Review

Behçet's syndrome: one year in review 2024

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ABSTRACT

The aim of this review is to provide a critical summary of studies published during 2023 that contribute to our understanding of Behçet's syndrome. An increase in the incidence of BS was reported in Northern Spain after 2014. Studies on patient perspectives showed the impact of Behçet's syndrome on quality of life, daily activities, education, work, and relationships. Differences in genetics among Behçet's syndrome patients with different types of organ involvement were reported and an association between HLA-B/MICA and SLCO4A1 polymorphisms and eye involvement and between DDX60L polymorphisms and nervous system involvement were observed. It was suggested that Integrin α9β1 plays a crucial role in the neutrophil-mediated inflammatory pathways underlying this syndrome and the dysfunction of the PDL1/PD-1 pathway may be associated with the hyperactivity of the Th-1/Th-17 axis. Vein wall thickness seems to be increased in patients with Behçet's syndrome, but its pathogenetic and clinical implications are not clear. There is growing evidence regarding the efficacy of TNF inhibitors in different types of organ involvement. A number of small case series point out to the potential role of TCZ and JAK inhibitors.

Epidemiology

A hospital-based prevalence study from Northern Spain identified a total of 120 patients with probable Behçet's syndrome (BS) according to expert opinion, through the screening of a clinical database from January 1980 to December 2018 (1). Among these patients, 59 (30 women, 29 men) fulfilled the ISG criteria. BS prevalence was estimated as 10.14 per 100,000. Yearly incidence was 0.49 per 100,000 between 1999 and 2018, and showed an upward trend from 2014 until the time of this study. The frequency of organ manifestations was similar to other Southern European cohorts with a frequency of 56% for uveitis, 17% for central nervous system involvement, 10% for vascular involvement and 7% for gastrointestinal involvement.

A systematic review revealed a total of 12 articles reporting on the epidemiology of BS in Latin American countries including Brazil, Colombia, Argentina, Chile and Mexico (2). Two of these were prevalence studies and reported an estimated prevalence of 0.3/100,000 in Brazil and 1.1/100,000 in Colombia. HLA B51 positivity among the BS patients *vs*. the general population was 38% *vs*. 14% in Argentina, 30% *vs*. 16% in Brazil, and 9% *vs*. 5% in Mexico. Clinical information was available for 532 patients form 5 cohorts and showed a mean age at onset of 33 years and a female to male ratio of 1.4. The overall frequency of manifestations was 99% for oral ulcers, 81% for genital ulcers, 69% for skin lesions, 53% for joint involvement, 28% for nervous system involvement, 20% for vascular involvement, 18% for gastrointestinal involvement and 5% for cardiac involvement.

Take home messages

- The prevalence of BS was reported as 10.14 per 100,000 and the incidence as 0.49 per 100,000 in Northern Spain, with an upward trend after 2014 (1).
- A systematic review showed that HLA B51 positivity among BS patients was 38% in Argentina, 30% in Brazil, and 9% in Mexico (2).

Patients' perspectives

A study assessed personal experiences and perspective of BS patients through analysis of the posts and comments in a BS subforum of the website Reddit among an anonymous community including 1100 members, using a Grounded Theory analysis (3). The recurrent

themes that were identified were looking for connectedness and different perspectives including experiences with different treatment options, diagnostic problems including experiences with physicians and other health care professionals, inquiries about symptoms including their severity, variety, and triggers, expression of emotions related to their experience with BS such as loneliness and feeling misunderstood, impact of BS on quality of life, daily activities, education, work, and personal relationships, and inquiries about COVID-19 and its vaccination.

Another study that explored patients' perspectives used an anonymous online survey designed by BS experts, patients and caregivers, with the narrative medicine approach with a semi-structured questionnaire and cluster analysis (4). A total of 207 patients (68 men, 139 women) answered the survey. Difficulties in diagnosis and unpredictable nature of the disease, impact of BS on their personal life, families, relationships, and work, patients' perception of themselves in terms of future and hopes, as well as emotions such as fear and anger. Cluster analysis additionally showed the important impact of accepting the disease or not, on daily life.

These are generally similar to what was observed through semi-structured interviews with BS patients (5), but may provide more information due to the anonymous nature of the interactions. These studies are important in increasing our understanding of the patients' perspective of BS and for developing better patient-reported outcome measures. On the other hand, the lack of diseased controls makes it impossible to determine whether any of these issues specific for BS, or can be observed in any chronic disease.

Take home messages

- Surveys exploring patients' perspectives revealed common themes such as loneliness, feeling misunderstood, fear, anger, and impact of BS on quality of life, daily activities, education, work, and relationships (3, 4).

Immunopathogenesis

Integrins are transmembrane receptors involved in the interaction between neutrophils and the vascular endothelium. More specifically, α9β1 is assumed to be related to inflammation, thus its role in different pathological processes has recently become subject of interest. Regarding BS, a cross-sectional study was performed with the aim of assessing the role of α9β1 in BS pathogenesis. (6) Higher serum levels of α9β1 integrin and its ligands were found in active BS patients compared to inactive patients and healthy controls. Moreover, laboratory findings like inflammatory markers, white blood cells (WBC) and platelet (PLT) values were higher in active patients, with a significant positive correlation between these values and serum levels of α9β1 integrin and its ligands. These results suggest that α9β1 may be an important marker for BS and further studies, especially those including diseased controls are necessary to assess the role of this integrin in helping the differential diagnosis and determining disease severity.

Several studies previously reported higher levels of interleukin (IL)-17 in serum and tissues of BS patients compared to healthy controls, suggesting that this cytokine may play an important role in the disease pathogenesis. A systematic review with meta-analysis (7) confirmed this observation, and showed that IL17A rs4711998 and rs8193036 polymorphisms were associated with BS susceptibility. However, no significant difference was found in circulating IL-17 levels in line with disease activity and severity.

It is known that dysregulated expression of co-stimulatory molecules on dendritic cells (DCs) surface is associated with hyperactivity of T helper (Th) 17 and hyperproduction of IL-17. The dysfunction of programmed death ligand-1 (PDL1)/programmed cell death 1 (PD-1) pathway is associated with multiple autoimmune diseases, and previous evidence showed that interferon (IFN) is effective in the treatment of these conditions due to the upregulation of DCs expression of PDL1, which is associated with Th17 hyperactivity and IL-17 hyperproduction. Based on these, a Chinese group evaluated the mechanism of IFN in the treatment of BS uveitis using *in vitro* experiments. (8) The authors found that the DCs expression of PDL1 in BS patients with active uveitis was significantly reduced, and that IFN significantly enhanced PDL1 expression in DCs resulting in CD4+ T cells apoptosis and lower frequencies of Th1 and Th17 cells. The longitudinal part of the study which showed the correlation of the decrease in Th1/Th17 cells with drug response supported these findings. Future *in vivo* experiments in animal models are expected to confirm the proposed mechanism of IFN and its clinical relevance, especially in local lesions of BS patients.

Take home messages

- Integrin α9β1 may have a crucial role in the neutrophil-mediated inflammatory pathway underlying BS (6).
- *In vivo* experiments should be performed to clarify the emerging *in vitro* evidence that the dysfunction of PDL1/PD-1 pathway may be associated with the hyperactivity of Th-1/Th-17 axis in BS pathogenesis (8).

Genetics

Sawalha *et al*. investigated the genetic features of the specific clinical manifestations of BS (9). They studied 436 patients from Turkey and genotyping was performed using the Infinium Immunoarray 24 bead chip. A weighted genetic risk score was calculated for each clinical feature. The genetic risk score was higher among patients with uveitis compared to those who did not have eye involvement and the previously determined HLA-B/MICA gene (rs11679906 OR: 1.85) and the newly found SLCO4A1 (rs6062789 OR:0.41) were the related associations. Neurological involvement went along with DDX60L (rs62334264 OR:4.12). The limitations of the study were the relatively small sample size of the clinical subgroups and the omission of the other clinical co-morbidities. Its major strength was its long follow-up duration. The authors suggested that genetic variability played an important role in disease pathogenesis and hypothesised that the findings may play a role in a personalised approach.

A paper on 'MHC-1-opathies" reconsidered the ideas surrounding this vague and heterogenous entity. The authors claimed that spondyloarthropathies, BS, psoriasis and birdshot uveitis were in the spectrum of MHC-1-opathies and suggested that together with the genes of the antigen processing aminopeptidases ERAP1 and ERAP2 they had similar pathways of antigen presentation to CD8 T cells. However, progress on the subject was hampered by phenotypic heterogeneity. The aims of this MHC-1-opathy multidisciplinary group were to form a standard annotation of disease symptoms, to perform a detailed phenotypic evaluation, integrating the GWAS data across a large number of existing cohorts, harmonisation of the nomenclature of ERAP allotypes, to improve disease classification, diagnostic criteria and prognostic biomarkers, evaluation of MHC-1-opathies in different ethnic backgrounds and to enable patient participation (10).

Burleigh *et al*. deployed a tailor-made WES genetic workflow for the identification of monogenic mimics of BS and HLA genotyping to better describe the genetic architecture of BS in an unselected UK cohort (11). 9/31 (29%) had monogenic disease presenting with a BS phenotype and the majority of these were patients with A20 haploinsufficiency, the best described monogenic mimic of BS. None of the cases with monogenic diagnoses were HLA-B51 positive; however, HLA-B51 positivity was confirmed in 8/22 (36%) of the remaining monogenic cases, in keeping with a typical polygenic BS phenotype. Thus, the application of this specific genetic workflow stratified UK patients into 3 broad groups: monogenic BS mimics, typical polygenic BS with HLA-B51 positivity and polygenic BS without HLA-B51 positivity. There was no significant association of age of disease onset with genetic associations. They suggested that their study provided a strong rationale for such combined genetic testing routinely before BS diagnosis in order to avoid misdiagnosis of such patients as BS. However, it should be noted that these patients had several clinical findings such as conjunctivitis, cervical lymph nodes, ulcerating lesions in the nostrils, neutropenia, hepatosplenomegaly, pulmonary interstitial emphysema, and skin lipodystrophy that would cause a clinician to suspect conditions other than BS, even without genetic testing.

Shi *et al*. assessed single-cell chromatin accessibility and transcriptomic characterisation of BS patients (12). They built their study on the idea that a comprehensive understanding of the gene regulatory profile of peripheral autoimmunity and the diverse immune responses across distinct cell types in BS were still lacking. They presented a multi-omic single cell study of 424817 cells in BS patients and non-BS individuals. They mapped chromatin accessibility and gene expression in the same biological samples and they observed vast cellular heterogeneity. Widespread cell type specific, disease associated active and pro-inflammatory immune responses were present. Integrative multi-omic analysis revealed putative TF regulators. They also predicted gene regulatory networks within nominated TF activators including AP-1, NF-κB and ETS transcript factor families. They proposed that their study illustrated the epigenetic and transcriptional landscape in peripheral blood of BS patients. The results have to be reproduced in further studies including BS patients with different types of organ involvement along with diseased controls.

Mitochondrial DNA (mtDNA) leakage into the cytoplasm occurs when cells are exposed to noxious stimuli. Specific censors recognise cytoplasmic mtDNA to promote cytokine production. Cytoplasmic mtDNA can also be secreted extracellularly leading to sterile inflammation. However, the mode of secretion of mtDNA out of cells upon noxious stimuli and its relevance to human disease remain unclear. Konaka *et al*. have shown that pyroptotic cells secrete mtDNA encapsulated within exosomes (13). Activation of caspase 1 leads to mtDNA leakage from the mitochondria into the cytoplasm via gasdermin-D. Caspase 1 also induces intraluminal membrane vesicle formation allowing for cellular mtDNA to be taken up and secreted as exosomes. Encapsulation of mtDNA within exosomes promotes a strong inflammatory response that is ameliorated upon exosome biosynthesis inhibition *in vivo*. The authors also showed that monocytes derived from BS patients showed enhanced caspase 1 activation leading to exosome mediated mtDNA secretion delineating a novel pro-inflammatory pathway.

Vlachogiannis *et al*. published a study on DNA damage response network in BS (14). Peripheral blood mononuclear cells from 26 patients and 26 age- and sex-matched healthy controls were studied. Endogenous DNA damage levels were increased in active BS patients compared to controls or patients in remission. In parallel, BS patients had defective nucleotide excision repair capacity. RNA sequencing revealed reduced expression of NEIL1 that negatively correlated with DNA damage accumulation. On the other hand, expression of the genes involved in senescence and senescence-associated secretory phenotype positively correlated with individual endogenous DNA damage levels. They concluded that the DNA damage response network contributed to the pro-inflammatory environment. A positive control group including patients with another inflammatory disease would have rendered the results more robust.

Ryu *et al*. investigated the role of ERAP1 in BS using a mouse model (15). ERAP1 incomplete expressing mice were inoculated with herpes simplex type 1. The model had significantly different expression levels of CD80, Ryu CD11b, Ly6G, RORγT, interferon gamma and IL-17 compared to asymptomatic controls showing that ERAP1 defective expressions played an important role in BS development through inappropriate regulation of Th17.

Take home messages

- Different subgroups of patients with BS may have different genetic make-ups (10).
- "MHC-1-opathies" continue to be discussed although it is still far from a unifying concept for the pathogenesis of BS (11).
- Mitochondrial DNA may be involved in a new inflammatory pathway (13).

Clinical manifestations

Eye involvement

In a study conducted using spectral domain optical coherence tomography (SD-OCT) and fluorescein angiography (FA) in Behçet uveitis (BU) related macular oedema (ME), eyes were divided into groups according to whether ME could be detected with these 2 modalities (16). Type of ME by SD-OCT and grade of macular leakage by FA were investigated. The study reported that SD-OCT was effective in detecting ME in 90% of eyes with BU.

In another OCT study, the authors analysed the development of macular OCT changes in BU patients and its relationship with visual acuity (VA) (17). They found that foveal atrophy related changes were correlated with VA and those patients had VA less than logMAR 1.0. Additionally, the authors report that some of the OCT changes can be reversed if aggressively treated in the early stages. The reversal of OCT changes before development of damage may be associated with better visual outcomes.

In 2023, a small number of studies evaluated OCT-A, a new technique, and different auxiliary methods in BU patients. Overall, OCT-A seems to be a promising but not fully standardised imaging method in the follow-up of BU (18, 19). The inability of OCT-A to detect vascular leakage limits its use in pathologies with retinal vasculitis. Furthermore, it is not suitable for use in pathologies where peripheral retinal vessels are frequently involved, including BU. Techniques that attempt to expand the image area with montage, lack the ability to provide optimal images due to artifacts. Moreover, the inability to obtain useful images in pathologies with anterior segment and vitreous inflammation such as BU limits its use in posterior uveitis.

In a multicentre retrospective study, the authors divided 175 BU patients into 3 different groups according to the age of disease onset (20). They compared the ocular findings and treatment results between the groups. It was observed that the ocular manifestations vary depending on the age of onset of the disease. Juvenile onset patients more commonly had non-occlusive retinal vasculitis, peripheral vessel occlusions, cataract and elevated intraocular pressure, whereas late-onset patients more commonly had anterior uveitis and macular ischaemia. The branch retinal vein occlusion was most common in adult and late onset patients. Interestingly, the visual outcome was similar between these groups. This may be related to the differences in treatment, since juvenile onset patients had used combination of immunosuppressive drugs and biologics more frequently.

In a large population-based cohort study using the Korea National Health Insurance Service database, the risk of blindness and sight-threatening ocular comorbidities were compared in BS and the general population (21). They found that BS patients have a 10.73-fold increased risk of blindness in 10 years.

In another retrospective study investigating the relationship between BU and neuro-Behçet's and including 108 BU patients, uveitis features, neurological symptoms, FA and MRI results were evaluated and the rate of neurological involvement associated with BU was reported to be approximately 24% (22). They reported that optic nerve leakage on FA and neurological symptoms were associated with an increased risk of neurological involvement.

Skin manifestations

A study based on the data obtained in the International Auto-Inflammatory Disease Alliance (AIDA) registry, evaluated clinical characteristics of 458 BS patients (23). Pseudofolliculitis was found to be associated with persistent skin involvement. Those with no skin involvement at disease onset did not develop skin lesions thereafter, suggesting that there is a cluster more prone to develop skin manifestations. Likewise, a retrospective study in an inception cohort of 188 patients revealed that the predominant clinical findings were skin-mucosa lesions and eye disease (24).

In a cross-sectional study involving 979 patients with BS from multiple countries, various factors including oral ulcer activity, genital ulcer activity, musculoskeletal involvement, gender, disease severity, smoking, and toothbrushing habits were analysed using a CART algorithm to predict treatment protocols (25). It was concluded that using immunosuppressives for oral ulcers was associated with irregular toothbrushing, especially among men.

Musculoskeletal involvement

According to the AIDA registry, among 141 juvenile BS patients, 26.2% had musculoskeletal manifestations such as arthritis, myalgia and sacroiliitis (26). Treatment responses varied; myalgia negatively affected response to biologic therapies.

Vascular involvement

- Vein wall

Prior work indicated that patients with BS had a higher thickness of the lower extremity vein walls in comparison with that observed in the HC and several other inflammatory diseases (27, 28). Atalay *et al*. confirmed increased vein wall thickness (VWT) in a small group of juvenile BS patients with definite (n=22) and incomplete BS (n=13) (29). To delineate more the structure of the venous wall, Sevik *et al*. measured this time, the intima-media thickness (IMT) of the common femoral vein in a group of BS patients and found it increased when compared to the healthy individuals (30). It has to be noted that IMT of common femoral vein (CFV) could not be discerned in 46.3% (n=19) of HC. Furthermore, the same concept was explored using MRI venography and a significant enhancement in the vein wall was observed in a group of BS patients in comparison with healthy individuals (31).

- Vascular disease

Clinical characteristics associated with cardiovascular (CV) involvement were investigated (32). Those with CV involvement (n=32) were found to be more hypertensive and more likely to have ascending aorta widening than those without (n=63). A retrospective study evaluated 28 patients with pulmonary artery involvement (33). Similar to what was previously reported (34), strong association with deep vein thrombosis (DVT), alveolar hemorrhage and/or ground-glass appearance in nearly half of patients, along with pulmonary artery aneurysms (n=7),

and pulmonary artery thrombosis (n=18) were observed. Five patients disclosed only pulmonary parenchymal involvement. Emekli et al. constructed flow-void probability maps of patients with cerebral venous sinus thrombosis (CVST) with and without BS to visually illustrate the impacted cerebral venous sinuses (35). Coşkun *et al*. analysed 15 paediatric patients with thrombi, focusing on clinical features, treatment responses, and prognosis (36). CVST was the predominant type, followed by DVT and pulmonary artery thrombosis (26.6%). Intracardiac thrombi occurred in 20% of male patients, mainly in the right heart cavity. Del Peral-Fanjul examined vascular involvement, evaluating CFV IMT via ultrasound, nailfold capillaroscopy (NFC) for microvascular involvement, and endothelial progenitor cells (EPC) in peripheral blood (37). CFV IMT assessment and NFC were deemed useful for evaluating vascular involvement, with EPC potentially serving as a biomarker for BS.

Gastrointestinal involvement

Among those with intestinal involvement, abdominal pain was the most commonly detected clinical manifestation, followed by reflux, diarrhoea, and nausea (38). Histopathological analysis revealed a high prevalence of vascular congestion through the gastrointestinal tract, although inflammation was less prevalent (38). Gastrointestinal dysmotility was reported in a small case series of 7 patients. These patients did not have intestinal involvement of BS and were effectively treated by apheresis. Six of them were women. No autoimmune features and auto-antibodies were reported in these patients, except for a speckled ANA in one of them (39).

Miscellaneous

Zhang *et al*. evaluated 4286 patients (390 had BS) who had total knee arthroplasty and observed higher rates of DVT, peri-prosthetic instability, aseptic loosening, and wound complications among BS patients compared to matched controls (40). Although there were no data on outcomes of knee arthroplasty in patients with other chronic diseases within the control group, it was reported that diabetes and hypertension were more common in this control group. In a cost-of-illness study conducted in 207 BS patients from Italy, mean overall costs were estimated to be €21,624.00 per patient/year, with direct non-health expenses accounting for 58% of the overall costs (41).

Cluster analysis

A study from Eastern Turkey, evaluated the clinical features and disease course using cluster analysis in a large cohort of 444 patients with a mean age of 35.8 ± 10.2 years (42). Four clusters were identified: vascular, ocular, musculoskeletal, and mucocutaneous as suggested previously (43). Male gender, superficial thrombophlebitis, and uveitis were associated with vascular involvement. Another study investigated BS across various age groups, categorised by onset: <3 years, 3–18 years, and >18 years, aiming to identify unique clinical patterns (44). Early-onset BS had higher rates of family history, perianal ulcers, fever, arthritis, and abdominal and ocular involvement. Late-onset BS showed increased neurologic involvement. Paediatric patients experienced gradual symptom onset, facilitating diagnosis with systemic involvement. In a multicentre retrospective study, five different clusters were reported in the juvenile BS patient group; C1, mucocutaneous type; C2, articular type; C3, ocular type; C4, vascular type; and C5, gastrointestinal type (45). The most common mucocutaneous cluster was predominant in girls, whereas ocular and vascular clusters were more frequently observed in boys. A higher disease activity at the time of diagnosis was reported in the ocular, vascular, and gastrointestinal clusters.

Diagnosis

A guideline by an international Delphi consultation was proposed on how to recognise oral ulcers specific for BS (46). Oral ulcers due to BS exhibited distinct features when compared to that seen in inflammatory bowel diseases and mucous membrane pemphigoid. On the other hand, differentiation from recurrent aphthous stomatitis was difficult. Vitale *et al*. evaluated pathergy test using intradermal self-saliva injection in 52 BS patients, 52 axial spondyloarthritis (axSpA) patients, and 26 healthy controls (HC) (47). BS patients showed significantly more skin erythema reactions compared to axSpA patients and HC. The Pediatric Behcet's Disease classification criteria (PEDBD) was attempted to be validated using an evidence-based approach (48). The ISG criteria had the highest specificity (1.00) followed by PEDBD criteria (0.99), while the ICBD criteria were more sensitive (0.79) than ISG (0.50) and PEDBD (0.58). The gold standard for diagnosis was consensus among a group of experts who reviewed patients' clinical and laboratory data. It should be noted that there was consensus on diagnosis among experts for only 66.2% of the patients.

Take home messages

- Venous system involvement appears to be generalised in BS (29-31).
- Cerebral venous sinus thrombosis was the predominant thrombus type in paediatric patients (36).
- Diverse clustering patterns of disease manifestations, suggest different underlying mechanisms (42, 44, 45).

Management

Azathioprine (AZA) is often the first choice in the treatment algorithm of BS when an immunosuppressive is indicated. Lately, mycophenolate (MMF) has become the first line immunosuppressive and has almost replaced cyclophosphamide and azathioprine in the treatment of various inflammatory diseases. However, experience with MMF in BS is limited to small studies and with conflicting results. In an observational study, 12 BS patients (8 men) with uveitis were treated with MMF or mycophenolic acid for a mean of 4 years (49). Seven of them received MMF for remission induction. MMF, combined with either adalimumab (ADA) or infliximab (IFX) in 3 patients was effective in inducing remission. However, 3 of the 4 patients using MMF as monotherapy switched to other drugs because of ongoing ocular attacks and the fourth patient discon-

tinued it because of diarrhoea. The remaining 5 patients received MMF for remission maintenance. Of the 4 patients receiving MMF as monotherapy only 1 maintained remission and the other 3 needed other drugs because of continuing ocular attacks. The last patient was on a combination with IFX and discontinued MMF 17 months later for long lasting remission. This limited experience suggests that the use of MMF in combination with anti TNF agents may be effective in the treatment of uveitis of BS. A controlled trial comparing MMF with azathioprine is needed to understand its place in the treatment of BS.

Several observational studies further supported the beneficial effect of ADA and IFX in the treatment of gastrointestinal involvement (50-54), uveitis (55-58) and neurologic involvement (59) of BS.

A retrospective study compared the frequency of relapses or development of new major organ involvement among BS patients receiving conventional immunosuppressives with those receiving biologics (60). The study cohort consisted of 806 patients (56% men) of whom 232 had major organ involvement at the time of diagnosis. During a median follow-up of 36 months 227 patients developed major organ involvement. Overall, 440 patients were treated with conventional immunosuppressives and/or biologics (interferon alpha or anti TNF agents). New major organ involvement developed in 51 patients and relapses occurred in 109 patients. Based on this, the authors considered that relapses and new events were more common under conventional immunosuppressives compared to biologics, and proposed earlier use of biologics at least in high-risk patients. However, the data presented lack detailed information on the time sequence and type of treatment preventing a definitive conclusion, since biologic agents are usually initiated when treatment with conventional immunosuppressives is inadequate and are often combined with conventional immunosuppressives.

A retrospective study reported experience among 127 BS patients (102 men) with vascular involvement treated with IFX 5 mg/kg between 2004 and 2022 (61). The majority of the patients (n=110) received IFX for remission induction and the remaining 17 patients for maintenance. IFX was combined with conventional immunosuppressives and glucocorticoids in 75% and 87% of the patients, respectively. The types of vascular involvement were pulmonary artery involvement (n=37), non-pulmonary arterial involvement (n=16), venous involvement (n=61), and venous ulcers (n=13). At month 12, the vascular remission rate was 63% for the whole group, 68% for pulmonary artery involvement, 70% for venous involvement and 63% for non-pulmonary arterial involvement. On the other hand, it was only 15% for venous ulcers which is currently the most difficult to treat complication of BS. The relapse rates were low under treatment with IFX and were managed with intensification of treatment. During a mean follow-up of 37 months, 63 patients (50%) were still receiving IFX. The main reasons for discontinuation were remission (22 patients), inefficacy (11 patients) and adverse events (14 patients). The high remission rates along with the low relapse rates during follow-up underline the efficacy of IFX in vascular involvement except for venous ulcers. The high remission rates especially for pulmonary artery involvement, the main cause of mortality in BS, raise the question whether IFX should be given as first line treatment to patients with this complication.

A multinational retrospective study that was conducted in referral hospitals in France, Spain, Italy and Turkey assessed the efficacy of tocilizumab (TCZ) in 30 BS patients (17 women) (62). The patients had either ocular involvement (18 patients), CNS involvement (5 patients), or mucocutaneous and/or joint involvement (7 patients) refractory to previous treatment including biologic agents. TCZ showed efficacy in the majority (15 of 18; 84%) of patients with uveitis, in all 5 patients with CNS involvement and in 5 of the 7 patients with mucocutaneous and/or joint disease. Thirteen patients (43%) continued TCZ after a median follow-up of 31 months whereas 5 patients discontinued it after achieving remission, and 12 patients due to side effects or failure/relapse.

Another multicentre, observational study from Spain aimed to compare the efficacy of ADA and IFX with TCZ in patients with refractory macular oedema (63). Forty patients received either ADA or IFX and 9 received TCZ. Seven patients in TCZ group had received anti TNF agents before.

The median follow-up was 24 months in anti TNF group and 13 months in TCZ group. Both treatments were effective in decreasing macular thickness and improving visual acuity. Not forgetting the small number of patients and the retrospective design of this study, the results suggest that TCZ might be a good alternative for patients with macular oedema that is refractory to treatment with anti TNF agents.

Observational studies, all from China, suggest that JAK inhibitors might be beneficial in the treatment of various organ manifestations of BS that are refractory to treatment including anti TNF agents. In a retrospective study, the pan-Jak inhibitor tofacitinib was found to be effective in 77% of patients with refractory uveitis during a follow-up of up to 38 months (64). Two observational studies both from the same centre in China, assessed the efficacy of the more selective JAK inhibitor baricitinib in the treatment of refractory vascular involvement and intestinal involvement (65, 66). The study on vascular involvement consisted of 17 patients (12 men) with refractory venous and/or arterial and/or cardiac involvement (65). Baricitinib was combined with immunosuppressives and glucocorticoids but was used at low dose of 2 mg/day because of the concerns of increased venous thromboembolism risk reported with JAK inhibitors. During a mean follow-up of 10.7 months approximately 90% of the patients achieved a complete response and radiologic response was seen in those with repeated imaging. Despite previous concerns regarding the thromboembolic risk of using JAK inhibitors, based on experience with rheumatoid arthritis patients, no thrombotic events or serious adverse events were record-

ed. In the second study, 13 patients (6 men) with refractory gastrointestinal involvement were treated with baricitinib 2-4 mg/day together with glucocorticoids and conventional drugs (66). During a mean follow-up of 11 months, 77% of the patients achieved complete response and endoscopic healing in the majority of patients with repeat colonoscopy. No serious adverse events and no thrombotic events were noted during follow-up. Interestingly, baricitinib was also effective in 3 patients who were refractory to previous treatment with tofacitinib. Finally, the new member of this family, the JAK-1 selective upadacitinib was given to 2 Chinese BS patients with panuveitis after failure of conventional immunosuppressives and ADA (67). Both patients responded well to upadacitinib 15 mg/day with improved visual acuity and resolution of macular oedema during follow-ups of 6 and 9 months, respectively.

Take home messages

- Studies are needed to understand whether infliximab might replace cyclophosphamide as a first line agent for pulmonary artery involvement (61).
- TCZ seems to be less effective for joint involvement and oral ulcers (62).
- With more evidence, JAK inhibitors might prove to be useful for all refractory manifestations of BS (64-67).

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