Biothérapies et Uvéites

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Biothérapies et Uvéites: Rationnel

- 10% de cécité dans les uvéites sévères
- Nombreux Immunosuppresseurs, prescription hors AMM++
- 30% formes réfractaires, corticodépendantes

Traitement des uvéites

< 2000	➢ 2000
Azathioprine	IFNα
MMF	Infliximab
Cyclophosphamide	Adalimumab, autres aTNF
Methotrexate	Anti-IL1, anti-IL6, anti-IL17, anti-IL12-23….
Cyclosporine	

CORTICOIDES

Autoimmun Rev. 2013 May;12(7):774-83

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

Grace Levy-Clarke, MD,[1] Douglas A. Jabs, MD, MBA,[2] Russell W. Read, MD, PhD,[3] James T. Rosenbaum, MD,[4,5] Albert Vitale, MD,[6] Russell N. Van Gelder, MD, PhD[7]

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2014

Infliximab (IFX) and adalimumab (ADA) can be used:

- In first line: uveitis associated with Behcet disease (strong recommendation)
- In second line:
  - uveitis associated with juvenile arthritis (strong recommendation)
  - Severe ocular inflammation in refractory uveitis (discretionary recommendation)

Biothérapies et Uvéites

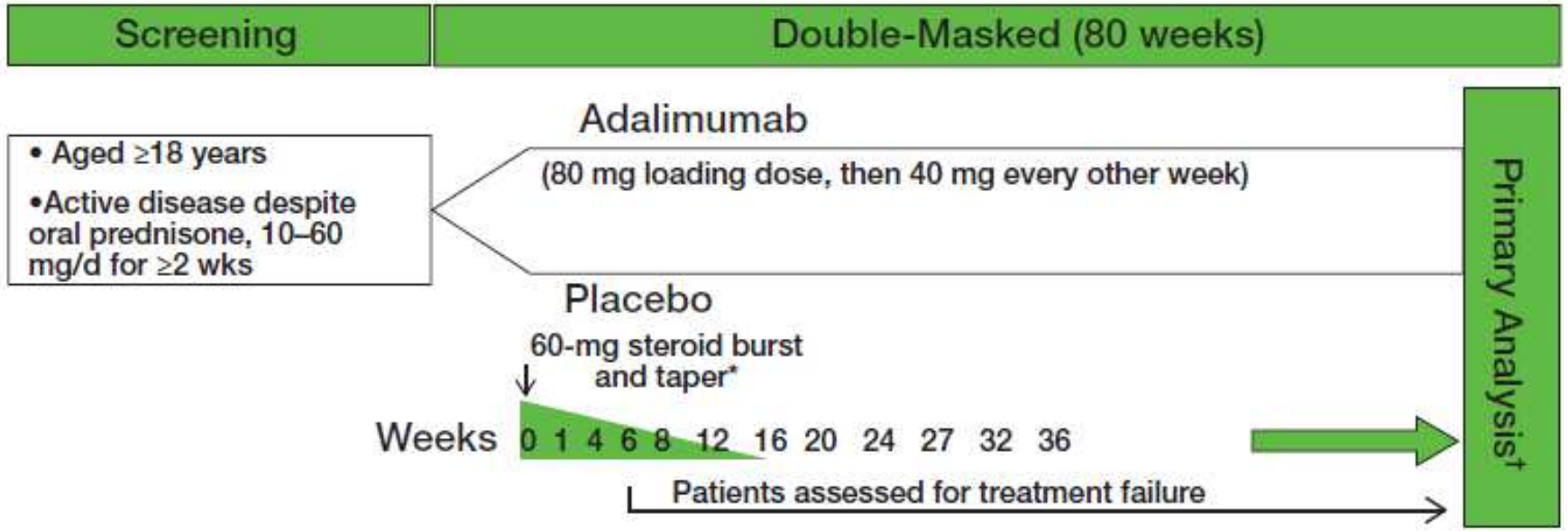
- Adalimumab dans les uvéites actives
- Adalimumab vs Infliximab dans les uvéites
- Quid des biosimilaires dans les uvéites?
- Les autres anti-TNF dans les uvéites?
- Les autres agents biologiques dans les uvéites?

Adalimumab et uvéites actives: Etude Visual 1

Adalimumab in Patients With Active, Non-infectious Uveitis Requiring High-Dose Corticosteroids: The VISUAL-1 Trial

Glenn J. Jaffe, MD,[1] Jennifer E. Thorne, MD, PhD,[2] David Scales, MD,[3] Pablo Franco, MD,[4] Samir Tari, MD,[5] Anne Camez, MD,[6] Alexandra P. Song, MD, MPH,[5]
Martina Kron, PhD,[6] Talin Barisani-Asenbauer, MD, PhD,[7] Andrew D. Dick, MBBS, MD, FMedSci[8]

Figure 1. Study Design

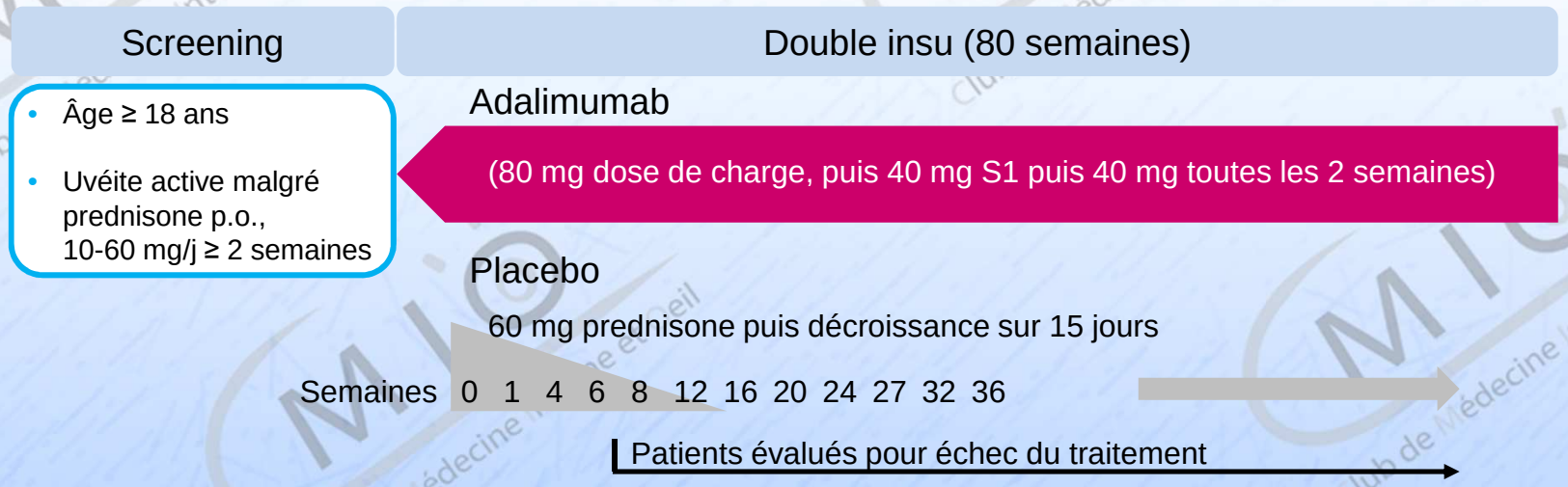


*Prednisone was tapered from weeks 2–15; all patients discontinued prednisone by week 15. Patients may have been using 1 immunosuppressive therapy and/or topical steroids at pre-defined, stable doses. All patients using a topical steroid at baseline underwent a mandatory taper schedule from weeks 1–9.

Jaffe GJ *et al.* N Engl J Med 2016,375: 932-43

Adalimumab dans le traitement des uvéites *(1)*

Étude VISUAL-1



- Étude multicentrique randomisée en double insu
  - Critère principal de jugement : temps jusqu'à la rechute
  - ⚠ Rechute définie par un critère composite fondé sur 4 critères
    - L'acuité visuelle
    - Une inflammation postérieure (choriorétinite ou vascularite rétinienne)
    - L'opacité vitréenne
    - L'inflammation de la chambre antérieure

Jaffe GJ *et al.* N Engl J Med 2016,375: 932-43

Caractéristiques de la pathologie à l'inclusion (population ITT)

M10-877	Placebo (N=107)	Adalimumab (N=110)	Total (N=217)
Type d'uvéite, n (%)			
Intermédiaire	23 (21,5)	24 (21,8)	47 (21,7)
Postérieure	37 (34,6)	36 (32,7)	73 (33,6)
Panuvéite	47 (43,9)	50 (45,5)	97 (44,7)
Etiologie, n (%)			
Idiopathique	45 (42,1)	36 (32,7)	81 (37,3)
Choriorétinopathie de birdshot	20 (18,7)	24 (21,8)	44 (20,3)
Syndrome de Vogt-Koyanagi-Harada	14 (13,1)	11 (10,0)	25 (11,5)
Sarcoïdose	8 (7,5)	10 (9,1)	18 (8,3)
Maladie de Behçet	4 (3,7)	12 (10,9)	16 (7,4)
Choroïdites et panuvéites multifocales	3 (2,8)	8 (7,3)	11 (5,1)
Autres	13 (12,1)	9 (8,2)	22 (10,1)
Œil affecté, n (%)			
Gauche	5 (4,7)	5 (4,5)	10 (4,6)
Droit	3 (2,8)	7 (6,4)	10 (4,6)
Les deux	99 (92,5)	98 (89,1)	197 (90,8)
Ancienneté du diagnostic à l'inclusion, mois			
Moyenne (ET)	51,0 (72,2)	40,2 (51,3)	45,5 (62,5)
Nombre de poussées au cours des 12 mois précédant l'inclusion, n (%)			
1	19 (17,8)	18 (16,4)	37 (17,1)
2	46 (43,0)	54 (49,1)	100 (46,1)
≥3	42 (39,3)	38 (34,5)	80 (36,9)

Jaffe GJ *et al.* N Engl J Med 2016,375: 932-43

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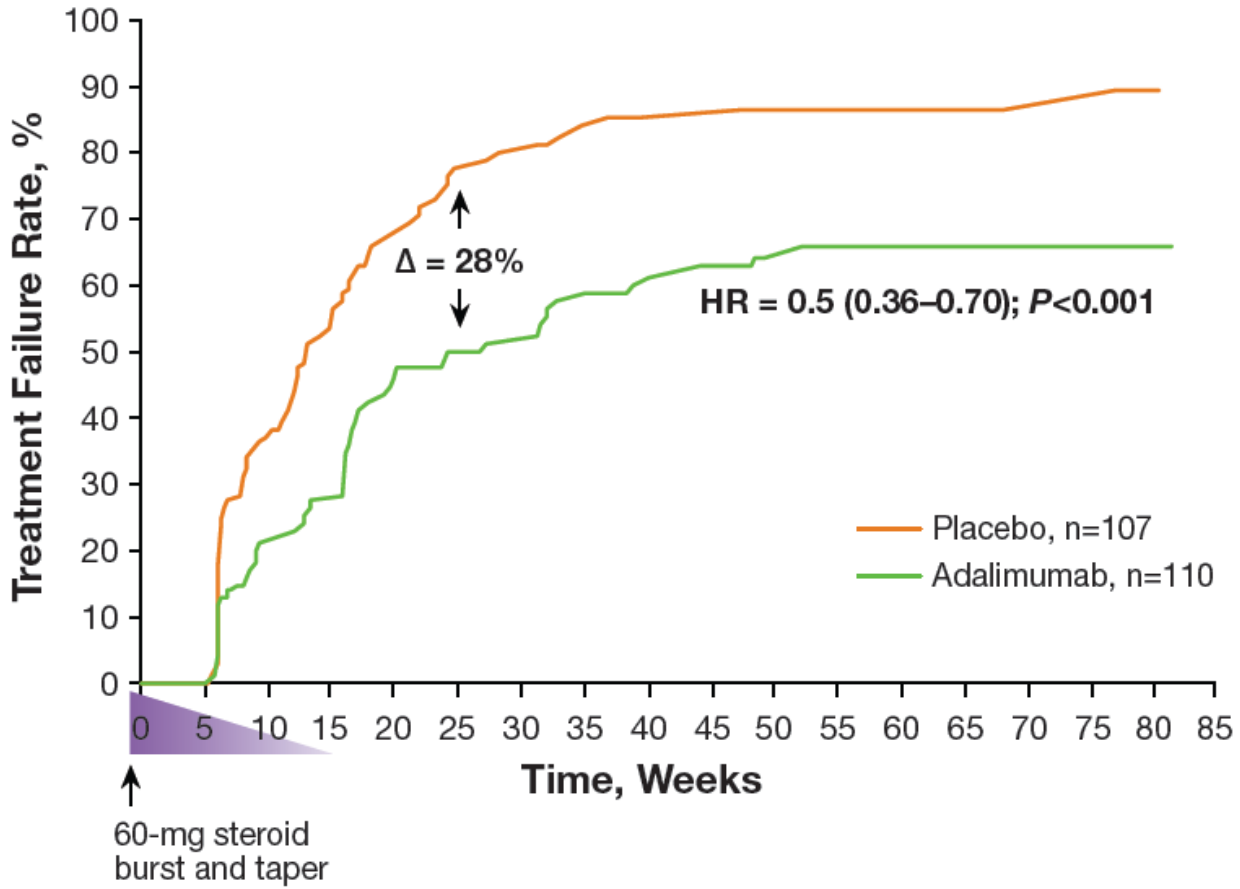
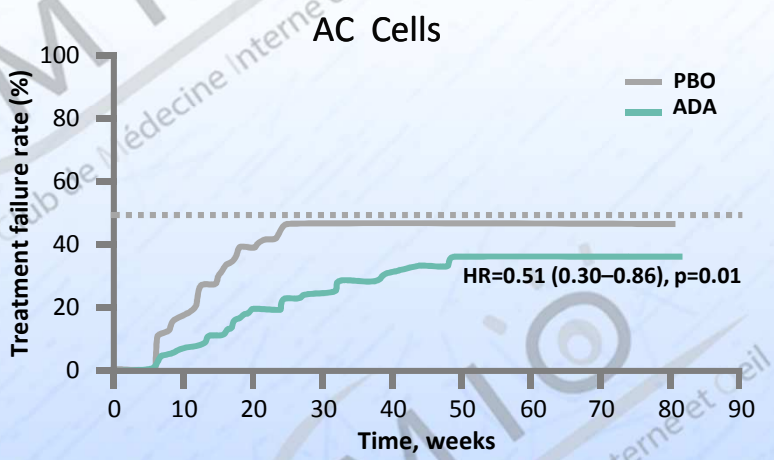
Résultat sur le critère principal de jugement : Délai de survenue de la rechute

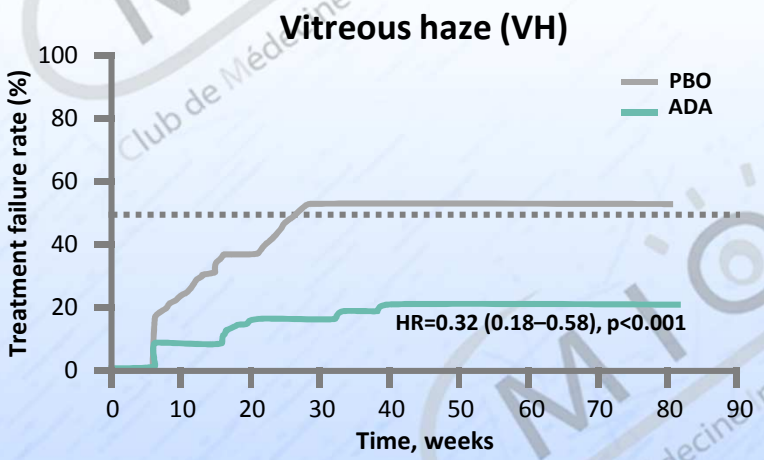
Figure 2. Treatment Failure On Or After Week 6, Kaplan-Meier Curve (Intent-to-Treat Population)

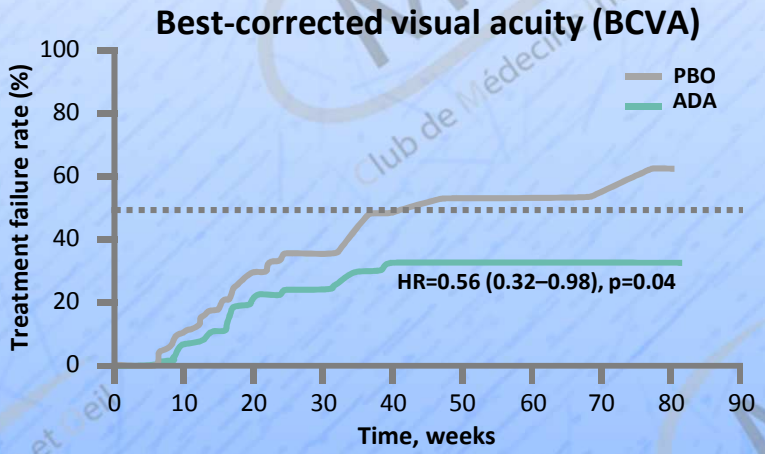


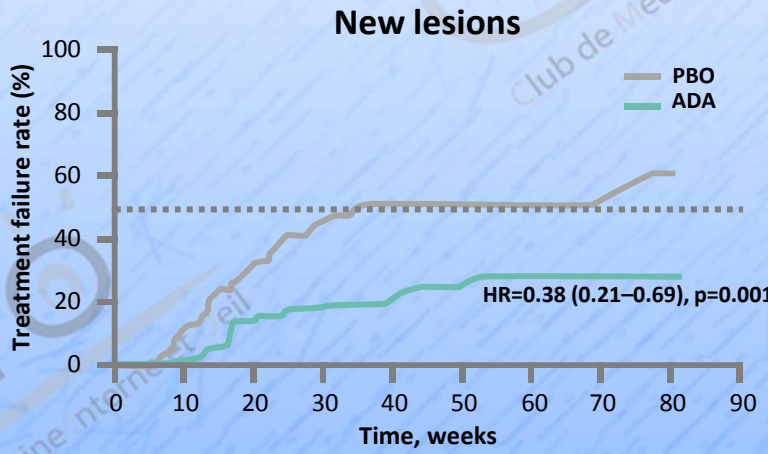
Jaffe GJ *et al.* N Engl J Med 2016,375: 932-43

Résultats selon les 4 composants du critère de rechute









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Traitements concomitants par immunosuppresseur et Réponse au Traitement

Visual I	Placebo (N=107) n (%)	Adalimumab (N=110) N (%)	Total (n=217)
Au moins 1 immunosuppresseur	33 (30,8)	34 (30,9)	67 (30,9)
Mycophenolate mofetil ou équivalent	14 (13,1)	11 (10,0)	25 (11,5)
Ciclosporine	3 (2,8)	10 (9,1)	13 (6,0)
Méthotrexate	12 (11,2)	9 (8,2)	21 (9,7)
Azathioprine	4 (3,7)	4 (3,6)	8 (3,7)
Tacrolimus	0	0	0

95% CI, 0.21 to 1.14; P=0.09). We also found the significantly greater than that of placebo in the subgroup of patients who were not using immunomodulatory therapies at baseline (hazard ratio, 0.49; 95% CI, 0.33 to 0.73; P<0.001) but not among patients who were using immunomodulatory therapies at baseline (hazard ratio, 0.55; 95% CI, 0.30 to 1.01; P=0.05).

Données de tolérance (population de tolérance)

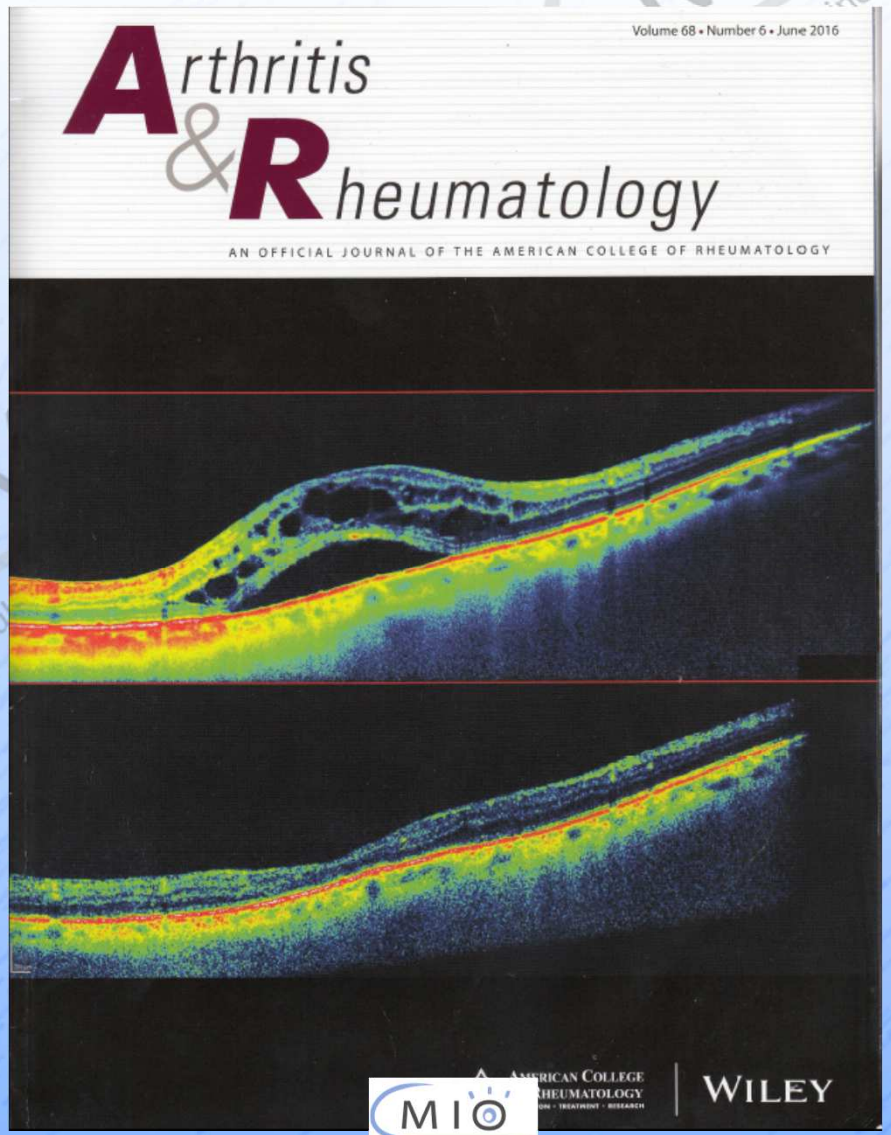
AE, events/100 PY	Placebo (n=112, PYs=44.3)	ADA (n=111, PYs=62.4)
AE	972	1052
AE leading to death	0	1.6
SAE	13.6	28.8
AE leading to discontinuation	11.3	20.8
Injection site reactions	15.8	44.9
Serious infectious AE	6.8	8 .0
Malignancy	0	3.2*
Demyelinating disorders	0	1.6
Opportunistic infections†	0	0

ADA=adalimumab; AE=adverse event; PY=patient-year; SAE=serious AE.
*One event each of carcinoid tumor of the gastrointestinal tract and glioblastoma multiforme.
†Excludes oral candidasis and tuberculosis.

Conclusions

- Dans les uvéites actives non controllées sous prednisone 10-60mg/j ≥2 semaines l'adalimumab diminue significativement l'inflammation oculaire et la survenue de nouvelles lésions inflammatoires.
- Les effets secondaires (dont les SAE) étaient plus fréquents dans le groupe adalimumab vs placebo.
- Le profile de tolérance de l'adalimumab était similaire à celui observé dans les autres indications (rhumatologiques…)

Infliximab vs Adalimumab: French Uveitis Network



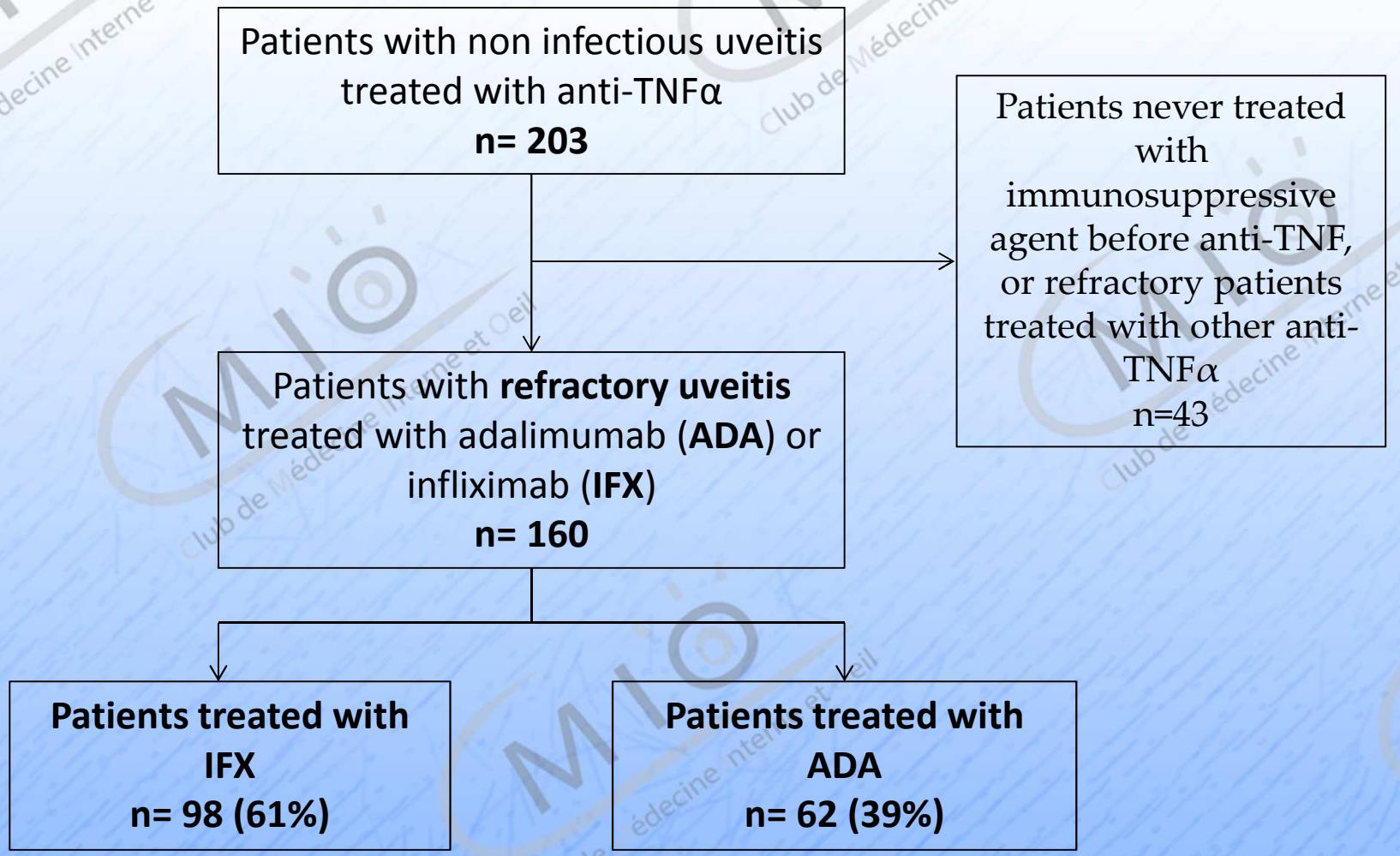
Objectifs

1. Analyser les facteurs prédictifs de réponse aux anti-TNF

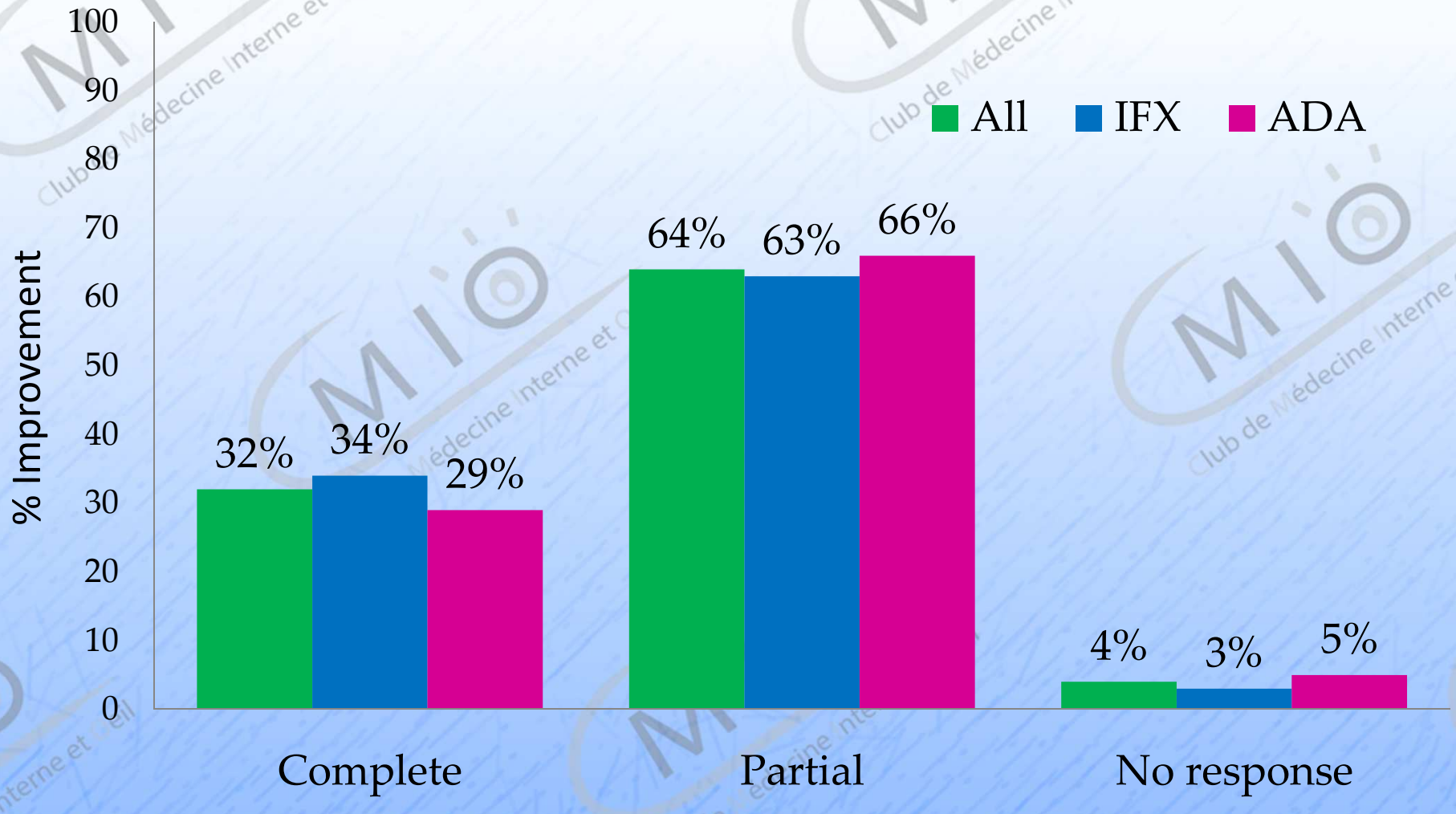
2. Comparer l'efficacité et la tolérance de l'IFX vs ADA (propensity score)

dans les uvéites non infectieuses réfractaires (≥ 1IS)

Résultats


Patients with non infectious uveitis treated with anti-TNFα
n= 203
Patients never treated with immunosuppressive agent before anti-TNF, or refractory patients treated with other anti-TNFα
n=43
Patients with refractory uveitis treated with adalimumab (ADA) or infliximab (IFX)
n= 160
Patients treated with IFX
n= 98 (61%)
Patients treated with ADA
n= 62 (39%)

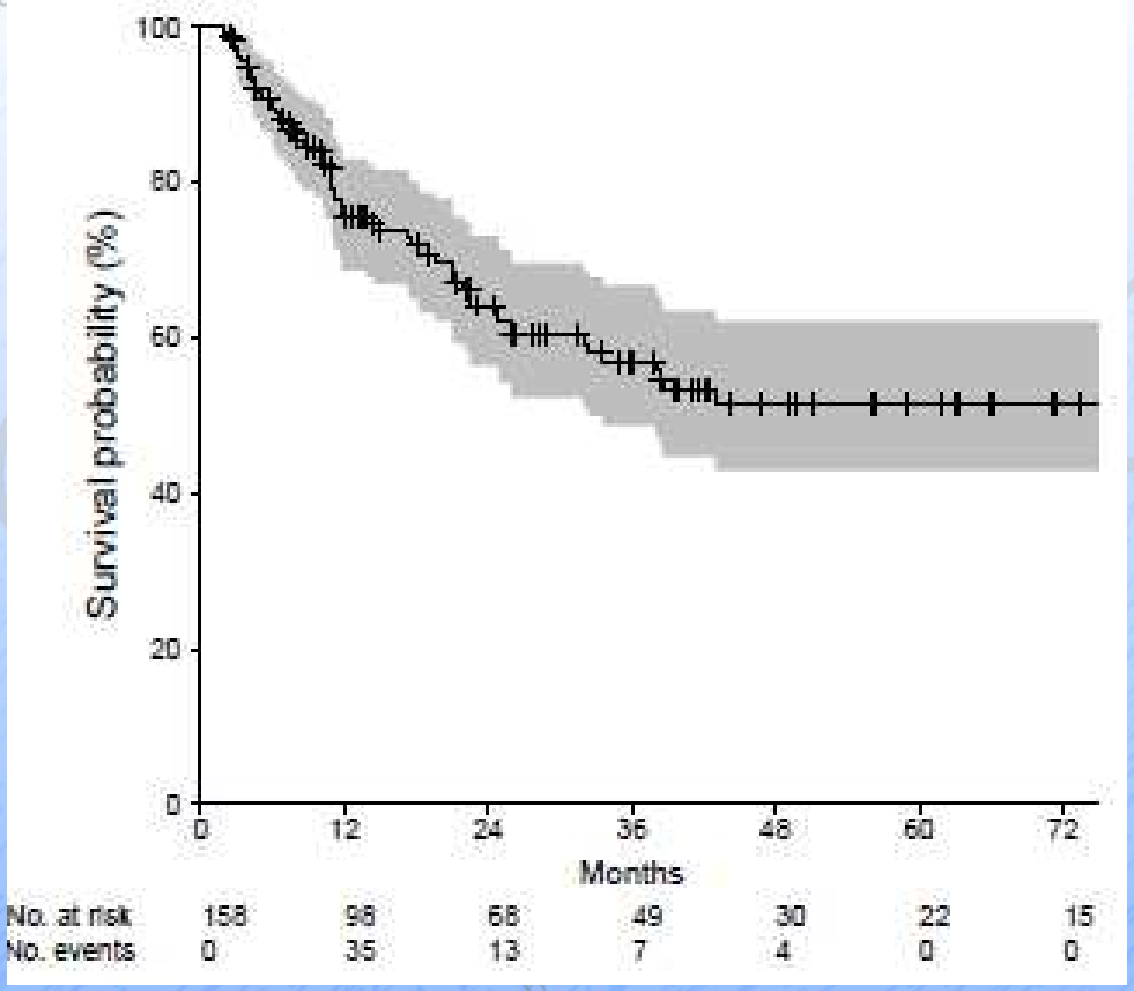
Réponse aux anti-TNFα



Facteurs associés à la réponse complète aux aTNF

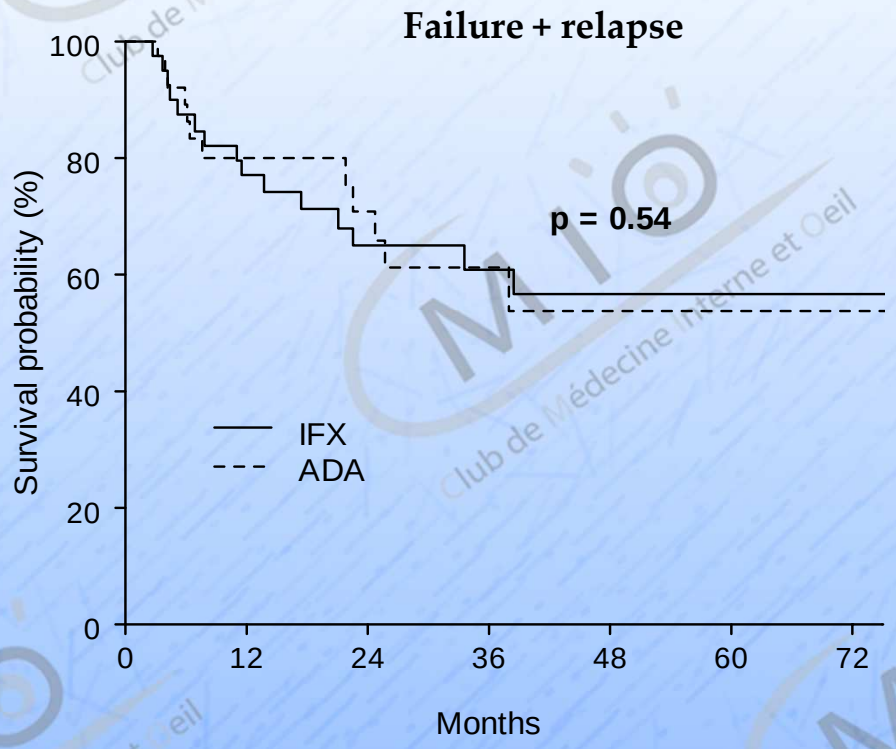
	Univariate analysis		Multivariate analysis	
	SHR 95%CI	P-value	OR 95%CI	P-value
Age	1.01 [0.99-1.02]	0.44		
Uveitis				
Panuveitis	1.50 [0.82-2.75]	0.19		
Bilateral	0.61 [0.31-1.20]	0.15		
Granulomatosis	1.19 [0.43-3.30]	0.73		
Vasculitis	0.88 [0.46-1.69]	0.70		
Macular edema	1.03 [0.50-2.12]	0.93		
Number of uveitis flares before anti-TNFα (>5)	1.90 [1.00-3.64]	0.052	2.25 [1.13-4.48]	0.022
Etiology				
JIA	1			
Behçet	3.95 [1.55-10.06]	0.004	2.52 [1.35-4.71]	0.004
Others	1.67 [0.6-4.6]	0.33		
Associated treatment				
Corticosteroid >20mg/d	2.10 [1.13-3.93]	0.019		
Immunosuppressant	0.46 [0.25-0.84]	0.012		

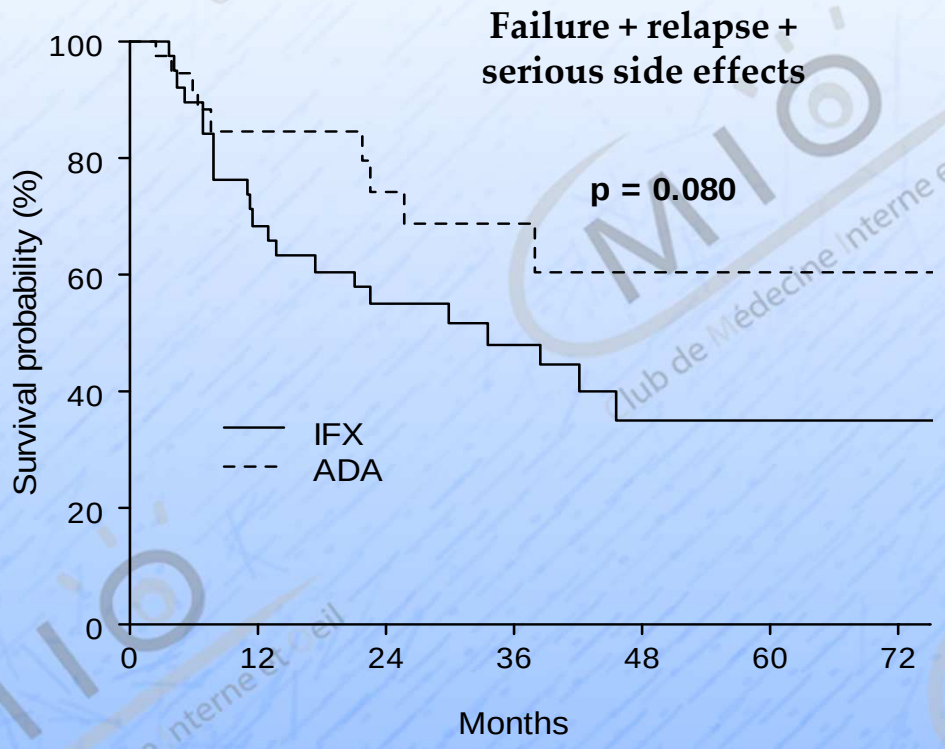
Survie sans evènement



EFS inclus rechutes, echecs and SAE

Comparaison efficacité IFX vs ADA





➔ **No significant difference regarding the event free survival**

Effets secondaires

	All n=160	IFX n=98	ADA n=62
Sides effects	45 (28)	30 (31)	11 (18)
Infections	18	14	1
Hypersensitivity reaction	10	7	3
Injection site reaction	1	0	1
Auto-immune disease	5	3	1
Neoplasia	4	3	1
Other	11	5	3
Serious sides effects	20 (12)	16 (16)	4 (6)
Infections	5	5	0
Hypersensitivity reaction	6	5	1
Auto-immune disease	4	3	1
Neoplasia	3	2	1
Other	2	1	1

Effets secondaires sévères

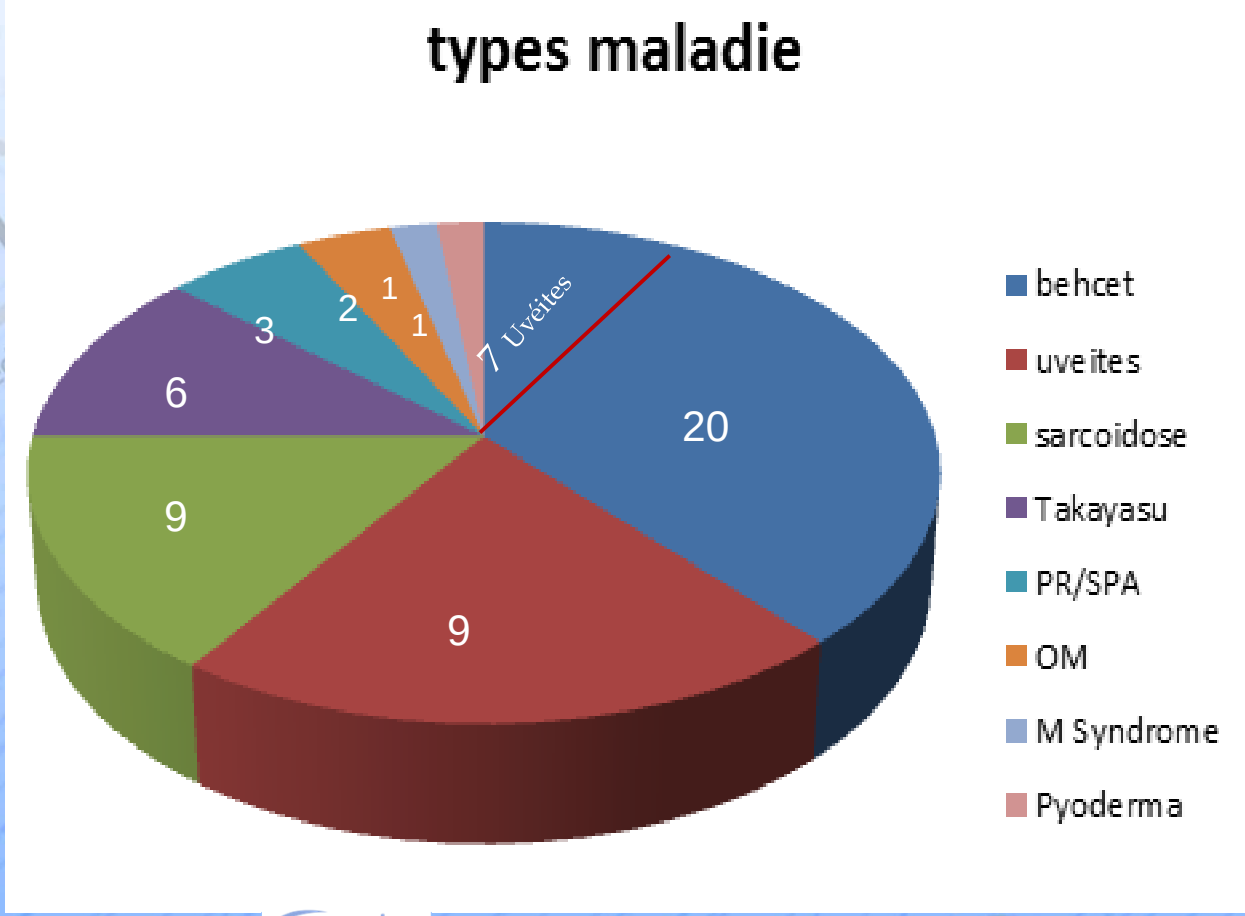
- Infections
  - Pneumonia/bronchitis
  - Urinary infection
  - Cholecystitis
  - Tuberculosis
- Hypersensitivity reaction
  - Pruritus
  - Hypersensitivity pneumonitis
- Auto-immune disease
  - Serum sickness
  - Lupus
  - Graves' disease
- Neoplasia
  - Uterine col dysplasia
  - Melanoma

Conclusions

- 96% d'efficacité globale (RC + RP) des anti-TNFα
- Facteurs de bonne réponse: maladie de Behçet disease et nombre de poussées d'uvéite (>5)
- Efficacité IFX et ADA semble équivalente
- Survie sans évènement = 60% à 2 ans

Quid des Biosimilaires dans les uvéites

- Mars à Aout 2016 GHPS
  - 51 patients Inflectra

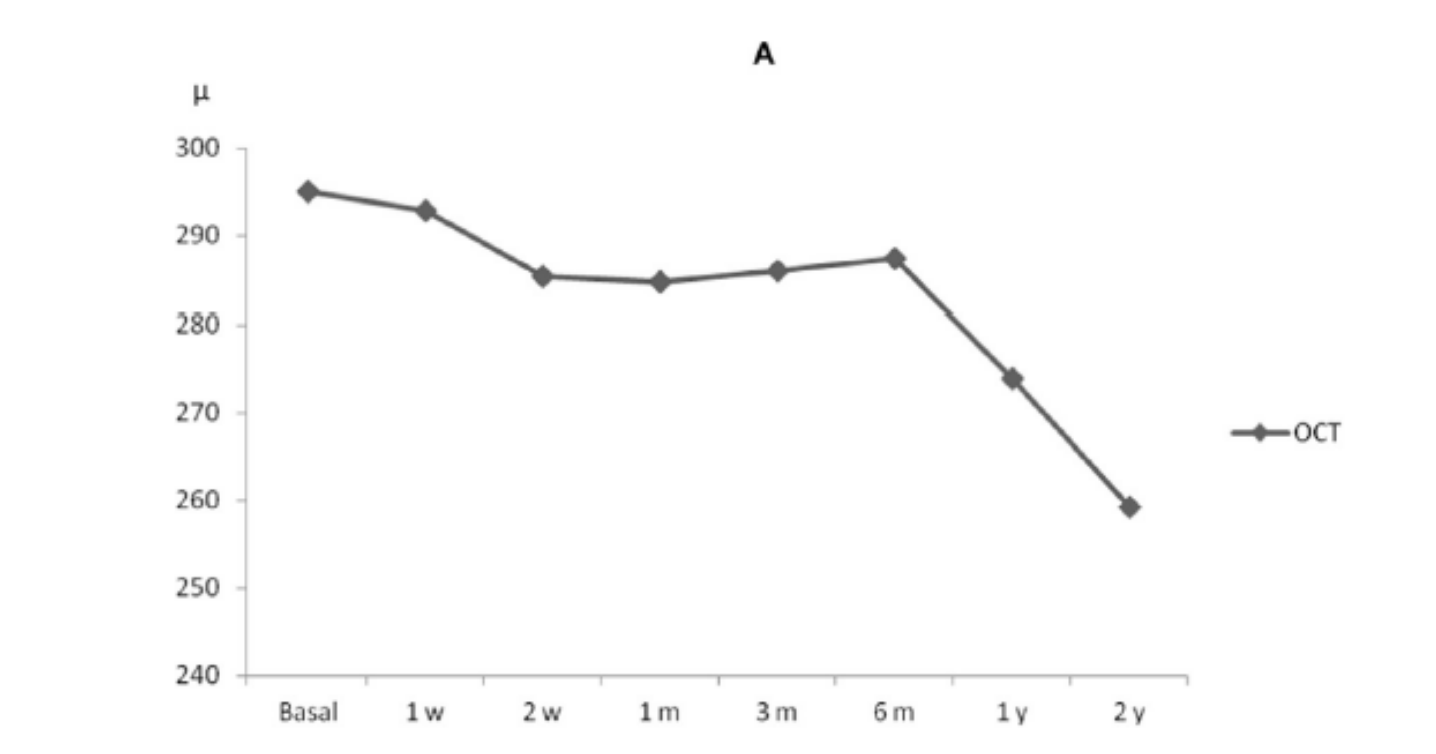


Les autres anti-TNF dans les uvéites

Golimumab in refractory uveitis related to spondyloarthritis. Multicenter study of 15 patients

Patient	Age	Sex	HLA-B27	Subtype of SpA	Pattern of uveitis	Ocular involvement	Previous IS to GLM	Indication for GLM
1	37	Man	+	AS	AU/chronic/unilateral	AC cells + vitritis + CME	MTX, SSZ	Uveitis
2	32	Man	+	AS	AU/chronic/bilateral	AC cells + CME	MTX, SSZ, ADA	Uveitis
3	45	Man	+	AS	AU/recurrent/unilateral	AC cells + CME	IFX, ADA, ETN	Uveitis
4	46	Man	+	AS	AU chronic/bilateral	AC cells + vitritis	MTX	Uveitis and articular activity
5	48	Man	+	AS	AU chronic/unilateral	AC cells	MTX, ETN, IFX	Uveitis and articular activity
6	42	Man	+	AS	AU recurrent/unilateral	AC cells + vitritis	MTX, AZA, ETN	Uveitis and articular activity
7	47	Man	+	AS	AU recurrent/unilateral	AC cells	MTX, AZA, LFN, SSZ, IFX	Uveitis and articular activity
8	39	Man	+	AS	AU recurrent/unilateral	AC cells	SSZ , AZA	Uveitis and articular activity
9	36	Man	+	PsA	AU recurrent/unilateral	AC cells + vitritis	MTX, SSZ, ADA	Uveitis and articular activity
10	31	Woman	−	PsA	AU recurrent/unilateral	AC cells	MTX, ADA, ETN, CZP, ETN	Uveitis and articular activity
11	36	Man	−	PsA	AU chronic/unilateral	AC cells	MTX, IFX, ADA, ETN	Uveitis
12	32	Man	+	PsA	AU chronic/unilateral	AC cells	MTX, LFN, ETN, IFX, ADA	Uveítis and psoriasis
13	35	Woman	−	PsA	AU chronic/unilateral	AC cells	MTX, SSZ	Uveitis and articular activity
14	40	Man	+	PsA	AU recurrent/unilateral	AC cells + retinal vasculitis	MTX, CsA, ETN, ADA, IFX	Uveitis
15	43	Man	−	nr-axSpA	AU recurrent/unilateral	AC cells	MTX	Uveitis

Golimumab in refractory uveitis related to spondyloarthritis. Multicenter study of 15 patients



Observed Incidence of Uveitis Following Certolizumab Pegol Treatment in Patients With Axial Spondyloarthritis

Table 2. Incidence of uveitis flares in axial SpA patients treated with CZP or placebo to week 24, and with CZP to weeks 48 and 96*

	Uveitis flare rate (95% CI)†	Uveitis flares, no.	Patients with uveitis flares, no.	Exposure, patient-years
Week 24				
CZP				
All patients (n = 218)	3.0 (0.6–8.8)	3	3	100.0
History of uveitis (n = 38)	17.1 (3.5–50.1)	3	3	17.5
No history of uveitis (n = 180)	0.0	0	0	82.5
Placebo				
All patients (n = 107)	10.3 (2.8–26.3)	4	4	38.9
History of uveitis (n = 31)	38.5 (10.5–98.5)	4	4	10.4
No history of uveitis (n = 76)	0.0	0	0	28.5
Week 48				

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Quid des autres agents biologiques dans les uvéites?

Tocilizumab in severe and refractory non-infectious uveitis

M. Papo[1], P. Bielefeld[2], H. Vallet[1], P. Seve[3], B. Wechsler[1], P. Cacoub[1], P. Le Hoang[5], T. Papo[4], B. Bodaghi[5], D. Saadoun[1]

Case*	Age (years)/ Sex	Eye inflammation	Previous treatments	Follow-up (months)	DMARDs	Initial prednisone dose (mg/day)	Prednisone dose at EOF (mg/day)
1	71/F	Birdshot	AZA, IVIg, MMF, ADA	11	MMF	12.5	7.5
2	40/M	Idiopathic bilateral panuveitis and retinal vasculitis	AZA	9	AZA	20	10
3	28/F	Granulomatous bilateral panuveitis	MTX, AZA, MMF, ADA	6	None	15	10
4	42/F	Granulomatous bilateral panuveitis	AZA,MMF, IFNα, MTX, IFX, ADA	8	MTX	30	15
5	47/M	AS bilateral macular oedema and panuveitis	MTX, CYC, CysA, ANA, IFX, ADA, ABA	25	MTX	17	10
6	40/M	Behçet's bilateral panuveitis and retinal vasculitis	CYC, MMF, IFNα, IFX, ADA	6	MMF	30	60
7	48/F	Idiopathic bilateral panuveitis and retinal vasculitis	AZA, MTX, CYC, IFNα, IFX, ADA	8	AZA	10	10
8	21/M	Bilateral macular oedema and panuveitis	MTX, AZA, IFX, ADA, ANA, CyA, IFNα	7	None	10	10

Tocilizumab in severe and refractory non-infectious uveitis

M. Papo[1], P. Bielefeld[2], H. Vallet[1], P. Seve[3], B. Wechsler[1], P. Cacoub[1], P. Le Hoang[5], T. Papo[4], B. Bodaghi[5], D. Saadoun[1]

Table II. Outcome of the 8 patients with severe and refractory non-infectious uveitis treated with tocilizumab.

Case *	Outcome	Visual acuity at baseline (R; L)	Visual acuity at EOF (R; L)	Side effects
1	Improvement	0.4; 0.15	0.045; 0	Bronchitis
2	Improvement	0; 0	0; 0	-
3	Improvement	0.22; 0	0.1; 0	-
4	Non response	1.0; 2.0	1.0; 2.0	-
5	Improvement	0.22; 1.3	0.1; 0.6	-
6	Non response	1.0 ; 2.0	1.0; 2.0	-
7	Improvement	0.7; 2.0	0.7; 2.0	-
8	Improvement	0.1; 0.22	0.1; 0.15	Leucopenia, thrombocytopenia

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Long-Term Effects of Tocilizumab Therapy for Refractory Uveitis-Related Macular Edema

Eye No.	Patient No.	Gender/ Age (yrs)	Uveitis Diagnosis	Uveitis Duration (yrs)	Previous Biologic Response Modifier(s)	Previous Intravitreal Therapy	Concomitant Treatment	Follow-up with Tocilizumab (mos)
1	1	F/31	JIA	25	CyA, ADA, RTX, ABT	Ozurdex (n = 2)	PDN 5 mg/day	14
2	2	F/56	Idiopathic panuveitis	30	CyA, MTX, IFX, ADA	Ozurdex (n = 1)	PDN 5 mg/day	18
3	3	F/60	Birdshot	8	CyA, MMF, ADA	Ozurdex (n = 2)	PDN 2.5 mg/day	16
4	3	F/60	Birdshot	8	CyA, MMF, ADA	Ozurdex (n = 3)	PDN 2.5 mg/day	16
5	4	F/70	Birdshot	6	CyA, MMF, ADA	Ozurdex (n = 2)	PDN 5 mg/day	15
6	4	F/70	Birdshot	6	CyA, MMF, ADA	Ozurdex (n = 3)	PDN 5 mg/day	15
7	5	F/40	Birdshot	2	CyA, IFX, ADA	Ozurdex (n = 1)	None	12
8	5	F/40	Birdshot	2	CyA, IFX, ADA	None	None	12
9	6	F/23	JIA	15	PDN, MTX, ADA	Avastin (n = 1)	PDN 5 mg/day, MTX	13
10	7	F/24	JIA	14	PDN, CyA, MTX, ADA, RTX	None	PDN 5 mg/day, MTX	18
11	7	F/24	JIA	14	PDN, CyA, MTX, ADA, RTX	None	PDN 5 mg/day, MTX	18

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Long-Term Effects of Tocilizumab Therapy for Refractory Uveitis-Related Macular Edema

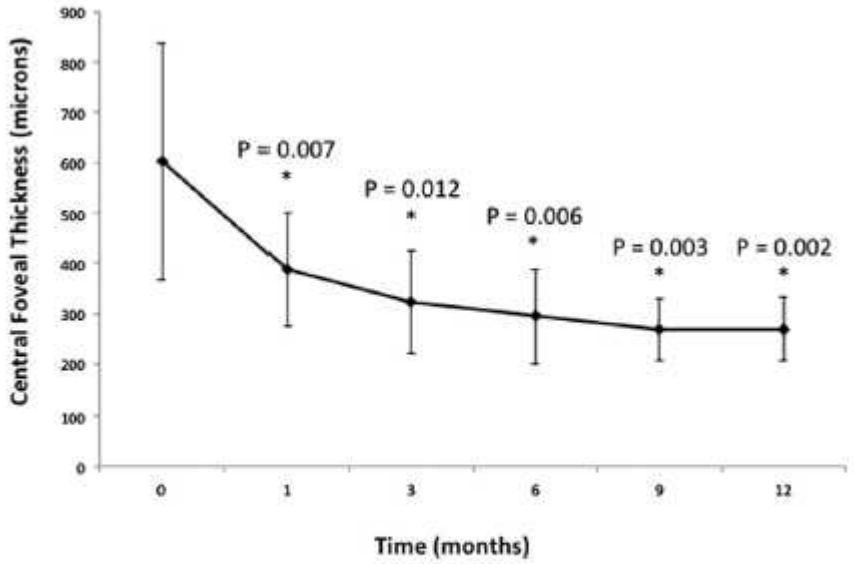


Figure 1. Graph showing the evolution of mean central foveal thickness (CFT) in study eyes (n = 11). Statistical analysis was conducted using the Wilcoxon test (*$P < 0.05$).

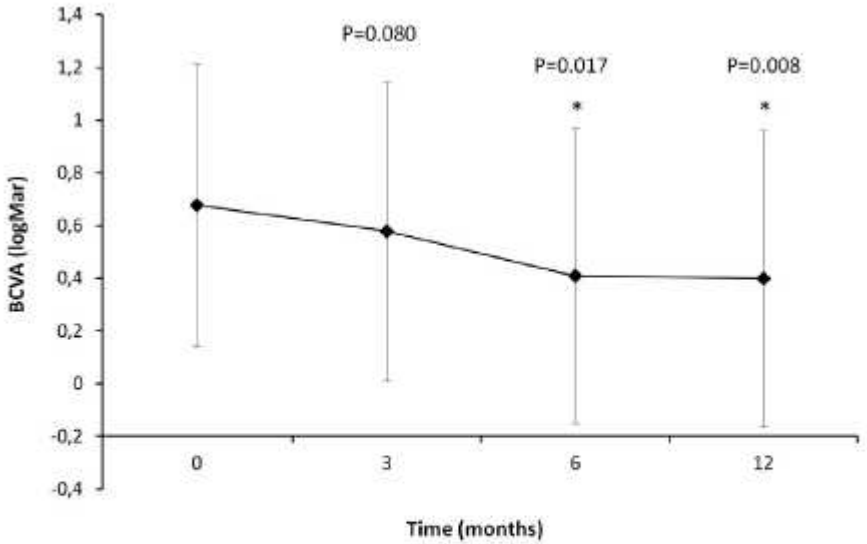
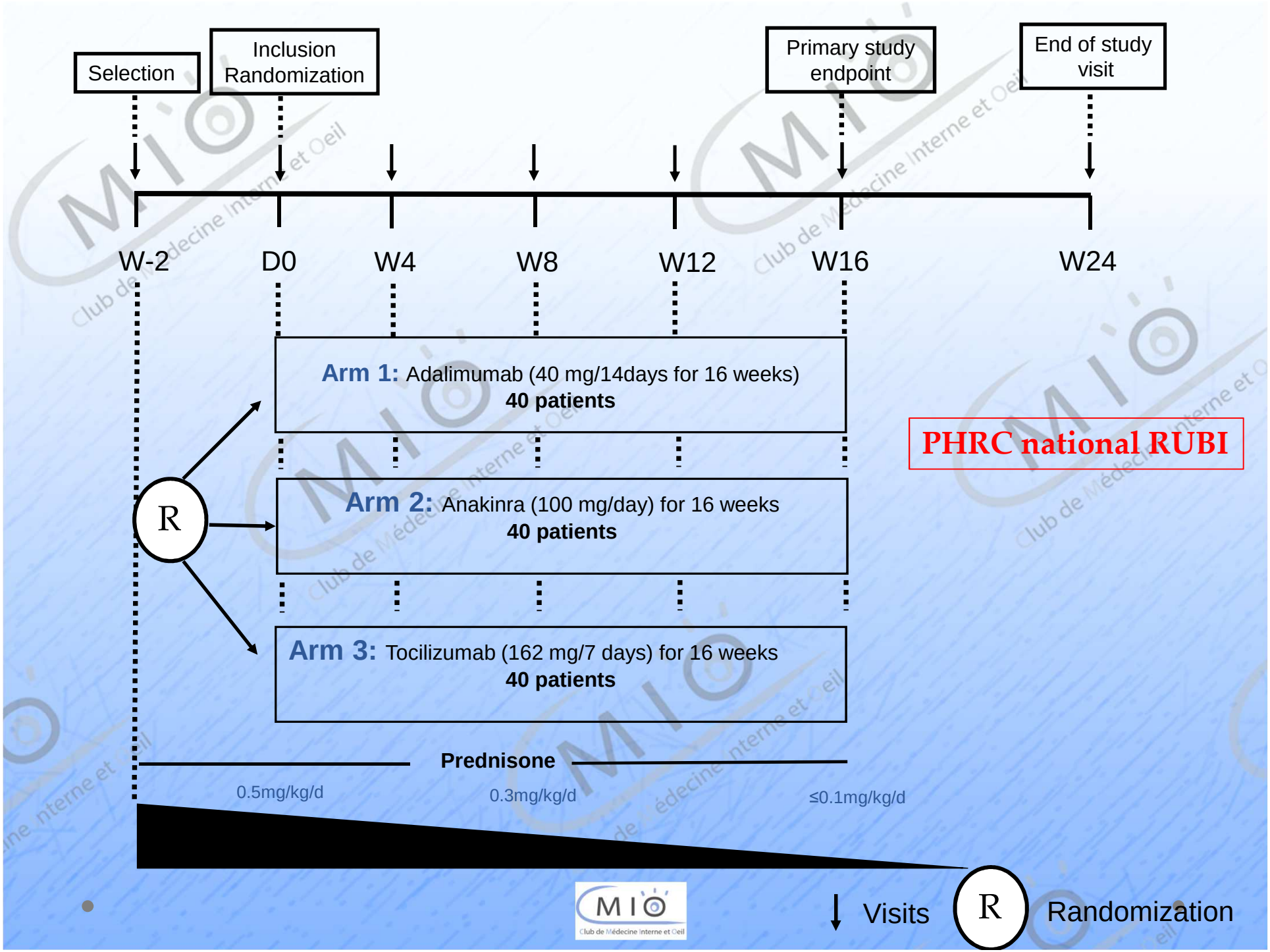


Figure 2. Graph showing mean changes in best-corrected visual acuity (BCVA) in the study eyes (n = 11). Statistical analysis was conducted using the Wilcoxon test (*$P<0.05$). logMAR = logarithm of the minimum angle of resolution.


Selection
Inclusion
Randomization
Primary study endpoint
End of study visit
W-2
D0
W4
W8
W12
W16
W24
Arm 1: Adalimumab (40 mg/14days for 16 weeks)
40 patients
R
Arm 2: Anakinra (100 mg/day) for 16 weeks
40 patients
Arm 3: Tocilizumab (162 mg/7 days) for 16 weeks
40 patients
PHRC national RUBI
Prednisone
0.5mg/kg/d
0.3mg/kg/d
≤0.1mg/kg/d
Visits
R
Randomization

Points clés

- Anti-TNF en première ligne dans les uvéites du Behçet+++

- AMM Adalimumab en première ligne dans les uvéites « sévères » et en seconde ligne dans les uvéites réfractaire et/ou corticodépendantes

- Place des Immunosuppresseurs à établir +++

  - Coût (~12000 euros/an vs 500 euros/an pour IS)
  - Efficacité/Tolérance des anti-TNF vs IS?
  - Survie sans événement sous anti-TNF (60% à 2 ans)

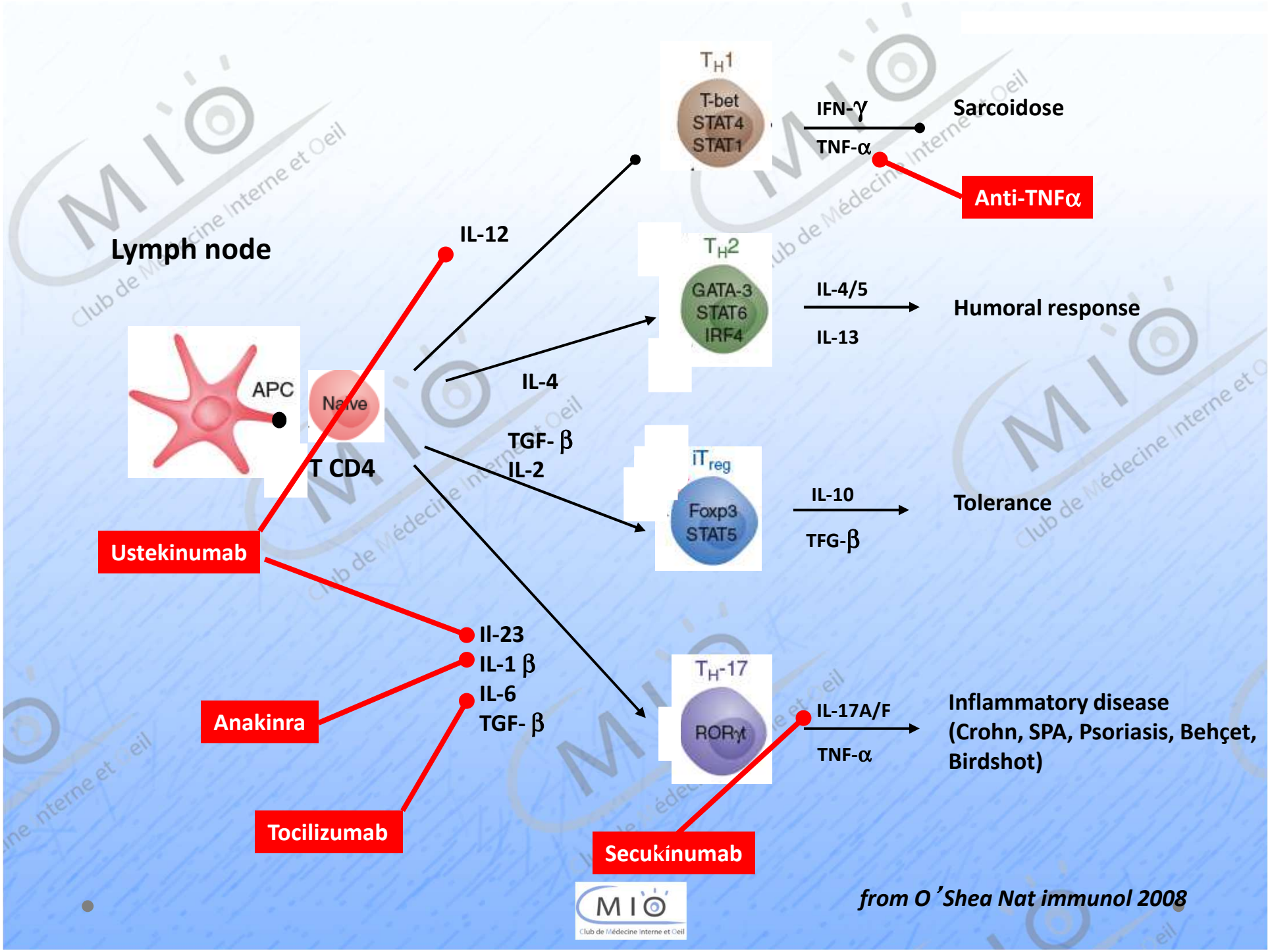
Interleukin 21, Interleukin 23, and Transforming Growth Factor β1 in HLA-A29-Associated Birdshot Retinochoroidopathy

AJO 2013

PAUL YANG AND C. STEPHEN FOSTER

TABLE. T-Cell and Proinflammatory Mediators in the Serum of Birdshot Retinochoroidopathy Patients and Control Volunteers[a]

		BSRC Geometric Mean (Range)			
Mediator	Control Geometric Mean (Range)	Active/Naïve	Active/IMT	Remission/IMT	Remission
IL-1β	2.6 (1.1-14.3)	7.3 (1.5-483.9)	1.4 (1.1-2.4)	4.7 (4.2-7.1)	4.3 (4.2-4.7)
IL-2	58.0 (17.3-311.3)	108.0 (5.0-369.1)	102.9 (68.9-229.7)	15.4 (2.2-68.9)	14.9 (2.2-74.0)
IL-4	12.1 (4.7-20.7)	18.7 (4.7-131.7)	7.1 (4.7-16.5)	10.0 (3.9-15.2)	10.8 (3.9-15.2)
IL-5	8.9 (1.8-82.1)	18.0 (1.8-109.1)	6.5 (1.8-84.5)	2.6 (0.9-3.8)	3.5 (0.9-12.1)
IL-6	16.4 (5.4-43.5)	28.6 (5.4-53.3)	11.0 (5.4-45.1)	10.4 (5.4-14.2)	11.3 (5.7-14.2)
IL-10	3.6 (1.9-8.6)	10.8 (5.5-37.2)	6.2 (1.9-19.4)	3.3 (1.7-4.5)	3.5 (1.7-4.5)
IL-12p70	2.9 (1.7-4.9)	9.5 (3.5-159.4)	4.2 (1.8-9.4)	3.8 (1.8-4.9)	4.2 (2.7-4.9)
IL-13	13.4 (5.9-24.1)	38.1 (19.3-167.8)	9.1 (5.9-21.8)	13.0 (5.9-18.0)	19.8 (14.6-36.2)
IL-17	14.9 (7.7-26.4)	12.8 (7.7-29.5)	13.1 (7.7-38.0)	14.2 (7.7-17.5)	15.8 (11.5-17.5)
IL-17F	13.6 (1.3-54.0)	69.6 (10.0-741.0)	30.4 (10.8-54.7)	8.7 (1.8-49.1)	14.3 (1.8-249.2)
IL-21[b]	613.5[b] (145.1-1475.2)	3699.6[b] (1621.0-8828.0)	540.4 (145.1-2012.3)	429.1 (145.1-726.9)	683.3 (493.2-1298.4)
IL-22	14.5 (9.6-42.7)	64.7 (32.0-282.5)	15.9 (9.6-43.4)	11.9 (8.5-13.6)	12.1 (8.5-13.6)
IL-23[c]	139.9[c] (36.7-1059.8)	1905.6[c] (1143.7-3028.0)	129.2 (36.7-1602.4)	62.0 (36.7-98.2)	172.2 (63.0-451.1)
IL-28	26.3 (11.3-41.8)	19.0 (11.3-29.1)	15.2 (11.3-27.7)	26.3 (9.7-41.8)	29.0 (9.7-41.8)
IFN-γ	107.2 (13.4-508.3)	113.8 (13.4-483.9)	37.6 (13.4-295.7)	49.3 (9.7-102.6)	78.5 (9.7-371.0)
TGF-β1[d]	639.3[d] (130.7-1274.8)	3703.6[d] (1135.9-11 860.0)	850.3 (130.7-2269.0)	513.6 (130.7-691.5)	827.9 (614.4-1599.1)
TNF-α	9.4 (3.1-45.5)	17.9 (3.1-64.6)	6.7 (3.1-31.5)	4.4 (2.7-5.4)	4.5 (2.7-5.4)
TNF-β	7.2 (2.6-33.2)	17.8 (2.6-51.9)	6.4 (2.6-38.2)	4.4 (2.6-5.1)	5.1 (4.8-6.1)
GM-CSF	19.3 (4.6-43.0)	19.6 (4.6-78.7)	14.6 (7.3-20.7)	28.1 (20.7-30.7)	20.4 (6.0-30.7)
MIP-3α	1.3 (0.5-28.8)	1.7 (0.5-6.1)	1.1 (0.5-5.3)	0.6 (0.5-0.6)	0.6 (0.5-0.6)


Lymph node
APC
Naive
T CD4
IL-12
IL-4
TGF- β
IL-2
Il-23
IL-1 β
IL-6
TGF- β
T_H1
T-bet
STAT4
STAT1
IFN-γ
TNF-α
Sarcoidose
Anti-TNFα
T_H2
GATA-3
STAT6
IRF4
IL-4/5
IL-13
Humoral response
iT_{reg}
Foxp3
STAT5
IL-10
TFG-β
Tolerance
T_H-17
RORγt
IL-17A/F
TNF-α
Inflammatory disease
(Crohn, SPA, Psoriasis, Behçet, Birdshot)
Ustekinumab
Anakinra
Tocilizumab
Secukinumab
from O'Shea Nat immunol 2008

Efficacité de l'adalimumab dans le traitement des uvéites d'AJI

Essai randomisé adalimumab (ADA) versus placebo dans les uvéites d'AJI actives malgré le MTX

- Traitement
  - Dose de MTX stable depuis au moins 12 semaines
  - ADA 20 mg (poids < 30 kg) ou 40 mg (poids ≥ 30 kg) en s.c. toutes les 2 semaines pendant 18 mois

  → Suivi 2 ans après randomisation

- Critère principal de jugement : temps jusqu'à la rechute

- Résultats
  - Essai arrêté sur l'analyse intermédiaire après inclusion de 90 patients pour efficacité nettement supérieure de l'ADA
    - HR = 0,27 (IC_{95} : 0,13-0,52) ; p < 0,0001
  - Tolérance sans particularité

→ **Démonstration de l'efficacité de l'ADA associé au MTX dans les uvéites des AJI**

Efficacité et immunogénicité des anti-TNF dans la SPA

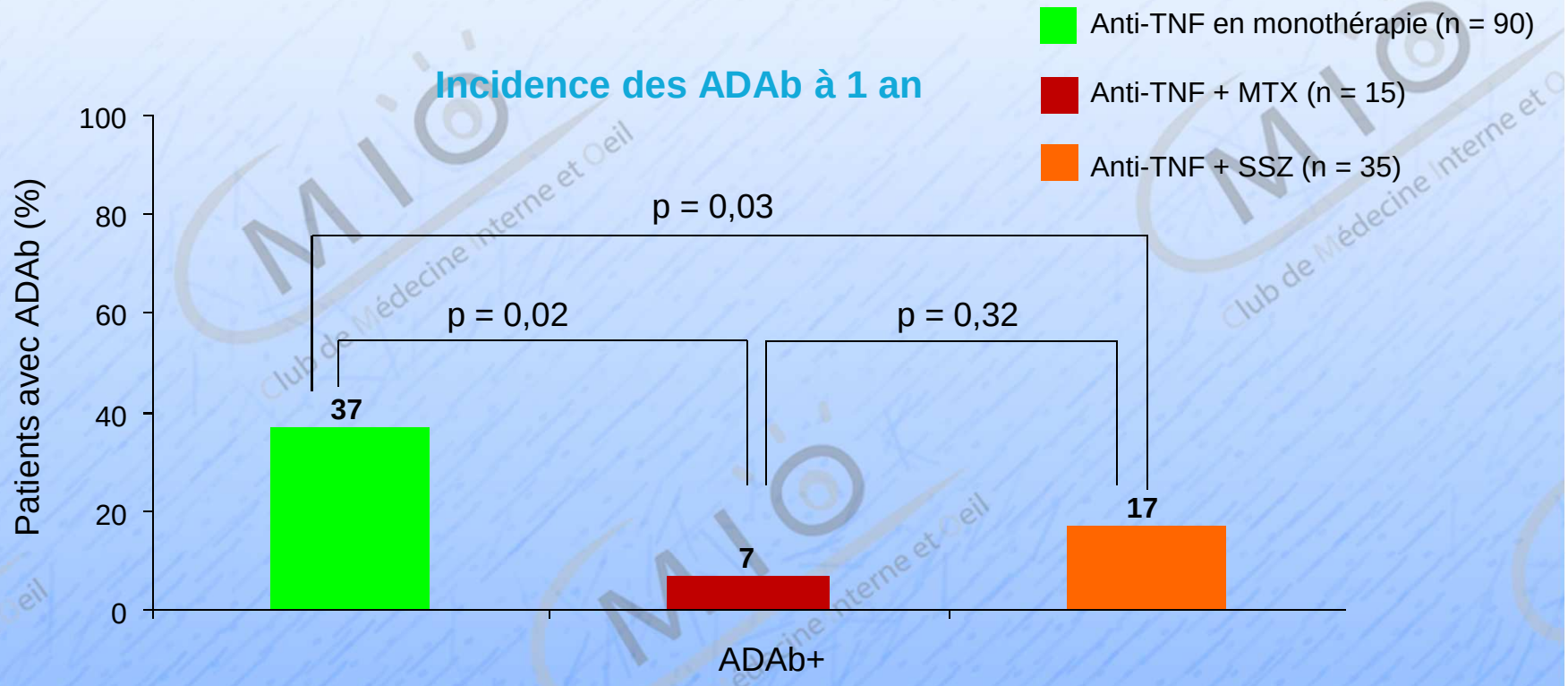
DMARD et immunogénicité des anti-TNF dans la SpA *(1)*

- Objectif
  - Étudier l'effet du MTX ou de la SSZ sur la formation d'anticorps anti-TNF (ADAb) dans une cohorte de SpA traitées par infliximab (IFX) ou adalimumab (ADA)
- Méthode
  - 204 SpA (2 cohortes, 1 espagnole et 1 néerlandaise), dont 117 SA
    - 75 traitées par IFX
    - 129 traitées par ADA

    → Suivi clinique et biologique à M0, M6 et M12
- Caractéristiques des 153 patients sur 204 inclus dans l'étude
  - Hommes : 61 % ; âge moyen : 47 ans ; HLA-B27+ : 72 % ; durée de la maladie : 11 ans ; durée du traitement par anti-TNF : 5,4 ans ; BASDAI : 5,9
  - Traitements associés
    - MTX : 10 %
    - SSZ : 23 %
    - MTX + SSZ : 8,5 %
    - Anti-TNF en monothérapie : 59 %

DMARD et immunogénicité des anti-TNF dans la SpA *(2)*

- Résultats
  - 40/153 patients ont développé des ADAb à 1 an (6 sous IFX et 34 sous ADA)
  - Aucune différence significative entre les caractéristiques des patients ADAb+ et ADAb–



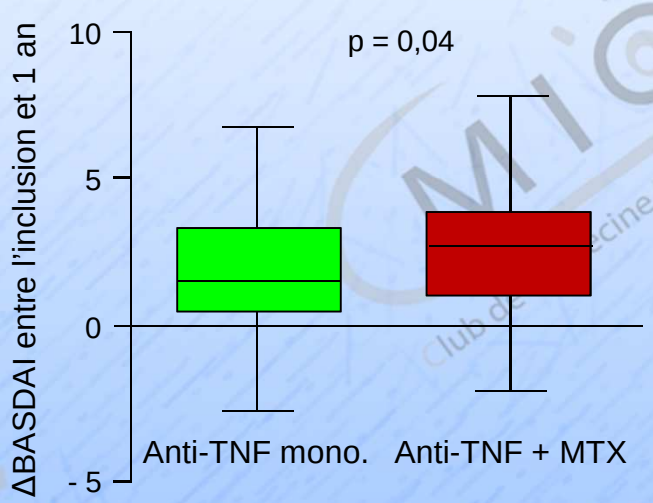
  - Pas de différence significative entre les groupes SSZ et MTX

ACR 2015 - D'après Martinez A (2147)

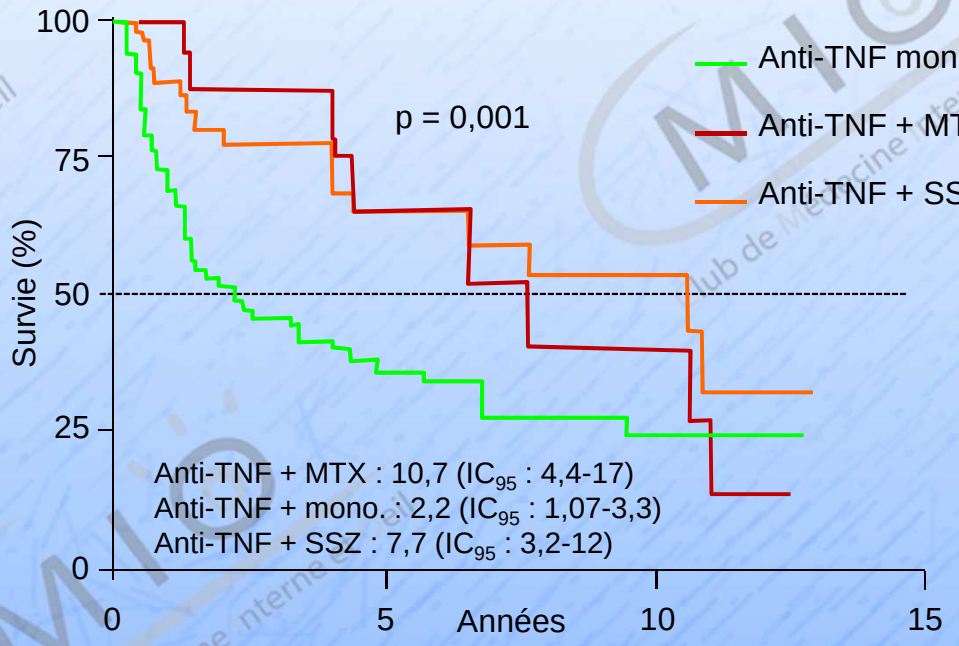
DMARD, réponse thérapeutique et survie des anti-TNF dans la SpA

- Résultats
  - Pourcentage de patients atteignant la LDA définie par BASDAI < 4 et CRP normale : 19 % dans le groupe ADAb+ et 34 % dans le groupe ADAb– (p = 0,03)

ΔBASDAI meilleur pour les patients traités par anti-TNF + MTX que par anti-TNF en monothérapie



Survie de l'anti-TNF plus longue pour les patients cotraités par SSZ ou MTX

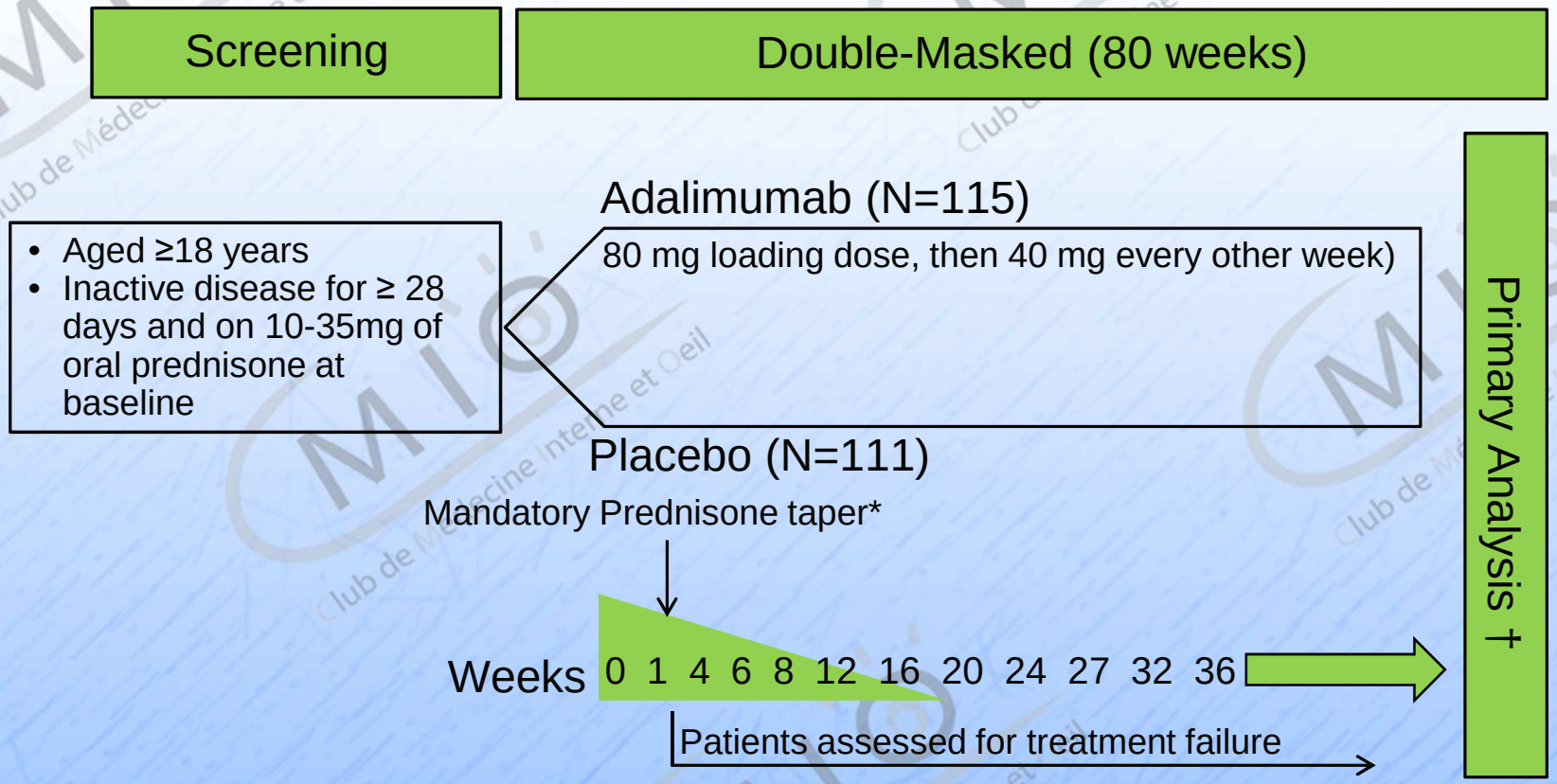


➔ **Le traitement concomitant par un DMARD (MTX ou SSZ) chez les patients sous anti-TNF est associé à une moindre formation d'ADAb, à une meilleure réponse et à une meilleure survie de l'anti-TNF**

ACR 2015 - D'après Martinez A (2147)

Adalimumab et uvéites: Etude Visual2

Schéma de l'étude VISUAL II



*Prednisone was tapered from weeks 2 to 19; all patients discontinued prednisone by week 19. Patients may have been using 1 immunosuppressive therapy and/or topical steroids at pre-defined, stable doses. †The study ended when the 106th treatment failure had occurred. Placebo (PBO).

Nguyen QD *et al*, Lancet 2016, 16 August, http://dx.doi.org/10.1016/S0140-6736 (16)31339-3

Critère principal de jugement : délai de survenue de la rechute

Parameter	Rechute At and After Week 2
Inflammatory, chorioretinal and/or inflammatory retinal vascular lesions	New active, inflammatory lesions relative to Baseline
Anterior Chamber Cell grade (SUN Criteria)	2-step increase relative to best state achieved**
Vitreous Haze grade (NEI/SUN criteria)	2-step increase relative to best state achieved**
Visual Acuity (ETDRS)	Worsening of BCVA by ≥ 15 letters relative to best state achieved

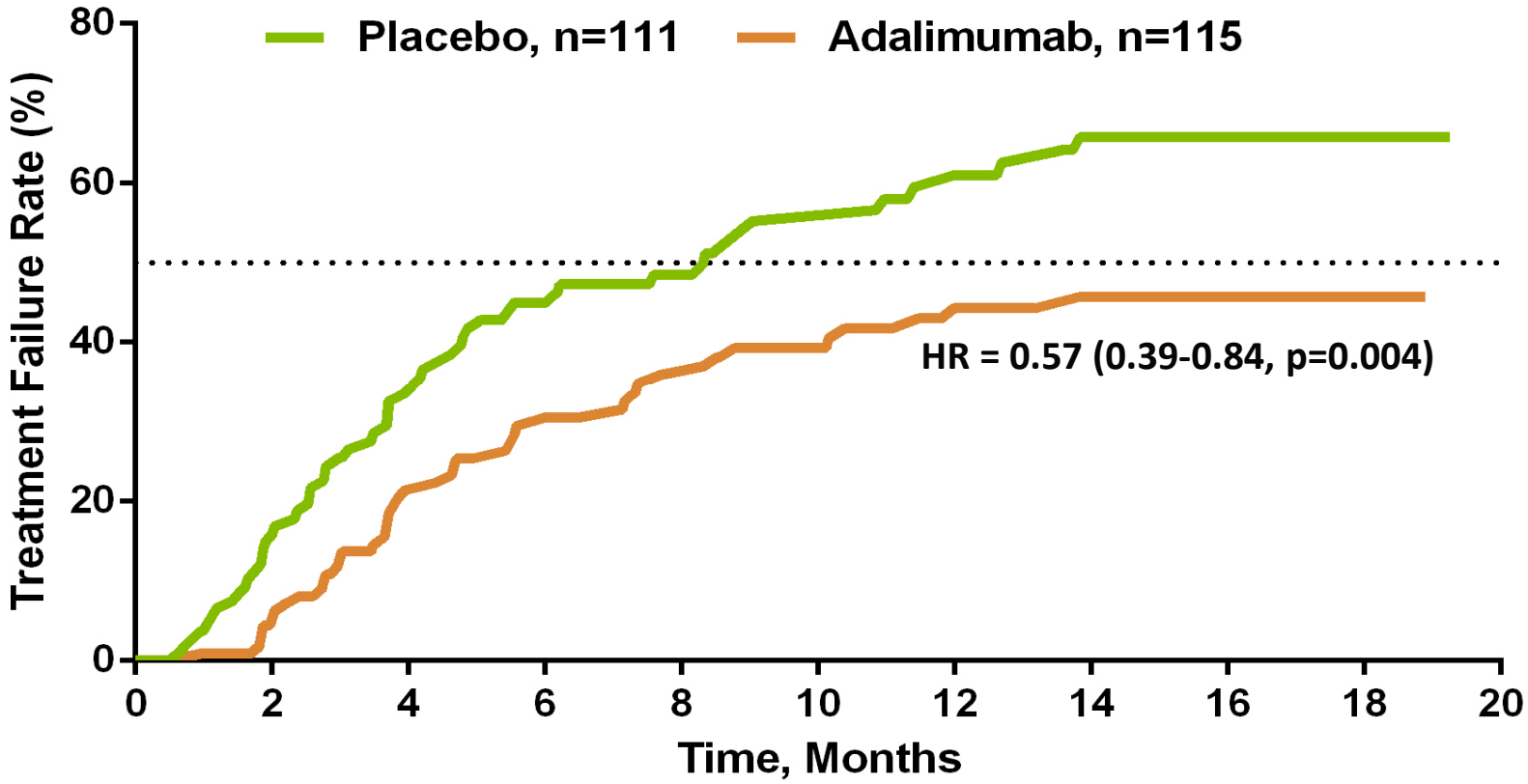
Caractéristiques de la population (ITT population)

	Placebo (n=111)	Adalimumab (n=115)
Sex, Female; n (%)	72 (64.9)	66 (57.4)
Race, White; n (%)	93 (83.8)	96 (83.5)
Age, years; mean ± SD	42.2±14.0	42.9±12.9
Type of uveitis, n (%)		
Intermediate	30 (27.0)	17 (14.8)
Posterior	34 (30.6)	39 (33.9)
Panuveitis	46 (41.4)	57 (49.6)
Diagnosis, n (%)		
Idiopathic	40 (36.0)	29 (25.2)
Birdshot Choroidopathy	15 (13.5)	15 (13.0)
Multifocal Choroiditis & panuveitis	2 (1.8)	5 (4.3)
Vogt Koyanagi Harada	25 (22.5)	26 (22.6)
Sarcoidosis	14 (12.6)	18 (15.7)
Behcet's	6 (5.4)	10 (8.7)
Other	9 (8.1)	12 (10.4)
Uveitis Duration, months; mean±SD	62.9±67.7	59.5±64.5

Nguyen QD *et al*, Lancet 2016, 16 August, http://dx.doi.org/10.1016/S0140-6736 (16)31339-3

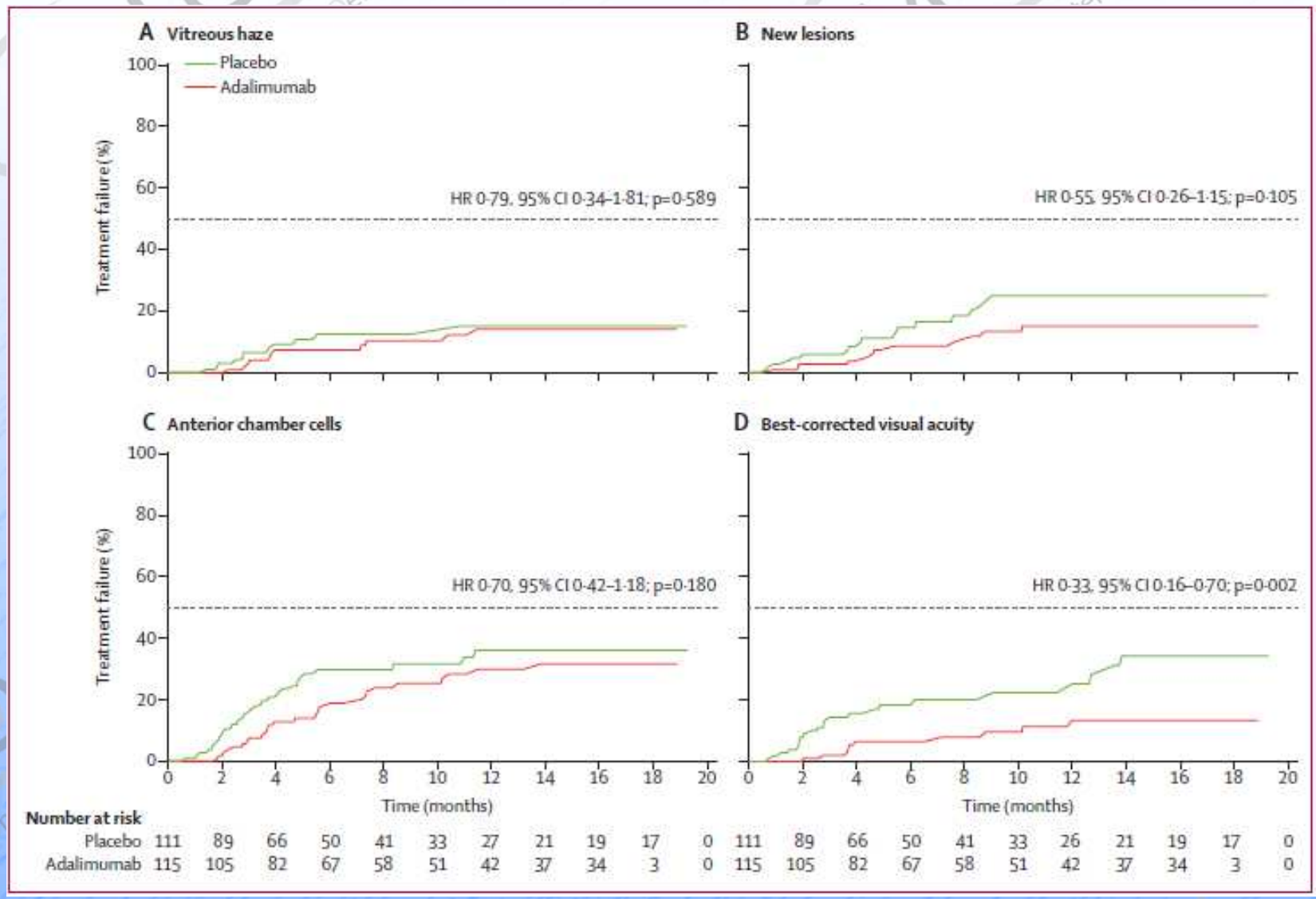
MIO
Club de Médecine Interne et Oeil

Résultats sur le critère principal de jugement : Délai de survenue de la rechute



- Decrease of 43% in the risk of having TF in the ADA group compared to PBO
- Median time to TF (PBO vs ADA); 8.3 months vs not estimable (more than half of the ADA-treated patients did not experience TF)

Résultats selon les 4 composants du critère principal de rechute



Tolérance

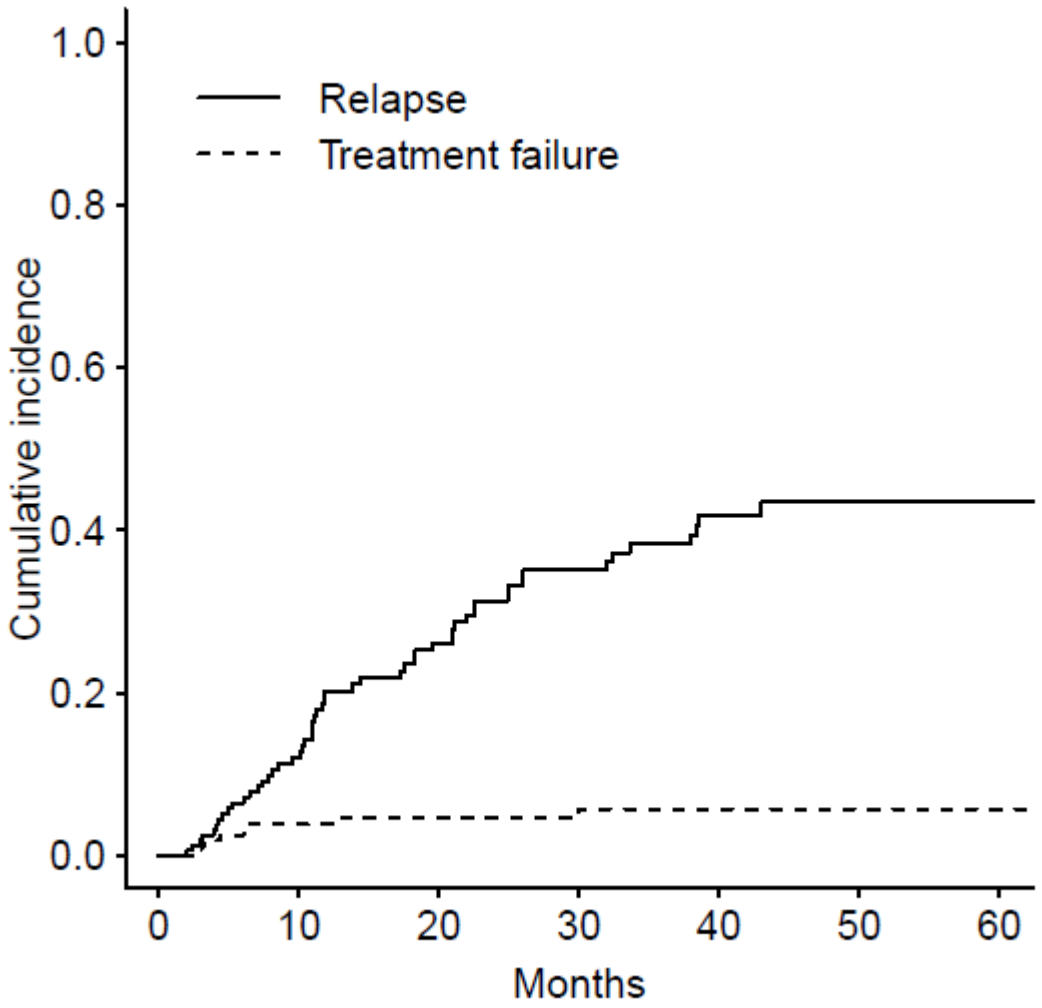
Adverse Events (AE)	Placebo (N=114) PYs=71.0 Events (E/100PY)	Adalimumab (N=115) PYs=94.5 Events (E/100PY)
Any AE	642 (905)	831 (879)
SAE	10 (14.1)	13 (13.8)
AE leading to discontinuation	7 (9.9)	11 (11.6)
Serious infections	2 (2.8)	3 (3.2)
Opportunistic infections (excluding oral candidiasis and TB)	0	0
Malignancy	0	1 (1.1)*
Any latent TB	1 (1.4)	3 (3.2)
Any demyelinating disease	0	0
Injection site reactions	16 (22.6)	36 (38.1)
AE leading to death	0	2 (2.1)**

* One event of non-serious squamous cell carcinoma of skin (day 210; resolved on day 215; ADA treatment was not interrupted).
** One death due to 2 fatal AEs of aortic dissection and cardiac tamponade (18 days after last ADA dose), not related to ADA treatment.

Conclusions

- In steroid-dependent patients with inactive, non-infectious uveitis, adalimumab significantly lowered the risk of uveitic flare or loss of visual acuity.
- Adverse events were similar between groups.
  No new safety signals were identified.

Response to anti-TNFα



Factors associated to relapse

	Univariate analysis		Multivariate analysis	
	SHR 95%CI	P-value	OR 95%CI	P-value
Age	1 [0.98-1.01]	0.69		
Uveitis				
Panuveitis	1.10 [0.61-1.97]	0.76		
Bilateral	0.51 [0.26-0.99]	0.046	0.55 [0.28-1.09]	0.086
Granulomatosis	0.84 [0.42-1.71]	0.64		
Vasculitis	0.59 [0.31-1.11]	0.10	0.63 [0.33-1.18]	0.15
Macular edema	1.07 [0.58-1.95]	0.84		
Number of uveitis flares before anti-TNFα treatment	1.33 [0.72-2.45]	0.37		
Etiology				
IJA	1			
Behçet	0.71 [0.35-1.44]	0.34		
Associated treatment				
Corticosteroid >20mg/d	0.96 [0.55-1.67]	0.89		
Immunosuppressant	1.15 [0.63-2.08]	0.65		

Systematic Review of Anti-Tumor Necrosis Factor-alpha Therapy for Treatment of Immune-mediated Uveitis

Miguel Cordero-Coma, MD, FEBOpth[1], Taygan Yilmaz, MPH[2], and Sumru Onal, MD, FEBOphth[3]

TABLE 1 Summary table reviewing the present evidence.

Treatment	Conclusion	Recommendation	Evidence level
Adalimumab	Effective in autoimmune uveitis	C	2b
Certolizumab	Not evaluated in autoimmune uveitis	N/A	N/A
Etanercept	Ineffective in autoimmune uveitis	A	1b
Golimumab	Effective in autoimmune uveitis	C	4
Infliximab	Effective in auto-immune uveitis	C	2b

Ocular Immunology & Inflammation, 21(1), 19–27, 2013