SRO
Rhumatismes inflammatoires

Actualités du semestre

5/10/2018

Dr Emmanuelle DERNIS

Polyarthrite Rhumatoïde

RESEARCH ARTICLE

Multi-biomarker disease activity score as a predictor of disease relapse in patients with rheumatoid arthritis stopping TNF inhibitor treatment

Marjan Ghiti Moghadam[1,2☯*], Femke B. G. Lamers-Karnebeek[3☯], Harald E. Vonkeman[1,2], Peter M. ten Klooster[2], Janneke Tekstra[4], Annemarie M. Schilder[5], Henk Visser[6], Eric H. Sasso[7], David Chernoff[7], Willem F. Lems[8], Dirk-Jan van Schaardenburg[9], Robert Landewe[10], Hein J. Bernelot Moens[11], Timothy R. D. J. Radstake[4], Piet L. C. M. van Riel[12], Mart A. F. J. van de Laar[1,2], Tim L. Jansen[13], on behalf of the Dutch National POET Collaboration[¶]

MULTI-BIOMARKER DISEASE ACTIVITY (MBDA) SCORE FOR RHEUMATOID ARTHRITIS (cont.)

Description:

Assessment of disease activity in rheumatoid arthritis (RA) is an important component of management with a goal of treatment being to maintain low disease activity or remission. One potential approach that has been investigated is the use of a multi-biomarker disease activity (MBDA) score. The Vectra® DA test (Crescendo Bioscience®) is a commercially available MBDA blood test that uses 12 biomarkers to construct a disease activity score ranging from 1 to 100.

The Vectra DA test consists of 12 individual biomarkers:

- CRP
- Epidermal growth factor (EGF)
- Interleukin-6 (IL-6)
- Leptin
- Matrix metalloproteinase 1 (MMP-1)
- Matrix metalloproteinase 3 (MMP-3)
- Resistin
- Serum amyloid A (SAA)
- Tumor necrosis factor receptor type I (TNFRI)
- Vascular cell adhesion molecule 1 (VCAM-1)
- Vascular endothelial growth factor A (VEGF-A)
- YKL-40

The Vectra DA test scores range from 1 to 100. Categories of scores were constructed to correlate with the DAS28-C-reactive protein scale:

- 45-100: high disease activity
- 30-44: moderate disease activity
- 1-29: low disease activity

MULTI-BIOMARKER DISEASE ACTIVITY (MBDA) SCORE FOR RHEUMATOID ARTHRITIS (cont.)

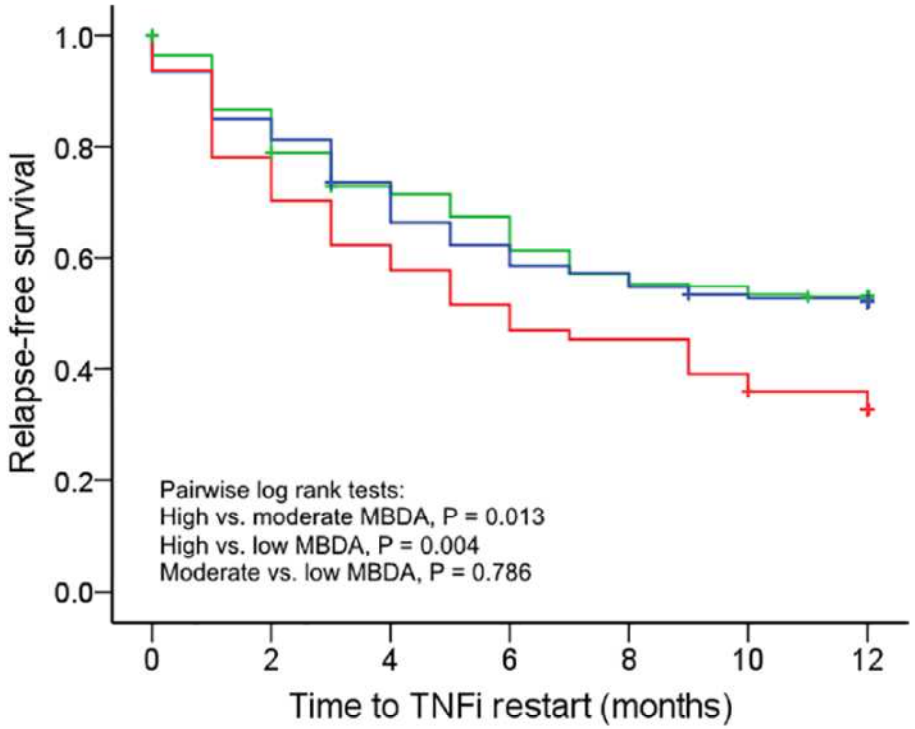
Criteria:

- The use of a multi-biomarker disease activity score for rheumatoid arthritis is considered ***experimental or investigational*** based upon:

  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  2. Insufficient evidence to support improvement of the net health outcome, and
  3. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  4. Insufficient evidence to support improvement outside the investigational setting.

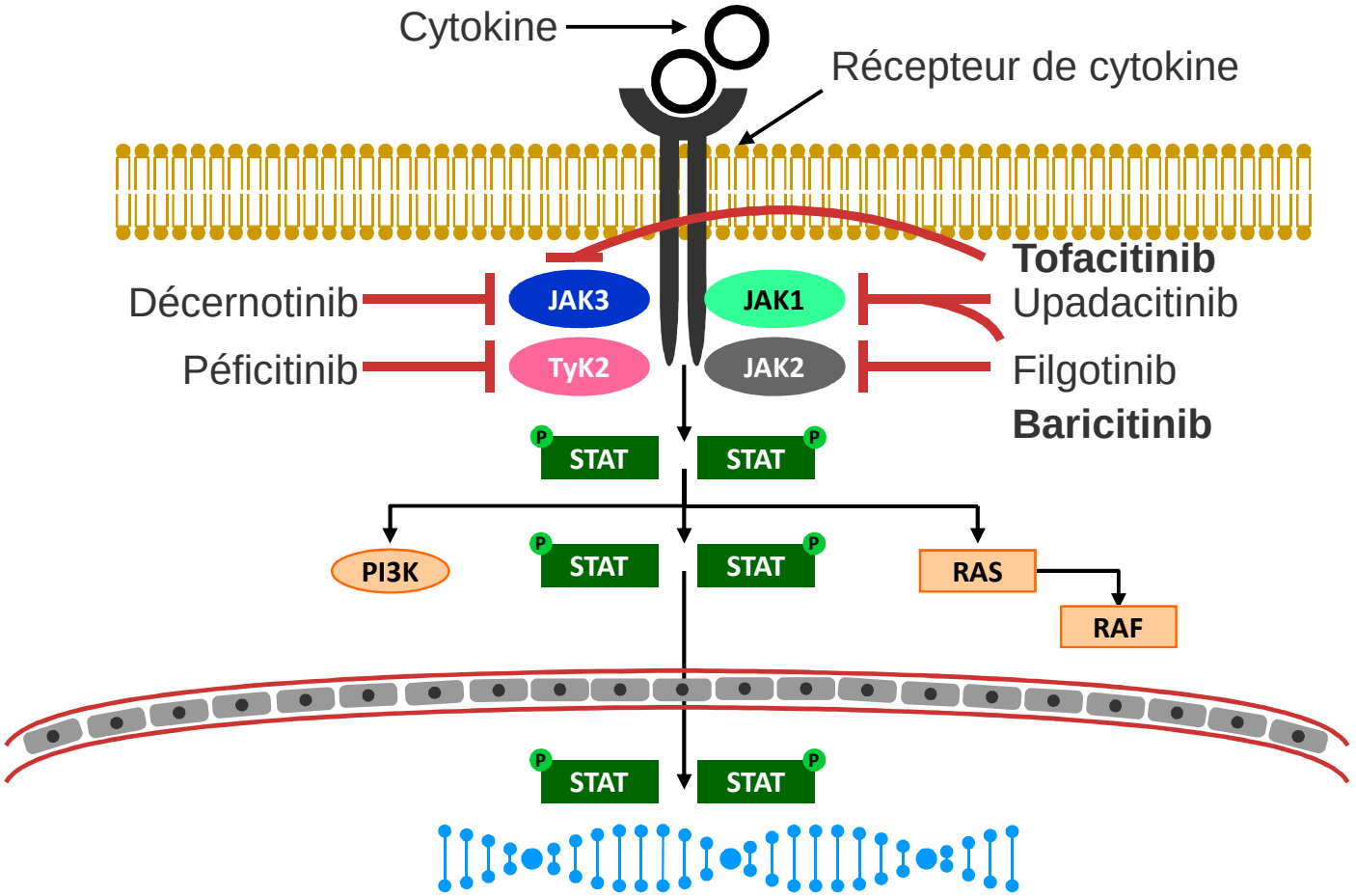
  These tests include, *but are not limited to*:

  - Vectra DA Score


Relapse-free survival
1.0
0.8
0.6
0.4
0.2
0.0
Pairwise log rank tests:
High vs. moderate MBDA, P = 0.013
High vs. low MBDA, P = 0.004
Moderate vs. low MBDA, P = 0.786
0
2
4
6
8
10
12
Time to TNFi restart (months)

Un nouvel inhibiteur de JAK : l'upadacitinib

La famille des JAKi comporte 6 molécules, dont l'upadacitinib



➔ **L'upadacitinib est un JAKi agissant principalement sur JAK1**

EULAR 2018 - D'après Lopez-Olivo MA et al., abstr. OP0032, actualisé

Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial

Mark C Genovese, Roy Fleischmann, Bernard Combe, Stephen Hall, Andrea Rubbert-Roth, Ying Zhang, Yijie Zhou, Mohamed-Eslam F Mohamed, Sebastian Meerwein, Aileen L Pangan

www.thelancet.com **Published online June 13, 2018** **http://dx.doi.org/10.1016/S0140-6736(18)31116-4**

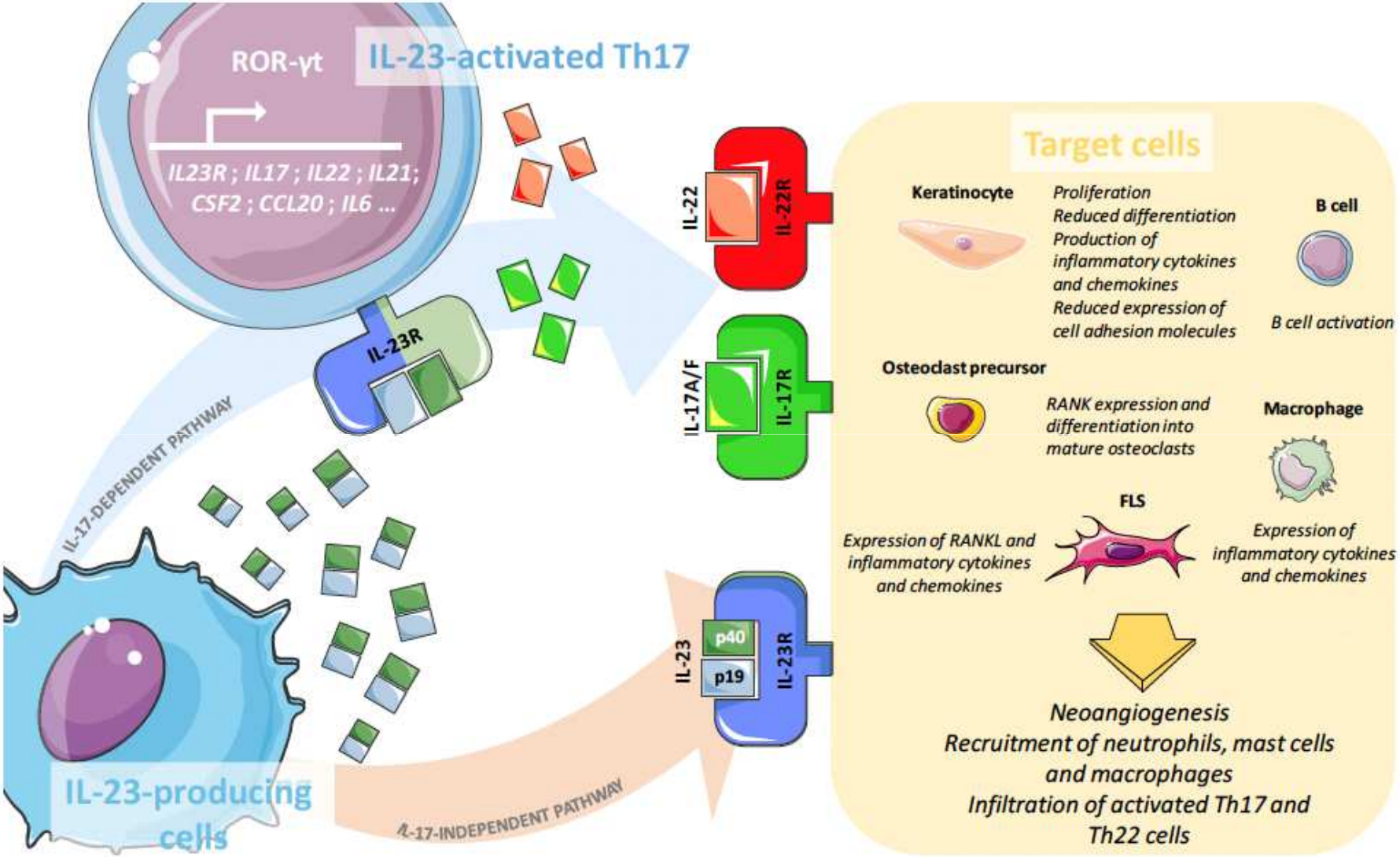
Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial

Gerd R Burmester, Joel M Kremer, Filip Van den Bosch, Alan Kivitz, Louis Bessette, Yihan Li, Yijie Zhou, Ahmed A Othman, Aileen L Pangan, Heidi S Camp

www.thelancet.com **Published online June 13, 2018 http://dx.doi.org/10.1016/S0140-6736(18)31116-4**

Rhumatisme psoriasique

Voie IL 23, IL 12 et IL 17



Int. J. Mol. Sci. 2018, 19, 530;

Biologiques ciblants les voies IL 23, IL 12 et IL 17

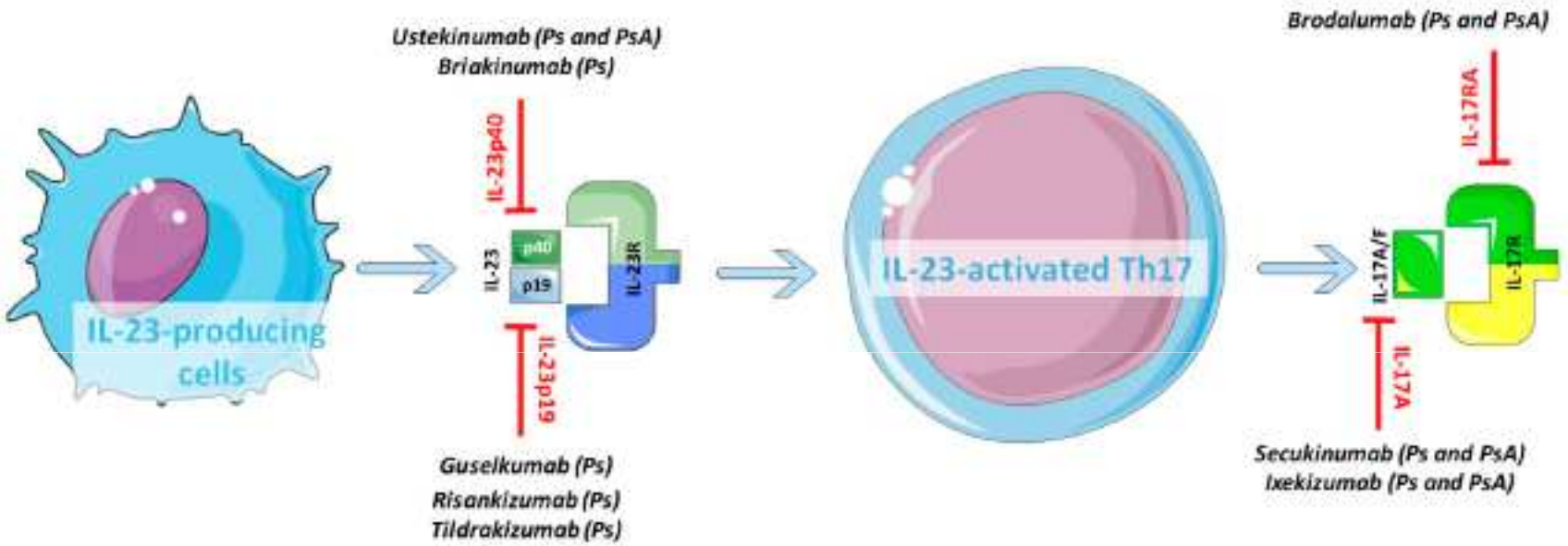
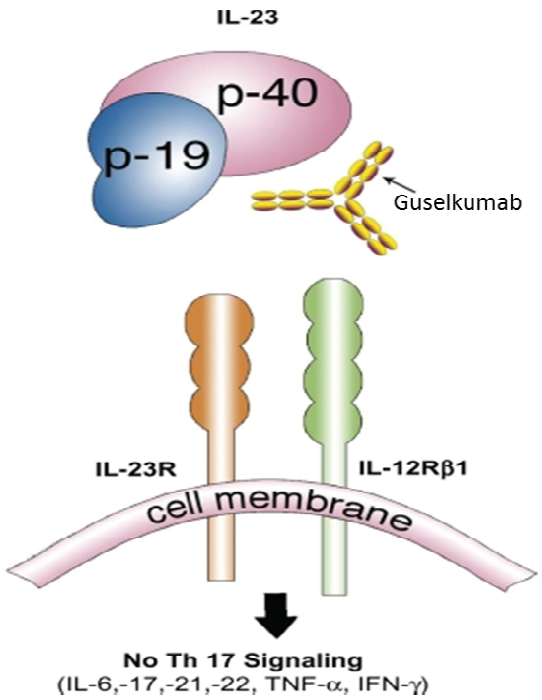


Figure 2. Biologics targeting the IL-23/IL-17 axis in Psoriasis (Ps) and Psoriatic Arthritis (PsA). Specific monoclonal antibodies targeting IL-23p40, IL-23p19, IL-17A or its receptor IL-17R have been developed and are currently used in clinical practice or still tested inclinical trials (see Table 1).

P40 commun avec IL23 et IL12
P39 commun avec IL23 et IL39

Efficacy and safety of guselkumab in patients with active psoriatic arthritis: a randomised, double-blind, placebo-controlled, phase 2 study

Atul Deodhar, Alice B Gottlieb*, Wolf-Henning Boehncke, Bin Dong, Yuhua Wang, Yanli Zhuang, William Barchuk, Xie L Xu, Elizabeth C Hsia, on behalf of the CNTO1959PSA2001 Study Group*

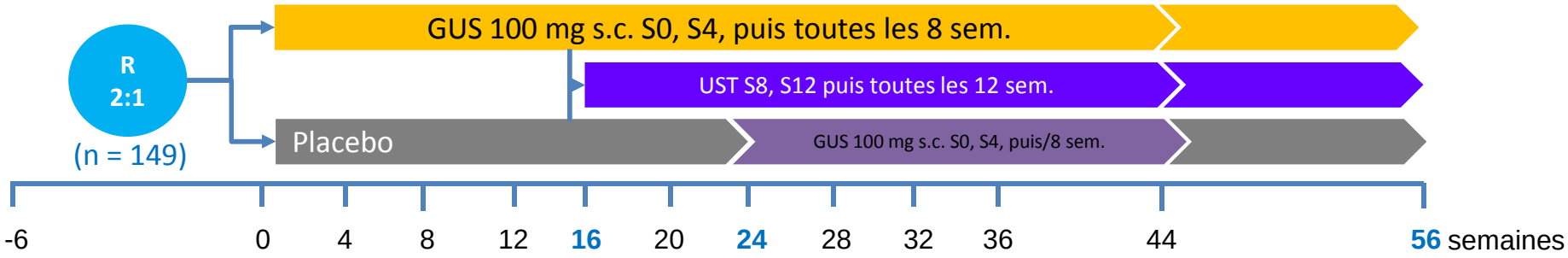


Anticorps monoclonal humain anti-IL23 (IgG1) p19

Lancet 2018; 391: 2213–24

Guselkumab dans le rhumatisme psoriasique

- Guselkumab, inhibiteur de la sous-unité p19 de l'interleukine 23
- Étude de phase II randomisée, en double insu, contrôlée versus placebo



- Critères d'inclusion
  - Rhumatisme psoriasique répondant aux critères CASPAR
  - NAD ≥ 3, NAG ≥ 3, CRP ≥ 3 mg/L
  - Psoriasis ≥ 3 % BSA
  - ≥ 1 atteinte suivante : atteinte des IPD, atteinte polyarticulaire, arthrite mutilante, oligoarthrite asymétrique, spondylite avec arthrite périphérique
  - Réponse insuffisante aux csDMARD
- Critère d'évaluation principal
  - ACR 20 à S24, analyse en ITT

Lancet 2018; 391: 2213–24

Guselkumab dans le rhumatisme psoriasique

149 pts

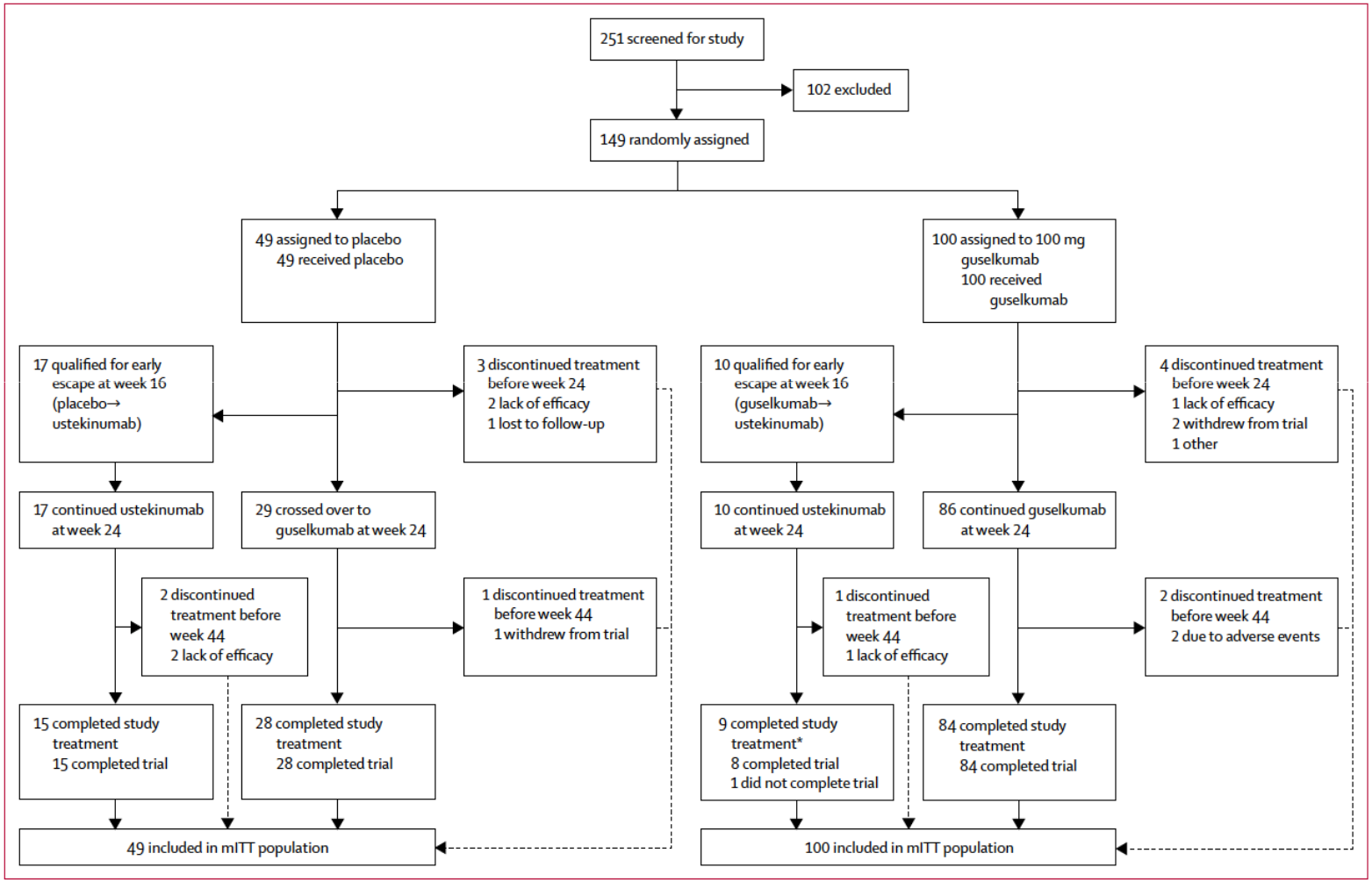


Figure 1: **Trial profile**
mITT=modified intention-to-treat. *One patient who completed 44 weeks of treatment with study drug was lost to follow-up and did not attend the week 56 follow-up visit.

Lancet 2018; 391: 2213–24

Guselkumab dans le rhumatisme psoriasique

	Placebo (n=49)	Guselkumab (n=100)
Age, years	44·2 (12·4)	47·4 (12·8)
Sex		
Men	24 (49%)	52 (52%)
Women	25 (51%)	48 (48%)
Race		
White	49 (100%)	100 (100%)
Bodyweight (kg)	86·3 (20·5)	84·4 (21·4)
Duration of psoriatic arthritis, years	6·9 (7·2)	7·0 (7·2)
Number of swollen joints (0–66)	10·6 (7·5)	11·9 (7·6)
Number of tender joints (0–68)	20·1 (12·5)	20·7 (12·2)
Patient's assessment of pain (0–100 mm VAS)	61·9 (20·2)	62·1 (21·5)
Patient's global assessment of disease activity (0–100 mm VAS)	64·7 (20·1)	67·0 (20·6)
Physician's global assessment of disease activity (0–100 mm VAS)	61·9 (15·9)	63·2 (16·8)
HAQ-DI score (0–3)	1·3 (0·5)	1·4 (0·6)
C-reactive protein (mg/dL)	0·9 (0·4–2·0)	0·9 (0·5–1·8)
Percentage of body surface area affected by plaque psoriasis	13·6% (12·5)	17·2% (15·6)
PASI score (0–72)*	9·9 (8·0)	12·0 (10·5)
Patients with enthesitis	31 (63%)	76 (76%)
Enthesitis LEI score (1–6)	2·6 (1·5)	2·7 (1·5)
Patients with dactylitis	23 (47%)	58 (58%)
Dactylitis score (1–60)	3·9 (3·0)	6·5 (6·2)
SF-36		
Physical component summary score	34·4 (8·0)	33·5 (7·1)
Mental component summary score	46·0 (12·5)	43·3 (11·5)
Previous drugs		
Anti-TNF α drug	4 (8%)	9 (9%)
DMARDs	41 (84%)	90 (90%)
Drugs taken at baseline		
Methotrexate	19 (39%)	47 (47%)
Methotrexate dose (mg per week)	16·1 (3·6)	15·1 (4·2)
Oral corticosteroids	8 (16%)	12 (12%)
Oral corticosteroid dose equivalent to prednisone (mg per day)	5·9 (1·9)	7·8 (2·6)
NSAIDs	36 (73%)	70 (70%)

Data are n (%), mean (SD), or median (IQR). VAS=visual analogue scale. HAQ-DI=Health Assessment Questionnaire-Disability Index. PASI=Psoriasis Area and Severity Index. LEI=Leeds Enthesitis Index. SF-36=36-item Short-Form Health Survey. TNF=tumour necrosis factor. DMARDs=disease-modifying antirheumatic drugs. NSAIDs=non-steroidal anti-inflammatory drugs. *48 patients in the placebo group and 98 patients in the guselkumab group had PASI measurements at baseline.

Table 1: **Baseline characteristics of the modified intention-to-treat population**

Caractéristiques des 149 patients Rh Pso

- Femmes : 49 % ;
- âge moyen : 46,3 ans ;
- poids : 85 kg
- NAD : 17 ; NAG : 9 ;
- CRP : 9,1 mg/L ; PASI : 11,3
- MTX : 44,3 % ;
- déjà exposé aux anti-TNF : 8,7 %

49 patients sous PCB
100 patients sous GUS

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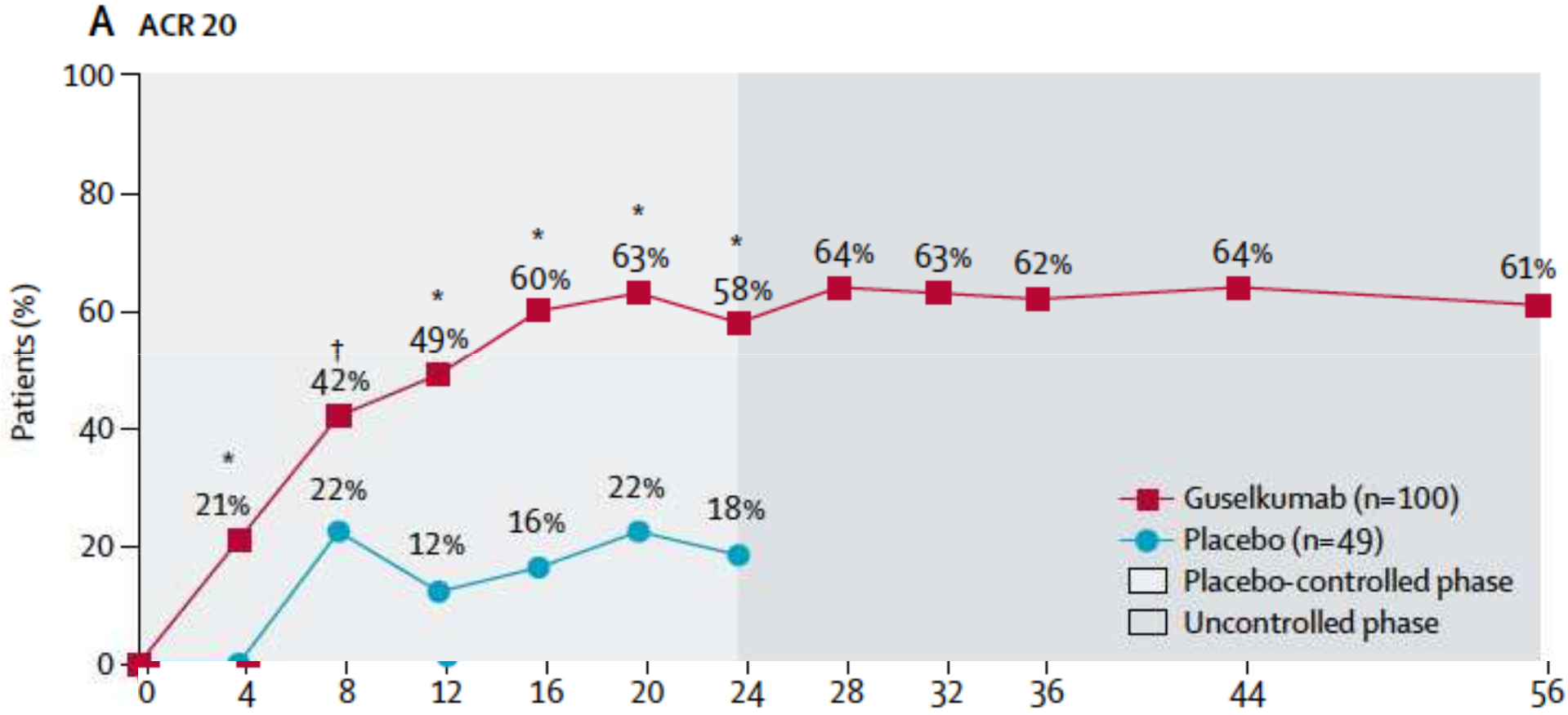
GUS vs PCB dans le RhPso : résultats

	Placebo (n=49)	Guselkumab (n=100)	Difference (95% CI)	p value
Primary endpoint				
ACR20	9 (18%)	58 (58%)	39·7% (25·3 to 54·1)	<0·0001
ACR20 with methotrexate at baseline	5/19 (26%)	27/47 (57%)		
ACR20 without methotrexate at baseline	4/30 (13%)	31/53 (58%)		
ACR20 with previous anti-TNF-α exposure	0/4	6/9 (67%)		
ACR20 without previous anti-TNF-α exposure	9/45 (20%)	52/91 (57%)		
ACR50	5 (10%)	34 (34%)	23·8% (11·3 to 36·3)	0·0021
ACR70	1 (2%)	14 (14%)	12·0% (4·2 to 19·9)	0·0228*
Secondary endpoints				
PASI75	6/48 (13%)	77/98 (79%)	66·1% (53·8 to 78·4)	<0·0001
PASI50	14/48 (29%)	85/98 (87%)	57·8% (43·6 TO 72·0)	<0·0001
PASI90	3/48 (6%)	65/98 (66%)	60·4% (48·9 to 71·9)	<0·0001
PASI100	3/48 (6%)	39/98 (40%)	33·6% (21·7 to 45·4)	<0·0001
HAQ-DI (change from baseline)	−0·06 (0·53)	−0·42 (0·51)	−0·31 (0·08)†‡	0·0002§
HAQ-DI responders (≥0·3 improvement from baseline)	14 (29%)	51 (51%)	22·2% (6·2 to 38·1)	0·0106
HAQ-DI responders (≥0·35 improvement from baseline)	14 (29%)	51 (51%)	22·2% (6·2 to 38·1)	0·0106*
Patients with enthesitis at baseline	31 (63%)	76 (76%)	..	..
Percentage change in enthesitis from baseline	−33·3% (−100·0 to 0·0)	−100·0% (−100·0 to −10·0)	..	0·0094¶
Resolved enthesitis	9/31 (29%)	43/76 (57%)	26·7% (7·2 to 46·1)	0·0124
Patients with dactylitis at baseline	23 (47%)	58 (58%)	..	..
Percentage change in dactylitis from baseline	−33·3% (−66·7 to 0·0)	−100·0% (−100·0 to −50·0)	..	0·0002¶
Resolved dactylitis	4/23 (17%)	32/58 (55%)	39·3% (19·4 to 59·2)	0·0014
SF-36				
Physical component summary score (change from baseline)	0·46 (6·51)	6·59 (7·47)	6·1 (3·7 to 8·6)‖	<0·0001‖
Mental component summary score (change from baseline)	0·42 (6·74)	4·95 (9·06)	4·5 (1·6 to 7·4)‖	0·0023‖
Patients with minimal disease activity**	1 (2%)	23 (23%)	21·2% (12·0 to 30·3)	0·0010
Patients with very low disease activity*	0	6 (6%)	6·1% (1·4 to 10·8)	0·0764

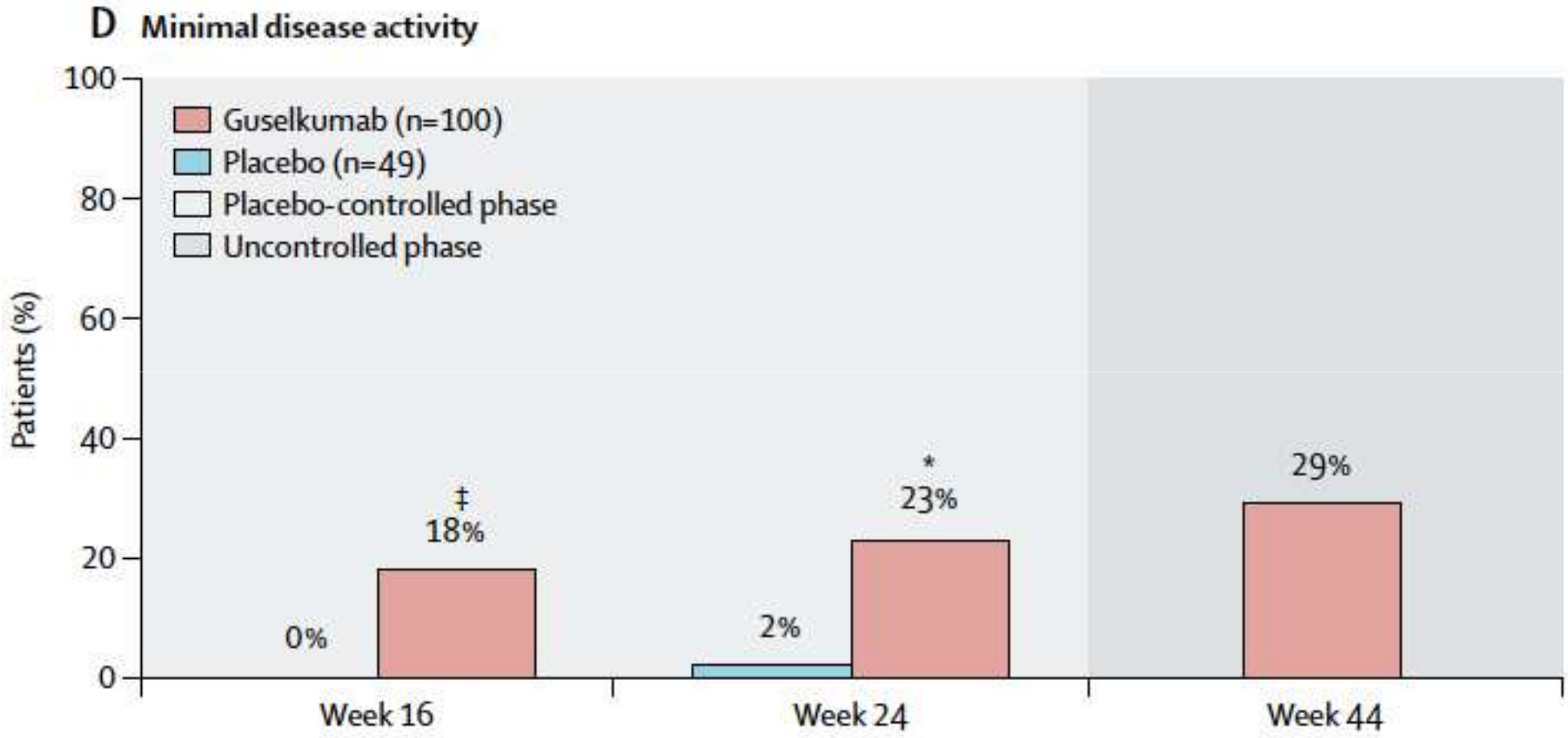
Lancet 2018; 391: 2213–24

GUS vs PCB dans le RhPso : résultats



Lancet 2018; 391: 2213–24

GUS vs PCB dans le RhPso : résultats



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GUS vs PCB dans le RhPso : effets secondaires

	Week 0–24		Week 0–56					
	Placebo* (n=49)	Guselkumab group† (n=100)	Placebo to guselkumab group‡ (n=29)	Guselkumab group§ (n=100)	Guselkumab groups combined (n=129)	Placebo to ustekinumab group¶ (n=17)	Guselkumab to ustekinumab group¶ (n=10)	Placebo or guselkumab to ustekinumab groups (n=27)
Duration of follow-up (weeks)	21·0 (4·3)	23·3 (2·5)	31·3 (4·5)	50·5 (13·6)	46·2 (14·6)	38·1 (7·0)	37·9 (5·0)	38·0 (6·2)
Number of injections	3·6 (0·5)	3·9 (0·4)	3·9 (0·6)	6·4 (1·4)	5·8 (1·7)	3·8 (0·5)	3·9 (0·3)	3·9 (0·5)
Patients with ≥1 adverse events	16 (33%)	36 (36%)	5 (17%)	46 (46%)	51 (40%)	8 (47%)	3 (30%)	11 (41%)
With methotrexate at baseline	6/19 (32%)	18/47 (38%)	2/12 (17%)	23/47 (49%)	25/59 (42%)	2/7 (29%)	1/3 (33%)	3/10 (30%)
No methotrexate at baseline	10/30 (33%)	18/53 (34%)	3/17 (18%)	23/53 (43%)	26/70 (37%)	6/10 (60%)	2/7 (29%)	8/17 (47%)
Common adverse events (>2% of patients guselkumab-treated patients between week 0 and week 56)								
Elevated transaminases‖	1 (2%)	4 (4%)	2 (7%)	9 (9%)	11 (9%)**	0	1 (10%)	1 (4%)
Nasopharyngitis	5 (10%)	6 (6%)	0	10 (10%)	10 (8%)	2 (12%)	0	2 (7%)
Leucopenia or decrease in WBC count	0	5 (5%)	1 (3%)	6 (6%)	7 (5%)††	0	0	0
Neutropenia or decrease in neutrophil count	0	5 (5%)‡‡	0	5 (5%)	5 (4%)‡‡§§	0	0	0
Upper respiratory tract infection	1 (2%)	1 (1%)	1 (3%)	3 (3%)	4 (3%)	0	0	0
Hepatic steatosis	0	1 (1%)	0	3 (3%)	3 (2%)	0	0	0
Serious adverse events								
Patients with ≥1 serious adverse events, n (%)	1 (2%)	1 (1%)	0	6 (6%)	6 (5%)	0	0	0
Joint (knee) injury	1 (2%)	0	0	0	0	0	0	0
Myocardial infarction	0	1 (1%)	0	1 (1%)	1 (1%)	0	0	0
Osteoarthritis	0	0	0	1 (1%)	1 (1%)	0	0	0
Pneumonia	0	0	0	1 (1%)	1 (1%)	0	0	0
Unequal pupils	0	0	0	1 (1%)	1 (1%)	0	0	0
Radius fracture	0	0	0	1 (1%)	1 (1%)	0	0	0
Ulcerative keratitis	0	0	0	1 (1%)	1 (1%)	0	0	0
Adverse events leading to discontinuation of study treatment								
Patients with adverse events resulting in study drug discontinuation	0	1 (1%)	0	2 (2%)¶¶	2 (2%)¶¶	0	1 (10%)¶¶	1 (4%)¶¶
Leucopenia	0	1 (1%)‖‖	0	1 (1%)	1 (1%)‖‖	0	0	0
Neutropenia	0	1 (1%)‖‖	0	1 (1%)	1 (1%)‖‖	0	0	0
Pneumonia	0	0	0	1 (1%)	1 (1%)	0	0	0
Osteoarthritis	0	0	0	0	0	0	1 (10%)	1 (4%)
Infections***	10 (20%)	16 (16%)	1 (3%)	26 (26%)	27 (21%)	5 (29%)	0	5 (19%)
Serious infections	0	0	0	1 (1%)	1 (1%)	0	0	0
Treated with oral or parenteral antimicrobial drugs†††	7 (14%)	10 (10%)	0	16 (16%)	16 (12%)	2 (12%)	0	2 (7%)
Injection-site reactions	1 (2%)	0	0	0	0	0	0	0

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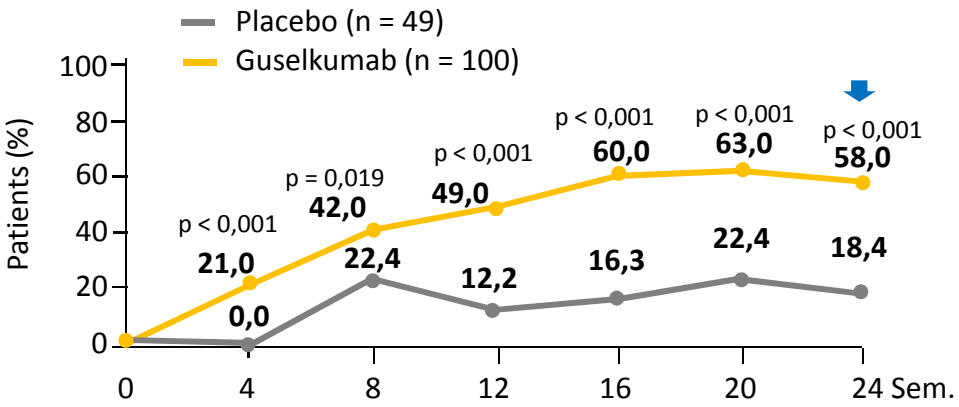
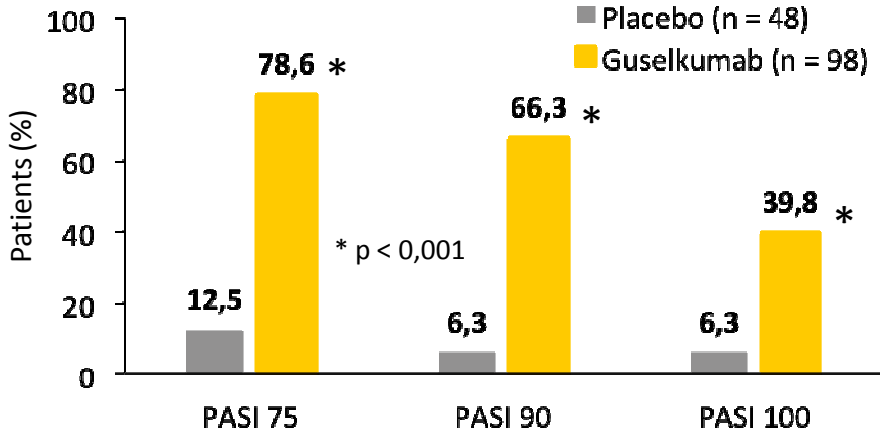
Guselkumab dans le rhumatisme psoriasique et le psoriasis

Réponse ACR 20



Réponse PASI à S24



- Tolérance
  - Absence d'infection sévère, de néoplasie ou de réaction anaphylactique
  - Plus de neutropénie (à suivre)

➔ Le guselkumab, inhibiteur spécifique de l'IL-23, a montré une efficacité significativement supérieure à celle du PBO dans tous les domaines du rhumatisme psoriasique

Lancet 2018; 391: 2213–24

PLOS ONE

RESEARCH ARTICLE

Dermatological guidelines for monitoring methotrexate treatment reduce drug-survival compared to rheumatological guidelines

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- Etude rétroleptive, sur dossier électronique, base de données de l'hôpital

- Effets des recommandations de suivi biologique du MTX en dermatologie et rhumatologie sur le maintien thérapeutique

Recommendations du suivi du MTX en dermatologie et rhumatologie au Pays Bas

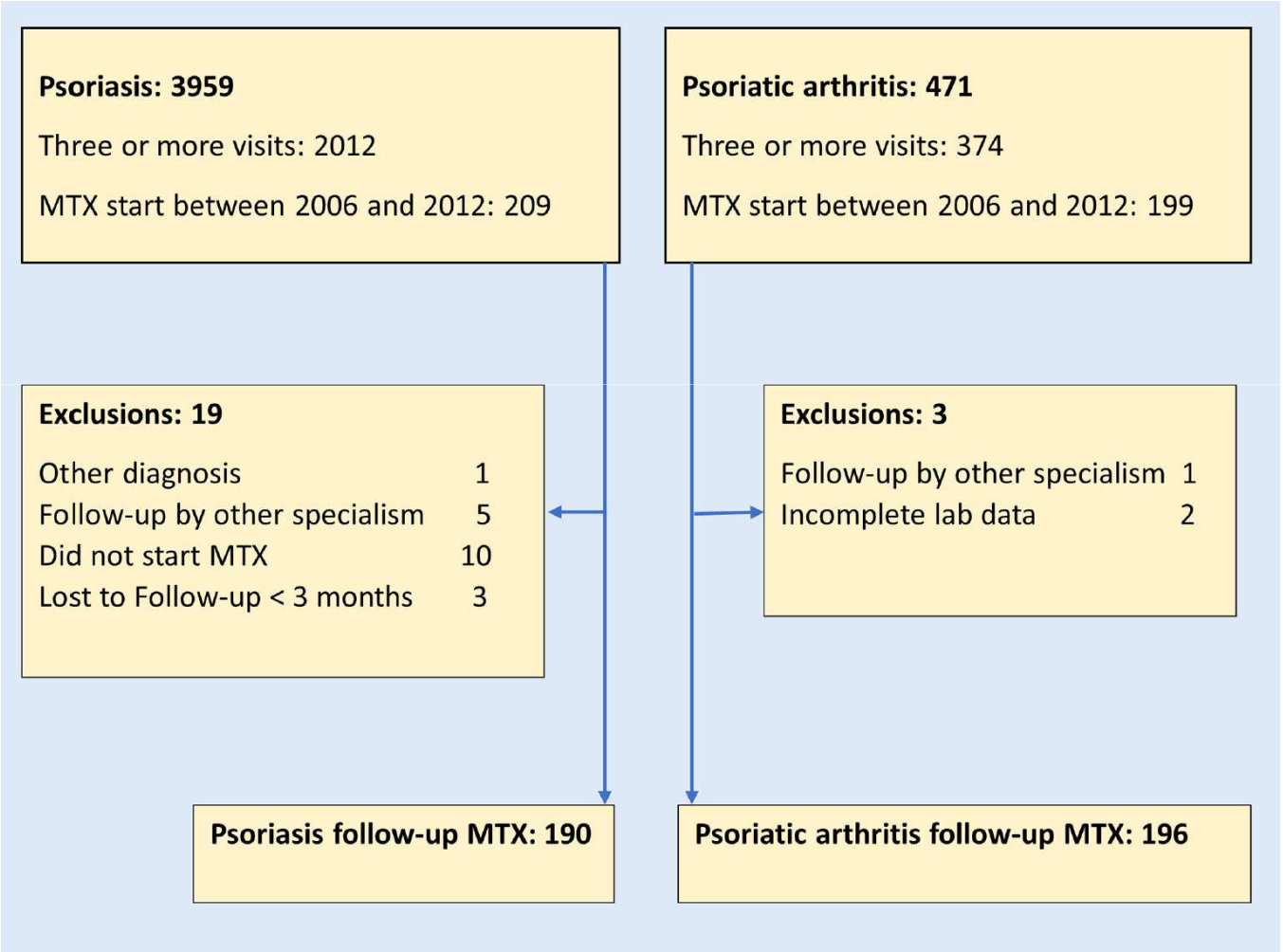
Table 1. Methotrexate monitoring guidelines used by dermatologists for psoriasis and by rheumatologists for psoriatic arthritis.

	Dermatology guideline [9]	Rheumatology guideline [10]
Starting dose MTX	5–10 mg-week	10–15 mg/week
Highest dose MTX	Oral 22,5 or SC 30 mg/wk	30 mg/week
Folic acid	5–10 mg/week	5–10mg/week
Initial monitoring	every two weeks	monthly
Monitoring long-term	every 2–3 months	every 3–4 months
Lab tests	ALAT, AF, γ-GT, full blood count, kreatinine	ALAT, Hb, leukocytes, thrombocytes, kreatinine
Advice when abnormal lab results	Reduce or withdraw when: leukocytes<3,0 or thrombocytes<100; Liver enzymes >2 times upper limit	Reduce or stop when: leukocytes<3,0 or thrombocytes<100 or ALAT>3ULN; withdraw when 2 times: ALAT>3 times upper limit
Liver biopsy/PIIIPN	Biopsy on clinical indication; PIIIPN 1x/3months	Biopsy on clinical indication; No PIIIPN

Dutch Society for Dermatology and Venereology. Guideline Psoriasis 2011. 2011;1–228. Available from: http://www.med-info.nl/Richtlijnen/Dermatologie/Psoriasis.pdf

Dutch Society for Rheumatology. Methotrexate Guideline update 2011. 2011;1–4. Available from: http://www.nvr.nl/wp-content/uploads/2014/11/NVR-Medicijnen-MTX-richtlijn-2009-update-2011.pdf

Diagramme de flux de l’étude (Dossiers électroniques)



Dossiers suivis par un dermatologue vs rhumatologue

Table 2. Characteristics of patients with psoriasis or psoriatic arthritis.

	Psoriasis	Psoriatic arthritis
	Treatment started by dermatologist	Treatment started by rheumatologist
	N = 190	N = 196
Men, N (%)	86 (45.3)	95 (48.5)
Age (y)	52.3 (16.2), 17–94	51.8 (13.8), 16–79
Prior treatment with MTX, N (%)	8 (4.2)	39 (19.9)**
MTX starting dose (mg/week)	12.2 (3.7), 2.5–15	15.2 (3.0), 5–30**
MTX maximal dose (mg/week)	15.6 (4.0), 5–25	21.5 (6.0), 5–40**
Folic acid starting dose (mg/week)	4.9 (0.7), 2.5–10	8.2 (5.4), 5–30**
Folic acid maximal dose (mg/week)	5.6 (2.9), 2.5–30	16.5 (10.4), 5–30**
Duration of first observed MTX course (months)	18.8 (19.1)	37.4 (30.0) **
Patients with 2 or more MTX courses, N (%)	12 (6.3)	25 (12.7) **

Rhum vs Derm : + d'utilisation du MTX, dose + élevée, + longtemps

Dossiers suivis par un dermatologue vs rhumatologue

Table 3. Laboratory monitoring during first treatment course with MTX.

	Psoriasis treatment by dermatologist N = 190	Psoriatic arthritis treatment by rheumatologist N = 196
Number of laboratory visits	1353	2609
Laboratory visits per treatment month	0.58 (0.74)	0.51 (0.34)
Number of abnormal laboratory results	227	121
Abnormal laboratory results per treatment month	0.14 (0.26)	0.03 (0.07) **
Abnormal laboratory results per laboratory visit [a]	0.26 (0.39)	0.06 (0.11)**
Any abnormal result N (%)	116 (61.1)	98 (50.0)*
alanine aminotransferase (ALT), N (%)	82 (43.2)	85 (43.4)
aspartate aminotransferase (AST), N (%)	48 (25.3)	4 (2.0)**
γ-glutamyl transpeptidase (γ-GT), N (%)	63 (33.2)	4 (2.0)**
Alkaline phosphatase (AP), N (%)	7 (3.7)	3 (1.5)
Leucocytes, N (%)	7 (3.7)	13 (6.6)
Thrombocytes, N (%)	2 (1.1)	7 (3.6)

Rhum vs Derm : + d'anomalie du bilan hépatique

Rhum vs Derm : + d'utilisation du MTX, dose + élevée, + longtemps

Dossiers suivis par un dermatologue vs rhumatologue

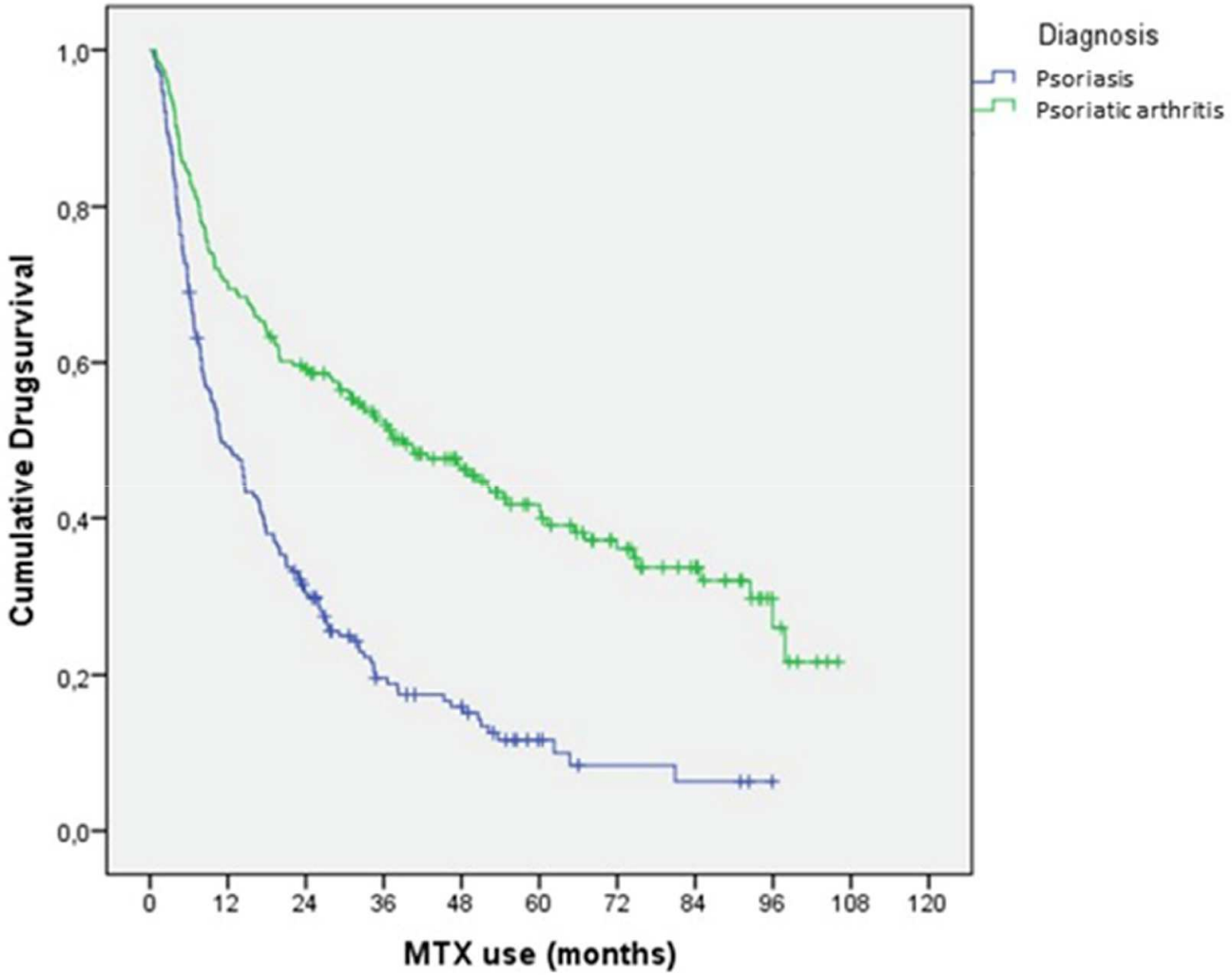


Fig 2. Continuation of methotrexate in first observed treatment course for psoriasis by dermatologists and psoriatic arthritis treated by rheumatologists (log-rank test: $p<0.001$).

Rhum vs Derm : + maintien du MTX

Dossiers suivis par un dermatologue vs rhumatologue

Table 4. Reasons for withdrawal from the first course of MTX in patients with psoriasis or psoriatic arthritis.

	Psoriasis	Psoriatic arthritis
	N = 190	N = 196
Ineffectiveness of MTX	46 (24.2%)	31 (15.8%) *
Disease remission	15 (7.9%)	23 (11.7%)
Abnormal laboratory result	30 (15.8%)	7 (3.6%) **
Other drug toxicity, e.g. nausea	45 (23.7%)	41 (20.9%)
Death not related to MTX	2 (1.1%)	4 (2.0%)
End of follow-up, unrelated to disease	4 (2.1%)	1 (0.5%)
Comorbid conditions	4 (2.1%)	3 (1.5%)
Other	15 (7.9%)	10 (5.1%)
Continued MTX to censor date	29 (15.3%)	76 (38.8%)**

Rhum vs Derm : + d'anomalie du bilan hépatique
Rhum vs Derm : + d'utilisation du MTX, dose + élevée, + longtemps
Rhum vs Derm : - d'inefficacité du MTX, - d'arrêts pour toxicité
Rhum vs Derm : - de surveillance hépatique, - d'arrêts pour toxicité

Spondylarthrite

Research Article

Whole-Body Cryotherapy Decreases the Levels of Inflammatory, Oxidative Stress, and Atherosclerosis Plaque Markers in Male Patients with Active-Phase Ankylosing Spondylitis in the Absence of Classical Cardiovascular Risk Factors

Agata Stanek[1], **Armand Cholewka**[2], **Tomasz Wielkoszyński**[3], **Ewa Romuk**[3], **and Aleksander Sieroń**[1]

[1]*School of Medicine with the Division of Dentistry in Zabrze, Department of Internal Medicine, Angiology and Physical Medicine, Medical University of Silesia, Batorego Street 15, 41-902 Bytom, Poland*
[2]*Department of Medical Physics, Chełkowski Institute of Physics, University of Silesia, 4 Uniwersytecka St., 40-007 Katowice, Poland*
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Mediators of Inflammation
Volume 2018, Article ID 8592532, 11 pages

Patients et méthodes : Cryothérapie

Table 1: Demographic data of the study subjects.

Characteristic	WBC group ($n = 16$)	Kinesiotherapy group ($n = 16$)	P value
Age (years), mean (SD)	46.63 ± 1.5	45.94 ± 1.24	0.114
Sex (M/F)	16/0	16/0	—
BMI (kg/m^2), mean (SD)	24.24 ± 4.4	23.76 ± 6.8	0.880
BASDAI	5.43 ± 1.61	5.28 ± 1.71	0.720
BASFI	5.20 ± 2.29	5.01 ± 2.06	1.00
Carotid IMT (mm)	1.1 ± 0.13	1.0 ± 0.14	0.925
Smoking (yes/no)	0/16	0/16	—
	Medication		
NSAID (yes/no)	16/0	16/0	—
DMARD (yes/no)	0/16	0/16	—
Biological agents (yes/no)	0/16	0/16	—

SD: standard deviation; BMI: body mass index; BASDAI: the Bath Ankylosing Spondylitis Diseases Activity Index; BASFI: the Bath Ankylosing Spondylitis Functional Index; IMT: intima-media thickness; NSAID: nonsteroidal anti-inflammatory drug; DMARD: disease-modifying antirheumatic drug.

WBC : 3 min (-110c) 10 j de suite puis kiné

kiné

Mediators of Inflammation
Volume 2018, Article ID 8592532, 11 pages

Cryothérapie : effets marqueurs de l'inflammation et paramètres cliniques

Table 2: Levels of inflammatory parameters as well as the value of BASDAI and BASFI (mean value ± standard deviation (SD)) in AS patients before and after the completion of a cycle of ten whole-body cryotherapy procedures with subsequent kinesiotherapy (WBC group) or a cycle of ten kinesiotherapy procedures only (KT group), with statistical analyses. (p): plasma; (s): serum; Δ: difference prior to post treatment.

Parameters		WBC group	KT group	*P*
hsCRP (s) (mg/l)	Before	13.5 ± 16.3	13.9 ± 15.2	0.942
	After	9.2 ± 15.3	13.6 ± 16.2	0.438
	**P*	**0.002**	0.623	
	Δ	−4.24 ± 5.68	−0.27 ± 3.25	**0.023**
CER (s) (mg/dl)	Before	62.83 ± 12.61	67.57 ± 12.60	0.296
	After	51.32 ± 10.74	53.51 ± 14.26	0.628
	**P*	**0.006**	**0.003**	
	Δ	−11.51 ± 16.6	−14.06 ± 14.47	0.646
IL-6 (p) (pg/ml)	Before	41.6 ± 8.86	41.8 ± 10.5	0.957
	After	36.6 ± 7.89	41.0 ± 10.4	0.191
	**P*	0.121	0.301	0.216
	Δ	−4.94 ± 11.9	−0.74 ± 5.71	
sICAM-1 (p) (ng/ml)	Before	79.0 ± 15.5	84.3 ± 21.9	0.432
	After	69.2 ± 14.2	83.9 ± 20.0	**0.023**
	**P*	0.088	0.642	
	Δ	−9.84 ± 23.0	−0.41 ± 16.1	0.191
BASDAI	Before	5.43 ± 1.61	5.28 ± 1.71	0.720
	After	3.29 ± 0.91	4.53 ± 1.62	**<0.05**
	**P*	**<0.001**	**<0.001**	
	Δ	−2.14 ± 1.23	−0.74 ± 0.38	**0.001**
BASFI	Before	5.20 ± 2.29	5.01 ± 2.06	1.00
	After	3.81 ± 2.20	4.35 ± 2.23	0.497
	**P*	**<0.001**	**<0.001**	
	Δ	−1.39 ± 1.03	−0.66 ± 0.39	**<0.01**

P: statistical significance of differences between both groups of patients; **P*: statistical significance of differences between values before and after treatment in particular groups of patients.

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Cryothérapie : effets marqueurs lipiques

Table 6: Levels of lipid profile parameters, atherosclerosis plaque markers, and atherosclerosis plaque instability and values of TG/HDL ratio (mean value ± standard deviation (SD)) in AS patients before and after the completion of a cycle of ten whole-body cryotherapy procedures with subsequent kinesiotherapy (WBC group) or a cycle of ten kinesiotherapy procedures only (KT group), with statistical analyses. (p): plasma; (s): serum; (e): erythrocyte lysates; Δ: difference prior to post treatment.

Parameters		WBC group	KT group	*P*
T-Chol (s) (mg/dl)	Before	221.3 ± 39.17	200.33 ± 21.33	0.074
	After	202.40 ± 24.40	190.70 ± 22.57	0.51
	**P*	**0.0006**	**0.04**	
	Δ	−18.90 ± 20.54	−9.63 ± 18.38	0.20
LDL-Chol (s) (mg/dl)	Before	125.2 ± 32.6	145.3 ± 28.3	0.073
	After	93.3 ± 36.9	132.4 ± 24.7	**0.002**
	**P*	**<0.001**	**0.005**	
	Δ	−31.9 ± 28.6	−12.9 ± 15.1	**0.027**
HDL-Chol (s) (mg/dl)	Before	50.5 ± 14.1	58.0 ± 18.0	0.198
	After	47.0 ± 9.0	56.4 ± 18.2	0.078
	**P*	0.079	0.109	
	Δ	−3.5 ± 9.1	−1.7 ± 10.1	0.590
TG (s) (mg/dl)	Before	185.1 ± 18.9	178.6 ± 15.9	0.299
	After	156.7 ± 11.2	165.2 ± 20.4	0.158
	**P*	**0.001**	**0.001**	
	Δ	−28.4 ± 22.4	−13.4 ± 19.7	0.053
TG/HDL ratio	Before	3.95 ± 1.18	3.32 ± 0.96	0.150
	After	3.44 ± 0.60	3.18 ± 0.99	0.320
	**P*	0.055	0.250	
	Δ	−0.51 ± 0.92	−0.14 ± 0.43	0.190
sCD40L(s) (mg/ml)	Before	9.21 ± 3.88	7.25 ± 2.20	0.180
	After	5.01 ± 2.55	5.85 ± 2.06	0.171
	**P*	**0.0004**	**0.006**	
	Δ	−4.19 ± 2.17	−1.4 ± 1.78	**0.0001**
PLGF(s) (pg/ml)	Before	30.17 ± 10.23	21.69 ± 3.54	0.007
	After	19.32 ± 5.53	18.31 ± 2.91	0.641
	**P*	**0.001**	**0.004**	
	Δ	−10.84 ± 7.05	−3.38 ± 2.13	**0.0001**
PAPP-A (s) (ng/ml)	Before	17.74 ± 7.78	14.48 ± 4.52	0.162
	After	11.24 ± 3.12	11.79 ± 3.72	0.920
	**P*	**0.0004**	**0.003**	
	Δ	−6.51 ± 8.40	−2.69 ± 3.65	**0.008**

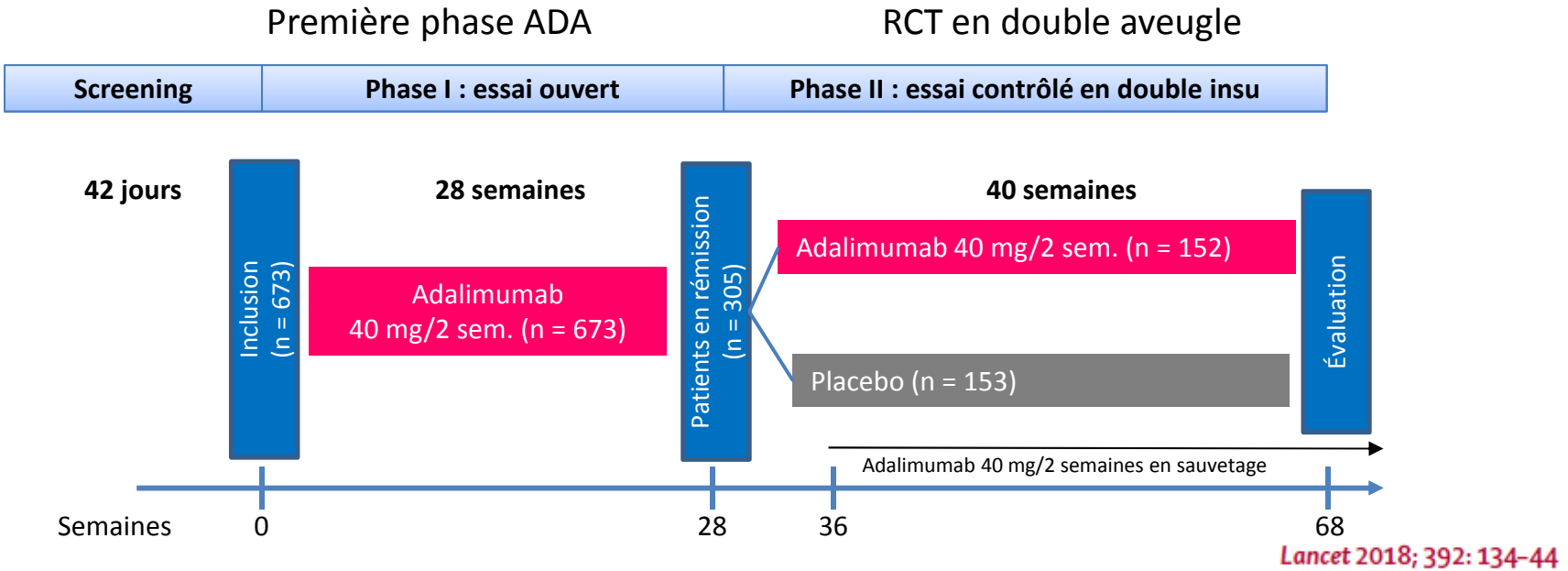
P: statistical significance of differences between both groups of patients; **P*: statistical significance of differences between values before and after treatment in particular groups of patients.

Mediators of Inflammation
Volume 2018, Article ID 8592532, 11 pages

Efficacy and safety of continuing versus withdrawing adalimumab therapy in maintaining remission in patients with non-radiographic axial spondyloarthritis (ABILITY-3): a multicentre, randomised, double-blind study

Robert Landewé, Joachim Sieper, Philip Mease, Robert D Inman, Robert G Lambert, Atul Deodhar, Helena Marzo-Ortega, Marina Magrey, Uta Kiltz, Xin Wang, Mei Li, Sheng Zhong, Nael M Mostafa, Apinya Lertratanakul, Aileen L Pangan, Jaclyn K Anderson

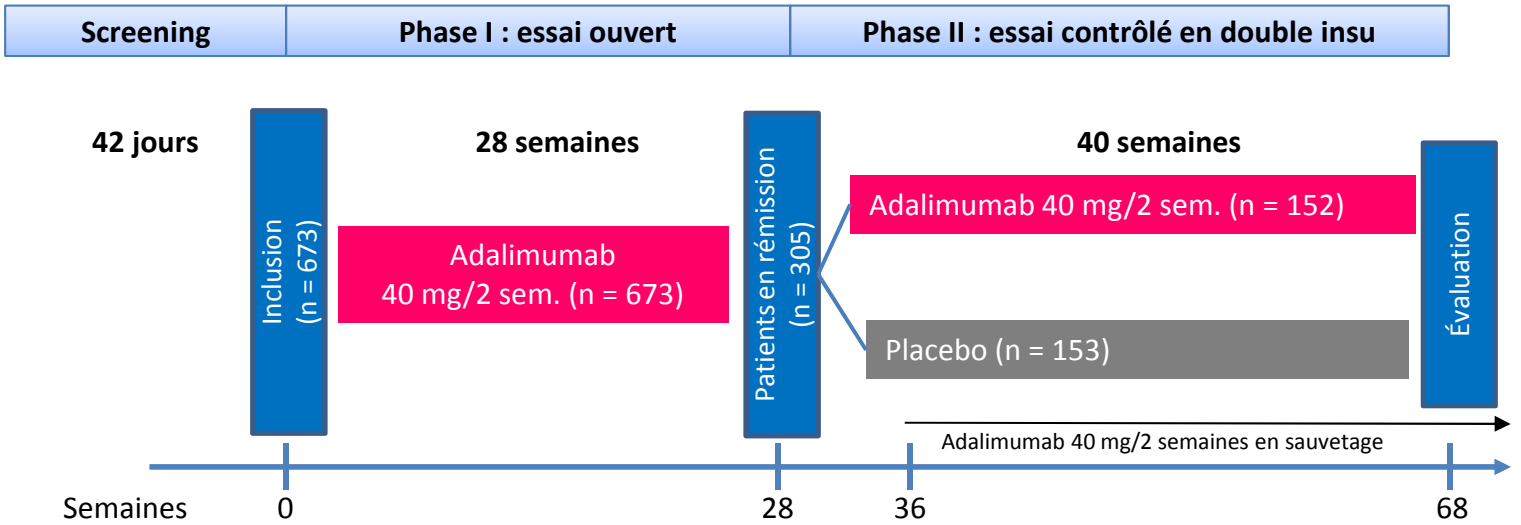
- Etude multicentrique contrôlée en 2 phases
- SpAnRX ASAS + NY – OSI + echec 2 AINS > 18 ans



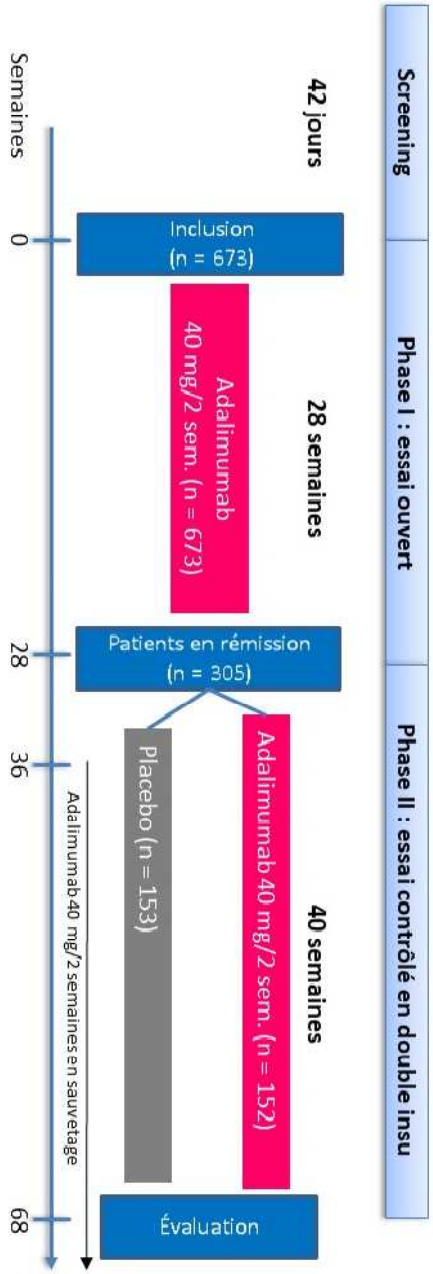
Lancet 2018; 392: 134–44

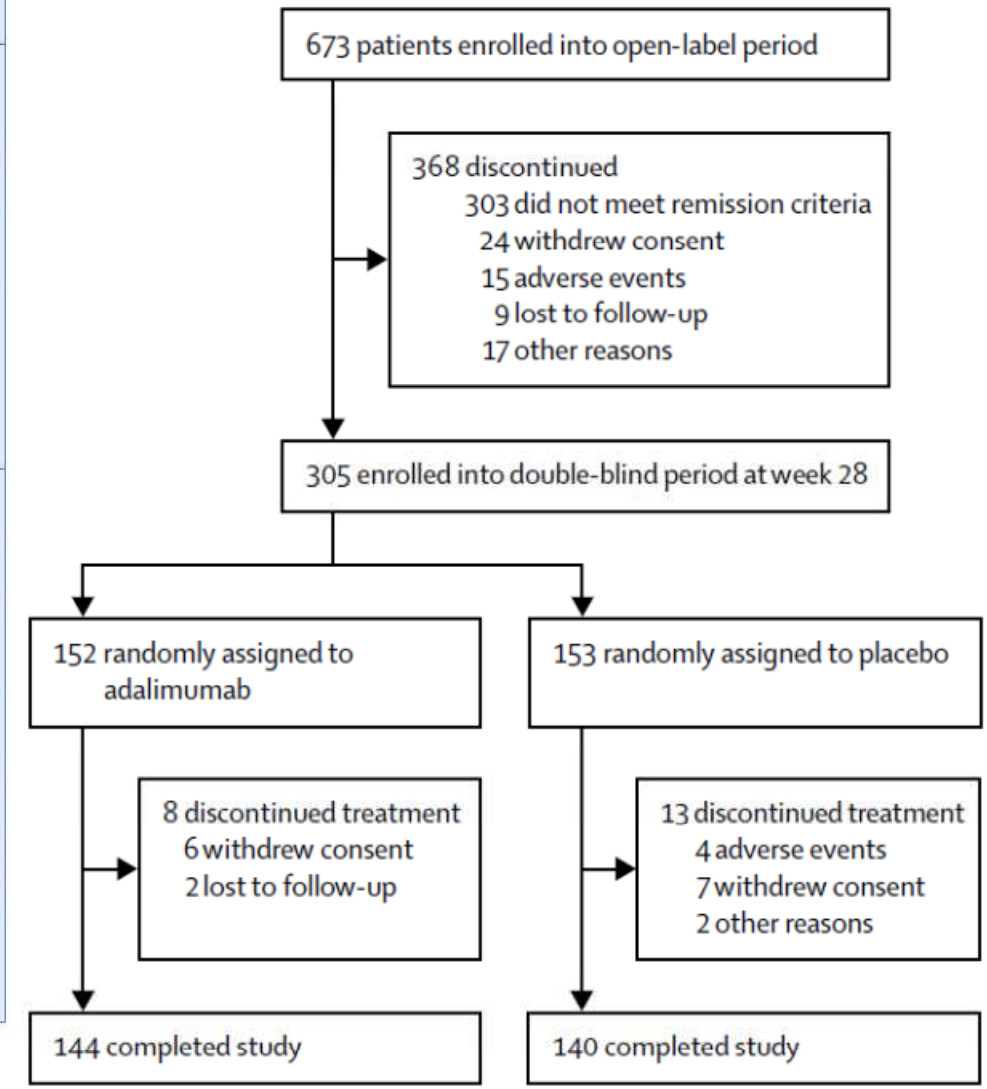
ABILITY 3 : arrêt de l'ADA après obtention de la rémission

- **Objectif**
  - Évaluer le taux de rémission (ASDAS-crp < 1,3) à 28 semaines de traitement par adalimumab puis
  - Évaluer l'absence de poussée (2 vistes conséctutives avec ASDAS >2.1) jusqu'à S 68



Étude Ability 3 : diagramme de flux





Lancet 2018; 392: 134–44

Étude Ability 3 : caractéristiques des malades

	Adalimumab (n=152)	Placebo (n=153)	Overall (n=305)
Baseline characteristics			
Sex			
Female	56 (37%)	60 (39%)	116 (38%)
Male	96 (63%)	93 (61%)	189 (62%)
Ethnicity			
White	149 (98%)	149 (97%)	298 (98%)
Other	3 (2%)	4 (3%)	7 (2%)
Age, years	34·7 (10·3)	35·3 (10·2)	35·0 (10·2)
Body-mass index (kg/m²)	24·6 (4·1)	25·0 (4·2)	24·8 (4·2)
Region			
USA and Canada	5 (3%)	12 (8%)	17 (6%)
Mexico and Brazil	3 (2%)	3 (2%)	6 (2%)
Europe	128 (84%)	119 (78%)	247 (81%)
Australia and New Zealand	16 (11%)	19 (12%)	35 (11%)
Spondyloarthritis symptom duration, years	6·4 (6·9)	7·1 (6·8)	6·7 (6·9)
Spondyloarthritis diagnosis duration, years	1·9 (2·9)	1·8 (2·9)	1·8 (2·9)
HLA-B27 positive	132 (87%)	134 (88%)	266 (87%)
Elevated high-sensitivity CRP	95 (63%)	84 (55%)	179 (59%)
MRI positive (sacroiliac joints or spine, or both)	104 (68%)	124 (81%)	228 (75%)

Lancet 2018; 392: 134–44

Étude Ability 3 : résultat

	Adalimumab (n=152)	Placebo (n=153)	Difference between groups	p value
Primary endpoint				
No flare mITT (NRI)	107 (70%)	72 (47%)	23%	<0·0001
Sensitivity analyses				
No flare mITT (observed)	107/129 (83%)	72/126 (57%)	26%	<0·0001
No flare per-protocol population (NRI)	106/149 (71%)	70/147 (48%)	23%	<0·0001
No flare mITT excluding major ICH deviations (NRI)	102/144 (71%)	69/144 (48%)	23%	<0·0001

Pas de poussée pendant le suivi

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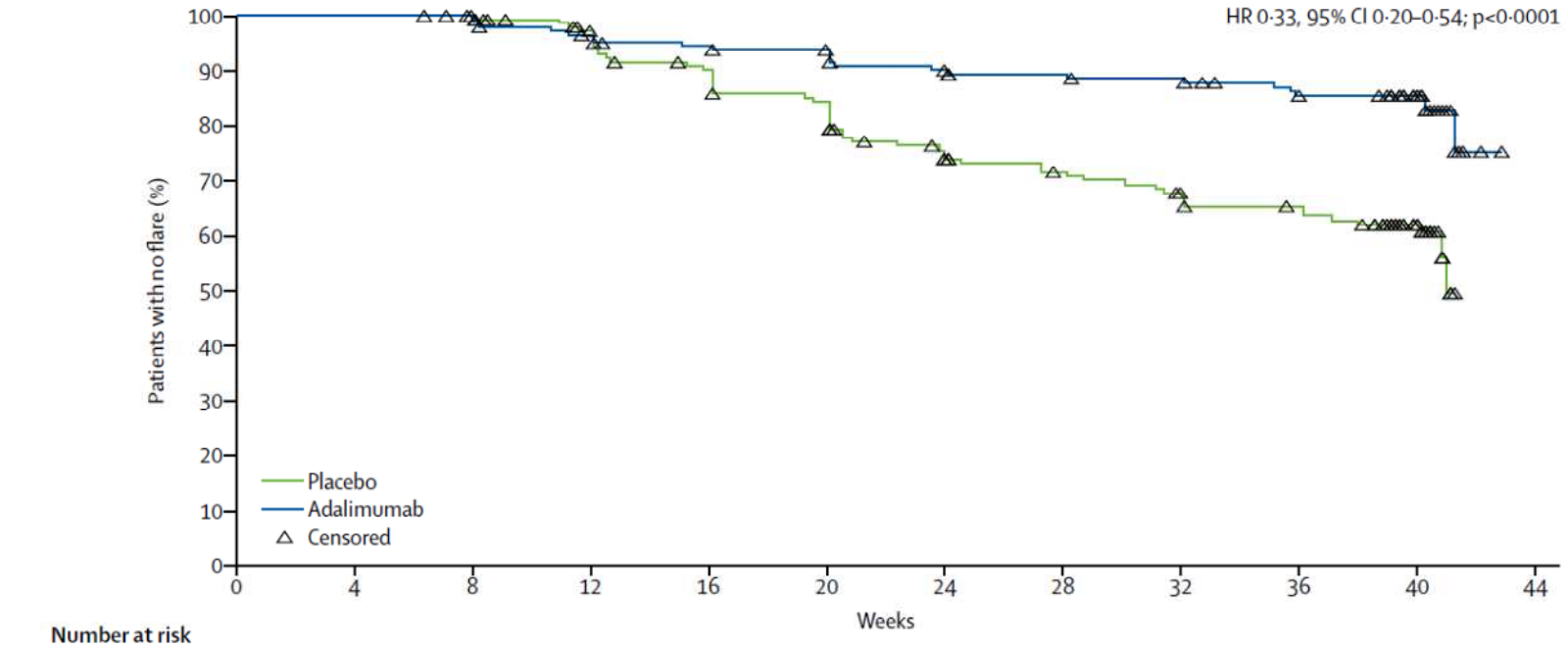
Étude Ability 3 : résultat

Secondary endpoints*				
ASDAS				
Inactive disease	87 (57%)	51 (33%)	24%	<0·0001
Major improvement	89 (59%)	49 (32%)	27%	<0·0001
Clinically important improvement	102 (67%)	69 (45%)	22%	<0·0001
ASAS				
20	107 (70%)	72 (47%)	23%	<0·0001
40	100 (66%)	70 (46%)	20%	0·0004
5/6	87 (57%)	49 (32%)	25%	<0·0001
Partial remission	64 (42%)	41 (27%)	15%	0·0049
BASDAI50	103 (68%)	72 (47%)	21%	0·0003
Mean (SE) change from baseline in BASFI†	−3·97 (0·11); n=111	−3·51 (0·13); n=77	−0·46	0·0069
Mean (SE) change from baseline in HAQ-S†	−0·71 (0·04); n=112	−0·61 (0·04); n=79	−0·10	0·0918

Lancet 2018; 392: 134–44

Étude Ability 3 : résultats



Number at risk (number censored)												
Placebo	153 (0)	153 (0)	152 (0)	140 (4)	127 (14)	118 (22)	101 (36)	93 (39)	87 (44)	81 (47)	60 (51)	0 (54)
Adalimumab	151 (0)	151 (0)	149 (0)	139 (5)	134 (8)	132 (9)	125 (14)	121 (15)	119 (16)	112 (20)	92 (20)	0 (22)

Figure 2: Time to first flare by week 68 (modified intention-to-treat population)

Lancet 2018; 392: 134–44

Étude Ability 3 : effets secondaires

	Adalimumab (n=152)	Placebo (n=153)	Any adalimumab exposure* (n=673)
Any adverse event	99 (65%)	105 (69%)	516 (77%)
Serious adverse event	1 (1%)	10 (7%)	28 (4%)
Any adverse event leading to discontinuation	0	4 (3%)	18 (3%)
Infectious adverse event	80 (53%)	70 (46%)	355 (53%)
Serious infection	0	2 (1%)	7 (1%)
Malignancy†	0	1 (1%)	1 (<1%)

*Adverse events occurring during administration of adalimumab and within 70 days of the last dose. †Event was gastric adenocarcinoma.

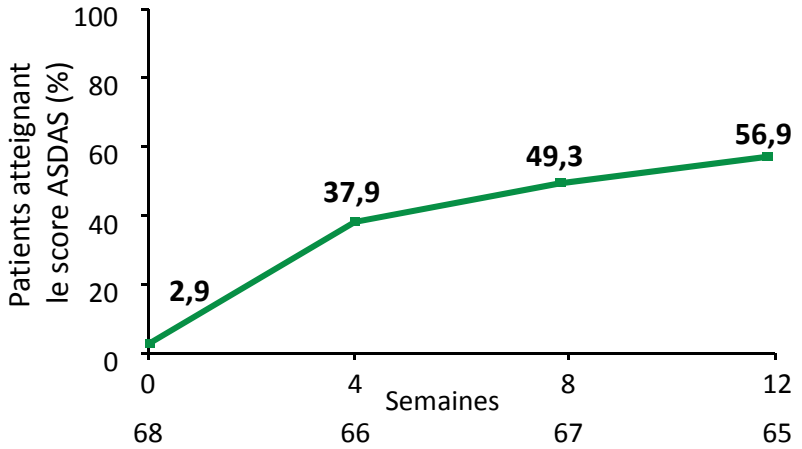
Table 3: **Number and percentage of adverse events during the double-blind period and during any adalimumab exposure**

Lancet 2018; 392: 134–44

Étude Ability 3 : effets secondaires

Significantly more patients in the withdrawal group received rescue therapy with open-label adalimumab than in the continuation group (68 [44%] of 153 patients *vs* 36 [24%] of 152 patients; p=0·0001). Overall, 37 (57%) of 65 patients regained ASDAS inactive disease in the placebo group after initiating open-label adalimumab rescue therapy for 12 weeks. Similarly, 20 (56%) of 36 patients in the adalimumab group regained ASDAS inactive disease after 12 weeks of open-label adalimumab rescue therapy (appendix). Improvement was also

Récupération de l'efficacité à la reprise de l'adalimumab

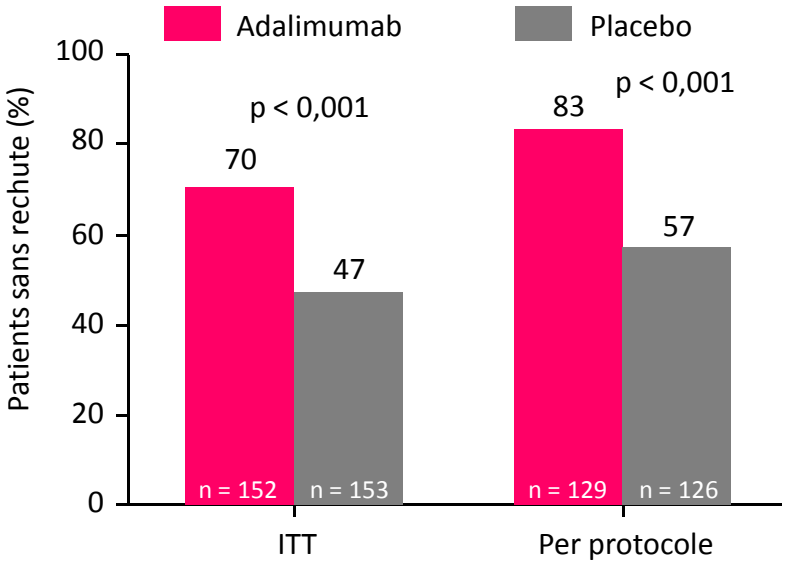


Lancet 2018; 392: 134–44

Étude Ability 3 :conclusions

- **Résultats**
  - "Rémission" obtenue chez 45 % des malades

Proportion de malades sans rechute à S68



Although 47% of patients in this study were able to stop treatment for at least a period of time, 44% of the patients who withdrew adalimumab treatment experienced a disease flare and received rescue therapy and 43% of these patients did not regain their previous state of clinical

n =

➔ **Fort risque de rechute en cas d'arrêt brutal de l'anti-TNF**

➔ **Environ 40 % des malades ne récupèrent pas l'effet à la reprise du traitement**

MISCELLANEES

ORIGINAL ARTICLE

Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout

William B. White, M.D., Kenneth G. Saag, M.D., Michael A. Becker, M.D., Jeffrey S. Borer, M.D., Philip B. Gorelick, M.D., Andrew Whelton, M.D., Barbara Hunt, M.S., Majin Castillo, M.D., and Lhanoo Gunawardhana, M.D., Ph.D., for the CARES Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Aspirin on Disability-free Survival in the Healthy Elderly

J.J. McNeil, R.L. Woods, M.R. Nelson, C.M. Reid, B. Kirpach, R. Wolfe, E. Storey, R.C. Shah, J.E. Lockery, A.M. Tonkin, A.B. Newman, J.D. Williamson, K.L. Margolis, M.E. Ernst, W.P. Abhayaratna, N. Stocks, S.M. Fitzgerald, S.G. Orchard, R.E. Trevaks, L.J. Beilin, G.A. Donnan, P. Gibbs, C.I. Johnston, J. Ryan, B. Radziszewska, R. Grimm, and A.M. Murray, for the ASPREE Investigator Group*

Aspirin has become one of the most popular agents used for the primary prevention of cardiovascular disease, largely on the basis of results from studies of secondary prevention of myocardial infarction and ischemic stroke. Large trials investigating primary cardiovascular prevention,[22-32] mainly involving participants younger than those in the ASPREE trial, have not shown a consistent effect of aspirin on cardiovascular outcomes. In many trials, the use of aspirin was accompanied by a higher bleeding risk, without any clear indication of overall benefit or harm.[23,25-28]

- Étude de phase II randomisée, en double insu, contrôlée versus placebo, multicentrique ‘34 USA, 16 Canada) durée 5 ans

Drs. McNeil and Woods contributed equally to this article.

This article was published on September 16, 2018, at NEJM.org.

McNeil JJ et al. NEJM sept 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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In conclusion, these results of the ASPREE trial indicate that, over a median follow-up of 4.7 years, the use of low-dose aspirin in persons 70 years of age or older who did not have cardiovascular disease did not prolong disability-free survival in a predominantly white population.

Drs. McNeil and Woods contributed equally to this article.

This article was published on September 16, 2018, at NEJM.org.

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Étude ASPREE : résultats

Table 2. Composite Primary End Point, Including the Components, and Secondary End Points of Death, Dementia, Persistent Physical Disability, and Major Hemorrhage.*

End Point	Aspirin (N = 9525)		Placebo (N = 9589)		Hazard Ratio (95% CI)	P Value
	no. of participants with event	*rate per 1000 person-yr*	*no. of participants with event*	*rate per 1000 person-yr*		
Primary end point†	921	21.5	914	21.2	1.01 (0.92–1.11)	0.79
Death from any cause	480	11.2	431	10.0	—	—
Dementia	274	6.4	275	6.4	—	—
Persistent physical disability	167	3.9	208	4.8	—	—
Secondary end points‡						
Death from any cause	558	12.7	494	11.1	1.14 (1.01–1.29)	—
Dementia	283	6.7	292	6.9	0.98 (0.83–1.15)	—
Persistent physical disability	188	4.9	224	5.8	0.85 (0.70–1.03)	—
Major hemorrhagic event	361	8.6	265	6.2	1.38 (1.18–1.62)	<0.001
Clinically significant bleeding	312	7.4	225	5.3	—	—
Hemorrhagic stroke	49	1.2	40	0.9	—	—

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Étude ASPREE : résultats

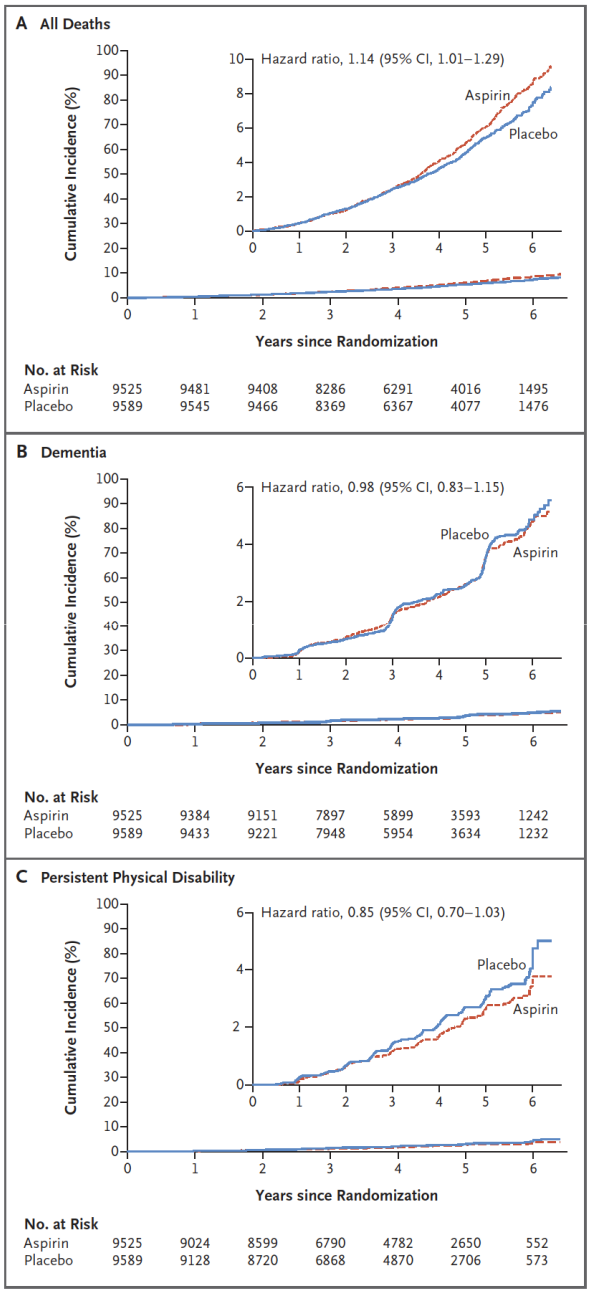

Figure 3. Cumulative Incidence of Death, Dementia, and Persistent Physical Disability.

Shown are the cumulative incidences of all events of death, dementia, and persistent physical disability that were observed during the trial. The 95% confidence intervals were not adjusted for multiple comparisons. Insets show the same data on an enlarged y axis.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Aspirin on All-Cause Mortality in the Healthy Elderly

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Étude ASPREE : résultats sur la mortalité

Table 1. Mortality According to the Underlying Cause of Death.*

Cause of Death	Overall (N = 19,114)	Aspirin (N = 9525)	Placebo (N = 9589)	Hazard Ratio (95% CI)
	no. of deaths	*no. of deaths (%)*		
Any	1052	558 (5.9)	494 (5.2)	1.14 (1.01–1.29)
Cancer†	522	295 (3.1)	227 (2.3)	1.31 (1.10–1.56)
Cardiovascular disease, including ischemic stroke‡	203	91 (1.0)	112 (1.2)	0.82 (0.62–1.08)
Major hemorrhage, including hemorrhagic stroke§	53	28 (0.3)	25 (0.3)	1.13 (0.66–1.94)
Other¶	262	140 (1.5)	122 (1.3)	1.16 (0.91–1.48)
Insufficient information‖	12	4 (<0.1)	8 (0.1)	—

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Efficacy and safety of ustekinumab, an IL-12 and IL-23 inhibitor, in patients with active systemic lupus erythematosus: results of a multicentre, double-blind, phase 2, randomised, controlled study

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Conclusion:

- Ustekinumab en supplément au SOC Stantard of Care (Plaquenil, Immunosuppresseurs, Glucocorticoides) est plus efficace que le placebo sur les paramètres cliniques et biologiques LED et est bien toléré
- Importance IL12 et IL23 dans LED
- Nécessité d'un large essai randomisé phase III évaluant Ustekinumab dans LED