Review

One year in review 2017: Behçet’s syndrome

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Abstract

A meta-analysis showed that methodological differences in prevalence studies such as a sample survey design or census design may be responsible for some of the variance in BS prevalence reported across countries, in addition to a true geographic variation. Efforts towards developing a data driven core set of outcome measures for clinical trials is continuing. Multimodal imaging using colour fundus photography, fluorescein angiography, and optical coherence tomography is essential in visualising diagnostic features, detecting structural changes, and monitoring disease activity and response to treatment in Behçet’s uveitis. Haemoptysis could also be due to bronchial artery enlargement in BS patients with pulmonary artery involvement and can be effectively treated with embolisation. Recent studies shed light on the link between immune system and thrombosis: fibrin clots seemed to be structurally different and plasmin resistant in BS. Newer genetic associations using immunochip were determined, but HLA-B51 is still the principal genetic link. Various studies on micro-RNAs, important molecules of immune regulation were published and discussed. Anti-TNF agents are still the key biologics for the treatment of various manifestations of BS. Two Phase III trials enrolling a small number of BS patients have shown the efficacy of adalimumab in the treatment of non-infectious, non-ocular uveitis. Interferon-alpha was found to induce long-lasting drug free remissions in a retrospective study. Small observational studies with non-TNF biologics such as ustekinumab, anakinra and canakinumab report beneficial results which await confirmation with further studies.

Epidemiology

Two studies that reported on the prevalence of Behçet’s syndrome (BS) were published from Korea, and Turkey during the last year (1, 2). These two studies used different methodologies to determine the prevalence. The study from Korea explored the prevalence of BS and the change in annual prevalence rate over time using the The Korea Healthcare Bigdata that consists of medical institution claims data concerning diagnosis, surgical treatment, and prescription medicines, and represents the total population. The database was reviewed for patients who had Korean Standard Classification of Diseases (KCD) diagnostic codes consistent with BS between 2011 and 2015. The prevalence was estimated as around 35.0 per 100,000 population. This is slightly higher than the previously reported BS prevalence in Korea which was 30.2 per 100,000. The current study pointed out to a gradual increase in annual prevalence rate between 2011 and 2015, from 32.8 in 2011, 34.0 in 2012, 34.6 in 2013, 35.5 in 2014, to 35.7 per 100,000 in 2015. The authors suggest that the prevalence may be even higher since the data is retrieved from a database and would be missing milder patients who had not sought medical attention. The prevalence was higher among women, with a men to women ratio of 0.54:1 in 2011 and 0.56:1 in 2015. This ratio is similar to what was reported previously by another group from Korea (0.63) (3). When the prevalence was compared between 5 districts, Seoul Metropolitan area had the highest prevalence and 60.3% of BS patients were recorded in this area.

The second prevalence study was a population based prevalence study from Northern Turkey that showed a BS prevalence of 600/100,000 (95% CI, 290–920/100,000) among individuals over the age of 20 (2). This is the highest BS prevalence reported until now. However this finding appears to be biased due to methodological problems. Individuals who were recorded in the 52 urban and 33 rural general...
practices of a city were randomly selected and invited to an interview and examination by 3 dermatologists. The authors report that since all individuals are recorded in general practices, the invited sample would well represent the whole population. Pathergy test and eye examination were performed in suspected individuals. Those who meet ISG criteria were diagnosed as BS. It was reported that 2428 individuals were interviewed and 2,325 (1,290 women, 1,035 men) were included in the study. However the total number of individuals who were invited for interview were not mentioned. Individuals with symptoms may have responded to the invitation more frequently, causing a higher prevalence estimate. Another interesting finding was that the prevalence was significantly higher among women (860/100,000 (95%CI 2.6–5.1). vs. 10.3/100,000 (95%CI 6.1–17.7). This is controversial to previous studies from Turkey reporting similar prevalence among men and women. Moreover none of the 14 BS patients reported in this study had vascular, gastrointestinal or nervous system involvement. These findings raise concern that some men with BS with these types of involvement may have been overlooked, resulting in a lower prevalence among men. Finally, a recent meta-analysis that included 45 prevalence studies disclosed that although there was clearly a wide variation across countries, methodological issues such as hospital or registry based prevalence studies in contrast to studies where a sample of individuals are directly contacted (also called population or field surveys) may be responsible for some of the variation (4). The overall pooled estimates of prevalence were 10.3/100,000 (95%CI 6.1–17.7), whereas it was 119.8/100,000 (95%CI 59.8–239.9) for Turkey, 31.8/100,000 (95%CI 12.9–78.4) for the Middle East, 4.5/100,000 (95%CI 2.2–9.4) for Asia and 3.3/100,000 (95%CI 2.1–5.2) for Europe. Studies with a sample survey design showed a strikingly higher prevalence (82.5/100,000 (95%CI 47.3–143.9) than those with a census design (3.6/100,000 (95%CI 2.6–5.1). The authors suggested that the true difference in BS prevalence may not be as great as reported, since all of the 8 BS studies from high-prevalence Turkey used a sample survey design whereas none of those from low-prevalence Europe used this approach. An analysis of prevalence proportions in areas where either study design were used such as Middle East and Asia, a 12-fold greater pooled BS prevalence was reported for sample surveys compared to census surveys. A meta-regression analysis showed that study design was an independent covariate for BS prevalence in these studies. Classification criteria, study period or reference type had a negligible effect. The authors concluded that methodological differences in addition to true geographic differences may be responsible for the large variation in BS prevalence across countries. Two studies reported on the clinical manifestations of BS patients according to gender (5, 7). In the first study differences between men and women with BS were explored in a retrospective chart review of 329 patients followed in the rheumatology department of a University hospital in Turkey (5). Data on demographic features of the patients, BS manifestations, pathergy positivity, age of onset, HLA B51 positivity and family history of BS were retrieved from patient charts. Among the 329 patients 199 (60.4%) were men. A family history of BS was reported by 9.7% of the patients and a family history of oral ulcers by 22.5%. Patients with a family history of BS had an earlier age of onset. This phenomenon known as genetic anticipation had already been observed in BS in earlier studies (6). This study showed that a family history of oral ulcers was also associated with earlier age of BS onset. The age at disease onset was lower among women compared to men (23.0 years vs. 25.2 years, p<0.05). Pathergy test was positive in 48.7% of the patients (52.4% among men and 43.4% among women, p=0.316). HLAB51 was positive in 44.1% of BS patients and the frequency was lower among men, but the difference was not significant (38.8% vs. 50.6%, p=0.106). Among the clinical findings ocular involvement and vascular involvement were more common among men (42.2% vs. 29.2%, p=0.014 for ocular involvement and 44.7% vs. 15.3%, p<0.001 for vascular involvement) whereas joint involvement and headache were common among women (70.0% vs. 49.2%, p<0.001 for joint involvement and 60.0% vs. 36.2%, p<0.001 for headache). The frequency of headache was quite high and it was not reported whether causes for headache other than BS were excluded. Frequency of genital ulcers, nodular lesions, papulopustular lesions and nervous system involvement were similar among men and women. Only patients who fulfilled the ISG criteria were included in this study. The second study was a retrospective chart review of 193 patients from Korea (7). The age of disease onset and HLA B51 status were studied in addition to gender, as possible predictors of disease phenotype. There were significantly more women (67%), and the mean age at onset, the mean disease duration, HLA-B51 carrier rate and the positivity of pathergy test were similar in both genders. Genital ulcers, peripheral joint involvement, and inflammatory back pain were more common in females while skin lesions were more frequent in males. In total, major organ involvement was present in 39% of the patients (uveitis: 27%, nervous system involvement: 7%, vascular involvement: 4%, and gastrointestinal involvement: 11%), with similar frequency in both men and women. When clinical findings were compared according to age of disease onset, those who had a late onset (>40 years) had more nervous system involvement compared to those with an early onset (15.9% vs. 4.2%, p=0.007). HLA-B51 positive patients had an earlier disease onset, but less nervous system and gastrointestinal system involvement compared to HLA-B51 negative patients (17.2% vs. 2.5%, p=0.02 for nervous system and 20.7% vs. 2.5%, p=0.01 for gastrointestinal involvement). A change in BS phenotype towards a milder disease course over the last decades has been suggested in different series (8, 9). A recent study from Japan also looked at the change in disease phenotype over time among BS patients treated in 7 hospitals in a
district in mid-Japan between 1991 and 2015 (10). The patients met the 1987 revised diagnostic criteria of the Behçet’s disease research committee, the Ministry of Health, Labor and Welfare of Japan (11). These criteria classify recurrent aphthous oral ulcers, skin lesions, ocular inflammation, and genital ulcers as “major symptoms”, and arthritis, intestinal ulcers, epididymitis, vascular lesions, and neuropsychiatric disease as “minor symptoms”. Those who have all four major symptoms during the clinical course are classified as complete, whereas those who have three major symptoms, two major and two minor symptoms, typical recurrent ocular inflammation and one or more major symptoms, or typical recurrent ocular inflammation and two minor symptoms are classified as incomplete BS. Patients were divided into three groups as group A: diagnosed before 2000, group B: diagnosed between 2000 and 2007, and group C: diagnosed after 2008. They observed a decrease in the number of patients with complete disease over time, suggesting a trend for milder disease in more recent years. This finding remained robust after adjustment for disease duration, by selecting symptoms appearing within 4.5 years after the onset of disease. Additionally frequency of genital ulcers and HLA B-51 positivity decreased and gastrointestinal involvement frequency increased. The male to female ratio or the age of disease onset, which are factors that could influence the clinical phenotype were not changed over time. The authors suggested that an increased use of biologics could have affected the disease phenotype by suppressing the emergence of additional symptoms, but they also suggested that this was probably not the case since most of their patients who started biologics already had established disease.

Disease criteria
A recent study from the UK compared the performance of the International Society Study Group (ISG) criteria that were developed in 1990 to the more recent International Criteria for Behçet’s Disease (ICBD) among their patients with BS (12-14). The ICBD was developed with the aim of improving the ISG criteria that did not include GI involvement, vascular involvement and nervous system involvement that are severe, but relatively uncommon complications of BS (14). However, despite providing an increase in sensitivity, this criteria set has a low specificity, causing several patients with other diseases to be misclassified as BS. The recent UK study showed that among 281 patients assessed for BS in Birmingham Centre of Excellence for Behçet’s disease between 2012 and 2015, 190 were diagnosed as BS, 7 as incomplete BS and 84 as not having BS (12). When the authors compared the performance of ISG and ICBD criteria in this cohort they observed that the sensitivity was higher for ICBD criteria (97.9%, 95% CI: 94.7–99.4) compared to ISG criteria (77.9%, 95% CI: 71.3–83.6), but the specificity of ICBD (19.1%, 95% CI: 11.3–29.1) was much lower compared to ISG criteria (69.1%, 95% CI: 58.0–78.7). The negative likelihood ratio was 0.32 for ISG and 0.11 for ICBD criteria whereas the positive likelihood ratio was 2.52 for ISG and 1.21 for ICBD. Thus, the authors concluded that the use of ICBD criteria may result in over-diagnosis of BS in the UK population.

Disease assessment
Efforts are ongoing for developing a data-driven core set of outcome measures to be used in clinical trials of BS. The OMERACT Vasculitis Working Group reported on the qualitative patient interviews that aimed to understand patients’ perspectives and priorities in order to determine patient-important candidate domains and sub-domains for a Delphi questionnaire and the results of the first round of the Delphi among BS experts and patients that aimed to identify domains, subdomains, and outcomes to be assessed in BS trials (15). The patient interviews were conducted among 20 patients with BS with different types of organ involvement. Several domains/subdomains were identified through these semi-structured interviews and when these were compared to items of the currently-used patient reported outcome measures (PROs) for BS, it was observed that several domains and concepts including work disability, difficulty in eating and drinking, difficulty in concentrating, suicidal ideation, anxiety, feeling judged or pitied by others, and sleep problems were missing from these PROs. For the Delphi exercise, a total of 74 BS experts from a wide range of specialties and 59 patients participated in Round 1. Several domains and subdomains were endorsed by the physicians and/or the patients. The group decided that these should be rated and ranked during the next rounds in order to achieve a reasonable set of instruments to be feasibly addressed in any one study.

Immunopathogenesis
The pathogenesis of BS has not been fully elucidated; however, BS has been mostly considered to be a typical Th1-mediated inflammatory disease, characterised by elevated levels of Th1 cytokines such as IFN-γ, IL-2, and TNF-α. A growing number of studies are reporting that Th17-associated cytokines are increased in BS, giving an important role to the IL17/IL23 in the pathogenesis of the disease. Recently, Deniz et al. have investigated the expression of Th17-related immunity in BS (16); specifically, peripheral blood mononuclear cells from 37 BS patients, and 25 healthy controls (HC) were cultured in Th17-inducing conditions (IL-6, Phytohemagglutinin (PHA), IL-1β, and IL-23) for 6 days. Cultured cells were stained with CD4, CD8, CD3, TCR gamma/delta, CD19, interferon-γ (IFN-γ), and IL-17 antibodies to determine the intracellular cytokine secretion by flow cytometry. The results showed that IL-17 expression by CD4+ and γδ+ T cells was higher in BD compared to HC (p=0.004, p=0.003, respectively). No differences were observed between the groups in the IL-17 production by B cells; moreover, under Th17-inducing conditions, production of IFN-γ by CD4+, CD8+, and γδ+ T cells was also higher in BD compared to HC. Globally, the results suggested that under Th17-stimulating conditions, T cells express both IL-17 and IFN-γ in BD; thus, more promi-
event IL-17 and IFN-γ production by all lymphocyte subsets in BD might be associated with the increased innate responses, early tissue neutrophil infiltrations and late adaptive immunity in BS. Data from other studies seem to suggest that imbalances in the expression of innate immunity as well as Th1- and Th17-related cytokines may play not only a pivotal role in BS pathogenesis but also can be important in disease severity (17). The serum levels of sixteen cytokines related to innate immunity, Th1, Th2 and Th17 cells in the sera of 44 patients with BS and 44 HC have been investigated using the cytokine array technique. Among the cytokines related to innate immunity, the levels of IL-1α, IL-1β, IL-6, IL-12, IL-15 and TNF-α were statistically higher in BS patients than HC. In the case of Th1- and Th17-related cytokines, IL-2, IFN-γ, IL-17 and IL-23 were significantly higher in patients. From Th2-related cytokines, only IL-13 showed statistically higher levels in patients than controls. In addition, the results showed that innate- and Th17-related cytokine were better indicators of cytokines imbalances in BD than each one of the innate- and Th17-related cytokines. Moreover, disease activity score and clinical activity index can also be affected by the levels of pro-inflammatory (IL-6) and anti-inflammatory (IL-4) cytokines. Also Shimizu et al. confirmed that helper Th17 cells in increased in patients with BS (18). They analysed whether T cells preferentially differentiate into Th17 cells in response to various inflammatory cytokines in patients with BS; exogenous IL-23 sustained the higher Th17 cell frequencies of CD4+CD45RO+ T cells after a 2-day culture in vitro in patients with BS, whereas the T cell subpopulation of normal individuals did not respond to IL-23 to sustain/increase Th17 cell frequencies. Another interesting study from Italy was aimed at investigating at mucosal level the T-cell responses from intestinal mucosa of 8 BS patients with early intestinal involvement (19). They isolated T cells from intestinal mucosa of 8 BS patients with intestinal symptoms which started within the previous 6 months, observing that in the early stages of the disease, both Th1 and Th17 cells drive inflammation leading to mucosal damage via abnormal and long-lasting cytokine production as well as via both perforin- and Fas-Fas ligand-mediated cytotoxicity. Moreover, all T cells at the mucosal level were able to produce large amount of TNF-α, perhaps having a therapeutic implication. Among the IL-1 cytokine superfamily, IL-33 plays an important role in inflammation. A recent study was aimed at further investigating serum IL-33 concentration in BS patients (20). The study included 54 BS patients, 31 with active disease, and 18 matched HC. Serum IL-33 levels were measured using an enzyme-linked immunosorbent assay (ELISA) and were significantly higher in patients with BS, particularly in the active stage. Other findings suggest that also IL-32 may play a minor role in the pathogenesis of BS (21), indicating a positive correlation between serum IL-32 levels and BDCAF. Growing interest exists regarding the role of natural killer (NK) cells, one of the major immunoregulatory cell groups of the innate immune system, in BS pathogenesis. Cosan et al. investigated the role of NK cell subsets and their cytokine secretion and cytotoxic activity, evaluating BS patients who had only mucocutaneous involvement and compared them with HC (22). The results of the study showed that although the cytokine secretion pattern was different, no difference was obtained in cytotoxic activity, expression of activatory receptors, or degranulation of NK cells. Further data come from a study by Hasan et al. (23), indicating that both BS activity and azathioprine therapy have significant independent depletive effects on the peripheral blood NK cell compartment. A recent study aimed studying B cell abnormalities in BS patients and the effect of TNF-blocking therapy (24). B cells in blood (n=36) and tissue (n=6) of BS patients were analysed with flow cytometry and/or immunohistochemistry and compared with HC (n=22). The results showed significant deviations in the memory B cell compartment, related to disease activity and therapeutic efficacy. Moreover, pronounced molecular impairments were seen in the fast-responding IgM(+) memory and the mucosal IgA(+) memory B cells. Because of the demonstrated abundance of B cells in affected tissue, the authors hypothesised relocation of memory B cells to the site of inflammation could account for the deviations found in peripheral blood of BS patients. Another interesting contribution to the knowledge of pathogenesis come from a work by Kahraman et al. (25); the study was aimed at exploring the association between circulating LL37 targets plasma extracellular vesicles (EV) to immune cells and disease severity. The results showed that disease activity was correlated with elevated levels of circulating LL37 and EV plasma concentration. Moreover, stimulation of healthy PBMC with active BS patient EVs induced heightened IL1β, IFNγ, IL6 and IP10 secretion compared to healthy and inactive BS EVs. Remarkably, when mixed with LL37, healthy plasma-EVs triggered a robust immune activation replicating the pathology inducing properties of BS EVs. It is well known that BS exhibits more severe disease course and higher mortality among male patients. However, underlying mechanisms of gender differences in clinical manifestations and disease severity are unclear. A recent study aimed at determining whether testosterone (T) has any role on BS pathogenesis (26). The authors studied peripheral blood mononuclear cells (PBMC) and neutrophils of BS patients and controls. Functional assay of neutrophils, cytokine measurements of culture supernatants and gene expressions on both cells were analysed before and after T incubation. Neutrophils were significantly activated after incubation with T in only BS patients. Incubation with T caused significantly elevated interleukin (IL)-12 and IL-2 in BS. The overall results that T seems to alter peripheral blood of BS patients. The peripheral blood of BS patients. Vascular inflammation, endothelial dysfunction and angiogenesis may in part be responsible for the pathogenesis of BS. Among endothelial biomarkers, angiopoietin-1 (Ang-1) is...
considered a recent angiogenic mediator and a recent study assessed Ang-1 in the plasma of BS and HC (27). The plasma level of Ang-1 in BS patients was significantly lower than healthy controls (p=0.005); moreover, plasma Ang-1 level in patients with vascular involvement was significantly lower than those without vascular involvement. Also anti-endothelial cell antibodies (AECA) are found in patients with BS (28). One of the endothelial cell antibodies was reported to recognize alpha-enolase. Kang et al. recently performed a study that aimed at investigating expression of alpha-enolase in the surface of peripheral blood cells and serum anti-alpha-enolase antibody (AEEA), and their association with clinical manifestations or disease activity of BS (29). Cell surface alpha-enolase expression was examined from several cell types of peripheral blood, including lymphocytes, monocytes, and neutrophils using flow cytometry. Moreover, IgG AEA levels were measured by enzyme-linked immunosorbent assay (ELISA) in sera from 110 patients with BS, and age/sex matched 110 HC. The results of the study showed that serum AEA was increased in BS patients and correlated with oral ulcers.

Genetics
A study from the US National Institutes of Health performed a dense genotyping of immune related loci among 1900 Turkish BS patients and 1779 controls using Immunochip. As expected, HLA-B51 conferred the main susceptibility to BS while other associations were also found. IL1A-IL1B, IRF8 and CEPBP-PTPN1 yielded a significant genome wide significance whereas imputation suggested the role of ADO-EGR2. Independent replication in Iranian patients and imputation in the Japanese further accentuated the role of ADO-EGR2 and IRF8 and meta-analysis additionally implicated RIPK2 and LACC1. rs4402765, the lead marker of IL1A-IL1B was associated with decreased IL-1α and increased IL-1β production. ABO non secretor genotypes for two ancestry specific FUT2 single nucleotide polymorphisms also showed strong disease association. These findings extended the list of susceptibility genes shared with Crohn’s disease and leprosy and implicated the role of mucosal factors and the innate immune response to microbial exposure in the pathogenesis of BS (30). Erer et al. tested whether killer immunoglobulin like receptors (KIR) regulated mechanisms contribute to BS by testing for association of KIR3DL1/ KIR3DS1 genotypes with disease in 1799 BS patients and 1710 healthy controls from Turkey. They showed that pathogenic mechanisms associated with HLA-B*51 do not primarily involve differential interactions with KIR3DL1 and KIR3DS1 receptors. They also claimed that they could not exclude a role for other types of KIR variation in the pathogenesis of BS due to the complexity of this locus (31).

Another genetic analysis with the Immunochip platform was performed in the Spanish population. 278 BS cases and 1517 controls were used and an independent replication cohort of 130 BS patients and 600 additional controls were utilised. HLA-B51 again showed the strongest association. HLA-B57 and HLA-A*03 were also independent markers. The amino acid model that explained the HLA class I associations included the position 97 of the HLA-B molecule and the position 66 of HLA-A. Non HLA loci were also implicated such as IL23R, JRKL/CNTN5 and IL12A (32).

Wilson et al. from the UK used literature mining techniques combined with various computational methodologies to identify the most likely regulation aspects that dictate gene activity, biological processes and disease pathways pertinent to BS. Their approach determined 247 genes, an amazing number, associated with BS and further analysis showed the ways how these genes may have affected the innate and immune responses. Additional algorithms identified potential therapeutic strategies such as NOD2, ICOS and IL18 signaling (33).

A Japanese group conducted a literature survey with the aim of determining the relationship between HLA-B51 and ocular involvement in BS. Eighteen articles written in English were reviewed. HLA-B51 was correlated with ocular lesions in the entire cohort of the reviewed articles (OR=1.76, p=0.000057). The correlation tended to become more prominent towards the east as can be seen from the odds ratios of the East-Eurasian, Middle-Eurasian and West-Eurasian populations (2.40 p=0.0030, 1.87 p=0.0045 and 1.28 p=0.35) (34).

Two Korean, two Chinese and one Turkish group explored the role of various microRNAs in the pathogenesis of BS. The first investigated the role of micro-RNA-155 on the regulation of the Th17 immune response (35). Forty-six BS patients and 23 healthy volunteers were used. They showed that microRNA-155 regulated the Th17 immune response by targeting Ets-1. Suppression of this micro RNA reduced the amount of pathogenic IL-17 expressing T cells. The authors suggested that this pathway could be the target of a new therapeutic strategy (35). Another Korean group studied the role of distinct microRNAs in the production of TNF-α and IL-6 in 21 patients with BS (10 stable and 11 active) and 8 controls (36). The levels of miR-638 and miR-4488 were reduced in patients with stable BS compared to healthy controls. The expression of miR-3591-3P increased in patients with active BS compared to the ones with stable BS. Transfection of miR-638 and miR-4488 inhibitors, together with miR-3591-3p mimics, increased IL-6 mRNA levels (36). A Chinese group investigated the association and functional roles of copy number variants (CNV) of several miRNAs in patients with BS and Vogt-Koyanagi-Harada syndrome (VKH) (37). No association of CNV of miR-23a, miR-146a and miR-301a was observed in BS patients while a significant relationship was found in VKH patients (37). Zou et al. studied the expression levels of 4 microRNAs in a group of patients with BS who had intestinal involvement (38). miR-196a2 was significantly decreased in BS patients who had an active intestinal ulceration compared to healthy controls. Moreover, the level of mRNA ho-1 was reduced. Levels of IFN-γ, IL-17, IL-10, IL-1β, and TNF-α were higher in patients with active intestinal
BS than those in healthy controls. This suggested that down regulated miR-196a2 may be involved in intestinal BS pathogenesis by targeting Bach1/ho-1 (38). Üğurel et al. studied the expression levels of complexin 1 (CPLX1) and miR-185, a target miRNA for CPLX1, after the recent identification of a CPLX1 polymorphism in BS patients (39). Twenty eight patients with neurological involvement, 28 without neurological involvement and 30 normal controls were used. PBMC expression levels of CPLX1 were significantly increased in BS with neurological involvement. The levels of miR-185 however, was reduced in both patient groups. They thought that CPLX1 had a proinflammatory action (39).

A Spanish group investigated the susceptibility of the functional variant R620W of the protein tyrosine phosphatase non receptor-22 (PTPN22) to BS in a Spanish cohort of 404 BS patients and 1,517 healthy controls. rs2488457 and several other single nucleotide polymorphisms were studied and a meta-analysis was performed. The results did not support a major role of the PTPN22 gene in BS (40).

In line with the previous GWAS studies, Qin et al. investigated the IL-23 receptor and the IL23R-IL12RB2 regions for potential genetic associations in 407 patients with BS and 421 healthy controls in a Chinese Han population (41). The SNP’s rs924080 and rs11209032 were studied. Both were related to the IL23R-IL12RB2 region and showed significant associations with BS (41).

Woo et al. analysed the differential expression of transcription factors which play a role in the production of TNF-α and IL-6 in 42 patients with BS (22 active and 20 stable) and 10 healthy controls (HC) (42). The transcript level of CCAAT-enhancer binding proteins (C/EBP) β was increased in PBMC’s of patients with active BS compared to the stable ones. The C/EBP δ transcript level was higher in active BS compared to HS. Activating transcription factor 3 (ATF3) was increased in stable BS compared to HC’s. The authors concluded that there was a differential expression of C/EBP β, C/EBP δ and ATF3 depending on disease activity (42).

A GWAS performed in 623 BS patients and 1074 controls in a Chinese Han population, evaluated the relationship between REL and PRKCQ genes and the susceptibility to BS (43). Three SNP’s of the REL gene (rs13031237, rs702873 and rs842647) and three of the PRKCQ gene (rs4750316, rs11258747, rs947474) were studied. rs842647 GG and rs842647 G were higher in patients compared to controls and rs842647 AG were lower in the patients than in controls. No statistically significant difference in the frequencies of rs702873, rs13031237, rs4750316, rs11258747 and rs947474 were observed between BS patients and controls. REL rs842647 polymorphism was associated with skin lesions. The conclusion was that REL rs842647 polymorphism was probably a susceptibility factor for BS and skin lesions, acting through the NF-kappa B pathway (43).

Göktaş et al. from Turkey investigated the cytochrome P450 enzyme CY-P2C19 levels and its polymorphisms in 59 patients with BS and 27 HC based on the hypothesis that alterations in cytochrome P450 enzyme activity may result in substances that may cause auto-immunity (44). They used lansoprazole 30 mg as a probe drug and additionally genotyped CYP2C19*2,*3 and 17 polymorphisms. They found that patients with BS had lower CY-P2C19 enzyme activity and a lower frequency of the CYP2C19*17 allele compared to normal controls, factors that may influence the immunological environment (44).

Hu et al. intended to identify a new biomarker for the diagnosis of BS using a microarray approach (45). They studied 40 BS patients, 5 patients with Takayasu arteritis, 5 with ANCA associated vasculitis and 5 with Sjögren’s syndrome along with 110 healthy controls. They validated CTDP1 (RNA polymerase II subunit A C-terminal domain phosphatase) as a BS-specific autoantigen (45).

Xu et al. performed a meta-analysis to investigate the association of IL-6, IL-12 and IL-18 gene polymorphisms in BS (46). Thirteen articles were utilised for the analysis. A significant association was observed for the dominant model for IL-6 rs1800795 and BS risk in four studies using 420 cases and 481 controls. The same association was discovered for IL-12B rs3212227 in another four publications (1088 cases and 1910 controls). AA genotypes of the IL-18 rs1946518 and the pooled AC vs. CC, AA+AC vs. CC and AA vs. AC+CC genotypes of the same gene showed a significant association with BS in five studies with 553 cases and 632 controls. IL-18 rs187238 did not show any significant association (46).

Ohnishi et al. from Japan reported a family with two members who had arthritis, fever of unknown origin, intestinal ulceration and oral and genital ulcers who had the TNFAIP3 mutation, originally described by Zhou et al. (47) but their juvenile onset, symmetrical synovitis of the carpal bones in both hands and skin lesions such as acrokeratoderma casts doubt on the diagnosis of BS (48).

Yamashita et al. reported a case with recurrent oral apthae, acne, erythema nodosum and recurrent epididymitis who had a heterozygous novel MEVF variant Q311H in exon 2 of the MEVF gene. To determine its relation to epididymitis needs further work (49).

Polymorphism studies conducted in small numbers of patients and controls showed associations with vitamin D receptor genes (50), TNF-α-857C and 238 a alleles (51), IL-8 gene polymorphisms (52), IL-17A gene polymorphisms in intestinal BS (53) and HLA-G 14b insertion/deletion polymorphism in Tunisians (54). These studies lacked power required for a sound analysis.

**Clinical manifestations**

**Eye involvement**

Horie et al. performed a meta-analysis to assess whether there is an association between HLA-B51 and the ocular manifestations of BS among various ethnic groups (55). The meta-analysis which included 18 articles, showed that there was a strong association between HLA-B51 expression and ocular involvement in reports originating from Middle and Far East. On the other hand, studies from North Africa and Europe showed no association.

Accorinti et al. investigated demo-
graphic and clinical trends of 385 patients with uveitis due to BS seen over 44 years in a referral unit at Sapienza University in Rome, Italy (56). The cohort was divided into cohort 1 (seen from 1968 to 1992), and cohort 2 (seen from 1993 to 2011). Compared to older cohort, in the recent cohort, there were more female patients, more patients with milder disease (more frequent isolated anterior uveitis, less frequent hypopyon) and more immunosuppressive use. Ocular complications such as optic atrophy, maculopathy and retinal neovascularisation, and retinal detachment were significantly more common in the older cohort. The visual acuity at final evaluation was better in the recent cohort. Through the whole cohort, males had signs of more severe disease (early onset, more complications and worse vision). These not surprising findings suggest that early and aggressive treatment may decrease rates of ocular complications and improve the outcome.

Tugal-Tutkun et al. systematically reviewed the use of multimodal imaging in Behçet uveitis (BU) (57). Authors suggest that multimodal imaging using color fundus photography, fluorescein angiography (FA), and optical coherence tomography (OCT) is essential in visualising diagnostic features, detecting structural changes, and monitoring disease activity and response to treatment, they also emphasise that FA is still the gold standard. Moreover, Khairallah et al. studied 44 eyes of 25 patients with BU having posterior segment involvement and found that OCT angiography was better than FA in identifying perifoveal microvascular abnormalities (58).

Laser flare photometry seems to be an alternative as a non-invasive and quantitative method to measure flare values. Yalcindag et al. evaluated the association between intraocular inflammation and laser flare photometry measurements in 78 eyes of 45 patients with BU and 50 healthy controls (59). Among the 78 eyes with BU, 58 eyes had active inflammation and 20 were in remission. Those with active inflammation had higher flare intensity. The flare levels were found to be higher in both BS groups compared with the values of healthy controls. Authors suggested that laser flare photometry may also be helpful in monitoring subclinical inflammation.

Vascular involvement

Seyahi and Yazici suggested that vascular disease is one of the several disease clusters in BS (60). In the vascular disease cluster, several types of vascular involvement may accumulate in the same individual. These may occur at once or step by step with each relapse. Lower extremity vein thrombosis (LEVT) is often present in these vascular clusters and may even precede other types of vascular involvement. Additionally, significant correlations exist between cerebral venous sinus thrombosis (CVST) and pulmonary artery involvement (PAI), intracardiac thrombi and PAI, Budd-Chiari syndrome (BCS), and inferior vena cava syndrome. PAI can manifest as pulmonary artery aneurysms (PAAs) or pulmonary artery thrombosis (PAT) (61). Haemoptysis along with other pulmonary symptoms (dyspnea, coughing, pleuretic chest pain) is the major and initial symptom of PAI. Haemoptysis could also be due to bronchial artery enlargement (BAE) in BS patients with PAI. In the latest survey of the Cerrahpasa group 47 BS patients with PAI, among the 35 patients who survived after a mean of 7 years, 8 continued to have recurrent small bouts of haemoptysis although there were no signs of active PAI such as increased acute phase response and PAAs or PAT images in the current thorax CT scans (61). Recently, Esatoglu et al. looked in more detail at the outcome and management of such patients (62). They identified 118 patients (111 M/7 F) diagnosed as having PAI (PAAs, PAT or the combination of PAAs and PAT). Among them, 9 had recurrent bouts of haemoptysis during follow-up, which could not be explained by a PAI relapse. All patients received immunosuppressive treatment and BAE was observed after a median of 9 years of follow-up. Six patients underwent embolisation of the bronchial arteries. There were more female patients who underwent embolisation, one died due to right heart failure as a complication of pulmonary hypertension and two experienced complications associated with the procedure, such as stroke and pulmonary infarction. Of the three patients who were followed without embolisation, one died due to massive bleeding from internal mammary artery. In conclusion, it should be remembered that haemoptysis during follow-up of a BS patient with PAI may be also related to BAE. Embolisation of the bronchial arteries even though carrying some serious risks, appears to be a valuable method of management.

Scientists from Peking Union Medical College, China, retrospectively analysed the clinical features of 21 patients (10 M/11 F; mean age 30.3±9.5) with CVST (63). Eighteen developed neurologic manifestations after a mean of 47.6 months. The major symptom was headache and intracranial hypertension. Transverse and superior sagittal sinus thrombosis along with hepatic vein thrombosis and the outcome is severe.

Thrombosis

Recent advances may help us understand why venous involvement in BS responds better to immunosuppressive treatment rather than anticoagulation. Becatti et al. in a pioneering study, examined whether neutrophil activation can lead to thrombosis by affecting fibrinogen modifications and whether there is a link between immune cell activation and thrombosis (66). Fibrinogen function and structure, fibrin susceptibility to plasmin-lysis, plasma redox status and leukocyte oxidative
stress markers are studied from the blood samples of 98 BS patients and 70 age and gender matched healthy controls. They found that thrombin-catalysed fibrin formation and fibrin susceptibility to plasmin induced lysis were significantly impaired in BS patients. These findings were associated with an increased plasma oxidative stress markers and carboxylation of fibrinogen. Neutrophils displayed an enhanced NADPH oxidase activity and increased reactive oxygen species production, which significantly correlated with fibrinogen clotting ability. Authors concluded that altered fibrinogen structure and impaired fibrinogen function are associated with neutrophil activation.

Atherosclerosis
The Cerrahpasa group reported that atherosclerosis was not appreciably increased in BS (67). Reasons for this assumption were summarised as: a. BS predominantly affects veins rather than arteries; b. The disease activity decreases in the majority of patients with the passage of time (68); c. contrary to what is observed in other chronic inflammatory diseases like RA and SLE, the increased mortality decreases with time (68); d) coronary calcification scores are not appreciably increased among patients with severe vascular disease (69); e) in a controlled study among BS, rheumatoid arthritis (RA), and ankylosing spondylitis patients and healthy controls, it was only among the RA patients that coronary atherosclerotic plaques and IMT were increased (67) and finally, f) in a controlled study, the frequencies of angina pectoris and myocardial infarction were not increased among BS patients compared to age and gender matched controls (70).

Yolbas et al. investigated carotid intima-media thickness (cIMT) and carotid artery stiffness among BS (n=49) patients, RA (n=64) patients and healthy controls (n=40) (71). When compared to the healthy controls, the mean cIMT was significantly higher only in the RA group. The CAS indices were similar across the study groups. Similar to that found in previous studies (67), results of the current study suggest that sub-clinical atherosclerotic markers such as arterial stiffness and increase in the cIMT are not features of BS.

A group from Sheba Medical Center, Tel-Hashomer, Israel, compared the frequency of ischaemic heart disease (IHD) among registered BS patients to that observed in a healthcare system population (72). A case-control study among 871 BS patients and 4,439 age- and gender-matched controls, revealed that the frequency of IHD amongst BS patients was almost similar compared with controls (11% vs. 8%, respectively); however the difference was found to be significant (p<0.001). BS patients with IHD were more likely to be male and younger than 70 years old.

Nervous system involvement
Bitik et al. observed that parenchymal neurological involvement (NBS) was preceded by posterior uveitis (PU) and investigated whether there was such a relationship in 30 BS patients with parenchymal NBS compared to 265 BS patients without (73). Patients with PU were found to be more likely to be associated with parenchymal NBS (63%) compared to those without (31%) (p<0.001). The frequency of PU was 21% and 22% among those with dural sinus thrombosis and vascular involvement, respectively.

Gastrointestinal involvement
It has always been difficult to distinguish Crohn’s disease (CD) from BS (75), since the two entities share a similar clinical picture and radiological features. Zhang et al. in a retrospective study described parameters useful to discern intestinal BS from CD and tried to build a statistical model accordingly (75). They studied 42 BS patients and 97 CD patients. The statistical model which included clinical, endoscopic and radiological parameters had quite high sensitivity and specificity values.

Audio-vestibular complications
Sota et al. at the frequency of sensorineural hearing loss (SNHL) defined as a deflection of at least 25 dB on pure-tone audiometry in 44 BS patients (76). SNHL was found in 28 (63%) patients and seemed to be associated with joint disease. Unfortunately this study had no control group.

Pregnancy complications
Yilmaz et al. investigated whether BS had any effect on the first and second trimester amniocentesis screening tests that are associated with Down syndrome risk and some of the pregnancy complications (77). They studied maternal serum levels of free beta-human chorionic gonadotropin, pregnancy-associated plasma protein-A, alpha fetoprotein and unconjugated estriol and fetal nuchal translucency by ultrasonography in 32 pregnant women with BS and 60 healthy pregnant women and found no significant difference. However, the sample size of the study is too small to detect an increased risk for Down syndrome or other perinatal adverse events.

Allergy
Horie et al. conducted a nationwide survey in Japan to investigate the prevalence of allergic diseases in patients who have BS (78). The authors studied 353 (255 M/98 F) patients with BS from 21 institutes of ophthalmology and found that 21% had histories of allergic diseases. This was lower than that found in a national survey conducted among the healthy population (48%) (OR: 0.29, 95% CI: 0.22–0.38).

Associations with other diseases
The co-existence of BS and FMF had been reported in several studies. Watad A et al. investigated whether there is an association between these two entities by using databases of a large health service organisation in Israel (79). In this database, the diagnoses of FMF and BS are based on data derived from hospital and primary care physicians’ clinical records. From this database, 892 BS patients were compared to age- and sex-matched 4444 controls without BS and frequency of FMF in patients with BS was found to be significantly increased in BS patients (6% vs. 0.23%, respectively, p=0.001). The study was not corrected for multiple testing. Interestingly, a multivariate regression analysis showed that this association was stronger among females, patients of Arab ethnicity and those with BMI.
>30. The main limitation of this study seems to be that the diagnoses are validated by the healthcare system, rather than the authors themselves.

**Reviews**

Comprehensive reviews focusing on general clinical findings (80, 81), recent epidemiological data (82), ocular involvement (83), vascular involvement (84) and neurological involvement (85) have been published. Additionally, one editorial criticising recent studies associated with pathogenesis was also published (86).

**Management**

Anti-TNF agents continue to be the key biologics for the treatment of various manifestations of BS (87). On the other hand, the biologic treatment spectrum seems to widen with newer agents such as IL-1 inhibitors and ustekinumab. Because of its multisystem nature various specialties are involved in the management of BS and this may lead to differences in therapy. The differences between rheumatologists and ophthalmologists in treating ocular involvement of BS has been recently assessed in a survey (88). An e-mail questionnaire containing the hypothetical case of a 45-year old male BS patient with a history of 3 episodes of retinal vasculitis and impaired visual acuity was sent to 852 rheumatologists and 934 ophthalmologists. Although the overall response rate was low (7.4%) there were considerable differences between both specialties. The most commonly first line therapy chosen was a biologic agent in both specialties. Methotrexate and azathioprine were chosen significantly more often as first line therapies by rheumatologists compared to ophthalmologists. The choice of an anti-TNF factor agent increased in both specialties when cost and prior authorisation issues were removed.

A retrospective study assessed adherence to EULAR 2008 BS treatment recommendations in 2 outpatient clinics in New York and Amsterdam by reviewing the records of 474 BS patients (89). The authors initially created a checklist based upon EULAR 2008 recommendations and categorised the recorded events of the patients according to their occurrence prior or after the publication of EULAR recommendations. The results showed substantial variation across different BS manifestations which was most remarkable in the treatment of eye disease and arthritides. These results suggest that the 2008 EULAR guidelines are not in line with current treatment practices which rely on the more frequent use of biologic agents. It is to be mentioned that an updated version of EULAR recommendations for BS has been already prepared and is expected to be published soon.

Adalimumab is now approved for the treatment of non-infectious intermediate uveitis, posterior uveitis and panuveitis in many countries worldwide based on the results of 2 double blind, placebo controlled multinational Phase III studies (90, 91). In both trials the patients received adalimumab at an initial dose of 80 mg followed by 40 mg every other week starting 1 week after the initial dose or placebo until treatment failure or the completion of 80 weeks treatment. Idiopathic uveitis, Birdshot chorioretinopathy and Vogt-Koyanagi-Harada made up the majority of patients in both trials and the percentage of BS patients enrolled in both trials was around 7%. The first trial (VISUAL I) studied patients having active uveitis despite treatment with corticosteroids for at least 2 weeks. Adalimumab significantly reduced the risk of treatment failure (primary outcome) compared to placebo (median time to treatment failure for adalimumab: 24 weeks, for placebo: 13 weeks). The second trial (VISUAL II) enrolled patients with inactive disease controlled by oral prednisolone 10-35 mg/day. Prednisolone dose was tapered starting at week 2 until week 17. Time to treatment failure was significantly better in the adalimumab group (median >18 months) compared to placebo group (median 8.3 months). Treatment failure occurred in 55% in the placebo group compared to 39% in the adalimumab group. The power of both studies does not allow to make a straightforward conclusion for BS patients but these results show a significant effect of adalimumab over placebo in reducing the risk of flare in patients with active or inactive uveitis following withdrawal of corticosteroid therapy.

A retrospective multicentre study reported the short (12 weeks) and long (24 months) term outcome of 100 patients treated with adalimumab for different manifestations of BS such as ocular, mucocutaneous, vascular, gastrointestinal and articular involvement (92). Previous treatments consisted of biologic agents (anti-TNF agents, rituximab, tocilizumab, anakinra) in 26 patients and conventional immunosuppressives in 69 patients. During treatment with adalimumab 36 patients used concomitant conventional immunosuppressives and 71 patients used corticosteroids. Clinical efficacy of adalimumab was evident in 81 patients at week 12 and 67 patients were still continuing to use adalimumab at month 24. Combination therapy with immunosuppressives was not judged to be superior to adalimumab monotherapy. The same group also reported good efficacy of adalimumab on the uveitis of BS in a separate retrospective study (93). A retrospective multicentre study from Spain reported 124 BS patients with uveitis treated with either adalimumab or infliximab (94). The majority (95%) of the patients responded successfully to these agents and only 7 patients had to be switched to another biologic agent (golimumab = 4 patients, tocilizumab = 2 patients, rituximab = 1 patient). The response to these agents was also satisfactory during a mean follow-up of 12 months. A retrospective study assessed the efficacy of infliximab in 16 patients with parenchymal CNS involvement who had at least two neurologic attacks during a median treatment of 20 months with conventional immunosuppressives (95). These patients initially received 1 gm methylprednisolone boluses for 7 to 10 consecutive days followed by infliximab 5 mg/kg at weeks 0, 2 and 6 and then every 8 weeks. Infliximab was given as monotherapy to 5 patients and in combination with azathioprine and/or prednisolone to 11 patients. One patient developed pulmonary and CNS tuberculosis at the second month of infliximab treatment and was excluded from the analyses (the study protocol mandated the use of infliximab for at
least 12 months). During a median treatment of 39 months (range 16-105 months) with infliximab, no neurologic attacks were seen in any of the patients. Disability measured by Expanded Disability Status Scale modified for Neuro-Behçet Syndrome (EDSS-NBS) was stable in 11 patients and improved in 4. No gadolinium enhancing lesions were detected in the brain MRIs that were performed during infliximab treatment. Only 1 patient who was urinary catheter dependent discontinued infliximab at the 47th month because of recurrent urinary infection. The results of this study suggest that infliximab might be a good option for patients with parenchymal CNS involvement who relapse under conventional immunosuppressives. The retrospective design of this study is surely a limitation but the long (8 years) recruitment period of these patients underlines the difficulty in conducting properly designed controlled trials for major organ involvements of BS.

A retrospective study examined the timing of initiation of infliximab for uveitis of BS. The results suggest that early treatment of uveitis with infliximab is more effective in maintaining visual acuity and reducing background vascular leakage (96). The study consisted of a total of 13 BS patients with uveitis treated with infliximab for 24 months. The duration of uveitis was less than 18 months (mean 15 months) in 6 patients and more than 18 months (mean 89 months) in the remaining 7 patients. Infliximab significantly decreased the frequency of ocular attacks in both groups with no statistical difference between them. The retinal and disc vascular leakage scores also decreased significantly in both groups but this was more pronounced among patients receiving infliximab early. The baseline visual outcome was better among patients with shorter duration of uveitis and this difference was preserved throughout the study. Because of the small number of the patients these encouraging results warrant further studies.

Despite the lack of controlled trials interferon-alpha is recommended for the treatment of refractory and severe uveitis of BS due its prompt and remarkable efficacy as well as the long-lasting remissions following its withdrawal (97, 98). A retrospective study from France assessed the long-term efficacy of interferon-alpha (IFN-α2a or IFN-α2b) in the treatment of severe uveitis of BS - defined as uveitis refractory to at least one conventional immunosuppressive drug and/or requiring intermediate doses of more than 10 mg/day oral corticosteroids (99). The main outcome measure was the number of relapses before, under, and after the discontinuation of IFN-alpha. The mean duration of IFN treatment (3 million units (MU) 3 times a week which was increased to 6 MU 3 times a week in case of insufficient response) was 54 months. The response to IFN treatment was 81% (31 of 36 patients). The mean frequency of uveitis relapses was significantly reduced from 1.39 person years before interferon and to 0.05 person years during interferon treatment. Twenty-one patients (58%) could discontinue IFN treatment and 81% of them never relapsed during 5 years following withdrawal. In the remaining 19% relapses responded to re-introduction of IFN. The visual acuity either improved or remained stable in 89% of the eyes during the entire study period. In line with previous reports from uncontrolled studies these results also support the value of IFN-alpha in the treatment of severe uveitis of BS. As suggested by the authors of this paper, further studies need to be undertaken to assess the efficacy of IFN-alpha as a first line treatment in the treatment of BS uveitis.

A retrospective study from Turkey compared 23 BS patients receiving aza-thioprine and cyclosporine combination with 16 patients on IFN-α-2a treatment after failure of combination therapy with conventional immunosuppressives (100). The mean number of uveitis attacks significantly decreased with the introduction of IFN and became similar to that of patients responding to conventional immunosuppressives indicating the potent effect of IFN in the treatment resistant uveitis of BS.

The efficacy of ustekinumab – a monoclonal antibody against IL-12 and IL-23 – was assessed in an open pilot study (101). Fourteen patients having at least one oral ulcer within 28 days before inclusion and at least 2 oral ulcers at the time of inclusion despite colchicine treatment were studied. Patients received subcutaneous injections of ustekinumab 90 mg at weeks 0, 4 and every 12 weeks (in 3 patients the dose was given as 45 mg because of lighter body weight). The median number of oral ulcers was 2 at baseline and dropped to 1 at week 12. Nine patients (69%) were free from ulcers at week 12 (complete response, primary outcome). Genital ulcers were present in 4 patients at baseline and in 1 patient at week 12. The median follow-up time was 7 months and 10 patients (71%) were still continuing ustekinumab. Four patients had to stop treatment either because of adverse effect (headache in 1 patient) or because of partial response or relapse (3 patients). For now it is too early to make any conclusions about the place of ustekinumab in the treatment of BS especially for the more serious manifestations.

Anti-IL1 agents appear to be a promising option in the treatment of BS with their good safety profile when considering the lack of tuberculosis reactivation as reported in a case report (102). A multicentre, retrospective study from Italy evaluated the efficacy of anakinra and canakinumab in 19 BS with uveitis (103). Thirteen patients (68%) received anakinra and 6 received canakinumab. In 7 patients (37%) IL-1 inhibition was the first line biologic whereas the remaining 12 had received other biologics before. Treatment with IL-1 inhibition significantly suppressed ocular attacks during the 12 months study period compared to 12 months before IL-1 inhibition. The number of eyes with retinal vascular involvement also decreased during the treatment period compared to pretreatment period. Anti-IL1 treatment was terminated early in 5 patients (4 anakinra, 1 canakinumab) because of lack or loss of efficacy. The safety profile was satisfactory and no serious adverse events occurred. However, it is too early to speculate on the efficacy of these agents on ocular involvement when remembering the failure of gevokizumab (another anti IL-1 antibody) in a phase III trial for ocular involvement of BS which was summarised in last year’s review (104).


13. OMERACT


27. HOŘE Y, MEGURO A, ORTA T et al.: HLA-B51 Carriers are susceptible to ocular symptoms of Behçet’s Disease and the association between the two becomes stronger towards the East along the Silk Road: a literature survey. *Ocul Immunol Inflamm* 2017; 25: 37-40.


