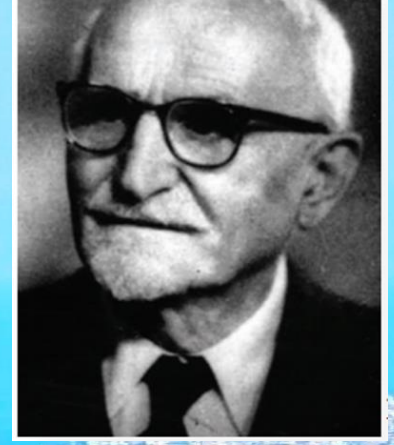
4ο ΣΥΝΕΔΡΙΟ ΕΠΕΜΥ, ΡΟΔΟΣ, 30-9-2022

Τι νεότερο στο σύνδρομο Αδαμαντιάδη-Behçet ?

Πέτρος Π. Σφηκάκης



19th International Conference, Athens, 2022, July 6-8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pharma


Bristol-Myers Squibb


gsk


ucb


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Boehringer
Ingelheim


Janssen
PHARMACEUTICALS
OF Johnson&Johnson


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PHARMACEUTICALS


ELPEN


Roche


AENORASIS
ntuition in Healthcare


ACTELION


SANOFI

ABD: υποτροπιάζουσα, πρωτοπαθής συστηματική αγγειιτίδα

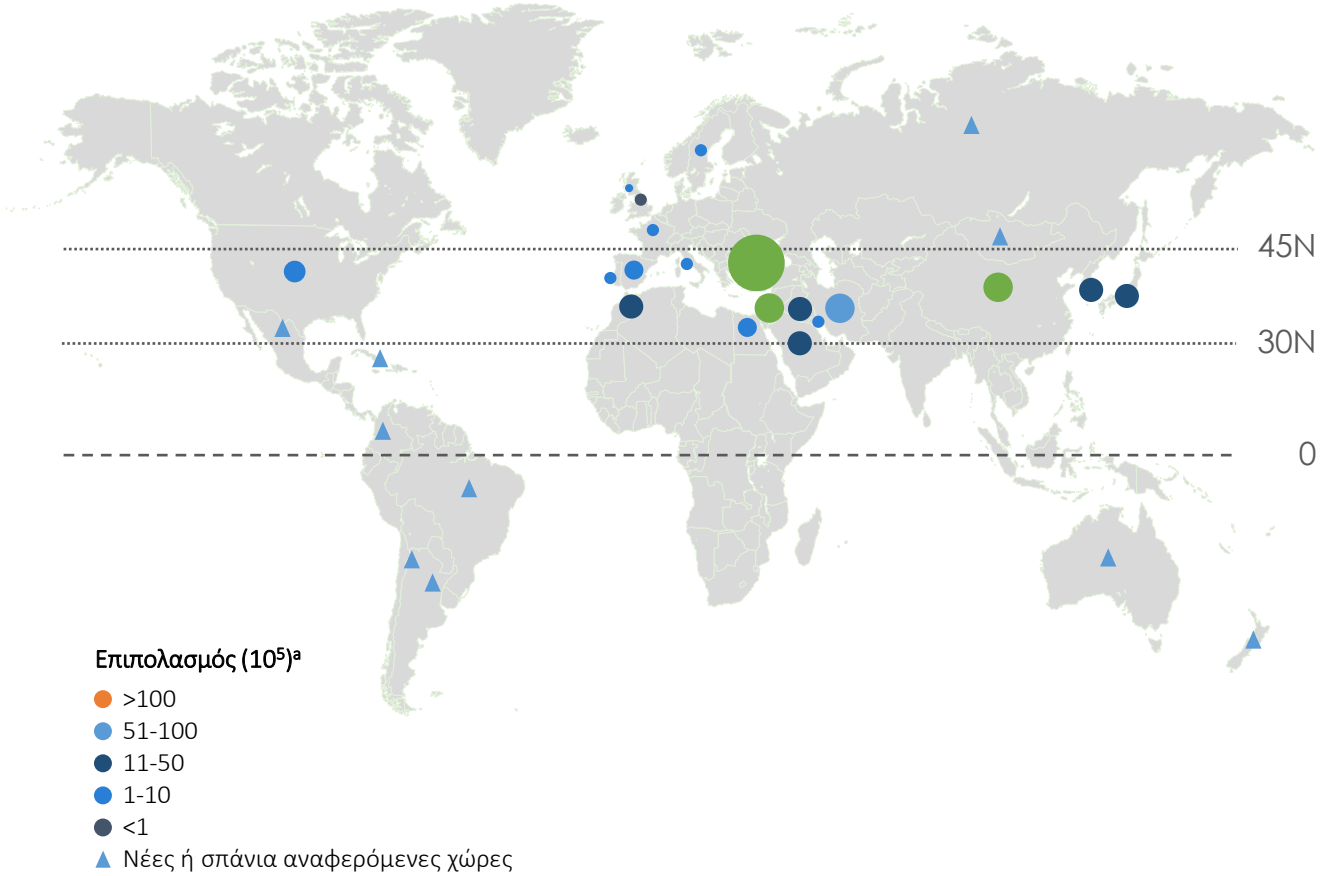
Hulusi Behçet (1889-1948)
Δερματολόγος

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

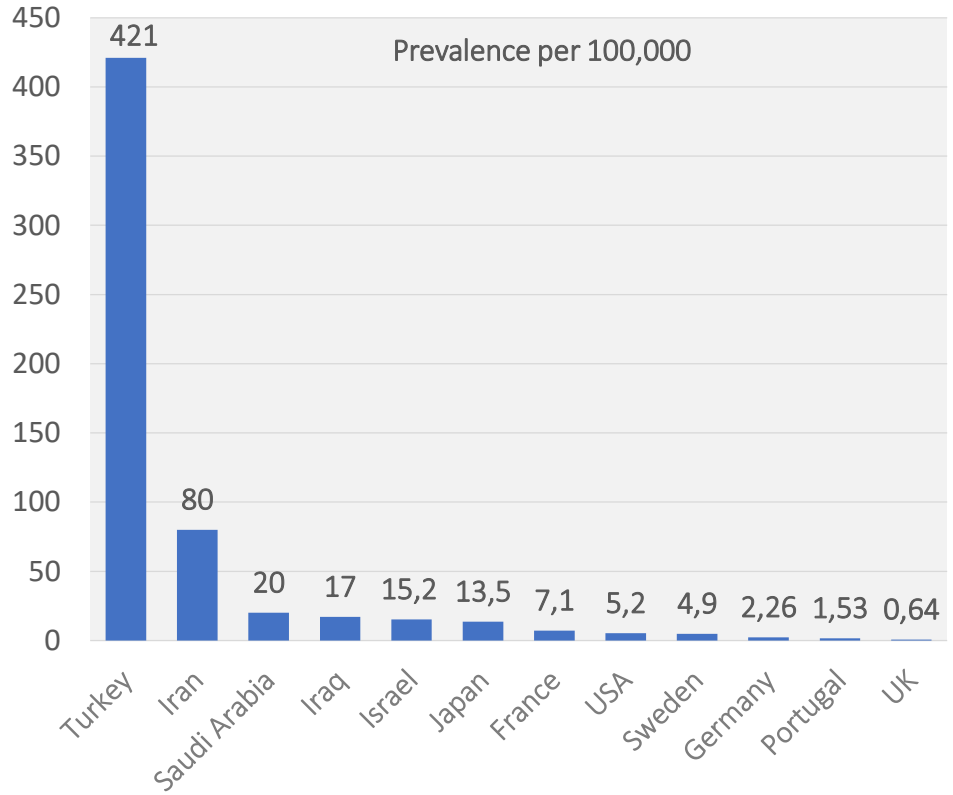
Βενέδικτος Αδαμαντιάδης (1875 – 1962)
Οφθαλμίατρος

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

Παγκόσμιος επιπολασμός



Επιπολασμός ανά χώρα

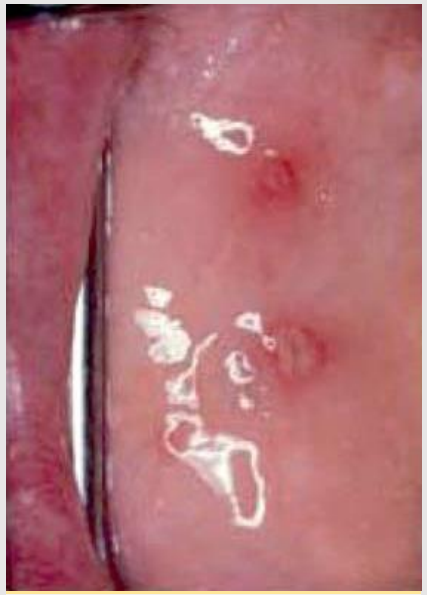


outline

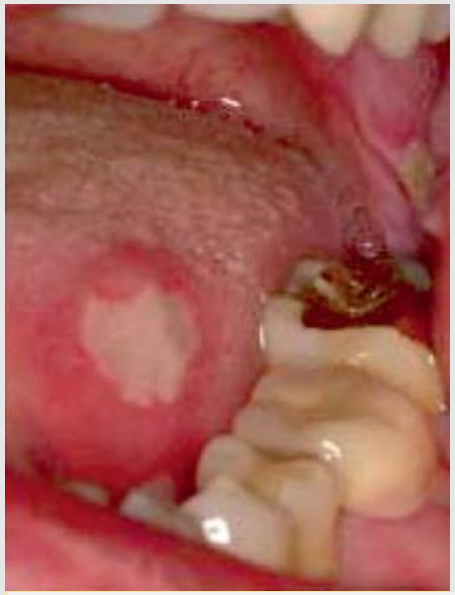
- Τι νεώτερο στη διάγνωση

- Τι νεώτερο στη θεραπεία
- Τι νεώτερο στην παθογένεια
- Μελλοντικές κατευθύνσεις

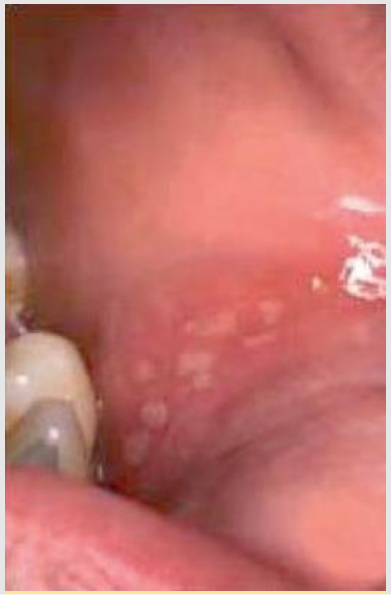
Σχεδόν κάθε ασθενής έχει υποτροπιάζοντα στοματικά έλκη



Minor-type oral aphthous ulcers[3]



Major-type oral aphthous ulcer[3]



Herpetiform oral aphthous ulcers[3]

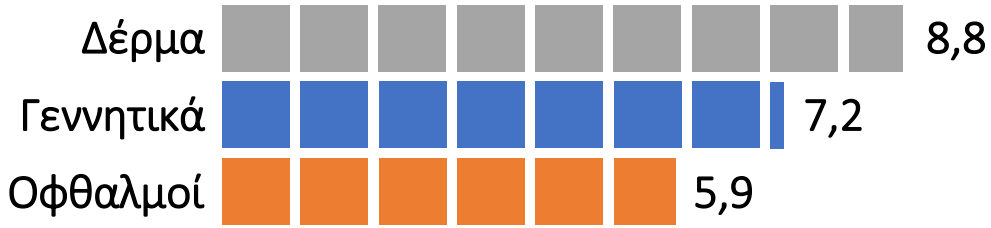
Τα υποτροπιάζοντα στοματικά έλκη της νόσου Behçet μπορεί να συρρέουν, να είναι επώδυνα, και (όχι συχνά) να αφήσουν ουλές

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

- *Αγγείιτις 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

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

HLA-B51 is not recommended for diagnosis

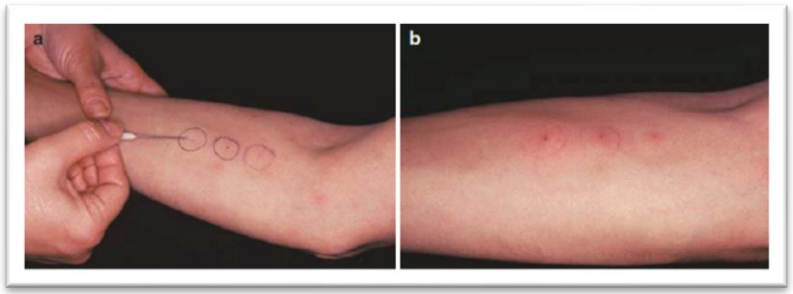
Lancet 1990;335:1078

- **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

Behçet Disease – Environmental Triggers (Pathergy Reaction)

- Induration and erythema at the needle (20G) prick (trauma) site



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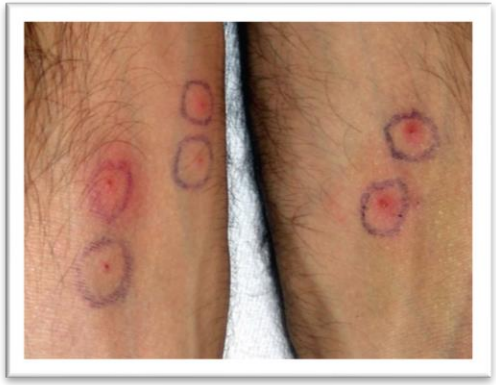
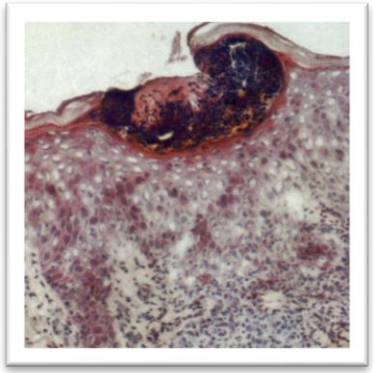
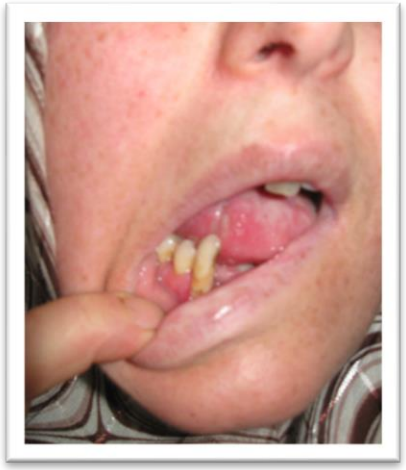
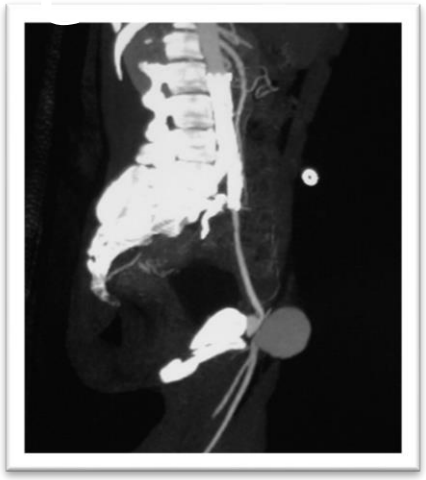




Gül et al. Br J Dermatol 1995; 132: 901-7.

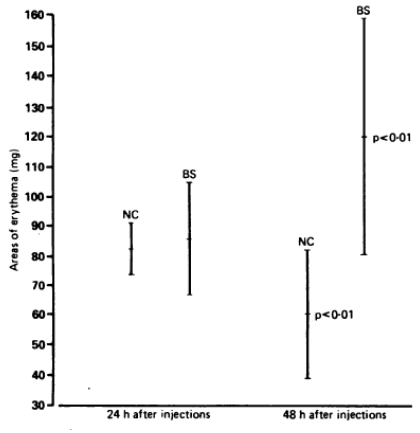
Induction of the disease manifestations following local trauma





Sahutoglu et al. Rheumatol Int 2019

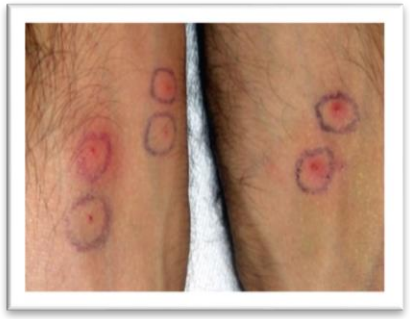
Increased reactivity to the uric acid crystals



Cakir et al. ARD 1991; 50: 634-6

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.

Sensitivity vs Specificity of diagnostic criteria

- UK, 281 BD in Birmingham Centre of Excellence for Behçet's disease
- 281 pt between 2012-2015
  - 190 were diagnosed as BD, 7 as incomplete BD, 84 as not having BD

- Sensitivity (=underdiagnosis when low..): ICBD criteria of 98% vs ISG criteria of 78%
- Specificity (=overdiagnosis when low): ICBD criteria of 19% vs ISG criteria of 69%
- Use of 2014 criteria may result in overdiagnosis of BD in the UK population….

Blake T et al. BMC Musculoskelet Disord 2017; 18: 101

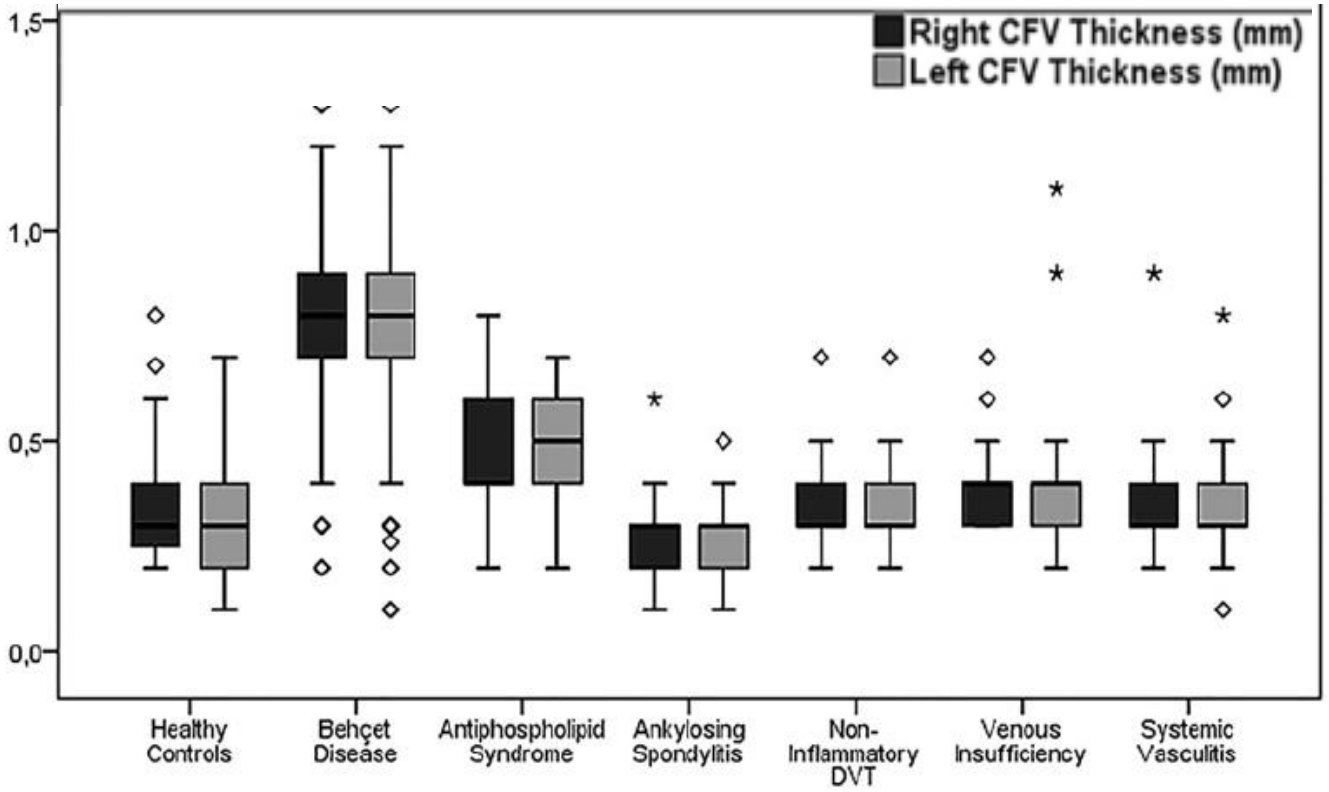
RHEUMATOLOGY

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

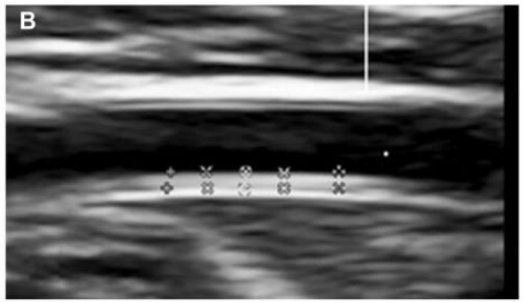
BD (n=152), A. spondylitis (n=27), systemic vasculitides (n=23), venous insufficiency (n=29), antiphospholipid syndrome (APS; n=43), deep vein thrombosis due to non-inflammatory causes (n=25) and healthy controls (n=51)

RHEUMATOLOGY

A new tool supporting the diagnosis of childhood-onset Behçet's disease: venous wall thickness

Rheumatology 2022;00:1–8

Erdal Atalay[1], Berna Oguz[2], Seher Sener[1], H. Nursun Ozcan[2], Erdal Sag[1], Ummusen Kaya Akca[1], Muserref Kasap Cuceoglu[1], Zeynep Balik[1], Jale Karakaya[3], Omer Karadag[4], Ozge Basaran[1], Ezgi Deniz Batu [1], Yelda Bilginer[1] and Seza Ozen[1]



Median (25p–75p) (mm)	Definite Behçet's disease (B) ($n = 13$)	Incomplete Behçet's disease (I) ($n = 22$)	Healthy controls (C) ($n = 27$)	*P*-value*
Right common femoral vein	0.87 (0.70, 1.05)	0.75 (0.66, 87)	0.58 (0.55, 0.62)	B–C=**<0.001** I–C=**<0.001** B–I = 0.14
Left common femoral vein	0.74 (0.60, 0.88)	0.71 (0.58, 0.81)	0.56 (0.52, 0.62)	B–C = **0.001** I–C = **0.01** B–I = 0.06

	Area under curve (AUC) (95% CI)	Best cut-off	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	*P*-value
Right CFV	0.89 (0.79, 0.96)	0.63	86 (70, 95)	89 (71, 98)	91 (76, 98)	83 (64, 94)	**<0.001**
Left CFV	0.76 (0.63, 0.86)	0.66	63 (45, 78)	93 (76, 99)	92 (73, 99)	66 (49, 80)	**0.001**

RHEUMATOLOGY

Rheumatology 2022;00:1–5
https://doi.org/10.1093/rheumatology/keac452
Advance access publication 9 August 2022

Concise report

Pulmonary arterial wall thickness increased in Behçet's disease patients with major organ involvement: Is it a sign of severity?

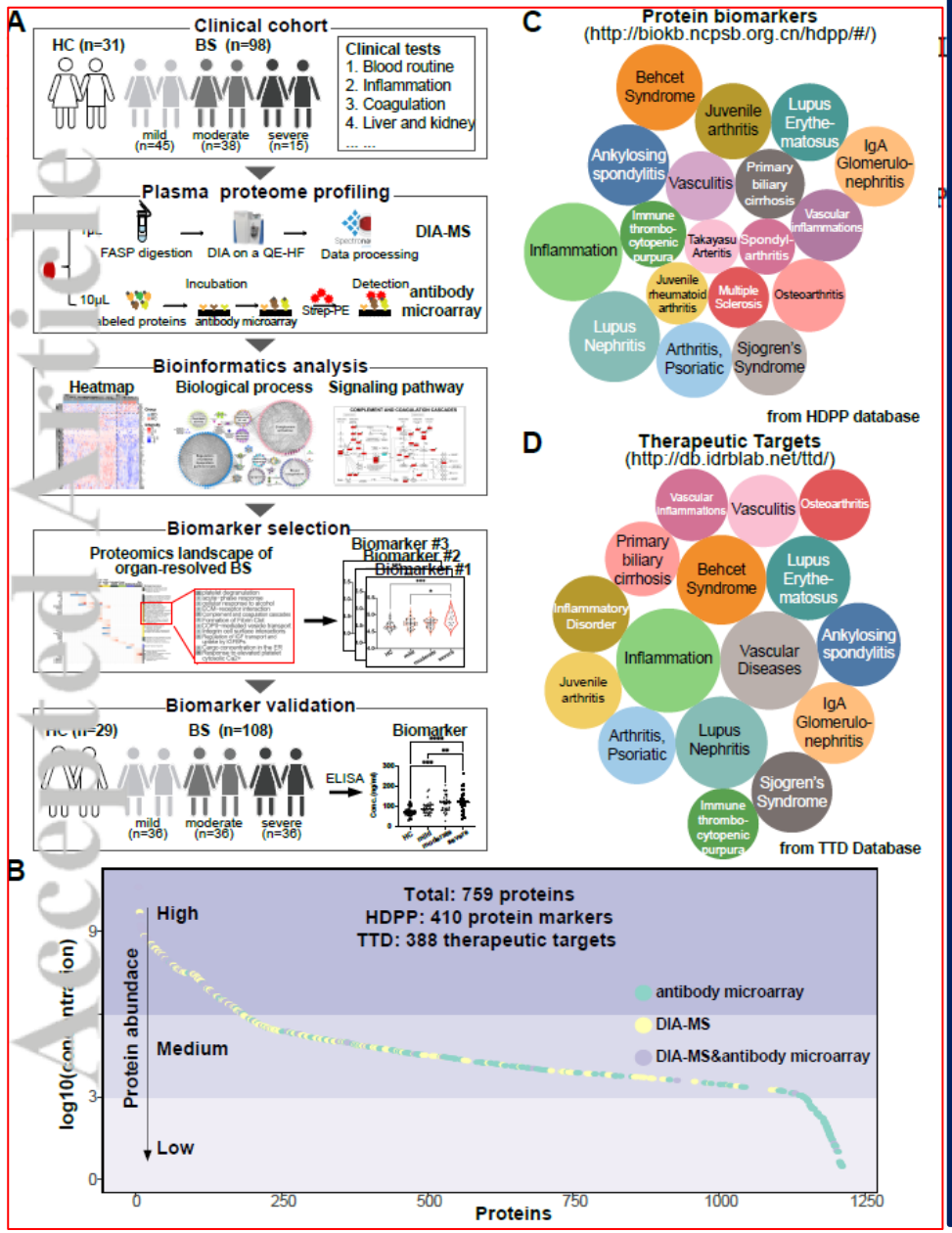
Seda Kutluğ Ağaçkıran [1], Murat Sünbül[2], Zekeriya Doğan[2], Derya Kocakaya[3], Semih Kayacı[3], Haner Direskeneli[1] and Fatma Alibaz-Oner [1]

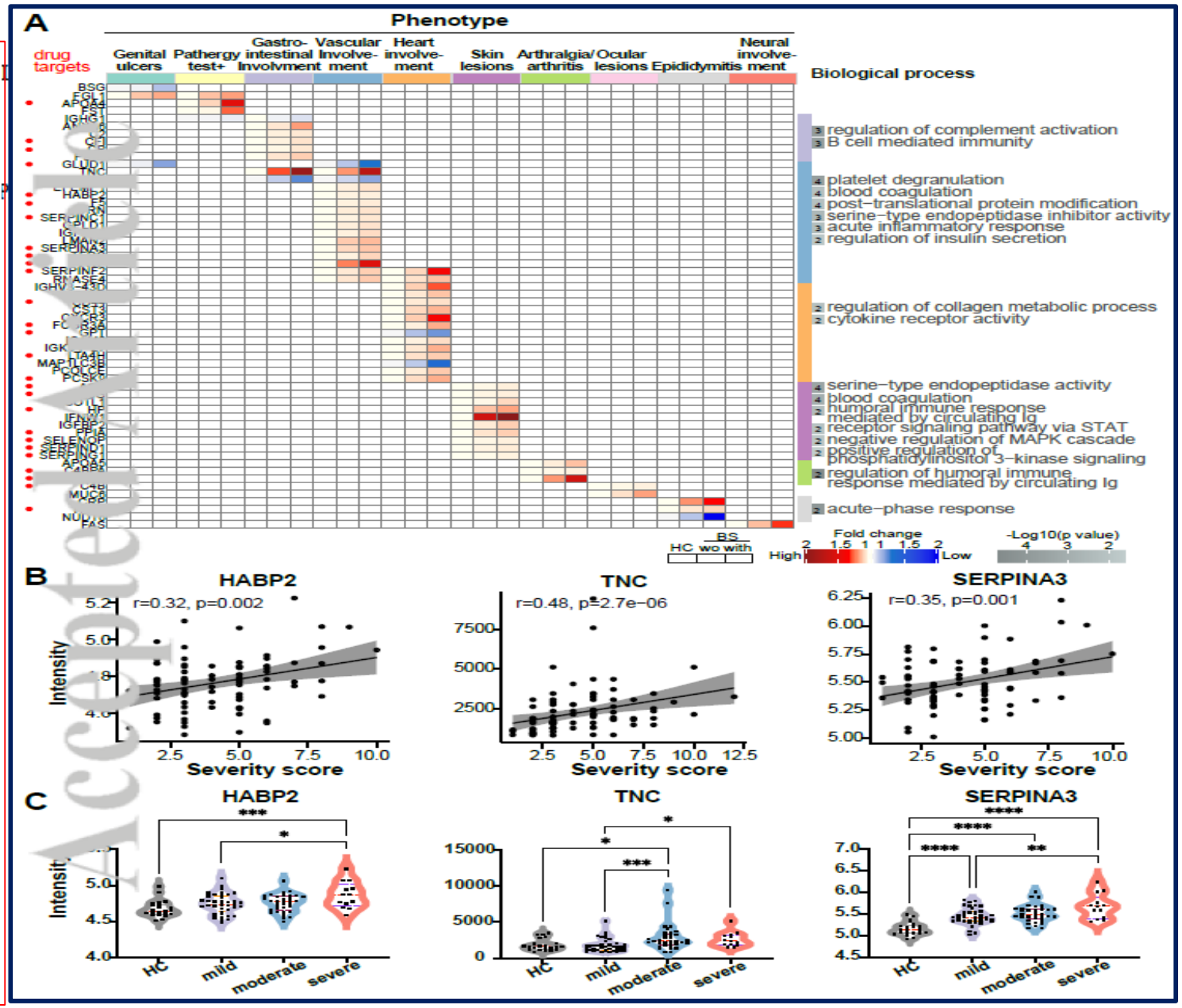
Rheumatology key messages

- Pulmonary artery (PA) wall thickness is increased in patients with BD compared with healthy controls and patients with thrombotic pulmonary disease.
- Increased PA wall thickness is mainly observed in patients with major organ involvement.
- Increased PA wall thickness may be a sign of a more severe disease spectrum in patients with BD.

Proteomic landscape mapping of organ-resolved Behçet's syndrome using in-depth plasma proteomics for identifying HABP2 expression associated with vascular involvement

Cheng et al. Arthritis Rheumatol 2022 in print





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- Μελλοντικές κατευθύνσεις

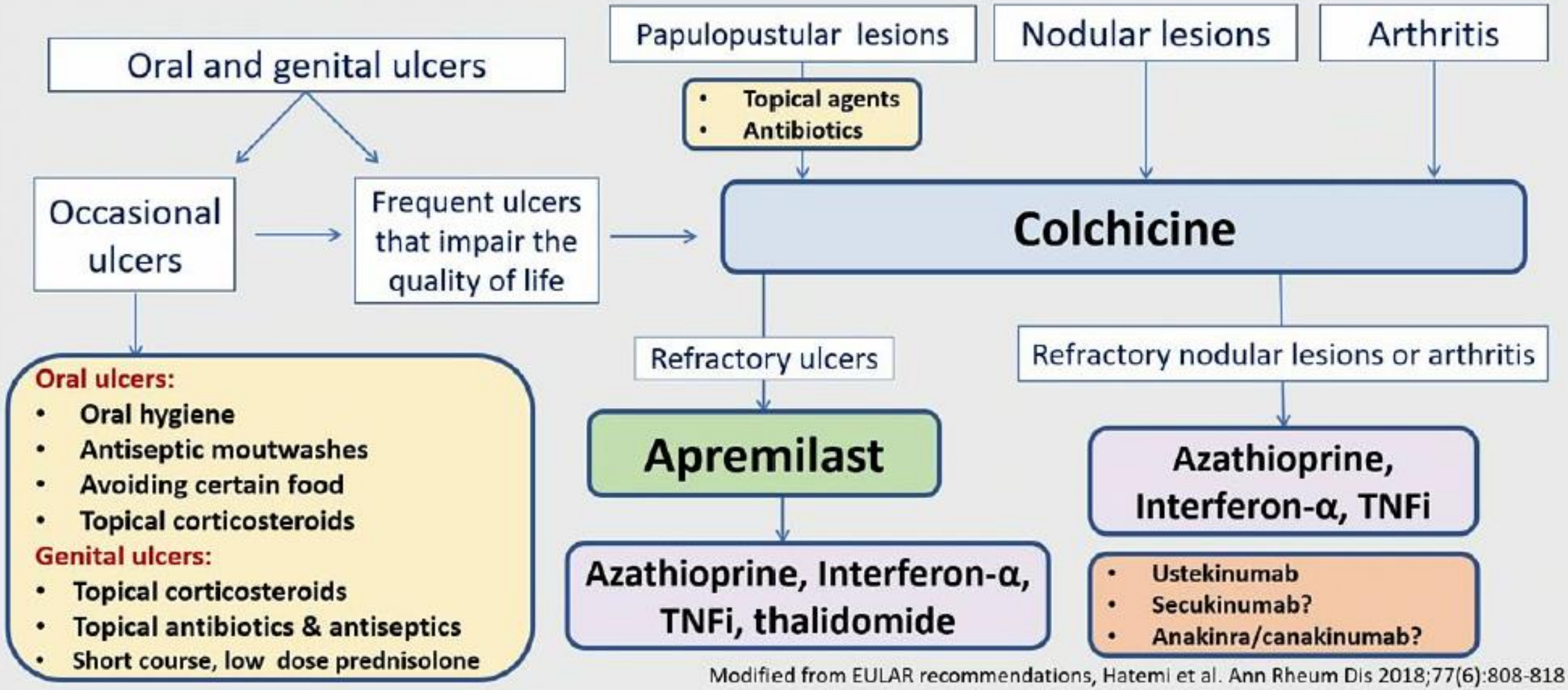
ARD Online First, published on April 6, 2018 as 10.1136/annrheumdis-2018-213225

Recommendation

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

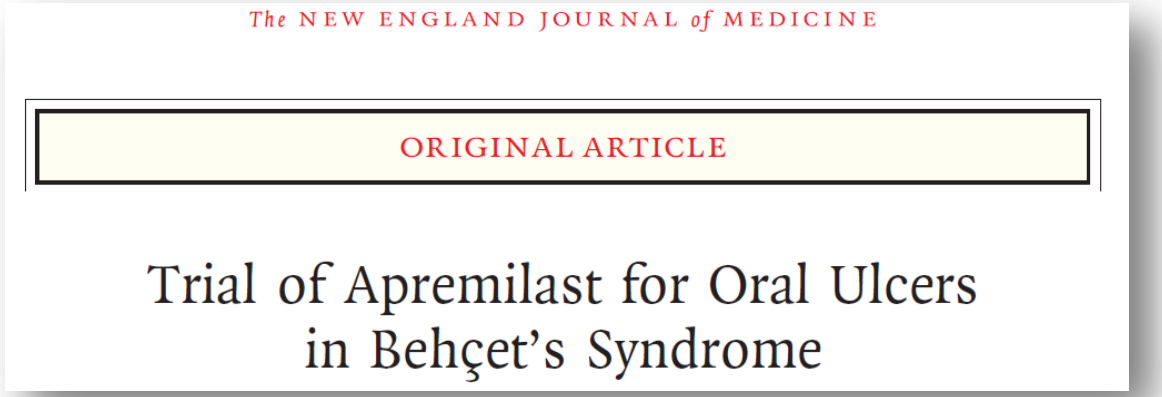
Gulen Hatemi,[1] Robin Christensen,[2] Dongsik Bang,[3] Bahram Bodaghi,[4] Aykut Ferhat Celik,[5] Farida Fortune,[6] Julien Gaudric,[7] Ahmet Gul,[8] Ina Kötter,[9] Pietro Leccese,[10] Alfred Mahr,[11] Robert Moots,[12] Yesim Ozguler,[1] Jutta Richter,[13] David Saadoun,[14,15,16,17] Carlo Salvarani,[18] 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]

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

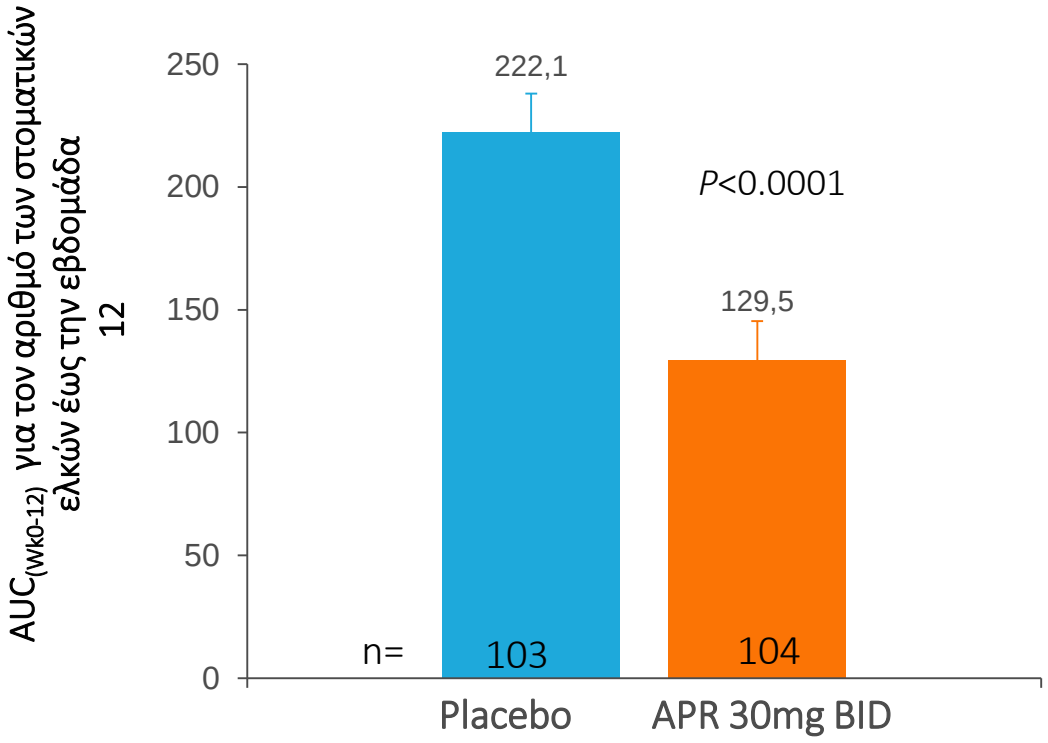
Gülen Hatemi, et al, N Engl J Med 2019; 381:1918-1928, DOI: 10.1056/NEJMoa1816594

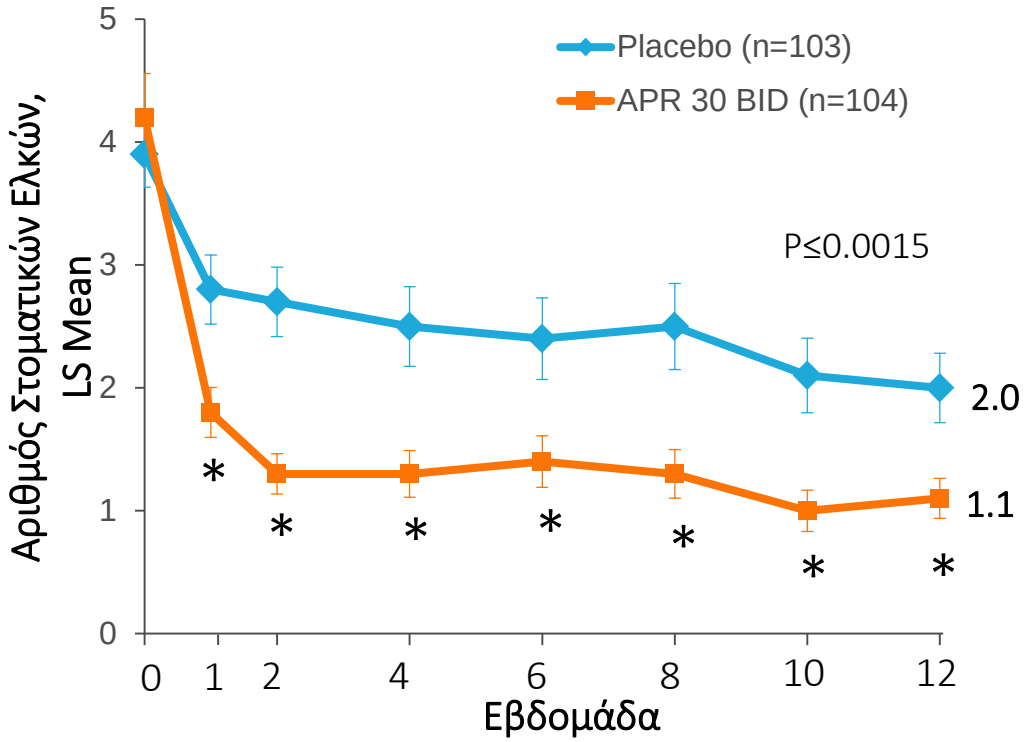


Η Απρεμιλάστη ενδείκνυται για τη θεραπεία των στοματικών ελκών που σχετίζονται με τη νόσο Behçet (BD) σε ενήλικες ασθενείς οι οποίοι είναι υποψήφιοι για συστηματική θεραπεία.

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

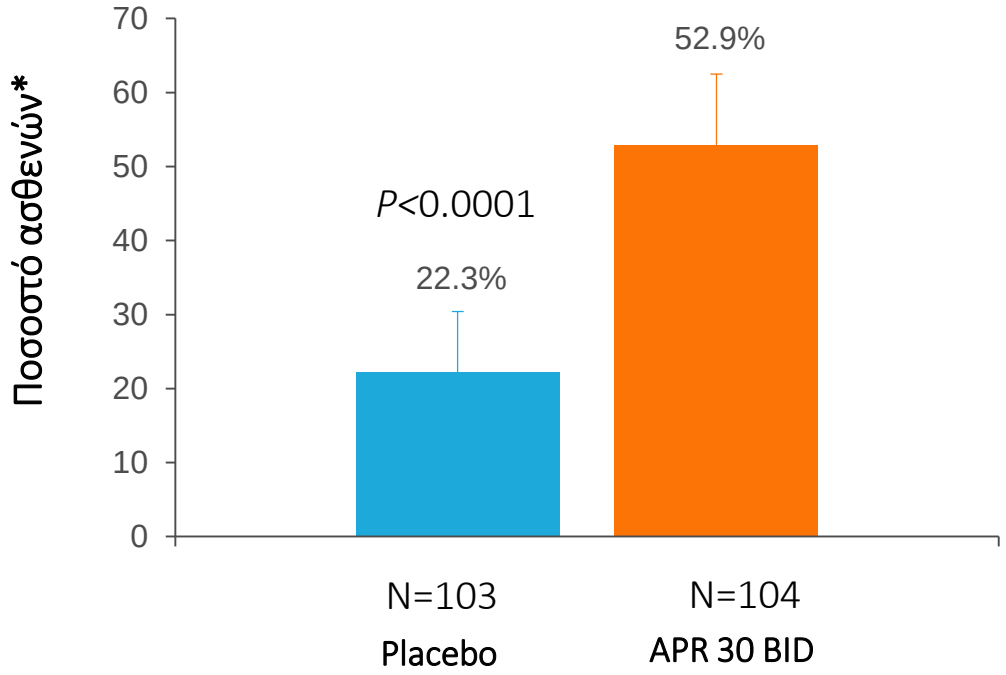




Hatemi et al, N Engl J Med 2019

Πλήρης αποδρομή στοματικών ελκών την εβδομάδα 12 στους μισούς ασθενείς

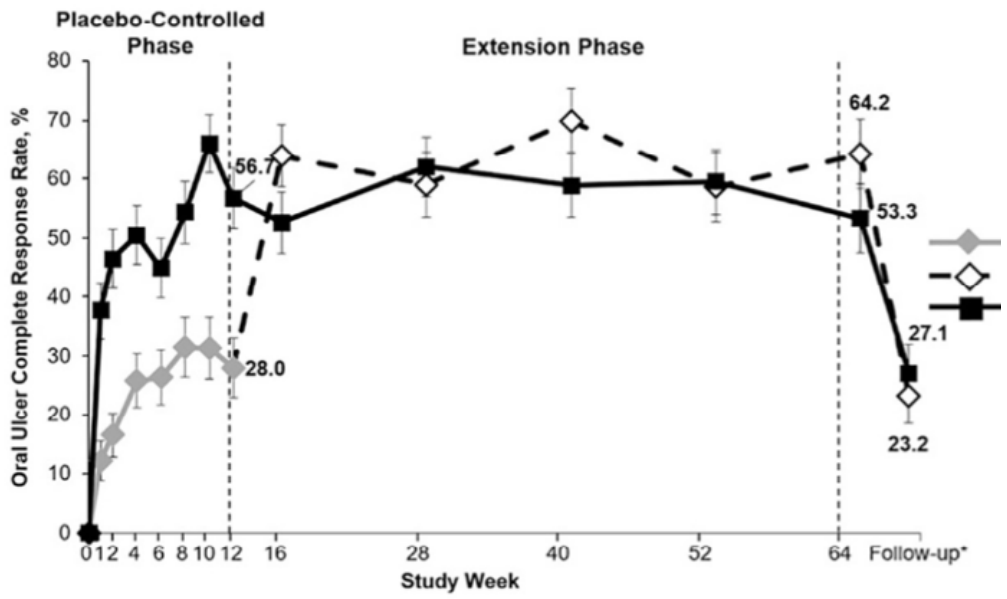
- 53% των ασθενών πέτυχε πλήρη ύφεση των στοματικών ελκών την εβδομάδα 12



Hatemi et al, N Engl J Med 2019

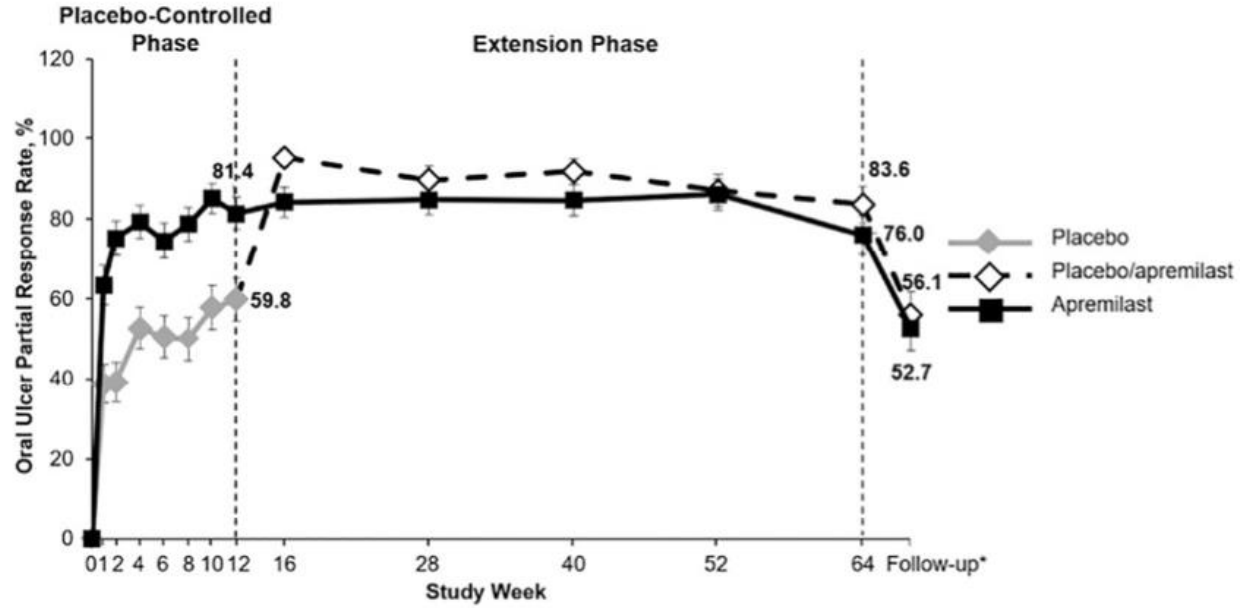
Apremilast for oral ulcers, 68 wks

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



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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

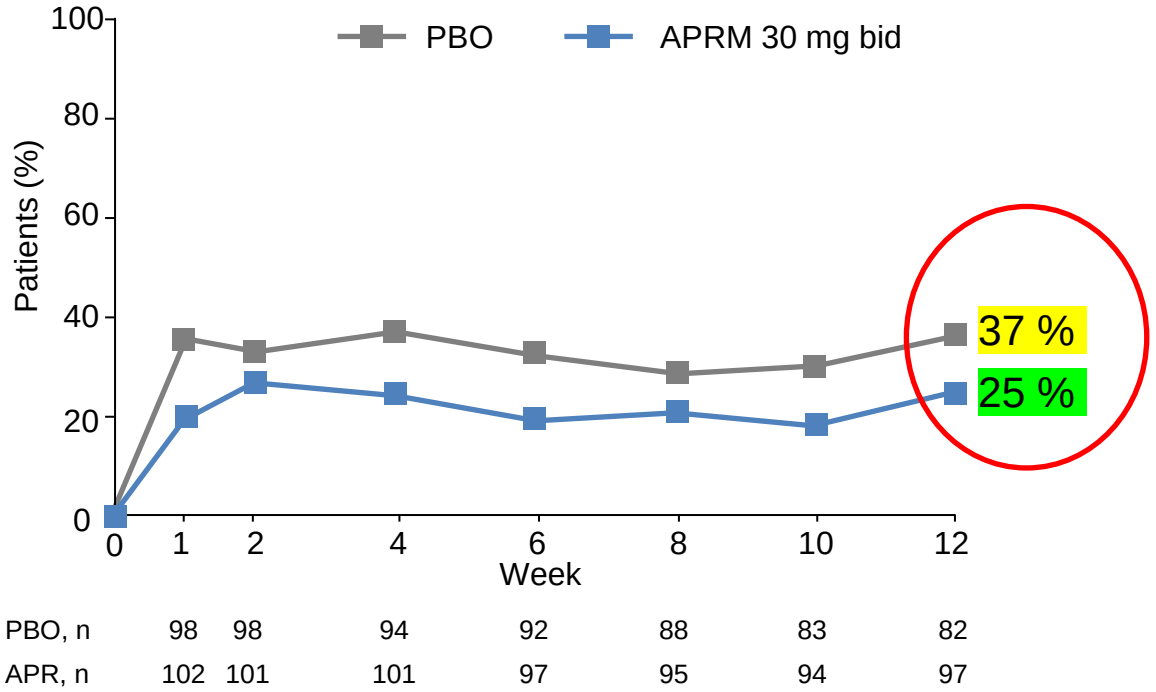
Efficacy of apremilast in beyond oral ulcers

- 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-OU manifestation during 12 weeks[a]



ITT population, data as observed

[a]Skin lesions, arthritis, uveitis, gastrointestinal, central nervous system, vascular

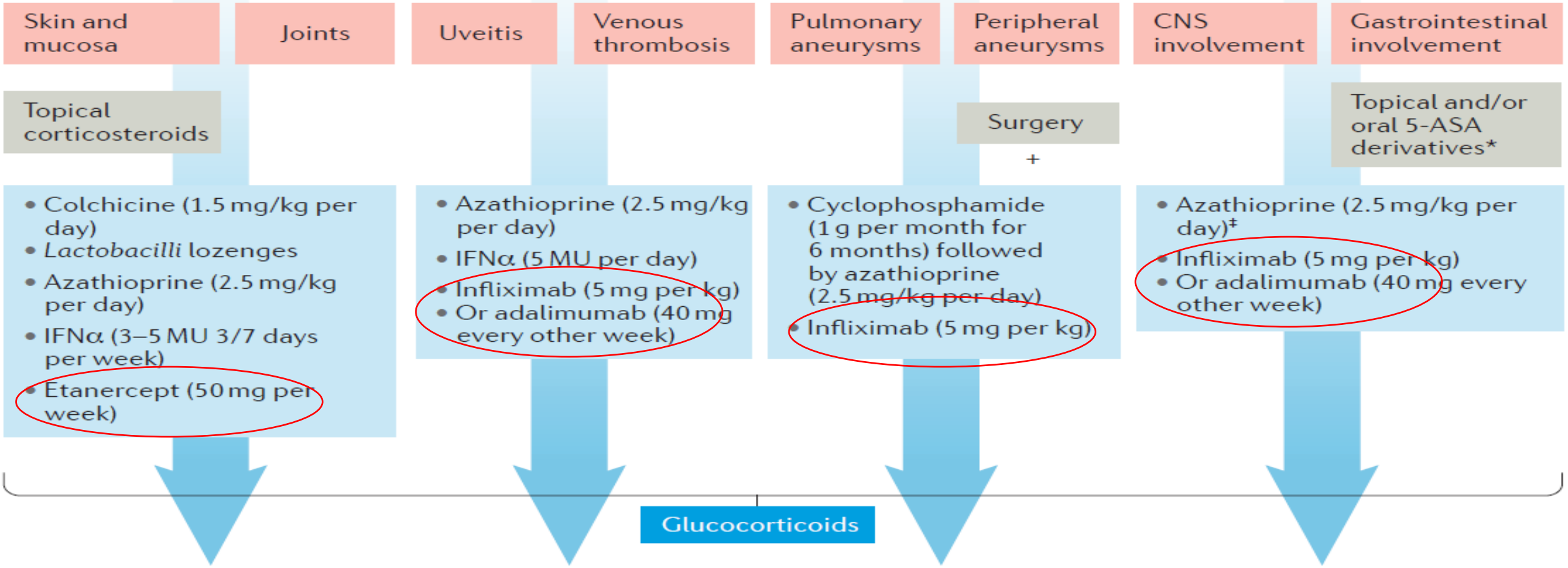
Hatemi G, et al. ACR 2020, #512

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



Visual I, II, III studies of Adalimumab

Adalimumab in patients with active noninfectious uveitis. *(VISUAL I)*

Jaffe GJ,Dick AD, Brezin AP, et al. N Engl J Med. 2016;375:932e943.

Adalimumab for prevention *of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial.*

Nguyen QD, Merrill PT, Jaffe GJ, et al. Lancet. 2016 ;388:1183e1192.

Long-term safety and efficacy of adalimumab in patients with noninfectious intermediate uveitis posterior uveitis or panuvietis (VISUAL III).

Suhler EB, Jaffe GJ, Fontin E et al. Ophthalmology. 2021; 128:899-909

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

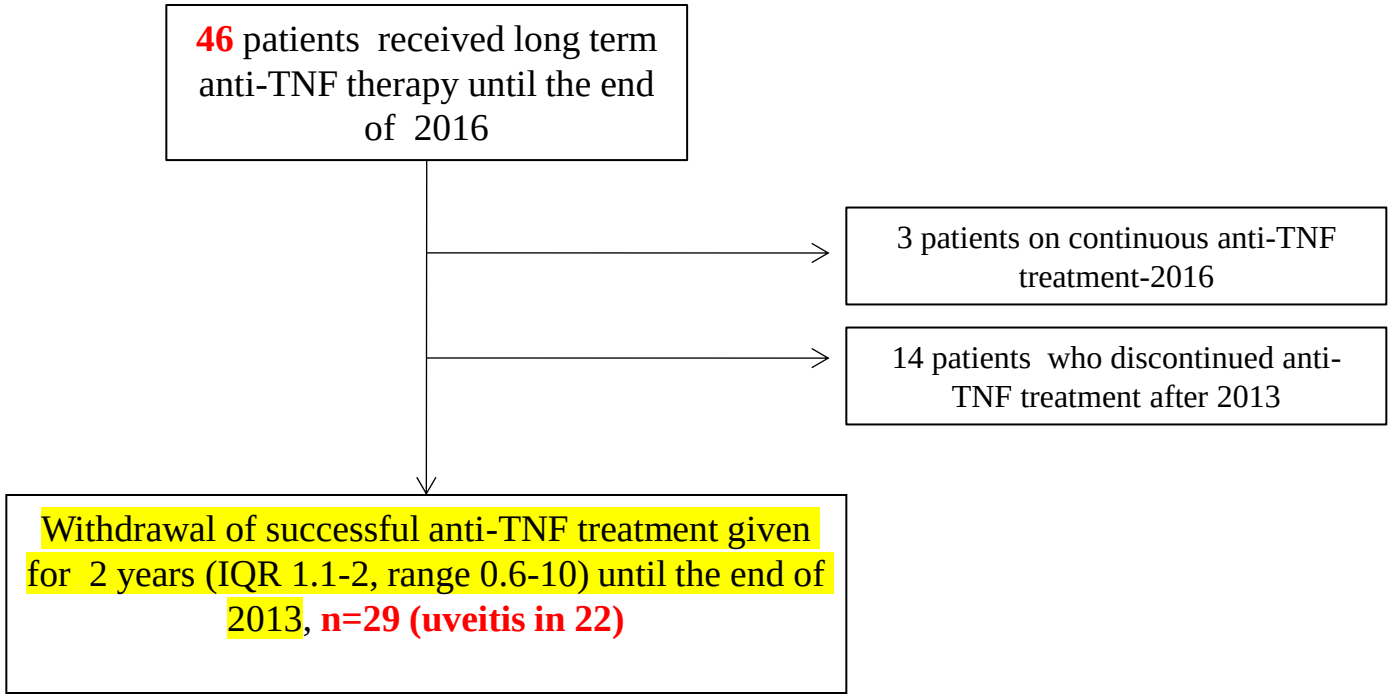
Petros P. Sfikakis, Aikaterini Arida, Stylianos Panopoulos, Kalliopi Fragiadaki, George Pentazos, Katerina Laskari, Maria Tektonidou, and Nikos Markomichelakis

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.



Sfikakis et al., Arthritis Rheumatol 2017

Out of the 29 patients in whom successful anti-TNF treatment was withdrawn after 2 years
16 patients in long-term remission (approx 7 years !) DRUG-FREE in 10 !

	Remission	
	Drug-free	Maintained with azathioprine
Male sex, no. (%)	10 (5)	6 (2)
Current age, median (IQR) years	36 (31–41)	45 (40–49)
Disease duration, median (IQR) years	12 (10–14)	14 (12–15)
Age at initiation of anti-TNF treatment, median (IQR) years	26.3 (24–31)	37.2 (32–38.3)†
Time between disease diagnosis and initiation of anti-TNF treatment, median (IQR) years	1 (0.5–3)	4.2 (3.3–8)‡
Main manifestations requiring anti-TNF therapy		
Ocular involvement	10	4
CNS involvement	0	1
Intestinal involvement	0	1
Overall disease manifestations		
Ocular involvement	10	4
CNS involvement	1	1
Deep vein thrombosis	2	3
Severe mucocutaneous involvement	8	4
Gastrointestinal involvement	0	1
Arthritis	4	0

* Except where indicated otherwise, values are the number of patients. BD = Behçet's disease; anti-TNF = anti–tumor necrosis factor; IQR = interquartile range; CNS = central nervous system.
† $P = 0.029$ versus drug-free.
‡ $P = 0.023$ versus drug-free.

Sfikakis et al., Arthritis Rheumatol 2017

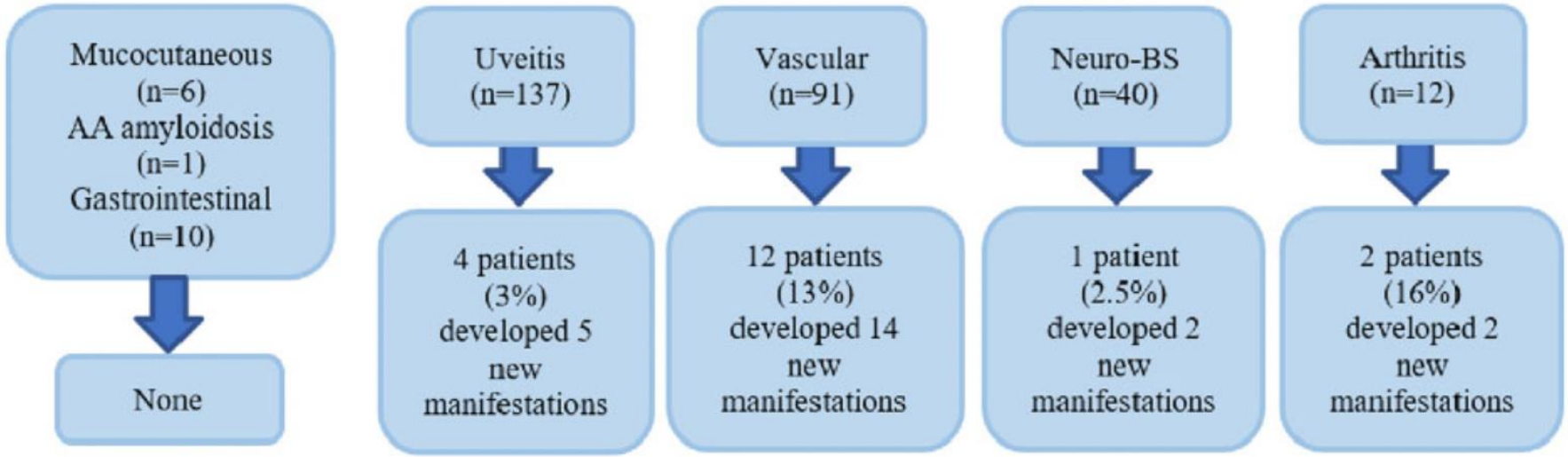
RHEUMATOLOGY
Rheumatology 2022;00:1–8
https://doi.org/10.1093/rheumatology/keab944
Advance access publication 27 December 2021

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
- New manifestations developed in:
  - 13% of patients with vascular involvement
  - 3% of patients with uveitis

Tukek et al. Rheumatology 2022

Optimal utilisation of biologic drugs in Behçet's Syndrome: a randomised controlled trial of infliximab (n=37) vs alpha interferon (n=37), with genotyping and metabolomic profiling, towards a stratified medicines approach to treatment

Robert J Moots[1, 2], Farida Fortune[3], Richard Jackson[4], Tony Thornburn[5], Ann Morgan[6], Dan Carr[7], Philip I. Murray[8], Graham Wallace[8], Deva Situnayake[9]

[1] Department of Academic Rheumatology, Liverpool University Hospitals NHS Foundation Trust, Liverpool UK
[2] Faculty of Health, Social Care and Medicine, Edge Hill University, Ormskirk, UK
[3] Queen Mary University of London, Barts Health, The London Hospital, London, UK
[4] Liverpool Clinical Trials Centre, University of Liverpool, UK
[5] Behçet's UK, Kemp House, 152-160 City Road, London, UK
[6] Institute of Cardiovascular and Metabolic Medicine, University of Leeds, UK
[7] Institute of Systems, Molecular and Integrated Biology, University of Liverpool, UK
[8] Institute of Inflammation and Ageing, University of Birmingham
[9] Department of Rheumatology, Sandwell and West Birmingham Hospitals, UK

Bio Behçet's Trial

- First head-to-head RCT of two biologic therapies in BS
- Both treatments comparable and effective
  - minor superiority for IFX in efficacy/tolerability
- Steroid sparing effects confirmed for both agents

- Biologically plausible but weak genomic signals for Roferon response in IFNL3/4 gene
- Potential metabolic markers of response to treatment with infliximab identified worthy of further study
- Is there a need to develop an alpha interferon 2a biosimilar..?

Bio Behçet's Trial

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

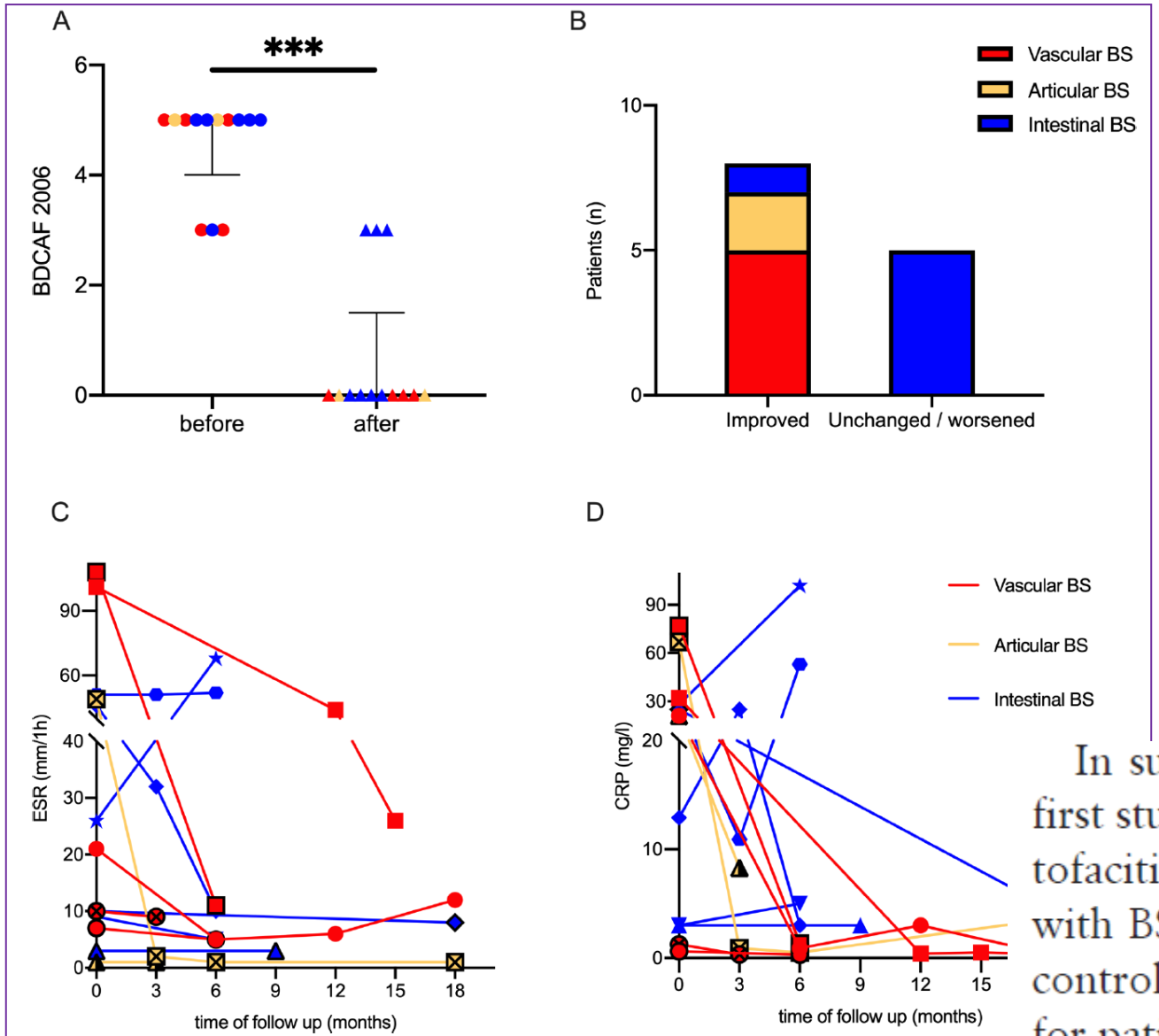


Figure 1 Efficacy of tofacitinib for patients with Behçet's syndrome (BS; presented with corresponding colours for various phenot BS; yellow: articular BS; blue: intestinal BS)). (A) Change in disease activity score (BDCAF 2006) from baseline (p=0.002). (B) Outcomes of three clinical phenotypes of BS.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

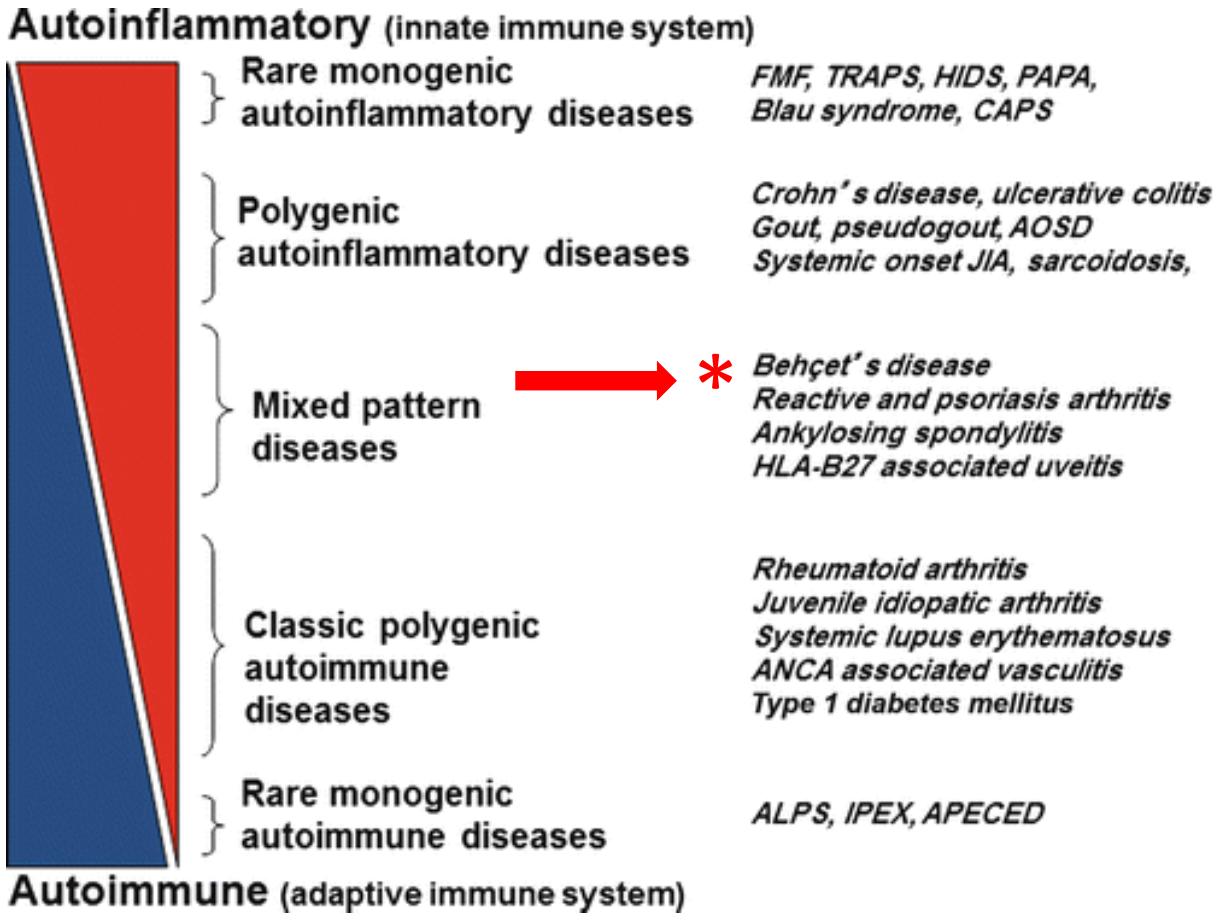
Case	Gender/age (years)	Clinical features and complications
1	M/37	O, S, V (AA, stenosis/occlusion of multiple arteries).
2	M/42	O, G, S, V (AA, stenosis of multiple arteries).
3	F/29	O, V (stenosis/occlusion of multiple arteries, PE).
4	F/42	O, G, S, V (ARD, AR, PVL).
5	M/64	O, G, V (ARD, AA, AR, coronary 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

- Τι νεώτερο στη διάγνωση
- Τι νεώτερο στη θεραπεία
- Τι νεώτερο στην παθογένεια
- Μελλοντικές κατευθύνσεις

- Polygenic autoinflammatory 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; Yazici H Clin Rev Allergy Immunol 2012

Impact of genetic component in the pathogenesis of BD :

- **BD heritability estimated to be at least 16%**
- **Known BD-associated loci explain ~ 60% implying that 40% remains to be identified**

Ortiz-Fernández L, Sawalha A. *Front Med* 2021

Journal of Autoimmunity 132 (2022) 102882

Contents lists available at ScienceDirect

Journal of Autoimmunity

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

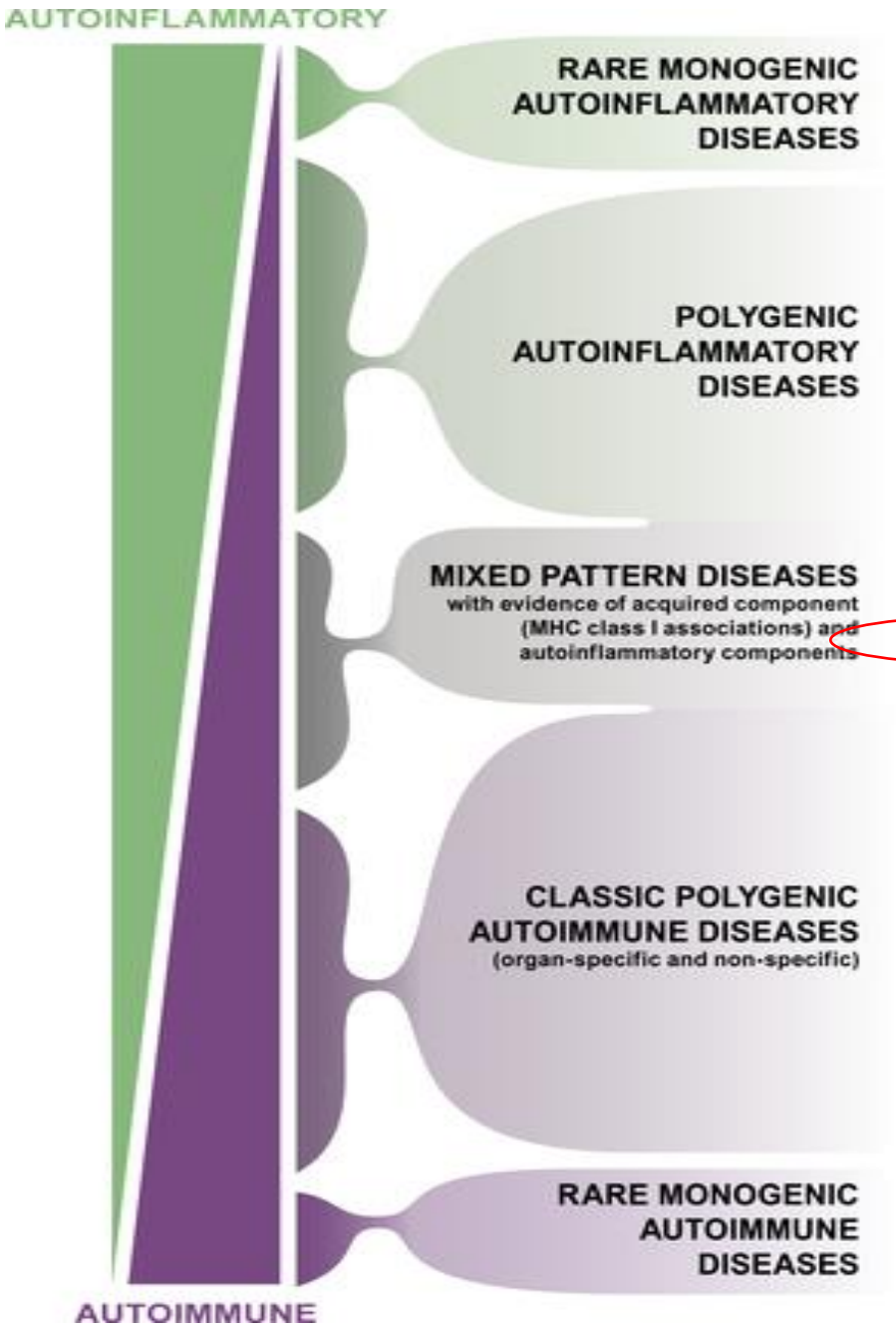
Sex-specific analysis in Behçet's disease reveals higher genetic risk in male patients

Yun Gun Jo [a], Lourdes Ortiz-Fernández [a], Patrick Coit [a], Vuslat Yilmaz [b], Sibel P. Yentür [b], Fatma Alibaz-Oner [c], Kenan Aksu [d], Eren Erken [e], Nursen Düzgün [f], Gokhan Keser [d], Ayse Cefle [g], Ayten Yazici [g], Andac Ergen [h], Erkan Alpsoy [i], Carlo Salvarani [j], Bünyamin Kısacık [k], Ina Kötter [l], Jörg Henes [m], Muhammet Çınar [n], Arne Schaefer [o], Rahime M. Nohutcu [p], Fujio Takeuchi [q], Shinji Harihara [r], Toshikatsu Kaburaki [s], Meriam Messedi [t], Yeong-Wook Song [u], Timuçin Kaşifoğlu [v], Javier Martin [w], María Francisca González Escribano [x], Güher Saruhan-Direskeneli [b], Haner Direskeneli [c], Amr H. Sawalha [a,y,z,aa,*]

OPEN ACCESS Freely available online
PLoS MEDICINE
Research in Translation

A Proposed Classification of the Immunological Diseases

Dennis McGonagle*, Michael F. McDermott



- colchicine
- corticosteroids
- anti-TNF agents
- apremilast

…. all have been shown to inhibit neutrophil chemotaxis and transmigration *in vitro* and *in vivo*…

RHEUMATOLOGY

Rheumatology 2021;60:4910–4919
doi:10.1093/rheumatology/keab052
Advance Access publication 26 January 2021

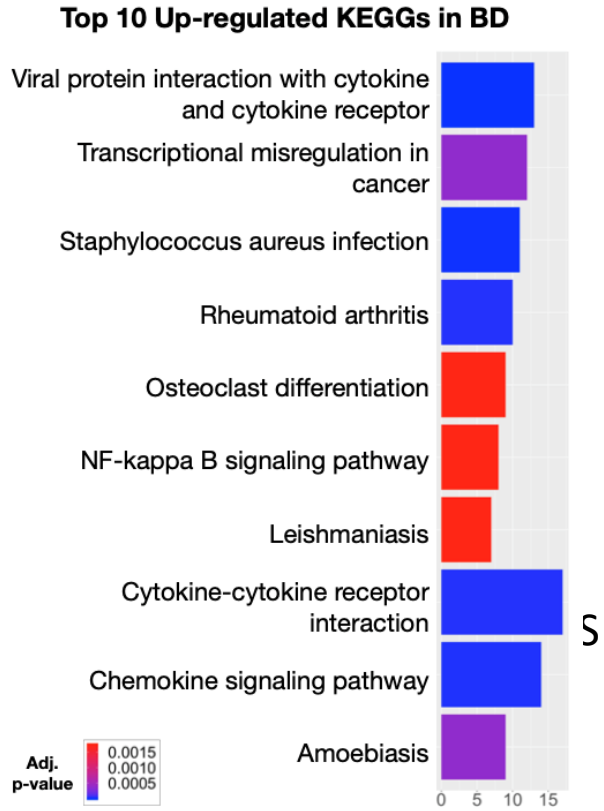
Original article

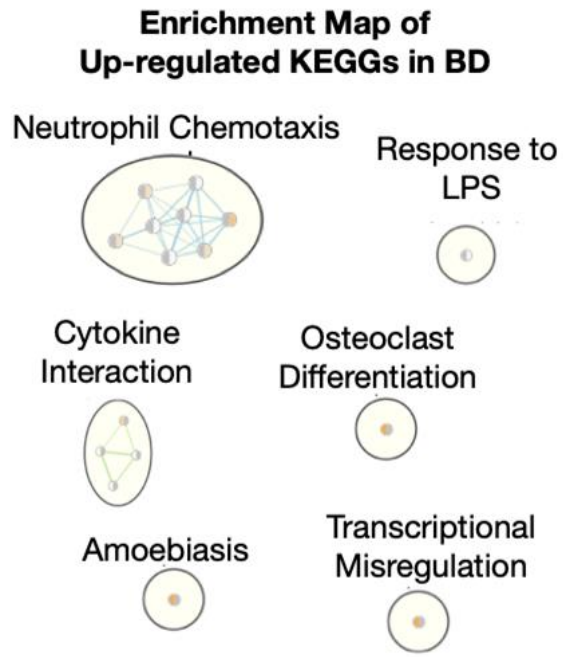
Distinct transcriptional profile of blood mononuclear cells in Behçet's disease: insights into the central role of neutrophil chemotaxis

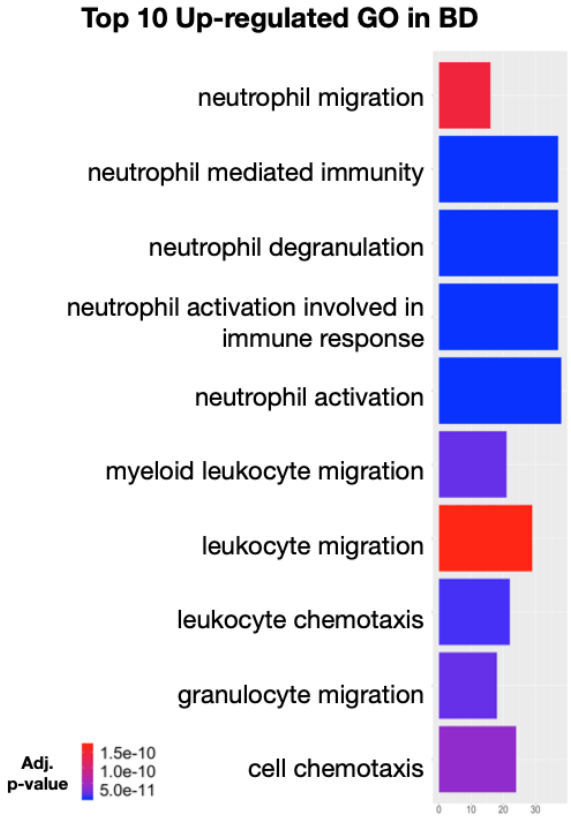
Kleio-Maria Verrou[1], Nikolaos I. Vlachogiannis [2], Giannis Ampatziadis-Michailidis[1], Panagiotis Moulos[1,3], Georgios A. Pavlopoulos[1,3], Pantelis Hatzis[1,3], George Kollias[1,4,5] and Petros P. Sfikakis [1,2]

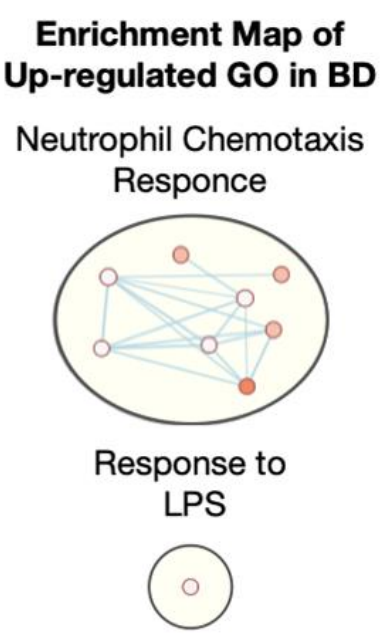
Rheumatology key messages

- 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.









<u>Enrichment analysis of up-regulated genes in BD patients</u>. 236 out of 17.591 non-zero protein coding genes were found upregulated in BD patients, with $\log_2$FC threshold equal to 1 and p-value <0.05 and became subject to the enrichment analysis. A. Barplot representation of Top 10 up-regulated KEGG pathways. Totally 22 pathways were found statistically significant enriched with DAVID (adj. p-value<0.05). The number of genes found in each pathway are described by x-axis, while color coding refers to the statistical significance of each term's enrichment. B. Enrichment map of upregulated KEGG pathways represented as network. With EnrichementMap and AutoAnnotate applications in cytoscape after DAVID analysis, the 22 up-regulated KEGG pathways were clustered into 2 major network clusters (Neutrophil Chemotaxis and Cytokine Interaction) and 4 single-element networks (Response to Lipopolysaccharide, Osteoclast Differentiation, Transcriptional Misregulation and Amoebiasis). C. Barplot representation of Top 10 up-regulated biological processes Gene Ontology (GO) terms. Totally 197 terms were found statistically significant enriched with DAVID (adj. p-value<0.05). The number of genes found in each pathway are described by x-axis, while color coding refers to the statistical significance of each term's enrichment. D. Enrichment map of upregulated biological processes GO terms represented as network. With EnrichementMap and AutoAnnotate applications in cytoscape after DAVID analysis, the 197 up-regulated GO terms were clustered into 1 major network clusters (Neutrophil Chemotaxis Response) and 1 single-element networks (Response to Lipopolysaccharide).

Taking into consideration both enrichments, **the most significant biological process that was identified as upregulated in BD is the neutrophil Chemotaxis response.**

PNAS

RESEARCH ARTICLE | IMMUNOLOGY AND INFLAMMATION

Single-cell analyses highlight the proinflammatory contribution of C1q-high monocytes to Behçet's disease

Wenjie Zheng[a,b,c,d,1,2], Xiaoman Wang[e,1,2], Jinjing Liu[a,b,c,d,1], Xin Yu[a,b,c,d,1], Lu Li[a,b,c,d,f], Heping Wang[e], Jijun Yu[g,h], Xiaoya Pei[e], Chaoran Li[a,b,c,d,i], Zhimian Wang[a,b,c,d], Menghao Zhang[a,b,c,d], Xiaofeng Zeng[a,b,c,d], Fengchun Zhang[a,b,c,d], Chenfei Wang[j], Hua Chen[a,b,c,d], and Hou-Zao Chen[e,2]

Edited by Yuta Kochi, Rikagaku Kenkyujo; received March 24, 2022; accepted April 15, 2022 by Editorial Board Member Tadatsugu Taniguchi

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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AC, MCK and YO contributed equally.

Received 31 January 2022
Accepted 27 June 2022

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.

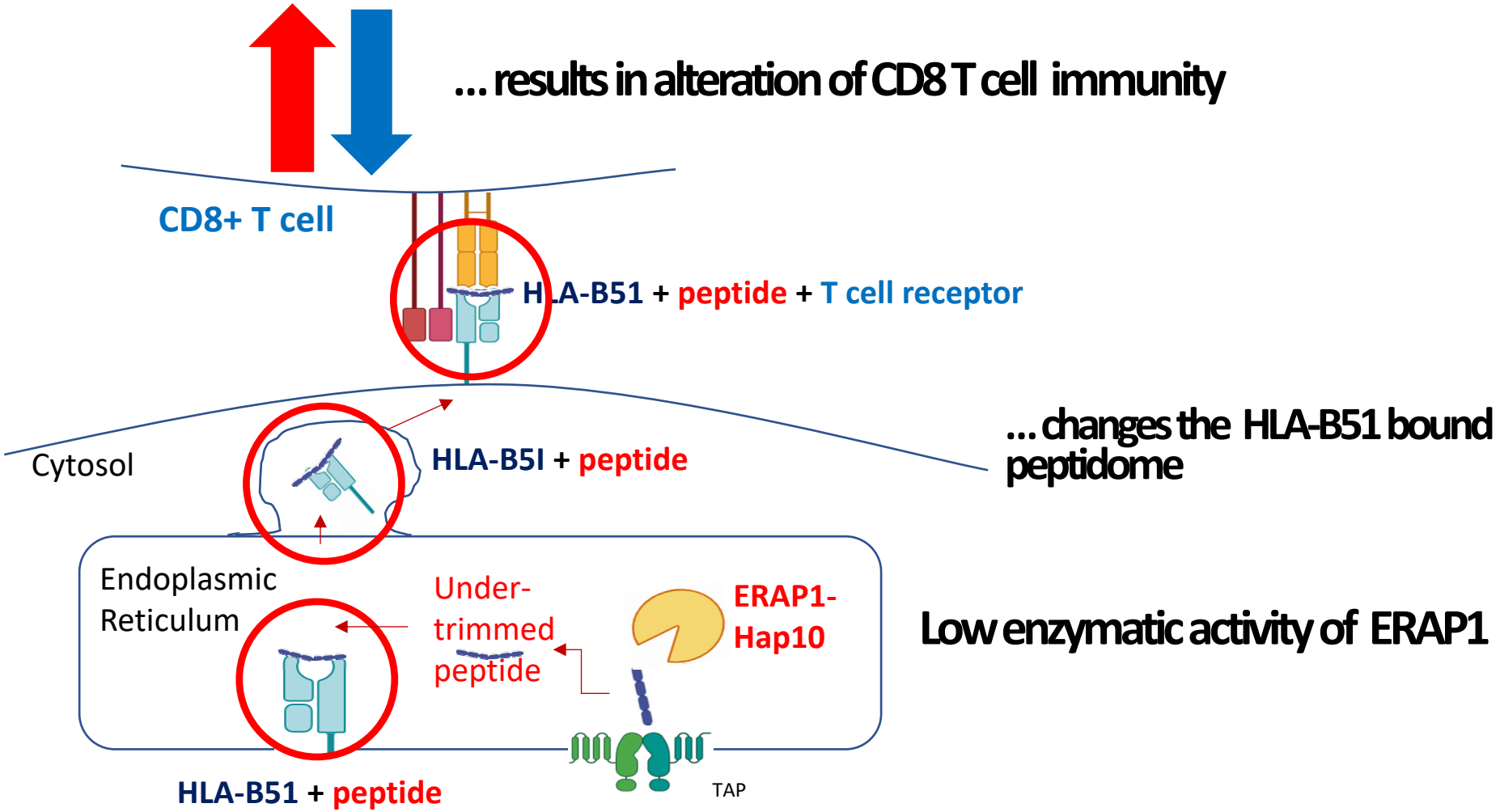
⇒ Knock-out of *ERAP1*—modelling hypofunctional ERAP1-Hap10—alters immunogenicity, mediated through an HLA class I-bound peptidome which is characterised by longer, that is, less trimmed peptides above 9mer.

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.

HYPOTHESIS



Nowatzky's group, ARD: Sept 2022

KEY POINTS

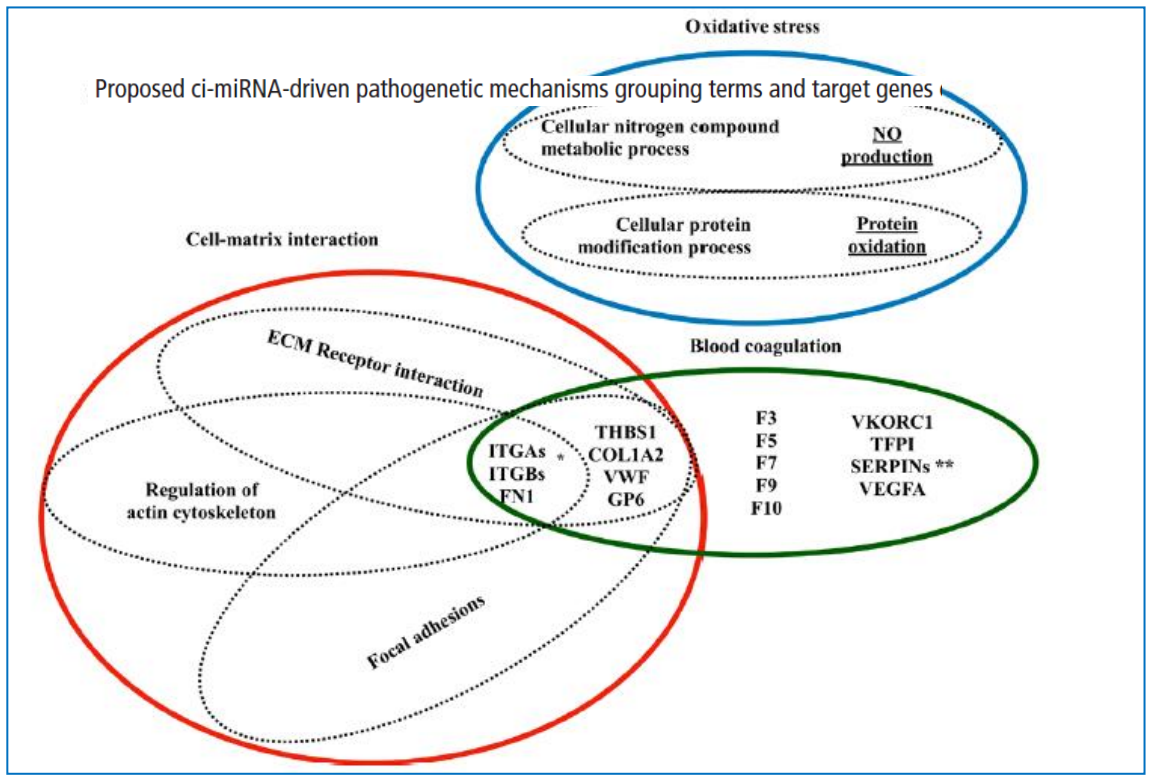
- Absence of functional ERAP1 alters immunogenicity to human CD8+ T cells
- Oligoclonally expanded, activated, HLA-restricted cytotoxic CD8 T cells are present in active BD uveitis; unlikely due to a stochastic effect
- Altered CD8 immune-phenotypes in ERAP1 Hap10/B51 carriers suggest biologic relevance of ERAP1 Hap10/ B51 in Behçet's disease (BD) as a disease endotype

Targeting ERAP1 activity in patient subsets defined by genotype rather than disease phenotype only may be become testable in clinical trials in the future

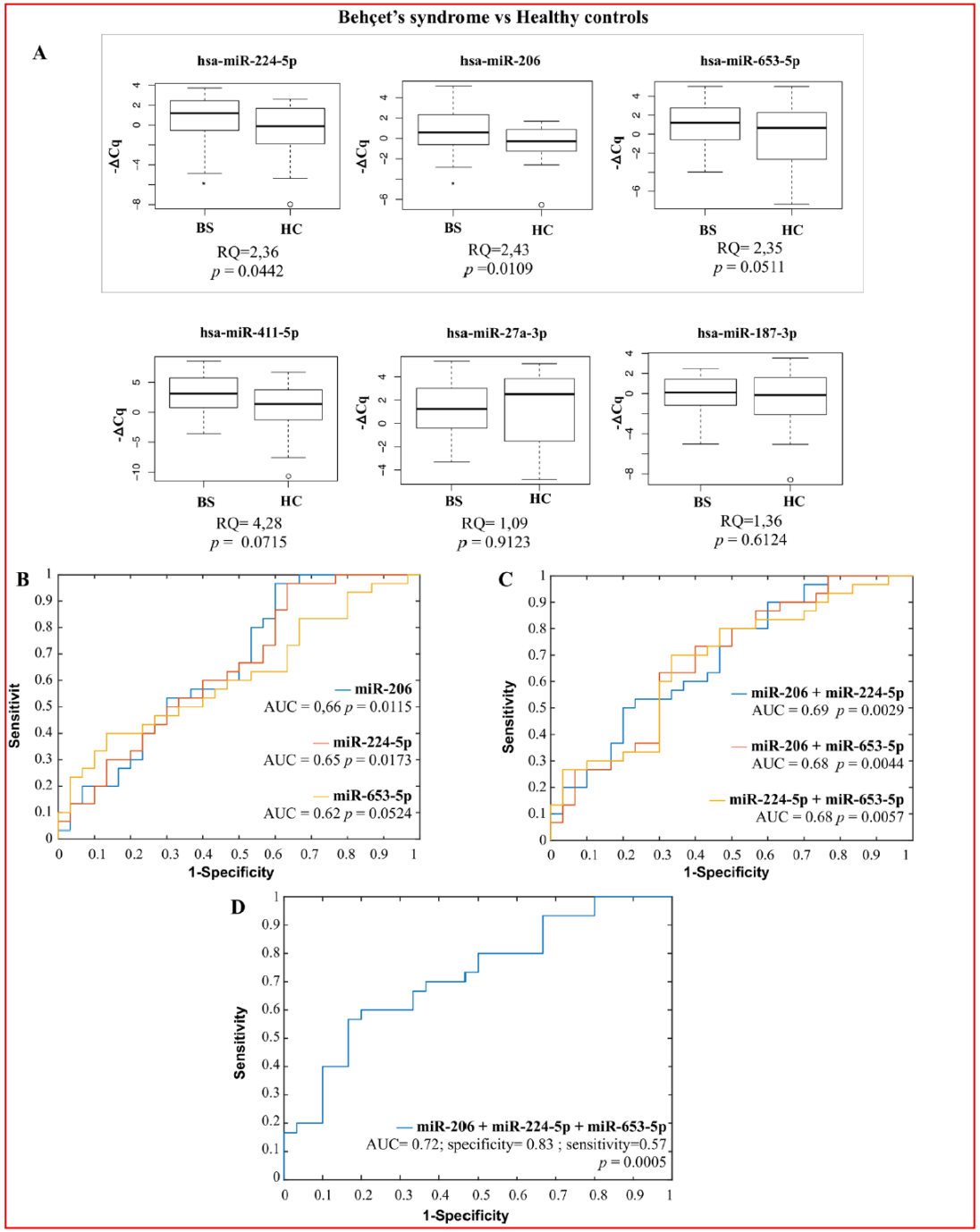
Nowatzky's group, ARD: Sept 2022

A unique circulating miRNA profile highlights thrombo-inflammation in Behçet's syndrome

Giacomo Emmi ,[1,2] Giacomo Bagni ,[1] Elena Lastraioli,[1]
Francesca Di Patti ,[3,4,5] Alessandra Bettiol ,[1] Claudia Fiorillo ,[6]
Matteo Becatti ,[6] Elena Silvestri ,[1,2] Maria Letizia Urban ,[1,2] Lorenzo Emmi,[7]
Domenico Prisco ,[1,2] Annarosa Arcangeli [1,4]

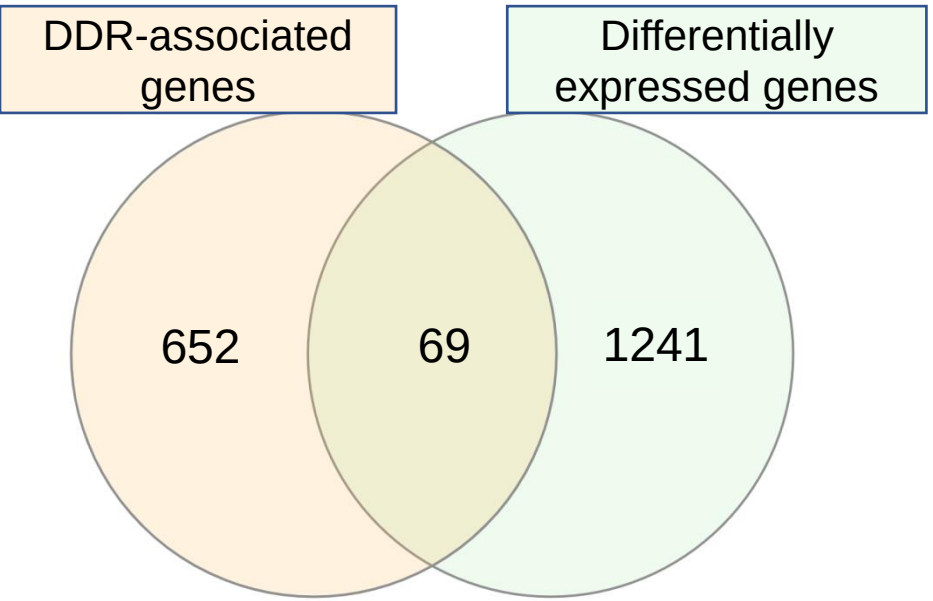


. Ann Rheum Dis 2021;0:1–12.

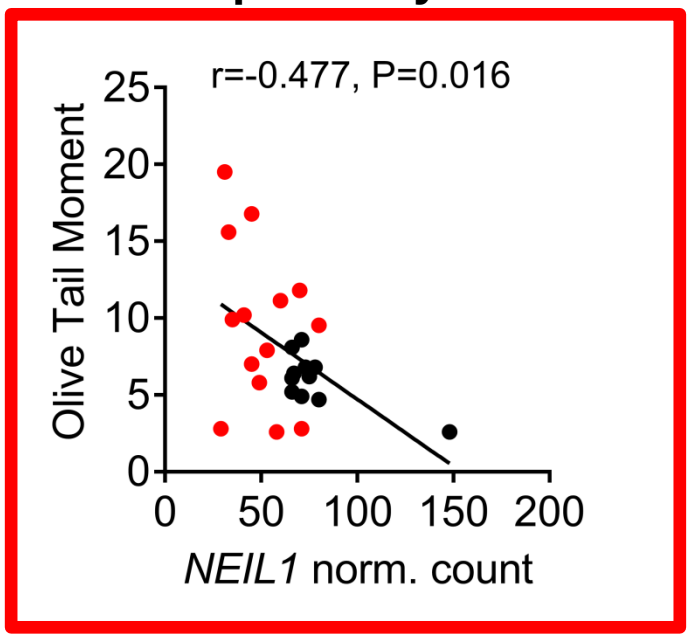


Association of increased endogenous DNA damage
with deregulated gene expression in patients with BD

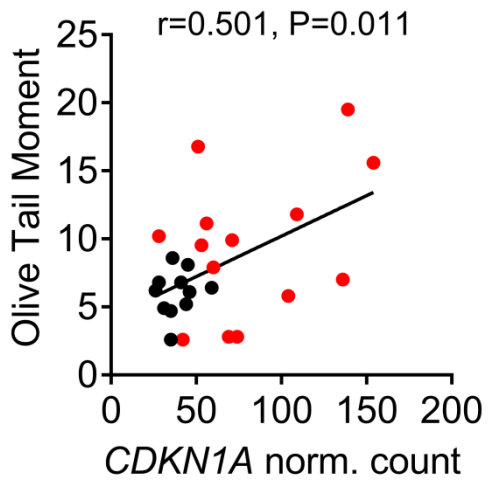
Vlachogiannis et.al, 2022

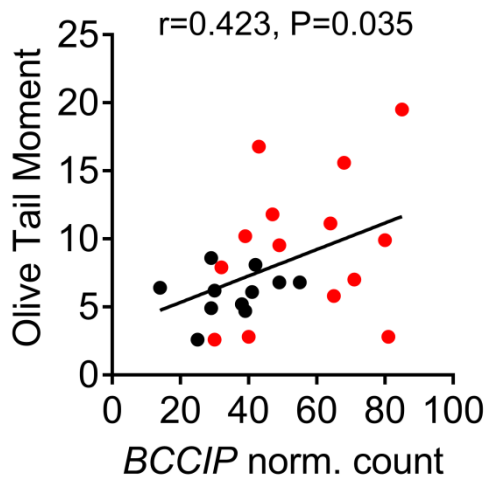


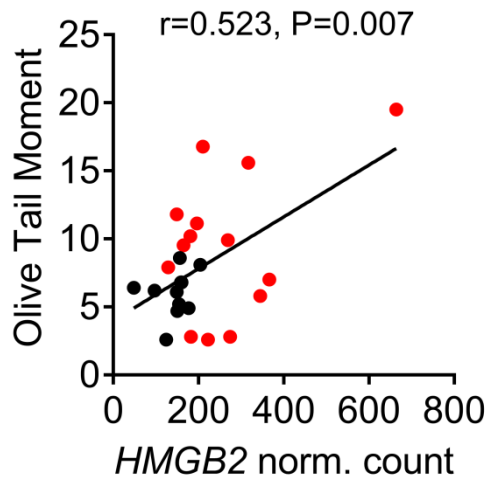
1. DNA repair enzyme NEIL1



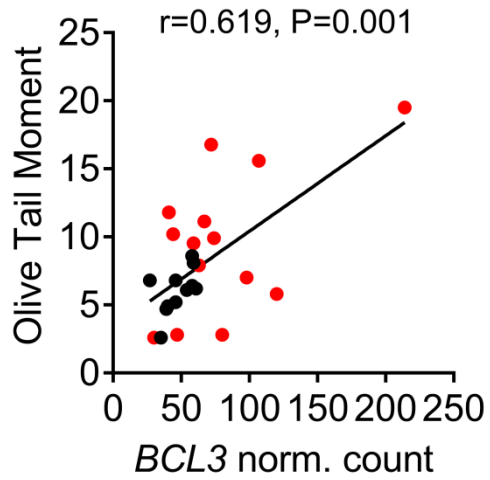
2. Senescence-associated factors

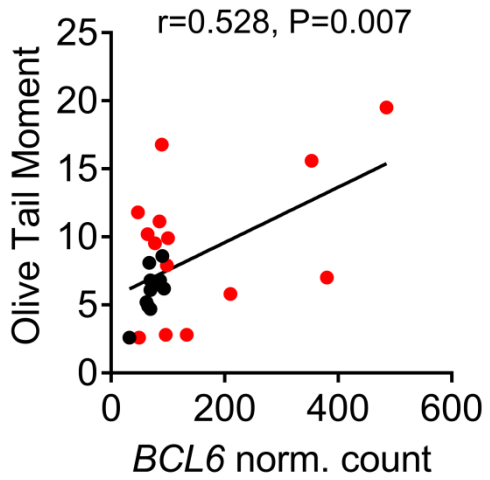






3. Anti-apoptotic factors





NEIL1 is associated with BD at the genetic level

The DNA repair enzyme **NEIL1** has been identified as one of the two genetic risk factors for BD by whole exome study in 3 independent patient cohorts

ARTHRITIS & RHEUMATOLOGY
Vol. 68, No. 5, May 2016, pp 1272–1280
DOI 10.1002/art.39545

Whole Exome Sequencing Identifies Rare Protein-Coding Variants in Behçet's Disease

Mikhail Ognenovski,[1] Paul Renauer,[1] Elizabeth Gensterblum,[1] Ina Kötter,[2] Theodoros Xenitidis,[3] Jörg C. Henes,[3] Bruno Casali,[4] Carlo Salvarani,[4] Haner Direskeneli,[5] Kenneth M. Kaufman,[6] and Amr H. Sawalha[1]

Methods. **Whole exome sequencing was performed in a discovery set comprising 14 German BD patients of European descent. For replication and validation, Sanger sequencing and Sequenom genotyping were performed in the discovery set and in 2 additional independent sets of 49 German BD patients and 129 Italian BD patients of European descent. Genetic association analysis was then performed in BD patients and 503 controls of European descent. Functional effects of associated genetic variants were assessed using bioinformatic approaches.**

Results. **Using whole exome sequencing, we identified 77 rare variants (in 74 genes) with predicted protein-damaging effects in BD. These variants were genotyped in 2 additional patient sets and then analyzed to reveal significant associations with BD at 2 genetic variants detected in all 3 patient sets that remained significant after Bonferroni correction. We detected genetic association between BD and *LIMK2* (rs149034313), involved in regulating cytoskeletal reorganization, and between BD and *NEIL1* (rs5745908), involved in base excision DNA repair ($P = 3.22 \times 10^{-4}$ and $P = 5.16 \times 10^{-4}$, respectively). The *LIMK2* association is a missense variant with predicted protein damage that may influence functional interactions with proteins involved in cytoskeletal regulation by Rho GTPase, inflammation mediated by chemokine and cytokine signaling pathways, T cell activation, and angiogenesis (Bonferroni-corrected $P = 5.63 \times 10^{-14}$, $P = 7.29 \times 10^{-6}$, $P = 1.15 \times 10^{-5}$, and $P = 6.40 \times 10^{-3}$, respectively). The genetic association in *NEIL1* is a predicted splice donor variant that may introduce a deleterious intron retention and result in a noncoding transcript variant.**

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pMedGR

ΑΠΟΡΡΥΘΜΙΣΗ ΤΩΝ ΕΠΙΔΙΟΡΘΩΤΙΚΩΝ ΜΗΧΑΝΙΣΜΩΝ ΤΗΣ ΒΛΑΒΗΣ ΤΟΥ DNA ΣΤΗ ΝΟΣΟ ΑΔΑΜΑΝΤΙΑΔΗ-ΒΕΗΣΕΤ

Βλαχόγιαννης Ν.Ι.*, Ντούρος Π.Α.*, Παππά Μ., Βέρρου Κ.-Μ., Αρίδα Α., Σουλιώτης Β., Σφηκάκης Π.Π.

14ο Ετήσιο Πανελλήνιο Συνέδριο ΕΠΕΜΥ – Ρόδος 2022

outline

- Τι νεώτερο στη διάγνωση
- Τι νεώτερο στη θεραπεία
- Τι νεώτερο στην παθογένεια

- Μελλοντικές κατευθύνσεις

SPECIAL SESSION - Towards A Treat-To-Target Strategy

Chairs: A. Gül, G. Fragoulis, P. Sfikakis

Treat to target in pleomorphic diseases – the lupus paradigm

George Bertsias

Measuring Behçet's disease activity

Gonca Mumcu

OMERACT - standardization of outcome measures

Gülen Hatemi

Therapeutic targets in Behçet's disease

Jan van Laar

Targeting remission in ocular manifestations

in Behçet's disease

Bahram Bodaghi

Implementing treat to target in treatment recommendations

and discussion

Petros Sfikakis & Audience

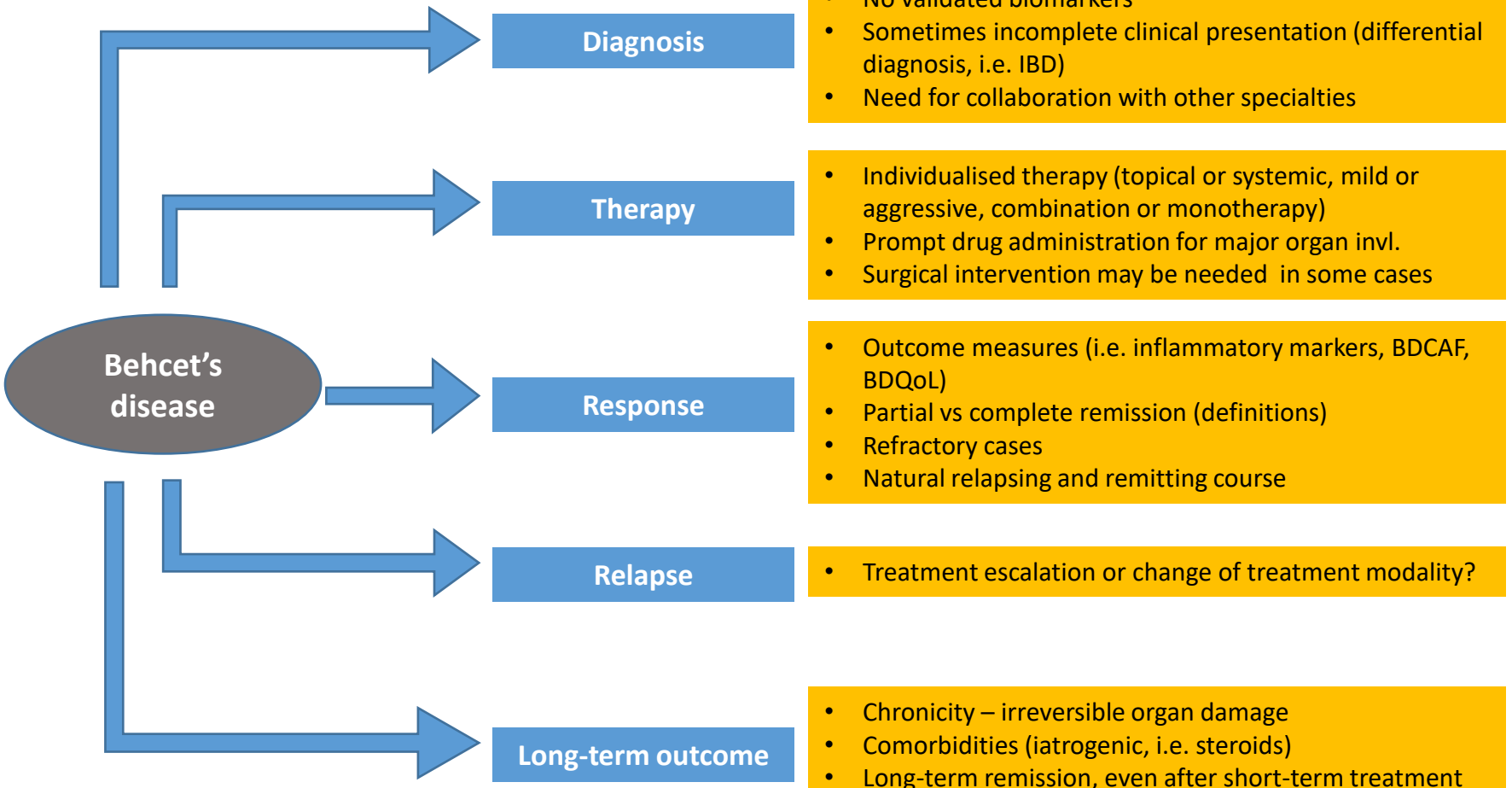
The "Treat-to-Target" strategy in chronic diseases is better than usual care

	Diabetes Mellitus	Hypertension	COPD	Rheumatoid Arthritis
At risk for	Loss of vision	Myocardial infarction Heart failure Stroke	Hospital admission Respiratory failure/Death	Disability
Underlying mechanism	Hyperglycemia	High blood pressure	Irritant-driven Inflammation	Inflammation
Biomarker / Outcome measure	HbA1c	Blood pressure	Exacerbations & FEV1 ≤ 50%	DAS 28
Target (threcshold)	**≤ 6%**	**≤ 140/90 mmHg**	**≤2 exacerbations per year; FEV1 ≤ 50%**	**≤ 3.2 ≤ 2.6**

	Diabetes Mellitus	Hypertension	COPD	Behcet's
At risk for	Loss of vision	Myocardial infarction Heart failure Stroke	Hospital admission Respiratory failure/Death	Disability Organ failure/dysfunction, poor QoL, death
Underlying mechanism	Hyperglycemia	High blood pressure	Irritant-driven Inflammation	Inflammation Thrombosis
Biomarker / Outcome measure	HbA1c	Blood pressure	Exacerbations & FEV1 ≤ 50%	???
Target	≤ 6%	≤ 140/90 mmHg	≤2 exacerbations per year; FEV1 ≤ 50%	???

…. 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.

Challenges in BD



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.

Different targets for different disease manifestations: a proposal

	Skin, mucosa	Arthritis
Treatment decision driving target/s	Function Quality of life	Function Quality of life
Monitoring instrument	Number of lesions? Pain? Quality of life indexes?	Joint count? Pain? Quality of life indexes?
Monitoring interval	3–6 months	3–6 months
Organ-specific goal	Preserving quality of life	Preserving function

Hatemi, Curr Opin Rheum. 2021

Different targets for different disease manifestations

	Uveitis	Venous	Arterial	CNS	Gastrointestinal
Treatment decision driving target/s	Remission Preventing relapses	Remission Preventing relapses	Remission Preventing relapses	Remission Preventing relapses	Remission Preventing relapses
Monitoring instrument	BOS24? Fluorescein angiography?	Clinical findings? Doppler USG?	Clinical findings? Acute phase response? MRI?	Clinical findings? MRI?	Endoscopy? Fecal calprotectin?
Monitoring interval	2–4 weeks at onset 3 months	1 month at onset 3 months	2–4 weeks at onset 3 months	2–4 weeks at onset 3 months	3 months
Organ-specific goal	Preserving visual acuity	Preventing postthrombotic syndrome	Preventing mortality	Preserving cognitive and motor function	Preventing perforation

To develop T2T recommendations many medical specialties should be involved

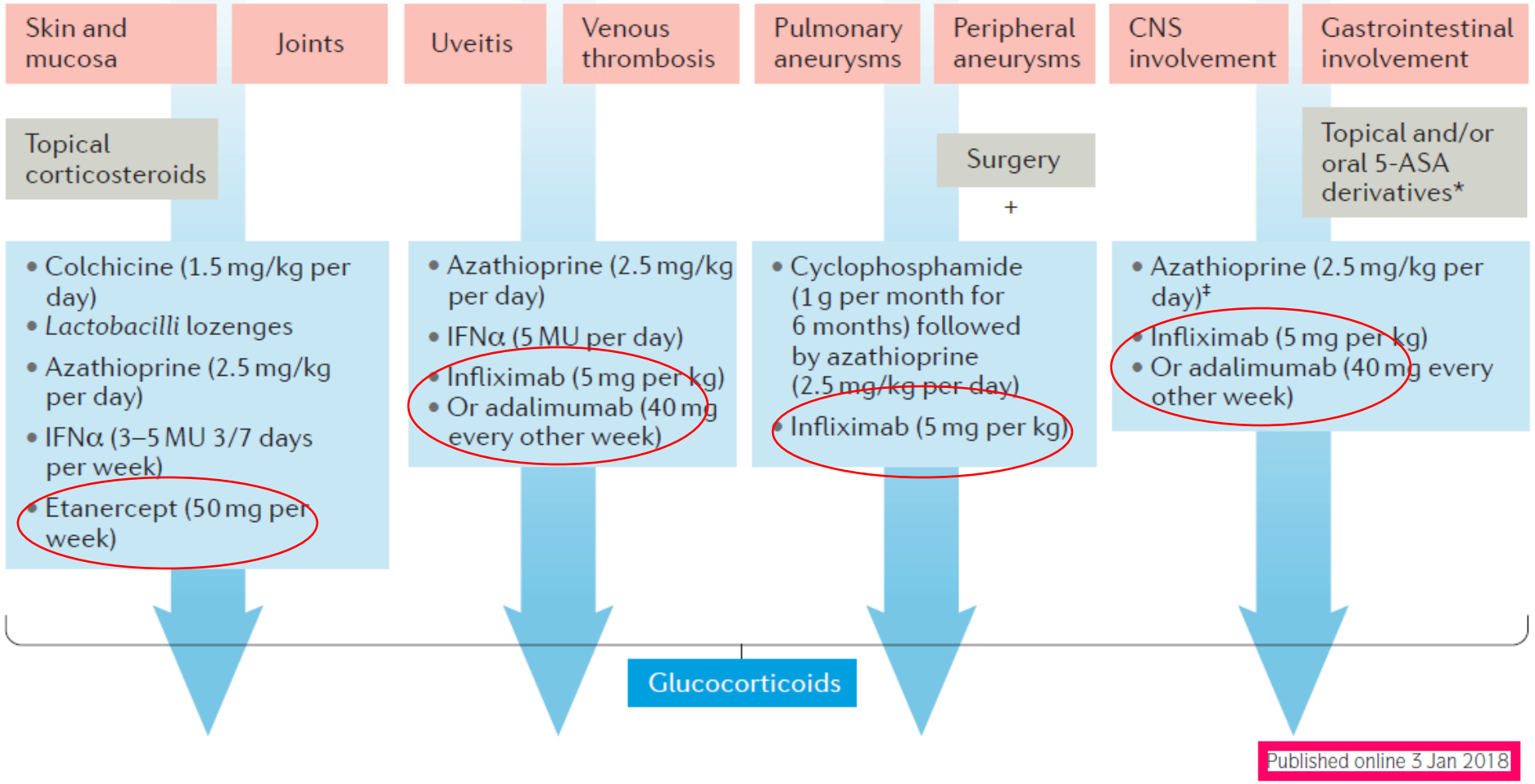
Hatemi, Curr Opin Rheum. 2021

The TREAT-To-TARGET STRATEGY requires having weapons = = EFFECTIVE TREATMENTS !

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

…. we need to agree on:

Measuring Behçet's disease activity

Gonca Mumcu

OMERACT - standardization of outcome measures

Gülen Hatemi

Therapeutic targets in Behçet's disease

Jan van Laar

Next Steps : application to EULAR to support a task-force to formulate recommendations/points to consider for T2T in BD

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- D. Ladas

- **EULAR task force for BD guidelines**
- **anti-TNF recommendations expert panel**
- **NeuroBD expert panel**
- **EULAR task force for T2T (?)**