VI Reunión GEAS

Terapias biológicas en la enfermedad de Behçet

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GEAS

SEMI

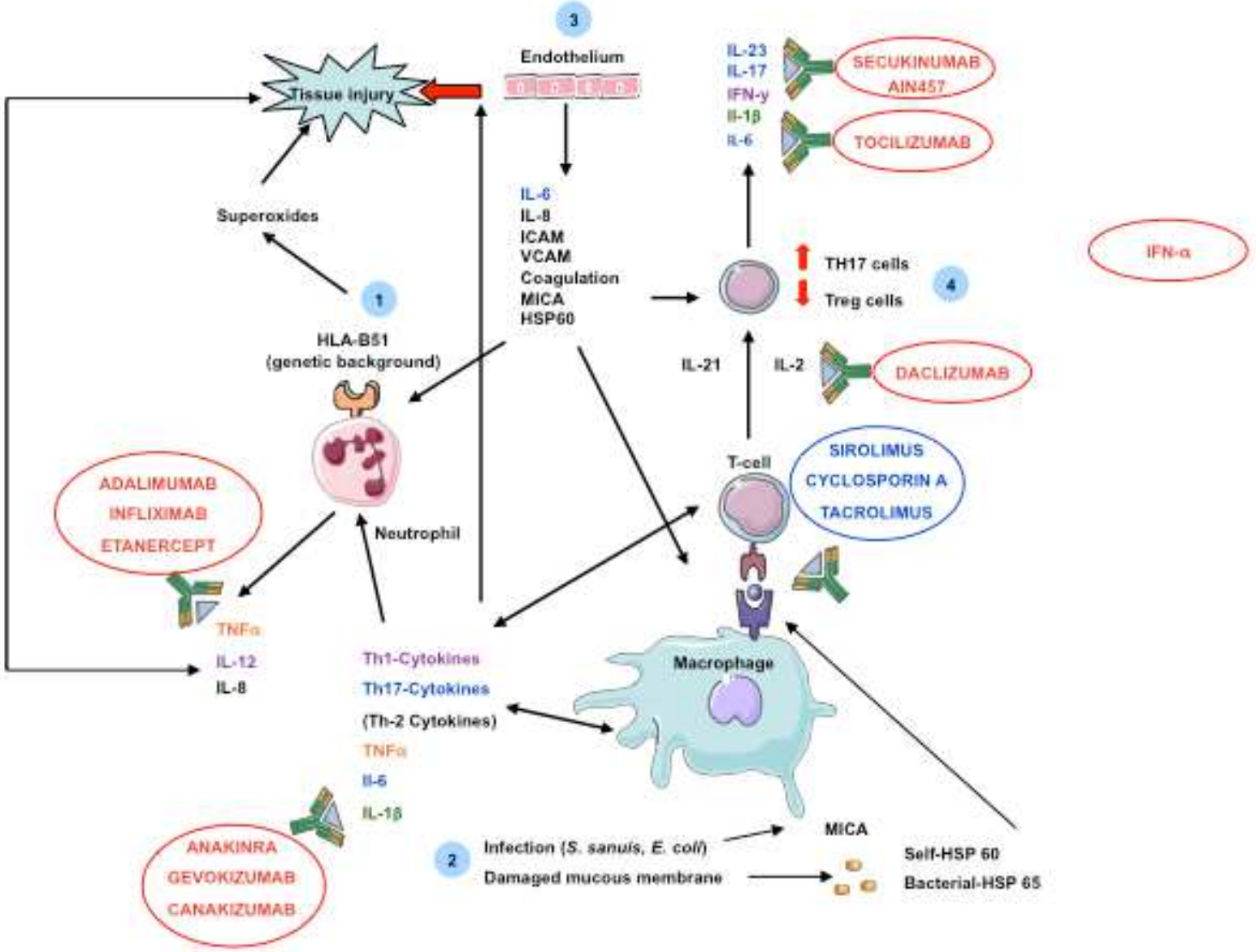
¿Por qué?

Medicina basada en la evidencia

Medicina basada en la eminencia

Medicina basada en la ocurrencia

Base fisiopatológica



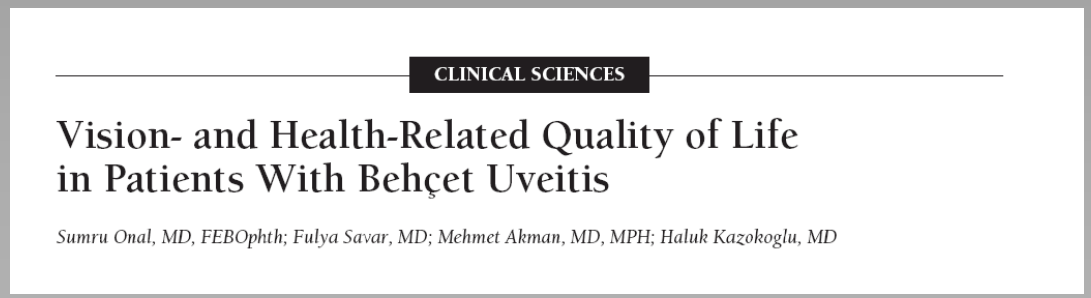
Mesquida M, et al. Int Ophthalmol. 2013 Jun 1. [Epub ahead of print]

Terapias biológicas en la enfermedad de Behçet
¿Por qué?

Refractariedad al tratamiento convencional

Intolerancia / efectos adversos

Calidad de vida



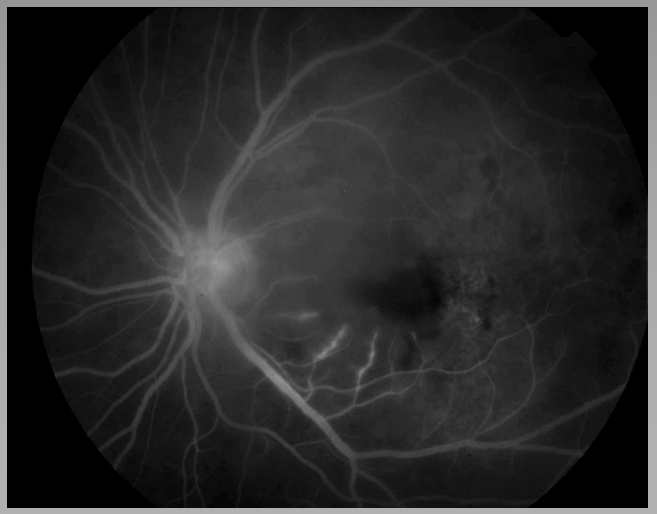
CLINICAL SCIENCES

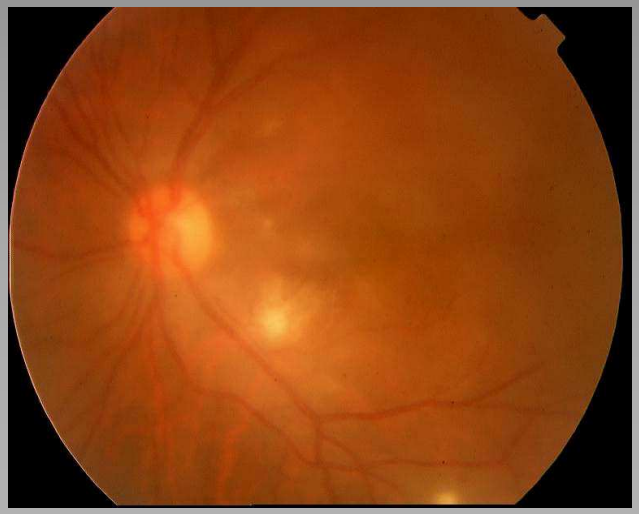
Vision- and Health-Related Quality of Life in Patients With Behçet Uveitis

Sumru Onal, MD, FEBOphth; Fulya Savar, MD; Mehmet Akman, MD, MPH; Haluk Kazokoglu, MD

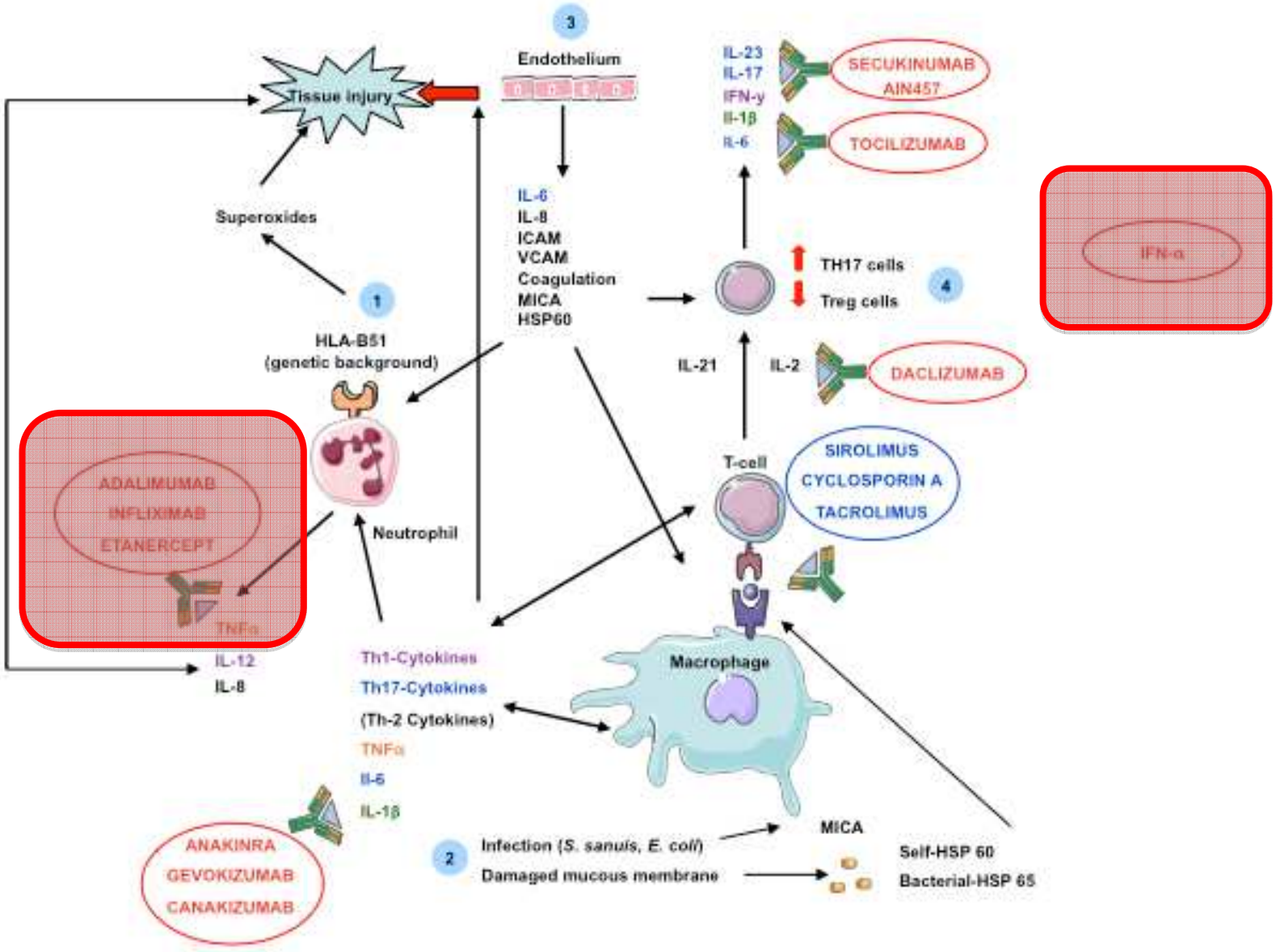
Terapias biológicas en la enfermedad de Behçet
¿Por qué?

- Afectación ocular en un 70%
  - 25% de los casos pérdida AV a los 10 años
- Ceguera legal (AV<20/200)
  - 50-90% casos en Japón y Turquía
  - 25% de los casos en USA





Evidencia



Mesquida M, et al. Int Ophthalmol. 2013 Jun 1. [Epub ahead of print]

Terapias biológicas en la enfermedad de Behçet

Recomendaciones de uso

EULAR recommendations for the management of Behçet disease

G Hatemi,[1] A Silman,[2] D Bang,[3] B Bodaghi,[4] A M Chamberlain,[5] A Gul,[6] M H Houman,[7] I Kötter,[8] I Olivieri,[9] C Salvarani,[10] P P Sfikakis,[11] A Siva,[12] M R Stanford,[13] N Stübiger,[14] S Yurdakul,[1] H Yazici[1]

Ann Rheum Dis 2008;67:1656-62

Terapias biológicas en la enfermedad de Behçet
Recomendaciones de uso

Recommendation
Any patient with BD and inflammatory eye disease affecting the posterior segment should be on a treatment regime that includes azathioprine and systemic corticosteroids.
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 ciclosporine A or infliximab be used in combination with azathioprine and corticosteroids; alternatively IFNα with or without corticosteroids could be used instead.
There is no firm evidence to guide the management of major vessel disease in BD. For the management of acute deep vein thrombosis in BD immunosuppressive agents such as corticosteroids, azathioprine, cyclophosphamide or ciclosporine A are recommended. For the management of pulmonary and peripheral arterial aneurysms, cyclophosphamide and corticosteroids are recommended.
Similarly there are no controlled data on, or evidence of benefit from uncontrolled experience with anticoagulants, antiplatelet or antifibrinolytic agents in the management of deep vein thrombosis or for the use of anticoagulation for the arterial lesions of BD.
There is no evidence-based treatment that can be recommended for the management of gastrointestinal involvement of BD. Agents such as sulfasalazine, corticosteroids, azathioprine, TNFα antagonists and thalidomide should be tried first before surgery, except in emergencies.
In most patients with BD, arthritis can be managed with colchicine.
There are no controlled data to guide the management of CNS involvement in BD. For parenchymal involvement agents to be tried may include corticosteroids, IFNα, azathioprine, cyclophosphamide, methotrexate and TNFα antagonists. For dural sinus thrombosis corticosteroids are recommended.
Ciclosporine A should not be used in BD patients with central nervous system involvement unless necessary for intraocular inflammation.
The decision to treat skin and mucosa involvement will depend on the perceived severity by the doctor and the patient. Mucocutaneous involvement should be treated according to the dominant or codominant lesions present.
Topical measures (ie, local corticosteroids) should be the first line of treatment for isolated oral and genital ulcers.
Acne-like lesions are usually of cosmetic concern only. Thus, topical measures as used in acne vulgaris are sufficient.
Colchicine should be preferred when the dominant lesion is erythaema nodosum.
Leg ulcers in BD might have different causes. Treatment should be planned accordingly.
Azathioprine, IFNα and TNFα antagonists may be considered in resistant cases.

Ann Rheum Dis 2008;67:1656-62

Terapias biológicas en la enfermedad de Behçet
Recomendaciones de uso

Recommendation no.	Category of evidence	Strength of recommendation
1 Eye involvement	Ib	A/D
2 Refractory eye involvement	Ib/IIb	C/D
3 Major vessel disease	III	C
4 Anticoagulation	IV	D
5 Gastrointestinal involvement	III	C
6 Joint involvement	Ib	A
7 Neurological involvement	III	C/D
8 Ciclosporine A neurotoxicity	III	C
9 Mucocutaneous involvement	Ib	A/C

Ann Rheum Dis 2008;67:1656-62

Terapias biológicas en la enfermedad de Behçet
Recomendaciones de uso

Anti-TNF therapy in the management of Behçet's disease—review and basis for recommendations

P. P. Sfikakis, N. Markomichelakis, E. Alpsoy[1], S. Assaad-Khalil[2], B. Bodaghi[3], A. Gul[4], S. Ohno[5], N. Pipitone[6], M. Schirmer[7], M. Stanford[8], B. Wechsler[3], C. Zouboulis[9], P. Kaklamanis and H. Yazici[4]

Rheumatology 2007;47:736-41

Terapias biológicas en la enfermedad de Behçet
Recomendaciones de uso

Subset	New manifestation	Recurrent/refractory cases
Posterior segment intraocular inflammation	In unilateral involvement with visual acuity <0.2 Infliximab[a] can be considered; in bilateral involvement Infliximab[a] can be used as first line treatment	In patients with two or more relapses/year despite, or intolerant to, adequate doses[b] of AZA and/or Cs, or, interferon α-2a, combined with prednisolone (<7.5 mg/day), infliximab[c] can be used
Anterior segment intraocular inflammation	Not recommended	Not recommended
Parenchymal CNS involvement	Not recommended	In patients refractory to treatment with pulse cyclophosphamide and prednisolone (1 mg/kg/day), or in those who relapse while on maintenance with AZA[b] and prednisolone (<7.5 mg/day) infliximab[c] may be tried
Intestinal inflammation	Not recommended	In patients that have failed two immunosuppressive agents[b] and require prednisolone at a dosage >7.5 mg/day, Infliximab[c] may be used
Major vessel involvement	Not enough data	Not enough data
Mucocutaneous manifestations	Not recommended	In patients with poor quality of life despite, or intolerant to, adequate doses[b] of AZA, colchicine or thalidomide and require prednisolone at a dosage >7.5 mg/day, etanercept[d] or Infliximab[c] may be used
Arthritis	Not recommended	In patients that have failed two immunosuppressive agents[b] including MTX and require prednisolone at a dosage >7.5 mg/day, etanercept[d] or Infliximab[c] may be used

Rheumatology 2007;47:736-41

Terapias biológicas en la enfermedad de Behçet

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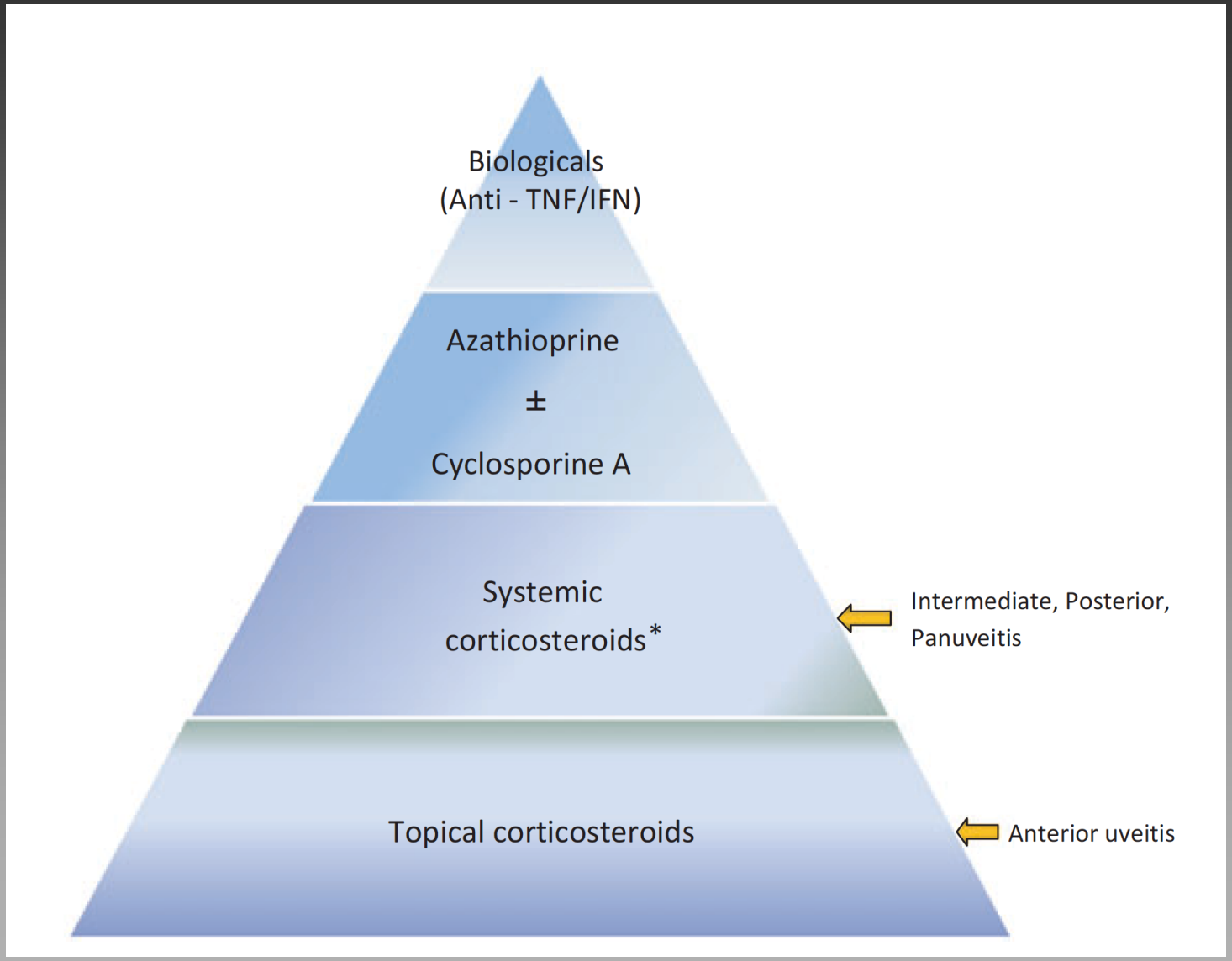
Terapias biológicas en la enfermedad de Behçet



Acta Ophthalmol 2013 ;91:297-306

Agentes anti-TNF en la enfermedad de Behçet

Anti-TNF Agents for Behçet's Disease: Analysis of Published Data on 369 Patients

Aikaterini Arida, MD, Kalliopi Fragiadaki, MD, Eirini Giavri, MD, and Petros P. Sfikakis, MD

Semin Arthritis Rheum 2011;41:61-70

Terapias biológicas en la enfermedad de Behçet
Agentes anti-TNF

Table 1 Disposition of Articles Appearing in Medline through March 2010 on the Use of Anti-TNF Agents in Patients[a] with Behçet's Disease

	Infliximab		Etanercept		Adalimumab	
	Studies	Patients	Studies	Patients	Studies	Patients
Case reports	53	59	9	11	8	8
Case series	11	30	2	6	3	9
Retrospective[b]	8	62	0	0	2	11
Prospective[b]	16	174	—	—	0	0
RCTs	—	—	1	20	—	—
Total articles	88	325	12	37	13	28

[a]Twenty patients received more than 1 anti-TNF agent.
[b]Studies describing 5 or more patients each.

Semin Arthritis Rheum 2011;41:61-70

Terapias biológicas en la enfermedad de Behçet
Agentes anti-TNF

Indicaciones y tasas de respuesta

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

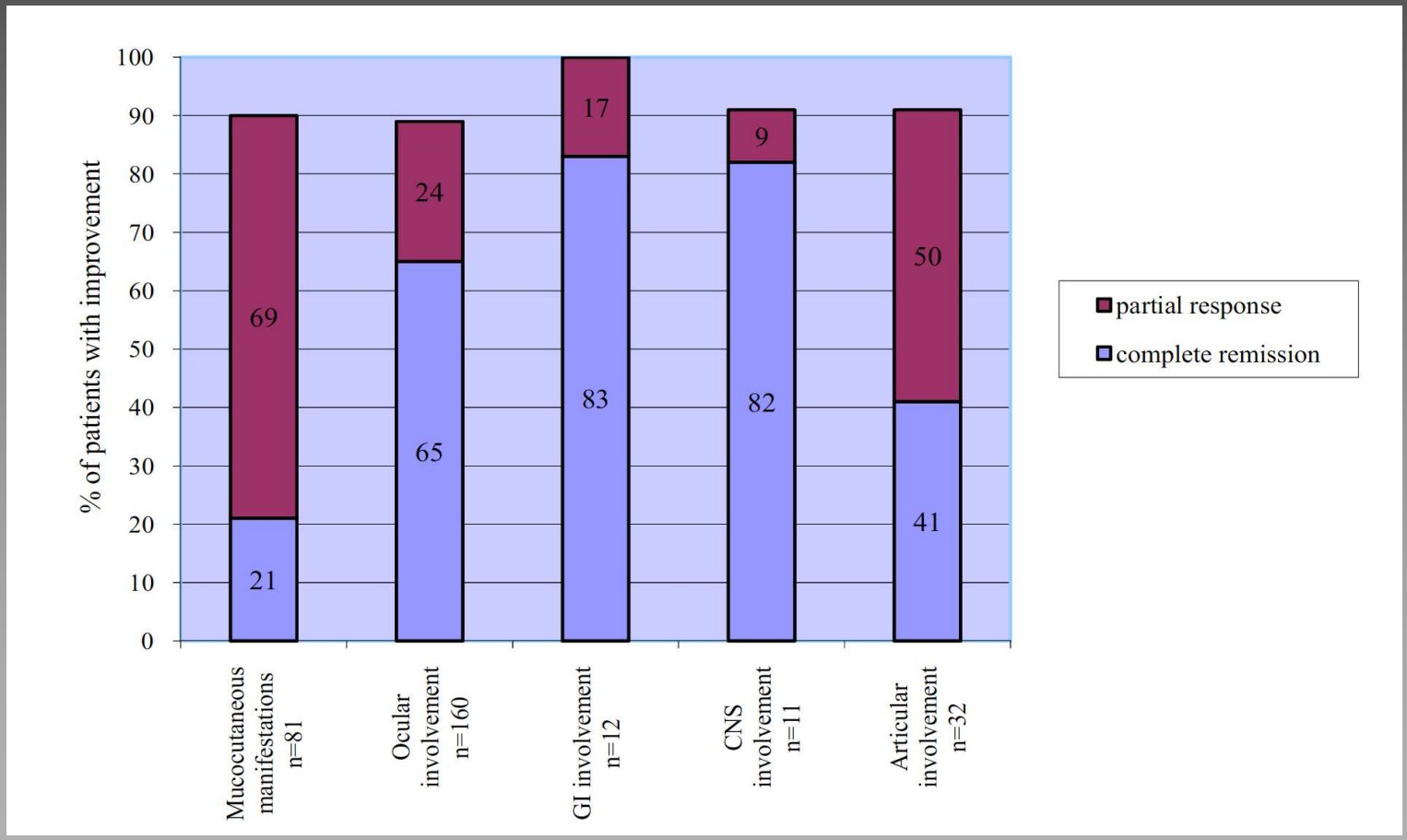
	Improving Patients/Treated Patients[a]		
	Infliximab	Etanercept[b]	Adalimumab
Oral ulcers	110/122 (91%)	8/10 (82%)	8/11 (73%)
Genital ulcers	76/80 (96%)	5/7 (71%)	6/7 (86%)
Skin involvement	51/67 (77%)	2/3 (67%)	4/5 (80%)
Erythema nodosum	13/16 (81%)	1/1 (100%)	1/1 (100%)
Ocular involvement	233/262 (89%)	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;41:61-70

Terapias biológicas en la enfermedad de Behçet
Agentes anti-TNF

Respuesta completa y parcial



Semin Arthritis Rheum 2011;41:61-70

Terapias biológicas en la enfermedad de Behçet
Agentes anti-TNF

Efectos adversos

Reported Adverse Reaction	Number of Patients (Ref. no.)
Respiratory track infection	14 (19,42,44,47)
Pneumonocystis carinii pneumonia	2 (13,48)
Legionella pneumophila pneumonia	1 (58)
Reactivation of TB	4 (14,38,45,58)
De novo TB	1 (90)
Non-Hodgkin lymphoma	1 (50)
Cryptococcal meningitis	1 (89)
Perianal abscess	1 (32)
Varicella zoster infection.	2 (18,88)
Upper arm pyomyostitis	1 (96)
Worsening of osteomalacia	1 (86)
CMV colitis	1 (57)
Psoriasis	2 (91)
Erythema nodosum (de novo)	2 (97)
Cellulitis of forearm (ETN)	1 (20)
Bacterial endocarditis by Staphylococcus warneri (ETN)	1 (24)
Urticaria and Angioedema (ADL)	1 (98)

Semin Arthritis Rheum 2011;41:61-70

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Terapias biológicas en la enfermedad de Behçet
Nuestra Experiencia

Paciente	Anti-TNF	Tiempo	IS Previos	IS actual	Remisión	Retirada anti-TNF
1 LBG	IFX	19 m	3	0	SI	SI
2 JPC	IFX, ADA	30 m	4	PDN	SI	NO
3 BAG	IFX, ADA	36 m	1	PDN	SI	NO
4 AIGC	IFX	16 m	3	0	SI	SI
5 JMAL	IFX, ADA	36 m	2	PDN	SI	NO
6 JBB	IFX, ADA	35 m	4	PDN, CSA	SI	NO
7 ARE	IFX, ADA	26 m	1	0	SI	NO
8 PCV	IFX	8 m	2	0	SI	NO
9 OGM	ADA	2 m	3	PDN, AZA	NO	NO
10 MALG	IFX	20 m	4	PDN, AZA	NO	NO

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Terapias biológicas en la enfermedad de Behçet
Nuestra Experiencia

Adalimumab for the treatment of Behçet's disease: experience in 19 patients

Daniela Perra[1,*], Marco A. Alba[1,*], José Luis Callejas[2], Marina Mesquida[3], Raquel Ríos-Fernández[2], Alfredo Adán[3], Norberto Ortego[2], Ricard Cervera[1] and Gerard Espinosa[1]

Rheumatology (Oxford) 2012;51:1825-31

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Terapias biológicas en la enfermedad de Behçet
Nuestra Experiencia

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Características generales

	n (%)
Sex, male/female	7/12 (37/63)
Age at diagnosis, median (IQR), years	34 (15)
HLA-B5 positivity	6 (31.6)
Clinical manifestations at the start of adalimumab[a]	
Ocular involvement	10 (50.6)
Panuveitis	8
Retinal vasculitis	3
Recurrent scleritis	1
Scleritis with recurrent anterior uveitis	1
Mucocutaneous involvement	9 (47.4)
Severe aphthosis	8
Severe folliculitis	3
Cutaneous vasculitis	2
Erythema nodosum	1
Gastrointestinal	2 (10.5)
Anal fistula	2
Peripheral nervous system	1 (5.3)
Immunosuppressive and immunomodulatory drugs used before adalimumab[b]	2 (1)
Colchicine	13
Prednisone	16
MTX	8
AZA	5
CSA	3
CYC	1
TNF-α inhibitor	7
Infliximab	5
Etanercept	2

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Terapias biológicas en la enfermedad de Behçet Nuestra Experiencia

Pacientes con afectación ocular

Patient	Age, years	Sex	Type of eye involvement	Eye	Initial BCVA	Final BCVA	Previous treatment	Final treatment	Response/time to response (weeks)	Time on adalimumab, months	Relapse
1	28	F	Panuveitis	R	0.4	0.7	PDN/AZA/colchicine	MTX	Complete (2)	5	No
				L	0.8	1.2					
2	40	F	Panuveitis	R	1.2	1	PDN/MTX/etanercept	MTX	Complete (4)	24	No
				L	0.15	0.05					
3	60	M	Panuveitis	R	1.2	0	CSA/colchicine	Colchicine	Complete (4)	12	No
				L	0.05	0.05					
4	26	M	Panuveitis	R	0.1	1	PDN/MTX/ infliximab	PDN/AZA	Complete (2)	29	Yes
				L	0.1	0.7					
5	26	M	Panuveitis + retinal vasculitis	R	0.15	0.15	PDN/CSA/infliximab/colchicine	PDN	Complete (4)	23	Yes
				L	1	0.1					
6	24	M	Panuveitis	R	0.15	0.2	PDN/infliximab	PDN	Complete (4)	27	Yes
				L	0.5	0.5					
7[a]	41	M	Panuveitis + retinal vasculitis	R	1	1	PDN/infliximab/colchicine	—	Complete (2)	10	No
				L	0.8	1					
8[a]	24	F	Panuveitis + retinal vasculitis	R	1	1	PDN/infliximab	PDN	Complete (4)	27	No
				L	0.4	0.2					

Rheumatology (Oxford) 2012;51:1825-31

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Terapias biológicas en la enfermedad de Behçet Nuestra Experiencia

Pacientes con afectación extra-ocular

Manifestation	*n*	Complete response, *n* (%)	Partial response, *n* (%)	Global response, *n* (%)
Severe aphthosis	8	5 (62.5)	3 (37.5)	8 (100)
Severe folliculitis	3	–	3 (100)	3 (100)
Cutaneous vasculitis	2	1 (50)	–	1 (50)
Erythema nodosum	1	–	1 (100)	1 (100)
Anal fistula	2	1 (50)	–	1 (50)
Peripheral neuropathy	1	1 (50)	–	1 (50)
Total	17	8 (47)	7 (41.2)	15 (88.2)

Rheumatology (Oxford) 2012;51:1825-31

REGEB

Terapias biológicas en la enfermedad de Behçet
Nuestra Experiencia

Pacientes: 496

Pacientes tratados con anti-TNF: 62 (12,5%)

infliximab	59
Adalimumab	3
Natalizumab	1

REGEB

Terapias biológicas en la enfermedad de Behçet
Nuestra Experiencia

Afectación ocular	29 (47%)
Retinitis	13 (21%)
Uveítis posterior	6 (10%)
Uveítis anterior	21 (34%)
Afectación articular	23 (37%)
Afectación SNC	9 (15%)
Meningitis	4 (6%)
Afectación parénquima SNC	5 (8%)
Afectación vascular	6 (10%)
Trombosis venosa	4 (6%)
Aneurisma	1 (1,6%)
Pseudoaneurisma	1 (1,6%)

Terapias biológicas en la enfermedad de Behçet
Nuestra Experiencia

	Infliximab	Etanercept	Adalimumab
Enfermedad de Behçet	C *	A	C
Nº de pacientes/RCT	133/28	26/20	9/0

* Mayor número de efectos adversos

Datos de 31-12-2007

Terapias biológicas en la enfermedad de Behçet

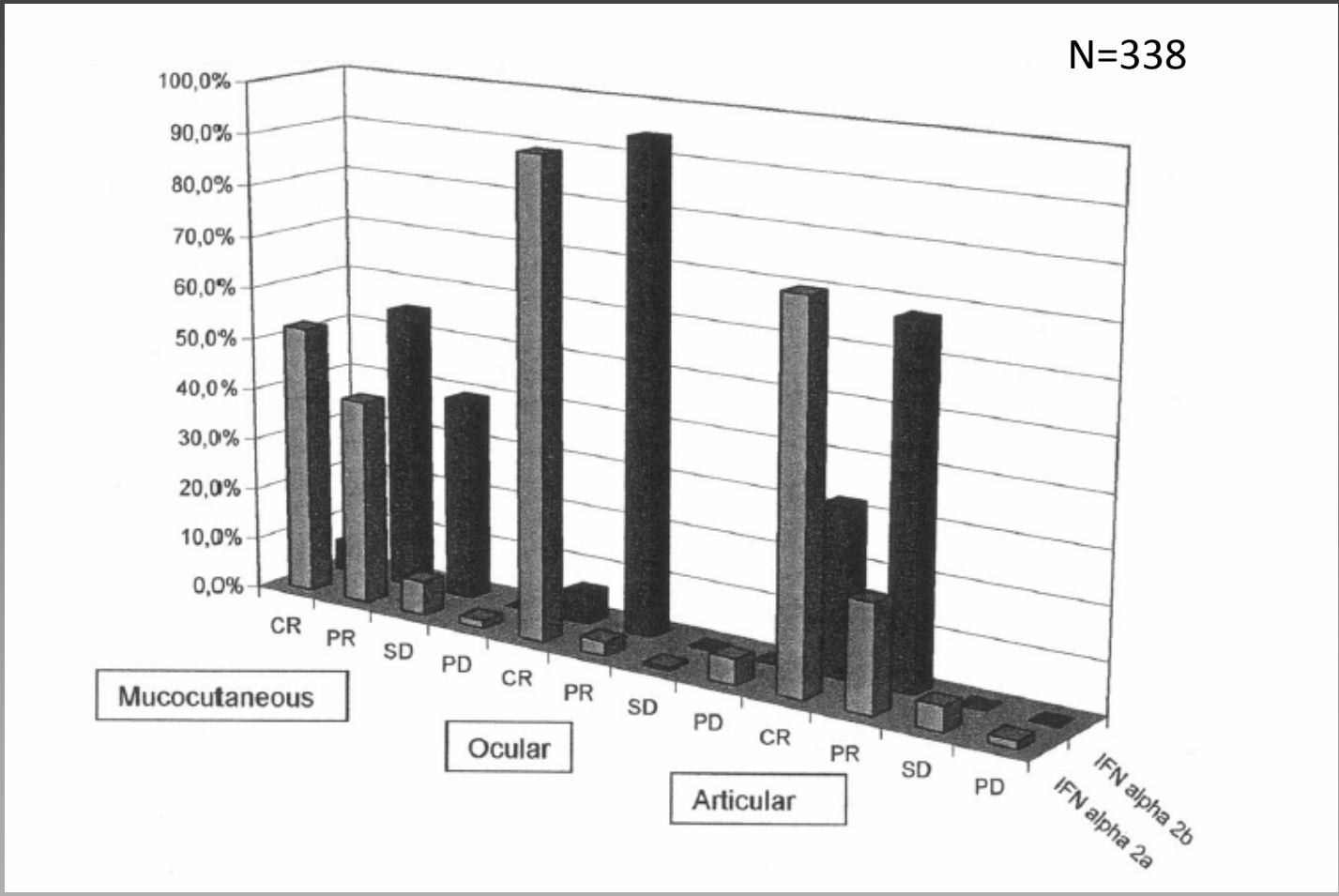
Interferón-α en la enfermedad de Behçet

The Use of Interferon α in Behçet Disease: Review of the Literature

Ina Kötter, Ilhan Günaydin, Manfred Zierhut, and Nicole Stübiger

Semin Arthritis Rheum 2004;33:320-35

Terapias biológicas en la enfermedad de Behçet
Interferón-α



Semin Arthritis Rheum 2004;33:320-35

Terapias biológicas en la enfermedad de Behçet

Interferón-α

Efectos adversos

Síndrome pseudogripal	84%
Leucopenia	25%
Neutropenia	0,05%
Anorexia	0,1%
Cefalea	0,05%
Alopecia	17,6%
Prurito	0,55%
Diarrea	0,02%
Amenorrea	0,02%
Depresión	0,3%
Artralgias/FM	0,33%
Generación de autoanticuerpos	0,33%

Semin Arthritis Rheum 2004;33:320-35

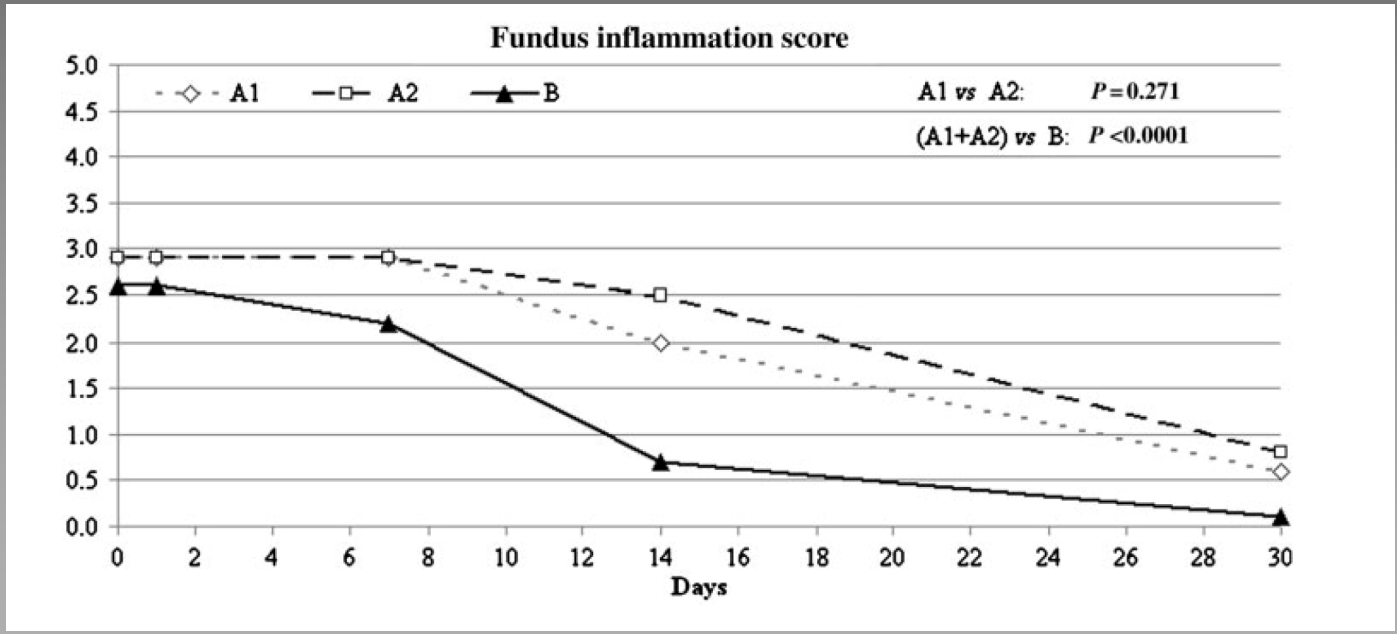
Take-home messages

- La terapia biológica en la enfermedad de Behçet representa una alternativa terapéutica eficaz y segura
- Tratamiento fuera de indicación
- Individualizar cada indicación
- Gravedad de la manifestación clínica
- Refractariedad a inmunosupresores
- Intolerancia al tratamiento convencional

Cuestiones por resolver

- Indicaciones como tratamiento de primera línea
- Asociación con inmunosupresores
- Pautas terapéuticas “específicas”
- Tipo de agente biológico
- Duración del tratamiento

A single infliximab infusion *vs* corticosteroids for acute panuveitis attacks in Behçet's disease: a comparative 4-week study



Rheumatology (Oxford) 2011;50:593-7

Terapias biológicas en la enfermedad de Behçet
Anti-TNF como primera línea

Rheumatology key messages

- Infliximab is faster and more effective than CSs in suppressing acute intra-ocular inflammation in BD.
- Unlike CSs, infliximab has an acceptable ocular safety profile.
- An i.v. infliximab infusion should be always considered for panuveitis attacks in BD.

Rheumatology (Oxford) 2011;50:593-7

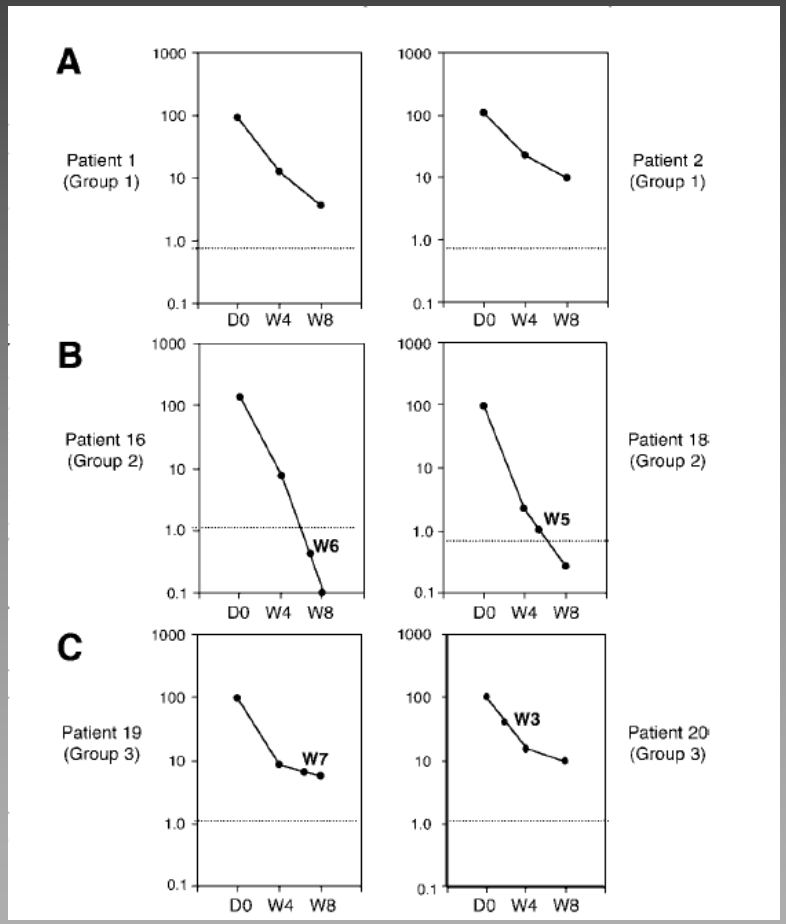
Terapias biológicas en la enfermedad de Behçet
Asociación de anti-TNF con inmunosupresores

Table 4 Sustained Organ-Specific Response to Repetitive Infliximab Injections, Given Either as Monotherapy or in Combination with Conventional Immunosupressants, in Patients with Available Data who Were Enrolled in Prospective Studies (90% under background steroids) each Describing 5 or More Patients with Behçet's Disease

	Responding Patients/Treated Patients[a]				
	INF Monotherapy	INF + AZA	INF + CsA	INF + MTX	INF + CsA + AZA
Ocular involvement	61/68	11/11	21/21	8/8	14/14
Gastrointestinal involvement	10/10	—	—	—	—
Central nervous system involvement	4/5		1/1	5/5	—
Articular involvement	14/15	1/3	3/3	2/2	—
Vascular involvement	1/1	—	—	1/1	—

Semin Arthritis Rheum 2011;41:61-70

Terapias biológicas en la enfermedad de Behçet
Pautas terapéuticas específicas



14 pacientes con niveles séricos elevado (>1.0 mg/ml) con remisión completa *GOOD RESPONDERS*

3 pacientes con niveles bajos en la semana 8 (brotes de uveítis entre la semana 5-8 antes de la siguiente infusión de IFX) *SHORT INTERVAL TREATMENT*

2 pacientes con brotes repetidos de uveítis a pesar de niveles séricos elevados de IFX
OTHER CYTOKINES RELATED: PRED/CyA

Br J Ophthalmol 2011;95:549-52

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Terapias biológicas en la enfermedad de Behçet
Duración del tratamiento

Paciente	Nº de Infusiones	Seguimiento IFX (meses)	Seguimiento tras stop IFX (meses)	Rebrote	Treatment After relapse
(1)	14	20	10	SI (a los 4 m)	Adalimumab
(2)	12	16	8	NO	-
(3)	11	16	6	SI (a los 6 m)	Adalimumab
(4)	14	17	6	NO	-

Int Ophthalmol 2010;30:577-81


"That's all Folks!"