Review

Behçet's syndrome: one year in review 2023

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ABSTRACT

This critical review of studies on Behçet's syndrome published during 2022 includes studies on epidemiology, patients' perspective, pathogenesis, diagnosis, clinical features and management. Studies on pathogenesis included potential biomarkers mostly related to macrophages, neutrophil and cytokine balance, new GWAS and polymorphism studies, and studies on miRNAs and long non-coding RNAs. Clinical studies showed that application of pneumococcal vaccine to the prick site increased the sensitivity and specificity of the pathergy test and the prevalence of AA amyloidosis had decreased over the years. Studies on management indicated that more data are needed to understand the effect of apremilast on BS manifestations other than oral ulcers, and new BS manifestations may develop during treatment with infliximab. Other biologics and Jak inhibitors might be an option for patients who are refractory to TNF-α inhibitors. Moreover, endovascular repair of arterial aneurysms might be an alternative to open surgery.

Epidemiology

A study from Wales reported that a total of 352 patients, 347 adults (77% women) and 5 children with BS were recorded in the Adult Rare Diseases Surveillance Registry for Wales, giving an estimated prevalence of 11.1 per 100,000 (1). There were no differences between men and women regarding survival, age at diagnosis and socioeconomic status. Median age at diagnosis was 42 (range 10-78) years. The relatively older age at diagnosis compared to other cohorts were attributed to a delay in diagnosis due to primary care physicians being unfamiliar with BS and to the possibility of more severe patients being diagnosed earlier and attending specialist centres in England rather than in Wales. Mortality rate was 6.6% at the end of the study period with a median survival of 101 months from diagnosis. In contrast to the previous observations indicating a more severe disease course among BS patients with an earlier age of onset, older age at diagnosis was the only factor associated with mortality. This finding was interpreted as a function of age itself. Causes of death and standard mortality ratio were not available.

A cross-sectional study that compared the prevalence of different systemic vasculitides between two vasculitis referral centres in Brazil and Peru included a total of 345 patients with systemic vasculitis in Brazil and 217 in Peru (2). The frequency of BS among the vasculitides was significantly higher in the Brazilian centre (37.9%) compared to the Peruvian centre (1.8%; $p<0.0001$). Takayasu's arteritis (TAK) and giant cell arteritis (GCA) were also more common in Brazil, whereas microscopic poliangiitis and renal-limited vasculitis were more common in Peru. BS and TAK were the most common forms of vasculitis in the Brazilian centre. The mean age at BS diagnosis was 31.0 years in Brazil, and 41.5 in Peru. Women comprised 62.7% of BS patients in Brazil compared to 75.0% in Peru. The retrospective and hospital-based design and start of inclusion in 1990 in Peru and 2003 in Brazil were potential sources of bias.

Take home messages

- The prevalence of BS in Wales was 11.1 per 100,000. There was no difference between sexes regarding age at diagnosis and survival, and 77% of the patients were women (1).
- The frequency of BS among patients with vasculitis was significantly higher in a Brazilian vasculitis referral centre (37.9%) compared to a Peruvian centre (1.8%; $p<0.0001$) (2).

Patients' perspective

A study that explored activities of daily living (ADL) and factors causing impaired ADL among 2960 BS patients registered in a Japanese dataset showed that ADL was normal in 59.7%, limited but not assisted ADL in 35.7%, partially assisted in 3.9%, and fully assisted in 0.6% (3). Multivariate analysis showed that chronic ocular lesions, paralysis, psychosis and arthritis were associated with impaired ADL.

Patient research partners are increasingly participating in designing studies, developing outcome measures and issuing management recommendations. A recent study that aimed to explore whether patients participating in meetings represent the general patient population showed that BS patients who participated in a patient convention had more severe disease, more frequent central nervous system involvement, vascular involvement, genital ulcers, erythema nodosa and cyclophosphamide use, and less frequently uveitis, gastrointestinal involvement and papulopustular lesions compared to BS patients attending a multidisciplinary BS outpatient clinic for their routine visits (4). EULAR advises that good communication skills, motivation and constructive assertiveness should be taken into account when selecting patient research partners. This study suggested that ensuring representation of the whole spectrum of the patient population is also important when selecting patient research partners for studies on multisystem heterogeneous conditions like BS.

Patient education is essential in the optimal management of patients with chronic diseases. A study that assessed readability, quality and reliability of online information on BS, using validated indexes showed that information on a total of 100 websites that included information on BS had moderate reliability and good quality, but were "difficult" to "very difficult" with regard to readability (5). A recent effort, the BehçetTalk educational programme that aims to create awareness about BS and its impact was developed together with patients, caregivers and patients' representatives (6). This programme involves webinars on different aspects of BS and support groups coordinated by a psychologist with expertise on BS.

Take home messages

- Activities of daily living are impaired in about 40% of patients with BS (3).
- Online information on BS had moderate reliability and good quality, but were problematic regarding readability (5).

Immunopathogenesis

Several studies have aimed to identify potential biomarkers implicated in the pathogenesis of BS. NK cells which provide interaction between adaptive and innate immune systems, are thought to be associated with immune attacks and remissions during the course of BS (7). Macrophages are also key innate immune cells implicated in the pathogenesis of BS and macrophage polarisation seems to play a pivotal role in the inflammatory response. Recently, Wu *et al*. (8) investigated the role of BS serum on the phenotypes and functions of macrophage polarisation. BS and healthy control (HC) serum-treated human monocyte-derived macrophages (HMDMs) were examined for M1/M2 phenotypes using flow cytometry and ELISA. BS serum-treated macrophages expressed higher levels of CD86, IL-12, and TNF-α and a lower level of CD163 compatible with the M1-like phenotype, showed enhanced phagocytic capacity and promoted more Th1 cell differentiation. Sixty-one differentially expressed genes were identified between BS and HC serum-treated macrophages and were enriched in NF-κB signalling. BS serum-treated macrophages showed upregulated p-p65 and downregulated IκBα. NF-κB inhibitor attenuated BS serum-stimulated M1-like phenotype. According to these results, and considering that BS serum promoted macrophage polarisation toward a proinflammatory M1-like phenotype through NF-κB signalling, M1 polarised macrophages may represent a potential therapeutic target for BS. An important limitation of this study was that there were no diseased controls.

Trying to identify further potential biomarkers related to the role of macrophages and T cells, a study which aimed to identify hub genes and biological processes, identified hub genes of inflammation and thrombosis pathways by bioinformatics analysis from gene expression profiles of immune cell subsets in BS (9). However, these preliminary findings of the complex transcriptional networks of BS need to be validated in future studies, in order to better understand the mechanisms underlying the dysregulated expression of target genes and their exact roles in the immune context.

γδ T cells are considered as a bridge between innate and adaptive responses and their role in the pathogenesis of BS has been known for some time (10). Abbasova *et al*. (11) investigated the role of γδ T cells in the cytokine-related mechanisms in BS in comparison to that of the CD4+ T cells, demonstrating a higher IFN-γ production of γδ T cells. This may point to a role of environmental triggers in BS pathogenesis, whereas the IL-17 related activity is mainly provided by the CD4+ T cells.

Neutrophils represent another recent target of study in the pathogenesis of BS. Yu *et al*. (12) observed an increased activation and chemotaxis of BS neutrophils characterised by the overexpression of CCL5, CCR6 and ETS1. Neutrophil activation and production of neutrophil extracellular traps (NET) were also associated with BS-related thrombosis as shown by another group (13).

A study exploring the association of lymphangiogenesis markers with disease pathogenesis in BS uveitis (BU) suggested that lymphatic vessel endothelial hyaluronan receptor 1 and podoplanin can be considered as potential representatives of ongoing inflammation in BU, and lymphangiogenesis may strongly contribute to inflammation (14). Similarly, IL-18, sCD40, PF4V1, and NGAL were suggested as potential biomarkers of ocular activity in BS (15). A comprehensive transcriptomic profiling of iris specimens from BS patients with the aim of providing some insight into intraocular immunopathogenesis highlighted the central role of T cell-mediated immunity and

previously unreported lymphocyte-specific protein tyrosine kinase (LCK) signalling in intraocular immunopathogenesis, and revealed the potential value of LCK as a new therapeutic target for BS patients (16).

Take home messages

- NK cells might be associated with immune attacks and remissions during the course of BS (7).
- M1 polarised macrophages may represent a potential therapeutic target for BS (8).
- Lymphangiogenesis and several interleukins may be involved in the ocular inflammation in BS (14).

Genetics

Jo *et al*. explored the genetic differences between male and female patients with BS using a genome wide approach in six different populations. They studied a total of 1762 male and 1216 female patients and found an association between carrying HLA-B/MICA (rs2848712) and being male. Other genes that were prominent in males compared to females were HLA-C and KLRC4. In contrast IFNGR1 was shown to confer a higher genetic risk in females. Whether these differences also affect disease manifestations needs further investigation (17).

Cavers *et al*. studied the effect of the risk variant of HLA-B51/ERAP-Hap10 on human CD8 T cell immunity in patients with BS. Previous studies had shown that there was an epistasis between HLA-B51 and the ERAP1-Hap10 that increased the risk of disease by 11-fold compared to carrying HLA-B51 alone. Taking into consideration that ERAP1-Hap10 has a low enzymatic activity compared to other ERAP variants, they hypothesised that a hypoactive ERAP1 leads to the loading of "undertrimmed" longer peptides onto Class I, resulting in an aberrant CD8 T cell response. They genotyped a cohort of untreated active patients with BS and healthy subjects, created an *in vitro* model system using CRISPR-Cas 9 genome editing and examined its effect on immunogenicity as assesed through CD8 T cell effector function. They showed that an altered HLA Class I peptidome induced by reduced ERAP1 function changed immunogenicity, skewing frequencies and phenotypes of human antigen stimulated *versus* naive CD8 T cells. They proposed that the study provided a rationale for the development of ERAP activity modulating therapy (18).

Takeno discussed the clinical and pathogenetic role of HLA-B51 in a review article and elaborated on several key points. It was a comprehensive text that clarified many concepts mentioned in Cavers's study described above (19).

Another review on the genetics of uveitis summarised the results of all data on the genetics of BS and gave a reference to the finding of a STAT4 polymorphism in a Chinese GWAS study. It used it as an explanation for the failure of secukinumab in BS uveitis and stressed that the presence of STAT4 pointed to the stimulation of IL-12 and the Th1 pathway rather than the activation of IL-17, a hypothesis that needs further clarification (20).

A group from China identified novel risk loci in BS uveitis in a recently performed GWAS study. The GWAS stage included 978 patients with BS uveitis and 4388 controls and the replication stage concerned 953 cases and 2129 controls. Three independent HLA alleles, HLA-B51, HLA A-26 and HLA C-0704 were associated with BS uveitis. Twenty-two novel susceptibility variants in 16 loci were identified in the non-HLA region. Meta analyses of the Chinese and Japanese cohorts showed significant associations with ZMIZ1, RPS6KA4, IL10RA, SIPA1-FIBP-FOSL1 and VAMP-1. Functional experiments showed that genetic variants of ZMIZ1were related to an enhanced transcription activity and increased expression of ZMIZ1. The current understanding of these relationships is not entirely clear and further replications and biological studies are needed to explore their perhaps causal role in the development of BS (21).

A letter to the editor described an association of VEXAS syndrome with BS. It was based on a 60-year-old Japanese man who developed painful erythematous nodules on the trunk and neck, spiking fever and oral and genital ulcers. He had pancytopenia and high ferritin levels and autoantibodies were absent. The bone marrow examination showed signs of myelodysplastic syndrome and also contained myeloid precursor cells with vacuolisation. Immunosuppressive therapy was ineffective and genetic sequencing revealed one of the UBA1 variants. This interesting observation in one 60-year-old patient obviously needs further validation (22).

Onaka *et al*. reported two cases of trisomy 8 positive myelodysplastic syndrome with incomplete BS disease who obtained long-term remissions after allogeneic stem cell transplantation. They summarised the literature on trisomy 8 and BS, emphasised its relationship with gastrointestinal involvement, described their resistance to conventional therapy and discussed the option of transplantation. The small number of patients reported need further consideration before a wider use of this method can be recommended (23).

A Chinese case control study examined cyclin dependent kinase polymorphisms (cyclins that may regulate the proinflammatory activity of various cytokines during the inflammatory response) among 542 patients with BS and 754 healthy controls. Individuals carrying the CDK6/rs2282983 and CDK6/rs42034 AG genotypes were protected against BS. Individuals with CDK6/rs2282983 TT genotype were at a higher risk of developing the disease. Stratified analysis showed that CDK6/rs2282983 was associated with skin lesions in BS. This study entails all the pros and cons of classical polymorphism studies, including the lack of diseased controls, and the functional significance and mechanisms of these polymorphisms remain unclear (24).

Another Chinese group made a meta-analysis on the reationship between Vitamin D receptor gene polymorphisms and BS among 478 cases and 666 healthy controls. Apal, Bsml and Fokl were associated with an increase risk for BS in the Caucasian populations while Fokl and Taql polymorphisms were protective especially in the African populations. Further studies based on a larger cohort with multiple ethnicities are required for more robust results (25).

Shan *et al*. conducted a meta-analysis to evaluate the relationship between miRNA-146a gene polymorphism rs2910164 with BS. A systematic search of published studies revealed 5 eligible studies involving 1167 BS cases and 1662 controls. The results suggested that the polymorphism rs2910164 was correlated with BS susceptibility in all genetic models. There were certain limitations of this study. First, it was only performed in Caucasian and Asian populations. Only one study was carried out among the Chinese. Secondly, three included studies did not meet the Hardy-Weinberg equilibrium expectations probably due to a relatively small number of diseased patients and controls. Thirdly, heterogeneity was detected in genetic models probably due to ethnicity (26).

Hou *et al*. examined the expression of mi-RNAs derived from plasma exosomes in patients with intestinal BS. A total of 43 BS patients who had gastrointestinal involvement and 23 healthy controls were enrolled. Fifteen miRNAs were found to be differentially expressed among the two groups. PCR analysis confirmed that miR-141-3p was down regulated and miR-122-5p, miR-150-3p, miR-183-5p, miR-224-5p and miR-342-5p were up-regulated. The authors concluded that they may serve as biomarkers of disease activity in gastrointestinal involvement (27).

Zhang *et al*. explored the effects of long non-coding RNA (lncRNA) related single nucleotide polymorphisms (SNPs) on BS disease susceptibility. A two-stage association study was performed among 1152 BS patients and 1152 healthy controls. The analysis showed a significantly decreased frequency of the A allele of SNP rs7130280 in BS patients and a potential role for a lncRNA-miRNA-mRNA regulatory network was suggested. The study had various limitations. First, the findings were mainly attributed to human peripheral blood specimens and common cell lines. Second the coverage genes by SNPs on GWAS arrays were not sufficient and the low frequency SNPs could not be addressed. Third the effect of lncRNA on all immune cells rather than only monocytes and macrophages should have been explored (28).

Take home messages

- Males and females with BS may have different genetic backgrounds (17).
- The HLA-B51/ERAP Hap10 risk variant may influence the immune response in BS by skewing the antigen related CD8 activity (18).
- Long coding RNA polymorphisms is a new area that needs to be explored in BS (28).

Clinical manifestations

Eye involvement

Fundus fluorescein angiography (FA) is the gold standard for the diagnosis and monitoring of retinal vasculitis and optical coherence tomography (OCT) is the most common modality for macula assessment. On the other hand, OCT angiography (OCTA) is still a developing modality for retinal and choroidal vascular imaging. Recent OCTA studies suggest subclinical changes in some patients without detectable ocular involvement based on decreased vessel density and outer retinal flow (29), as well as changes in the macular microvascular, radial peripapillary capillary, and optic nerve head structures (30). Another study among non-ocular patients showed no deficit in retinal microcirculation by OCTA, and suggested that choroidal vascularity index by OCT may be a more reliable marker of choroidal perfusion. (31). The mean density of the subbasal nerve plexus was significantly lower, and nerve tortuosity was significantly higher in patients with ocular involvement (32).

The foveal avascular zone (FAZ) was enlarged, and vessel density (VD) was lower both in the superficial and deep retinal layers in angiographically quiescent BS patients. Larger FAZ size and lower width around the FAZ were correlated with higher visual acuity in BU. VD of choriocapillaris was lower in 6 locations in the peripheral fundus of BU compared to controls. In FA of peripheral fundus, vascular leakage was detected in 54.4% and retinal non-perfusion in 66.7% of the patients (33).

Zeng *et al*. showed that macrophage-like cells density was elevated in BU and may serve as a non-invasive indicator of the severity of fluorescein leakage and retinal inflammation (34).

In a cross-sectional study, significant thinning in the outer retinal layers and thicker inner nuclear layer was reported in patients with BU. The authors found a negative correlation between the duration of uveitis and the thickness of the outer retinal layer and positive correlation between visual acuity and central macular, the total inner layer, and the outer retinal layer thicknesses. They proposed spectral domain-OCT retinal segmentation as a predictor of visual loss in patients with BU (35).

In a retrospective study a high correlation was detected between widefield fluorescein angiography and laser flare photometry (LFP) in BS patients. The authors concluded that an elevated anterior chamber flare on LFP in the absence of clinical signs of active inflammation indicates subclinical inflammation in the posterior segment and a high risk of macular oedema (36).

Ultra-widefield fluorescein angiography (UWFA) was used to monitor the efficacy of adalimumab in BU and significant improvement in grading of anterior chamber cells, vitreous haze and UWFA score was observed (37).

Studies on the clinical characteristics and visual outcome of BU showed bilateral involvement in 60.0% and vitritis in 68.0% of the patients in the UK (38), uveitis in 47.5% of BS patients at initial examination with male gender, younger age at onset, panuveitis, posterior uveitis, retinal vasculitis, and longer duration of uveitis as poorer visual prognostic factors in Iran (39) and more severe ocular manifestations among women in Oman (40). A study from Korea showed 10.73-fold increased risk of blindness in 10 years and a higher risk of ocular comorbidities including glaucoma, cataract and retinal disorders that are potential threats to vision among BS patients compared to the general population (41).

Skin and mucosa

Recurrent oral ulcers (OU) continue to appear during the course even though several other lesions disappear. In a retrospective survey including 155 BS patients followed between 1989-2020, young age at disease onset, being non-

smoker, presence of genital ulcers, positive pathergy test and not using disease modifying anti-rheumatic drugs were identified as factors that prevent OU remission (42). Pharyngeal scarring with stenosis is a rare complication in BS. Pharyngeal reconstructive surgeries using flaps were suggested as an effective and safe approach in BS patients with such condition (43).

Pathergy

The sensitivity of skin pathergy test (SPT) is decreasing over years. Stimulation by 23-valent polysaccharide pneumococcal vaccine and a 20G needle prick exhibited a more sensitive (64.3%) and specific (100%) reaction compared to the standard approach, particularly among those with active BS (44).

Vascular involvement

Vascular involvement in BS is more common among males, venous involvement is more frequent than arterial involvement, and superficial thrombophlebitis is strongly associated with vascular involvement (45-47). These were confirmed in retrospective chart surveys among both juvenile and adult cohort studies (48-50). Pulmonary artery involvement (PAI) can occur as aneurysms (PAA) with or without thrombosis or may present as isolated pulmonary artery thrombosis (PAT) (51). Previous studies have indicated that thrombus develops as a complication of the underlying endothelial dysfunction or vasculitis (52-54). An interesting report is about a post-mortem examination of a patient who apparently died from acute complete obstruction of the pulmonary arteries due to a pulmonary embolus (PE) originating from a thrombus in the inferior vena cava (55). The authors propose that this report is the ever first documentation of a histologically documented PE in BS. It is important to note this patient also had locally formed thrombi and was undergoing lymphocyte apheresis therapy. The issue of a possible dehydration during the plasmapharesis is not discussed. Nevertheless, this publication should prompt yet more research scrutiny into pulmonary artery lesions in BS. The mortality rate is significantly increased among patients with PAI and Budd-Chiari syndrome (BCS) (56). In a case series of 10 patients with arterial aneurysms followed for a mean of 3 years, 4 patients died due to aneurysm rupture (3 pulmonary, 1 iliac) (57). Four patients died (19%) after a mean follow-up of 7 years in a case series that included 21 patients with BCS (58). Intra-cardiac thrombosis (ICT) affects usually the right side of the heart and the right ventricle more often than the right atrium (59). Wu and Lulu described a patient who presented with ICT attached to the pulmonary valve and on the apex of the left ventricle (60). A case control study showed that male gender, young age of onset, high acute phase response and positive pathergy reaction were associated with vena cava superior (VCS) thrombosis and patients with VCS thrombosis had a better survival and lower relapse rates than those with arterial involvement (61). A comparison of two cohorts from Turkey (n=160) and France (n=131) revealed that Turkish patients were more likely to have a family history, HLA-B51 and pathergy positivity whereas, French patients tend to have more neurological involvement and higher recurrence risk (HR=1.64; 95%CI 1.1–2.44, p=0.014) (62).

Cardiac function and valvular abnormalities

As previously reported (63), aortic regurgitation was the most common cardiac valvular lesion (64), associated with aortic valve prolapse, echo-free spaces within the aortic annulus, vegetation-like lesions and aortic root aneurysm. BS patients had functional impairment in both sides of the heart on echocardiography (65, 66).

Gastrointestinal system involvement

Myelodysplastic syndrome (MDS) with trisomy 8 has been observed in patients with BS, particularly in those with gastrointestinal system (GIS) involvement (67, 68). Recently, the association of BS with polycythemia vera and trisomy 8 has been reported in a 70-year-old woman with GIS involvement (69). Patients with MDS and GIS involvement are reported to have an unfavourable outcome and seem to have a more favourable response to treatment approaches directed at MDS (70, 71). Another study reported that the region of patients rather than having the trisomy 8 played a more important role in the prognosis of GIS-MDS (72).

Nervous system involvement

Factors associated with relapse among 208 patients with neuro-BS were identified as young age of onset and cranial nerve dysfunction (73). After a median of 68 months, 23 patients (18.4%) had a poor outcome. Indicators of a poor outcome were higher initial modified Rankin score and progressive parenchymal neuro-BS.

Juvenile-onset BS

Skin mucosa lesions and ocular disease occurred less frequently and family history was more common in juvenile-onset BS, whereas vascular and neurological involvements were more common in adult-onset BS (74).

Pregnancy

Women with BS appear to have a favourable outcome during pregnancy (75). Recent data collected from 33 pregnancies in 16 women are in line with this observation (76).

Amyloidosis and mortality

The prevalence of AA amyloidosis was found to be decreased over the years (1976-2000:24/3820 *vs*. 2001-2017: 3/5590) based on a retrospective chart survey (77). Male gender, vascular involvement and increased mortality were associated with AA amyloidosis as indicated in the accompanying systematic review (77). A total of 328 death certificates collected between 1979 and 2016 by the French Epidemiological Centre showed an earlier mean age of death in BS, compared to the general population (78). The age-standardised mortality rate was 0.15/million person-years and the most frequent associated causes were infections, organ dysfunction, and arterial events.

Quality of life and psychiatric disorders

Quality of life is impaired (79) and fatigue, sleep disorders, depression and

anxiety occur more frequently in BS patients than in the general population (80-82). Young patients and those with low socio-economic status are more severely affected (80). A multicentre cohort study of 189 patients with BS revealed that organ damage increased over 2 years of follow-up, resulting in impairment of the perceived physical and mental health (79). In a cross-sectional multi-national study evaluating 364 patients with BS and 143 with recurrent aphthous stomatitis (RAS), presenteeism was found to be associated with increased disease activity, comorbidities and smoking in BS, whereas with oral ulcer activity and long disease duration in RAS (83).

COVID-19

Although there is an increased risk for COVID-19 infection compared to the general population, the course of infection among BS patients is relatively mild with lower admission rates, no exacerbation of thrombotic events or increased mortality (84, 85). Higher rates of symptomatic COVID-19 and more hospitalisation were observed among colchicine users compared with controls despite similar sero-positivity for SARS-CoV-2 (86). This was also true for those patients who use daily hydroxychloroquine, suggesting that neither of the drugs exerted a protective effect against COVID-19 infection. The frequency and profile of adverse effects after COVID-19 vaccination were similar between BS, FMF and other rheumatic patients, flare rate after vaccination was significantly higher among BS and FMF patients, suggesting defects in innate immunity in BS and FMF (87, 88). Seroprevalence rates after vaccination with Pfizer/BioNTech or Sinovac/CoronaVac were similar among BS patients and healthy controls. Antibody titres were significantly elevated after Pfizer/BioNTech (89).

Take home messages

- OCT, OCTA and laser flare photometry are being investigated as potential imaging modalities that may replace FA, which is an invasive method for the assessment of BS patients with uveitis (29-36).
- Sensitivity and specificity of the pathergy test improve with the addition of pneumococcal vaccine (44).
- Patients with VCS thrombosis have a better survival and lower relapse rates compared to those with arterial involvement (61).
- The prevalence of AA amyloidosis has decreased over the years (77).

Treatment

Apremilast

A subanalysis of the phase 3 apremilast study showed significant improvements on patient quality of life (90, 91). A randomised controlled study (RCT) confirmed the efficacy of apremilast in suppressing oral ulcers and overall disease activity in Japanese patients (92). A meta-analysis showed that apremilast is effective for mucocutaneous lesions and arthritis as well as overall disease activity (93). It should be underlined that apremilast was used in combination with immunosuppressives and TNF inhibitors in some studies included in this meta-analysis.

TNF-α inhibitors

A 32-week, open, multicentre, prospective study from Korea evaluated the efficacy of infliximab in 33 BS patients with refractory GI involvement (94). Response to infiximab was evident within 2 weeks and was maintained thereafter and repeat colonoscopies showed significant mucosal healing. Three different meta-analyses coming from China provide further support for the efficacy and acceptable safety of adalimumab and infliximab in the treatment of intestinal involvement of BS (95-97).

A multicentre retrospective study from France compared uveitis relapse rates with adalimumab (initially 80 mg and then 40 mg every other week) and infliximab (5 mg/kg every 4-6 weeks following a loading dose at weeks 0.2 and 6) in a cohort of 330 patients with sight-threatening noninfectious uveitis, including 89 patients with BS, during median 74 months follow-up (98). Relapse risk was lower with infliximab (35%) compared to adalimumab (46%) but the response rates were similar. The study suggested lower relapse risk in BS patients compared to idiopathic uveitis (HR=0.53, 95%CI 0.33–0.85, p=0.009). The complete response of BS patients was also better than idiopathic uveitis (OR=2.04, 95%CI 1.16–3.58, p=0.014). A systematic literature review showed that relapse rates were lower with TNF-α inhibitors (adalimumab and infliximab) compared to conventional immunosuppressives, but similar to interferon-α (99).

Although TNF-α inhibitors have become the standard treatment for severe manifestations in BS, new manifestations may occasionally develop during their use. A retrospective study of 282 BS patients (220 men) treated with infliximab between 2004-2020 showed new manifestations in 13% of patients with vascular involvement and 3% of patients with uveitis. Eleven (48%) of the new manifestations were vascular, 5 were arthritis, 3 were gastrointestinal, 3 patients had erythema nodosum and 1 had CNS involvement. Pulmonary artery involvement was the most frequent new vascular manifestation. New manifestations were managed by either intensifying the infliximab treatment, adding glucocorticoids, immunosuppressives or switching to another agent. Interestingly no uveitis occurred as a new manifestation.

Tocilizumab

A retrospective study from China looked at the efficacy of intravenous tocilizumab in 10 BS patients with arterial involvement who were either refractory or intolerant to treatment with classical immunosuppressives and corticosteroids (101). A complete or partial response was observed in 9 patients at 24 weeks and no complications were observed in 5 patients who underwent surgery during 24 months of follow-up. A systematic review showed that tocilizumab was effective in 87% of 29 anti-TNF-α naive and in 80% of 45 anti-TNF-α experienced patients. However, negative response to tocilizumab in 3 consecutive BS patients with refractory uveitis led to early termination of an observational trial from China (103).

Tofacitinib

A retrospective study from China looked at the efficacy of tofacitinib in

13 BS patients with GI involvement refractory to previous treatments including TNF-α inhibitors (104). During a mean treatment duration of 10 months improvement in abdominal and systemic symptoms was observed in all patients. Follow-up colonoscopy of 11 patients revealed mucosal healing or improvement in 10 patients. Another report from China reported satisfactory response to tofacitinib in 4 BS patients with GI involvement (105). It should be underlined that a previous retrospective study from China reported negative responses with tofacitinib for GI involvement in BS patients (106).

Ustekinumab

The efficacy of ustekinumab in recurrent oral or genital ulcers was assessed in 15 BS patients in an open, prospective study from France. The patients were either treatment-naive or refractory to colchicine and/or glucocorticoids (107). At week 24, a complete response was observed in 11 patients (73%) that was maintained at week 52 in 10 patients. Elevated baseline CRP levels were associated with a poor response.

Invasive interventions for arterial involvement

Arterial aneurysms in BS are traditionally treated with open surgery in addition to immunosuppressives. Development of anastomotic aneurysms and graft thromboses necessitating re-operations are well known complications of surgery. Endovascular repair might be a suitable alternative. A retrospective single-centre study including 21 patients (16 males, median age 42 years) reported endovascular arterial repair among 4 patients with peripheral artery involvement and 1 patient with infrarenal aortic occlusion treated with tube endografts or balloon-expandable stents, 8 patients with thoracic arterial aneurysms treated with thoracic endovascular aortic repair and 8 with abdominal aortic aneurysms treated with endovascular aortic repair (108). Except in emergency cases with ruptured aneurysms, all elective interventions were performed after the patients achieved normal levels of acute phase reactants with medical treatment and all patients continued their medications following surgery. During a mean follow-up of 50 months, 3 patients required re-intervention and 1 of them underwent open surgery for the repair of a pseudoanerysm at the access site. Re-intervention free survival rate was 94% at 1 year and 68% at 5 years. The authors concluded that endovascular repair of arterial complications of BS when supported by medical treatment provides good mid-term outcome with low re-intervention rates.

A retrospective study from Egypt reported 1-year results of stent graft repair for carotid artery pseudoaneurysm in 6 BS patients (5 men) collected over 11 years (109). All patients received immunosuppressives for at least 1 month before the intervention and continued them postoperatively. The intervention was technically successful in 5 patients but open surgery was required in 1 patient because of failure to cannulate the internal carotid artery. Development of false aneurysm and thromboses at the puncture site were short term complications in 2 patients, respectively. A computed tomography angiography at 1 year revealed that 4 of the 5 stents were patent and 1 stent was occluded but the patient was not symptomatic and no intervention was needed.

A retrospective study from China reported the outcome of 19 BS patients with aortic involvement including 13 with aortic valve pathology at echocardiography (110). Eleven patients were operated 22 times. Aortic valve replacement was performed in 6 patients, 3 of them required a second valve replacement operation and 2 required a Bentall procedure as the third operation. Four patients had died during follow-up. Only 5 patients received pre- and post-operative immunosuppressive treatment, and 7 patients did not receive any immunosuppressives. The authors underlined the importance of post-operative immunosuppressive treatment to reduce mortality and post-operative complications.

Take home messages

- New BS manifestations may develop during treatment with TNF-α inhibitors (100).
- More data are needed to understand the role of biologics other than TNF-α inhibitors and JAK inhibitors in BS (101-107).
- Pre- and post-intervention immunosuppressive treatment improves the outcome of BS undergoing endovascular repair of arterial complications (108-110).

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