Meeting Report

Highlights of the 18th International Conference on Behçet's syndrome

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The 18th International Conference on Behçet's Disease was held in Rotterdam, Netherlands between 13th and 15th of September 2018 under the auspices of the International Society for Behçet's Disease. The president of the conference was Professor Jan van Laar. There were around 300 participants, including rheumatologists, dermatologists, ophthalmologists, gastroenterologists and epidemiologists. In addition to 23 plenary lectures, 9 oral and 131 e-poster presentations were presented, 3 sponsored sessions and 7 Meet the Professor sessions were conducted.

Epidemiology

A decrease in the prevalence, severity and clinical expression of Behçet's syndrome (BS) over the last decades has been reported previously. A Tunisian study reported a significant increase in male to female ratio from 1.59 to 3, a significant decrease in articular involvement (49.6% *vs*. 35.1%) and a slight increase in ocular involvement (33.1% *vs*. 45.4%) in their recent cohort compared to their previous cohort (1). The Cerrahpasa group compared the initial presentation findings of BS patients who were registered at 4 different decades (2). While mean age at presentation did not change, the median disease duration got shorter over time. In addition to the severity of vascular and ocular involvement, the frequency of BS manifestations other than genital ulcer and neurologic involvement tended to decrease. The frequency of pulmonary artery involvement decreased from 1.9% to 1.4% (3). The recent cohort had more pulmonary artery thrombosis and received more biologic agents and had a more favourable outcome. Visual prognosis of BS patients with ocular involvement also got better in the recent cohort in a Turkish study (4). Although demographics, clinical characteristics and the frequency of posterior uveitis did not differ between the cohorts, biologics and combination therapy of azathioprine and cyclosporine were more commonly used in the recent cohort suggesting that the good outcome may be associated with more intensive treatment. Dilşen *et al*. analysed the demographic and clinical characteristics of BS patients with non-oral aphthous beginning (5). Males and patients with early disease onset were at higher risk for major organ involvement, as was shown for BS patients in general more than 30 years ago (6). The same group also reported that BS patients with non-oral aphthous beginning had a more severe disease course with an increased frequency of ocular and cardiovascular involvement (7). Additionally, there were more smokers among patients with non-aphthous beginning and smoking was associated with more frequent ocular involvement and genital ulcers (8).

The influence of sex and age on BS manifestations was analysed using a Japanese nationwide survey database of 7950 BS patients (9). A lower frequency of ocular involvement and HLA-B51 positivity and a higher frequency of intestinal and neurologic involvement were observed in this recent cohort compared to the previous ones. The male predominance in HLA-B51 positivity, pathergy positivity and ocular involvement disappeared in the elderly. Articular, vascular, neurologic and intestinal involvement tended to increase with aging. Skin manifestations, genital ulcers and epididymitis had a peak incidence at 20 and 50 years of age. A Tunisian study reported that male patients tended to develop ocular and vascular involvement while females were more likely to have erythema nodosum and articular manifestations (10). Posterior uveitis,

deep vein thrombosis and papulopustular lesions were more frequent in males whereas erythema nodosum, arthralgia and intestinal involvement were more common in females in an Italian study (11). Ocular and vascular involvement, papulopustular lesions and HLA-B51 positivity were more common in males while genital ulcers and arthralgia were more common in a United Kingdom (UK) study (12).

Older onset BS patients were evaluated in a Turkish study (13). Females tended to be more frequent in the older cohort. The frequencies of skin, joint, eye involvement were less common in older onset patients with a lower total activity scores. There was no difference regarding the finding among male and female patients. Male to female ratio was investigated by a meta-analysis of population-based prevalence surveys. There was no a significant sex predilection in BS occurrence (14).

Patients with manifestations suggestive of BS but not fulfilling International Study Group (ISG) criteria were assessed to find predictive manifestations for the fulfillment of ISG criteria over time in NewYork and Amsterdam cohorts (15). Over a mean follow-up of 9.4 years, 38% of the 189 patients fulfilled ISG criteria. Presence of morning stiffness, genital ulcers, skin lesions, and eye disease at initial presentation were associated with increased odds of ISG fulfillment. In a study from Amsterdam, 37% of the patients fulfilled ISG criteria at initial visit, 47% of the patients had a probable BS and BS was excluded in the rest of the patients (16). The demographic and clinical manifestations other than eye involvement presenting with visual loss were similar with the previous cohorts reported from non-endemic regions. A Moroccon cohort of 1646 patients had similar demographic and clinical findings with other endemic regions (17).

A Japanese study described three different clusters using data from a Japanese clinical database of patients receiving financial aid for treatment (18). These subsets were as follows: group A (male, ocular inflammation, HLA-B51-positivity, neurologic involvement), group B (female, genital ulcers, onset age <30 years, no ocular inflammation, HLA-B51-negativity, no neurologic involvement), and group C (onset age: 30-39 years, skin lesions, arthritis). The authors aim to look at the prognosis of these clusters in the following years. The same group also identified 3 distinct clusters by a principal component analysis: group A: patients having eye or neurological lesions without vascular and intestinal lesions, Group B: patients having vascular or intestinal lesions without eye and neurological lesions, and Group C: patients without eye involvement and special type of BS (19). Group A and B had more male patients and received more biologic agents. The frequencies of complete type of BS and HLA-B51 positivity were more frequent in Group A. There was a declining trend in the frequency of Group A and an increasing trend in Group B over years.

The comparative analysis of two cohorts from the Unites States (US) and Iran showed that genital ulcers, skin, joint, neurologic, vascular, cardiac and pulmonary artery involvement but not ocular involvement were more commonly observed in the US cohort (20). Moreover, a higher rate of multi-organ involvement was present in the US cohort. The most interesting finding of this study was the more severe disease course in a non-endemic region with a female predominance. 2018 update of the German registry of BS estimated a prevalence of BS of 1.1 per 100,000 in Germany (21). Turkish patients had significantly more uveitis and folliculitis compared to Germans while prostatitis/epididymitis was more frequent in German patients. An Austrian study reported that BS patients with Turkish and Austrian background had similar features, however those with Turkish background living in Austria had a milder disease course compared to BS patients living in Turkey (22).

Pathogenesis

Both innate and adaptive immune systems are thought to play role in the pathogenesis of BS and this year there were several studies that explored the role of the innate immune system. A study conducting whole-genome imputation of the Turkish genome-wide association study (GWAS) identified TLR2-RNF175 as a susceptibility locus for BS (23). Peripheral blood mononuclear cells homozygous for the risk allele of rs1869947 in TLR2-RNF175 locus were more likely to produce tumour necrosis factor (TNF) suggesting that increased production of TNF through Toll-like receptor (TLR) 2 pathway signaling in response to microbial stimulations are involved in the pathogenesis. On the other hand, another study evaluated TLR2 and TRL4 expression level and DNA methylation rate in BS patients (24). TLR4 expression was significantly higher in the BS patients (n=47) than in healthy controls (n=61) while TLR4 methylation rates were significantly lower in BS patients. TLR2 expression and TLR2 methylation rates did not differ between the groups. The third study about TLR found a significant elevated expression of TLR1 and TLR2 in B-lymphocytes, TLR1, TLR2 and TLR4 in both CD4 and CD8 positive T-lymphocytes, TLR1, TLR2, TLR4 and TLR6 in granulocytes and TLR2 and TLR4 in monocytes of BS patients compared to healthy controls (25). TLR5 expression was significantly increased on B and T-lymphocytes, granulocytes and monocytes in patients with pathergy positivity compared to those without. A previous GWAS study has identified CCR1 locus as the disease susceptibility gene (26). A study analysed the protein expression of CCR1 by a herpes simplex virus-induced mouse model of BS (27). The CCR1+ cells in BS mice were significantly down-regulated compared to the normal control and symptom-free control mice. A gut microbiome study also supported the role of innate immunity by showing an association between microbial genes and signaling pathways that are involved in innate immunity (28).

Phenotypes of neutrophils, natural killer cells, CD4 and CD8 cells were examined in 1 study each. Phagocytic capacity and ROS production after stimulating neutrophils were reduced in BS and Ocular Mucus Membrane Pemphigoid (OcMMP) patients compared to healthy controls and BS and OcMMP patients had a heterogeneous population of neutrophils (29). The Italian group sug-

gested that the percentages of NK, NKT and T cells expressing NKG2D may differentiate BS patients from healthy controls (30). However, this finding should be confirmed with a diseased control group. A subgroup CD4+ populations with non-activated HELIOS+FOXP3+ and non-proliferating Treg were found to be useful in differentiating BS from healthy subjects (31). Non-Treg CD25+ cell populations were more indicative of BS *vs*. uveitis due to non-BS as well as of clinically active BS while non-BS disorders were associated with high CD39 expression. The gene expression of the senescent CD8+ T cells was also found to differ from that of non-senescent CD8+ T cells (32).

Several studies investigated the impact of various single gene polymorphisms (SNPs) in BS. There was a different distribution of the most significant ERAP1 coding variants within BS and ankylosing spondylitis (AS) patients in an Italian study (33). A higher frequency of rs17482078 was found in the BS group compared to the AS group. Interestingly, this SNAP was found to be associated with BS susceptibility and protective against AS. The same group also investigated the frequency of IL10 SNPs and demonstrated that genotypic distributions of IL10 rs1800872 heterozygous genotype were different between BS and healthy controls (34). Another study form Iran showed that hypomethylation of IL-10 gene promoter contributes to the low expression of IL-10 mRNA in BS patients (35). Four candidate loci including 3p12, 6q25.1, 12p12.1 and 22q11.22 in non-HLA region has been reported to be associated with the susceptibility of BS in a genome-wide association study with a Japanese population (36). A Japanese GWAS study once again confirmed 3p12 and 6q25 (37). Fifteen SNPs from six genes including STAT3, UBAC2, TCFBR3, PTPN22, GIMAP4 and IL10 which have been identified as high risk factors in BS patients were assessed (38). There was a wide variation among British, Turkish and Han-Chinese populations that may explain the different phenotypes among the different ethnic groups. The frequency of IL-17 gene SNP did not differ between BS patients and healthy controls while there was a higher tendency of IL-17 A genotype A frequency in BS (39). SNP at positions–607 (C/A) but not 137 (G/C) in the promoter region of the IL-18 gene was associated with a susceptibility to BS while there was no association regarding both SNPs in recurrent aphthous stomatitis (40). An immunochip study again showed that HLA-B51 is the strongest association and identified HLA-A*68 as a protective allele for ocular involvement (41). A study from UK analysed KIR3DL1/S1 allelic variation in order to investigate the functional effects of HLA-B*51 in BS and suggested an interaction of KIR3DS1 with HLA-F (42). A BS family study found a probably damaging variant (NM_000022: exon4:c.A251G:p.Y84C) in the in ADA gene, however functional testing of this variant was not done yet (43).

BS has been shown to be associated with an altered serum metabolomics profile (44). It was suggested that levels of phosphatidylcholines and polyunsaturated fatty acids may be helpful in the diagnosis of BS while the two omega-6 polyunsaturated fatty acids may be promising as a therapeutic agent (45). Serum and urinary metabolic profiles were found to be clearly different between BS patients and patients with early inflammatory arthritis, supporting the contention that BS is not an autoimmune condition (46).

BS patients had significantly higher levels of immunoglobulin D (IgD) compared to healthy controls (47). IgD levels were also more likely to be elevated in patients with active mucocutaneous involvement and in those with high serum amyloid A levels. The serum levels of epidermal growth factor (EGF) receptor and its ligands were examined in non-infectious uveitis patients (48). Serum levels of epiregulin, amphiregulin, betacellulin, transforming growth factor-alpha and heparin-binding epidermal growth factor were significantly elevated in BS, sarcoidosis and Vogt-Koyanagi-Harada disease than in healthy controls. However, EGF levels were significantly higher in only BS and sarcoidosis.

A debate took place on the role of genetic versus environmental factors in the pathogenesis of BS. Although there was no definite conclusion due to inadequate data, there was general consensus that both may be playing role.

Clinical findings

Skin, mucosa and joint involvement

A group from Turkey had reported a low probability of complete remission in BS and showed that most BS patients continue to have oral ulcers during follow-up (49). This finding was supported by a multinational study, and it was suggested that not receiving immunosuppressive treatment is an independent risk factor for ongoing oral ulcer activity (50). The same group also evaluated the factors associated with mucocutaneous activity index (MI) and composite index (CI) scores, they had previously developed as patient-reported outcome instruments for assessing mucocutaneous involvement in BS. Female gender, smoking and disease duration were associated with higher MI scores (51) while, mild disease course was associated with immunosuppressive use and severe disease course with no immunosuppressive use. Disease duration less than 5 years and being a non-smoker were predictive factors for low CI scores (52). This is interesting since smoking was previously reported to decrease oral ulcers (53). A group from UK announced an attempt to delineate the clinical features of oral ulcers of BS that may help to discriminate them from oral ulcers due to other causes by an international Delphi process (54).

The role of menstruation as triggers of BS manifestations was studied in an Irish study (55). Nine of 18 patients reported a correlation between menstruation and flare. The most common manifestations that were correlated with menstruation were oral ulcers (89%), followed by arthralgia (56%), genital ulcers (44%), lethargy (44%), skin lesions (11%) and headaches (11%).

The skin prick test with self-saliva has been proposed as a diagnostic test by a Japanese group (56). Cutaneous reaction with self-saliva was more pronounced in 25 BS patients compared to controls including 7 patients with RAS and 12 diseased controls (herpes simplex virus infection, Lipschutz genital

ulceration and erythema nodosum) (57). The authors speculated that this reaction is linked with allergic reaction to oral microbes owing to the absence of reaction with sterilised self-saliva. Another study found an association between oral health and disease severity supporting the microbes in the pathogenesis of BS (58).

Eye involvement

A Korean population-based cohort study including 14,408 patients with new incident uveitis showed that legal blindness that was defined as best-corrected visual acuity less than 20/400 was higher among patients with uveitis due to BS compared to those with uveitis due to non-BS causes (3.7% *vs*. 1%) (59). BS, older age and low income were significantly associated with legal blindness by cox proportional hazard regression analyses.

The findings of optical coherence tomography (OCT) in BS patients were reported in 2 studies. The first study investigated macular vascular changes in BS patients without uveitis and healthy controls and demonstrated macular vascular changes even in BS patients without uveitis (60). The second study examined the findings of OCT during active and remission phases of uveitis in BS (61). Macular oedema was the most common macular pathology in the active period while epiretinal membrane was more often detected during remission. Macular thickness was less common during remission and there was no correlation between macular oedema during the active phase and macular damage during remission.

The management of idiopathic branched retinal vein occlusion (BRVO) includes laser photocoagulation, intravitreal injection of anti-vascular endothelial growth factor agents and dexamethasone implant (62). Long-term results suggested that BS patients with BRVO are more likely to respond to immunosuppressive therapy compared to patients with idiopathic BRVO (63).

The Cerrahpasa group attempted to find the predictors of damage progression in uveitis due to BS using a standard screening method (64). Posterior and panuveitis attacks, attacks causing severe vitreous opacity, retinal infiltrates and haemorrhage in the arcuate region and hypopyon attacks were predictors of damage whereas anterior uveitis attacks were not associated with damage. A new uveitis damage score was developed by the same group (65). Intra and inter-observer agreement of this tool was considerably good with a good correlation between damage scores and the visual acuities.

Finally, a Tunisian study analysed their BS patients with ocular involvement and found genital ulcers, deep venous thrombosis and mucocutaneous onset as protective factors for the development of ocular involvement (66).

Vascular involvement

Lower extremity vein wall thickness (LEVWT) was found to be significantly increased among BS patients with or without lower extremity venous thrombosis compared to healthy controls in 2 studies from Turkey (67, 68). LEVWT was more pronounced in patients with deep vein thrombosis than in those without. Given that AS patients had a similar LEVWT with healthy controls, this was thought to be specific for BS. Longer follow up of patients with increased LEVWT will answer its predictive role for the development of deep vein thrombosis.

The role of thrombophilic factors in thrombosis due to BS was investigated by a systematic literature review (69). Among the several prothrombotic factors that were studied in BS, factor V Leiden mutations, high homocysteine levels and high von Willebrand factor levels were found to be associated with thrombosis.

A Tunisian study reported a lower frequency of recurrent deep vein thrombosis in BS compared to non-BS (70). It was somewhat interesting since a prospective study of BS patients with deep vein thrombosis reported a relapse rate of 54% over a mean follow-up period of 40.7±13.4 months as mentioned below (71).

A survey of 24 BS patients highlighted the difficulties in the management of leg ulcers due to BS (72). Ulcers did not heal despite several treatment strategies in 54% of the patients and were associated with unemployment in 46% of the patients.

Nervous system involvement

Two studies from South Korea (n=85) and China (n=42) reported the clinical characteristics of parenchymal neuro-BS (NBS) patients (73, 74). The findings of both studies were comparable with the previous cohorts regarding demographics, mean age at diagnosis, site of involvement and disease course. The Chinese study also compared NBS patients with BS patients without neurologic involvement and confirmed the clustering of NBS and ocular involvement (74).

There is no consensus on the duration of treatment for NBS. A study from Turkey tried to answer this question by investigating the relapse rate over time (75). Forty-one percent of the 285 patients with parenchymal NBS and 14.0% of 89 patients with cerebral venous sinus thrombosis had at least one relapse within a mean follow-up of 5.4±0.7 years and 13.7±1.3 years, respectively. They recommended discontinuing the treatment after 7 years since the risk of relapse was very low after seven years.

Parenchymal lesions in NBS tend to locate in ponto-mesencephalic junction. This was also confirmed by probability mapping using brain magnetic resonance imaging (MRI) (76).

The mechanism of the sustained elevation of interleukin (IL)-6 in chronic progressive NBS was evaluated by an autopsy study (77). The histopathologic features of a patient with chronic progressive NBS were compared with a patient with acute NBS who was in a long-term remission at the time of death. Perivascular infiltration of CD68+ monocytes throughout the whole brain tissue was found to be a characteristic finding of chronic progressive NBS and was suggested to be the reason for the sustained elevation of IL-6.

A multicentre study from Turkey reported on 8 patients with pseudotumour cerebri without cerebral venous sinus thrombosis that was evaluated by contrast enhanced MRI and MR-venography (78). Four of these 8 patients presented with pseudotumour cerebri and then were diagnosed with BS. The authors suggested that the differential diagnosis of pseudotumour cerebri should

include BS in countries with a high prevalence of BS.

Optic neuritis which is a rare finding in BS was described in two studies. The first study including 25 patients divided patients into 2 groups: those having optic neuritis after BS diagnosis (Group 1) and those diagnosed with BS during evaluation of the aetiology of optic neuritis (Group 2) (79). Group 1 (n=12) was significantly older than Group 2 (n=13). Bilateral involvement of optic nerve was rare, observed with a similar rate among the two groups (3/12 *vs*. 5/13). Disc oedema was more often detected in group 2 (3/12 *vs*. 10/13). Eight of the patients had an improvement with immunosuppressive and corticosteroid therapy. A study from Morocco found the frequency of optic retrobulbar neuritis as 3% among their 287 patients with neurologic involvement (80). Different from the former study, all 8 patients had a bilateral involvement. All patients received high dose corticosteroid treatment. Four achieved complete remission, 3 had a stable course and the last one did not respond to therapy.

Life impact

Work outcomes in BS were presented in 4 studies. Patients with four or more clinical manifestations of BS had a statistically significant increased risk of unemployment in the British study (81). Male gender, increase in the frequency of visits, being a current smoker, having a vascular involvement and early period of the disease were predictive factors for work-day loss in BS patients in the Turkish study (82). Work productivity was found to be impaired in two studies from Turkey and was associated with major organ involvement in the multinational study (83) and with eye involvement in the single centre study (84).

A study from Ireland including 28 patients looked at the mood of BS patients (85). Fifty percent of patients scored their mood as low. The most commonly reported reason for the low mood was exacerbations of BS (71.4%), followed by other health reasons (50%), family issues (35.7%) and problems related to work (21.4%).

Sexual dysfunction and mental health status were investigated in 50 BS patients with healthy controls in an Iranian study (86). Sexual dysfunction was more common in females but not in males compared to healthy controls. Regarding mental status, only aggressive behaviour was more frequent in BS group.

A study from the UK looked at the longitudinal relationship between disease activity and psychological status in BS patients (87). Disease activity was assessed by Behçet's disease activity index (BDAI), clinician's and patient's perception of disease activity and psychological status by a number of validated quality of life instruments. BDAI weakly correlated with the psychological status while clinician and patient perception of disease were significantly correlated with each other and with all of the validated quality of life instruments. Longitudinal changes in BDAI reflected only a small proportion of changes in psychological status.

Paediatric Behçet's syndrome

A surveillance study was undertaken in the UK and Republic of Ireland to study the performance of 3 criteria sets for the diagnosis of BS in paediatric patients (88). The sensitivity of ISG and Paediatric Criteria for Behçet's Disease criteria was similar when the gold standard was chosen as the fulfillment of International Criteria for Behçet's Disease. However, both had a low sensitivity (55.4% *vs*. 51.8%). Mucocutaneous involvement was the most common type with a less frequency of ocular involvement compared to other paediatric cohorts.

Two studies from Iran (n=203) and Morocco (n=60) presented the characteristics of juvenile onset BS patients (89, 90). Both studies reported similar rates regarding gender, mean age at diagnosis, ocular involvement and family history of BS, but differed in the frequency of venous involvement (6% *vs*. 10%), neurologic involvement (5% *vs*. 18%), arthritis (31% *vs*. 55%) and genital ulcers (42% *vs*. 88%).

Comorbidities

A study from Korea compared 5,576 BS patients with 27,880 age- and sex-matched non-BS patients (91). None of these patients had a history of cardiovascular disease and they were followed for up to 5 years for incident cardiovascular disease. Myocardial infarction (HR: 1.717; 95%CI 1.08–2.73), stroke (HR: 1.653; 95%CI 1.094–2.498), mortality rate due to cardiovascular diseases (HR: 1.823; 95%CI 1.4–2.373) but not congestive heart failure (HR: 1.202 95%CI 0.737–1.958) were significantly higher in BS patients compared to non-BS controls.

The Cerrahpasa Group reported a decrease in the frequency of secondary amyloidosis in BS patients (92). Its frequency was 0.62% among the 3820 patients registered between 1976-2000 and declined to 0.054% among the 5590 patients registered between 2000-2017. However, mortality due to amyloidosis was high and nearly 50% of the patients had died within a median of 3 years. The same centre also evaluated the frequency of obstructive sleep apnea (OSA) among male patients with superior vena cava syndrome (SVCS) and controls using the Berlin questionnaire which is a screening test for OSA with a high sensitivity and modest specificity (93). OSA was significantly higher in BS patients with SVCS (57%, 16/28) than in those with vascular involvement other than SVCS (13%, 13/100), those without vascular involvement (6%, 6/93) and healthy controls (9%, 9/100). The authors suggested that external pressure of the large venous collaterals on the upper airways may explain the increased prevalence of OSA among patients with SVCS.

An Iranian study described 18 BS patients with osteonecrosis and found that vascular involvement was more common in these patients compared to BS patients in general (94). However, information on corticosteroid use, a common cause of osteonecrosis was not reported.

A study of 154 consecutive patients (10 with pulmonary artery involvement) aimed to determine the prevalence and causes of pulmonary hypertension (PH) in BS (95). The presence of PH was evaluated by transthoracic echocardiography and defined as an estimated sPAB ≥ 40 mmHg. Seventeen (11%) patients had PH. Group II PH (n=9) was the most common cause followed by group IV (n=4). Only 1 of 4 patients with group 4

PH was symptomatic hence the authors recommended to screen patients with pulmonary artery involvement for PH even if the patients are asymptomatic.

Disease assessment

The OMERACT core set of domains for clinical trials in BS were reported (96). These included five mandatory domains to be assessed in all trials and additional sub-domains for specific types of organ

Biomarkers

Endothelial function was assessed as a potential predictive factor for the development of major organ involvement in young male patients with only mucocutaneous involvement (97). Thirty-six BS patients, 35 AS patients and 36 healthy subjects were prospectively followed and assessed by carotid Doppler ultrasonography in each visit. At baseline, markers of endothelial dysfunction, flow mediated dilatation (FMD) and nitroglycerine-induced vasodilation, were similar between the groups whereas carotid intima media thickness was significantly higher in BS. During a mean follow-up of 56.6 months, only 5 patients developed major organ involvement (3 vascular and 2 ocular). Lower baseline FMD was associated with a higher probability of immunosuppressive requirement during the follow-up.

The association of alpha-melanocyte stimulating hormone (α-MSH), vasoactive intestinal peptide (VIP), IL-1β, IL-6, IL-10, and TNF-α with disease activity, fatigue and quality of sleep were assessed (98). α-MSH, VIP, and IL-6 were significantly elevated in BS patients compared to healthy subjects. Both α-MSH and IL-6 were associated with fatigue and quality of sleep while VIP was associated with quality of sleep and disease activity, but not with fatigue.

Immunogenicity

There were three studies about immunogenicity of anti-TNFs in BS. The first study investigated the prevalence of anti-drug antibodies against infliximab (IFX) in patients with BS together with controls (99). Anti-IFX antibodies were detected in 4/66 (6%) BS, 5/27 (18.5%) rheumatoid arthritis, 3/25 (12%) Crohn's disease, and 1/53 (%2) AS patient, and in none of the healthy subjects (n=32). The median serum IFX trough level was significantly lower in patients with anti-IFX antibodies compared to those without antibodies. However, the therapeutic effect of antibodies could not be evaluated due to the small number of BS patients with antibodies. The second study from Japan looked at the correlation between the clinical response and the trough level of adalimumab (ADA) or the presence of anti-ADA antibody in 10 patients with refractory non-infectious uveitis (100). However, there was only 1 patient with uveitis due to BS. Four of the 10 patients had anti-ADA antibodies and mean serum ADA trough level was significantly lower in patients with anti-ADA antibodies compared to those without antibodies. However, clinical response was not different between patients with anti-ADA antibodies and those without. The third study from the Netherlands followed 9 refractory patients treated with ADA up to 5 years and observed no anti-ADA antibodies in any of the patients (101). Overall, three studies suggest that immunogenicity does not seem to be an important problem in BS patients treated with infliximab and adalimumab.

Management

There were several reports on the efficacy and safety of traditional drugs such as cyclophosphamide, methotrexate and interferon-alpha and biologic agents including anti-TNFs, IL-1 blockers, secukinumab and the oral phosphodiesterase inhibitor apremilast.

The phase III, multicentre, randomised, placebo-controlled, double-blind study of apremilast (RELIEF) in BS patients without major organ involvement and with active oral ulcers despite at least one previous medication showed a significant benefit of apremilast over placebo on the number and pain of oral ulcers, overall disease activity and quality of life (102, 103). The proportion of patients with treatment-emergent adverse events was similar between apremilast and placebo groups during the placebo-controlled period. The subgroup analysis of Japanese patients was also reported and showed similar results (104).

There were four studies on the management of vascular involvement. A multicentre study from Turkey analysed 23 refractory patients with vascular involvement treated with anti-TNFs (21 IFX and 2 ADA) (105). Eleven patients had pulmonary aneurysms (4 with additional cardiac involvement) and 12 had venous involvement. All patients obtained remission within 3 months. Three of the 21 patients who were treated with IFX had to switch to ADA due to secondary unresponsiveness in 2 patients and allergic reaction in 1 patient. Two patients had stopped the treatment due to remission, however, one of them had a relapse 6 months after the cessation of treatment. There was an additional relapse and a tuberculosis under anti-TNFs. Overall, 20 (2 ADA, 18 IFX) patients were still using anti-TNFs at the end of a median follow up of 14 (3-67) months and all were in remission. Tocilizumab was assessed in 7 refractory patients with arterial involvement other than pulmonary artery involvement (106). Two of them also had venous lesions. Tocilizumab was administrated at 8mg/kg iv every 4 weeks for a median follow-up of 19.4±9.0 months and all patients had clinical and acute phase response improvement. Radiologic improvement was observed in one patient. The number and the dose of immunosuppressive agents could be tapered in 3 patients each. None of the patients experienced a serious adverse event. A prospective survey of 33 patients with lower extremity deep vein thrombosis followed for a mean of 40.7±13.4 months showed that relapse rate under azathioprine therapy (45%, 13/29) was considerably high within a mean follow-up of 20.2±15.8 months while there were only 2/17 (11%) patients who had a relapse under interferon-alpha therapy within a mean follow-up of 29±20 months (71). A systematic literature review of BS patients who underwent endovascular or surgical procedures for venous thrombosis pointed out the importance of pathergy reaction with invasive procedures in BS (107). Fifty percent of the 30 patients had unfavourable results and many of the case reports with favourable results had a small duration of follow-up.

The subgroup analysis of VISUAL III study, an open label extension phase of VISUAL I/II studies (108, 109), was presented (110). Patients involving VISUAL I/II studies and who were defined as treatment failure or who completed without treatment failure were eligible. Among the 371 patients with non-infectious uveitis treated with ADA, 27 patients had a uveitis due to BS. The proportion of patients with quiescent disease that was defined as no active inflammatory lesions and anterior chamber cell grade ≤0.5+ and vitreous haze grade ≤0.5+ increased from 44.4% at week 0 to 77.8% at week 12 and remained stable through week 78. Mean logMAR best corrected visual acuity of both eyes remained stable over time. Serious adverse events and serious infections were observed at 8.8 and 5.8 events per 100 patient-years respectively. Two patients experienced 5 vasculitic events.

A study from Greece had reported that long-term remission is achievable after discontinuation of successful continuous anti-TNFs (111). This time the same group investigated whether short-term IFX also provides long-term remission for ocular involvement (112). Among the 13 patients who received one (n=2), two (n=1) and three (n=10) infusions, 12 achieved complete remission subsequently. Out of 12 patients with remission, only 1 had a relapse 6 months after IFX infusion. The remaining 11 patients achieved sustained remission for a mean of 7±3.8 years and 4/11 was able to stop azathioprine. A case series including 3 paediatric BS patients with uveitis showed that IFX or ADA was successful and safe in these patients (113).

A previous study on the concomitant use of interferon-alpha and azathioprine was early terminated due to adverse events (114). This time, a study looking at the safety and efficacy of interferon-alpha as an add-on treatment for uveitis reported that 26 patients did not experience any serious adverse events when interferon-alpha was used together with conventional immunosuppressive agents (115). Immunosuppressive agents could be tapered in 88.5% of the patients and were completely withdrawn in 19% of the patients.

Two retrospective studies comparing anti-TNFs and interferon-alpha for uveitis due to BS were presented. In the first study the mean duration of treatment was 20.8±18.1 months in 20 patients treated with IFX (Group 1) and 29.5±22.3 months in 33 patients with interferon-alpha (Group 2) (116). The proportion of patients achieving remission was similar among the groups (Group 1 *vs*. Group 2: 80% *vs*. 85%). Intraocular inflammation that was assessed by frequency of relapses, aqueous flare levels, anterior chamber cells, vitreous haze score, macular oedema and retinal vasculitis significantly decreased with both agents. Adverse events that required switching to another agent were also comparable in Group 1 *vs*. Group 2 (15% *vs*. 18%). In the second study, 31 refractory eyes treated with anti-TNFs (mainly adalimumab) and 12 refractory eyes treated with interferon-alpha were compared at 10-year follow-up (117). Interferon-alpha group had a worse visual acuity at presentation compared to anti-TNFs group (0.3±0.4 *vs*. 0.5±0.4) and provided a significant improvement in visual acuity over 10 years. Although this was not true for anti-TNFs group, 10-year outcome of visual acuity did not differ between the groups. Both studies concluded that interferon-alpha and anti-TNFs have comparable treatment effects. However, it should be noted that the results of these indirect comparisons may be hampered by differences in baseline characteristics and severity between patients who were prescribed interferon-alpha or infliximab.

A retrospective study looking at the long term safety of cyclophosphamide underlined the need for safer and effective alternatives to cyclophosphamide for serious organ involvement in BS (118). Among the 198 patients who were treated for mainly vascular involvement, 26% of the patients had died and 50% of these had died due to disease-related causes. Malignancies and infertility occurred in 7% and in 21.5% of the patients, respectively.

Low dose prednisolone (10-15 mg prednisolone) was reported to be effective in 5 patients with esophageal involvement (119). All patients tapered prednisolone by 5 mg every week and discontinued. Clinical and endoscopic remission was achieved after 8 weeks. Another study proposed methotrexate as an effective treatment in refractory gastrointestinal involvement (120). Among the 10 patients, 5 were treated with only methotrexate and the remaining 5 received methotrexate in addition to ADA. At month 6, 70% achieved steroid free remission.

Canakinumab was studied in an open-label pilot study (121). Eight of the 10 refractory patients did not reach the final visit due to relapses or primary inefficacy. Mucocutaneous and articular symptoms were more likely to respond to canakinumab while this was not true for severe ocular involvement. The Italian group evaluated the efficacy of secukinumab on refractory mucocutaneous and articular involvement in 5 patients (122). Four patients also had ankylosing spondylitis and the fifth had psoriatic arthritis. The dose of 300 mg provided complete remission in the patient with psoriatic arthritis and in 3 patients who started at a dose of 150 mg. Bosentan, an endotheline-1 receptor antagonist, was studied in 10 patients in a randomised placebo controlled study (123). Only 1 patient who was treated with Bosentan responded clinically and endothelin levels remained elevated during the treatment without a correlation with disease activity.

A new multicentre longitudinal German registry of BS that aims to assess long-term efficacy and safety of treatment modalities was announced (124).

Conclusion

Several new and exciting studies that aim to help our understanding of the epidemiology, pathogenesis, clinical manifestations and disease course of BS, and to improve our management strategies were reported during the 18th International Conference on Behçet's Disease. Further research on the pathogenesis of BS, especially aiming to delineate possible differences between the pathogenesis of types of organ involvement, more studies with appropriate control groups and randomised controlled trials with different treatment modalities are awaited.

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