Maladie de Behçet

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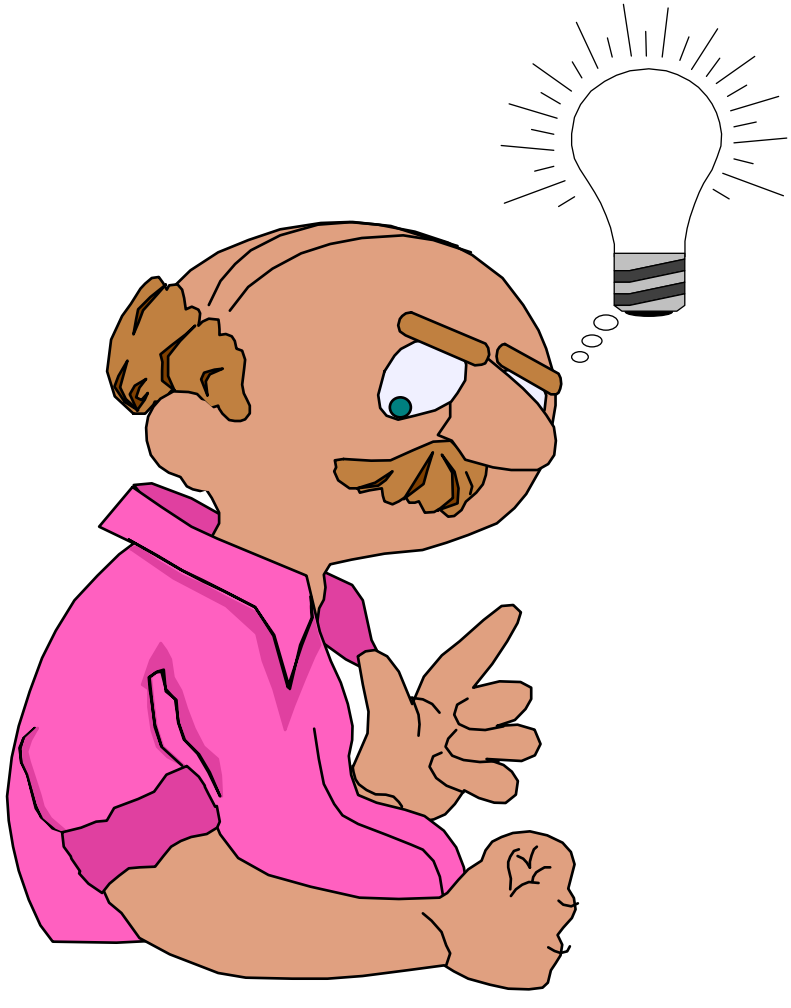
Quel(s) est(sont) le(s) éléments(s) diagnostic(s) à prendre en considération pour la maladie de Behçet?

1. ***Aphtose buccale récidivante,***
2. ***CRP, VS***
3. ***HLA B51***
4. ***Uvéite***
5. ***Hypersensibilité cutanée (Pathergy test)***



LA BIOLOGIE

NFS
VS
HÉMOSTASE
HLA B5
ANTICARDIOLIPINE
ANCA
ASCA

Année de publication	International Study Group	International criteria for Behçet's disease
	1990	2013
Eléments de classification		
Aphtose buccale (AB)	Obligatoire	2 points
Aphtose génitale (AG)	Facultatif	2 points
Atteinte oculaire	Facultatif	2 points
Atteinte cutanée	Facultatif	1 point
Test pathergique positif	Facultatif	1 point
Arthrite/arthralgie		
Atteinte vasculaire		1 point
Thrombophlébite		
Atteinte cardiovasculaire		
Atteinte neurologique		1 point
Atteinte digestive		
Orchi-épididymite		
Critères BD si	AB et au moins 2 items facultatifs	Au moins 4 points

Stratégie thérapeutique de la maladie de Behçet

1. Eliminer les diagnostics différentiels ++

2. Quel patient?

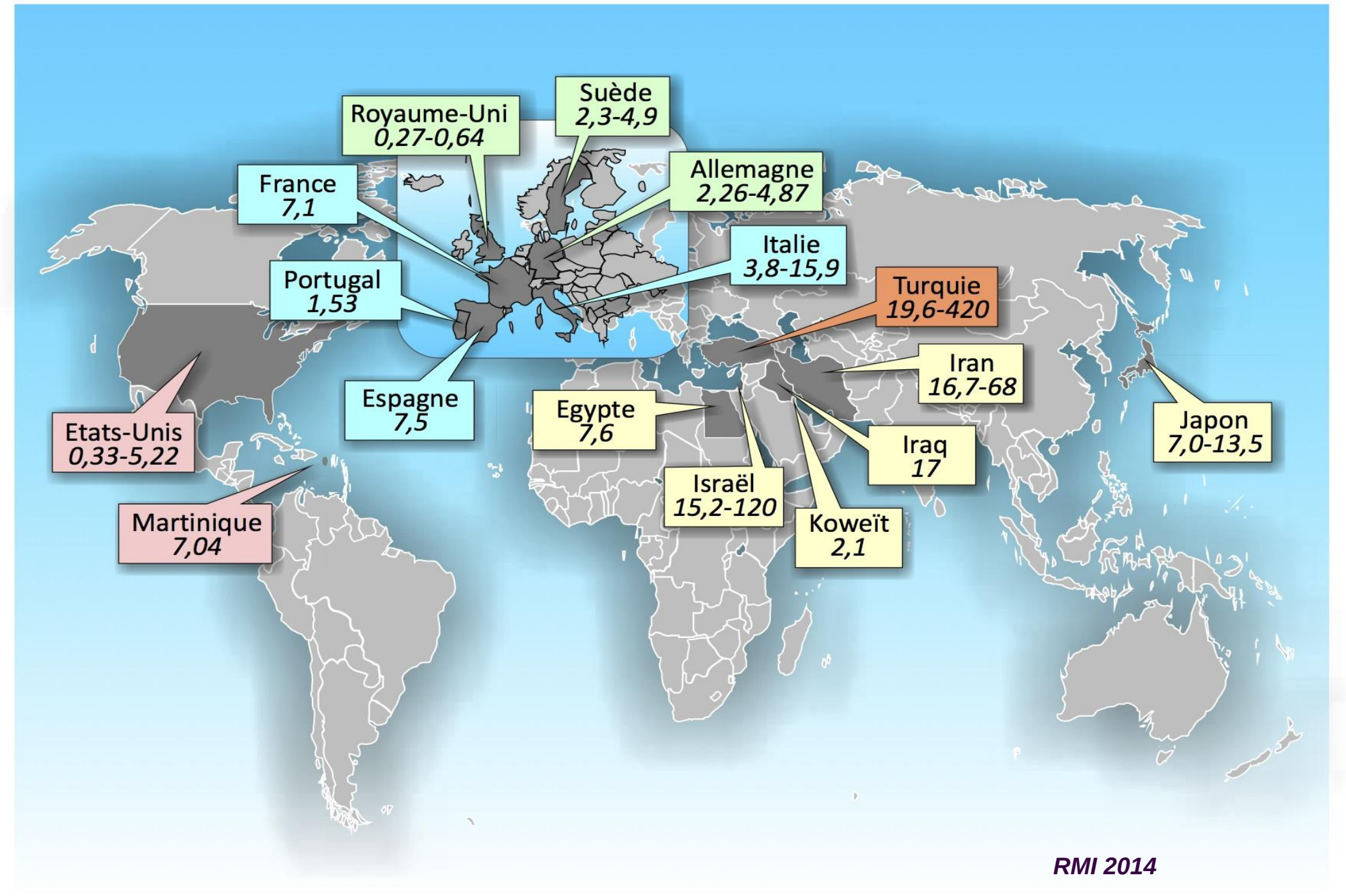
Homme jeune vs femme, Forme B7 sévère vs réfractaire?
Origine géographique (Afrique du nord…), ATCD cancer, BK?, observance…

3. Quel type d'atteinte?

Formes peu sévères	Risque Fonctionnel	Risque Vital
Atteintes cutanéo-muqueues Et/ou Articulaire	Œil+++ SNC	Cardiovasculaire++ SNC

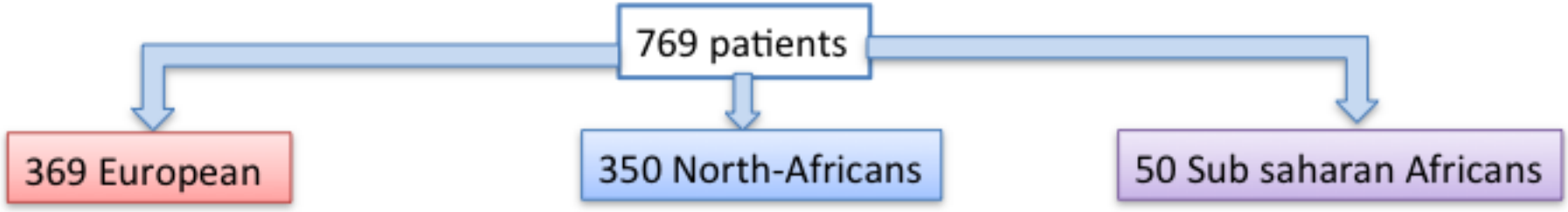
4. Coût du/des traitement(s)

L'origine géographique a-t-elle un impact sur le phénotype de la maladie de Behçet?


Suède
2,3-4,9
Royaume-Uni
0,27-0,64
Allemagne
2,26-4,87
France
7,1
Italie
3,8-15,9
Portugal
1,53
Turquie
19,6-420
Iran
16,7-68
Espagne
7,5
Egypte
7,6
Japon
7,0-13,5
Etats-Unis
0,33-5,22
Iraq
17
Israël
15,2-120
Martinique
7,04
Koweït
2,1
RMI 2014

Ethny and association with disease manifestations and mortality in Behçet's disease

- Monocentric retrospective study
- Clinical records of 769 consecutive patients fulfilling the international criteria of classification for BD were analyzed



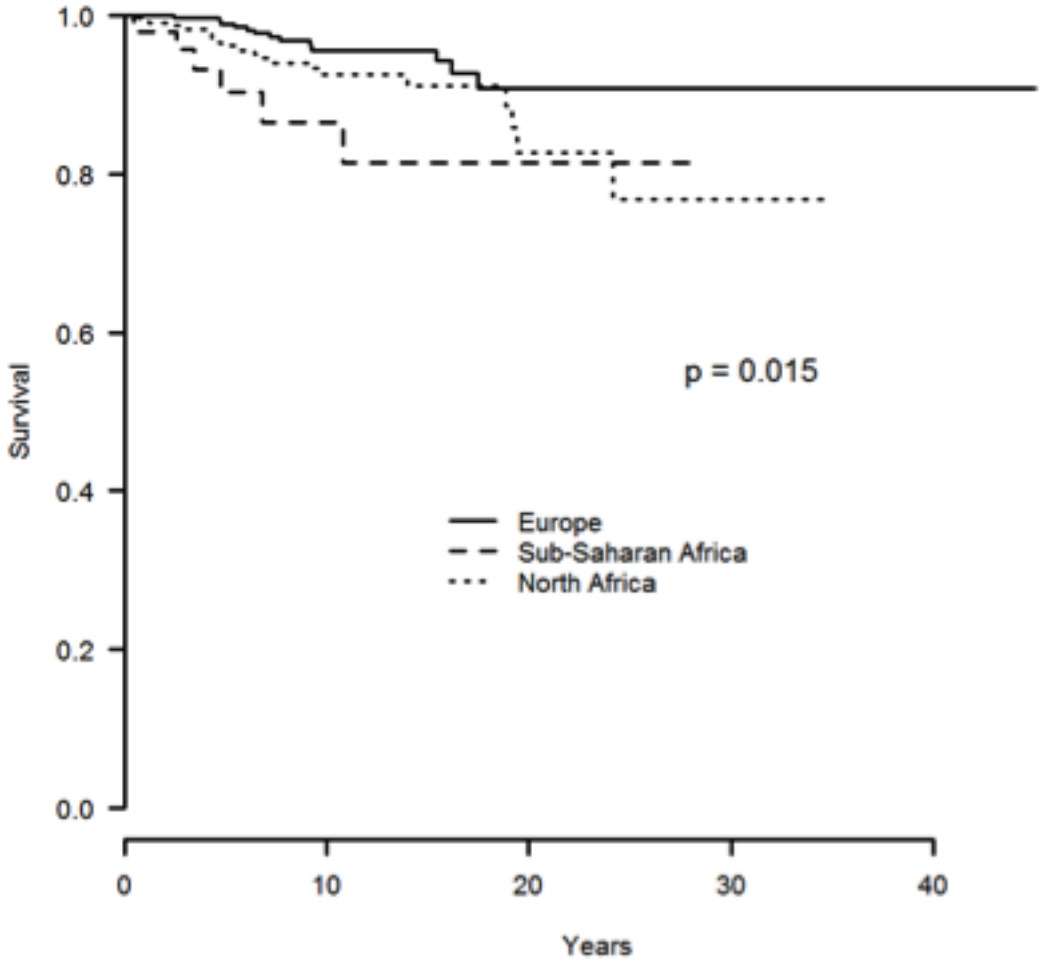
Ethnicity was defined as the country of origin of the patient's parents and grandparents

Savey et al OJRD 2014

Ethny and association with disease manifestations and mortality in Behçet's disease

Parameters	Europe	Sub saharan africa	North africa	*P*
Age at diagnostis (yrs)	30.6	32.2	30.6	0.55
Time from 1st symptoms to Diagnosis (yrs)	3.12 [0.28; 7.95]	1.99 [0.04; 7.68]	1.99 [0.04; 7.68]	0.059
Male gender	193 (52.3%)	39 (78%)	273 (78%)	<0.0001
Genital ucerations	217 (58.8%)	31 (62%)	217 (62%)	0.66
Joint involvement	188 (51.09%)	23 (46%)	163 (46.7%)	0.47
Cardiovascular	152 (41.2%)	27 (54%)	149 (42.57%)	0.22
CNS involvement	108 (29,5%)	24 (48%)	112 (32.3%)	0.035
HLAB51	163/292 (55.8%)	10/34 (29.41%)	119/242 (49.2%)	0.009
Nb of flares	3 (2;5)	3 (2;4.5)	3 (2;5)	0.81
Immunosuppressants	178 (48.24%)	26 (52%)	206 (58.8%)	0.016
Glucocorticosteroids	239 (64.77)	33 (66%)	238 (68%)	0.66
Anticoagulation	27 (7.32%)	2 (4%)	20 (5.71%)	0.63
Death	13 (3.52%)	6 (12%)	21 (6%)	0.029

Ethny and association with disease manifestations and mortality in Behçet's disease



Survival rate :

Sub Saharan Africa:
5 years: 90 %
10 years: 87%
15 years: 81%

North-Africa & Europe:
5 years: 99%
10 years: 96%
15 years: 94%

Savey et al OJRD 2014

Mme M 39 ans

• Behçet diagnostiqué devant une Aphtose bipolaire récidivante, des arthralgies inflammatoires et pseudo-folliculite

Problème d'aphtose bipolaire récidivante et très invalidante (1 à 2 poussées mensuelle très douloureuses)

Quelle(s) mesure(s) thérapeutique(s) proposez vous en première intention?

1. ***Colchicine 1 à 2mg/j***
2. ***Traitements symptomatiques locaux.***
3. ***Prednisone 40mg/j PO***
4. ***Imurel (2mg/kg/j)***
5. ***Roféron 9mUI/semaine sc***

Yurdakul et al A&R 2001

A double-blind trial of colchicine in Behçet's syndrome.

- *116 patients BD (60H/56F) avec manifestations cutanéo-muqueuses actives et sans atteinte oculaire ni atteinte d'organe majeur.*
- *Colchicine (1 à 2mg/j selon poids) vs placebo pendant 2 ans*
- *Objectifs: survie sans lésions cutanéo-muqueuses et articulaires*

Résultats : *45H et 39F, 72% suivis jusqu'à 24 mois*

•Diminution nombre poussées d'aphtose buccale et génitale, de lésions papulo-pustuleuses, de lésions nodulaires (EN) et d'arthrites chez les femmes

•Diminution nombre poussées d'arthrites chez les hommes

•Effets secondaires équivalents entre Colchicine et placebo

Aktulga et al Haematologica 1980

A double-blind study of colchicine in Behçet's disease.

- *28 patients BD avec manifestations cutanéo-muqueuses actives et sans atteinte oculaire ni d'organe majeur.*
- *Colchicine (1.5 mg/j) vs placebo pendant 6 mois*

Résultats :

•Diminution nombre poussées de lésions nodulaires (EN) et d'arthrites

•Effets secondaires équivalents entre Colchicine et placebo

Les ulcérations buccales et génitales persistent sous Colchicine 2mg/j et traitements locaux. Quelle(s) solution(s) thérapeutique(s) pouvez vous proposer ?

1. ***Torental LP 400mg x2/j***
2. ***Dapsone 100mg/j***
3. ***Prednisone 40mg/j PO***
4. ***Thalidomide***
5. ***AINS***
6. ***Anti-TNFa***

Sharquie et al J Dermatol 2002

Dapsone in Behçet's disease: a double-blind, placebo-controlled, cross-over study

- ***20 patients BD avec manifestations cutanéo-muqueuses actives et sans atteinte oculaire ni atteinte d'organe majeur.***
- ***Dapsone (100mg/j) vs placebo pendant 3 mois puis cross over pendant 3 mois***

<u>Résultats :</u>

Diminution significative du nombre de poussées d'aphtose buccale et génitale, et des lésions cutanées dans le groupe Dapsone

Hamuryudan et al Annal Intern Med 1998

Thalidomide in the treatment of mucocutaneous lesions of the Behçet's syndrome: a randomized, double-blind, placebo-controlled trial

- ***96 (H) patients BD avec manifestations cutanéo-muqueuses actives et sans atteinte d'organe majeur.***
- ***Thalidomide (100mg/j, n=32) vs Thalidomide (300mg/j, n=32) vs placebo (n=32) pendant 24 semaines***

Table 2. Study Outcomes*

Outcome	Placebo Group (*n* = 32)	100-mg Thalidomide Group (*n* = 32)	300-mg Thalidomide Group (*n* = 31)	*P* Value†
	← *n* (%) →			
Sustained absence of any oral or genital ulceration				
At visits and between visits	0 (0) [0–10.9]	2 (6.3) [0.8–20.8]	5 (16.1) [5.5–33.7]	0.031
At visits only	0 (0) [0–10.9]	10 (31) [16.1–50]	9 (29) [14.2–48]	0.001
Activation in either eye	9 (28) [13.7–46.7]	2 (6.3) [0.8–20.8]	3 (9.7) [2–25.8]	0.041
Visual acuity scorings other than perfect	5 (15.6) [5.3–32.8]	1 (3.1) [0–16.2]	0 (0) [0–11.2]	0.045

Hamuryudan et al Annal Intern Med 1998

Thalidomide in the treatment of mucocutaneous lesions of the Behçet's syndrome: a randomized, double-blind, placebo-controlled trial

- ***Pas de différence significative d'efficacité entre Thalidomide 100 et 300mg/j***
- ***Efficacité persistante pendant la durée du traitement mais rechutes précoces à l'arrêt***
- ***Polyneuropathies (n=4 patients, dont 3 avec Thali 300mg/j et 1 avec Thali 100mg/j)***

Mme M 39 ans suite et fin

- ***Behçet diagnostiqué devant une Aphtose bipolaire récidivante, des arthralgies inflammatoires et pseudo-folliculite***

Colchicine plus Torental (echec)
Thalidomide 100mg/j (neuropathie)
Imurel puis MTX et CT 10mg/j (echec AB et articulations)
Efficacité des anti-TNF (Humira 40mg/15j sc)

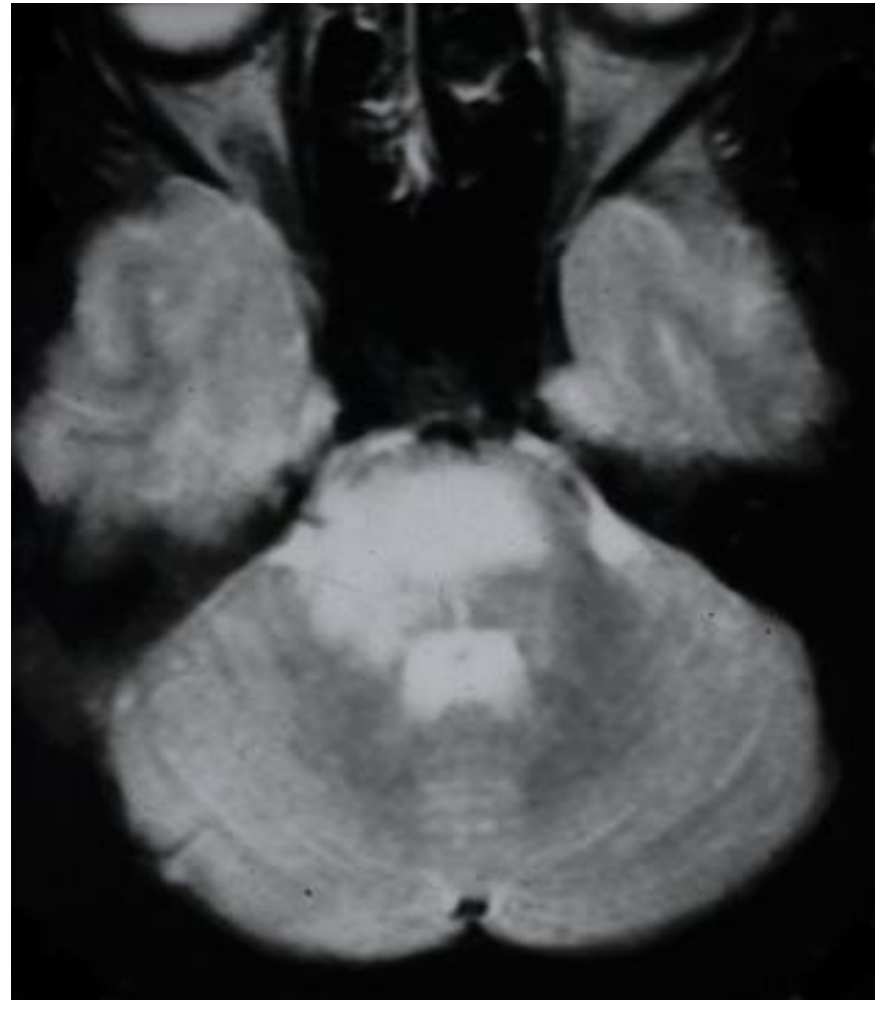
Mr A 41 ans

Behçet diagnostiqué en réanimation devant

•une Aphtose buccale récidivante,

•des arthralgies inflammatoires et

• une rhombencéphalite (diplopie, dysarthrie, troubles de la déglutition, ataxie, hémiparésie G)



Patient sous assistance respiratoire

Quel Traitement?

Mr A 41 ans

- ***3 bolus Solumédrol (1g) puis relais 1mg/kg/j et décroissance progressive***
- ***Cyclophosphamide IV (6 cures) puis relais Imurel (2.5mg/kg/j)***

Guérison sans séquelles cliniques

Traitements utilisés dans le neuro-Behçet…

- **Corticoides**

Hamza M et al. *Ann Med Interne* 1992;143:438-441

- **Endoxan**

Du LT et al. *Presse Med* 1990;19:1355-1358

- **Imurel**

Yazici H et al. *NEJM* 1990;322:281-285. Hamuryudan V et al. *Arthritis Rheum* 1997;40:769-774

- **MTX**

Hirohata S et al. *J Neurol Sci*1998;159:181-185. Kikuchi H et al. *Adv Exp Med Biol* 2003;528:575-578

- **Anti-TNF**

Borhani-Haghigih A et al. *Clin rheumatol* 2011;30:1007-12
Pipitone N et al. *Arthritis Rheum* 2008;59:285-290
Sfikakis PP et al. *Rheumatology (Oxford)* 2007;46:736-741

- **Thalidomide**

Ranselaar CG et al. *Br J Dermatol* 1986;115:367-70

Traitements utilisés dans le neuro-Behçet…

- **Pas de consensus réel**
- Recommendations EULAR (Hatemi G, ARD 2008)

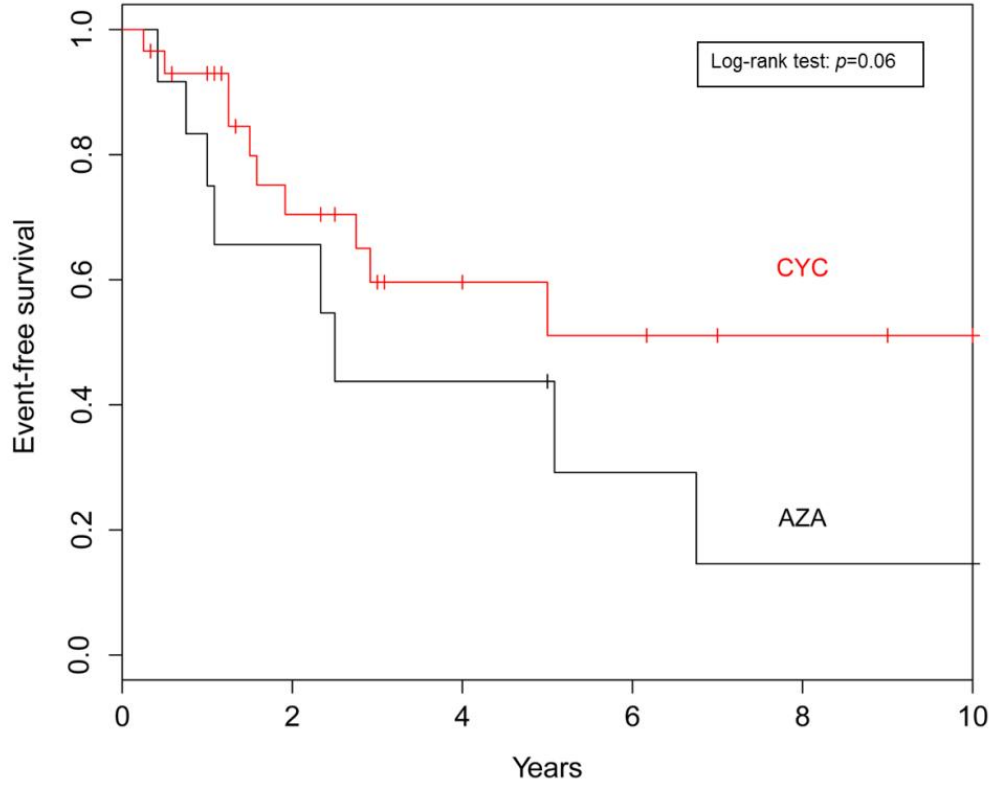
Corticoides plus IFNa ou AZA ou CYC ou MTX ou aTNF

- **Formes peu sévères:**
  - Corticoïdes (prednisone 1mg/kg/j)
  - Immunosuppresseurs (AZA, MMF, MTX…)
- **Formes sévères d'emblée (Rankin initial ≥ 3):**
  - Impact du cyclophosphamide i.v. en première ligne?
  - Données suggérées par les recommandations européennes

Quel immunosuppresseur?

- Globalement, pas d'impact dans les formes peu sévères

Patients sévères au diagnostic (Rankin initial ≥3)



EFS groupe CYC

1 an: 93%

5 ans: 56%

7 ans: 56%

10 ans: 56%

EFS groupe AZA

1 an: 75%

5 ans: 44%

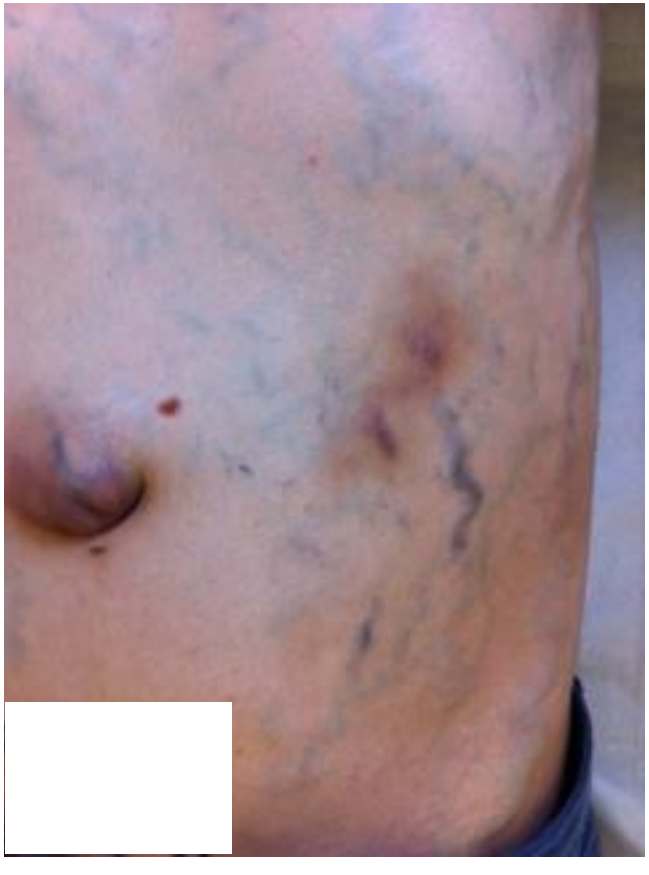
7 ans: 15%

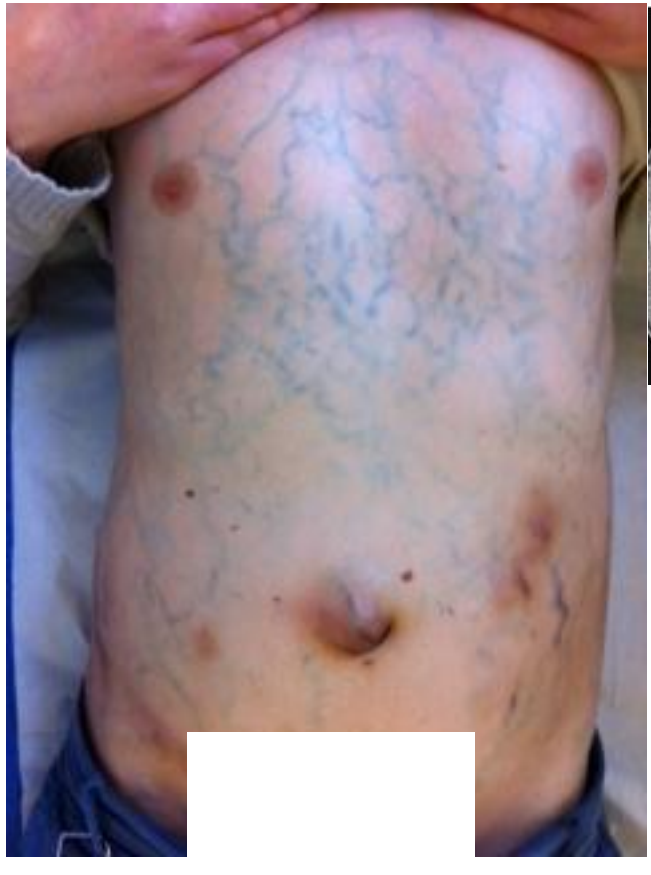
10 ans: 15%

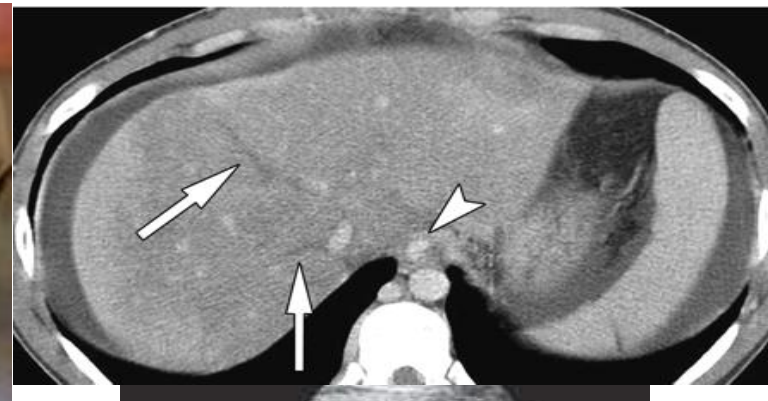
Noel et al Arthritis & Rheumatology 2014

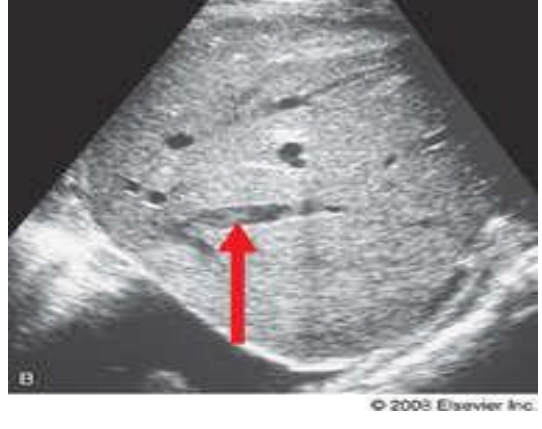
Mr A 36 ans

AB récidivants, pseudofolliculite, douleurs abdominales fébriles, syndrome oedémateux. Quel Traitement?







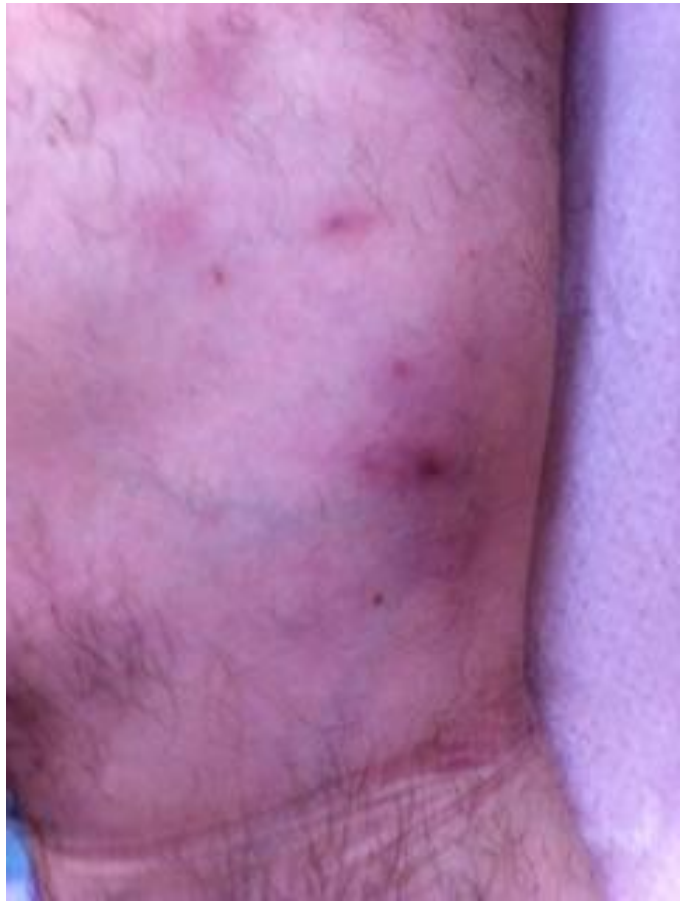


Mr A 41 ans

- ***3 bolus Solumédrol (1g) puis relais 1mg/kg/j***
- ***Cyclophosphamide IV (6 cures)***
- ***Anticoagulation efficace,***
- ***Ligatures de VO itératives, traitement HTP***

Mr A 41 ans (suite)

Rechute à C6 Endoxan et sous prednisone 20mg/j. Thrombose iliofémorale bilatérale, épisodes d'EH et thrombophlébites superficielles.



- ***Remicade (5mg/kg S0, S2, S6 puis tous les S5) et stabilisation IHC et HTP.***
- ***Behçet quiescent***
- ***Retirer liste TH***

Recommendations EULAR 2008
Traitement maladie Behçet

Thombose veineuse membre	Corticoides ± Imurel
Thombose veineuse gros Vx	Corticoides plus Endoxan
Thombose veineuse cérébrale	Corticoides

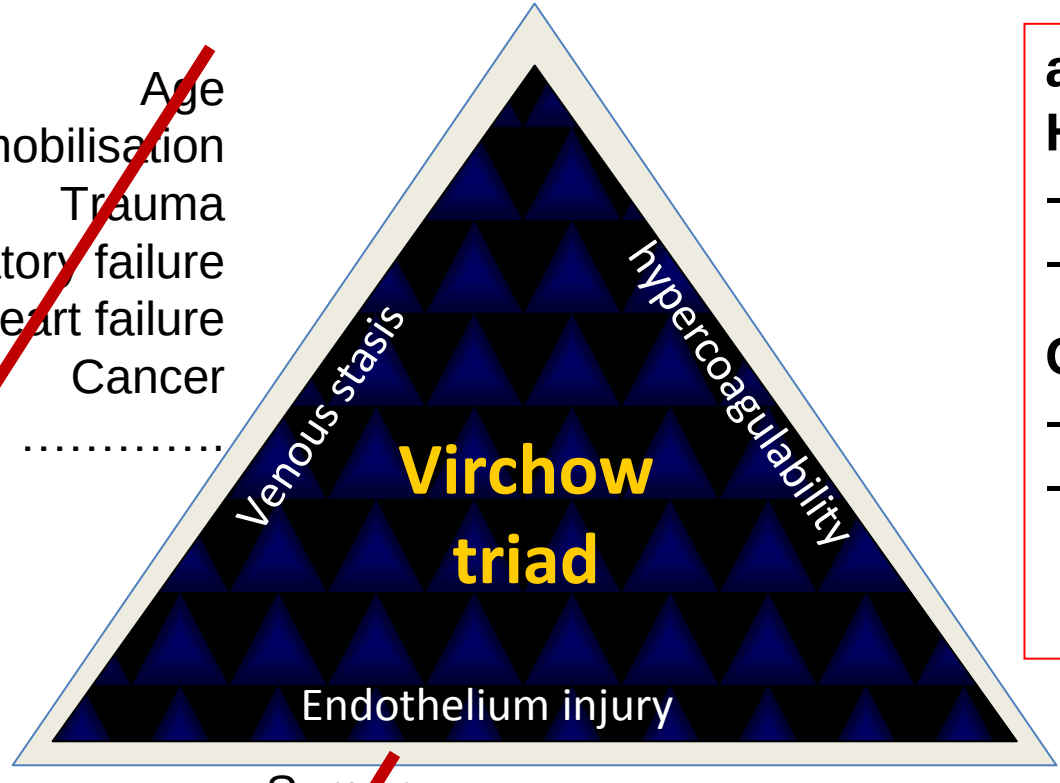
Quid de l'anticoagulation?

Atteinte anévrysmale	Corticoides plus Endoxan ou Imurel

Quid de l'anticoagulation?

Pathogenesis of thrombosis in Behçet's disease

Age
Immobilisation
Trauma
Respiratory failure
Heart failure
Cancer
……



Surgery
Trauma
Sepsis
Vasculitis

aPL ➔ inconsistent data
Hyperhomocysteinemia
-Negative studies
-Positive metaanalysis

Genetic thrombophilia
-Negative studies +++
-Positive studies : Turkey
-Factor V Leiden
-Factor II mutation

ML Regina et al. Arterioscl Thrombo Vasc Biol 2010
Houman H et al. Adv Exp Med Biol 2003,
Ozdemir R et al. Am J Cardiol 2004
Leiba M et al. Ann Rheum Dis 2004
Ates A et al. Pathophysiol Haemost Thromb 2003
Espinosa G et al. Am J Med 2002
Mader R et al. J Rheumatol 1999
Gull et al. Br J Rheumatol 1996; Rheumatol 1999

Management of venous thrombosis in Behcet's

No RCT
Observational studies
Retrospective analysis

The EULAR recommandations

Hatemi G et al. Ann Rheum Dis 2008

Corticosteroids ± Immunosuppressive agents

yes

- Bleeding risk +++
30% associated aneurisms
- Low risk of « PE »
inflammatory thrombus
- No thrombophilic factors
- Relapses on VKA

Anticoagulant

« non »

Immunosuppressants Reduce Venous Thrombosis Relapse in Behçet's Disease

Table 4. Factors associated with venous thrombosis relapse*

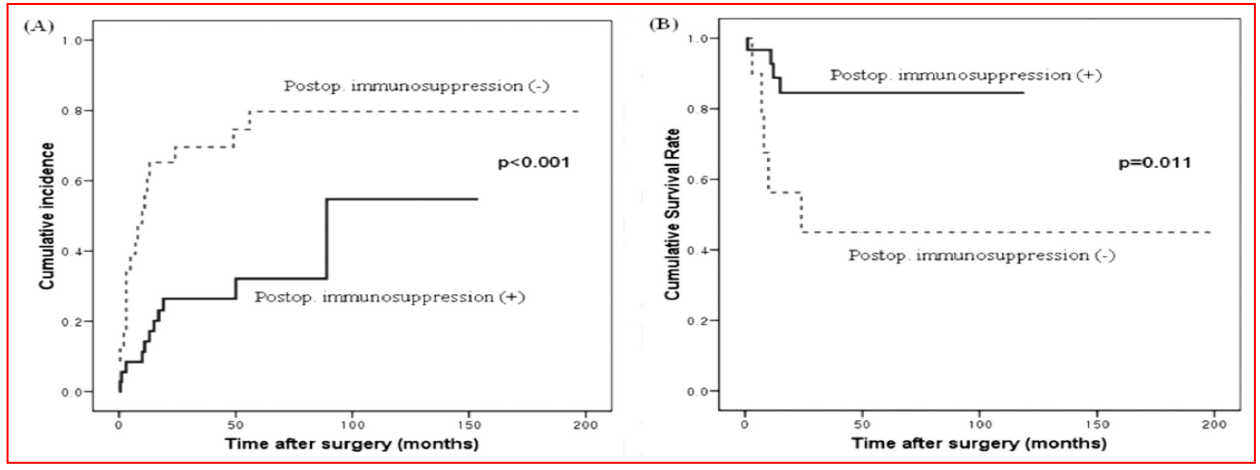
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	0.99 (0.97–1.01)	0.30	–	–
Location/type of thrombosis				
Upper limb veins	0.96 (0.35–2.6)	0.94	–	–
Lower limb veins	1.28 (0.86–1.92)	0.23	–	–
Pulmonary embolism	0.93 (0.56–1.56)	0.79	–	–
Cerebral veins	1 (0.58–1.73)	0.99	–	–
Cervical veins	0.91 (0.33–2.45)	0.84	–	–
Superior vena cava	0.97 (0.43–2.2)	0.94	–	–
Inferior vena cava	0.6 (0.31–1.15)	0.12	–	–
Budd-Chiari syndrome	1.52 (0.37–6.21)	0.56	–	–
Right atrium	1.34 (0.19–9.59)	0.77	–	–
Right ventricle	0.62 (0.09–4.44)	0.63	–	–
Other locations	0.37 (0.12–1.15)	0.086	–	–
Associated involvement				
Oral ulcerations	0.27 (0.04–1.94)	0.19	–	–
Genital ulcerations	1.12 (0.79–1.6)	0.52	–	–
Articular	1.05 (0.74–1.49)	0.78	–	–
Ocular	0.82 (0.58–1.15)	0.24	–	–
Neurologic	1.52 (1.07–2.14)	0.018	2.07 (1.36–3.15)	0.0028
Arterial	1.06 (0.69–1.62)	0.79	–	–
Cardiac	0.72 (0.35–1.47)	0.36	–	–
Treatment				
Glucocorticoids	0.71 (0.47–1.07)	0.099	0.62 (0.40–0.97)	0.058
Immunosuppressive agents	0.26 (0.14–0.49)	<0.0001	0.27 (0.14–0.52)	0.00021

Desbois et al Arthritis & Rheumatology 2012

Peripheral artery aneurysms / surgery

Aggressive medical treatment
Corticosteroids + IS
peri et post-operatory

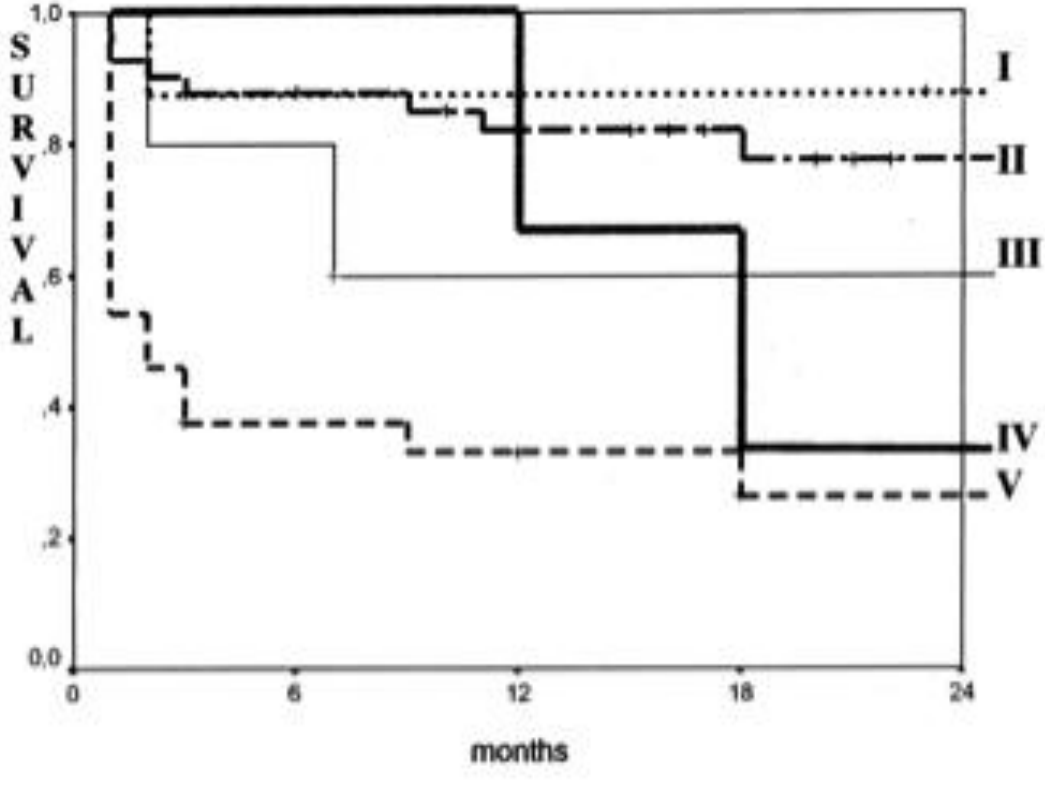
- Surgery
  - Mortality : 5-30% -
  - Anastomotic relapses: 50% 0-10%
  - Graft thrombosis : 40% 10-15%



MC Park et al. Clin Rheumatol 2007
HJ. Ho et al. Clin Exp Rheum 2012

Pulmonary Vasculitis in Behçet Disease*: A Cumulative Analysis

Chest. 2005;127(6):2243-2253. doi:10.1378/chest.127.6.2243



Embolization ± IS (n=8)

IS (n=36)

AC ± IS (n=5)

Embolization, AC, IS (n=3)

Surgery ± IS (n=19)

Figure Legend:

Quid de la Chirurgie?

Interventions cardiothoraciques	n=221
Chirurgie Cardiovasculaire	**176 (79%)**
Valve	74 (42)
IAo	60
Anévrysme	58 (33)
Aorte	40
Art coronaire	7
Art Pulmonaire	7
Thrombus (VD et OD)	23 (13)
Pontage coronaire	10 (5.7)
Geste Endovasculaire	**31 (14%)**
Embolisation Art Pulm	11
Stent coronaire	8
Stent V cave	3

Complications post-opératoires	n=44 22%	Réintervention 11%	Mortalité 15%
Déhiscence prothèse valvulaire	23 (52)	10 (52.6)	7 (70)
Occlusion	7 (16)	2 (10)	0
Thrombose	3 (7)	0	0
Anévrysme	5 (11)	3 (16)	1 (10)
Autre	6 (14)	4 (21)	2 (20)

Yuan Clin Exp Rheum 2014

Lesquel(s) de ces traitements peut(vent) être utilisé(s) dans le traitement d'une uvéite postérieure (sans critère de gravité) du Behçet?

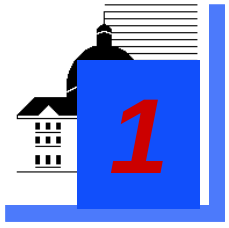
1. ***Infliximab***
2. ***Etanercept***
3. ***Adalimumab***
4. ***Corticoides seuls***
5. ***Corticoides plus Azathioprine***

EULAR Recommendations for the Management of Behçet's Disease

Report of a Task Force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT)

G. Hatemi, A. Silman, D. Bang, B. Bodaghi, A. M. Chamberlain, A. Gul, M. H. Houman, I. Kötter, I. Olivieri, C. Salvarani, P. P. Sfikakis, A. Siva, M. R. Stanford, N. Stübiger, S. Yurdakul and H. Yazici

Ann Rheum Dis 2008



Any patient with BD and inflammatory eye disease affecting the posterior segment should be on a treatment regime, which includes azathioprine and systemic corticosteroids

*Category of evidence**: Ib***

*Strength of Recommendation**: A/D***

Level of Agreement:

among the whole group: 9.57 ± 0.51

among "experts": 9.73 ± 0.47 (n=11)

Azathioprine in Severe Uveitis of Behçet's Disease

D. SAADOUN,[1] B. WECHSLER,[1] C. TERRADA,[1] D. HAJAGE,[2] D. LE THI HUONG,[1] M. RESCHE-RIGON,[2] N. CASSOUX,[1] P. LE HOANG,[1] Z. AMOURA,[1] B. BODAGHI,[1] AND P. CACOUB[1]

Table 1. Characteristics of the 157 patients with BD*

	Value
Age at diagnosis, mean ± SD years	29.9 ± 10.1
Male sex	112 (71.3)
Ethnic origin	
North Africa	70 (44.6)
Africa	5 (3.2)
Europe	77 (49.0)
Others	5 (3.2)
HLA–B5 (n = 120)	73 (60.8)
Characteristics of uveitis	
Unilateral	25 (15.9)
Bilateral	132 (84.1)
Panuveitis	66 (42.0)
Retinal vasculitis	54 (34.4)
Clinical features of BD	
Oral ulcerations	157 (100)
Genital ulcerations	83 (52.9)
Arthralgias	80 (51.3)
Skin lesions	97 (61.8)
Arterial involvement	13 (8.3)
Venous thrombosis	39 (24.8)
CNS involvement	52 (33.3)

* Values are the number (percentage) unless otherwise indicated. BD = Behçet's disease; CNS = central nervous system.

Arthritis 2010

Azathioprine in Severe Uveitis of Behçet's Disease

D. SAADOUN,[1] B. WECHSLER,[1] C. TERRADA,[1] D. HAJAGE,[2] D. LE THI HUONG,[1] M. RESCHE-RIGON,[2] N. CASSOUX,[1] P. LE HOANG,[1] Z. AMOURA,[1] B. BODAGHI,[1] AND P. CACOUB[1]

Table 4. Comparison of patients with Behçet's disease and severe uveitis who were complete responders versus partial/nonresponders*

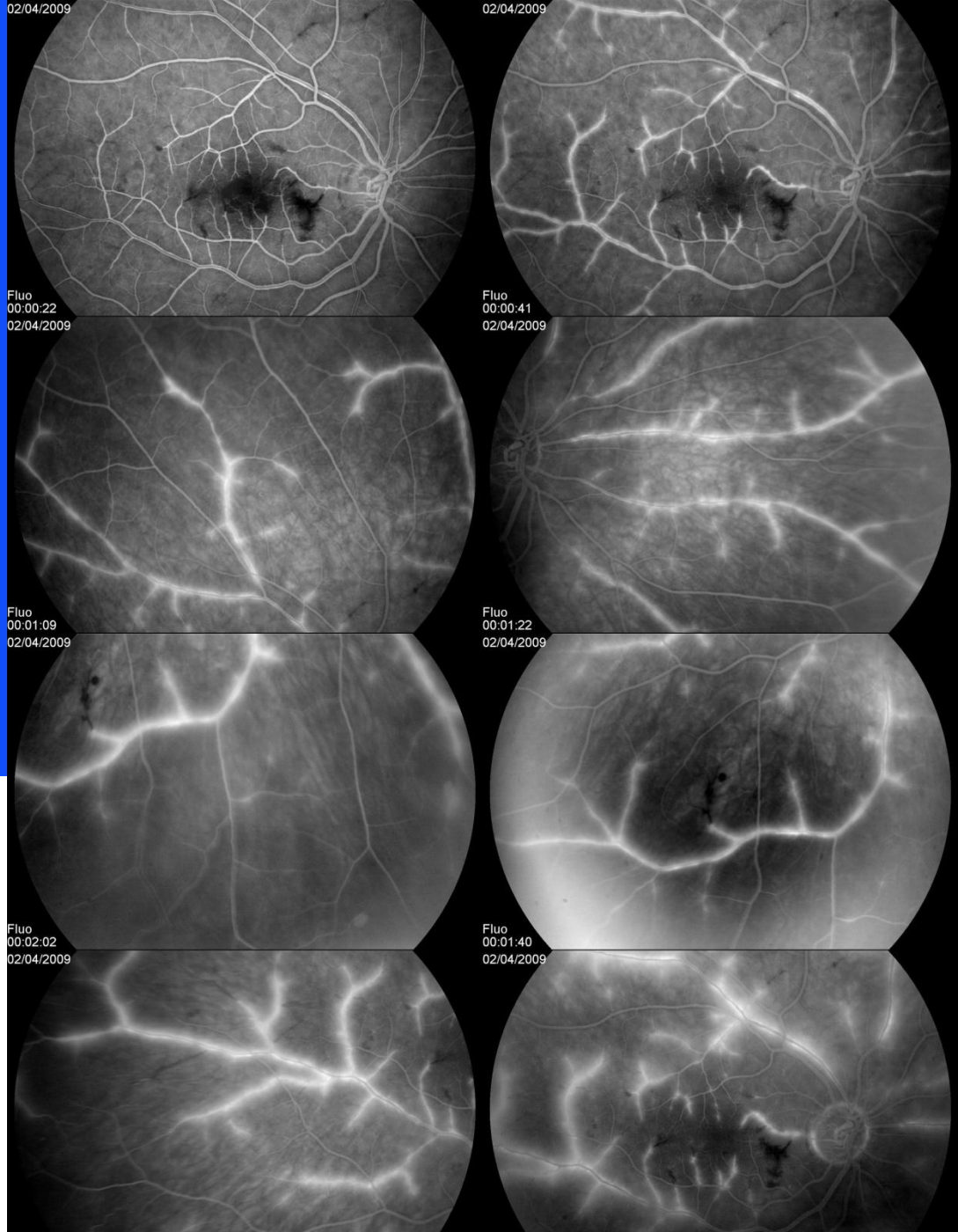
	All (n = 157)	Complete responders (n = 81)	Partial/nonresponders (n = 76)	OR (95% CI)	*P*
Age, mean ± SD years	29.9 ± 10.1	29.3 ± 9.3	30.7 ± 10.9	0.98 (0.9–1.1)	0.37
Male sex	112 (71.3)	56 (69.1)	56 (73.7)	0.80 (0.4–1.7)	0.59
HLA–B5	72 (60.5)†	36 (60)	36 (61)	0.95 (0.4–2.1)	1
Previous immunosuppressant	31 (19.7)	14 (17.3)	17 (22.4)	0.71 (0.5–3.1)	0.55
Retinal vasculitis	54 (34.4)	21 (25.9)	33 (43.4)	0.45 (0.2–0.9)	0.02
Bilateral uveitis	132 (84.1)	66 (81.5)	66 (86.8)	0.66 (0.2–1.7)	0.39
Visual acuity, mean ± SD	4.3 ± 3.6	5.4 ± 3.2	3.1 ± 3.4	0.28 (0.2–0.7)	< 0.0001
Oral ulceration	157 (100)	81 (100)	76 (100)	–	–
Genital ulceration	83 (52.9)	40 (49.4)	43 (56.6)	0.75 (0.4–1.5)	0.42
Articular involvement	80 (51.3)	42 (51.9)	38 (50.7)	1.04 (0.5–2.1)	1
Venous involvement	39 (24.8)	23 (28.4)	16 (21.1)	1.48 (0.6–3.3)	0.35
Arterial involvement	13 (8.3)	10 (12.5)	3 (3.9)	1.47 (1.2–1.7)	0.08
CNS involvement	52 (33.3)	32 (39.5)	20 (26.7)	1.78 (0.8–3.7)	0.12

* Values are the number (percentage) unless otherwise indicated. OR = odds ratio; 95% CI = 95% confidence interval; CNS = central nervous system.
† N = 120.

Arthritis 2010

Mr C 26 ans

- Vasculite rétinienne OD
AV 1/10eme
- Aphtose Buccale récidivante,
- Pseudo Folliculite



Lesquel(s) de ces traitements peut(vent) être utilisé(s) dans le traitement de cette atteinte oculaire grave du Behçet?

1. ***Corticoides plus Infliximab***
2. ***Corticoides plus Cyclophosphamide***
1. ***Corticoides plus IFNa***
1. ***Corticoides seuls***
2. ***Corticoides plus Azathioprine***

If the patient has severe eye disease defined as >2 lines of drop in visual acuity on a 10/10 scale and/or retinal disease, (retinal vasculitis or macular involvement), it is recommended that either cyclosporine A or infliximab be used in combination with azathioprine and corticosteroids; alternatively interferon-alpha with corticosteroids could be used

*Category of evidence**: II***

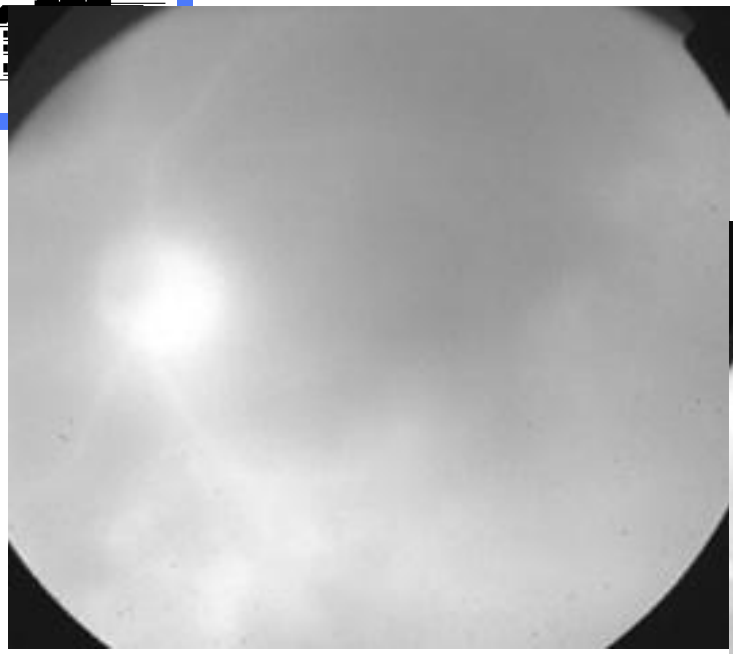
*Strength of Recommendation**: C/D***

Level of Agreement:

among the whole group: 8.71 ± 0.91

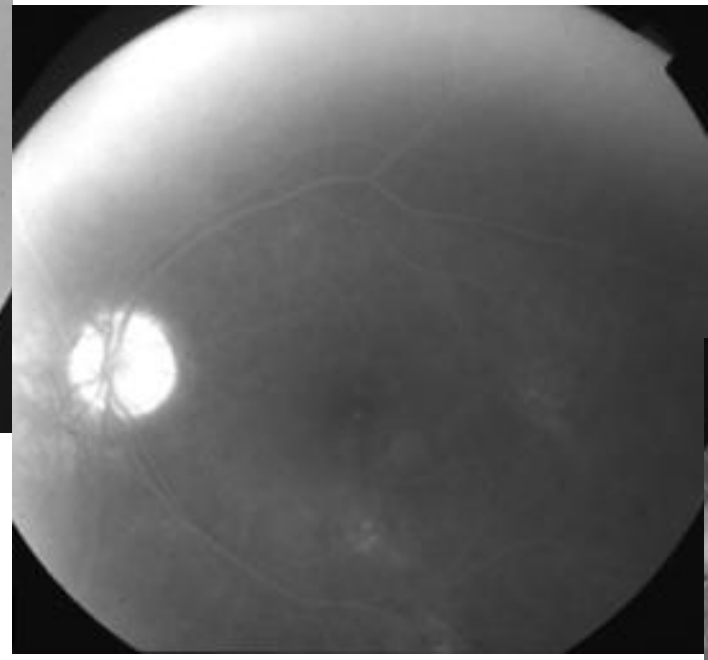
among "experts": 8.9 ± 0.83 (n=11)

INFLIXIMAB



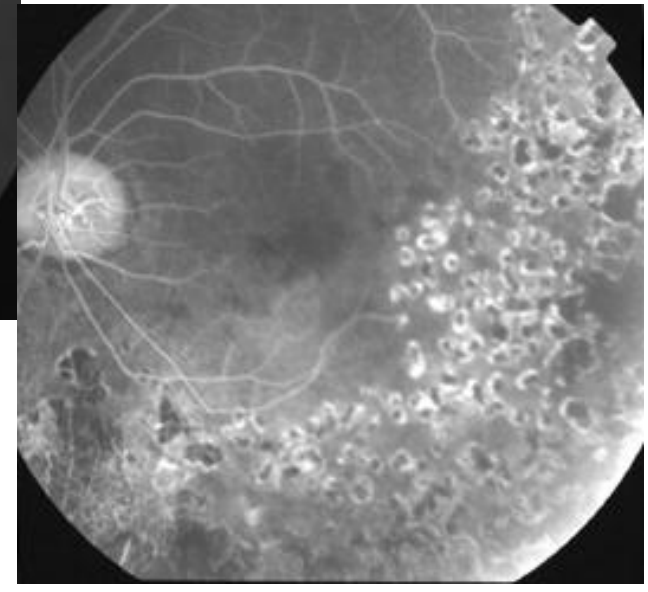
10/2

Rechute sous EDX
Hyalite++



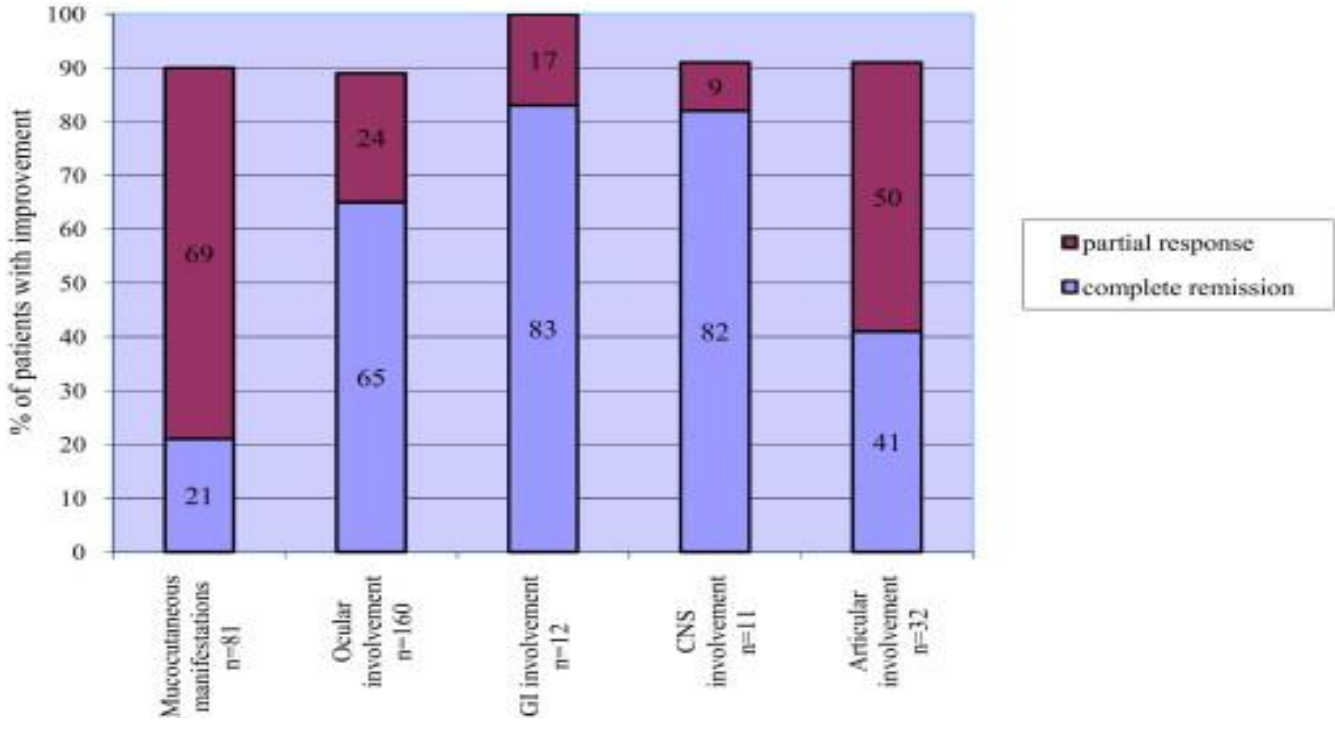
10/4

48h après aTNFa



10/25

S3 après aTNFa

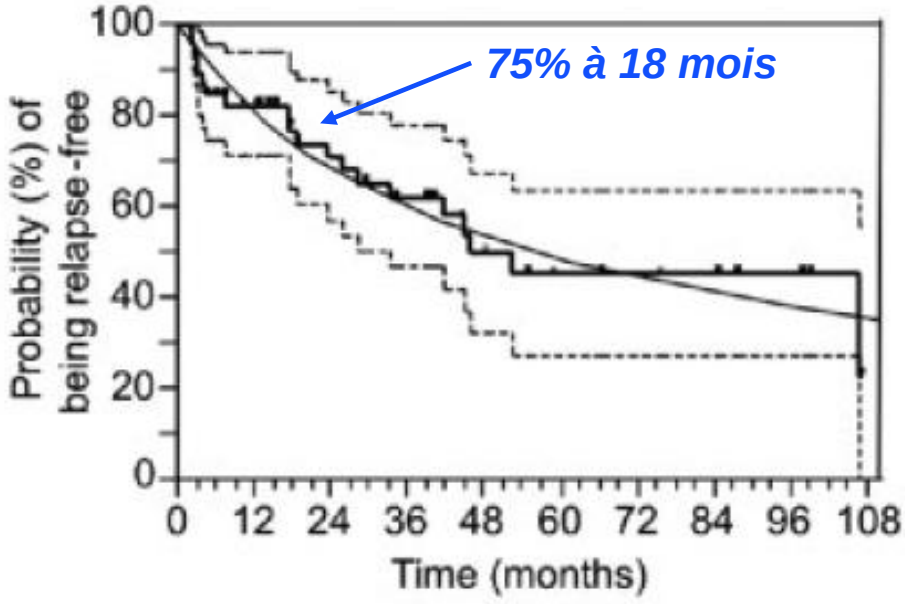


Organ-specific response to repetitive infliximab infusions in 174 patients with refractory BD enrolled in prospective studies, describing 5 or more patients each (median follow up of 16.2 ± months).
369 patients in total – 325 infliximab 37etanercept 28 adalimumab

Arida et al Semin Arthritis Rheum, 41 2011, 61-70

Long-Term Remission After Cessation of Interferon-α Treatment in Patients With Severe Uveitis Due to Behçet's Disease

Christoph M. E. Deuter,[1] Manfred Zierhut,[1] Antje Möhle,[1] Reinhard Vonthein,[2] Nicole Stübiger,[1] and Ina Kötter[1]



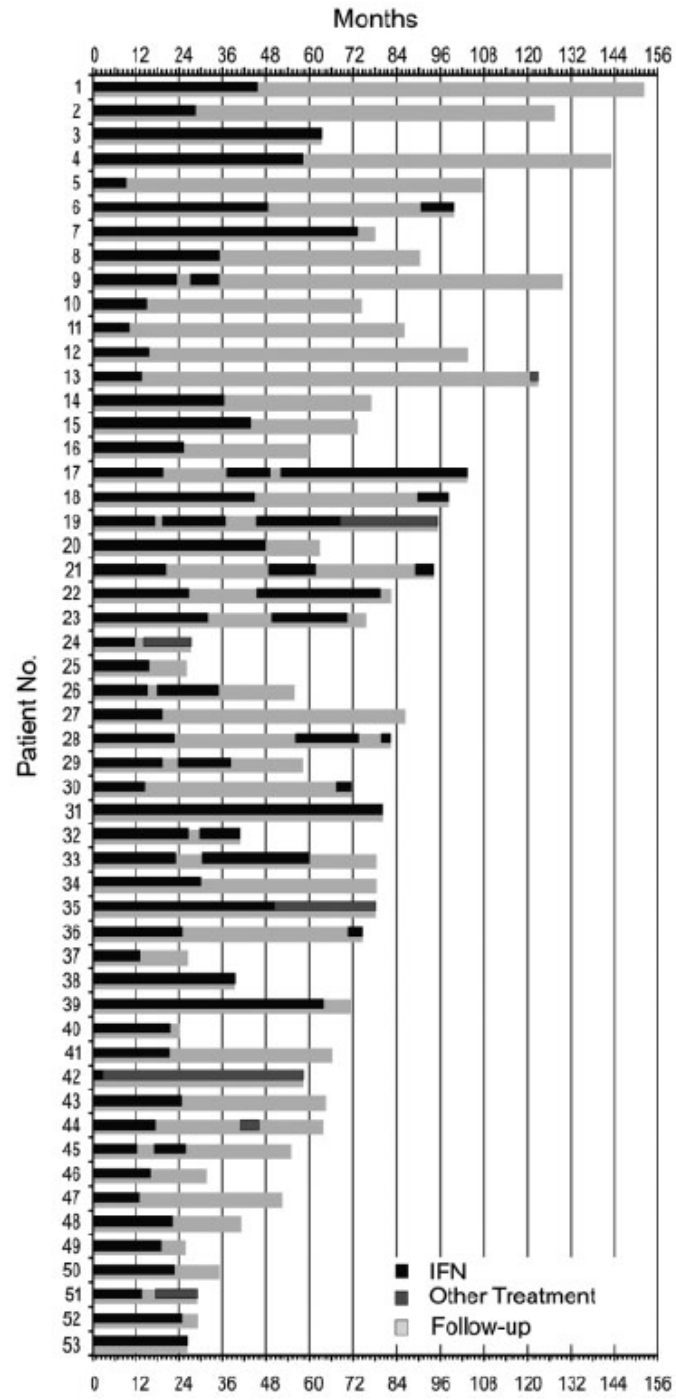


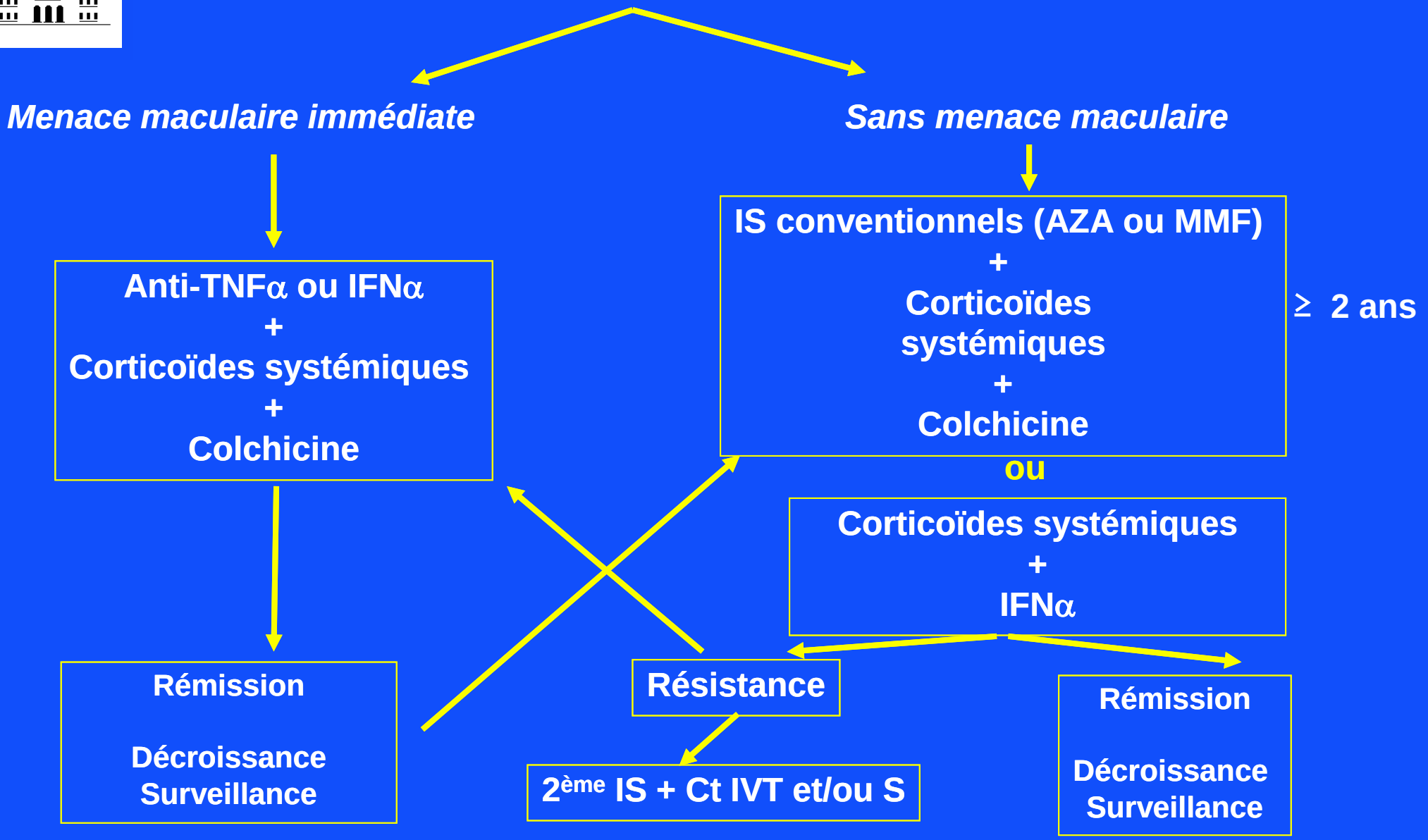
Tableau 50-IV. Études ouvertes évaluant l'interféron α pour le traitement des uvéites associées à la maladie de Behçet.

Auteur Pays	Kotter [29] Allemagne	Tugal-Tutkun [55] Turquie	Gueudry [19] France	Krause [30] Allemagne	Sobaci [47] Turquie	Deuter [15] Allemagne	Onal [40] Turquie
Nombre de patients	50	44	32	45	53	53	37
Dose initiale IFN-α2a (MUI)	6/jour	6/jour	3 × 3/semaine	6-9 × 3/semaine	4,5 × 3/semaine	6/jour	3/jour
Rémission complète	46 (92 %)	40 (91 %)	28 (88 %)	62/79* (78 %)	45 (85 %)	52 (98 %)	35 (95 %)
Pas de rechute sous traitement d'entretien	41 (82 %)	16 (36,4 %)	23 (71,6 %)	–	–	48 (90 %)	13 (35 %)
Arrêt du traitement par IFN-α2a	20 (40)	9 (22,5 %)	19 (59,5 %)	–	–	47 (88,7 %)	17 (49 %)
Durée du traitement (mois)	16,4 (3-58)	22,2 ± 13,4	32 (16-50)	30 (1,1-101)	–	22,4 (9,2-79,9)	21 (2-24)

Tableau 50-IV. Études ouvertes évaluant l'interféron α pour le traitement des uvéites associées à la maladie de Behçet.

Auteur Pays	Kotter [29] Allemagne	Tugal-Tutkun [55] Turquie	Gueudry [19] France	Krause [30] Allemagne	Sobaci [47] Turquie	Deuter [15] Allemagne	Onal [40] Turquie
Suivi moyen après arrêt	29,5 mois (7-58)	≥ 24 mois	43 mois (11-64)	6,67 ans	65 mois (12-130)	6 ans (2-12,6)	17,1 mois (5-24)
Nombre de patients en rémission en l'absence de traitement	20/50 (40 %)	8/40 (20 %)	13/28 (46,4 %)	9/45 (20 %)	15/53 (28,3 %)	39/53 (75 %)	10/37 (27 %)
Arrêt de la corticothérapie	81 %	40-60 %	Aucun	–	100 %	–	9/17 (53 %)
Effets secondaires							
– Syndrome pseudo-grippal	50 (100 %)	44 (100 %)	17 (53,1 %)	43 (96 %)	53 (100 %)	53 (100 %)	37 (100 %)
– Dépression	4 (8 %)	0 (0 %)	3 (9,4 %)	13 (29 %)	3 (5,6 %)	4 (7,5 %)	0 (0 %)
– Leucopénie	20 (40 %)	6 (13,6 %)	6 (18,8 %)	–	3 (5,6 %)	53 (100 %)	2 (5 %)

Maladie de Behçet avec uvéite postérieure



Lesquel(s) de ces anti -TNF peut(vent) être utilisé(s) dans le traitement du Behçet oculaire grave?

1. ***Infliximab***
2. ***Etanercept***
3. ***Adalimumab***

Expert Panel Recommendations for the Use of Anti-Tumor Necrosis Factor Biologic Agents in Patients with Ocular Inflammatory Disorders

Grace Levy-Clarke, Douglas A. Jabs, Russell W. Read, James T. Rosenbaum, Albert Vitale, Russell N. Van Gelder.

Topic: To provide recommendations for the use of anti-tumor necrosis factor a (TNF-a) biologic agents in patients with ocular inflammatory disorders.

Clinical Relevance: Ocular inflammatory diseases remain a leading cause of vision loss worldwide. Anti-TNF-a agents are used widely in treatment of rheumatologic diseases. A committee of the American Uveitis Society performed a systematic review of literature to generate guidelines for use of these agents in ocular inflammatory conditions.

Methods: A systematic review of published studies was performed. Recommendations were generated using the Grading of Recommendations Assessment, Development, and Evaluation group criteria.

"Infliximab and adalimumab can be considered as first-line immunomodulatory agents for the treatment of ocular manifestations of Behçet's disease."

Ophthalmology 2014;121:785-796 2014

Table 3 Anti-TNF Therapy-Induced Improvement of Various Clinical Manifestations in Patients with Behçet's Disease, Published through March 2010

	Improving Patients/Treated Patients[a]		
	Infliximab	Etanercept[b]	Adalimumab
Oral ulcers	110/122 (91%)	8/10 (82%)	8/11 (73%)
Genital ulcers	76/80 (96%)	5/7 (71%)	6/7 (86%)
Skin involvement	51/67 (77%)	2/3 (67%)	4/5 (80%)
Erythema nodosum	13/16 (81%)	1/1 (100%)	1/1 (100%)
Ocular involvement	233/262 (89%)	6/10 (60%)	16/16 (100%)
Gastrointestinal involvement	29/32 (91%)	—	3/3 (100%)
Central nervous system involvement	27/30 (90%)	2/2 (100%)	3/3 (100%)
Joint involvement	50/53 (94%)	6/6 (100%)	3/5 (60%)
Thrombophlevitis	7/10 (70%)	—	1/1 (100%)

[a]Patients with variable degree of improvement according to treating physicians are shown.
[b]Patients treated in the course of the RCT were excluded since they were not refractory to conventional immunosuppressants.

Semin Arthritis Rheum. 2011 Aug

Efficacy of anti-TNF alpha in severe and/or refractory Behçet's disease: Multicenter study of 124 patients

Table 2
Improvement of clinical manifestations in BD patients treated by anti-TNF therapy.

	All		IFX		ADA	
	Improvement n/n (%)	CR/PR %/%	Improvement n/n (%)	CR/PR %/%	Improvement n/n (%)	CR/PR %/%
Uveitis	77/80 (96.3)	44.6/51.8	54/56 (96.4)	44.6/51.8	23/24 (95.7)	56.5/43.5
Macular edema	28/29 (96.6)	27.6/69.0	25/25 (100.0)	32.0/68.0	3/4 (75.0)	0/75
Retinal Vasculitis	46/49 (93.9)	36.7/57.1	37/39 (94.9)	38.5/56.4	9/10 (90.0)	30.0/60.0
Mucocutaneous	22/25 (88.0)	56.0/32.0	14/15 (93.3)	53.3/40.0	6/8 (75.0)	50.0/25.0
Joint	21/30 (70.0)	46.7/23.3	9/11 (81.8)	54.5/27.3	6/10 (60.0)	20.0/40.0
Gastro-intestinal	7/9 (77.8)	55.6/22.2	5/6 (83.3)	50.0/33.3	/	/
CNS	12/13 (92.3)	53.8/38.5	9/10 (90.0)	40.0/50.0	3 (100)	100/0
Cardiovascular	4/6 (66.7)	50.0/16.7	3/4 (75.0)	75.0/0	1 (50.0)	0/50

CNS, central nervous system. IFX: infliximab. ADA: adalimumab. CR: complete response. PR: partial response.

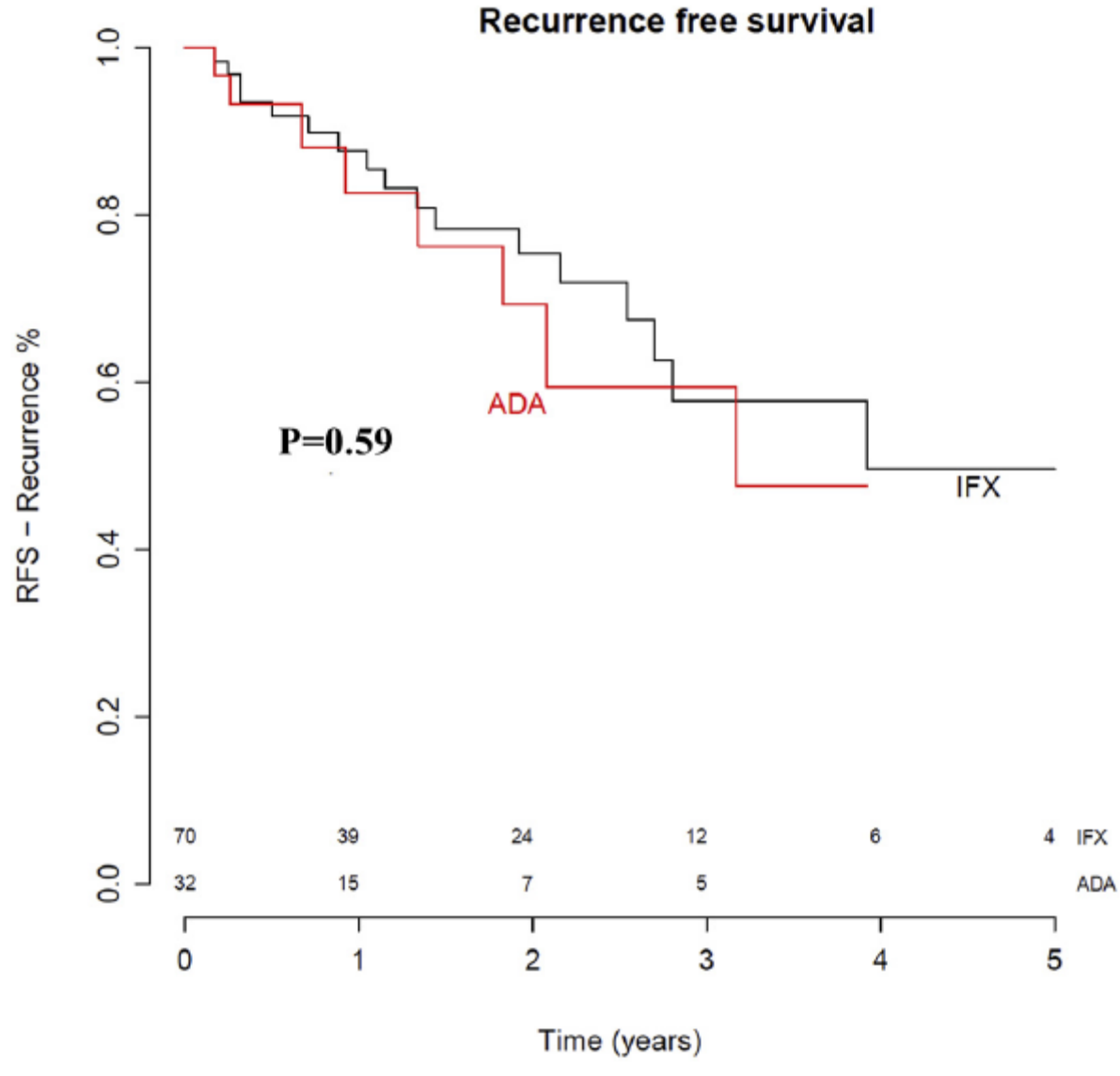


Fig. 1. Kaplan–Meier analysis of relapse free survival according to the anti-TNFα used [infliximab (IFX) and adalimumab (ADA)].

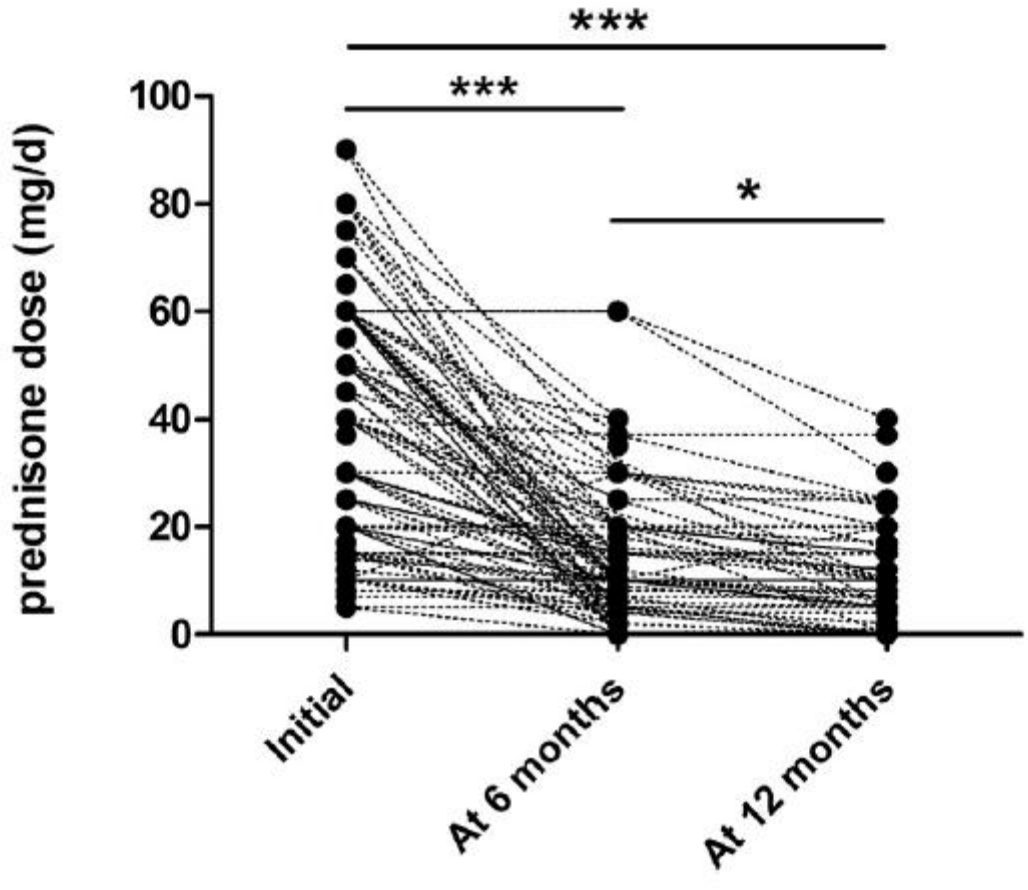


Fig. 2. Corticosteroid sparing effect in BD patients treated with anti-TNFα.

Lesquel(s) de ces immunomodulateurs est(sont) utilisé(s) avec succès dans le traitement de la maladie de Behçet?

1. ***Anti-IL-1***
2. ***Anti-IL6***
3. ***Mabthera***
4. ***Belimumab***
5. ***Apremilast***

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apremilast for Behçet's Syndrome — A Phase 2, Placebo-Controlled Study

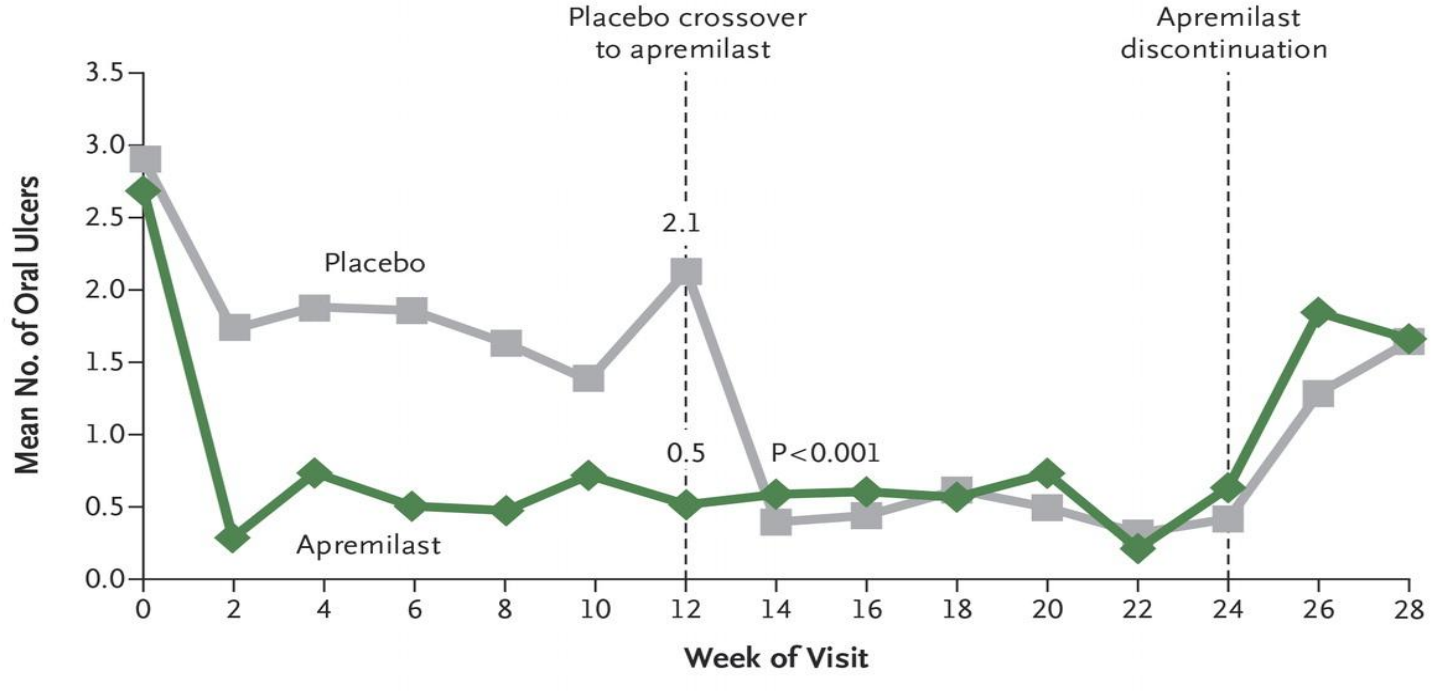
BACKGROUND

Oral ulcers, the hallmark of Behçet's syndrome, can be resistant to conventional treatment; therefore, alternative agents are needed. Apremilast is an oral phosphodiesterase-4 inhibitor that modulates several inflammatory pathways.

METHODS

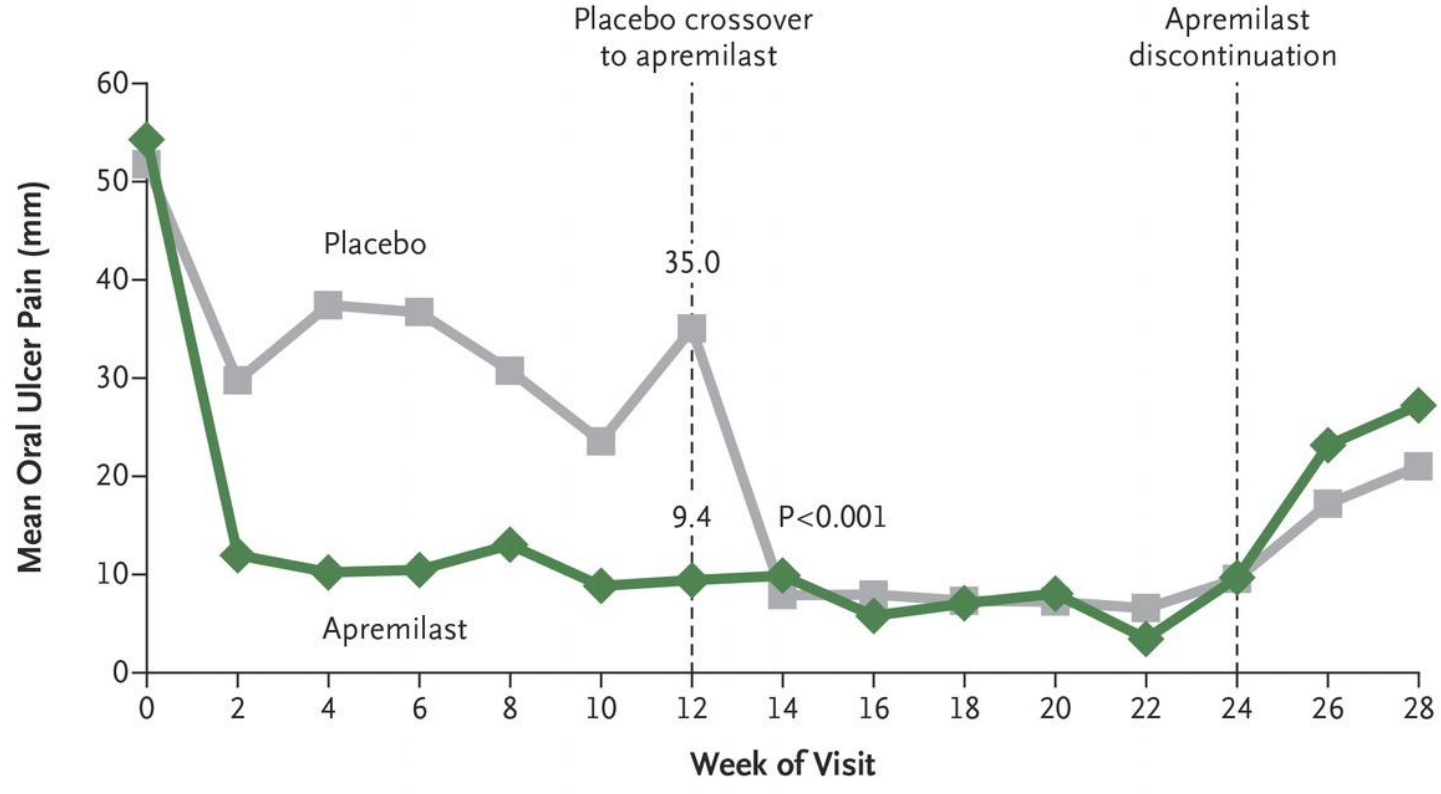
We conducted a phase 2, multicenter, placebo-controlled study in which 111 patients with Behçet's syndrome who had two or more oral ulcers were randomly assigned to receive 30 mg of apremilast twice daily or placebo for 12 weeks. This regimen was followed by a 12-week extension phase in which the placebo group was switched to apremilast and a 28-day post-treatment observational follow-up phase. The patients and clinicians were unaware of the study assignments throughout the trial. The primary end point was the number of oral ulcers at week 12. Secondary outcomes included pain from these ulcers (measured on a 100-mm visual-analogue scale, with higher scores indicating worse pain), the number of genital ulcers, overall disease activity, and quality of life.

Mean Number of Oral Ulcers Per Patient, According to Study Group.



No. at Risk															
Placebo	56	56	53	51	44	42	45	45	36	45	36	34	45	38	54
Apremilast, 30 mg	55	55	50	53	48	47	50	49	41	49	38	37	47	40	54
Mean No. of Oral Ulcers															
Placebo	2.9	1.7	1.9	1.9	1.6	1.4	2.1	0.4	0.4	0.6	0.5	0.3	0.4	1.3	1.6
Apremilast, 30 mg	2.7	0.3	0.7	0.5	0.5	0.7	0.5	0.6	0.6	0.6	0.7	0.2	0.6	1.9	1.7

Mean level of Pain from Oral Ulcers Per Patient, According to Study Group.



No. at Risk															
Placebo	56	56	53	51	44	42	45	45	36	45	36	34	45	38	54
Apremilast, 30 mg	55	55	50	53	48	47	51	49	41	49	38	37	47	40	54

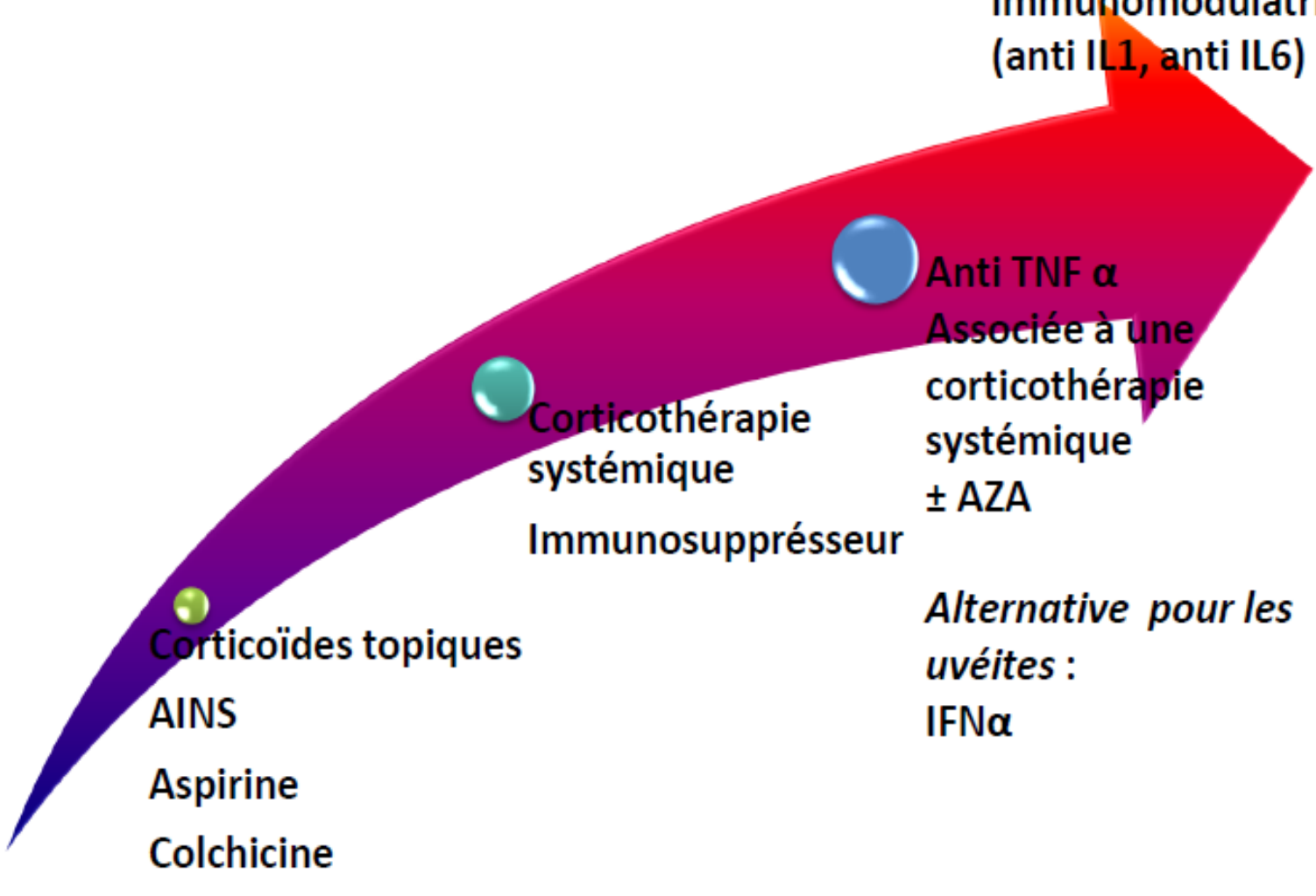
Mean Oral Ulcer Pain (VAS)															
Placebo	51.7	29.8	37.4	36.7	30.7	23.5	35.0	7.9	7.9	7.3	7.2	6.6	9.6	17.2	21.0
Apremilast, 30 mg	54.3	12.0	10.2	10.5	13.0	8.8	9.4	9.9	5.8	7.1	8.1	3.4	9.7	23.2	27.2

Stratégie thérapeutique

MB sévère ou réfractaire

Uvéite postérieure/ Atteinte Digestive/ Neurologique/ Vasculaire

Atteinte cutanéo-muqueuse/ Articulaire



Interleukin-1β-regulating antibody XOMA 052 (gevokizumab) in the treatment of acute exacerbations of resistant uveitis of Behçet's disease: an open-label pilot study

Table 1 Patient characteristics

Patient	Gender	Age	Previous treatment	Prednisolone dose (mg/day)	History
1001	M	25	AZA, CysA	10	Recurrent attacks with hypopyon, experiencing rebound attacks after missing one dose of CysA or prednisolone
1002	M	37	CysA	7.5	Intolerant to AZA and more than 100 mg CysA; recurrent retinitis attacks
1003	F	33	AZA, CysA, Colch	10	No light perception in the right eye, presented with counting fingers from 2 m in the left eye
1004	M	37	AZA, CysA	5	Recurrent uveitis attacks despite the combination of AZA + CysA
1005	M	26	AZA	5	Sight-threatening severe attack involving macula
1006	M	29	AZA, Colch	20	Recurrent attacks of uveitis on 20 mg prednisolone and AZA, intolerant to CysA
1007	M	25	AZA, CysA	10	Recurrent uveitis attacks despite the combination of AZA + CysA

AZA, azathioprine; Colch, colchicine; CysA, ciclosporin.

Gul et al, ARD 2011

Interleukin-1β-regulating antibody XOMA 052 (gevokizumab) in the treatment of acute exacerbations of resistant uveitis of Behçet's disease: an open-label pilot study

7 uvéites réfractaires et/ou vascularite rétinienne BD traitées par Gevokizumab 1 injection (0.3mg/kg)

- Régression complète de l' inflammation oculaire :100% cas
- Délai de réponse: 4-21 jours (médiane 14j)
- Aucun effet indésirable rapporté
- Durée médiane de réponse 49 jours (21-97j)
- Rechutes dans 6 cas/7

Gul et al, ARD 2011

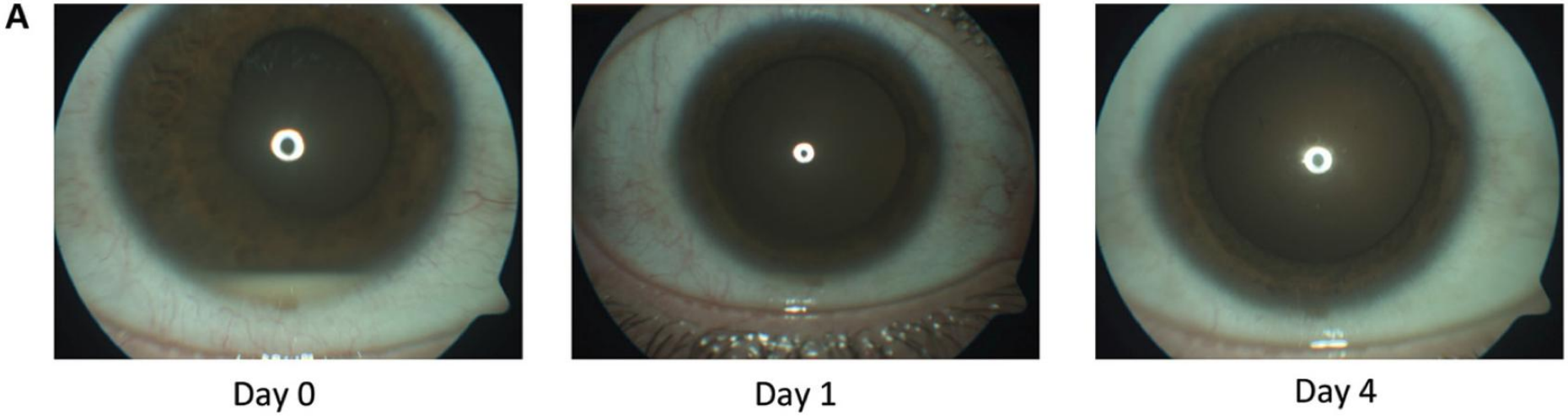


Figure 1 Resolution of panuveitis with hypopyon in the right eye of patient 1001 following XOMA 052 infusion.

Gul et al, ARD 2011

Anti-IL1 et maladie de Behçet

- ≈ 20-30 cas rapportés dans la littérature
- Anakinra (100 à 150mg/j sc) >> Canakinumab 150mg/6 à 8 sem) plus corticoides
- Efficacité surtout sur l'atteinte oculaire du Behçet
- Réactions locales++
- Suspensif

Arida et al Clin Exp Rheum 2014

Anti-RIL6 et maladie de Behçet

- ≈ 10-15 cas rapportés dans la littérature
- Tocilizumab (8mg/4 sem IV) plus corticoides
- Données intéressantes surtout sur l'atteinte oculaire et neurologique du Behçet

Papo et al Clin Exp Rheum 2014 ; Arida et al Clin Exp Rheum 2014

	Cutanéo-muqueuse (CM) ou Articulaire (A)	Oculaire sévère (BAV et/ou vasculite)	Neurologique (N) ou Cardiovasculaire (CV)
1ere Ligne	TT locaux Colchicine Infiltrations (A) AINS (A)	Cx plus aTNF (IFX ou ADA) et AZA ou Cx plus IFNa	Formes sévères: Cx plus CYC ou aTNF Formes peu sévères: Cx plus AZA ±Chirurgie (CV) ±Anticoagulation

	Cutanéo-muqueuse (CM) ou Articulaire (A)	Oculaire sévère (BAV et/ou vasculite)	Neurologique (N) ou Cardiovasculaire (CV)
1ere Ligne	TT locaux Colchicine Infiltrations (A) AINS (A)	Cx plus aTNF (IFX ou ADA) et AZA ou Cx plus IFNa	Formes sévères: Cx plus CYC Formes peu sévères: Cx plus AZA ±Chirurgie (CV) ±Anticoagulation
2nde Ligne	Torental (CM) Dapsone (CM) MTX (A)	Changement d'anti-TNF ou anti-IL1	Anti-TNF

	Cutanéo-muqueuse (CM) ou Articulaire (A)	Oculaire sévère (BAV et/ou vasculite)	Neurologique (N) ou Cardiovasculaire (CV)
1ere Ligne	TT locaux Colchicine Infiltrations (A) AINS (A)	Cx plus aTNF (IFX ou ADA) et AZA ou Cx plus IFNa	Formes sévères: Cx plus CYC Formes peu sévères: Cx plus AZA ±Chirurgie (CV) ±Anticoagulation
2nde Ligne	Torental (CM) Dapsone (CM) MTX (A)	Changement d'anti-TNF ou anti-IL1	Anti-TNF
3eme Ligne	Thalidomide (CM) Anti-TNF	Anti-R IL6, CYC?	Anti-R IL6 (N)

MERCI ++

- Bertrand WECHSLER
- Cloé COMARMOND
- Anne Claire DESBOIS
- Hélène VALLET
- Nicolas NOEL
- Léa SAVEY
- Jacky NYZARD
- Pascal SEVE
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- David KLATZMANN
- Aurélie PLESSIER
- Dominique VALLA
- Mathieu RESCHE RIGON
- Bahram BODAGHI
- Phuc Le HOANG
- Fabien KOSKAS
- Laurent CHICHE
- Julien GAUDRIC

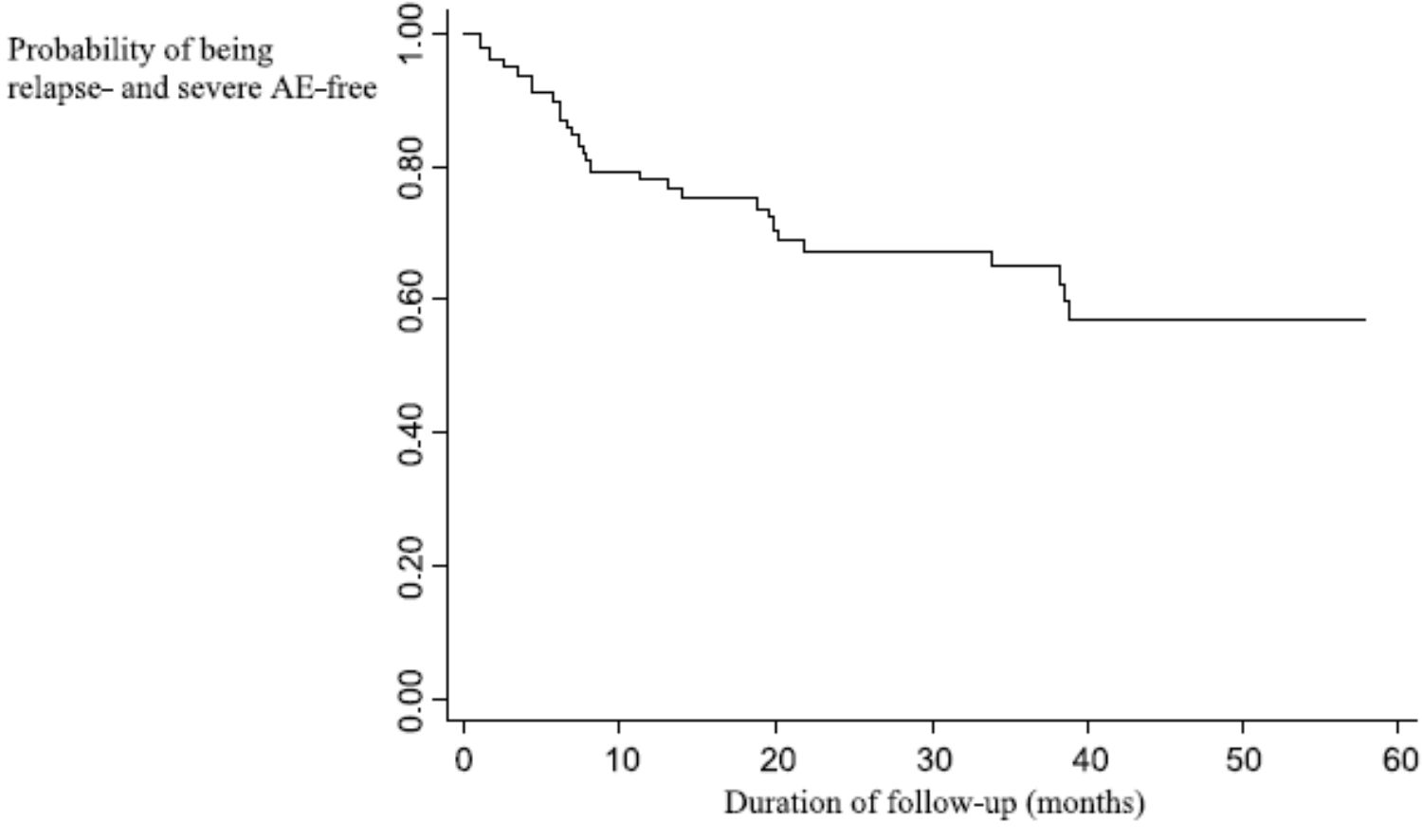
Use of Thalidomide for Severe Recurrent Aphthous Stomatitis

A Multicenter Cohort Analysis

Medicine 2010

Muriel Hello, MD, Sébastien Barbarot, MD,* Sylvie Bastuji-Garin, MD, PhD, Jean Revuz, MD, and Olivier Chosidow, MD, PhD*

92 patients inclus dont 16 maladies de Behçet



Traitement par Thalidomide « faible dose » en traitement d'entretien efficace sur les aphtoses récidivantes et avec une tolérance acceptable

Neuro-Behçet's disease	Licata G [102]	n = 1	Pyramidal tract involvement, hemiplegia	IFX 5 mg/kg	Complete remission
	Ribi C [103]	n = 1	Hemiparesis, aphasia	IFX 5 mg/kg + bolus MP + CYC	Complete remission, relapse after cessation of IFX but rapid resolution after reintroduction
	Sarwar H [104]	n = 1	Disorientation, cognitive dysfunction, cerebral vasculitis	IFX 3 mg/kg + pred. 60 mg/day	Complete remission: clinical (neurological manifestations and bipolar ulcerations) and MRI radiological signs (disappearance of con trast enhancement in the left capsula interna)
	Fujikawa K [105]	n = 1	Pyramidal tract involvement, cerebellar ataxia	IFX 3 mg/kg	Remission
	Tognon S [64]	n = 1	Meningoencephalitis, posterior uveitis	IFX 3–5 mg/kg/6–8 wk + AZA 100–150 mg/day + pred. 5–15 mg/day	Remission of posterior uveitis and extraocular manifestations including CNS, oral ulcerations, erythema nodosum, folliculitis, arthritis
	Kikuchi H [106]	n = 5	Dementia, psychosis, dysarthria, ataxia, myoclonus, spasticity with gait disturbance, depression, urinary incontinence	IFX 5 mg/kg (4 infusions) + MTX 10–17.5 mg/kg + pred. 0 to 10 mg/day	Clinical remission and reduction in MRI le-sions
	Pipitone [107]	n = 8	Hemiparesis, epilepsy, cerebellar signs, headache, vertigo, diplopia, altered mental status	IFX 5 mg/kg + MTX 20 mg/wk (n = 2) + CsA 2.5 mg/kg/day (n = 1) + pred. 5–50 mg/day (n = 6) + MP 1 g during 3 days (n = 1)	Clinical (n = 8, 100%) and radiological (n = 7, 87.5%) improvement
	Giardina A [47]	n = 5	Cerebral vasculitis	IFX 5 mg/kg/8 wk	Complete remission (n = 5, 100%)
	van Laar JA [108]	n = 2	CNS	IFX then ADA 40 mg/2 wk + CsA (n = 1) + AZA (n = 1) + pred. (n = 2)	Complete remission (n = 2, 100%)
	Belzunegui J [109]	n = 1	Spastic paraparesia	IFX 3 mg/kg (4 infusions) then AZA in maintenance (2.5 mg/kg/day) then ADA 40 mg/wk	Clinical and radiological (MRI) improvement
	Alty JE [110]	n = 1	Headache, diplopia, hemiparesis, dysarthria, aseptic meningitis	IFX 3 mg/kg + MTX 10 mg/wk then ETA 25 mg twice weekly	Complete remission, rechute à l'arrêt de l'ETA à nouveau en rémission à la reprise de l'ETA

Behçet and pulmonary artery aneurysms (PAA)	Baki K [120]	n = 1	Life-threatening hemoptysis	IFX 5 mg/kg	Complete remission (six months later, the size of the pulmonary aneurysms was markedly reduced)
	Lee SW [59]	n = 1	Hemoptysis, dyspnea, thoracic pain	ADA 40 mg/2 wk	Complete remission (reduction in size of PAA)
	Schreiber BE [121]	n = 1	Hemoptysis (refractory to pred. + CYC)	IFX 5 mg/kg + MTX 20 mg/wk	Complete remission (resolution of femoral and pulmonary artery aneurysms)
	Tolosa-Vilella C [122]	n = 1	Fever, cough, dyspnea, thoracic pain	IFX 5 mg/kg + MP 0.5 g/day during 3 days, then pred. + AZA	Clinical and radiological remission (thickening of pulmonary artery wall, reduction in size and number of PAA and thrombosis)
Behçet and Budd-Chiari	Seyahi E [123]	n = 3	Suprahepatic and hepatic vein thrombosis ± inferior vena cava (IVC): abdominal pain, ascites, hepatosplenomegaly, hepatic encephalopathy	IFX 3–5 mg/kg + MP then pred. 1 mg/kg	Failure (death, n = 2, and resolution of thrombus in IVC but extension of the thrombus in the inferior vena cava and formation of new thrombus in the brachiocephalic vein, then complete remission under (CYC), n = 1)

Anti-IL17

Secukinumab in the Treatment of Noninfectious Uveitis: Results of Three Randomized, Controlled Clinical Trials

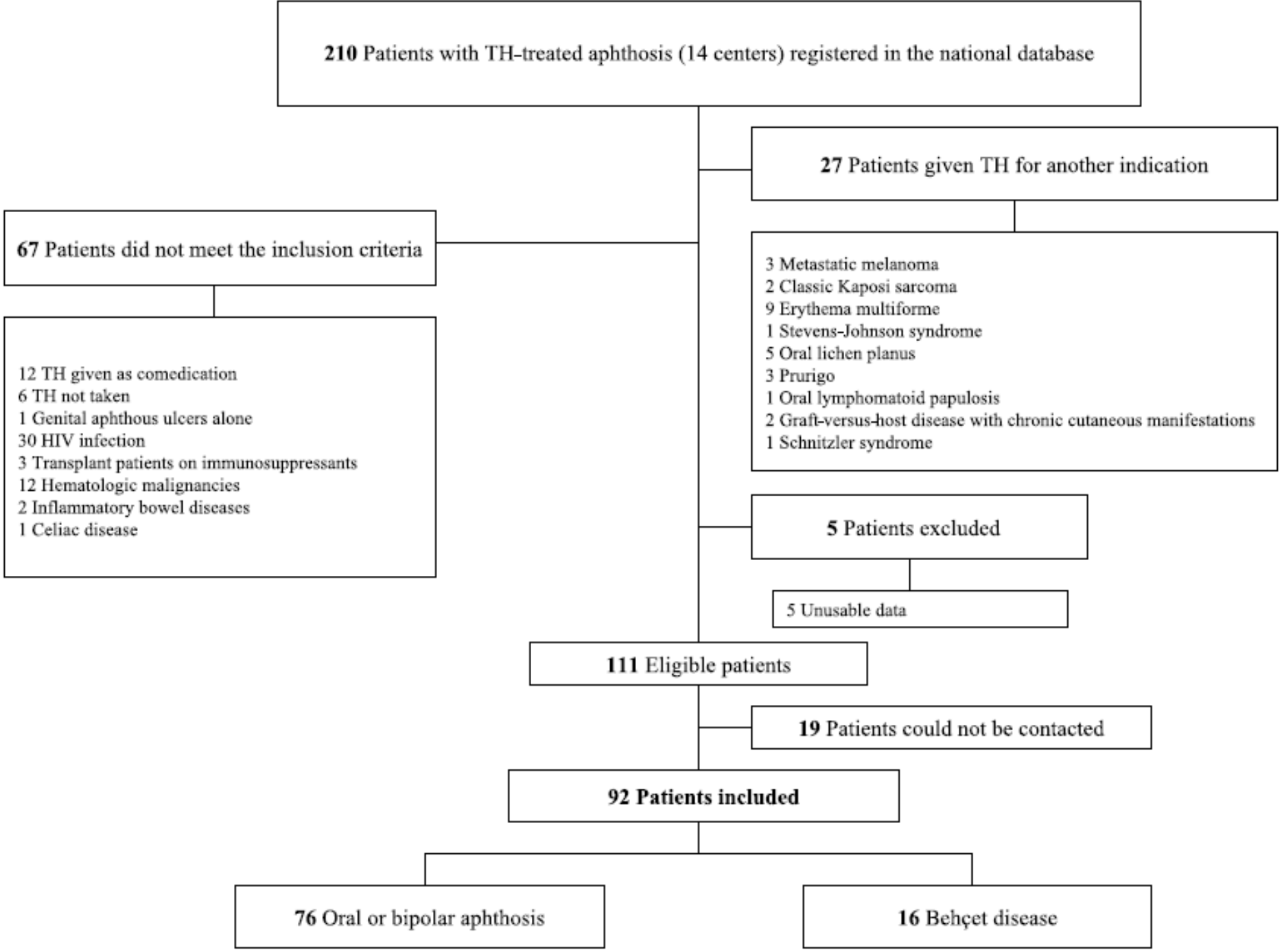
Andrew D. Dick, MD,[1,2] Ilknur Tugal-Tutkun, MD,[3] Stephen Foster, MD,[4,5] Manfred Zierhut, MD,[6] S. H. Melissa Liew, MB, BS,[7] Vladimir Bezlyak, PhD,[8] Sofia Androudi, MD[9]

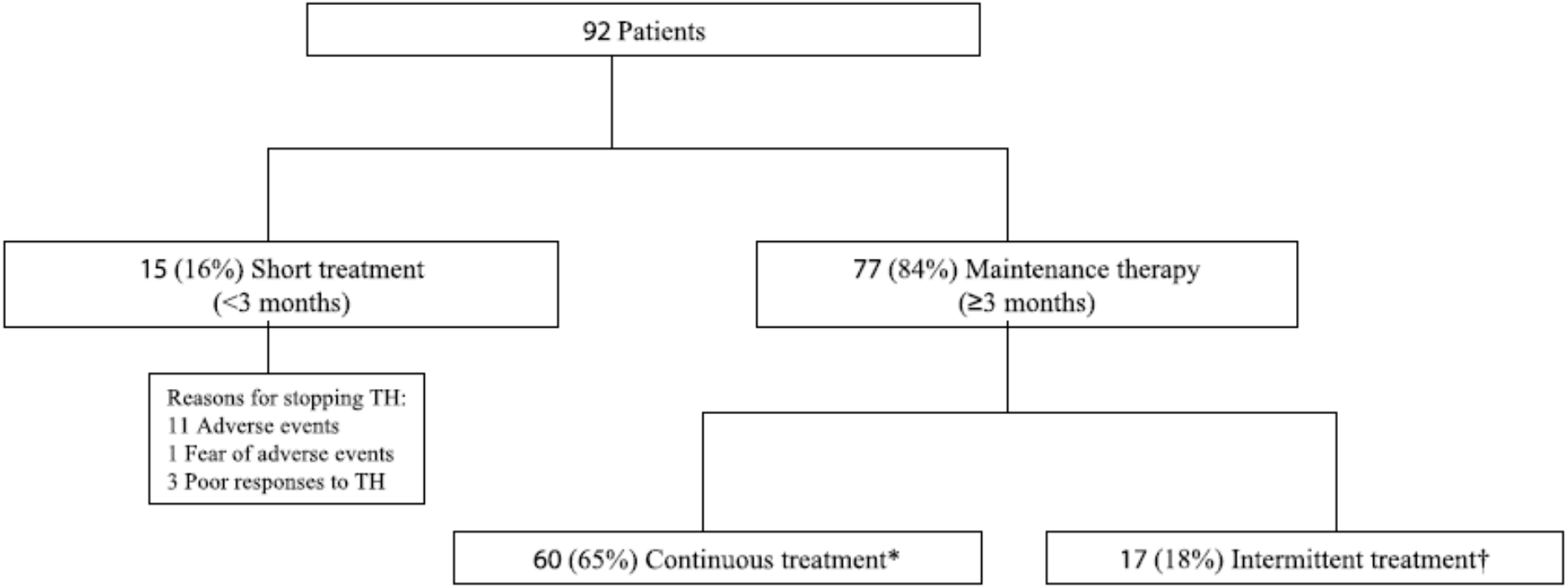
- Secukinumab : high affinity fully human mAb
- 3 RCT
- Shield : 118 patients with BD
- Insure : 31 patients with active noninfectious uveitis
- Endure : 125 patients with quiescent noninfectious uveitis

Secukinumab did not separate from placebo

Poorly designed study, low dose secukinumab

Dick et al. Ophthalmology, 2013


210 Patients with TH-treated aphthosis (14 centers) registered in the national database
27 Patients given TH for another indication
3 Metastatic melanoma
2 Classic Kaposi sarcoma
9 Erythema multiforme
1 Stevens-Johnson syndrome
5 Oral lichen planus
3 Prurigo
1 Oral lymphomatoid papulosis
2 Graft-versus-host disease with chronic cutaneous manifestations
1 Schnitzler syndrome
67 Patients did not meet the inclusion criteria
12 TH given as comedication
6 TH not taken
1 Genital aphthous ulcers alone
30 HIV infection
3 Transplant patients on immunosuppressants
12 Hematologic malignancies
2 Inflammatory bowel diseases
1 Celiac disease
5 Patients excluded
5 Unusable data
111 Eligible patients
19 Patients could not be contacted
92 Patients included
76 Oral or bipolar aphthosis
16 Behçet disease



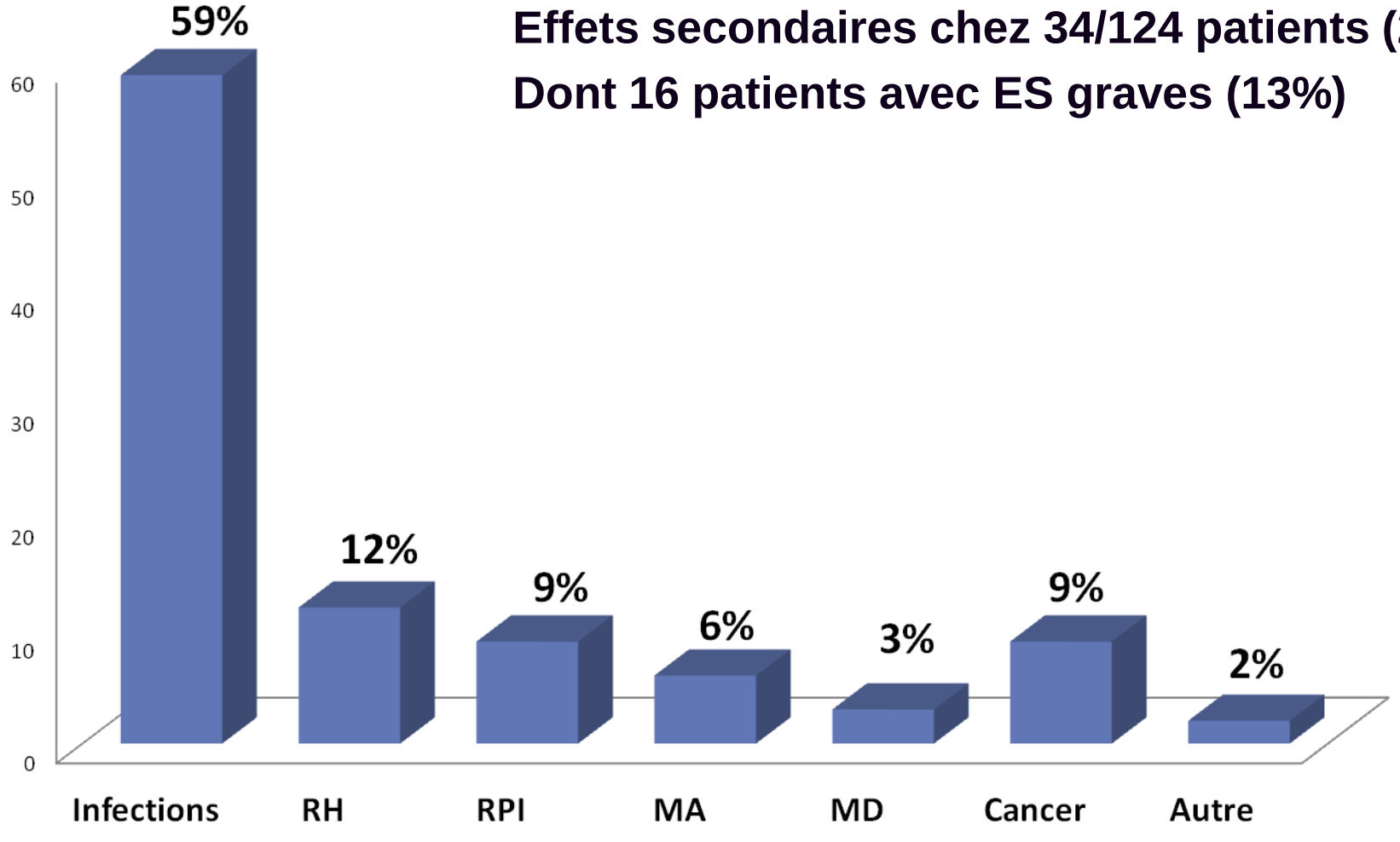
Dose médiane 150mg/sem
Mean AE/patient =2.2
Neuropathie 17%
Thrombose 1%

Dose médiane 19mg/sem
Mean AE/patient =1.4

Tolérance

Effets secondaires chez 34/124 patients (27%)

Dont 16 patients avec ES graves (13%)



Traitement des uvéites

< 2000	2000
Azathioprine	**IFN α**
MMF Cyclophosphamide	**Infliximab** **Adalimumab**
Methotrexate	**Anti-IL1, anti-RIL6….**
Cyclosporine	

CORTICOIDES

Saadoun D, et al Autoimmun Rev. 2013 May;12(7):774-83

Aggressive long-lasting anti-inflammatory and IS strategies

- Behçet disease
- Multifocal choroiditis and panuveitis
- Non TB serpiginous choroiditis
- Birdshot
- JIA-associated uveitis
- Idiopathic posterior uveitis / retinal vasculitis
- Sarcoidosis (37% vasculite, ischémie <4%)

Vascularite rétinienne
Facteurs Pronostiques

1. Ischémie rétinienne+++
2. Oedeme maculaire
3. Occlusions

Risque X 6 de perte visuelle sévère

Palmer et al Eye 1996