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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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Conclusion. The majority of studies related to major organ involvement that informed the updated EULAR recommendations for the management of BS were observational studies.

Key words: Behçet's syndrome, treatment, eye involvement, uveitis, vascular involvement, nervous system involvement, gastrointestinal involvement

Rheumatology key messages

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

Introduction

Behçet's syndrome (BS) is a multisystem vasculitis that has a relapsing and remitting course. The main goal of management is to prevent relapses and to suppress inflammation rapidly for major organ involvement that may cause damage and even be fatal.

A substantial amount of new data was published on the management of BS, especially with biologics, over the past years. This led to the update project of the EULAR recommendations for the management of Behçet's disease, now termed Behçet's syndrome, as explained in the recommendations manuscript [1]. This article reports the results of the systematic review (SR) and meta-analyses, when possible, that formed the base for updating the recommendations on major organ involvement including eye, vascular, nervous and gastrointestinal system involvement.

Methods

The protocol for this SR was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42015027033. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines [2]. The electronic databases that were searched, the keyword combinations that were used, eligibility criteria, study selection and data collection process are provided in the supplementary data, section 'Methods of systematic literature review', available at *Rheumatology* online. Risk of bias was assessed using the Cochrane risk of bias assessment tool [3] for randomized controlled trials (RCTs) and the Newcastle-Ottawa Scale for cohort and case–control studies [4].

Data analysis

A meta-analysis was performed whenever more than one study was available for a specific Patients, Interventions, Comparison and Outcomes question. A random effects model was applied to pool overall effect estimate by using Review Manager 5.3. For continuous outcomes, we summarized data using the mean difference (MD) with 95% CI [5]. For dichotomous outcomes, we presented the risk ratio (RR) and its 95% CI [6]. A two-sided *P* value of 0.05 was considered as the threshold for statistical significance.

Results

The initial electronic database search yielded 3927 articles, and 161 studies met the inclusion criteria (Fig. 1). Study characteristics of the nine RCTs are summarized in Table 1 and the main outcomes are summarized in Table 2. The quality assessment and risk of bias assessment of these RCTs are provided as Supplementary Figs S1 and S2, available at *Rheumatology* online.

Eye involvement

Non-biologic agents

Among the 83 studies that reported on outcomes assessing eye involvement, nine were RCTs. AZA (2.5 mg/kg/day) was effective in decreasing the number of patients with hypopyon uveitis (RR 0.06, 95% CI 0.01, 0.43) and the development of new eye disease (RR 0.14, 95% CI 0.02, 0.93) [7]. None of the patients in the AZA group experienced serious adverse events whereas one patient died due to ruptured pulmonary artery aneurysm in the placebo group.

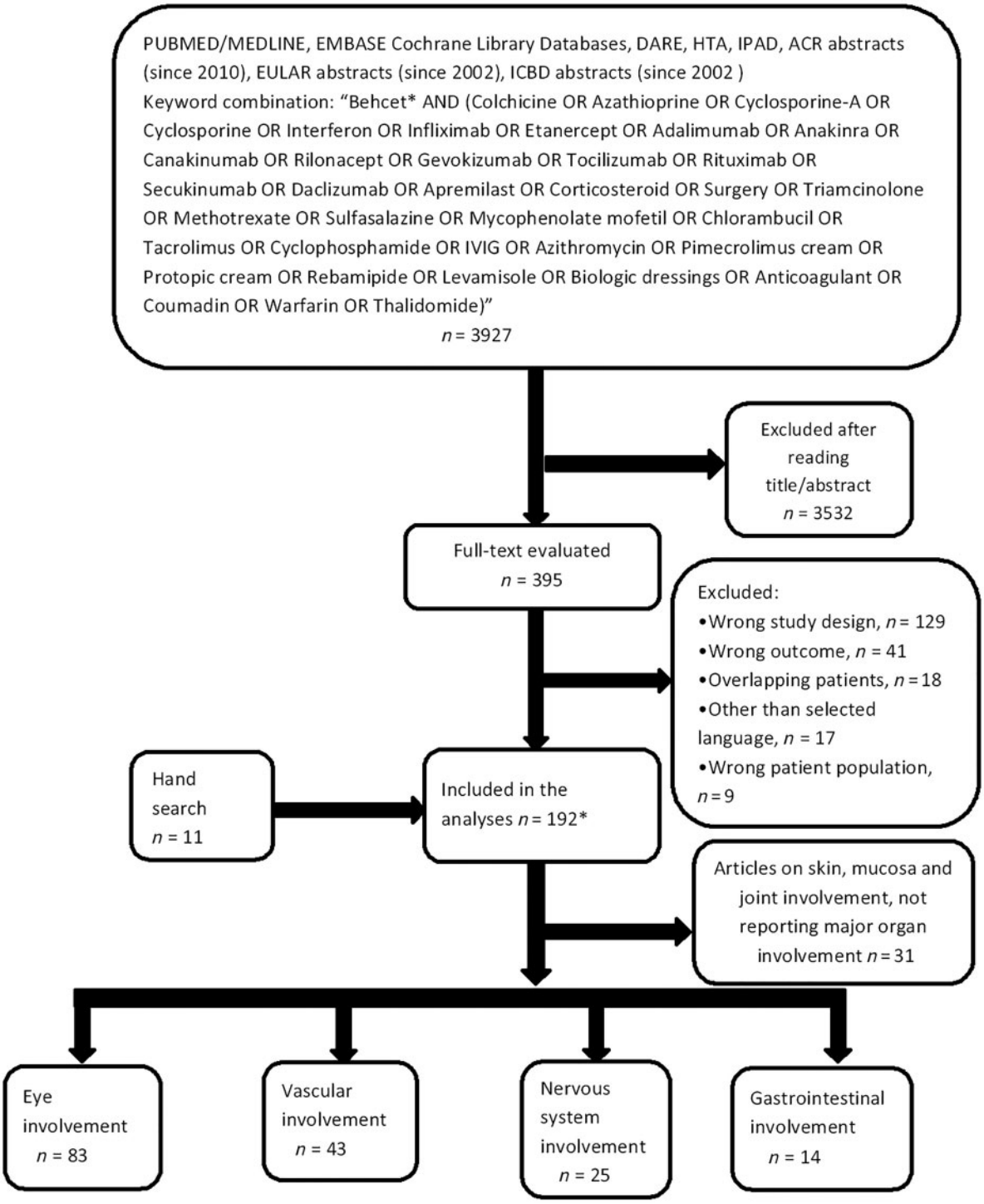
CSA was studied in three RCTs (details in the supplementary data, section 'Treatment for eye involvement', available at *Rheumatology* online) [8–10]. CSA decreased the frequency (RR 2.47, 95% CI 1.68, 3.64) [8] and severity of ocular attacks (RR 2.11, 95% CI 1.44, 3.10) [8]. There was also a trend for a decrease in worsening of ocular condition with CSA (RR 0.25, 95% CI 0.06, 1.02) [10]. Visual acuity at month 6 improved significantly more in the CSA group [MD 2.99 (95% CI 0.58, 5.39) lines on Snellen chart] [9]. Renal dysfunction was more frequent in the CSA group (RR 5.50, 95% CI 1.29, 23.45), but withdrawal of CSA was required in only one patient [8].

In a small observational study MTX improved visual acuity in 68% of patients [11]. However, the same group reported that this rate decreased to 46.5% in long term follow-up [12].

Biologic agents

The only prospective head to head RCT with a biologic agent was the single-blind INCYTOB study that compared IFN-α 3–9 MU 3 times per week with CSA 3–5 mg/kg

FIG. 1 Flow-chart of study selection process



*Some studies assessed more than one type of involvement.

(details in the supplementary data, section 'Treatment for eye involvement', available at *Rheumatology* online) [13]. IFN-α was superior to CSA in the number of patients who achieved ocular remission (RR 1.44, 95% CI 1.01, 2.08), visual acuity and posterior uveitis score.

The only other controlled study with a biologic was a non-randomized observational study that compared infliximab (5–10 mg/kg) with CSA (3–5 mg/kg) [14]. The number of ocular attacks was significantly lower [MD −0.80 (95% CI −1.50, −0.91) attacks during 6 months] and the number

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	

[a]Group 1: patients without eye involvement; group 2: patients with eye involvement. CHL: cholrambucil; CTr: conventional treatment; DAC: daclizumab; F: female; IQR: interquartile range; IS: immunosuppressant; M: male; PBO: placebo; PegIFN: pegylated IFN; RTX: rituximab; SEC: secukinumab; TADAI: Total Adjusted Disease Activity Index.

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)	PBO (39)	MD 0.0 (−9.9, 9.9)	7.7 (22.4) *vs* 7.7 (22.4)	Low
	SEC (q4wk) (40)		MD 3.80 (−7.41, 15.01)	11.5 (28.2) *vs* 7.7 (22.4)	
Change in IS score from baseline to week 24	SEC (q2wk) (39)		MD −1.67 (−3.84, 0.50)	−1.7 (4.9) *vs* −0.03 (4.9)	
	SEC (q4wk) (40)		MD −2.97 (−5.0, −0.93)	−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.

of patients achieving complete remission was significantly higher in the infliximab arm (RR 1.83, 95% CI 1.07, 3.12). There were no differences between infliximab and CSA in improvement of visual acuity (RR 1.05, 95% CI 0.94, 1.17).

There were no studies comparing infliximab and IFN-α. However several open label uncontrolled studies and retrospective case series had studied the efficacy of both agents (details in the supplementary data, section 'Treatment for eye involvement', available at *Rheumatology* online) [15–51]. Remission rates were similar for infliximab and IFN-α, but the sustained remission rate was higher with IFN-α (71%) compared with infliximab (43%) among the seven studies with IFN-α [20, 26, 27, 31, 33, 36, 40] and six studies with infliximab [25, 29, 32, 47, 48, 50] that addressed this question (Table 3). The success rate for improving visual acuity was 76% for infliximab [22–24, 43] and 46% for IFN-α [20, 27, 35, 40]. However, it should be noted that there was heterogeneity in the reporting of visual acuity. Most of the infliximab studies reported the patient as the unit of measure whereas most of the IFN-α studies reported the involved eye as the unit of measure. CS cessation rate was higher in the IFN-α group (66%) [20, 26, 31, 40] when compared with infliximab (33%) [29, 42, 49].

A prospective observational study showed that infliximab is a rapidly acting agent when compared with methylprednisolone in suppressing ocular inflammation [39]. The effect of infliximab started within the first 24 h for suppressing ocular inflammation, as well as in decreasing anterior chamber cells, clearing retinal vasculitis and resolution of retinitis and cystoid macular oedema [17, 23, 32, 39]. There were no studies that specifically explored the time of onset of action with IFN-α but three open studies indicated that retinal infiltrates resolved within 2 weeks and infiltration of anterior chamber, vasculitis and macular oedema resolved within 4 weeks with IFN-α treatment [15, 20, 27].

Most frequent adverse events were infections including tuberculosis with infliximab and flu-like symptoms, depression, leukopenia, thrombocytopenia, alopecia and transaminase elevations with IFN-α.

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.

Adalimumab was evaluated in patients with non-infectious uveitis in a RCT [52]. This study included BS patients but their results were not reported separately and were not provided by the study sponsor with the explanation that the study was not powered to detect the effect in uveitis of differing aetiologies and it would be difficult and inaccurate to make any inferences from these data. Based on a few case series and reports, adalimumab seems to improve visual acuity [51, 53–55].

Pegylated IFN-α, secukinumab, daclizumab and gevokizumab did not meet the primary endpoints for uveitis compared with placebo in four RCTs (details in the supplementary data, section 'Treatment for eye involvement', available at *Rheumatology* online) [56–59].

Rituximab (RTX) in combination with MTX and prednisolone was compared with cytotoxic combination group using CYC, AZA and prednisolone in a single-blind trial in 20 patients [60]. Although there was a significant difference in 'Total Adjusted Disease Activity Index' score favouring RTX in the *t* test conducted by the authors, when we calculated the RR and MD, the difference was not statistically significant for primary (MD −5.10, 95% CI −21.01, 10.81) and secondary endpoints (visual acuity: RR 0.67, 95% CI 0.14, 3.17; posterior uveitis: RR 0.86, 95% CI 0.45, 1.64; retinal vasculitis: RR 1.17, 95% CI 0.61, 2.23). In the RTX group, one patient had pneumonia, one patient had herpes zoster and one patient dropped out due to a severe infusion reaction. In the cytotoxic combination group, none of the patients experienced severe adverse events.

Tocilizumab was reported in three case reports including four patients [61–63]. Visual acuity improved in two patients, macular oedema improved in two patients and one patient did not benefit from tocilizumab.

Intravitreal triamcinolone treatment, which may be used in addition to systemic immunosuppressives in severe patients, was assessed in five studies that included 86 patients (96 eyes) [64–68]. Improvement in visual acuity was observed in 54%. However complications were frequent (49%), with cataracts in 36%, increased intraocular pressure in 43% and glaucoma in 9% of the patients.

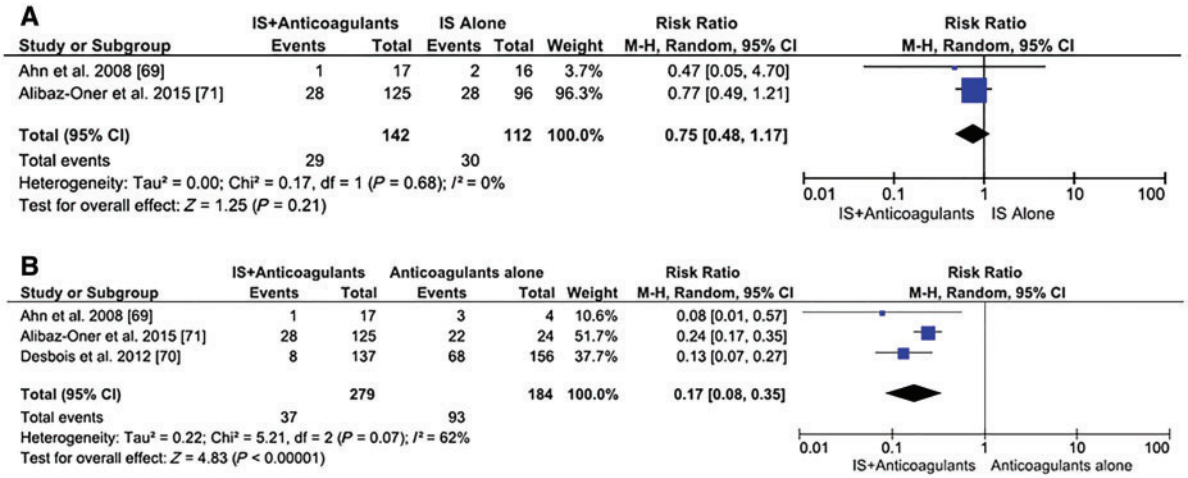
Vascular involvement

Venous thrombosis

There were three retrospective studies that reported on the efficacy of immunosuppressives and anticoagulants for preventing relapses of deep vein thrombosis in BS patients (see supplementary data, section 'Treatment for vascular involvement', available at *Rheumatology* online) [69–71]. We pooled these three studies to obtain an estimate of the efficacy of immunosuppressives and anticoagulants in preventing relapses. Meta-analysis of these studies showed that immunosuppressives significantly reduced the relapse risk (RR 0.17, 95% CI 0.08, 0.35) whereas anticoagulants did not (RR 0.75, 95% CI 0.48, 1.17) (Fig. 2). Bleeding occurred in 2.4% and 4.5% of the anticoagulated patients in two of these studies [70, 71].

One retrospective study looked at the risk of post-thrombotic syndrome (PTS) among BS patients who

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.

experienced deep vein thrombosis and suggested that not having used anticoagulants in addition to immunosuppressives seems to increase the risk of PTS (odds ratio 3.8, 95% CI 1.04, 14.1) [72]. However this finding was not supported by a more recent study, which did not report a significant effect of anticoagulation for preventing PTS [73].

Intracardiac thrombosis

A small study that compared the use of immunosuppressives together with anticoagulants ($n = 9$) to immunosuppressives alone ($n = 12$) for intracardiac thrombosis showed no difference (RR 1.29, 95% CI 0.91, 1.82) [74].

Pulmonary artery aneurysms and thrombosis

Two retrospective studies evaluated the mortality rate in BS patients with pulmonary artery involvement treated with CYC compared with other interventions (surgery or AZA and CSs) (details in Supplementary Table S1, available at *Rheumatology* online) [75, 76]. In the first study 6 out of 17 patients in the CYC group and all patients ($n = 5$) in the other interventions group died (RR 0.35, 95% CI 0.19, 0.67). In the second study, one patient (25%) in the CYC group and all patients ($n = 5$) in the other intervention group died (RR 0.25, 95% CI 0.05, 1.36).

Mortality rate with embolization and open surgery during emergency pulmonary haemorrhage was reported in retrospective series. Three studies including a total of 78 patients reported on emergency embolization in seven (9%) BS patients with pulmonary haemorrhage and four of them died [77–79]. Mortality rate with open surgery was reported in three other studies including 79 patients with pulmonary artery aneurysms [75, 76, 79]. Eight (10%) patients had open surgery and six of them died within the first month after surgery.

Infliximab was tried in 13 BS patients who were refractory to CYC and 11 had a good response [80]. In four patients, infliximab was stopped due to remission but two of them relapsed after cessation. In two patients infliximab had to be stopped due to tuberculosis and aspergillosis.

Peripheral artery aneurysms

Unlike pulmonary arteries, surgical intervention is usually required for peripheral artery aneurysms. Perioperative use of immunosuppressives with or without CSs is an important issue that was assessed in retrospective studies (see supplementary data, section 'Treatment for vascular involvement', and Supplementary Table S1, available at *Rheumatology* online) [78, 81, 82]. Immunosuppressives and CSs decreased postoperative complication rate significantly when compared with no medical treatment [RR 0.08 (95% CI 0.01, 0.55) and 0.30 (95% CI 0.12, 0.77), respectively] [78, 82].

The possible types of interventions in such patients are endovascular graft, bypass surgery, ligation and graft interposition. Peripheral arterial ligation was reported in four retrospective series [78, 83–85]. Among a total of 20 patients, relapses occurred in five and death in one. Bypass was performed in overall 32 patients [78, 83, 85–87]. Relapses occurred in 11 (34%), occlusion in five (16%) and death in six (14%) patients. Graft interposition was performed in overall 48 patients.[83–85, 87, 88] Fourteen (29%) patients experienced graft occlusion, 13 (27%) relapsed and seven (15%) died.

Nervous system involvement

Parenchymal involvement

No RCTs were available for the treatment of nervous system involvement in BS. In one retrospective study, patients who used CYC had a trend for a lower relapse rate compared with AZA during the first year (RR 0.62, 95% CI 0.38, 1.01). However, this difference was not observed at

the 5th, 7th and 10th years (see supplementary data, section 'Treatment for neurologic involvement', available at *Rheumatology* online) [89]. In another retrospective study, adding CYC to CSs did not provide additional benefit to CSs alone [90]. This is interesting since CYC is used as first line in other CNS vasculitides.

Case series reported the efficacy of infliximab in the management of patients with parenchymal involvement. In a large published case series, it was shown that in patients with NBS who had ongoing clinical relapses on single or multiple immunosuppressives, a switch to infliximab was beneficial in preventing further relapses and stabilized disability [91]. It is of interest that in the same centre among 74 BS patients without nervous system involvement, who were put on infliximab for either arterial or eye involvement because of failure of other immunosuppressives, none had developed nervous system involvement at the time of last follow-up. The efficacy of infliximab for patients with severe nervous system involvement and resistance to standard immunosuppressive regimens was also shown in another recent case series. Collectedly, 56 out of 60 patients had a good clinical response [37, 51, 91–94]. Furthermore, infliximab showed a CS sparing effect and a rapid onset of action. Two patients (3.3%) stopped infliximab due to adverse events and in two patients serious adverse events were reported. Beneficial results were reported in case reports and case series with IFN-α, mycophenolate mofetil, tocilizumab, anakinra and MTX (see supplementary data, section 'Treatment for neurologic involvement', available at *Rheumatology* online) [95–101].

There were four studies that evaluated the risk of developing nervous system involvement among BS patients who use CSA (see supplementary data, section 'Treatment for neurologic involvement', available at *Rheumatology* online) [102–105]. A meta-analysis of these studies showed that the risk of developing nervous system involvement was significantly higher among BS patients who used CSA compared with those who did not (RR 8.26, 95% CI 4.45, 15.32) (Fig. 3).

Cerebral venous thrombosis

There were three retrospective studies evaluating the efficacy of CSs plus anticoagulants in the treatment of cerebral venous thrombosis [106–108]. Among a total of 80 patients, 74 (92.5%) showed a good response. Bleeding complications were reported in four patients (6.4%), but they recovered without sequelae. In a retrospective study involving 36 patients with cerebral venous thrombosis treated with CSs alone, a good response was observed in all [109].

Gastrointestinal system involvement

Non-biologic agents

Three retrospective studies reported on the efficacy of AZA and 5-ASA derivatives in the treatment of gastrointestinal involvement [110–112]. In the first study, the treatment outcome was evaluated in 16 patients with mild gastrointestinal involvement who initially received 5-ASA derivatives (3–4 g/day) and in 37 patients with active moderate-severe gastrointestinal involvement who initially received AZA (2–2.5 mg/kg/day). Ten patients (62.5%) in the 5-ASA group and 24 patients in the AZA group (65%) achieved complete clinical and endoscopic remission without relapse during a mean follow-up of 89.3 (64.5) months and 68.6 (43.6) months, respectively. No withdrawals due to adverse events were reported. In the second study, the cumulative relapse rates at 1, 3, 5 and 10 years among 143 patients who achieved remission with 5-ASA compounds (3–4 g/day) for at least 6 months were 8.1%, 22.6%, 31.2% and 46.7%, respectively. In the third study among 39 patients who achieved remission with first line AZA, the cumulative relapse rates were 5.8%, 28.7%, 43.7% and 51.7% at 1, 2, 3 and 5 years, respectively.

A SR and case series reported on thalidomide use in a total of 19 BS patients with refractory gastrointestinal involvement [113]. Clinical remission was achieved in 84%.

Postoperative CS use was found to be associated with higher re-operation rates in a retrospective study (hazard ratio 2.85, 95% CI 1.21, 6.75) [114]. Thiopurine decreased post-operative recurrences compared with 5-ASA (RR 0.56, 95% CI 0.33, 0.95), but not the rates of reoperation, readmission, and death [115]. Whether this is associated with thiopurine being prescribed to more severe patients was not assessed.

Biologic agents

Five case series reported on the use of infliximab (5 mg/kg at week 0, 2, 6 and then every 6–8 weeks) for gastrointestinal involvement refractory to conventional therapy [113, 116–119]. Among the total of 63 patients treated with infliximab, 34 (54%) obtained clinical remission. Safety data were available for 49 patients and one had stopped treatment due to an adverse event.

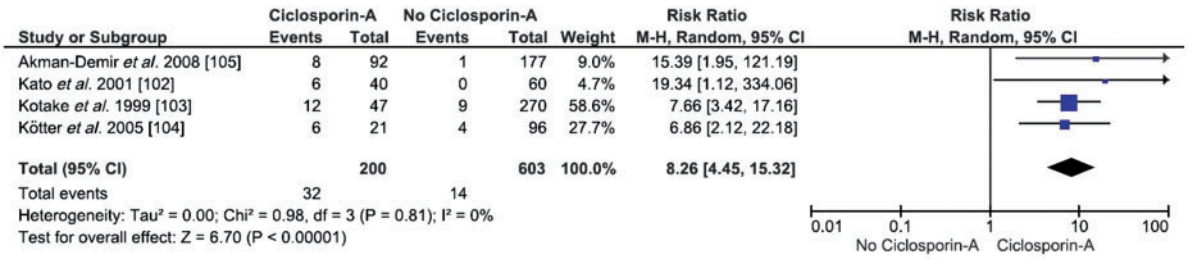
Adalimumab (160 mg at week 0, 80 mg at week 2, and 40 mg every other week thereafter) was evaluated in an open-label study in 20 BS patients with active gastrointestinal involvement refractory to CSs and/or standard immunosuppressive therapy [120]. After 24 weeks of treatment, clinical and endoscopic improvement was observed in nine patients (45%) and complete remission in four (20%). There were two withdrawals due to adverse events.

Etanercept (25 mg twice a week) was compared with conventional treatment (MTX 15 mg/week or prednisolone) in an open study [121]. Higher clinical remission rate (RR 1.74, 95% CI 1.22, 2.49) and healing of intestinal ulcers (RR 1.66, 95% CI 1.22, 2.25) was observed with etanercept. No withdrawals due to toxicity were reported.

Discussion

Major new findings of this SR compared with the one performed during the previous EULAR recommendations for BS were increased evidence for the use of biologics and especially TNF inhibitors in patients with all types of major organ involvement refractory to conventional

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



BS: Behçet's syndrome.

treatment modalities, review of surgical intervention types for arterial aneurysms and the meta-analysis showing that immunosuppressives rather than anticoagulants decreased the recurrence rate of deep vein thrombosis.

Although there are no RCTs comparing IFN-α and TNF inhibitors in BS patients with eye involvement, there were two studies that compared and showed superiority of these agents to CSA. There were several observational studies that assessed these two agents for eye involvement. Methodological differences in studies, such as the unit of measure, hamper the comparability of these findings. Moreover, the higher CS cessation rate may be related to the old contention that CSs may decrease the efficacy of IFN-α. An important issue that is operative in choosing one of these two agents is the difference in the adverse event profile. Increased risk of tuberculosis and other infections with infliximab and difficulty in tolerating IFN-α due to flu-like symptoms and depression are the major concerns.

Unfortunately, the three recent RCTs with promising biologic agents, pegylated IFN-α, secukinumab and gevokizumab, failed to meet their primary endpoints. Whether these agents are completely ineffective for BS patients or these disappointing results are related to trial design or the choice of outcomes is not clear.

Anticoagulation for the treatment of venous thrombosis in BS is a controversial issue. Our meta-analysis showed that there was no beneficial effect of adding anticoagulation to immunosuppressives when compared with immunosuppressives alone for preventing relapses. Two retrospective studies assessed whether anticoagulation may decrease PTS in BS patients who experienced venous thrombosis and showed conflicting results [72, 73]. Prospective studies are needed to ascertain the role of anticoagulation in preventing venous thrombosis relapses and PTS in patients with BS.

CSs are frequently used during the perioperative period in BS patients with the aim of decreasing postoperative complication risk related to the pathergy phenomenon induced by surgical intervention. It was previously observed that immunosuppressive and CS use decreased postoperative complication rate in BS patients undergoing surgery for peripheral artery aneurysms. Surprisingly one retrospective study suggested that CS use may increase recurrence risk in the post-operative period in BS patients with gastrointestinal involvement [114]. We think that this finding may be confounded by indication since those patients who required steroids in the postoperative period were probably those with more severe gastrointestinal involvement.

The main limitation of this SR was the rarity of RCTs and the lack of head-to-head trials with biologic agents. Another limitation was the heterogeneity in the methodology of studies including patient selection, unit of measure and the outcomes and outcome measures that were used.

In conclusion, we have updated the evidence on efficacy and safety of pharmacological and surgical treatment modalities for major organ involvement of BS. The majority of the studies were observational studies.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Hatemi G, Silman A, Bang D *et al*. EULAR recommendations for the management of Behçet disease. Ann Rheum Dis 2008;67:1656–62.

2 Shamseer L, Moher D, Clarke M *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;349:g7647.

3 Higgins JPT, Sterne JAC, eds. Chapter 8: assessing risk of bias in included studies. In: Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. London: The Cochrane Collaboration, 2011.

4 Wells GA, Shea B, O'Connell D *et al*. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in metaanalyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (March 2018, date last accessed).

5 Guyatt GH, Thorlund K, Oxman AD *et al*. GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles-continuous outcomes. J Clin Epidemiol 2013;66:173–83.

6 Guyatt GH, Oxman AD, Santesso N *et al*. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol 2013;66:158–72.

7 Yazici H, Pazarli H, Barnes CG *et al*. A controlled trial of azathioprine in Behçet's syndrome. N Engl J Med 1990;322:281–5.

8 Masuda K, Nakajima A, Urayama A *et al*. Double-masked trial of cyclosporin versus colchicine and long-term open study of cyclosporin in Behçet's disease. Lancet 1989;1:1093–6.

9 Ozyazgan Y, Yurdakul S, Yazici H *et al*. Low dose cyclosporin A versus pulsed cyclophosphamide in Behçet's syndrome: a single masked trial. Br J Ophthalmol 1992;76:241–3.

10 BenEzra D, Cohen E, Chajek T *et al*. Evaluation of conventional therapy versus cyclosporine A in Behçet's syndrome. Transplant Proc 1988;20(3 Suppl 4):136–43.

11 Davatchi F, Shahram F, Chams H *et al*. High dose methotrexate for ocular lesions of Behçet's disease. Preliminary short-term results. Adv Exp Med Biol 2003;528:579–84.

12 Davatchi F, Shams H, Shahram F *et al*. Methotrexate in ocular manifestations of Behçet's disease: a longitudinal study up to 15 years. Int J Rheum Dis 2013;16:568–77.

13 Kötter I, Vonthein R, Schoenfisch B *et al*. AB0545 interferon alpha2a versus cyclosporin A for the treatment of severe ocular Behçet's disease—a prospective, randomised, single blind, National Multicenter Trial (INCYTOB). Ann Rheum Dis 2016;75:1091.2.

14 Yamada Y, Sugita S, Tanaka H *et al*. Comparison of infliximab versus ciclosporin during the initial 6-month treatment period in Behçet disease. Br J Ophthalmol 2010;94:284–8.

15 Kötter I, Eckstein AK, Stubiger N, Zierhut M. Treatment of ocular symptoms of Behçet's disease with interferon alpha 2a: a pilot study. Br J Ophthalmol 1998;82:488–94.

16 Wechsler B, Bodaghi B, Huong DL *et al*. Efficacy of interferon alfa-2a in severe and refractory uveitis associated with Behçet's disease. Ocul Immunol Inflamm 2000;8:293–301.

17 Sfikakis PP, Theodossiadis PG, Katsiari CG, Kaklamanis P, Markomichelakis NN. Effect of infliximab on sight-threatening panuveitis in Behçet's disease. Lancet 2001;358:295–6.

18 Calguneri M, Ozturk MA, Ertenli I *et al*. Effects of interferon alpha treatment on the clinical course of refractory Behçet's disease: an open study. Ann Rheum Dis 2003;62:492–3.

19 Krause L, Turnbull JR, Torun N *et al*. Interferon alfa-2a in the treatment of ocular Adamantiades-Behçet's disease. Adv Exp Med Biol 2003;528:511–9.

20 Kotter I, Zierhut M, Eckstein A *et al*. Human recombinant interferon-alpha2a (rhIFN alpha2a) for the treatment of Behçet's disease with sight-threatening retinal vasculitis. Adv Exp Med Biol 2003;528:521–3.

21 Sfikakis PP, Kaklamanis PH, Elezoglou A *et al*. Infliximab for recurrent, sight-threatening ocular inflammation in Adamantiades-Behçet disease. Ann Intern Med 2004;140:404–6.

22 Ohno S, Nakamura S, Hori S *et al*. Efficacy, safety, and pharmacokinetics of multiple administration of infliximab in Behçet's disease with refractory uveoretinitis. J Rheumatol 2004;31:1362–8.

23 Lindstedt EW, Baarsma GS, Kuijpers RW, van Hagen PM. Anti-TNF-alpha therapy for sight threatening uveitis. Br J Ophthalmol 2005;89:533–6.

24 Abu El-Asrar AM, Abboud EB, Aldibhi H, Al-Arfaj A. Long-term safety and efficacy of infliximab therapy in refractory uveitis due to Behçet's disease. Int Ophthalmol 2005;26:83–92.

25 Tugal-Tutkun I, Mudun A, Urgancioglu M *et al*. Efficacy of infliximab in the treatment of uveitis that is resistant to treatment with the combination of azathioprine, cyclosporine, and corticosteroids in Behçet's disease: an open-label trial. Arthritis Rheum 2005;52:2478–84.

26 Tugal-Tutkun I, Guney-Tefekli E, Urgancioglu M. Results of interferon-alfa therapy in patients with Behçet uveitis. Graefes Arch Clin Exp Ophthalmol 2006;244:1692–5.

27 Bodaghi B, Gendron G, Wechsler B *et al*. Efficacy of interferon alpha in the treatment of refractory and sight threatening uveitis: a retrospective monocentric study of 45 patients. Br J Ophthalmol 2007;91:335–9.

28 Accorinti M, Pirraglia MP, Paroli MP *et al*. Infliximab treatment for ocular and extraocular manifestations of Behçet's disease. Jpn J Ophthalmol 2007;51:191–6.

29 Niccoli L, Nannini C, Benucci M *et al*. Long-term efficacy of infliximab in refractory posterior uveitis of Behçet's disease: a 24-month follow-up study. Rheumatology (Oxford) 2007;46:1161–4.

30 Tognon S, Graziani G, Marcolongo R. Anti-TNF-alpha therapy in seven patients with Behçet's uveitis: advantages and controversial aspects. Ann N Y Acad Sci 2007;1110:474–84.

31 Krause L, Altenburg A, Pleyer U *et al*. Longterm visual prognosis of patients with ocular Adamantiades-Behçet's disease treated with interferon-alpha-2a. J Rheumatol 2008;35:896–903.

32 Al-Rayes H, Al-Swailem R, Al-Balawi M *et al*. Safety and efficacy of infliximab therapy in active Behçet's uveitis: an open-label trial. Rheumatol Int 2008;29:53–7.

33 Gueudry J, Wechsler B, Terrada C *et al*. Long-term efficacy and safety of low-dose interferon alpha2a therapy in severe uveitis associated with Behçet disease. Am J Ophthalmol 2008;146:837–44 e1.

34 Tabbara KF, Al-Hemidan AI. Infliximab effects compared to conventional therapy in the management of retinal vasculitis in Behçet disease. Am J Ophthalmol 2008;146:845–50.e1.

35 Sobaci G, Erdem U, Durukan AH *et al*. Safety and effectiveness of interferon alpha-2a in treatment of patients with Behçet's uveitis refractory to conventional treatments. Ophthalmology 2010;117:1430–5.

36 Deuter CM, Zierhut M, Mohle A *et al*. Long-term remission after cessation of interferon-alpha treatment in patients with severe uveitis due to Behçet's disease. Arthritis Rheum 2010;62:2796–805.

37 Giardina A, Ferrante A, Ciccia F *et al*. One year study of efficacy and safety of infliximab in the treatment of patients with ocular and neurological Behçet's disease refractory to standard immunosuppressive drugs. Rheumatol Int 2011;31:33–7.

38 Yamada Y, Sugita S, Tanaka H *et al*. Timing of recurrent uveitis in patients with Behçet's disease receiving infliximab treatment. Br J Ophthalmol 2011;95:205–8.

39 Markomichelakis N, Delicha E, Masselos S *et al*. A single infliximab infusion vs corticosteroids for acute panuveitis attacks in Behçet's disease: a comparative 4-week study. Rheumatology (Oxford) 2011;50:593–7.

40 Onal S, Kazokoglu H, Koc A *et al*. Long-term efficacy and safety of low-dose and dose-escalating interferon alfa-2a therapy in refractory Behçet uveitis. Arch Ophthalmol 2011;129:288–94.

41 Handa T, Tsunekawa H, Yoneda M *et al*. Long-term remission of ocular and extraocular manifestations in Behçet's disease using infliximab. Clin Exp Rheumatol 2011;29:S58–63.

42 Keino H, Okada AA, Watanabe T, Taki W. Decreased ocular inflammatory attacks and background retinal and disc vascular leakage in patients with Behçet's disease on infliximab therapy. Br J Ophthalmol 2011;95:1245–50.

43 Cantini F, Niccoli L, Nannini C *et al*. Efficacy of infliximab in refractory Behçet's disease-associated and idiopathic posterior segment uveitis: a prospective, follow-up study of 50 patients. Biologics 2012;6:5–12.

44 Okada AA, Goto H, Ohno S, Mochizuki M; Ocular Behcet's Disease Research Group of Japan. Multicenter study of infliximab for refractory uveoretinitis in Behcet disease. Arch Ophthalmol 2012;130:592–8.

45 Capella MJ, Foster CS. Long-term efficacy and safety of infliximab in the treatment of Behçet's disease. Ocul Immunol Inflamm 2012;20:198–202.

46 Takeuchi M, Asukata Y, Kawagoe T *et al*. Infliximab monotherapy versus infliximab and colchicine combination therapy in patients with Behçet's disease. Ocul Immunol Inflamm 2012;20:193–7.

47 Al Rashidi S, Al Fawaz A, Kangave D, Abu El-Asrar AM. Long-term clinical outcomes in patients with refractory uveitis associated with Behçet disease treated with infliximab. Ocul Immunol Inflamm 2013;21:468–74.

48 Kawaguchi T, Kawazoe Y, Kamoi K *et al*. Clinical course of patients with Behçet's uveitis following discontinuation of infliximab therapy. Jpn J Ophthalmol 2014;58:75–80.

49 Takeuchi M, Kezuka T, Sugita S *et al*. Evaluation of the long-term efficacy and safety of infliximab treatment for uveitis in Behçet's disease: a multicenter study. Ophthalmology 2014;121:1877–84.

50 Calvo-Rio V, Blanco R, Beltran E *et al*. Anti-TNF-alpha therapy in patients with refractory uveitis due to Behçet's disease: a 1-year follow-up study of 124 patients. Rheumatology (Oxford) 2014;53:2223–31.

51 Vallet H, Riviere S, Sanna A *et al*. Efficacy of anti-TNF alpha in severe and/or refractory Behçet's disease: multicenter study of 124 patients. J Autoimmun 2015;62:67–74.

52 Jaffe GJ, Dick AD, Brezin AP *et al*. Adalimumab in patients with active noninfectious uveitis. N Engl J Med 2016;375:932–43.

53 Bawazeer A, Raffa LH, Nizamuddin SH. Clinical experience with adalimumab in the treatment of ocular Behçet disease. Ocul Immunol Inflamm 2010;18:226–32.

54 Perra D, Alba MA, Callejas JL *et al*. Adalimumab for the treatment of Behçet's disease: experience in 19 patients. Rheumatology (Oxford) 2012;51:1825–31.

55 Interlandi E, Leccese P, Olivieri I, Latanza L. Adalimumab for treatment of severe Behçet's uveitis: a retrospective long-term follow-up study. Clin Exp Rheumatol 2014;32:S58–62.

56 Lightman S, Taylor SR, Bunce C *et al*. Pegylated interferon-alpha-2b reduces corticosteroid requirement in patients with Behçet's disease with upregulation of circulating regulatory T cells and reduction of Th17. Ann Rheum Dis 2015;74:1138–44.

57 Dick AD, Tugal-Tutkun I, Foster S *et al*. Secukinumab in the treatment of noninfectious uveitis: results of three randomized, controlled clinical trials. Ophthalmology 2013;120:777–87.

58 Buggage RR, Levy-Clarke G, Sen HN *et al*. A double-masked, randomized study to investigate the safety and efficacy of daclizumab to treat the ocular complications related to Behçet's disease. Ocul Immunol Inflamm 2007;15:63–70.

59 Tugal-Tutkun I, Pavesio C, De Cordoue A *et al*. Use of gevokizumab in patients with Behcet's disease uveitis: An International, Randomized, Double-Masked, Placebo-Controlled Study and Open-Label Extension Study. Ocul Immunol Inflamm 2018:1–11.

60 Davatchi F, Shams H, Rezaipoor M *et al*. Rituximab in intractable ocular lesions of Behçet's disease; randomized single-blind control study (pilot study). Int J Rheum Dis 2010;13:246–52.

61 Hirano T, Ohguro N, Hohki S *et al*. A case of Behçet's disease treated with a humanized anti-interleukin-6 receptor antibody, tocilizumab. Mod Rheumatol 2012;22:298–302.

62 Calvo-Rio V, de la Hera D, Beltran-Catalan E *et al*. Tocilizumab in uveitis refractory to other biologic drugs: a

study of 3 cases and a literature review. Clin Exp Rheumatol 2014;32(4 Suppl 84):S54–7.

63 Papo M, Bielefeld P, Vallet H *et al*. Tocilizumab in severe and refractory non-infectious uveitis. Clin Exp Rheumatol 2014;32:S75–9.

64 Karacorlu M, Mudun B, Ozdemir H, Karacorlu SA, Burumcek E. Intravitreal triamcinolone acetonide for the treatment of cystoid macular edema secondary to Behçet disease. Am J Ophthalmol 2004;138:289–91.

65 Atmaca LS, Yalcindag FN, Ozdemir O. Intravitreal triamcinolone acetonide in the management of cystoid macular edema in Behçet's disease. Graefes Arch Clin Exp Ophthalmol 2007;245:451–6.

66 Ohguro N, Yamanaka E, Otori Y, Saishin Y, Tano Y. Repeated intravitreal triamcinolone injections in Behçet disease that is resistant to conventional therapy: one-year results. Am J Ophthalmol 2006;141:218–20.

67 Tuncer S, Yilmaz S, Urgancioglu M, Tugal-Tutkun I. Results of intravitreal triamcinolone acetonide (IVTA) injection for the treatment of panuveitis attacks in patients with Behçet disease. J Ocul Pharmacol Ther 2007;23:395–401.

68 Park UC, Park JH, Yu HG. Long-term outcome of intravitreal triamcinolone acetonide injection for the treatment of uveitis attacks in Behçet disease. Ocul Immunol Inflamm 2014;22:27–33.

69 Ahn JK, Lee YS, Jeon CH, Koh EM, Cha HS. Treatment of venous thrombosis associated with Behçet's disease: immunosuppressive therapy alone versus immunosuppressive therapy plus anticoagulation. Clin Rheumatol 2008;27:201–5.

70 Desbois AC, Wechsler B, Resche-Rigon M *et al*. Immunosuppressants reduce venous thrombosis relapse in Behçet's disease. Arthritis Rheum 2012;64:2753–60.

71 Alibaz-Oner F, Karadeniz A, Ylmaz S *et al*. Behçet disease with vascular involvement: effects of different therapeutic regimens on the incidence of new relapses. Medicine (Baltimore) 2015;94:e494.

72 Seyahi E, Cakmak OS, Tutar B *et al*. Clinical and ultrasonographic evaluation of lower-extremity vein thrombosis in Behçet syndrome: an observational study. Medicine (Baltimore) 2015;94:e1899.

73 Alibaz-Oner F, Aldag B, Aldag M *et al*. Post-thrombotic syndrome and venous disease-specific quality of life in patients with vascular Behçet's disease. J Vasc Surg Venous Lymphat Disord 2016;4:301–6.

74 Emmungil H, Yaş ar Bilge NŞ, Küçükş ahin O *et al*. A rare but serious manifestation of Behçet's disease: intracardiac thrombus in 22 patients. Clin Exp Rheumatol 2014;32:S87–92.

75 Hamuryudan V, Yurdakul S, Moral F *et al*. Pulmonary arterial aneurysms in Behçet's syndrome: a report of 24 cases. Br J Rheumatol 1994;33:48–51.

76 Saba D, Saricaoğlu H, Bayram AS *et al*. Arterial lesions in Behçet's disease. Vasa 2003;32:75–81.

77 Hamuryudan V, Er T, Seyahi E *et al*. Pulmonary artery aneurysms in Behçet syndrome. Am J Med 2004;117:867–70.

78 Le Thi Huong D, Wechsler B, Papo T *et al*. Arterial lesions in Behçet's disease. A study in 25 patients. J Rheumatol 1995;22:2103–13.

79 Seyahi E, Melikoglu M, Akman C *et al*. Pulmonary artery involvement and associated lung disease in Behçet disease: a series of 47 patients. Medicine (Baltimore) 2012;91:35–48.

80 Hamuryudan V, Seyahi E, Ugurlu S *et al*. Pulmonary artery involvement in Behçets syndrome: effects of anti-Tnf treatment. Semin Arthritis Rheum 2015;45:369–73.

81 Saadoun D, Asli B, Wechsler B *et al*. Long-term outcome of arterial lesions in Behçet disease: a series of 101 patients. Medicine (Baltimore) 2012;91:18–24.

82 Park MC, Hong BK, Kwon HM, Hong YS. Surgical outcomes and risk factors for postoperative complications in patients with Behçet's disease. Clin Rheumatol 2007;26:1475–80.

83 Kalko Y, Basaran M, Aydin U *et al*. The surgical treatment of arterial aneurysms in Behçet disease: a report of 16 patients. J Vasc Surg 2005;42:673–7.

84 Tuzun H, Seyahi E, Arslan C *et al*. Management and prognosis of nonpulmonary large arterial disease in patients with Behçet disease. J Vasc Surg 2012;55:157–63.

85 Tüzün H, Beş irli K, Sayin A *et al*. Management of aneurysms in Behçet's syndrome: an analysis of 24 patients. Surgery 1997;121:150–6.

86 Alpagut U, Ugurlucan M, Dayioglu E. Major arterial involvement and review of Behçet's disease. Ann Vasc Surg 2007;21:232–9.

87 Yang SS, Park KM, Park YJ *et al*. Peripheral arterial involvement in Behçet's disease: an analysis of the results from a Korean referral center. Rheumatol Int 2013;33:2101–8.

88 Koksoy C, Gyedu A, Alacayir I *et al*. Surgical treatment of peripheral aneurysms in patients with Behçet's disease. Eur J Vasc Endovasc Surg 2011;42:525–30.

89 Noel N, Bernard R, Wechsler B *et al*. Long-term outcome of neuro-Behçet's disease. Arthritis Rheumatol 2014;66:1306–14.

90 Yoon DL, Kim YJ, Koo BS *et al*. Neuro-behçet's disease in South Korea: clinical characteristics and treatment response. Int J Rheum Dis 2014;17:453–8.

91 Zeydan B, Uygunoglu U, Saip S *et al*. Infliximab is a plausible alternative for neurologic complications of Behçet disease. Neurol Neuroimmunol Neuroinflamm 2016;3:e258.

92 Pipitone N, Olivieri I, Padula A *et al*. Infliximab for the treatment of Neuro-Behçet's disease: a case series and review of the literature. Arthritis Rheum 2008;59:285–90.

93 Borhani Haghighi A, Safari A, Nazarinia MA, Habibagahi Z, Shenavandeh S. Infliximab for patients with neuro-Behçet's disease: case series and literature review. Clin Rheumatol 2011;30:1007–12.

94 Al-Araji ASA, Saip S *et al*. Treatment of neuro-Behçet's disease with infliximab: an international multi-centre case-series of 18 patients. Clin Exp Rheumatol 2010;28(Suppl 60):S119.

95 Monastirli A, Chroni E, Georgiou S *et al*. Interferon-alpha treatment for acute myelitis and intestinal involvement in severe Behçet's disease. QJM 2010;103:787–90.

96 Nichols JC, Ince A, Akduman L, Mann ES. Interferon-alpha 2a treatment of neuro-Behçet disease. J Neuroophthalmol 2001;21:109–11.

97 Shugaiv E, Tuzun E, Mutlu M *et al*. Mycophenolate mofetil as a novel immunosuppressant in the treatment of neuro-Behçet's disease with parenchymal involvement: presentation of four cases. Clin Exp Rheumatol 2011;29(4 Suppl 67): S64–7.

98 Addimanda O, Pipitone N, Pazzola G, Salvarani C. Tocilizumab for severe refractory neuro-Behçet: three cases IL-6 blockade in neuro-Behçet. Semin Arthritis Rheum 2015;44:472–5.

99 Cantarini L, Vitale A, Scalini P *et al*. Anakinra treatment in drug-resistant Behçet's disease: a case series. Clin Rheumatol 2015;34:1293–301.

100 Hirohata S, Kikuchi H, Sawada T *et al*. Retrospective analysis of long-term outcome of chronic progressive neurological manifestations in Behçet's disease. J Neurol Sci 2015;349:143–8.

101 Kikuchi H, Aramaki K, Hirohata S. Effect of infliximab in progressive neuro-Behçet's syndrome. J Neurol Sci 2008;272:99–105.

102 Kato Y, Numaga J, Kato S *et al*. Central nervous system symptoms in a population of Behçet's disease patients with refractory uveitis treated with cyclosporine A. Clin Exp Ophthalmol 2001;29:335–6.

103 Kotake S, Higashi K, Yoshikawa K *et al*. Central nervous system symptoms in patients with Behçet disease receiving cyclosporine therapy. Ophthalmology 1999;106:586–9.

104 Kötter I, Günaydin I, Batra M *et al*. CNS involvement occurs more frequently in patients with Behçet's disease under cyclosporin A (CSA) than under other medications—results of a retrospective analysis of 117 cases. Clin Rheumatol 2006;25:482–6.

105 Akman-Demir G, Ayranci O, Kurtuncu M *et al*. Cyclosporine for Behçet's uveitis: is it associated with an increased risk of neurological involvement? Clin Exp Rheumatol 2008;26:S84–90.

106 Saadoun D, Wechsler B, Resche-Rigon M *et al*. Cerebral venous thrombosis in Behçet's disease. Arthritis Rheum 2009;61:518–26.

107 Mossadeq R, Karouache A, Bouraza A *et al*. [Neuro-Behçet's syndrome and thrombosis of Rosenthal's basilar vein: a report of twelve cases]. Rev Neurol (Paris) 2004;160:935–8.

108 Ferro JM, Canhao P, Stam J *et al*. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). Stroke 2004;35:664–70.

109 Yesilot N, Bahar S, Yilmazer S *et al*. Cerebral venous thrombosis in Behçet's disease compared to those associated with other etiologies. J Neurol 2009;256:1134–42.

110 Hatemi I, Esatoglu SN, Hatemi G *et al*. Characteristics, treatment, and long-term outcome of gastrointestinal involvement in Behçet's syndrome: a strobe-compliant observational study from a dedicated multidisciplinary center. Medicine (Baltimore) 2016;95:e3348.

111 Jung YS, Hong SP, Kim TI, Kim WH, Cheon JH. Long-term clinical outcomes and factors predictive of relapse after 5-aminosalicylate or sulfasalazine therapy in patients with intestinal Behçet disease. J Clin Gastroenterol 2012;46:e38–45.

112 Jung YS, Cheon JH, Hong SP, Kim TI, Kim WH. Clinical outcomes and prognostic factors for thiopurine maintenance therapy in patients with intestinal Behçet's disease. Inflamm Bowel Dis 2012;18:750–7.

113 Hatemi I, Hatemi G, Pamuk ON, Erzin Y, Celik AF. TNF-alpha antagonists and thalidomide for the management of gastrointestinal Behçet's syndrome refractory to the conventional treatment modalities: a case series and review of the literature. Clin Exp Rheumatol 2015;33(6 Suppl 94): S129–37.

114 Baek SJ, Kim CW, Cho MS *et al*. Surgical treatment and outcomes in patients with intestinal Behçet disease: long-term experience of a single large-volume center. Dis Colon Rectum 2015;58:575–81.

115 Lee HW, Cheon JH, Lee HJ *et al*. Postoperative effects of thiopurines in patients with intestinal Behçet's disease. Dig Dis Sci 2015;60:3721–7.

116 Naganuma M, Sakuraba A, Hisamatsu T *et al*. Efficacy of infliximab for induction and maintenance of remission in intestinal Behçet's disease. Inflamm Bowel Dis 2008;14:1259–64.

117 Iwata S, Saito K, Yamaoka K *et al*. Efficacy of combination therapy of anti-TNF-alpha antibody infliximab and methotrexate in refractory entero-Behçet's disease. Mod Rheumatol 2011;21:184–91.

118 Lee JH, Cheon JH, Jeon SW *et al*. Efficacy of infliximab in intestinal Behçet's disease: a Korean multicenter retrospective study. Inflamm Bowel Dis 2013;19:1–8.

119 Kinoshita H, Kunisaki R, Yamamoto H *et al*. Efficacy of infliximab in patients with intestinal Behçet's disease refractory to conventional medication. Intern Med 2013;52:1855–62.

120 Tanida S, Inoue N, Kobayashi K *et al*. Adalimumab for the treatment of Japanese patients with intestinal Behçet's disease. Clin Gastroenterol Hepatol 2015;13:940–8 e3.

121 Ma D, Zhang CJ, Wang RP, Wang L, Yang H. Etanercept in the treatment of intestinal Behçet's disease. Cell Biochem Biophys 2014;69:735–9.