The 17th International Conference on Behçet's Disease
Casa di Spiritualità Sant'Anna, Matera, Italy, 15–17 September 2016

Delegates from all over the world attended the 17th International Conference on Behçet's Disease in the beautiful southern Italian city of Matera. The programme included 26 oral presentations of accepted abstracts, as well 125 posters and 29 presentations from ISBD invited speakers.

Hasan Yazici (Turkey) started proceedings with a special lecture entitled 'Behçet's disease in the 2000s'. He explained how Behçet's disease (BD) has often been 'lumped' together with other diseases, spondylarthropathy being one example. However, although there are many similarities between these diseases, there are also some important differences. Several chronic inflammatory disorders share particular genes, but it is important to analyse genotype data in the light of detailed clinical information, considering the differences as well as the similarities. Drugs that work in one disorder may or may not work in another with genes in common. Professor Yazici pointed out that conditions such as BD are constructs rather than single entities. In future, researchers should do hypothesis-driven research, splitting diseases instead of lumping them together.

Basic science

The first session was devoted to basic science. Graham Wallace (UK) spoke about cytokines and intracellular mechanisms of inflammation, saying that certain tumour necrosis factor alpha (TNFα) and interleukin (IL)-10 polymorphisms have been shown to be associated with susceptibility to BD. These cytokines have multiple effects on different cell populations. Other cytokines implicated in BD include IL-23, which contributes to the development of Th17 cells (critical mediators of the cellular immune response) and also targets cells involved in the innate immune response to stimulate production and release of neutrophils. IL-22 is high in patients with active uveitis, and IL-1β, IL-27, IL-28A and IL-33 all have potential roles. However, most studies have not been large enough to relate particular cytokines to individual manifestations of BD. More than an association with BD is needed – it is also necessary to look at function. Several different cytokines have been identified and targeted for treatment, but future research should aim at understanding what specific therapies are targeting

in particular groups of patients. For this, longer follow-up of the effect of treatment on different BD manifestations is needed.

Haner Direskeneli (Turkey) then gave a presentation on immune response and tissue-specific factors, explaining that the microbiome is the collection of genes encoded by the microbiota (the population of microbes in the human body). Changes in the microbiome are seen in many immune disorders. Colonisation with *Streptococcus mutans* has been found to be associated with oral ulcers in BD, while pustular skin lesions in BD contain microbes and the gut microbiome in BD is less diverse than in healthy controls. However, no significant difference in the microbiome is seen following improvements in oral health or after immunosuppressive treatment. Factors affecting the intestinal microenvironment can affect the differentiation of TH17 cells, which are involved in BD. The enzyme FUT2 is involved in the interaction between genes and the environment, playing a role in the symbiosis between host and microbiota, and it may be a risk factor for BD.

Next, Lorenzo Emmi (Italy) spoke about inflammation and vascular thrombosis, saying that inflammation and haemostasis (the body's normal physiological response for the prevention and stopping of bleeding/haemorrhage) are closely related. Inflammation leads to increased pro-coagulant activity, endothelial dysfunction and platelet hyperactivity, all of which increase the risk of thrombosis. Chronic inflammation results in oxidative stress and damage to endothelial cells, with release of cytokines. The neutrophils produced cause tissue damage, resulting in vascular disease and modification of fibrinogen. The altered fibrinogen seen in BD has impaired function and increases the risk of thrombus formation.

In the first oral presentation of an abstract, Orso Maria Lucherini (Italy) described the serum cytokine profile in BD.[1] The researchers looked at the levels of 25 cytokines in 46 BD patients and 19 healthy controls. They found that TNF receptor 1 and 2 were higher in both active and inactive BD than in controls, while IL-26 was elevated only in BD patients with active disease. Graham Wallace returned to the stage to present findings on ocular disease phenotyping.[2] His group used machine learning algorithms to identify markers (such as IL-22, TNFα and IL-23R) that can distinguish BD from healthy controls and other diseases with a similar aetiology, and to distinguish ocular and non-ocular BD. The next step is to do longitudinal analyses in treated patients. Finally in this session, Lesley Ann Bergmeier (from Farida Fortune's group in London) presented on the expression of homing markers on peripheral blood lymphocytes in BD patients and healthy controls.[3] This research is investigating receptors in the oral mucosa that are responsible for the tropism (homing) of γδ T cells to the oral mucosa and drive the inflammatory processes in BD.

Epidemiology and genetics

The first presentation in this session was by Ahmet Gül (Turkey) on the genetic contribution to the phenotype of BD. BD has a complex phenotype; it is a multisystem disorder with several subsets of patients with different manifestations such as mucocutaneous symptoms and neuro-BD. BD has many symptoms in common with Crohn's disease, but the latter has predominantly gastrointestinal involvement. The main genetic association with BD is the MHC Class 1 region, with HLA-B51 being the most important. Peptides derived from degraded cell proteins through the action of ERAP-1 have varying affinities for HLA-B51 depending on the polymorphisms of ERAP-1 present. One particular

type of ERAP-1 (haplotype 10) confers a 10-fold increased risk of BD, while types 1–3 are associated with psoriatic arthritis and ankylosing spondylitis. It seems that HLA-B51 positivity and the particular type of ERAP-1 combine to define the disease phenotype expressed.

Alfred Mahr (France) continued the examination of phenotype in a presentation entitled "Behçet's disease worldwide: is it the same disease?", a question that he answered "yes or maybe". There is no strong evidence for genuine genetic disparity in different parts of the world, although most of the studies have been small. The evidence for commonly cited differences such as higher rates of gastrointestinal involvement in Japan than in Turkey and higher rates of positive pathergy tests in Silk Road countries than elsewhere is not very convincing. Studies in France and the Netherlands have found little difference between disease phenotypes in European and non-European populations. HLA-B51 is more common in the background population in countries along the Silk Road, as well as in BD patients, and seems to be associated more with some manifestations (e.g. genital ulcers, and eye and skin involvement) than others. Dr Mahr concluded that there is insufficient evidence to support different expression of BD clinical phenotypes in different ethnic groups.

Next, Hasan Yazici (Turkey) spoke about criteria and the definition of disease, saying that criteria are needed for diagnosis and research, and to raise awareness. However, he suggested that while inflammatory bowel disease and gastrointestinal BD are difficult to distinguish from each other, both respond to TNF inhibitors so treatment does not depend on a precise diagnosis. BD is a construct involving stronger and weaker components, and it may be impossible to devise universally applicable criteria. Professor Yazici suggested that criteria tailored to a particular purpose may be more useful in the long term.

The session finished with three oral presentations of abstracts. Masaki Takeuchi (USA) described a genotyping study that identified several novel loci associated with BD in Turkish, Iranian and Japanese patients.[4] Some of these genes conferring susceptibility to BD are related to the FUT2 non-secretor phenotype associated with Crohn's disease and gut microbiome composition, suggesting that an impaired host response to the microbiome may contribute to BD susceptibility. Takahiro Yamane (Japan) presented another genotyping study, which identified candidate risk loci for specific BD manifestations.[5] Finally, Elaine Rimmers (UK) showed evidence that homozygosity for a single ERAP-1 allotype greatly increase the risk of BD in people positive for HLA-B51.[6]

Vascular disease

Kenneth Calamia (USA) gave an overview of the clinical manifestations of vascular disease in BD. Vascular manifestations occur in about a quarter of patients, contributing to BD mortality, and differ from non-Behçet's vascular disease. Systemic and pulmonary arterial vasculitis are seen, as is venous occlusion. Up to 90% of vascular BD patients have deep venous thrombosis (DVT). In Turkey, 77% of patients with vascular BD have only DVT; treatment may prevent progression to more serious complications. BD patients with DVT are more likely to smoke than other patients, and they may develop post-thrombotic syndrome due to lower anticoagulant use in BD. Vena cava thrombosis occurs in less than 10% of BD patients with DVT, while most have DVT in the extremities. Portal vein thrombosis, intracardiac thrombosis and cerebral venous thrombosis are also seen. About 5% of cases of Budd-Chiari syndrome are caused by BD, although this figure is higher in countries with

higher rates of BD. This syndrome has haemodynamic and ischaemic consequences, and has a 61% mortality rate. Treatment with immunosuppressants and anticoagulants improves the prognosis, and surgical intervention (shunts and stents) is also possible. Arterial disease in BD affects multiple vessels. Occasionally, patients may have several aneurysms before BD is diagnosed; immunosuppressive treatment can prevent further aneurysms. There is still no clear answer on the best way to treat BD patients at high risk of vascular events, but prevention and treatment of vascular BD is improving all the time.

In the next presentation, Dorian Haskard (UK) spoke about vascular imaging and vessel wall changes. The usual mechanism of thrombosis in BD is injury to the vascular endothelium. Oxidative stress in the vessel wall leads to vessel dilatation, suppression of platelet activation, and inflammation. Imaging is useful for early diagnosis, to guide treatment and monitor treatment response, as an outcome measure in clinical trials and for research into pathophysiology. Ultrasound is the standard method in thrombophlebitis. Good images can be obtained with MRI, but it is technically more difficult with veins than arteries due to skeletal muscle movement during respiration. MRI has been used to investigate potential cardiovascular effects of interferon treatment, showing a possible vasculoprotective effect (decreased carotid volume and increased flow-mediated dilatation). There is potential for molecular imaging techniques (such as SPECT, PET and NIRF) and targeted ultrasound and MRI using contrast agents, to provide information on biological changes such as inflammatory activity. NIRF (near infrared fluorescence) scanning may be suitable for monitoring superficial vessels.

Emire Seyahi (Turkey) then gave a presentation on pulmonary vascular disease, saying that pulmonary artery involvement (PAI) is very rare but is nevertheless the most common type of arterial involvement in BD. It has a high mortality rate and its management is challenging. PAI is becoming more common in female BD patients but is still uncommon in Japan. PAI is present before fulfilment of BD criteria in about 10% of cases, appears around the same time in another 20% and develops up to 5 years later in the remaining 70%. More patients are now being found to have isolated pulmonary artery thrombosis, possibly due to advances in imaging. This is part of PAI and has similar symptoms to pulmonary artery aneurysm, which it can transition into. It may disappear with immunosuppressive therapy without the need for anticoagulation. Mild pulmonary artery hypertension is often seen in patients with PAI; severe pulmonary artery hypertension is rare and suggests small vessel involvement. Early diagnosis is important to improve the prognosis of PAI, but mortality is still around 25%. Immunosuppression is the mainstay of treatment; TNF inhibitors are very effective and are now being used earlier.

Three oral presentations of abstracts completed this session. Fatma Alibaz Oner (Turkey) presented data showing that post-thrombotic syndrome is increased and venous disease specific quality of life is impaired in patients with vascular BD; anticoagulation had no benefit in these patients.[7] Enes Kurt (Turkey) showed findings from an outcome survey of 100 patients (81 males) with cerebral venous sinus thrombosis due to BD.[8] Forty-eight of the patients developed this complication before or at fulfilment of BD criteria, and the average age of the patients was 28; 18 patients had juvenile onset BD. Other vascular involvement was common. To conclude the first day of the conference, Emon Khan (UK) described research into microparticles, which are increased in BD patients and particularly in those with vascular involvement.[9] They may represent a biomarker for thrombotic risk assessment.

Ocular Behçet's disease

This session began with a presentation from Iknur Tugal-Tutkun (Turkey) on the diagnosis and differential diagnosis of BD eye disease. There is no specific test for ocular BD, and diagnosis is based on the association with non-ocular symptoms of BD. The presence of uveitis and suggestive symptoms can result in an incorrect diagnosis of BD, and hence the wrong treatment, especially in areas where BD has a high prevalence. Certain features, such as iris nodules, can rule out BD uveitis. Uveitis is the first manifestation in about 20% of BD patients, and it is important to recognise it in patients who have not yet fulfilled the criteria. Anterior uveitis with hypopyon is very characteristic of BD uveitis, as is a relapsing and remitting course. Non-granulomatous acute anterior uveitis is often bilateral. Other common features include recurrent transient retinal infiltrates (which must be distinguished from infectious uveitis), inferior pearl-like precipitates after diffuse uveitis (usually in a linear pattern) and recurrent occlusive periphlebitis. In response to a questionnaire sent to 37 uveitis specialists, smooth hypopyon was the top-ranked feature characterising BD uveitis. Development of diagnostic criteria for ocular BD is underway with the aim of preventing misdiagnosis and allowing early and appropriate treatment.

Kenichi Namba (Japan) then gave a presentation entitled "Treatment in the biologic era", explaining that the aim of treatment is to decrease the frequency of ocular attacks and maintain visual function. Cyclosporine is effective in 40–50% of cases, but it is associated with severe and common adverse effects and is not used as a first-line treatment. Infliximab has been used in more than 1000 Japanese BD patients since 2007, with excellent efficacy. Precautions need to be taken in patients with a high risk of infection (especially tuberculosis), and infusion reactions are common. Ocular attacks decrease in frequency and severity during infliximab treatment, and visual acuity increases. Some patients have attacks in the week or two before their next infusion. Interferon is not much used in Japan but is used in Europe and in Turkey. It has 80–90% efficacy, and 20–40% of patients can discontinue treatment without relapsing. Adverse effects include a flu-like syndrome in more than half of patients. Compared with the older immunosuppressive therapies, biologics are more effective and have fewer adverse effects. Several new biologics are emerging, including anti-IL-1 and IL-6 agents. For example, gevokizumab (an anti-IL-1 agent) produced rapid and durable resolution in seven patients. Biologics are costly and they suppress disease rather than curing it (although interferon may cure it in a proportion of patients). Mild cases of ocular BD can be treated with azathioprine, but specialists do not hesitate to use biologics in patients with severe uveitis.

Next, Moncef Khairaliah (Turkey) spoke about unmet needs in ocular BD. All BD criteria require the presence of non-ocular symptoms for diagnosis of BD, but at least 20% of patients have isolated ocular BD. This can delay diagnosis and hamper the inclusion of patients in clinical trials. In addition, the current criteria are not precise enough about the ocular findings. There are several methods that could be used to define ocular BD more precisely. A vitreous haze scale has been accepted by the US Food and Drug Administration for use in clinical trials, with a score of $\geq$2 indicating ocular BD; however, many patients with BD uveitis have a score below 2. Chorioretinal lesions can be graded using the Behçet's disease ocular attack score 24 (BOS24), although this has not yet been validated. Fluorescein angiography is the gold standard technique, but it is invasive and quantitative assessment is limited. Laser flare photometry has no validated score, and there is no consensus on its use. Optical coherence tomography, which shows macular changes, is used as an endpoint in clinical trials, but it needs further investigation. Best corrected visual acuity is a standard assessment in

clinical trials, along with the Visual Function Questionnaire (VFQ-25). However, visual acuity is an imperfect indicator of day-to-day visual function. In terms of treatment, interferon and TNF inhibitors are very effective but costly, and some patients are refractory to these drugs. There is as yet very little evidence on the newer agents. Overall, better therapeutic approaches are needed, as well as specific diagnostic criteria and validated scores for disease activity and clinical trial endpoints.

In the first of three oral presentations of abstracts, Gul Guzelant (Turkey) showed evidence that earlier use of infliximab in BD uveitis is associated with better outcomes.[10] Patients who started treatment after 2013 had significantly shorter duration of uveitis than those treated before 2013 and had better visual acuity after infliximab treatment. Tatiana Lisitsyna (Russia) described an evaluation of BOS24 for assessing ocular disease activity.[11] The average BOS24 score in 31 patients with an ocular attack fell from 9.1 before treatment to 2.7 afterwards; the pre-treatment score was correlated with the number of ocular attacks in the previous year, severity of BD and vascular involvement. To finish the session, Masaru Takeuchi (Japan) showed data on cellular immune responses in BD patients with uveitis during infliximab therapy.[12] The researchers measured the pattern of cytokines before and after an infusion of infliximab, concluding that this might help to quantify the efficacy of infliximab treatment of uveitis.

Neuro-Behçet's disease

Afshin Borhani-Haghighi (Iran) reviewed the history, epidemiology and clinical features of neuro-BD. Neuro-BD is diagnosed in patients with relevant neurological symptoms confirmed by MRI and with no better explanation. It was first described in 1941 and is present in 5–13% of BD patients, varying by geography and ethnicity, and affecting more men than women. The usual age of onset is the 20s to the 40s, and it predates other BD symptoms in about 3% of cases. Neuro-BD can affect the central or peripheral nervous system. The former can be parenchymal (e.g. affecting the brainstem) or non-parenchymal, while the latter can manifest as neuropathy or myopathy. Headache is the most common manifestation of parenchymal neuro-BD, although most headaches in BD patients are migraines or tension headache and are not neuro-BD. Less common manifestations include seizures (generalised or focal) in 2.2%, movement disorder, tumour-like manifestations and cognitive impairment. Brainstem manifestations include cranial nerve palsies. Spinal manifestations, which occur in about 11% of neuro-BD patients and have a poor prognosis, include sphincter and sexual dysfunction. Optic neuritis, cochlear hearing loss and bladder dysfunction can also occur. Non-parenchymal manifestations include cerebral venous sinus thrombosis, which has a good prognosis, and intracranial hypertension. Early diagnosis of neuro-BD is important to prevent progression.

Gulsen Akmar-Demir (Turkey) followed with a presentation on diagnosis and treatment of neuro-BD, pointing out the risk of over-diagnosis as not every neurological symptom in a patient with BD is caused by neuro-BD. International consensus recommendations for the diagnosis and treatment of neuro-BD were published in 2014. According to these, definite neuro-BD is present in patients who satisfy the criteria for BD and have characteristic neurological symptoms confirmed by neuroimaging (MRI), cerebrospinal fluid (CSF) examination or both. About 70% of neuro-BD patients have parenchymal disease, and 25% have dural sinus thrombosis. MRI scans in parenchymal disease show very characteristic features. CSF findings are usually abnormal in parenchymal disease (e.g. increased IL-6 levels) and normal in dural sinus thrombosis. Diagnosis is quite straightforward in patients with

typical symptoms, but it is necessary to be aware of common co-morbidities such as a primary headache disorder or rarer ones such as a brain tumour. Red flags suggesting possible misdiagnosis include risk factors for stroke, atypical MRI features and lack of response to steroids. There is no good clinical trial evidence on the treatment of neuro-BD, but several days of high-dose intravenous methyl prednisolone is usually followed by gradual tapering and weekly then monthly pulses while long-term treatment with azathioprine is started. Mycophenolate mofatil and cyclophosphamide are alternatives to azathioprine, and TNF inhibitors such as infliximab are used in refractory patients.

Adnan Al-Araji (UK) then presented some clinical cases. The first case was a patient with definite BD who presented with headaches. This patient had a history of migraine and did not have neuro-BD. It is important to take a good history in such patients, who may present repeatedly. The case of a patient with risk factors for stroke illustrated the importance of not starting immunosuppressive therapy in patients who have had a stroke and do not have neuro-BD. In the third case, MRI showed a brainstem abnormality indicating probable neuro-BD and the CSF had an elevated white blood cell count. This patient had been treated for ocular BD with cyclosporine, which can sometimes trigger neuro-BD. The patient responded well to infliximab but later had an apparent relapse that was actually caused by an infection. MRI and CSF were normal, and the patient responded to antibiotics and continued on infliximab. The final case was a patient who had a massive cerebral venous thrombosis after seven infusions of natalizumab to treat multiple sclerosis. This patient, who had a history of mouth and genital ulcers and skin lesions, and was pathergy-positive, had neuro-BD but had MRI features typical of MS. The patient was treated with alemtuzumab, which is effective in both BD and MS.

The oral presentations of abstracts began with Hirotoshi Kikuchi (Japan) describing MRI findings in patients with chronic progressive neuro-BD.[12] The results indicated that the hippocampus, as well as the brainstem, is a common site for lesions in these patients, accounting for the progressive cognitive dysfunction seen. Rosaria Talarico (Italy) then presented results from a study looking at psychiatric disorders in neuro- and non-neuro-BD.[13] The prevalences of bipolar disorder, obsessive-compulsive disorder, depression and sleep disorder were surprisingly high in both groups. Finally, Klii Rim (Tunisia) reported that cochlear involvement in BD is common, particularly in older patients with later onset of BD.[14]

Locomotor system disease

This short session opened with a clinical overview of musculoskeletal manifestations of BD by Fereydoun Davatchi (Iran). Musculoskeletal involvement can be peripheral – such as arthralgia and mono-, oligo- or poly-arthritis – or can involve the spine, as in ankylosing spondylitis. Reports of the prevalence of joint symptoms in BD have varied widely, but a large Iranian study in 2010 found a prevalence of 37% and an international cohort study including 27 countries in 2006 reported a figure of 43%. Peripheral presentations other than chronic polyarthritis follow a pattern of attacks and remissions, and erosive disease is unusual. Attacks usually respond well to non-steroidal anti-inflammatory drugs (NSAIDs), which can be tapered after a response is obtained and stopped once remission is achieved. Colchicine may be effective in NSAID-resistant patients; patients refractory to this may respond to low-dose prednisolone, which can be tapered and followed by methotrexate.

Rarely, azathioprine or a combination of immunosuppressants may be needed, with biologics such as etanercept reserved for the very rare cases resistant to all the above.

Next, Pietro Lessese (Italy) spoke about BD and spondyloarthritis. The question of whether BD forms part of the spondyloarthritis spectrum of diseases has been debated for many years. Spondyloarthritis is a complex group of disorders that overlaps with inflammatory bowel disease, BD and other conditions such as Reiter's disease. Early reports of a high frequency of sacroiliitis in BD have been contradicted by more recent findings, and BD is accepted as being a form of vasculitis rather than spondyloarthritis (although the two may coexist). An increased rate of enthesopathy (a symptom of spondyloarthritis) is seen in BD patients with acne and arthritis. Among 74 Italian BD patients, seven fulfilled the ASAS criteria for spondyloarthritis, which is higher than the general population prevalence of spondyloarthritis. So it seems that the two conditions may coexist more often than would be expected by chance, although the reason for this is not yet clear.

In the only oral presentation of an abstract in this session, Jimyung Seo (South Korea) described the predictive value of bone scintigraphy for the detection of joint involvement in BD.[16] This technique detects inflammatory bone remodelling and was found to correlate fairly well with joint complaints in 211 patients. It is simple to perform and may help dermatologists and other non-rheumatologists to detect joint involvement in BD patients.

Mucocutaneous disease

Eun-So Lee (South Korea) began this session with a presentation on the significance of mucocutaneous manifestations of BD. These manifestations are a hallmark of BD, with oral ulcers being the most common initial symptom. Mucocutaneous lesions usually precede potentially more serious manifestations, so careful follow-up is important. Recurrent aphthous stomatitis (oral ulcers) occurs in 97–100% of BD patients and precedes diagnosis by 6–7 years. Frequent oral ulcers in the initial years may predict the development of major organ involvement in male patients. The 2–3% of BD patients who do not have recurrent oral ulcers are more likely to develop eye disease. Oral ulcers decrease with age in many patients; they also decrease with immunosuppressive therapy, but many doctors are reluctant to use such therapy in patients without other symptoms. Genital ulcers occur in 50–85% of patients; these patients are more likely to have ocular disease and less likely to have gastrointestinal or joint manifestations than those without genital ulcers. Pathergy (an exaggerated skin injury occurring after minor trauma) has a high prevalence and intensity in young male patients in areas such as Turkey, the Middle East and Japan. It is not associated with a more severe disease course. Other skin manifestations include erythema nodosum, popular pustules and superficial thrombophlebitis. Mucocutaneous symptoms of BD affect patients' quality of life; their recognition may permit early diagnosis and treatment of BD.

Next, Erkan Alpsoy (Turkey) spoke about the diagnostic aspects of mucocutaneous manifestations, pointing out that in most patients the diagnosis can be made clinically on the basis of these symptoms. In about 15% of patients, more than one mucocutaneous symptom appears at the same time. The oral ulcers of BD have a characteristic appearance and tend to heal in 1–4 weeks. Genital ulcers are less often recurrent. They tend to occur on the scrotum in male patients and on the labia major (and minor) in females, but the groin and perineal area can also be affected. Erythema

nodosum is more common in women and is often seen on both lower legs. The lesions do not ulcerate; they resolve spontaneously and recurrence is common. Superficial thrombophlebitis most often involves veins and manifests as nodular lesions; this is clinically important as it may be associated with other vascular symptoms such as deep venous thrombosis. A pathergy test is positive if a papule or pustule at least 2 mm in diameter appears within 48 hours of a needle prick. Diagnosis of BD is primarily based on clinical criteria and relies heavily on mucocutaneous symptoms. Differential diagnosis can be difficult, as oral and genital ulceration occurs in many different disorders (such as herpes simplex). Complex aphthosis can be difficult to distinguish from BD, and careful follow-up is needed to make the correct diagnosis. The pathergy test is still important for diagnosis of BD in Turkey, but not in Northern Europe or the USA.

Andreas Altenburg (Germany) then described the therapeutic aspects of mucocutaneous manifestations. Topical therapies are the first-line treatment for isolated ulcers, but controlled studies are lacking. General measures include avoiding toothpastes containing sodium lauryl sulphate. There are no reliable studies on the effect of diet, but patients should try to avoid possible triggers such as hard, acidic, salty and spicy foods. Topical anaesthetics offer good pain relief, while antiseptic and anti-inflammatory mouthwashes can reduce ulcer pain/severity and promote healing. Cauterisation can provide immediate pain relief but does not speed up healing. Tetracycline mouthwash has been shown to increase the number of pain-free and ulcer-free days. Topical steroids can also be used. As regards systemic treatment, colchicine is helpful for both oral and genital ulcers in most patients, while sucralfate leads to rapid healing and decreased pain. Steroids reduce pain as well as the number and size of ulcers, and methylprednisolone is also effective for erythema nodosum. There have been a few small studies using pentoxifylline, doxycycline, dapsone, azathioprine, methotrexate and rebamipide. Cyclosporine is effective at high doses but has adverse effects, while thalidomide is also effective but is only used in exceptional cases. Interferon can induce partial or complete remission, and combination with colchicine is possible. TNF inhibitors are very effective in refractory patients. Apremilast led to complete remission in 71% of patients and partial remission in 89% in a placebo-controlled trial, and a larger study is recruiting patients.

In the first of three oral presentations of abstracts, Jean-Baptist Fraison (France) showed results from questionnaires on triggers of oral ulcers returned by 81 BD patients.[17] Fatigue/stress (37%) and food (32%) were the most commonly cited triggers. The most frequently mentioned foods were nuts and peanuts, cheese, pineapple and citrus foods. These foods trigger release of histamine from mast cells, which are also activated by stress. Gonca Mumcu (Turkey) presented a long-term follow-up study of oral hygiene education in BD, suggesting that a more aggressive approach to oral health would be beneficial.[18] Finally, Yesim Ozguler (Turkey) showed results from a study on papulopustular lesions in BD.[19] These occurred more often on the legs of BD patients compared with rheumatoid arthritis (RA) patients or healthy controls, and the number of lesions decreased with age.

Gastrointestinal disease

This session began with a clinical overview of gastrointestinal (GI) manifestations by Makoto Naganuma (Japan). GI lesions occur in 3–16% of BD patients, usually presenting as deep, round ulcers in the ileocaecal area. The incidence is higher in Japan and Taiwan than in Turkey. The current criteria for BD do not include GI manifestations, meaning that about 30% of patients with GI symptoms are

not diagnosed as having BD. For example, a patient with oral and genital ulcers plus GI symptoms would not fulfil the criteria for BD and could only be described as having probable BD. In a nationwide survey in Japan, GI symptoms were more common in males than females, and abdominal pain was the most common symptom (reported in 82%). The most common location was the ileocaecum (69%), followed by the ileum. Surgery is needed in 37% of patients – for example, for intestinal perforation – but recurrence rates are high (~75% within 2 years). Treatments used for GI manifestations include 5-aminosalicylic acid, colchicine, steroids, azathioprine, TNF inhibitors, cyclosporine and surgery. In patients with severe symptoms, steroid induction therapy should be considered, followed by tapering and cessation; however, some patients become steroid-dependent. Azathioprine can be useful for maintenance of remission or to reduce recurrence after surgery. Infliximab is often effective in refractory patients; there have been several studies showing mucosal healing, including in post-surgery patients. One study in 121 patients showed clinical improvement in 81% of patients and endoscopic improvement in 52%. Adalimumab is also effective, achieving a 20% complete remission rate in one study. A Japanese consensus statement published in 2014 recommended that infliximab and adalimumab should be considered as a standard therapy for intestinal BD.

Next, Jae Hee Cheon (South Korea) gave a presentation on differential diagnosis. BD and Crohn's disease (CD) have many similarities to each other, as well as to intestinal tuberculosis, and all of these conditions are prevalent in East Asia. Differentiation is important because, for example, TNF inhibitors should not be used in intestinal tuberculosis. In all three conditions, the ileocaecal region is the most commonly affected area and extra-GI manifestations are common. Colonoscopy is the most useful method for differentiation. If tuberculosis is suspected, appropriate treatment should lead to clinical and colonoscopic improvement. On colonoscopy, BD ulcers are usually deep and penetrating, round or oval in shape, with discrete, elevated borders. CD ulcers tend to be shallow and longitudinal, with a cobblestone appearance and irregular, ill-defined borders. In addition, fistulas or strictures are more common in CD, while perforation is more common in BD.

This session finished with an oral presentation by Jae Hee Cheon (South Korea) of an abstract on the use of faecal calprotectin as a non-invasive biomarker for GI involvement in BD.[20] Levels of this substance, which is released into the intestines when inflammation is present, were higher in BD patients with (versus without) ulcers on colonoscopy and were higher in those with typical (versus atypical) lesions.

Paediatric Behçet's disease

Opening this short session, Isabelle Koné-Paut (France) spoke about the diagnosis and classification of paediatric BD. BD is a frequently missed diagnosis in children and is a clinical diagnosis of exclusion. Periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) is a syndrome that consists of recurrent episodes of fever, sore throat, mouth sores and swelling of the glands in the neck. PFAPA syndrome is benign and usually resolves before the age of 5 years, but it can occasionally mask BD in a young child. There is a strong genetic component in paediatric BD, with familial aggregation rates of 9–42%. Up to a quarter of children with BD fulfil the criteria before the age of 16. Uveitis is less common in children than in adult BD patients, while recurrent fever is common in children but rarely seen in adults. The PED-BD international cohort study began in 2007

and now includes 219 patients, of whom 156 have a confirmed diagnosis. Genital ulcers are more common in girls, while ocular and vascular involvement is seen more often in boys. Those with definite BD were older when the first symptom appeared. Oral ulcers were usually the first symptom, followed by skin lesions and genital ulcers. Preliminary criteria for paediatric BD have been developed, in which a score of 1 is given to each of recurrent oral aphthosis, genital ulceration, ocular signs, skin lesions, neurological manifestations and vascular signs, with a score of $\geq$3 needed for a diagnosis of BD. Unmet needs in this area include biomarkers, outcome measures, treatment trials, and studies of disease burden and quality of life.

The second day of the conference finished with an oral presentation of an abstract on an Italian paediatric BD cohort.[21] Of the 129 children included, 73 were boys and 56 girls. The average age at disease onset was 9 years and the average age at diagnosis was 13. Only 14 of the cases had a positive family history of BD. Almost all (94%) had mucocutaneous symptoms, 42% had ocular involvement, 36% had musculoskeletal problems, 35% had GI symptoms and 24% had neurological involvement.

Outcome measures

The final morning of the conference started with a presentation by Maarten Boers (Netherlands) entitled “Developing a core set of outcome measures for clinical trials”. Trials of potential treatments are essential to improve the prognosis of patients with BD, and these trials need to use appropriate outcome measures (OMs). The heterogeneity of OMs used and the lack of standardisation reduce the ability to summarise and pool the results of trials. There is a potential for bias if researchers can choose which OMs to report, and it is also important that measures used in trials are relevant to clinical practice and meaningful to patients. A core set is a minimum set of OMs that should be reported in all clinical trials of a particular condition. OMERACT (outcome measures in Rheumatology) is developing core sets of OMs in rheumatology, starting with RA in 1992. The RA core set includes measures of disease activity, joint damage and patient functioning; uptake has increased over time. Input from patients began in 2002 and identified missing areas such as fatigue and sleep quality. The main question is which areas are core, and whether OMs are generic or specific to the particular condition. Challenges in BD include the multisystem nature of the disease, the pattern of exacerbation and remission, the difficulty of operationalising the concept of disease activity and the fact that BD is a rare disease in much of the world. OMERACT set up a BD special interest group in 2014 to look at how to overcome these challenges.

Gülen Hatemi continued the theme with a presentation on the challenges of developing OMs in BD. The OMERACT special interest group began by doing a systematic review of 249 studies in BD, which had used 139 different OMs. At least 12 indices were used for measuring overall disease activity, and many researchers used their own definitions of disease activity. Many different scales are used to assess mucocutaneous symptoms, ocular symptoms are usually assessed by visual acuity and number of attacks, GI measures are often borrowed from inflammatory bowel disease, and multiple sclerosis scales are sometimes used for neurological symptoms. Generic measures of disease-related quality of life are also used. All this makes comparing and combining results from different trials very difficult. Developing a core set of OMs for BD will not be easy. The various manifestations of BD respond differently to treatments. A study looking at eye disease also needs to consider the effects

on mucocutaneous symptoms, for example. A composite index giving a single overall score would result in a reduced sensitivity to changes in a particular severe manifestation. A meeting at the Paris conference in 2014 began the process with a preliminary survey of physicians (60% rheumatologists) to establish some priorities. Surveys and interviews with patients then identified seven broad themes, the top four of which were symptoms, impact on function and activity, psychological impact and social impact. A Delphi consensus process with 74 participants was then used to agree on what needs to be measured in all BD trials and in trials in particular manifestations. The next step is to rank the long list of OMs produced and validate the domains and subdomains identified. It may be possible to develop a composite measure that could be weighted for use in particular manifestations. Specific BD OMs that have not been validated also need to be compared with validated non-BD-specific OMs, and a new patient-reported outcome would be useful.

In the first of two oral presentations of abstracts, Matteo Piga (Italy) reported results of study which found that impaired quality of life was related to disease activity only for the physical component, which was similar to that in RA and lupus.[22] The mental component was more impaired in BD than in RA and lupus, but was not related to disease activity; further studies are needed to determine the reasons for this. Fereydoun Davatchi (Iran) then showed some results using the Iran BD Disease Dynamic Activity Measure.[23]

Treatment

The last, and longest, session of the conference began with a presentation by Petros Sfikakis (Greece) on anti-TNF and anti-IL-1 agents. A causal relationship between TNFα and arthritis led to clinical trials of TNF inhibitors (such as infliximab) in RA two decades ago, and about 4 million patients worldwide have been treated with these drugs. IL-1 has been shown to act in series with TNFα in a mouse model of arthritis. The first use of infliximab in BD was in patients with sight-threatening pan-uveitis; a single infusion led to a great improvement. Infliximab was reintroduced when patients relapsed; azathioprine was then added and patients became relapse-free. Many trials of infliximab in BD have taken place since then, and the European League Against Rheumatism (EULAR) recommends its use in patients with a definite diagnosis of BD, active disease and objective signs of inflammation, and previous failure of or inability to tolerate standard BD treatments. Infliximab seems to be effective in all manifestations of BD, adalimumab has comparable efficacy to infliximab, and etanercept also showed efficacy in a single randomised controlled trial (RCT), but there is little evidence for certolizumab pegol. Infliximab produces a very rapid response in ocular disease, preventing relapse and increasing visual acuity, with complete remission in 60% of patients. As a result, very few BD patients now lose their sight. Intravitreal injections are also effective, but they have a slower action than intravenous infusions because the disease is systemic rather than local in origin. The effect on skin and joint manifestations is less good than on ocular, neurological and gastrointestinal symptoms. Treatment with infliximab (plus azathioprine) is usually continued for 2 years, after which the intervals between infusions may be increased; treatment may be stopped in the third or fourth year if no relapses have occurred. TNF inhibitors have a good safety record, but caution is needed in patients at risk of infections. IL-1 inhibitors (anakinra and canakinumab) are effective in most patients, whether or not they have previously been treated with a TNF inhibitor. A clinical trial

suggested that they may be a promising approach in patients who do not respond to or cannot tolerate TNF inhibitors.

Yusuf Yazici (Turkey) then described the use of apremilast, which inhibits the enzyme phosphodiesterase 4 and prevents spontaneous production of TNFα. It was approved in the USA in 2014 for the treatment of psoriasis and psoriatic arthritis and has been used in US BD patients. An RCT in BD patients showed that the number of oral ulcers was reduced after apremilast treatment, as was the pain caused by ulcers; 71% of patients had complete remission after 12 weeks, and 89% had partial remission. However, the ulcers returned when treatment was stopped. There were also effects on genital ulcers, disease activity and quality of life. Apremilast has a very good safety profile and no monitoring is needed. In Yazici's own practice, of nine BD patients treated with apremilast (none with ocular symptoms), two did not respond but others have been able to stop their other treatments. Another clinical is ongoing, but much more data is needed to determine the potential role of apremilast in BD.

Next, Ina Kötter (Germany) gave a presentation on interferon. It is an anti-proliferative, antiviral agent that acts on lymphocytes and neutrophils, leading to anti-inflammatory effects. Ocular symptoms improved in BD patients treated with interferon for viral infections. An observational study in 50 patients found a 92% response rate, and 42% of patients discontinued treatment without relapsing. Further studies found lower remission rates for mucocutaneous symptoms. There have been two RCTs and many case series of the use of interferon for ocular BD symptoms. In one retrospective study of 53 patients with severe uveitis, 52 initially responded to interferon; 47 were able to stop treatment, and 20 of these needed a second course of interferon over 6 years of follow-up. Another study compared interferon and cyclosporine; remission was seen in all 13 patients who received interferon and 9/13 who received cyclosporine, which was a statistically non-significant difference. Depression was noted as an adverse effect of interferon. More head-to-head trials of interferon versus other drugs are needed. Doses and tapering schedules differ, as do use of concomitant steroids, which makes indirect comparisons between studies difficult. Studies are also needed to clarify understanding of interferon's mechanism of action and to identify the patients who are most likely to benefit. There have been a few case reports of the use of interferon in neuro-BD; it may be preferable to a TNF inhibitor in patients with possible multiple sclerosis, but probably not in other patients.

Gülen Hatemi then described the updating of the 2008 EULAR recommendations for management of BD. A systematic literature search was carried out to identify new data, and a Delphi process was used to reach a consensus among a task force with representatives from all the different specialties involved in treating BD. Some overarching principles have been added to the recommendations, such as the need for a multidisciplinary approach. For mucocutaneous disease, management of leg ulcers and use of apremilast have been added. Intravitreal glucocorticoid injections and treatment of isolated anterior uveitis have been added for ocular disease, while confirmation by endoscopy or imaging has been added to the gastrointestinal recommendations. For vascular manifestations, management of arterial aneurysms has been included, as has the possible use of anticoagulants in refractory patients; immunosuppressive therapy decreases the risk of relapse, whereas anticoagulants do not. The level of evidence is good and the strength of recommendations high for mucocutaneous, ocular and joint symptoms, but not for other manifestations.

The conference concluded with oral presentations of three abstracts on the treatment of BD. Shunsei Hirohata (Japan) reported the effect of infliximab in patients with chronic progressive neuro-BD (CPNBD).[24] Delay in introduction of infliximab led to irreversible functional disability, so infliximab should be used as soon as possible in patients with CPNBD who do not respond to methotrexate. Next, Yoshiaki Ishigatsubo (Japan) described a multicentre, prospective study of infliximab in 18 BD patients with neurological, vascular and intestinal involvement who had responded poorly to standard therapies.[25] Eleven (61%) of the patients showed complete response to infliximab. Finally, Luca Cantarini (Italy) showed the results of a retrospective study of the use of anti-IL-1 agents (anakinra and canakinumab) in 30 BD patients.[26] After 12 months, 13 of the patients were in complete remission.

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