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Management of skin, mucosa and joint involvement of syndrome: A systematic review for update of the EULA recommendations for the management of Behçet's syn

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ABSTRACT

Objectives: The aim of this systematic review was to Rheumatism (EULAR) Recommendations for the manag for the treatment of skin, mucosa and joint involveme
Methods: A systematic literature search, data extract quality of evidence were performed according to a pre Studies that assessed the efficacy of an intervention in

This paper is dedicated to the memory of Ignazio Olivieri.

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Original article

Management of major organ involvement of Behçet's syndrome: a systematic review for update of the EULAR recommendations

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Abstract

Objective. To assess the efficacy and safety of treatment modalities for major organ involvement of Behçet's syndrome (BS), in order to inform the update of the EULAR recommendations for the management of BS.

Methods. A systematic literature review of all randomized controlled trials, controlled clinical trials, or open label trials assessing eye, vascular, nervous system or gastrointestinal system involvement of BS was performed. If controlled trials were not available for answering a specific research question, uncontrolled studies or case series were also included.

Results. We reviewed the titles and abstracts of 3927 references and 161 studies met our inclusion criteria. There were only nine randomized controlled trials. Observational studies with IFN-α and monoclonal anti-TNF antibodies showed beneficial results for refractory uveitis. Meta-analysis of case–control studies showed that immunosuppressives decreased the recurrence rate of deep vein thrombosis significantly whereas anticoagulants did not. CYC and high dose glucocorticoids decreased mortality in pulmonary arterial aneurysms and postoperative complications in peripheral artery aneurysms. Beneficial results for gastrointestinal involvement were obtained with 5-ASA derivatives and AZA as first line treatment and with thalidomide and/or monoclonal anti-TNF antibodies in refractory cases. Observational studies for nervous system involvement showed improved outcome with immunosuppressives and glucocorticoids. Meta-analysis of case–control studies showed an increased risk of developing nervous system involvement with ciclosporin-A.

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Recommendation

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

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ABSTRACT

Several new treatment modalities with different mechanisms of action have been studied in patients with Behçet's syndrome (BS). The aim of the current effort was to update the recommendations in the light of these new data under the auspices of the European League Against Rheumatism (EULAR) Standing Committee for Clinical Affairs. A task force was formed that included BS experts from different specialties including internal medicine, rheumatology, ophthalmology, dermatology, neurology, gastroenterology, oral health medicine and vascular surgery, along with a methodologist, a health professional, two patients and two fellows in charge of the systematic literature search. Research questions were determined using a Delphi approach. EULAR standardised operating procedures was used as the framework. Results of the systematic literature review were presented to the task force during a meeting. The former recommendations were modified or new recommendations were formed after thorough discussions followed by voting. The recommendations on the medical management of mucocutaneous, joint, eye, vascular, neurological and gastrointestinal involvement of BS were modified; five overarching principles and a new recommendation about the surgical management of vascular involvement were added. These updated, evidence-based recommendations are intended to help physicians caring for patients with BS. They also attempt to highlight the shortcomings of the available clinical research with the aim of proposing an agenda for further research priorities.

INTRODUCTION

Behçet's syndrome (BS) is a systemic variable vessel vasculitis that involves the skin, mucosa, joints, eyes, arteries, veins, nervous system and the gastrointestinal system. Physicians from several different disciplines are involved in the care of patients with BS. The disease shows geographic differences in its clinical features. Thus a multicentre collaboration of experts from different specialties and from different parts of the world is necessary for the optimisation of the recommendations for managing BS.

The first European League Against Rheumatism (EULAR) Recommendations for the management of Behçet's disease that were published in 2008 has gained a lot of interest and helped physicians from different disciplines in the management of patients with BS.[1] At that time a total of nine recommendations were formed after a literature review, a Delphi exercise and two expert consensus meetings by a task force that included rheumatologists, ophthalmologists, dermatologists, a neurologist and a patient. In five of the nine recommendations, the strength of the recommendation was 'D', indicating that it was based only on expert opinion for the whole or at least a part of the recommendation.

The task force felt that there was a need for updating these recommendations as there had been several related new publications and data with new agents were available. Especially the experience with the use of biological agents in BS has substantially increased during the recent years. There is also more evidence to guide us in the management of gastrointestinal involvement and about other issues such as the use of anticoagulants in BS patients with vascular involvement. One of the shortcomings of the previous recommendations was that it lacked guidance regarding the surgical and interventional treatment options for vascular involvement.

The objective of the current project was to update and improve the EULAR Recommendations for the management of BS in the light of the new studies, in addition to identifying the hitherto uncovered areas for future research. The target population for these recommendations includes all physicians and surgeons who are involved in the treatment of BS.

METHODS

The standard operating procedures for developing EULAR-endorsed recommendations was followed and when applicable the Appraisal of Guidelines, Research and Evaluation instrument was used.[2] A task force was formed including 20 BS experts from seven European countries and Korea, 1 healthcare professional (a nurse), 2 patients with BS, 2 fellows responsible for the systematic literature review who are EMEUNET members and 1 senior methodologist. The experts were from various specialties that are involved in the management of patients with BS including internal medicine, rheumatology, ophthalmology, dermatology, neurology, gastroenterology, oral health medicine and vascular surgery.

An initial Delphi was conducted among the task force members to identify the questions and problem areas which were not covered by

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Table 3 Nine recommendations on Behçet disease (BD) that were developed after two anonymous Delphi rounds

No.	Recommendation
1	Any patient with BD and inflammatory eye disease affecting the posterior segment should be on a treatment regime that includes azathioprine and systemic
2	
3	
9	8 Ciclosporine A neurotoxicity III C 8.79 (0.70) 8.78 (0.68)

Table 4 Category of evidence, strength of recommendations and level of agreement of recommendations

Recommendation no.	Category of evidence	Strength of recommendation	Level of agreement (VAS, mm)	
			Whole committee	Experts in the field

- Bu dönemde biyolojik kullanımı artmış
- Yeni ajanlar kullanıma girmiş
- GIS tutulumu veya antikoagülan kullanımı gibi alanlarda daha fazla kanıt elde olunmuş
- Ayrıca eski öneriler vasküler tutulumda cerrahi veya girişimsel tedavi seçeneklerini de içermiyormuş

Amaç:

- 2008 önerilerini güncellemek

Hedef kitlesi:

- Behçet tedavisinde yer alan tüm hekim ve cerrahlar

surgeons who are involved in the treatment of BD. whole group were calculated to determine the level

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

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- 20 Behçet uzmanı (Avrupa ve Kore)
- 1 hemşire
- 2 hasta
- 2 fellow (EMEUNET üyesi)
- 1 senior metodolog

2 SLR yapılıyor

- MEDLINE (>1950)
- EMBASE (>1980)
- Cochrane

- SLR'lerinin sonuçları 1.5 günlük bir toplantıda «task force»'a sunuluyor
- Tartışma sonuçlarına göre draft önerielr şekillendiriliyor
- SOR belirleniyor (A [meta-analizlere veya en az RCT'ye dayalı] to D [categori IV] kanıt)
- Uzmanların >%70 mutabık kaldıkları öneriler konsensusa ulaşıldığı şeklinde yorumlanmış ve LoA (kapalı oyla) belirlenmiş

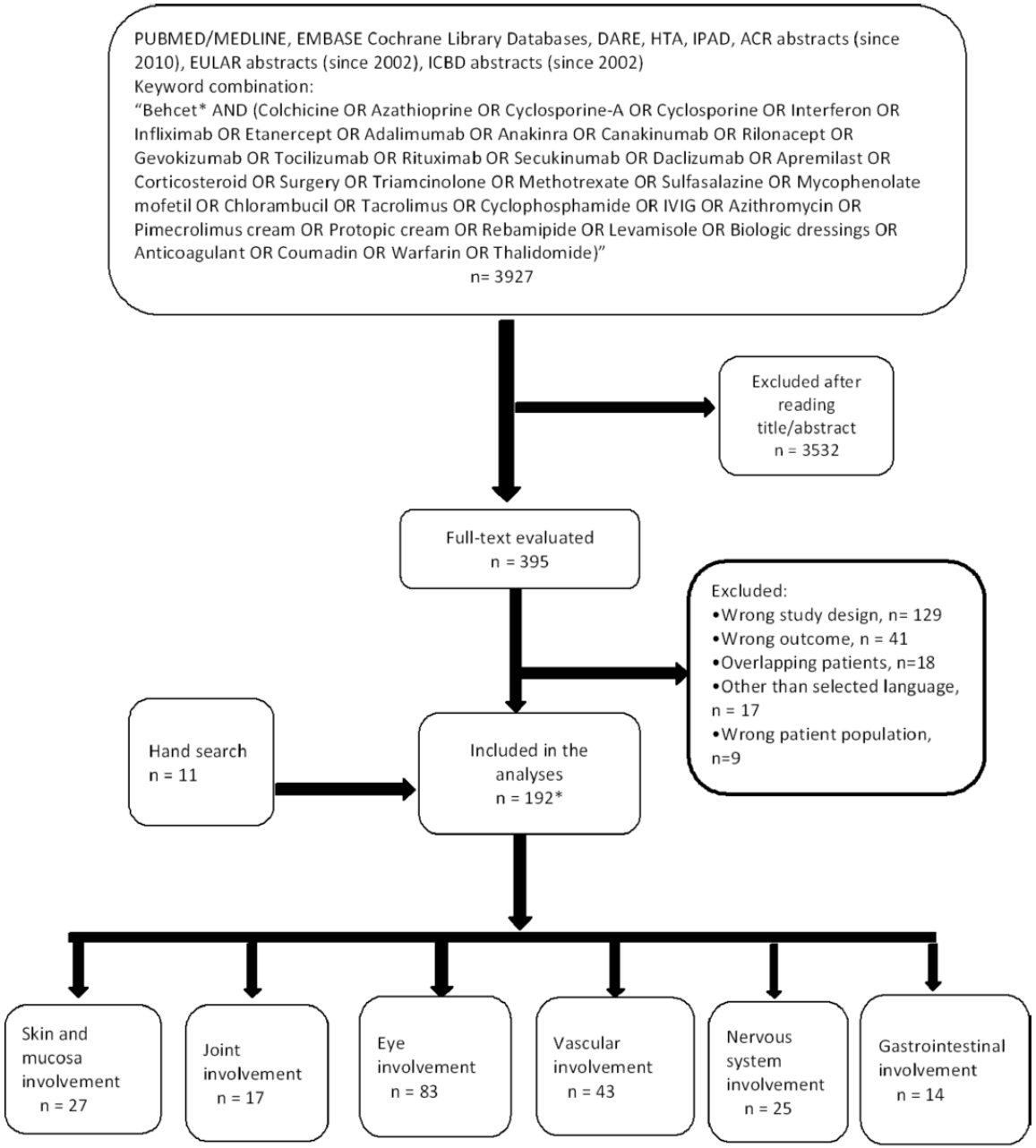


Figure 1 Flow chart of the study selection process. ACR, American College of Rheumatology; DARE, Database of Abstracts of Reviews of Effects; EULAR, European League Against Rheumatism; HTA, Health Technology Assessments; ICBD, The International Criteria for Behçet's Disease; IPAD, International Pharmaceutical Abstracts Database.

Table 1 Updated European League Against Rheumatism recommendations for the management of Behçet's syndrome, with levels of evidence, grade of recommendations, voting rates and level of agreement

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

- Yalnızca cilt, mukoza ve eklem tutulumu varlığında hastaların ihtiyacı veya semptomların QoL üzerindeki etkisi ve tedavi yan etkisine göre tedavi karırı verilir
- Göz, damar veya nörolojik tutulum gibi manifestasyonlarda hızla inflamasyonu baskılamak, rekürransa engel olmak (fonksiyon kaybının engellenmesi) ve bazen yaşamı korumak için hızla immünsupresif başlamak (erkeklerde, genç yaşta daha agresif tedavi) gerekebilir ve zaman içinde artırmak gerekli olabilir

1. Mucocutaneous involvement	Topical measures such as steroids should be used for the treatment of oral and genital ulcers. Colchicine should be tried first for the prevention of recurrent mucocutaneous lesions especially when the dominant lesion is erythema nodosum or genital ulcer (IB). Papulopustular or acne-like lesions are treated with topical or systemic measures as used in acne vulgaris (IV).	IB/IV	A/D	9.4±0.8
	Leg ulcers in BS might be caused by venous stasis or obliterative vasculitis. Treatment should be planned with the help of a dermatologist and vascular surgeon.	IV	D	
	Drugs such as azathioprine, thalidomide, interferon-alpha, TNF-alpha inhibitors or apremilast should be considered in selected cases.	IB	A	

- Mukokutanöz lezyonların tedavisinde:

- Bacak ülseri tedavisi:

1. Tamamen uzman görüşüne dayalı
2. Tedavi dermatolog ve vasküler cerrah ile birlikte planlanmalı; gerekirse immünsupresif, enfekte ise Ab, LH debritman ve oklusive (kompresif bandajlama vb) uygulanabilir

5. SEC etkisiz
6. Tosilizumab kötüleştirmiş

sistemik tedaviler gündeme gelebilir

Table 1
Characteristics of RCTs for mucocutaneous and joint involvement of Behçet's syndrome

Author, year	Drug	Dose	Trial duration (weeks)	Sex M/W	Age (mean ± SD years)	Disease duration, (mean ± SD years)	Number of patients	Main outcomes
Aktulga, 1980 [9]	Colchicine	1 mg/day	36	9/5	34.2 ± 7.2	NA	14	Improvement in each mucocutaneous lesion, eye and joint involvement
	Placebo			13/1	33 ± 12.8		14	
Yurdakul, 2001 [10]	Colchicine	1–2 mg/day	104	30/0	Men 27 ± 5.5	Men 8.2 ± 8.4	30	Complete remission of each mucocutaneous lesion and arthritis
	Placebo			30/0	Men 27.3 ± 5.3	Men 10.3 ± 8.3	30	
	Colchicine	1–2 mg/day		0/28	Women 26.7 ± 4.8	Women 8 ± 8.8	28	
	Placebo			0/27	Women 27.2 ± 5.5	Women 6.8 ± 6.8	27	
Davatchi, 2009 [11]	Colchicine	1 mg/day	16	NA	32.1 ± 8.29	6.4 ± 5.52	136	IBDDAM score
	Placebo			NA			146	
Yazici, 1990 [12]	Azathioprine	2.5 mg/kg/day	104	34/0	Group 1 31.8 ± 4.3 Group 2 32.1 ± 5.3	Group 1 2.7 ± 2.6 Group 2 8.6 ± 6.3	34	Withdrawal due to eye disease
	Placebo			23/0	Group 1 30.5 ± 5.2 Group 2 31.5 ± 6.5	Group 1 5.2 ± 3.4 Group 2 6.9 ± 6.8	23	
Alpsoy, 2002 [13]	Systemic Interferon alpha-2a	6 × 10^6/3 times per week	12	16/7	32.82 ± 8.17	6.54 ± 5.70	23	Frequency and duration of each mucocutaneous lesion and articular symptom
	Placebo			11/10	31.89 ± 7.85	6.33 ± 5.83	21	
Hamuryudan, 1991 [22]	Topical alpha Interferon	1 × 10^5 U/g t.i.d.	24	NA	NA	NA	30	Number of oral ulcers
	Placebo			NA	NA	NA	31	
Melikoglu, 2005 [14]	Etanercept	50 mg/week	4	20/0	28.5 ± 5.3	2.8 ± 2.6	20	Suppression of the pathergy response and monosodium urate tests
	Placebo			20/0	30.8 ± 6.2	4.3 ± 3.2	20	
Hamuryudan, 1998 [15]	Thalidomide	100 mg/day	24	32/0	27.6 (25.7–29.4)	2.97 (2.05–3.89)	32	Complete remission of oral or genital ulcer
	Placebo			32/0	26.7 (24.8–28.6)	2.72 (2.18–3.26)	32	
	Thalidomide	300 mg/day	24	31/0	27.8 (25.9–29.6)	2.71 (2.11–3.33)	31	
	Placebo			32/0	26.7 (24.8–28.6)	2.72 (2.18–3.26)	32	
Matsuda, 2003 [16]	Rebamipide	300 mg/day	24	9/10	46.7 ± 14	8.9 ± 10.7	19	Number and pain of oral ulcers
	Placebo			5/11	44.3 ± 11.2	8.8 ± 8.3	16	
Sharquie, 2002 [17]	Dapsone	100 mg/day	12	16/4	30.9 (16–48)	NA	10	Number, size, duration and frequency of each mucocutaneous lesion
	Placebo						10	
Mat, 2006 [18]	Depot corticosteroids	40 mg methylprednisolone acetate i.m. every 3 week	27	20/21	31.7 ± 7	3.9 ± 4.7	41	Number of genital ulcers
	Placebo			22/22	29.4 ± 6	2.8 ± 3.3	44	
Hatemi, 2015 [19]	Apremilast	30 mg BID	12	16/39	34.3 Mean	4.92	55	Number of oral ulcers
	Placebo			18/38	34.7 Mean	5.72	56	
Alpsoy, 1999 [21]	Topical sucralfate	5 mL × 4 times/day	12	8/8	33 ± 9.3	9.9 ± 5.6	16	Frequency, healing time and pain of oral and genital ulcers
	Placebo			8/6	34.1 ± 5.3	8.8 ± 5.9	14	
Kılıc, 2009 [23]	Topical Interferon alpha	2000 IU/day	12	7/19	36 ± 9.4	NA	26	Efficacy on the total ulcer burden
	Topical Interferon alpha	1000 IU/day		11/20	37 ± 10.2	NA	31	
	Placebo			7/20	36 ± 8.6	NA	27	
Fani, 2012 [24]	Topical phenytoin syrup	2 teaspoon t.i.d.	1	8/22	38.77 ± 9.4	NA	30	Efficacy on oral ulcers
	Topical triamcinolone acetonide	0.1% triamcinolone acetonide ointment t.i.d.		8/22	35.4 ± 8.85	NA	30	
Ergun, 1997 [25]	Topical cyclosporine-A	70 mg per g of orobase	8	NA	36.5 ± 6.5	NA	12	Efficacy on oral ulcers
	Placebo			NA		NA	12	

Table 2
Efficacy of interventions for oral ulcers

Outcome	Intervention (*n*)	Comparator (*n*)	Effect	Number of events/mean values	Risk of bias
Improvement in ulcer score at 3 months [9]	Colchicine (*n* = 14)	Placebo (*n* = 14)	RR 0.75 (0.48 to 1.17)	14/14 vs 12/14	LOW
Number of oral ulcers during 2 years [10]	Colchicine (*n* = 30 men, 28 women)	Placebo (*n* = 30 men, 27 women)	Men MD 0.80 (−7.83 to 9.47) Women MD −5.73 (−12.6 to 1.16)	Men 25.7 ± 14 vs 24.9 ± 19.7 Women 15.6 ± 12.3 vs 21.3 ± 13.6	LOW
IBDDAM score at week 16 [11]	Colchicine (*n* = 136)	Placebo (*n* = 146)	MD −0.55 (−0.99 to 0.10)	1.83 ± 1.56 vs 2.4 ± 2.2	UNCLEAR
Numbers of patients with oral ulcers at 24 months [12]	Azathioprine (*n* = 34)	Placebo (*n* = 23)	RR 0.34 (0.12–0.99)	4/34 vs 8/23	UNCLEAR
Complete remission of oral ulcers at 3 months [13]	Systemic Interferon alpha-2-a (*n* = 23)	Placebo (*n* = 21)	RR 4.58 (0.23–90.3)	2/23 vs 0/21	UNCLEAR
Total number of oral ulcers at week 24 [22]	Topical alpha Interferon (*n* = 30)	Placebo (*n* = 31)	MD 1.50 (−10.43 to 13.43)	41.8 ± 24.5 vs 40.3 ± 23	UNCLEAR
Remission of oral ulcers at week 4 [14]	Etanercept (*n* = 20)	Placebo (*n* = 20)	RR 9 (1.25–64.6)	9/20 vs 1/20	UNCLEAR
Remission of oral and genital ulcers during 24 weeks at and between visits [15]	Thalidomide 100 mg/day (*n* = 32)	Placebo (*n* = 32)	RR 5 (0.25–100)	2/32 vs 0/32	LOW
Remission of oral and genital ulcers during 24 weeks at visits [15]	Thalidomide 100 mg/day (*n* = 32)	Placebo (*n* = 32)	RR 21 (1.28–343)	10/32 vs 0/32	LOW
Remission of oral and genital ulcers during 24 weeks at and between visits [15]	Thalidomide 300 mg/day (*n* = 31)	Placebo (*n* = 32)	RR 11.3 (0.65–196.9)	5/31 vs 0/32	LOW
Remission of oral and genital ulcers during 24 weeks at visits [15]	Thalidomide 300 mg/day (*n* = 31)	Placebo (*n* = 32)	RR 19.6 (1.19–322)	9/31 vs 0/32	LOW
Improvement of oral ulcers at 6 months [16]	Rebamipide (*n* = 19)	Placebo (*n* = 16)	RR 1.85 (0.81–4.21)	11/19 vs 5/16	UNCLEAR
Number of oral ulcers at week 12 [17]	Dapsone (*n* = 10)	Placebo (*n* = 10)	MD −2.70 (−3.75 to −1.65)	0.5 ± 0.8 vs 3.2 ± 1.5	UNCLEAR
Duration of oral ulcers at week 12 [17]	Dapsone (*n* = 10)	Placebo (*n* = 10)	MD −1.40 (−3.47 to 0.67)	7 ± 3 vs 8.4 ± 1.5	UNCLEAR
Frequency of oral ulcers at week 12 [17]	Dapsone (*n* = 10)	Placebo (*n* = 10)	MD −1 (−1.72 to −0.27)	0.7 ± 0.6 vs 1.7 ± 1	UNCLEAR
Number of oral ulcers during 27 weeks [18]	Depot corticosteroids (*n* = 41)	Placebo (*n* = 44)	MD 0 (−0.46 to 0.46)	1.8 ± 1 vs 1.8 ± 1.2	LOW
Number of oral ulcers at week 12 [19]	Apremilast (*n* = 55)	Placebo (*n* = 56)	MD −1.60 (−2.33 to 0.86)	0.5 ± 1 vs 2.1 ± 2.6	LOW
Complete remission of oral ulcers at week 12 [19]	Apremilast (*n* = 55)	Placebo (*n* = 56)	RR 2.48 (1.59–3.88)	39/55 vs 16/56	LOW
Pain of oral ulcers at week 12 (0–100) [19]	Apremilast (*n* = 55)	Placebo (*n* = 56)	MD −28.7 (−39.3 to −18)	−44.7 ± 24.3 vs −16 ± 32.5	LOW
Frequency of oral ulcers [20]	Benzathine penicillin + colchicine (*n* = 94)	Colchicine (*n* = 60)	MD −0.29 (−0.86 to 0.26)	1 ± 1.8 vs 1.3 ± 1.7	UNCLEAR
Number of oral ulcers [20]	Benzathine penicillin + colchicine (*n* = 94)	Colchicine (*n* = 60)	MD 0.10 (−0.20 to 0.40)	0.9 ± 1 vs 0.8 ± 0.9	UNCLEAR
Duration of oral ulcers [20]	Benzathine penicillin + colchicine (*n* = 94)	Colchicine (*n* = 60)	MD −0.20 (−1.29 to 0.89)	3.1 ± 3 vs 3.3 ± 3.6	UNCLEAR
Severity of oral ulcers [20]	Benzathine penicillin + colchicine (*n* = 94)	Colchicine (*n* = 60)	MD 0.2 (−0.07 to 0.47)	0.9 ± 0.9 vs 0.7 ± 0.8	UNCLEAR
Frequency of oral ulcers at week 12 [21]	Topical sucralfate (*n* = 16)	Placebo (*n* = 14)	MD −0.80 (−2.12 to 0.52)	3.56 ± 1.3 vs 4.36 ± 2.2	LOW
Pain of oral ulcers at week 12 [21]	Topical sucralfate (*n* = 16)	Placebo (*n* = 14)	MD −0.38 (−0.86 to 0.10)	0.69 ± 0.5 vs 1.07 ± 0.8	LOW
Healing time of oral ulcers at week 12 [21]	Topical sucralfate (*n* = 16)	Placebo (*n* = 14)	MD −1.09 (−2.61 to 0.43)	7.19 ± 1.9 vs 8.28 ± 2.3	LOW
Efficacy on oral ulcers at week 1 [24]	Topical Phenytoin Syrup (*n* = 30)	Topical triamcinolone acetonide (*n* = 30)	RR 0.62 (0.43–0.88)	16/30 vs 26/30	LOW

Table 3
Efficacy of interventions for genital ulcers

Outcome	Intervention (n)	Comparator (n)	Effect	Number of events/mean values	Risk of bias
Improvement in ulcer score at 6 months [9]	Colchicine ($n = 14$)	Placebo ($n = 14$)	RR 1 (0.37–2.70)	5/14 vs 5/14	LOW
Number of genital ulcers during 2 years [10]	Colchicine ($n = 30$ men, 28 women)	Placebo ($n = 30$ men, 27 women)	Men MD −1.10 (−4.10 to 1.90) Women MD −2.50 (−4.24 to −0.75)	Men 2.4 ± 4.3 vs 3.5 ± 7.2 Women 0.1 ± 0.5 vs 2.6 ± 4.6	LOW
IBDDAM score at week 16 [11]	Colchicine ($n = 90$)	Placebo ($n = 98$)	MD −0.22 (−0.4 to 0.003)	0.46 ± 0.64 vs 0.68 ± 0.89	UNCLEAR
Number of patients with genital ulcers at 24 months [12]	Azathioprine ($n = 34$)	Placebo ($n = 23$)	RR 0.08 (0.01–0.63)	1/34 vs 8/23	UNCLEAR
Remission of genital ulcers at week 4 [14]	Etanercept ($n = 20$)	Placebo ($n = 20$)	RR 0.82 (0.59–1.16)	14/20 vs 17/20	LOW
Number of genital ulcers at week 12 [17]	Dapsone ($n = 10$)	Placebo ($n = 10$)	MD −0.50 (−1.02 to −0.02)	0.1 ± 0.3 vs 0.6 ± 0.8	UNCLEAR
Number of genital ulcers at week 27 [18]	Depot corticosteroids ($n = 41$)	Placebo ($n = 44$)	MD 0 (−0.17 to 0.17)	0.3 ± 0.4 vs 0.3 ± 0.4	LOW
Complete remission of genital ulcers at week 12 [19]	Apremilast ($n = 10$)	Placebo ($n = 6$)	RR 2 (0.90–4.45)	10/10 vs 3/6	LOW
Frequency of genital ulcers at week 12 [21]	Topical sucralfate ($n = 14$)	Placebo ($n = 13$)	MD 0.02 (−0.63 to 0.67)	1.31 ± 0.9 vs 1.29 ± 0.9	LOW
Healing time of genital ulcers at week 12 [21]	Topical sucralfate ($n = 14$)	Placebo ($n = 13$)	MD −3.92 (−9.02 to 1.18)	14 ± 3.9 vs 18 ± 8.6	LOW
Healing time of genital ulcers at week 4 [34]	Pimecrolimus cream ($n = 45$)	Placebo ($n = 45$)	MD −10 (−14.68 to −5.32)	10.7 ± 9.23 vs 20.7 ± 13.1	UNCLEAR
Healing time of genital ulcers at week 4 [35]	Pimecrolimus cream + colchicine ($n = 38$)	Colchicine ($n = 38$)	MD −0.52 (−1.3 to 0.25)	4.27 ± 1.51 vs 4.79 ± 1.88	HIGH
Pain duration of genital ulcers at week 4 [35]	Pimecrolimus cream + colchicine ($n = 38$)	Colchicine ($n = 38$)	MD −1.3 (−1.28 to −0.88)	4.2 ± 0.5 vs 5.5 ± 1.2	HIGH
Frequency of genital ulcers [20]	Benzathine penicillin + colchicine ($n = 94$)	Colchicine ($n = 60$)	MD −0.30 (−0.53 to −0.07)	0.1 ± 0.7 vs 0.4 ± 0.7	UNCLEAR
Number of genital ulcers [20]	Benzathine penicillin + colchicine ($n = 94$)	Colchicine ($n = 60$)	MD −0.50 (−1.19 to 0.19)	0.3 ± 1.4 vs 0.8 ± 2.5	UNCLEAR
Duration of genital ulcers [20]	Benzathine penicillin + colchicine ($n = 94$)	Colchicine ($n = 60$)	MD −0.30 (−0.86 to 0.26)	1 ± 1.8 vs 1.3 ± 1.7	UNCLEAR
Severity of genital ulcers [20]	Benzathine penicillin + colchicine ($n = 94$)	Colchicine ($n = 60$)	MD −0.10 (−0.55 to 0.35)	1.6 ± 1 vs 1.7 ± 1.6	UNCLEAR

Table 4
Efficacy of interventions for skin lesions

Outcome	Intervention (*n*)	Comparator (*n*)	Effect	Number of events/mean values	Risk of bias
Papulopustular lesions					
Improvement in papulopustular lesions at 6 months [9]	Colchicine ($n = 14$)	Placebo ($n = 14$)	RR 0.07 (0.24–1.86)	4/14 vs 6/14	LOW
Mean number of papulopustular lesions during 2 years [10]	Colchicine ($n = 30$ men, 28 women)	Placebo ($n = 30$ men, 27 women)	Men MD 2.60 (−1.65 to 6.85)	Men 15.7 ± 8.5 vs 13.1 ± 8.3	LOW
			Women MD −1.80 (−4.15 to 0.55)	Women 4.1 ± 3.5 vs 5.9 ± 5.2	
IBDDAM score at week 16 [11]	Colchicine ($n = 67$)	Placebo ($n = 73$)	MD −0.06 (−0.23 to 0.11)	0.47 ± 0.33 vs 0.53 ± 0.67	UNCLEAR
Numbers of patients with papulopustular lesions at 24 months [12]	Azathioprine ($n = 34$)	Placebo ($n = 23$)	RR 1.07 (0.80–1.45)	27/34 vs 17/23	UNCLEAR
Remission of papulopustular lesions at week 4 [14]	Etanercept ($n = 20$)	Placebo ($n = 20$)	RR 0.05 (0.05–5.08)	1/20 vs 2/20	LOW
Number of papulopustular lesions at week 27 [18]	Depot corticosteroids ($n = 41$)	Placebo ($n = 44$)	MD 0.10 (−0.17 to 0.37)	1.1 ± 0.7 vs 1 ± 0.6	LOW
Erythema nodosum					
Improvement in erythema nodosum at 6 months [9]	Colchicine ($n = 14$)	Placebo ($n = 14$)	RR 2 (0.20–19.6)	2/14 vs 1/14	LOW
Mean number of erythema nodosum lesions during 2 years [10]	Colchicine ($n = 30$ men, 28 women)	Placebo ($n = 30$ men, 27 women)	Men MD −1.30 (−3.70 to 1.12)	Men 0.7 ± 1.5 vs 2 ± 6.6	LOW
			Women MD −4.60 (−10 to 1.20)	Women 1.4 ± 3.9 vs 6 ± 14.9	
IBDDAM score at week 16 [11]	Colchicine ($n = 31$)	Placebo ($n = 35$)	MD −0.35 (−0.57 to −0.12)	0.26 ± 0.31 vs 0.61 ± 0.6	UNCLEAR
Remission of erythema nodosum lesions at week 4 [14]	Etanercept ($n = 20$)	Placebo ($n = 20$)	RR 3.40 (1.56–7.43)	20/20 vs 5/20	LOW
Number of erythema nodosum lesions at week 27 [18]	Depot corticosteroids ($n = 41$)	Placebo ($n = 44$)	MD −0.20 (−0.37 to −0.02)	0.1 ± 0.3 vs 0.3 ± 0.5	LOW
Frequency of erythema nodosum [20]	Benzathine penicillin + colchicine ($n = 94$)	Colchicine ($n = 60$)	MD −0.40 (−0.49 to −0.30)	0.1 ± 0.4 vs 0.5 ± 0.2	UNCLEAR
Number of erythema nodosum [20]	Benzathine penicillin + colchicine ($n = 94$)	Colchicine ($n = 60$)	MD −0.10 (−0.51 to 0.31)	0.4 ± 1.6 vs 0.5 ± 1	UNCLEAR
Duration of erythema nodosum [20]	Benzathine penicillin + colchicine ($n = 94$)	Colchicine ($n = 60$)	MD −1 (−1.55 to −0.44)	0.1 ± 0.8 vs 1.1 ± 2.1	UNCLEAR
Severity of erythema nodosum [20]	Benzathine penicillin + colchicine ($n = 94$)	Colchicine ($n = 60$)	MD −0.10 (−0.18 to −0.01)	0.1 ± 0.4 vs 0.2 ± 0.1	UNCLEAR

RR: risk ratio; MD: mean difference.

	Overarching principles and recommendations	Level of evidence*	Strength of recommendation †	Level of agreement
10. Joint involvement	Colchicine should be the initial treatment in BS patients with acute arthritis. Acute monoarticular disease can be treated with intra-articular glucocorticoids. Azathioprine, interferon-alpha or TNF-alpha inhibitors should be considered in recurrent and chronic cases.	IB	A	9.0±1.0

- Akut artritili Behçet hastalarında:

1. İlk tedavi kolşisin olmalı
2. Bazı üyeler kolşisin ile kontrol edilemeyen hastalarda sürekli düşük doz KS kullanımını önerirken bazıları AZA, IFN-a veya TNFi kullanımı lehine görüş bildirmişler
3. Akut ataklarda İA KS yararlı olabilir ancak sıklıkla akut ataklar 2-3 hafta içinde kendini sınırlayacağı için çoğu vakada İA KS gerekli olmayabilir

Table 5
Efficacy of interventions for arthritis

Outcome	Intervention (*n*)	Comparator (*n*)	Effect	Number of events/mean values	Risk of bias
Improvement in arthritis at month 6 [9]	Colchicine (1.5 mg/d) ($n = 5$)	Placebo ($n = 5$)	RR 3 (0.45–19.93)	3/5 vs 2/5	LOW
Complete response of arthritis at month 24 [10]	Colchicine (1-2 mg weight adjust) ($n = 30$ men, 28 women)	Placebo ($n = 30$ men, 27 women)	Men RR 1.53 (1.16–2.02) Women RR 1.47 (1.11–1.97)	Men 26/30 vs 17/30 Women 26/28 vs 17/27	LOW
Mean number of arthritis during 24 months [10]	Colchicine (1-2 mg weight adjust) ($n = 30$ men, 28 women)	Placebo ($n = 30$ men, 27 women)	Men MD −1.60 (−4.45 to 1.25) Women MD −2.10 (−4.39 to 0.19)	Men 2.8 ± 1.1 vs 4.4 ± 7.9 Women 0.3 ± 1.1 vs 2.4 ± 6.0	LOW
IBDDAM score at week 16 [11]	Colchicine (1 mg/d) ($n = 45$)	Placebo ($n = 45$)	MD −0.21 (−0.49 to 0.07)	0.59 ± 0.67 vs 0.8 ± 0.7	UNCLEAR
Number of patients with new arthritis episode during 24 months [12]	Azathioprine (2.5 kg/d) ($n = 34$)	Placebo ($n = 31$)	RR 0.13 (0.02–1.00)	1/34 vs 7/31	UNCLEAR
Complete response of arthritis at week 4 [14]	Etanercept ($n = 20$)	Placebo ($n = 20$)	RR 1.06 (0.88–1.26)	19/20 vs 18/20	LOW
Mean number of swollen joints at week 4 [14]	Etanercept ($n = 20$)	Placebo ($n = 20$)	MD −0.10 (−0.43 to 0.23)	0.1 ± 0.45 vs 0.2 ± 0.6	LOW
Mean number of arthritis during 27 weeks [18]	Depot corticosteroids (40 mg IM every 3 week) ($n = 41$)	Placebo ($n = 44$)	MD 0 (−0.15 to 0.15)	0.1 ± 0.4 vs 0.1 ± 0.3	LOW
Mean number of arthritis during 24 months [36]	Benzathine penicillin (1.2 MU IM every 3 week)-colchicine (0.5 mg t.i.d.) ($n = 60$)	Colchicine (0.5 mg t.i.d.) ($n = 60$)	MD −0.60 (−0.92 to −0.28)	0.2 ± 0.6 vs 0.8 ± 1.1	LOW
Total number of new arthritis attacks during 24 months [36]	Benzathine penicillin (1.2 MU IM every 3 week)-colchicine (0.5 mg t.i.d.) ($n = 22$)	Colchicine (0.5 mg t.i.d.) ($n = 24$)	RR 0.16 (0.02–1.26)	1/22 vs 7/24	LOW
Mean duration of arthritis attacks (months) [36]	Benzathine penicillin (1.2 MU IM every 3 week)-colchicine (0.5 mg t.i.d.) ($n = 13$)	Colchicine (0.5 mg t.i.d.) ($n = 49$)	MD −0.50 (−2.45 to 1.45)	8.9 ± 3.1 vs 9.4 ± 3.5	LOW
Number of patients with arthritis during 24 weeks [15]	Thalidomide (100 mg/d) ($n = 32$)	Placebo ($n = 32$)	RR 1.25 (0.37–4.23)	5/32 vs 4/32	LOW
Number of arthritis episodes during 24 weeks [15]	Thalidomide 100 mg/day ($n = 32$)	Placebo ($n = 32$)	RR 0.64 (0.28–1.43)	7/32 vs 11/32	LOW
Number of patients with arthritis during 24 weeks [15]	Thalidomide (300 mg/d) ($n = 31$)	Placebo ($n = 32$)	RR 0.52 (0.10–2.62)	2/31 vs 4/32	LOW
Number of arthritis episodes during 24 weeks [15]	Thalidomide (300 mg/d) ($n = 31$)	Placebo ($n = 32$)	RR 0.38 (0.13–1.05)	4/31 vs 11/32	LOW
Number of patients with persistence of arthritis during 3 weeks [37]	Azapropazone (300 mg t.i.d.) ($n = 28$)	Placebo ($n = 29$)	RR 1.29 (0.74–2.25)	15/28 vs 12/29	UNCLEAR
Number of patients with new arthritis attacks during 3 weeks [37]	Azapropazone (300 mg t.i.d.) ($n = 28$)	Placebo ($n = 29$)	RR 0.69 (0.28–1.69)	6/28 vs 9/29	UNCLEAR
Mean duration of arthritis attacks (days) [37]	Azapropazone (300 mg TID) ($n = 28$)	Placebo ($n = 29$)	MD 2.90 (−1.11 to 6.91)	19.9 ± 8.3 vs 17 ± 8.2	UNCLEAR

RR: risk ratio; MD: mean difference; TID: three times a day.

2. Eye involvement	Management of uveitis of BS requires close collaboration with ophthalmologists with the ultimate aim of inducing and maintaining remission. Any patient with BS and inflammatory eye disease affecting the posterior segment should be on a treatment regime such as azathioprine (IB), cyclosporine-A (IB), interferon-alpha (IIA) or monoclonal anti-TNF antibodies (IIA). Systemic glucocorticoids should be used only in combination with azathioprine or other systemic immunosuppressives (IIA).	IB/IIA	A/B	9.5±0.6
	Patients presenting with an initial or recurrent episode of acute sight-threatening uveitis should be treated with high-dose glucocorticoids, infliximab or interferon-alpha. Intravitreal glucocorticoid injection is an option in patients with unilateral exacerbation as an adjunct to systemic treatment.	IIA	B	9.4±0.7

- Göz tutulumu:

1. Bazı uzmanlar TNFi ile AZA veya CsA kulanımın sonuçları iyileştirdiğini düşünse de retrospektif bir çalışmada herhangi bir katkı bulunmamış
2. Gevokizumab ve SEC çalışmaları pimer sonlanımını karşılamamaış
3. İntravitreal KS akut alevlenmelerde yalnızca adjunctive olabilir
4. Anti-inflamatuvar etkisi olmasa bile (konsensasyon, koagüle hemraji, retinal detachment), vitro-retinal-epiretinal membran vb) komplikasyon halinde vitrektomi yapılabilir
5. 2 yıl AZA+TNFi ile remisyonda olan hastalarda ilacın kesilmesi denenmiş

3. Isolated anterior uveitis	Systemic immunosuppressives could be considered for those with poor prognostic factors such as young age, male sex and early disease onset.	IV	D	9.0±0.8

- İzole AAU:

1. Topikal tedavi edilebilir
2. Ancak bazı AAU hastaları şiddetli hastalık (hipopiyonlu AAU) geliştirebilir ve bazıları zaman içinde post üveit geliştirebilir
3. Genç erkekler, hastalığın başlangıcında genç yaşta olanlar post üveit için riskli olabilir
4. Bu hastalarda AZA gündeme gelebilir (yeterli kanıt yok)

TABLE 2 Efficacy of randomized controlled trials for eye involvement in Behçet's syndrome

Outcomes	Intervention (*n*)	Comparator (*n*)	Effect (95% CI)	Number of events/mean values (s.d.)	Risk of bias
Withdrawal due to eye disease [7]	AZA (Group 1: 12, group 2: 25)	PBO (Group 1: 13, group 2: 23)	[a]Group 2 RR 0.15 (0.02, 1.18)	Group 2 *vs* PBO (0/25 *vs* 6/23)	Unclear
Visual acuity at year 2 [7]			Group 2 MD −0.91 (−2.10, 0.28)	Group 2 *vs* PBO 0.17 (1.39)[b] *vs* 1.08 (2.59)[b]	
Hypopyon uveitis episode [7]			Group 2 RR 0.06 (0.01, 0.43)	Group 2 *vs* PBO (1/25 *vs* 15/23)	
Development of new eye disease [7]			Group 1 RR 0.14 (0.02, 0.93)	Group 1 *vs* PBO (1/12 *vs* 8/13)	
Improvement in frequency of ocular attack [8]	CSA + Colch (46)	Colch alone (46)	RR 2.47 (1.68, 3.64)	42/46 *vs* 17/46	Unclear
Improvement in severity of ocular attack [8]			RR 2.11 (1.44, 3.10)	38/46 *vs* 18/46	
Mean number of ocular attacks [9]	CSA (12)	CYC (11)	MD −0.14 (−0.34, 0.06)	0.48 (0.28) vs 0.62 (0.22)	High
Visual acuity at 6 month [9]			MD 2.99 (0.58, 5.39)	6.82 (2.98) *vs* 4.14 (3.09)	
Worsening of ocular condition [10]	CSA (18)	CTr (18)	RR 0.25 (0.06, 1.02)	2/18 *vs* 8/18	High
Visual acuity improvement [11]	RTX+ MTX +CS (10)	CYC+ AZA + CS (10)	RR 0.67 (0.14, 3.17)	2/10 *vs* 3/10	High
ME improvement [11]			RR1.50 (0.87, 2.59)	9/10 *vs* 6/10	
PU improvement [11]			RR 0.86 (0.45, 1.64)	6/10 *vs* 7/10	
RV improvement [11]			RR 1.17 (0.61, 2.23)	7/10 vs 6/10	
TADAI [11]			MD −5.10 (−21.01, 10.81)	34.7 (16.7) *vs* 39.8 (19.5)	
Ocular attack [12]	DAC+ std IS (9)	PBO (std IS) (8)	RR1.33 (0.58, 3.07)	6/9 *vs* 4/8	Unclear
Tapering IS [12]			RR 0.30 (0.08, 1.07)	2/9 *vs* 6/8	
Ocular attack [13]	SEC (q2wk) (39) SEC (q4wk) (40)	PBO (39)	MD 0.0 (−9.9, 9.9) MD 3.80 (−7.41, 15.01)	7.7 (22.4) *vs* 7.7 (22.4) 11.5 (28.2) *vs* 7.7 (22.4)	Low
Change in IS score from baseline to week 24	SEC (q2wk) (39) SEC (q4wk) (40)		MD −1.67 (−3.84, 0.50) MD −2.97 (−5.0, −0.93)	−1.7 (4.9) *vs* −0.03 (4.9) −3 (4.3) *vs* −0.03 (4.9)	
N of pts those required prednisolone ⩽10 mg/day at month 10–12 [14]	PegIFN (36) (N of pts on >10 mg CS at baseline = 29)	PBO (36) (N of pts on >10 mg CS at baseline = 32)	RR 1.05 (0.72, 1.53)	19/29 *vs* 20 /32	High
Rate of ocular relapse at 1 year [14]	PegIFN (36) (No. of pts with ocular inv. = 13)	PBO (36) (No. of pts with ocular inv. = 19)	RR 1.17 (0.39, 3.55)	4/13 *vs* 5/19	
Remission [15]	IFN (13)	CSA (13)	RR 1.44 (1.01, 2.08)	13/13 *vs* 9/13	High
Switch between study drugs			RR 0.14 (0.02, 1.0)	1/13 *vs* 7/13	

[a]Group 1: patients without eye involvement; group 2: patients with eye involvement. [b]Snellen chart.; CTr: conventional treatment; DAC: daclizumab; IS: immunosuppressant; ME: macular oedema; PBO: placebo; PegIFN: pegylated IFN; PU: posterior uveitis; RTX: rituximab; RV: retinal vasculitis; SEC: secukinumab.

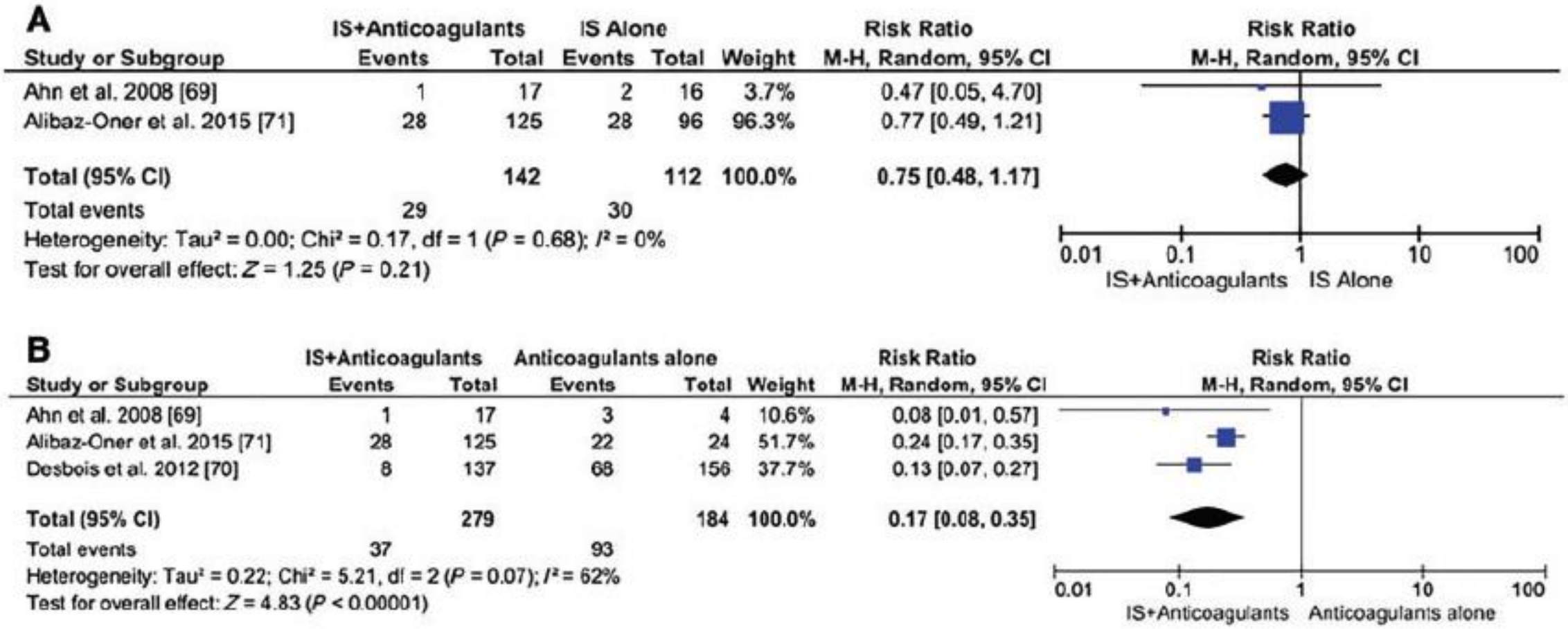
Table 3 Comparisons of observational studies of IFN-α and IFX in BS uveitis

Outcome	IFN (%)	IFX (%)
Onset of action	2–4 weeks	Within first 24 h
Visual acuity improvement	133/291 (46) (eyes)	71/94 (76) (patients)
Complete remission	149/233 (64)	123/216 (57)
Complete + partial remission	280/310 (90)	120/126 (95)
Sustained remission	90/127 (71)	24/54 (44)
CS cessation	95/144 (66)	28/84 (33)
Withdrawal due to side effect	17/310 (5.5)	18/332 (5)

BS: Behçet's syndrome; IFX: infliximab.

4.Acute deep vein thrombosis	For the management of acute deep vein thrombosis in BS, glucocorticoids and immunosuppressives such as azathioprine, cyclophosphamide or cyclosporine-A are recommended.	III	C	9.3±0.8

FIG. 2 Relapse risk of deep vein thrombosis



(A) Relapse risk of deep vein thrombosis with immunosuppressives and anticoagulants compared to anticoagulants alone (B) Relapse risk of deep vein thrombosis with immunosuppressives and anticoagulants compared to immunosuppressives alone.

5. Refractory venous thrombosis	Monoclonal anti-TNF antibodies could be considered in refractory patients. Anticoagulants may be added, provided the risk of bleeding in general is low and coexistent pulmonary artery aneurysms are ruled out.	III	C	8.7±0.8

- Refrakter VT:

1. Böyle hastaların tedavisinde data yok
2. Refrakter arteriel olgulardan projeksiyon ile TNFi kullanılabilir
3. Antikoagülanın IS tedaviye ilavesi relapsı önlemese de posttrombotik komplikasyonları azaltıyor (OR 3.8, 95% CI 1.04 to 14.1) olabilir. Bu nedenle task force AK aleyhine görüş bildirmemiş
4. Ancak özellikle arteriyel anevrizması olanlarda olmak üzere kanam riski konusunda dikkatli olunmalı (anevrizması olan hastaların hemen hepsinin öyküsünde DVT olduğundan bu hastalar zaman içinde anevrizma gelişimi açısından dikkatle izlenmelidir)

6. Arterial involvement	For the management of pulmonary artery aneurysms, high-dose glucocorticoids and cyclophosphamide are recommended. Monoclonal anti-TNF antibodies should be considered in refractory cases. For patients who have or who are at high risk of major bleeding, embolisation should be preferred to open surgery.	III	C	9.2±0.9
	For both aortic and peripheral artery aneurysms, medical treatment with cyclophosphamide and corticosteroids is necessary before intervention to repair. Surgery or stenting should not be delayed if the patient is symptomatic.	III	C	9.0±1.0

- Pulmoner arter anevrizması:

1. İlk sıra tedavisi yüksek doz KS (3 gün 1 gr IV pulse ardından 1 mg/kg/gün) ve Cy (aylık IV pulse)
2. Gözlemsel çalışmalar refrakter hastalarda TNFi (INF) etkili olabileceğini göstermiş
3. Cerrahinin mortalitesi yüksek

- Pulmoner veya periferik arter anevrizması tamir yöntemi (gerftleme, ligasyon, bypass vb):

1. Lokasyon, boyut ve cerrahin tecrübesine göre değişebilir
2. Ancak venzö greftin tromboz rsiki fazal olacağı için sentetik greftler tercih edilebilir

- Pulmoner veya periferik arter anevrizması tamir öncesi KS (RR 0.30; %95 CI 0.12-0.77) ve IS (RR 0.08; %95 CI 0.01-0.55) başlanması post op komplikasyon olasılığını anlamlı şekilde azaltabilir

7. Gastrointestinal involvement	Gastrointestinal involvement of BS should be confirmed by endoscopy and/or imaging. NSAID ulcers, inflammatory bowel disease and infections such as tuberculosis should be ruled out.	III	C	9.2±0.9

- GIS tutulumu:

1. En zor kısmı tanı koymak gibi görülüyor (karın ağrısı, ishal, intestinal ülser vb sıklıkla kullanılan NSAID'ler, IS alan hastalarda görülebilecek Tb vb GIS enfeksiyonları ile de ilişkili olabilir
2. Tanıyı doğrulamak özellikle IS'lerin etkisinin yıkıcı olabileceğinden enfeksiyon durumlarından uygunsuz tedaviye engel olmak için esansiyel

8. Refractory/ severe gastrointestinal involvement	Urgent surgical consultation is necessary in cases of perforation, major bleeding and obstruction. Glucocorticoids should be considered during acute exacerbations together with disease-modifying agents such as 5-ASA or azathioprine. For severe and/or refractory patients, monoclonal anti-TNF antibodies and/or thalidomide should be considered.	III	C	8.8±0.9

- Reftakter/ciddi GIS tutulumunda:

1. Tedavi retrospektif/gözlemsel çalışmalara, kontrolsüz dataya dayanıyor
2. İlk tedavi tutulumun şiddetine göre değişir
3. KS, akut alevlenmelerde ülser iyileşmesine yardımcı olabilir (yüksek riskli hastalarda perforasyon riskini srtıracağı düşünülse de bu yönde kanıt yok)
4. Hafif vakalarda 5-ASA, daha ciddi vakalarda AZA kullanılabilir
5. Ciddi veya AZA'ya refrakter olgularda INF, ADA ve talidomid yararlı olabilir
6. Seçilmiş vakalarda talidomid+INF kullanılabilir (!)
7. Bir kohort çalışmasında 1/3 olgunun kanama, perforasyon veya obstrüksiyon ile cerrahi ihtiyacı olabileceğini göstermiş. Böyle hastalarda eş zamanlı IS kullanımı post op komplikasyon/nüsk oranını azaltıyor olabilir

9. Nervous system involvement	Acute attacks of parenchymal involvement should be treated with high-dose glucocorticoids followed by slow tapering, together with immunosuppressives such as azathioprine. Cyclosporine should be avoided. Monoclonal anti-TNF antibodies should be considered in severe disease as first-line or in refractory patients.	III	C	9.1±1.2
	The first episode of cerebral venous thrombosis should be treated with high-dose glucocorticoids followed by tapering. Anticoagulants may be added for a short duration. Screening is needed for vascular disease at an extracranial site.	III	C	9.0±0.8

- Akut serebral venöz tromboz atağı tedavisinde:

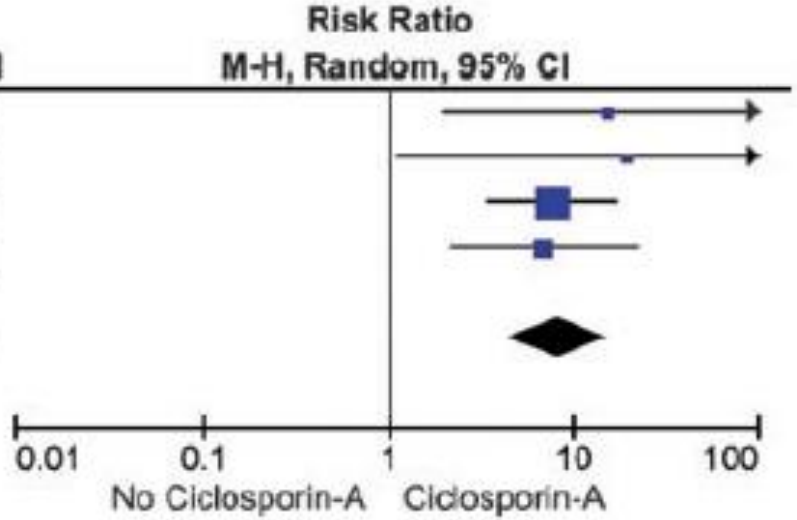
1. Task force hızlı remisyon için yüksek doz KS kullanımı konusunda görüş birliğine varmış

FIG. 3 Risk of nervous system involvement among BS patients using CSA

Study or Subgroup	Ciclosporin-A Events	Total	No Ciclosporin-A Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Akman-Demir *et al.* 2008 [105]	8	92	1	177	9.0%	15.39 [1.95, 121.19]
Kato *et al.* 2001 [102]	6	40	0	60	4.7%	19.34 [1.12, 334.06]
Kotake *et al.* 1999 [103]	12	47	9	270	58.6%	7.66 [3.42, 17.16]
Kötter *et al.* 2005 [104]	6	21	4	96	27.7%	6.86 [2.12, 22.18]
Total (95% CI)		**200**		**603**	**100.0%**	**8.26 [4.45, 15.32]**
Total events	32		14			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.98$, $df = 3$ ($P = 0.81$); $I^2 = 0\%$

Test for overall effect: $Z = 6.70$ ($P < 0.00001$)



BS: Behçet's syndrome.

Table 1 Characteristics of randomized controlled trials for major organ involvement in Behçet's syndrome

Authors (year)	Drug	Dose	Trial duration, weeks	Sex, M/F	Age, mean (s.d.), years	Disease duration, mean (s.d.), weeks	Number of patients	Primary outcome
Yazici (1990) [7]	AZA	2.5 mg/kg/day	96	96 M	[a]Group 1: 31.8 (4.3) Group 2: 32.1 (5.3)	Group 1: 0.8 (1.3) Group 2: 4.4 (4.2)	Group 1: 12 Group 2: 25	Withdrawal due to eye disease
	PBO	—			Group 1: 30.5 (5.2) Group 2: 31.5 (6.5)	Group 1: 0.7 (1.0) Group 2: 3.2 (3.6)	Group 1: 13 Group 2: 23	
Masuda (1989) [8]	CSA + Colch	10 mg/kg/day + 1 mg/day	16	NA	NA	NA	46	Improvement in frequency of ocular attack
	Colch alone	1 mg/day		NA	NA	NA	46	
Ozyazgan (1992) [9]	CSA	5 mg/kg/day	24	12 M	29 (6)	2.64 (1.68)	12	Mean number of ocular attacks
	CYC	1000 mg/month		6 M/5 F	32 (6)	2.39 (2.37)	11	Visual acuity at 6 month
BenEzra (1988) [10]	CSA	10 mg/kg/day → 5 mg/kg/day	144	NA	NA	NA	20	Worsening of ocular condition
	CTr	CS: 1.0–1.5 mg/kg/day CHL: 0.1–0.2 mg/kg/day		NA	NA	NA	CS = 17 CHL = 3	
Davatchi (2010) [11]	RTX+ MTX +CS	RTX: 1000 mg day 0–15; MTX: 15 mg/week; CS: 0.5 mg/kg/day	24	6 M/4 F	28.8 (11.3)	NA	10	TADAI score
	CYC+ AZA + CS	CYC: 1000 mg/month; AZA: 2–3 mg/kg/day; CS: 0.5 mg/kg/day		7 M/3 F	30.9 (12.0)	NA	10	
Buggage (2007) [12]	DAC+ std IS	1 mg/kg Every 2 weeks for 6 weeks	Median 15 month (1–34 month)	4 M/5 F	32.6 (13.9)	NA	9	Number of ocular attacks
	PBO (std IS)	NA		4 M/4 F	33.4 (17.0)		8	Immunosuppressive tapering
Dick (2013) [13]	SEC	300 mg q2w or q4w	24	q2w = 27 M/12 F q4w = 29 M/11 F	q2w: 36.2 (11.0) q4w: 34.0 (11.9)	NA	q2w: 39, q4w: 40	Number of ocular attacks
	PBO	NA		24 M/15 F	32.5 (10.3)	NA	39	
Lightman (2015) [14]	PegIFN	0.3 μg/kg/week for 26 weeks	52	14 M/22 F	38.9 (8.4)	Median (IQR) 7 (4–11)	25	Number of patients who required prednisolone ⩽10mg/day at month 10–12
	PBO	NA		16 M/20 F	38.9 (8.5)	Median (IQR) 10 (6–15)	25	
Kötter (2015) [15]	IFN	3–9 MU/day → 3 MU 3/7	31	NA	NA	NA	13	Remission of eye involvement
	CSA	3–5 mg/kg		NA	NA	NA	13	

Table 2 Research agenda

Eye involvement	Head-to-head trial comparing interferon-alpha to TNFis
	Controlled trials with IL-1 and IL-6 blockers
	Controlled trials assessing the comparative efficacy and safety of different TNFis
	Determining how long TNFis or interferon-alpha should be continued after remission is obtained
	Defining remission regarding a decision to switch to a maintenance therapy or considering treatment discontinuation for eye involvement
	Controlled trials determining whether glucocorticoids reduce the efficacy of interferon-alpha
Vascular involvement	Controlled trials to assess the efficacy and safety of anticoagulation for preventing relapses of venous thrombosis, post-thrombotic syndrome and recurrent arterial occlusive events
	Observational studies to identify individual differences (saccular/diffuse fusiform/large vs small) that guide the choice of surgical intervention
	Determining the optimal dose and duration of immunosuppressives after surgical intervention for peripheral artery aneurysms
	Determining the optimal treatment of postoperative recurrent anastomotic aneurysms (extra-anastomosis bypass vs local aneurysm repair)
	Determining the optimal management of intracardiac thrombosis
Nervous system involvement	Controlled studies for determining the optimal management of initial, refractory and recurrent parenchymal nervous system involvement and cerebral venous thrombosis
	Determining the role of MRI and other laboratory tests in making treatment decisions and follow-up of patients with nervous system involvement
Gastrointestinal system involvement	Controlled studies for determining the optimal management of initial, refractory and recurrent gastrointestinal system involvement
	Determining the role, optimal dose and duration of corticosteroids in acute relapses and whether they increase the risk of perforation
	Determining whether a control colonoscopy is needed in patients with clinical remission and the optimal timing for control colonoscopy
Overall	Controlled trials to assess the benefit of concomitant immunosuppressive use with TNFis
	Controlled trials assessing the efficacy of treatment modalities for patient important outcomes such as fatigue

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