

Behçet's syndrome: a critical digest of the recent literature

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ABSTRACT

A similar disease severity among men and women in Brasil, a high frequency of gastrointestinal involvement in China, Japan and USA, a low frequency of pathergy positivity in Japan and USA underline the ethnic variations reported in recent studies. Polymorphisms pertaining both to innate and adaptive immunity in genome wide association studies, clusters in phenotype, and new mechanisms for emerging therapeutic implications have been reported. A Th17 dominance seems to be likely with the exception of gastrointestinal involvement. Infliximab, interferon-alpha and cyclosporine-A may be showing their beneficial effects also by affecting the Th17 cells. The clinical course and outcome of isolated pulmonary artery thrombosis is similar to pulmonary artery aneurysms. Parenchymal lesions (nodules, consolidations, cavities and ground glass lesions) are common in patients with pulmonary involvement. Pericarditis is a frequent cardiac manifestation in France. Treatment of BS became more intensive than before. Immunosuppressives and corticosteroids seem to prevent relapses of venous thrombosis. Studies are needed to understand the role of anticoagulants. Interferon alpha-2a appears to be effective at lower dosage, which brings the advantage of decreased cost and increased tolerability. Switching between anti-TNF agents, when needed, is possible. Interleukin-1 and interleukin-6 are new promising targets.

Introduction

A list of manuscripts have been published during the last 2 years which improved our understanding of Behçet's syndrome (BS). We reviewed all articles published during the last 2 years on BS and selected the most relevant manuscripts regarding the epidemiology, pathogenesis including genetics and

the work on Th 17 dominance, vascular involvement and management of BS.

Epidemiology

It is well known that BS is most prevalent along the ancient Silk Road, including the Mediterranean countries, the Middle East and extending to the Far East, to Korea and Japan (1). It has a much lower prevalence in Northern European countries and the United States (US). Disease expression may also differ across different geographies. Examples to these are pathergy positivity and gastrointestinal involvement with different frequencies in series from the Far East, the US and the Mediterranean countries.

In the study from Brasil, the frequency of disease manifestations were somewhat similar to those in Mediterranean countries (2). Arthritis and erythema nodosum were more common among women, and papulopustular lesions were more common among men. Different from other reports, the frequencies of severe manifestations were reported to be similar between men and women. Still the use of immunosuppressives was significantly more frequent among men compared to women (85.2% vs. 57.6%; $p=0.020$). It is worth underlying that in all comparative studies it is important to record the type and the severity of organ lesions as well as its site. For example, the frequency of eye disease may well be similar between patients from the USA and Japan while we know that the frequency of severe eye disease is considerably less among the US patients (3).

The other report from China involved 334 BS patients (4). The hospital based prevalence was calculated to be 14/100,000. HLA-B51 was positive among 17% of the tested. The high frequency of gastrointestinal involvement (17%) was similar to that reported from Japan and Korea. Interestingly, 10

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of their patients had pulmonary hypertension, defined as a systolic pressure over 40 mmHg with echocardiography. Similar to reports from the other parts of the world, eye and vascular involvement were more common among men. A recent publication compared BS patients from USA and Japan with regard to fulfilling ISG criteria and the Japanese criteria, clinical manifestations and treatment modalities (5). A total of 634 multi-ethnic patients from USA and 135 patients from Japan were included. The frequency of fulfilling both the ISG and the Japanese criteria were similar in the 2 cohorts (61.5% of patients from the US and 63.7% of patients from Japan for ISG and 69.2% of the patients from US and 72.6% of patients from Japan for the Japanese criteria).

The mean age at onset was 35.2 years among patients from USA and 38.1 years among patients from Japan whereas 77% of US patients were women compared to 58% of the Japanese. Genital ulcers were more common among the former, whereas epididymitis and pulmonary involvement were more common among the latter. Gastrointestinal involvement was frequent in both cohorts, 34% in the USA and 37% in Japan. This is higher than many of the previous series and was interpreted as due to the recent development of more advanced techniques for detecting gastrointestinal lesions. The pathergy phenomenon was low in either cohort, 9% in the USA and 11% in Japan.

Colchicine, sulfasalazine/mesalazine and non-steroidal anti-inflammatory drugs were more commonly used in Japan, whereas methotrexate, mycophenolate mofetil, dapsone, hydroxychloroquine and TNF-alpha inhibitors were more commonly used in the USA. Among the TNF-alpha inhibitors, infliximab which is approved for refractory uveitis and gastrointestinal involvement in Japan, was used with the same frequency in either country. In general, the use of first-line immunosuppressives was more frequent in the USA. Saadoun *et al.* reported the 10 year mortality of 817 French BS patients (6). The mean age at diagnosis was 31.5 years, 66% were men, and 40% were HLA-B51 positive. Forty-one of the

patients (5%) had died after a median follow-up of 7.7 years. Ninety-five percent of these patients were men and the mean age at death was 34.8 years. The standardised mortality ratios compared to the matched general population were highest among the 15–24 years age group (2.99) followed by the 25–34 years age group (2.9). The main causes of death were major vessel involvement such as arterial aneurysms and Budd-Chiari syndrome in 44%, malignancies in 15%, CNS involvement in 12% and sepsis in 12%. Multivariate analysis showed that male sex, arterial involvement, and the number of flares were associated with mortality.

These findings are somewhat similar to a previous mortality study from Turkey reporting a mortality rate of 9.8% over 20 years with 93% of the dead being men (7). Main causes of death were again major vascular involvement and neurologic involvement. The mean age at diagnosis of the patients who died was 34.8 years compared to those who were alive (31.4 years) in the French study, a finding that is somewhat against the contention that BS runs a more severe course among those developing the disease at younger age. However this difference may be due to the fact that age at diagnosis does not necessarily reflect the age of disease onset.

Genetics

Most of BS is sporadic. However the occasional presence of familial occurrence (in families of 1/10 patients), the peculiar distribution of the disease along the so called Silk Road (30–45° latitude north; from Japan to the Mediterranean Basin) and the association between HLA-B51 and BS in different populations favour the role of genetic factors (8). A higher prevalence of BS among immigrants of North African and Asian ancestry compared to the European population in Paris (9) and a lower prevalence of BS in Armenians when compared to the frequency of the general population living in the same environment (Istanbul, Turkey) (10) also suggest a hereditary basis.

Initial analyses of multicase families had not demonstrated a Mendelian inheritance pattern. However paediatric

patients seemed to fit more an autosomal recessive inheritance model and there was an excess of familial cases among the paediatric group compared to adults suggesting an increased genetic load in children (11).

Studies on twins in BS are scarce and a recent report showed that the pairwise concordance rate for BS was 2/6 for monozygotic twins and 1/8 for dizygotic twins, again suggesting a genetic predisposition. However, the persistence of discordance in the remaining monozygotic twins after 8 years of follow-up pointed to the presence of non-genetic factors as well, like in any true to form complex disease (12). Larger twin series are required for a more firm analysis.

HLA-B51, a class I major histocompatibility complex (MHC) is strongly associated with BS. A recently published meta-analysis has shown that the pooled odds ratio of HLA-B51/B5 carriers to develop BS compared to non-carriers was 5.78 (95% CI 5.00–6.67). The risk was consistent across different populations with varying frequencies of BS, further supporting the hypothesis that the allele is one of the primary risk determinants (13).

The exact role of HLA B51 in the pathogenesis is not known. The main function of the HLA Class I system is to present peptides to CD8⁺ T cells. However a specific peptide related to BS has not been identified. The interactions between KIR (killer immunoglobulin like) receptors of natural killer (NK), CD8⁺, and gamma delta T cells with selective inhibition of NK and T cell mediated toxicity is another mode of action (14). HLA B51 has also been linked to neutrophil hyperfunction (15).

It has been debated whether the strong association between HLA B51 and BS is due to the transmission of other genes in linkage disequilibrium with HLA B51, a phenomenon common in the Class I MHC region. Many genes have been implicated along this line (*e.g.* MICA 009 allele and its transmembrane microsatellite polymorphism A6). However fine mapping of the region among different ethnic groups has shown that HLA B-51 has the strongest association. The only exception to this is the HLA-A26 allele and the HLA-

A*26-F*010101-G*010102 haplotype which associates with BS independently from HLA B51 (16).

The relationship between the clinical characteristics of BS with HLA B51 has been the subject of intense research. However the analyses were usually done in small samples and in heterogeneous groups of patients. A recent meta-analysis evaluated this relationship in 72 studies representing 74 populations. The results showed that HLA B51/B5 was moderately associated with genital ulcers, eye and skin involvement and with being male. Interestingly, the serious manifestations of the disease such as uveitis and major vessel disease did not seem to be related to the presence of HLA B51 although they are more frequent in males (17). A Korean study among 223 BS patients and 1398 healthy controls showed that HLA-A*02:07, A*26:01 and A*30:04 were associated with skin lesions, arthritis, uveitis, vascular lesions and a positive pathergy test (odds ratios: 2.37, 2.32, 3.01, 9.80 and 4.10) (18).

Non-HLA genes also contribute to the pathogenesis of BS. Case control studies among small numbers of patients and controls have suggested associations with candidate genes. However these studies lack statistical power. Moreover only a few of them have been replicated in different ethnic groups. IL-18 (19), MDR1 (ABCB1) gene encoder P-glycoprotein (20), Intron F G79A of the Protein Z gene (21), promoter-2518 of monocyte chemoattractant protein-1 (22), TGFBR3 (23), matrix metalloproteinase-2-9 and tissue inhibitor of metalloproteinase 2 (24), JAK2 and STAT3 (25,26), Platelet Glycoprotein Receptor PLA1/A2 (27), IL-2,4 and TGF-beta (28), SUMO4 C438T (29) polymorphisms and NOD2 expression in bronchoalveolar lavage cells (30) should be evaluated in this context.

Copy number variation (CNV) is defined as deletions or duplications of DNA segments larger than 1 kilobase and up to several megabases in size that are present in variable copy numbers compared to a reference genome. CNV may influence the susceptibility to disease. DEFA1 defensin gene copy number was associated with suscepti-

bility to intestinal involvement in BS (31) whereas β -defensin and Fc-gamma receptor copy numbers were not risk factors (32, 33).

Recently several genome-wide association studies (GWAS) have been reported. The first one was conducted in a small number of Turkish patients (156 with BS and 167 controls). The single nucleotide polymorphisms (SNPs) KIAA1529, CPVL, LOC100129342, UBASH3B and UBAC2 were associated with BD. The functions of two of these genes were unknown. UBASH3B and UBAC2 were involved in the ubiquitination pathway whereas CPVL encoded a carboxypeptidase (34). The same group repeated the study in 376 patients and 369 controls and the association between UBAC2 and BS was confirmed (35). It was also demonstrated in two independent Chinese sets of patients with BS (36).

The second and third GWAS studies were done in 1215 BS patients and 1278 controls by Remmers *et al.* (37) and in 612 Japanese individuals with BS and 740 controls by Mizuki *et al.* (38). Both studies revealed similar results. The most significant association was in the HLA region on chromosome 6 as expected. A second association was seen around the HLA-A region, supporting the previous finding of Meguro concerning HLA-A26. The third concerned the IL-10 gene. Remmers demonstrated that the IL-10 polymorphism was associated with a decreased production of IL-10 from mononuclear cells and monocytes. The defect in IL-10 may play a part in the dysregulated immune response of BS. Moreover, a drug that has the potential to increase IL-10 production can be beneficial. Interferon-alpha may act in this manner. On the other hand, and curiously, the production of IL-10 decreases significantly with age (39). This is of course somewhat counterintuitive for a major and pervasive role for this cytokine in BS, a condition more active in younger years (40). The fourth interesting association observed in the two studies concerned the IL-23R gene. IL-23 is a proinflammatory cytokine that stimulates T helper cells and increases the production of IL-1, IL-6, IL-17 and

TNF-alpha. Polymorphisms of this gene are associated with ankylosing spondylitis, inflammatory bowel disease and psoriasis and remind us the old conundrum that BS belongs to the family of spondylarthritides (41).

Recently our group has shown that the clinical cluster of acne/arthritis/enthesitis also clusters in families (42). This is also reminiscent of the spondylarthritides concept. On the other hand, what we call BS might not be all one disease as we have also recently suggested and further genetic studies also give the due emphasis to the phenotype as well (43). It is quite possible that the genetic heterogeneity at hand might well be explained by the heterogeneity in disease expression. Recent data presented in the 15th International Conference of Behçet's disease (see the article by Fresko on page S-118) also reported associations with CCR1, STAT4 and KLRC4, encoding a chemokine receptor, a transcription factor implicated in IL-12 and IL-23 signalling and a natural killer cell receptor and with ERAP1 which is an endoplasmic reticulum expressed aminopeptidase that trims peptides and loads them to MHC Class I. An epistatic interaction between HLA B51 and ERAP was demonstrated and MEFV, NOD2 and TLR4, loci pertinent to innate immunity, were also implicated (unpublished observations). A more complete listing of common and rare variants associated with BS 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 emerged as potential areas of research.

Role of TH17

There are several studies pointing out to a Th1 dominance in BS, showing increased Th1 cytokines and chemokines in the peripheral blood and different lesions of active BS patients (44). However there has been growing evidence that Th17 cells which proliferate from naive T cells through IL-6 and TGF- β stimulation and which produce IL-17 also play a role in the development of BS (44, 45).

Geri *et al.* studied the nature of T cells and cytokines in peripheral blood, cerebrospinal fluid (CSF), parenchymal brain lesions and cerebral blood vessels of BS patients with neurological involvement (46). They observed that IL-21 has an important role in BS, by promoting Th17 and suppressing regulatory T cells (Tregs). There was a significant increase in Th17 cells and a significant decrease in Tregs in the peripheral blood of active BS patients and these changes were induced by IL-21 production.

They also showed that IL-21- and IL-17A-producing T cells were present in the CSF, parenchymal brain lesions and cerebral blood vessels of BS patients with active neurological involvement. When CD4⁺T cells were stimulated with IL-21, Th17 and Th1 cells increased and Tregs decreased. They also tried to block IL-21 with an IL-21R-Fc, and showed that this attempt resulted in reversal of the Th17 and Treg state. Thus, they suggested that IL-21 may be a promising target for the treatment of BS.

In another study which aimed to determine the relative roles of Th1, Th2 and Th17 cells in BS patients, Kim *et al.* studied peripheral blood mononuclear cells of active BS patients with those of rheumatoid arthritis patients and healthy controls (47). They analysed the surface markers and intracellular levels of IL-17, IFN- γ and IL-4 in isolated CD4⁺ T cells. The peripheral blood Th17/Th1 ratio of BS patients was significantly higher than in healthy controls. The Th1/Th2 and Th17/Th2 ratios were similar among the groups. BS patients who had uveitis or folliculitis had higher Th17/Th1 compared to patients who did not have these manifestations. The Th17/Th1 ratio was increased among patients using azathioprine. However this increase was interpreted as associated with uveitis itself since there was no difference regarding the Th17/Th1 ratio among uveitis patients who were using azathioprine and who did not.

In contrast to these studies, Ferrante *et al.* reported a Th1 dominance instead of Th17 in intestinal lesions of BS patients with gastrointestinal involvement (48). They aimed to evaluate the

IL-17/IL-23 axis in parallel with Th1 and IL-27 responses in BS patients with gastrointestinal involvement, ankylosing spondylitis (AS), Crohn's disease (CD) and healthy controls. They studied the serum levels of Th1 and Th17 as well as ileal biopsy specimens of BS. IL-23 mRNA levels were normal in ileal biopsies of BS patients in contrast to AS and CD patients. STAT-3 and IL-17A mRNA were also normal in BS patients. However, TNF- α , IFN- γ , and IL-12p35 mRNA levels in BS specimens were similar to those of CD patients and were significantly higher than those of healthy controls and AS patients. It is interesting that, in contrast to the similarities regarding the clinical, endoscopic and histological findings of gastrointestinal involvement of BS and CD, the cytokine profile was quite different.

Due to the potential role of Th17 cells in the pathogenesis of BS, treatment modalities targeting the Th17/IL17 axis were suggested (45). Three papers that were recently published claim that anti-TNF agents, interferon-alpha (IFN-alpha) and cyclosporine-A may show their effect through inhibition of this pathway.

Sagita *et al.* aimed to determine whether infliximab inhibits Th17 differentiation in BS patients with eye involvement (49). They measured the inflammatory cytokines in ocular fluid samples of BS patients with uveitis who were using infliximab, BS patients with active uveitis who had not been treated with immunosuppressives and patients who were having eye surgery for non-inflammatory conditions. They observed high levels of inflammatory cytokines such as IFN- γ , IL-2, TNF-alpha, IL-6, and IL-17 in the ocular fluids of active BS patients who were not yet treated. On the other hand there were no inflammatory cytokines in the ocular fluid of uveitis patients treated with infliximab. Similarly activated CD4⁺ T cells of active uveitis patients produced high levels of TNF- α and IL-17, whereas T cells of BS patients did not. Altogether their data suggest that infliximab may be showing its effect through the inhibition of Th17 cytokines.

In a recent study which aimed to de-

termine whether IFN-alpha affects the IL-23/Th17 pathway, peripheral blood mononuclear cells of BS patients and controls were cultured alone or with IFN-alpha and the levels of IL-17 and IL-10 were determined (50). The IL-17 and IL-10 levels were significantly higher in BS patients compared to controls. They observed that IFN-alpha caused a significant decrease in IL-17 and an increase in IL-10 in both BS patients and controls. Similar results were obtained with CD4⁺ T cells from controls cultured with and without IFN-alpha. IFN-alpha significantly increased the p-STAT2 expression. These results suggest that IFN-alpha may be showing its beneficial effects in BS through inhibition of IL-17 and increased production of IL-10.

Another study aimed to determine the effect of cyclosporine-A on IL-17 and IFN- γ production in BS patients with uveitis (51). They showed that IL-17 and IFN- γ levels were significantly higher in active BS patients compared to controls. The production of both cytokines and uveal inflammation decreased with cyclosporine-A. They also studied the effects of cyclosporine-A *in vitro* and showed that it again inhibited the production of IL-17 and IFN- γ . The authors concluded that the effect of cyclosporine-A in BS uveitis could be through the inhibition of these cytokines.

Clues from clinical research

We have previously shown that: **a.** papulopustular lesions are more common among BS patients who have arthritis; **b.** the papulopustular lesion-arthritis association is one of the clusters of disease expression shown by factor analysis; **c.** the papulopustular lesions which were previously thought to be sterile were infected with bacteria; **d.** enthesopathy is also part of this papulopustular lesion-arthritis association; and **e.** HLA B27 positivity and sacroiliitis were not more frequent among these patients (52-56). These observations led to the hypothesis that the papulopustular lesion-arthritis cluster of BS may have a pathogenesis similar to the acne associated reactive arthritides (57).

A recent study by Karaca *et al.* have used factor analysis to identify symptom clusters in familial and non-familial BS patients (42). Familial BS patients who had a first-degree relative with BS and non-familial BS patients were questioned for the BS symptoms they experienced during the previous 3 months. The previously shown clusters were confirmed in this study and only the papulopustular skin lesions and joint involvement association had a significantly higher frequency among familial BS patients (39.2% vs 21.5%, $p < 0.001$). Moreover it was concomitantly present in both family members in 5 of the 17 (29%) familial related pairs compared to only 5 of the 110 (4.5%) unrelated pairs of the non-familial group ($p = 0.004$, RR=6.47 95% CI 2.15-18.89).

This study, together with the above mentioned observations supports the idea that there may be different clusters of disease expression in BS with different biologic pathways involved in their pathogenesis.

Vascular involvement

A comprehensive review updated recent developments in vascular involvement (58). Vascular involvement is reported to be less frequent and milder in Japan compared to other populations (59). In a chart review of 412 patients registered in two university hospitals between 1991 and 2007 vascular involvement was found in 26 (6%) patients with venous lesions (81%) being more common than the arterial lesions (31%). Eye involvement was significantly less and gastrointestinal involvement was more frequent among patients with vascular disease.

Arterial involvement

Saadoun *et al.* reported 101 patients with arterial disease among a cohort of 820 BS patients who were followed between 1976 and 2009 (60). Male preponderance and association with venous disease were again noted. The median time to arterial involvement was 4 years. Arterial lesions were frequently single (68%) and consisted of aneurysms (47%), occlusions (37%) or stenosis (14%). The most commonly

Table. Highlights of recent literature on management of BS.

Highlight	Reference
Current drug treatment of BS became more intensive.	70
Rheumatologists from countries with a low prevalence of BS use more frequent and more prolonged anticoagulation in the treatment of venous thrombosis compared to those from countries with a high prevalence.	71
Immunosuppressives and corticosteroids seem to be effective in decreasing recurrences of venous thrombosis.	72
Interferon alpha-2a appears to be effective at lower dosage in the treatment of severe uveitis of BS, which might decrease the cost and dose dependent adverse events.	76
The effect of infliximab in suppressing ocular inflammation seems to start faster than that of iv or intra-ocular corticosteroids.	83
Intra-vitreous use of infliximab might be of value in decreasing systemic adverse events related to the use of this drug.	84
Adalimumab seems to be effective for most manifestations of BS even in patients who fail to respond to infliximab.	77
Interleukin-1 and interleukin-6 appear to be promising targets for severe complications of BS.	91,92,93
Surgical treatment of peripheral aneurysms gives satisfactory results at the long-term	95

involved artery was the aorta followed by femoral, pulmonary and iliac arteries. The majority of the patients were treated with glucocorticoids (86%) and immunosuppressive agents (78%). Additional anticoagulants (47%) were used mainly for occlusive lesions. Arterial disease significantly decreased the survival. After a median follow-up of 8 years, 39% of patients achieved complete remission, 28% relapsed and 14% died. Relapses were less frequent among patients treated with immunosuppressives.

We recently studied 47 patients with pulmonary artery involvement (PAI) registered at our center between 2000 and 2007 (61). The mean age of the patients was 29.4 ± 8.2 , and the disease duration at the onset of PAI was 3.6 ± 4.8 SD years. The majority (72%) of the patients had pulmonary artery aneurysms (PAA) either isolated or accompanied by pulmonary artery thrombosis (PAT) and the remaining (28%) had isolated PAT. Twenty-five percent of the patients with isolated PAT developed PAA during follow-up. Thorax CT scans were more helpful than chest radiographs in the diagnosis. Aneurysms were partially or totally thrombosed in about one third of the cases. The involvement was usually bilateral and affected mostly inferior lobes. Thorax CT scans also showed parenchymal lesions such as nodules, consolidations, cavities and ground glass lesions. Mediastinal lym-

phadenopathy, mild pleural and pericardial effusions and intracardiac filling defects were also observed. Ventilation-perfusion lung scans showed perfusion defects that persisted for several years, a finding that is not expected in true to form pulmonary emboli. All patients received immunosuppressive treatment combined with glucocorticoids. Additionally, 2 patients underwent endovascular embolisation and 3 others required surgical operations for various complications. After a mean follow-up of 7 years, 26% of the patients were dead, 34% were symptom free and the remaining 40% continued to complain of dyspnea or small bouts of hemoptysis. Relapses occurred in 20% of the patients. Our experience shows that the mortality of PAI is still high and the prognosis of isolated PAT and PAA is similar except that hemoptysis is less frequent and less abundant in patients with isolated PAT.

Moreover, we also recently observed that the mean systolic pulmonary artery pressure (sPAP) was significantly higher among those who had died due to PAI compared to those who had survived. In another cross-sectional controlled study we measured the sPAP in BS patients with PAI and suitable healthy and diseased controls (62). The cut-off value to define elevated sPAP with echocardiography was set as ≥ 35 mmHg. The frequency of elevated sPAP was significantly higher

among patients with systemic sclerosis (SSc) (26%) and BS patients with PAI (17%) as compared to the BS without PAI (8%) and healthy controls (0%). sPAP levels were mildly elevated in BS patients and ranged between 35 and 45 mmHg. Also the DLCO was decreased and pro-BNP levels were increased among BS patients with PAI similar to patients with SSc, suggesting that BS involves the small/micro vessels in the cardio-pulmonary system as well as the larger arteries.

Cardiac involvement

Geri *et al.* surveyed 52 BS patients with cardiac lesions from a cohort of 807 (63). The patients were young, male and were more likely to have both arterial and venous involvement elsewhere in the body. Pericarditis was the most common cardiac lesion. Endocarditis causing aortic insufficiency, intracardiac thrombosis, myocardial infarction, endomyocardial fibrosis and myocardial aneurysm were also common. Complete remission was observed in 46% (24/52) and was associated with the use of anticoagulants and immunosuppressive treatment. Eight patients (15%) died during a median follow-up of 3 years. The 5-year survival rate was significantly less (84%) among patients with cardiac involvement compared to those without cardiac involvement (96%).

Cerebral venous thrombosis (CVT)

De Souza *et al.* made a systematic review of 23 studies including 249 patients with CVT reported between 1966 and 2009 (64) and Saadoun *et al.* evaluated retrospectively 64 patients with CVT among a cohort of 820 (65). The prevalence of CVT among patients with neurological involvement was calculated as 13%. CVT usually presents with symptoms of increased intracranial pressure such as severe headache, papilloedema, sixth nerve palsy and nausea/vomiting. CVT may also cause focal deficits, seizures, confusion and fever. The most frequent locations were superior sagittal sinus followed by transverse sinuses. CVT is usually treated with corticosteroids with or without immunosuppressives. About 74% of the cases received additional antico-

agulation in the acute phase (64). Optic nerve atrophy, persistent headache, reduced visual acuity, and tinnitus were late findings. CVT is closely associated with major vessel involvement and less likely with parenchymal CNS disease (65). Dural sinus thrombosis is also the predominant type of neurological involvement in juvenile BS patients (66). This type of neurological involvement has a more favourable outcome than the parenchymal type (67). A recent study compared CVT in patients with BS and in non-BS cases (68). BS patients were younger and more likely to be male. Focal deficits and venous infarcts were more common among those with non-BS patients. While the outcome was good in both groups recurrences were more common in BS cases.

Evolution of clinical manifestations

A retrospective survey from Japan analysed the evolution of clinical manifestations in 412 patients (69). Time from the initial symptom to diagnosis was 9 ± 10 SD years. Oral ulcers, the most common initial manifestation, preceded the diagnosis by 8 ± 10 SD years. Genital ulcers, eye and skin involvement appeared 1 or 2 years before diagnosis, whereas gastrointestinal, CNS, or vascular involvement developed later. No particular combination of symptoms predicted the development of organ involvement.

Management

Physician surveys

The results of a new physician survey suggest that current treatment of BS became more intensive in terms of immunosuppressive use when compared to 10–20 years ago but also showed a rather low agreement among the physicians in their approach to treating different clinical scenarios and adherence to EULAR guidelines (70).

The prevalence of BS in a certain country might explain the differences among the physicians in their approaches to the treatment of thrombosis according to the results of another survey (71). In this survey, the case histories of 3 BS patients with major vein thrombosis were mailed to rheumatologists from countries with low (USA), intermedi-

ate (Israel) and high (Turkey) prevalence of BS and asked them about their choice for treatment as well as about the duration of anticoagulation if this was their choice. The majority of rheumatologists from Israel and USA stated that they would give anticoagulants at the time of diagnosis of venous thrombosis compared to only 40–44% of the Turkish rheumatologists. Also, the percentage of rheumatologists giving life-long anticoagulation was remarkably higher among rheumatologists from USA and Israel compared to those from Turkey.

Immunosuppressives

A retrospective study from France reported that immunosuppressives might decrease venous thrombosis relapse in BS (72). Out of 807 patients, 296 (37%) had venous thrombosis. Almost all (99%) patients had received anticoagulants, 47% received additional immunosuppressives and 63% received corticosteroids. One hundred (34%) of these patients had experienced at least 1 venous relapse during follow-up. In multivariate analysis, factors that prevented relapse of venous thrombosis were the use of immunosuppressives (HR 0.27; 95%CI: 0.14–0.52) and corticosteroids (HR 0.62; 95%CI: 0.40–0.97). Bleeding complications occurred in 7 (2.4%) patients.

A retrospective study reported the efficacy of azathioprine (2.5 mg/kg/day) combined with prednisolone at an initial dose of 0.5–1 mg/kg/day in 157 consecutive BS with active posterior uveitis or panuveitis (73). The dose of prednisolone was tapered down according to the response to treatment. After a mean follow-up of 71.5 months, 93% of the patients had either partial or complete response. Treatment with azathioprine significantly improved the visual acuity and decreased the percentage of patients who had loss of useful vision compared to baseline values. Patients having retinal vasculitis (OR=0.45; 95% CI=0.2–0.9) and severe visual loss (OR=0.28; 95%CI=0.2–0.7) at baseline were less likely to be complete responders.

In an open study, treatment with enteric-coated mycophenolate sodium for 6 months led to significant decreases in

disease activity of 10 BS patients with active mucocutaneous symptoms (74). Disease-free remissions for up to 24 months following high-dose cyclophosphamide treatment (200 mg/kg iv given in 4 consecutive days) without stem cell rescue were reported in 2 BS patients who had severe manifestations refractory to immunosuppressives and anti-TNF agents (75).

Biological agents

Most of the adverse effects of IFN alpha are dose dependent and a lower dose might be of value in decreasing the cost of treatment while increasing tolerability. In an open study, 37 BS patients with severe panuveitis were treated with 3 million units (MIU) daily IFN alpha-2a for 14 days. The maintenance dose was 3MIU 3 times a week. In case of relapses, the dose was increased sequentially to 4.5, 6.0 and 9.0 MIU 3 times weekly. The duration of treatment was 24 months. This regimen stopped the uveitis relapses in 15 (41%) patients (76).

According to an observational study, the use of infliximab approaches 30% (69 of 230 BS patients) in a tertiary referral center in Italy (77). A literature review as of March 2010 found 113 articles on the use of anti-TNF agents in 369 BS patients in peer-reviewed journals (78).

In January 2007, the Japanese Ministry of Health, Labour and Welfare approved infliximab for the treatment of refractory uveoretinitis of BS. As a condition of approval, the health authority mandated the collection of data on all BS patients using infliximab and the results of the first year treatment on 63 patients (56 men) from 8 tertiary referral centres were published (79). The efficacy analysis at the end of the first year showed that uveoretinitis improved in 92% of the patients and was unchanged in the remaining 8%. Infliximab significantly decreased the mean numbers of ocular attacks and 44% of the patients remained attack free during the 1-year treatment period.

Other groups have also reported similar beneficial results obtained with infliximab in the treatment of refractory ocular involvement (80-82).

In BS, rapid suppression of inflammatory attacks is important for the prevention of the development of irreversible lesions in the retina and optic disk. Infliximab's time to response seems to be faster than that of corticosteroids (83). In an open study, the efficacy of a single infliximab infusion (5 mg/kg) given at the onset of eye attack was compared with high-dose iv methylprednisolone (1 g/day for 3 days) and intra-vitreous triamcinolone acetonide (4 mg) in 35 eyes of 22 BS (males, 14) patients. At the end of follow-up (4 weeks) all treatment arms showed equal efficacy on visual acuity. However, compared to corticosteroids, infliximab began to work significantly earlier in suppressing ocular inflammation. The authors' conclusion was to consider infliximab, also as an adjunct therapy, for the control of acute panuveitis attacks of BS. This surely awaits confirmation.

Intra-vitreous use of infliximab may be of value in decreasing the systemic adverse effects associated with TNF blockage when considering the small concentration of the drug used and its minimal systemic absorption. Infliximab given as an intra-vitreous injection (1mg/0.05 ml) at the onset of a posterior uveitis attack was found to be effective in 15 patients in a pilot study with no ocular or extra-ocular side effects (84).

The use of infliximab in BS is not limited to severe posterior uveitis only. Infliximab combined with methotrexate was effective in the treatment of 10 patients with refractory intestinal involvement. Its effect was rapid and all patients showed clinical improvement at 4 weeks. Furthermore, ileocecal ulcerations disappeared in 9 of the 10 patients at 12 months (85).

Infliximab showed rapid effect in inducing and maintaining vasculitic activity in 7 BS patients with diverse vascular complications (2 patients had retinal vasculitis, 3 had aortic involvement, 1 each had recurrent pelvic vein thrombosis and recurrent venous and arterial thrombosis of the thigh) (86). Resolution of pulmonary artery aneurysms, disappearance of cardiac thrombi (87, 88) and sustained remission of neurologic involvement for 4 years, all

with infliximab treatment, have been reported in case reports (89).

The use of adalimumab is also increasing in the treatment of diverse manifestations of BS (90). Case reports also suggest successful switching to adalimumab in case of inefficacy or adverse events associated with infliximab (77). The success of anti-TNF agents in the treatment of BS has led the investigators to search for other cytokine targets. Gevokizumab, a recombinant humanised anti interleukin-1 β antibody has recently been used successfully in a pilot trial of 7 patients with active uveitis and retinal vasculitis who were resistant to combination of azathioprine and cyclosporine-A (91). Canakinumab, another humanised anti-interleukin-1 β antibody, has been also reported to be effective in the treatment of uveitis that was refractory to treatment with conventional immunosuppressives and biologic agents (92).

Recently, tocilizumab, an anti-IL-6 antibody was reported to be effective in the treatment of refractory neurological involvement in one BS patient (93).

Miscellaneous

Intestinal involvement is an important complication of BS that is more prevalent among patients from the Far Eastern countries. 5-aminosalicylate and less often sulfasalazine are used in the treatment of intestinal BS empirically. In a retrospective study this treatment was found to have a salutary effect in maintaining remission in 143 Korean BS patients with intestinal involvement (94). A younger age at diagnosis (<35 years of age), higher CRP levels (≥ 1.5 mg/dl) and higher disease activity index score for intestinal involvement (≥ 60) at the initiation of treatment were independent predictors of relapse during maintenance.

A retrospective study from Turkey reported the outcome of 25 patients (24 men) with non-pulmonary large arterial disease who had been followed-up for a mean of 7.4 years after surgery (95). The preferred surgical intervention was aorto-bi-iliac by-pass when the aneurysm was in the infrarenal aorta. Extremity aneurysms were treated with synthetic graft insertion. Ligation was

used in selected cases with satisfactory results but postoperative claudication was common. In 3 patients with small saccular aneurysms, aneurysms were managed medically without surgery. Occlusion of synthetic grafts, aneurysms occurrence at the anastomotic site and development of new aneurysms at other sites were seen during follow-up. The authors underlined the importance of concomitant immunosuppressive therapy in the prevention of relapses.

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