Review

Behçet's syndrome: one year in review 2022

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ABSTRACT

This review highlights publications on different aspects of Behçet's syndrome (BS) that appeared in 2021 and provides a critical view. These publications include works on the epidemiology of BS across different continents, newly developed instruments to assess damage in BS, studies highlighting the immunopathogenesis, genetics and epigenetic factors, histopathology of the pathergy lesion, clinical and imaging aspects of vascular involvement, and safety and efficacy of therapeutic agents including tocilizumab, apremilast and direct oral anticoagulants.

Introduction

Behçet's syndrome (BS) is a variable vessel vasculitis that involves several organs and systems, causing ulcers on the oral, genital and intestinal mucosa, skin lesions that are most commonly in the form of papules, pustules or nodules, arthritis, uveitis, central nervous system lesions, venous and arterial thrombosis and arterial aneurysms. Here we aim at critically reviewing the most recent research on the epidemiology, disease assessment, immunopathogenesis, genetics, clinical features, and treatment of BS, as we had done in previous years (1, 2). We used PubMed to identify manuscripts on BS published between January 1st and December 31st, 2021.

Epidemiology

Epidemiology of BS in the USA was investigated using data acquired between 2014–2018 by the Rheumatology Informatics System for Effectiveness which stores data from rheumatologists representing more than 30% of the clinical rheumatology workforce in the USA (3). This is the largest BS dataset from this country, but the only data reported here are demographic features and the drugs that were prescribed. Among the 1323 patients, female to male ratio was 3.8:1. This is an interesting finding, since the frequency of BS seems to be similar among men and women in other parts of the world. Frequency of biologic and glucocorticoid use was similar between men and women. Overall, TNF inhibitors (TNFi) were used by 29.4% of the cohort, while glucocorticoids were used by 67.6%, conventional DMARDS by 48.0%, and colchicine by 55.0%. The dose and duration of glucocorticoids or other medications were not provided.

In a prevalence study of rheumatic diseases in Iran, a specific population of Zoroastrian individuals, a protected minority group was addressed (4). This study was part of a WHO initiative for recognising and preventing rheumatic diseases in developing countries, the Community Oriented Program for Control of Rheumatic Diseases (COPCORD). A total of 2000 individuals were interviewed, and no patients with BS were detected. This is interesting, since Iran is among the countries with a high BS prevalence. In another prevalence study within COPCORD, the estimated BS prevalence was 80/100,000 population. This difference may be interpreted as supporting the role of genetics in BS pathogenesis, assuming environmental factors were similar between Zoroastrian and other populations of Iran. However, this study was powered to estimate the prevalence of more frequent rheumatic conditions, and screening 2000 individuals might not have been enough to capture patients with BS.

A single-centre study from Tunisia reported on all patients with BS hospitalised over a period of 26 years (5). Among the 130 patients that were identified, the mean age at disease onset was 30.3±8.8 and the mean age at diagnosis was 34.6±9.4 years. Men made up 71% of the cohort and had more

uveitis, venous involvement, corticosteroid, immunosuppressive and anticoagulant use and more relapses. Two out of 35 patients who were anticoagulated experienced bleeding complications. Poor prognosis was associated with the male sex, uveitis, venous involvement, cardiovascular disease, longer follow-up and a delayed diagnosis.

Take home messages

- A large dataset from the United States showed an almost four-fold higher frequency of women among patients with BS. Biologic and immunosuppressive use was similar between men and women, with an overall 29% TNF inhibitor use (3).
- No patients with BS were detected among 2000 Zoroastrian individuals from Iran, a country with a high BS prevalence (4).

Outcome measures

Two different indices for the assessment of overall damage in BS have recently been published (6, 7). The first one, the BS overall damage index (BODI) was developed by an Italian multicentre group, through a multistep process (6). Candidate items were identified with a systematic literature review and highly ranked items were selected through a multi-round Delphi exercise among experts from different disciplines including rheumatology, ophthalmology, immunology and neurology. Following a reliability analysis using clinical vignettes, the instrument was validated in a multicentre cohort of consecutive patients by testing for correlation with vasculitis damage index, lack of correlation with Behçet's Disease Current Activity Form (BDCAF) and analysis of damage accrual over 5 years. The final index comprises 37 items that score damage in different types of organ involvement of BS as well as amyloidosis and potentially treatment related damage items such as gonadal failure, osteoporotic fractures, diabetes and malignancy. However, some items such as hepatic failure that can be seen in BS patients with Budd-Chiari syndrome, pulmonary parenchymal lesions, pulmonary hypertension and right heart failure secondary to pulmonary artery thrombosis, post-thrombotic syndrome secondary to deep vein thrombosis, cataract, glaucoma, renal failure and hypertension are missing.

The other damage index, Behçet's Disease Damage Index (BDI) was developed by a group of rheumatologists from Egypt (7). This time the candidate items were derived and modified from VDI by a group of experts. The instrument was prospectively validated among 1252 patients with various organs involved. In this instrument items are scored if they are present for at least 3 months, different from BODI that requires 6 months. This instrument does not capture some damage items such as parenchymal lung lesions, glaucoma, hypertension, and liver failure.

These are important efforts for standardisation of damage assessment in BS. Prospective validation of these instruments in different cohorts is needed and there seems to be room for improvement for both instruments.

Take home message

- Two new instruments were developed for overall damage assessment in BS. Both may benefit from some modifications, as certain damage items related to BS itself or to its treatment are missing (6, 7).

Immunopathogenesis

Two studies investigated immunepathogenetic aspects of herpes simplex virus type 1-induced BS in mouse models. One determined whether administration of the butyrate-producing bacteria *Eubacterium rectale* (*E. rectale*) could regulate dendritic cell activation and systemic inflammation (8). *E. rectale* was administered to these mice and peripheral blood leukocytes (PBL) and lymph node cells were isolated and analysed by flow cytometry. 16S rRNA metagenomic analysis was performed in the feces to determine the differences in the composition of the microbial population between normal and BS mice. Administration of *E. rectale* reduced the frequency of CD83+ cells and significantly increased the frequency of NK1.1+ cells with the improvement of symptoms. Moreover, the co-administration of colchicine and *E. rectale* also significantly reduced the frequency of CD83+ cells. Another study investigated the effects of environmental factors on the incidence of BS (9). The incidence of BS was tracked by adding different stressors and analysing DC activation markers using flow cytometry. The combination of conventional environment, noise stress, and HSV resulted in the highest rate of BS among all groups, suggesting that environment and stress may influence the incidence of HSV-induced BS in mouse models.

Neutrophil hyperactivation mediates vascular BS pathogenesis, via both a massive reactive oxygen species (ROS) production and neutrophil extracellular traps (NETs) release. Recently, neutrophil-mediated mechanisms of damage in non-vascular BS manifestations were investigated. NETs and intracellular ROS production were assessed in blood samples from 80 BS patients (46 with active non-vascular BS, 34 with inactive disease) and 80 healthy controls (10). Isolated neutrophils were incubated for 1 hour with an oxidating agent and the ability of pure colchicine pretreatment (100 ng/ml) to counteract oxidation-induced damage was assessed. Patients with active non-vascular BS showed increased NET levels compared to patients with inactive disease and controls. Moreover, in active non-vascular BS, NETs correlated with neutrophil ROS production and were particularly increased in patients with active mucosal, articular and gastrointestinal symptoms. These results suggest that neutrophil-mediated mechanisms might be directly involved in non-vascular BS, and NETs, more than ROS, might drive the pathogenesis of mucosal, articular and intestinal manifestations. A study investigated the potential role of NETs in promoting macrophage activation in BS, via quantifying NETs by measuring double-stranded DNA (dsDNA) levels using PicoGreen and calculating the proportion of NETosis (11). Macrophages were stimulated with BS- or HC-derived NETs, and IL-8 and TNF-α production and IFN-γ+ CD4+ T cell differentiation were measured using

ELISA and flow cytometry, respectively. Circulating NETs and neutrophil-derived NETs were significantly higher in BS than HC and BS NETs stimulated macrophages produced higher levels of IL-8 and TNF-α, and promoted IFN-γ+ CD4+ T cells differentiation, suggesting that higher levels of Histone H4 and oxidised DNA in BS NETs might mediate macrophage hyperactivation.

Innate lymphoid cells (ILCs) are lymphoid cells that have important effector and regulatory functions in innate immunity and tissue remodeling. Cell surface and cytotoxic granules (perforin and granzyme) expression of NK cells and ILCs were evaluated and labeled according to whole blood lysing protocol in peripheral blood samples obtained from BS patients and HC and cytokine levels of NK cells were investigated in stimulated peripheral blood mononuclear cells (13). Total ILC and ILC3+ cells were increased in active BS patients compared to inactive BS patients and HC. Since it is known that ILC3+ cells are similar to Th17 subset regarding their cytokine profile and transcription factor expression patterns, these findings may suggest that inflammatory microenvironment in BS patients might direct ILC cells to differentiate into ILC3+ subset, and IL-17 released by NK cells might have a role in neutrophilic infiltration.

The orientation of T cell subpopulations in paediatric BS was explored, focusing on regulatory T lymphocyte (Treg)/Th17 imbalance (14). A bias towards Th17 polarisation in active and remitting BS was observed. Although an increase in the number of Tregs was not detected, their Tregs limit CD4+ T cell differentiation into Th1 and Th17 cells.

The key players of ocular BS seem to be highly polarised Th1 and Th17 lymphocytes, natural killer T cells and γδ T cells, since they contribute to a highly destructive inflammatory environment (15). Another group studied the metabolite composition of sweat in BS (16) by metabolomics analysis and liquid chromatography tandem mass spectrometry and showed significant differences between BS and HCs in l-citrulline, l-pyroglutamic acid, urocanic acid, 2-oxoadipic acid, cholesterol 3-sulfate, and pentadecanoic acid levels.

Finally, a study using 3' mRNA next-generation sequencing-based genome-wide transcriptional profiling followed by analysis of differential expression signatures, Kyoto Encyclopedia of Genes and Genomes pathways, GO biological processes and transcription factor signatures highlighted the action of aberrant innate immune responses with a central role played by upregulated neutrophil chemotaxis. It did not support a major pathogenetic role for adaptive immunity-driven mechanisms (17).

Take home messages

- Emerging data seem to suggest that environment and stress may influence the incidence of HSV-induced BS in mouse models (8, 9).
- There is growing evidence that neutrophil-mediated mechanisms might be directly involved in BS, and NETs might drive the pathogenesis of both vascular and non-vascular involvement (10, 11).

Genetics

A genetic association study among 3477 patients with BS and 5967 controls recruited from 7 regions (Turkey, Spain, Italy, Korea, Tunisia, Japan and Western Europe) identified 2 novel genetic susceptibility loci: IFNGR1 (a binding sub-unit of the interferon gamma receptor that plays a role in the activation of the JAK/STAT signalling pathway) (rs4896243) and LNCAROD/DKK1(a long intergenic non-protein coding RNA acting as an active regulator of DKK1 and Wnt signalling, a pathway important in immune mediated diseases) (rs1660760) (18). The risk variants in IFNGR1 increased IFNGR1 messenger RNA expression in lipopolysaccharide stimulated monocytes. They also replicated the association of 6 previously identified loci (IL-10, IL23R, IL-12AS1, CCR3, ADO and LACC1) and determined 30 additional loci with a suggestive level of association that required further validation. The replication of the findings in populations of different ancestries was the strong point of the study. The functional significance of the findings was again not very clear (18).

The same authors wrote a comprehensive review about the history and methods of genetic analyses in BS starting from candidate gene association studies and culminating in various levels of genome wide association approach (19). They also elaborated on the recent advances in statistical genetics and imputation algorithms and proposed that determining the functional consequences of the findings presented a challenge since most of the BS related polymorphisms resided in the non-coding regions of the genome. They performed a regulatory enrichment analysis where they checked the frequency of epigenetic markers and they found 40 significantly over-represented histone marks in 27 cell types and tissues, denoting activation. The stronger enrichment patterns were observed in NK cells, lymphoblastoid cell lines, monocytes, B cells, T cells and neutrophils suggesting active roles for these in the pathogenesis. Other tissues implicated were the brain and the digestive tissue. They proposed that the total variance explained by the currently known genetic susceptibility loci for BS accounted for 58.75%of the genetic contribution to the development of BS, implying that approximately 40% of the genetic aetiology of BS still needs to be identified (19).

A high resolution next-generation sequencing was performed in 60 Egyptian patients with BS and 160 HC (20). HLA-B 51:08, HLA-A 68:02, HLA-C 16:02 and the HLA class 2 alleles DRB1 13.01, DQB1 06:03 were associated with BS while HLA-A 03:01 and HLA-DPB1 17:01 were protective. HLA-B 51:08 was the main susceptibility allele and was related to eye involvement and was in strong linkage disequilibrium with HLA-A 02:01 and HLA-C 16:02. The association with various Class 2 alleles was interesting but the relatively small sample size and the lack of replication in other ancestries were the weak points of the study (20).

An Italian group studied the relationship between a circulating mRNA profile (ci-miRNA) (a class of small non-coding RNA that acts as an inhibitory post-transcriptional regulator of gene expression) and BS (21). The

profile was evaluated by microarray in a screening cohort of 16 patients with BS and 18 HC and validated by PCR in a validation cohort of 30 patients with BS, 30 HC, 30 patients with systemic lupus and 30 giant cell arteritis. The microarray showed 29 differentially expressed human ci-mRNAs in BS. PCR analysis confirmed the de-regulation of miR-224-5p, miR-206 and miR-653-5p. The functional annotation analyses showed that the most affected pathways by these miRNAs were cell-matrix interactions, oxidative stress and blood coagulation, all related to thrombo-inflammatory mechanisms. The results suggested an attractive theory of a possible epigenetic control of BS-related thromboembolism but the small number of patients studied and the absence of a predominance of clinically apparent thromboembolic phenomena cast doubt on its significance (21).

A review article by Mehmood and Wallace discussed the microbiome data in BS and its possible interaction with their genetic background (22). There was a long list of increased and decreased bacteriae in the gut and oral microbiota of patients with BS but the main principles were: a) The discovery of a significant reduction in the alpha diversity and depletion of butyrate producing bacteria in the gut microbiome of BS patients compared to controls and a parallel finding of a reduction of butyrate levels in faecal samples. This seemed to be important because butyrate is responsible in inhibiting intestinal pro-inflammatory cytokines and in promoting a regulatory T cell lineage; b) The fact that a reduction in butyrate causes downstream effects of promoting immune-pathologic-T effector responses leading to gut inflammation; c) The finding that Toll like receptors, IL-23, IL-22 and fucosyltransferase play a role in the potential pro-inflammatory effects of various microbiomes. The available data on the subject is very variable and further studies are needed for a more rational framework (22).

Işık and Görmez worked on a method of diagnosing BS using a combination of genetical data obtained from genome wide analyses with biological information and machine learning classifiers (23). They used several feature selection algorithms to find the best subsets that will aid discrimination, reduced the number of SNP's to 13611 out of 311459 and claimed to obtain a 99.64% of accuracy of disease prediction. The genes which were significant were HLA-B (rs1058026), HCP5 (rs1131896, rs2848713), KIR-REL3 (rs522686), LAMP5-AS1 (rs16995979), MICA (rs2256028) and SCD5 (rs6535384). They presented their work as an important tool in the so-called era of personalised medicine but diagnosis of BS according to clinical criteria seemed more robust in the final analysis (23).

A group from China searched for gene signatures that would aid in the early diagnosis of BS and that would cast light on its pathogenesis (24). They identified a so-called hub gene after examining 82 differentially expressed genes and situated CCL4 as the central hub. Gene-set enrichment and immune cell subset analyses were applied on high and low CCL4 expression groups. Higher expression of CCL4 was accompanied by larger fractions of CD8+ T cells, natural killer cells, M1 macrophages and activated mast cells. They also identified a group with down regulated NPY2R m RNA expression. They concluded that CCL4 and NPY2R could be diagnostic biomarkers for BS but this again does not seem to have the advantage of diagnosing the condition on a clinical basis. Moreover, there was no mention of the universal association of HLA-B51 with BS (24).

An informatic analysis to determine various molecular and genetic overlaps with BS and other "autoimmune" diseases utilised a convergent functional genomics approach and were able to ascertain 7 BS consensus genes and 16 overlap areas (25). The 7 BS consensus genes were HLA-B, IL-10, IL23R, HLA-A, STAT4, MICA and ERAP1 as expected while the overlap areas entailed conditions such as sarcoidosis, uveitis, Sjögren's syndrome, haemolytic anaemia and myositis. The idea that all inflammatory diseases could share various genetic mechanisms was an attractive hypothesis, but the absence of autoimmune features in BS and the lack of any clinical or pathologic association of BS with any of the mentioned conditions other than uveitis cast doubt on its validity (25).

IL33/ST2 polymorphisms were studied in 585 BS patients with uveitis and 834 healthy controls since IL33 is an emerging pro-inflammatory cytokine and the so-called polymorphism has been implicated in the pathogenesis of various autoimmune diseases such as rheumatoid arthritis and systemic sclerosis (26). rs3821204 was associated with BS uveitis whereas the frequency of rs2210463G was lower in patients with genital involvement. Complete and incomplete BS patients had varying associations suggesting a different genetic background among the two populations. The limitation of the study to Chinese Han patients and the possible selection bias due to patient enrolment from only tertiary ophthalmological centres were the weak aspects of the study (26).

Take home messages

- Two novel susceptibility loci were identified in a group of patients with BS who were recruited from 7 different regions: IFNGR1, a sub-unit of a receptor that plays a role in the activation of the JAK-STAT pathway and LNCAROD/DKK1, a regulator of DKK1 and Wnt signalling (18).
- A study showed deregulation of 3 micro RNAs (miR-224-5p, miR-206 and miR-653-5p) in BS and suggested that it was related to thromboembolic disease (21).
- A review of microbiome data in BS emphasised a significant reduction in the alpha diversity and depletion of butyrate producing bacteria in the gut microbiome and a parallel finding of a reduction of butyrate levels in faecal samples leading to gut inflammation (22).

Clinical features

Eye involvement

Standardisation of Uveitis Nomenclature (SUN) Working Group used machine-learning to develop diagnosis criteria for Behçet's uveitis (BU) (27). They developed a set of criteria that in-

cludes a compatible uveitic syndrome and evidence of systemic BS according to International Study Group Criteria.

Significantly higher subfoveal choroidal thickness (SFCT) was observed in BU patients compared to patients without uveitis, using enhanced depth imaging optical coherence tomography (EDI–OCT), a non-invasive method that may be useful for assessing subclinical choroidal involvement (28). Elevated SFCT did not show BU activity, but may predict future ocular involvement. The study had some limitations, including small sample size and case heterogeneity.

Fluorescein angiography (FA) findings were compared with BS ocular attack score 24 (BOS24) for predicting visual acuity in BU (29). BOS24 scores ≥6 (p<0.0001), severe posterior pole leakage (p<0.004), and arterial narrowing (p<0.0001) were significantly correlated with poor visual prognosis. They found no significant link between disc leakage and VA. FA and the BOS24 scoring system may be useful for predicting poor vision. Another study assessed ultra-widefield FA (UWFA) in monitoring adalimumab response in 38 patients with BU (30). There was significant improvement in anterior chamber cell grading, vitreous haze, vascular and capillary leakage ratings at weeks 6, 14, and 30 UWFA scores improved even more in patients without clinical inflammation. Retinal vascular leakage may be used as a surrogate marker for adalimumab efficacy and may play a role in making treatment decisions.

Studies using OCT-A for the assessment of BU reported a significant decrease in foveal density and superficial and deep capillary plexus vessel density (VD), increase in foveal avascular zone (FAZ), parafoveal microvascular alterations, a correlation between visual acuity and VD, correlation between FAZ area and central macular thickness (CMT), as well as correlation of FAZ area and capillary VD with age, BCVA, duration of uveitis, CMT, and FA score (31-37). One of these studies additionally investigated retinal and choroidal microvascular features in both macular and peripapillary areas of BU (35). The authors reported a significant peripapillary VD decrease in BU patients compared to HC. They found a positive correlation with BCVA and peripapillary VD and proposed peripapillary radial capillary density as a novel indicator of disease progression for BU.

In a study that compared changes in retinal microvasculature (OCTA) and choroidal thickness (EDI-OCT) during active disease and remission, although deep capillary plexus (DCP) density and FAZ area were more useful as prognostic indicators, superior capillary plexus (SCP) density was more indicative of activity (36). Sub foveal choroidal thickness was an indicator of visual function, but its change did not precisely reveal disease activity.

Another study which analysed the correlation of OCT parameters with FA reported that central subfield macular thickness, peripapillary retinal thickness and peripapillary retinal nerve fiber layer thickness as well as visual acuity were significantly correlated with angiographic inflammatory activity (37).

A study assessed macular cone density and regularity with an adaptive optics scanning light ophthalmoscope (AOSLO) in BS patients (38) with a visual acuity of 20/20 or above (38). AOSLO detected hyporeflective patches in BS patients with and without a history of uveitis that were not visible on colour fundus photography or OCT; these were not seen in the control group. Cone density was significantly lower in BU patients compared to controls. The proportion of hexagonal Voronoi domains in BS eyes with and without uveitis was significantly lower than in controls. This first study of photoreceptor morphology in BS using AOSLO and revealed macular photoreceptor loss in BS patients with and without uveitis.

Inflammatory markers were evaluated in a retrospective study including 50 patients with BU and 52 with HLA-B27-related uveitis (39). Both groups had elevated ESR, CRP, and C-reactive protein/albumin ratio during active uveitis, whereas white blood cell count, albumin, NLR, and LR were not different. These findings require confirmation in a larger cohort.

A study from the United Kingdom showed that the yearly incidence of BU was 0.04/100,000. 60% of the patients had bilateral uveitis, 68% had vitritis, and 46% had anterior uveitis (40). Cystoid macular oedema, vitritis, and retinal ischaemia were the leading causes of visual morbidity. A retrospective study of 21 patients with late-onset BU showed that uveitis was bilateral in 17 eyes, panuveitis was the most common presentation affecting 13 eyes, and macula was involved in 14 eyes (41). Although the course of ocular involvement in late-onset BS is thought to be relatively mild, blindness was observed in 4 patients.

A nationwide multicentre study including 3363 patients compared sociodemographic features of patients with BU and other non-infectious uveitis (42). BU patients had lower education and socioeconomic levels than the other non-infectious uveitis. Another study from Turkey reported higher depression scores, but similar anxiety scores in patients with posterior segment involvement (43).

Skin and mucosa

A skin histopathology study of pathergy positive and negative patients showed dermal vasculitis indicated by fibrinoid necrosis in pathergy positive (55%) as well as negative patients (39%) (44).

Musculoskeletal

A multicentre retrospective study of 151 BS patients with joint involvement showed that knees, ankle, and proximal interphalangeal joints were most commonly affected (45).

Clinical phenotypes

BS may not be a single disease, but rather a multi-system complex disorder composed of distinct clinical phenotypes each with probably different disease mechanisms (46, 47). A total of 4 clinical phenotypes were previously suggested as indicated by a cluster analysis (48): 1) skin-mucosa; 2) eye; 3) vascular and 4) papulopustular lesions and arthritis. These clusters were confirmed 10 years later in a different cohort as well as in patients with familial BS (49). Several studies reappraised the notion of clinical phenotypes in 2021 (50-54). Gastrointestinal (GI) subgroup

emerged alone as a distinct phenotype in China and Japan in addition to the previously described phenotypes. Additionally, well known age and gender characteristics of BS were described in retrospective cohort studies (55, 56). There are certain differences between cluster studies regarding the identified phenotypes. Further work is needed to delineate whether these are real differences or result from methodological differences such as statistical methods, setting, disease criteria used, and definition, timing and the ascertainment method of manifestations.

Vascular involvement

A multicentre retrospective study showed a post-thrombotic syndrome (PTS) frequency of 62% and severe PTS of 18% among 205 BS patients with lower extremity DVT (57). Bilateral involvement, residual iliofemoral thrombi, older age and high activity scores were predictors of PTS whereas increased BMI and not using immunosuppressives were independently associated with severe PTS. Use of interferon-α was associated with better recanalisation compared with azathioprine alone as previously reported (58). Another multicentre retrospective study reported the vascular findings among 61 BS patients with Budd-Chiari syndrome (59). The low mortality rate (14.8%) compared to previous reports (14-47%) (60, 61) may be due to the relatively high frequency of silent cases (45/61) and the short follow-up.

A cross-sectional uncontrolled study of cardiac MRI in a small cohort of asymptomatic BS patients (n=30) showed that 20/30 patients had some level of pericardial, endocardial or myocardial abnormalities (62). A retrospective study investigated the clinical characteristics and outcome of 22 BS patients with aortic regurgitation and/or aortic involvement (63). The risk of ischaemic heart disease was found to be comparable between BS (n=1554) and controls (n=3108), after propensity score matching for confounding factors in a study based on Taiwan National Health Insurance Database (64). Another study using nationwide population data of 10 505 818 individuals between 2009 and 2012 showed that the incidence of BS was reduced in subjects with metabolic syndrome (65). Clinical significance is unclear since no diseased controls were included and the data is based on diagnosis codes, carrying the risk of misdiagnosis.

Growing evidence indicates that venous wall thickness (VWT) of the lower extremity veins is increased in BS compared to that found in several inflammatory diseases and healthy controls (66-71). VWT was especially increased among those BS patients with no apparent vascular involvement suggesting that VWT could be an early indication of vascular inflammation (66, 71). Furthermore, Alibaz *et al*. suggested that VWT could be used as a distinctive diagnostic tool for the differentiation of BS from other inflammatory diseases (68). A letter to the editor (72) commented on these findings and suggested that an overestimation of diagnostic accuracy and absence of external validation were the main issues in this study.

Nervous system involvement

A study that explored association of cranial MRI findings with clinical features of 55 BS patients with parenchymal nervous system involvement showed that the most frequently affected structures were the rostral pons, mesencephalon, and diencephalic region (73). Use of non-standardised MRIs of different qualities and resolutions instead of standardised 3D FLAIR was the main limitation of the study.

The width of the third ventricle was measured in consecutive cranial MRIs of 13 BS patients with parenchymal nervous system involvement, 5 with relapsing remitting multiple sclerosis (RRMS), and 9 HC (74). They observed a faster rate of enlargement of the third ventricle in the chronic progressive type than that observed in the acute type and RRMS. Small sample size and unblinded measurements were the main limitations of the study.

A study including 24 BS patients with cerebral venous sinus thrombosis showed a high prevalence of deep CVST (n=18; 75%) confirmed by angiographic demonstration of basal vein of Rosenthal thrombosis (75). The results need to be reproduced in a larger cohort and in different ethnic populations.

Gastrointestinal (GI) involvement

A cross-sectional study of 1232 consecutive BS patients who routinely underwent voluntary endoscopy showed that 22% had GI ulcers (76). Another retrospective study of 163 patients with intestinal BS showed that 27.6% did not fulfil intestinal Behçet's Disease criteria (77).

Juvenile-onset BS

A retrospective study with a short follow-up of 2 years comparing 64 juvenile-onset and 332 adult-onset BS patients showed that juvenile-onset patients had less major organ involvement and less severe disease course (79).

Pregnancy

Two retrospective case-controlled studies evaluated the outcome, complications and disease flares associated with pregnancies with BS and found contradictory results (79-80).

COVID-19

A number of cohort studies and case series from Turkey, USA, Spain, Iran and Italy reported the incidence and outcome of BS patients with COVID-19 (81-88). Although the incidence of COVID-19 was increased compared to the general population, the outcome was mild with no increased mortality or thrombotic events.

Take home nessages

- OCT-A is a novel imaging technique, but it still needs enhancement and standardisation in Behçet's uveitis (31-37).
- Fibrinoid necrosis can be found in the histopathologic examinations of pathergy positive as well as negative patients (44).
- Evidence indicates that BS may be composed of distinct clinical phenotypes each with probably different disease mechanisms (50-54).
- Silent forms of Budd-Chiari syndrome due to BS result in a more favourable outcome (59).
- Immunosuppressive treatment is essential to prevent severe PTS (57).

- Wall thickness of lower extremity veins is increased compared to several inflammatory diseases and could be a distinctive feature of BS (66-71).
- Rostral pons, mesencephalon, and diencephalic regions were most frequently affected structures as shown in 3-D MRI study (73).
- Gastrointestinal involvement can be found in 22% of asymptomatic patients when evaluated with routine endoscopy (76).
- Juvenile-onset patients had less major organ involvement and less severe disease course (79).
- COVID-19 usually runs a mild course among BS patients (81-88).

Management

TNF inhibitors

According to the updated EULAR recommendations TNFi can be given as first-line treatment to patients with sight threatening posterior uveitis, but in clinical practice they are usually preserved for patients who are refractory to conventional immunosuppressives (89). In a retrospective study from China the efficacy of immunosuppressives was compared with that of adalimumab plus immunosuppressives in treatment-naïve patients with retinal vasculitis (90). Forty-five patients (61% women) with very short median disease duration (2 weeks) were followed-up for a median of 17 months. Both treatments were effective, but improvement in BCVA, anterior chamber inflammation, vitritis and fluorescein angiography scores were more pronounced in the adalimumab group. The diversity of conventional treatments, short follow-up and female predominance of the patients necessitate further studies. Similarly, a retrospective study from Japan reported a better long-term outcome (median 132 months) among 7 patients who received infliximab early during the course of BS uveitis (<18 months) (91). A multicentre observational study from Spain reported that infliximab led to rapid and sustained improvement of BCVA, macular thickness and intraocular inflammation in 117 BS patients with refractory uveitis and 78 patients achieved ocular remission at 32 months (92). Remission was maintained in 18 patients receiving Infliximab at 5 mg/kg after dose optimisation (reducing the dose or prolonging the infusion intervals). The results of a systematic literature review based on 13 observational studies suggest that monoclonal TNFi are effective in providing clinical remission and mucosal healing in the treatment of GI involvement of BS (93). Despite the lack of controlled trials monoclonal TNFi have become standard treatment for all refractory manifestations of BS. Their place as first-line agents and dose optimisation in responders await further studies.

Tocilizumab

A multicentre, observational study from France compared the efficacy of TNFi (infliximab and adalimumab; 149 patients) with tocilizumab (55 patients) in refractory macular oedema of diverse aetiologies (94). Thirty-five patients (17%) had BS and only 3 received tocilizumab. The complete response rate was found to be 22% with TNFi and 36% with tocilizumab. Tocilizumab was twice as effective as TNFi for macular oedema, but it should be underlined that 76% of patients treated with tocilizumab had previously been refractory to TNFi. The number of BS patients was small, but showed an increased risk for low visual acuity when compared to the whole cohort. A multicentre retrospective study from Spain looked at the efficacy of tocilizumab in 16 BS patients who were refractory to previous treatments including biologics (95). The main indications for tocilizumab treatment were ocular involvement (n=14) and CNS involvement (n=5) followed by active mucocutaneous lesions and arthritis. Tocilizumab was effective in achieving complete ocular and CNS remission but its effect was less pronounced for oro-genital ulcerations and arthritis. Unlike monoclonal TNFi, which appear to be effective for all manifestations of BS, tocilizumab's effect appears to be limited mainly to ocular and CNS involvement.

Apremilast

Apremilast, an oral inhibitor of phosphodiesterase 4, is approved for the treatment of oral ulcers of BS based on the results of a 12-week placebo-controlled Phase 3 trial (96). This trial also included a 52-week extension phase with all patients in the placebo group switching to apremilast and a 4-week post-treatment observational period. Of the 207 patients enrolled in this trial, 178 (86%) entered the extension phase and 143 (80%) completed week 64 (97). The improvement in the number of oral ulcers obtained with apremilast in the controlled phase were maintained in the extension phase and patients switching from placebo to apremilast also showed similar response regarding suppression of oral ulcers. However, the number of oral ulcers increased after discontinuation of apremilast. Data were not available regarding the efficacy of apremilast on other manifestations of BS. Diarrhoea, nausea and headache were the main side effects.

A multicentre, observational study from France assessed the efficacy of apremilast in 50 patients with active mucocutaneous and/or joint involvement refractory to other treatment modalities including biologics (98). Apremilast was mainly combined with colchicine (36%), prednisolone (28%), methotrexate (6%) and biologics (6%). A completers analysis revealed that complete or partial response of joint involvement was 82% at 6 months whereas complete response for oral ulcers and genital ulcers was 73% and 94%, respectively. The discontinuation rate of apremilast was high (46%) with side effects (30%) as the main reason. A retrospective, multicentre study from Spain assessed the efficacy of apremilast on orogenital ulcers (99). Included were 51 patients with mainly active orogenital ulcers but also with joint and skin manifestations who were refractory to previous treatment modalities including biologics. Apremilast was mostly combined with colchicine and glucocorticoids followed by immunosuppressives and biologics. Treatment with apremilast was effective in reducing the numbers of orogenital ulcers and skin lesions but the effect was inconsistent on joint symptoms. There was no difference between apremilast monotherapy and combination treat-

ment. Continuation of apremilast was 78% at 8.5 months. Since data on oral and genital ulcers were combined, the effect of apremilast on genital ulcers specifically could not be assessed. The study also seems to suffer from selection bias because it included only patients continuing apremilast. A systematic literature review and meta-analysis of 8 articles looked at the efficacy of apremilast on oral ulcers and other manifestations of BS (100). Two of the selected 8 articles were RCT's and the remaining 6, including 1 abstract in Japanese, were observational studies. Compared to baseline, at week 12 apremilast was effective not only for oral ulcers but also for genital ulcers, erythema nodosum, follicular lesions, joint symptoms and for disease activity assessed by BDCAF.

It appears that apremilast might be an option especially for treatment resistant oral ulcers and perhaps for other mucocutaneous and joint symptoms of BS. Whether it should be added to existing treatment or used as mono-therapy awaits further studies. Also, studies comparing apremilast with immunosuppressives will help us to understand its place in the treatment of BS.

Anticoagulants

The experience so far suggests that anticoagulation with vitamin K antagonists does not prevent the risk of venous thrombosis relapses but might be beneficial in decreasing the risk of post-thrombotic syndrome (101). The results of a multicentre, retrospective study assessing the efficacy of direct oral anticoagulants (DOA) in the treatment of venous thrombosis may challenge this notion (102). The study included 44 patients (75% men) having a wide variety of venous thrombi, mostly (57%) in the lower extremities and 50% had multiple thrombi. The most frequently used DOA was Rivaroxaban (34 patients) followed by Apixaban (6 patients). DOA treatment was combined with colchicine (25 patients), corticosteroids (26 patients), classical immunosuppressives (19 patients) and TNFi (20 patients). Eleven patients experienced 13 relapses during a median follow-up of 21 months, defined as a new venous thrombosis occurrence at another site or an extension of the current thrombosis on imaging. Eight of these relapses occurred when treatment with DOA was stopped. Cox analysis showed a significantly reduced risk of venous thrombosis recurrence with DOA that was more pronounced when DOA was used in combination with immunosuppressives. These results seem to be encouraging, but the cumulative incidence of relapse which was 44% at 4 years is similar to a previous study reporting 37% relapse rate at 5 years under immunosuppressive and classical anticoagulant treatment (103).

Ustekinumab

The efficacy of ustekinumab, an anti-IL12/23 antibody, was tested in 15 BS patients with active, treatment-resistant oral and/or genital ulcers in an open-label prospective, 52 weeks study (104). Ustekinumab appeared to be effective in reducing the number and pain of oral ulcers, genital ulcers, skin involvement and articular symptoms justifying further studies.

Surgery for aortic valve involvement

Aortic valve involvement is almost only confined to BS patients from Far-East countries. Aortic valve replacement (AVR) is often complicated by valve dehiscence leading to re-operations. A retrospective study of 20 BS patients from China points out to the importance of pre-operative diagnosis of BS as the cause of aortic valve involvement (105). Thirteen of the 15 pre-operatively undiagnosed patients who underwent classical AVR developed valve dehiscence and underwent re-operation within a mean of 11 months. However, pre-operatively diagnosed 5 BS patients underwent modified AVR and none developed valve dehiscence during follow-up.

Another retrospective study from China reported that biologics (TNFi or tocilizumab) given pre-operatively or within 3 months post-operatively with concomitant immunosuppressives were associated with significantly reduced paravalvular leakage after surgery (106).

Take home messages

- Early initiation of TNFi might lead to better visual prognosis at long-term (90-91).
- Tocilizumab seems to have a variable treatment response in different disease phenotypes of BS (94, 95).
- Whether apremilast is superior to immunosuppressives in terms of oral ulcer suppression warrants further studies (97-99).
- Further studies are needed to understand the place of direct oral anticoagulants in preventing venous thrombosis recurrences (102).
- Ustekinumab might be an emerging option for treatment of resistant mucocutaneous and joint manifestations (104).
- Modification of the operation technique and pre-operative use of biologics seem beneficial in decreasing the risk of paravalvular leakage after AVR (105-106).

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