Επικαιροποίηση συστάσεων για την θεραπεία του συνδρόμου Behcet (EULAR 2018)

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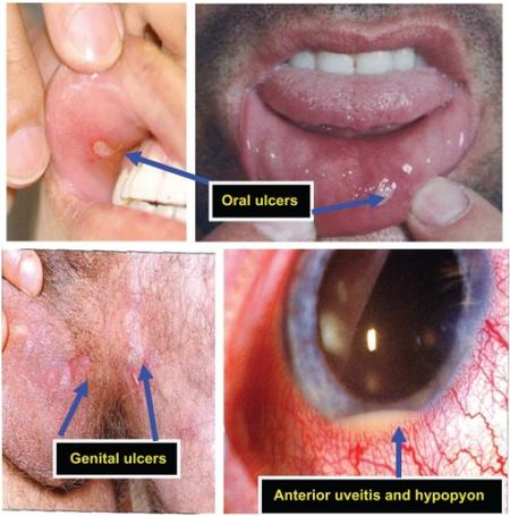
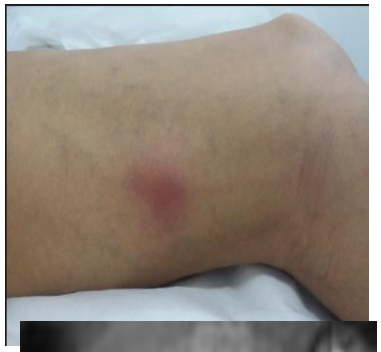
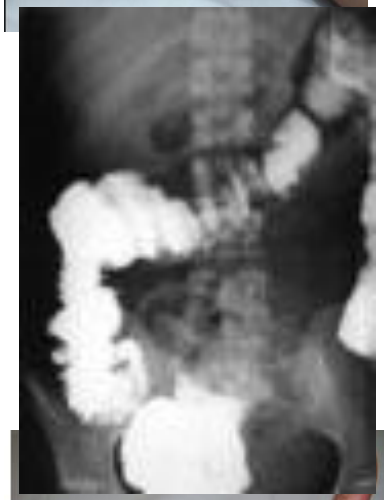
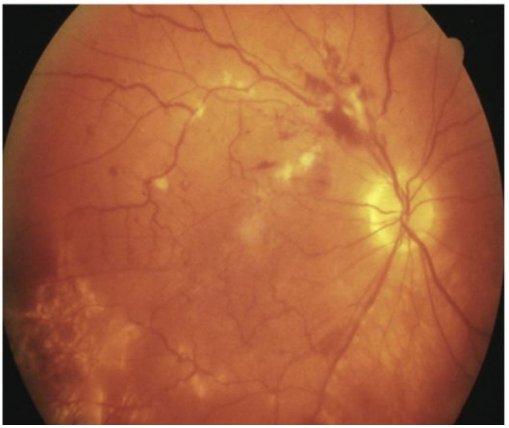
Behcet Syndrome

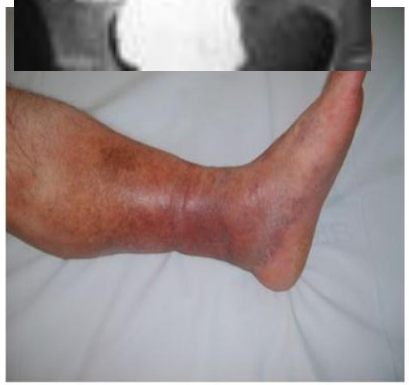


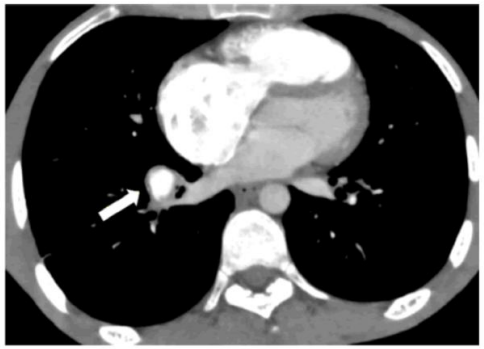


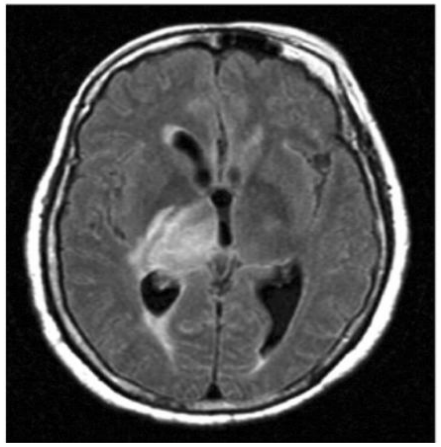


Manifestation	Frequency (%)
Oral ulcers	97–99
Genital ulcers	85
Genital scar	50 (probably more prevalent in men)
Skin lesions	
Papulopustular lesions	85
Erythema nodosum	50
Pathergy reaction	60 (Mediterranean countries and Japan)
Uveitis	50
Arthritis	30–50
Subcutaneous thrombophlebitis	25
Deep vein thrombosis	15
Arterial occlusion/aneurysm	5–10
Central nervous system involvement	20
Epididymitis	5
Gastrointestinal lesions	1–58 (more prevalent in Japan)









EDITOR'S CHOICE

EULAR recommendations for the management of Behçet disease

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Ann Rheum Dis 2008

Nine recommendations on Behçet disease (BD) that were developed after two anonymous Delphi rounds

No.	Recommendation
1	Any patient with BD and inflammatory eye disease affecting the posterior segment should be on a treatment regime that includes azathioprine and systemic corticosteroids.
2	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.
3	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.
4	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.
5	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.
6	In most patients with BD, arthritis can be managed with colchicine.
7	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.
8	Ciclosporine A should not be used in BD patients with central nervous system involvement unless necessary for intraocular inflammation.
9	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.

CNS, central nervous system; IFN, interferon; TNF, tumour necrosis factor.

Recommendation

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

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Handling editor Josef S Smolen

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ABSTRACT

Several new treatment modalities with different mechanisms of action have been studied in patients with Behçet's syndrome (BS). The aim of the current effort was to update the recommendations in the light of these new data under the auspices of the European League Against Rheumatism (EULAR) Standing Committee for Clinical Affairs. A task force was formed that included BS experts from different specialties including internal medicine, rheumatology, ophthalmology, dermatology, neurology, gastroenterology, oral health medicine and vascular surgery, along with a methodologist, a health professional, two patients and two fellows in charge of the systematic literature search. Research questions were determined using a Delphi approach. EULAR standardised operating procedures was used as the framework. Results of the systematic literature review were presented to the task force during a

different disciplines in the management of patients with BS.[1] At that time a total of nine recommendations were formed after a literature review, a Delphi exercise and two expert consensus meetings by a task force that included rheumatologists, ophthalmologists, dermatologists, a neurologist and a patient. In five of the nine recommendations, the strength of the recommendation was 'D', indicating that it was based only on expert opinion for the whole or at least a part of the recommendation.

The task force felt that there was a need for updating these recommendations as there had been several related new publications and data with new agents were available. Especially the experience with the use of biological agents in BS has substantially increased during the recent years. There is also more evidence to guide us in the management of gastrointestinal involvement and about other issues

Rationale for updating the EULAR Recommendations of 2008

- Several new publications and data with new agents
- The use and experience of anti-TNF in BS has substantially increased
- There is more evidence to guide us in :

i. the management of GI involvement

ii. use of anticoagulants in patients with venous involvement

iii. Surgical and interventional treatment options

Categories of evidence

Category	Evidence
Ia	Meta-analysis of randomised controlled trials
Ib	Randomised controlled trial
IIa	Controlled study without randomisation
IIb	Quasi-experimental study
III	Non-experimental descriptive studies, such as comparative, correlation and case–control studies
IV	Expert committee reports or opinion or clinical experience of respected authorities or both

Strength of recommendations

Strength	Based on
A	Category I evidence
B	Category II evidence or extrapolated recommendations from category I evidence
C	Category III evidence or extrapolated recommendations from category I or II evidence
D	Category IV evidence or extrapolated recommendations from category II or III evidence

Overarching principles

	Level of evidence	Strength of recommendation	Level of agreement
➢ BS is a condition that typically runs a relapsing and remitting course and the goal of treatment is to promptly supress inflammatory ecaxerbations and recurrences to prevent organ damage	***NA***	***NA***	***9.5±0.7***
➢ A multidisciplinary approach is necessary for optimal care			
➢ Treatment should be individualised according to age, gender, type and severity of organ involvement and patient's preferences.			
➢ Ocular, vascular, neurological and gastrointestinal involvement may be associated with a poor prognosis.			
➢ Disease manifestations may ameliorate over time in many patients			

1.Mucocutaneous Involvement

	Level of evidence	Strength of recommendation
➢ Topical measures such as steroids should be used for the treatment of oral and genital ulcers. Colchicine should be tried first for the prevention of recurrent mucocutaneous lesions especially when the dominant lesion is erythema nodosum or genital ulcer (IB). Papulopustular or acne-like lesions are treated with topical or systemic measures as used in acne vulgaris (IV).	***IB/IV***	***A/D***
➢ Leg ulcers in BS might be caused by venous stasis or obliterative vasculitis. Treatment should be planned with the help of a dermatologist and vascular surgeon.	***IV***	***D***
➢ Drugs such as azathioprine, **thalidomide**, interferon-alpha, TNF-alpha inhibitors or **apremilast** should be considered in selected cases.	***IB***	***A***

**Level of agreement 9.4±0.8*

The NEW ENGLAND JOURNAL of MEDICINE

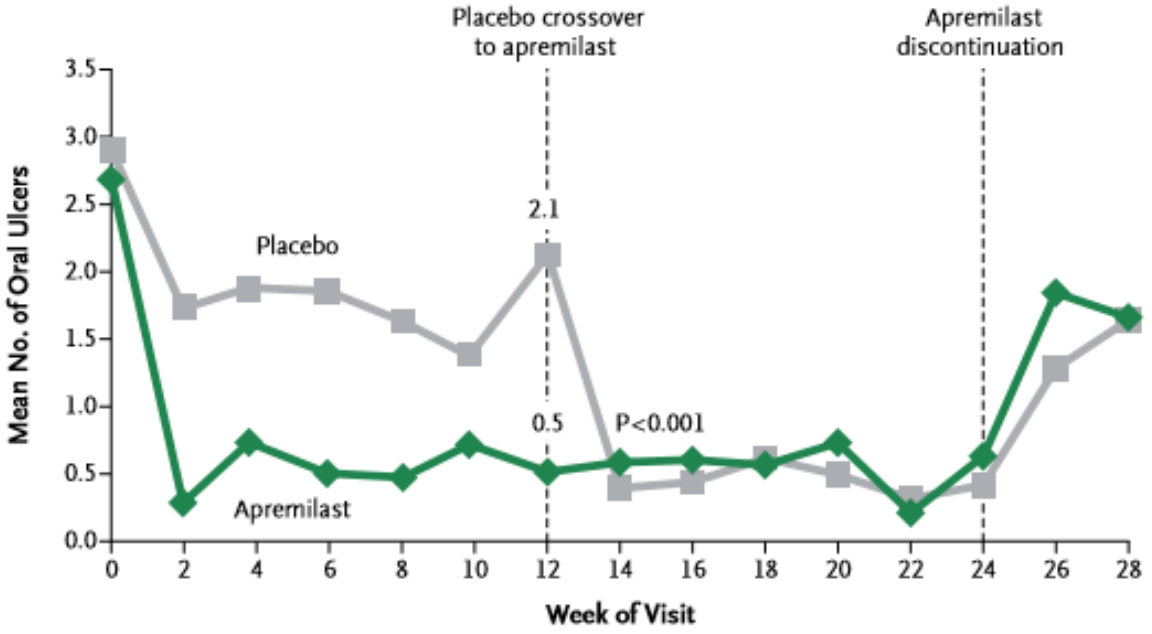
ORIGINAL ARTICLE

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

Gulen Hatemi, M.D., Melike Melikoglu, M.D., Recep Tunc, M.D., Cengiz Korkmaz, M.D., Banu Turgut Ozturk, M.D., Cem Mat, M.D., Peter A. Merkel, M.D., Kenneth T. Calamia, M.D., Ziqi Liu, Ph.D., Lilia Pineda, M.D., Randall M. Stevens, M.D., Hasan Yazici, M.D., and Yusuf Yazici, M.D.

- 4 PDE inhibitor / Approved for Psoriasis and PsA
- 2015, Phase 2 , Placebo-controlled study
- N=111, no major organ involvement, ≥2 oral ulcers
- Two arms: APR 30 mg BID (n=55) or PBO for 12 weeks (n=56). from 12 to 24 week all pts on active-treatment.

- At week 12, more pts on APR had complete response (ulcer-free) (71% APR v.s 29% PBO; $p<0.0001$).
- At week 14 PBO pts who received APR had significant decrease of ulcers
- 10/10 with genital ulcers receiving APR had a complete response at week 12 vs 3/6 receiving PBO ($p=0.036$).



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

Figure 1. Mean Number of Oral Ulcers Per Patient, According to Study Group.

The mean number of oral ulcers per patient was significantly lower in the apremilast group than in the placebo group during the placebo-controlled phase (baseline to week 12). At week 12, patients in the placebo group were switched to apremilast therapy, after which the mean number of oral ulcers in those patients decreased. After apremilast was discontinued at week 24, the mean number of oral ulcers started to increase within 2 weeks. A repeated-measures analysis performed with data from baseline to week 12 showed consistent results.

Other non Anti-TNFa Biologic agents for mucocutaneous BS

- Interleukin 1 blockade potential benefit

Grayson PC et al. Treatment of mucocutaneous manifestations in Behçet's disease with anakinra: a pilot open-label study. Arthritis Res Ther 2017

Emmi G et al. Efficacy and safety profile of anti-interleukin-1 treatment in Behçet's disease: a multicenter retrospective study. Clin Rheumatol 2016

- IL 12/23 blockade potential benefit

Mirouse A et al. Ustekinumab for Behçet's disease. J Autoimmun 2017

- Il 6 blockade innefective/deterioration

Diamantopoulos AP, Hatemi G. Lack of efficacy of tocilizumab in mucocutaneous Behçet's syndrome: report of two cases. Rheumatology 2013

Cantarini L, Lopalco G, Vitale A, et al. Paradoxical mucocutaneous flare in a case of Behçet's disease treated with tocilizumab. Clin Rheumatol 2015

- Il 17 blockade controversial

Di Scala G et al. Efficacy of the anti-IL 17 **secukinumab** in refractory Behçet's syndrome: A preliminary study. J Autoimmun. 2019 Feb

2. Eye involvement

	Level of evidence	Strength of recommendation
➢ Management of uveitis of BS requires close collaboration with ophthalmologists with the ultimate aim of inducing and maintaining remission. Any patient with BS and inflammatory eye disease affecting the posterior segment should be on a treatment regimen such as azathioprine (IB), **cyclosporine-A (IB), interferon-alpha (IIA) or monoclonal anti-TNF antibodies (IIA).** Systemic glucocorticoids should be used only in combination with azathioprine or other systemic immunosuppressives (IIA).	**IB/IIA**	**A/B**
➢ Patients presenting with an initial or recurrent episode of acute sight-threatening uveitis should be treated **with high-dose glucocorticoids, infliximab or interferon-alpha**. Intravitreal glucocorticoid injection is an option in patients with unilateral exacerbation as an adjunct to systemic treatment.	***IIA***	***B***

**Level of agreement* 9.5±0.6

3. Isolated anterior uveitis

	Level of evidence	Strength of recommendation
➢ Systemic immunosuppressives could be considered for those with poor prognostic factors such as young age, male sex and early disease onset.	***IV***	***D***

**Level of agreement* 9.0±0.8

Anti-TNFa agents for BS uveitis

- 2001-2008 15 articles >120 pts with BS uveitis treated succesfully with anti-TNFa agents

- 2009-2018 >40 studies, **>1100 pts with BS uveitis treated with anti-TNFa** agents:
  - IFX 5 mg/kg 0-2-6 wks / ADA 40 mg/2 wks
  - Rapid improvement
  - 90% response at 6 months follow up/ sustained remission
  - Corticosteroid sparing effect
  - Comparable efficacy between IFX and ADA
  - possible withdrawal after 2 years and sustained remission

- Anti-TNFa agents **first line** treatment for BS uveitis

  Levy-Clarke G et al. **Expert panel recommendations** for the use of **anti TNFa** biologic agents in patients with ocular inflammatory disorders.Ophthalmology. 2014 Mar

- 06/2016 FDA approval (2 RCTs) of Adalimumab for non infectious uveitis

4. Acute deep vein thrombosis

	Level of evidence	Strength of recommendation
➢ For the management of acute deep vein thrombosis in BS glucocorticoids and immunosuppressives such as azathioprine, cyclophosphamide or cyclosporine-A are recommended.	***III***	***C***

*Level of agreement 9.3±0.8

5. Refractory venous thrombosis

	Level of evidence	Strength of recommendation
➢ **Monoclonal anti-TNF antibodies** could be considered **in refractory** patients. **Anticoagulants may be added**, provided the risk of bleeding in general is low and coexistent pulmonary artery aneurysms are ruled oud.	***III***	***C***

**Level of agreement 8.7±0.8*

- In acute DVT: meta-analysis of 3 retrospective studies revealed significant efficacy of IMS (4-fold decrease of relapse risk) but not of anticoagulants in the prevention of recurrence of acute DVT
- Equal efficacy of AZA, CYC, CsA. For large veins (i.e vena cava) CYC may be preferred

- In refractory cases: AntiTNFa (high vascular response rates)

  Emmi et al.: Adalimumab-based treatment versus DMARDs for venous thrombosis in Behçet syndrome. A retrospective study of 70 patients with vascular involvement. Arthritis Rheum 2018.

  ± anticoagulants (possibly decreases the risk of post thrombotic syndrome, OR 3.8)

  Seyahi E et al. Clinical and ultrasonographic evaluation of lower-extremity vein thrombosis in Behcet syndrome: an observational study. Medicine 2015.

!!! exclude aneurysms

6. Arterial Involvement

	Level of evidence	Strength of recommendation
➢ For the management of pulmonary artery aneurysms, high-dose glucocorticoids and cyclophosphamide are recommended. **Monoclonal anti-TNF antibodies should be considered in refractory cases. For patients who have or who are at high risk of major bleeding, embolisation should be preferred to open surgery.**	***III***	***C***
➢ *For both aortic and peripheral artery aneurysms, medical treatment with cyclophosphamide and corticosteroids is necessary before intervention to repair. Surgery or stenting should not be delayed if the patient is symptomatic.*	***III***	***C***

**Level of agreement 9.2±0.9*

Arterial involvement

- Hamuryudan V et al. Pulmonary artery involvement in Behçet's syndrome: Effects of anti-Tnf treatment. Semin Arthritis Rheum 2015.
  - Retrospective study, 13 BS patients with refractory PAI (all men)
  - Infliximab 5 mg/kg, 0-2-6 wks
  - remission in 11 (84%)
  - 2 pts relapsed within 3 years after anti-TNFa withdrawal.
  - Corticosteroid sparing effect

- Desbois AC et al. Efficacy of anti-TNF alpha in severe and refractory major vessel involvement of Behcet's disease: A multicenter observational study of 18 patients. Clin Immunol.2018.
  - Retrospective study, 18 BS patients with refractory major vessel involvement
  - Infliximab 5 mg/kg, 0-2-6 wks
  - remission in 16 (89%) pts, event free survival in 87% pts after 1 year
  - 4 pts relapsed, 2 while on treatment.
  - Lower 9 and 12-month relapse risk of Anti-TNFa compared to conventional IMS [OR = 5.62 at 12 months, p = 0.04]
  - Corticosteroid sparing effect

Arterial Involvement II

- Saadoun et al. Long-term outcome of arterial lesions in Behçet disease: a series of 101 patients. Medicine 2012.

  Postoperative complications less frequent in pts receiving IMS (28% v.s 71% p<0,001)
  Post thrombotic events less in pts receiving anticoagulants (40% vs. 75%, p<0,001)

- Park M-C et al. Surgical outcomes and risk factors for postoperative complications in patients with Behcet's disease. Clin Rheumatol 2007.

  IMS decreased the risk of postoperative complication compared to those that were not followed by medical treatment (P < 0.05)

- Voiriot G et al Transcatheter embolotherapy of pulmonary artery aneurysms as emergency **treatment** of hemoptysis in **Behcet** patients: experience of a referral center and a review of the literature.Intern Emerg Med. 2018

  Transcatheter embolotherapy of PAA was successful for immediate control of hemoptysis in all 17 patients,
  Hemoptysis recurred in 7 pts (41%) within 12 months, 4 died
  15/17 received IMS after embolectomy, overall 1 year survival rate 76%

7. Gastrointestinal Involvement

	Level of evidence	Strength of recommendation
➢ *Gastrointestinal involvement of BS should be confirmed by endoscopy and/or imaging. NSAID ulcers, inflammatory bowel disease and infections such as tuberculosis should be ruled out.*	***III***	***C***

**Level of agreement 9.2±0.9*

8. Refractory/severe/gastrointestinal involvement

	Level of evidence	Strength of recommendation
➢ Urgent surgical consultation is necessary in cases of perforation, major bleeding and obstruction. Glucocorticoids should be considered during acute exacerbations together with disease-modifying agents such as 5-ASA or azathioprine. **For severe and/or refractory patients, monoclonal anti-TNF antibodies and/or thalidomide** should be considered.	***III***	***C***

**Level of agreement 8.8±0.9*

- For mild to moderate involvement 5 ASA or AZA ± Cs

- Anti-TNFa agents:

Infliximab

- 7 retrospective (2 multicentre)/ 1 prospective study, n=139 pts with refractory GI involvement
- 5 mg/kg 0-2-6 week
- Response rate 50-80%, complete remission 40-60%

Adalimumab

- 160 mg week 0, 80 mg week 2, 40 mg from week 4
- 2 retrospective and 2 prospective studies, n=56 pts with refractory GI involvement
- Response rate 60-75% , complete remission 20%

- *May 16, 2013: Adalimumab officially approved for intestinal BD in Japan.*

- Hatemi I et al. Characteristics, treatment, and longterm outcome of GI involvement in Behcet's syndrome: an observational study from a dedicated multidisciplinary center. Medicine 2016

- N=60 pts,30% of pts presented with acute abdomen and required emergency surgery
- IMS decrease the risk of postoperative flares and complications, 90% relapse in pts without IMS

9. Nervous system involvement

	Level of evidence	Strength of recommendation
➢ Acute attacks of parenchymal involvement should be treated with *high-dose* glucocorticoids followed by slow tapering, together with immunosuppressives such as azathioprine. Cyclosporine should be avoided. **Monoclonal anti-TNF antibodies should be considered in severe disease as first-line or in refractory patients.**	*III*	*C*
➢ The first episode of cerebral venous thrombosis should be treated **with high-dose glucocorticoids** followed by tapering. **Anticoagulants may be added for a short duration**. Screening is needed for vascular disease at an extracranial site.		

**Level of agreement 9.1±1.2*

Management of BS CNS disease

- High Cs doses: Daily pulses 1 gr /day follwed by p.os prednisolone 1 mg/kg with progressive tapering

- **Anti-TNFa agents <u>first line drugs</u> for severe CNS involvement**

- Giardina A et al. One year study of efficacy and safety of infliximab in the treatment of patients with neurological Behçet's disease refractory to standard immunosuppressive drugs. Rheumatol Int 2011.

N=5 pts, 52 weeks of treatment with Infliximab 5mg/kg, 5/5 response, 2pts relapsed

- Vallet H et al. Efficacy of anti-TNF alpha in severe and/ or refractory Behçet's disease: Multicenter study of 124 patients. J Autoimmun 2015

N= 13 pts, infliximab 5mg/kg, 12/13 response, significant cs reduction (40 mg to 10 mg after 6 months)

- Zeydan B et al. Infliximab is a plausible alternative for neurologic complications of Behçet disease. Neurol Neuroim Neuroinflamm 2016

N=15 pts, Infliximab 5mg/kg, mean duration of treatment 39 months, 15/15 response, 0 relapse

- Desbois AC et al. Efficacy of Anti-TNFα in Severe and Refractory Neuro-Behcet Disease: An Observational Study. Medicine (Baltimore). 2016

N= 17, infliximab 5mg/kg, 16/17 response (6 complete remission), significant cs reduction (>50% at 12 months)

Management of BS CNS disease II

- Cerebral venous thrombosis usually coexists with other vascular lesion. Screening for other vascular lesions is mandatory
- No benefit from use of IMS in first episode of cerebral venous thrombosis. Relapses are rare
- Anticoagulants especially indicated in pts with prothrombotic conditions.

10. Joint involvement

	Level of evidence	Strength of recommendation
➢ Colchicine should be the initial treatment in BS patients with acute arthritis. Acute monoarticular disease can be treated with intra-articular glucocorticoids. Azathioprine, interferon-alpha or TNF-alpha inhibitors should be considered in recurrent and chronic cases.	***IB***	***A***

**Level of agreement 9.0±1.0*

Unmet needs / Research Agenda

- Head-to-head trial between interferon-alpha and TNFis or different TNFis
- Controlled trials:
- Efficacy of IL-1 and IL-6 blockers
- optimal duration of TNFis or interferon-alpha after remission
- efficacy and safety of anticoagulation for preventing relapses
- optimal dose and duration of IMS after surgery for artery aneurysm
- optimal management of initial, refractory and recurrent CNS or GI involvement
- role,dose and duration of corticosteroids in acute relapses and whether they increase the risk of GI perforation
- benefit of concomitant IMS use with TNF

Conclusions

- Apremilast for mucocutaneous BS
- In sight-threatening posterior uveitis, Anti-TNFa agents or Interferone-alpha are first line treatments
- Anticoagulants not indicated in DVT. Anticoagulants may be useful in recurrent DVT to prevent PTS
- Anti-TNFa should be used in refractory cases of DVT or PAI.
- Embolisation is preferable than open surgery in case or high risk of major bleeding
- For severe and/or refractory GI and CNS involvement monoclonal anti-TNF antibodies are first choice

ΣΑΣ ΕΥΧΑΡΙΣΤΩ ΠΟΛΥ