROXYCHLOROQUINE
- Moins de CORTICOIDES

CORTICOIDES



Brain/CNS:
Depression
Psychosis

Eye:
Glaucoma

Endocrine system:
↓ LH, FSH release
↓ TSH release
↓ GH secretion

GI tract:
Peptic ulcerations

Carbohydrate/lipid metabolism:
↑ hepatic glycogen deposition
↑ peripheral insulin resistance
↑ gluconeogenesis
↑ free fatty acid production
Overall diabetogenic effect

Adipose tissue distribution:
Promotes visceral obesity

Cardiovascular/Renal:
Salt and water retention
Hypertension

Skin/muscle/connective tissue:
Protein catabolism/collagen breakdown
Skin thinning
Muscular atrophy

Bone and calcium metabolism:
↓ bone formation
↓ bone mass and osteoporosis

Growth and Development:

Why patients hate them

Quand vous prescrivez des corticoides…

Fred Houssiau

EXTENDED REPORT

Factors associated with damage accrual in patients with systemic lupus erythematosus: results from the Systemic Lupus International Collaborating Clinics (SLICC) Inception Cohort

Ian N Bruce,[1,2] Aidan G O'Keeffe,[3] Vern Farewell,[4] John G Hanly,[5] Susan Manzi,[6] Li Su,[4] Dafna D Gladman,[7] Sang-Cheol Bae,[8] Jorge Sanchez-Guerrero,[7] Juanita Romero-Diaz,[9] Caroline Gordon,[10] Daniel J Wallace,[11] Ann E Clarke,[12] Sasha Bernatsky,[13] Ellen M Ginzler,[14] David A Isenberg,[15] Anisur Rahman,[15] Joan T Merrill,[16] Graciela S Alarcón,[17] Barri J Fessler,[17] Paul R Fortin,[18] Michelle Petri,[19] Kristjan Steinsson,[20] Mary Anne Dooley,[21] Munther A Khamashta,[22] Rosalind Ramsey-Goldman,[23] Asad A Zoma,[24] Gunnar K Sturfelt,[25] Ola Nived,[25] Cynthia Aranow,[26] Meggan Mackay,[26] Manuel Ramos-Casals,[27] Ronald F van Vollenhoven,[28] Kenneth C Kalunian,[29] Guillermo Ruiz-Irastorza,[30] Sam Lim,[31] Diane L Kamen,[32] Christine A Peschken,[33] Murat Inanc,[34] Murray B Urowitz[7]

Bruce IN, *et al*. *Ann Rheum Dis* 2015;**74**:1706–1713.

Facteurs de risque de dommages

- 1722 patients avec lupus incident.
- Dommages initiaux => nouveaux dommages (p<0,001).
- Age, sexe masculin, blacks US, **score SLEDAI-2K, corticoïdes et l'HTA** => Dommages
- **HCQ** => effet protecteur (HR 0,63; IC95%: 0,44 – 0,89).

RHEUMATOLOGY

Rheumatology 2014;53:1470–1476
doi:10.1093/rheumatology/keu148
Advance Access publication 27 March 2014

Original article

Glucocorticoids and irreversible damage in patients with systemic lupus erythematosus

Ioana Ruiz-Arruza[1], Amaia Ugarte[1], Ivan Cabezas-Rodriguez[1], Jose-Alejandro Medina[1], Miguel-Angel Moran[1] and Guillermo Ruiz-Irastorza[1]

- 188 patients (82%) traités par prednisone
- 87 **(38%) ont des dommages à 5 ans**
- Dose moyenne (> 7,5mg/j) / pas de CT : OR 9,9, IC95% 1,1-84 d'avoir des dommages
- **Faibles doses (<7,5 mg/j) :** pas associée aux dommages
- Dose cumulée de BSM : pas associée aux dommages

Doses de Corticoides (rein)

- CT : 0,5 - 1 mg/kg/j (max : 60 mg/j) voire beaucoup moins.
- Dose d'entretien :
  - Arrêt à M6 si possible (USA)
  - Maintien de 5 mg à 7,5 mg au long cours (Europe)

Empirique…

Doses de Corticoides (rein)

- **Maintain (F Houssiau, 2010):** 3 BSM (750 mg/j) puis CT : 0,5 mg/kg/j puis enlever 2,5mg toutes les 2 semaines => 7,5 mg/j à M6 et 5 mg/j à M12 puis diminuer et stopper si possible
- **Multi-target (Liu, 2015, Ann Intern Med):** 3 BSM (500 mg/j) puis CT : 0,6 mg/kg/j puis enlever 5mg toutes les 2 semaines jusqu'à 20 puis 2,5 toutes les 2 semaines jusqu'à 10mg à 6 mois
- **Tacro vs MMF (Mok, ARD, 2016):** 0,6 mg/kg/j/6 semaines puis enlever 5mg/j chaque semaine jusqu'à <10 mg/j à 6 mois
- **Rituxilup…**

Tableau 12. Schémas indicatifs pour la corticothérapie

	CORTICOTHERAPIE USUELLE					
M0	J1, J2, J3	Solumédrol 500 à 1000 mg/j				
	Poids (kg)	80	70	60	50	40
		Prednisone en mg/j				
	J4 à J14 (S1 et S2) (1/2mg/kg/j)	40	35	30	25	20
	J15 à J28 (S3 et S4)	35	30	25	22,5	17,5
M1	J29 à J42 (S5 et S6)	30	25	22,5	20	15
	J43 à J56 (S7 et S8)	25	22,5	20	17,5	15
M2	J57 à J70 (S9 et S10)	22,5	20	17,5	15	12,5
	J71 à J84 (S11 et S12) (1/4mg/kg/j)	20	17.5	15	12.5	10
	J85 à J98 (S13 et S14)	15	15	12,5	12.5	10
	J99 à J112 (S15 et S16)	12,5	12.5	12.5	10	7.5
	J113 à M6	10			7.5	
	M7 M8 M9	7.5				
	M10 M11 M12	5				
	1 an	Arrêt à discuter				

CORTICOTHERAPIE POUR LES FORMES SEVERES (INSUFFISANCE RENALE AIGUE ET/OU ACTIVITE HISTOLOGIQUE >50%)					
J1, J2, J3	Solumédrol 500 à 1000 mg/j				
Poids (kg)	80	70	60	50	40
	Prednisone en mg/j				
J4 à J14 (S1 et S2) (1mg/kg/j)	80	70	60	50	40
J15 à J28 (S3 et S4)	60	50	45	35	30
J29 à J42 (S5 et S6) (1/2mg/kg/j)	40	35	30	25	20
J43 à J56 (S7 et S8)	30	25	20	20	17,5
J57 à J70 (S9 et S10)	25	20	17.5	17,5	15
J71 à J84 (S11 et S12)	25	20	17,5	15	12,5
J85 à J98 (S13 et S14) (1/4mg/kg/j)	20	17,5	15	12.5	10
J99 à J112 (S15 et S16)	15	15	12.5	10	7.5
J113 à M6	10			7.5	
M7 M8 M9	7.5				
M10 M11 M12	5				
1 an	Arrêt à discuter				

J : Jour ; S : semaine ; M : mois

Autoimmun Rev. 2017 Aug;16(8):826-832. doi: 10.1016/j.autrev.2017.05.017. Epub 2017 May 28.

Repeated pulses of methyl-prednisolone with reduced doses of prednisone improve the outcome of class III, IV and V lupus nephritis: An observational comparative study of the Lupus-Cruces and lupus-Bordeaux cohorts.

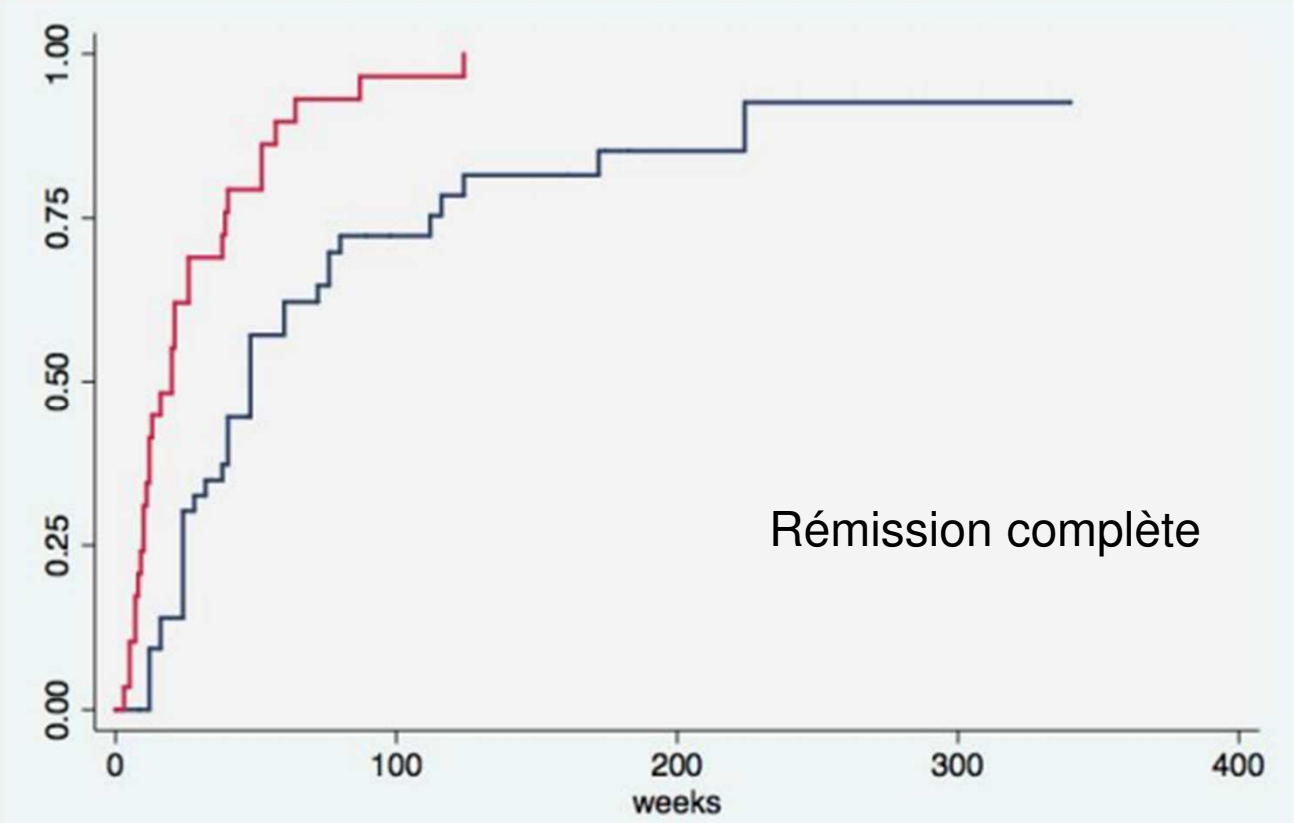
Ruiz-Irastorza G[1], Ugarte A[2], Saint-Pastou Terrier C[3], Lazaro E[4], Iza A[2], Couzi L[5], Saenz R[2], Richez C[6], Porta S[7], Blanco P[8].

Ruiz-Irastorza, *et Bordeaux*. Autoimmun Rev. 2017;16:826-32.

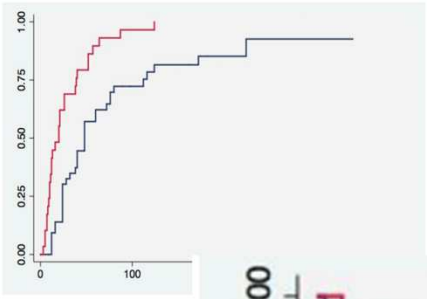
- GN lupiques classe III, IV et V
- **Schéma Cruces (n=29)** : BSM 125mg x 3 + avec chaque CYC (Euro-lupus) + prednisone ≤30mg/j => 2,5-5mg/j à M3.
  - Dose max moyenne : 21 mg/j
  - Dose M6 moyenne : 8 mg/j
  - Nb moyen BSM : 9,3
- **Schéma Bordeaux (n=44)** : classique (prednisone + MMF ou CYC puis prednisone et IS).
  - Dose max moyenne: 42,5 mg/j
  - Dose M6 moyenne : 21 mg/j
  - Nb moyen BSM : 3

HCQ: 100% vs 64% (p<0,001)

Seule variable indépendamment associée à la rémission complète : nombre de BSM (HR ajusté 1,09, IC95% 1,03-,1,15).



HR ajusté 3,8, IC95% 2,05-7,09



Toxicité liée aux corticoïdes

Voies génomique (toxicité, maximale à 30mg/j)
et extra-génomique (efficacité rapide, obtenue si >100mg/j)

HR ajusté 0,19, IC95% 0,04-0,89

Doses de Corticoides (rein)

Schéma Fred Houssiau (et Cochin) :

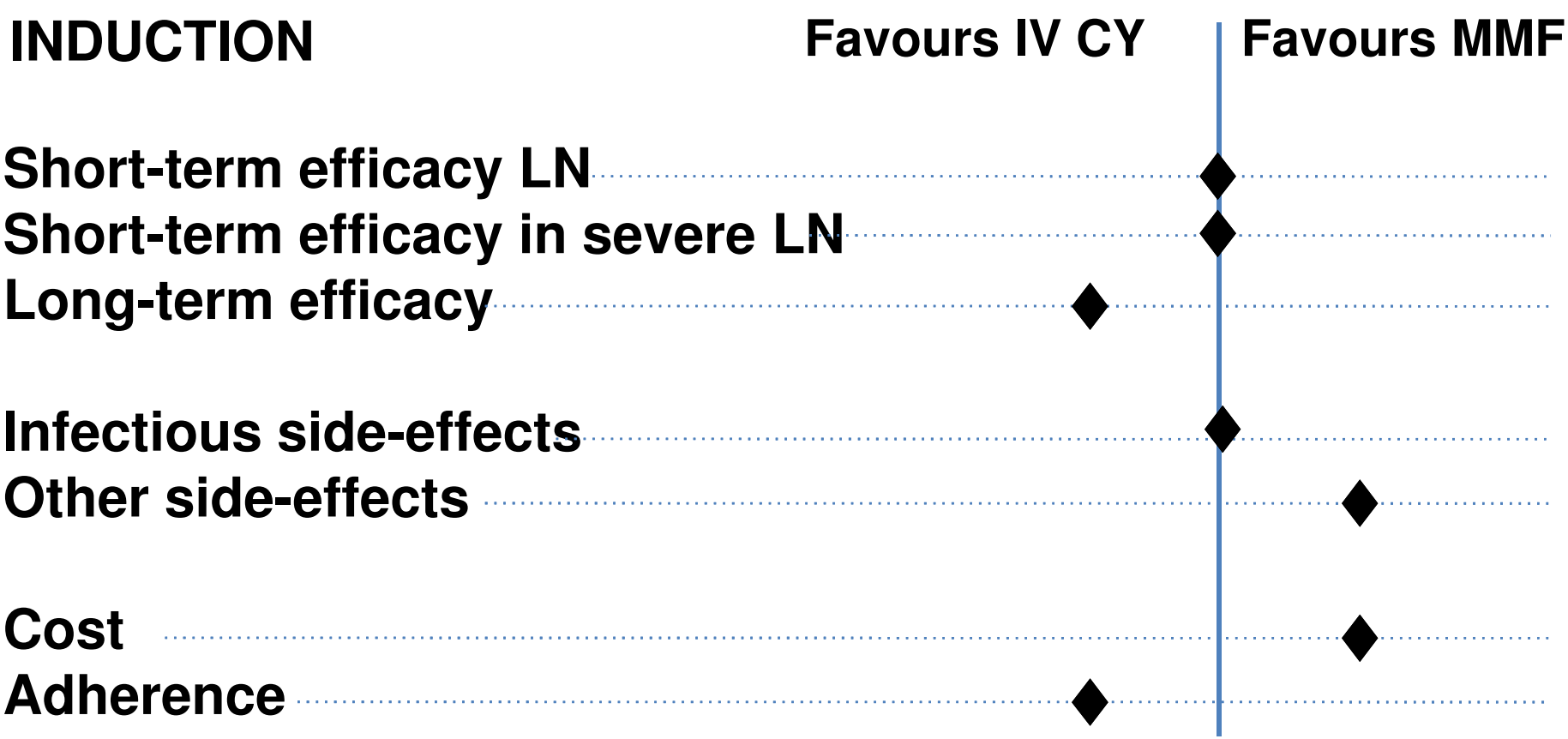
- Bolus de méthylprednisolone
  (750 mg x 3)
- Puis 20 mg/j
- 10 mg à 2 mois
- 5 mg à 3 mois
- 2,5 mg à 6 mois
- 0 à 1 an

Week	Prednisolone mg/day
1-4	20
5-6	15
7-8	10
9-10	7.5
11-24	5
24-52	2.5
At w 52	possibly 0

Traitement du lupus

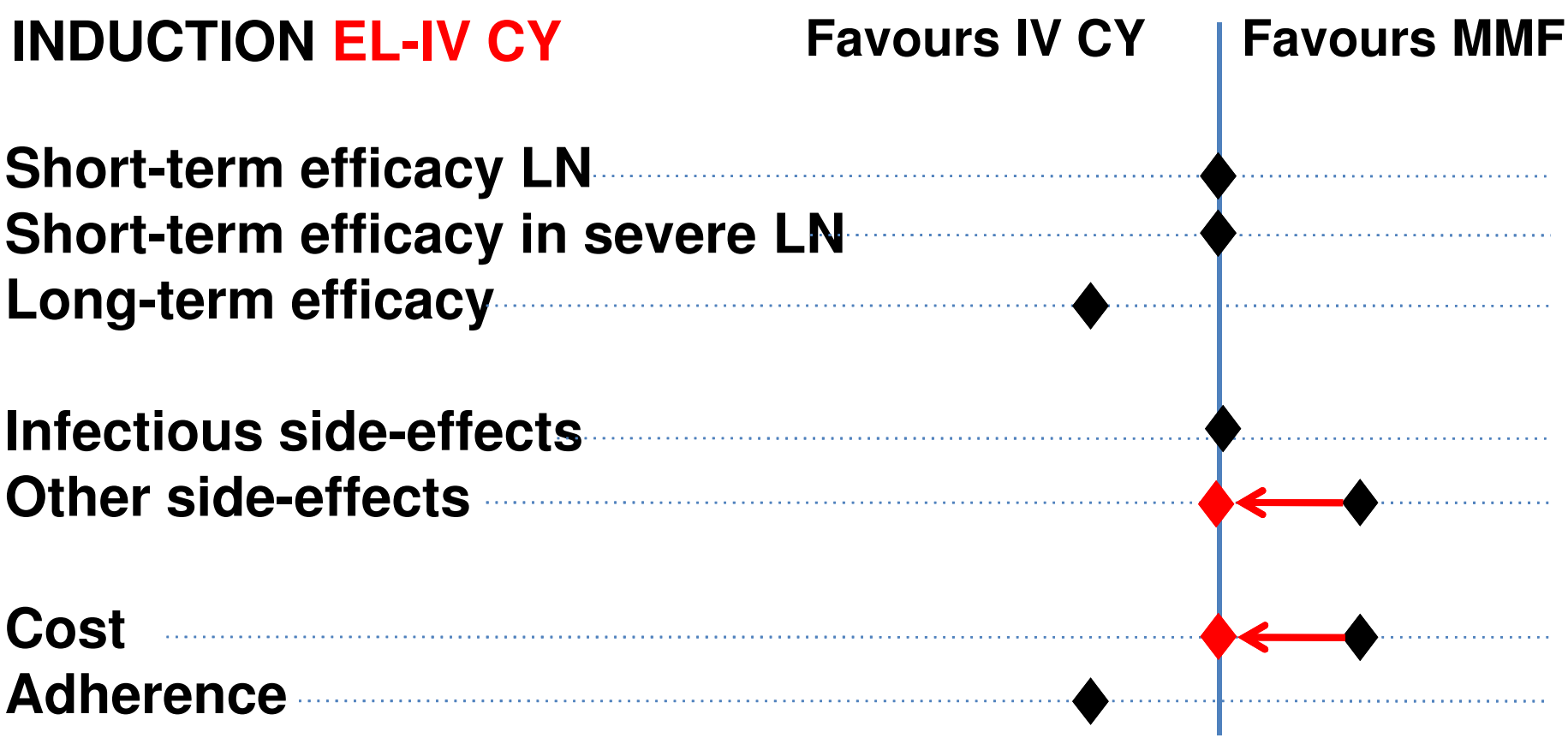
- Plus d'HYDROXYCHLOROQUINE
- Moins de CORTICOIDES
- Quel IMMUNOSUPPRESSEUR ?
  - INDUCTION (CYC vs MMF)
  - ENTRETIEN (AZA vs MMF)

My eminence-based forest plots in LN



Fred Houssiau

My eminence-based forest plots in LN



Fred Houssiau

Traitement du lupus

Le reste

ARTHRITIS & RHEUMATOLOGY
Vol. 67, No. 6, June 2015, pp 1577–1585
DOI 10.1002/art.39070

Serious Infections Among Adult Medicaid Beneficiaries With Systemic Lupus Erythematosus and Lupus Nephritis

Candace H. Feldman,[1] Linda T. Hiraki,[2] Wolfgang C. Winkelmayer,[3] Francisco M. Marty,[4] Jessica M. Franklin,[4] Seoyoung C. Kim,[4] and Karen H. Costenbader[4]

Medicaid database (2000–2006; 47 US states),

Adults (18–64 years) with SLE

Incidence des infections

- **33565 patients** avec un lupus systémique
- 9078 infections sévères chez 5068 patients
- **10,8 pour 100 personnes-années** (23,9 rein)
- **96% bacteriennes:** pneumonies (n=3337), cellulites (n=2322), ou bactériémies (n=2200)

Feldman et al. Arthritis Rheum, 2015; 1577

Facteurs de risque d'infections

Le risque d'infections sévères : **iatrogène.**

Augmenté par les corticoides même à faibles doses

Diminué par l'hydroxychloroquine (même après ajustement)

Feldman et al. Arthritis Rheum, 2015; 1577-85
Ruiz-Irastorsza, Arthritis Res Ther, 2009, 11:109
Herrington et al. J Rheumatol 2016;43:1503–9

Recommendation

EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases

S van Assen,[1] N Agmon-Levin,[2] O Elkayam,[3,4] R Cervera,[5] M F Doran,[6] M Dougados,[7] P Emery,[8,9] P Geborek,[10] J P A Ioannidis,[11–14] D R W Jayne,[15] C G M Kallenberg,[16] U Müller-Ladner,[17] Y Shoenfeld,[2,4] L Stojanovich,[18] G Valesini,[19] N M Wulffraat,[20] M Bijl[12]

Ann Rheum Dis 2011;**70**:414–422.

The highest strength of these recommendations is B

ARTHRITIS & RHEUMATOLOGY
Vol. 67, No. 6, June 2015, pp 1577–1585
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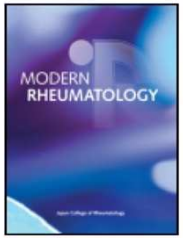
Serious Infections Among Adult Medicaid Beneficiaries With Systemic Lupus Erythematosus and Lupus Nephritis

Candace H. Feldman,[1] Linda T. Hiraki,[2] Wolfgang C. Winkelmayer,[3] Francisco M. Marty,[4] Jessica M. Franklin,[4] Seoyoung C. Kim,[4] and Karen H. Costenbader[4]

Resultats

- 33 565 patients avec un lupus prévalent
- 9 078 infections sévères chez 5 068 patients lupiques
- 10,8 per 100 personnes-années

- **18 cas de pneumocystose (0,05%)**
- **Statut HIV non connu**



Japan College of Rheumatology
MODERN RHEUMATOLOGY

http://informahealthcare.com/mor
ISSN 1439-7595 (print), 1439-7609 (online)

Mod Rheumatol, 2016; 26(4):557–561

DOI: 10.3109/14397595.2015.1112467

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Safety and efficacy of upfront graded administration of trimethoprim–sulfamethoxazole in systemic lupus erythematosus: A retrospective cohort study

Yasuhiro Suyama[1], Masato Okada[1], Ryo Rokutanda[1], Chisun Min[1], Belinda Sassé[1], Daiki Kobayashi[2], Osamu Takahashi[2], Gautam A. Deshpande[2], Kazuo Matsui[3], Yasushi Kawaguchi[4], and Mitsumasa Kishimoto[1]

Trimethoprim-sulfamethoxazole et lupus

- Etude rétrospective de 59 patients lupiques + TMP/SMX
- L'incidence des effets II^{aires} : **41,9% posologie classique**, vs. 10,7% si augmentation progressive ($p = 0.009$)
- Réduction du risque de fièvre, anomalies du bilan hépatique, dyspnée, et hospitalisations si augmentation progressive de la posologie

Suyama et al. Mod Rheumatol. 2016;26:557-61

Versus 3% dans la population générale

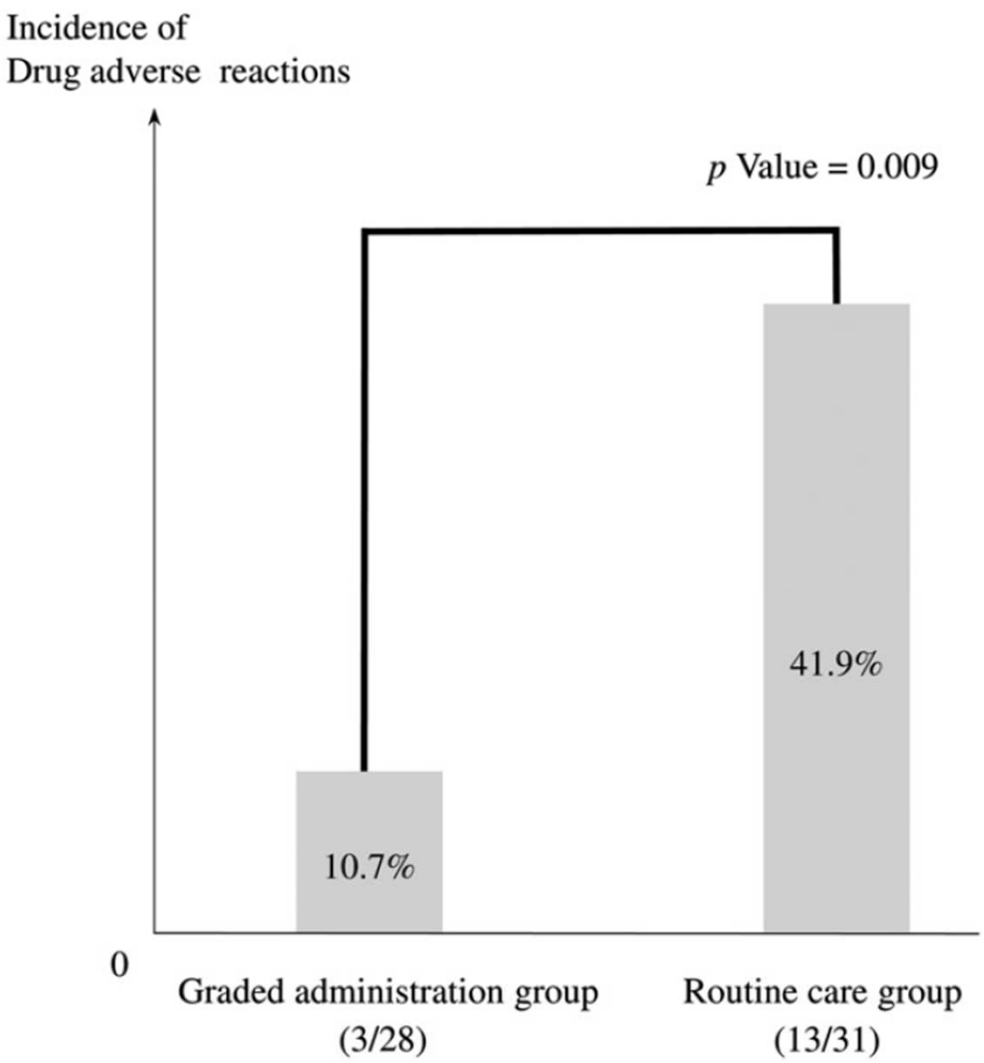


Figure 1. Incidence of adverse drug reactions in systemic lupus erythematosus patients.

Primary prophylaxis?

Clinical and epidemiological research

OPEN ACCESS

EXTENDED REPORT

Prophylactic effect of trimethoprim-sulfamethoxazole for pneumocystis pneumonia in patients with rheumatic diseases exposed to prolonged high-dose glucocorticoids

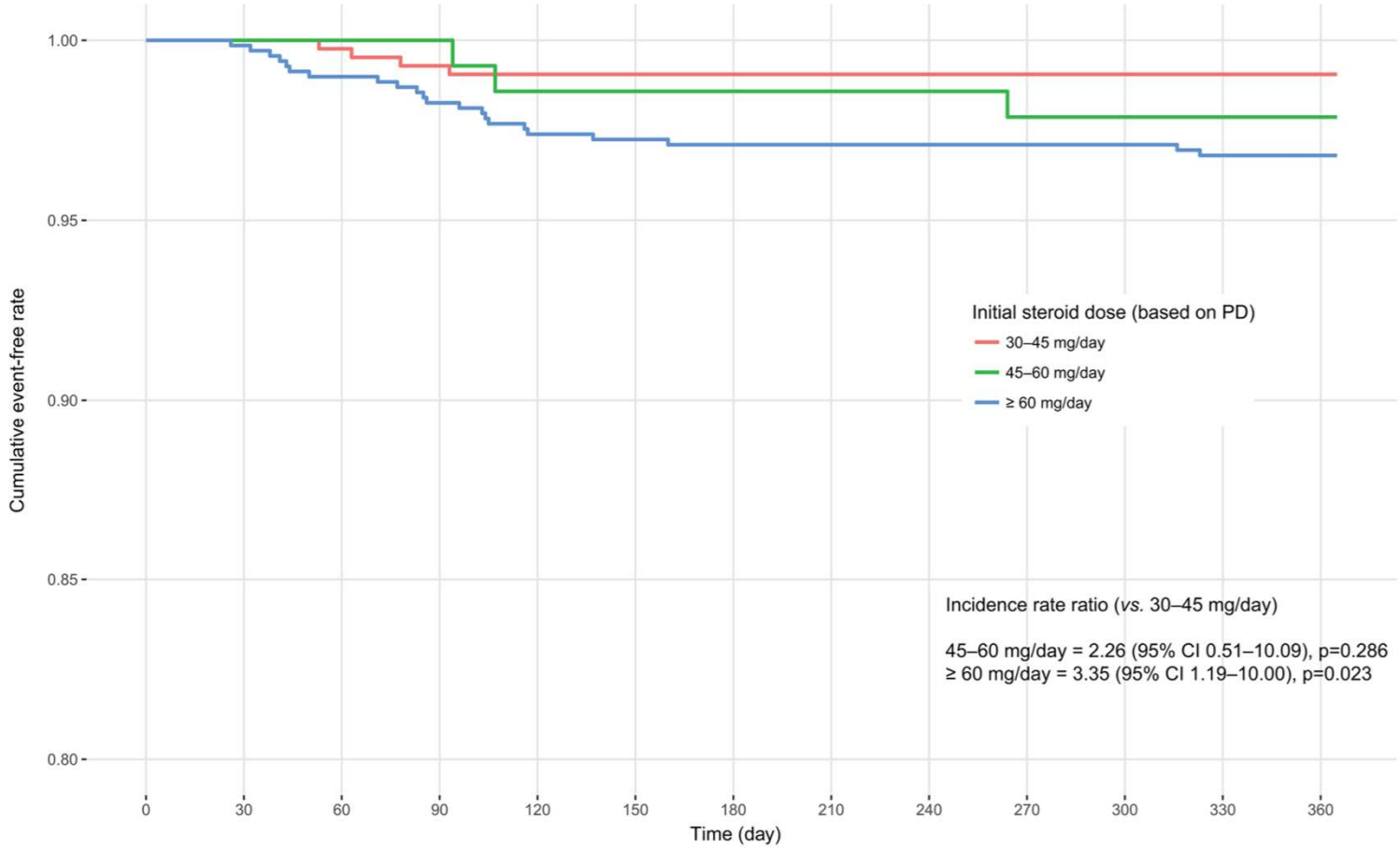
Jun Won Park,[1] Jeffrey R Curtis,[2] Jinyoung Moon,[1] Yeong Wook Song,[1] Suhnggwon Kim,[3,4] Eun Bong Lee[1]

M & M

- Seoul electronic database
- All patients with RD treated by HD steroids ≥ 4 weeks, January 2004 → December 2015
- Exclusion of : history of PCP, cancer, organ transplant, HIV
- 2 groups : w/wo PCP prophylaxis
- Follow up : 1 year from baseline (first day of PCP prophylaxis or HD steroids)
- Primary outcome : incidence of PCP

PCP incidence

N=1522 treatment episodes



GCA > SSc > DM > SLE

Results

Table 3 Effect of TMP-SMX prophylaxis on 1-year PCP incidence and related mortality in the propensity score-matched population (n=470)

	1-year PCP incidence		1-year PCP-related mortality*	
	HR (95% CI)		HR (95% profile likelihood CI)	
	Univariable analysis	Multivariable analysis†	Univariable analysis	Multivariable analysis‡
TMP-SMX prophylaxis	0.07 (0.01 to 0.54)	0.07 (0.01 to 0.53)	0.07 (0.0005 to 0.55)	0.08 (0.0006 to 0.71)
P value for HR	0.010	0.010	0.007	0.019

*"In the subgroup with a higher initial steroid dose (**≥60mg/day prednisone**) (n=261), TMP-SMX led to a **significant reduction in PCP incidence** after adjusting for GPA (adjusted HR=0.05; 95% profile likelihood CI 0.0004 to 0.40)."*

Limits

- PCP prophylaxis patients had more often lymphopenia, GCA, DM, history of immunosuppressive treatments…

- No clear message on when to stop : « *stopped when the daily steroid dose (…) was tapered: to 30mg in 35 (13.6%) treatment episodes, 25mg in 6 (2.3%), 20mg in 26 (10.1%), 15mg in 53 (20.6%) and <15mg/day in 113 (44.0%)* »

- **High dose steroid treatment for lupus can be avoided**

TMP/SMX et lupus

- Pas d'indication de TMP/SMX du fait du très faible risque d'infections et du fort risque d'effets secondaires.

- Si nécessaire (HIV): augmentation de posologie progressive.

Kapoor et al Lupus. 2017
Suyama et al. Mod Rheumatol. 2016;26:557-61

Toujours

- Attention à la iatrogénie
- Prévention des infections : vaccinations (pneumocoque, grippe, HPV…).
- Attention aux vaccins vivants
- Cotrimoxazole-Bactrim très discutable
- Prise en compte des facteurs de risques cardio-vasculaires
- Prise en compte du SAPL éventuellement associé.
- Information, éducation, soutien, disponibilité

Exercice physique et lupus

Métananalyse de 2 études randomisées + 1 étude expérimentale (aerobic)

- Diminution de la fatigue (-0.52, 95%IC: [-0.91, -0.13], p=0.009)
- Augmentation de la vitalité (14.98, 95%IC [7.45, 22.52], p<0.001).
- 12 semaines mieux que 8
- Mieux si avec supervision
- Au moins 20 minutes x 3 par semaine

Wu ML, et al Worldviews Evid Based Nurs. 2017.

Prescription (en rémission)

- **Immunosuppresseur**
- **Corticoïdes**
- **Plaquénil**
- **Potassium**
- **Calcium**
- **Vitamine D**
- **Biphosphonates**
- **Anti-acides**
- **Aspirine**
- **Contraception**
- **Statine (?)**

Mlle S., 22 and, lupus renal remission (pas de truquage)

Who is refractory ?

Traitement du lupus

Et l'adhésion ?

Dynamic Patterns and Predictors of Hydroxychloroquine Nonadherence among Medicaid Beneficiaries with Systemic Lupus Erythematosus

Candace H. Feldman, MD, ScD[1,2], Jamie Collins, PhD[3], Zhi Zhang, MS[1], SV Subramanian, PhD[2], Daniel H Solomon, MD, MPH[1], Ichiro Kawachi, MB.ChB., PhD*[2], Karen H. Costenbader, MD, MPH*[1]

Feldman CH*, et al. Semin Arthritis Rheum*. 2018.

Méthodes

- Données U.S. Medicaid entre 2000-2010
- Lupus, 18-64 ans, prescription récente d'HCQ
- Mauvaise adhésion : « taux de possession moyen » (MPR) <80%.

Feldman CH, *et al. Arthritis Care Res (Hoboken)*. 2015;67:1712-21.

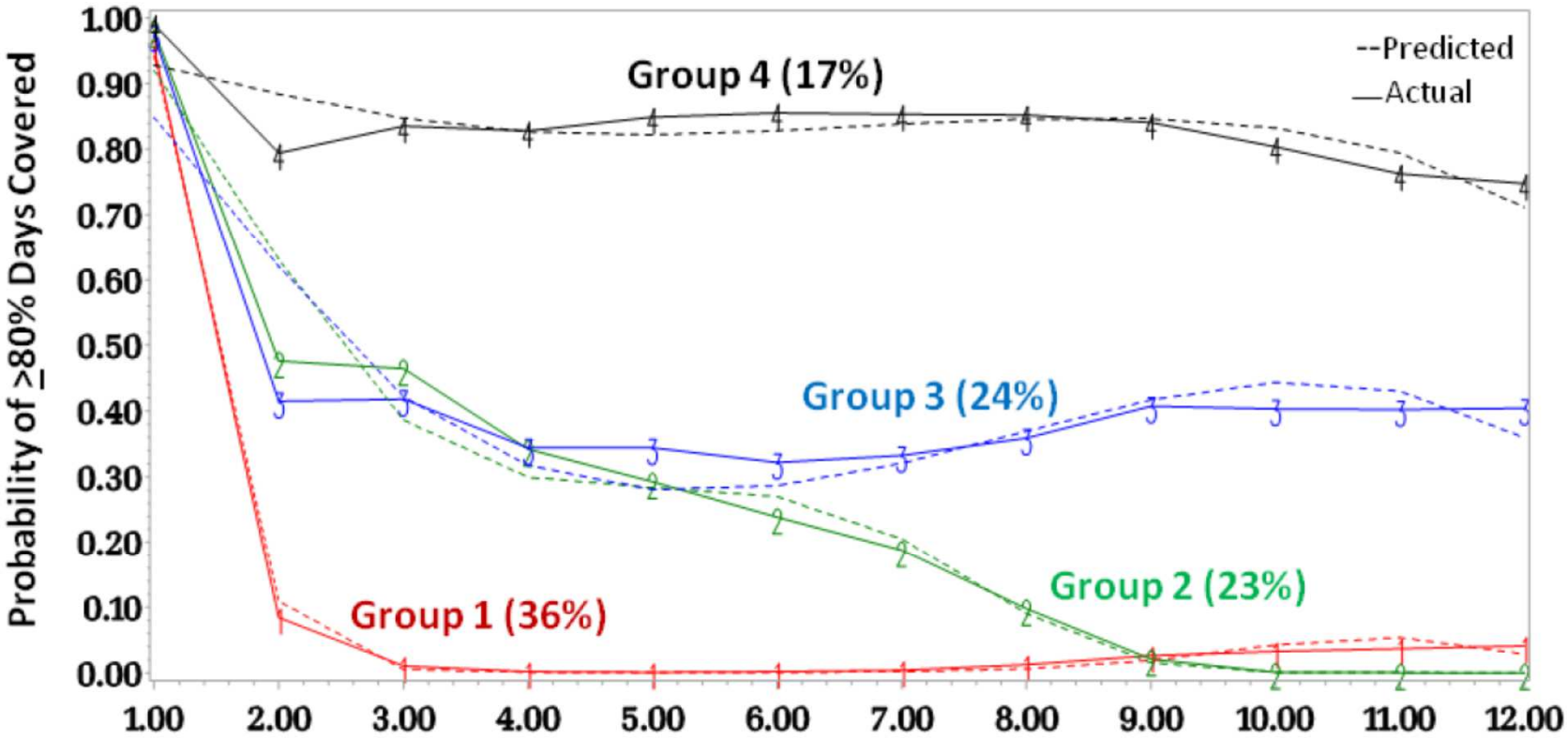
Résultats

- 10 406 patients lupiques primo-traités *(non adhésion primaire éliminée)*
- **Non-adhésion : 85%**
- L'adhésion diminue pour la plupart des patients au cours de la première année

PDC: proportion of days covered.

Feldman CH*, et al. Semin Arthritis Rheum*. 2018.

Résultats



Durant la période de suivi de 1 an, le taux de possession moyen était de 42 ± 29 %

Feldman CH, *et al. Semin Arthritis Rheum*. 2018.

Rétinopathie infra-clinique

Dépend de la dose journalière et de la durée d'exposition

En théorie et sur la population totale : pour avoir 5 mg/kg/j d'HCQ réellement dispensée en pharmacie, il faudrait prescrire 11,1 mg/kg à tous les patients

Marmor et al. Ophthalmology. 2016;123:1386-94

A Prospective International Study on Adherence to Treatment in 305 Patients With Flaring SLE: Assessment by Drug Levels and Self-Administered Questionnaires

Nathalie Costedoat-Chalumeau[1], Frédéric Houssiau[2], Peter Izmirly[3], Véronique Le Guern[1], Sandra Navarra[4], Meenakshi Jolly[5], Guillermo Ruiz-Irastorza[6], Gabriel Baron[7], Eric Hachulla[8], Nancy Agmon-Levin[9], Yehuda Shoenfeld[9], Francesca Dall'Ara[10], Jill Buyon[3], Christophe Deligny[11], Ricard Cervera[12], Estibaliz Lazaro[13], Holy Bezanahary[14], Gaëlle Leroux[15], Nathalie Morel[1], Jean-François Viallard[13], Christian Pineau[16], Lionel Galicier[17], Ronald Van Vollenhoven[18], Angela Tincani[10], Hanh Nguyen[19], Guillaume Gondran[14], Noel Zahr[20], Jacques Pouchot[21], Jean-Charles Piette[15], Michelle Petri[22] and David Isenberg[19]

CLINICAL PHARMACOLOGY & THERAPEUTICS

Costedoat-Chalumeau N*, et al. Clin Pharmacol Ther*. 2018.

Objectif

Etude prospective internationale évaluant l'adhésion

chez **305 patients lupiques en poussée** avec :

- Dosages d'HCQ et DCQ
- Et auto-questionnaires

HCQ: hydroxychloroquine;
DCQ: desethylchloroquine.

Costedoat-Chalumeau N*, et al. Clin Pharmacol Ther*. 2018.

Taux de non-adhésion

- Les dosages d'HCQ et de DCQ identifiaient une non-adhésion sévère chez **près de 1 patient sur 5.**

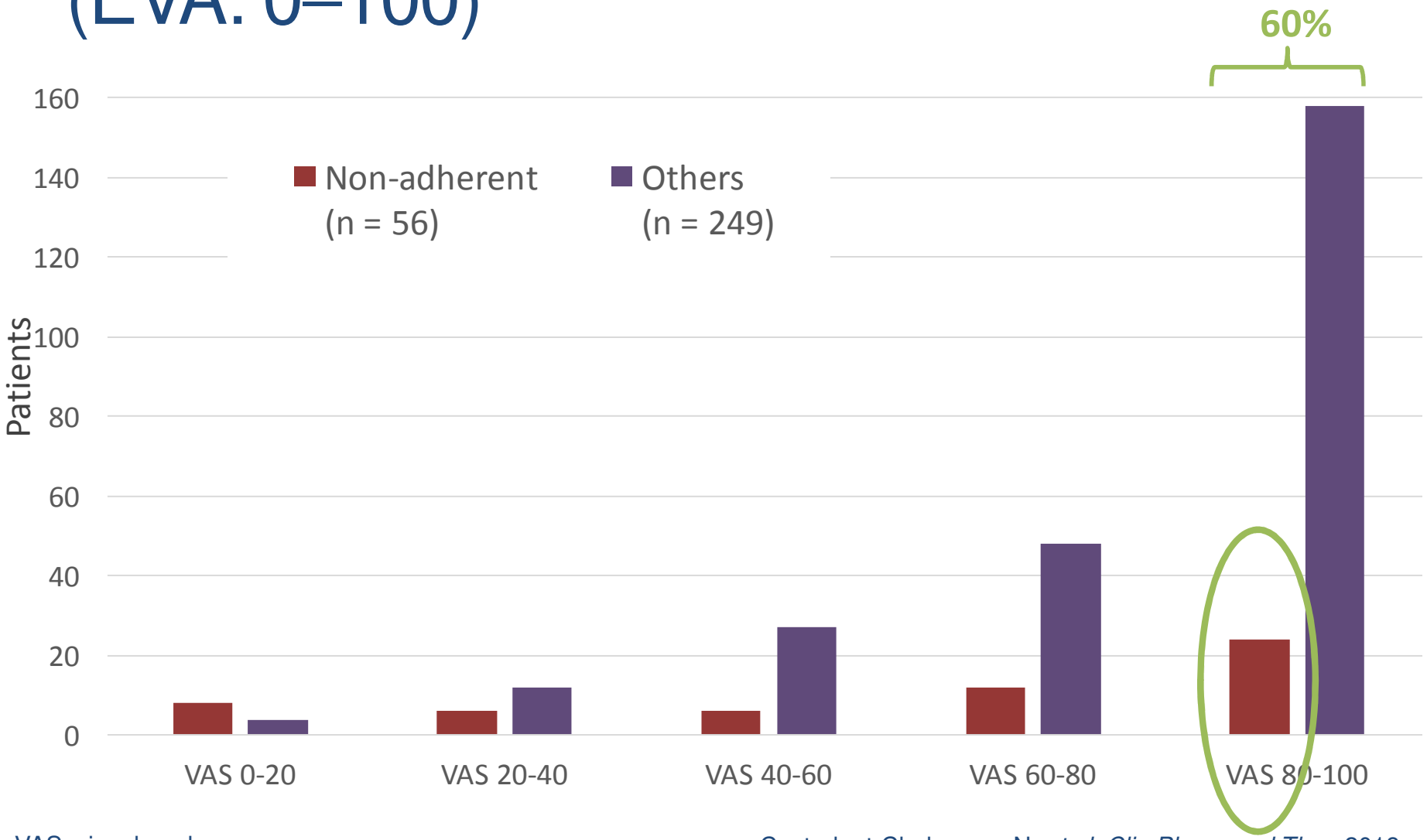
- Avec les auto-questionnaires, **environ 1/3 des patients** étaient non-adhérents

Costedoat-Chalumeau N*, et al. Clin Pharmacol Ther*. 2018.

Certains patients avec des **taux d'HCQ et DCQ indétectable avaient un score MASRI > 80%,** montrant qu'il peut être très difficile d'admettre une non-adhesion sévère.

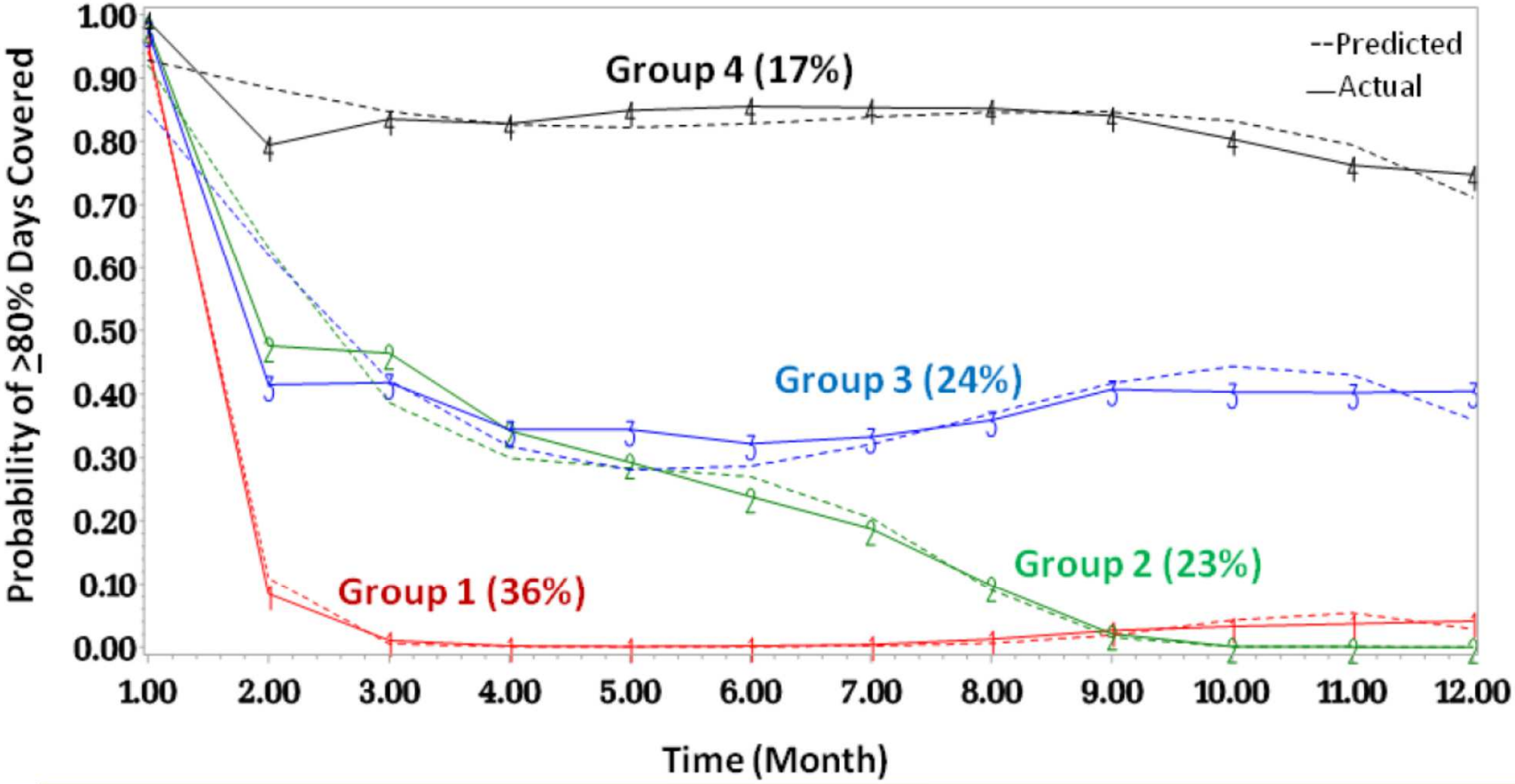
Costedoat-Chalumeau N*, et al. Clin Pharmacol Ther*. 2018.

Evaluation par le médecin (EVA: 0–100)



VAS: visual analogue score.

Costedoat-Chalumeau N, *et al. Clin Pharmacol Ther*. 2018.



Nous sommes très optimistes !

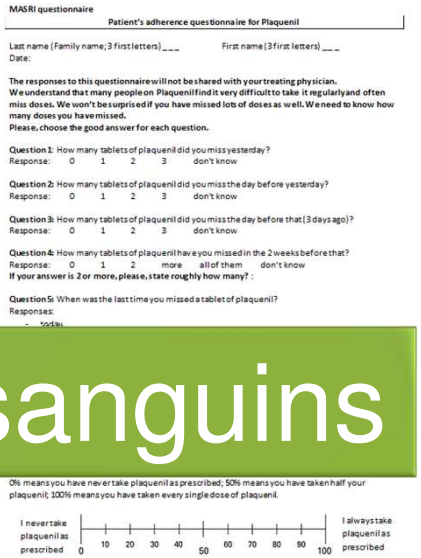
Costedoat-Chalumeau N, *et al. Clin Pharmacol Ther*. 2018.

Correlations

Rs: 0.19
Très faible

Rs: 0.37
Modérée

Rs: 0.43
Modérée


MASRI questionnaire

Patient's adherence questionnaire for Plaquenil

Last name (Family name; 3 first letters) ___ First name (3 first letters) ___
Date:

The responses to this questionnaire will not be shared with your treating physician.
We understand that many people on Plaquenil find it very difficult to take it regularly and often miss doses. We won't be surprised if you have missed lots of doses as well. We need to know how many doses you have missed.
Please, choose the good answer for each question.

Question 1: How many tablets of plaquenil did you miss yesterday?
Response: 0 1 2 3 don't know

Question 2: How many tablets of plaquenil did you miss the day before yesterday?
Response: 0 1 2 3 don't know

Question 3: How many tablets of plaquenil did you miss the day before that (3 days ago)?
Response: 0 1 2 3 don't know

Question 4: How many tablets of plaquenil have you missed in the 2 weeks before that?
Response: 0 1 2 more all of them don't know
If your answer is 2 or more, please, state roughly how many? :

Question 5: When was the last time you missed a tablet of plaquenil?
Responses:

0% means you have never take plaquenil as prescribed; 50% means you have taken half your plaquenil; 100% means you have taken every single dose of plaquenil.

I never take plaquenil as prescribed 0 10 20 30 40 50 60 70 80 90 100 I always take plaquenil as prescribed

Nous avons besoin des taux sanguins

Rs: spearman coefficient of correlation score.

Les auto-questionnaires et les taux sanguins mesurent deux choses différentes.

Deux types de non-adhesion sont décrits :

- Oublis plus ou moins fréquents
- Arrêt complet ou prise très occasionnelle

Merci pour votre attention