4ο Διαπανεπιστημιακό Πρόγραμμα Εκπαίδευσης στη Ρευματολογία
9ος Κύκλος Μαθημάτων, 18-3-2023

Νόσος Αδαμαντιάδη-Behçet's

("Silk Road" Disease, Behçet's Disease)

Πέτρος Π. Σφηκάκης
Α' Προπαιδευτική Παθολογική Κλινική
Ιατρική Σχολής ΕΚΠΑ

ABD: υποτροπιάζουσα, πρωτοπαθής συστηματική αγγειιτίδα

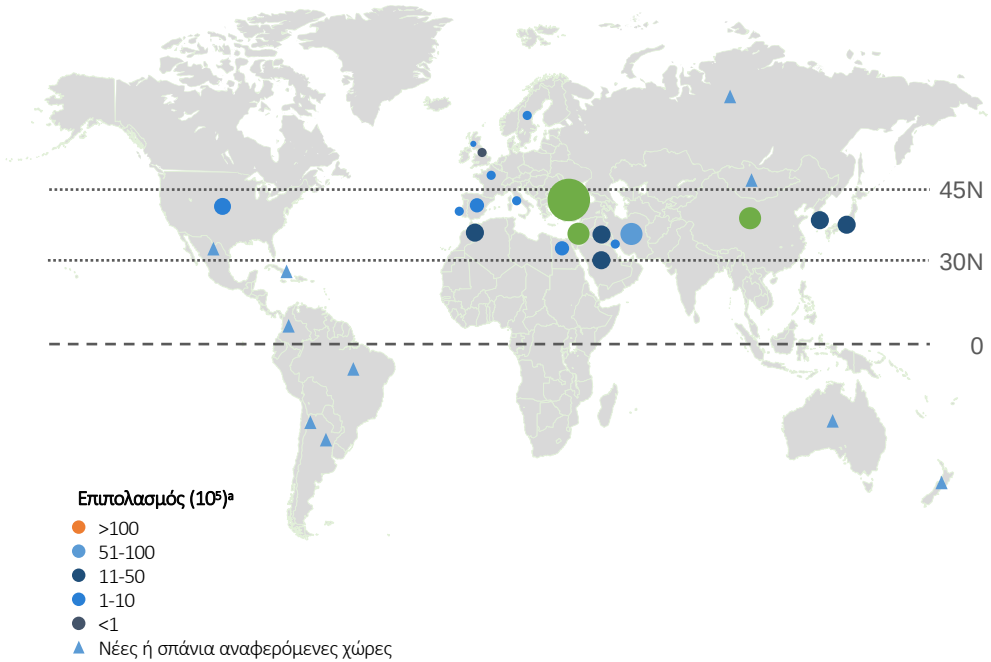
Hulusi Behçet (1889-1948)
Δερματολόγος

- Δερματικά εξανθήματα (βλατιδώδη, φλυκταινώδη, οζώδη)
- Χαρακτηρίζεται από υποτροπιάζοντα αφθώδη έλκη βλεννογόνων στόματος, γεννητικών οργάνων, & εντέρου
- Φλεγμονή σε οφθαλμούς, ΚΝΣ, αρθρώσεις
- Προσβάλλει τόσο αρτηρίες (θρομβώσεις & ανευρύσματα), όσο και τις φλέβες (θρομβώσεις)
- Σοβαρή νοσηρότητα και θνητότητα

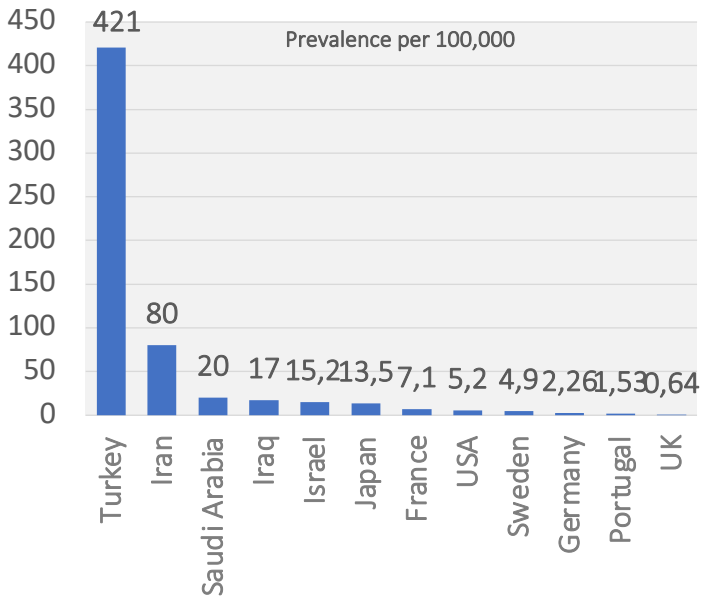
Βενέδικτος Αδαμαντιάδης (1875 – 1962)
Οφθαλμίατρος

Γεωγραφική κατανομή: συχνότερη σε περιοχές κατά μήκος του ‘Δρόμου του Μεταξιού’ (silk-road disease)

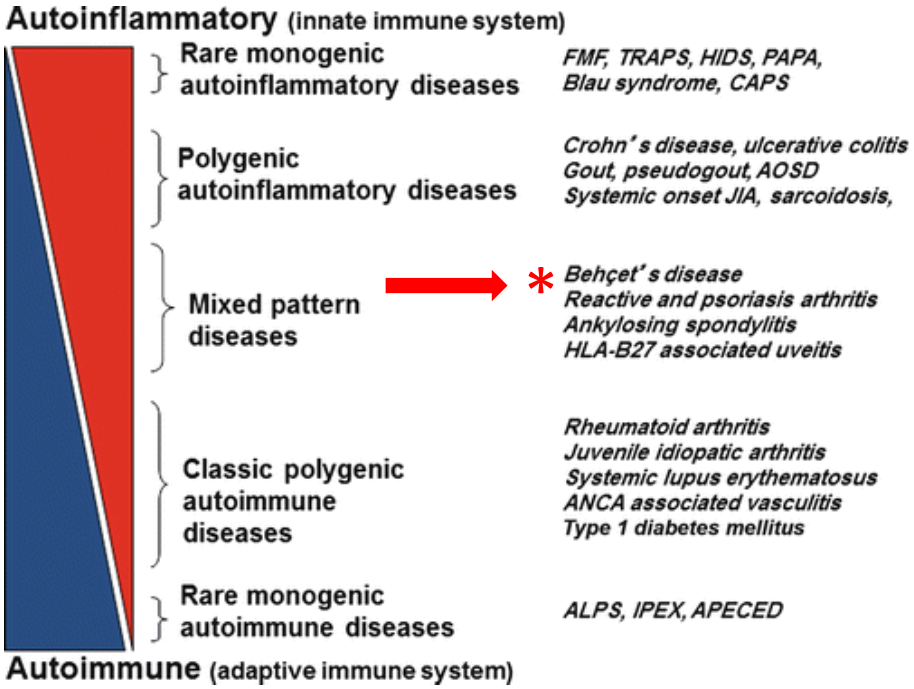
Παγκόσμιος επιπολασμός



Επιπολασμός ανά χώρα



- Polygenic autoinflammatory/autoimmune condition
- Pathologic pathways of BS remain largely unknown
- No single common denominator has been identified



Innate immunity components	Players	Involvement in BD
Cells	Neutrophils	Activated by a subset of IL-8 producing T cells (Keller et al)
	Macrophages	Produce IL-1β through activation of the NLRP3 inflammasome by ROS
	Monocytes	Increased P2X7r-dependent IL-1β secretion in BD
Cytokines	IL-1	Significantly higher in patients with both active and inactive BD compared to HC Polymorphism of IL-1 gene have shown to be significantly more represented in patients with BD
	IL-33	Increased in serum from BD patients along with its soluble ligand sST2 The soluble ligand correlates with BD activity Highly expressed in the epidermis and dermis of patients with BD
Intracellular proteins	NLRP3 Inflammasome	Its components are significantly increased in peripheral blood mononuclear cells from BD patients and in BD skin lesions, compared to HC and erythema nodosum patients, respectively IL-1β secretion in BD appears related with NLRP3 inflammasome activation IL-1β production by monocyte-derived macrophages via NLRP3 inflammasome is induced by ROS
Surface receptors	TLR	TLR-2 and -4 upregulate IL-1β production through a ROS-NLRP3 inflammasome pathway TLR-4 and TLR-9 gene polymorphisms are significantly more frequent in BD patients than HC
	P2X7r	Higher monocyte surface expression in BD than HC Higher sensitivity to stimulation when compared to HC Increased P2X7r-dependent IL-1β secretion in BD

McGonagle D Nat Rev Rheumatol 2015; Giza M Clin Exp Immunol 2018; Direskeneli H Rheumatology 2006; Y

A recessive model of epistatic interaction between ERAP1 and HLA-B51 has been described

Kirino Y, Bertsias G, Ishigatsubo Y, et al. *Nat Genet* 2013

Enzyme encoded by ERAP1 trims peptides for loading onto MHC class I molecules in the endoplasmic reticulum

Takeuchi M, Ombrello M, Kirino Y, et al. *Ann Rheum Dis* 2016

Behçet's disease risk-variant HLA-B51/ERAP1-Hap10 alters human CD8 T cell immunity

Ann Cavers,[1] Matthias Christian Kugler,[2] Yesim Ozguler,[1,3,4] Arshed Fahad Al-Obeidi,[5] Gulen Hatemi ,[3,4] Beatrix M Ueberheide,[6] Didar Ucar,[4,7] Olivier Manches,[8,9] Johannes Nowatzky [1,10]

Handling editor Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/ard-2022-222277).

For numbered affiliations see end of article.

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ABSTRACT

Objectives The endoplasmic reticulum aminopeptidase (*ERAP1*) haplotype *Hap10* encodes for a variant allotype of the endoplasmic reticulum (ER)-resident peptide-trimming aminopeptidase ERAP1 with low enzymatic activity. This haplotype recessively confers the highest risk for Behçet's diseases (BD) currently known, but only in carriers of *HLA-B*51*, the classical risk factor for the disease. The mechanistic implications and biological consequences of this epistatic relationship are unknown. Here, we aimed to determine its biological relevance and functional impact.

Methods We genotyped and immune phenotyped a cohort of 26 untreated Turkish BD subjects and 22 healthy donors, generated CRISPR-Cas9 *ERAP1* KOs from *HLA-B*51*$^+$ LCL, analysed the HLA class I-bound peptidome for peptide length differences and assessed immunogenicity of genome-edited cells in CD8 T cell co-culture systems.

Results Allele frequencies of *ERAP1-Hap10* were similar to previous studies. There were frequency shifts between antigen-experienced and naïve CD8 T cell populations of carriers and non-carriers of *ERAP1-Hap10* in an *HLA-B*51* background. *ERAP1* KO cells showed peptidomes with longer peptides above 9mer and significant differences in their ability to stimulate alloreactive CD8 T cells compared with wild-type control cells.

Conclusions We demonstrate that hypoactive ERAP1 changes immunogenicity to CD8 T cells, mediated by an HLA class I peptidome with undertrimmed peptides. Naïve/effector CD8 T cell shifts in affected carriers provide evidence of the biological relevance of *ERAP1-Hap10/HLA-B*51* at the cellular level and point to an HLA-B51-restricted process. Our findings suggest that variant ERAP1-Hap10 partakes in BD pathogenesis by generating HLA-B51-restricted peptides, causing a change in immunodominance of the ensuing CD8 T cell response.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ *ERAP1-Hap10* encodes for a hypoactive endoplasmic reticulum aminopeptidase (ERAP1) resembling a functional KO, and recessively confers the highest risk for Behçet's disease (BD) in the presence of *HLA-B*51* (epistasis).

WHAT THIS STUDY ADDS

⇒ ERAP1-Hap10/HLA-B51 skews frequencies and phenotypes of human antigen-experienced versus naïve CD8 T cells in vivo, pointing to the biologic relevance of this variant and suggesting its importance in HLA-B51-restricted CD8 T cell activation.

⇒ Knock-out of *ERAP1*—modelling hypofunctional ERAP1-Hap10—alters immunogenicity, mediated through an HLA class I-bound peptidome which is characterised by longer, that is, less trimmed peptides above 9mer.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ The study provides rationale for the development of ERAP1 activity modulating therapy targeted to BD patient subsets defined by genotype as opposed to disease phenotype alone.

⇒ The findings have relevance to understanding, risk stratifying and treating other, clinically distinct HLA class I-associated diseases in whom epistasis between *ERAP1* haplotypes and disease-associated *HLA class I* alleles has been shown to be linked to risk and protection, such as ankylosing spondylitis and psoriasis.

RHEUMATOLOGY

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Advance Access publication 26 January 2021

Original article

Distinct transcriptional profile of blood mononuclear cells in Behçet's disease: insights into the central role of neutrophil chemotaxis

Kleio-Maria Verrou[1], Nikolaos I. Vlachogiannis [2],
Giannis Ampatziadis-Michailidis[1], Panagiotis Moulos[1,3],
Georgios A. Pavlopoulos[1,3], Pantelis Hatzis[1,3], George Kollias[1,4,5] and
Petros P. Sfikakis [1,2]

Rheumatology key messages

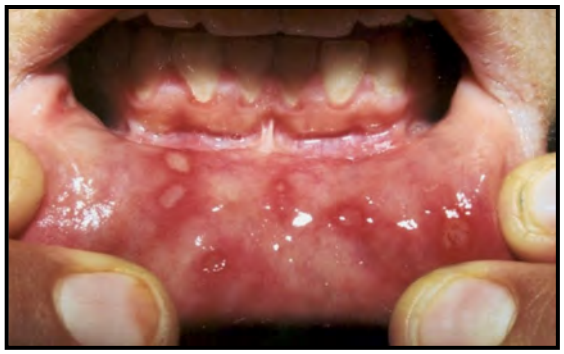
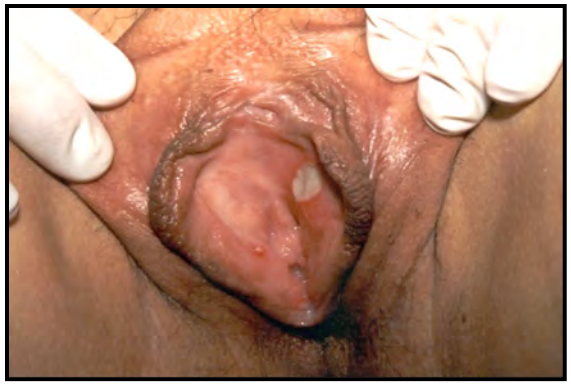
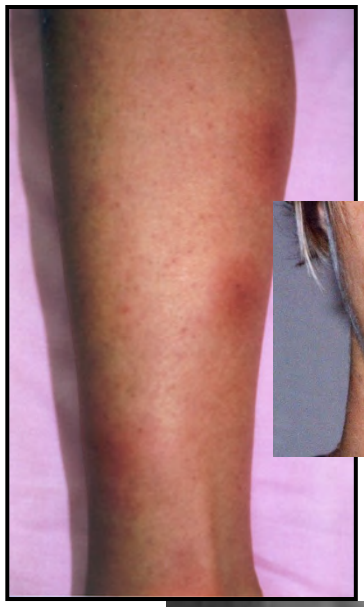
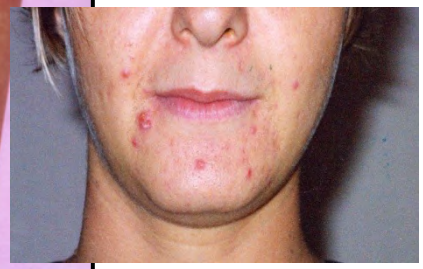
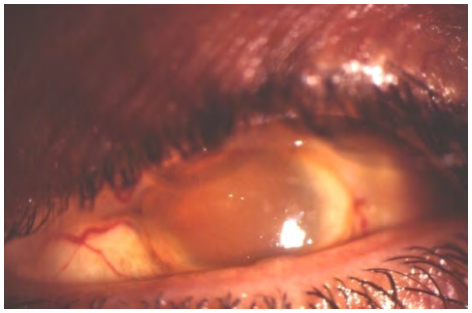
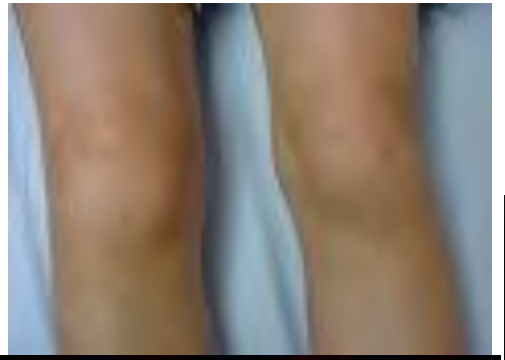
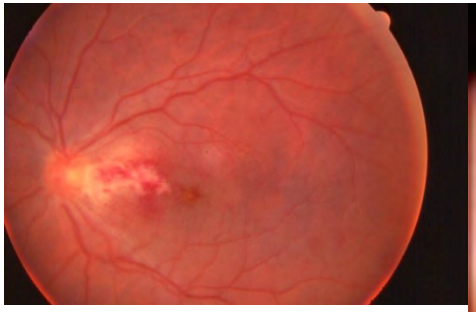
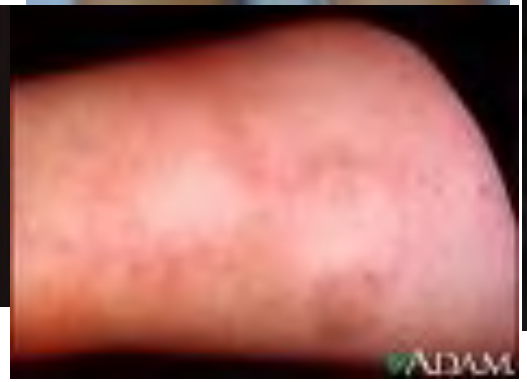
- The most upregulated genes in Behçet's disease peripheral blood mononuclear cells comprised an abundance of CC- and CXC-chemokines.
- Of 10 top upregulated biological processes in Behçet's disease, 5 involved leucocyte recruitment to peripheral tissues, especially for neutrophils.
- The NF-kB p65/RELA subunit action was found to underlie the observed differences in the Behçet's disease transcriptome.

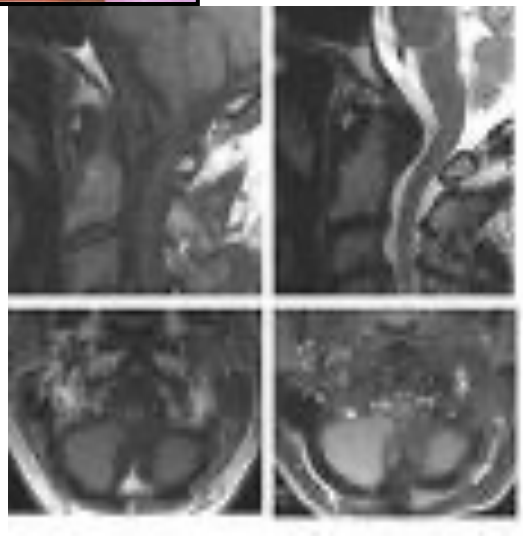
outline

- Μια νόσος με ευρύ φάσμα και αποκλειστικά κλινική Διάγνωση
- Τι νεώτερο στη θεραπεία
- Σύνοψη: 4 περιστατικά

- Μελλοντικές κατευθύνσεις

- BD: distinct, chronic, relapsing, multisystem inflammatory disorder
  … small and large vessels of venous and arterial systems affected
  … muco-cutaneous, ocular, arthritic, vascular, intestinal, CNS

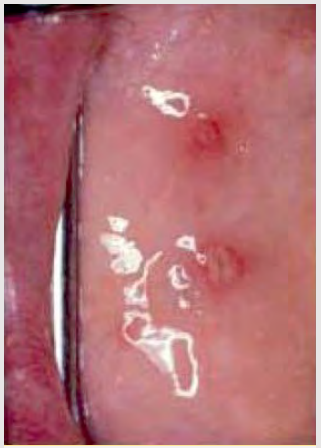



wide range of clinical manifestations* – strong **ethnic differences**

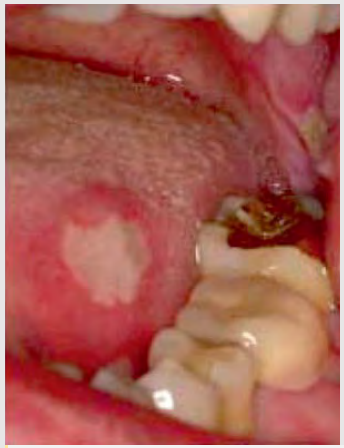
• Oral ulcers	95-100 %
• Genital ulcers	75 - 85 %
• Papulopustular lesions	55%
• Erythema nodosum	45%
• Uveitis	35-80 %
• Arthritis	35-60 %
• Superficial thrombophlebitis	25 %
• Deep vein thrombosis	5-10 %
• Aneurysms	3-8 %
• CNS involvement	10-20 %
• Epididymitis	5-15 %
• GI involvement	5-25 %

…various changes as treatment options become more effective…

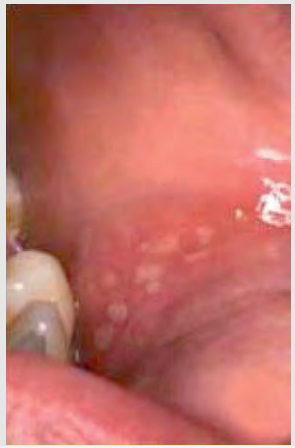
Σχεδόν κάθε ασθενής έχει υποτροπιάζοντα στοματικά έλκη



Minor-type oral aphthous ulcers[3]



Major-type oral aphthous ulcer[3]



Herpetiform oral aphthous ulcers[3]

Τα υποτροπιάζοντα στοματικά έλκη της νόσου Behçet μπορεί να συρρέουν, να είναι επώδυνα, και (όχι συχνά) να αφήσουν ουλές

Η διάγνωση είναι ΚΛΙΝΙΚΗ ….. και μπορεί να καθυστερήσει πολλά χρόνια

Μέση διάρκεια από την έναρξη των συμπτωμάτων μέχρι την διάγνωση[1,a]

Η διάγνωση καθυστερεί περισσότερο σε ασθενείς που έχουν μόνο βλεννογονικές βλάβες (1,13 ± 2,4 έτη)
παρά σε ασθενείς με συμμετοχή άλλων οργάνων (0,88 ± 1,9 έτη)[1,a,b]

Χρόνος έως τη δεύτερη εκδήλωση σε ασθενείς με υποτροπιάζοντα στοματικά έλκη (έτη)[2,c]

[a] Study of 661 patients at the Behçet's Disease Units of Akdeniz, Çukurova, Firat, Gazi, İnönü, and Mersin Universities; [b]Mean ± SD; [c]Study of 67 patients with only a history of recurrent oral ulcers at the time of their first visit to the Behçet's Disease Specialty Clinic in Severance Hospital, Yonsei University, Seoul, Korea.

SD = standard deviation.

1. Alpsoy E et al. *Br J Dermatol.* 2007;157:901-906; 2. Bang D et al. *J Dermatol.* 1995;22:926-929.

η βιοψία ΔΕΝ βοηθά στη διάγνωση….

Ιστοπαθολογία

- *Αγγείτις πάντα*
  - αγγεία (συμπλβ. φλέβες και πνευμονική αρτηρία)
  - οφθαλμοί
  - επιδυδιμίτιδα
- *Αγγειίτις συχνά*
  - έλκη στόματος
  - έλκη γεννητικών οργάνων
  - οζώδες ερύθημα
  - έντερο
  - ΚΝΣ
- *Αγγειίτις ποτέ*
  - υμενίτιδα
  - ψευδοακμή-θυλακίτιδα
  - παθεργία

HLA-B51 (up to 20% positivity in Greek population)

- strong association with BD (x2-x3), confirmed in 2 GWAS *
- … HLA-B51 association accounts for less than 20% of the genetic risk
- **not recommended for diagnosis !**

* Mizuki N et al. *Nat Genet.2010;42:703-6* &
Remmers EF et al. *Nat Genet. 2010;42:698–702*

1990 classification-diagnostic criteria (sensitivity 85%; specificity 96%)

HLA-B51 is not recommended for diagnosis

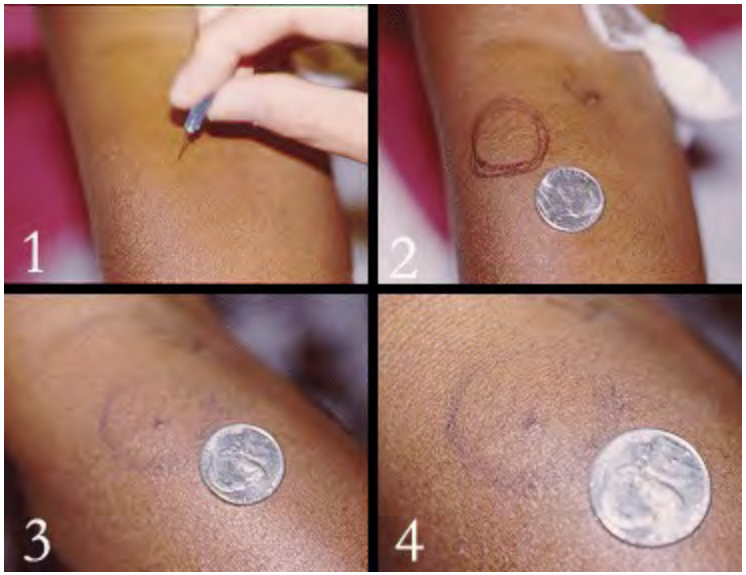
Lancet 1990;335:1078

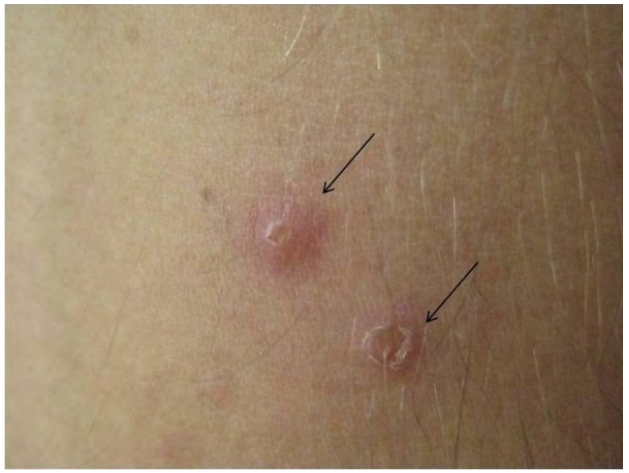
- **recurring oral ulcerations (aphthous or herpetiform) observed by the physician or reliably reported by the patient at least 3 times/year**
    - **plus at least any two of the following:**

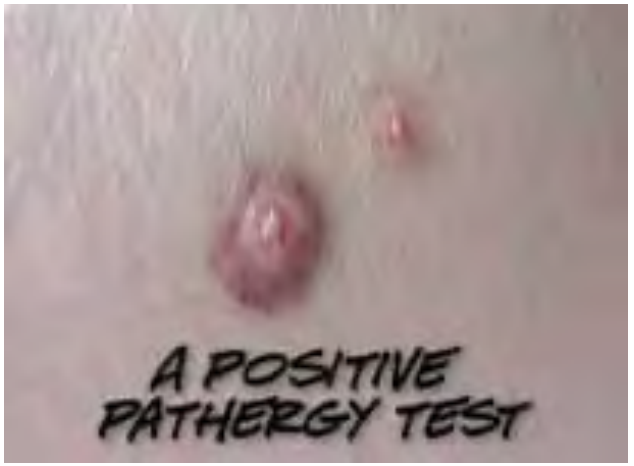
- a) recurrent genital ulceration or scarring
- b) eye lesions: anterior uveitis, posterior uveitis, cells in the vitreous by slit lamp examination or retinal vasculitis observed by an ophthalmologist
- c) skin lesions: erythema nodosum, pseudofolliculitis, papulopustular lesions or acneiform nodules in postadolescent patients not on corticosteroids
- d) a positive pathergy test

pathergy test (prick skin test): non-specific skin hyper-reactivity in response to minor trauma read by a physician at 24–48 hours

> 2 mm pustule, after forearm skin (5 mm depth) prick with 20-22 g needle



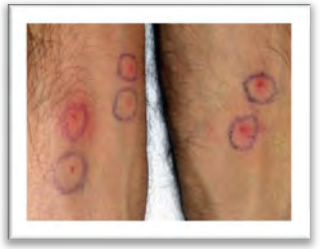




a relevant criterion ?

Behçet Disease – Pathergy Reaction

- Skin microbiome may play a role in the pathergy reaction ?
  - A decrease in positive test results
    - From 65-80% to 30-40%



  - Surgical cleaning of the skin has a negative effect on the pathergy reaction

Pathergy reaction under different conditions

Povidone iodine (10%) (n=93)*				*Chlorhexidine (100%)† (n=47)*				*Chlorhexidine (4%)‡ (n=42)*			
Surgically cleaned forearm	*Conventionally cleaned forearm*	*First observer*	*Second observer*	*Surgically cleaned forearm*	*Conventionally cleaned forearm*	*First observer*	*Second observer*	*Surgically cleaned forearm*	*Conventionally cleaned forearm*	*First observer*	*Second observer*
–	+	23§	19§	–	+	14¶	13§	–	+	5‖	9‖
+	–	3§	3§	+	–	3¶	1§	+	–	2‖	3‖
+	+	22	22	+	+	14	14	+	+	22	11
–	–	45	49	–	–	16	19	–	–	13	19

*Interobserver agreement, 89·8%; κ value, 0·74. †Interobserver agreement, 88·3%; κ value, 0·743. ‡Interobserer agreement 79·2%; κ value, 0·58.
§Significant at p=0·01. ¶Significant at p=0·05. ‖Significant at p=0·25.

Fresko I, et al. Ann Rheum Dis 1993;52:619-20

2014 International Criteria for BD （ ICBD ） – point score system: scoring 4 indicates Behçet's diagnosis

HLA-B51 is not recommended for diagnosis

Sign/symptom	Points
Ocular lesions	2
Genital aphthosis	2
Oral aphthosis	2
Skin lesions	1
Neurological manifestations	1
Vascular manifestations	1
Positive pathergy test*	1*

*Pathergy test is optional and the primary scoring system does not include pathergy testing. However, where pathergy testing is conducted one extra point may be assigned for a positive result.

When it looks like Behçet's syndrome but is something else: Differential diagnosis of Behcet's syndrome: a two-centre retrospective analysis

Authors: Fabian Lötscher[1*/], Floor Kerstens[2,3**], Martin Krusche[4], Nikolas Ruffer[4], Ina Kötter[4,5], Franktien Turkstra[2,3], EULAR study group on MHC-I-opathy.**

Rheumatology 2023

Results: In total 202 patients were included and categorized as follows: 58 patients (28.7%) as 'probable BS', 57 (28.2%) skin disease, 26 (12.9%) chronic pain syndrome, 14 (6.9%) eye disease, 11 (5.4%) spondyloarthropathy, 9 (4.5%) gastrointestinal disease, 7 (3.5%) neurological disease, 4 (2%) arthritis, 3 (1.5%) auto-inflammation, 3 (1.5%) connective tissue disease, 10 (5.0%) miscellaneous disease. *HLA-B51* was positive in 55/132 (41.6%); 75/202 (37.1%) of the patients fulfilled the ICBD criteria.

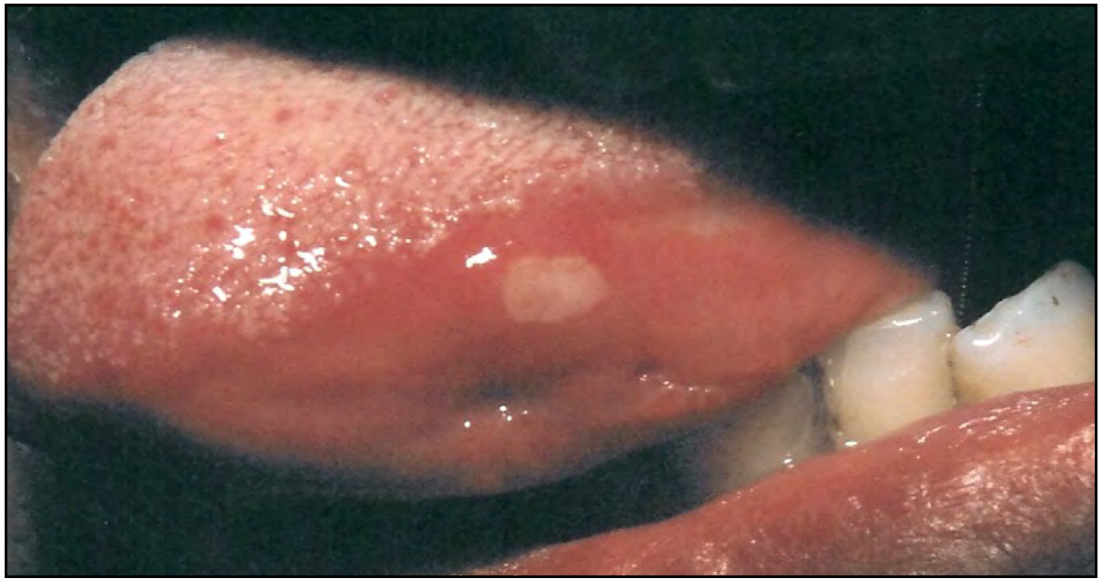
Conclusion: In a low disease prevalence setting the straightforward application of the ICBD criteria may lead to overdiagnosis of BS. The differential diagnosis of BS is enormously broad. Clinicians should be aware that *HLA-B51* positivity is still not considered as a diagnostic feature in BS.

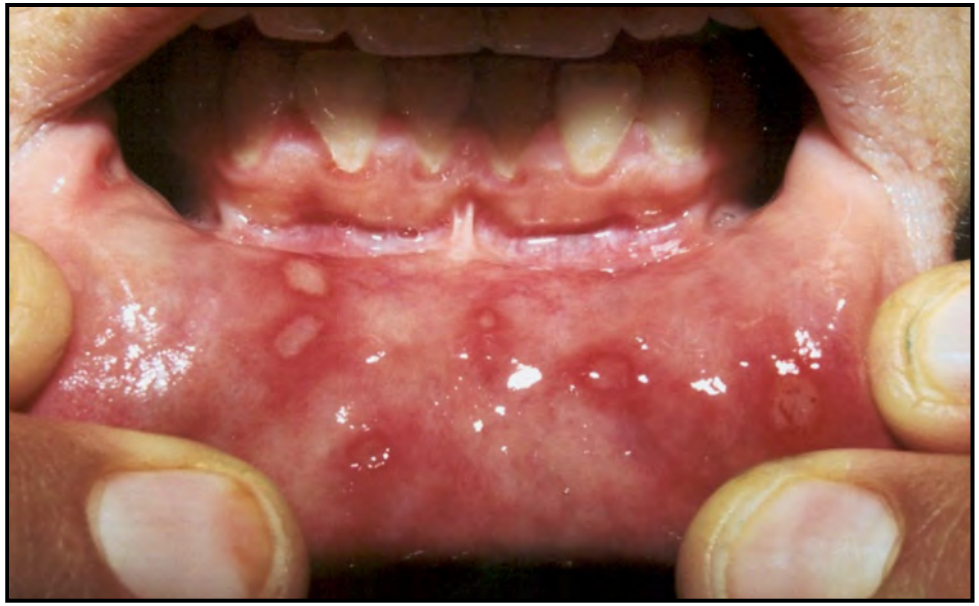
- Arthritis-arthralgias
- Epididymitis
- Vascular thromboses - aneurysms
- GI
- CNS

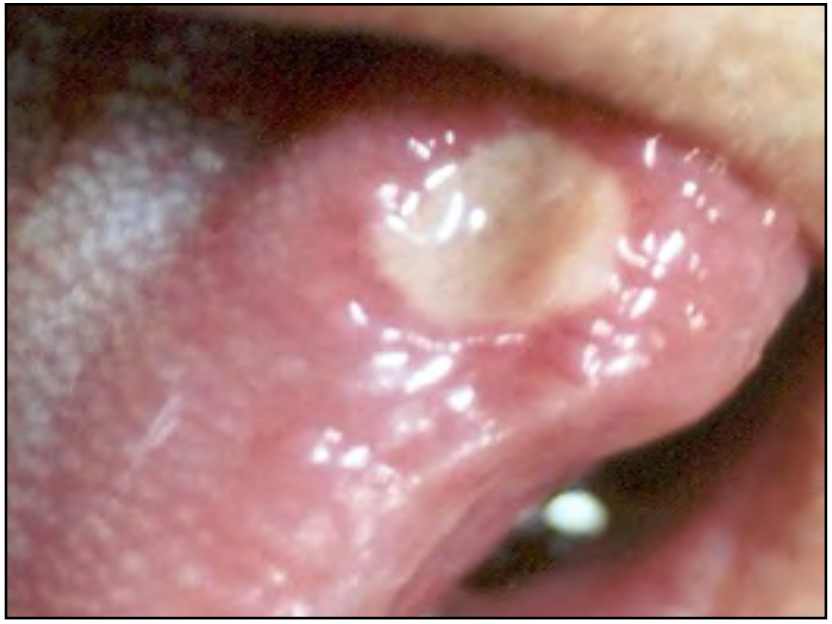
ATTN: not included in classification criteria

oral ulcers >95 %

more often painful

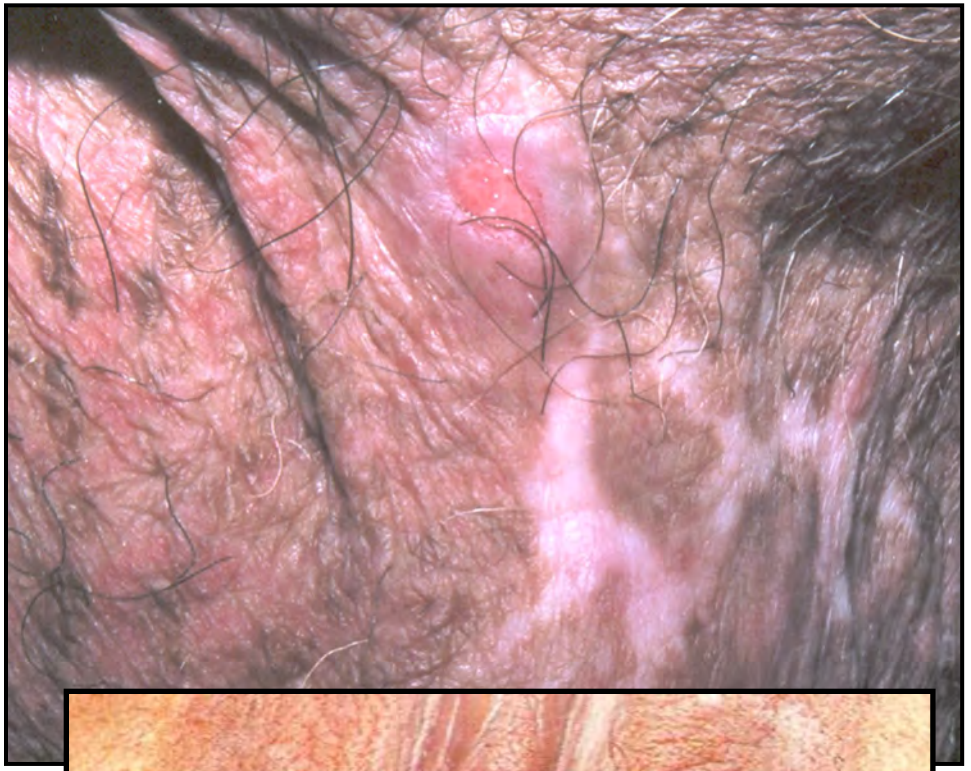


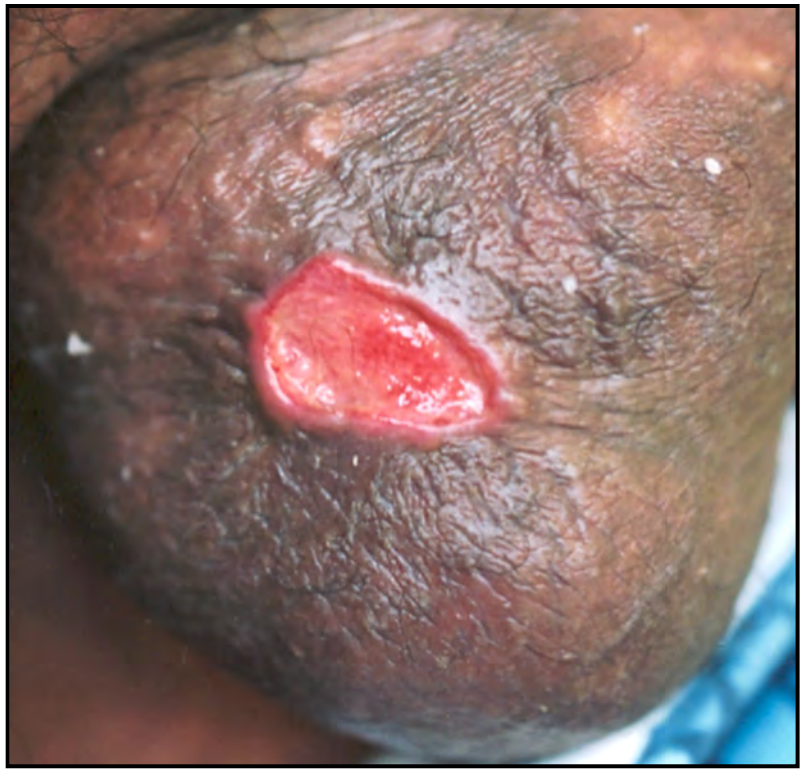


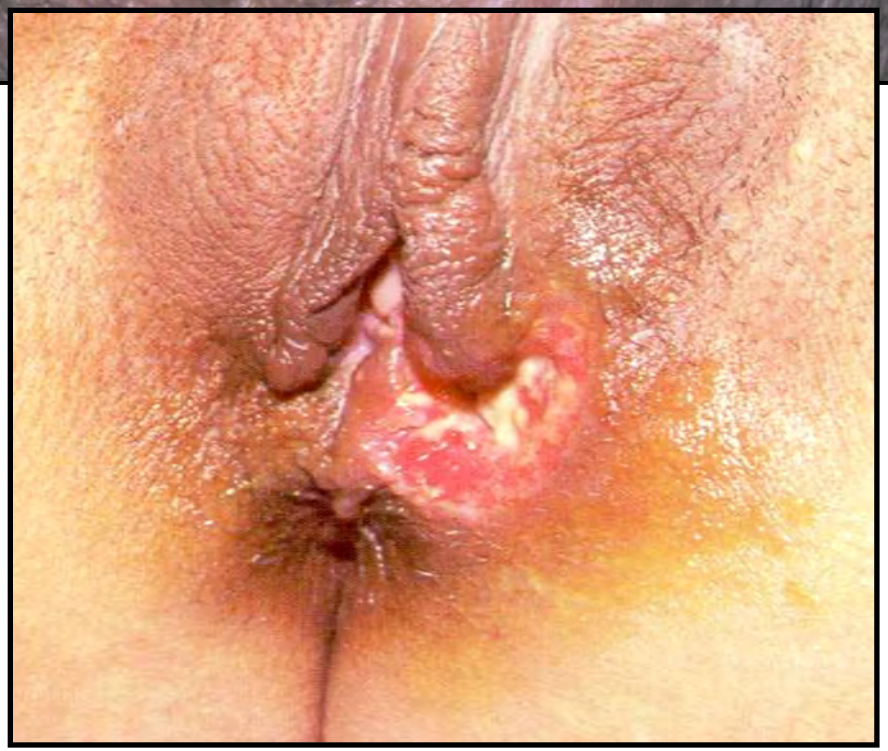


genital ulcers >75%

painful or painless,
significant morbidity …







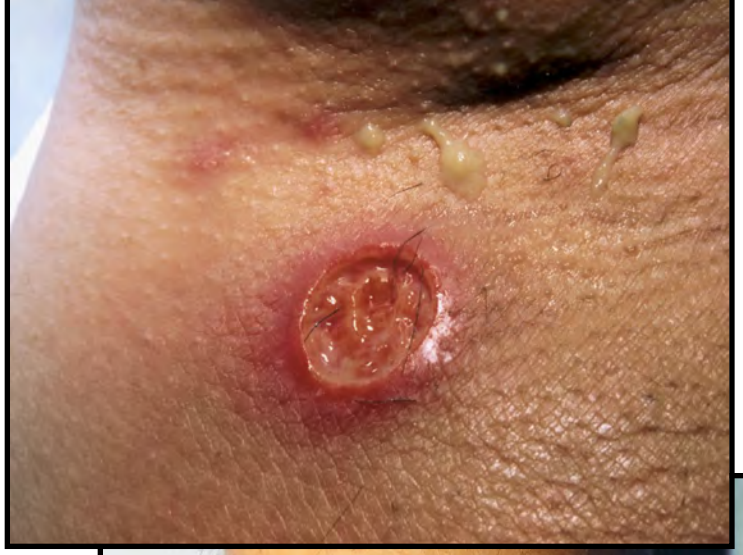
any skin lesion >60 %

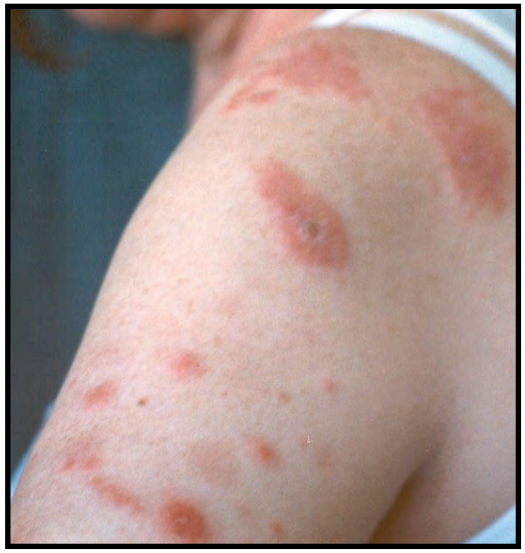
erythema nodosum

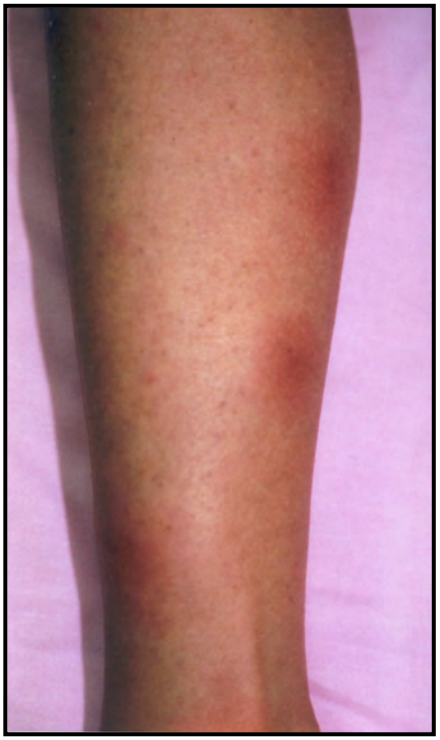
papulopustular lesions-pseudofolliculitis-acne

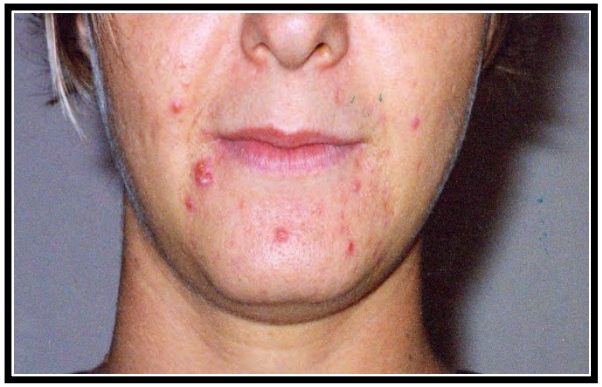
vasculitis

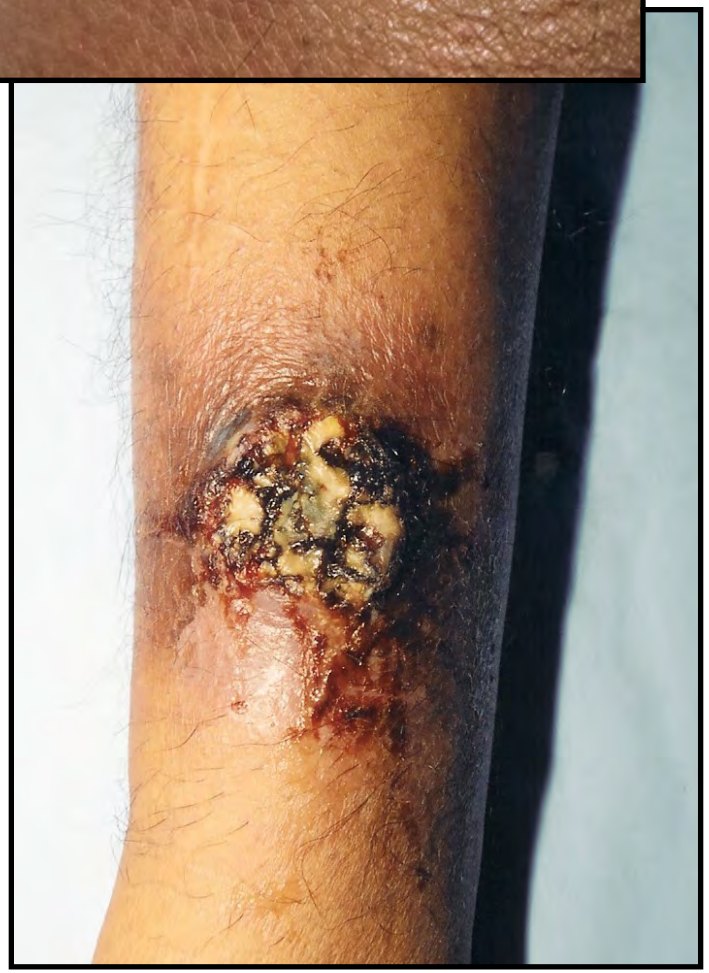
pyoderma gagrainosum





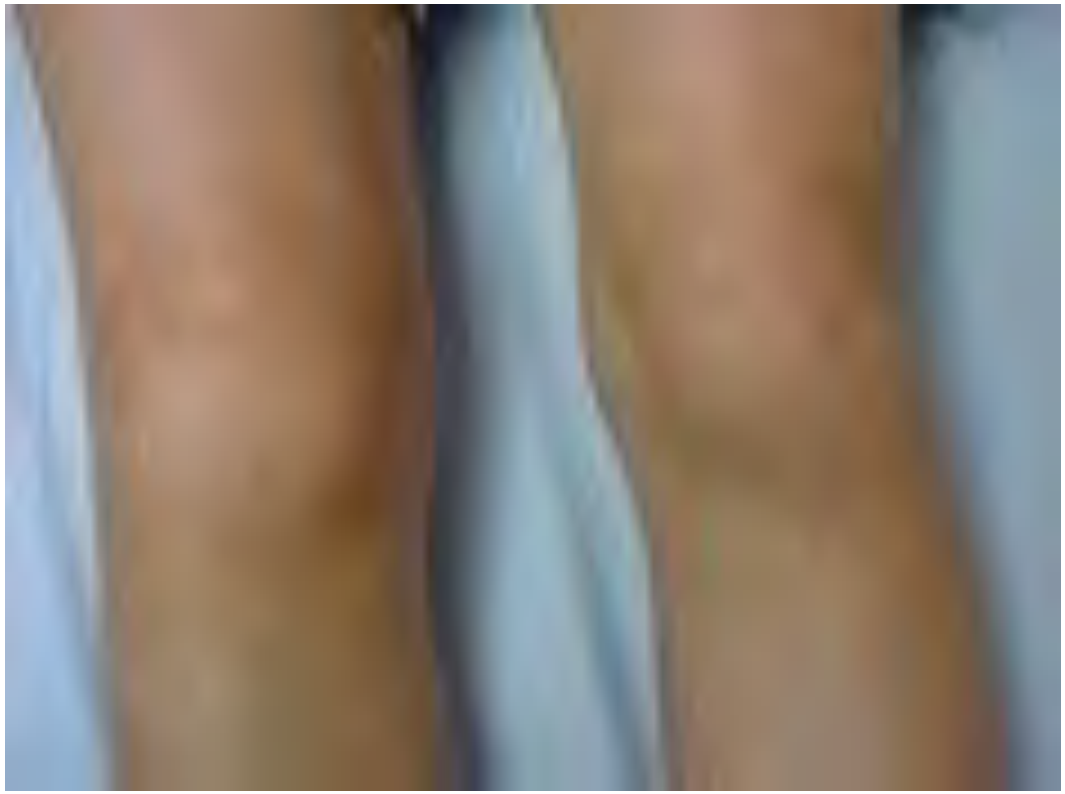




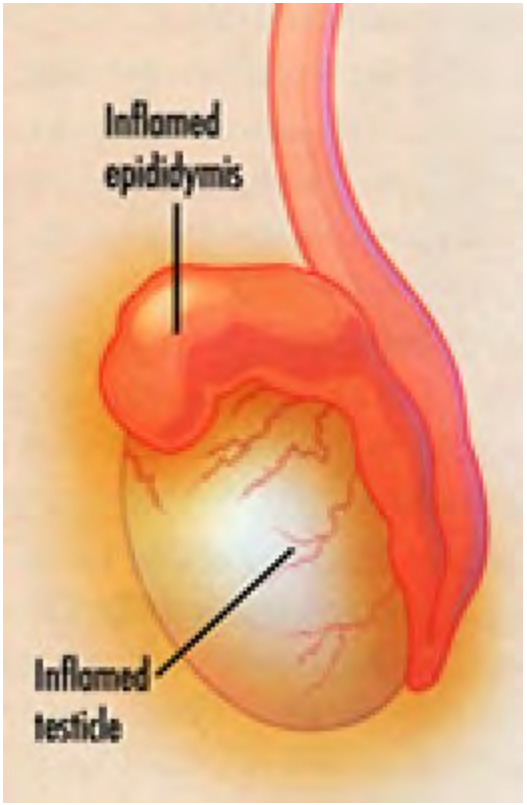


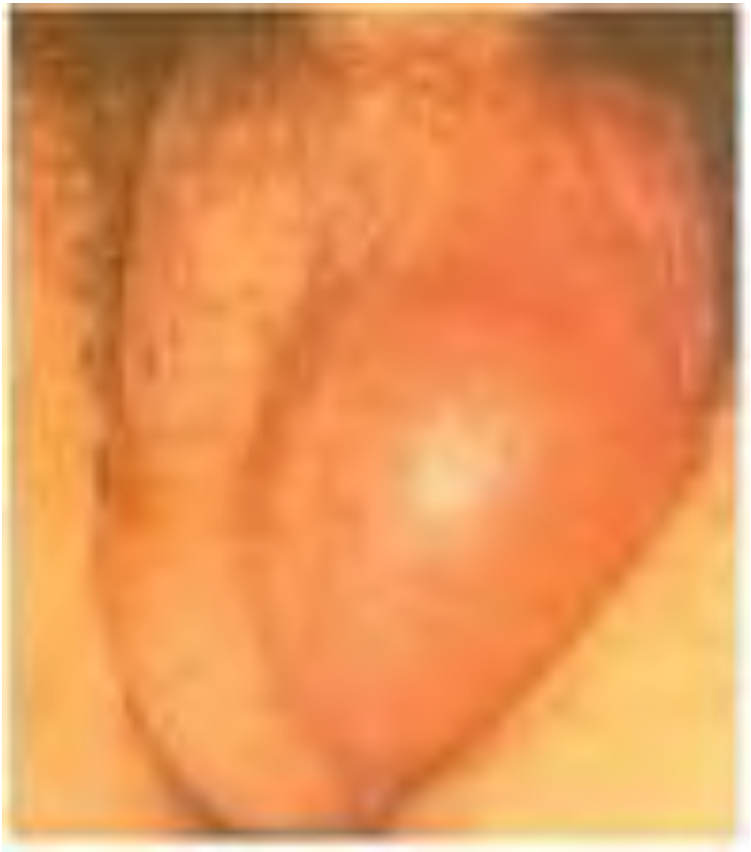
Arthritis or arthralgias: >50 %

-not deforming arthitis
-usually mono-arthritis
-Knees>Ankles>Feet>Hands
-axial invl.: less frequent

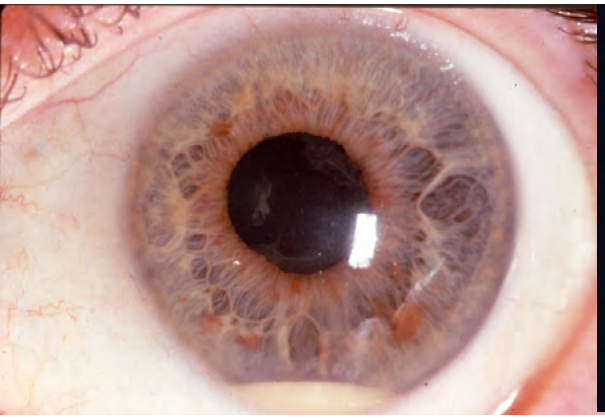
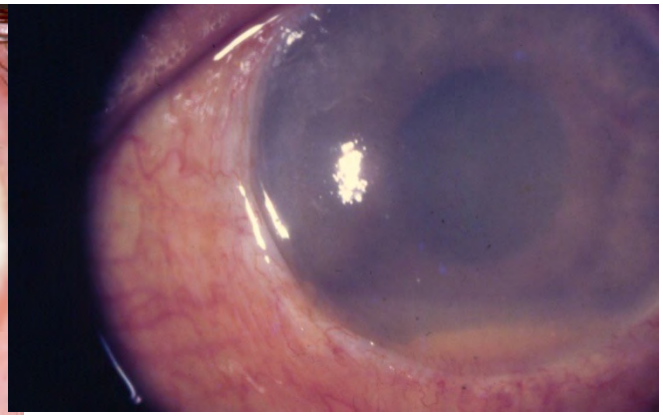
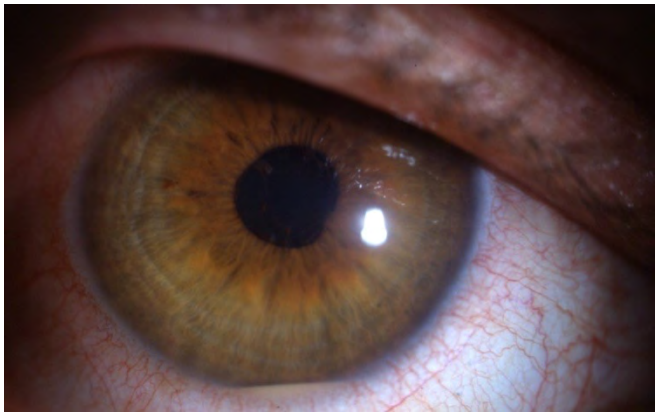
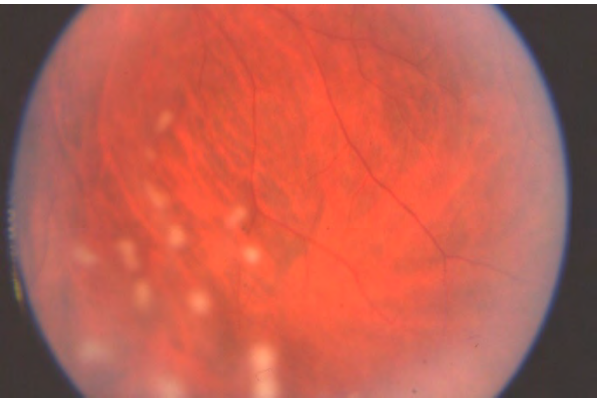
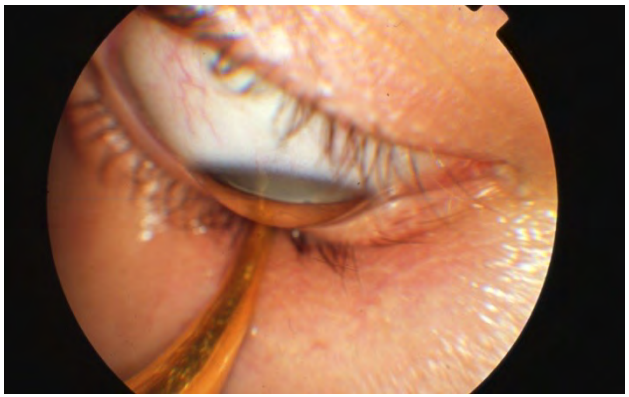
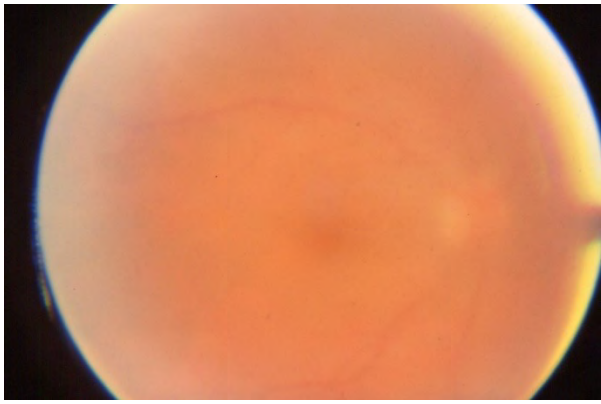
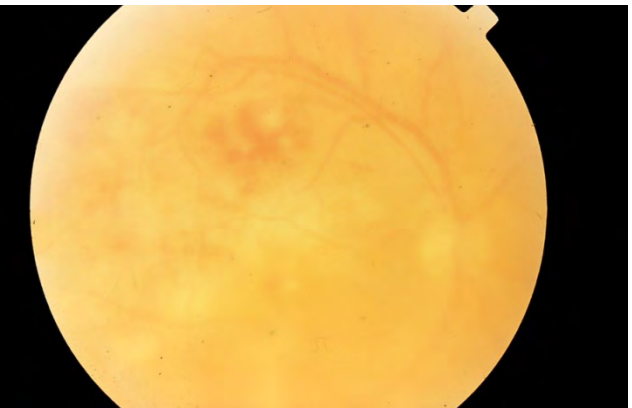
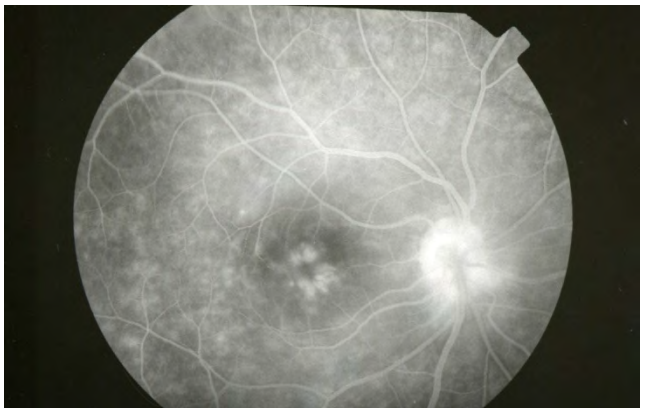
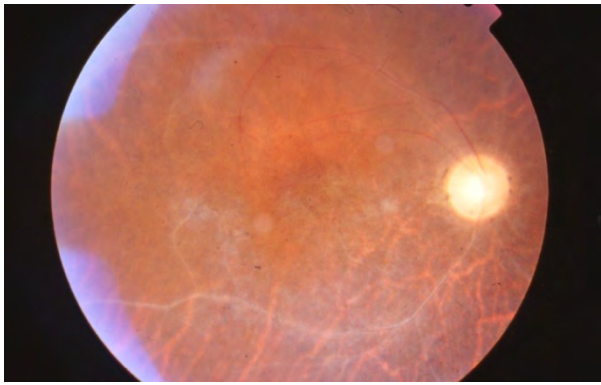


Epididymitis (15 % men)





… any part of the EYE may be affected …

Types of large vessel involvement in BD patients affected

Event Type	N	%
Deep vein thrombosis	889	69.9
Pulmonary artery aneurysms	92	7.2
Superior vena cava syndrome	67	5.3
Budd-Chiari syndrome	48	3.8
Peripheral artery aneurysm	46	3.6
Inferior vena cava syndrome	45	3.5
Cerebral venous sinus thrombosis	31	2.4
Other arterial & venous events	30	2.4
Aortic aneurysms	19	1.5
Carotid aneurysms	4	0.3
Total	1271	

… the cumulative risk of a recurrent vascular event was 38.4% at 5 years !

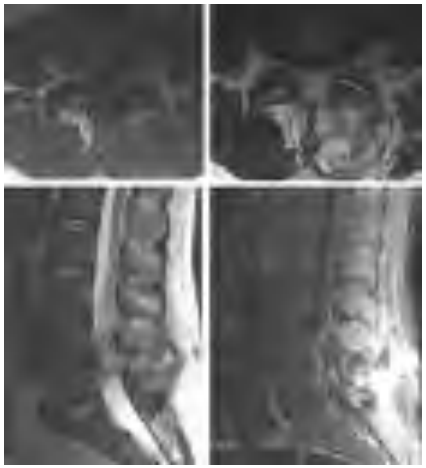
K Taşçılar et al. *Rheumatology 2014[Epub ahead of print]*

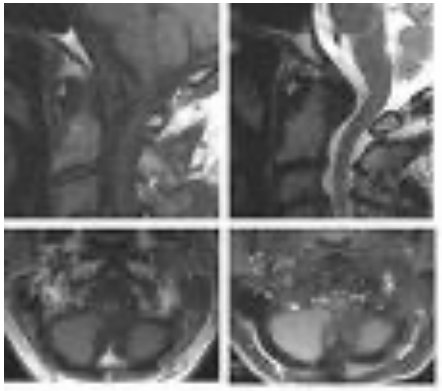
J Neurol
DOI 10.1007/s00415-013-7209-3

REVIEW

Diagnosis and management of Neuro-Behçet's disease: international consensus recommendations

Seema Kalra · Alan Silman · Gulsen Akman-Demir · Saeed Bohlega · Afshin Borhani-Haghighi · Cris S. Constantinescu · Habib Houman · Alfred Mahr · Carlos Salvarani · Petros P. Sfikakis · Aksel Siva · Adnan Al-Araji





Classification of Neuro-Behçet's disease (10-20%)

Central Nervous System

Parenchymal * (bad prognosis)

- **Brainstem**
- **Diffuse ("brainstem plus")**
- **Spinal cord**
- **Cerebral**
- Asymptomatic ("silent")

Non-parenchymal **

- **Cerebral venous thrombosis: intracranial hypertension**
- **Intracranial aneurysm**
- **Extracranial aneurysm/dissection**

Mixed parenchymal and non-parenchymal disease (uncommon)

Peripheral nervous system (relation to Behçet's disease uncertain)

- Peripheral neuropathy and mononeuritis multiplex
- Myopathy and myositis

Other uncommon but recognised syndromes

- Acute meningeal syndrome
- Tumour-like NBD
- Optic neuropathy

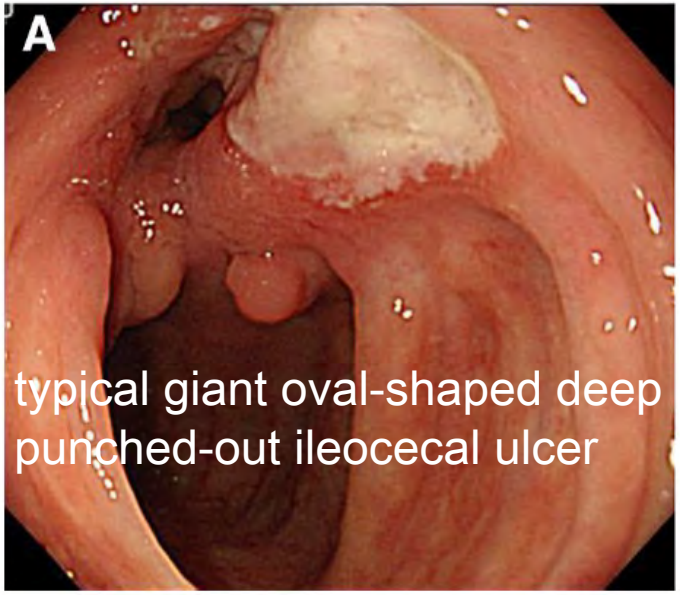
*** 80 %, inflammatory meningo-encephalitis, progressive (relapsing remitting pattern) OR monophasic**

**** 20%, secondary to vascular involvement, usually monophasic**

GASTROINTESTINAL INVOLVEMENT:10 % (40% ?)

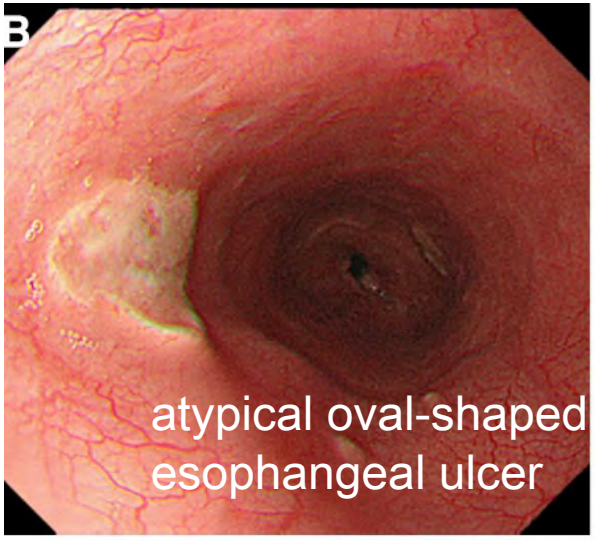
Gut mucosal ulcerations, frequent

Crohn's disease-like may lead to perforation



VERY RARE MANIFESTATIONS: < 2%

- amyloidosis
- renal invl.
- serositis
- cardiac invl.
- pulmonary invl.



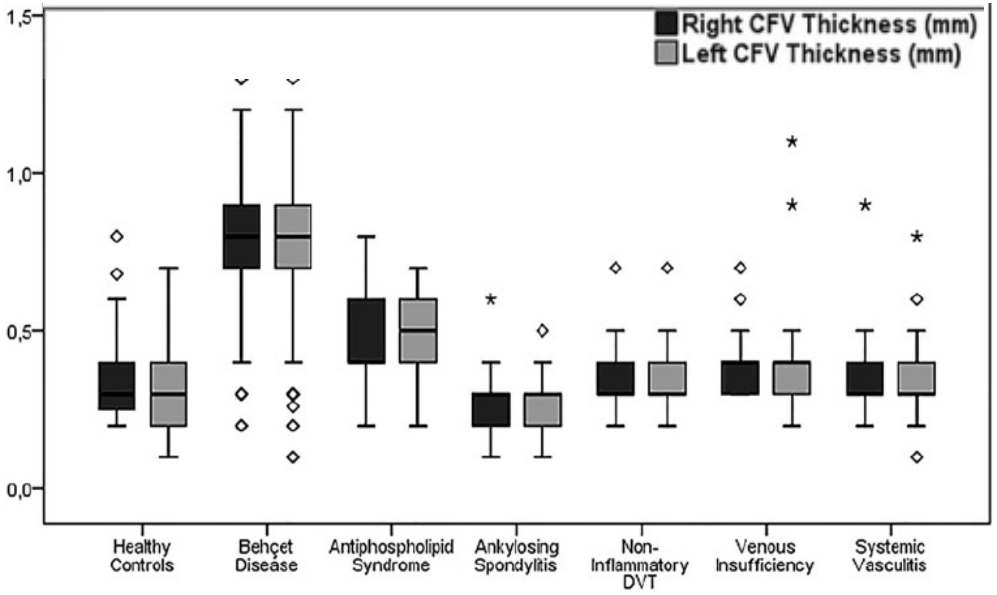
RHEUMATOLOGY

Rheumatology 2021;60:288–296

Femoral vein wall thickness measurement: A new diagnostic tool for Behçet's disease

Fatma Alibaz-Oner [1], Rabia Ergelen[2], Yasin Yıldız[1], Mustafa Aldag[3], Ayten Yazici[4], Ayşe Cefle[4], Ertan Koç[5], Bahar Artım Esen[6], Gonca Mumcu[7], Tulin Ergun[8] and Haner Direskeneli[1]

- 350 patients/controls



- BD vs HC, A. Spondylitis, systemic vasculitis and venous Insufficiency: $p < 0.001$
- BD vs AP Syndrome with DVT: $p < 0.01$

BD (n=152), A. spondylitis (n=27), systemic vasculitides (n=23), venous insufficiency (n=29), antiphospholipid syndrome (APS; n=43), deep vein thrombosis due to non-inflammatory causes (n=25) and healthy controls (n=51)

• Oral ulcers	97-100 %
• Genital ulcers	75 - 85 %
• Papulopustular lesions	55%
• Erythema nodosum	45%
• Uveitis	35-70 %
• Arthritis	35-60 %
• Superficial thrombophlebitis	25 %
• Deep vein thrombosis	5-10 %
• Aneurysms	3-8 %
• CNS involvement	10-20 %
• Epididymitis	5-15 %
• GI involvement	5-25 %

…any patient presenting with one of the above may have BD !

relapsing/remitting disease course; retrospective diagnosis is common ….

rule out other diagnoses…..no specific lab tests exist … careful history ….

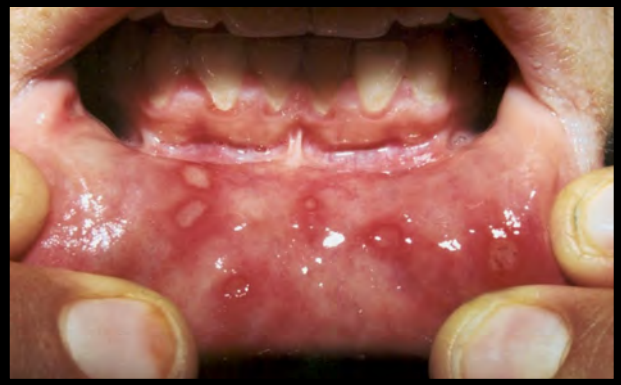
outline

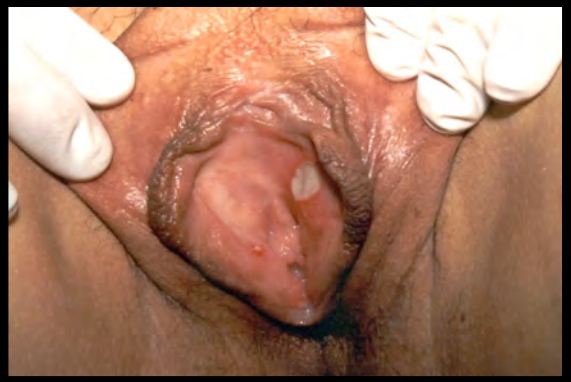
- Μια νόσος με ευρύ φασμα και αποκλειστικά κλινική Διάγνωση
- Τι νεώτερο στη θεραπεία
- Σύνοψη: 4 περιστατικά

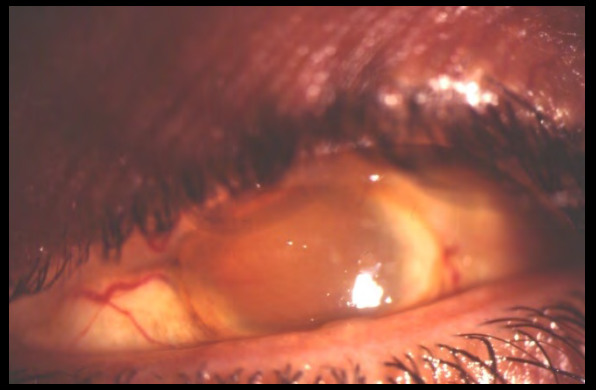
- Μελλοντικές κατευθύνσεις

Management of BD is a complicated issue and needs to be individualized, balancing the risks of therapy with the putative efficacy of a given approach

(few RCTs)

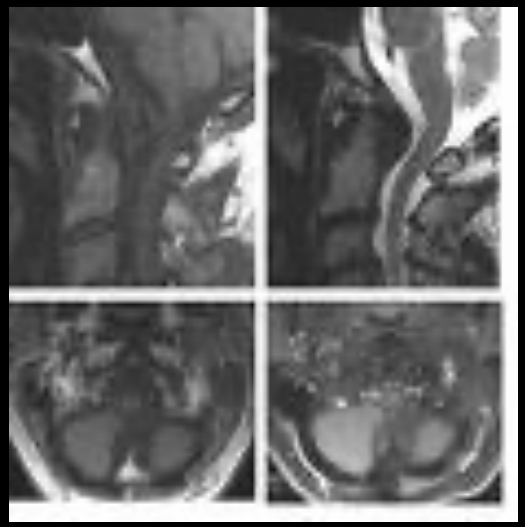


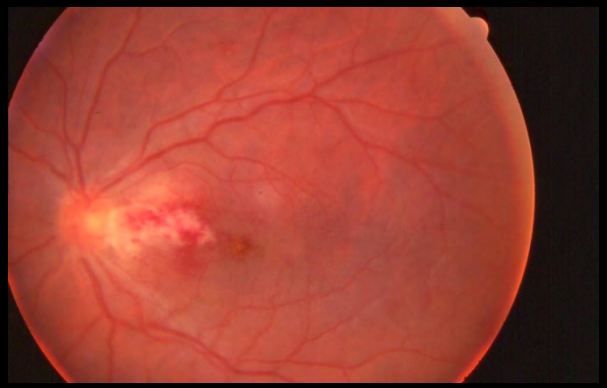




Unmet medical needs for some patients with

a) poor quality of life, and/or
b) vital organ involvement





any drug(s) (combinations) used in rheumatology has been tried….

- **topical measures**
- **antibiotics**
- **NSAID's**
- **thalidomide**
- **corticosteroids**
- **colchicine**
- **cyclosporin-A**
- **azathioprine**
- **interferon-a**
- **cyclophosphamide**
- **anti-TNF agents**

- methrotrexate
- sulphasalazine
- chlorambucil
- mycophenolate mofetil

- anti-IL-1 & IL-1R mAbs
- anti-IL-6 mAb
- anti-IL-17 mAbs
- anti-IL-2R mAb
- JAK-i
- stem cell transplantation

Colchicine: widely used (1-2 mg/d) for mucocutaneous manifestations and arthritis (2 placebo-controlled double blind RCTs *)

- **Women**: Effective in genital ulcers & erythema nodosum
  Less effective for arthritis

- **Men**: Partial efficacy in mucocutaneous lesions
  Effective for arthritis

* Aktulga E, et al. Haematologica 1980
Yurdakul S, et al. Arthritis Rheum 2001

AZATHIOPRINE: used for eye disease †, arthritis †, chronic progressive CNS disease, large vessel disease

- In the placebo-controlled double-blind RCT (75 men) azathioprine 2.5 mg/kg/day for 2 years

- decreased hypopyon uveitis attacks – no effect on existing ocular damage
- prevented deterioration of visual acuity
- decreased the development of new eye disease
- decreased new genital ulcers, arthritis, thrombophlebitis

Yazici H et al NEJM 1990

- The beneficial effect continued during the following 7 years (Hamuryudan et al Arthritis Rheum 1997)

†efficacious in controlled clinical trials.

Cyclophosphamide: for major vascular and CNS involvement

- Positive retrospective data only, no RCT

! side effects

Corticosteroids: the most widely used immunosuppressive drugs

- no controlled data …
- considered effective for mucocutaneous manifestations (alone) and for serious internal organ involvement in combination with AZA/CsA/CYC and biologics

! do not improve the long-term outcome

! side effects

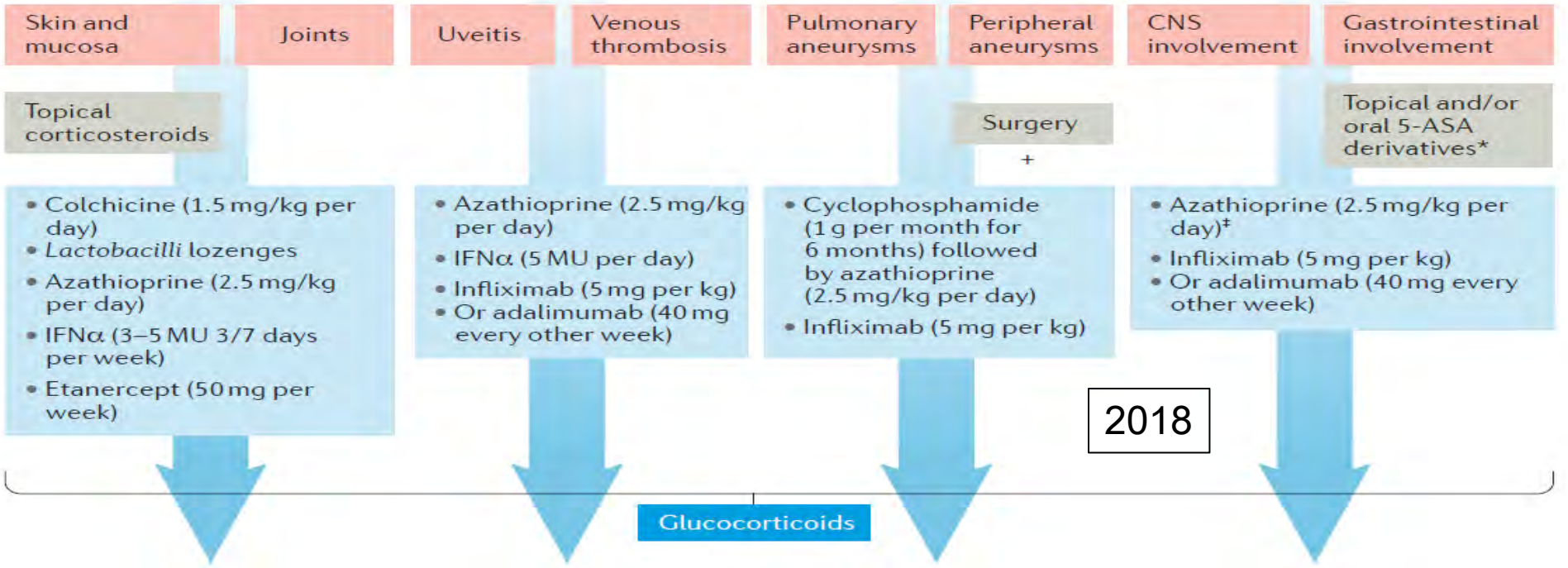
Rheumatology 2007; 1 of 6 doi:10.1093/rheumatology/kem034

2007

Review

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]



2018

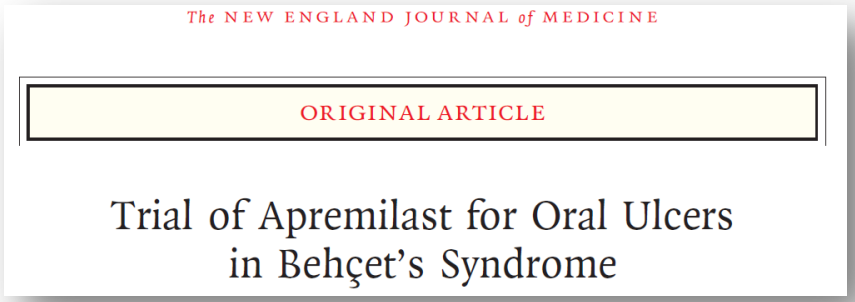
ARD Online First, published on April 6, 2018 as 10.1136/annrheumdis-2018-213225

Recommendation

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

Gulen Hatemi,[1] Robin Christensen,[2] Dongsik Bang,[3] Bahram Bodaghi,[4] Aykut Ferhat Celik,[5] Farida Fortune,[6] Julien Gaudric,[7] Ahmet Gul,[8] Ina Kötter,[9] Pietro Leccese,[10] Alfred Mahr,[11] Robert Moots,[12] Yesim Ozguler,[1] Jutta Richter,[13] David Saadoun,[14,15,16,17] Carlo Salvarani,[18] Francesco Scuderi,[19] Petros P Sfikakis,[20] Aksel Siva,[21] Miles Stanford,[22] Ilknur Tugal-Tutkun,[23] Richard West,[24] Sebahattin Yurdakul,[1] Ignazio Olivieri,[25] Hasan Yazici[1]

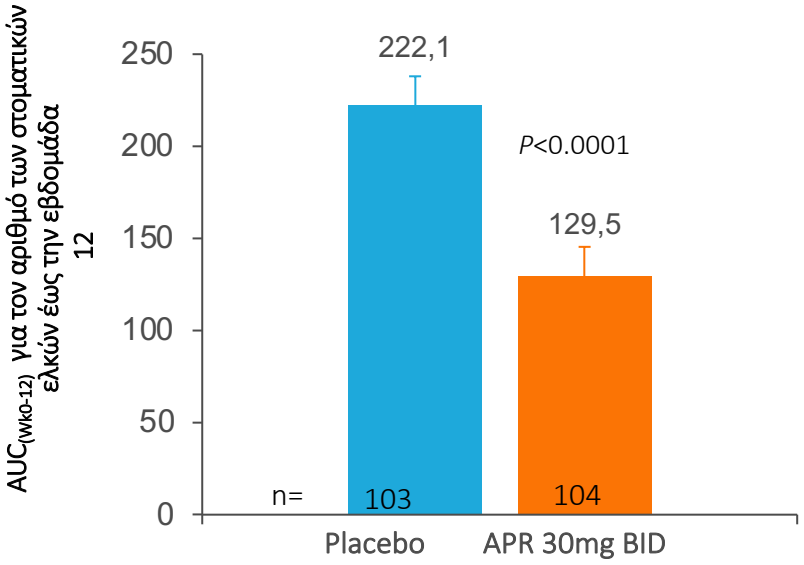
Gülen Hatemi, et al, N Engl J Med 2019; 381:1918-1928, DOI: 10.1056/NEJMoa1816594

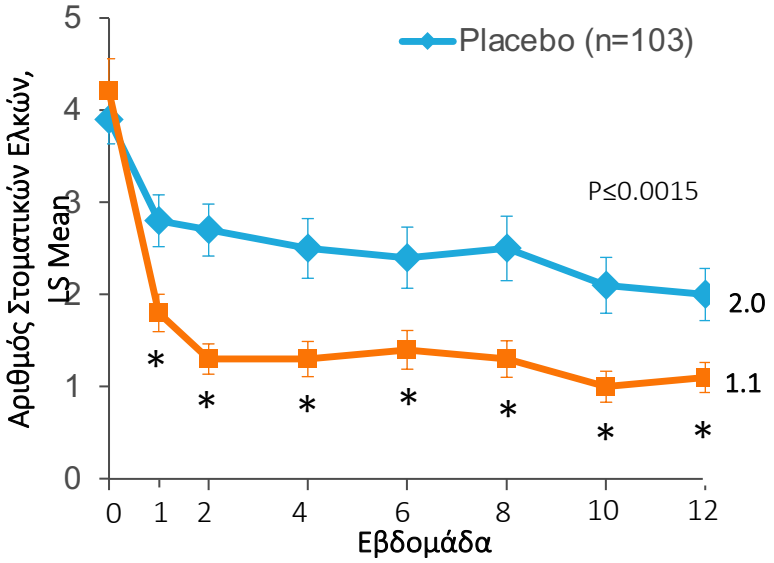


Η Απρεμιλάστη ενδείκνυται για τη θεραπεία των στοματικών ελκών που σχετίζονται με τη νόσο Behçet (BD) σε ενήλικες ασθενείς οι οποίοι είναι υποψήφιοι για συστηματική θεραπεία.

Κύριο καταληκτικό σημείο: $AUC_{(WK\ 0–12)}$ για τον αριθμό των στοματικών ελκών έως την εβδομάδα 12

Η θεραπεία με απρεμιλάστη οδήγησε σε στατιστικά σημαντική μείωση του αριθμού των στοματικών ελκών την εβδομάδα 12 σε σχέση με placebo

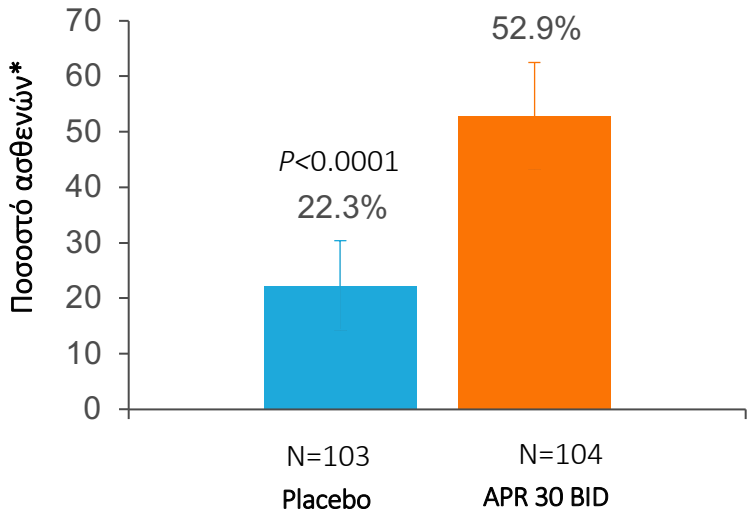




Hatemi et al, N Engl J Med 2019

Πλήρης αποδρομή στοματικών ελκών την εβδομάδα 12 στους μισούς ασθενείς

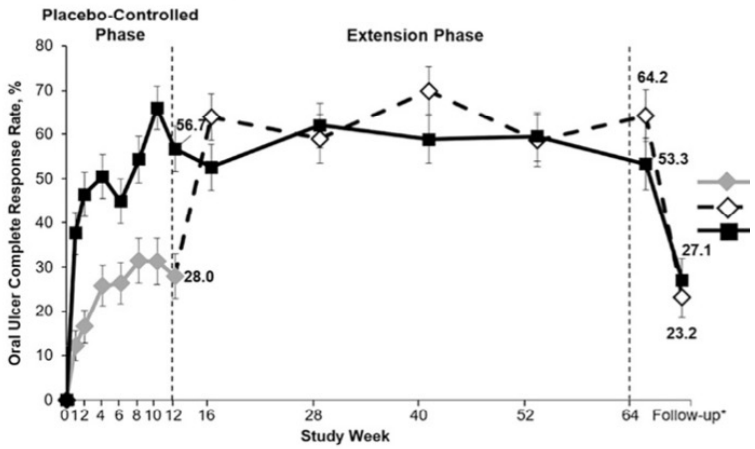
- 53% των ασθενών πέτυχε πλήρη ύφεση των στοματικών ελκών την εβδομάδα 12



Hatemi et al, N Engl J Med 2019

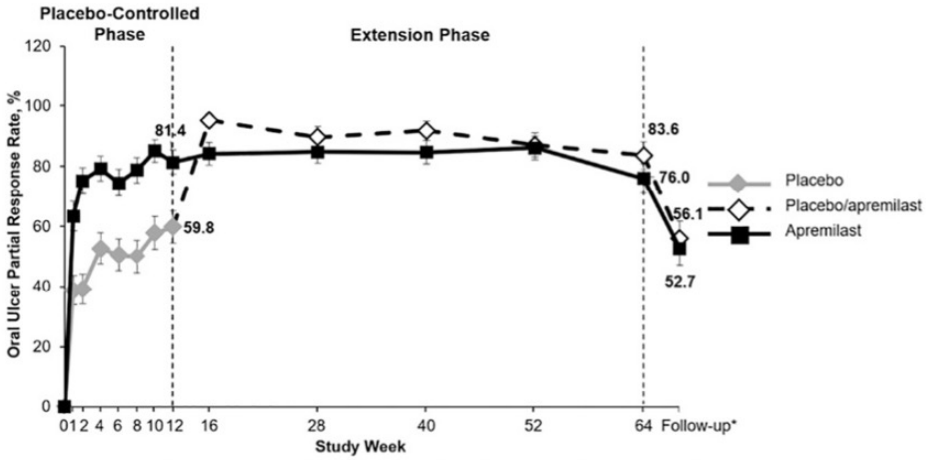
Apremilast for oral ulcers, 68 wks

A Proportions of patients achieving complete resolution of oral ulcers over 64 weeks



Week	0	1	2	4	6	8	10	12	16	28	40	52	64	Follow-up*
Placebo, n	103	98	97	93	91	86	83	82						
Placebo/apremilast, n									83	78	73	70	67	82
Apremilast, n	104	101	101	101	98	94	94	97	95	92	85	79	75	85

B Proportions of patients achieving partial resolution of oral ulcers over 64 weeks



Week	0	1	2	4	6	8	10	12	16	28	40	52	64	Follow-up*
Placebo, n	103	98	97	93	91	86	83	82						
Placebo/apremilast, n									83	78	73	70	67	82
Apremilast, n	104	101	101	101	98	94	94	97	95	92	85	79	75	85

Hatemi G, et al. Clin Exp Rheumatol 2021

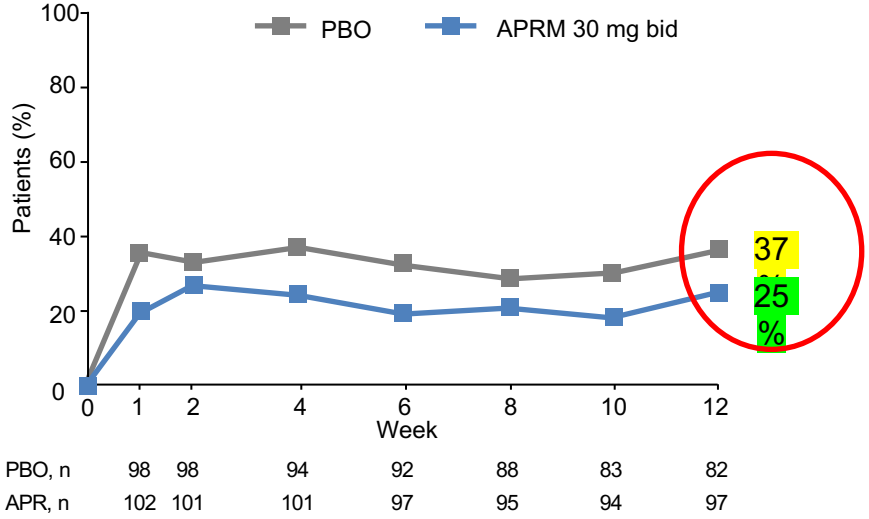
Efficacy of apremilast in beyond oral ulcers

- Assessed new, recurrent, or worsening of non-OU manifestations through Week 12 of a DBRCT[3]
  - APRM 30 mg bid n=104, PBO n=103

Baseline history of non-OU manifestations, n (%)

	PBO (n=103)	APRM 30 mg bid (n=104)
Skin	102 (99.0)	102 (98.1)
Musculoskeletal	80 (77.7)	70 (67.3)
Ocular	19 (18.4)	17 (16.3)
Gastrointestinal	11 (10.7)	8 (7.7)
Central nervous system	8 (7.8)	12 (11.5)
Vascular	1 (1.0)	2 (1.9)

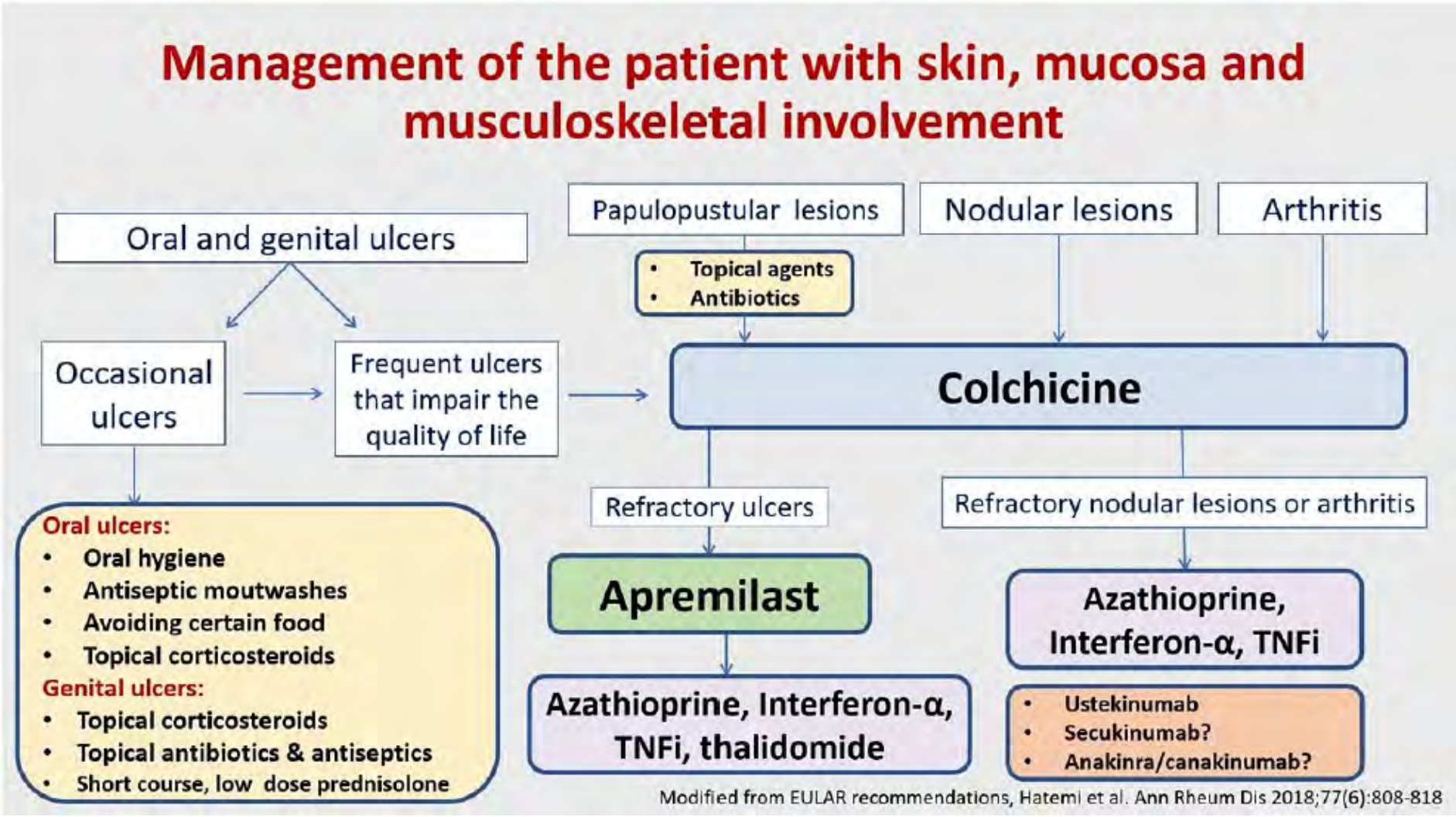
Patients in overall population with ≥1 new, recurrent, or worsening non-Oral Ulcer manifestation during 12 weeks[a]



ITT population, data as observed
[a]Skin lesions, arthritis, uveitis, gastrointestinal, central nervous system, vascular

Hatemi G, et al. ACR 2020, #512

Management of the patient with skin, mucosa and musculoskeletal involvement



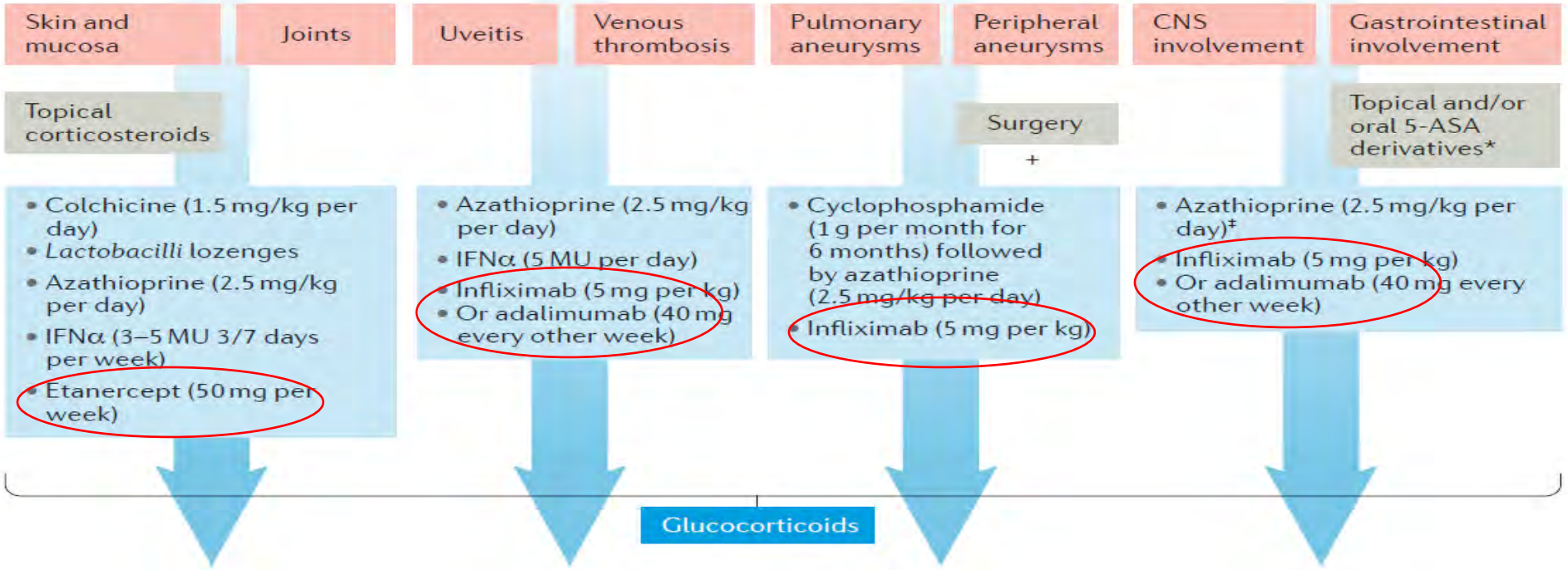
Modified from EULAR recommendations, Hatemi et al. Ann Rheum Dis 2018;77(6):808-818

Behçet syndrome: a contemporary view

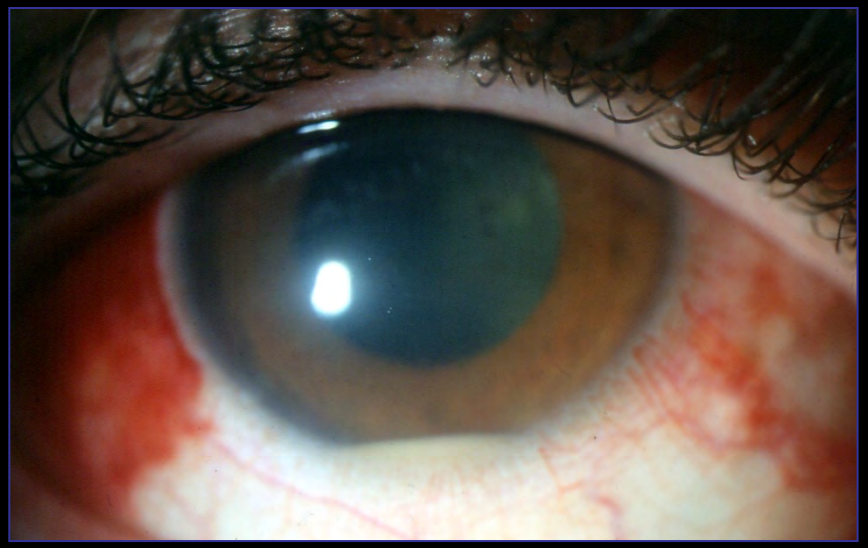
NATURE REVIEWS | RHEUMATOLOGY

Hasan Yazici[1], Emire Seyahi[2], Gulen Hatemi[2] and Yusuf Yazici[3]

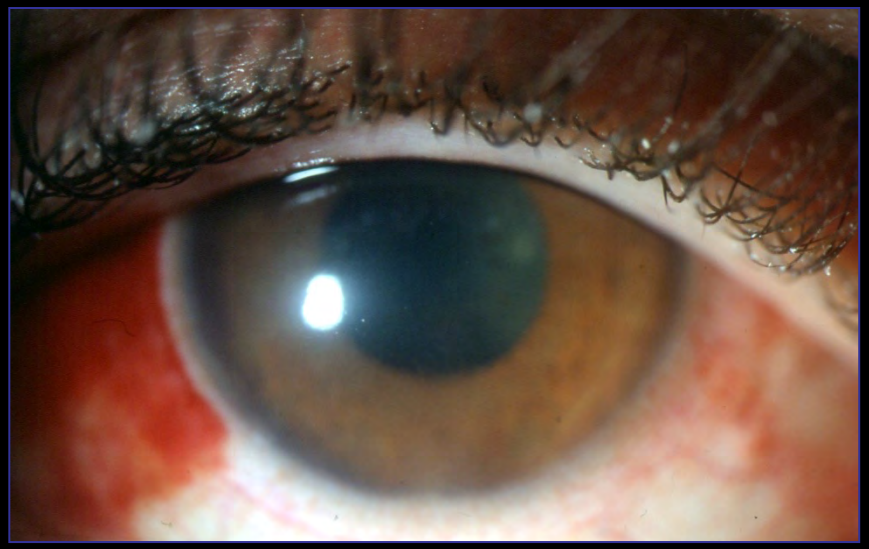
Published online 3 Jan 2018



Infliximab – cells in anterior chamber



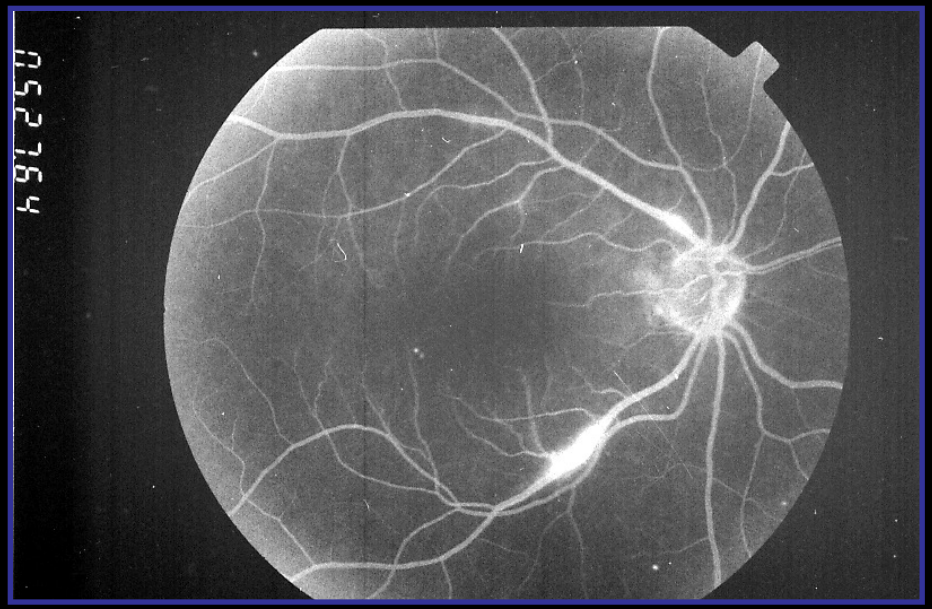
Before Infliximab

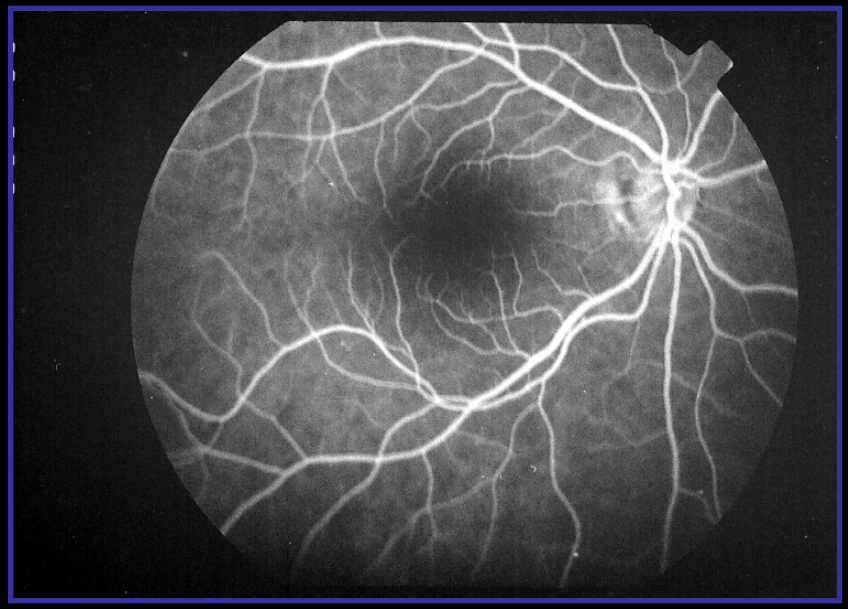


One day later

Sfikakis et al, Ann Intern Med 2004

Infliximab - retinal vasculitis





Before Infliximab

14 days later

Sfikakis et al, Ann Intern Med 2004

ARTHRITIS & RHEUMATOLOGY
Vol. 69, No. 12, December 2017, pp 2380–2385
DOI 10.1002/art.40235

Drug-Free Long-Term Remission in Severe Behçet's Disease Following Withdrawal of Successful Anti–Tumor Necrosis Factor Treatment

Petros P. Sfikakis, Aikaterini Arida, Stylianos Panopoulos, Kalliopi Fragiadaki, George Pentazos, Katerina Laskari, Maria Tektonidou, and Nikos Markomichelakis

Methods

- This retrospective longidutinal study was performed in 2016 and included all 46 patients who received successful long-term anti-TNF treatment for refractory BD in our center, the first being treated in 2000
  - Information on clinical manifestations, treatment and disease course was recorded.
- **Endpoint : the proportion of patients achieving sustained disease remission for at least 3 years** after discontinuation of anti-TNF treatment.

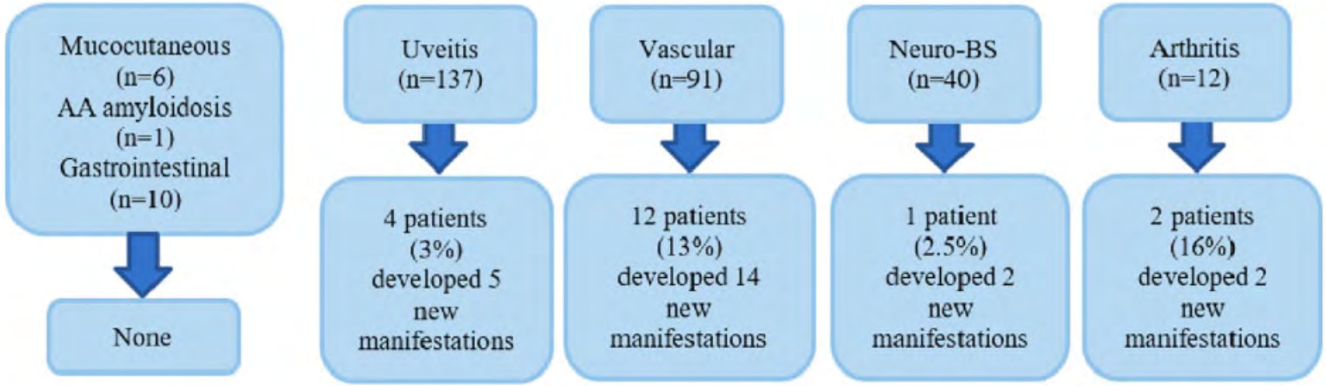
RHEUMATOLOGY

Original article

Emergence of new manifestations during infliximab treatment in Behçet's syndrome

Nur Beyza Tukek[1], Sinem Nihal Esatoglu[2], Gulen Hatemi [2], Elif Buse Calıskan[1], Yılmaz Ozyazgan[3], Didar Ucar[3], Yesim Ozguler[2], Emire Seyahi[2], Melike Melikoglu[2], Ugur Uygunoglu[4], Aksel Siva[4], Zekayi Kutlubay[5], İbrahim Hatemi[6], Aykut Ferhat Celik[6], Serdal Ugurlu [2], Izzet Fresko[2], Sebahattin Yurdakul[2], Hasan Yazici[2] and Vedat Hamuryudan [2]

Indications for IFX use in 282 patients and new manifestations during 3 years (median) under IFX



- The most frequent indications for IFX:
  - Uveitis and vascular involvement
- 19 pts (7%…ONLY !) experienced 23 new manifestations during 3 years
- New manifestations developed in:
  - 13% of patients with vascular involvement
  - 3% of patients with uveitis

Tukek et al. Rheumatology 2022

Anti-IL-1 agents (ANAkinra & CANacinumab) for 12 anti-TNF experienced pts

	Gender Age	Previous treatment	Target clinical manifestations	Biologic agent and concomitant treatment	Clinical outcome	Follow up period
Botsios 2008	F, 75	CSA intolerance, AZA+PDN, IFX+MTX,	Oral and genital ulcers, arthralgias, fever	ANA 100mg/d +PDN 5mg/d	Remission	20 months
Emmi 2013	F, 27	AZA, PDN, IFX intolerance, ADA, RTX	Mucocutaneous, arthralgia, abdominal symptoms, bilateral panuveitis	ANA 100mg/d	Remission and restoration of visual acuity	12 months
Caso, 2013	M, 36	CSA,CS, NSAIDs, IFX	Oral and genital ulcers, sacroiliitis	ANA100mg/d + PDN 5mg/d	Remission	6 months
Cantarini 2013	F, 21	SSZ, MTX, CSA, AZA, ETN/IFX intolerance	Mucocutaneous, arthritis, abdominal symptom, fever	ANA 100mg/d +low dose PDN	Remission, deep vein thrombosis after 16 months	28 months
Vitale 2013	F, 20	PDN high dose, SSZ, MTX, CSA, AZA, LFM, ETN/ IFX intolerance	Mucocutaneous, arthritis, abdominal symptoms, fever	ANA100mg/d	Partial remission; discontinuation due to adverse event	Few weeks
				CAN 150mg/8 weeks	Remission. DVT relapse. Remission with CAN increase	22 months
Cantarini 2013	M, 7	THD+ MMF +PDN, ADA	Mucocutaneous, abdominal symptoms, arthralgias	ANA 2.5 mg/kg/d +PDN 15mg/d	Partial remision	7 months
Cantarini 2013	M, 47	LFM, CSA, AZA, ETN, IFX	Mucocutaneous, uveitis, retinal vasculitis	ANA150mg/d+ PDN 25mg/d	Partial remission	unknown
Caso, 2013	F, 41	PDN, AZA, CSA+ADA, MTX, CTX, IFX	Mucocutaneous, fever, uveitis, arthralgias, pemphigus foliaceus	ANA100mg/d	Partial remission. Relapse.	20 days
Ugurlu 2012	F, 16	AZA+CSA+PDN, IFN, IFX, ADA	Bilateral panuveitis, retinal vasculitis,	ANA 2mg/kg/d	No response	1 month
				CAN 150mg	Remission	2 months
Vitale 2013	F, 41	CS, MTX, AZA, ETN, ADA	Oral and genital ulcers, fever, abdominal symptoms, arthralgia	ANA100mg/d	No response	8 weeks
				CAN 150mg/6 weeks	Remission	12 months
Cantarini 2013	F, 41	CS, MTX, AZA, ETN, ADA	Oral and genital ulcers, arthralgias, fever, abdominal symptoms	ANA 100mg/d	No response	8 weeks
				CAN 150mg/ 8 weeks	Partial remission	2 weeks
Sfikakis, unpublished	F, 56	PDN, AZA, MTX, CSA, CTX, IFX, ADA	Posterior uveitis	ANA 100mg/d	No response	4 months

Arida & Sfikakis *ClinEexp Rheumatol, 2014*

IL-6 blockade for Behçet's disease: review on 31 anti-TNF naive and 45 anti-TNF experienced patients

A. Arida[1], D. Saadoun[2], P.P. Sfikakis[1]

Clin Exp Rheumatol 2022; 40: 1575-1583.

Tocilizumab was effective in 87% of anti-TNF naive (13 and 14 with complete and partial remission, respectively) and in 80% of anti-TNF experienced patients (17 and 19 with complete and partial remission, respectively).

TOFFACITINIB: PILOT STUDY IN REFRACTORY ABD

Ann Rheum Dis November 2020 Vol 79 No 11

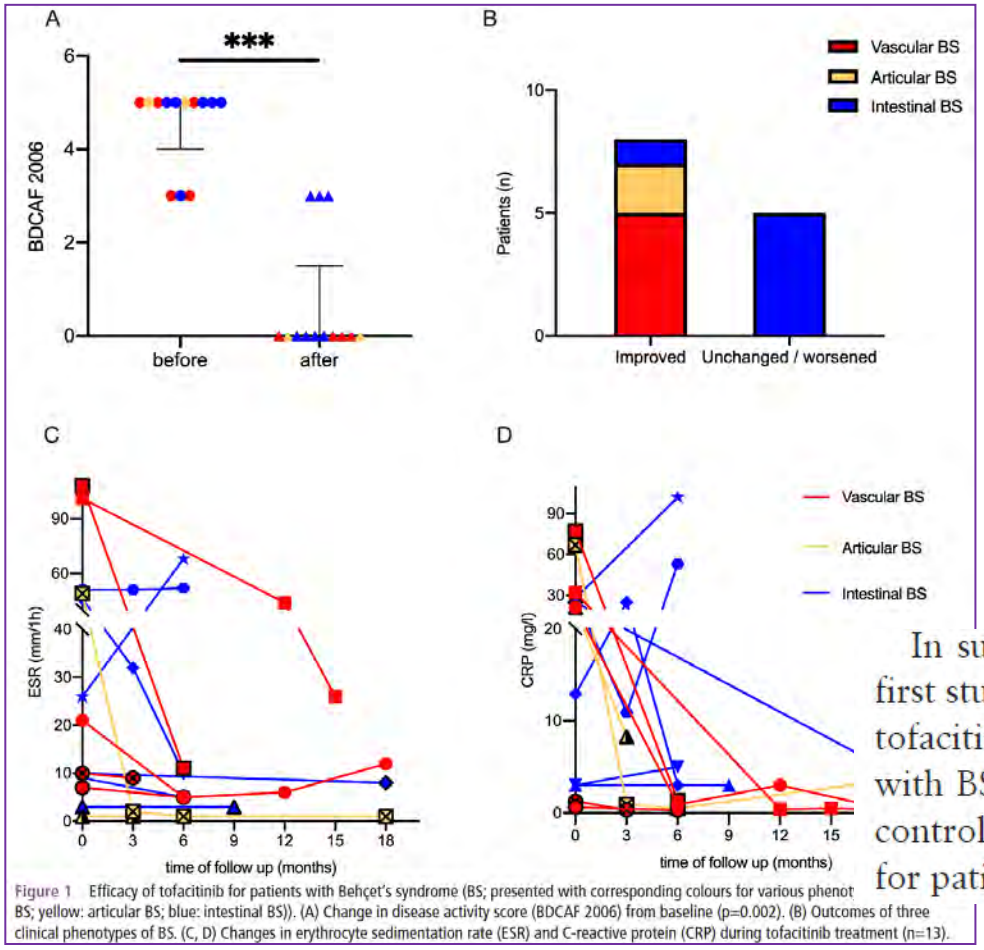


Figure 1 Efficacy of tofacitinib for patients with Behçet's syndrome (BS; presented with corresponding colours for various phenot BS; yellow: articular BS; blue: intestinal BS)). (A) Change in disease activity score (BDCAF 2006) from baseline (p=0.002). (B) Outcomes of three clinical phenotypes of BS. (C, D) Changes in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) during tofacitinib treatment (n=13).

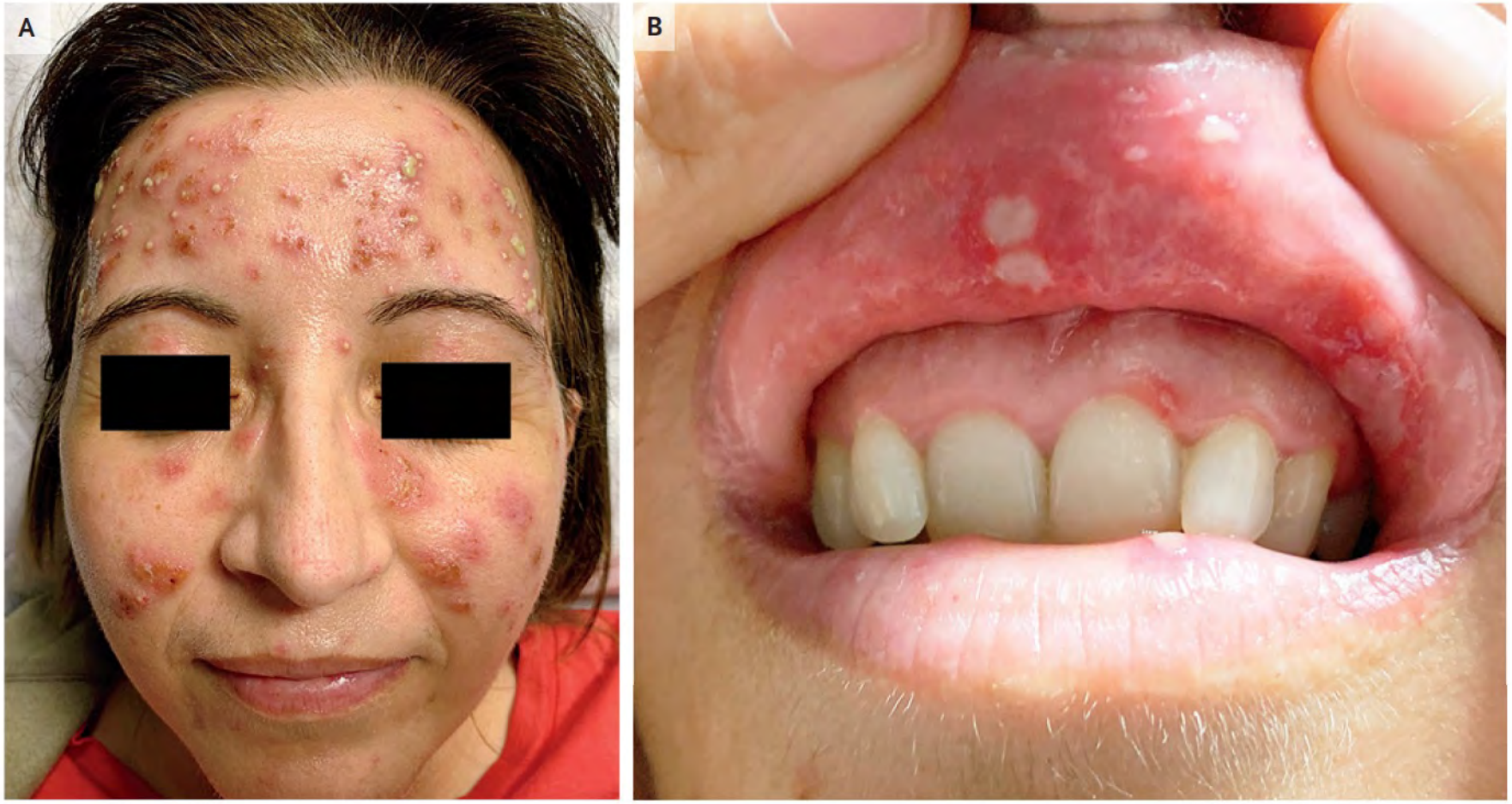
Case	Gender/age (years)	Clinical features and complications
1	M/37	O, S, V (AA, stenosis/occlusion of multiple arteries).
2	M/42	O, G, S, V (AA, stenosis of multiple arteries).
3	F/29	O, V (stenosis/occlusion of multiple arteries, PE).
4	F/42	O, G, S, V (ARD, AR, PVL).
5	M/64	O, G, V (ARD, AA, AR, coronary sinus aneurysm, perforation, PH).
6	M/42	O, G, polyarthritis.
7*	M/30	O, S, GI, scleritis, polyarthritis.
8	M/73	O, G, GI ulcers (ileum, ileocecal junction, cecum, colon
9	F/59	O, GI ulcers (oesophagus, ileocecal junction, colon).
10	M/48	O, G, GI ulcers (ileocecal, colon, fistula formation).
11	F/22	O, G, GI ulcers (ileocecal, colon, perforation, fistula formation).
12	F/37	O, G, MDS, GI ulcers (ileocecal, colon).
13	F/23	O, G, GI ulcers (ileocecal, GI bleed, perforation, fistula formation).

In summary, our study, to the best of our knowledge, is the first study on tofacitinib for refractory BS. Our data suggest that tofacitinib is well tolerated and might be effective for patients with BS with vascular and articular involvement. A prospective controlled study to confirm the therapeutic benefit of tofacitinib for patients with BS is warranted.

outline

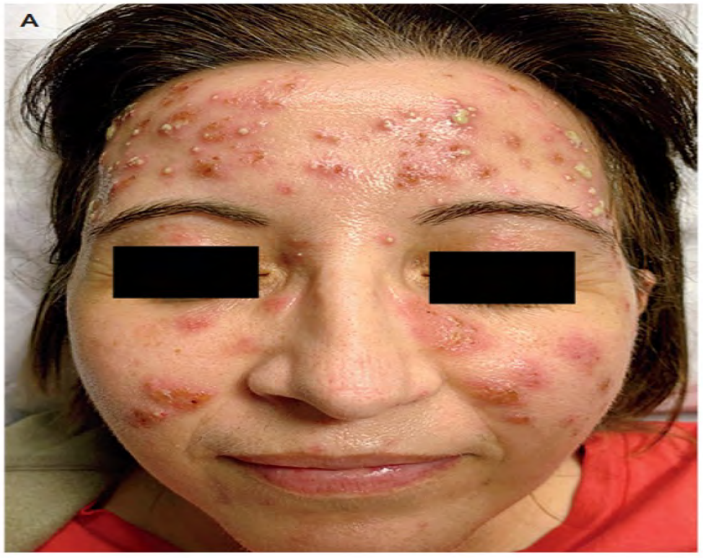
- Μια νόσος με ευρύ φάσμα και αποκλειστικά κλινική Διάγνωση
- Τι νεώτερο στη θεραπεία
- Σύνοψη: 4 περιστατικά

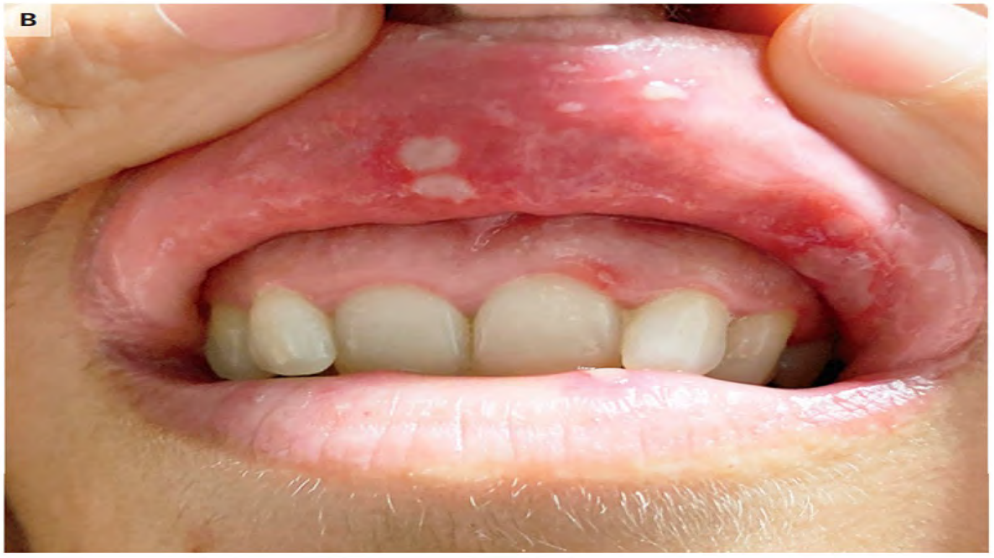
- Μελλοντικές κατευθύνσεις

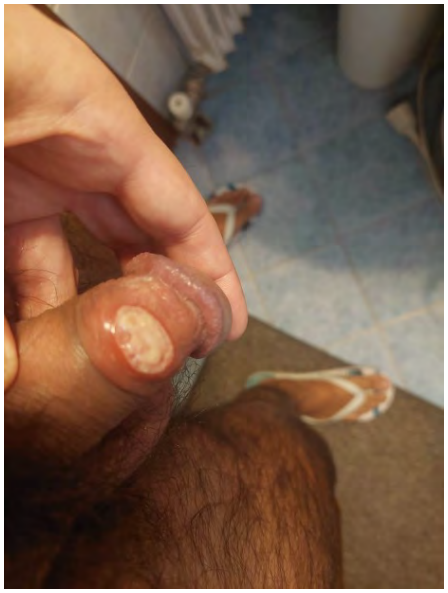

A
B

A 44-YEAR-OLD WOMAN PRESENTED TO THE EMERGENCY DEPARTMENT with a 1-week history of a pustular rash. The rash had initially appeared on her face and subsequently appeared on her lower legs. She also reported ankle pain and odynophagia. Further history revealed that she had had recurrent bouts of oral ulcers over the past few years. She had never had genital ulcerations. On physical examination, a papulopustular rash was noted on the patient's face (Panel A) and lower legs. Aphthous ulcers were also seen on the inner lips and gingiva when the patient lifted her lip (Panel B). There was no uveitis or retinal vasculitis on ophthalmologic evaluation. Antinuclear antibody, antineutrophil cytoplasmic antibody, human immunodeficiency virus, syphilis, herpes simplex virus, and pregnancy tests were negative. A pathergy test was not performed. Skin biopsy of a pustular lesion on the right calf revealed focal small-vessel vasculitis. A diagnosis of probable Behçet's disease was made according to the international criteria for Behçet's disease. The skin manifestations of Behçet's disease are varied and include erythema nodosum, pseudofolliculitis, acneiform nodules, and papulopustular lesions, as seen in this patient. Treatment with glucocorticoids and colchicine was initiated. At 2 months of follow-up, the rash had abated.

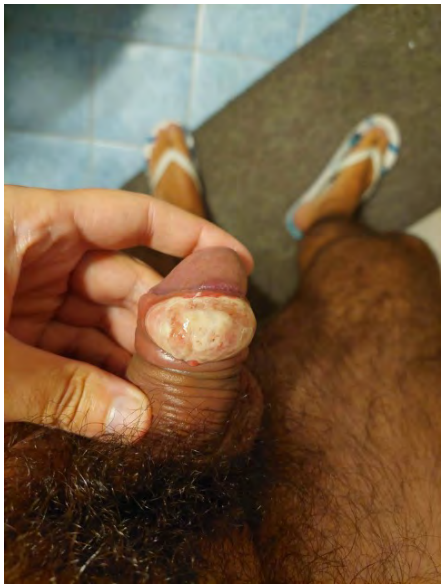
DOI: 10.1056/NEJMicm2209759



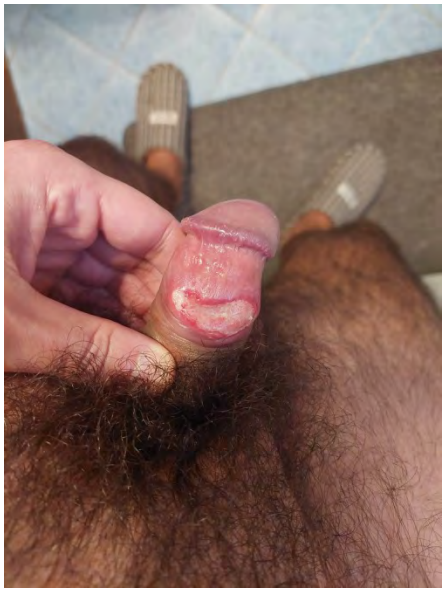




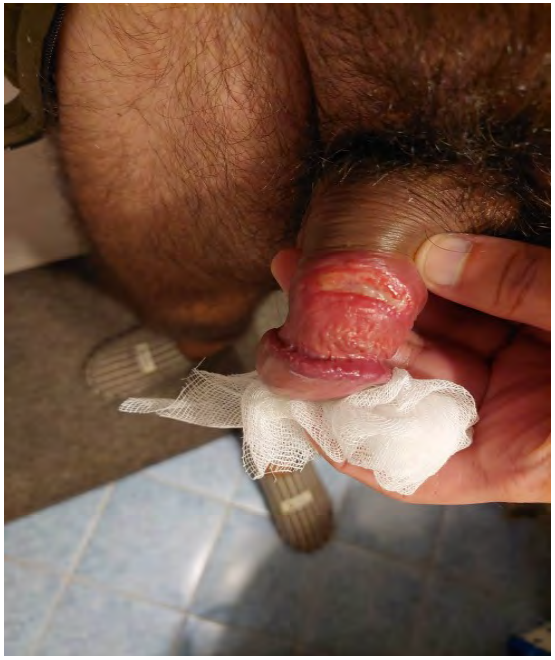
27/10/2022



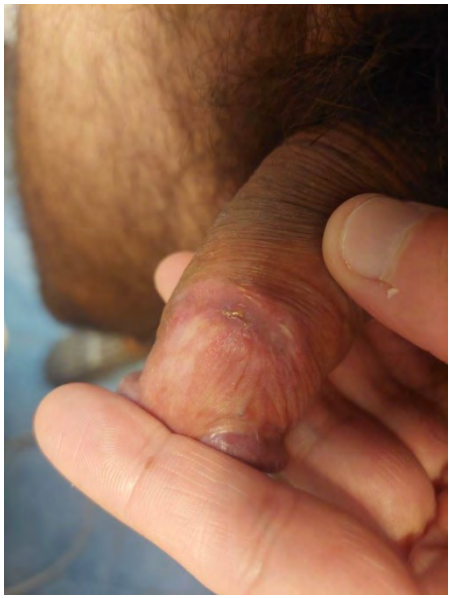
27/11/2022: presolon 10mg & AZA 150 mg



28/12/2022: Pr &AZA



24/01/2023: Pr & AZA



25/02/2023: 15 d after Infliximab 5mg/kg

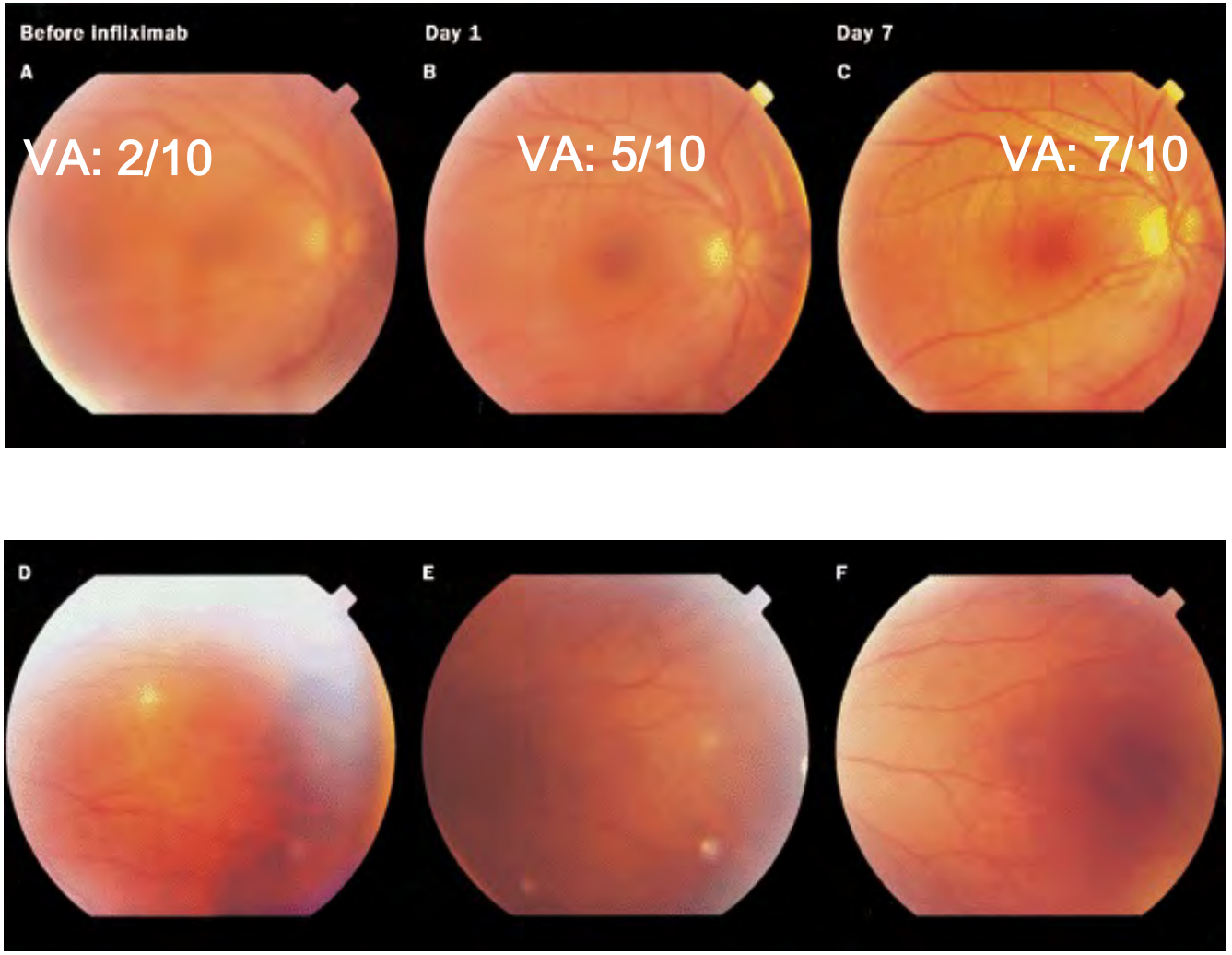
A young man with uveitis

- Spyros S, 22 y, student, Agrinio, central Greece
- 19 y: BD diagnosis (oro-genital ulcerations & uveitis)

- for 8 months: 20-35 mg prednisolone & AZA (2.4 mg/Kg) for recurrent episodes of unilateral/bilateral panuveitis
- …. upon prednisolone decrease continuous relapses, addition of CsA (3 mg/kg, 2 months)

- new relapse of bilateral panuveitis, under the triple combination therapy
  - visual acuity: 4/10 (L) and 2/10 (R)
  - anterior chamber cells: 2 (0-4) both eyes
  - vitreous haze: 2 (0-3) both eyes
  - vasculitis: + both eyes
  - number of retinal lesions: 2 (L) and 3 (R)

Sight-threatening BD panuveitis under Pred+AZA+CsA and complete suppression by a single infliximab infusion (5 mg/kg)



Sfikakis PP et al, Lancet 2001

A young man with uveitis

- suppression of panuveitis attack after infliximab, continuation of triple therapy, new relapse after 12 weeks
- repetitive infliximab at day 0, 30, and every 2 months (first year)

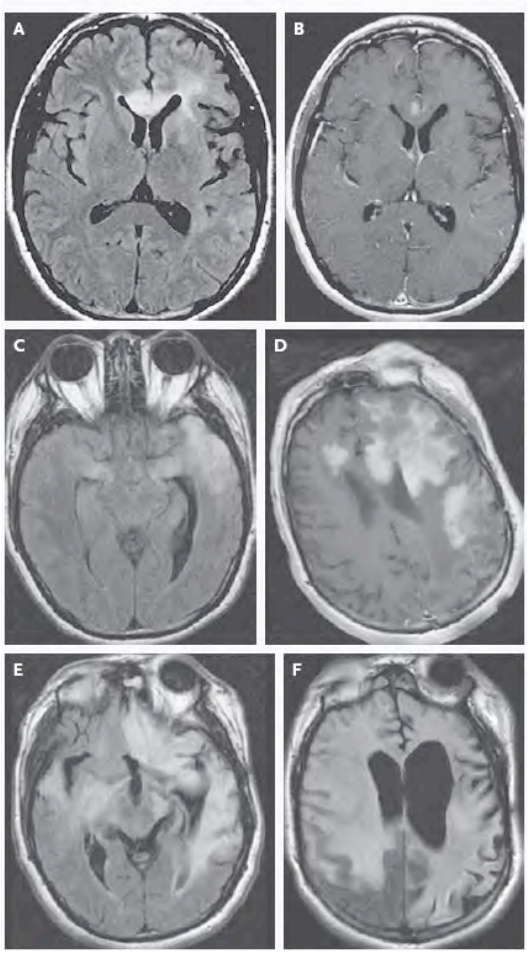
Result: free of relapses, discontinuation of CsA, tapering of corticosteroids

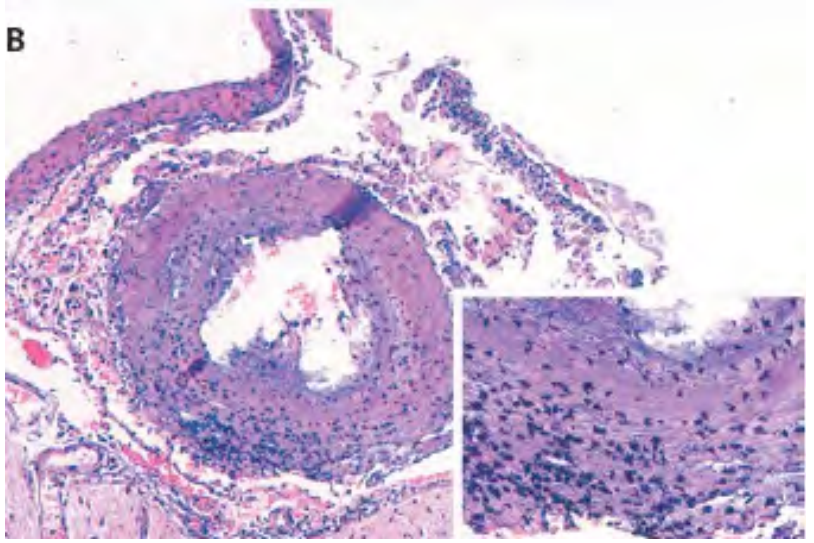
- repetitive infliximab every 3 months for the second year (plus AZA) Result: disease-free, he decides to discontinue both

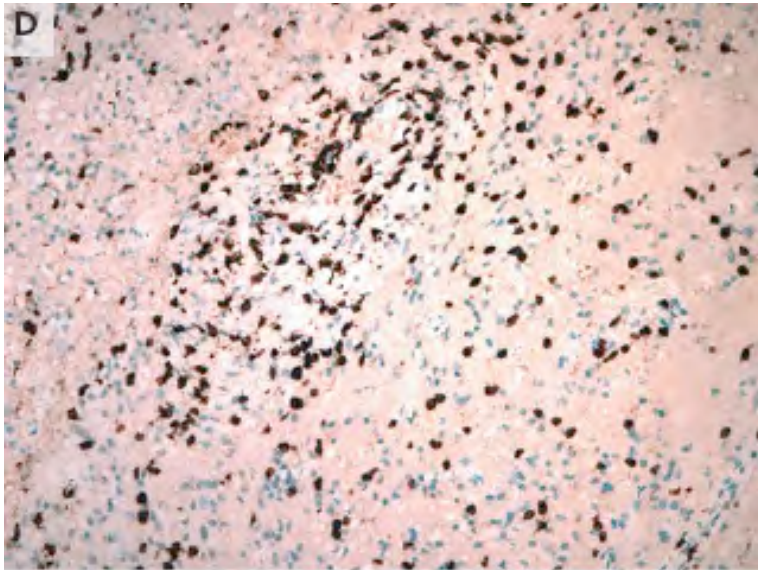
- … after 3 years disease-free w/o treatment bilateral panuveitis relapses
- successful re-introduction of infliximab plus AZA for 1 more year; successful replacement of infliximab by adalimumab for 2 more years

- At present (39 y): relapse-free with AZA (50 mg daily for the past 11 years)

Patient with CNS manifestations

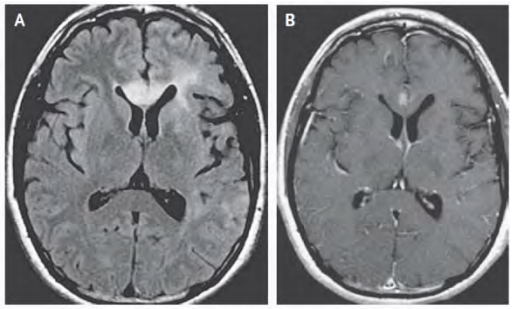






Case 17-2009: A 30-Year-Old Man with Progressive Neurologic Deficits

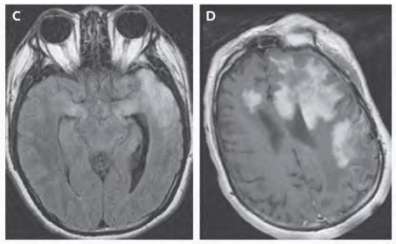
The NEW ENGLAND JOURNAL of MEDICINE



An axial fluid-attenuated inversion recovery (FLAIR) image from an MRI of the brain performed 10 months before this admission (Panel A) reveals increased signal intensity of the genu of the corpus callosum and left forceps minor. After the administration of gadolinium, an axial T_1-weighted image (Panel B) reveals nodular enhancement of the genu and right cingulate gyrus.

- 26 y: fever, fatigue, painful oro-genital ulcers, arthritis, nodular skin lesions
- persisting BD activity despite colchicine, MMF, steroids; effective control with MTX (25 mg/w)
- 29 y: gradual onset of difficulty with word finding and writing, inflammatory LP findings, MRI : parenchymal NBD, exclusion of infections

- What would you do ? Cyclosporine –A ?



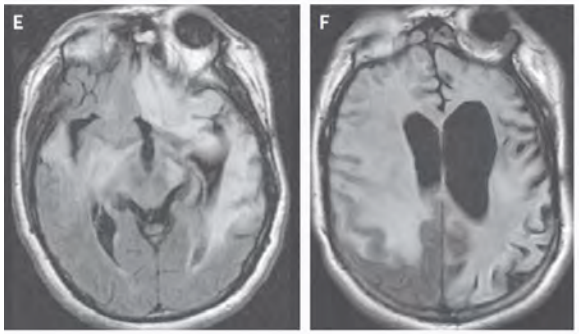
An axial FLAIR image of the brain at the time of the patient's second admission, 5.5 months before this admission (Panel C), reveals new areas of high signal intensity in the left anterior temporal lobe and bilateral hippocampus. After the administration of gadolinium, an axial T_1-weighted image (Panel D) reveals confluent enhancement of the left frontal lobe, corpus callosum, caudate, temporal lobe, and the white matter in the right frontal lobe. An axial FLAIR image from an MRI

- Infliximab (5 mg/kg) every 4 w (x3) and every 6 w thereafter

… within one month language difficulties resolved; MRI and CSF findings improved; very good clinical condition for 6 months…

- after 6 m: Grand-mal followed by status epilepticus, fever 40C with inflammatory LB findings and MRI +, exclusion of infection: partial response to antiepileptic drugs and additional infliximab

- Replacement of MTX and infliximab by interferon alfa: uncontrolled disease for 3 more months
- Present admission: rapid progression of neurologic events…coma, intubation, antibiotics….. Brain biopsy findings consistent with NBD



reveals extensive signal abnormality involving both cerebral hemispheres, edema of the left cerebral hemisphere, and encephalomalacia of the left cerebral hemisphere. An axial T_1-weighted image after the administration of gadolinium (Panel F) shows extensive bihemispheric involvement.

- Pulse steroids and CYC

… recurrent infections…..after 102 days he was transferred to a rehabilitation hospital

- CY discontinued, further neurologic decline and recurrent status epilepticus; transient only control with infliximab and pulse steroids

- Multiple bilateral infracts, with edema and encephalomalacia (consecutive venous infarctions ?) in MRI 3 w before his **death** (aged 32..) **- 3 years after the onset** of neurologic symptoms…

outline

- Μια νόσος με ευρύ φάσμα και αποκλειστικά κλινική Διάγνωση
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- Μελλοντικές κατευθύνσεις

Clinical Immunology 246 (2023) 109186

Contents lists available at ScienceDirect

Clinical Immunology

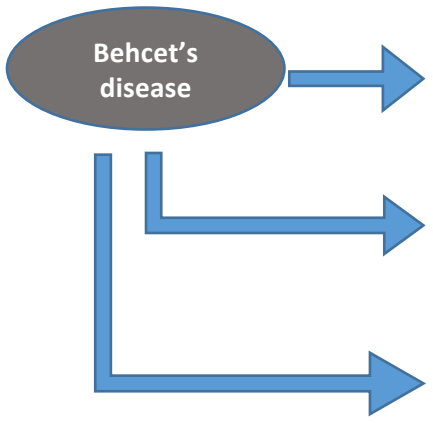
journal homepage: www.elsevier.com/locate/yclim

Treat to target in Behcet's disease: Should we follow the paradigm of other systemic rheumatic diseases?

George E. Fragoulis [a], George Bertsias [b], Bahram Bodaghi [c], Ahmet Gul [d], Jan van Laar [e], Gonca Mumcu [f], David Saadoun [g], Ilknur Tugal-Tutkun [h,i], Gulen Hatemi [j,k,*,1], Petros P. Sfikakis [a,**,1]

Taking the main strands together, we believe that there is a need for the formulation of recommendations about a T2T strategy in BD, by experts in the field, including rheumatologists, ophthalmologists, dermatologists, oral medicine specialists,neurologists and gastroenterologists, who will reach a consensus, when plausible,to the above-mentioned challenges.

Challenges in BD



Diagnosis

- Clinical diagnosis (caution in major organ involvement)
- No validated biomarkers
- Sometimes incomplete clinical presentation (differential diagnosis, i.e. IBD)
- Need for collaboration with other specialties

Therapy

- Individualised therapy (topical or systemic, mild or aggressive, combination or monotherapy)
- Prompt drug administration for major organ invl.
- Surgical intervention may be needed in some cases

Response

- Outcome measures (i.e. inflammatory markers, BDCAF, BDQoL)
- Partial vs complete remission (definitions)
- Refractory cases
- Natural relapsing and remitting course

Relapse

- Treatment escalation or change of treatment modality?

Long-term outcome

- Chronicity – irreversible organ damage
- Comorbidities (iatrogenic, i.e. steroids)
- Long-term remission, even after short-term treatment (natural history)

What the **target** would be ? ... it is a key goal to validate target state definitions, such as low disease activity and remission, and test their implementation in clinical practice and clinical trials.

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EULAR Center of Excellence 2021-2026

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- S. Panopoulos
- M. Pappa
- A. Protogerou
- K. Verrou
- N. Vlachogiannis

- N. Markomichelakis
- E. Masselos
- P. Theodossiadis
- D. Ladas

- **EULAR task force for BD guidelines**
- **anti-TNF recommendations expert panel**
- **NeuroBD expert panel**