Terapéutica en la enfermedad de Behçet refractaria.

- Mónica Rodríguez Carballeira
- Madrid 20-21 enero 2023

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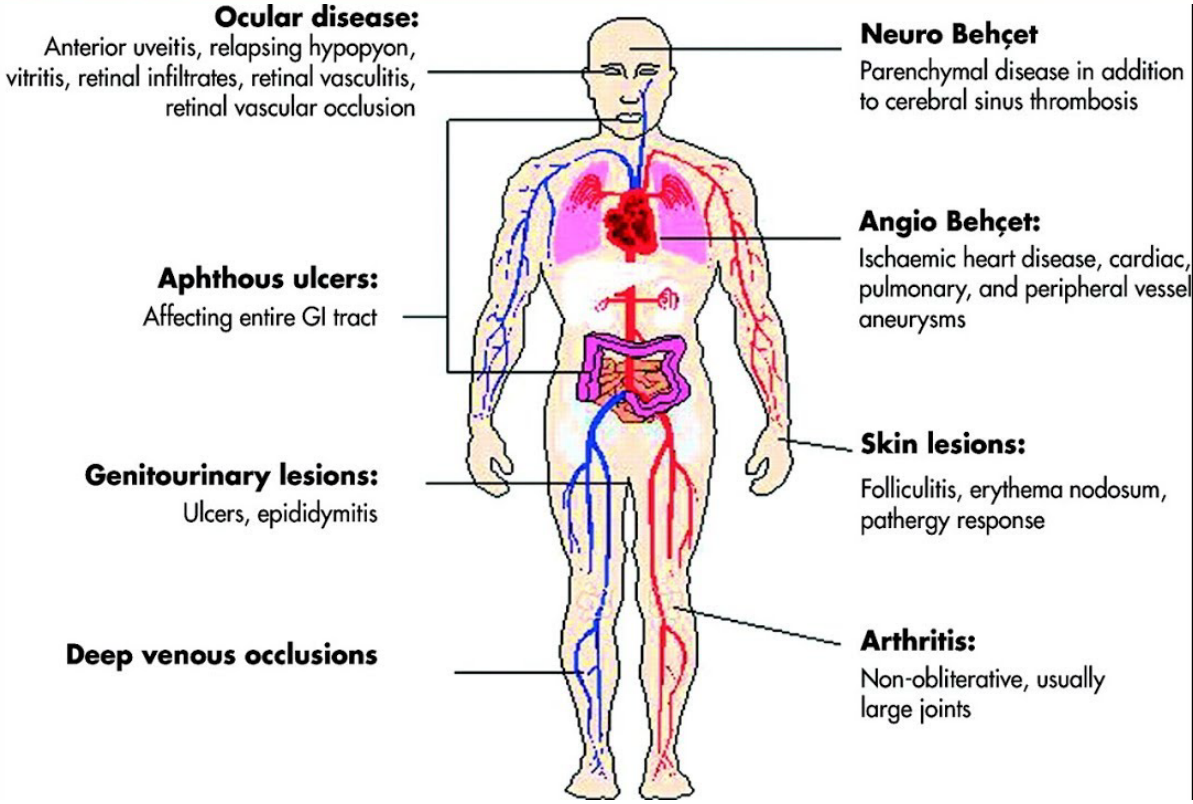
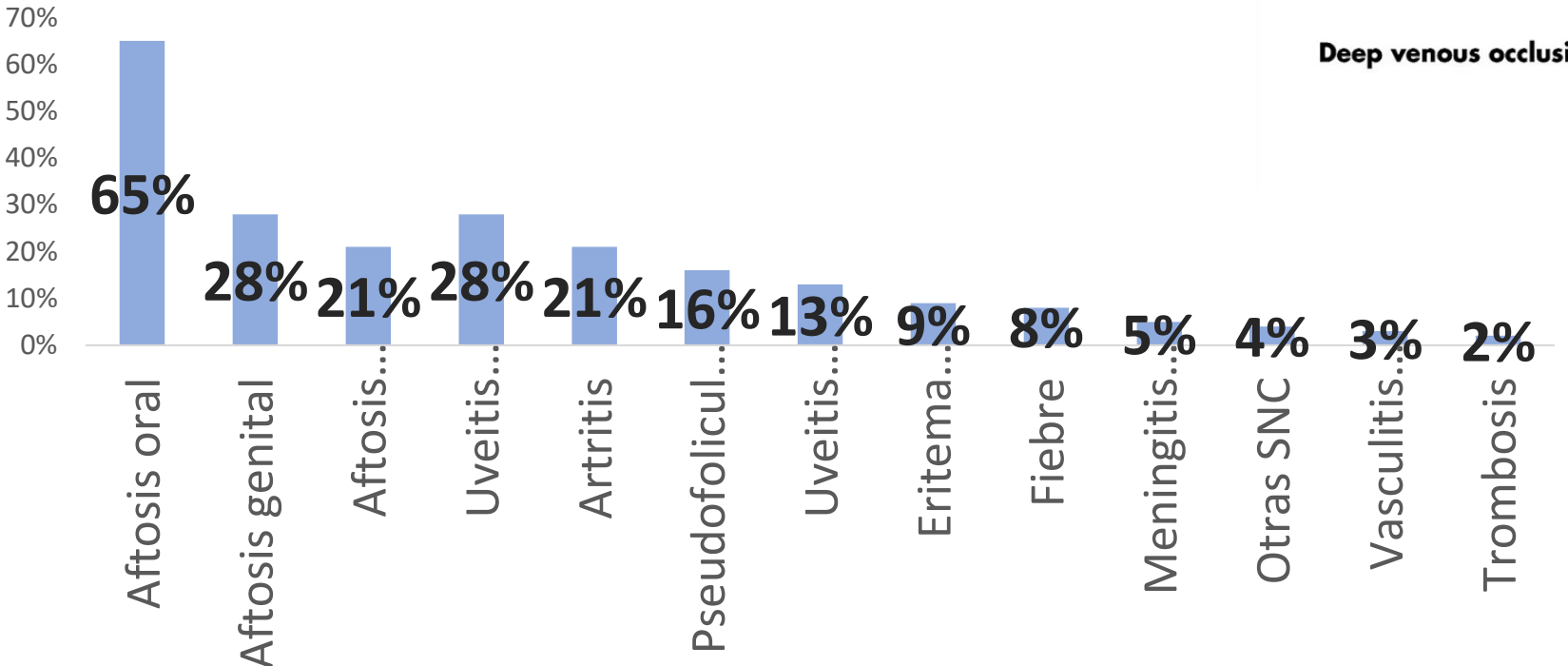
regEB



Manifestaciones clínicas DEBUT



Registry of the Spanish network of Behçet's disease: a descriptive analysis of 496 patients

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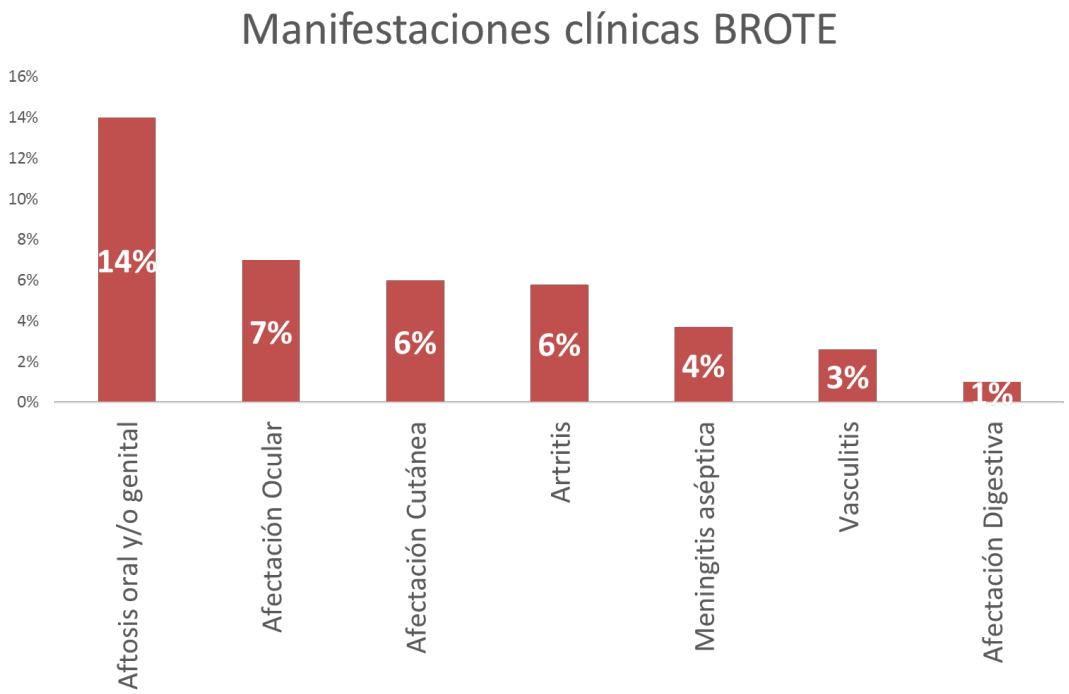
Seguimiento

regEB

- Seguimiento prospectivo de 273
- Brotes = inicio o modificación de tratamiento inmunosupresor, o corticoides 10mg/d, > 1mes
- Corticoides al inicio del seguimiento: 69%
  Inmunosupresores al inicio del seguimiento: 40%

- 18% presentan brote



Tratamiento (%)	
	Corticosteroides (14,3)
	Azatioprina (7,7)
	Ciclofosfamida (7.3)
	Terapia biológica (3,7) (refractariedad)
	Metotrexato (2,6)
	Anticoagulantes (2,3)
	Ciclosporina A (1.8)

42º Congreso SEMI 2021

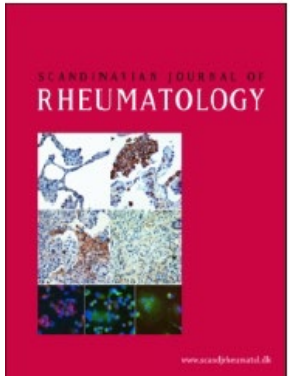
regEB

Afectación de órgano mayor: 40,6%

Ocular posterior	133	(24,3%)
Vascular	94	(17,2%)
SNC	65	(11,9%)
Digestivo	11	(2%)

Análisis Multivariado	OR	IC 95%	p
Hombres	1,99	1,39-2,84	<0,001
Uveítis anterior	1,47	1,01-2,15	0,009
Colchicina	0,50	0,33-0,74	<0,001

AOM (≥1) : 51,8%
Multiavariado :
•Sexo masculino
•Tabaco



Scand J Rheumatol 2021;00:1–9

Patients characteristics in Behçet's Syndrome and their associations with major organ involvement: a single-centre experience of 2118 cases

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Arsenal terapéutico para Behçet

corticoides

colchicina

azatioprina

ciclofosfamida

CS-A

metotrexate

INFLIXIMAB

adalimumab

SIN CONFLICTOS DE INTERÉS

Recommendation

2018 update of the EULAR recommendations for the management of Behçet's syndrome

Rheumatology key messages

- Major organ studies in Behçet's syndrome included in the updated EULAR Recommendations were mostly observational.
- Biologic treatments, mostly TNF-inhibitors, have started to gain importance in the treatment of Behçet's syndrome.

- 5 Principios y recomendaciones

SB cursa a brotes: objectivo suprimir inflamación recurrencias para prevenir daño orgánico.

Tratamiento individualizado

Peor pronóstico asociado a manifestaciónes oculares, vasculares, neurológicas y gastrointestinales

Las manisfestaciones puede mejorar con el tiempo

Es necesario un manejo multidisciplinar

- Agenda

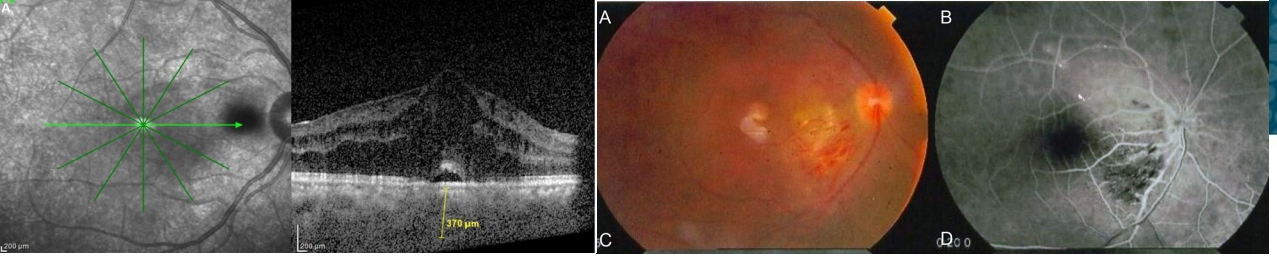
- Ocular
  - Comparar INF& vs iTNF
  - Estudios controlados entre iTNF, con IL1,IL6
  - Duración tratamiento
- Vascular
  - Anticoagulación
  - IQ, tto post-IQ
  - Duración
  - Tratamiento Trombosis intracardiaca
- SNC:
  - papel RMN,
  - estudios controlados
- GI:
  - estudios controlados,
  - riesgo perforación con cortis,
  - indicaciones de FCS

Afectación mucocutanea

- **Tratamiento tópico** para aftas aisladas.
- Acne-like : tratamiento tópico como en acné vulgar.
- **Colchicine** de elección frente a Eritema Nudoso.
- Úlceras en EEII: valorar con cirugía

- **Casos refractarios** :AZA, IFN& and antiTNF.

Alternativas para casos refractarios		
Thalidomida	Úlceras orales y genitales, lesiones papulopustulares.	
antiTNF	Etanercept:manifestaciones mucocutáneas (*Ther Adv Chronic Dis* 2014; 5: 112-34.)	
	Adalimumab eficacia en ulceras genitales (*Clin Rheumatol* 2017; 36: 451-5).	
IFN&:	Resultados contradictorios	
IL1 anakinra	Úlceras orogenitales (*Rheumatol Int.(2019) 39:971–90).*	
IL17 secunikumab	Manifestaciones mucocutáneas (J *Autoimmun* 2019; 97: 108-13.)	
IL12 Ustekinumab	Manifestaciones mucocutáneas (*J Autoimmun* 2017; 82: 41-6)	
APREMILAST	Aprovado para úlceras orales . Eficaz en casos reales *Clin Exp Rheumatol 2020; 38 (Suppl. 1,27): S69-S75.* N=51 *Mod Rheumatol. (2021) 32:1153–62.* . Metaanálisis	



Afectación ocular

- Descenso rápido de corticoides sistémicos!!
- Uveitis posterior: AZA, CS-A, INF&, anti-TNF.
- Cortis solo con IS.
- Corticoides intravitreos en caso de afectación unilateral.
- **Refractariedad o gravedad** extrema
  - bolus corticoids + IFX/CS-A,
  - IFN&

If the patient has severe eye disease it is recommended that either ciclosporine A or infliximab be used in combination with azathioprine and corticosteroids; alternatively IFNa with or without corticosteroids could be used instead.

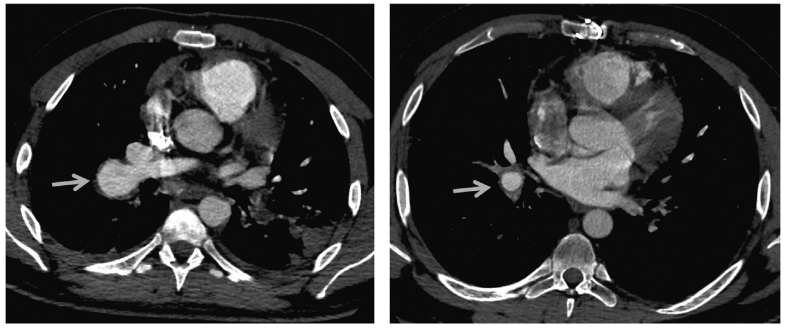
Alernativas para casos refractarios	
Cortis intravitreo (inyección/implantes)	Edema macular refractario *Ophthalmologica. (2019) 241:190–94.*
Adalimumab	Aprobado para uveitis no infecciosa (2016) *Ophtalmology 2018:125(9):1445*
ADA vs IFX	ADA mejor adherencia *Arthritis Rheumatol. (2019) 71:2081–9.*
Golimumab	Promete *Ocul Immunol Inflamm. (2019) 27:58–63.*
Tocilizumab	En casos refractarios CON EDEMA MACULAR *Am J Ophthalmol. (2017) 183:71–80* . *Clin Exp Rheumatol 2021; 39 (Suppl. 132): S37-S42* N=16 *Sem in Art and Rheum 58 (2023)* N=49 EM (cohorte177)
Anakinra y canakinumab	Mejor en uveitis que en otras manifestaciones (IL1 encels dendriticas) *Clin Rheumatol. (2017) 36:191–7*
Secukinumab	SHIELD trial no eficaz pero reduce IS concomitantes
JAK inhibitors	Tofacitinib: éxito en estudio piloto uveitis refractaria *Ann Rheum Dis. (2021).*

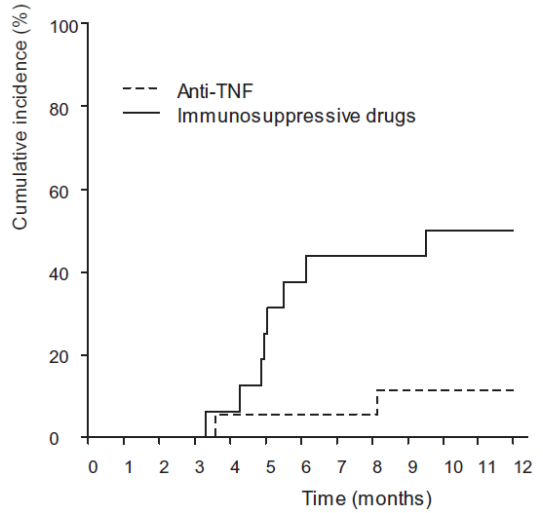
TVP

- Corticoides e IS (AZA, CFM o CS-A).
- Casos refractarios: considerar anti-TNF.
- Valorar anticoagulantes si se ha descartado aneurisma arteria pulmonar y el riesgo hemorrágico es bajo.

There is no firm evidence to guide treatment

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.





N=18 refractarios

Clin Immunol . 2018 Dec;197:54-59

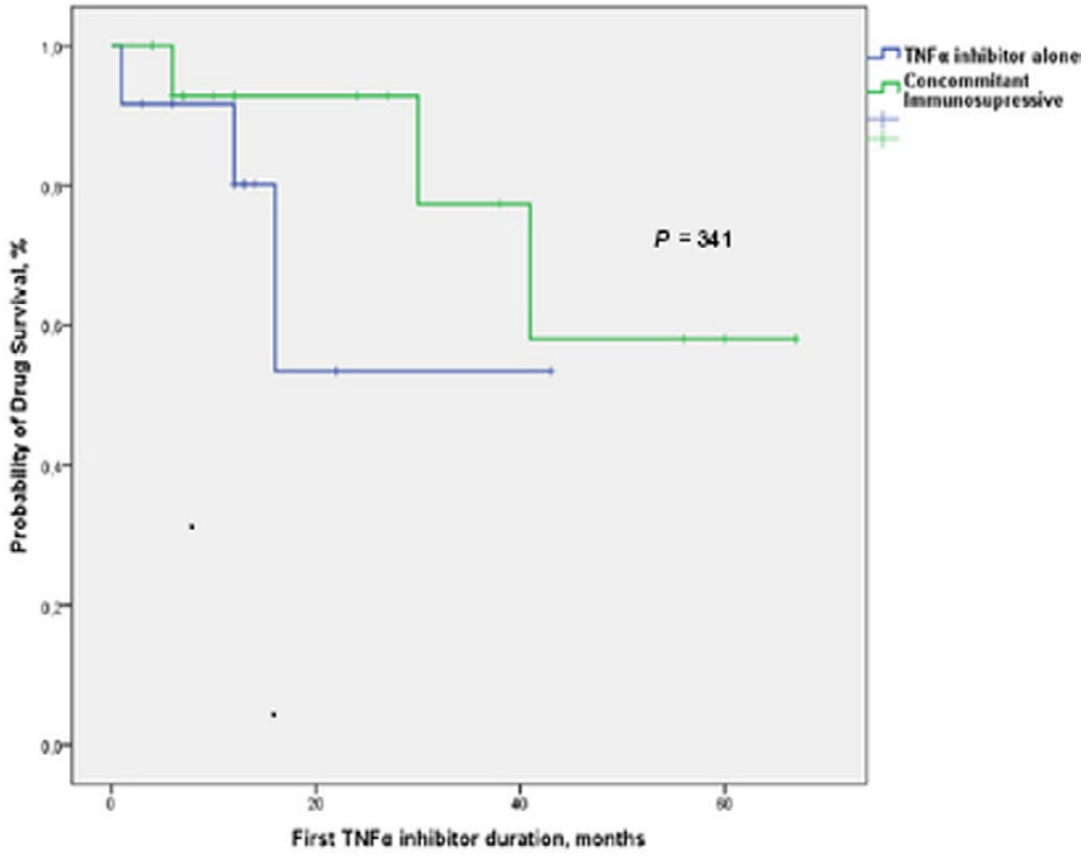
Afectación arterial

Clinicians should manage pulmonary artery aneurysms with high-dose **glucocorticoids and cyclophosphamide**.

In **refractory cases**, consider monoclonal anti-TNF antibodies.

Embolization should be used over open surgery in patients who have or are at high risk for major bleeding.

Artery aneurysms: cyclophosphamide and corticosteroids before intervention to repair. If the patient is symptomatic, **surgery** or stenting should not be delayed.

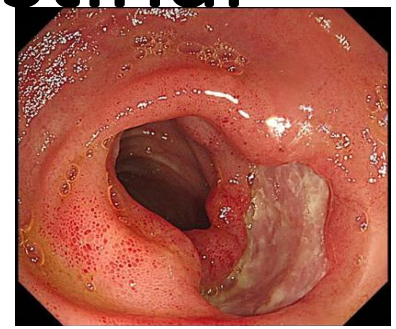


N=27, revisan 127, 80% responden a aTNF
Int J Rheum Dis. 2020;00:1–6.

Infliximab	
Adalimumab	
Certolizumab	

Afectación Gastrointestinal

- FGS o prueba de imagen para descartar EII, úlceras por AINES o infección como TBC.



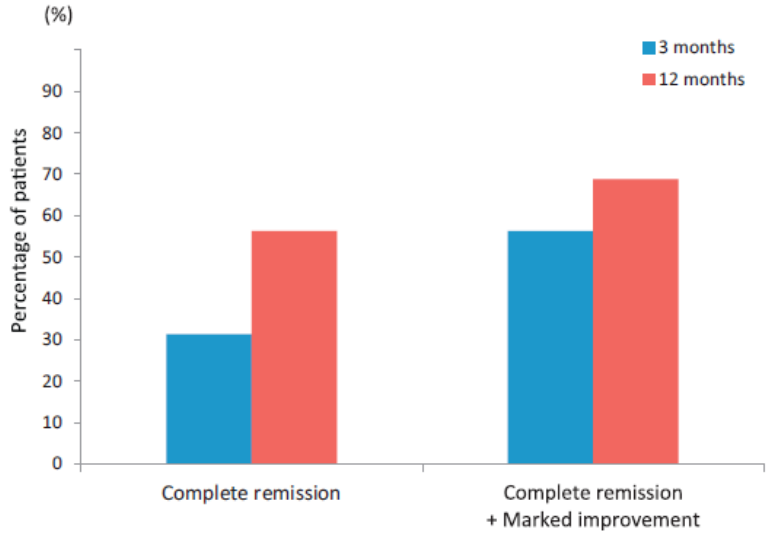
There is no evidence-based treatment

Sulfasalazine, corticosteroids, azathioprine, TNFa antagonists and thalidomide should be tried first before surgery, except in emergencies.

Perforation, major bleeding, or obstruction → surgical consultation.

Consider glucocorticoids in patients with acute exacerbations...+ 5-aminosalicylic acid (5-ASA) or azathioprine.

In severe or refractory cases, clinicians should consider monoclonal anti-TNF antibodies and/or thalidomide.



N. Sugimura et al. / Digestive aldLiver sDisease 2019, 51 (7), 967-971

antiTNF	• *Ther Adv Gastroenterol 2022, Vol. 15: 15.* Metaanálisis. 1ª linea? • Journal of Gastroenterology and Hepatology 37 (2022) 608–619 Metaanalisis : remisión 60% al año y efectos adversos 22% total. • *N. Sugimura et al. / Digestive aldLiver sDisease 2019,* 51 (7), 967-971: N=*22 ;* responden, sugieren 1ª linea • *Intest Res (2021) 19:301–12.* No responden los más graves graves
JAK	*Front. Immunol. 13:981502. N=4;* responden

Afectación de SNC

There is no firm evidence ...

Acute attacks of parenchymal involvement with high-dose glucocorticoids + IS (AZA)

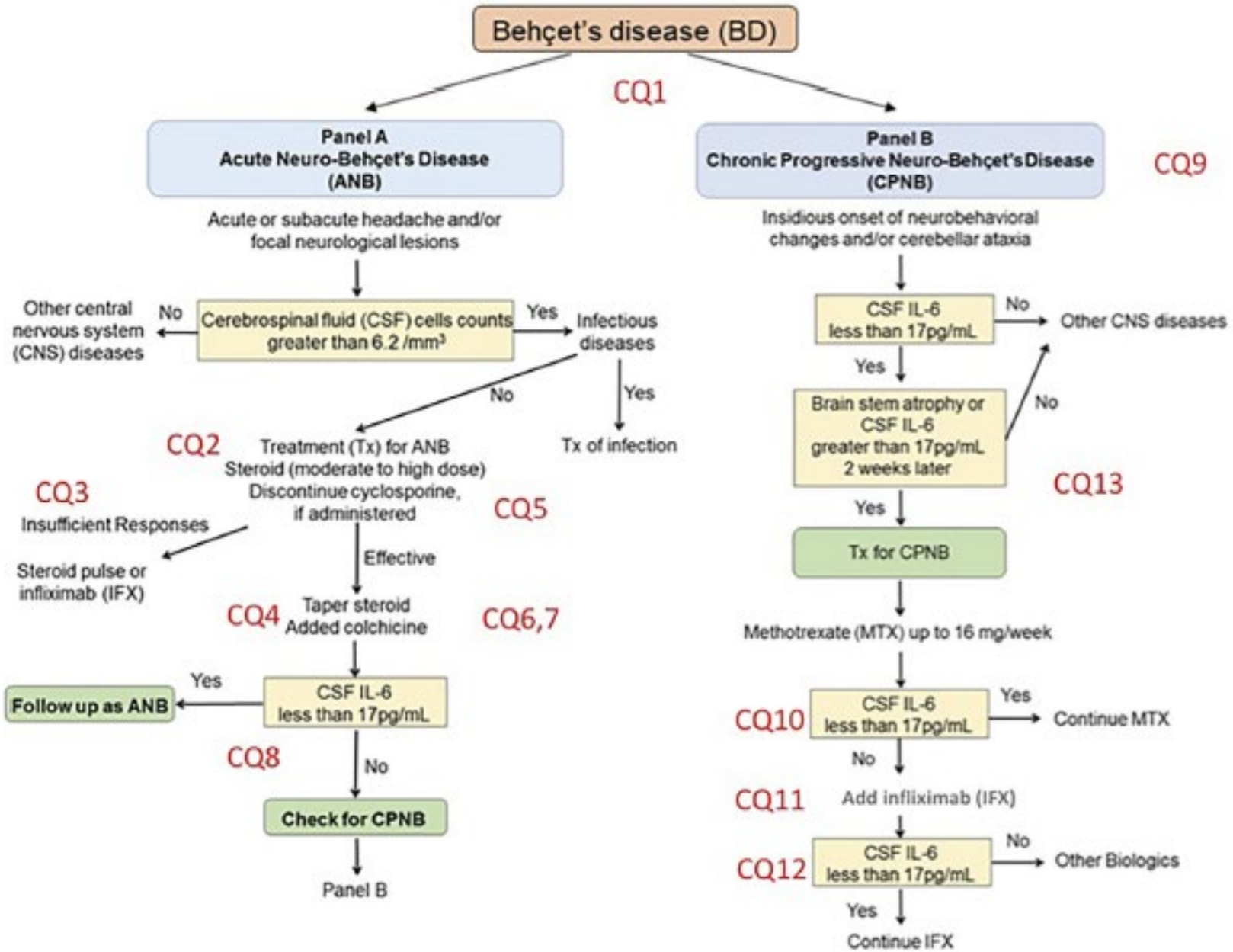
1st cerebral venous thrombosis with high-dose glucocorticoids ...may add anticoagulants for a short time.

Consider treating patients with monoclonal **anti-TNF antibodies in severe cases as first-line or refractory treatment**.

Intern Med 59: (19):2359-2367 **Recommendations for the Management of Neuro-Behçet's Disease by the Japanese National Research Committee for Behçet's Disease**

- Agudo: corticosteroides + colchicine para prevenir recurrencias
- Crónico: metotrexato.
- Infliximab si no mejoría y LCR IL-6 > 17 pg/mL
- Objetivos:
  - stop progresión de síntomas,
  - LCR IL-6 <17 pg/mL y
  - no progresión de la atrofia de tronco en RMN
- RMN y LCR IL-6 anualmente, mínimo

Tocilizumab	*Clin Exp Rheumatol 2021; 39 (Suppl. 132): S37-S42* *N*=16; mejoran
TB	*Grupo de NeuroB ...GGay, Ricarco Blanco Rheumatology (Oxford). 2022 Nov 2;61(11):4427-4436* N=41; 90% remisión a 57 meses


Behçet's disease (BD)
CQ1
Panel A
Acute Neuro-Behçet's Disease
(ANB)
Acute or subacute headache and/or
focal neurological lesions
Cerebrospinal fluid (CSF) cells counts
greater than 6.2 /mm3
No
Other central
nervous system
(CNS) diseases
Yes
Infectious
diseases
Yes
Tx of infection
No
CQ2
Treatment (Tx) for ANB
Steroid (moderate to high dose)
Discontinue cyclosporine,
if administered
CQ5
CQ3
Insufficient Responses
Steroid pulse or
infliximab (IFX)
Effective
CQ4
Taper steroid
Added colchicine
CQ6,7
CSF IL-6
less than 17pg/mL
Yes
Follow up as ANB
CQ8
No
Check for CPNB
Panel B
Panel B
Chronic Progressive Neuro-Behçet's Disease
(CPNB)
CQ9
Insidious onset of neurobehavioral
changes and/or cerebellar ataxia
CSF IL-6
less than 17pg/mL
No
Other CNS diseases
Yes
Brain stem atrophy or
CSF IL-6
greater than 17pg/mL
2 weeks later
No
CQ13
Yes
Tx for CPNB
Methotrexate (MTX) up to 16 mg/week
CQ10
CSF IL-6
less than 17pg/mL
Yes
Continue MTX
No
CQ11
Add infliximab (IFX)
CQ12
CSF IL-6
less than 17pg/mL
No
Other Biologics
Yes
Continue IFX

En resumen:

Infliximab Adalimumab ADA>IFX Etanercept Apremilast	Adalimumab Tocilizumab (edema) Corticoides iv, iJAK	aTNF Cirugía Anticoagulación ??	aTNF, Tocilizumab RMN y LCR IL-6	aTNF Cirugía. iJAK?

Gracias

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