Review

One year in review 2016: Behçet's syndrome

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ABSTRACT

Several articles highlighting the epidemiology, pathogenesis, clinical features, treatment modalities and disease assessment of Behçet's syndrome (BS) have been published during the last year. Clinical and radiological features of lower extremity deep vein thrombosis due to BS can be quite different than those found in thrombosis due to other causes; additionally, frequency of post-thrombotic syndrome is significantly increased in BS. Some clinical and colonoscopic features are useful in differentiating BS from Crohn's disease. Barkhof criteria may be helpful in differentiating neurologic involvement due to BS from multiple sclerosis. Anatomical localisation of papulopustular lesions but not histology has been found to be helpful in differentiating papulopustular lesions of BS from those found in acne vulgaris. Several studies looked at the ovarian reserve with contradicting results. A population-based cohort study found higher risk of haematological malignancies only among female BS patients living in Taiwan. The role of genetic factors and environment is discussed and both autoimmune and autoinflammatory features are underlined in the pathogenesis of BS. New data on the epistatic interactions between ERAP and HLA B51 is available and information on the microbiome have started to appear. New uncontrolled data suggest beneficial effects of anti-TNFs for refractory extra-ocular complications of BS such as pulmonary artery, gastrointestinal and central nervous system involvement. Uncontrolled studies suggest promising results with interleukin-1 inhibition but gevokizumab, a humanised anti IL-1β antibody, failed to meet the primary endpoint of time to first ocular exacerbation in a phase III trial. The debate on anticoagulation continues with new observational data.

Epidemiology

The relatively high prevalence of Behçet's syndrome (BS) along the Silk Road from the Mediterranean to the Far East had led to the hypothesis that it had spread over centuries through this ancient trade route. A recent study aims to provide a first clue towards genetic evidence for this hypothesis by testing it via an anthropological evolutionary genetics approach (1). BS patients who fulfilled ISG criteria and were of Italian origin for several generations and with no consanguinity were studied. Characterisation of BD variation at ancestry informative mitochondrial DNA control region and haplogroup diagnostic sites of these 185 patients revealed that they were more closely related with some middle eastern and central asian populations settled along the ancient Silk Road rather than with healthy Italians.

Recently, the first study reporting the prevalence of BS in the Netherlands became available (2). This was a hospital-based prevalence study where the number of BS patients with different ethnic backgrounds living in the Rotterdam area and recorded in 4 hospitals in this area was compared to the number of people with that ethnic background living in the same area. The prevalence was calculated as 1 per 100,000 among Dutch-Caucasians, 71 per 100,000 among Turks and 39 per 100,000 among Moroccans. The authors suggest that the prevalence among Turks is comparable to what was reported from Western Turkey and the prevalence among Moroccons to what was reported from Morocco. Such prevalence studies among immigrants give important clues regarding the role of genetics *versus* environment in the pathogenesis of a disease. It is indicated that only 11 of the 52 Turkish origin patients and 3 of the 30 Moroccon origin patients were born in the

Netherlands. Whether they are second or third generation immigrants is not stated. It would be interesting to know the prevalence among those who had migrated to the Netherlands recently compared to the second or third generation immigrants to better understand the role of environment.

BS is generally known to be very rare in Sub-Saharan Africa. A study from Dakar challenges this contention by reporting a case series of 50 patients with BS that were recorded between 2000 and 2013 (3). The authors calculated a yearly incidence of 3.84. The mean age was 32 years, male to femaile ratio was 1.6 and a positive family history was present in 2 of the patients. All of the patients had oral and genital ulcers, 32% had a positive pathergy test and 42% had uveitis. Nervous system involvement was reported as 24%, but most of these were patients with headache which is a common symptom in BS even without nervous system involvement.

Community Oriented Program for Control of Rheumatic Diseases (COPCORD) is a WHO initiative started for the recognition, prevention and control of rheumatic diseases in developing countries. Recently results of the the first stage of this study in 1 rural and 3 urban areas of Iran aiming to determine the prevalence of rheumatic diseases was published (4). This study confirmed the previously reported prevalence of BS in Iran as 80 per 100,000 (95%CI 50 to 130).

A consensus classification criteria for paediatric BS was developed by an international expert group (5). According to the new criteria for paediatric BS, patients with at least three of the following 6 manifestations are classified as BS: at least 3 oral ulcers per year, genital ulcers typically with scars, skin lesions in the form of necrotic folliculitis, acneiform lesions or erythema nodosum, uveitis in the form of anterior uveitis, posterior uveitis or retinal vasculitis, nervous system involvement except for isolated headache and vascular involvement in the form of venous or arterial thrombosis or arterial aneurysms. Among the 219 individuals whose data were analysed, 156 were classified as BS by the expert group. When tested in this group, International Study Group criteria had a sensitivity of 73.7% and specificity of 100%. The new criteria had a higher sensitivity (91.7%), but a much lower specificity (42.9%). Despite this substantially low specificity the expert committe propose it for future therapeutic trials. Although it is mentioned in the methods that the EUROFEVER registry would be used for determining the external validity of these criteria, only the frequency of each BS manifestation among different autoinflammatory conditions are reported in this paper.

A retrospective case series of 46 paediatric BS patients was reported from a tertiary referral centre in the UK, a country with a relatively low BS prevalence (6). The frequency of having a first degree relative with BS was 17%, much higher than that reported in adults with BS (7), reflecting genetic anticipation that was previously reported in BS (8). Regarding the clinical manifestations, frequency of gastrointestinal involvement (56.5%) and nervous sytem involvement (28.3%) are rather high. However it seems that very few of these patients have documented gastrointestinal or nervous system involvement. Reporting of transient abdominal pain as gastrointestinal involvement and headache as nervous system involvement in BS patients without further documentation may be misleading.

Disease assessment

One of the major contraversies in disease assessment in BS is the use of outcome measures developed for other conditions with similar types of involvement to BS *versus* developing Behçet's specific outcome measures for each type of organ involvement (9). An ocular attack score for assessing uveitis specifically in BS patients had been developed by our Japanese colleagues (10). This instrument called "Behçet's disease ocular attack score 24" assesses Behçet's uveitis through 6 domains which are cells in the anterior chamber, vitreous opacity, peripheral fundus lesions, posterior pole lesions, subfoveal lesions and optic disc lesions. The authors suggest that this instrument has the advantages of evaluating both anterior and posterior involvment, reflecting the total number of attacks as well as the severity of each attack, the ability of being added to show the disease state during a certain amont of time, being simple and available for retrospective assessment. Recently, they tested the ability of this instrument to predict visual acuity in BS patients with uveitis using the retrospectively collected data of 50 patients over a preiod of 5 years (11). A low, but significant correlation (R2=0.334, $p<0.001$) was observed between the BOS24 score and change in the best corrected visual acuity (BCVA) over time. The domains that determined the change in visual acuity were BOS24 score over 5 years, baseline BCVA and age. Among the domains of BOS24 score, posterior segment lesions had the strongest correlation with the deterioration of VA ($p=0.002$).

The other study published this year about the asessment of eye involvement in BS tested the interobserver variability of scoring ultra-wide-field fluoescein angiography (UWFA) in BS patients (12). The Angiography Scoring for Uveitis Working Group (ASUWG) had developed standards for recording fundus florescein angiography findings (13) and this study tested the usefulness of the ASUWG scoring system for scoring UWFA, which has the advantage of requiring less patient cooperation and technical expertise and visualising the peripheral retina compared to standard FA. Both the standard FA and UWFA images of BS patients with retinal vasculitis were scored by 3 independent observers. Intraclass correlation coefficient (ICC) was used to assess the inter-observer variability. There was good correlation between the observers for both standard FA (ICC=0.874, $p<0.001$) and UWFA (ICC 0.928, $p<0.001$). The ICC was higher for UWFA compared to standard FA for scoring the angiographic signs of peripheral retinal vascular staining leakage, peripheral capillary leakage, and neovascularisation. Although the correlation seem to be better for UWFA, the retrospective nature of the study and the fact that stand-

ard FA and UWFA were not performed on the same day were limitations.

Another organ specific outcome measure that was recently developed for BS was the Genital Ulcer Severity Score (GUSS) (14). This score was developed by modification of the Oral Ulcer Severity Score that had been developed for assessing recurrent aphtous stomatitis (15). GUSS assesses the number, size, duration, ulcer-free period, pain and the site of genital ulcers within the previous 4 weeks. In addition, evidence of scarring, discharge, quality of life assessed by measuring difficulty in sitting, walking, passing urine and sexual activity on a VAS scale are also recorded. The overall score showed the strongest correlation with pain (r=0.936, p<0.0001). On multivariate regression analysis, pain related to ulcers, size and site were the main characteristics that influence the genital health quality of life (R2 0.60, p<0.0001). The duration and number of genital ulcers showed a moderate correlation with the BDCAF (r=0.375, p=0.003 and r=0.368, p=0.004 respectively) while the other domains of GUSS showed a weak correlation.

The two most commonly used instruments for the assessment of overall disease activity in BS are the Behçet's Disease Current Activity Form (BDCAF) and the Behçet's Syndrome Activity Scale (BSAS) (9). The first is a composite physician and patient reported outcome measure whereas the latter is completely patient reported. Two recent studies reported the adaptation and validation of these 2 instruments in Korea (16, 17). In the first study the BDCAF was forward and backward translated to Korean by 2 independent translators for cross-cultural adaptation (16). Then the Korean form was tested and retested in a group of 46 BS patients who attended the clinic for their routine controls. The total score was compared using intraclass correlation coefficient (ICC) with the patient's and clinician's perception of disease activity and the Behçet's Disease Quality of Life (BDQoL) Scale score to assess the validity. Although the test-retest reliability was good for several items, it was moderate for eye (κ 0.427) and nervous system involvement (κ 0.502) and fair for arthritis (κ 0.355) and major vessel involvement (κ 0.330). The authors do not provide detailed information on these discrepancies. They may be due to a lack of prior knowledge of the previous examination that is needed to determine if this is a "new" manifestation, the difficulty of differentiating active disease from damage in eye involvement without ophthalmologic examination, assessing nervous system involvement without a neurologic examination and assessing major vessel involvement without imaging. There was a fair correlation between the BDCAF and BDQoL (ICC = 0.836, p<0.001), and poor correlation with physicians's VAS (ICC = 0.362, p=0.005) and patient's VAS (ICC = 0.311, p=0.005). A similar approach was used for validation of the Korean version of the BSAS by the same authors and published in a second paper (17). Here the instrument seemed to have performed better, altough it is hard to make a reliable comparison since this time the authors chose to use ICC in stead of Cohen's kappa to assess test-retest reliability and Pearson's correlation instead of ICC to compare BSAS with BDQoL, patient VAS and physician VAS. The test-retest reliability was good except for the item concerning gastrointestinal involvement. There was a good correlation with BDCAF (r=0.701, p<0.001), and moderate correlation with BDQoL (r=0.522, p=0.002), patient VAS (r=0.450, p=0.011) and physician VAS (r=0.441, p=0.001). This better performance of BSAS compared to BDCAF may be related to the fact that BSAS also asesses how much each lesion bothers the patient, in addition to the number of lesions.

Finally, 2 papers were published reporting the adaptation, reliability and validity of the Turkish versions of the Compliance questionnaire on Rheumatology (CQR) and Beliefs About Medicine questionnaire (BMQ) in patients with BS (18, 19). Turkish version of the CQR showed acceptable internal consistency (Cronbach's alpha 0.832), moderate test-retest reliability (ICC=0.630) and criterion validity tested by its correlation with the Morisky Medication Adherence Scale (r=-0.389, p<0.001) (18). The authors used a similar methodology and concluded that Turkish version of the BMQ is a valid and reliable tool for BS patients (19).

Immunopathogenesis

Although several inflammatory molecules have been studied, current biomarkers are largely insensitive in BS and unable to predict disease progression and response to treatment. Within the previous year, a study was conducted to explore serum levels of soluble CD40 L (sCD40L), soluble intracellular adhesion molecule (sICAM-1), monocyte chemoattractant protein-1 (MCP-1), myeloperoxidase (MPO), leptin, resistin, osteoprotegerin (OPG), soluble type 1 tumour necrosis factor receptor (sTNFR), interleukin (IL)-6 and serum amyloid A (SAA) in a cohort of BS patients. Serum concentrations of sTNFR, leptin, sCD40L and IL-6 were significantly higher in BS patients than in healthy controls (HC), while no difference was found in MCP-1, MPO and resistin serum levels. Moreover, the authors observed significantly higher sTNFR serum concentrations in BS patients with inactive disease than HC. Moreover, a correlation between sTNFR and age was also found. sTNFR levels were higher among BS patients over the age of 40 years compared to healthy controls (20). Another interesting attempt to explore the role of potential biomarkers in BS was by a study aimed at evaluating serum levels of IL-8, IL-18, IFN-α2a, IL-6, IFN-γ, CXCL10, CXCL11, CXCL9, and SAA levels in patients with BS, in comparison to HC, and to correlate their levels to disease activity. Compared to HC, BS patients showed elevated levels of IL-8, IL-18, IFN-α2a, and IL-6, and low levels of CXCL11. Moreover, active BS patients with SAA levels >20 mg/L exhibited elevated levels of inflammatory mediators, suggesting that a relationship between SAA and pro-inflammatory cytokines may exist in the intricate scenario of BS pathogenesis (21). Different study groups have reported conflicting results about NK cell activity in BS, however, contribution of NK cells to BS is still unclear.

Recently, a Turkish group studied NK cells from BS patients with uveitis as well as age and gender-matched healthy controls, purified to determine intracytoplasmic cytokine levels of TNF-α, IFN-γ, IL-2, IL-4, IL-10, IL-12 and IL-13. The results of the study showed that NK cells seem to be important in BS with their NK1 profile in relapse periods, and also with their NK2 profile in remission periods, in patients with uveitis. (22) A Korean study assessed CD11a and CD11c in $CD4^+$ and $CD8^+$ subpopulations in BS patients; the rational of this study was the hypothesis that single nucleotide polymorphisms of CD11a and CD11c were susceptibility loci in BS. The results showed that the frequencies of $CD11a^+$ and $CD11c^+$ cells were significantly increased in the $CD4^+$ and $CD8^+$ cell populations of active-BS patients, respectively, than that among the HCs. Additionally, both CD11a and CD11c mRNA and protein levels were significantly elevated in the $CD8^+$ T cells of active-BS patients than among the HC (23). It has been proposed that classical phagocytic functions are constitutively stimulated in patients with BS; specifically, it seems that patients with severe active BS do exhibit phagocytic dysfunction and some evidence of constitutive activation regarding oxidative burst and cytokine production (24).

Interleukin genes have also been frequently studied. A Turkish study looked at IL-8 gene polymorphisms in 88 patients with BS and 112 HC. Although large cohort studies are needed to confirm the hypothesis, analysis of the results indicated that IL-8 gene polymorphisms may affect susceptibility to BS (25). Similarly, another study investigated the effects of the IL-1β, IL-1Ra, IL-2, IL-6, IL-10 gene polymorphisms on BS occurrence and the association between the polymorphisms and the phenotype. Although the sample sizes were low, the correlations between articular involvement and IL-1RN, ocular involvement and IL-1β, and the age of disease onset and the IL-2 and IL-10 gene polymorphisms, suggest that these polymorphisms could be associated with the disease symptoms and even used as prognostic factors (26). Finally, in order to investigate the association of cytokine gene polymorphisms with the risk of BS, a comprehensive meta-analysis was performed. A total of 13 eligible articles including 2,065 BS patients and 1,559 controls were included. This meta-analysis found that IL-6 rs1800795 and IL-18 rs1946518 polymorphisms decreased the risk of BS. However, IL-12B rs3212227 increased BS susceptibility (27).

So far, genome-wide association studies (GWAS) and candidate gene studies have identified the REL and PRKCQ genes as risk loci for various autoimmune diseases. A case-control study was conducted in a total of 623 BS patients and 1,074 healthy controls to investigate the association of the REL and PRKCQ genes with BS in a Chinese Han population. Three single nucleotide polymorphisms (SNPs), (rs13031237, rs702873, and rs842647) of the REL gene and three SNPs (rs4750316, rs11258747, and rs947474) of the PRKCQ gene were studied using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Stratification analysis indicated that the REL rs842647 polymorphism was associated with BS patients with skin lesions, while no significant association of the other five SNPs between BS patients with other extra-ocular findings, including genital ulcers, arthritis, and positive pathergy test was found. On the light of these data, REL rs842647 polymorphism may be a susceptibility factor for BS pathogenesis and skin lesions, which, in turn indicates that c-Rel may be involved in the pathogenesis and skin lesions of BS through the NF-κB pathway (28).

A study explored the post-transcriptional regulation of the peripheral blood mononuclear cells (PBMCs) transcriptome by microRNAs in BS. The results showed that miR199-3p and miR720 may be promising as biomarkers for BS. The unique microRNA signature displayed by PBMCs from active BS patients may indicate their role in regulation of innate immunity activation and T-cell function (29).

FOXP3 is a key transcription factor in the development and function of Treg cells. Recent studies have shown that SNPs in the FOXP3 contribute to the susceptibility to some autoimmune disorders. Fifty patients diagnosed with BS and 50 healthy controls from north-western Iran were genotyped by PCR-RFLP for two SNPs including rs3761547 (-3499T/C) and rs3761548 (-3279 C/A) in the promoter region of the FOXP3 gene. In addition, a 506 bp nucleotide sequence of FOXP3 promoter was analysed. Notably, the study results showed that the SNP rs3761548 in the FOXP3 gene appears to contribute to the risk of BS among the north-western Iranian population (30). Despite the identification of multiple common genetic variants associated with BS, rare genetic variants have been less explored. Recently, a multicentre study investigated the role of rare variants in BS by performing whole exome sequencing in BS patients of European descent. Whole exome sequencing was performed in a discovery set comprising 14 German BS patients of European descent. For replication and validation, Sanger sequencing and Sequenom genotyping were performed in the discovery set and in 2 additional independent sets of 49 German BS patients and 129 Italian BS patients of European descent. Genetic association analysis was then performed in BS patients and 503 controls of European descent. Using whole exome sequencing, the authors identified 2 rare putative protein-damaging genetic variants associated with this disease. Interestingly, the identified genetic variants might influence cytoskeletal regulation and DNA repair mechanisms in BS and might provide further insight into increased leukocyte tissue infiltration and the role of oxidative stress in BS (31).

Recently, an association of variants of the JAK1 and TNFAIP3 genes with the disease has been reported in the Chinese Han population. Therefore, a European study was aimed at assessing whether the association described in Asian populations could be replicated in Europeans. The study included 1155 Spanish subjects of European origin (372 BS and 783 unrelated healthy individuals). Interestingly the association of variants of the genes JAK1 and the TNFAIP3 with BS which has been de-

scribed in the Chinese population was not replicated in Europeans (32).

Genetics

Two extensive reviews on the immunogenetics of BS were published (33, 34). Both re-emphasised the role of environmental and genetic factors in the pathogenesis and proposed that the syndrome has both autoimmune and autoinflammatory aspects. The effectiveness of classical immunosuppressives such as azathioprine and cyclosporine and the role of human heat shock protein 60 (HSP60) were evidence for autoimmunity, on the other hand the lack of high-titer autoantibodies or antigen-specific T cells, strong involvement of major histocompatibility complex (MHC) class I molecules, clinical episodes of unprovoked inflammatory attacks driven by neutrophils, the possible contribution of M694V MEVF mutation to disease susceptibility and the therapeutic effectiveness of colchicine supported autoinflammation. In addition to the positive association of HLA-B51, recent data report additional links with HLA-B15, B27, B57 and A26. HLA-B49 and A03, on the other hand, seem to be protective. Genome wide associations have identified significances in the IL-23R-IL12RB2, IL-10, STAT-4, CCR1-CCR3, KLRC4, ERAP1, TNFAIP3 and FUT2 loci and targeted next generation sequencing has revealed the rare non-synonymous variants of IL23R, TLR4, NOD2 and MEVF. They claim that these genes encompass both innate and adaptive immunity and confirm the polarisation of helper T cell (Th1) *versus* Th2 cells and the involvement of the Th17 lineage. Moreover, they accentuate that the epistatic interactions between HLA-B51 and the risk coding haplotype of the endoplasmic reticulum associated protease ERAP1 provides the clue to the role of HLA class-1 peptide presentation. Another review article written by Dennis McGonagle and colleagues propose the concept of "MHC-I-opathy" as a unified concept for spondylarthritis, psoriasis and BS and suggest that these diseases share the clinical features of disease localisation to sites of contact between the body and the external environment (oral mucosa, gut, skin) or to sites of physical stress such as entheses, including mini-enthesis in the eye, vessel wall and valve regions (35). They suppose that the bridge between them is their asociation with MHC class I alleles such as B51, C0602, B27 and epistatic ERAP-1 interactions. They do not, however, consider the fact that a substantial number of BS patients are B-51 negative (36) and that the association between entesopathy and arthritis was prominent among the HLA-27 negative patients (37).

A Portuguese-Iranian study group tried to replicate the findings of the main whole-genome wide association studies among 973 Iranian BS patients and 828 controls and confirmed that CCR1, KLRC4, IL12A-AS1, STAT4, ERAP1, MHC, IL-10 and IL23R-IL12RB2 were disease susceptibilty loci (38).

A Spanish group investigated the role of Toll-like receptor 8 (TLR), a mediator of innate inflammatory response in BS and in Crohn's disease (CD). A total of 844 CD, 371 BS and 1385 controls were genotyped for single nucleotide polymorphisms in the TLR8 locus. Rs2407992 and rs5744067 were associated with susceptibility to BS and CD (OR=1.34 and OR=0.82). However, statistically significant differences were observed only in females. The data was interpreted as a common pathogenic link between the two diseases (39).

Kim *et al*. from Korea evaluated the expression of the NLRP3 inflammasome components and its link with IL-1 beta hypersecretion in 15 active and 15 stable patients with BS and 15 healthy volunteers. They found that the NLRP3 inflammasome components increased at both mRNA and protein levels compared to controls (40).

Nitric oxide synthase gene polymorphisms (NOS2 and NOS3) were investigated in 733 Han Chinese patients with BS and 1359 healthy controls. The results showed a decreased frequency of the NOS3/rs1799983 GG genotype and an increased frequency of NOS3/rs1799983 GT genotype in patients with BS. These findings suggested that the NOS3/rs1799983 polymorphism was associated with the syndrome (41).

The same group also studied the polymorphisms of cell adhesion molecules among 1149 BS patients and 2107 controls. A higher frequency of the CT genotype and a lower frequency of the CC genotype and C allele of CD6 rs11230563 were observed in BS compared to controls. Functional experiments showed an increased CD11c expression and an increased production of TNF-alpha and IL-1beta in GG carriers of CD11c rs2929 compared to AA/AG carriers. The findings showed that CD6 and CD11c were involved in susceptibility to BS (42).

Another study involved five NLR family genes (NOD1, NOD2, NLRP1, NLRP3 and CIITA). The study was among 950 BS patients and 1440 controls. The first stage of the study showed significantly decreased frequencies of the CIITA/rs12932187 C and NOD1/rs2075818 G alleles. The second stage validation study confirmed the association of CIITA/rs12932187 and NOD/rs2075818 with BS. Functional experiments showed that carriers with the CC genotype in CIITA/rs12932187 had a lower CIITA mRNA expression level and an enhanced IL-10 secretion as compared to GG and CG carriers (43).

The last experiment from this Chinese group evaluated several modulatory factors in the TLR signalling pathway including IRF3, IRF7, IRF8, TRIM20, MYD88 and NFkB. Two SNP's near IRF8 were associated with BS (rs17445836 GG genotype and rs11647823 AA genotype). Functional studies revealed an increased mRNA expression of IRF8 and IFN-gamma production and a decreased production IL-10 in rs17445836 carriers with the GG genotype and increased production of URF8 and decreased IL-10 in individuals carrying the rs11642873/AA genotype (44).

A microarray analysis performed in 41 Japanese BS patients revealed elevated levels of IL-23 receptor mRNA. DNA sequencing around rs12119179 tightly linked to BS, revealed an elevated frequency of the C phenotype, consistent with a previous report that IL23R is a susceptibilty locus for BS (45).

Another group looked at whether IL-

23 gene polymorphism was associated with an enhanced inflammatory response in 27 BS patients and 32 controls with three genotypes. The expression of IL-23R was significantly higher in both BS patients and in controls with the GG phenotype compared to the AG and AA phenotypes. There was an elevated secretion of TNF-alpha, IL-6 and IL-17 in BS patients and healthy controls with the GG phenotype showing that this phenotype intensifies proinflammatory cytokine responses (46).

A meta-analysis of 8 studies obtained from 2538 BS patients and 2792 healthy controls, evaluated the prevalence of MEVF mutations among patients with BS. M694V (pooled OR 1.74) and M680I (pooled OR 1.26) were associated with BS in the overall analysis. E148Q was not linked to BS. M694V and M680I were risk loci especially among the Turks (47).

The peptides presented by HLA-B51 and their processing by ERAP1 has been the subject of new research. A study from Spain intended to characterise the peptidome of the HLA-B51:01 allotype and their subsets and their distinct ERAP-1 mediated processing. They used 721221 transfected cells for this purpose and showed that the major peptide motif consisted of Pro and Ala at position 2, aliphatic/aromatic position 3 residues and Val and Ile at the C-terminal position. The ligands with Pro and Ala at position 2 constituted 2 distinct peptidomes. Both peptide subsets differed drastically in their susceptibility of their position 1 residues to ERAP1 and this provided a mechanism for the epsitatic interaction between B51:01 and ERAP1 (48). In another study looking at the naturally occurring ERAP1 protein allotypes and the contribution to BS, genotypes of all reported missense ERAP1 gene variants with 1000 Genomes Project EUR superpopulation frequency >1% were determined in 1900 BS cases and 1779 controls. It was seen that one ERAP1 protein allotype with five non-ancestral amino acids was recessively associated with disease (OR 2.55). The association was absent in individuals who lacked HLA-B51 and these findings suggested that an ERAP1 allotype contributed to the BS risk by altering the peptides available for binding to HLA-B51 (49).

A group from China and the Netherlands investigated the genetics of a family of intracellular non-receptor tyrosine kinases called TAM kinase (Tyro3, Axl, Mer) and its two ligands (Gas6 and PROS1) among 907 patients with BS and 1780 healthy controls. The frequency of the C allele and CC genotype of rs9577873 in GAS6 and A allele and AA genotype of rs4857037 in PROS1 were significantly increased in BS, suggesting that TAM-GAS6/PROS1 signal pathway may be important in pathogenesis (50).

A group at the National Institutes of Health (USA) described a new syndrome caused by high penetrance heterozygous germline mutations in the NFkB regulatory protein TNFAIP3 (A20) in families with a systemic inflammation that resembled BS. The mutant truncated proteins acted by haploinsufficiency and increased the inflammatory cascade since A20 is a potent inhibitor of the NFkB signalling pathway. However BS usually does not show a Mendelian pattern of inheritance and the chorioretinal scarring and macular fibrosis was not typical for this condition (51). A Japanese group identified a heteozygous C243Y mutation in A20/TNFAIP3 in 6 patients with BS from the same family over four generations. They pointed to the potentiating effect of this mutation on NFkB signalling and proposed that corticosteroids were beneficial in these patients because of their role in the suppression of the so called NFkB dependent inflammatory cascade (52). Different from the previous report by Zhou, the C234Y mutation seems to cause less loss of function.

Being in linkage disequilibrium with HLA-B51, the major histocompatibility complex class-1 chain-related gene A (MICA) has frequently been considered as a candidate gene for BS susceptibility. Three meta-analyses reassessed this relationship. The first included 12 studies and showed that the MICA-TM A6 allele was associated with BS susceptibility in European and Asian populations whereas MICA*0009 showed this association only in Europeans. It reaffirmed their linkage disequibilibrium with HLA-B51 and suggested their possible role in the pathogenesis (53). The second also looked at the MICA A6 allele in a total of 12 case control studies involving 752 cases and 1175 controls and demonstrated that its frequency was higher in BS patients compared to controls (OR 2.43) especially in Asians and Caucasians. It also suggested that it may serve as an early diagnostic marker (54). The third review delineated the contradictory nature of several studies and focused on MICA-A4, A5, A5.1, A6 and A9. It pooled the results of 1555 BS patients and 2086 controls and again emphasised that MICA-A6 showed a strong correlation with BS (OR 0.71) The remaining alleles exhibited negative associations (55).

A group from Thailand tried to provide a pathogenic link between MICA and HLA-B51. They showed that the MICA-TM nonapeptide (AAAAAIFVI) served as the anchor for the peptide accomodated at the binding groove of the BS associated HLAs (mainly HLA-B51:01). In addition, they demonstrated that the residues 70, 73, 99, 146, 147 and 159 of the BS associated alleles provided the conserved interaction for this binding (56).

Copy number variations are a source of genetic diversity and have been reported to confer susceptibility to various inflammatory diseases. It was investigated in the context of apoptosis-related genes including FAS, CASPASE8, CASPASE3 and BCL2 in 1014 BS and 1051 Vogt Koyanagi Harada (VKH) patients along with 2076 controls. An increased frequency of FAS copy number was found in both BS and VKH and a significant upregulated mRNA expression of FAS was observed in individuals carrying a high copy number. The pathogenetic significance of this finding was not clear (57). Another study evaluated the copy number variations of complement components again in patients with BS and VKH. This study showed that the frequency of having more than two copies of C3 was significantly increased in BS and VKH whereas the variation in C5 was

only associated with BS (58). Finally, a study from Iraq investigated the association of BS with defensin β-4 (DEFB4) genomic copy numbers among 50 patients and 27 controls. The copy numbers were higher in BS compared to controls. Clinical subgroups did not confer special risks (59).

New data from epigenetic studies come from investigations on the hypomethylation that seems to lead to activation of interspersed repetitive sequences (IRSs) such as LINE-1 and Alu, contributing to the pathologies in autoimmune diseases and cancer. The epigenetic changes of IRSs in BS were evaluated using combined bisulfite restriction analysis-interspersed repetitive sequences (COBRA-IRS). DNA from neutrophils and peripheral blood mononuclear cells (PBMCs) of BS patients with ocular involvement that were in active or inactive states and healthy controls were used to analyze LINE-1 and Alu methylation levels. For Alu sequences, significant differences were observed in the frequency of (u)C(u)C alleles between PBMCs of patients and controls, and between inactive patients and controls. Thus, changes in the methylation level of IRS elements might contribute to the pathogenesis of BS (60).

The search for a specific antigen in BS has always been popular. A Chinese group worked with hnRNP A1 as an endothelial cell auto-antigen and demonstrated that the IgG reactivity against this moiety was higher in BS compared to controls (p<0.0001). Deep vein thrombosis inferred a special risk (p<0.05) (61).

Coit and colleagues presented the evaluation of the salivary microbiome of 31 patients with BS and 15 healthy controls using high throughput sequencing of the V4 region of the bacterial 16S rRNA gene. In 9 BS patients, a second saliva sample was collected following dental and periodontal treatment. Sequence analysis identified a total of 908 operational taxonomic units (OTUs) present across all samples. It was observed that BS patients had a microbial structure that was less diverse than that of the healthy controls. The most abundant species in BS was Haemophilus parainfluenza while the most depleted were Alloprevotella rava and Leptotrichia (62).

Clinical manifestations

Skin involvement

Previous studies showed that clinical and histopathological features of papulopustular lesions in patients with BS were not much different than those observed in individuals with acne vulgaris (AV) (63). Kutlubay *et al*. re-assessed this issue with a higher number of patients (64). A dermatologist who was blind to the patients' diagnosis examined formally dermatological lesions in 58 patients with BS and 31 patients with AV and 2 pathologists analysed the skin biopsies. Facial lesions were found to be more common in patients with AV, whereas those on the back and on the extremities were more common in patients with BS. Histopathological description was not found to be useful in differentiating BS from AV however, comedone formation which was more frequent in AV was an exception. It has to be noted that the interobserver agreement for histologic assessment was considerably low.

Eye involvement

Fluorescein angiography (FA) allows the recognition of retinal vascular inflammation based on fluorescein dye leakage from damaged retinal vessels. Kim *et al*. investigated whether there is correlation between changes of FA findings and visual acuity (VA) in BS patients with retinal vasculitis (65). In this retrospective study of 48 patients, there was a more severe and diffuse pattern of vascular leakage in vasculitis in the posterior pole as compared to vasculitis in the peripheral vessels. Retinal vascular leakage, optic disc hyperfluorescence, and macular leakage were found to be significantly associated with a decreased VA.

Vascular involvement

Lower extremity deep vein thrombosis (LEVT) is the most common form of vascular involvement in BS. The Cerrahpasa group (Istanbul) studied clinical and radiological characteristics of LEVT due to BS compared to those due to other causes (66). BS patients were more likely to be young males, whereas controls were mostly females. In addition there was significantly less complete recanalisation, more collateral formation and more bilateral involvement among BS patients, which could be attributed to frequent relapses. 51% of the BS patients suffered from severe post-thrombotic syndrome and 32% from venous claudication while these were present in 8% and 12%, respectively, among the controls (66).

Israeli colleagues reported a case series of 23 children who presented with cerebral venous sinus thrombosis (CSVT) due to BS (67). Patients were mostly males with a mean age of 12 years. CVST was the first event in three-quarters of the patients. Thrombosis at other sites was found in 5 children. The presenting symptom and signs included persisting headache, papilledema, seizures and personality changes. Co-existence with parenchymal CNS involvement was observed in 2 of the 23 patients. The authors suggest that CVST due to BS should be included in the differential diagnosis of children who present with persisting headache even with no prior diagnosis of BS.

Celik *et al*. investigated the frequency of publications about pulmonary artery aneurysms (PAA) due to BS and assessed whether there was a geographic clustering at specific geographies (68). They found that the number of PAA-BS articles from Turkey were higher than expected, whereas those from Japan were significantly lower indicating that PAA could be rare in Japan. It has to be noted that this study did not include the largest series of pulmonary artery involvement in BS reported from Turkey (69). It was interesting to note that this 'cheap methodology' was able to pick up the relative rarity of PAA in Japan, as had previously been suggested (70).

Recently investigators from non-endemic geographies were interested with some rare forms of vascular involvement in patients with BS. A Spanish group reported a 55-year-old woman with BS who presented with acute coronary syndrome due to spontaneous coronary artery dissection (SCAD) of the left anterior descending artery

(71). They suggested that SCAD could be another cause of coronary artery disease, in addition to aneurysms and thrombosis. A group of English thoracic surgeons has brought to our attention the presence of thoracic aortic aneurysm in BS as a potential cause of mortality (72). In their editorial, they emphasised its silent presentation and suggested that imaging of the thoracic aorta should be included in the screening of BS patients.

Atherosclerosis

A recent meta-analysis of 9 studies reported that subclinical atherosclerosis was increased in BS as evidenced by impaired flow mediated dilatation and increased intima media thickness (73). An important limitation of this study is the acknowledged heterogeneity of the studies included in the meta-analysis. A more important issue is whether this subclinical atherosclerosis translates into clinical coronary artery disease in time and the available evidence indicates that this is not so (74-76).

Gastrointestinal involvement

Gastrointestinal involvement is another serious and difficult to treat complication of BS. The frequency of this complication shows a marked variability around the globe with the highest prevalence rates coming from the Far-Eastern countries like Japan and Korea. A recent study from Turkey showed that among almost 9000 BS patients registered in a single multidisciplinary Behçet's centre, 60 patients were diagnosed with GI involvement (77). Although a formal screening of all BS patients was not performed in this study, the results suggest a frequency of less than 1% among Turkish patients. Patients with gastrointestinal symptoms were evaluated by the gastroenterologists in this multidisciplinary group and among the 82 patients with gastrointestinal symptoms and endoscopic lesions that may mimick gastrointestinal involvement of BS, 22 were diagnosed with other conditions such as NSAID ulcers, antibiotic associated haemorrhagic colitis or gastrointestinal tuberculosis. Among the remaining 60 patients who were diagnosed to have gastrointestinal involvement of BS, 19 were diagnosed after emergency surgery for perforations or massive bleeding.The most common endoscopic finding in BS patients with gastrointestinal involvement was the presence of big oval ulcer(s) at the ileocecal region (61%).

Another diagnostic challenge regarding gastrointestinal involvement is distinguishing BS from Crohn's disease. A group from China tried to find discriminative factors between intestinal BS and Crohn's disease (CD) in a retrospective study among 35 patients with BS and 106 patients with CD seen between 1983 and 2010 (78). Massive gastrointestinal haemorrhage, fever, and extraintestinal systemic manifestations were more common in BS patients, while diarrhoea, intestinal obstruction, and perianal lesions were more common in CD. Regarding colonoscopic findings, focal involvement, ileocecal valve deformity, solitary ulcers, large ulcers (>2 cm), and circumferential ulcers were more common in BS patients while segmental involvement, longitudinal ulcers, a cobblestone or nodular appearance, and pseudo-polyps were more common in CD patients.

Arimoto *et al*. from Japan, investigated clinical value of capsule endoscopy in detecting small bowel lesions in 19 patients with intestinal BS and 19 healthy controls (79). Capsule endoscopy revealed significantly more lesions among BS patients such as reddened lesions, erosions and ulcers. Additionally, authors noted that the frequency of ulcers tended to increase towards the distal intestine.

Lee *et al*. from Korea evaluated the seasonal pattern of exacerbations in 268 patients with intestinal BS and found that the flares were more frequent in spring and autumn (80).

Nervous system involvement

Patients with nervous system involvement may present with white matter lesions similar to that seen in multiple sclerosis (MS). Using the Barkhof MRI criteria, (a: at least 1 gadolinium-enhancing lesion or at least 9 lesions on T2-weighted images, b: at least 3 periventricular lesions, c: at least 1 juxtacortical lesion, and d: at least 1 infratentorial lesion) Akman-Demir *et al*. retrospectively studied, MRIs of 84 BS patients with nervous system involvement (81). Those who fulfilled the criteria (n=11) and those who did not (n=73) were compared.Those who fulfilled the criteria were more likely to be female, were more likely to have increased number of attacks, higher rate of oligoclonal band positivity and less pleocytosis in CSF. Additionally, these patients showed reduced frequency of brainstem symptoms and an increased frequency of hemiparesis, hemihypoesthesia and spinal cord symptoms. Those who do not fulfill the criteria, on the other hand, displayed typical large lesions covering brainstem, diencephalon and basal ganglia. Their neurological findings were consistent with brainstem involvement. Authors suggested that, Barkhof criteria may help in differentiating nervous system involvement of BS from MS.

Joint involvement

A group of dermatologists from Korea, used bone scintigraphy to assess the presence of joint involvement in 211 patients with BS (82). The total kappa value was fairly good (0.604), between joint complaints and scintigraphy results. The rheumatologist confirmed 91% (95/104) of the cases as joint involvement.

Gynaecologic complications

There were 3 recent studies which assessed overian reserve in BS by measuring anti-Mullerian hormone (AMH) levels (83-85). Henes *et al*. studied 30 BS patients along with 33 rheumatoid arthritis patients, 32 spondyloarthropathy patients and age matched healthy controls (83). At the time of the study, patients were immunsuppressive or cytotoxic treatment naïve. They had had significantly lower levels of AMH compared to controls indicating diminished ovarian reserve. Similarly, Mont'Alverne *et al*. studied 10 BS patients and 22 healthy controls and found somewhat decreased – albeit not significant – levels of AMH compared to the controls (84). On the other hand, Sahin

et al. found no difference with regard to AMH levels among 35 BS patients and age matched 35 healthy controls (85).

Fatigue

Fatigue affects the quality of life in many inflammatory diseases and is becoming increasingly an issue of interest in the recent years. This year 2 centres from Turkey investigated the presence of fatigue in BS (86, 87). Cerrahpasa group (86) studied fatigue severity and its impact in BS in both diseased and healthy controls. Diseased controls included patients with rheumatoid arthritis, systemic lupus erythematosus and ankylosing spondylitis. Fatigue severity and impact scores of BS patients were similar to that found in diseased controls and significantly higher than that found among the healthy controls. No difference was found between the several subgroups of BS with different types of organ involvement. This was also true when males and females were separately analysed. The other group used Multidimensional Assessment of Fatigue (MAF) questionnaire to assess fatigue and included only healthy controls as a comparator group (87). They found that BS patients had significantly higher MAF. Additionally, those with active disease had significantly higher MAF scores compared to those without active disease. Depression, anxiety and physical dysfunction were found to be positively correlated with fatigue.

Malignancies

Wang *et al*. conducted a nationwide population-based cohort study using the Health Insurance Research Database of Taiwan (88). They identified 1314 new patients with BS without a previous diagnosis of cancer during 2000 and 2009. They observed that 30 patients developed malignancies (9 M/21 F) during 2000 and 2011. Standardised incidence ratio (SIR) of overall cancers was calculated as 1.5 (95% CI: 1.03–2.11). However, when females and males were separately analysed, only females were found to have significantly higher SIR values. Among the cancer types, haematological malignancies and breast cancer were significantly more common. Interestingly, the cancer risk was highest within the first years of follow-up.

Reviews

Several reviews about gastrointestinal involvement (89-91) and one comprehensive update about eye involvement (92) were published.

Management

Anti-TNF agents

Refractory ocular involvement still continues to be the main indication for anti-TNF treatment in BS, but reports on the beneficial effects of these agents in extra-ocular manifestations of BS are increasing. In a recent retrospective study the Cerrahpasa group reported their experience with anti-TNF agents on 13 BS patients with pulmonary artery involvement (PAI) (all males) who continued to have haemoptysis despite treatment with conventional immunosuppressives (93). Twelve patients received infliximab at a dose of 5 mg/kg and 1 patient received adalimumab at a dose of 40 mg every other week (eow). Overall, the response to this treatment was good for 11 patients and treatment could be stopped in 4 patients after a mean period of 23 months. Of the 4 patients stopping treatment, 2 relapsed within 3 years. In 2 patients serious infections (lung tuberculosis and aspergillosis) necessitated withdrawal of anti-TNF agents. These results suggest that TNF inhibition, appears beneficial in PAI. In addition to these promising results, it should be noted that in the same paper 2 additional patients who had developed PAI while using infliximab for large vein thrombosis and CNS involvement are reported. A recent paper on 2 BS patients with refractory PAI also reported satisfactory outcome with TNF inhibition (94).

The report on gastrointestinal involvement of BS mentioned above also reported on the management and outcome of those 60 patients (77). One-third of the patients, judged as having mild disease, initially received 5-ASA derivatives whereas the remaining 62% who were considered to have moderate-severe disease received azathioprine at baseline. Twenty-two patients (36%) underwent emergency surgery due to perforations or massive bleeding. Nine patients did not receive post-operative immunosuppressives and 8 of those patients relapsed. At the end of a mean follow-up of 7.5 years, 48 of 60 patients (80%) were in remission. This study, being the first large study on GI involvement of BS outside the Far-East, showed that the clinical and endoscopic findings of Turkish patients were not different from those reported from Far-Eastern countries. On the other hand, the lower relapse rate of these patients is probably a result of the more frequent use of azathioprine as the initial treatment and the less frequent use of corticosteroids. In a subsequent paper by the same group, the course of 13 patients with GI involvement who were treated with anti-TNF agents and/or thalidomide because of an inadequate response to initial conventional treatment was reported (95). Thalidomide, which exerts its activity by inhibiting TNF-alpha secretion from leukocytes, was used for refractory mucocutaneous and GI involvement before the availability of anti-TNF agents. Of these 13 patients, 6 received thalidomide (mainly 100 mg/day) resulting in remission in 4 of them. The fifth patient was switched to infliximab after 5 years of thalidomide use and the last patient underwent surgery because of a duodenal ulcer that did not heal during 6 months under treatment with azathioprine and thalidomide. Anti-TNF agents, mostly infliximab (5 mg/kg), were given to 10 patients and switch from infliximab to adalimumab was needed for 3 patients during follow-up. At the end of the survey clinical and endoscopic remission was obtained in 10 patients (77%). One patient receiving infliximab and high dose steroids died with sepsis. A systematic literature review, as reported in this article showed clinical remission among 47 of 91 patients (51%) using anti-TNFs. Unfortunately, the data in the literature did not allow to understand whether immunosuppressives added to anti-TNFs improved the outcome.

Two uncontrolled studies from Japan assessed the efficacy of adalimumab on GI involvement in BS (96, 97). The first was a multicentre study evaluating 20 patients with GI disease refractory

to conventional treatment for 52 weeks (96). Adalimumab was initially given at a loading dose of 160 mg, followed by 80 mg 2 weeks later and 40 mg eow thereafter. Improvement of GI symptoms was seen as early as at week 4 and marked improvement was achieved by 12 patients (60%) at week 52. Eight patients (40%) had marked endoscopic improvement between weeks 8 to 12 and this increased to 65% at week 52. Steroids could be completely withdrawn in 8 of the 9 patients taking these drugs at baseline. In 6 patients the dose of adalimumab had to be increased to 80 mg eow because of inadequate response or flare with 3 of them responding satisfactorily at week 52. The second study retrospectively evaluated the efficacy of adalimumab in 8 BS patients with refractory GI involvement for 52 weeks (97). The dose of adalimumab was similar to that in the previously mentioned study. Six patients (75%) showed marked improvement and 2 (25%) achieved complete remission at week 52. Complete endoscopic ulcer healing was also evident in 4 patients (50%). Taken together all of these studies suggest that infliximab and adalimumab as well as thalidomide are of value in the treatment of BS patients with refractory GI involvement.

A retrospective and multicentre study evaluated the efficacy and safety of long-term anti-TNF treatment in 124 BS patients (52% being women) having ocular (65%) and different extra-ocular (45%) manifestations such as mucocutaneous, articular, neurological, GI, cardiovascular involvement, with 12 patients having both ocular and extra-ocular complications (98). Seventy-five percent used at least 1 previous immunosuppressive drug before starting anti-TNF treatment. The median duration between the diagnosis and initiation of anti-TNF treatment was 36 months. The first anti-TNF agent was infliximab (62%), followed by adalimumab (30%) and etanercept (7%). Switch between anti-TNF agents was made in one fifth of the patients. After a median follow-up of 21 months the overall response rate was 90% with the highest figures being obtained for ocular involvement (96%) and the lowest for cardio-vascular involvement (66.7%). The efficacy of adalimumab and infliximab appeared to be similar. Adverse events necessitated withdrawal of treatment in 16 patients (13%). The same group compared the efficacy of adalimumab and infliximab in another multicentre retrospective study (99). The study included 160 patients with refractory inflammatory uveitis associated with various aetiologies –including 58 BS patients (36%) – that have been treated with infliximab (98 patients) or adalimumab (62 patients) between 2001 and 2013. The overall response rates for all patients at 6 and 12 months were 87% and 93%, respectively. Multivariate analysis showed a better response for BS patients and for those who had frequent uveitis attacks (more than 5) previously. Infliximab and adalimumab did not seem to differ in terms of complete response, event-free survival and the development of adverse events. Finally, a high response rate of 94% was reported in a retrospective multicentre study on 17 BS patients with severe and refractory neurological involvement with anti-TNF agents (100).

Interferon alpha

Interferon alpha (IFN-) is the first biologic agent introduced to the armamentarium of BS especially for ocular involvement since 1986 (101). Despite the lack of controlled evidence, it is recommended for the treatment of severe eye involvement of BS in the light of several uncontrolled studies showing a fast onset of action and high remission rates that may also persist after withdrawal (102). However, frequent injections along with interferon's common adverse effects like flu-like reactions, fever, depression and thyroiditis often cause compliance problems (101). A pegylated form of interferon (peg-IFN) which allows once weekly injections is reported to have better tolerability. A recent single blind, controlled trial including 72 BS patients has looked at the corticosteroid and immunosuppressive sparing effect of peg-IFN-2b (103). Patients were randomised to peg-IFN-2b plus standard care or to standard care only groups for 26 weeks and were then followed 6-monthly for 3 years with BS activity scores and quality of life scores. The authors did not give any data on the visual or other clinical outcomes. At the end, the study failed to meet its primary endpoint and show the corticosteroid sparing effect of peg-IFN. The quality of life and fatigue scores were also found similar between the 2 groups. A *post hoc* subgroup analysis of patients who were using corticosteroids at baseline seemingly suggested lower corticosteroid dose for these patients in the peg-IFN group but the baseline steroid dose was already lower in this group compared to the control group. When considering the positive background experience with IFN in BS so far, one can suspect that the negative results of this study may be related to the study design. Recently, an uncontrolled study on 5 BS patients with uveitis reported satisfactory results with peg-IFN-2a (104).

Emerging targets

The resemblance of some characteristics of BS to those of the auto-inflammatory conditions, like the undulating course with spontaneous remissions and exacerbations, has made interleukin-1 inhibition a promising target in managing BS. The pathogenic, clinical and therapeutic data supporting the use of IL-1 inhibition in BS has been reviewed in detail recently (105). Until now, 3 anti-IL-1 agents have been tested in BS. These are the IL-1 receptor antagonist anakinra, the anti-IL-1β monoclonal antibody canakinumab and the recombinant humanised anti-IL-1β, gevokizumab. A retrospective, multicentre study reported the efficacy and safety of anakinra and canakinumab in 30 BS patients (106). Briefly, 60% of the patients were women and 19 (63%) had used another biologic drug before anakinra or canakinumab. Mucocutaneous involvement followed by eye and joint involvement were the main indications for anti IL-1 treatment. The first anti IL-1 agent was anakinra for 27 patients (90%) and canakinumab for 3 patients (10%). Overall, 13 (43%) patients remained on anti IL-1 for at least 12 months with good results. Increasing the dose of anakinra from 100 mg/d to 200 mg/d or decreasing the interval

between the infusions of canakinumab from 8 weeks to 6 weeks as well as switching from anakinra to canakinumab seemed to be beneficial. Both drugs were well tolerated with adverse events being mainly related to injection site reactions caused by anakinra. These salutary results seem to open new horizons in the treatment of BS patients but they should be interpreted with caution until the availability of controlled data, especially when considering the unexpected negative experience with gevokizumab. A proof-of-concept study showing rapid and sustained inhibition of intraocular inflammation with a single infusion of gevokizumab in 7 BS patients with posterior uveitis led to an open-label, multicentre, phase 2 trial on 21 BS patients with posterior uveitis in which gevokizumab was added at a dose of 30 or 60 mg every 4 weeks to a stable regimen of conventional immunosuppressives and corticosteroids (107). The results of this trial suggested again good tolerability and rapid efficacy of gevokizumab. However, in a phase III randomised placebo controlled trial (Eyeguard-B trial) gevokizumab failed to meet the primary endpoint of time to first acute ocular exacerbation even though there were some signals of drug activity such as preserved visual acuity or less severe ocular inflammation in patients treated with gevokizumab (www.genengnews.com July 22, 2015). Tocilizumab, a humanised IL-6 receptor blocking agent, seems to be promising especially for central nervous system involvement of BS (108). The current state of emerging drugs for BS treatment can be further read in a comprehensive review published recently (109).

Anticoagulation

The fact that BS predominantly involves veins especially of the lower extremities had started the still unresolved debate whether anticoagulation should be used in such patients to prevent recurrences, pulmonary thromboembolism and the development of post-thrombotic syndrome. This hot topic was discussed in detail in a recent letter (110) in the context of the rather surprising findings of a Doppler study comparing the characteristics of DVT in BS patients with those of non-BS patients (66). This uncontrolled study with small patient numbers gave a hint for significantly less frequent occurrence of post-thrombotic syndrome among BS patients when anticoagulation is added to immunosuppressives. This finding again underlines the need for formal prospective studies to understand the place of anticoagulation in the treatment of venous involvement of BS.

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