Review

One year in review 2020: Behçet’s syndrome

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ABSTRACT

Behçet’s syndrome is a variable vessel vasculitis with multi-system involvement that shows important heterogeneity among patients regarding demographic features, organ manifestations, frequency and severity of relapses, disease course, response to treatment and prognosis. This heterogeneity has made it difficult to interpret and compare the results of studies, to standardise disease assessment and to develop management strategies. Several new studies have been published during the previous year exploring the epidemiology, pathogenesis, clinical manifestations, diagnosis, and management of Behçet’s syndrome. The aim of this review is to provide an overview of the most relevant recent research in Behçet’s syndrome from a critical perspective.

Introduction

Behçet’s syndrome (BS) is a multi-system variable vessel vasculitis with heterogeneity among patients regarding demographic features, organ manifestations, frequency and severity of relapses, disease course, response to treatment, and prognosis. Skin and mucosa lesions comprising oral and genital ulcers, papulopustular lesions, and erythema nodosum-like lesions are observed in the majority of patients. They show frequent relapses that usually last a few weeks, may be multiple and may reduce quality of life. On the other hand, organ/system involvement including uveitis, venous thrombosis, arterial thrombosis and aneurysms, nervous system involvement, and gastrointestinal involvement occur in a smaller proportion of patients, have much less frequent recurrences, but can cause damage with permanent impairment of function, and even death. Interpretation and comparison of study findings, standardisation of disease assessment and developing management strategies for BS have been challenging due to the important variation among patients. During the previous year several studies have been published expanding our understanding of BS. Main topics that these studies tried to elucidate were epidemiology, pathogenesis including immunopathology, genetics and epigenetics, advances in laboratory and imaging modalities for diagnosis and monitoring, and management issues regarding efficacy and safety of newer treatment modalities and long-term outcome with older agents. The aim of this review, as in the previous years (1-8), is to provide an overview of the recent research from a critical perspective, elaborate on the implications of these in light of the previous studies and provide suggestions on how these may be advanced with future studies. Literature search was conducted in PubMed with “Behçet*” as the keyword, including all articles in English, published between July 2019 and January 2020. Articles published during 2019, before July were already covered in the previous “One year in review” (8), and those published between January 2020 and January 2021 will be included in next year’s review. Each author selected the articles related to their preassigned topic at their own discretion.

Epidemiology

Differences in incidence, prevalence, frequency of manifestations and disease severity of BS between countries has been of interest to researchers for a long time. Recently, a study comparing 163 BS patients recorded in Tehran University Medical Center in Iran and 56 patients in Stanford University Hospital in the United States (US) between the years 2000 and 2016 was published (9). All patients that were recorded in Stanford University were included, whereas the Iranian patients were se-

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selected with stratified randomisation according to follow-up duration. Genital ulcers, skin lesions, joint, nervous system, and vascular involvement as well as cardiopulmonary manifestations and having early age of onset were more frequent in the US cohort. Interestingly, although there was a higher proportion of women in the US cohort (70% vs. 39%), US patients had more severe disease. This is similar to a previous study comparing Turkish patients to US patients followed in New York University and the National Institute of Health (10). This may be considered to be associated with the diagnosis of more severe patients in US compared to countries with high BS prevalence such as Turkey and Iran, where milder patients are more easily recognised.

Patients’ perspective
Individual patient interviews were conducted with 20 patients with BS with various types of organ and system involvement to represent the heterogeneous disease spectrum of BS with the aim of expanding the understanding of patients’ experiences with BS and the impact of physical symptoms of BS on other patient-centered health domains, as well as helping outcome measure development for the assessment of BS in clinical trials (11). The impact of BS on patients’ daily activities, physical function, social and family life, psychological well-being, and coping strategies were questioned. Four main themes and the related subdomains that were identified through the analyses of these interviews were skin problems, pain, vision problems, fatigue, sleep disturbances, gastrointestinal concerns and weight loss within the symptoms domain; impact on speech and vision, mobility, energy for tasks, adaptations, and self-care within the function domain; fear, anxiety, stress, depression, and anger within the psychological impact domain; and decreased ability to socialise, negative impact on social duties, family life and work within the social impact domain.

Take home message
- A study comparing BS patients from Iran with patients from the US showed more severe disease among US patients despite a higher proportion of women (9). This may be associated with diagnosis of only more severe patients in areas where the prevalence is low and physicians are less familiar with BS.

Pathogenesis
BS is considered as the prototype of a systemic inflammation-induced thrombotic condition whose pathogenesis cannot be explained just by coagulation abnormalities. Circulating haematopoietic progenitor cells (CPC) are mobilised in response to vascular injury and play a key role in tissue repair. In cardiovascular and thrombotic diseases, low circulating CPC number and reduced CPC function have been observed. Moreover, oxidative stress may be one of the relevant culprits that account for the dysfunctional and numerically reduced CPC in these conditions. So far, the detailed mechanisms underlying CPC number reduction are unknown. Recently a study was conducted in order to explore the possible relationship between CPC dysfunction and oxidative stress in BS patients (12). It was noted for the first time that CPC from BS patients show signs of oxidative stress and apoptosis and that a reduced CPC number is present in BS patients with respect to controls. Interestingly, these data support the hypothesis that oxidative-stress-mediated CPC dysfunctioning may counteract their vascular repair function, thereby contributing to the pathogenesis and the progression of vascular disease in BS. Moreover, exploration of the role of circulating endothelial cells (CEC) was the primary aim of another recent study, considering their implications in conditions with vascular damage such as systemic vasculitis (13). Specifically, the study investigated if EPC, CEC, and/or its subgroups activated CEC (aCEC) or resting CEC (rCEC) related with vascular involvement in BS. A total of 60 patients were studied, including BS patients with a history of vascular involvement, BS patients with mucocutaneous involvement, patients with history of thrombosis due to other causes, and healthy subjects as controls. EPC and rCEC levels resulted higher in patients with vascular BS and patients with thrombosis due to other causes, compared with mucocutaneous BS and control groups. These data may suggest that CEC, EPC, aCEC and rCEC may have a role in the assessment of vascular involvement in BS. Other interesting considerations emerged from the exploration of neutrophil extracellular traps (NETs), which are prothrombotic elements (14). NET components, including cell-free DNA (cfDNA) and neutrophil enzymes myeloperoxidase (MPO), were assessed in serum or in purified neutrophils from the study population and, notably, patients with active BS had elevated serum cfDNA levels and MPO-DNA complexes compared to patients with inactive disease and healthy controls. In addition, levels of cfDNA and MPO-DNA complexes were significantly higher in BS patients with vascular involvement compared to those without vascular symptoms. Biopsy specimens from patients with BS showed NETs production in areas of vasculitic inflammation and thrombosis. These data might give us important clues in terms of potential therapeutic target for the reduction or prevention of BS-associated thrombotic risk. Considering also other molecules implicated in the angiogenic process, another recent study tried to assess CCN2/CTGF (connective tissue growth factor) plasma concentrations in BS patients and to analyse their association with clinical disease features activity and laboratory parameters (15). The plasma concentrations of CCN2 in BS patients were significantly elevated compared to healthy controls and the mean plasma CCN2 levels in patients with major organ involvement were significantly higher than those without. A peculiar aspect was that patients who received steroids or cyclophosphamide showed a significant reduction in CCN2 levels. This needs further scrutiny and might lead to new therapeutic approaches. More and more information is available regarding the role that various cytokines have in the pathogenesis of BS. IL-38, a new member of IL-1 cytokine family, may have anti-inflammatory properties. Preliminary data were provided regard-
ing its role in BS (16). A total of 81 patients with BS and 81 age- and sex-matched healthy subjects were studied. However, the results of the study seem to provide different considerations, since healthy controls showed higher IL-38 serum levels than patients, suggesting a protective anti-inflammatory role of IL-38 in BS. On the other hand, a positive association between IL-38 serum levels and eye involvement was noted. There is an inverse relationship between the amount of transcription of a particular gene and its degree of methylation. An Iranian group from Tabriz studied the methylation and expression profile of various genes in 47 patients with BS and 61 healthy controls. They investigated the forkhead box P3 (Foxp3) gene, an important tool in Treg cell function (17). The level of expression of the gene was lower and the methylation level higher among BS compared to the controls although the increase in methylation did not reach statistically significant. A study exploring the expression and methylation status of the vitamin D receptor gene showed that the level of VDR expression was significantly lower in BS patients compared to controls as expected, whereas there was no difference in the amount of methylation among the two groups. No correlation was observed between VDR gene expression rate and disease activity (18).

A Chinese group compared genome-wide DNA methylation profiles between 60 BS patients and 60 healthy controls. A total of 4332 differentially methylated CpG were associated with BS. Four CpG sites with aberrant methylation status had the potential to serve as a diagnostic marker for BS. A significant inverse correlation was found between the degree of methylation and FKBP5 mRNA expression, the gene which plays an important role in the TNF-alpha NF-kappa B signalling pathway. FKBP5 was also the most significant differentially methylated site (19).

Killer Ig-like receptor molecules expressed on NK cells (KIR) have also attracted attention because they are natural ligands of HLA Class I molecules (including HLA-B51) and have the potential of influencing the immune response. Petrushkin et al. examined the association of various KIR alleles with BS in 267 patients and 445 matched controls. Low expressing KIR3DL1/S1 alleles in combination with KIR3DS1 increased the risk of developing BS (OR:2.47, 95% CI 1.43–4.25) whereas high expressing KIR3DL1/S1 alleles in combination with a null expressing KIR3DL1 reduced the risk of the disease (OR: 0.53, 95% CI 0.33–0.87). KIR3DL1 (low)/KIR3DS1 increased the risk of ophthalmic disease (OR:3.92, 95% CI 2.06–7.47) whereas KIR3DL1 (high)/KIR3DL1 (null) reduced the risk of having purely mucocutaneous disease (OR:0.45, 95% CI 0.25–0.81). The authors thought that this provided insight into the pathogenetic role of HLA B51 and its interaction with KIR3DL1/S1 (20). Castano-Nunez et al. also investigated the contribution of certain KIR functional polymorphisms to the susceptibility of BS. 466 BS patients and 444 healthy individuals were studied. The frequency of KIR3DL1*004 was lower in patients compared to controls (OR:0.70, 95% CI 0.54–0.90) (21). Autoinflammation and BS was also the subject of a number of studies. Li et al. made a case control association study of CARD9 gene polymorphisms in 480 patients with BS, 1150 patients with acute anterior uveitis (AAU) and 1440 healthy controls among the Han Chinese. None of the individual SNP’s in the CARD9 gene showed an association with either BS or AAU. There was a significant decrease of the frequency of a CARD9 gene haplotype CGCCA among patients with BS, suggesting a protective effect (22). Given the hypothesis that MEVF gene mutations may act as disease modifiers in BS, a Japanese group looked for these among patients with BS-like symptoms were reported in two of the families. One patient who presented with oculomotor nerve palsy and painful legs, progressed to recurrent genital ulcers, arthralgias and fever and erythema nodosum. Her sister had erythema nodosum, recurrent oral ulcers, arthralgia, folliculitis and livedoid rash in her hands (25).

Kaburaki et al. identified two peptides with high affinity to HLA-B*51:01 using computerised binding predictions. These peptides (HSP65PD, derived from heat shock protein-65A and B51PD derived from HLA-B*51:01) showed significantly high responses in HLA-B51:01 patients with BS. They concluded that computerised simulations might be useful in determining autoreactive peptides for HLAs (26).

A Korean group examined differences in the expression of HLA Class II subtypes and T cell subsets among 25 patients with BS and arthritis compared to diseased (rheumatoid arthritis) and healthy controls. They found that HLA-DQ presenting cells were decreased in BS patients compared to healthy controls and proposed that this finding may as well be a risk factor for BS arthritis. The improvement of BS arthritis may as well be a risk factor for BS arthritis. The improvement of BS arthritis may as well be a risk factor for BS arthritis.
Additionally reversed the concentrations of effector and central memory T cells (27). A letter to the editor by Leccese et al addressed the issue of HLA-B51 frequency and subtypes in 152 BS patients and 320 healthy controls in Lucania, Italy. HLA-B51 was more frequent in patients as expected (RR 3.82 95% CI 2.92-5.01), and B*51:08 was the most common subtype (RR 2.88 95% CI 2.30-3.61) (28).

Recently, some disease related single nucleotide peptides (SNPs) have been reported to mediate disease risk through modulating the expression of long non-coding RNAs (lncRNAs) which are a type of non-coding RNAs regulating gene expression. An Iranian study performed in 212 patients with BS and 200 healthy controls tested the potential association of two SNPs of transmembrane immunoglobulin and mucin-domain 3 (TIM) a Th1 related cellular immune response gene. They did not determine any difference in allele and genotype frequencies among the two groups (29).

Two separate groups performed meta-analyses on the association between interleukin-10 polymorphisms and susceptibility to BS, with similar results. The -819 T>C and the -592 A>C polymorphisms decreased BS risk while the -1082 A>G was not associated with a change in risk. The data suggested that the former two polymorphisms had the potential to influence the pathogenesis (30, 31). Gong et al. performed a meta-analysis of case control studies to determine the association between IL-23R gene polymorphisms and BS susceptibility. Twelve case control studies among 6926 BS patients and 10211 controls and 5 loci were investigated. rs17375018 (G/A) and rs924080 (T/C) were associated with BS risk (32).

Take home messages
- Epigenetic modifications of various genes increase and complicate the genetic armamentarium of BS and need to be addressed in more detail (17).
- Various KIR alleles (natural ligands of HLA-B51) and their functional polymorphisms influence the risk of presenting with various subtypes of BS (20,21).
- The -819 T>C and the -592 A>C polymorphisms of IL-10 decrease the BS risk while the -1082 A>G is not associated with a change in risk (30, 31).

Clinical findings
Eye involvement
Imaging modalities have an important role in the diagnosis and follow-up of Behçet uveitis. Laser flare photometry (LFP) is used in the assessment of the anterior chamber inflammation, fluorescein angiography (FA) for the detection of retinal vasculitis, indocyanine green angiography (ICGA) for possible choroid pathologies, and optical coherence tomography (OCT) for detecting macular pathologies. Optical coherence tomography angiography (OCTA) is used increasingly to assess retinal and choroidal vasculature including superficial capillary plexus (SCP), deep capillary plexus (DCP), outer retina, and choriocapillaris (33, 34). Additionally, it can measure foveal avascular zone (FAZ) area, capillary non-perfusion areas, vessel densities in both SCP and DCP, and flow area of the choriocapillaris. Projection resolved OCTA (PR-OCTA) - a recently developed technique - provides a better visualisation of retinal vessels by mitigating artifacts (75). Two studies investigated the role of OCTA in demonstrating lesions of BU (33, 34). Vessel densities in both SCP and DCP were found to be decreased; and an even lower vessel density in DCP, compared to that in SCP was detected in patients with BS compared with healthy controls. The FAZ area in both superficial and deep plans, FAZ perimeter and FAZ acircularity index were found to be increased (33). OCTA also revealed perifoveal capillary hyperperfusion, perifoveal capillary network disorganisation and FAZ irregularity in ocular BS (34).

Several studies described early microvascular changes in the retinal vascular plexus and choriocapillaris using OCTA among patients with non-ocular BS (35-37). Thinning of the choroid relative to normal eyes in non-ocular BS has also been shown. These results indicate that there could be both retinal and choroidal involvement in non-ocular BS patients before the emergence of overt clinical findings.

Shirahama et al. investigated whether retinal FA leakage sites are correlated with subfoveal choroidal thickness (SCT) measured using enhanced depth imaging (EDI) OCT (38). Twenty-two BS patients with uveitis underwent EDI-OCT and FA. The changes in FA leakage scores in the macula were correlated with the changing rates in SCT. By contrast, there were no significant associations between the changes in SCT and those in leakage from the peripheral retina or the optic disc on FA. These suggest that changes in SCT may reflect macular vasculitis or inflammation in BS.

Yang et al. investigated the clinical characteristics and outcome of primary optic neuropathy among 61 (38 M/23 F) patients with BS (39). Different from what has previously been reported by Akdal et al. (40), none of the patients had CNS involvement or MS-like disease. Among 67 eyes with optic nerve abnormalities, MRI showed perineural enhancement around the orbital optic nerve in 46 (68.7%) eyes and signal in the optic nerve itself in 31 eyes (46.3%), the sunflower-like sign being a distinctive MRI feature. Relapse was rare (3.6%), however severe visual loss was common and more likely to occur among males (males: 62.5% vs. females: 14.7%).

Vascular involvement
Qi et al. studied characteristics of the vascular lesions (mainly aneurysms) using multi-slice CT among 45 BS patients (37 M/8 F; median age: 40 years) (41). Of the 45 patients, 38 had aneurysms, 18 had arterial thrombosis and 7 venous thrombosis. A total of 14 patients (31.1%) had multiple vascular lesions. In total there were 42 aneurysms. Twenty-eight aneurysms were located in the aorta (67%) (thoracic aorta: 20, abdominal aorta: 8) while 14 were in the large arteries. Their mean diameter was 43 mm. Aortic aneurysms were more likely to form a mural thrombus, have a thicker wall, unclear borders and asymmetric bulging of the right part of the wall and have a longer extension than aneurysms occurring in the peripheral arteries.
Chen investigated the clinical features and potential risk factors of coronary involvement in BS (42). Among 476 (296 M/180 F) BS patients, 19 (17 M/2 F) with coronary involvement were identified either by coronary angiography and (or) computed tomography angiography. The median duration from onset of BS to coronary involvement was 2.8 years. Coronary stenosis, aneurysm, and occlusion were presented in 13, 9, and 3 patients, respectively. Smoking (36.8%) was the major traditional risk factor. Coronary involvement was found to be associated with being male, a positive pathergy test, and a high acute phase response. Lee et al. investigated the prevalence of atrial fibrillation among 6636 newly diagnosed BS patients registered in the Korean National Health Insurance Service database between 2010 and 2014 (43). During a mean follow-up of 3.6±1.5 years, the incidence of non-valvular atrial fibrillation was calculated as 2.3 and 1.1 per 1000 person-years, in BS and healthy controls, respectively. After adjustment, the BS group showed a 1.8-fold higher risk of atrial fibrillation compared to the control group, however when males and females were separately analysed, only male patients had an increased risk, which was 2.5-fold.

Ayar et al. studied arterial stiffness by measuring pulse wave velocity (PWV) and augmentation index (AIx) among 54 BS patients and 34 healthy controls (44). While PWV values were not different between BS patients and healthy controls, AIx was significantly higher in all patients with BS. Additionally, PWV and disease duration were found to be correlated.

Nervous system involvement
A study from South Korea and another from China investigated the clinical characteristics and outcome of patients with nervous system involvement and revealed similar results (45, 46). Kim et al. investigated the clinical characteristics of patients with nervous system involvement using a large database in Seoul, South Korea, registered between 2000 and 2017 (45). Of 9,817 patients with the diagnosis code for BS, 1,682 (17.1%) visited the neurology clinic and 110 (1.1%) were diagnosed with nervous system involvement. A total of 98 patients exhibited parenchymal and 12 exhibited non-parenchymal involvement. Brainstem lesions (43.9%) were the most common lesions. The majority (72.4%) of the patients presented with acute nervous system involvement, while the remaining had a progressive disease course. Pyramidal signs (52.0%), headache (45.9%), dysarthria (42.9%), and fever (31.6%) were the most common signs. Yan et al. investigated the clinical features of 42 (25 M, 17 F) patients with parenchymal nervous system involvement and compared them to 84 age- and sex-matched BS patients without nervous system involvement (46). All patients were admitted to Peking Union Medical College Hospital, China between 2000 and 2016. Pyramidal signs (50.0%) and headache (33.3%) were the most common manifestations. On MRI, the lesions were mainly in the brainstem with hyperintense midline attenuation in T2-weighted images. Spinal cord involvement which was mainly cervical was observed in five cases. Ocular involvement was more common in parenchymal nervous system involvement. All patients received aggressive treatment with corticosteroids and immunosuppressives (cyclophosphamide: 39/42, biological agents: 6/42). Within a median follow-up of 28 months, 22 patients (61.1%) achieved clinical improvement, while 10 (27.8%) relapsed and 4 died (11.1%). Diffusion-weighted imaging (DWI) is an MRI technique that has been introduced during the last decade (47). It helps to evaluate the diffusiveness of water in the extracellular space. Owing to DWI, specific diffusion capacity of a biologic tissue could be quantitatively measured using apparent diffusion coefficient (ADC) on ADC maps. Alis et al. studied 58 patients with nervous system involvement using DWI MRI between 2013 and 2018 (47). Of the 58 patients, 42 had parenchymal involvement, and 24 of these were found eligible for the study. A total of 45 parenchymal lesions (25 acute, 20 chronic) were detected in these 24 patients. The study found that the acute and chronic parenchymal lesions had significantly higher ADC values compared with the contralateral normal brain parenchyma. Moreover, although acute lesions had numerically higher ADC values than chronic ones, no statistically significant differences were observed between them. Hence, authors suggested that DWI MRI-derived ADC measurements might be beneficial in differentiating acute nervous system lesions of BS from an acute infarct, since increased diffusiveness is expected to be seen in nervous system involvement of BS, different from what is seen in acute arterial infarcts.

Wu et al. investigated the prevalence of stroke among BS patients in Taiwan using a nationwide population-based database encompassing the years from 2000 to 2010 (48). The study cohort included 306 patients with newly diagnosed BS and 1224 controls. During the 10-year follow-up, and after adjusting for comorbidities and demographic characteristics, Cox regression analysis revealed that patients with BS had a 2.77-fold risk of ischemic stroke (CI 95%: 1.38–5.57) compared with control subjects. Akinc et al. studied brainstem changes in BS patients with nervous system involvement using electro-physiological tests (49). Electrically-induced blink reflex (eBR), auditory blink reflex (aBR) and electrically-induced masseter inhibitory reflex (eMIR) were evaluated in 16 BS patients with nervous system involvement. However, these neurophysiological tests were found to have a poor overall sensitivity compared to neuroimaging for the diagnosis of brainstem lesions. They also showed low sensitivity for the differential diagnosis of focal pontine lesions versus diffuse brainstem disease in nervous system involvement of BS.

Intestinal involvement
Zhang et al. investigated the predictors of long-term flare-ups, poor outcome and event-free survival in 109 BS patients (median age: 35 years; median disease duration: 7 year) with intestinal involvement (50). Ileoecal/colorectal ulcers, a high erythrocyte sedimentation
rate (>24 mm/h), treatment with infliximab and poor compliance were found to be independently correlated with a poor outcome. Adverse events were observed in 41% of the patients and were found to be associated with early disease onset and poor compliance.

Audio-vestibular complications
Karadağ et al. studied 44 (26 M/18) patients (mean age: 40.13±8.82 years) with BS and 42 (23 M/19 F) healthy controls (mean age: 39.59±8.27 years) (51). The exclusion criteria were all conditions that may interfere with sensorineuronal hearing deficit such as diabetes, hypertension, endocrinological disorders, liver and kidney dysfunction, malignancy, neurological involvement, any congenital, traumatic or infectious ear disease and immunosuppressive use other than colchicine.

The hearing levels of all participants were measured with high-frequency audiometry and transient auto-acoustic emission tests. Additionally, the level of tinnitus-induced annoyance and the effects of tinnitus on daily life were evaluated using a visual analog scale and the Tinnitus Reaction Questionnaire. The study showed that the sensorineural hearing loss and tinnitus were significantly more frequent among BS patients.

Ertugrul et al. showed that the audio-vestibular system was affected in 31 patients with BS compared with 31 healthy individuals (52). Similar inclusion criteria applied in this study. All study participants were evaluated via pure tone audiometry, video head impulse test, post head shake nystagmus test and dizziness handicap inventory. The study showed that the audio-vestibular system was affected in BS. In particular an isolated horizontal canal involvement was observed.

Obstructive sleep apnea
Gokturk et al. studied the frequency of obstructive sleep apnea among patients with BS and healthy controls using the Berlin questionnaire (53). BS patients were all male and included three different clinical groups (group 1: 28 patients with superior vena cava syndrome (SVCS), group 2: 129 patients with other vascular involvement and group 3: 151 patients with no vascular involvement. BS patients with SVCS were found to carry a significantly higher risk for obstructive sleep apnea (57%), compared with other BS groups and healthy controls (17%, 17% and 11%, respectively). While the etiology of this phenomenon is unclear, the external pressure to the upper airways by the abundant venous collaterals is thought to play role.

Pregnancy
A retrospective cohort study was done to estimate the prevalence of BS in pregnancy and evaluate maternal and fetal outcomes (54). The 1999-2013 Healthcare Cost and Utilization Project-Nationwide Inpatient Sample which is the largest public all-payer database in the USA was used. The study revealed an overall prevalence of 1.14 cases/100,000 births (144 women with BS/12,592,676 pregnancies) which gradually increased from 0.5 to 2.4 over the study period. Women with BS were more likely to be Caucasian, and be of the upper income quartiles. They were at greater risk for pre-term labour and postpartum venous thromboembolism, while their newborns were more likely to be born premature.

Take home messages
• Optical coherence tomography angiography (OCTA) can demonstrate significant microvascular changes in the retinal vascular plexus and choriocapillaris among patients with and without uveitis (33, 34).
• Diffusion-weighted imaging MRI could be helpful in the diagnosis of acute parenchymal nervous system involvement (47).
• Maternal and fetal morbidity is increased and the risk for postpartum venous thromboembolism seems to be high (54).

Treatment
TNF-α inhibitors
A systematic review from China looked at the efficacy of TNF-α inhibitors for the treatment of BS uveitis (55). They included articles that included a minimum of 10 patients with at least 6 months follow-up. The search in Embase, Medline and Cochrane databases between January 2010 and December 2019 revealed 504 publications, of which 18 (15 retrospective studies and 3 prospective studies) were selected for meta-analysis. Ten studies evaluated infliximab, 4 evaluated adalimumab and 4 evaluated both drugs. Overall, treatment with TNF-α inhibitors was found to be effective in inducing remission, improving visual acuity, decreasing macular edema and reducing the need for glucocorticoids (55). Although properly conducted randomised trials are lacking, accumulating evidence so far suggests that especially monoclonal TNF-α inhibitors are a good option for various refractory manifestations of BS.

Cyclophosphamide
Cyclophosphamide (CYC) is a potent immunosuppressive agent that has been widely used for serious complications of BS, including vascular, ocular and central nervous system involvement.

Because of its severe adverse effects, current CYC use in our unit is limited to only induction treatment of BS patients with life threatening vascular involvement and is replaced by other immunosuppressives or biologic agents once clinical response is achieved.

Recently, in a retrospective study our group assessed the long-term outcome of 198 BS patients (93% men) who had received CYC between 1976 and 2006 (56). Main indications were vascular (67%) and eye involvement (27%). The median duration of CYC use was 12 months with a median cumulative dose of 13.5 grams. CYC was given intravenously to 102 patients and orally to 69 patients with the rest of the patients receiving both routes. Outcome information could be obtained in 165 patients (83%) after a median period of 17 (IQR: 9-26) years. Fifty-two (26%) of these 165 patients had died after a median duration of 4 (IQR: 1-12) years following the initiation of CYC. The main causes of death were malignancies in 7 (14%), serious infections in 5 (10%) and vascular involvement in 27 (52%) patients. Malignancies consisted of lung adenocarcinoma in 3 patients and acute myeloid leukemia, lymphoma, bladder.
cancer, carcinoma of unknown primary origin, each in one patient. The cumulative dose of CYC was higher among those with adverse events than those who had no adverse events. Short-term adverse events were seen in 17 (9%) patients. The most common short-term adverse event was haemorrhagic cystitis and was seen in 7 patients. These 7 patients received CYC without mesna prophylaxis and 6 of them were using oral CYC which is today rarely used because of its more frequent toxicity compared with intravenous CYC. Infections, leukopenia, azoospermia, nausea and vomiting were the other adverse events at short term. Malignancies (17 in 15 patients; 8%) and infertility (26 of 86 patients; 30%) defined as not having a child despite attempts were the leading adverse events at long term. At least 15% of deaths could be attributed to CYC which can actually be higher considering the retrospective nature of the study. CYC is still among the most potent drugs for life threatening complications of BS, but restricting its use only to induction therapy appears to be wise when considering its serious short and long-term adverse events.

Take home messages

- TNF-α inhibitors, especially infliximab and adalimumab, seem to be effective for refractory manifestations of BS (55).
- Cyclophosphamide is still valuable for life-threatening vascular involvement of BS, but its potential serious adverse effects necessitate short term use only (56).

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