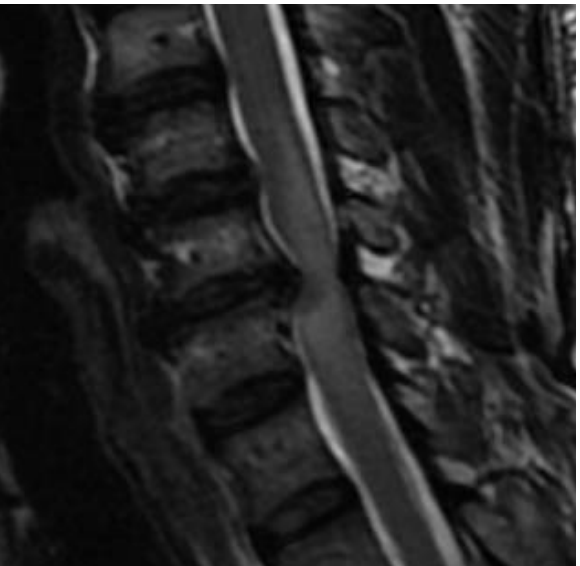
Atteintes neurologiques au cours de la sarcoïdose : quels traitements fondés sur les preuves ?



Fleur Cohen Aubart
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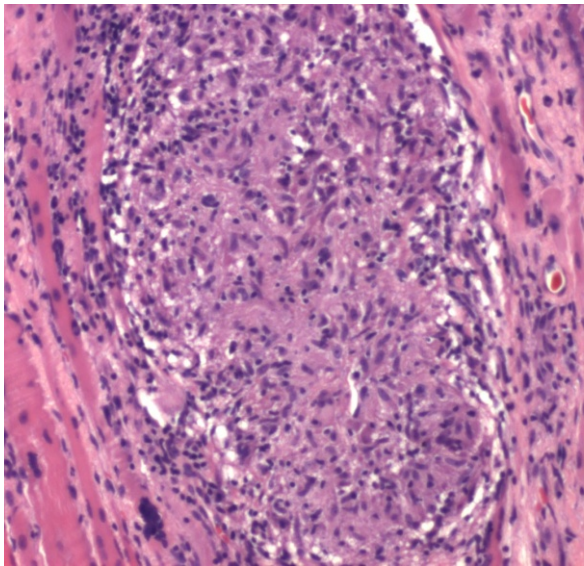
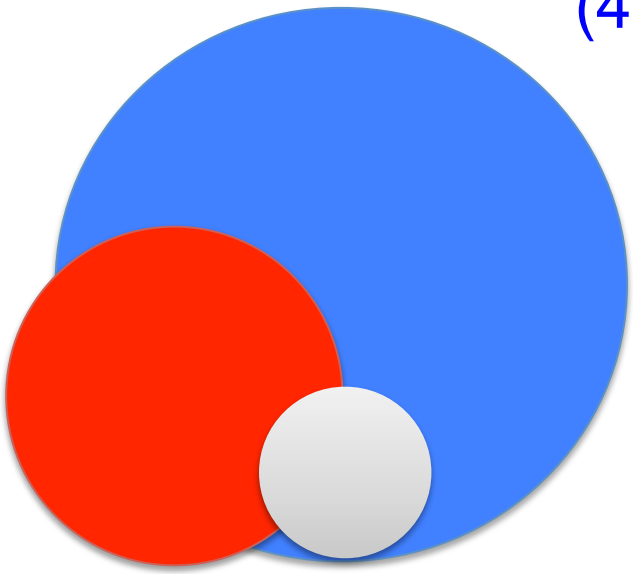


Difficultés générales au cours de la sarcoïdose

- Maladie rare
- Affection hétérogène : multisystémique, présentations hautement variables
- Difficulté à distinguer les lésions actives et chroniques
- Pas de gold standard pour évaluer l'activité (pas de score d'activité)
- Les granulomes sont sensibles à la corticothérapie
- L'évolution peut être spontanément favorable
- Très faible nombre d'essais randomisés

Atteintes thoraciques (85-95%)

Thoraciques isolées (40-50%)



Extrathoraciques isolées <15%

Signes généraux : EN, hypercalcemie: <20%

Atteintes extra-thoraciques 30-50%

Valeyre D Lancet. 2014;383(9923):1155-67

Atteintes extra thoraciques 30-50%

>15%	Œil, peau, ganglions lymphatiques, foie
5-10%	Rate, sinus
~5%	Parotides, coeur
<5%	**SNC**, toutes les autres localisations

Valeyre D Lancet. 2014;383(9923):1155-67

JAMA Neurology | Special Communication

Definition and Consensus Diagnostic Criteria for Neurosarcoidosis From the Neurosarcoidosis Consortium Consensus Group

Barney J. Stern, MD; Walter Royal III, MD; Jeffrey M. Gelfand, MD, MAS; David B. Clifford, MD; Jinny Tavee, MD; Siddharama Pawate, MD; Joseph R. Berger, MD; Allen J. Aksamit, MD; Allan Krumholz, MD; Carlos A. Pardo, MD; David R. Moller, MD; Marc A. Judson, MD; Marjolein Drent, MD, PhD; Robert P. Baughman, MD

Probable

1. The clinical presentation and diagnostic evaluation s
neurosarcoidosis, as defined by the clinical manifest
MRI, CSF, and/or EMG/NCS findings typical of granu
inflammation of the nervous system after rigorous e
of other causes.
2. There is pathologic confirmation of systemic granulo
disease consistent with sarcoidosis.

Possible

1. The clinical presentation and diagnostic evaluation suggest neurosarcoidosis, as defined by the clinical manifestations and MRI, CSF, and/or EMG/NCS findings typical of granulomatous inflammation of the nervous system and after rigorous exclusion of other causes.
2. There is no pathologic confirmation of granulomatous disease.

Definite

1. The clinical presentation and diagnostic evaluation suggest neurosarcoidosis, as defined by the clinical manifestations and MRI, CSF, and/or EMG/NCS findings typical of granulomatous inflammation of the nervous system after rigorous exclusion of other causes.
2. The nervous system pathology is consistent with neurosarcoidosis.
Type a. Extraneural sarcoidosis is evident.
Type b. No extraneural sarcoidosis is evident (isolated CNS sarcoidosis).

Diagnostic de sarcoïdose sans documentation histologique = situation à risque majeur d'erreur

Stern BJ JAMA Neurol. 2018 Dec 1;75(12):1546-1553

Traitement = modalités

- Souvent non nécessaire au cours de la sarcoïdose

- Indications formelles
  - Hypercalcémie
  - Localisations engageant le pronostic vital (ORL, cœur)
  - **Retentissement fonctionnel** (poumon, atteintes neurologiques)

Traitement = modalités

Table 3 Treatment and outcome

Characteristic	n/N[a] (%)	Characteristic	n/N[a] (%)
No treatment	99/655 (15)	Other treatment modalities	
First line therapy	434/539 (81)	Neurosurgical intervention	30/230 (13)
Second line therapy	144/539 (27)	Anti-epileptic medication	14/106 (13)
Third line therapy	49/539 (9)	Hormonal substitution	18/227 (8)
Overall treatment		Follow-up, yr., mean (SD)	4.4 (SD 3.15)
Corticosteroids	546/655 (83)	Outcome	
Methotrexate	105/655 (16)	Remission	126/415 (27)
Azathioprine	54/655 (8)	Improvement	147/415 (32)
(Hydroxy) chloroquine	24/655 (4)	Stable disease	100/415 (22)
Mycophenolate mofetil	12/655 (2)	Deterioration	19/415 (4)
Cyclosporine A	10/655 (2)	Mortality	42/826 (5)
Cyclophosphamide	40/655 (6)		
TNF-alpha antagonists	24/655 (4)	Favourable outcome per treatment group	
Treatment switches		First line therapy	161/227 (71)
First to second or third line	88/363 (24)	Second line therapy	47/85 (55)
Second to third line	14/104 (13)	Third line therapy	7/18 (39)
Between third line	7/23 (30)		

Fritz D. BMC Neurol. 2016 Nov 15;16(1):220.

Objectifs du traitement

- Diminuer la masse granulomateuse (corticoïdes) pour limiter les conséquences fonctionnelles
- Limiter l'apparition de fibrose : pas de traitement spécifique et aucune démonstration pour aucun traitement
- Eviter les rechutes (fréquentes dans certaines situations comme les atteintes neurologiques)

Traitement : modalités

Corticothérapie seule

- Poumon
- Hypercalcémie
- Atteintes rénales

Immunosuppresseur associé (?)

- Atteintes neurologiques
- Formes multisystémiques (en particulier si atteinte ORL)
- Cœur

Intérêt de l'immunosuppresseur

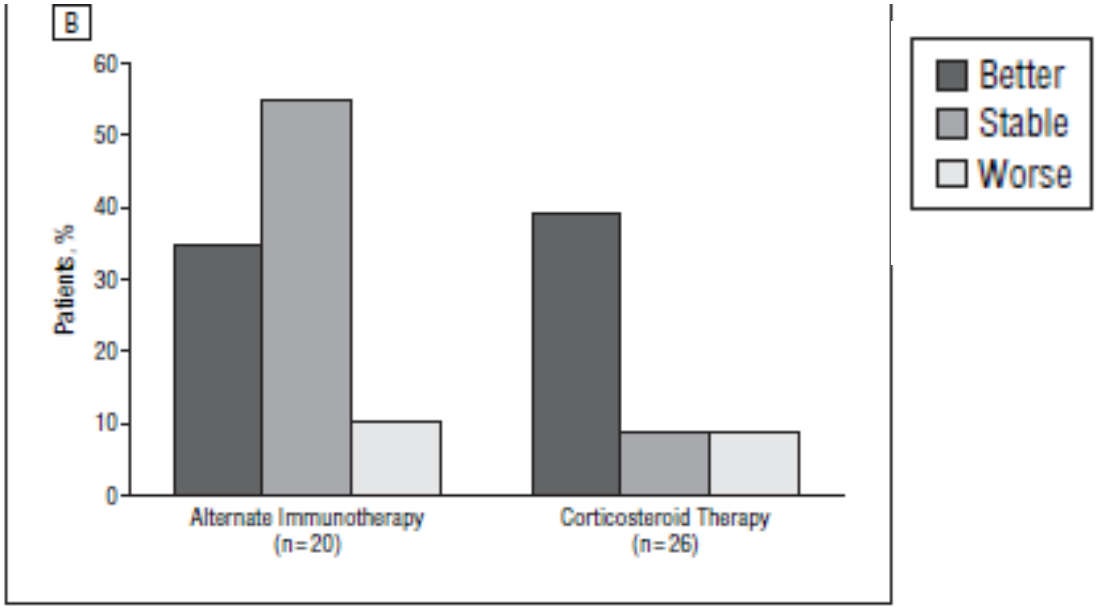


Figure 5. Percentages of patients with changed or stable outcomes for the total group (A) and treatment groups (B) according to Disease Steps in Multiple Sclerosis and Rankin scores before and after treatment. Two patients who received no treatment are not included in the figure. NS indicates neurosarcoidosis.

Scott TF Arch Neurol. 2007 May;64(5):691-6.

Quel immunosuppresseur ?

Première ligne

Méthotrexate

Azathioprine

Mycophenolate

(Cyclosporine, n=6)

Deuxième ligne

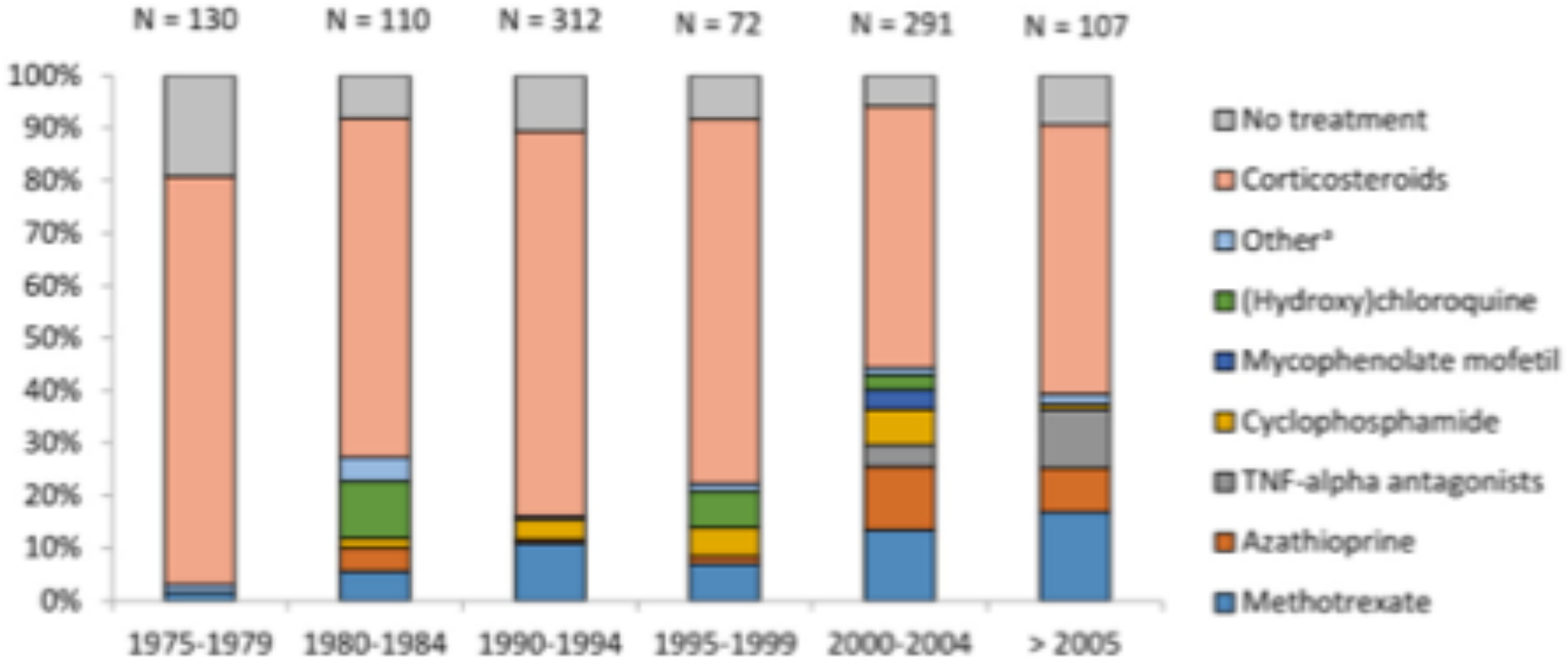
Cyclophosphamide

Infliximab (pas le récepteur)

AntiCD20

AntiIL12/IL23

Inhibiteurs de mTOR
Leflunomide
JAKi



[a] Cyclosporin A (n=10), Chloorambucil (n=2), IVIG (n=2) and rituximab (n=1)

Fritz D. BMC Neurol. 2016 Nov 15;16(1):220.

Intérêt du méthotrexate

24 patients traités mais 15 traités au moins 6 mois (autres perdus de vue)
Sur ces 15 patients
Corticothérapie diminuait dans le bras methotrexate
(First 6 months: Median 26 (Range 15-37) mg/day)
Second 6 months 8 (1-22) mg/day, $p < 0.01$)
Et dans le bras placebo
(First 6 Months 28 (24-33) mg/day;
Second 6 months 16 (11-22) mg/day, $p < 0.02$)
dose totale de corticoïdes moins élevée dans le bras méthotrexate ($p < 0.01$). Moins de prise de poids dans le bras méthotrexte
Pas de différence dans les effets indésirables
Pas de différence dans l'analyse en intention de traiter (donc sur les 24 patients)

Baughman RP Sarcoidosis Vasc Diffuse Lung Dis. 2000 Mar;17(1):60-6.

Mais largement utilisé

Question #6: The second-line agent that I add to corticosteroids or replace corticosteroids with in patients with sarcoidosis who have an inadequate response to corticosteroids is: ($n = 36$)

- Methotrexate (24, 67%)
- Azathioprine (6, 17%)
- Hydroxychloroquine (2, 6%)
- Indicated more than one response,including methotrexate, hydroxychloroquine, and infliximab (3, 8%)
- Infliximab (1, 3%)
- Chloroquine (0)
- Thalidomide (0)
- Leflunomide (0)

Schutt AC Respir Med. 2010 May;104(5):717-23.

Méthotrexate versus azathioprine

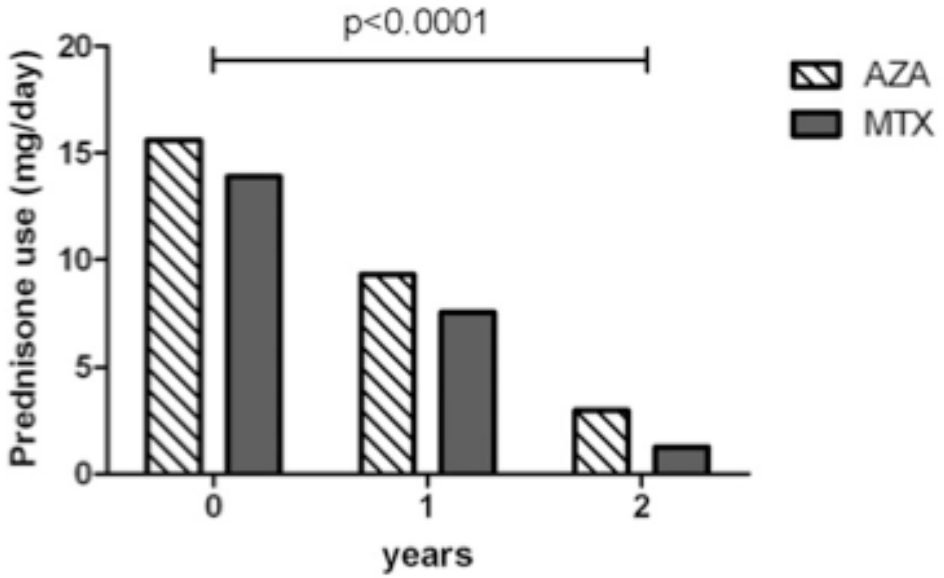


FIGURE 2. Effect of AZA and MTX on daily prednisone dose. Daily prednisone use decreased with 6.32 mg/year (SE, 0.63; $P < .0001$). The difference between AZA and MTX was not significant ($P = .139$). See Figure 1 legend for expansion of abbreviations.

Vorselaars ADM Chest. 2013 Sep;144(3):805-812.

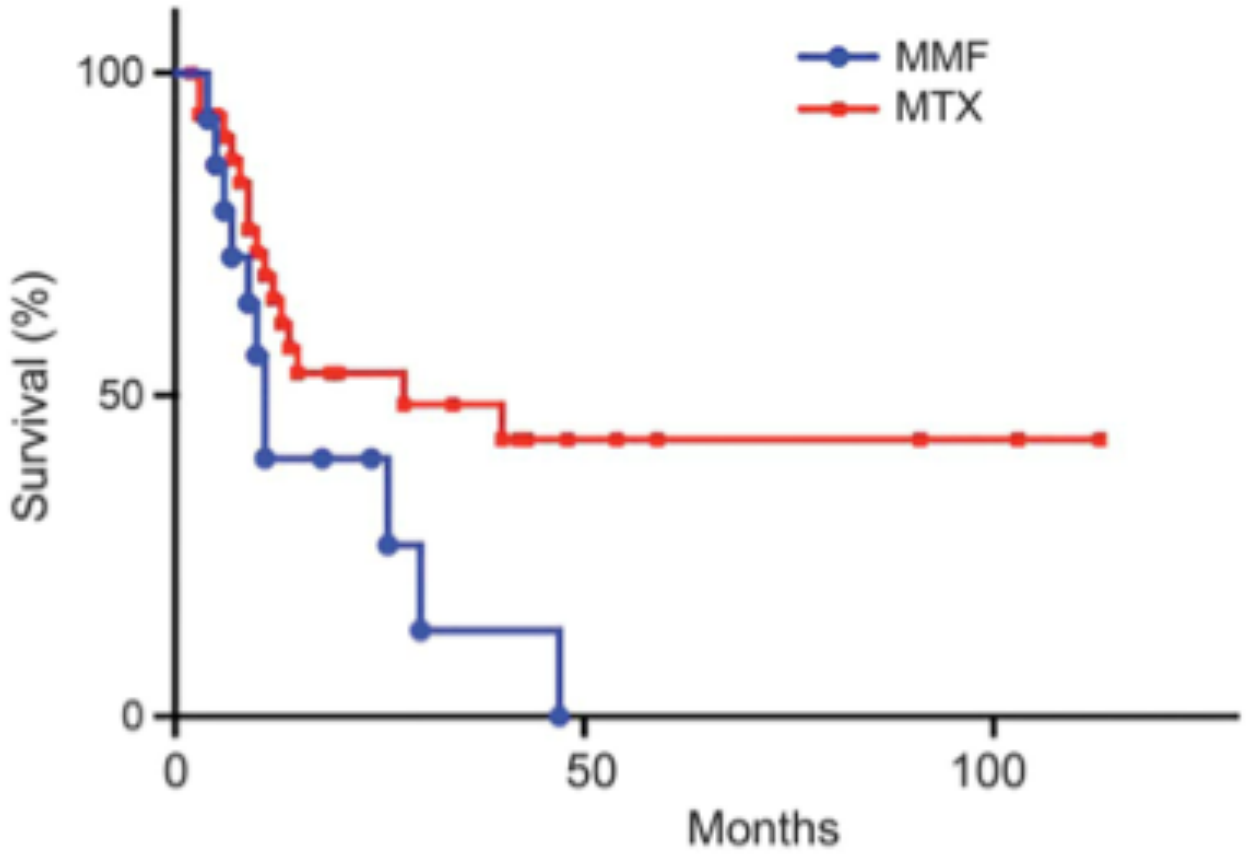
Mycophénolate

Patients	Previous treatment	Reason for MMF initiation	Steroids dosage at MMF initiation, mg/d	Duration of MMF treatment/ follow-up,[a] mo	Duration of treatment with steroids,[a] mo	Response of neurologic symptoms to MMF	Steroids dosage at the end of the follow-up, mg/d
1	None	Induction	0	16/16	0	Clinical: CR	0
						MRI: CR	
2	S	Maintenance	35	30/70	8	Clinical: maintenance of CR	0
						Persistent hormonal dysfunction	
						MRI: maintenance of CR	
3	S	Maintenance	0	15/15	0	Clinical: maintenance of CR	0
						MRI: maintenance of PR	
4	S	Maintenance	80	40/40	40	Clinical: maintenance of CR	10
						Persistent hormonal dysfunction	
						MRI: maintenance of PR	
5	S	Rescue therapy	60	21/21	17	Clinical: CR	0
						Persistent hormonal dysfunction	
						MRI: CR of cerebral lesions, PR of spinal cord lesion	
6	S	Rescue therapy	60	18/31	31	Clinical: failure	20
						Persistent hormonal dysfunction	
						MRI: failure	
7	S, Cy, A	Rescue therapy	0	17/17	0	CR: PR	0
						Persistent hormonal dysfunction	
						MRI: stability	
8	S, Mtx	Rescue therapy	60	22/22	15	Clinical: CR	0
						MRI: CR	
9	S, A	Rescue therapy	15	8/77	77	Failure	15
10	S, Cy, A	Rescue therapy	20	24/60	60	Failure	10

Androdias G Neurology. 2011 Mar 29;76(13):1168-72.

MTX versus MMF

Figure 1 Survival curve of relapse occurrence in patients treated with methotrexate (MTX) or mycophenolate mofetil (MMF)



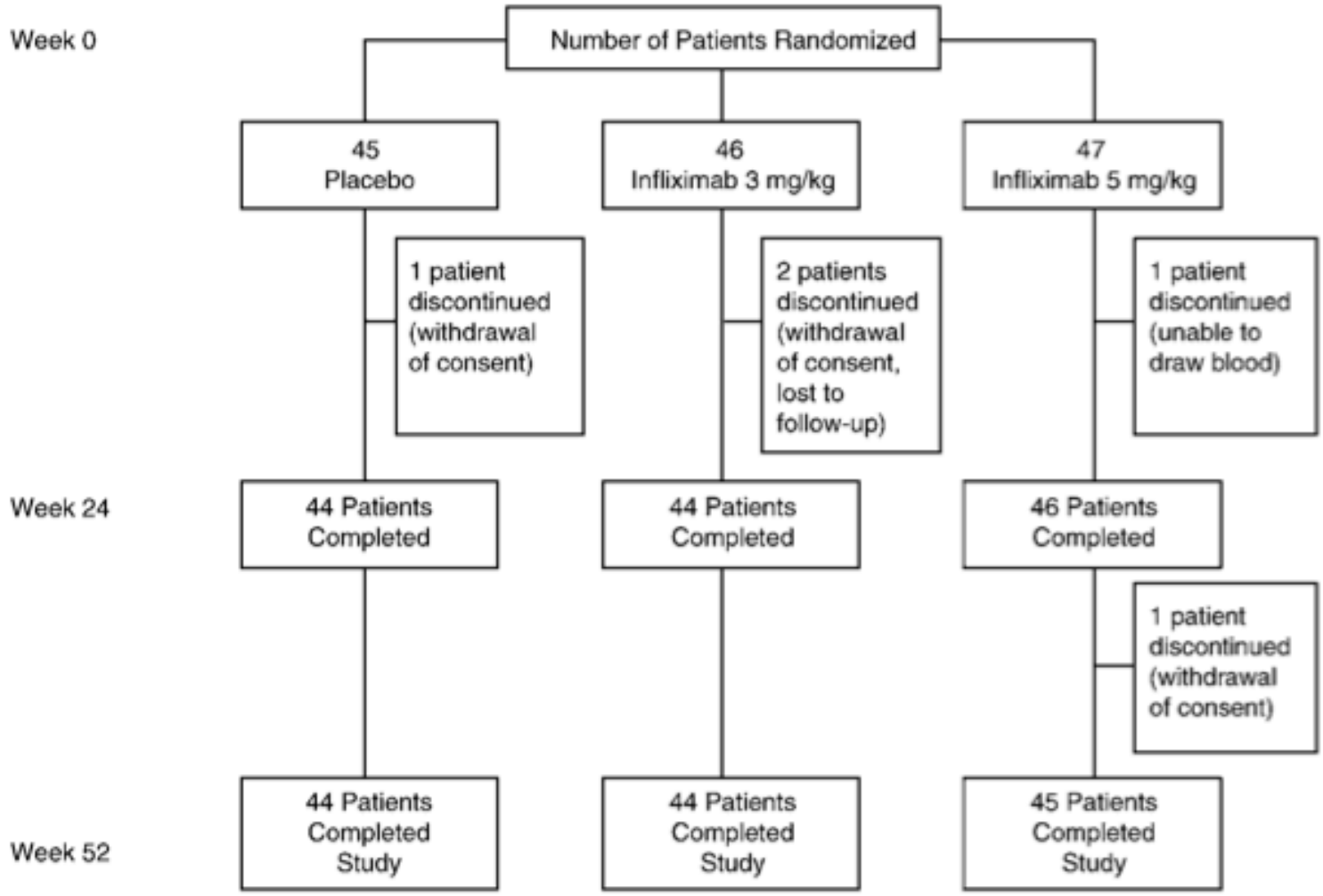
Bitoun S. Neurology. 2016;87(24):2517-2521.

MTX versus MMF

nombre	MMF (N= 14)	MTX (N=32)	p
Effets indésirables N (%)	1 (7)	8 (25)	0, 13
Hépatique N (%)	0	2 (6)	0, 22
Infectieux N (%)	0	6(19)	**0, 02**

Bitoun S. Neurology. 2016;87(24):2517-2521.

Traitement par infliximab



Baughman R. Am J Respir Crit Care Med. 2006 Oct 1;174(7):795-802.6

Traitement par infliximab

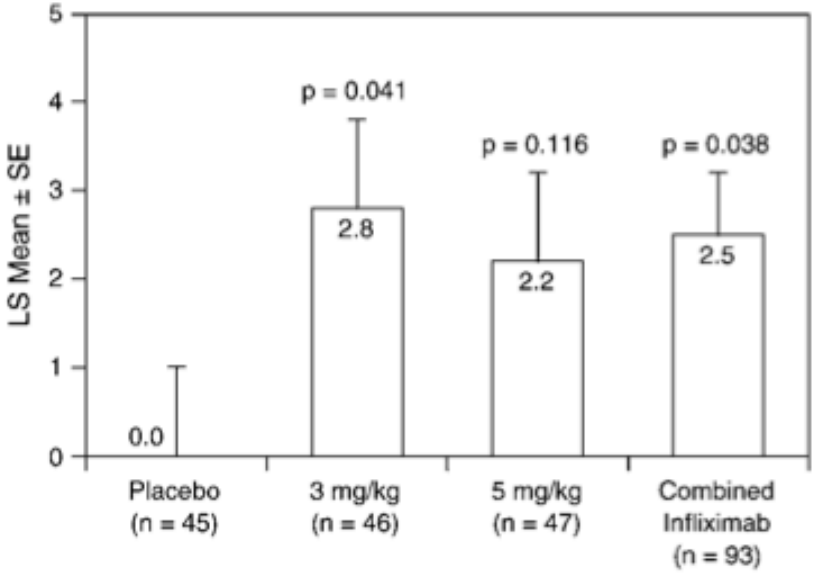


Figure 2. Summary of change from baseline to Week 24 in percent of predicted FVC with last observation carried forward. LS mean = least square mean.

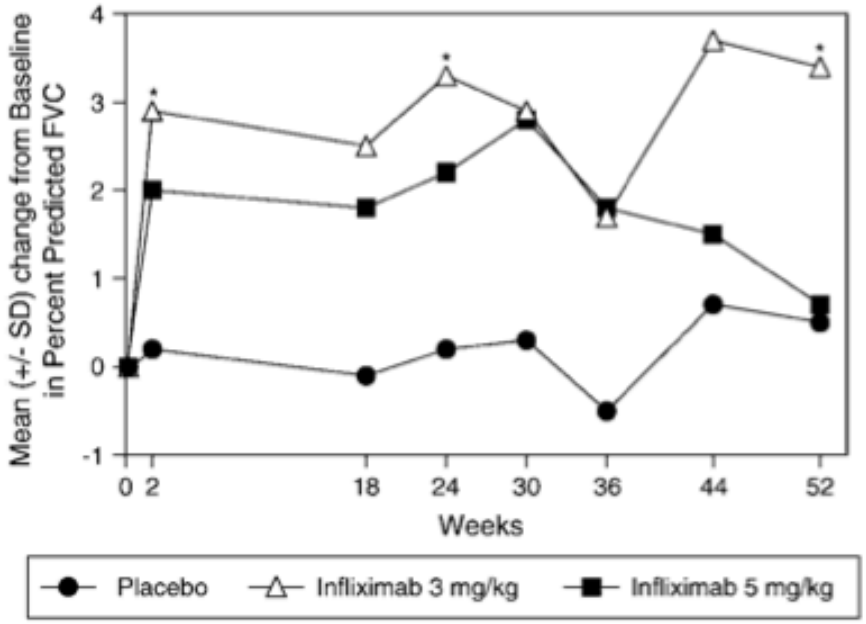


Figure 3. Mean (± SD) changes from baseline in percentage of predicted FVC through Week 52 (randomized patients, no imputation for missing data). *p < 0.05 versus placebo group.

Baughman R. Am J Respir Crit Care Med. 2006 Oct 1;174(7):795-802.6

TABLE 4 Frequencyement at baseline

Organ	Patients affected
Lungs	136 (100)[#]
Peripheral lymph nodes	50 (37)
Skin	36 (26)
Bone/joint	27 (20)
Liver	19 (14)
Eyes	19 (14)
Muscle	18 (13)
Cardiac	12 (9)
Peripheral nervous system	11 (8)
Nose	11 (8)
Central nervous system	9 (7)
Spleen	8 (6)
Renal	8 (6)
Bone marrow	5 (4)
Throat	3 (2)
Parotid/salivary glands	3 (2)
Ear	1 (1)
Gastrointestinal	1 (1)

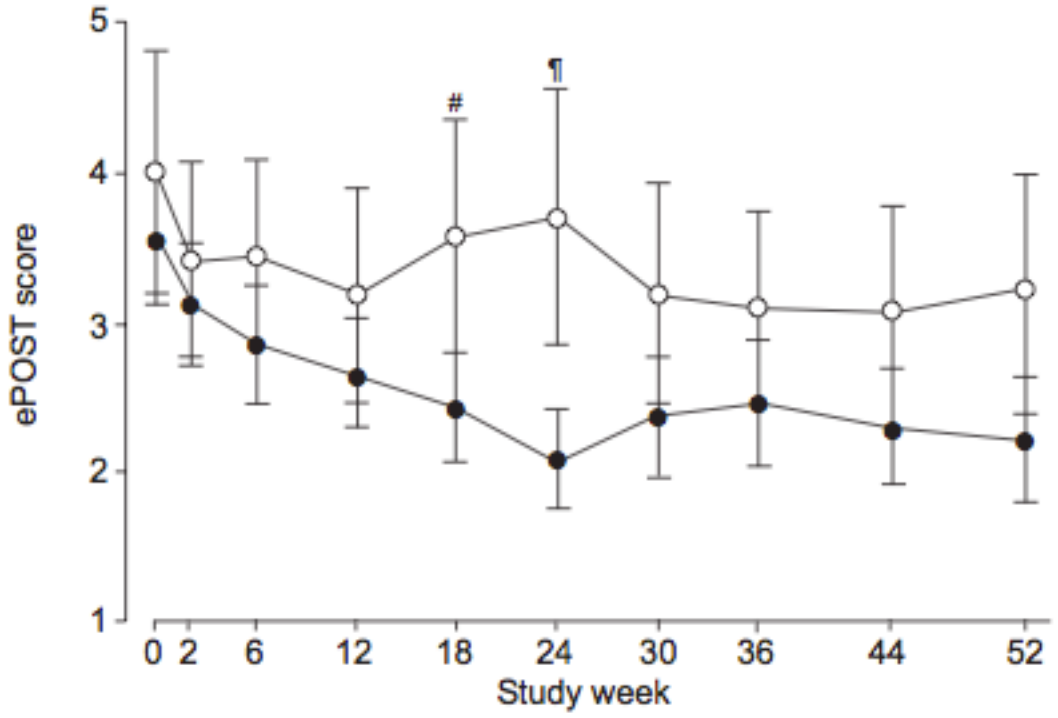


FIGURE 2. Mean extrapulmonary physician organ severity tool (ePOST) scores, with SEM bars, at each assessment visit, according to treatment group. ○: placebo group; ●: combined infliximab groups. [#]: p=0.0247; [¶]: p=0.0019. If not specified, p>0.05. Comparisons between groups are based upon change from baseline values.

Judson MA Eur Respir J. 2008 Jun;31(6):1189-96.

TABLE 6 Mean change in sarcoidosis organ score for each organ

Organ	Placebo[#]			Combined infliximab[¶]			Wilcoxon p-value
	Mean±SD (range)	Baseline[+]	Week 24[+]	Mean±SD (range)	Baseline[+]	Week 24[+]	
Bone/joint	-0.1±0.85 (-2–4)	8	8	-0.2±0.57 (-3–1)	19	11	0.580
Bone marrow	0.0±0.46 (-2–2)	3	3	0.0±0.24 (-1–2)	2	3	0.524
Cardiac	0.0±0.30 (0–2)	4	4	-0.1±0.36 (-2–1)	8	4	0.111
Central nervous system	0.1±0.78 (-1–4)	3	5	0.0±0.15 (-1–0)	6	5	0.582
Eyes	0.0±0.46 (-1–2)	7	9	-0.1±0.61 (-3–2)	12	10	0.841
Liver	0.0±0.30 (-1–1)	3	3	-0.2±0.54 (-3–1)	15	8	0.096
Peripheral lymph nodes	-0.4±0.79 (-3–0)	19	14	-0.3±0.75 (-3–2)	31	23	0.390
Muscle	-0.1±0.47 (-2–1)	7	6	-0.1±0.44 (-2–1)	11	9	0.588
Nose	0.1±0.59 (-2–3)	3	4	-0.1±0.63 (-4–1)	7	6	0.236
Peripheral nervous system	0.0±0.51 (-3–1)	4	4	-0.1±0.38 (-2–1)	7	6	0.281
Renal	0.0±0.15 (0–1)	1	2	0.0±0.32 (-1–2)	7	5	0.293
Skin	-0.1±0.69 (-4–1)	8	8	-0.3±0.90 (-5–2)	26	17	0.087
Spleen	0.0±0.15 (0–1)	0	1	-0.1±0.38 (-2–0)	8	5	0.061

[#]: n=44; [¶]: n=89; [+]: number of patients with involvement of that organ, *i.e.* organ score ⩾1.

Judson MA Eur Respir J. 2008 Jun;31(6):1189-96.

Adalimumab

11 patients 52 semaines

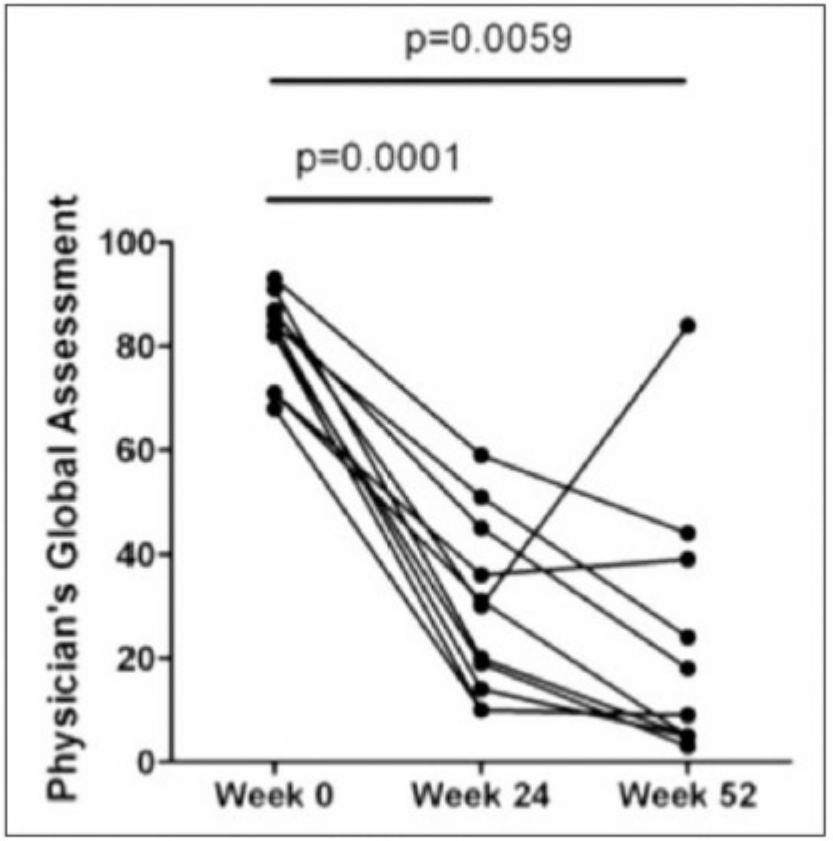


Fig. 3.
Physician's global assessment scores are significantly reduced at Weeks 24 and 52.

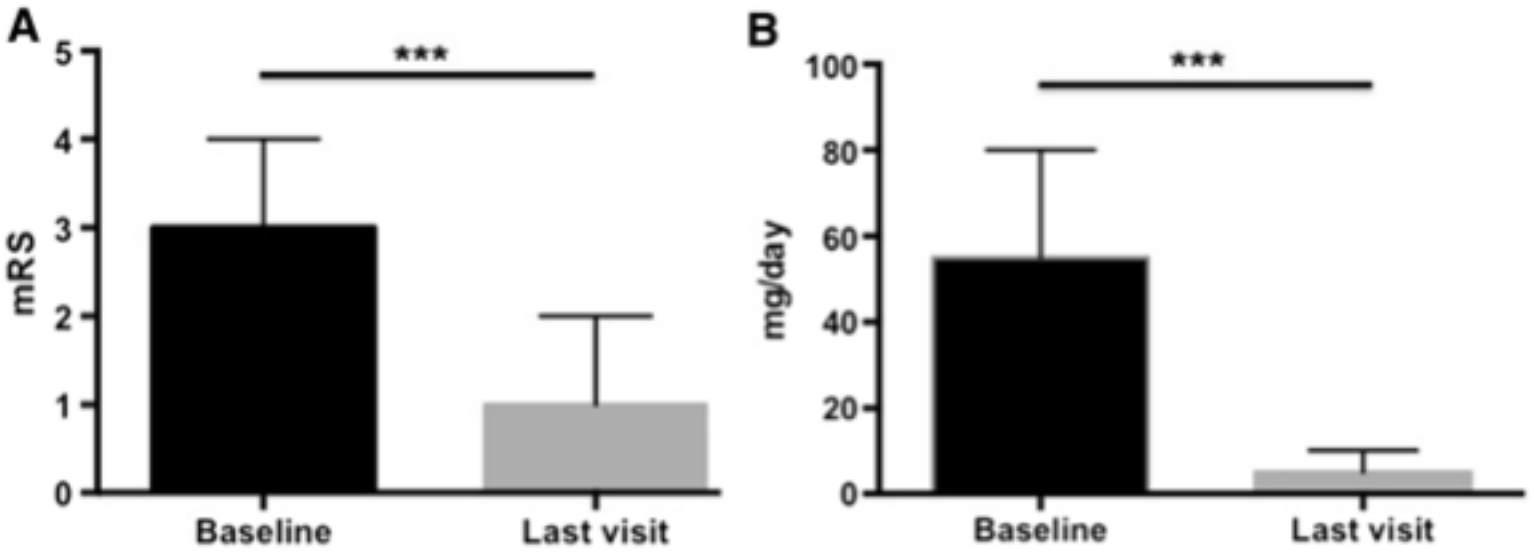
Sweiss NJ Sarcoidosis Vasc Diffuse Lung Dis. 2014 Apr 18;31(1):46-54

Recommandations d'experts

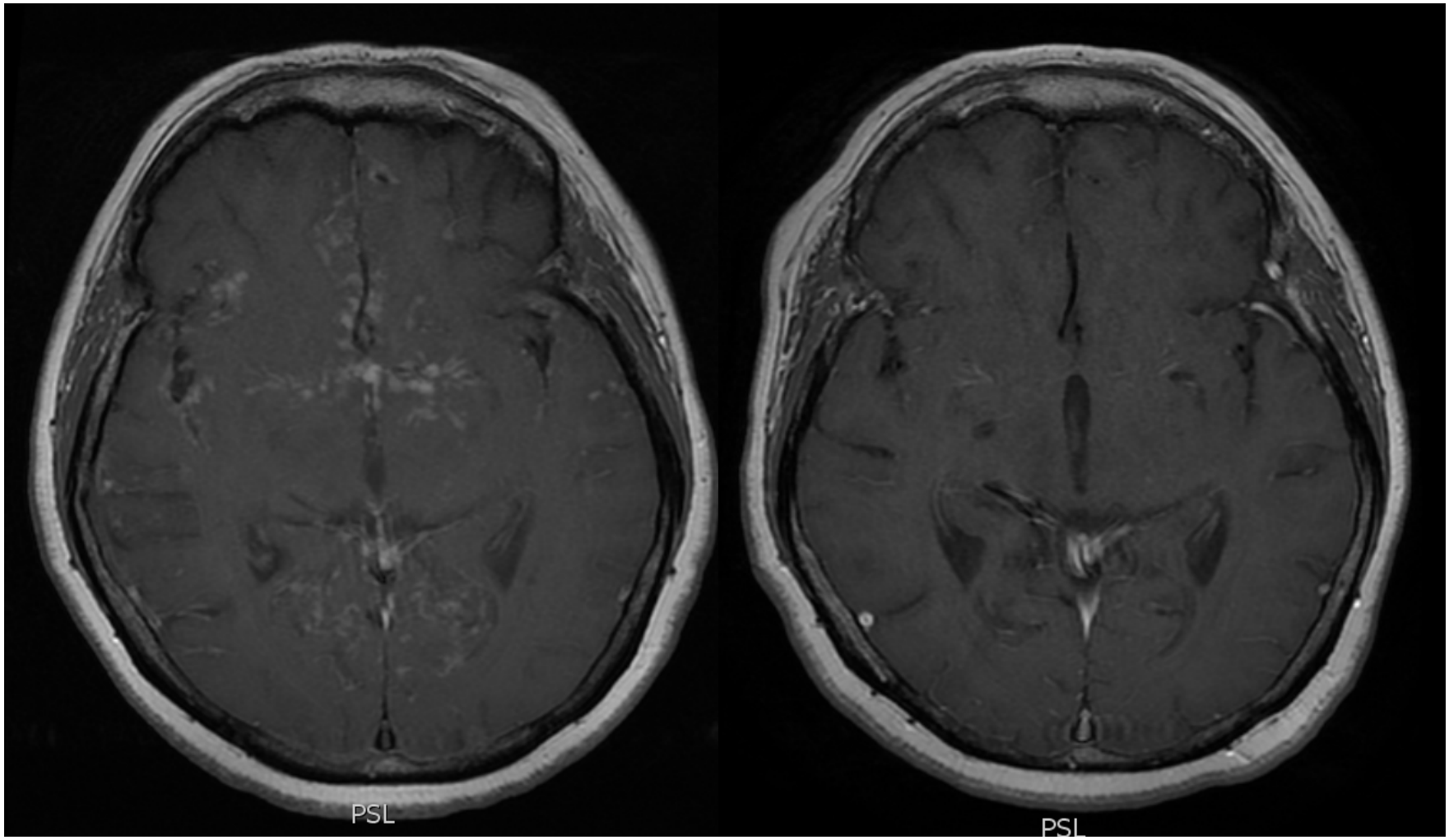
Dosing	
Infliximab	
Dosage	
-5 mg/kg body weight	15/18 (83.3%)
-3 mg/kg body weight	2/18 (11.1%)
-Depending on response	1/18 (5.6%)
Induction regimen	
-Week 0, 2, 6	18/18 (100%)
Maintenance regimen	
-Every 4 weeks	7/17 (41.2%)
-Every 6 weeks	6/17 (35.3%)
-Every 8 weeks	3/17 (17.6%)
-Depending on response	1/17 (5.9%)

Drent M. Sarcoidosis Vasc Diffuse Lung Dis. 2014 Jul 8;31(2):91-107.

Infliximab dans les atteintes neurologiques de la sarcoïdose

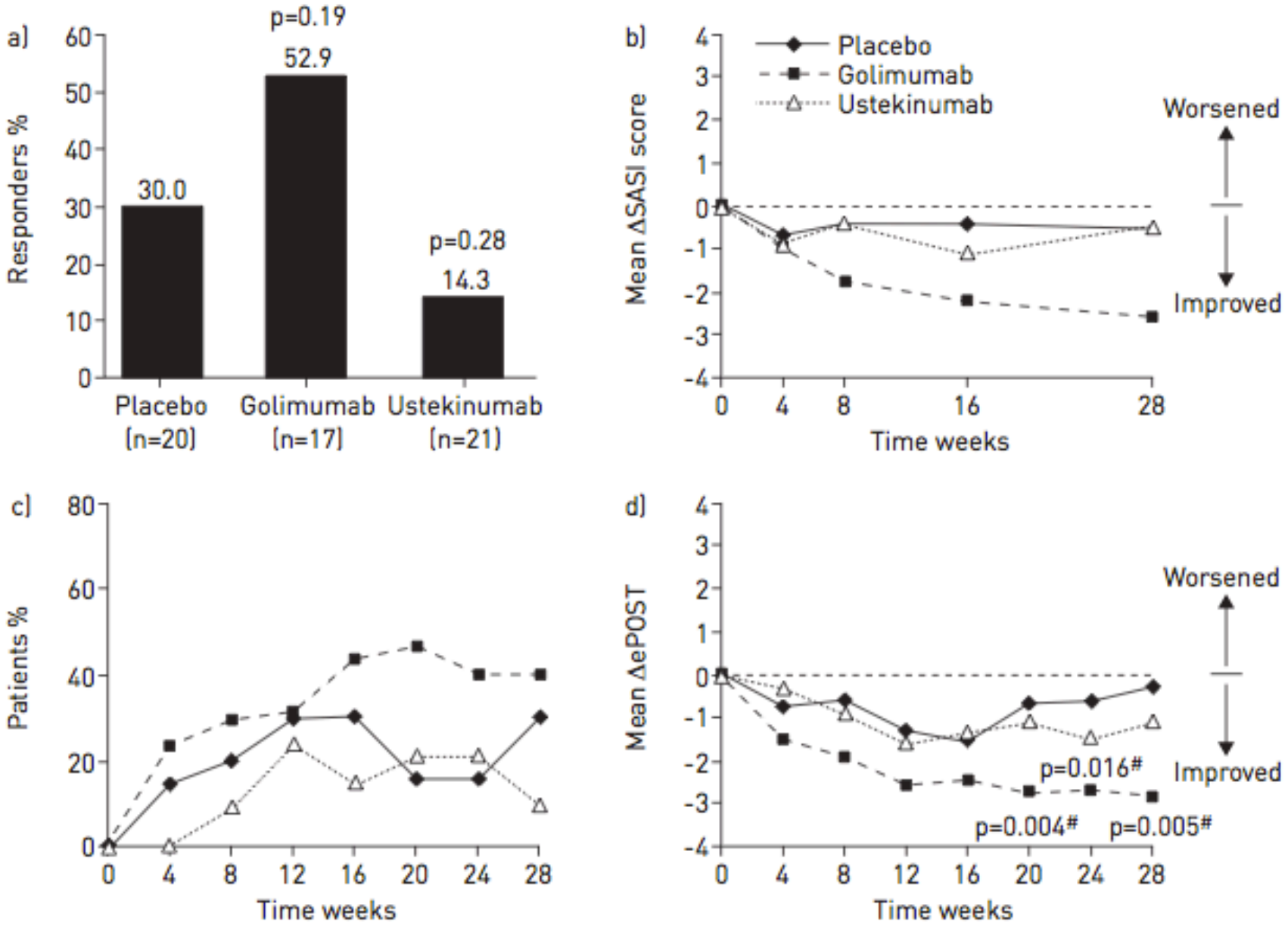


Cohen Aubart F J Neurol. 2017 May;264(5):891-897

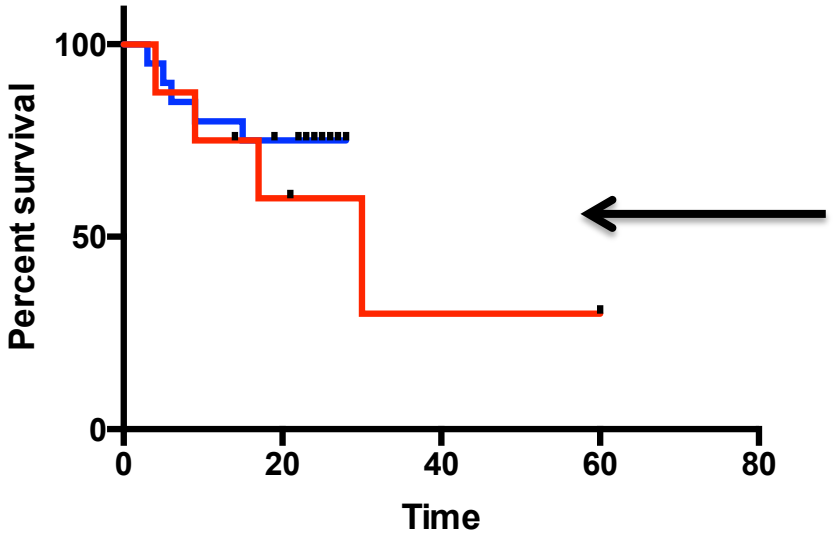

PSL
PSL

MRI response, n (%)	
Worsened	2 (3)
No change	8 (12.1)
Partial improvement	17 (25.8)
Complete Remission	29 (43.9)
Incomplete imaging follow-up	10 (15.2)
Clinical response, n (%)	
Worsened	2 (3)
Stable	12 (18.2)
Improvement with some residual neurologic disability	32 (48.5)
Complete recovery	19 (28.8)
Lost to follow-up	1 (1.5)

Gelfand JM Neurology. 2017 Nov 14;89(20):2092-2100



Judson MA, Eur Respir J. 2014 Nov;44(5):1296-307.



Durée du traitement ?

Utilisation possible des biosimilaires

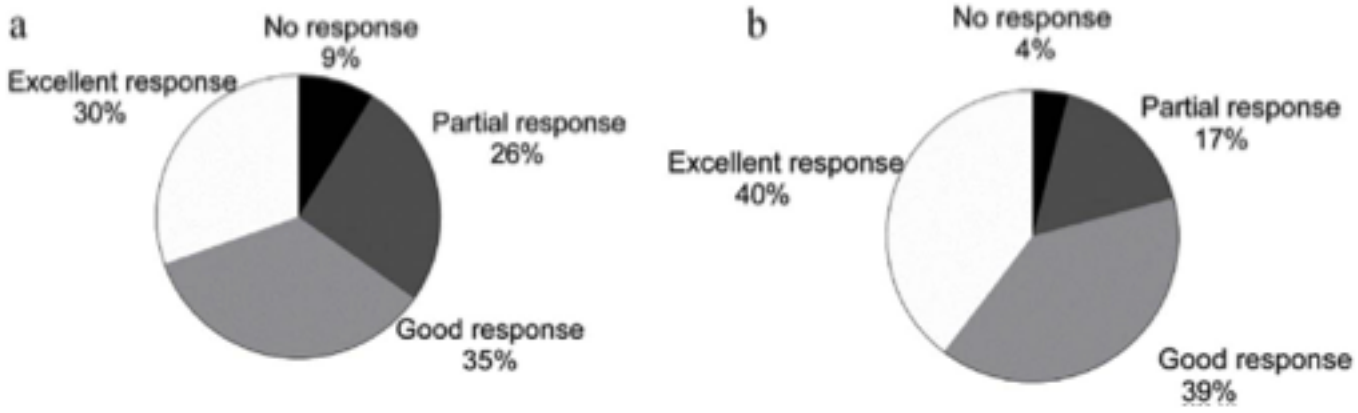
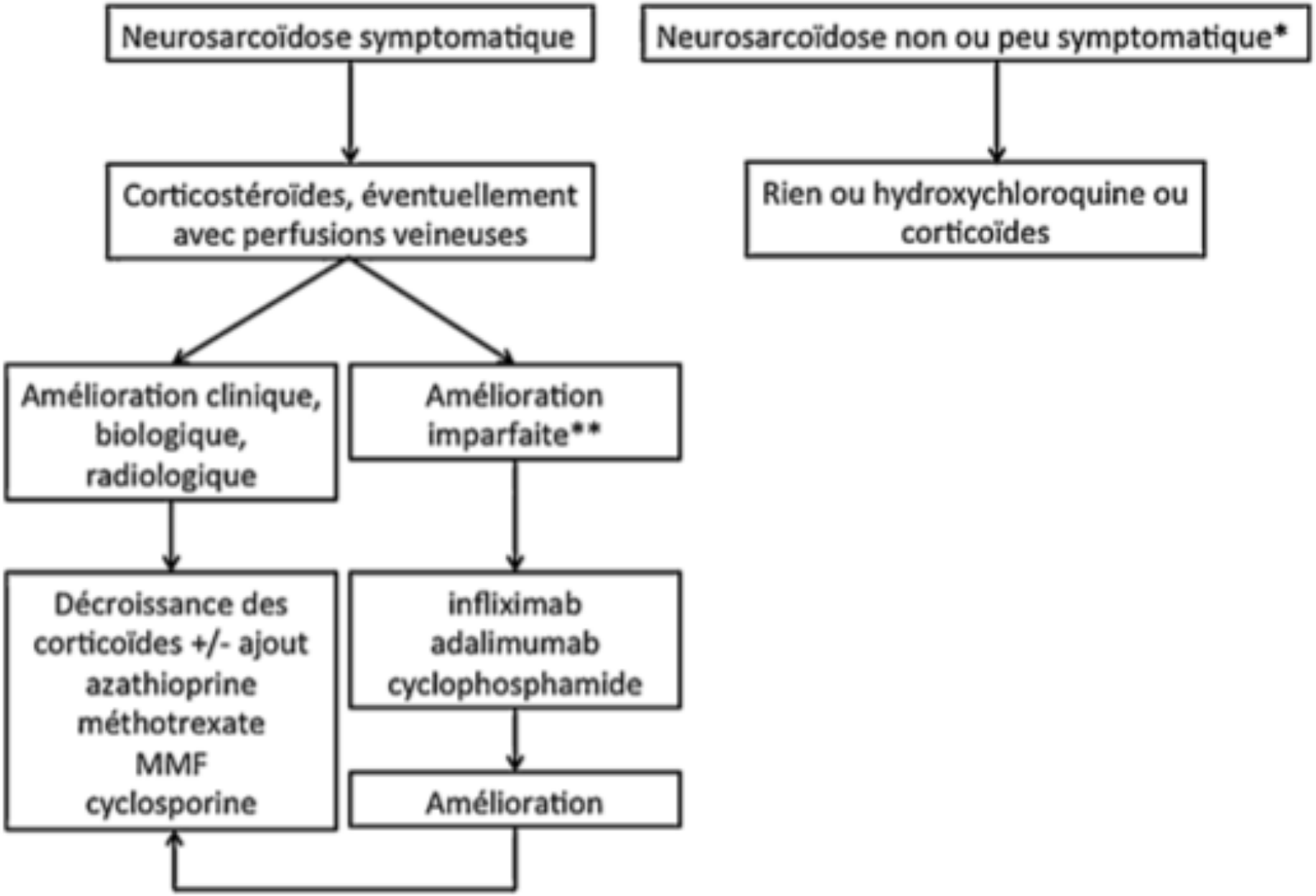
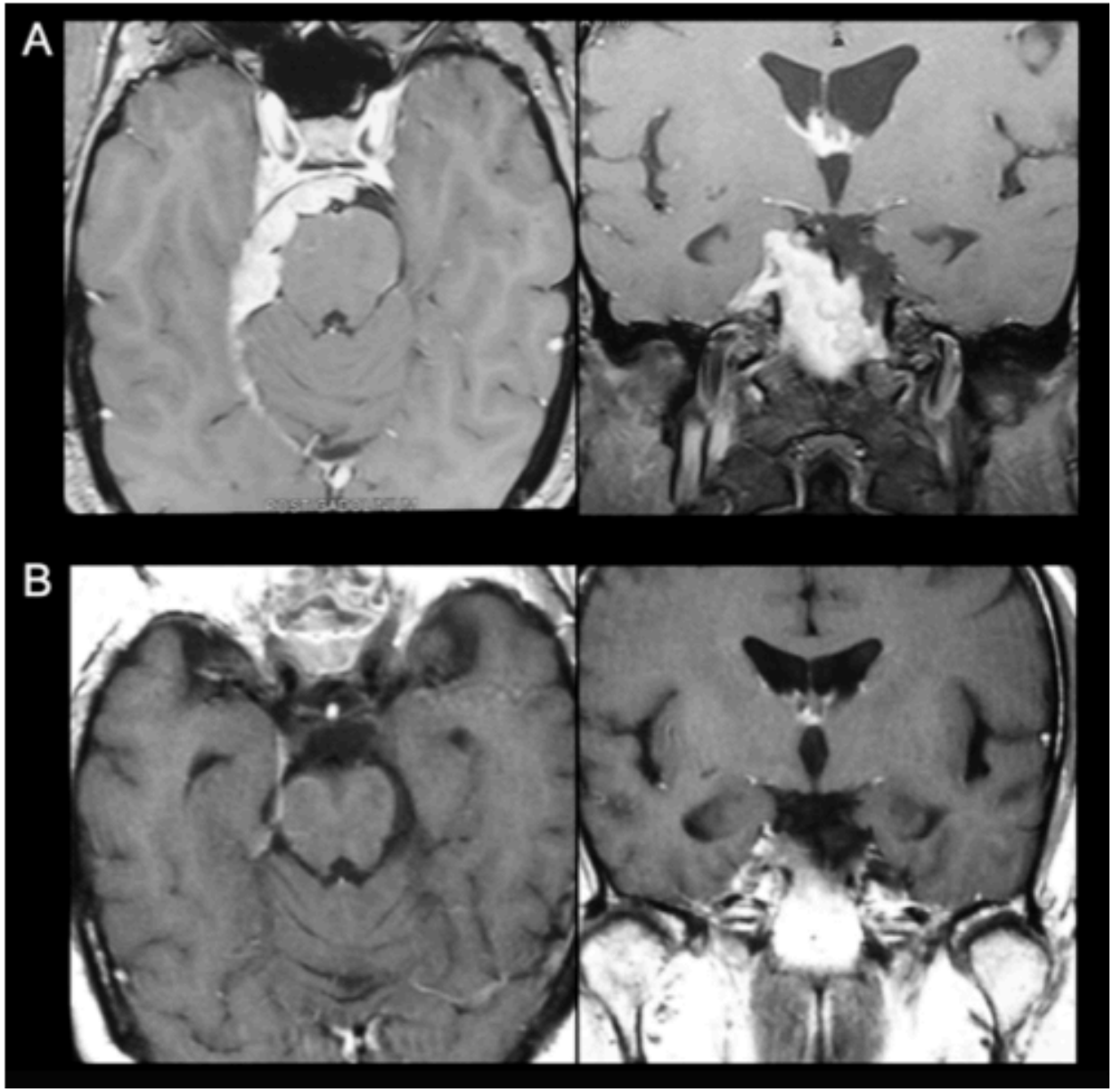


Fig. 6. (a) Response after 26 weeks of Inflectra® therapy. (b) Response after 26 weeks of Remicade® therapy.

Riller Q. J Neurol. 2019 Feb 9 **Schimmelpennink MC**. Respir Med. 2018 May;138S:S7-S13.



Cohen Aubart F. Rev Med Interne. 2017 Jun;38(6):393-401.



Bhagwan S. Clin Neurol Neurosurg. 2015 Sep;136:79-81
The use of cladribine in neurosarcoidosis: A report of two cases.

Leflunomide

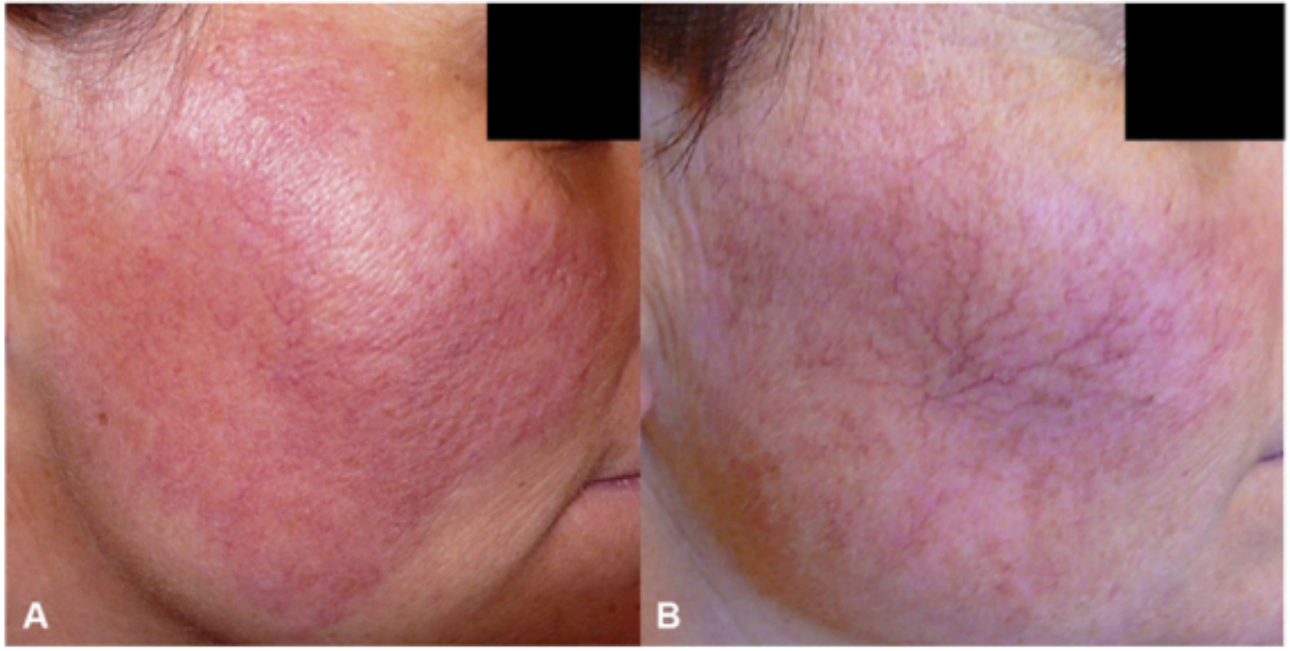


Fig 1. **A**, Sarcoidosis skin lesions on the right cheek in patient 1 before leflunomide treatment. **B**, Complete remission in patient 1 after 12 months of leflunomide treatment.

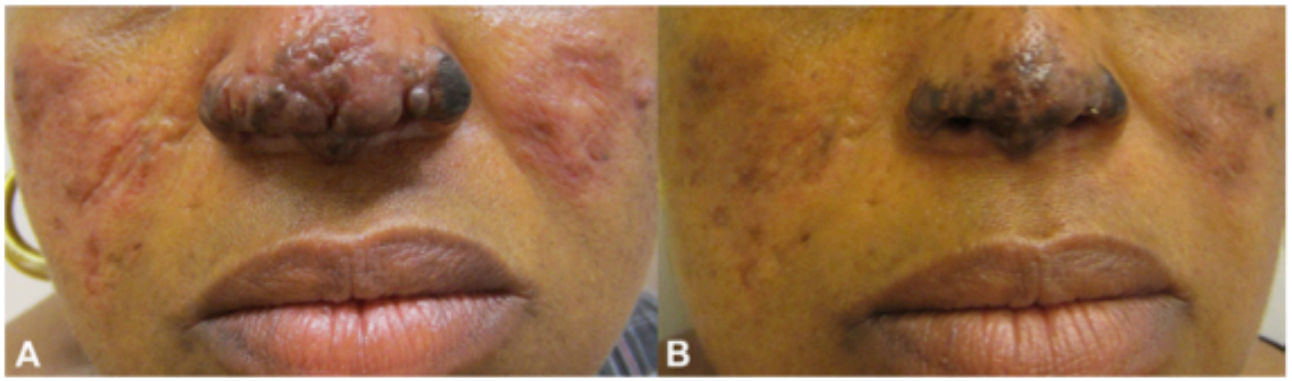


Fig 2. **A**, Severe facial lupus pernio in patient 2 before combined leflunomide and methotrexate treatment. **B**, Rapid partial response of the facial lupus pernio in patient 2 after 4 months of combined leflunomide and methotrexate treatment.

Bohelay G J Am Acad Dermatol. 2014 May;70(5):e111-3

	Complete (>90%)	Partial (50–89%)	No response (<49%)
Cutaneous	6	5	1
Eye	5	2	0
Sinonasal	4	2	0
Cardiac	2	1	0
CNS	1	0	2
Gastric	1	0	0
PNS	0	0	1
Liver	0	1	0
Vasculitis	0	1	0
MSK	0	0	1
Total[#]	19	12	5

Side-effect[#]	
Total n	68[¶]
None	45 (66)
Diarrhoea, nausea or bloating	17 (25)
Hepatic enzyme elevation	5 (7)
Neuropathy	2 (3)
Hair loss	2 (3)
Visual disturbance	1 (1)
Arthralgia	1 (1)

Sahoo DH. Eur Respir J. 2011 Nov; 38(5):1145-50.

Rituximab in the treatment of refractory pulmonary sarcoidosis

The current study was the first prospective phase I/II clinical trial to evaluate the use of rituximab in patients with refractory pulmonary sarcoidosis. We observed the clinical response to rituximab therapy to be inconsistent among patients with refractory pulmonary sarcoidosis. Respiratory function improved in only a subset of our study cohort: five patients had >5% absolute improvement in FVC and five patients improved by >30 m in 6MWD (seven responders total; some patients improved in only FVC or 6MWD, others improved in both). We were not able to correlate response to rituximab with pre-treatment immunoglobulin levels. Further studies are required to assess whether rituximab may be a viable alternative to anti-TNF antibodies for refractory sarcoidosis. In addition, it should be defined which subgroup of patients is likely to respond to rituximab therapy.

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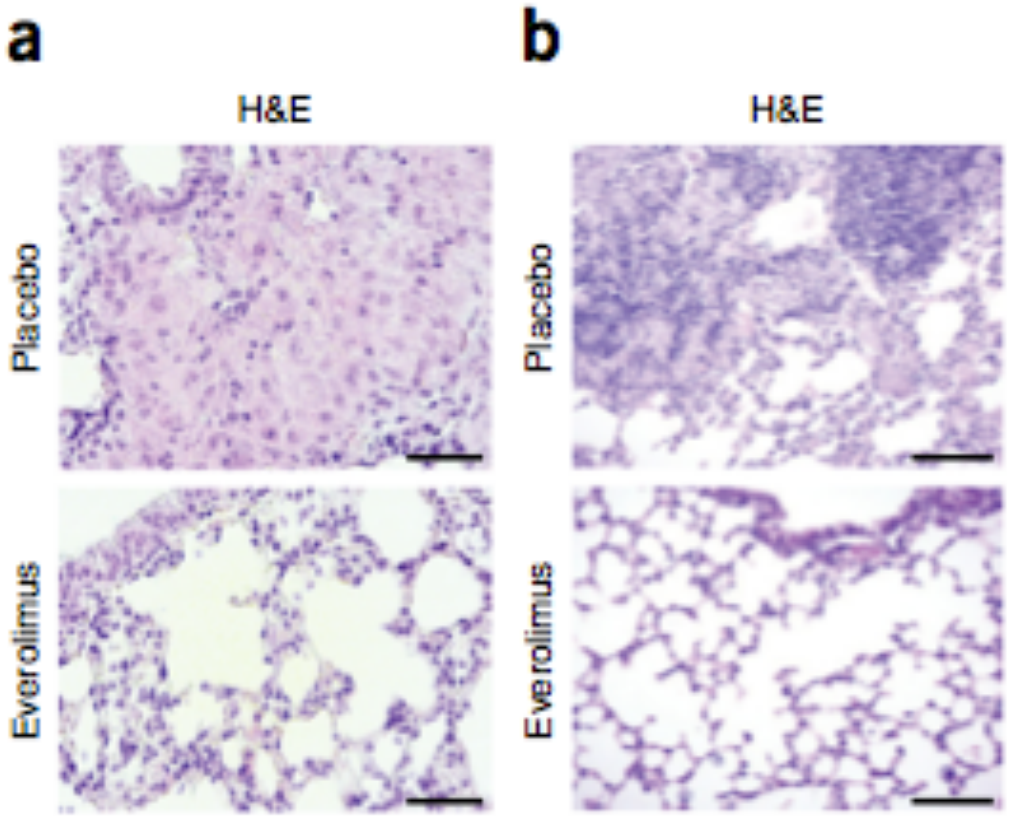
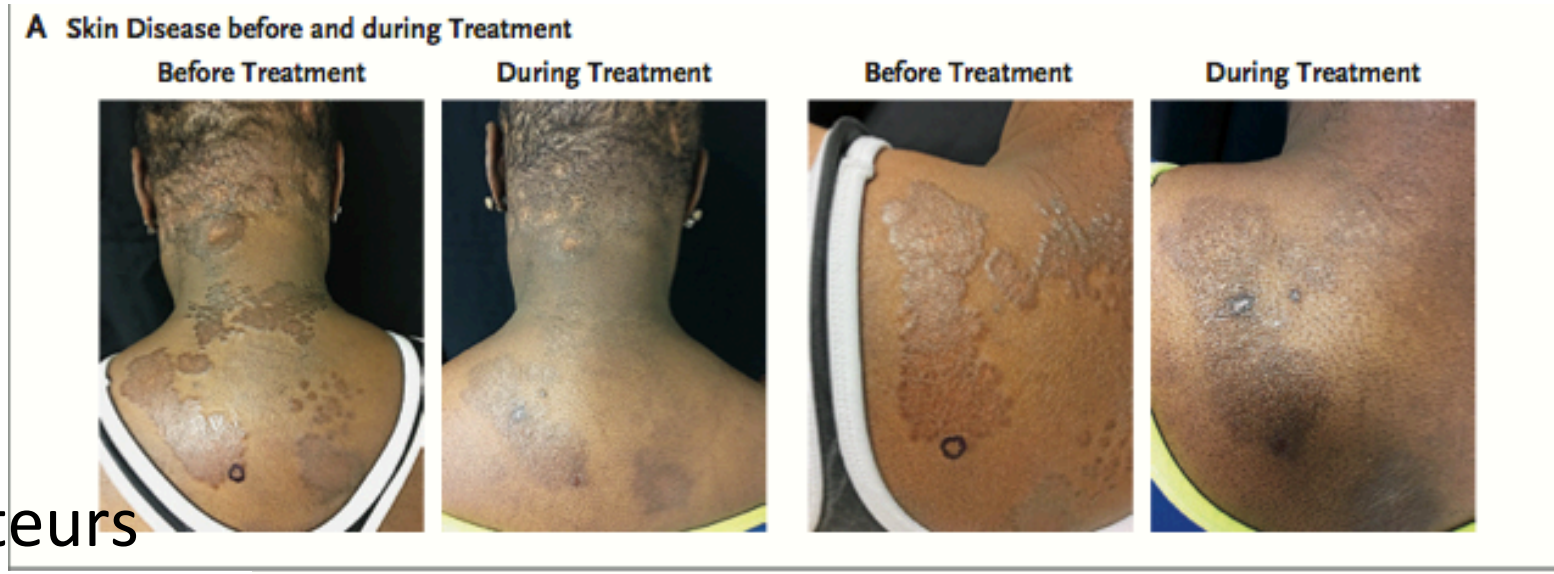
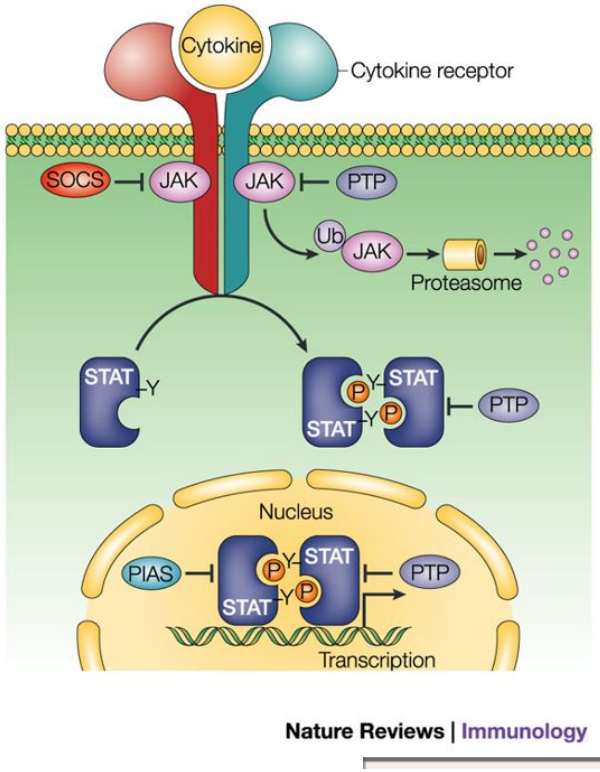


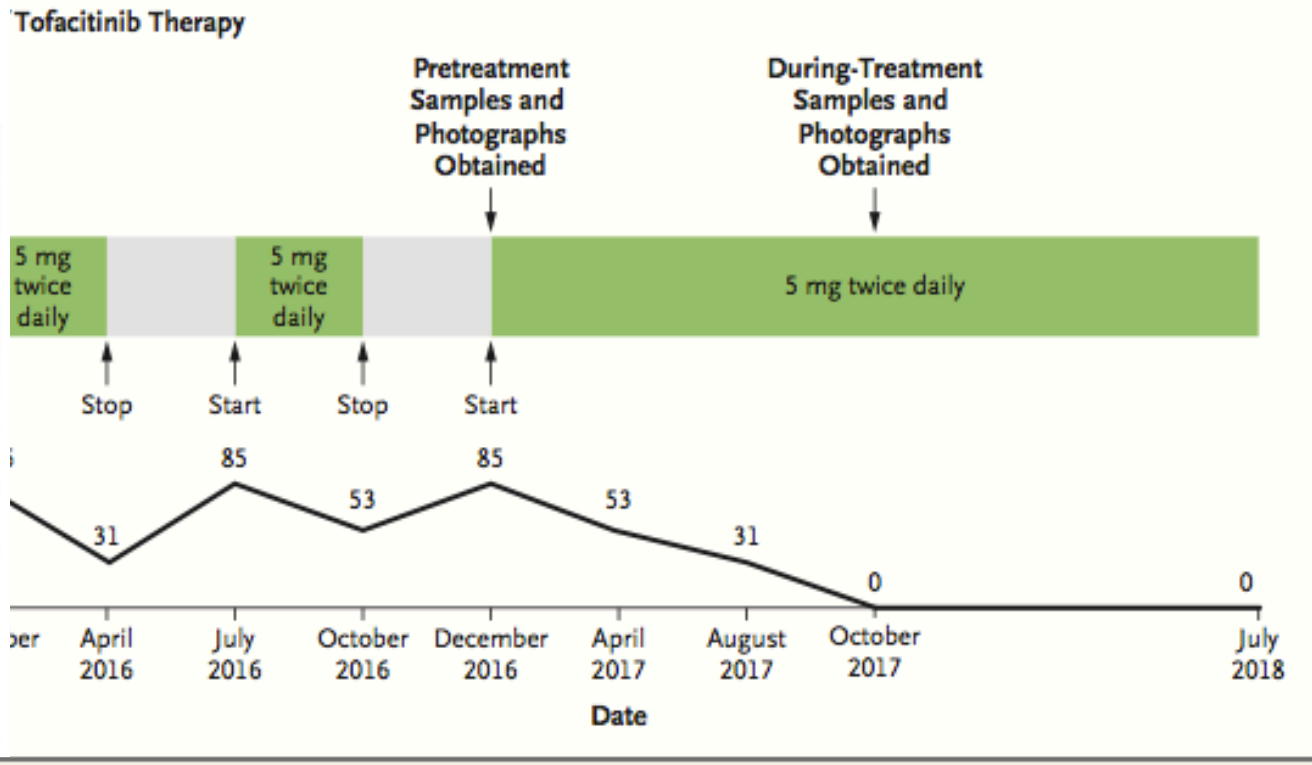
Chronic signaling via the metabolic checkpoint kinase mTORC1 induces macrophage granuloma formation and marks sarcoidosis progression

Monika Linke[1], Ha Thi Thanh Pham[1], Karl Katholnig[1], Thomas Schnöller[1], Anne Miller[2], Florian Demel[1], Birgit Schütz[1], Margit Rosner[1], Boris Kovacic[1], Nyamdelger Sukhbaatar[1], Birgit Niederreiter[3], Stephan Blüml[3], Peter Kuess[4], Veronika Sexl[5], Mathias Müller[6], Mario Mikula[1], Wolfram Weckwerth[7], Arvand Haschemi[2], Martin Susani[8], Markus Hengstschläger[1], Michael J Gambello[9] & Thomas Weichhart[1]

JAK inhibiteurs







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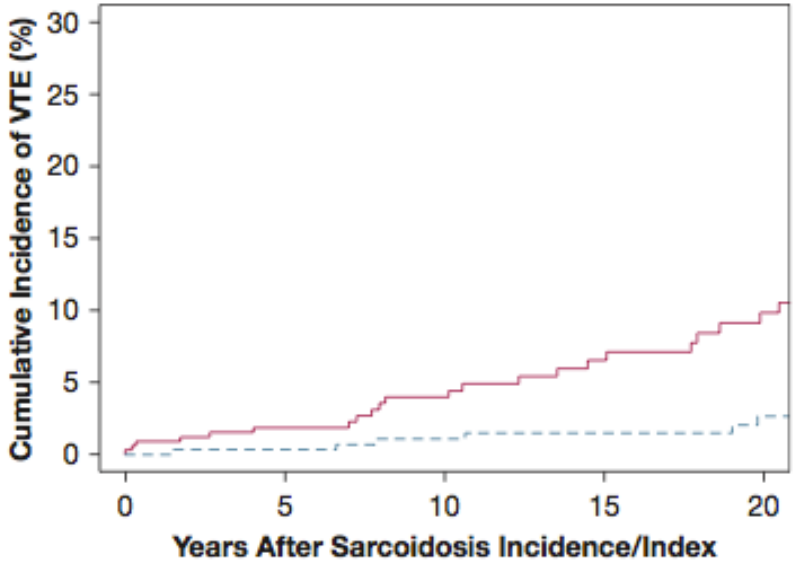
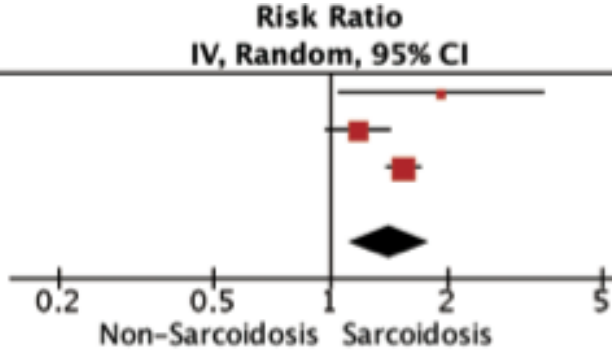
Risque thrombo-embolique



Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI	Year
Crawshaw et al.	0.6523	0.3079	11.7%	1.92 [1.05, 3.51]	2011
Johannesdottir et al.	0.1625	0.0953	39.6%	1.18 [0.98, 1.42]	2012
Zoller et al.	0.4318	0.0486	48.8%	1.54 [1.40, 1.69]	2012
Total (95% CI)			**100.0%**	**1.42 [1.12, 1.79]**	

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 7.13$, df = 2 (P = 0.03); $I^2 = 72\%$
Test for overall effect: Z = 2.95 (P = 0.003)



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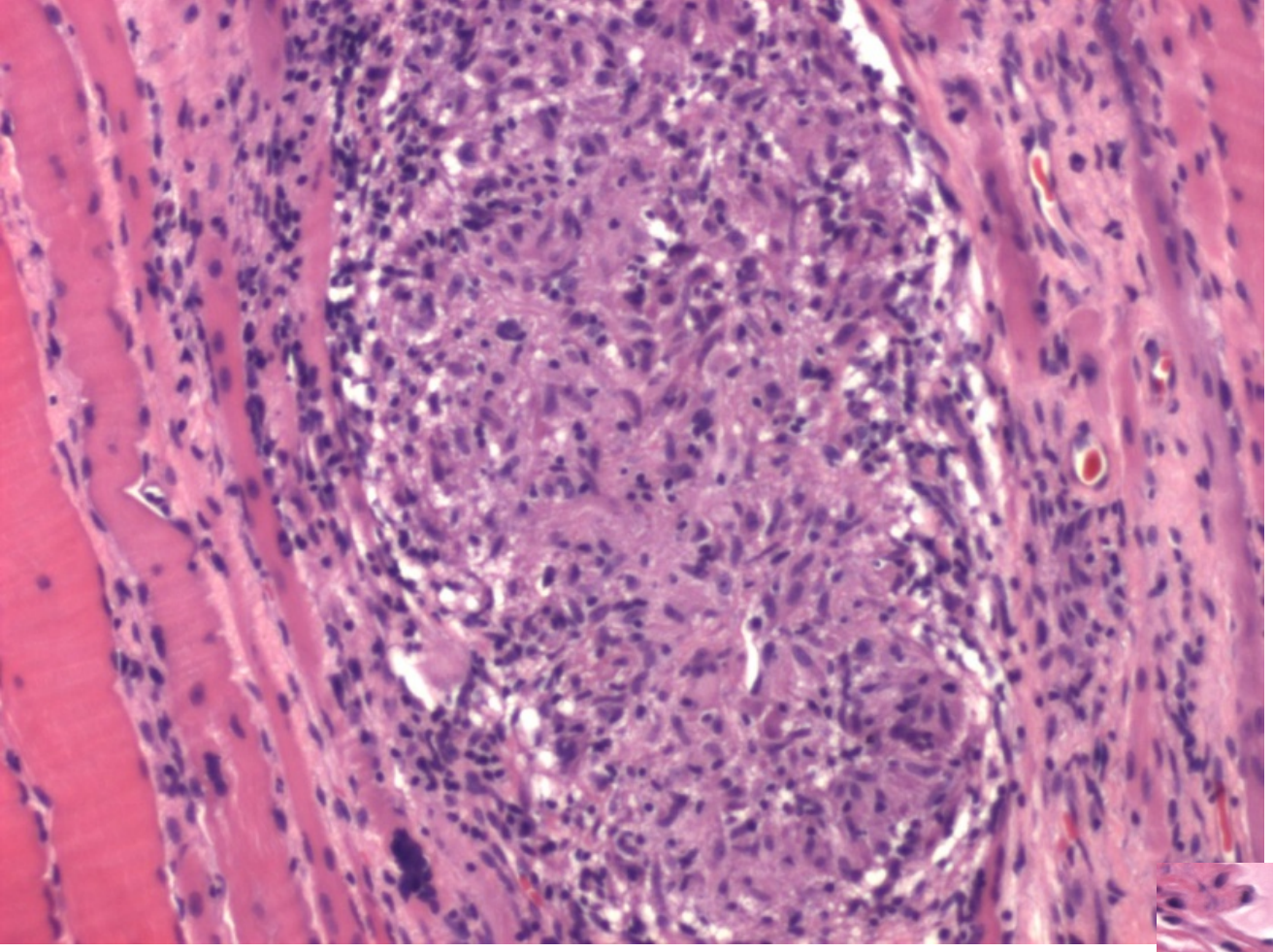
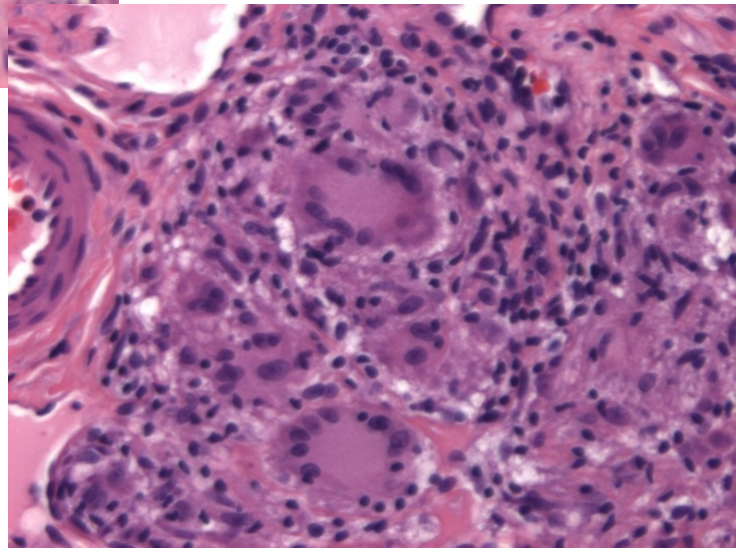


Formes réfractaires

définition+++



Messages clés

Savoir évoquer (et confirmer) le diagnostic

La corticothérapie reste le traitement de première intention même sans preuve

L'ajout d'un immunosuppresseur reste la règle même sans preuve

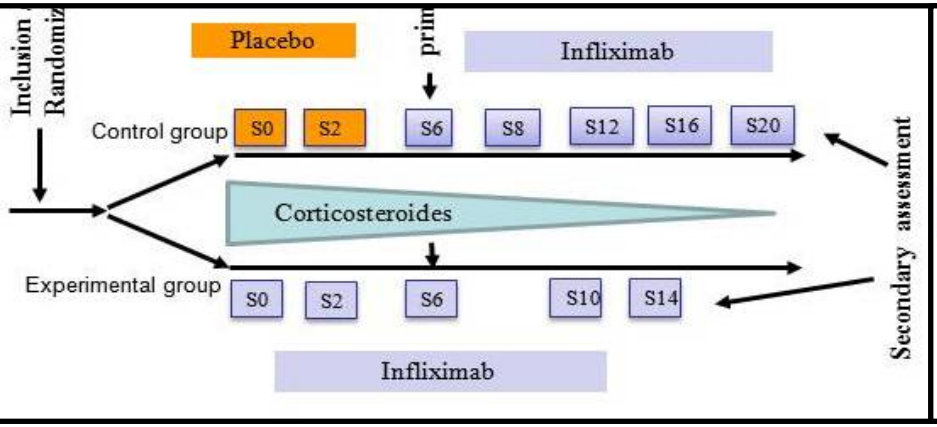
L'infliximab est utile mais jamais en première ligne

Maintien d'un traitement prolongé

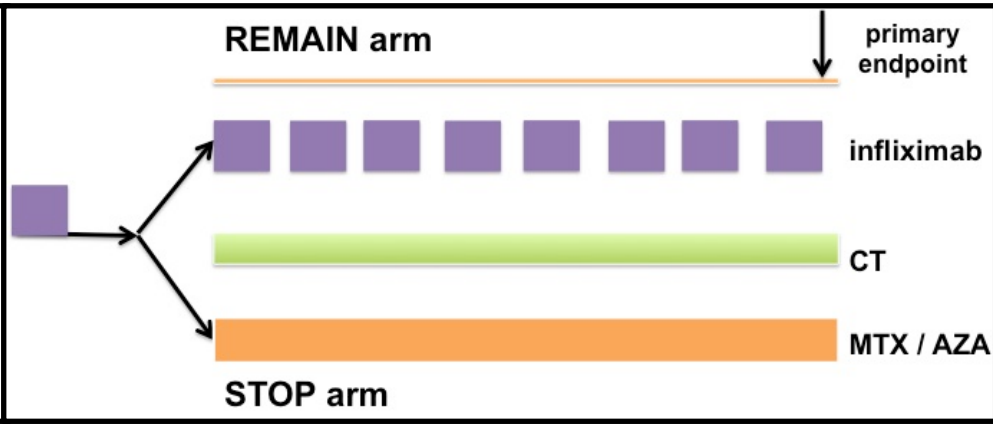
Attention aux formes réfractaires = erreur diagnostique jusqu'à preuve du contraire

En cours…

PHRC N EFIRTES



PHRC N TAWIS

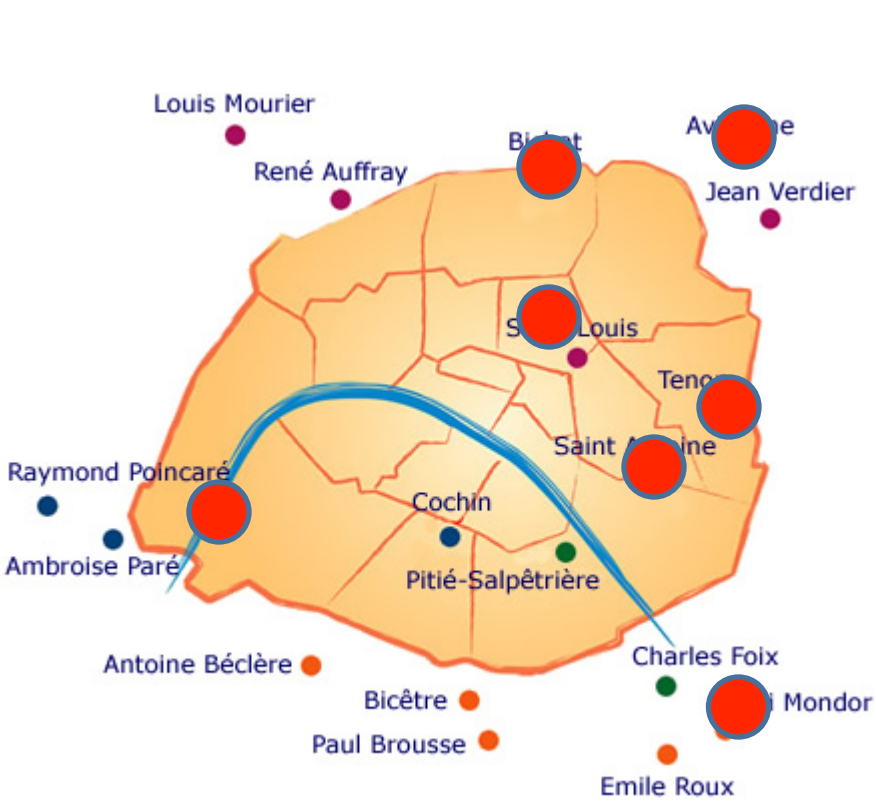


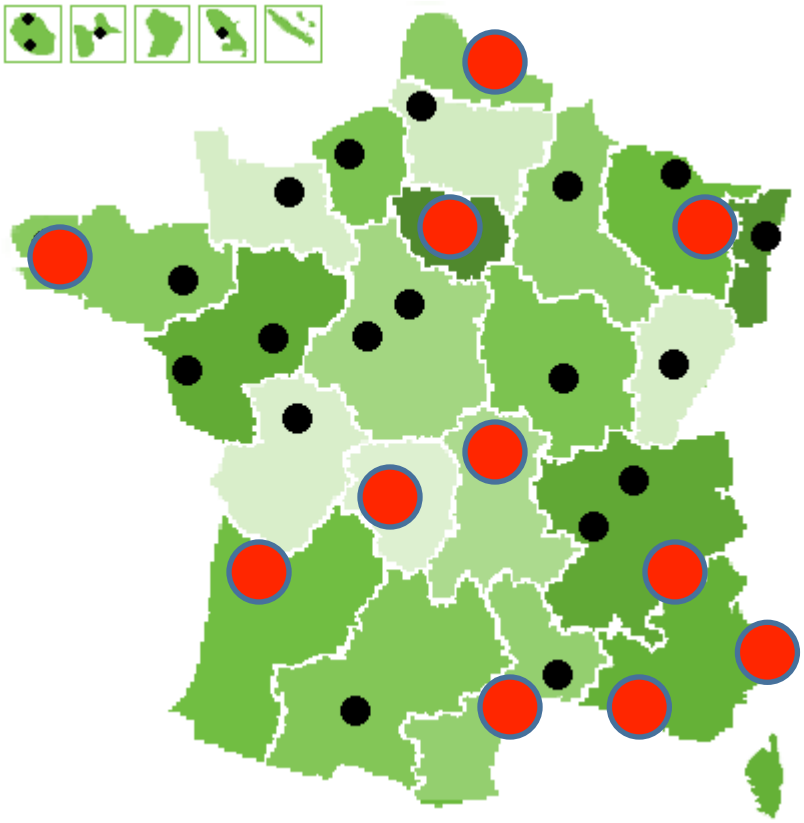
EpiSarc

Scores d'activité

Dosages du TNF-alpha (Simoa) comme marqueur d'activité (CIMI)

IA : apprentissage des règles des experts pour outil diagnostique





Registre prospectif des formes extra-pulmonaires

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RCP sous l'égide de la filière RESPIFIL

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