The 16th International Conference on Behçet’s Disease was attended by delegates from all over the world. Fifteen abstracts were presented orally and 39 in poster talks, with 133 other posters also presented. There were also a number of presentations from ISBD invited speakers.

**Immunology**

The first day of the conference was devoted to basic science. Fabio Martinon (Switzerland) got the first session underway with a presentation on innate immunity. The innate immune system detects pathogens and other danger signals, activating toll-like receptors (TLRs) in the cell membrane and NOD-like receptors within the cell. These receptors regulate inflammatory responses and apoptosis (programmed cell death). An example of this process is gout, where uric acid crystals trigger interleukin-1β (IL1β)-dependent inflammation. Other factors that can cause cells to become stressed include ageing, viral infections, drugs, metabolic imbalance and genetic mutations. In these situations, the repair processes within cells lead to inflammation.

Capucine Picard (France) also spoke about TLRs, showing how herpes simplex virus 1 (HSV1), a double-stranded DNA virus, can act on TLR3 to cause viral encephalitis (acute inflammation of the brain). This mainly occurs in children under 6 years old and results from an impaired interferon response to HSV1 infection in fibroblasts. Deficiencies in signalling through other TLRs, via interleukin-1 receptor-associated kinase 4 (IRAK4) and myeloid differentiation primary response gene 88 (MyD88), are associated with susceptibility to invasive bacterial infections with a high mortality rate in young children. These immune deficiencies seem to improve with age, possibly due to adaptive immunity.

Gilles Kaplanski (France) gave a presentation on IL1 and IL18. IL1β is produced from a precursor in response to infection, while IL1α is present in cells and is released by membrane rupture, leading to IL1β activation and hence inflammation. Increased IL1β production has been seen in active Behçet’s disease (BD), and polymorphisms of the genes for both IL1α and IL1β are associated with BD. Anakinra and gevokizumab are IL1 receptor antagonists that have been shown to reduce eye and joint symptoms in BD. IL18 is another member of the IL1 superfamily that is increased in BD.

Farida Fortune (UK) spoke about the role of the microbiota in BD. Different microorganisms are found on different surfaces inside the mouth. The oral cavity is sterile at birth but rapidly becomes colonised, first with Streptococcus salivarius and then with Strep mutans and Strep sanguinis. The flora increases in complexity until
Oral microbial factors may act as a trigger of BD. Streptococci have a possible role in relapses of BD; dental treatment can sometimes trigger a flare, and poor oral health is a risk factor for severe disease. High levels of \textit{Strep mutans} are seen in severe disease, with increased concentration around oral ulcers. Analysis of DNA from salivary samples from BD patients shows around 90 different microorganisms, with little difference between patients. Certain organisms are increased in orally active disease, while others are decreased. \textit{Rothia dentocariosa} is the organism that varies most, whereas other Rothia species are not affected. The picture is complex, and future studies need to look at subgroups of microorganisms.

In the first oral presentation of an abstract, Kitaichi Nobuyoshi (Japan) described how echinochrome, a pigment present in the shells and spines of sea urchins, can protect cells from oxidative damage. Injection of the pigment significantly reduced the number of inflammatory cells and the concentration of TNF\(\alpha\) and NF\(\kappa\)B in an animal model of uveitis. Echinochrome may therefore be a promising candidate for the treatment of uveitis, particularly as these parts of the sea urchin are usually wasted. Next, Toz Bahtiyar (Turkey) presented research to determine the serum levels of various acute phase reactants and their possible correlation with clinical activity in BD. The researchers found that levels of C-reactive protein (CRP) and serum amyloid A (SAA) were significantly higher in serum samples from patients with active BD than in those with inactive disease and healthy controls. These proteins may have potential for monitoring clinical manifestations and response to treatment in BD.

The second basic science session began with a presentation on adaptive immunity from David Saadoun (France). While the innate immune system is primarily involved in autoimmunity, the adaptive immune system plays an important role in autoinflammation. Infiltration of neutrophils leads to venous and arterial vasculitis. CD4 cells and T cells are also prominent. In BD, many pro-inflammatory cytokines are increased, while the anti-inflammatory IL10 is decreased. T-cell apoptosis is impaired, leading to prolongation of the autoinflammatory response. Interferon-alpha (IFN\(\alpha\)) is pro-inflammatory in some situations and anti-inflammatory in others. In BD, IFN\(\alpha\) promotes a Th1 adaptive immune response and induces IL10, which has an anti-inflammatory effect; in systemic lupus erythematosus, it is pro-inflammatory.

Graham Wallace (UK) gave a presentation entitled “Tumour necrosis factor: one cytokine to rule them all”. TNF\(\alpha\) promotes inflammation, cell infiltration, angiogenesis and acute phase responses (for example, CRP). Of its two most important receptors, TNFR1 is ubiquitous and TNFR2 is present on lymphocytes. TNFR1 is responsible for the pro-inflammatory and apoptotic functions of TNF. Blocking the binding of TNF to its receptor (for example, with infliximab) has been shown to reduce manifestations of BD patients with refractory disease. An expert panel recently concluded that infliximab and adalimumab can be considered as first-line treatment for ocular manifestations of BD.

Romaric Lacroix (France) spoke about the role of microparticles in arterial and venous thrombosis. Microparticles are extracellular vesicles resulting from blebbing
of the cell membrane in response to cell activation or apoptosis. They have a diameter of 0.1–1 μm and have a key role in cellular communication relating to inflammation and thrombosis. They represent a possible biomarker of arterial and venous thrombotic risk. Both pro- and anticoagulation properties of microparticles have been demonstrated, and the ratio of the two may be important. However, no mechanism is yet known by which microparticles can be changed from being predominantly pro-coagulation to being predominantly fibrinolytic.

In an oral presentation of an abstract, Samiul Hasan (UK) described phenotype and functional differences in circulating natural killer (NK) cells in BD. NK cells are the first line of defence in adaptive immunity and are activated early during inflammation. Percentages of NK cells were found to be significantly lower in BD patients than in healthy controls. In addition, CD3-CD56+ bright NK cells were increased, whereas CD3-CD56+ dim cells were decreased. The bright cell population was significantly higher in active BD, while the dim cell population did not differ between active and inactive patients.

**Genetics and epidemiology**

Alfred Mahr (France) gave a presentation on the epidemiology of Behçet’s disease. He discussed a meta-analysis of 31 studies of the prevalence of BD (also presented as a poster). The overall pooled prevalence was 46 per 100,000 people, ranging from 2 in Northern Europe to 162 in Turkey. Census surveys found a much lower prevalence than sampling surveys (5 vs. 117 per 100,000). There is no evidence to suggest that the incidence of BD is declining, but more data is needed. The phenotype of BD differs between the sexes, with males having more ocular manifestations and females more joint symptoms and genital ulcers. Ethnicity is a risk factor for BD and may also affect the phenotype. People of Turkish origin in Germany have a 50-fold higher prevalence of BD compared with the local population, and the prevalence in Paris is higher in those of North African or Asian background. HLA-B51 confers a sixfold risk of BD and is more common in high prevalence areas, but it does not on its own explain the differences and has little impact on phenotype.

Ivona Aksentijevich (USA) spoke about her search for a single disease-causing gene in a Canadian family with BD. Of 21 candidate genes, two were not present in unaffected family members. One of these genes is involved in the tumour necrosis factor receptor superfamily member 9 (TNFRSF9)/CD137 pathway and the other in the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway. Similar mutations have been seen in families from Japan and Turkey.

In an oral presentation of an abstract, Elaine Remmers showed more data related to her genome-wide association study. HLA-B51, known to be associated with BD, is a ligand for a pair of allelic killer immunoglobulin-like receptors present on cytotoxic cells – KIR3DL1, which inhibits cytotoxicity, and KIR3DS1, which activates cytotoxicity. However, PCR assays showed no disease association of KIR3DS1 with
BD, so the role of HLA-B51 in BD is independent of this particular polymorphism. Michael Ombrello (USA) also presented research on HLA types.\textsuperscript{6} Using data from 1190 BD cases and 1257 healthy controls, the researchers identified seven amino acid positions in HLA-A and B molecules that seem to account for the associated risk of BD. Haner Direskeneli (Turkey) presented research on DNA methylation showing that epigenetic modification of cytoskeletal dynamics may underlie the pathogenesis and therapeutic response in BD.\textsuperscript{7}

Isabelle Koné Paut presented the latest data from the PEDBD cohort study.\textsuperscript{8} The cohort includes 230 children, 159 (70%) of them classified as having definite BD with another 12% being probable BD. The average age at onset of disease was 7.8 years, and the average age at definite BD was 14.8 years. Apart from oral ulcers, which were the first symptom in 43%, the most common symptoms in the 159 patients were genital ulcers (55%), ocular (45%), fever (45%), joints (42%), neurological (41%), gastrointestinal (31%) and skin (26%). The best predictive combinations with oral ulcers for a diagnosis of BD were uveitis (97%), skin (80%) and genital ulcers (77%).

Laurent Abi-Rached (France) gave a special lecture entitled “Mixture between modern and archaic humans and the origin of Behçet’s disease”. The MHC class I system (HLA-A, B and C) is the most polymorphic system in humans. For example, there are more than 2500 HLA-B molecules. HLA-B73 contains sequences similar to those seen in chimpanzees and gorillas; it is strongly linked to HLA-C15, which is much more modern. It seems possible that modern humans acquired B73 from archaic humans. Around 1–4\% of the modern human genome in Europe and Asia is of Neanderthal origin, while 6\% of the Papuan genome is of Denisovan origin. Denisovan HLA-A and C haplotypes exist in some modern Asian and Oceanian populations but are rare in Africa, while HLA-B and C alleles from the Neanderthal genome are common in Europe and Asia. All modern HLA-A11 is derived from Denisovan A11; the sequence is identical. HLA-B51:01 and 08, both of which are associated with BD, are found in the Neanderthal genome. This raises the question of whether BD is a Neanderthal disease that did not exist in modern humans before admixture with Neanderthals occurred. However, it seems more likely that Neanderthal admixture increased the incidence of pre-existing BD in the human population by introducing the effect of HLA-B51. The emergence of BD may be linked to changes that are now fixed in modern populations but were not a problem in the absence of B51.

**Clinical sessions**

To start the first clinical session, Gülen Hatemi (Turkey) spoke about quality of life and the socioeconomic impact of BD, and how these can be measured. Quality of life (QoL) can be measured with generic instruments such as SF-36 or EQ-5D or with the BDQoL, a disease-specific instrument. There are also organ-specific instruments to assess the impact of oral or visual manifestations, for example. Vision-related QoL has been shown to improve significantly following treatment with infliximab. The
apremilast study described below also included patient-reported outcomes (presented as a poster), showing that apremilast improved QoL (SF-36 and BDQoL), physical function and patient-reported disease activity. Research also presented as poster found that predictors of worse BDQoL scores included high disease activity, work disability, low household income and neurological damage. Several studies in Turkey have found an association between BD and low socioeconomic status, although it is not clear whether this is a consequence of the disease or a predisposing factor. Work loss and productivity is an area that needs further study.

Eldad Ben-Chetrit (Israel) gave a presentation on contraception, pregnancy and BD. There have been five case reports of BD patients taking the oral contraceptive pill. In three of the cases, the pill suppressed oral and genital ulcers as well as erythema nodosum-like skin lesions. Two other patients taking the contraceptive pill had thrombotic events. It is recommended that patients who have already had a thrombotic event should avoid the contraceptive pill. Twenty-five case reports of pregnancies in BD patients suggest that pregnancy may improve or adversely affect the disease course in almost equal numbers. In seven of 11 case series, the disease course was ameliorated in most patients. Exacerbations are mainly mucocutaneous lesions. A poster reported on a series of 3167 Iranian patients, with 200 pregnancies among them. Half of the patients remained unchanged during pregnancy, a quarter improved and a quarter had aggravated disease. Regarding the effect of BD on pregnancy outcomes, only two out of eight case series reported poor outcomes. No clear predictive factors have been found. There is a non-significant tendency towards more miscarriages and Caesarean deliveries. The former may be due to small thrombotic events in the placenta and the latter to obstetricians wanting to avoid local trauma to the perineum.

Gonca Mumcu (Turkey) presented a new mucocutaneous activity index for BD. The mucocutaneous index (MI) has subscales for genital ulcers, erythema nodosum and oral ulcers. Questionnaire and clinical examination data from 137 BD patients were used to validate the index. The new index was associated with self-reported health status, and a moderate correlation was seen between MI score and Behçet’s Syndrome Activity Score. Emire Seyahi (Turkey) gave a preliminary report on 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scans in large vessel disease due to BD. This type of scan detects hypermetabolism. In a study of 33 BD patients with large vessel disease, the scan was positive in 15 (45%), including 11 (79%) of the 14 patients with pulmonary artery disease. Of 19 patients with venous large vessel, only 4 (21%) had positive scans.

The second clinical session began with a presentation on vital emergencies by Zoubida Tazi-Mezalek (Morocco). Thrombophlebitis was recognised early on as a symptom of BD and is one of the main causes of mortality. Vascular manifestations of BD need to be identified and treated as early as possible to reduce this risk. Vasculo-BD is more common in European and Middle Eastern populations than in Japan, where it is very rare. Venous involvement includes deep vein thrombosis (mainly in the legs) and cerebral vein thrombosis leading to raised intracranial pressure. The latter accounts for about 30% of neurological manifestations of BD.
Budd–Chiari syndrome is caused by occlusion of the hepatic veins; it has a severe presentation with abdominal pain and acute liver problems. Arterial events include aortic, peripheral and pulmonary aneurysms. Pulmonary artery aneurysms occur almost exclusively in men and are the inaugural BD symptom in 10–15% of cases. They can be asymptomatic, so at-risk patients should have regular CT scans. About 10% of patients with vasculo-BD have systemic arterial disease, and 75% of them present as emergencies. Vascular manifestations are not included in the ISG criteria for BD, but they are the inaugural symptom in 10–30% of patients. Inclusion of vascular disease in the new criteria may lead to earlier diagnosis, and thus treatment. EULAR recommends corticosteroids and immunosuppressive therapies, but not anticoagulants. However, the risk of bleeding with anticoagulation is probable overestimated and can be reduced by immunosuppressive therapy.

Vedat Hamuryudan (Turkey) described a patient with fatal pulmonary artery involvement in BD. The 33-year-old man may have died as a result of bleeding from the bronchial arteries. Bronchial artery enlargement is part of the pulmonary vasculitis seen in BD, and can be fatal. Embolisation can be life-saving and has a high success rate (73–99%), but 10–55% of patients will have a recurrence.

Gulen Hatemi (Turkey) then spoke about outcome measures in BD. Many measures are used in clinical trials, but an agreed minimum core set of validated measures is needed to ensure consistency and allow comparisons and combination of data. A recent systematic review identified 139 outcome measures used in BD clinical trials. A group of 35 experts were in agreement that a composite measure for overall disease is needed and that this should include input from patients. Data need to be collected to make this possible. Organ-specific outcome measures are also needed. Patient-reported outcomes are essential, but studies are needed to understand their utility.

In an oral presentation of an abstract, Yilmaz Ozyazgan (Turkey) proposed a new uveitis damage score for BD. The score is graded from 0 (no ocular involvement) to 5 (total optic atrophy, end-stage vaso-occlusive changes and massive pigment alterations). The score was tested retrospectively in a cohort of 50 patients with BD eye disease, and a good correlation was seen between damage scores and changes in visual acuity over time. To finish this session, Seema Kalra (UK) described the development of the new international consensus recommendations for the diagnosis and management of neuro-Behçet’s disease. A systematic literature search was followed by a consensus process, and 16 recommendations were agreed. Definite and probable neuro-BD are defined and classified as parenchymal, non-parenchymal and peripheral.

**Therapeutics**

Following on from the presentation by Seema Kalra, Adnam Al-Araji (UK) presented some of the new neuro-BD consensus recommendations. There have been no randomised controlled trials in this area, as it is an uncommon manifestation of a
rare disease. Headache is the most common neurological symptom of BD, but only about 10% of headaches in BD patients are due to neuro-BD; most are migraine or tension-type headaches. Diagnosis of neuro-BD involves MRI scanning and lumbar puncture. The recommendations on management of neuro-BD are numbers 11, 12 and 13. For a parenchymal neuro-BD attack, corticosteroid treatment is recommended, with a disease-modifying therapy such as azathioprine in the case of a relapse. Biologic agents are recommended when first-line therapies are ineffective. Corticosteroid is also recommended for cerebral venous thrombosis, with consideration of anticoagulation and disease-modifying therapy.

Ilknur Tugal-Tutkun (Turkey) spoke about new therapeutic perspectives in BD eye disease. Uveitis affects about half of patients with BD and follows a relapsing-remitting course. The number and severity of attacks determine the long-term prognosis. Male patients have a greater risk of visual loss, but the risk is now lower than it was in the 1990s, mainly due to more aggressive treatment. A trend to milder disease in recent years has been reported in Japan and Korea. The goals of management are to treat acute attacks and chronic inflammation, prevent recurrences and achieve sustained remission. A single infliximab infusion has been shown to be effective in acute uveitis. Interferon-alpha has been shown to produce a rapid and dramatic improvement of intraocular inflammation, has been successful in treating refractory BD uveitis, and has the potential to induce long-term remission in around half of patients. However, there is no consensus on the optimal dose or duration of treatment, adverse effects can be a problem, and about 10% of patients do not respond to interferon. Infliximab also has the potential to induce long-term remission and has been licensed for BD uveitis in Japan. A US expert panel has recently recommended infliximab (and adalimumab) for first-line treatment of ocular manifestations of BD, while another expert panel recommends interferon first line. There are case reports of successful treatment of BD uveitis with newer drugs such as tocilizumab, sarilumab and alemtuzumab. The most promising seem to be anakinra, canakinumab and gevokizumab. Clinical trials are underway with these agents.

Mitsuhiro Takeno (Japan) presented research in 160 BD patients treated with infliximab, in whom drug concentrations and antibodies against infliximab were measured.16 Infusion reactions were more common in the patients with antibodies. Drug concentrations were lower in patients with persistent symptoms, and these patients were also more likely to have anti-infliximab antibodies. Shortening the interval between infusions restored efficacy in some patients, while others benefitted from a switch to adalimumab. Hélène Vallet (France) presented data on the efficacy and safety of anti-TNF agents in uveitis from a French multicentre registry.17 Among 213 patients with inflammatory uveitis, 38 had BD; the uveitis was mainly bilateral (80%) and chronic (88%). Most patients (60%) were treated with infliximab, with 37% receiving adalimumab. A complete response was seen in 56% and a partial response in 33%, and patients were able to reduce their corticosteroid doses. The relapse rate was significantly reduced. About a quarter of patients had adverse effects, the most common being infection.
Petros Sfikakis (Greece) gave a presentation on advances in the treatment of BD with biologics. BD patients most likely to benefit from anti-TNF therapy are those with a definite diagnosis, active disease and signs of inflammation, and an inadequate response to immunosuppressive drugs. The best candidates are patients with acute, sight-threatening eye disease; EULAR recommends anti-TNF agents as an add-on therapy in patients with refractory eye disease. Both infliximab and adalimumab have also now been shown to be effective in major vessel disease. A Japanese consensus statement recommends them as standard treatment for gastrointestinal involvement, while the new neuro-BD consensus recommends them as second-line treatment. Infliximab is the most used TNF inhibitor, but adalimumab is also effective and there are some case reports of success with golimumab. Infliximab is faster and more effective than steroids as rescue therapy in acute uveitis, and a single infusion should be considered for attacks of pan-uveitis. A single intravitreal injection of infliximab is also effective, but less so than an intravenous infusion. Infliximab is also effective against skin, gastrointestinal, central nervous system and joint manifestations. Non-TNF biologics that are being tested in BD include secukinumab (anti-IL17), XOMA (anti-IL1) and tocilizumab (anti-IL6).

The programme concluded with oral presentations of two abstracts on studies of new potential therapies for BD. Ahmet Gül (Turkey) showed data from an open-label study of gevokizumab (anti-IL1) in BD uveitis. The study randomised 21 BD patients (17 with acute uveitis and 4 considered to be at risk) to receive 30 or 60 mg of gevokizumab, intravenously or subcutaneously, every month for a year on top of stable immunosuppressive therapy and corticosteroids. All evaluable patients experiencing an acute exacerbation responded to gevokizumab, most of them within a week and all within 3 weeks. Marked improvement in visual acuity was seen, as well as improvement in retinal lesions. No serious adverse events related to gevokizumab were reported. Finally, Gulen Hatemi (Turkey) reported a randomised, double-blind trial of apremilast (an oral phosphodiesterase 4 inhibitor) versus placebo in BD. Patients (n=111) with active oral ulcers but no major organ involvement were randomised to receive apremilast or placebo for 12 weeks, after which all patients received apremilast for a further 12 weeks. At week 12, apremilast-treated patients had significantly fewer oral ulcers, with 71% achieving a complete response compared with 29% for placebo. All 10 apremilast-treated patients with genital ulcers achieved a complete response. Apremilast was generally well tolerated.

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References


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