Meeting report

Highlights of the 19th International Conference on Behçet's Syndrome

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The 19th International Conference on Behçet's Disease has been scheduled for 2020 but could not be held due to COVID-19 pandemic. After a 2-year postponement, the conference organised by the International Society for Behçet's Disease was held in Athens, Greece on July 6-8, 2022. The president of the conference was Prof. Petros Sfikakis from the National and Kapodistrian University of Athens Medical School. For the first time, the meeting was a hybrid event and ended with a half-day virtual conference.

There were 261 participants from 24 countries, including rheumatologists, ophthalmologists, dermatologists, gastroenterologists, immunologists and epidemiologists. Six oral, 27 poster-tour and 85 poster presentations, in addition to 29 plenary lectures and 6 "Difficult to treat Behçet's disease" sessions were presented. The abstracts of the conference have been published in the Mediterranean Journal of Rheumatology.

The opening lecture was presented by George Tsokos. Although his talk was mainly on systemic lupus erythematosus (SLE), he also mentioned that researchers in Behçet's syndrome (BS) face the same problems they face in SLE. He explained one of these problems as a "synchronicity" problem. A pathogenic pathway or a parameter which is involved in disease expression, by definition, should precede the disease. Even though there are some clues for mice, the time between the pathogenic parameters and disease expression is not known in humans yet. On the other hand, clinical trials which target these pathogenetic parameters are usually carried out, when these parameters disappear but the clinical manifestations persist. He also mentioned that the disease process in BS and other chronic inflammatory diseases begins long before the clinical diagnosis. Therefore, the patients included in a clinical study assuming that they have the same disease duration may not actually have the same disease duration. Finally, he stated that he disagreed with the idea that the mission was accomplished in a clinical trial when you find a "statistically significant p-value" which is overvalued by FDA and all clinical trials.

John Ioannidis gave a very comprehensive talk with many messages on reproducibility and transparency problems in clinical studies in the special lecture session on Day 1. First, he listed some important problems in scientific publications. He pointed out some transparency problems. Very few articles have registered protocols while many authors do not let other researchers reach out to their raw data. He said 96% of the biomedical literature claims that they have statistically significant *p*-values while most clinical research is not useful and has almost no effect on changing the clinical practice. He also mentioned the importance of external validation studies, how small sample size undermined the reliability of the studies, also how overpowered sample size caused problems. Finally, he gave recommendations such as large-scale collaboration, adoption of a replication culture, registration of protocols, sharing of data, reproducibility practices, more appropriate statistical methods. Briefly, the proportion of true research findings should be increased.

Immunology and genetics

Omics, single-cell RNA sequencing and immunosenescence in BS made up the main studies in the basic science section in this conference. Cheng *et al*. from China presented their results

on proteomics analysis in BS patients with different organ involvement in order to identify the biomarkers for clinical assessment and treatment of BS patients (1). They measured the expression levels of proteins in plasma in their discovery cohort which included 98 BS patients and 31 healthy controls (HCs). They found 220 differentially expressed proteins which discriminate 88.6% of BS patients and 95.5% of HCs. These differentially expressed proteins were involved in a variety of biological functions related to BS pathogeneses, including complement activation, regulation of plasma lipoprotein particle levels, wound healing, angiogenesis, and leukocyte-mediated immunity, according to bioinformatic analyses. Vascular involvement has the largest differentially expressed proteins which were mainly related with platelet degranulation, blood coagulation, post translational protein modification. Finally, they found and validated HABP2, TNC and SERPINA3 as potential biomarkers for the clinical assessment of vascular BS and treatment targets. In the other omics study, transcriptomic changes were evaluated in erythema nodosum-like lesions (ENL) in BS patients (2). A total of 7 ENL and 3 non-lesional samples was analysed by using bulk tissue RNA sequencing. They found upregulated genes in ENL related to activated innate immune system and increased myeloid compartment, particularly M1 macrophages. Zheng *et al*. from China presented the contribution of C1q-high monocyte subsets in BS pathogenesis by using single-cell RNA sequencing (scRNA-seq) (3). They performed both scRNA-seq (4 BS and 4 HCs) and bulk RNA-seq (9 BS and 10 HCs) to profile peripheral blood mononuclear cells (PBMCs) and isolated CD14+ monocytes from BS patients and HCs. They found C1qhi monocyte subset was significantly increased in BS and positively correlated with high disease activity, and high ESR levels also decreased with remission. When they compared this new subset with CD16+ monocyte, C1qhi monocytes exhibited enhanced phagocytosis, antigen presentation and proinflammatory cytokine secretion (IL-6 and TNF-alpha). They also found out overexpression of interferon-alpha inducible genes and increased expression of STAT1 and IRF1 in BS C1qhi monocytes. Finally, they tested whether C1qhi monocytes respond to tofacitinib, a JAK-STAT signalling inhibitor, and showed decrease in interferon-alpha stimulated C1qhi monocytes. In another scRNA-seq study, Nowatzky *et al*. aimed to find out whether HLA class I-restricted CD8 T cells in BS are present at an important effector site (the eye) and tried to define their clonality and activation-dependent phenotypes and also their relationship with ERAP1-Hap10/HLA-B*51 carrier status (4). For this purpose, they obtained anterior chamber fluid cells from BS uveitis patients for scRNA-seq and PBMCs from 26 untreated BS patients and 22 HCs. They also generated CRISPR-Cas9 ERAP1 knocked out (KO) immortalised lymphoblastoid cell lines (LCL) resembling the hypotrimming ERAP1-Hap10 allotype in an HLA-B51 restriction context, and assessed their effects on CD8 T cell function. They found oligoclonal CD8 T cell expansions in the aqueous humour during BS uveitis and their clonotypes matched highly expanded clones in autologous, time-matched PBMCs. They also reported CD8 T cell phenotypes in blood showed shifts between antigen-experienced and naive CD8 T cells, which depended on ERAP1-Hap10/HLA-B*51 carrier status. Finally, they showed ERAP1 KO altered immunogenicity to CD8 T cells in assays assessing proliferation, cytokine secretion, and toxic degranulation. The same group reported another scRNA-seq study to identify highly BS/HCs discriminating immune cells with the same study subjects used in the previous study (5). They identified CD16+, CD14low, CD4low, CD3-, CD19- cells are the only BS/HCs discriminant cellular expression pattern by using flow-cytometry and CITRUS analysis. They found decreased non-classical (CD14lowCD16hi) and intermediate (CD14+CD16+) monocytes, and CD16+ dendritic cells in BS patients' PBMCs compared to HCs. They also showed an abundance of CD14+ cells with CD16 co-expression in the eye during uveitis but not in CD14+ cells in PBMCs which suggested their transmigration into or, less likely, interconversion within the eye during BS uveitis. This was probably not a stochastic process.

Immune senescence in BS was discussed in the basic and translational science session and also in an oral presentation. Lee *et al*. from South Korea briefly mentioned the process of immunosenescence, role of age and inflammation in immunosenescence, changes in immune cells during immunosenescence and immunosenescence in other immune disorders and then presented her published data on immunosenescence in BS. She showed that senescent CD8+T cells were increased in active BS patients compared to the inactive BS patients while senescent CD4+ T cells and CD19+ B cells were not different between the groups. She also showed increased activation of cAMP-mediated signalling pathway in senescent CD8 T cells in BS patients compared to HCs. Her group also presented their data on the efficacy of apremilast, a phosphodiesterase-4 inhibitor related to cAMP pathway, in senescent CD8 T cells (6). They collected PBMCs from 9 HCs based on their age group (ranging from 40s to 60s). Half of the samples were treated with IL-6, anti-CD3 and anti-CD28 to mimic the BS conditions. All samples were treated with various doses of apremilast. They found the proportion of senescent CD8+ T cells were decreased when treated with apremilast, with partial correlation to dosage increment only in BS mimic condition.

Sawalha *et al*. presented their multiethnic genetic data which they looked at if there is evidence for genetic influence for sex bias in BS (7). They performed a case-case analysis which means they compared male BS patients with female BS patients and control males with control females separately. Their discovery cohort and also the majority of their data consisted of Turkish BS patients (2213 cases and 1533 controls). They also had 5 additional multiethnic cohorts (Spanish, Korean, Japanese, Italian, Tunisian). They found out

an association with male sex in MICA/HLA-B within the HLA region when comparing Turkish male BS patients with female BS patients (rs2848712, OR=1.46, p=1.22x10-8) but not in the control group comparison. They said they confirmed their result in other ethnic cohorts in a meta-analysis. However, it seems that the significance of this meta-analysis came from the largest patient cohort (Turkish cohort) and all the other cohorts crossed the line of null effect in their forest plot. They also found out higher genetic risk in HLA-B/MICA, HLA-C, and KLRC4 in male BS patients and IFNGR1 in female BS patients. In another study from China, contribution of neutrophils in the sex-biased ocular involvement in BS was investigated. They observed expansion of chemotactic and inflammatory neutrophils subsets in male BS patients, increased proportions of type I interferon responding neutrophils in female BS patients (8). Neutrophil extracellular traps (NETs) in BS were reported in 2 studies. In the first, the authors found increased NETs levels in BS patients compared to HCs (9). However, they couldn't show any significant differences between NETs levels and disease activity or vascular manifestations in BS patients. In the second, immunolabeling of myeloperoxidase and histone citrullination proteins was performed on the skin biopsies of three BS patients who had skin biopsy-proven superficial vein thrombophlebitis in their ENL lesions (10). NETs were found in neutrophils of panniculitis concurrent with superficial vein thrombophlebitis. Vitamin D is a frequently studied, controversial subject in immune diseases. Fifty-two Italian BS patients were studied in order to genotype the mutational hot spot (3' end) of vitamin D receptor (VDR) gene (11). The authors found a novel VDR variation in heterozygosity state in 3/52 BS patients but couldn't show any association between disease clinical manifestations and genotypes.

A group from Greece investigated whether there was a role of deregulated DNA damage response-repair network in BS (12). They studied PBMCs from 26 BS patients with various disease activity and 26 age-sex matched HCs. They found out higher levels of single-/double-strand DNA breaks, increased oxidative stress levels and abasic sites in BS patients compared to HCs. Their functional analysis revealed defects in central DNA repair mechanisms. The study also showed decreased expression of central DNA repair enzymes (ATM, NEIL1) and increased expression of senescence gene p21/CDKN1A in next generation RNA-seq analysis. A study from United Kingdom compared the frequency of Tfh-like γδ T cells in ocular and mucocutaneous BS patients and HCs (13). PBMCs from 15 mucocutaneous and 13 ocular BS patients and 10 age-sex matched HCs were analysed and no differences were observed in the frequencies of total γδ T cells and their subpopulations in BS patients compared to HCs. On the other hand, the authors found increased levels of cell markers (CXCR5 and PD-1) which define Tfh cells in ocular BS patients compared to mucocutaneous BS and HCs. Another group from United Kingdom reported their preliminary results on usefulness of measuring lymphocytes subsets in BS (14). Among 909 samples from 635 patients, the CD3, CD4, CD8 cells were often above and B and NK cells were often below the normal range. They have not yet interpreted their results in terms of disease status and treatment. Fortune *et al*. reported their results on genital and oral microbiome in BS (15). They studied 153 BS patients' samples; 70 matched oral and genital samples and 12 non-matched samples; and applied 16S rRNA-seq to all specimens. They found alpha and beta diversity significantly different between oral and genital samples but couldn't find differences between ulcer vs non-ulcer samples. They reported *Gardnerella*, *Lactobacillus*, and *Atopobium* were significantly increased in females than in males, while *Peptoniphilus* and *Corynebacterium* were significantly increased in males in the genital ulcer group. They also found the presence of *Staphylococcus* is associated with BS disease activity. The only BS animal model (mouse infected with HSV-1) study in the conference investigated the influence of the environmental factors on BS induction (16). Mice were maintained in either a conventional or a specific pathogen free (SPF) facility; other stressors such as noise, cold, anxiety and oxidative stress were added. The authors showed that the combination of conventional environment, noise stress, and HSV had the highest rates of developing BS (38.1%) among all groups. They also found noise stress increased the frequencies of CD83+ cells and different gut microbial compositions between SPF and conventional environments.

Effects of nanocurcumin supplementation on T-helper 17 cells inflammatory response in 36 BS patients was evaluated in a randomised, double-blind, placebo-controlled trial (17). No relevant clinical data such as type of organ involvement and other treatments was specified in the abstract. The authors claimed that the number of Th17 cells, RORγt, IL-17, IL-23, miRNA-155, miRNA-181, and miRNA-326 mRNA expression, disease activity decreased in nanocurcumin group compared to baseline and placebo group.

It should be stated that the absence of diseased control groups in all of the basic science abstracts stood out as an important drawback in this conference.

Epidemiology

Distinct clinical phenotypes with clustering of certain organ manifestations were suggested in BS. Ethnicity and geographic region may simply explain heterogeneity between studies regarding the clusters that were defined. A study from Russia evaluated 6 predefined clusters (mucocutaneous, articular, ocular, vascular, neurological and gastrointestinal) in different ethnic groups. A neurological and gastrointestinal phenotype were more likely to be observed in Russians, ocular phenotype in Azerbaijanis, and vascular phenotype in Dagestanis. Severe disease was more common in Azerbaijanis and indigenous residents of Dagestan than in Russians, Armenians and Chechens (18). A late-onset study from Morocco showed that females or patients with gastrointestinal involvement tended to be more common while ocular involvement was less frequent in the late-onset cohort than in the classic-onset group

(19). On the other hand, an Iranian study found a lower frequency of mucocutaneous and joint involvement, a higher frequency of ocular involvement and no difference regarding gender distribution in the late-onset cohort (20).

A Japan multicentre registry identified 5 clinical subsets based on residual symptoms by machine learning cluster analysis. These were subsets of complete remission, of oral ulcers, of arthralgia, of oral ulcers and arthralgia, and oral ulcers, arthralgia and cutaneous symptoms (21). Similarly, oral ulcers were found to be the main reason for not achieving complete remission in BS in another study from Japan (22). Finally, a systematic review identified other possible predictors of the differences in the reported clusters. These were study design, statistical analysis method, patient population, setting, diagnostic criteria, disease duration, definition of organ involvement, and ascertainment of manifestations (23).

Diagnosis

A study from United Kingdom investigated the saliva proteome of patients with BS, inflammatory bowel disease and mucous membrane pemphigoid and identified over expressed and under expressed proteins specific to BS. A secondary and complementary technique is being planned to verify the results and to assess saliva proteomics as a new diagnostic tool (24).

Although skin pathergy test is a highly specific diagnostic tool for BS, its sensitivity has decreased over the past decades. A study from Turkey aimed to improve its diagnostic performance and reported that skin pathergy test induced by 20G needle-prick and 23-valent polysaccharide pneumococcal vaccine has the highest sensitivity and specificity for BS patients (25).

The Marmara group from Istanbul previously proposed an increased common femoral vein (CFV) thickness (≥0.5 mm) as a diagnostic tool for BS. They reported that CFV thickness measurement is not affected by the patient position and can be done accurately in an erect or supine position (26). Prospective follow-up of their patients showed that CFV thickness remains stable over time, however, patients with mucocutaneous involvement with higher CFV tended to develop major organ involvement during follow-up (27). They assessed its diagnostic performance in patients with incomplete BS. Among the 48 incomplete BS patients followed at their clinic, an increased CFV thickness was not observed in only 2 patients (28). CVF measurement was also useful in differentiating BS uveitis from other forms of inflammatory uveitis (29) and the gastrointestinal involvement of BS from inflammatory bowel disease (30). Both intima-media and whole wall thickness of CFV were increased in BS patients compared to HCs suggesting a full layer venous wall inflammation (31). Increased inferior vena cava thickness (32) and pulmonary artery wall thickness (33) were also observed in BS patients suggesting extensive vascular inflammation. While all these impressive findings need to be replicated in other cohorts, our group detected venous halo sign in 13 of the 16 BS patients with superficial thrombophlebitis with superb microvascular imaging again suggesting venous wall inflammation (34).

Twelve different classification criteria sets were examined with regard to their sensitivities in 900 BS patients registered in the German Registry of Adamantiades-Behçet's disease. There was a wide variation in the sensitivity of sets to diagnose BS, ranging from 25% and to 90%. This finding confirmed most of the existing classification criteria is inappropriate for diagnostic use in routine clinical care at least in Germany (35).

Differential diagnosis

Diagnosis of BS may be challenging especially in non-endemic areas and the differential diagnosis includes several diseases. In a study from London, the final diagnoses of 9 patients who were referred with a probable diagnosis of BS to the London Behçet's Centre of Excellence were bullous pemphigoid in 2 patients, Majeed syndrome, erythema multiforme, chronic iron deficiency anemia, illness triggered by Epstein Barr virus, morsicatio buccarum and self-harm, erosive lichen planus, and recurrent oro-genital ulceration in 1 patient each (36). Another study included 202 patients from two referral centers in Hamburg and Amsterdam who did not fulfill ISG criteria and had a clinical diagnosis with a score of <5 points in the ICBD criteria set. Patients having oro-genital ulcers without an alternative diagnosis were defined as probable BS in case of HLA-B51 positivity, origin from an endemic area, typical BS symptom that is not part of the any classification criteria or with 3-4 points scored in the ICBD criteria. These 202 patients were categorised as: 58 (29%) probable BS, 57 (28%) skin disease, 26 (13%) chronic pain syndrome, 14 (7%) eye disease, 11 (5%) spondyloarthropathy, 9 (4.5%) gastrointestinal disease, 4 (2%) auto-inflammatory disease, 3 (1.5%) connective tissue disease, and 17 (8%) miscellaneous disease. Overall, 75 (37%) of these 220 patients also fulfilled the ICBD criteria. These findings underlined the disadvantage of the use of ICBD criteria for making clinical diagnosis in non-endemic areas (37).

Cerebral venous sinus thrombosis, the second most common type of neuro-BS, may be the initial manifestation in BS and its differentiation from other pro-thrombotic diseases is essential. A MR-venography study from Turkey constructed flow void probability maps of patients with CVST due to BS and other causes. Transverse sinus thrombosis was more common while venous infarction and haemorrhage were less common in BS. Headache due to the elevated intracranial pressure was the only clinical symptom in BS patients while focal neurologic findings were only found in patients with CVST due to other causes (38).

Life impact

Work outcome was evaluated in a subcohort of 148 patients enrolled from the Behçet's syndrome Overall Damage Index (BODI) study. Female gender, higher patient global assessment and an increased BODI score in the last 2 years of follow-up were associated with work impairment. BODI ocular damage was the only factor associated with absenteeism. Finally, younger age

at enrolment, higher disease activity and fibromyalgia were factors associated with patients' daily activity impairment (39).

Quality of life (QoL) in BS was addressed in 4 studies. Among the 103 BS patients, moderate to severe depression, moderate to severe anxiety and moderate to high fatigue were identified in 55%, 35% and 98% of the patients, respectively. Time Trade-Off and Standard Gamble methods showed that BS patients would forgo 28% of their remaining life or run a 30% risk of death to avoid the disease. Psychological factors such as depression, anxiety and fatigue rather than disease activity seem to influence patients' willingness to take risks associated with treatment (40). In the second study from United Kingdom, the most common problems reported by the patients were anxiety, depression and fatigue. Arthropathy, neurological problems, pathergy reaction, stomach/bowel symptoms and skin lesions were the symptoms that had negative impact on QoL according to 3 surveys in 2009, 2014 and 2020 (41). QoL was also found to be impaired among Egyptian BS patients (42).

Sexual dysfunction was investigated in 57 BS patients with HCs in a Turkish study. Sexual dysfunction was more common in males but not in females compared to the HCs (43).

The Behçet Clinic of Pisa, Italy, together with the Italian patients' association for Behçet's disease developed BehçeTalk, an educational program, to improve the knowledge of the patients and their caregivers about BS. The group announced that a new edition of BehçeTalk in English was on the way (44).

Pregnancy

Two retrospective studies from Italy and Russia reported pregnancy outcomes in BS patients. In the first study, 152 pregnancies in 96 patients were assessed and the authors concluded that BS manifestations do not appear to aggravate during pregnancy and gestational complications while adverse maternal-foetal outcomes are not increased in BS patients (45). The second study from Russia, 118 pregnancies in 45 BS patients with 10 controls were assessed. BS patients tended to terminate pregnancy more commonly compared to the control group and unfavourable pregnancy outcome was not associated with disease activity (46).

COVID-19

Previous studies could not find an increased risk of worse COVID-19 outcome in BS patients. Two studies from German and Iran reported similar results. Among the 900 BS patients registered in the German Registry of Adamantiades-Behçet's disease, there were only 2 patients who were infected with COVID-19. One of them recovered without a need for hospitalisation and the other needed intensive care for 12 days (47). In the second study, there were 107 Iranian patients with COVID-19 among the 7789 patients. Only one patient died due to respiratory failure (48).

Another study looked at the impact of the pandemic on BS patients using Maslow's hierarchy of needs. The authors found a decrease in weekly working hours, frequency of exercise, employment rate and patients experienced sleeping less and feeling lonely during the lockdown. They also recommended strategies such as tele-medicine for patient empowerment to better cope with the pandemic (49).

Whether immune response after COVID-19 vaccines is impaired in BS patients is of particular interest. The humoral response after 2 doses of inactivated or mRNA vaccines against COVID-19 in 166 BS patients was studied in a Turkish study. Most of the BS patients and all HCs had detectable antibodies after either CoronaVac (96%) or BioNTech (99%). Antibody titers were significantly lower in BS patients vaccinated with CoronaVac compared to the HCs while they did not differ among BS patients and HCs vaccinated with BioNTech. Among the patients vaccinated with CoronaVac, the antibody titers were significantly less among patients treated with TNF inhibitors. There was no significant difference between treatment regimens among patients vaccinated with BioNTech (50).

Disease assessment

The results of prospective follow-up of patients recruited in the BODI validation study showed that the duration of glucocorticoid therapy and ≥1 disease relapse were independently associated with damage accrual while immunosuppressive use was protective. Damage accrual was also associated with an impaired QoL (51).

A group from Turkey translated BODI into Turkish language and proved its construct validity. BODI was also reliable to be used for retrospective studies. Hypertension, lymphedema, liver failure, glaucoma, damage due to venous interventions and lung parenchymal involvement were found to be items that were not captured by BODI (52).

Evidence-Based Behçet's Disease Activity (EBDA), a new instrument for disease activity and remission assessment, was presented. EBDA was moderately correlated with BDCAF, however, EBDA was able to identify moderate to severe and severe disease activity more regularly (53).

In a special session, a need for treat-to-target strategy for BS was discussed. There was agreement on the need for a treat-to-target strategy for BS and an initiative to develop one, led by Professor Gulen Hatemi and Professor Petros Sfikakis was proposed.

Management

Professor Robert Moots presented the first randomised controlled study of infliximab and interferon-alpha. Thirty-seven patients with different types of involvement who were refractory or intolerant to first-line therapy were included in each arm. The primary outcome was the modified Behçet's disease activity index (mBDAI) at 12 weeks of therapy. There was no significant difference between treatment arms with respect to change in mBDAI at 12 or 24 weeks. However, there were significantly more patients who had to be switched another drug in the interferon-alpha arm than in the infliximab arm (11 (33%) *vs*. 3 (9%); p=0.01). Regarding secondary outcomes, median reduction in oral ulcer activity score and genital ulcer activity score, im-

provement in QoL, and glucocorticoid sparing effect were similar between the arms. Adverse events were observed more frequently in interferon-alpha arm (n=169 *vs*. n=101; *p*=0.224). However, the trial was not powered to look at individual organ manifestations (54).

A retrospective study from Turkey reported their experience with infliximab in 127 BS patients with vascular involvement who were followed up for a median of 24 months. The primary endpoint was remission at month 6 and the remission was defined as (i) no new clinical symptoms/findings associated with vascular lesion, (ii) no worsening of the primary vascular lesion and no new vascular lesion on imaging and (iii) a CRP<10 mg/L. Relapse was defined as development of new vascular lesion or recurrence of the primary vascular lesion. Overall, the remission rate was 73% and 63% at month 6 and 12, respectively. Regarding remission rates for each type of vascular involvement, infliximab was highly effective for venous thrombosis and pulmonary artery involvement while less effective for non-pulmonary artery involvement and no remission could be achieved in patients with venous ulcers (55).

In a case series from India, rituximab was tried in 11 patients who had refractory oro-genital ulcers. Two doses of 1 gr rituximab provided complete remission of mucocutaneous lesions without recurrences during the one-year follow-up (56).

Apremilast was previously shown to be effective for oral ulcers in phase-3 randomised controlled study. Its efficacy on other BS manifestations were studied in 15 Spanish patients who were refractory to conventional or biologic therapies in a retrospective study. Clinical improvement was 93% for oral ulcers, 100% for genital ulcers, and 70% for articular symptoms at month 3. Organ manifestations including uveitis in 4 patients, neuro-BS in 3 patients and venous thrombosis in 1 patient remained inactive during a median follow-up of 12 months (57).

A study from Italy explored the reasons of withdrawal failure of glucocorticoids in 100 patients who were using glucocorticoids at initial visit. During the follow-up, glucocorticoids could not be stopped in 40 patients at the last evaluation. The main reason for withdrawal failure of glucocorticoids in these patients was glucocorticoid addiction defined as occurrence of manifestations that were non-BS related (40%), followed by recent relapse while being on glucocorticoid therapy (30%), and disease recurrence while tapering glucocorticoids (30%) (58).

As the survival of BS patients with pulmonary artery involvement improves, we may see more patients with pulmonary hypertension due to chronic thromboembolic pulmonary hypertension (CTEPH). The results of pulmonary endarterectomy in BS patients, a potentially curative treatment for CTEPH, seems to be promising. Among the 20 patients who underwent pulmonary endarterectomy, all improved to the New York Heart Association functional class I and II. There was no perioperative mortality, however, 1 patient died four weeks after surgery due to massive haemorrhage. Only one patient experienced a relapse during a median follow of 55 months (59).

A pilot study from China conducted a pilot study of baricitinib in 11 patients with gastrointestinal involvement who were refractory to biologic therapies. Eight patients achieved complete remission on global gastrointestinal symptom assessment after a median follow-up of 9 months. Among the 7 patients who underwent a colonoscopy after 5-6 months of therapy, 5 achieved mucosal healing. Glucocorticoids could be tapered in 8 patients and no severe adverse event was observed. The longer follow-up of these patients with colonoscopic and safety evaluation will be more informative (60).

A study from Turkey assessed the frequencies of relapses and new major organ involvement in 440 patients who were on immunosuppressive therapy and followed up at least 6 months. New major organ involvement, relapse or both occurred in 160 (36%) patients. These events were significantly more common in patients receiving conventional therapies than among those receiving biologic therapies including interferon-alpha. The authors suggested that earlier and more aggressive treatment of major organ involvement may prevent relapses and new major organ involvement (61).

BS patients may have vitreous cells without any other posterior involvement and their prognostic importance is unknown. In a study including 42 patients with vitreous cells in either eye, posterior uveitis developed in 13 patients. Among these 13 patients, 4 patients had posterior uveitis in the other eye and 4 patients had both isolated anterior uveitis and vitreous cells in the same eye. As EULAR recommends initiating immunosuppressive therapy for patients with isolated anterior uveitis who have poor prognostic factors including young age, early disease onset and male sex, vitreous cells may be added as a poor prognostic factor (62)

The causes of hospitalisation may provide valuable information on the treatment-related adverse events. A hospitalisation study from Turkey surveyed BS patients who were hospitalised between 2002 and 2019. Of 414 patients, hospitalisation reason was BS-related in 304 (57%) patients and non-BS related in 223 (42%) patients. The most common BS-related and non-BS related reasons were vascular involvement and infections, respectively. Interestingly, opportunistic infections such as CMV and PCP were extremely rare (63).

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