

One year in review 2019: Behçet's syndrome

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ABSTRACT

Several epidemiologic studies report on the prevalence of Behçet's syndrome (BS) and demographic and clinical findings in patients from different countries and ethnicities. Although these studies point out geographic differences in disease course, methodologic differences make it difficult to compare the results of these studies. Recent data suggest that neutrophil extracellular trap levels are elevated in patients with BS, and that it may be a potential therapeutic target for the reduction or prevention of BS-associated thrombotic risk. Details on the mode of functioning of ERAP have been delineated and further epigenetic data reported. Wall thickness of lower extremity veins is increased among BS patients without any apparent clinical involvement. Magnetic resonance (MR) venography and Doppler ultrasonography (USG) were comparable in the diagnosis of chronic deep vein thrombosis, while MR venography is more effective in detecting collateral formations. Results were also collected on some dietary and non-dietary factors in triggering oral ulcers, while smoking seems to have a protective role. With regards to the therapy, it has been demonstrated that endovascular interventions carry the risk of inducing pathergy phenomenon. Apremilast has been convincingly shown to be useful for oral ulcers of BS and classical immunosuppressives are effective as first line therapy in more than half of patients with uveitis. While infliximab and adalimumab seem to be equally effective in the treatment of refractory uveitis of BS, the combination of adalimumab and immunosuppressives appears to be superior to immunosuppressives alone for venous thrombosis of the extremities. In addition, tocilizumab might be an alternative to anti-TNF agents for patients with arterial involvement refractory to immunosuppressives. On the

other hand, the place of IL-17 inhibition in the treatment of BS still remains questionable.

Introduction

Behçet's syndrome (BS) is a multisystem variable vessel vasculitis that can cause oral and genital ulcers, papulopustular and nodular skin lesions, arthritis, uveitis, venous and arterial thrombosis, arterial aneurysms, central nervous system lesions and gastrointestinal ulcers. It has a distinct geographic spread along the ancient Silk Route (1, 2). It usually starts during the second or third decade of life, but the demographic features of patients and frequency of clinical manifestations show important differences across countries and ethnicities. The exact pathogenesis is not understood and the heterogeneity of clinical manifestations and disease course (3, 4) highly impacts on the quality of life (5, 6) and makes it difficult to advocate a uniform treatment strategy. Management is planned according to the age and sex of the patients and the organs that are involved. Many new studies have been published over the last year highlighting the epidemiology, immunopathogenesis/genetics, clinical findings and management of BS. As the previous yearly reviews published in this supplement (1, 7), the aim of this manuscript is to provide a compendium of the most relevant studies that have been published in this field in the last year.

Epidemiology

Various studies have addressed the epidemiological complexity of BS with different aims and methodologies. A longitudinal cohort study from the midwest region of Ireland aimed to determine the natural course of their patients with BS and compare it to cohorts from Europe and other Mediterranean countries (8). Twenty-five patients who

fulfilled the International Study Group (ISG) or International Classification for Behçet's Disease (ICBD) criteria were included and followed longitudinally for clinical features, disease activity and outcome. Except for one patient from Syria, all of the patients had Irish ancestry. The point prevalence of BS was calculated as 6.5 per 100,000 population and, if only patients who fulfilled ISG criteria were included, the prevalence was 6.2 per 100,000. This was higher than the prevalence previously reported from Dublin (2.3 per 100,000) and from other northern countries such as Scotland (0.36 per 100,000) and the UK (0.64 per 100,000) (9-11). Whether this difference between the 2 reports from Ireland 22 years apart reflects increased awareness for BS among physicians, differences in the criteria used for including patients or a real increase in prevalence, is not clear. Among their 25 patients with BS, 16 were women, 9 were men and the median age was 40.0 years. The frequencies of clinical features were comparable to other European BS cohorts with oral ulcers in all of the patients, genital ulcers in 92%, skin lesions in 92%, joint involvement in 40%, eye involvement in 32%, thrombosis in 12% and pathergy positivity in 8%. An unusual finding was that 5 of their patients (20%) had structural laryngeal changes that were attributed to BS. Only one of the 25 patients was HLA-B51 positive.

Another study from Egypt attempted to estimate the prevalence of BS, identify the frequency of clinical manifestations and the impact of sex and age of onset on the frequency of these manifestations (12). Although the authors suggest that this is a population-based study, the patients included were adults who were registered to one of the included centres and fulfilled the International Study Group criteria. A total of 1526 patients were identified from 26 centres. The overall estimated prevalence was 3.6 per 100,000 population. The authors indicate that this may be an underestimate, as patients treated in private clinics and ophthalmology and dermatology clinics are not included. It is known that the prevalence of BS generally increases from north to south (13). One

of the aims of this study was to compare the prevalence of BS in northern and southern parts of Egypt. However, a significant difference was not observed between the north and south of the country. The prevalence was highest in the two main cities, Alexandria and Cairo as 15.3 and 8.7 per 100,000, respectively. It was commented that this may be due to referrals from other parts of the country. Patients had moderate disease activity with a mean Behçet's Disease Current Activity Form (BD-CAF) score of 4.48 ± 4.28 during this cross-sectional analysis. The male to female ratio was 2.6:1. Major organ involvement including venous, nervous system and gastrointestinal system were more common among men and joint involvement was more common among women. Frequency of clinical manifestations was similar between juvenile-onset and adult-onset patients. The demographic and clinical features of patients with BS was analysed in Iran and compared to cohorts from other countries included 7641 patients with BS diagnosed according to expert opinion (14). Patients were referred from all over Iran and followed at Tehran University. Among these patients 56% were men, the mean age at disease onset was 25.6 ± 9.8 years and the mean disease duration was 11.7 ± 8.9 years. The most common manifestation was oral ulcers (97.5%) followed by genital ulcers (64.4%), skin lesions (62.2%), eye involvement (55.6%), joint involvement (38.1%), vascular involvement (8.9%), gastrointestinal manifestations (6.8%), epididymitis (4.6%), and nervous system involvement (3.9%). Gastrointestinal manifestations included findings not specific for BS such as gastroduodenitis and peptic ulcer. The pathergy test was positive in 50.4% of the patients. The authors noted a decrease in pathergy positivity in their cohort, from 71.8% among the first 1,000 patients recorded between the years 1977 and 1989, to 37.8% in the last 1,141 patients recorded between 2010 and 2018. They had reported the number of BS patients in their registry as 6,500 in 2010 and in that report the number of new patients per year was 282 (15). Interestingly since their report in 2010, the number

of new patients per year has dropped to 143. The authors do not comment on whether this is related to a difference in referral patterns or a real decrease in the incidence of BS in Iran. HLA-B5 was positive in 53.5%, HLA-B51 was positive in 48.2% and HLA-B27 in 8.4% of the patients who were studied. There was no difference in clinical manifestations according to age of onset.

A small cohort of 47 patients with BS over the age of 14 who were followed in a tertiary centre in southwestern Saudi Arabia between 2012 and 2017 were reported in a retrospective study (16). The authors indicate that their cohort was comparable to Middle East cohorts especially regarding demographic features such as male predominance (1.24:1), however, there were interesting differences in the frequency of some of the features. Gastrointestinal involvement, which is an infrequent manifestation among BS cohorts from the Middle East, was seen in 34% of their patients. However, it is not clear whether these patients had confirmed gastrointestinal involvement of BS or only nausea and vomiting. On the other hand, in contrast to other cohorts erythema nodosum-like lesions were seen in only 4.3% of the patients. Additionally, they reported pulmonary involvement in 8 patients (17%) and 4 of these had chest pain and 4 had shortness of breath with no explanation of the underlying pathology. Family history was frequent at 10.9%, however, they did not report whether this number also included second-degree relatives.

Another study on the prevalence of BS comes from Switzerland, where patients with BS followed at the University Hospital of Bern were identified and rheumatologists in the same area as well as departments of other specialties taking care of patients with BS in the same University were contacted with the aim of including all BS patients in the canton of Bern and the neighbouring cantons (17). A total of 60 patients fulfilled the ICBD criteria and the prevalence was calculated as 4.03 per 100,000 inhabitants. This is similar to what was previously reported from South Switzerland (18). On the other hand, the prevalence in non-Swiss indi-

viduals from high-risk countries of BS was calculated as 19.5 per 100,000. Fifty-two patients followed at the University of Bern whose diagnosis was confirmed by the expert rheumatologists in the unit were included in a database and their clinical and laboratory data were analysed. Forty-six of these patients fulfilled the ICBBD criteria. Thirty-one patients were of Swiss origin. The median age at first symptom was 21.4 years and the median disease duration was 19 years with a mean diagnostic delay of 8 years. The diagnostic delay was 2 years longer in patients of Swiss origin compared to patients of non-Swiss origin. On the other hand, there was no difference in frequencies of organ involvement across different ethnicities. Overall, oral ulcers were the most common symptom (92%) followed by skin lesions (79%), joint involvement (77%), genital ulcers (67%), eye involvement (48%), vascular involvement (52%), nervous system involvement including headache and cerebral sinus thrombosis (42%) and gastrointestinal complaints (31%). Pathergy was positive in 65% of the patients. Interestingly anti-TNFs were used in 64% of the patients.

In a study from a tertiary referral centre in Southwestern United States the estimated prevalence was reported as 8.9 per 100,000 when ISG criteria were used and 10.9 per 100,000 when ICBBD criteria were used (19). This is higher than the prevalence reported in a previous study from the US as 5.2 per 100,000 population (20). Fifty-two of the 63 patients who fulfilled ISG criteria (82.5%) were women. This female predominance was previously observed in other US cohorts and it was thought to be associated with higher health care utilisation by women (21). The mean age at diagnosis was quite high, 41.0 ± 14.9 years. Among these patients 49.2% were Hispanic Americans, 31.7% were non-Hispanic European Americans (European Americans), 14.3% were Native Americans, and only 4.7% were Silk Route Americans with ancestry from Middle East and the Silk Route through Asia. HLA-B51 was positive in 74.2%, 42.1%, 89.0% and 100% of the patients in these ethnic groups, respectively. High frequency of

HLA-B51 positivity in the general population was previously shown among Native Americans, but an increased frequency of BS had not been shown (22-24). Despite the differences in HLA-B51 positivity rates, the frequency of clinical manifestations was quite similar between the Hispanic Americans and European Americans. On the other hand, among Americans of Silk Road descent ocular involvement rate was higher than in the other groups. Overall, the most common manifestations were oral ulcers (100%), genital ulcers (61.9%), acneiform lesions (69.8%), papulopustular lesions (52.4%), arthritis (41.3%), anterior uveitis (23.8%), posterior uveitis (15.9%), deep vein thrombosis (14.3%), erythema nodosum (7.9%), arterial thrombosis (6.3%), and retinal vasculitis (1.6%). Pathergy was positive in 15.9% of the patients. Regarding medications, interestingly 39.7% of the patients were using or had used hydroxychloroquine for BS. However, it was impossible to comment on its efficacy due to the study design, but the authors suggested that the fact that 27.9% of the patients continued to use the drug in the long term is an indication of its success.

Interestingly, a retrospective study from Japan reported on the patterns of uveitis among patients admitted to the ophthalmology unit of the University of Tokyo between 2013 and 2015, and compared it to those between 2004 and 2012, showing that BS was the third most common cause of uveitis (4.4%) after herpetic iridocyclitis (7.5%) and sarcoidosis (6.1%) in the recent cohort of 750 new patients with uveitis (25). A definite diagnosis could not be made in 39.1% of the patients. There was a progressive decrease in the frequency of BS among uveitides over the years. The frequency was 4.9% in the 2004-2006 and 2007-2009 cohorts, and 4.7% in the 2010-2012 cohort compared to 4.4% in their recent cohort (26, 27). The authors indicated that they could not find adequate reasons for this decrease. However, the age of their new patient cohorts had increased over the years with 38.5% of the patients over the age of 60 in the 2004-2006 cohort and 51.1% in the 2013-2015 cohort. This may be a

reason for the relative decrease in the frequency of Behçet's uveitis, which usually starts around the age of 20. In a recent report from France on clinical and aetiologic characteristics of *de novo* uveitis among 283 patients who were 60 years or above, there were no patients with BS (28). A similar study from Italy reported on 278 patients with non-infectious uveitis admitted to 2 tertiary referral rheumatology centres between January 2016 and January 2017 (29). Half of these patients had bilateral uveitis and the diagnosis was anterior uveitis in 54.3% of the patients, posterior uveitis in 24.1, intermediate uveitis in 5.4 and panuveitis in 16.2% of the patients. A systemic disease could be diagnosed in 41.7% of the patients and overall the main diagnosis was BS (40/116) followed by ankylosing spondylitis (22/116) and juvenile idiopathic arthritis (14/116). The frequency of BS among anterior uveitis patients was 9/83 (18.8%), among intermediate uveitis 3/4, among posterior uveitis 16/33 (48.5%) and among panuveitis 12/23 (52.3%). The authors note that this high prevalence of BS in their cohort may be due to a referral bias, as their departments are national and regional reference centres for BS.

Although several studies are reported each year on the epidemiology of BS, the methodological differences in these studies make it difficult to compare the results. When reporting the frequency of some of the clinical manifestations, such as gastrointestinal or nervous system involvement, it is often not clear whether this is a real involvement of BS or just a non-specific symptom, such as transient abdominal pain or hearing loss associated with age, or a complication of the medications that are used, such as in cataract. Another problem is the age of onset, since some studies use the first symptom, others the fulfillment of criteria and yet others the diagnosis at the time of disease onset. Additionally, family history is reported without providing whether only first-degree or other relatives are included. Finally, laboratory results that could show an important variation according to disease activity, infections or other causes are reported as abnormal

without any explanation of the clinical scenario they are associated with, such as disease activity or infections, and sometimes mean values are calculated for these laboratory parameters using values of patients in different disease states. These and other issues make it difficult to interpret and compare the results of cohort studies. Standardisation is needed for reporting observational and epidemiologic studies in BS.

Pathogenesis

The pathogenesis of BS is poorly understood and evidence supporting a role of different molecules in the different types of organ involvement is growing. Regarding the thrombotic risk related to BS, a work was recently published on the role of neutrophil extracellular traps (NETs); as a matter of fact, to respond to inflammatory insults, neutrophils release web-like structures, known as NETs, which are prothrombotic. The study evaluated the role of NETs and markers of NETs in BS. Blood samples were collected and NET components, including cell-free DNA (cfDNA) and neutrophil enzymes myeloperoxidase (MPO), were assessed in serum or in purified neutrophils from patients with BS and healthy donors (HD). Patients with active BS had elevated serum cfDNA levels and MPO-DNA complexes compared with patients with inactive BS and with HD. Moreover, levels of cfDNA and MPO-DNA complexes were significantly higher in patients with BS with vascular involvement compared with those with no vascular symptoms. Thrombin generation in BS plasma was significantly increased and positively correlated with the levels of MPO-DNA complexes and cfDNA. Notably, DNase treatment significantly decreased thrombin generation in BS plasma but not in HD plasma, suggesting that, since NETs and markers of NETs levels are elevated in patients with BS, targeting NETs may represent a potential therapeutic target for the reduction or prevention of BS-associated thrombotic risk (30).

A recent meta-analysis compared mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) between

patients with BS and healthy controls, evaluating these parameters in BS according to disease activity and thrombosis. In total, 14 studies were included; MPV was not higher in the BS group than in the control group, while NLR was significantly higher in the BS group than in the control group and PLR showed a non-significant trend of association with BS. MPV did not differ between patients with active and inactive BS, and between patients with BS with and without thrombosis. Conversely, NLR was significantly higher in patients with active BS than in those with inactive BS, but not significantly higher in patients with BS with thrombosis than in those without thrombosis. This finding suggests that NLR may be a potential index to evaluate the disease activity of BS, although there are limitations of small number of studies and heterogeneity of individual characteristics (31).

Maintaining the topic of the pathogenetic mechanisms of vascular involvement, another study was conducted in order to compare vascular endothelial growth factor (VEGF) and soluble vascular endothelial growth factor receptor-1 (sVEGFR-1) levels in BS, among patients with active disease and especially vascular involvement. Fifty-five patients with BS, 25 of whom were accompanied by vascular involvement, and 31 control subjects were included in the study. Disease activity was assessed with the Turkish version of Behçet's Disease Current Activity Form (BDCAF) and active vasculitis lesions at the time of study were recorded. The authors suggested that elevated serum VEGF, sVEGFR-1, and more importantly VEGF/sVEGFR-1 ratio could play an important role in the development of thrombosis in BS and therefore they should be evaluated together (32). However, the VEGF and sVEGFR-1 levels, and the VEGF/sVEGFR-1 ratio were not significantly different between BS patients with and without vascular involvement. The VEGF/sVEGFR-1 ratio especially was quite similar in these 2 groups. Moreover, the lack of a diseased control group with thrombosis due to other causes lessens the robustness of the conclusions. The current

understandings on cellular and molecular biology suggest that Th17 axis may play a pivotal role in BS pathogenesis. Recently the role of serum amyloid-A (SAA) as a potential marker of disease activity in BS patients has been explored, and it has been reported that the occurrence of specific clinical features is significantly associated with high serum levels of this inflammatory mediator. In this regard, an interesting study investigated the cytokine-like activity of SAA in inducing Th17 differentiation from CD4⁺ T naïve cells in BS. Purified peripheral monocytes from BS and healthy controls (HC) were stimulated with SAA *in vitro*, and secreted IL-8, TNF- α , IL-18, IFN- α , IFN- γ , IL-1 β and IL-6 were measured using a Bio-Rad multiplex cytokine immunoassay. Monocytes-derived supernatants from BS patients, but not HC, could promote Th17 but not Th1 differentiation from CD4⁺ T cells. However, SAA did not induce up-regulation of Th17 specific mRNA transcript such as IL-17A and (ROR)- γ t in PBMCs from both HC and BS. The overall results showed that SAA induced Th17 polarisation rather than Th1 differentiation from CD4⁺ T cells in BS patients and these data suggest that a critical regulation of Th17 may be the functional link between acute SAA increase and the induction of Th17 mediated inflammatory response in BS (33). This study also lacks diseased controls and it is not clear whether these findings are specific for BS or if they can be observed in any inflammatory condition. Other suggestions related to the pathogenetic mechanisms underlying disease activity derive from the evaluation of CCN2/CTGF (connective tissue growth factor), which is one of the CCN family members that carry out pro-angiogenic biological functions and play an important role in inflammatory and autoimmune diseases. Specifically, a recent study assessed CCN2 plasma concentrations in BS patients and analysed their association with clinical features of disease activity and laboratory parameters. The study included 87 BS patients and 60 age- and gender-matched HCs. The plasma concentrations of CCN2 in BS patients were significantly

elevated compared to HC and the mean plasma CCN2 levels in patients with major organ involvement were significantly higher than those without. Interestingly, patients who received steroids or cyclophosphamide showed a significant reduction in CCN2 levels (34).

There have been several studies still exploring the role that the cytokine network plays in the disease pathogenesis, also related to specific types of organ involvement. Among these, one study evaluated the level of T-helper type 9 (Th9) cells and the cytokine interleukin (IL)-9 in peripheral blood and in bronchoalveolar lavage (BAL) of patients with BS affected by pulmonary manifestations (35). Among the 18 patients with pulmonary involvement, 5 were indicated to have pulmonary embolism, but how pulmonary artery thrombosis was excluded in these patients is not clear. Providing evidence that Th9 T cells are increased in BS patients with pulmonary manifestations, the study results suggest that the expansion of the Th9 cell subset, up-regulation of the PU.1 transcription factor and increased secretion of the IL-9 cytokine may contribute to the pathogenesis of BS, which may be supported by the increased release of IL-17 and TSLP. However, the BAL Th9 levels were quite similar in BS patients without pulmonary findings and healthy controls. It is not possible to conclude that these findings are related to BS, rather than the pulmonary condition as controls with other diseases causing pulmonary involvement were not studied. Other literature data published in the last months have confirmed the important role of proinflammatory cytokines in the genesis of BS; among these, the data suggested that serum MiR-181b could be utilised as potential biomarker for diagnosis and therapeutic targeting of BS (36). However, this is a premature conclusion, as there are no controls in this study to show the specificity of serum MiR-181b. Another study suggested that IL-20 could have an important role in the complex process of the settlement and activation of the disease, again without a diseased control group (37). It was proposed that cerebrospinal fluid IL-10 may be considered as an early

stage discriminative marker between multiple sclerosis and BS (38). Based on the proposal that higher serum levels of IL-15 and lower expression levels of IL-15 receptor alpha (IL-15R α) may be correlated with pathogenesis of BS, a group of researchers tested whether up-regulating IL-15R α + cells could be used as novel therapeutic strategy in a mouse model infected with HSV and showing symptoms similar to BS (39). The authors observed that these symptoms improved with IL-15R α + upregulation. Moreover, encouraging data from an Iranian study demonstrated that curcumin reduces the expression of interleukin 1 β and the production of interleukin 6 and TNF-alpha by M1 macrophages in patients with BS (40).

An interesting study from Brazil (41) assessed IgM anti-alpha-enolase antibodies (AAEA) in BS and their possible association with clinical manifestations and disease activity. Ninety-seven consecutive BS patients were compared to 36 enteropathic spondyloarthritis (ESpA) [24 Crohn's disease (CD) and 12 ulcerative colitis (UC)] patients and 87 healthy controls. IgM AAEA was detected by immunoblotting. Higher IgM AAEA prevalence was found in 97 BS (17.7%) compared to ESpA patients (2.8%) and HCs (2.3%), and BS patients with mucocutaneous and articular symptoms presented higher IgM AAEA positivity in the first and second evaluations (64.7% vs. 27.5%, $p=0.005$; 36.4% vs. 7.1%, $p=0.039$, respectively). These data suggest that alpha-enolase may be considered a target antigen in BS, particularly associated with disease activity, mucocutaneous and articular involvement. In addition, IgM AAEA may distinguish BS from ESpA, especially in patients with high disease activity.

Microbial agents have been considered to contribute to the pathogenesis of this disease, but the underlying mechanisms remain unclear. The association of gut microbiome composition with BS as well as its possible roles in the development of this disease was reported in a study from China (42) which explored faecal and saliva samples collected from 32 active BS patients and 74 healthy controls. DNA extracted from faecal samples was subjected to

metagenomic analysis, whereas DNA extracted from saliva samples was subjected to 16S rRNA gene sequencing analysis. Faecal samples from active BS patients were shown to be enriched in *Bilophila* spp., a sulfate-reducing bacteria (SRB) and several opportunistic pathogens (*e.g.* *Parabacteroides* spp. and *Paraprevotella* spp.) along with a lower level of butyrate-producing bacteria (BPB) *Clostridium* spp. and methanogens (*Methanoculleus* spp. *Methanomethylophilus* spp.). Analysis of microbial functions revealed that capsular polysaccharide transport system, oxidation-reduction process, type III, and type IV secretion systems were also increased in active BS patients. Globally, the result of the study showed that BS seems to be associated with considerable gut microbiome changes; interestingly, the authors proposed a model explaining the association of the gut microbiome composition with BS pathogenesis. The lack of diseased controls renders the specificity of these findings questionable for BS. Another perspective by which the pathogenesis of BS has been evaluated is the exploration of immunoglobulin D (IgD). A study from an Italian group assessed the role of IgD in BS by comparing circulating levels of IgD in a cohort of BS patients and HC, as well as by correlating IgD levels with BS activity and different clinical presentations. Serum IgD levels were significantly elevated in BS patients, especially among patients with active mucocutaneous manifestations, suggesting a possible role of IgD in BS pathogenesis and in the onset of mucosal and skin lesions (43).

As summarised, a number of studies were published exploring the immunologic basis of BS pathogenesis. However, lack of disease controls, pooling together the results of patients with different manifestations at the time of blood or sample collection, poor definition of active and inactive disease and lack of prospective longitudinal data reduce the information we get from these studies.

Genetics

Previous genome wide association studies had shown genetic associations with IL-10 and C-C chemokine recep-

tor 1 (CCR1) in BS and the results were independently replicated in various populations. A Japanese study sought to clarify the pathological roles of CCR1 and IL-10 expression and showed that the BS associated CCR1 and IL10 loci are responsible for defective M2 monocytes and a skewed polarisation towards M1 monocytes given the fact that the first cell population is anti-inflammatory whereas the second is pro-inflammatory. They discussed future therapeutic strategies that could increase the local production of the inhibitory cytokine IL-10 and that could restore the monocyte balance, and commented on the potential role of apremilast in attaining this objective (44).

An Iranian group investigated the promoter methylation status of the IL-10 gene in 61 patients with BS and 61 healthy controls, taking into account the epigenetic mechanism of hypermethylation that results in transcriptional gene repression. They determined that BS patients had both a lower IL-10 expression and a higher promoter methylation compared to healthy controls ($p < 0.001$) (45). The same group also published a paper on the hypomethylation of the IL-6 gene promoter in BS patients, a finding that may have caused an increased state of inflammation (46).

Two studies from Egypt investigated the role of miRNA in BS. The first group looked at the relationship of miRNA155 expression (a negative regulator of inflammation) to BS activity (measured by BDCAF) in 33 patients with BS and 15 healthy subjects. The miRNA155 levels in BS patients as a whole did not differ from those of the controls although BS patients with more serious manifestations and a higher BDCAF score tended to have lower levels (47).

The second group investigated microRNA-146a expression and microRNA-146a rs2910164 polymorphism in 47 BS patients and 50 healthy controls. The microRNA-146a expression was significantly higher in BS patients compared to controls ($p < 0.001$) with a preponderance of ocular and vascular involvement. The GG genotype of rs2910164 was increased in BS while the CC genotype was decreased conferring a susceptibility to the former and a

protective role to the latter (48).

A Turkish group studied serum IL-37 levels and IL-37 gene polymorphisms, a recently identified suppressor of innate inflammation and acquired immunity, in 223 patients with BS and 80 HC. Serum IL-37 levels were not different between BS and HC ($p > 0.05$) and its level was not associated with disease activity although patients with mucocutaneous disease tended to have a higher level. The gene polymorphisms were also similar among the two groups (49). A letter to the editor on this subject accentuated the discrepancies of the literature and described the data obtained from various studies that showed down-regulated IL-37 expression and increased rs3811047 population in various BS populations (50).

In addition, the mutual relationship of the endoplasmic reticulum peptidases ERAP1 and ERAP2 in the processing of an HLA-bound peptidome and evaluated their differential association with BS was evaluated by a joint Spanish-Israeli group. The results showed that both enzymes had distinct but complementary and partially redundant effects on the B*51:01 peptidome, leading to its optimisation and maximal surface expression. An interesting finding was that a large majority of B*51:01 ligands were present in the endoplasmic reticulum even in the absence of ERAP1/ERAP2 (51).

An Italian group genotyped the whole ERAP structure in 50 consecutive BS and 50 ethnically matched healthy controls. They identified two novel heterozygous missense single nucleotide variations (SNVs) of ERAP 1 exon 3. The first novel variation was a heterozygous glutamate to valine SNV at 18169 nucleotide position that was found in 7/50 (14%) of the cases and the second variation was a heterozygous thymine to cytosine at 18217 nucleotide position determined in 3/50 (6%) of the patients. They concluded that the functional and pathogenic role of these SNVs needed to be validated in a larger study (52).

Two reviews were published on polymorphisms and mutations in gene encoding. A review article examined the literature on autosomal dominant familial BS and haploinsufficiency A20, mu-

tations in the TNFAIP3 gene encoding A20. They reviewed 45 cases and highlighted the similarities and differences between this genetic auto-inflammatory disease and classic BS. It resembled BS if recurrent oral ulcers (87%), genital ulcers (67%), arthralgia or arthritis (42%) skin involvement (53%) and gastrointestinal findings (60%) were taken into account but differed when its ubiquitous geographical distribution, its female preponderance, the usual occurrence of the first symptoms in early childhood, its association with recurrent fever, the over-representation of abdominal symptoms, the rarity of the HLA-B51 antigen and its inconsistent response to colchicine were considered. They concluded that more studies needed to be performed to clarify these discrepancies (53). A systematic review was published by a Chinese group regarding the major and minor polymorphisms observed in BS in various populations and emphasized the special preponderance of immunoregulatory genes. An exhaustive discussion on HLA and related genes, IL family genes, genes involved in transcription activation and immune regulation and their possible roles on the pathogenesis formed the main content of the article (54).

Another Chinese study investigated the characteristics of BS patients who had a myelodysplastic syndrome (MDS) among a total of 805 cases. 16/805 (2%) had MDS and 81% of the 16 had trisomy 8. Patients with MDS were more likely to be female and older, displayed fever and intestinal lesions, had lower leukocyte, haemoglobin and platelet counts and higher acute phase reactants. Ulcers in the ileocecal region were also more frequent (55). A previous systematic review of the association of BS with MDS and trisomy 8 had shown that gastrointestinal involvement was present in majority of such cases and the presence of trisomy 8 was associated with fever (56).

Two papers were also published on the association of BS with HLA. The first study comes from an Egyptian group who performed a genetic association study of the HLA Class I alleles among 57 patients with BS and 221 healthy controls. They found a relationship

Table I. Main results of the studies investigating VWT.

Study author, year	Seyahi, 2019			Alibaz-Oner, 2019		
	BS (vascular involvement) n=50; 43 M/7 F	BS (without vascular involvement) n=50; 43 M/7 F	Healthy controls n=50; 43 M/7 F	BS (n=59 ; all male)	AS (n=27; all male)	HC (n=37; all male)
Mean age \pm SD, years	37.2 \pm 5.2	37.0 \pm 4.5	36.0 \pm 6.8	32.6 \pm 5.9	30.5 \pm 5.5	30.1 \pm 5.1
VWT (CFV), mean \pm SD	0.98 \pm 0.57	0.68 \pm 0.11	0.56 \pm 0.05	0.8 \pm 0.3	0.3 \pm 0.2	0.4 \pm 0.2
VWT (FV), mean \pm SD	0.83 \pm 0.28	0.62 \pm 0.10	0.49 \pm 0.06	*	*	*
VWT (GSV), mean \pm SD [§]	0.63 \pm 0.17	0.53 \pm 0.09	0.44 \pm 0.06	*	*	*
Width (GSV) [§]	*	*	*	3.3 \pm 1.2	2.5 \pm 0.6	2.2 \pm 0.6
Width (SSV) [§]	*	*	*	3 \pm 1.2	1.9 \pm 0.6	1.6 \pm 0.6

SD: standard deviation; VWT: vein wall thickness; CFV: common femoral vein; FV: femoral vein; GSV: great saphenous vein; SSV: small saphenous vein. *not assessed; [§]measurements from right side were displayed. All measurements are expressed as mm.

with HLA-A*24, A*68, B*15, B*42 and B*51. They claimed that A*03 and B*52 were protective for BS while B*51 and A*68 were associated with severe eye involvement (57).

Angioni *et al.* from Sardinia performed another study with 64 consecutive BS patients, 43 HLA-B51 positive HD and 70 random HC with the aim of identifying other genes of susceptibility in the HLA region. The human Allograft Inflammatory Factor-1 (AIF-1) gene variants were examined. HLA-B51 was the only allele with significantly higher frequency in BS patients (40.6% vs. 9.8%). No significant difference in the distribution of AIF-1 SNPs haplotypes was observed between BS patients and healthy controls and between HLA-B51 positive BS patients and B51 positive healthy controls (58).

Kallel *et al.* from Tunisia evaluated beta defensin-1 (hBD-1) levels (an antimicrobial peptide involved in epithelial host defense) and DEFB1 -20G/A polymorphism in 106 BS patients and 156 controls. Plasma hBD-1 concentrations were higher in BS patients compared to controls ($p < 0.001$) with highest levels in patients with neurological involvement. The GA and AA genotypes of the polymorphism conferred a higher risk of BS compared to the GG phenotype suggesting a possible role for hBD-1 in the pathogenesis (59).

Another Turkish study investigated the role of Vitamin D receptor gene polymorphisms in 150 BS patients and 150 HC. Significant differences between patients and controls in genotypes rs1544410, rs2228570 and rs731236 were observed.

Patients with ocular lesions had a higher percentage of rs1544410 A allele whereas those with oral aphthae, a positive pathergy test and arthritis had more rs2228570 C allele (60).

Overall, the same methodological problems underlined for immunology studies are also true for genetic studies. Methodological weaknesses in BS studies were surveyed in a study on BS publications between 1999 and 2009, and several issues were raised (61). It is disappointing to see that these findings are still valid 10 years later.

Clinical findings

Skin and mucosa lesions

Kecici *et al.* evaluated skin pathergy tests comparing naked eye examination with dermatoscopy in 100 patients with a suspicion of BS (62). All patients were seen by two dermatologists separately at 48th hour of the test. The pathergy scores, meaning the number of positive ones among the 6 pricks, were similar between naked eye examination and dermatoscopic examination for both dermatologists. However, the scores with the naked eye examination showed a significant difference between the 2 dermatologists ($p = 0.038$), whereas the scores of 2 dermatologists were similar with dermatoscopy. This may point out to a better inter-observer reliability with dermatoscopy, but a formal analysis for inter-observer or intra-observer variation was not done.

Eye disease

Emre *et al.* evaluated 32 eyes of 16 patients with BS uveitis and 30 eyes

of 15 HC using optical coherence tomographic angiography (OCTA) (63). In line with what has been previously reported (64, 65), they showed that deeper capillary plexuses were affected more intensely than superficial capillary plexus in BS. In addition, capillary vessel density among BS patients was significantly lower than in HC.

Vascular involvement

Two centres from Istanbul, Turkey worked on vein wall thickness (VWT) among BS patients who do not have any vascular involvement (66, 67). Table I summarises the results of these two works. Seyahi *et al.* studied 50 (43 M/7 F) BS patients with lower extremity deep vein thrombosis (LE DVT), 50 (43M/7F) BS patients without any vascular involvement, and 50 (43M/7F) age- and sex-matched apparently healthy controls (66). Two radiologists blinded to the diagnosis of the study participants used ultrasonography (USG) to measure the VWT of the common femoral vein (CFV), femoral vein (FV), and great saphenous vein (GSV) in both legs and their agreement was found to be good. Those with LE DVT had the highest VWT which was rather expected considering the remodelling process after having an acute thrombi. The most important finding was that the mean VWT among those without apparent vascular involvement was significantly increased compared with that found among the HC. Additionally, ROC curve analysis pointed out a cut-off value of 0.62 mm for CFV, 0.56 mm for FV, and 0.45 mm for GSV

among BS patients with no vascular disease.

Alibaz-Oner *et al.* studied 61 male patients with BS, 27 patients with ankylosing spondylitis (AS) and 37 HC using USG (67). About half of the BS patients had vascular involvement (n=30) while the remaining had only skin-mucosa involvement (n=31). One radiologist blinded to the diagnoses of study participants measured the VWT of CFV and diameters of GSV and small saphenous vein (SSV). All measurements were found to be significantly higher in BS compared to AS and HC ($p<0.001$ for all), while there was no difference between AS and HC. Among BS patients although all venous measurements were found to be greater among those with vascular involvement than those without, only left CFV VWT and the width of right GSV were found to be statistically significant. ROC curve analysis identified cut-off values of 0.49 and 0.48 mm, respectively, for right and left CFV VWT among BS patients. In conclusion, 2 studies independently found that thickness of proximal deep and superficial LE veins are increased in BS patients without any evidence of vascular involvement (66, 67). It is unknown whether the thickness is a precursor to a DVT or simply results from vascular inflammation. Further prospective studies are needed to elucidate these findings.

The clinical course of 12 (11M/1F) BS patients with abdominal aortic aneurysms (AAA) among 1224 BS patients followed between 1988 and 2011 was investigated by Sahutoglu *et al.* (68). Follow-up data was available for 11 patients (median age: 43 years; median follow-up time: 4.3 years). All aneurysms were in the infra-renal segment of the abdominal aorta, except for one patient who had a second aneurysm located superior to the celiac trunk. The median transverse diameter of aneurysms was 4.3 (1.3-8.2) cm. All aneurysms were saccular and irregular in shape, and contained mural thrombus. Tutar *et al.* compared the diagnostic value of true fast imaging with steady-state precession magnetic resonance (True-FISP MR) venography and Doppler USG in the assessment of chronic

DVT among 28 patients with BS (69). CFV and femoral vein (FV) on both right and left sides were examined for the presence of thrombosis, recanalisation, collaterals and reflux. Doppler USG showed signs of chronic DVT in all 28 patients, while MR venography detected chronic thrombotic changes in 26/28 (93%) patients. Collateral veins were detected in 19 patients (19/28) with MR venography, whereas they were present in only 7 (7/28) with USG ($p=0.003$). Moreover, collateral formations on the MR were more prominent among those with severe post-thrombotic syndrome. The study showed that true-FISP MR venography and Doppler USG were comparable in the diagnosis of chronic DVT in patients with BS and collateral circulation is significantly more apparent on MR venography compared to USG.

Kızıldag *et al.* retrospectively reviewed chest MDCT scans of 44 BS patients referred to a radiology department for chest symptoms between 2009 and 2016 (70). Pulmonary artery involvement (PAI) was the most common type of involvement being found in 12 patients (thrombosis in 8 and aneurysms in 4). Other findings included bronchial artery collaterals (50%), subpleural alveolar opacities (56.2%), focal atelectasis (50%) and ill-defined nodular opacities (31.2%) and cardiac filling defects (18.7%).

Calik *et al.* studied 62 patients with BS and 32 healthy controls using echocardiography and investigated whether any association exists between inflammatory markers and echocardiographic parameters (71). The authors demonstrated that there may be correlation between inflammatory markers (pentraxin-3 and homocysteine levels) and echocardiographic parameters such as the left ventricular diastolic functions, atrial conduction times, and aortic stiffness parameters in BS patients.

Nervous system involvement

A multicentre study from Turkey determined the frequency of BS-related cerebral venous sinus thrombosis (CVST) among 1144 patients with CVST due to several aetiologies registered in neurology departments (72).

BS was determined to be a causative factor of CVST in 108 (9.4%) patients. Patients with BS were younger (mean age: 35.27 years) and showed a male predominance (males: 68.5%). The onset was more likely to be subacute. The transverse sinuses were the most common sites of thrombosis, followed by the superior sagittal sinuses. The most common symptom was headache (96.2%), followed by visual field defects (38%). The functional outcome of CVST among BS patients was found, albeit non-significant, to be better than those without BS, with only 12% having a poor outcome.

Aykac *et al.* investigated the pyramidal tract integrity using diffusion tensor imaging (DTI) among 28 BS patients (parenchymal neurological involvement: n=10, vascular neurological involvement: n=9 and without neurological involvement: n=9) and 14 healthy controls (73). The study could not demonstrate any difference between the study groups. The authors concluded that the failure of the study was perhaps due to the small sample sizes.

Gastrointestinal involvement

Ye and Guan retrospectively analysed clinical manifestations and endoscopic findings of 111 patients with intestinal BS and 81 patients with Crohn's disease (CD) (74). Gastrointestinal symptoms were significantly more common in CD compared to those with intestinal BS ($p<0.001$). Independent factors that distinguished intestinal BS from CD were solitary ulcer in the ileocecal area, perianal abscess, single segment involvement, round intestinal ulcer, intestinal obstruction, and fistula formation. Although a multivariate logistic regression analysis was performed to determine the independent predictors of intestinal BS, the effect size was not provided and only p -values were given.

The same group also reported that the frequency of anaemia (60%) in newly-diagnosed patients with intestinal BS (n=106) was significantly higher (28%) than that found among those with non-intestinal BS (n=241) (75).

A study that evaluated faecal and serum calprotectin levels as a biomarker for active gastrointestinal involvement

among 39 BS patients with gastrointestinal involvement and 47 patients with CD showed that faecal calprotectin, but not serum calprotectin, may be a promising non-invasive tool for assessing gastrointestinal disease activity (76).

Juvenile Behçet's syndrome

A comparison between the clinical features of adult and juvenile onset BS (JBS) in a UK population (77) was performed by Mahkmur *et al.* The JBS database was collected at the Great Ormond Street Hospital for Children, London (n=46), whereas the adult database was at the Hammersmith Hospital, London (n=560). The authors observed that the JBS cohort was more likely to have gastrointestinal involvement (21.7% vs. 4.5%, $p<0.001$) and arthritis (21.7% vs. 9.6%, $p=0.021$) compared to the adults. On the other hand, the juvenile patients were less likely to have eye (4.3% vs. 37%, $p<0.001$), skin (21.7% vs. 55.4%, $p<0.001$) and vascular involvement (6.5% vs. 17.5% $p=0.063$). Moreover, girls had a higher frequency of genital ulcers than boys among the juvenile patients (87.5% vs. 59.1%, $p=0.044$).

Triggering factors

Two groups assessed triggering factors in BS. Iris *et al.* assessed triggering factors for oral ulcers among 92 (42 F/ 50 M) patients with BS with the help of a questionnaire (78). Major self-reported triggering events were found to be stress (78.3%), dental treatments (17.4%), tooth brushing (14.1%), infection (31.5%), and menstruation (10.9%). A total of 148 different dietary factors were reported, of which eggplant, walnut, sodas, tomato, hot pepper, spices, sunflowers, peanut, almond, chocolate, mandarin, and zucchini were the most frequent. Additionally, among patients with active oral ulcers (n=63), non-smokers were more frequent than the smokers (47 vs. 16) and this was true for both males (21 vs. 12) and females (26 vs. 4).

The second group investigated the incidence of BS in a Korean adult population according to smoking status using nationwide population data (79). They reported that BS developed in 10.888

never-smokers, 1.108 ex-smokers, and 1.218 current smokers between 2009 and 2012. The incidence rates of BS per person-years were calculated as $1.42/10^4$ in never smokers, $0.68/10^4$ in ex-smokers, and $0.41/10^4$ in current smokers. Current smokers were found to have a decreased risk of BS (HR 0.29; 95% CI: 0.27–0.31) compared with never-smokers. This risk persisted after adjusting for age, gender, regular exercise, drinking, BMI, and the presence or absence of diabetes mellitus, hypertension, dyslipidaemia, and history of stroke or ischaemic heart disease.

Reviews

There have been some comprehensive reviews about clinical phenotypes in BS (80) and eye disease in BS (81).

Patients' perception

In order to investigate how BS patients perceive their disease, different studies were performed. A study reported on semi-quantitative interviews with 20 patients with BS selected to ensure representation of patients with all types of organ involvement with the aim of better understanding patients' perception of and experiences with BS and how these affect their lives, and how these could be incorporated into outcome measures for use in clinical trials (82). Several domains were identified including physical functioning, psychological state, and social identity, associated with the variety of symptoms depending on the different organs and systems that are involved. Symptoms related to oral ulcers and genital ulcers, pain, fatigue, lack of energy, sleep problems, impact on vision, speech, eating, visual impairment and mobility, and psychological and social impact especially on family life and work. These will help the foundation for selection and development of patient reported outcome measures for BS trials. Patients' illness perception and beliefs about their disease and its consequences on their life may affect their perception of disease severity. The relationship between patients' perception of disease and self-assessment of disease activity or symptom severity may have an impact on how they score

patient reported outcome measures. A study from Turkey assessed the relationship between illness perception and disease course and symptoms in 110 patients with BS (83). It was demonstrated that the identity score and consequences score were higher in patients with musculoskeletal involvement and the timeline score (acute / chronic) was higher in patients with eye involvement. It was concluded that patients' beliefs and emotional responses may affect the outcome measures especially in patients with musculoskeletal and eye involvement. Another recent study explored the association of psychological representation and illness perception of patients with self-assessment of severity of symptoms in 273 patients with BS from the UK (84). It was demonstrated that the relationship between disease activity and pain was mediated by cognitive components of illness perception and between disease activity and perceived energy level by emotional components. It is suggested that this information may help in developing support programmes for patients with BS. More work is needed to make use of these findings for disease assessment in clinical trials.

Treatment

During the drafting of this year's review, the US Food and Drug Administration (FDA) has approved the use of apremilast, an oral selective inhibitor of phosphodiesterase-4, for the treatment of oral ulcers associated with BS, making it the first ever drug licensed for BS in the US (FDA OKs apremilast (Otezla) for Oral Ulcers of Behçet's Disease – Medscape – Jul 22, 2019). This approval was based on the results of a 12-week placebo controlled, double-blind phase 3 trial on 207 BS patients with active oral ulcers that was first presented at the EULAR 2018 meeting (85). Apremilast 30 mg twice daily was effective in reducing pain of oral ulcers, decreasing their numbers and in achieving oral ulcer free complete response compared to placebo. The results also suggested beneficial results for genital ulcers, but the study was not powered for this and other less frequently occurring manifestations of BS.

Eye involvement

Despite the increasing use of biologic agents in BS, classical immunosuppressives still reserve their place as the first line treatment in most centres for patients with uveitis (86). A single-centre, retrospective study from Turkey looked at the switch rate from classical immunosuppressives (mostly azathioprine and cyclosporine A) to interferon alpha (IFN) followed by adalimumab or infliximab among BS patients with eye involvement (87). The study group consisted of 76 patients, of whom 44 (59%) continued their treatment with classical immunosuppressives during a mean follow-up of 39 months (range 6–96 months), whereas 31 (41%) did not respond to classical agents and switched to IFN. Eight of these patients further remained refractory to IFN and switched to anti-TNF treatment. Panuveitis and bilateral ocular involvement were significantly more frequent among the patients switching to biologic agents compared to those remaining on classical immunosuppressives. The finding that more than half of BS patients with uveitis can be effectively treated with classical immunosuppressives is important especially when considering the high cost of biologic agents.

Interferon alpha (IFN) has been in use for a long time especially for the treatment of BS uveitis affecting the posterior segment. The usual practice is to use this drug as mono treatment or when necessary in combination with corticosteroids. We previously reported that combination of IFN with azathioprine is effective but carries the risk of increased myelosuppression (88). A retrospective study from a single centre in China looked at the efficacy and safety of IFN given as an add-on treatment to 30 BS patients with uveitis refractory to steroids and at least to one of the classical immunosuppressives, namely cyclosporine A, azathioprine, cyclophosphamide, methotrexate or tacrolimus (89). The initial dose of IFN was 3 MIU daily for 4 weeks followed by 3 MIU every other day. At the initiation of IFN treatment 19 patients (63%) were on 2 immunosuppressives and 2 patients were on 3 immunosuppressives. The response to treatment in

terms of reductions of ocular inflammation and uveitis relapse rates was observed in 87% of the patients during a mean follow-up of 22 months. IFN could be successfully tapered down in 8 patients and completely withdrawn in 6 patients without any recurrence of uveitis attacks during a mean follow-up of 9 months after discontinuation. Suppression of leukocyte and platelet counts were observed in only 4 patients (13%) necessitating temporary withdrawal of IFN in one. The authors concluded that IFN is effective and relatively safe as an add-on treatment to steroids and immunosuppressives. However, the numbers of patients using azathioprine and the frequencies of laboratory monitorisations could not be retrieved from the paper. Another retrospective study from Turkey attempted to look at factors predicting response to IFN treatment in 32 BS patients with uveitis. The response rate was 94% and increasing age was found to be associated with a good response (90).

A multicentre observational study from Spain compared the efficacy and safety of infliximab and adalimumab in 177 BS patients with uveitis refractory to classical immunosuppressives (91). The dose for infliximab was 3–5 mg/kg at weeks 0, 2 and 6 and every 4–8 weeks thereafter (103 patients) and for adalimumab 40 mg every other week without a loading dose (74 patients). During a 1-year observation period, 78 patients in the infliximab group (77%) and 52 (70%) in the adalimumab group continued with conventional immunosuppressives. The choice of adalimumab or infliximab was based on a physician and patient agreement. There were no significant differences at baseline between the 2 groups except significantly more frequent use of azathioprine among patients receiving infliximab. After 1 year both groups showed improvement in anterior chamber inflammation, vitritis and better-corrected visual acuity. The improvement in better-corrected visual acuity was significantly better in patients receiving adalimumab compared to those receiving infliximab but the onset of improvement was more rapid in the infliximab group probably due to the loading dose. Serious adverse ef-

fects leading to drug withdrawal were similar for both agents and were comparable to the literature. The authors, acknowledging the uncontrolled design of their study, concluded that both drugs were effective in refractory uveitis of BS at 1 year, with adalimumab appearing to be associated with a better visual outcome. A multicentre study from Italy also compared the efficacy of adalimumab and infliximab albeit in a heterogeneous group of 107 patients with non-infectious, non-anterior uveitis of whom 74 had BS uveitis (92). The mean follow-up was 57 months for infliximab and 26 months for adalimumab. Both drugs showed similar efficacy in controlling uveitis relapses, but the corticosteroid use was significantly less in the infliximab group compared to adalimumab group at 12 months and at the last visit. Similarly, the number of patients with macular oedema was also significantly less in the infliximab group at 12 months and at the last visit. These 2 studies give further clues as to the effectiveness of infliximab and adalimumab in the treatment of BS uveitis but whether one could be preferred over the other warrants further studies.

Infliximab and adalimumab have significantly improved the outcome of BS patients refractory to classical immunosuppressives but some patients remain also resistant to these agents. Although inhibition of IL-1 appears to be a suitable target for such patients previous reports with IL-1 inhibitors have been inconsistent. A retrospective study from Italy aimed to identify predictive factors for a sustained efficacy to IL-1 inhibitors anakinra and canakinumab by dividing patients according to their response into 2 groups (93). Group 1 consisted of 18 patients showing a sustained clinical response for at least 12 months, while Group 2 consisted of 18 patients who discontinued IL-1 treatment because of inefficacy. There were no baseline differences between the 2 groups regarding demographic factors, disease activity and previous treatments. Eye involvement was significantly more frequent (67%) in Group 1 compared to Group 2 (17%). The frequencies of joint involvement, cutaneous manifestations, fever, gastrointestinal involve-

ment and vascular involvement did not differ between groups at baseline. At month 3, all 18 patients in Group 1 had a complete response whereas this was the case only for 7 patients (39%) in Group 2. The mean time to disease relapse was 80 weeks in Group 1 and 19 weeks in Group 2. Some relapsing patients in Group 1 responded to dose adjustments, which was not the case for those in Group 2. A better response to IL-1 inhibition was seen in patients with ocular involvement. These results suggest that IL-1 inhibition might be a good therapeutic option for patients with refractory eye involvement but also remind us of a previous proposal of diverse immunologic pathways for different organ involvements of BS (94). A systematic review on IL-1 inhibitors showed that these agents might have a potential benefit for ocular, mucocutaneous and articular manifestations of BS (95).

Gastrointestinal involvement

Gastrointestinal involvement is a classic example for the geographical variation of disease expression of BS being more frequent in patients from the Far-East countries compared to those from Mediterranean countries. A retrospective study looked at the efficacy of 5-aminosalicylic acid (5-ASA) as first-line remission induction and maintenance therapy in BS patients with mild to moderately severe gastrointestinal involvement (96). The study included 41 patients with active intestinal lesions on colonoscopy and excluded those using corticosteroids, immunosuppressives and anti-TNF agents. The daily dose of 5-ASA ranged between 750 to 4000 mg. The response parameters were disease activity indexes, endoscopic response, rescue-treatment free survival and surgery-free survival at 52 weeks. Seven patients withdrew early from the study due to adverse events. Evaluation at week 8 showed that 16 patients (57%) were in clinical remission. The endoscopic evaluation of 17 patients showed that 6 patients (35%) achieved complete mucosal healing whereas 5 patients (29%) had no response and the remaining patients had partial response. Thirteen patients (32%) needed res-

cue therapy with corticosteroids and/or anti-TNF agents during a median follow-up ranging between 35 and 52 weeks with no patient needing intestinal surgery. The probability of rescue therapy free survival among all patients was calculated as 73%. Higher disease activity index was negatively associated with clinical response. The most frequent adverse effects related to therapy were fever and diarrhoea (4 patients) which resolved after cessation of 5-ASA. Despite the small number of patients studied, this study suggests that BS patients with mild to moderate intestinal involvement could be managed effectively with 5-ASA without any concomitant corticosteroids and immunosuppressives. However, patients with high baseline disease activity might need more intensive therapy to prevent recurrences.

Vascular involvement

Venous involvement can be seen in up to 50% of BS patients, has a recurrent nature and can result in significant morbidity and even mortality. Systemic inflammation rather than a coagulation defect seems to be the underlying cause of thrombosis making immunosuppressives the mainstay of treatment, but the response to these agents is also far from satisfactory. A retrospective study from a single centre in Italy compared the efficacy of adalimumab based treatment (adalimumab as a single agent or combined with immunosuppressives) with classical immunosuppressives (azathioprine, cyclosporine A, cyclophosphamide, methotrexate) in a large cohort of BS patients with recurrent deep vein thrombosis and/or superficial vein thrombosis of the extremities (97). Patients with co-existent arterial involvement or those with large vein thrombosis were excluded. The patients were evaluated periodically every 4 weeks in the first 3 months and then every 3 months or whenever they had a recurrence. The response to treatment was stratified according to clinical and ultrasonographic evaluations. There were 35 patients each in the adalimumab arm and immunosuppressive arm, respectively. The response to treatment during a mean follow-up of 26 months

was significantly more frequent and more rapid among patients in the adalimumab based treatment arm compared to those in the immunosuppressive arm. The corticosteroid sparing effect was also significantly more in the adalimumab based treatment arm. The use of anticoagulants was not found to be associated with response but the numbers of patients receiving additional anticoagulants were low. These results support the use of adalimumab for venous thrombosis of BS and warrants further studies. Another multicentre, retrospective study from France assessed the efficacy of anti-TNF agents in 18 BS patients with severe vascular involvement refractory to classical immunosuppressives (98). The patients had arterial aneurysms (pulmonary, aorta, peripheral), arterial occlusions, intracardiac thrombosis and large vein thrombosis either as a single complication or concomitantly. Infliximab was the most frequently chosen anti-TNF agent (n=15) and adalimumab was given to 3 patients only. Anti-TNF agents were combined with immunosuppressives (mostly azathioprine or methotrexate) and/or corticosteroids. All patients but 1 with venous thrombosis received anticoagulant therapy and 7 underwent surgical or endovascular interventions. Vascular remission, defined as the resolution of clinical and laboratory features of active disease and the absence of new vascular lesion or progression of pre-existing vascular lesion in imaging, was achieved in 16 patients (90%) following initiation of anti-TNF treatment. Two patients, initially not responding to anti-TNF therapy had a favourable response when the interval between infusions was shortened. Fifteen patients underwent radiological assessment which showed that 13 patients had complete or partial improvement and 2 had stable disease. Anti-TNF treatment also allowed a significant decrease in daily corticosteroid dosage. The median follow-up under anti-TNF treatment was 15 months. One patient stopped treatment because of heart failure and a second one because of non-compliance. A retrospective study from a single centre in China reported the efficacy of the IL-6 receptor antagonist tocilizumab in

7 BS patients with multiple arterial lesions (aneurysms, occlusions, stenosis) of whom 2 had also concomitant venous involvement (99). All patients had previously received at least 2 classical immunosuppressives combined with corticosteroids and 2 patients underwent endovascular stenting (EVS). One patient was also prescribed etanercept for 3 months with no response. Tocilizumab was given as infusions at a dosage of 8 mg/kg monthly and previous treatments were also continued. After a mean follow-up of 19 months all patients showed improvement. Re-evaluation of 6 patients showed complete response in 3 and partial response in the other 3. Treatment with tocilizumab also allowed reduction of corticosteroid dosage and other concomitant immunosuppressives. These findings, if supported by other studies, suggest that tocilizumab might be an alternative to anti-TNF treatment for BS patients with vascular involvement who are refractory to classical immunosuppressives. A retrospective study from a single centre from Istanbul, also mentioned above, in the clinical section of this review, looked at the outcome of AAA in 11 BS patients (68). Two patients underwent emergency surgical resection and polytetrafluoroethylene graft interposition due to spontaneously ruptured aneurysms. Both received immunosuppressive treatment only after the intervention and were reported to have symptomatic response without any complication during follow-ups between 4.7 to 7.2 years, respectively. Seven patients underwent EVS. Six of them received induction treatment (iv methylprednisolone and cyclophosphamide pulses) before the intervention and all received maintenance treatment (oral methylprednisolone combined with azathioprine or cyclophosphamide) after the intervention. One patient developed stent infection and died after 8 months following the intervention, another one developed a femoral artery aneurysm at the catheter insertion site 2.7 years following the intervention and a third patient developed a new aneurysm at the proximal site of the stent 4.7 years following the intervention. Two further patients continued to complain of low

back pain which the authors attributed to mechanical irritation of EVS on the aortic wall. The 2 remaining patients were treated only with a drug regimen containing steroids and azathioprine with follow-ups of 5 and 6 years, respectively. The reasons why these 2 patients did not receive any invasive intervention have not been explained. The development of new aneurysms even after 4.7 years following EVS in 2 patients despite continuing immunosuppressive treatment underlines the importance of pathergy phenomenon in the pathogenesis and clinical features of BS. A case report from Spain on a patient who developed extensive venous thrombosis along with intracardiac thrombosis shortly after a percutaneous thrombectomy and venous stent replacement might be another example of pathergy phenomenon (100).

Secukinumab

Some data suggest a role of IL17 in the pathogenesis of BS. A retrospective study looked at the efficacy of secukinumab, an IL17 inhibitor, in 5 BS patients (all female) with articular and mucocutaneous lesions who had been refractory to previous therapy with colchicine, immunosuppressives and at least one anti-TNF agent (101). The dose of secukinumab was 150 mg/month in 4 patients with co-existing AS and the fifth patient with a history of psoriasis received secukinumab 300 mg/month. At 3 months, only the patient receiving the high dose of secukinumab had a clinical response that was maintained during follow-up. On the other hand, the partial response to low dose secukinumab at month 6 required an increase of the dose to 300 mg in 3 patients, which gave satisfactory results. These results can be considered to indicate that secukinumab might be an option for refractory articular and mucocutaneous manifestations of BS, but the female gender and old age (4 patients were between 48-62 years old) of the study patients together with their co-existing diseases of the reported patients are not typical for our usual patients with BS.

The expanding spectrum of biological agents has undoubtedly improved the prognosis of chronic immune mediated

diseases in general but it should be kept in mind that these agents might induce various paradoxical adverse events such as psoriasis, uveitis and Crohn's disease (102). We have reported 2 AS patients, the first with exacerbation of concomitant BS and the second with emergence of *de novo* BS during secukinumab treatment (103). This limited experience underlines the importance of close observation in patients receiving biological agents for the unpredictable occurrence of such reactions.

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