Meeting report

15th International Congress on Behçet's Disease

13-15 July 2012, Yokohama, Japan

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Received and accepted on August 30, 2012.

Clin Exp Rheumatol 2012; 30 (Suppl. 72): S118-S128.

Key words: Behçet, immunology, genetics, therapy

Competing interests: none declared.

The 15th International Congress on Behcet's Disease (BD) was held in Yokohama, Japan between 13th and 15th of July 2012 under the auspices of The Japanese Behçet's Disease Study Group and its president was Prof. Yoshiaki Ishigatsubo from Yokohama City University. There were 270 participants and the venue was the home to many lively discussions and ideas. Forty-one oral presentations and 116 posters were presented and the programme was enriched by a special lecture by Daniel Kastner on the immunogenetics of BD.

Genetics and Immunology

The Immunology and Genetics section was dominated by new data from various genome wide association studies (GWAS). Elaine Remmers from the NIH group presented three new BD susceptibility loci when approximately 800000 single nucleotide polymorphisms were investigated. These were CCR1, STAT4 and KLRC4, encoding a chemokine receptor, a transcription factor implicated in IL-12 and IL-23 signaling and a natural killer cell receptor. ERAP1 which is an endoplasmic reticulum expressed aminopeptidase that trims peptides and loads them to MHC Class I was the fourth association that was observed when patients with uveitis were analysed.

A strong interaction between HLA-B51 and the ERAP1 genotypes were suggested and homozygosity for ERAP1 conferred an odds ratio for BD of 3.78 in HLA-B51 positive individuals versus 1.48 in B51 negatives. This was a finding that drew similarities between BD, ankylosing spondylitis and psoriasis (1). Targeted deep re-sequencing of the IL23R and IL10 regions by the same group also showed that MEVF, NOD2 and TLR4 loci pertinent to innate immunity, were also related to BD (2). Kappen *et al*. performed a GWAS in 336 BD cases (western Caucasians, Jordanians and Turks) and 5843 controls and identified two significant signals on chromosome 6 and one weak signal on chromosome 18. The chromosome 6 signals were related to the HLA region (3). A Japanese group who had previously shown associations with IL-10, IL23R-IL12RB2, HLA-B51 and HLA-A26 in a GWAS, investigated the relationship between these loci and various clinical manifestations of BD. They demonstrated that the homozygosity for the IL10 risk allele was significantly more common among patients with complete type BD compared to non-complete patients and severe BD and uveitis were strongly associated with IL-10 and IL23R-IL12RB2 alleles (4). Alekberova *et al*. did not find any association with HLA-A 26 or a relationship between HLA-B51 and A26 in a group of Russian patients (5) whereas Saruhan Direskeneli's group in Istanbul confirmed the association of the IL23R (rs17375018) polymorphism independent of HLA-B51 in 217 BD patients in a case control study (6). A Portuguese Iranian collaboration involving 973 BD patients and 637 controls also independently confirmed the relationship between BD, IL-10 and IL23R-IL12RB2 single nucleotide polymorphisms (7).

An interesting hypothesis in the immunogenetics of BD concerns the slow folding and promiscuous peptide binding phenomena, factors related to an aberrant immune response in relation to peptides presented by HLA molecules to effector cells. Gül from Istanbul investigated this in 84 BD patients and controls by looking at XBP1 (a transcription factor) splicing, BiP and HLAB expression. Spliced forms were seen in 20% of BD patients and in none of the controls suggesting an unfolded

protein response related inflammatory reaction. The phenomenon was not related to HLA-B51 (8). An Iranian study was not able to confirm a previous relationship between plasma homocysteine levels and HLA-B51 in BD (9) and a Turkish study was not able to replicate TIR-domain containing adaptor protein gene TIRAP S180 L polymorphism previously reported in Caucasian populations (10).

Daniel Kastner commented on the recent GWAS findings in BD and emphasised that both innate and adaptive immune responses were involved in the pathogenesis. He stressed that HLA-B51 was strongly related to BD in both Turkish and Japanese patients whereas a second independent Class I MHC association was also present (eg HLA-A26 previously delineated by Meguro *et al*). Non MHC loci were also operative exemplified by IL-10, IL-23R, CCR1, KLRC4, STAT 4 and ERAP 1 and innate immune loci such as TLR4, NOD2 and MEVF played an additional role. Interesting functional consequences were also discussed: a) deficient IL-10 production leading to impaired inhibition of inflammation and its potential amelioration by interventions that increase its level such as alpha interferon b) IL-23R association and its possible role in the activation of the IL-17 pathway (similar to ankylosing spondylitis, inflammatory bowel diseases and psoriasis) c) the possible peptide presentation aberrations that may be caused by ERAP 1 mutations especially in patients who are HLA-B51 positive. A more complete listing of common and rare variants associated with BD susceptibility and their copy numbers, the delineation of the exact function of the HLA-B51 molecule and its interactions with the host microbiome and the pathogenic relationships with ankylosing spondylitis and psoriasis were described as potential areas of future research (11).

IL-23 and STAT3 are involved in the activation of Th17 cells, a subset of T cell described in 2005 that play important proinflammatory and protective roles in rheumatoid arthritis, psoriasis, multiple sclerosis and inflammatory bowel diseases. This has fueled in interest in the characterisation of these cells in BD. Yasuoka *et al*. have looked at the recruitment mechanisms of Th17 cells in BD and have examined the peripheral blood samples of 20 patients with BD and 14 controls. Plasma IL-17 levels were higher in BD patients. Expression levels of RORC mRNA (transcription factor of Th17 cells), intercellular $CD4^+$IL-17 T cells and the various chemokines such CCR6 and CCR20 were all increased (12). Shimizu *et al*. studied mRNA expression of several cytokines and their signaling molecules in BD T lymphocytes. They found that $CD4^+$T cells in BD over-respond to Th17 related cytokines and differentiate into IL-17 and IFN gamma co-expressing $CD4^+$ T cells. IL-23/IL23 receptor pathway plays an important role in this transformation (13). A Chinese group from Chongqing evaluated the role of 1-25-dihydroxyvitamin D3 on Th17 and Th1 cell differentiation. They showed that the vitamin inhibited Th17 cell differentiation, RORC, IL-17, IL-23R, CC6 production in naïve CD4*T cells and resulted in an increased production of IL-10. Dendritic cells were also involved. They speculated that VitD might have a therapeutic effect (14). An Iranian group measured the 25 (OH) Vitamin D levels of 48 patients with BD and 47 age and sex matched controls and found that BD patients had lower levels compared to the controls (15). Nakamura *et al*. looked for an interleukin 17A single nucleotide polymorphism in BD and found a slightly higher tendency of the IL-17A genotype A frequency (16). A French group investigated regulatory T cell/Th17 cell balance among a group of pediatric BD patients (24 active and 12 inactive compared 25 healthy controls) and found that Th17 polarisation with normal Treg and IL-21 values were important in driving the inflammation. This was in contrast to adults where suppression of Tregs mediated by IL-21 was more prominent (17).

Farida Fortune's group reported two studies on the expression of Toll like receptors (TLR) 2 and 4 and suppressor of cytokine signalling (SOCS) 1 and 3 among groups of approximately 50 BD patients and healthy controls. In the initial study they demonstrated that splice variants of TLR 2 and 4 were found in BD that were probably defective in function; a factor that may impair the innate immune response (18). In the second study the inhibitory SOCS 1 and 2 showed inconsistent bands in western blot analysis in both neutrophils and peripheral blood mononuclear cells leading to a predominance of a pro-inflammatory cytokine profile (19). Another Chinese group found a decreased expression of miR-155 (an inhibitory micro RNA) in the peripheral blood mononuclear and dendritic cells of a group of patients with BD and none in patients with the Vogt Koyanagi Harada syndrome. It was proposed that down regulated miR-155 may lead to an increased production of pro-inflammatory cytokines (20). However So Young Na *et al*. from Ajou University Korea found a higher level of miR-155 expression in $CD4^+$T cells of 5 patients with BD patients compared to 4 with recurrent aphthous stomatitis and 5 healthy controls (21). A Korean group evaluated the membrane expression of the RNA binding protein hnRNP A2B1 in human dermal microvascular endothelial cells (HDME) in response to sera derived from BD patients and Streptococcus sanguis. They found that the protein increased in both the cytoplasm and the membrane of the cells in response to BD and the microorganism. They proposed that this molecule may behave as a novel antigen in BS although an epiphenomenon not specific to BD and related to endothelial cell destruction was also a possibility (22). The same group also demonstrated that sera from BD and Streptococcoccus sanguis stimulated the expression of alpha enolase in the membranous compartment of HDME. The potential interaction with alpha enolase antibodies was also discussed (23).

The CD 14+ cells of BD uveitis patients expressed substantial amount of alpha enolase compared to those patients with other forms of uveitis. The levels were not different when CD3+, CD11c+, CD19+, CD56+ cells were studied (24). A microarray analysis on the peripheral blood nuclear cells of BD patients with active uveitis, in re-

mission and of healthy controls was performed to examine the role of inducible co-stimulator (ICOS), an important regulator of T cell activation. BD patients with uveitis showed high ICOS expression whereas the other groups did not. It was proposed that abnormal ICOS stimulation contributed to the IFN-gamma, IL-17 and TNF-alpha production in patients who had ocular involvement (25). Another group suggested that the TGFbeta/Smad signaling pathway was overactive in BD, another finding that is important in the differentiation and maintenance of Th17 cells (26). A group from Netherlands investigated the role of B cells in 25 patients with BD and 25 controls and found a reduced number of total B cells and especially the natural effector, IgM only and germinal center derived IgA+ subgroups in BD patients. They speculated that B cells were drawn to the inflammation site and that they had a role in pathogenesis (27). A group from Armenia investigated the aqueous humour of patients with BD and Fuchs uveitis. BD patients had more gamma delta T cells and CD5+CD19+ positive B cells whereas patients with Fuchs uveitis had an abundance of $CD3+CD4^+$ T helper and CD3+CD+ cytotoxic T cells. The cells observed in BD were more suggestive of an innate immune response (28). The effect of osteopontin blockade, a molecule that promotes Th1 and Th17 responses, and its effects on uveitis were examined in mice with experimental autoimmune uveoretinitis (EAU). Osteopontin blockade by siRNA improved both the clinical picture and the amount of Th1 and Th17 cytokines (29). Another study measured the amount of glyceraldehyde derived advanced glycation end products (Glycer-AGE) in patients with uveitis (31 Vogt Koyanagi Harada, 21 with HLA-B27 associated uveitis, 14 with BD and 37 with sarcoidosis) and the effect of pyridoxamine in a mice model of EAU. Pyridoxamine was expected to decrease the levels of Glycer-AGE. Glycer-AGE levels were elevated in sera of all uveitis patients regardless of etiology and the systemic administration of pyridoxamine ameliorated EAU (30).

Ohno's group from Japan evaluated the possible effect of natural killer cells in the same uveitis model in mice. EAU was induced by immunising wild type or NK T cell deficient mice with a peptide of the interphotoreceptor retinoid-binding protein. EAU exacerbated in NK deficient mice but not in the wild type mice because of the probable inhibitory effects of NK cells. The exact nature of the receptor ligand interaction was not determined (31). Another experimental uveitis model was induced by endotoxin (by injection of LPS of Escherichia coli to Lewis rats). IkappaB stimulation in this model was believed to stimulate Ikappab kinases in turn leading to the production of proinflammatory cytokines. IMD-0354 was known to suppress the kinases and its administration in various doses decreased uveal inflammation. It was speculated that it was a promising mode of therapy for the uveitis of BD (32). CCR7, its ligand CCL21 and CD8+ memory cells were effective in the regulation of BD symptoms in Herpes Simplex virus induced BD like inflammation in mice (33).

Two studies looked at the inflammasome induced IL-1 activation pathway; an important aspect of the innate immune response in BS. The first examined the relationship between the reactive oxygen species (ROS) from mitochondria and the stimulation of the NLRP3 inflammasome. They showed that the ROS from mitochondria of monocyte derived macrophages was significantly increased in BD patients with uveitis and they in turn produced increased amounts of IL-1 beta (34). Another Turkish study explored alternative (non-TLR) stimulation mechanisms of the inflammasome and showed that NOD1/NOD2 and RIG-1 activations were not as prominent as those induced by TLR's in patients with BD (35). A study investigated the effect of transmembrane and soluble CXCL16 on interferon secretion from dendritic cells in patients with BD, spondylarthritides and healthy controls. They had previously shown that this chemokine had played a role in the intracellular transport of CpG D ODN and the secretion of interferon. However no meaningful relationship was found in any of the groups studied (36). Hasegawa *et al*. investigated the bioactive molecules that promote the induction of human tolerogenic dendritic cells and found that PPAR-gamma, dexamethasone and indirubin suppressed allogeneic T cell responses whereas protein kinase C inhibitor, bisindolylmaleimide I, prostaglandin and GSK 3-beta inhibitors enhanced the production of the inhibitory cytokine IL-10 from dendritic cells (37). Serum S100A8/A9 heterodimer levels (a heterodimer of two calcium binding immunogenic proteins expressed and secreted by neutrophils and monocytes) were significantly elevated in a group of BD patients with mucocutaneous lesions compared to healthy controls and their levels correlated with CRP (38). B cell activating factor belonging to the TNF family (BAFF) levels in the cerebrospinal fluids of 18 patients with neuro-Behçet's disease, 27 with epidemic aseptic meningitis, 24 multiple sclerosis and 34 healthy controls were compared. BAFF levels were higher in patients with BD whereas the levels were not different from those observed in diseased controls. The levels were especially prominent among those with a slowly progressive neurological course (39). Miles Stanford *et al*. examined the MICA levels in BD and their relationship with natural killer, gamma delta and $CD8^+$ cytotoxic cells bearing the NKG2D receptor. The same group also investigated the interaction between NKG2D expressing Chinese Hamster Ovary (CHO) cells with HLA-B51, peripheral blood mononuclear cells of BD and controls. B51+ BD sera resulted in less killing of CHO cells as expected but the response was not consistent with any pattern, the level of killing showed extensive inter-patient variation and serum MICA levels were not increased (40, 41).

Eye involvement

Tugal Tutkun *et al*. collected 59 ophthalmic photographs from patients with Behçet's uveitis, non Behçet uveitis and non-inflammatory retinal vasculopathy and measured the agreement among uveitis specialist. Smooth

layered hypopyon, superficial retinal infiltrate with retinal hemorrhages and branch retinal vein occlusion with vitreous haze were correctly recognised as BD signs by the majority of observers, whereas non-inflammatory branch retinal vein occlusion with soft exudates were mislabeled as Behçet by most observers. They claimed that some ocular signs of BD could be distinguished even in the absence of other clinical information (42). A Tunisian group found 47% of ocular involvement in their series of BD patients, claimed that it was lower than that observed in other North African countries and showed that patients with eye disease had less genital ulcers, positive pathergy test and vascular involvement compared to those without uveitis. The confounding effect of therapy however was not evaluated (43). Alekberova from Russia showed that uveitis was more common in males as expected, was more frequently associated with HLA B-51, was negatively associated with gastrointestinal involvement and was usually observed during the first 5 years of the disease course (44). A Turkish group presented the contents of a national registry for uveitis. The registry had 5071 patients with 1266 with BD (25%), BD being the most common cause of uveitis. Eight hundred and sixty one of these (68%) were male and thirty-two (2.5%) were children (45). Yalcindag *et al*. did not find any difference in serum fibronectin levels among a group of patents with BD uveitis compared to controls (46). The inspection of the registry of the Low Vision Clinic in Japan showed that the number of patients that needed low vision care decreased during the last decade, an observation compatible with the finding that BD is getting milder in this country (47).

Vascular involvement

Tascılar from Turkey presented data on the type, time and sequence of vascular events obtained from the chart reviews of the BD patients. There were 1272 episodes of vascular involvement in 882 patients among 5970 registered BD patients in the period between 1977 and 2006. Deep vein thrombosis (DVT) was the most frequent type (69%). Pulmonary artery involvement was frequent among patients with vena caval and dural sinus thrombosis. Non-pulmonary artery events occurred at an older age than venous and pulmonary artery events (39.4 years vs 31.3 and 31.4 years) and were less commonly associated with DVT. Five year risk of a recurrent event was 38%. Male gender was the only predictor of recurrence. The relationship between pulmonary artery aneurysms, vena caval and dural sinus thrombi favoured the presence of a venous disease cluster of disease expression (48). A Japanese group also evaluated the vascular manifestations of their series. They had 105 patients with large vessel involvement with a predominance of males (68%). The venous system was most frequently affected (71%) followed by arterial (31%) and pulmonary disease (25%). Only eight patients died in their series prompting them to conclude that vascular involvement is milder and has a better prognosis in Japan compared to other countries. Another important factor of the Japanese series was their routine use of anticoagulants in patients with venous thrombosis contrary to some areas where BD is prevalent (49). A Tunisian group examined the demographic and clinical features of (DVT) in their series and found DVT in 119 among 430 (28%). Ninety-eight of the cases were male, it was the first manifestation of the disease in 65 and the lower limbs were most frequently involved. This group also used anticoagulants in the management of this condition although they admitted that anticoagulants combined with corticosteroids were more beneficial in preventing recurrences (50). Mezalek *et al*. from Morocco reported arterial involvement among 10% of their patients with BD with a predominance of males. There were 28 aneurysms, 14 in the pulmonary area, 4 in the infrarenal abdominal aorta, 3 cases each in the superficial femoral and carotid arteries, 2 subclavian and one each in the thoracic and coronary arteries. Arterial disease was strongly associated with deep vein thrombosis as expected and 4 patients died from ruptured pulmonary arterial aneurysms (51). Ozguler *et al*. followed the clinical course of lower extremity deep vein thrombosis (LEDVT) after an acute and subacute first episode in 30 patients for a course of 13.4±6.2 months. The most common vascular relapse after an episode of LEDVT was superficial thrombophlebitis. Relapses of a superficial thrombophlebitis occurred earlier than relapses of deep vein thrombosis. Poor recanalisation of the index LEDVT at 3 months was again associated with relapses (52). Hamzaoui *et al*. from Tunisia recapitulated the rare occurrence of cardiac involvement in BD (16 patients among a cohort of 480) and showed that there were 7 cases with pericarditis, 5 with intracardiac thrombi, 2 with coronary aneurysms and 2 with a myocardial infarction. All patients were male (53). Another group from Istanbul Turkey evaluated the clinical characteristics, course and management of abdominal aortic aneurysms (AAA). There were 12 patients with AAA among 1200 patients (1%) and data from 10 patients (9 males) were available. All lesions were located in the infrarenal aorta except one with an additional suprarenal aneurysm. All of them contained an intramural thrombus. Presentation symptoms included abdominal pain, lower back pain, groin pain and weight loss. Two patients received only medical treatment, one had partial and the other had a complete resolution. Eight patients underwent interventional treatments, six had endovascular stent insertion and two had surgery. Three received interventional treatments followed by surgery. Only one patient died following a misdiagnosis of abscess resulting in an attempt at percutaneous sampling, and one developed a pseudoaneurysm and arteriovenous fistula at the catheter site and was treated surgically. The prognosis was good although complications were possible (54). Endarterectomy of an obstructed pulmonary artery from a patient with BD revealed a huge, rock hard in situ sticky thrombus, quite different from those observed in other thromboembolic diseases. It supported the previous notion of the inflammatory nature of thrombi in this condition (55). Pierce *et al*. from the UK investigated the potential usefulness of high resolu-

tion MR in identifying inflammation in the venous walls of BD patients. Seven normal subjects and 5 with BD were included. A standard MR was obtained from the popliteal vein with metronome-guided breathing that generated a regular respiratory variation. Vein scores ranked from 1= normal to 5=diseased. However repeated images gave variable results and metronome guided breathing lacked standardisation (56).

Neurological involvement

Bitik from Turkey presented the clinical and radiological features of four patients (3 males and 1 female) with transverse myelitis, a rare complication of neurological involvement in BD. It affected the cervical and thoracic levels of the spinal cord. It involved multiple segments in 4 cases and developed at any stage of the disease, even as an initial presentation. The longest interval between diagnosis of BD and myelitis was 10 years. All cases were associated with pan uveitis and cyclophosphamide and steroid therapy was the mainstay of treatment. The outcomes were variable and only one recovered without sequelae (57). Hirohata *et al*. compared cyclosporine related and unrelated acute neurological events among 76 patients (20 with CyA and 50 without). Sixty-nine patients had uveitis. There were no significant differences in demographic features, clinical, radiological and cerebrospinal fluid findings between the two groups. CyA related events showed a higher relapse rate than those without CyA (58). Akman Demir *et al*. surveyed arterial disease among 17 patients with BD out of 400 with neurological involvement. Fourteen were male and 3 were female. Their age of onset of arterial CNS involvement ranged between 25 and 65 years (median 43). Fourteen of the patients presented with an acute hemiparesis/hemiplegia, accompanied by aphasia in two, ataxia in one and brainstem syndrome with contralateral hemiparesis in two. One had an asymptomatic intracranial aneurysm, one presented with seizures due to anterior cerebral artery infarct and one presented with multiple cranial neuropathies due to external carotid artery aneurysms. Vasculitic involvement in angiography was present in two patients. They concluded that other etiological factors unrelated to BD should be extensively sought before attributing a stroke to BD (59). Ben-Salem *et al*. from La Rabta hospital in Tunisia found neurological involvement among 121 patients with BD among 430 (28%). Seventy-eight of the patients were males. Parenchymal involvement was seen in 48, cerebral venous thrombosis in 24 and arterial involvement in 6. The pattern was consistent with what has been observed in other North African and Middle Eastern countries (60). A Moroccan group identified 34 patients with neurological involvement among their pool of 292 cases (15%). Males dominated and the first symptom was headache in 70% of the cases. Eighty percent of the patients had parenchymal and the remaining had thrombotic lesions. Peripheral neuropathy was also common contrary to expectations (61). Three males from Turkey with pseudotumor cerebri were presented. All had severe cases with papilloedema for at least a month and 2 presented with bilateral sixth nerve palsy. The lumbar CSF opening patient was measured in only 2 patients and was 35 and 30 cm water. The superior saggital sinus was thrombosed in one patient (62). The same group also evaluated the occasional patient with a white matter lesion; a factor that is important in the differential diagnosis of multiple sclerosis and BD. There were 43 patients (32 female and 11 male) who had white matter lesions. Twenty-two had an abnormal neurological exam (Group I) whereas the remaining had a primary headache disorder (Group II). In Group I, 16 patients fulfilled the Barkhof-Tintore criteria with 10 with periventricular and 6 with subcortical lesions. In Group II none fulfilled the Barkhof-Tintore criteria and all showed non-specific deep white matter lesions. CSF oligoclonal band positivity was also more prominent in Group I and their clinical pictures were closer to MS (63). One study found a higher frequency of restless leg syndrome than expected among patients with BD who had neurological involvement (64). Aseptic meningitis, bilateral optic neuritis, anterior spinal cord syndrome and cognitive impairment were discussed in case presentations (65-68).

Gastrointestinal involvement

Hatemi *et al*. presented data on the treatment and outcome of gastrointestinal involvement of BD patients in Istanbul, Turkey. There were 51 patients with endoscopy proven gastrointestinal BD among the 8000 registered cases. Surgery was performed in 20 patients. Drugs used in the initial management were azathioprine and 5 ASA compounds. Patients who had relatively severe symptoms and persistent large ulcers for at least six months could be managed with thalidomide, infliximab or adalimumab. Forty-two patients (84%) were in remission after a mean follow up of approximately seven years and 14 (28%) were not receiving any treatment. Four patients (8%) were still active (69). A Brazilian group investigated the presence of anti-saccharomyces cerevisiae antibodies (ASCA) in 87 patients with BD and 43 with other causes of entero-arthritis (EA). The prevalence of ASCA antibodies were around 30% in both groups and male patients with gastrointestinal lesions had higher titres (70). An Egyptian group presented the clinical and colonoscopic characteristics of a group of patients with BD. The most common complaint was abdominal pain (9 in 20 patients). Bloody diarrhoea was seen in 2. Fistulisation, severe bleeding and perforation were observed and were discussed in the context of the need for early endoscopy (71). A Japanese series reported their experience on 30 patients. The most frequent initial manifestations were again abdominal pain (13 cases), melena/bloody stool (11 cases), diarrhoea (6 cases), dysphagia, gastric distress and weight loss (each one case). The most frequent ulcerations were observed in the ileo-caecal area as expected although ulcerations throughout the gastrointestinal tract were also seen (72).

Pediatric BD and Epidemiology

Isabelle Kone-Paut from France presented her data on pediatric BD. There

were 206 patients obtained from 22 centers in 12 countries and diagnosis was performed by an international expert committee on the basis of clinical findings. The cohort was characterised by an equal sex ratio, a high rate of familial aggregation and marked phenotypic differences by gender exemplified by a higher prevalence of uveitis among males (73). Fujikawa *et al*. also examined their pediatric cohort of 157 patients and demonstrated that genital ulcers and ocular lesions were less in children while gastrointestinal involvement was more frequent (74). A Korean group evaluated the clinical findings of their series of 1061 patients with BD and compared the performance of the International Study Group criteria (ISG) with Japanese criteria. One hundred and ninety five patients did not fulfill the former whereas they were classified as BD in the latter (75). Altenburg and Mahr updated the German registry for BD. There were 721 patients, 258 of German and 308 of Turkish descent. Turkish patients had more uveitis compared to Germans whereas the latter had more epididymitis, prostatitis and gastrointestinal involvement. The frequency of family history was 13% with Turks having a higher frequency compared to Germans (15% vs 3.8%). HLA B51 was positive in 58% of the patients and was mostly related to the presence of uveitis (76). Kobashigawa *et al*. found an association between HLA-A 26 and uveitis among 69 patients with BD (77) whereas a study from Seoul among 58 patients could not demonstrate this relationship (78). D'Angelo *et al*. from Italy conducted an epidemiological study on BD in Basilicata in southern Italy with the aim of comparing it to the data obtained in Reggio Emilia in the north. A prevalence of 9.2 cases for 100000 was obtained which was higher than that seen in Reggio Emilia. This was interpreted in favour of an increased prevalence of BD in the south (79). A Japanese and an American group compared the clinical characteristics of BD patients between the two countries (630 patients in the US and 142 in Japan). They found that age of onset was higher in the Japanese (47 *vs*. 36), there were more males and they had less genital ulcers and arthritis compared to their American counterparts. They also had more epididymitis, pulmonary disease and HLAB51, B52 and A26 positivity (80). A group in Korea looked for the frequency of malignancy in patients with BD and found a lower morbidity related to cancer compared to that observed in the general population (81). Shahram *et al*. from Iran compared the clinical characteristics of 61 pairs of BD patients with familial occurrence with an age and sex matched cohort of sporadic cases. There were no differences in the clinical profiles between the 2 groups (82). A German French collaborative study explored the effect of gender on BD phenotype by doing a meta-analysis. Six hundred and thirty-three publications were evaluated and 27 met the eligibility criteria. Males had a slightly higher frequency of eye involvement, papulopustular lesions and pseudofolliculitis and a 2-2.5 fold higher prevalence of vascular involvement, in particular thrombophlebitis. Females were characterised by more genital ulcers, erythema nodosum and joint involvement (83).

Defining clinical activity is an important issue in BD and a collaborative study from the United States and Turkey compared the Behcet's Disease Current Activity Form (BDCAF) with Behçet Syndrome Activity Score (BSAS) and Routine Assessment of Patient Index Data 3 (RAPID 3). They showed that the BSAS questionnaire, composed of patient responses only, had a strong positive correlation with the BDCAF, a questionnaire completed by a clinical assessor. They proposed that an outcome score derived of only patient derived observations was advantageous in a routine clinical setting (84). Mumcu *et al*. suggested that patient reported outcomes should always complement the data of clinical trials and advocated the use of a mucocutaneous index based on a self-reported evaluation (85).

Mucocutaneous, musculoskeletal and renal findings

An Iranian group evaluated iron deficiency in a group of BD patients with oral aphthae. Two hundred and twenty patents were divided into resistant (n=75) and responder (n=145) groups based on their response to conventional therapy. Iron deficiency was found in 33% of the patients and was more frequent in the resistant group compared to the responders (39% *vs*. 30%). The results however did not reach statistical significance (86). A group from Turkey evaluated fibromyalgia among BD patients, based on the new ACR criteria published by Wolfe *et al*. Thirty three BD patients were enrolled and 24 with systemic lupus and 23 healthy controls were used. Ten patients with BD (30%), 4 with SLE (17%) and one healthy control (4%) met the 2010 ACR criteria. The prevalence of fibromyalgia in BD was higher than that observed in previous studies (87). Another study confirmed the high frequency of fibromyalgia among patients with BD and stressed that it was more prevalent in females and was not related to a specific subgroup of the disease (88). Two studies from Turkey measured fatigue in BD. The Marmara group demonstrated that fatigue was similar in magnitude to that observed in systemic lupus patients and healthy controls (89) whereas the Cerrahpaşa group reported that it was an important problem. It was equally severe in subgroups of patients with eye, vascular, joint and mucocutaneous symptoms (90). Hamuryudan *et al*. showed that large numbers of oral aphthae in the initial years of the clinical course was predictive of severe organ involvement in a group of Turkish patients with BD although the data was confounded by the younger age of onset of the disease (91). Naito from Japan investigated the prevalence of oral apthae and oral health related quality of life in patients with BD and in the normal population. Oral aphthae were seen in 83% of BD patients and in 32% of the general population. The mean number of oral apthous ulcers per year was 12±31 in BD and 1±3 among the healthy. The General Oral Health Assessment Index was lower than the Japanese normal in patients who had more than 2 oral apthae/year (92). Olivieri *et al*. examined the frequency of spondyloarthritis in Italian patients with BD

using the ASAS criteria. Seven out of 74 patients (9.4%) met the ASAS classification criteria. Of these 1 had axial disease with features of AS and 6 with peripheral SpA. Two had acute anterior uveitis and 4 had psoriasis, dactylitis, enthesitis or inflammatory chronic low back pain in addition to peripheral arthritis. Two patients were HLA B27 positive (93). The occasional occurrence of myositis in BD was recapitulated in two cases and the role of contrast MR in its evaluation was specified (94). The rare association of Sweet syndrome with the myelodysplastic syndrome in patients with BD was reported (95).

Choi *et al*. from Korea presented the renal manifestations of 2007 Korean patients with BD. Hematuria was noted in 20% and proteinuria in 29%. Multivariate analysis showed that older age, female sex and a high erythrocyte sedimentation rate were associated with renal findings. The most common pathologic finding was IgA nephropathy (96), a finding confirmed by an Iranian observation (97).

Management

Infliximab was the most commonly evaluated biological agent probably due to its license in Japan for BD. Olivieri from Italy presented a series on 68 patients with BD who used the drug. Being non-responsive to conventional therapy was the pre-requisite of enrollment and the dose was 5 mg/kg at weeks 0,2,6 and every 6 to 8 weeks. The drug was used for uveitis (n=35), severe mucocutaneous manifestations (n=14), central nervous system (CNS) vasculitis (n=11), optic neuritis (n=1), intestinal involvement (n=2), arthritis (n=2), seizure (n=2) and unspecified vascular involvement in the remaining one patient. The median duration of treatment was 25.5 months (range 1-106). Response to therapy was evaluated by expert opinion and was graded as remission, response, no response and worsening. The drug resulted in remission in 20 patients with uveitis, 6 with CNS involvement, in 3 with mucocutaneous manifestations and in one each with optic neuritis, arthritis and vascular involvement. A response was observed in 4 patients with mucocutaneous involvement. The drug was stopped for lack of efficacy in 4 patients with severe mucocutaneous manifestations, 2 with uveitis, 2 with CNS vasculitis and 1 with seizure. Seventeen patients stopped therapy for loss of efficacy, six because of adverse events (5 infusion reactions and 1 pneumonia). Milder adverse events that did not require drug discontinuation were also observed (mild infusion reactions in 2, upper respiratory tract infection in 6, urinary tract infection in 1) (98). Takemoto from Japan also showed that infliximab was beneficial in 90% of 30 patients with uveitis again unresponsive to conventional treatment. The dose intervals needed to be shortened to 6 weeks in some patients instead of 8 because of loss of efficacy (99). The need for shortening the dose interval was confirmed in another study (100). Fluorescein angiography showed a decrease in optic disk hyperfluorescence, macular oedema, retinal vascular staining or leakage and capillary leakage in response to the drug (101). A study evaluated the effectiveness of infliximab in relation to baseline TNF alpha levels and serum infliximab concentrations in a small sample of 16 patients. The clinical efficacy of the drug was not related to these, contrary to what is observed in other inflammatory diseases such as rheumatoid arthritis (102). Intractable gastrointestinal involvement was another area that infliximab was utilised. Saito *et al*. used the drug in 18 patients with intestinal involvement who were refractory to conventional treatment, who had adverse events with conventional drugs and who could not taper their steroid doses. The drug had a beneficial effect on ileocecal ulcerations, decreased surgical complications and enabled the reduction of the steroid dose from a mean of 12.7 to 2.7 mg/day (103). The efficacy of infliximab in aggressive gastrointestinal involvement was replicated in other centers, and a case report reported improvement in a sigmoido-vesical fistula (104, 105, 106). Adalimumab was beneficial in a case with ileocolonic ulcer resistant to infliximab (107). The relationship between the development of antinuclear antibodies (ANA) in response to infliximab and clinical efficacy was studied in 17 patients with uveitis who used the drug for a period of 2 years or longer. ANA was observed in 65% of the patients 6 months after the initiation of therapy. The patients who showed seroconversion had recurrent uveitis attacks whereas the ones without antibodies were in remission. The authors suggested that ANA positivity could be a predictor of therapeutic efficacy (108). The effect of the drug on the expression of toll like receptors and pro-inflammatory cytokines were measured in 33 patients with uveitis. Toll like receptors 2 and 4 decreased significantly in monocytes obtained from patients whereas the concentrations of pro-inflammatory cytokines (Gamma interferon, IL-10, IL-17) did not change (109). Neurological involvement was another area where infliximab was used. There were no controlled studies, but two case reports showed beneficial effects in parenchymal involvement, one especially prominent in the chronic progressive variant (110, 111). A patient who underwent endovascular treatment because of a ruptured aneurysm of the left subclavian artery, benefited from infliximab after surgery and went into a remission (112). Constitutional symptoms, erythema nodosum, polyartrhritis, and oral and genital ulcers all improved in another observation (113). A monthly infusion of the IL-6 inhibitor tocilizumab (8 mg/kg) was given to two patients for 12 to 18 months in Italy. The results were not spectacular and although uveitis responded in the initial stages, fever, fatigue, recurrent oral aphthosis persisted and erythema nodosum lesions exacerbated (114). Golimumab was administered to 2 patients with bilateral retinal vasculitis who had not previously received any biological drugs. The drug was given at a dose of 50 mg/month subcutaneously and a complete resolution of retinal findings in 3 out of 4 eyes was seen at the end of 3 months (115).

Several papers evaluated the efficacy and safety of alpha interferon in BD. Yalçındağ *et al*. from Turkey analysed the medical records of 12 patients treated with the drug. It was initially

administered at a dose of 4.5 million units daily and the dose was tapered according to the clinical response. The mean duration of therapy was 13.3 months (range 3-28 months) and 83% of the patients with ocular involvement achieved a partial or complete response. Best corrected visual acuity improved or remained stable in all patients. Flu like symptoms that responded to acetaminophen was observed in all cases, hair loss developed in 58% while a psoriatic skin rash was seen in 25% (116). Another Turkish group, who used the drug more liberally, evaluated its adverse effects. The mean duration of interferon treatment was 3 years (range 1-15 years). Flu like symptoms were observed in 26% increases in liver enzymes occurred in 26% and mild leukopenia in 11% of the patients (117). A Korean study evaluated the effect of the drug on 4 patients with uveitis resistant to conventional treatment. One patient started therapy with 9 million units whereas the remaining with 6 million units/day. The mean duration of treatment was 24 weeks. Two patients went into a remission for a period of 6 years whereas the remaining 2 relapsed albeit to a lesser state of inflammation than that observed initially. Flu-like syndromes and myalgias were again encountered (118).

Sohee Jehon *et al*. from Korea investigated the changes in the intraocular levels of vascular endothelial growth factor (VEGF) and inflammatory cytokines after intravitreal bevacizumab treatment for macular oedema with uveitis. Nine eyes of 8 patients who underwent at least 2 serial bevacizumab treatments were studied. Intraocular VEGF decreased to very low levels in response to treatment whereas TGF beta and TNF alpha concentrations increased. The authors concluded that the use of bevacizumab for macular oedema might aggravate inflammation due to its effect on the local cytokine milieu (119). Sharquie *et al*. from Iraq conducted a single blinded study on isotretinoin on 30 patients with BD. All patients received 20 mg isotretinoin orally for 3 months followed by a period of placebo for another 3 months. The drug was beneficial for mucocutaneous manifestations and decreased the positivity of the pathergy test and CRP (120). The same group also claimed that the drug was beneficial for recurrent aphthous stomatitis of non-Behçet origin (121). Mycophenolate mofetil was used in 5 patients who had the parenchymal form of neurological involvement resistant to other immunosuppressive drugs. The patients benefited and the response was sustained during 2-8 years of follow up (median 6.5 years) (122). The observation that colchicine decreases serum cholesterol levels was re-evaluated in a 12 week study in 19 patients with FMF and 15 patients with BD. Colchicine did not alter the lipid levels in either group (123).

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