The 18th International Conference on Behçet's Disease
De Doelen, Rotterdam, Netherlands, 13–15 September 2018

The 18th International Conference on Behçet's Disease took place in the Dutch port city of Rotterdam. The programme included three keynote lectures, 22 presentations from ISBD invited speakers, 10 oral presentations of accepted abstracts, 140 e-posters, one debate and three sponsored symposiums.

Mihai Netea (Netherlands) started proceedings with a keynote lecture entitled 'Innate immunity'. The innate immune system provides the first line of defence from infection in a non-specific manner. Unlike adaptive immunity, which responds more slowly to specific threats, the innate system does not build memory. Although improved response on a second exposure (the basis of vaccination) is an evolutionary advantage, only vertebrates (about 5% of all species) have an adaptive immune system, whereas innate immune systems are found in all classes of plants and animals. However, some plants and invertebrates that survive infections become more resistant. Mice with a deficiency in adaptive immunity can develop some protection against future infections. This is known as trained immunity, a form of innate immune memory with features distinct from classical adaptive immune memory. It involves reprogramming of myeloid cells, with activation of the cholesterol synthesis pathway. A metabolite called melavonate is important in this process. Monocytes of patients with hyper immunoglobulin D syndrome (HIDS), who are deficient in mevalonate kinase and accumulate mevalonate, have a constitutive trained immunity phenotype. There is also evidence that BCG vaccination against tuberculosis provides non-specific protection against other infections through a training effect on monocytes and bone marrow progenitor cells. Finally, trained monocytes produce pro-inflammatory cytokines and may contribute to chronic inflammation.

Basic science

As usual, the first session of the conference was devoted to basic science. Andre Uitterlinden (Netherlands) spoke about the complex genetics of common diseases. Human DNA is highly variable, with more than 150 million variable loci contributing to the necessary heterogeneity of the

population. The Rotterdam Study has been running for 25 years and includes around 20,000 people aged over 45. With more than 2 billion data points, this is an example of 'big data' and is examining how DNA changes as a result of environmental factors. Osteoporotic fractures, for example, have a complex phenotype. Risk factors include bone strength, fall risk and impact force, and these are influenced by genetic factors (DNA) and dynamic genomics (RNA, epigenetics, DNA methylation, etc). The populations of Holland and Belgium have similar genetics but a different diet, with different calcium intake affecting bone strength, for example. Monogenic diseases, such as cystic fibrosis and sickle cell disease, arise from mutation in a single gene and can be investigated by whole genome sequencing. The common diseases have more complex genetics and are investigated by genome-wide association studies (GWAS), which look for associations with genetic variants. A study of 140,000 people in the UK Biobank found genetic variants that accounted for about 20% of the heritability of bone mineral density. The cost of DNA analysis has decreased in recent years, and the time has come to start using it as a clinical tool. It is also necessary for researchers to collaborate and publish meta-analyses of large amounts of data rather than multiple publications of small amounts of data.

Eun Ha Kang (Korea) then gave a presentation on the genetic aspects of Behçet's disease (BD) in Asia. The strongest evidence is for HLA-B51, with the prevalence of BD in a population largely depending on the prevalence of HLA-B51. This association is lower in Korea than in the rest of Asia. Another association, especially in B51-negative people, is with HLA-A26. This association is higher in Japan than in Korea, and is not seen in Chinese people. Two MICA polymorphisms are also important – one of these seems to be associated with HLA-B51 while the other is independent. MICA has a role in the pathogenesis of BD. TNFα also plays a central role in BD, but the TNFα promoter polymorphism has a lower association in Asia than in other populations. In addition, a GWAS in Korea did not find any association with the IL10 and IL23R-IL12RB2 variants seen elsewhere.

Next, Ivona Aksentijevitch (USA) spoke about BD-like diseases and their genetic association with BD. There are several rare monogenic diseases with similarities to BD. A family in Canada has several members diagnosed with BD, but the inheritance is dominant and the family members are HLA-B51 negative. Two candidate genes have been identified – tumour necrosis factor (TNF) receptor and TNFα-induced protein-3 (TNFAP3). Another family (also HLA-B51 negative) has systemic lupus erythematosus (SLE) and BD-like features, and a mutation in the TNFAP3 gene has been identified. Low-prevalence single-nucleotide polymorphisms (SNPs) in this gene are associated with multiple autoimmune diseases, including SLE, psoriasis, type 1 diabetes, inflammatory bowel disease (IBD) and rheumatoid arthritis (RA), as well as with protection against asthma and allergies. A20 is an anti-inflammatory protein that regulates cell death and has a tumour suppressive function. Patients with haploinsufficiency of A20 (i.e. only one copy of the gene is functional) have several BD-like features. Onset is usually in childhood, and fever, autoantibodies and polyarthritis are more common than in BD.

To round off the session, Ahmet Gül (Turkey) gave an overview of the genetics of BD and the consequences for disease phenotypes. HLA-B51 and ERAP1 are the most important genetic factors in defining the phenotype, while other factors are important as triggers of disease. The distribution of HLA-B51 in populations is similar to the distribution of BD. B51 has a strong association with 'classic' symptoms of BD such as mucocutaneous, joint and eye symptoms, but less association with gastrointestinal, vascular and neurological manifestations. HLA-B15, B27 and B57 are also risk alleles,

while HLA-A26 confers risk in Asian populations. There are also protective HLA alleles, including B49 and A03. B51-positive people can also have polymorphisms in ERAP1. ERAP1 haplotype 10 is particularly associated with BD, while haplotypes 1 and 3 are associated with ankylosing spondylitis (AS) and psoriasis. The link between ERAP1 haplotypes and hyperinflammatory responses has not yet been elucidated. However, it is clear that genetic susceptibility combined with environmental triggers lead to a hyperinflammatory response involving the innate and adaptive immune systems, which results in the clinical manifestations of BD and similar diseases.

In the first oral presentation of an abstract, Elaine Remmers (USA) reported on a whole-genome imputation study looking for new genetic loci contributing to BD.[1] The researchers used data from the original Turkish GWAS study, including 311,459 markers in 1278 BD patients to impute genotypes of over 5.9 million markers. They identified a marker in the TLR2 locus that seems to confer risk for BD by increasing the innate immune response against microbes. The morning was completed by Maria Padula (Italy), who presented results from a study of ERAP1 polymorphisms in BD and AS in Italian patients.[2] Using DNA from 51 BD patients and 53 AS patients, the group found a different distribution of the most common ERAP1 coding variants in the two diseases. In particular, the rs17482078 genotype was more common in the BD patients; this SNP is thought to be associated with risk of BD but protective against AS.

The basic science session continued in the afternoon, with a presentation on microbiomes from Marcel de Zoete (Netherlands), who described the microbiota as the forgotten organ. Each microbiota is unique and is composed of 100 to 200 bacterial species, as well as 150 times more genes than human cells. The microbiota affects health and disease in many ways, being involved in obesity, colon cancer, IBD, metabolic syndrome and possibly autism. Patients with IBD have been shown to have an altered (dysbiotic) microbiota, with some species being absent and some extra species being present. The hypothesis is that an 'inflammatory' member of the microbiota causes low level inflammation that leads to chronic disease. Immunoglobulin A (IgA) secreted into the gut neutralises bacteria and can be used to identify the species by staining and sequencing the IgA-coated bacteria. This approach has been validated in mice and has been used to show a lot of extra IgA-coated bacteria in the faeces of IBD patients. Healthy volunteers have fewer IgA-coated bacteria, and a different pattern. Cultures of IgA-positive bacteria from IBD patients trigger severe colitis in germ-free mice, while IgA-negative cultures trigger mild colitis; IgA-positive cultures from healthy people trigger only mild colitis. IgA-positive *Bacillus fragilis* has been shown to adhere to intestinal cells and to be enriched in enzymes that degrade mucus. BD patients have more IgA-positive Bifidobacteria species than healthy people, and this could represent a future target for treatment.

Giacomo Emmi (Italy) then spoke about the role of the microbiome in BD. He explained that short-chain fatty acids such as butyrate have an important role in maintaining gut health. BD patients have decreased diversity of gut microbiota species, with depletion of genera that produce butyrate. The salivary microbiota is also less diverse; immunosuppressant treatment increases some species, but improving oral health does not increase diversity. However, in Japan, no difference in diversity was seen between BD patients and healthy controls, and immunosuppressants had no effect on diversity. Vegetarians have more butyrate-producing species and decreased inflammatory markers. Approaches to improving the microbiota include prebiotics (compounds that induce the growth or activity of beneficial bacteria) and probiotics (live bacteria), as well as postbiotics which contain bacterial metabolites such as butyrate. A lacto-ovo vegetarian diet and supplementation with

butyrate both increase the ability of plasmin to degrade thrombus, which decreases the risk of inflammation-induced thrombosis.

Next, Haner Direskeneli (Turkey) gave a presentation on epigenetics, which involves changes in phenotype without genetic changes, brought about by environmental factors such as ageing or smoking. One example is DNA methylation, which suppresses gene expression; it is decreased in BD and can be restored by colchicine treatment. Hypermethylation of the promoter region of the interleukin (IL)-10 gene leads to reduced production of IL-10 (an anti-inflammatory cytokine) in BD patients, while hypomethylation of the IL-6 promoter region results in increased IL-6 (a pro-inflammatory cytokine). Ocular BD is associated with aberrant methylation of IRF8, a transcription factor that plays a critical role in myeloid cell maturation. Another epigenetic mechanism involves micro RNAs, which are small, non-coding RNA molecules involved in RNA silencing and post-transcriptional regulation of gene expression. There are more than 900 miRNAs in mammals, and they are affected by inflammatory responses. For example, miR155 is decreased in the peripheral blood mononuclear cells and dendritic cells of BD patients with active uveitis. Some miRNAs are increased in BD, while others are decreased, and miRNA profiling in BD patients shows many affected genes and pathways, such as neutrophils, cell adhesion and oxidative stress. However, most of these studies have not been replicated, and the functional effects have not been studied. DNA methylation inhibitors have been investigated in some cancers, but have not yet been looked at in autoinflammatory diseases.

Two more oral presentations of abstracts followed. First, Seonghyang Sohn (Korea) showed data on the chemokine receptor CCR1 and its ligand CCL3 in a mouse model of BD,[3] suggesting the upregulation of CCR1-positive cells is related to the control of systemic inflammation in BD. However, an audience member questioned the validity of mouse models in BD. Harry Petrushkin (UK) then presented interesting research on the role of the KIR gene cluster, which co-evolved with HLA and is expressed in innate immune cells.[4] This work used DNA from 267 UK BD patients and 445 healthy controls. The combination of low expressing KIR3DL1 allotype and KIR3DS1 was associated with ocular BD, whereas high KIR3DL1 and null KIR3DR1 provided protection against mucocutaneous disease. This research may offer insight into the pathogenic role of HLA-B51 and its interaction with KIR3DL/S1.

The first day of the conference finished with a special lecture by Graham Wallace (UK) on the biomechanisms of BD. He began by pointing out that the association of HLA-B51 with BD is well known, but the exact role of B51 is not well understood and many BD patients are B51-negative. B51 is a very old protein, so it must be important to have been conserved during evolution. In addition to B51, and other common polymorphisms in IL-10 and IL-12R/23R, more than 45 SNPs have been found to be associated with BD, some of them only in particular parts of the world. For example, PTPN22 (protein tyrosine phosphatase, non-receptor type 22) is found in 18% of BD patients in northwestern Europe but is not seen in the Far East. However, many of the different genes identified may be involved at different places in the same pathways. For example, PTPN22 in Europe and GIMAP in the Far East are both involved in lymphocyte regulation. This means that it is important to look at pathways rather than individual genes. A similar situation is seen with the influence of the microbiome and dietary on BD. Certain foods trigger oral ulcers in BD patients, with different foods triggering the same pathways (e.g. histamine release) in different countries. Metabolomic analysis is the large-scale study of small molecules (metabolites), within cells, biofluids, tissues or organisms. A

clear separation is seen between patients with BD and early arthritis, and this may help to identify pathways for further investigation. Research is trying to link polymorphisms to metabolomics differences in different parts of the world. Dr Wallace concluded by saying that greater understanding is needed of the role of HLA-B51, the cells involved in BD, and the role of the microbiome and the diet.

Nature versus nurture

The second day began with a debate entitled "Nature or nurture: does migration change the prevalence of BD?". Yohei Kirino (USA) began by making the case for the role of nature, laying out six reasons why BD can be considered a hereditary disease. These are prevalence depending on ethnicity, the association with HLA-B51, identification of identical IL-10 and IL-23R SNPs in Turkey and Japan, familial cases of BD, reduction of heterogeneity by population stratification (e.g. ERAP1), and the evolving genotype in Japan (and other phenotype clusters, such as ocular and neurological manifestations versus gastrointestinal and vascular symptoms). Haner Direskeneli (Turkey) then presented a case for the role of the environment, pointing out that migration changes the prevalence of BD. The prevalence of BD is decreasing worldwide, with good data from Korea showing a reduction from 7.4 to 2.5 per 100,000 between 2006 and 2015. In Japan, the rate of HLA-B51 positivity in BD patients is also decreasing, and BD is evolving to become more like IBD. It is likely that changes in phenotype are related more to environmental factors than to genetics. The discussion that followed unsurprisingly concluded that both nature and nurture are important. Environmental factors alone will not trigger BD in a person with no genetic tendency. Shigeaki Ohno (Japan), who has looked at BD among descendants of Japanese emigrants in Hawaii and Brazil, pointed out that the incidence of BD is very low in these groups, although their prevalence of HLA-B51 is the same as in Japan. It may be that the early immigrants had a high prevalence of BD, but after three or generations the effect of the environment has reduced the incidence. It is notable that the incidence of other genetic diseases is the same as in Japan. It was agreed that environmental factors are important in determining the severity of BD, but that a genetic predisposition is essential for the disease to develop.

The oral presentations of abstracts continued with Yutaro Soejima presenting the data on clustering of BD types in Japanese patients that had been discussed in the preceding debate.[5] Analysis of 691 patients identified three subgroups: group A includes ocular and neurological manifestations, group B includes gastrointestinal and vascular symptoms, and group C patients have primarily mucocutaneous symptoms (oral/genital ulcers and skin lesions). The group A cluster has declined in incidence since the 1990s, while the B cluster has increased. It was pointed out that gastrointestinal symptoms are a minor feature in the Middle East and are not included in the international criteria for BD. Gülem Hatemi (Turkey) had presented the main results of a clinical trial of apremilast in BD (207 patients) at the 2016 conference, showing a significant effect on oral ulcers. This time, she showed the results for patient-reported outcomes, including measures of disease activity and quality of life.[6] Significant improvements were seen in all the measures, showing that the reduction in oral ulcers with apremilast was associated with decreased disease activity and increased quality of life. To finish the session, Farhad Shahram (Iran) reported on 204 paediatric cases from the Iran registry of BD.[7] These cases, 2.7% of the 7504 patients in the registry, represent the largest paediatric BD cohort

reported. The mean age of disease onset was 10.5 years. Ocular lesions were more common than reported in other cohorts, while genital ulcers, skin lesions and gastrointestinal involvement were less common.

Organ involvement in BD

The first clinical session began with a talk on large vessel vasculitis by David Saaduin (France), who explained that BD can involve both arteries and veins of all sizes. Vascular manifestations include deep vein thrombosis (DVT), pulmonary artery aneurysm (PAA)/thrombosis and dural sinus thrombosis. Vascular infiltrates include neutrophils, T cells and NT cells, and imaging shows inflammation of the vessel wall. There is geographical variation in the incidence of vasculo-BD, and both incidence and severity are higher in male patients. Large vessel vasculitis tends to be recurrent. The most common vascular manifestation is venous thrombosis, especially DVT in the legs. Aortic aneurysm is the most common arterial manifestation. Superficial thrombophlebitis, caused by a blood clot just below the surface of the skin, is a risk factor for DVT and must be recognised and treated. Cerebral venous thrombosis represents 30% of neuro-BD and 10% of vasculo-BD; it is strongly associated with DVT in the legs. Budd–Chiari syndrome is a rare but severe presentation that is often associated with inferior vena cava thrombosis; early treatment improves the prognosis. Another manifestation that must be diagnosed as soon as possible is pulmonary embolism, which is caused by pulmonary venous thrombosis and associated with pulmonary artery thrombosis and aneurysm. The new EULAR recommendations say that vasculo-BD should be treated with corticosteroids and immunosuppressive drugs, with anti-TNF agents in refractory cases and possible use of anticoagulants. In DVT, immunosuppression and anticoagulation have been shown to be better than anticoagulation alone, while PAA is best treated by embolization and immunosuppression. Anti-TNF therapy can produce regression of PAA, avoiding surgery and reducing the risk of relapse. Overall, early diagnosis and aggressive treatment can improve the prognosis of vasculo-BD.

Farida Fortune (UK) then spoke about oral manifestations, emphasising their effect on quality of life, ability to work and psychosocial functioning. Examination of the mouth is not well taught in medical schools, and many dentists are not trained in clinical medicine. The mouth is complex, including several different types of tissue in the tongue, hard palate and cheeks. On top of all the tissue is the saliva, which is different from other mucosa in the body (e.g. gut or vagina), while the salivary glands are different from other glands. Periodontal disease is important, with Gram-negative bacteria being involved, while different organisms are found in the saliva of BD patients with active ulcers. Oral ulcers occur in 15–25% of the population and in 30–40% of relatives of BD patients. They can be caused by many factors, such as trauma, infection, nutritional deficiency or cancer, and patients can be wrongly diagnosed with BD. One distinction is that the outside of the lips is not affected in BD. The ulcers in patients with Crohn's disease are similar to those in BD, whereas ulcers seen in ulcerative colitis patients are quite different. SLE patients also have distinctive ulcers with 'star flaming'. The 2014 criteria allow patients to be diagnosed with BD on the basis of having both oral and genital ulcers, but they may not have BD. It is important that the unique features of BD are recognised.

The session continued with a presentation on the eye by Ilknur Tugal-Tutkun (Turkey). He said that uveitis is a result of intraocular inflammation, and 90% of cases of uveitis in BD are in males. BD uveitis can be both anterior and posterior; it is usually bilateral, although isolated anterior uveitis occurs (about 10% of cases, often female). Around 90% of BD uveitis has posterior segment involvement, and a minority of patients have conjunctival ulcers and other manifestations. BD uveitis typically manifests as recurrent acute episodes, which can be explosive; spontaneous resolution is common. Macular ischaemia can lead to permanent visual loss, while chronically leaky retinal capillaries increase the risk of macular oedema. The differential diagnosis of BD uveitis includes several other diseases, and BD patients can also develop uveitis from other causes. Fundus fluorescein angiography is useful in the differential diagnosis, while optical coherence tomography is a quick and non-invasive method of visualising the characteristic features of retinal infiltrates in BD. Colour fundus photography shows the transient nature of retinal infiltrates. Work is ongoing to define and validate criteria for the diagnosis of ocular BD.

Next, Gulsen Akman-Demir (Turkey) spoke about neurological aspects of BD, pointing out that not every neurological symptom in BD patients represents neuro-BD. A thorough history and examination, including magnetic resonance imaging (MRI) and analysis of cerebrospinal fluid (CSF), are needed to make a diagnosis. About 70% of neuro-BD is parenchymal, involving the brainstem and/or the spinal cord; another 20% is represented by dural sinus thrombosis (presence of a blood clot in the dural venous sinuses, which drain blood from the brain), and 10% have atypical multiple sclerosis (MS)-like symptoms. The CSF is usually abnormal in parenchymal disease and normal in dural sinus thrombosis, and the prognosis is better in the latter. Particular care needs to be taken regarding complications of treatment and of common co-morbidities in patients with atypical neuro-BD. Care is also needed in patients with typical neuro-BD symptoms who do not fulfil the criteria for BD. Headache in BD patients is usually migraine or tension headache rather than a symptom of neuro-BD. Neuro-BD can present with headache, however, but other neurological findings are needed for the diagnosis to be made. MS-like neuro-BD should be treated more like MS than BD, and anti-TNF agents should be avoided. Any MRI features that do not respond to steroids are not neuro-BD. There is no class I evidence for treatment of neuro-BD. The recommended approach is high-dose intravenous methylprednisolone for an acute attack, followed by tapering of the steroid and introduction of immunosuppressive therapy. First-line immunosuppressants are the conventional drugs such as azathioprine, with interferon or a TNF inhibitor in refractory patients.

The last presentation in this session was on the skin and was given by Bing Thio (Netherlands). Mucosal lesions (skin lesions and oral or genital ulcers) are not life-threatening and do not cause serious damage, but they reduce quality of life. They are also important in the diagnostic criteria for BD; 97% of patients have oral ulcers, and 75% have genital ulcers. The microbiome plays a large role in these ulcers; it has been proposed that a ‘disease-associated microbial community’, deficient in butyrate-producing bacteria, can induce epithelial barrier damage, allowing entry of damaging molecules. Autoinflammatory processes in the skin involve neutrophils, macrophages and IL-1. Manifestations such as pyoderma gangrenosum and erythema nodosum are typical of BD. The risk of post-thrombotic syndrome (redness, swelling, ulcers and chronic leg pain following DVT) may also be increased. Treatment of skin lesions in BD usually involves topical corticosteroids, colchicine and azathioprine, with biologics such as TNF inhibitors and the IL-1 inhibitor apremilast also having a role.

‘Capita selecta in BD’

This session included a variety of clinical topics, starting with Eldad Ben-Chetric (Israel) speaking about pregnancy and contraception in BD patients. Most people with BD are in their reproductive years, so this is an important issue. Both the effect of pregnancy and contraception on BD and *vice versa* are matters of concern. Some retrospective case series have been published, but very few include comparisons with controls. In one series, four out of six cases reported a decrease in mucocutaneous symptoms with oral contraceptive use, while the other two worsened. In case reports of 32 pregnancies in BD patients, 14 had reduced disease activity, 16 worsened and two were unchanged; it cannot be excluded that these findings were simply due to chance. In 15 case series including 1164 pregnancies, 37% improved, 23% worsened and 40% were unchanged. However, there is a possibility that cases of deterioration are more likely to be reported. In addition, some patients have a different disease course in different pregnancies. If disease exacerbation occurs, it can be in any trimester. In 11 case series, outcomes of pregnancy were similar to those in healthy women, with a possible tendency to increased rates of miscarriage and caesarean section. The risk of miscarriage may be related to thrombotic events, while caesarean sections may be due to fetal distress or risk of perineal trauma.

Annet van Rooyen (Netherlands) then spoke about BD in children, which accounts for between 3% and 36% of cases. The average age of onset is 7–8 years, and oral ulcers are the first symptom in 80%. BD in children is more likely to be familial than it is in adults. It is usually 2–3 years before the second symptom appears, which can delay diagnosis. However, there is a large overlap with other autoinflammatory diseases, so it is important not to rush to a diagnosis. Among a cohort of 219 children with possible BD in 12 countries, 156 have a confirmed diagnosis. Fever is reported as a symptom in almost 44%, which is very different from BD in adults. Genital ulcers are less common than in adults (55% versus 80%), as are ocular symptoms. This cohort has been used to develop new PEDBD criteria, in which fulfilment of 3/6 items represents BD. All suspected BD in children should be documented and followed up to confirm the diagnosis. Treatment of paediatric BD is similar to that in adults, with short courses of steroids, immunosuppressants such as azathioprine and mycophenolate mofetil, TNF inhibitors and IL-1 or IL-6 inhibitors. Clinical trials never include children, but this needs to be reconsidered so that data can be collected.

Next was a presentation on cardiovascular risk factors and surgery in BD patients, given by ISBD President Dorian Haskard (UK). Any operative procedures in BD patients carry a risk of a pathergy reaction, including insertion of cannulas and catheters. Dental procedures can trigger oral ulcers, while general and cardiovascular surgery may lead to postoperative aneurysms or saphenous vein graft thrombosis. Vascular surgery can cause graft thrombosis, aneurysm, vessel occlusion or fistula formation. Gastrointestinal surgery has a 50% recurrence rate and can cause perforation, fistula formation and obstruction. Poor surgical outcomes in BD result from amplified inflammatory responses. There is ‘cross-talk’ between inflammation and thrombosis, which are linked by tissue factor. Tissue factor-bearing microparticles in blood plasma increase the thrombogenic potential, with a positive feedback loop leading to increased inflammation. In addition, corticosteroids, immunosuppressant drugs and biologics increase the risk of infection and impair wound healing. It is nevertheless important to suppress inflammation as much as possible before planned surgery, but this is more difficult for emergency surgery.

The second day of the conference was completed by the final three oral presentations of abstracts. Tom Missotten (Netherlands) described a study comparing interferon and anti-TNF therapy in a cohort of 52 BD patients with uveitis.[8] Of the 100 eyes, 31 were treated mainly with anti-TNF agents (mostly adalimumab) and 12 were treated mainly with interferon. The 10-year visual outcomes did not differ between the two groups, and neither did the inflammatory activity. Fatma Alibaz-Oner (Turkey) then presented data on venous vessel wall thickness in the legs in male BD patients.[9] Venous thrombosis due to vascular inflammation is the most common form of vascular involvement in BD, and this study showed that vascular wall thickness was increased in 61 male BD patients (30 with vascular involvement) compared with 37 healthy controls and 27 patients with AS. If it can predict future vascular involvement, this may be a useful diagnostic tool. The final presentation of the day was by Amal Senusi (UK), on the association of alpha-melanocyte stimulating hormone (α-MSH) and vasoactive intestinal peptide (VIP) with fatigue and quality of sleep in BD.[10] The study included 100 BD patients and 30 healthy controls, and found that both α-MSH and VIP were higher in the BD patients. α-MSH (as well as IL-6) was associated with both fatigue and poor sleep quality, while VIP was associated with poor sleep quality and disease activity. A better understanding of these complex interactions might lead to the development of novel approaches to manage fatigue and sleep disorders as well as disease activity in BD patients.

New therapeutic strategies

The final morning of the conference was dedicated to treatment of BD. The first presentation, by Marjan Versnel (Netherlands), was on targeting interferon type I and II pathways in autoimmune diseases. Type I interferons include interferon alpha and beta, while interferon gamma is type II. Type I interferons are produced by plasma B cells and activated T cells, monocytes and macrophages. A 'signature' of interferon type I-induced gene expression has been identified in Sjögren's syndrome, allowing patients to be classified as type I-positive or negative. Type I-positive patients have increased disease activity compared with negative patients. The signature is not specific to Sjögren's syndrome, and type I-positive SLE and RA patients have also been identified. A type I receptor blocker is being tested in SLE; 34% of patients met the primary endpoint in a phase 2 study, and a phase 3 trial is ongoing. A type II signature has also been identified in Sjögren's syndrome, and some patients are positive for both types. Type I interferonopathies are rare monogenic immunodeficiencies, and the TBK1 (TANK binding kinase-1) pathway (involving TLR7/9 signalling) has been identified as playing an important role. TBK1 is increased in type I-positive patients with Sjögren's syndrome, SLE and systemic sclerosis; a TBK1 inhibitor is a potential treatment. Janus kinase (JAK) inhibitors block both type I and II interferons and are a potential treatment for patients positive for both signatures. The JAK/STAT pathway is activated in BD, and type I interferon is used as a treatment for BD. Research is needed to look at interferon signatures in BD and determine whether subgroups based on these might be useful in selecting and monitoring treatment.

Martin van Hagen (Netherlands) then spoke about biosimilars in BD, explaining that while generic forms of small molecule drugs are identical to the original drug, biosimilars are highly similar, but not identical, to the original biologics. Biologics are defined as proteins containing more than 40 amino acids and manufactured using DNA technology. They are a mix of structurally related isoforms, with differing glycosylation, and even the reference products change over time. In some cases, a

biosimilar may look more like the original reference product than the current reference product does. An infliximab biosimilar was approved for use in RA, spondyloarthritis and IBD in 2016. No clinical trials of biosimilars have been done in rare diseases. One observational study looked at 48 patients with rare autoinflammatory diseases (12 with BD) who were switched from infliximab originator (Remicade) to biosimilar (Remsima). Two patients switched back due to adverse events; after 6 months, another six had switched back and five had stopped treatment. No differences in various efficacy and safety measures were seen (including BD activity), but two patients with sarcoidosis experienced seizures and two had worsening polyneuropathy. A systematic review of 57 studies of biosimilars in any disease identified important evidence gaps around the safety of switching between biologics and their biosimilars. A report of three BD cases documented rapid disease relapse after switching from Remicade to Remsima, possibly due to cross-reaction of anti-infliximab antibodies.

Next, Peter Sfikakis (Greece) gave an update on anti-TNF therapy, concentrating on timing of tapering. TNF inhibitors, especially infliximab, are the key biologic drugs used in BD and have been used since 2001 to treat BD uveitis. Tapering of therapy is possible, as some early patients have remained relapse-free for 10 years when treatment was stopped after 3 years. Infliximab has been shown to be effective in long-term treatment of uveitis, with 41% of patients not relapsing during 4 years' treatment, and it has also been shown to be more effective than adalimumab. Earlier use of infliximab achieves better outcomes, and it is a useful therapy for gastrointestinal, vascular and neurological manifestations of BD as well as uveitis. A Japanese study found that safe, pre-planned discontinuation of infliximab therapy can be performed in patients with Behçet's uveitis. In a study of infliximab therapy in severe ocular BD, 11/13 patients responded and achieved long-term remission for a mean of 7 years; four of them were drug free. Dr Sfikakis has also published a study showing that drug-free, long-term remission after withdrawal of successful anti-TNF treatment is feasible in patients with severe BD. Of 46 patients on long-term anti-TNF treatment, 29 discontinued and 12 of them remained in remission for at least 3 years. Of the other 17 patients, 14 were re-treated and four these subsequently achieved drug-free remission. It seems that younger patients with shorter disease durations are more likely to achieve long-term, drug-free remission.

Finally, Gülem Hatemi (Turkey) summarised the use of molecular designed agents in BD, beginning with TNF inhibitors. These are well established in the treatment of BD, especially refractory ocular symptoms. Good effects have also been reported in patients with vascular problems such as pulmonary artery involvement. A recent study evaluating anti-TNF therapy in refractory BD patients with major vessel involvement reported that vascular remission was achieved in 16/18 patients. Among patients with gastrointestinal BD symptoms who received anti-TNF therapy in another study, clinical remission was obtained in 47/91 (51%) patients, while endoscopic remission was observed in 21/46 (45%). TNF inhibitors have also been shown to be effective in the treatment of neuro-BD. Most of these studies used infliximab, and sometimes adalimumab, but recent studies have also reported good results with golimumab and certolizumab. Immunogenicity (production of antibodies against the anti-TNF drug) seems to be less of a problem in BD than in RA or Crohn's disease. Another class of biologic drugs that has been used in BD is the IL-1 inhibitors anakinra, canakinumab and gevokizumab. These have been shown to be effective against oral/genital ulceration; they also have some effect in uveitis, but much less than is seen with TNF inhibitors. The IL-17 inhibitor sekukinumab did not reduce disease activity in BD patients. In contrast, the IL-12/23 inhibitor ustekinumab brought about complete remission in 9/14 BD patients with oral ulcers refractory to

colchicine. Finally, tocilizumab, an IL-17 inhibitor, has also been shown to be effective in refractory BD, particularly for neurological involvement and uveitis.

The ethics of genetic analysis

To conclude the conference, James Stacy Taylor (a moral philosopher) gave a keynote lecture on the ethics of genetic analysis, stressing that he could only provide a framework for discussion and not absolute answers. Questions arising from genetic testing include whether patients have a right not to know about incidental findings, and whether they have a responsibility to disclose information to other people affected by it. The principles at play here are respect for autonomy, beneficence, non-maleficence and justice. In a case where only the patient is affected, there is no difficulty, but such cases are rare. In most cases, patients may have a moral obligation to disclose information to others affected, which may mean that they do not have the right not to know. A duty of disclosure may deter some people from being tested. It may also depend on whether the disease is treatable; many people would prefer not to know if they have a degenerative disease that cannot be treated. A useful framework (which can be used by ethics committees) is to identify the issue, determine whose interests deserve moral consideration, and decide which of the above principles can be used to support the decision.

Closing remarks

ISBD President Dorian Haskard closed the conference, noting the important themes of big data and improvements in the treatment of BD with biologics. The hope for the future is that these two aspects will come together to provide individualised treatment, ensuring the right treatment for the right patient at the right time. It was announced that the 19th ICBD will take place in Athens on 2–4 July 2020.

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