Review

One year in review 2021: Behçet's syndrome

G. Hatemi[1], E. Seyahi[1], I. Fresko[1], R. Talarico[2], D. Uçar[3], V. Hamuryudan[1]

[1]Division of Rheumatology, Department of Internal Medicine, and Behçet's Disease Research Centre, Istanbul University-Cerrahpasa, School of Medicine, Istanbul, Turkey; [2]Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Italy; [3]Division of Ophthalmology, and Behçet's Disease Research Centre, Istanbul University-Cerrahpasa, School of Medicine, Istanbul, Turkey.

Gulen Hatemi, MD
Emire Seyahi, MD
Izzet Fresko, MD
Rosaria Talarico, MD
Didar Uçar, MD
Vedat Hamuryudan, MD

Please address correspondence to:
Vedat Hamuryudan,
Division of Rheumatology,
Department of Internal Medicine,
Istanbul University-Cerrahpasa,
School of Medicine,
34750 Istanbul, Turkey.
E-mail: vhamuryudan@yahoo.com

Received on May 21, 2021; accepted in revised form on July 14, 2021.

Clin Exp Rheumatol 2021; 39 (Suppl. 132): S3-S13.

Key words: Behçet's syndrome, epidemiology, pathogenesis, outcome assessment, clinical findings, management

Competing interests: G. Hatemi has received research grant from Celgene, honoraria consulting or speaker fees from AbbVie, Amgen, Celgene, Lilly, Novartis and UCB Pharma. E. Seyahi has received honoraria from Novartis, Pfizer, AbbVie and Gilead. D. Uçar has received honoraria from AbbVie. V. Hamuryudan has received speaker fees and honoraria from Amgen, AbbVie, Celltrion, MSD, Johnson & Johnson, Gilead, Pfizer, Lilly and UCB Pharma. The other co-authors have declared no competing interests.

ABSTRACT

This review aims to provide a critical digest of the recent studies that enhance our understanding of Behçet's syndrome by evaluating time trends, differences in disease course between men and women, and between patients with an early and late disease onset, progress in disease assessment, novel findings on immunopathogenesis and genetics, clinical features and differential diagnosis of eye, vascular, nervous system and gastrointestinal system involvement, and new data on treatment modalities including TNF-alpha, IL-17 and IL-6 inhibitors, tofacitinib, and apremilast, as well as surgical interventions.

Introduction

Behçet's syndrome (BS) is classified as a variable vessel vasculitis based on inflammation of arteries and veins of all sizes. It is a complex condition of heterogeneous nature that manifests with recurrent skin and mucosa lesions in the majority of the patients, and additionally with arthritis, uveitis, vascular, neurologic, and gastrointestinal involvement with varying frequencies in different parts of the world. In this review, we aimed to present a critical digest of the recent studies highlighting the epidemiology, disease assessment, pathogenesis, clinical findings, and treatment of BS, as in the previous years (1, 2). We searched PubMed for manuscripts on BS published in English between January 1st and December 31st, 2020 and selected the most relevant ones for this review.

Epidemiology

A number of studies on incidence, prevalence, time trends, differences in disease characteristics between men and women, and between patients with early and late disease onset were published last year.

Although BS is classically known to be more prevalent along the ancient Silk Route, most of the previous epidemiologic studies had come from the beginning and end of this route with little data on the prevalence in countries along the middle of the Silk Route. This year there was one study from Mongolia and another from Kazakhstan (3, 4). The study from Mongolia provided an estimated prevalence of 2.4 per 100,000 population, acknowledging that milder patients may be missing from this study which was conducted in secondary and tertiary centres (3). Demographic features and frequency of each clinical manifestation were in general similar to that in other Behçet's cohorts. Interestingly 55.4% of the patients had ulcers in their nasal mucosa, which was considered to be associated with extreme temperature conditions and the dust in Mongolia.

The study from Kazakhstan was not a formal prevalence study, but an extrapolation based on the HLA B51 positivity in the general population (4). They found an allelic HLA B51 frequency of 8.14% and carrier rate of 15.28% and speculated that the prevalence of BS in Kazakhstan would be at least 10-15 per 100,000 population. Prevalence of BS in a population is thought to be associated with the frequency of HLA B51 in the general population, although there are no formal studies showing a linear correlation. Environmental factors are also thought to play role in BS pathogenesis and it would be interesting to see a formal prevalence study from Kazakhstan.

There is little data on BS from South America. A recent study from Colombia reported on 523 patients with BS syndrome who were registered to the Ministry of Health registry between 2012 and 2106 (5). The estimated prevalence was 1.10 per 100,000 among individuals over the age of 18. Prevalence was highest among the 45-

49 years age group. The women to men ratio was 2.2 to 1.

A vasculitis registry from Portugal including patients from 13 centres showed that BS is the most common vasculitis in this registry (298/687, 42.5%), despite the longest diagnostic delay (82.5±110.1 months) (6). The authors suggest that a new prevalence study of BS in Portugal is warranted, as the 2 previous prevalence studies showing 1.5 per 100,000 in 1991 (7) and 2.4 per 100,000 in 1997 (8) may not be reflecting the true prevalence.

Another study suggesting a higher prevalence than previously thought came from the United Kingdom (9). This study was based on a large primary care database and showed a prevalence of 14.6 per 100,000 population, much higher than the previous prevalence study from the United Kingdom showing 0.64 per 100,000 (10). The authors point out that more patients with BS were additionally coded as stroke/transient ischaemic attacks, vein thrombosis, and pulmonary emboli compared to age and gender-matched randomly selected controls from the general population. Most of these events had occurred before a diagnosis of BS, and at a quite early age. However, the likely possibility that the stroke/transient ischaemic attack codes may be due to nervous system involvement of BS and the pulmonary emboli codes may be due to the *in situ* pulmonary artery thrombosis of BS, were overlooked.

A study from Egypt challenged the contention that BS runs a more severe course among men (11). Medical files of 255 BS patients (85% men) who were admitted to the rheumatology departments of Cairo University and Tanta University between 2002 and 2018 were retrospectively analysed. Papulopustular lesions and vascular involvement were more common among men, while pathergy positivity and parenchymal central nervous system involvement were more common among women. The frequency of severe disease according to Krause's severity score, intravenous methylprednisolone, immunosuppressive or biologic use, and organ damage including blindness were similar among men and women. In addition to the possibility of a real geographic difference regarding an equally severe disease among women with BS, these results may be biased by the fact that this was a hospital-based study, and all participants, independent of their sex, may be severe patients.

A study that assessed disease manifestations according to the age of onset and gender among 489 patients came from China (12). Eye involvement, vascular involvement, pseudofolliculitis, and pathergy positivity were more common among men, while genital ulcers were more common among women. A stratified analysis according to age showed that eye involvement was more common among men between the age of 20 and 30, vascular lesions between the age of 30 and 40, and genital ulcers were more common among women between the age of 30 and 40. The difference between genders disappeared after these ages. Overall, vascular and gastrointestinal involvement were relatively late manifestations, which were more common after the age of 40. It should be noted that all data regarding manifestations were those recorded at the time of registration to the database and there was no follow-up.

Two studies reported changes in disease manifestations over time. A retrospective study from Tunisia evaluated the change over time in the disease phenotype of their patients with BS by comparing the 147 patients who were registered between the years 1995 and 2005, with 99 patients registered between 2006 and 2017 in a University Hospital (13). All patients fulfilled ISG criteria. The proportion of men and women and HLA B51 positivity were similar in the earlier and latter cohorts. They observed a decrease in the frequency of genital ulcers, erythema nodosum, joint involvement and pathergy positivity over time. The frequency of eye involvement did not change, but there were fewer patients with posterior uveitis and blindness, with better visual acuity in the latter cohort.

The study from South Korea utilised data from a rare intractable disease and a claims database to see the change in incidence and mortality of BS over 3 time periods between 2004-2006, 2007-2010, and 2011-2017 (14). They observed a decrease in yearly incidence from 8.15 per 100,000 in 2004 to 1.51 in 2017. This decrease was more prominent among women and among patients in their 40'ies. There are several clues from basic and clinical studies on the role of infections in the pathogenesis of BS (15). The authors also suggest that the decrease in incidence may be associated with a decrease in infections and improvement of oral health in South Korea. On the other hand, the standardised mortality rates increased from 1.04 between 2004-2006, to 1.14 between 2011-2017. The authors speculate that the increase in mortality despite a decrease in incidence shows that the incidence of patients with mild disease decreased more than patients with severe manifestations. However, the causes of death and data on the change of disease manifestations over the years were not provided. These findings are in contrast with previous studies suggesting a milder disease course and better prognosis in more recent years, especially for eye involvement.

Take home messages

- Data from a vasculitis registry from Portugal and a primary care database from UK, suggested a higher prevalence of BS than previously reported from these countries (6, 9).
- A study from Egypt suggested that BS has a more severe course among men (11).
- A study from Tunisia showed a decrease in the proportion of BS patients who became blind over the decades from 1995 to 2007 (13).
- A study from Korea showed an increase in mortality despite a decrease in incidence over three-time intervals between 2004 and 2017 (14).

Disease assessment

The need for validated, reliable, and widely used outcome measures for BS trials have led to the development of a core set of domains by a large group of experts from different disciplines through a multi-stage project, and finally endorsement by OMERACT (16). The domain set included 5 domains that are mandatory for all trials, as well

as sub-domains that are mandatory for studies of specific organs or systems. The mandatory domains for all studies were disease activity, new organ involvement, quality of life, adverse events, and death. The final aim of this ongoing project is to develop a core set of outcome measures that match these domains, in order to harmonise studies and enable to compare their findings.

Take home message

- The recently developed core set of domains for BS trials consists of 5 mandatory domains for all trials, and subdomains specific for organs or systems (16).

Pathogenesis

Immunopathogenesis

It is well known that BS shares some features with other diseases belonging to the autoinflammatory disorders group. Recent data have explored whether IL-1β/Caspase-1 may play a cardinal role in the pathogenesis of BS (17). The authors studied the mechanism underlying the involvement of xanthine oxidase (XO) and uric acid (UA) in BS and the direct effects of UA and XO inhibitor allopurinol on nitric oxide (NO) and caspase-1-mediated IL-1β release in peripheral blood mononuclear cells (PBMCs) of BS patients. With this purpose, plasma of BS patients and healthy controls (HC) were used to measure XO activity, UA, advanced oxidised proteins products (AOPP), and NO levels; moreover, PBMCs of BS patients and HC were treated or not with either UA or allopurinol. Notably, a significant positive correlation between XO and UA was observed in BS patients. Additionally, while UA has markedly increased NO, IL-1β, and Caspase-1 activity levels in PBMCs of BS patients, allopurinol has exerted an immunomodulatory effect resulting in reduced NO, IL-1β, and Caspase-1 levels in PBMCs of BS patients, particularly during the active stages. Although confirmatory studies are needed, these data suggest a potential use of XO in the assessment of BS activity.

While some reports suggest that neutrophil extracellular traps (NETs) seem to represent a potentially promising area of research in the framework of the pathogenetic mechanisms of BS (18, 19), other studies report interesting results regarding the expression of different elements. A recent study by Kim *et al*. (20) used global gene expression analysis to identify candidate genes that might be related to pathogenesis or that can represent putative biomarkers in two CD8+ T cell subsets from BS patients and HCs. By means of performing RNA sequencing analysis, CD8+CD27-CD28- and CD8+CD27+CD28+ T cell subsets were isolated from a group of BS patients and HCs. The authors found that 1,103 genes and 652 genes were differentially expressed in the CD8+CD27-CD28- and CD8+CD27+CD28+ T cell subsets of patients with BS, respectively. Additionally, they validated the differential expression of COL5A1 in CD8+CD27-CD28- T cells and TRPV3 and ARHGEF10 in CD8+CD27+CD28+ T cells. Furthermore, Ingenuity Pathway Analysis indicated that eleven pathways were more active in BS CD8+CD27-CD28- T cells and more suppressed in BS CD8+ CD27+CD28+ T cells than in the HCs. These results encourage further research on novel genes that might be related to BS pathogenesis.

Previous data have shown that BS patients have abnormal FcγR polymorphisms, the implication of which remains to be fully elucidated. Further confirmation came from a study aimed at exploring FcγRIIb expression on neutrophils, monocytes, B cells, natural killer cells, dendritic cells and T cells, and FcγRI and FcγRIII expression on monocytes in BS patients and HCs using flow cytometry (21). The authors found that BS monocytes expressed a lower level of FcγRIIb and a higher level of FcγRIII, which were correlated with erythrocyte sedimentation rate and C-reactive protein levels and were rescued after treatment. Furthermore, LPS- and IgG-stimulated BS monocytes produced higher levels of IL-6 and TNF-α than HC monocytes. Globally, these data indicate that BS monocytes downregulated FcγRIIb expression and upregulated FcγRIII expression, which seems to be correlated with disease activity (21).

Previous microbiota studies had suggested differences in the gut microbiota of BS patients compared with controls. Recently a study looked at this based on the types of organ involvement (22). They observed significantly more *Actinomyces, Libanicoccus, Collinsella, Eggerthella, Enetrohabdus, Catenibacterium, and Enterobacter*, as well as significantly less *Bacteroides, Cricetibacter, Alistipes, Lachnospira, Dielma, Akkermansia, Sutterella, Anaerofilum, Ruminococcease-UCG007, Acetanaerobacterium, and Copropaacter* in BS patients compared with healthy controls. Further analyses showed increased *Lachnospiraceae NK4A136* in patients with uveitis group, *Dialister, Intestinomonas*, and *Marvinbryantia* in patients with isolated mucocutaneous involvement, and *Gemella* in patients with vascular involvement (22). However, the possible impact of differences in the drugs used for the different organ manifestations is not clear.

Take home messages

- The putative auto-inflammatory nature of BS has been suggested in further studies on TLR response and IL-1β/Caspase-1 (17).
- Emerging data suggest that NETs seem to represent a potentially promising area of research in the framework of pathogenetic mechanisms of BS (18, 19).
- Lack of diseased controls continue to dominate basic science studies in BS.

Genetics

Endoplasmic reticulum aminopeptidase 1 (ERAP1) influences the peptidome of the MHC Class 1 antigen presentation pathway. It trims the proteins degraded in the cytoplasm to eight or ten amino acids, loads them onto MHC Class 1 molecules and presents them to CD8+ cells. Genome wide association studies have shown an epistatic interaction between various ERAP polymorphisms and HLA-B51 in BS. Newly defined polymorphisms, the presence or absence of ERAP in different tissues, and its effect on the peptide repertoire continue to draw attention. Dimopoulo *et al*. determined a

rare 1-bp deletion, rs140416843 in the promoter region of ERAP1 in a patient with oral ulceration, psychosis and inflammatory bowel disease and claimed that it was the first genetic variant that down-regulated its production as a whole. They proposed it as a diagnostic marker but the single patient studied and the dubious nature of its clinical characteristics cast significant doubt on its significance (23). Riahi *et al*. used a novel data mining method called Model-Based Multifactor Dimension Reduction Algorithm (an alternative to logistic regression and a new way of analysing very large numbers of SNP-SNP interactions among an unlimited number of genes and polymorphisms) among 748 BS patients and 776 HCs. This study showed that among the ERAP1 SNP's, the TT genotype of rs1065407, CC genotype of rs2287987 and GG genotype of rs1065407 increased the susceptibility for BS. They proposed that these polymorphisms affected the trimming effect of ERAP1. However, they did not study the effects of gender, drug use and clinical characteristics (24). Padula *et al*. studied 109 consecutive Italian patients with BS and 106 matched HCs and determined two novel SNPs (p.Glu 337 Gln and p.Phe360Cys). The first variation was benign whereas the second was pathogenic damaging the protein active site that is pivotal for the enzymatic activity of ERAP. Additional analyses showed decreased protein stability related to the second variant. They concluded that this was only one of the multitude of gene variations within the coding region of the ERAP gene and that it was a fertile area of research with yet unknown functional consequences (25). Chen *et al*. used a HLA-ABC-triple knockout cell model, isolated HLA-B51 and silenced ERAP1. They determined an unconventional type of peptide bound to ERAP1 comprising of non-Pro/Ala2 moities, showed that this formed around 20% of HLA-B51 bound peptides and that knockdown of ERAP1 increased the length of non-pro/Ala2 and Ala2 peptides but not that of Pro2. They also determined that ERAP-1 regulation of HLA-B51 cell surface expression was cell type dependent. They proposed that the knock-down of ERAP1, which mimics the loss-of-function of ERAP1 variants associated with BS, causes the substitution of 30–40% of HLA-B51 peptides by new ones. However, the human implications of this model were not evident (26).

Autoinflammation and BS was also the subject of a list of studies. Manthiram *et al*. did a genetic analysis of one Turkish and two European American cohorts (total n=231) with the PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis). They found various genetic susceptibility variants and determined that there were shared risk loci with BS and recurrent aphthous stomatitis at IL12A, STAT4, IL-10 and CCR1-CCR3. They proposed that it was part of a family of Behcet's spectrum disorders without discussing any of the clinical discrepancies between various autoinflammatory diseases and BS (27). A Dutch group investigated leukocyte toll like receptor expression in pathergy positive and negative BS patients. TLR1, 2, 4, 5 and 6 were increased in the lymphoid and myeloid cells of BS compared to controls. Pathergy positive patients displayed even higher TLR5 expression on B, CD4+, CD8+ and granulocytes compared to pathergy negative patients. The researchers claimed that the exaggerated inflammatory cutaneous response seen in a positive pathergy test could be triggered via the upregulated TLR5 in leukocytes, by skin-derived flagellin (due to a microorganism) and/or high mobility group box 1 (HGMB1) released from necrotic cells. They also concluded that this showed the importance of the innate immune response in at least some of the phenomena of BS. The major drawback of this study was the small number of patients studied (28). Gur *et al*. did molecular dynamic simulations to provide insights into the mode of action of HLAB51 in BS. They compared it to HLAB52 which differs in two amino acids from B51 and showed that peptide binding of B51 is "looser" compared to the latter giving a chance to HLA-B51 to select a multitude of loosely bound and more promiscuous peptides. They further speculated that the improper folding of the HLA-peptide complex due to this instability may have a role in the inflammatory response in general, and especially in endoplasmic reticulum stress associated inflammation. They concluded that further studies were required to determine the universality of this floppiness (29). A proteomic study was done in the peripheral blood mononuclear cells of 59 patients with BS (33 with active disease and 26 in remission) by a Turkish group. They underlined the problem of irreproducibility of the results of these type of experiments due to the heterogeneity of the condition, the absence of specific laboratory tests and the complex inheritance pattern at least in a subgroup of patients. They determined 16 differentially expressed proteins, they performed comparisons among active and inactive patients and controls, and suggested that at least some of the findings were related to down-regulation of protein folding and endoplasmic reticulum stress process proteins. They again emphasised the possible role of endoplasmic stress associated inflammation (30).

Kato *et al*. evaluated the role of HLA-A26 as a risk factor for BS ocular lesions in 557 patients (42.7% male and 57.3% female). The prevalence of ocular lesions was higher among HLA-A26 carriers compared to non-carriers. It had a similar impact on ocular lesions in B51 positive and negative patients. Iridocyclitis and retinochoroiditis conferred the highest risk. It was not clear whether any controls were used or not in the study (31). Recently, some disease-related SNP's have been reported to mediate disease risk through modulating the expression of long non-coding RNAs (lincRNAs) which further regulate gene expression. Wang *et al*. studied 28 Vogt Koyanagi Harada (VKH) patients, 22 BS patients with uveitis, and 97 normal controls. They showed that the SNP rs12469232 was associated with the expression of linc00467 and that linc00467 was up-regulated in PBMCs and CD4+T cells in both VKH and BS patients. Over-expression of linc00467 increased the viability of CD4+T cells, although its exact role in the pathogenesis of BS

could not be determined. The absence of any longitudinal data or data from patients in remission were weaknesses that needed to be addressed (32).

Take home messages

- Variations in the genes of ERAP, the presence or absence of ERAP in specific organs and the nature of its peptidome draw considerable attention (23-26).
- BS as an autoinflammatory disease is the subject of various publications, although severe drawbacks in definition continue to exist (27).
- Various effector mechanisms including non-coding RNAs seem to be operative in the pathogenesis but the characteristics and the numbers of the studied patients and controls set a limit to its validity (32).

Clinical findings

Eye involvement

Işik and Yalçındağ compared the spectral domain (SD) OCT findings and laser flare photometer (LFP) measurements in 12 HC (Group 1), 31 BS patients with eye involvement (Group 2), 17 patients with active uveitis (Group 3), and 18 patients with uveitis who were in remission (Group 4) (33). They observed that the choroidal thickness in group 3 was higher than that found in groups 1 and 2. Central macular thickness (CMT) and disease duration were negatively correlated, while CMT and flare values were positively correlated. The most frequent OCT finding in groups 3 and 4 was "epiretinal membrane". The most frequent angiographic sign in FFA was "peripheral retinal vascular staining/leakage".

In a further SD-OCT study Yalcindag *et al*. retrospectively searched macular structural changes in 69 eyes of 35 patients with Behcet's uveitis (BU) during the active and remission periods (34). They evaluated the macular structural changes as macular oedema, RPE damage, ellipsoid zone (EZ) damage, external limiting membrane (ELM) damage, presence of epiretinal membrane (ERM), presence of atrophy, the structure of foveal contour, and central macular thickness (CMT). Twenty-six eyes (37.7%) had normal SD-OCT and 43 eyes (62.3%) had any kind of macular pathology in the active uveitis period. In the remission period, 32 eyes (46.3%) had normal SD-OCT and 37 eyes (53.6%) had any kind of macular pathology. They reported that the mean CMT in the remission period was significantly lower than in the active uveitis period and there was a negative correlation between EZ damage and visual acuity in both active and remission periods.

OCTA is a novel technique, which demonstrates retinal microvascular structure based on the amount of light returned from moving blood cells. As a non-invasive and easily applicable method, it is very useful for monitoring retinal microvascular involvement in patients with BU. There were 4 studies published in 2020, that investigated the role of OCTA in BU (35-38). In all studies, superficial and deep capillary vessel density (VD) were reduced in patients with both active and inactive BU, especially for deep capillary plexus (DCP), and there was also enlargement of the foveal avascular zone.

Ozbek-Uzman *et al*. evaluated anterior segment parameters using Scheimpflug camera among 120 patients with inactive BU and 121 HCs (39). Corneal thickness and corneal volume were found to be significantly decreased and corneal astigmatism was significantly higher in the BS group. No evidence of dry eye or endothelial dysfunction which could be related to corneal thickness was shown. The authors could not provide an explanation other than the inflammatory background.

Tugal-Tutkun *et al*. proposed an algorithm for the diagnosis of BU with a multi-centre retrospective study, using classification and regression tree analysis (40). The aim was to improve the diagnosis of characteristic signs using clinical and angiographic findings in BU. The authors reported the most relevant indicators for the diagnosis of BU as the presence of superficial retinal infiltrate or its sequela, retinal nerve fiber layer thickness defect, signs of occlusive retinal vasculitis, and diffuse retinal capillary leakage on FA in the absence of granulomatous anterior uveitis or choroiditis in patients with vitritis.

Ata *et al*. measured femoral cartilage thickness among 20 BS patients with uveitis and 20 patients without uveitis (41). None of the patients had a previous history of joint involvement. They found that the femoral cartilage was significantly thinner among those with uveitis. Although the result was interesting, the hypothesis behind this study is not clear and no adjustments were made for body mass index, corticosteroid use, or any other potentially relevant parameters.

Nakahara *et al*. compared records of 68 newly diagnosed patients with BU registered in the 2000s to those of 107 patients diagnosed during the 1990s in terms of clinical characteristics and treatment (42). They found that the frequency of iridocyclitis had increased in the recent cohort. Similar trends were also true for intestinal, vascular, and neurological involvements. These results are in contrast with some previous studies suggesting a milder disease course in BS, although an increase in intestinal involvement was also observed in those studies (43, 44). Additionally, in the recent cohort, the use of cyclophosphamide had decreased, while the use of oral corticosteroids and biological treatment had increased and cataract and glaucoma surgeries were performed more frequently.

Researchers from Siena, Italy examined clinical characteristics and long-term outcome in a cohort of Italian patients with BU (n=47; 23 M/24 F) (45). Of the 94 eyes, 84 were affected. uveitis was mostly bilateral (78.7%). Panuveitis (40/84) followed by posterior uveitis (24/84) was the most common type of involvement. Researchers reported that the best corrected visual acuity (BCVA) and the retinal vasculitis were significantly improved at the last follow-up. Complications such as cataract, epiretinal membranes, and cystoid macular oedema were frequently observed. HLA- B51, panuveitis, and uveitis duration of more than 15 years were poor prognostic factors. Similarly, a group from Cairo, Egypt, studied predictors of visual morbidity in a group of 40 patients with BU (46). Bilateral involvement, posterior involvement, delay in diagnosis and

frequent attacks were identified as poor prognostic factors.

Abd El Latif *et al*. reported the clinical patterns of 1301 eyes of 681 patients with BU, seen at a tertiary eye care centre between June 2010 and June 2018 in a retrospective Egyptian cohort (47). They divided the cohort into 2 groups, depending on the referral time (below or above 18 months from the diagnosis of uveitis) as Group 1 (≤18 months; 267 patients; 39.2%) and Group 2 (>18 months; 414 patients; 60.8%). Bilateral involvement (96.4 *vs*. 82.8%), panuveitis (87.1 *vs*. 68.1%), ocular complications and immunosuppressive (96.9 *vs*. 57.7%) and biologic (12.3 *vs*. 4.5%) use were significantly more common among group 2. And the authors especially emphasised that a higher percentage of Group 2 eyes had a final visual acuity <20/200, compared to Group 1 (32.2% *vs*. 20.3%). They reported no statistically significant difference between the 2 groups with respect to the systemic manifestations of the disease, except that deep vein thrombosis was more common among Group 2 patients.

HLA-B51 and organ associations

Mizuki *et al*. investigated HLA-B51 association in a database of 3044 BS patients (48). Overall, 45% were positive for HLA-B51. HLA-B51carriers were shown to have a higher risk for ocular involvement and a lower risk for genital ulceration and gastrointestinal symptoms. On the other hand, a retrospective study of 396 patients from Italy found no difference between HLA-B51 positive and negative patients (49). The study also investigated potential association among the different manifestations and looked at whether there are specific disease clusters. Oral ulcers were associated with erythema nodosum and pseudofolliculitis, whereas uveitis emerged as a distinct feature. Negative associations were detected between genital ulcers and vascular involvement and between arthritis and papulopustular lesions. Interestingly, a previous factor analysis from Turkey had shown that arthritis and papulopustular lesions formed a cluster together, which was later shown to be associated with enthesopathy and was shared by first-degree relatives of BS patients who also had BS (50-52).

Vascular involvement

Ozguler *et al*. prospectively studied 33 patients with lower extremity deep vein thrombosis (DVT) during a mean of 40±13 months (53). The relapse rates were calculated as 29%, 37% and 45% at 6, 12 and 24 months, respectively. Poor recanalisation was the only significant predictor for relapse. Overall, 29 patients were treated with azathioprine (AZA) and 17 with interferon (IFN)-alpha. The relapse rate was lower and recanalisation rate was higher among those who used IFN-alpha compared with those who used AZA (12% *vs*. 45% and 86% *vs*. 45%, respectively).

Lin *et al*. described clinical characteristics of 47 BS patients with vascular involvement (DVT: n=25, arterial aneurysms: n=21 and arterial occlusion: n=12) registered in a cohort of 836 BS patients (54). Late onset and arterial involvement were associated with poor prognosis. Treatment with biological treatment rather than conventional agents seemed to provide better results.

In a retrospective study from Spain clinical characteristics of 12 patients with DVT were compared with 45 patients without DVT (55). During a mean follow-up of 10 years, 26 episodes of venous thrombosis were observed. Erythema nodosum, fever, and the absence of immunosuppressive treatment were associated with thrombotic relapses.

Sakr *et al*. identified differential characteristics of BS patients with Budd-Chiari syndrome (BCS) (56). They studied 232 patients with BCS without BS and 39 patients with BCS due to BS between 2005 and 2016. BS patients with BCS were more likely to have jaundice, collateral vessel formation (on the abdominal and intrahepatic veins), DVT, and IVC thrombosis. Immunosuppressive treatment, anticoagulation, and IVC stenting were more common among BS patients. During a median 4 years of follow-up, BCS with BS had a more severe outcome with a higher frequency of mortality rate and hepatocellular carcinoma.

Alibaz *et al*. measured lower extremity vein wall thickness in 69 patients with BS, 38 patients with Crohns's disease (CD), and 38 HCs using USG (57). The study revealed that the mean CFV thickness was significantly higher in BS compared to that seen in CD and HCs. There was no difference between patients with CD and HCs. The authors suggested that CFV wall thickness could be a distinctive diagnostic tool for the differentiation of BS and CD. However, the study had some limitations. First, as also pointed out by the authors the sample sizes were quite small for formulating a diagnostic marker. More importantly, 22/69 of BS patients also had vascular involvement as a confounding factor.

Nervous system involvement

Bolek *et al*. investigated the outcome of 77 patients with nervous system involvement (NBS) followed between 2014 and 2018 (58). Of the 77 patients 61, had definite NBS and 47 had parenchymal involvement. Chronic progressive course was seen in a minority. A considerable portion of the patients had received aggressive immunosuppressive treatment. A total of 14 BS patients (all with parenchymal involvement) had died during a median 9.4 years of follow-up.

Gunduz *et al*. aimed to find a surrogate marker for brain atrophy in patients with NBS (59). For this purpose, they investigated 17 BS patients with NBS, 15 BS patients without neurological involvement, 19 patients with RA, and 17 HCs. The study showed that the cognitive skills, particularly memory and language domains were severely affected among patients with NBS. No correlation was found between hippocampal volume loss and memory scores. Brain MRI volumetry data in the NBS group showed brain stem and cerebellar atrophy with ventricular enlargement, however volume loss was not found to be associated with impaired cognition or laboratory tests.

Toledo-Samaniego *et al*. described the clinical characteristics of 25 patients with neurological symptoms compared to 32 patients without neurological symptoms diagnosed and followed be-

tween 2006 and 2019 in a tertiary hospital in Madrid (60). NBS was defined as the presence of any neurological symptom which could not be explained by the presence of another disease. Neurological findings included headache, aseptic meningitis, typical lesions in imaging studies, depression, cranial and peripheral neuropathies. During a mean follow-up of 8±7 years, 56 neurological symptoms were observed in 25 patients and these were found to be associated with fever and papulopustular lesions. Mortality was not increased. Moreover, the medical treatment and prognosis were not different among those with neurological involvement compared to those without.

Juvenile BS

A study found significant differences among paediatric patients from Turkey compared to those from Israel (61). A total of 205 patients (165 from Turkey; 40 from Israel) were studied. HLA-B51 positivity, male gender, and skin involvement were more frequent among patients from Turkey. Moreover, Turkish patients had higher disease activity at initial presentation. However, significantly more patients were treated with corticosteroids with or without immunosuppressives in Israel than in Turkey. In total, ICBD criteria (73%) were found to have the highest sensitivity followed by paediatric BS criteria (48%), and the ISG (42%) criteria sets.

Gezgin Yıldırım *et al*. evaluated the long-term outcome of 57 patients with juvenile onset BS, diagnosed between 2008 and 2018 (62). Similar to the study by Butbul Aviel, ICBD criteria (95%) were found to have the highest sensitivity followed by paediatric BS (60%), and the ISG (54%) criteria sets. The authors observed that disease activity decreased significantly over the years. Twenty-one patients experienced ≤3 events (defined as the emergence of a new clinical symptom), however of these only 4 were serious. Specificity of these criteria, which is known to be especially problematic for ICBD was not studied, as there were no control groups in either of the studies.

Miscellaneous conditions

Baser *et al*. observed that the lower urinary tract symptoms (urgency: 55%, nocturia: 80% and urinary incontinence: 31%) were frequent in BS and were associated with high disease activity (63). The study included 55 BS patients who did not have a history of urinary or prostate disease or neurological involvement. In a retrospective cohort study, Yeh *et al*. observed that the risk of obstructive sleep apnoea was significantly increased among patients with BS as well as Sjögren's syndrome (64). Guven *et al*. demonstrated an increased cancer risk in BS (65). A high frequency of sexual dysfunction in BS especially among those with neurological involvement was observed (66). Similarly, a systematic literature review revealed that sexual dysfunction was considerably frequent in BS and was strongly associated with depression (67). The absence of diseased controls precludes any definitive conclusion in the majority of these studies (63, 65, 66).

Coronavirus disease 2019 (COVID-19)

Yurttaş *et al*. reported clinical characteristics, management, and outcome of 10 BS patients who were diagnosed with COVID-19 during the first month of the pandemic in Turkey (68). Eight out of ten patients were hospitalised, six were diagnosed with pneumonia and one died due to severe respiratory failure. One patient developed *de novo* DVT, while three reported mild exacerbations associated with BS. Similarly, Espinosa *et al*. reported four BS patients with COVID-19 at the beginning of the pandemic in Spain (69). All four had mild infection. Two of the four patients experienced mild BS attacks.

Take home nessages

- Optical coherence tomography angiography (OCTA) can demonstrate significant microvascular changes in the retinal vascular plexus and choriocapillaris among patients with and without uveitis (35-38).
- There are positive and negative associations between different clinical manifestations suggesting the presence of distinct clinical clusters in BS (49).
- Wall thickness measurement of lower extremity veins could be a distinctive feature for BS (57).
- Venous thrombotic relapse rate may go up to 45% in 2 years (53).
- A recent study reported an increased cancer risk compared to age and gender-matched general population (65).

Treatment

TNFα inhibitors

A multi-centre, retrospective study from Italy reported the efficacy of adalimumab both for posterior and anterior uveitis related to BS and other aetiologies during a period of more than 12 months (70). In a retrospective study, the 10-year continuation rate of infliximab was 70% among 27 BS patients and there was no difference in the retention rates and efficacy parameters between infliximab monotherapy and its combination with colchicine and/or glucocorticoids (71). Another retrospective study evaluated the effect of infliximab treatment on 16 patients regarding the duration of uveitis prior to infliximab (72). Overall, infliximab was effective in decreasing ocular attacks and increasing BCVA during a median follow-up of 132 months. However, because of the less favourable BCVA scores at baseline, the improvement of patients with a long duration of uveitis (>18 months) was not as satisfactory as in patients with a short duration of uveitis (up to 18 months), underlining the importance of early treatment before the development of irreversible changes. A retrospective study focused on 8 BS patients from a group of 25, who discontinued infliximab after achieving continuous ocular remission for at least 12 months (73). Five of these patients also had complete remission confirmed with fluorescence angiography. During a mean follow-up of 47 months after discontinuing infliximab, 4 patients maintained their remission and remained completely attack free, but the other 4 patients experienced ocular attacks within a median of 9 months after discontinuing infliximab. Two of these patients received interferon α-2a and the other 2 received adalimumab with satisfactory control of ocular inflammation. It was sug-

gested that TNF inhibitors may also be beneficial for inflammatory scleritis in a retrospective study that included 19 patients, 3 of whom had BS (74)

A prospective, multicentre study from Japan reported the efficacy of adalimumab in 85% of 383 BS patients with GI involvement during a mean follow-up of 580 days (75). Endoscopic evaluation revealed more than 50% reduction in the size of the largest ulcer in 68% of the patients. Another single-centre retrospective study from Japan reported 17 BS patients with GI involvement treated with infliximab or adalimumab for up to 6 years (76). Thirteen patients (76%) were categorised as responders and 11 of them had mucosal healing at endoscopy. Five patients (38%) developed mucocutaneous and joint symptoms despite GI response during follow-up.

A multi-centre, retrospective study from Turkey looked at the efficacy of TNFα inhibitors in 27 BS patients with various types of refractory vascular involvement (77). The initial TNFα inhibitor was infliximab in all patients excluding 3 starting adalimumab. More than half of the patients received concomitant azathioprine and 70% received anticoagulant treatment. Complete remission rate was 80% at the third month, but information on the baseline status of the patients was not given. Combination of TNFα inhibitors with immunosuppressives or the use of anticoagulants did not seem to be beneficial on vascular relapse or TNFα inhibitor drug survival. A single-centre, retrospective study from Turkey reported experience with infliximab in 18 BS patients with vascular involvement (arterial involvement, thrombosis of cerebral veins, vena cava, and hepatic veins) (78). Seventeen patients reached remission with a new vascular event developing in only one patient. The diversity of vascular involvement, lack of information on the clinical status of patients at the initiation of TNFα inhibitors, and short follow-up duration were the main limitations of both studies.

Tocilizumab

A systematic literature review of the IL-6 receptor antibody tocilizumab showed the heterogeneous response of different organ manifestations of BS to treatment (79). This review included 20 publications about 47 BS patients with different organ involvements refractory to previous treatment with conventional immunosuppressives and biologic agents. Tocilizumab was given intravenously (8 mg/kg/month) to all but one patient. It was used as monotherapy in 6 patients and in combination with steroids and immunosuppressives in the remaining. After a mean observation period of 12 months, tocilizumab was found to be effective for ocular, neurological, vascular involvement, and amyloidosis but it was not effective for oral and genital ulcers, skin findings, arthritis, and gastrointestinal involvement, with even aggravation of symptoms in some patients. Additionally, a retrospective case series of 5 BS patients with CNS involvement from China reported a beneficial effect of tocilizumab (80). These divergent findings support the hypothesis that disease clusters in BS have different pathogenic mechanisms.

Secukinumab

Case reports of paradoxical reactions, such as exacerbation of BS symptoms or *de novo* appearance of BS-like symptoms have been reported in psoriasis or ankylosing spondylitis patients during treatment with secukinumab (81). However, in a multicentre, retrospective study of 15 BS patients with refractory manifestations secukinumab led to a complete or partial response in 90% during a follow-up of 18 months (82). Interestingly, 60% of these patients had intestinal involvement and they responded completely to secukinumab, an agent that might induce or exacerbate Crohn's disease. On the other hand, it should be underlined that the demographic characteristics of the patients (87% were women with a median age of 51 years at the beginning of secukinumab treatment) as well as their clinical characteristics (60% had inflammatory back pain) do not fit the classical clinical picture of BS. Hence, more work is necessary to understand the role of IL-17 in the pathogenesis of BS.

Tofacitinib

A retrospective study from China reported 13 BS patients with refractory uveitis who were treated with tofacitinib 5 mg twice daily along with prednisone 30 mg daily (83). This treatment led to a rapid and sustained improvement in visual acuity and ocular inflammation during a follow-up duration ranging between 24 and 38 months. There was no documented thromboembolism. Another retrospective study from China looked at the efficacy of tofacitinib 5 mg twice daily with background glucocorticoids and immunosuppressives in 13 BS patients with refractory cardiac/vascular, gastrointestinal or articular involvement (84). Tofacitinib significantly improved overall disease activity after a median of 8 months and led to remission in patients with cardiac/vascular and articular involvement, but had no effect on GI involvement. This was attributed to the resemblance of the gastrointestinal involvement of BS to Crohn's disease for which tofacitinib is already known to be ineffective. A surprising result of this study was the efficacy of tofacitinib on vascular involvement that was almost only on the arterial side. It is known that the majority of vascular involvement in BS occurs on the venous site and reports of increased thromboembolism with tofacitinib might still be a concern despite the favorable results obtained in these studies. We definitely need more studies to understand the value of tofacitinib in treating BS.

Apremilast

A prospective study from Japan assessed the efficacy of apremilast in 14 BS patients with refractory oral ulcers (85). Apremilast was added to background treatment consisting of colchicine, prednisolone, immunosuppressives and TNF inhibitors (used by 93%, 21%, 29%, and 14% of the patients, respectively). Complete remission of oral ulcers was achieved in 64% of the patients at 3 months, with improvements in the mean disease activity scores, genital ulcers, skin lesions, and articular symptoms. Similar beneficial results were also reported in an open, multi-centre study from Spain

on 51 BS patients with active mucocutaneous lesions despite treatment with colchicine, glucocorticoids, at least 1 classic immunosuppressive and also a biologic agent in some (86). Apremilast was used either as monotherapy or in combination with colchicine, glucocorticoids, immunosuppressives, and biologic agents. This treatment led to rapid improvement of oral and genital ulcers and reduction of glucocorticoid dose with no difference between monotherapy and combination therapy. Other BS manifestations such as skin lesions and intestinal symptoms also improved but the effect of apremilast on arthritis was less remarkable. These results suggest that apremilast can be added to ongoing treatment in BS patients. However, whether this is superior to apremilast monotherapy awaits further studies.

Surgical interventions for peripheral artery involvement

A retrospective study from Korea reported 17 patients with peripheral arterial involvement (excluding pulmonary arteries) (87). Eight of these patients underwent a total of 17 operations. The first operation was an emergency surgery for all patients (aneurysm rupture 6 patients, acute ischaemia 2 patients) and complications such as fistula formation or rupture at the anastomotic site were the main causes of re-operations. The 5-year mortality rate in this surgically treated group was 63% and all deaths were related to arterial complications. Aneurysm formation was associated with low survival. Eight of the 9 medically treated patients had arterial occlusions or stenoses and 1 had bilateral internal carotid artery aneurysms. The mortality rate of this group during a mean follow-up of 8 years was 22% and the causes of death have not been directly attributed to arterial complications. Immunosuppressive treatment consisting mainly of prednisolone was given to 7 surgically treated patients. The authors discussed the adverse effects of immunosuppressives such as delayed wound healing and increased susceptibility to infections, but whether these drug-associated adverse events had been observed in their study was not mentioned. A single-centre study from France reported 23 patients with peripheral artery involvement (aneurysms in 22 patients) undergoing 47 surgical procedures during a mean follow-up of 8 years (88). Seventeen patients experienced a total of 24 recurrences and 92% of the recurrences occurred at the anastomosis site. The use of pre- or post-operative immunosuppression was associated with a statistically significant decrease in the recurrence rate compared to patients not receiving immunosuppressives. A study from Egypt reported 22 patients with peripheral artery aneurysms treated with endovascular stent-graft treatment (89). The early patency rate was high (91%) but stent-graft complications occurred in 8 patients (36%) during a mean follow-up of 23 months. Pre-operative and post-operative immunosuppressives were given only to patients judged as having active disease.

Take home messages

- Infliximab and adalimumab continue to be the most frequently used biologic agents for severe manifestations of BD (70-78).
- More work is needed to understand the value of other biologics in the treatment of BS.
- Apremilast may also be used in combination with other agents, but this needs confirmation with controlled studies (85, 86).
- Surgery of peripheral arteries is complicated with a high rate of recurrences occurring at the anastomosis site (87).

Acknowledgement

We thank Professor Hasan Yazıcı for his critical reading of this review.

References

1. HATEMI G, SEYAHI E, FRESKO I, TALARICO R, HAMURYUDAN V: One year in review 2019: Behçet's syndrome. *Clin Exp Rheumatol* 2019; 37 (Suppl. 121): S3-17.
2. HATEMI G, SEYAHI E, FRESKO I, TALARICO R, HAMURYUDAN V: One year in review 2020: Behçet's syndrome. *Clin Exp Rheumatol* 2020; 38 (Suppl. 127): S3-10.
3. BALT J, JAMYANJAV B, JAV S *et al*.: Clinical features of Behcet's disease in Mongolia: a multicenter study. *Clin Rheumatol* 2020; 39: 2697-706.
4. PODDIGHE D, TURGANBEKOVA A, MUKUSHEVA Z, ABDIRAKHMANOVA A, ASSYLBEKOVA M, ABDRAKHMANOVA S: HLA-B*51 allelic and carrier frequency in Kazakhstan: insights into Behçet's disease prevalence in Central Asia. *Intern Emerg Med* 2021; 16: 325-31.
5. FERNÁNDEZ-ÁVILA DG, RINCÓN-RIAÑO DN, BERNAL-MACÍAS S, DÁVILA JMG, ROSSELLI D: Prevalence and demographic characteristics of Behcet disease in Colombia: data from the national health registry 2012-2016. *Rheumatol Int* 2020; 40: 17-20.
6. PONTE C, KHMELINSKII N, TEIXEIRA V et al.: Reuma.pt/vasculitis - the Portuguese vasculitis registry. *Orphanet J Rare Dis* 2020; 15: 110.
7. DE SOUZA-RAMALHO P, D'ALMEIDA MF, FREITAS JP, PINTO J: Behçet's disease in Portugal. *Acta Medica Port* 1991; 4: 79-82.
8. Grupo Nacional para o Estudo da Doença de Behçet, Jorge Crespo Behçet's disease - a national casuistic. *Med Int* 1997; 4: 225-32.
9. THOMAS T, CHANDAN JS, SUBRAMANIAN A et al.: Epidemiology, morbidity and mortality in Behçet's disease: a cohort study using The Health Improvement Network (THIN). *Rheumatology* (Oxford) 2020; 59: 2785-95.
10. CHAMBERLAIN MA: Behcet's syndrome in 32 patients in Yorkshire. *Ann Rheum Dis* 1977; 36: 491-9.
11. ATTIA DHS, ABDEL NOOR RA: Severe Behçet's disease equally affects both genders in Egyptian patients: A multicentre retrospective follow-up study. *Reumatismo* 2020; 71: 218-25.
12. LI C, LI L, WU X *et al*.: Clinical manifestations of Behçet's disease in a large cohort of Chinese patients: gender- and age-related differences. *Clin Rheumatol* 2020; 39: 3449-54.
13. KSIAA I, KECHIDA M, ABROUG N *et al*.: Changing pattern of clinical manifestations of Behçet's disease in Tunisia: comparison between two decades. *Reumatologia* 2020; 58: 87-92.
14. JUN JB, KIM HJ, KAZMI SZ *et al*.: Significant Decline in the Incidence of Behcet's Disease in South Korea: A Nationwide Population-Based Study (2004-2017). *Arthritis Care Res* (Hoboken) 2020 Aug 8 [Online ahead of print].
15. HATEMI G, YAZICI H: Behçet's syndrome and micro-organisms. *Best Pract Res Clin Rheumatol* 2011; 25: 389-406.
16. HATEMI G, MEARA A, OZGULER Y *et al*.: The OMERACT Core Set of Domains for Outcome Measures in Behçet Syndrome. *Arthritis Care Res* (Hoboken) 2020 Nov 17 [Online ahead of print].
17. CHEKAOUI A, BELGUENDOUZ H, LAHMAR K *et al*.: Uric acid increases IL-1β secretion and Caspase-1 activation in PBMCs of Behçet's disease patients: The in vitro immunomodulatory effect of xanthine oxidase inhibitor Allopurinol. *Int Immunopharmacol* 2020; 80: 106119.
18. LE JONCOUR A, SAADOUN D, BOULAFTALI Y: Response to: 'Correspondence on 'Critical role of neutrophil extracellular traps (NETs) in patients with Behcet's disease'' by Chen *et al*. *Ann Rheum Dis* 2020 Dec 24 [Online ahead of print].
19. CHEN J, LIU T, HE J, LIU Y: Correspondence on 'Critical role of neutrophil extracellular

traps (NETs) in patients with Behcet's disease'. *Ann Rheum Dis* 2020 Dec 24 [Online ahead of print].
20. KIM SM, PARK MJ, PARK S, CHENG JY, LEE ES: Differential expression of novel genes and signalling pathways of senescent CD8+ T cell subsets in Behçet's disease. *Clin Exp Rheumatol* 2020; 38 (Suppl. 127): S17-25.
21. HUANG L, YU X, LI L et al.: Aberrant FcγRIIb and FcγRIII expression on monocytes from patients with Behçet's disease. *Clin Immunol* 2020; 219: 108549.
22. DIMOPOULOU C, LUNDGREN JD, SUNDAL J *et al*.: Variant in ERAP1 promoter region is associated with low expression in a patient with a Behçet-like MHC-I-opathy. *J Hum Genet* 2020; 65: 325-35.
23. YASAR BILGE NS, PÉREZ BROCAL V *et al*.: Intestinal microbiota composition of patients with Behçet's disease: differences between eye, mucocutaneous and vascular involvement. The Rheuma-BIOTA study. *Clin Exp Rheumatol* 2020; 38 (Suppl. 127): S60-8.
24. RIAHI P, KAZEMNEJAD A, MOSTAFAEI S *et al*.: ERAP1 polymorphisms interactions and their association with Behçet's disease susceptibly: Application of Model-Based Multifactor Dimension Reduction Algorithm (MB-MDR. *PLoS One* 2020; 15: e0227997.
25. PADULA MC, LECCESE P, LASCARO N *et al*.: From structure to function for the characterization of ERAP1 active site in Behçet syndrome. A novel polymorphism associated with known gene variations. *Mol Immunol* 2020; 117: 155-9.
26. CHEN L, SHI H, KOFTORI D *et al*.: Identification of an unconventional subpeptidome bound to the Behçet's disease-associated HLA-B*51:01 that is regulated by endoplasmic reticulum aminopeptidase 1 (ERAP1). *Mol Cell Proteomics* 2020; 19: 871-83.
27. MANTHIRAM K, PREITE S, DEDEOGLU F *et al*.: Common genetic susceptibility loci link PFAPA syndrome, Behçet's disease, and recurrent aphthous stomatitis *Proc Natl Acad Sci USA* 2020; 117: 14405-11.
28. VAN DER HOUWEN TB, DIK WA, GOEIJENBIER M *et al*.: Leukocyte toll-like receptor expression in pathergy positive and negative Behçet's disease patients. *Rheumatology* (Oxford) 2020; 59: 3971-9.
29. GUR M, GOLCUK M, GUL A, ERMAN B: Molecular dynamics simulations provide molecular insights into the role of HLA-B51 in Behçet's disease pathogenesis. *Chem Biol Drug Des* 2020; 96: 644-58.
30. KIRECTEPE AYDIN A, ÖZGÜLER Y, UÇAR D *et al*.: Peripheral blood mononuclear cell proteome profile in Behçet's syndrome. *Rheumatol Int* 2020; 40: 65-74.
31. KATO H, TAKEUCHI M, HORITA N *et al*.: HLA-A26 is a risk factor for Behçet's disease ocular lesions. *Mod Rheumatol* 2021; 31: 214-8.
32. WANG Q, YI S, DU Z *et al*.: The Rs12569232 SNP Association with Vogt-Koyanagi-Harada Disease and Behcet's Disease is probably mediated by regulation of linc00467 expression. *Ocul Immunol Inflamm* 2020 May 13 [Online ahead of print].
33. IŞIK MU, YALCINDAG N: Comparison of spectral domain optical coherence tomography (SD OCT) findings with laser flare photometry (LFP) measurements in Behçet's iveitis. *Ocul Immunol Inflamm* 2020; 28: 194-9.
34. YALÇINDAĞ FN, TEMEL E, ŞEKKELI MZ, KAR I: Macular structural changes and factors affecting final visual acuity in patients with Behçet uveitis. *Graefes Arch Clin Exp Ophthalmol* 2021; 259: 715-21.
35. TÜRKCÜ FM, ŞAHIN A, KARAALP Ü *et al*.: Automated quantification of foveal avascular zone and vascular density in Behçet's disease. *Ir J Med Sci* 2020; 189: 349-54.
36. ACCORINTI M, GILARDI M, DE GERONIMO D, IANNETTI L, GIANNINI D, PARRAVANO M: Optical coherence tomography angiography findings in active and inactive ocular Behçet disease. *Ocul Immunol Inflamm* 2020; 28: 589-600.
37. ESER-OZTURK H, ISMAYILOVA L, YUCEL OE, SULLU Y: Quantitative measurements with optical coherence tomography angiography in Behçet uveitis. *Eur J Ophthalmol* 2021; 31: 1047-55.
38. AKSOY FE, BASARIR B, ALTAN C *et al*.: Retinal microvasculature in the remission period of Behcet's uveitis. *Photodiagnosis Photodyn Ther* 2020; 29: 101646.
39. OZBEK-UZMAN S, KARATAS SUNGUR G, YALNIZ-AKKAYA Z, ORMAN G, BURCU A, ORNEK F: Anterior segment parameters in Behçet's patients with ocular involvement. *Int Ophthalmol* 2020; 40: 1387-95.
40. TUGAL-TUTKUN I, ONAL S, STANFORD M *et al*.: An algorithm for the diagnosis of Behçet disease uveitis in adults. *Ocul Immunol Inflamm* 2020 Apr 14.
41. ATA E, KOSEM M, OZSOY-UNUBOL T: Ultrasonographic assessment of femoral cartilage thickness in patients with and without uveitis in Behçet's disease. *Rheumatol Int* 2020; 40: 75-80.
42. NAKAHARA H, KABURAKI T, TANAKA R *et al*.: Comparisons of clinical features in Japanese patients with Behçet's uveitis treated in the 1990s and the 2000s. *Ocul Immunol Inflamm* 2020; 28: 262-9.
43. KIRINO Y, IDEGUCHI H, TAKENO M *et al*.: Continuous evolution of clinical phenotype in 578 Japanese patients with Behçet's disease: a retrospective observational study. *Arthritis Res Ther* 2016; 18: 217.
44. KIM DY, CHOI MJ, CHO S, KIM DW, BANG D: Changing clinical expression of Behçet disease in Korea during three decades (1983- 2012): chronological analysis of 3674 hospi¬tal-based patients. *Br J Dermatol* 2014; 170: 458-61.
45. SOTA J, CANTARINI L, VITALE A *et al*.: Long-term outcomes of behçet's syndrome-related uveitis: a monocentric Italian experience. *Mediators Inflamm* 2020; 2020: 6872402.
46. ALLAM RSHM, MEDHAT BM: A clinical audit on the predictors for visual morbidity in patients with Behçet's disease attending cairo university hospitals. *Semin Ophthalmol* 2020: 1-7.
47. ABD EL LATIF E, ABDEL KADER FOULY GALAL M *et al*.: Pattern of uveitis associated with Behçet's disease in an Egyptian cohort. *Clin Ophthalmol* 2020; 14: 4005-14.
48. MIZUKI Y, HORITA N, HORIE Y *et al*.: The influence of HLA-B51 on clinical manifestations among Japanese patients with Behçet's disease: A nationwide survey. *Mod Rheumatol* 2020; 30: 708-14.
49. SOTA J, RIGANTE D, EMMI G *et al*.: Behçet's syndrome in Italy: a detailed retrospective analysis of 396 cases seen in 3 tertiary referral clinics. *Intern Emerg Med* 2020; 15: 1031-9.
50. TUNC R, KEYMAN E, MELIKOGLU M, FRESKO I, YAZICI H: Target organ associations in Turkish patients with Behçet's disease: a cross sectional study by exploratory factor analysis. *J Rheumatol* 2002; 29: 2393-6.
51. HATEMI G, FRESKO I, TASCILAR K, YAZICI H: Increased enthesopathy among Behçet's syndrome patients with acne and arthritis: an ultrasonography study. *Arthritis Rheum* 2008; 58: 1539-45.
52. KARACA M, HATEMI G, SUT N, YAZICI H: The papulopustular lesion/arthritis cluster of Behçet's syndrome also clusters in families. *Rheumatology* (Oxford) 2012; 51: 1053-60.
53. OZGULER Y, HATEMI G, CETINKAYA F *et al*.: Clinical course of acute deep vein thrombosis of the legs in Behçet's syndrome. *Rheumatology* (Oxford) 2020; 59: 799-806.
54. LIN CH, LUO D, MA HF, SHEN Y, ZOU J, GUAN JL: Clinical characteristics and factors influencing the prognosis of Behçet's disease complicated with vascular involvement. *Vasa* 2020; 49: 309-18.
55. TOLEDO-SAMANIEGO N, GALEANO-VALLE F, PINILLA-LLORENTE B *et al*.: Clinical features and management of venous thromboembolism in patients with Behçet's syndrome: a single-center case-control study. *Intern Emerg Med* 2020; 15: 635-644.
56. SAKR MA, REDA MA, EBADA HE *et al*.: Characteristics and outcome of primary Budd-Chiari syndrome due to Behçet's syndrome. *Clin Res Hepatol Gastroenterol* 2020; 44: 503-12.
57. ALIBAZ-ONER F, ERGELEN R, ERGENC I *et al*.: Femoral vein wall thickness measurement may be a distinctive diagnostic tool to differentiate Behçet's disease with intestinal involvement and Crohn's disease. *Dig Dis Sci* 2021; 66: 2750-5.
58. BOLEK EC, SARI A, KILIC L *et al*.: Clinical features and disease course of neurological involvement in Behcet's disease: HUVAC experience. *Mult Scler Relat Disord* 2020; 38: 101512.
59. GÜNDÜZ T, KÜRTÜNCÜ M, MATUR Z *et al*.: Laboratory and clinical correlates of brain atrophy in Neuro-Behçet's disease. *J Neurol Sci* 2020; 414: 116831.
60. TOLEDO-SAMANIEGO N, GALEANO-VALLE F, ASCANIO-PALOMARES P, GONZÁLEZ-MARTÍNEZ B, VALENCIA-KRUSZYNA A, DEMELO-RODRÍGUEZ P: Neurological manifestations of Behçet's disease: Study of 57 patients. *Med Clin* (Barc) 2020; 154: 488-92.
61. BUTBUL AVIEL Y, BATU ED, SÖZERI B *et al*.: Characteristics of pediatric Behçet's disease in Turkey and Israel: A cross-sectional cohort comparison. *Semin Arthritis Rheum* 2020; 50: 515-20.
62. GEZGIN YILDIRIM D, BAKKALOĞLU SA, HASANREISOGLU M, BUYAN N: Disease activity and outcomes in juvenile Behçet's dis-

ease: 10 years' experience of a single centre. *Clin Exp Rheumatol* 2020; 38 (Suppl. 127): S105-11.
63. BASER A, ZUMRUTBAS AE, OZLULERDEN Y *et al*.: Is there a correlation between Behçet disease and lower urinary tract symptoms? *Int Neurourol J* 2020; 24: 150-5.
64. YEH TC, CHEN WS, CHANG YS *et al*.: Risk of obstructive sleep apnea in patients with Sjögren syndrome and Behçet's disease: a nationwide, population-based cohort study. *Sleep Breath* 2020; 24: 1199-205.
65. GUVEN DC, BOLEK EC, ALTINTOP SE *et al*.: Cancer incidence in Behçet's disease. *Ir J Med Sci* 2020; 189: 1209-14.
66. SORGUN MH, KUZU M, ERDOĞAN S, YUCESAN C: Sexual dysfunction in Neuro-Behcet's disease. *J Clin Neurosci* 2020; 78: 211-4.
67. TALARICO R, ELEFANTE E, PARMA A, TAPONECO F, SIMONCINI T, MOSCA M: Sexual dysfunction in Behçet's syndrome. *Rheumatol Int* 2020; 40: 9-15.
68. YURTTAŞ B, OZTAS M, TUNC A *et al*.: Characteristics and outcomes of Behçet's syndrome patients with Coronavirus Disease 2019: a case series of 10 patients. *Intern Emerg Med* 2020; 15: 1567-71.
69. ESPINOSA G, ARAUJO O, AMARO S *et al*.: COVID-19 and Behçet's disease: clinical case series. *Ann Rheum Dis* 2020 Jul 21 [Online ahead of print].
70. SILVESTRI E, BITOSSI A, BETTIOL A *et al*.: Adalimumab effectively controls both anterior and posterior noninfectious uveitis associated with systemic inflammatory diseases: focus on Behçet's syndrome. *Inflammopharmacology* 2020; 28: 711-8.
71. HORIGUCHI N, KAMOI K, HORIE S *et al*.: A 10-year follow-up of infliximab monotherapy for refractory uveitis in Behçet's syndrome. *Sci Rep* 2020; 10: 22227.
72. KEINO H, WATANABE T, NAKAYAMA M, KOMAGATA Y, FUKUOKA K, OKADA AO: Long-term efficacy of early infliximab induced remission for refractory uveoretinitis associated with Behçet's disease. *Br J Ophthalmol* 2020 Sep 24 [Online ahead of print].
73. KÖSE HC, YALÇINDAĞ N: Clinical follow-up of patients with Behçet uveitis after discontinuation of infliximab therapy. *Ocular Immunol Inflamm* 2020; Aug 11 [Online ahead of print].
74. FABIANI C, SOTA J, SAINZ-DE-LA-MAZA M *et al*.: Effectiveness of TNF-α blockade in the treatment of refractory non-infectious scleritis: a multicentre study. *Clin Exp Rheumatol* 2020; 38: 1138-44.
75. SUZUKI Y, HAGIWARA T, KOBAYASHI M, MORITA K, SHIMAMATO T, HIBI T: Long-term safety and effectiveness of adalimumab in 462 patients with intestinal Behçet's disease: results from a large real-world observational study. *Intest Res* 2020 Aug 20 [Online ahead of print].
76. KAMBAYASHI H, OMORI T, SAITO S *et al*.: The efficacy of medium to long-term anti TNF-α antibody based maintenance therapy in Behçet's disease patients with intestinal lesions. *Intern Med* 2020; 59: 2343-51.
77. AKSOY A, YAZICI A, OMMA A *et al*.: Efficacy of TNFα inhibitors for refractory vascular Behçet's disease: A multi center observational study of 27 patients and a review of the literature. *Int J Rheum Dis* 2020; 23: 256-61.
78. KEHRIBAR DY, OZGEN M: Infliximab treatment in refractory vascular Behcet's disease: a single-center experience. *Vascular* 2020; 28: 829-33.
79. AKIYAMA M, KANEKO Y, TAKEUCHI T: Effectiveness of tocilizumab in Behcet's disease: a systematic literature review. Semin *Arthritis Rheum* 2020; 50: 97-804.
80. LIU J, YAN D, WANG Z *et al*.: Tocilizumab in the treatment of severe and refractory parenchymal neuro-Behçet's syndrome: case series and literature review. *Ther Adv Musculoskel Dis* 2020; 12: 1-8.
81. BARRADO-SOLIS N, RODRIGO-NICHOLAS B, DE LA MORENO-BARRIO L et al.: Report of two cases of Behçet's disease developed during treatment with secukinumab. *J Eur Acad Dermatol Venereol* 2020; 34: e587-9.
82. FAGNI F, BETTIOL A, TALARICO R *et al*.: Long-term effectiveness and safety of secukinumab for treatment of refractory mucosal and articular Behçet's phenotype: a multicentre study. *Ann Rheum Dis* 2020; 79: 1098-104.
83. ZOU J, LIN CH, WANG Y, SHEN Y, GUAN JL: Correspondence on 'A pilot study of tofacitinib for refractory Behçet's syndrome'. *Ann Rheum Dis* 2021 Jan 25 [Online ahead of print].
84. LIU J, HOU Y, SUN L *et al*.: A pilot study of tofacitinib for refractory Behçet's syndrome. *Ann Rheum Dis* 2020; 79: 1517-20.
85. HIRAHARA L, KIRINO Y, SOEJIMA Y *et al*.: Efficacy and safety of apremilast for 3 months in Behçet's disease: A prospective observational study. *Mod Rheumatol* 2020; 16: 1-6.
86. ATIENZA-MATEO B, MARTIN-VARILLAS JL, GRANA J *et al*.: Apremilast in refractory urogenital ulcers and other manifestations of Behçet's disease. A national multicentre study of 51 cases in clinical practice. *Clin Exp Rheumatol* 2020; 38 (Suppl. 127): S69-75.
87. CHUNG SW, BAE M, LEE CW *et al*.: Surgical experience of Behçet's Disease involving the peripheral artery. *Ann Vasc Surg* 2020; 69: 246-53.
88. GAUDRIC J, JAYET J, SAADOUN D *et al*.: Factors influencing the recurrence of arterial involvement after surgical repair in Behçet disease. *J Vasc Surgery* 2020; 72: 1761-9.
89. ELESHRA A, ABDELGAWWAD MS, REGAL S, SOLIMAN M, KHAFAGY T: Short-term outcome of primary stent-graft for peripheral arterial aneurysm in patients with Behcet's disease. *J Vasc Surg* 2021; 73: 279-84.