The 19th International Conference on Behçet's Disease
Royal Olympic Hotel, Athens, Greece, 6–8 July 2022

The 19th International Conference on Behçet's Disease took place in Athens in July 2022, two years after it was originally scheduled. It was a hybrid conference, with both in-person and virtual sessions. The abstract book included 119 abstracts, of which 113 were presented as e-posters and six were selected for oral presentations. A quarter of the abstracts came from Turkey, followed by Morocco with 20% and the UK with 12%.

After the conference was opened by its president, Petros Sfikakis, the opening lecture was given by George Tsokos (US). Prof Tsokos spoke about immune cell signalling, gene transcription and mechanisms of tissue injury in systemic lupus erythematosus (SLE), suggesting that Behçet's and SLE face many of the same challenges. As with Behçet's, several different organs are affected in SLE and the diagnostic criteria have been revised several times. Genetic, environmental, immunoregulatory, hormonal and epigenetic factors are involved in the pathogenesis. More than 200 genetic variants are associated with SLE (most in non-coding regions of the genome), and it shares genetic loci with rheumatoid arthritis (RA), systemic sclerosis and Sjögren's syndrome (and probably Behçet's). People with SLE are inherently immunocompromised, and infectious agents are also implicated in the disease process. SLE signatures in the gut microbiota have been identified, and faecal microbiota transplantation is being studied as a treatment. Prof Tsokos explained that there is a move towards personalised medicine in SLE, with targeted therapies being delivered directly to the tissues that need it.

Basic and translational science

Session 1 of the conference was devoted to basic science, starting with a presentation on immunology, inflammation and thrombosis by Giacomo Emmi (Italy). Behçet's is a systemic vasculitis that mainly affects the veins, rather than the arteries as in most vascular diseases. NETosis, a type of regulated cell death dependent on the formation of neutrophil extracellular traps (NETs), plays an

important role in Behçet's. It is increased in active Behçet's, especially in angio-Behçet's, and is associated with hypercoagulation. Neutrophil-mediated oxidative stress is another important factor, with increased production of reactive oxygen species resulting in resistance to degradation of fibrin in blood clots in Behçet's patients. MicroRNA is involved in cell-to-cell communication; a distinct microRNA profile has been identified in Behçet's, associated with enrichment of pathways involved in thromboinflammation. Finally, Dr Emmi spoke about the role of the microbiome in Behçet's, including a depletion of bacterial species involved in the production of butyrate. A small study of a diet promoting butyrate production or addition of butyrate to the diet suggested that such an approach could reduce the production of reactive oxygen species and improve fibrin degradation.

The microbiome was discussed further by Graham Wallace (UK) in his presentation on Behçet's and microbes. Ho pointed out that it is uncertain whether changes in the microbiota are a cause or a result of disease. In the case of Behçet's, changes in gut and oral microbiota are very variable and cannot be linked to any particular manifestations. Faecal transplants from Behçet's patients have been shown to cause uveitis in mouse models. Dr Wallace considered whether diet could be used to alter the microbiome in Behçet's. Butyrate is a short-chain fatty acid that inhibits inflammation via generation of T regulatory cells. The Mamba trial is a larger follow-up to the small study mentioned by Dr Emmi, in which 90 Behçet's patients were randomised to an ovo-vegetarian diet or a Mediterranean diet with or without butyrate supplements. Preliminary results suggested a reduction in symptoms with a butyrate-enriched diet, but no changes in the microbiota have yet been seen. Adherence to the diets was good, and no adverse effects were reported, but a longer intervention may be needed to alter the microbiome.

Ahmed Gül (Turkey) spoke about the immunopathogenesis of Behçet's, explaining that this is multifactorial involving environmental triggers leading to a hyperinflammatory response in people with a genetic susceptibility. One example of this is the pathergy response, whereby local trauma such as skin pricks using a sterile needle lead to development of an inflammatory papule. The strongest genetic association with Behçet's is human leukocyte antigen (HLA)-B51, one of a complex of genes on chromosome 6 that encode cell-surface proteins responsible for regulation of the immune system. HLA-B51 is too common in the population to be useful as a diagnostic tool in Behçet's, but it may be important in determining the clinical phenotype. ERAP-1 is a protein involved in protein processing and transport in the endoplasmic reticulum, and a strong association has been found between a particular ERAP-1 haplotype and HLA-B51 positivity in Behçet's. ERAP-1 haplotype 10 genes code for a peptidome with a lower affinity for HLA-B51; this leads to misfolding of HLA-B51, which is thought to result in endoplasmic reticulum stress and autoinflammation.

Next, Eun-So Lee (Korea) gave a presentation on immune senescence in Behçet's. The function of the immune system declines with age, and the cell senescence involved leads to inflammation and associated age-related diseases. Premature senescence of T cells has been shown to result in increased morbidity in RA and psoriasis. Some symptoms of Behçet's seem to increase with age while others decrease, and cases of late-onset Behçet's have been reported. In healthy controls, there is a correlation between chronological age and the frequency of senescent cytotoxic (CD8+) T cells, and the frequency of senescent CD8+ T cells is higher in active Behçet's than in healthy controls. It might be that T-cell senescence is triggered by a viral infection or some other factor as part of the aetiology of Behçet's, or that local inflammation during flare-ups of Behçet's brings about senescence. Premature T-cell senescence has been observed during chronic viral infections, autoimmune diseases

and cancer. The changes in genetic profile between non-senescent and senescent T-cells differ between Behçet's patients and healthy controls, with different genes being up-regulated and down-regulated. Specifically, cAMP-mediated signalling seems to be affected, suggesting that activation of cAMP-mediated pathways (sustained by senescent T cells) may cause cellular dysfunction in Behçet's. The possible use of apremilast to reduce T-cell senescence was discussed later in the conference (oral presentation of abstract O05).

The session concluded with the first two oral presentations of abstracts. Linlin Chen (China) described a proteomic landscape mapping study that identified potential biomarkers for vascular Behçet's (abstract O01). Wenjie Zheng (China) then presented a study that used single-cell analyses to highlight the pro-inflammatory contribution of C1q-high monocytes to hyperinflammation in Behçet's (O02).

Special lecture: The expanding role of apremilast in the treatment of Behçet's

Yusuf Yazici (USA) said that apremilast was licensed for treating oral ulcers of Behçet's in the USA in 2019. Results of the first clinical trial were published in 2015, showing a reduction in the mean number of oral ulcers per patient from ~2.7 at baseline to 0.25 after 2 weeks' treatment with apremilast, as well as a reduction in oral ulcer pain and significant benefits for overall disease activity and quality of life. Apremilast has been extensively used in psoriasis and psoriatic arthritis, with a good safety profile and no requirement for monitoring. A second, larger trial confirmed these findings and showed that benefits were sustained for more than a year. Patients who responded more rapidly had better long-term outcomes, allowing for the possibility of a 4–6-week treatment trial. Some efficacy for other symptoms was seen, with non-significant decreases in recurrences of skin lesions and arthritis. A small open-label study in Spain showed that doses of prednisolone could be decreased during apremilast therapy. Apremilast thus seems to be a good option for mucocutaneous and joint manifestations of Behçet's, and its safety profile allows it to be used in combination with other drugs.

Satellite lecture: Unravelling the management of non-infectious uveitis

Dimitrios Ladas (Greece) explained that uveitis is a diverse group of intraocular diseases of the uveal tract, a layer of tissue located between the outer layer (cornea and sclera) and the inner layer (the retina) of the eye. After an infectious cause (such as herpes simplex or toxoplasmosis) has been ruled out, Behçet's is one of many possible non-infectious causes. Up to 90% of people with Behçet's have ocular involvement. The first aim of treatment is to manage the acute attack, the second is to preserve vision and prevent chronic complications, and the third is to determine the best treatment for the eye and for the patient's overall disease. The risk of vision loss depends on the duration and severity of uveitis, the number of recurrences and the site of inflammation, with posterior uveitis carrying the greatest risk. Steroids, which can be given locally or systemically, are used as a rescue treatment and can save vision. For longer-term treatment, immunosuppressants such as methotrexate or mycophenolate can be used. By 2014, there were >6000 publications on the use of anti-TNF agents to treat uveitis, and an expert panel recommended their first-line use in Behçet's

uveitis. Adalimumab was approved for the treatment of non-infectious uveitis in the USA and EU in 2016 after phase 3 clinical trials showed it to be effective in controlling inflammation and improving vision, with a good corticosteroid-sparing effect and no significant safety issues. Expert recommendations in non-infectious uveitis support the use of adalimumab, infliximab and interferon-alpha. Potential alternatives with favourable results in case series include certolizumab, golimumab, tocilizumab, anakinra, canakinumab, rituximab and tofacitinib.

Genetics and epidemiology: Is it all in the genes?

The first presentation in this session was given by Kalpana Manthiram (USA) on the subject of shared genetic findings between PFAPA and Behçet's. PFAPA stands for periodic fever, aphthous stomatitis, pharyngitis, adenitis syndrome, and it is the most common periodic fever syndrome in childhood. Febrile episodes occur at regular intervals, accompanied by aphthous ulcers, pharyngitis and/or cervical lymphadenitis. PFAPA is probably underdiagnosed, often being misdiagnosed as recurrent tonsillitis. Around 25% of patients have a family member with PFAPA, and aphthous ulcers are common in first-degree relatives. The genetics are complex, with overlaps in genotype and phenotype between PFAPA, recurrent aphthous ulcers (RAU) and Behçet's. Screening 231 patients with PFAPA for genetic risk variants identified loci associated with IL12A, STAT4 and IL10, which are also linked to RAU. Dr Manthiram proposed that a spectrum of disorders of aphthous ulcers exists, with RAU at one end, Behçet's at the other end and PFAPA in between. This spectrum includes patients who do not meet the criteria for either PFAPA or Behçet's. HLA may be a factor that affects phenotype along the spectrum, with stronger HLA associations at the Behçet's end of the spectrum. A genome-wide association study (GWAS) is planned for PFAPA to compare the genetic architecture of the disorders.

Next Martin Van Hagen (Netherlands) spoke about the similarities and differences between Behçet's and primary immunodeficiencies (PIDs). He explained that most PIDs are antibody deficiencies; they are characterised by recurrent infections and many comorbidities including inflammatory bowel disease (IBD), allergies, and autoimmune and autoinflammatory diseases. PIDs thus involve immune dysregulation as well as deficiency. There are several similarities between PIDs, IBD and Behçet's, including oral and genital ulceration, and ocular and gastrointestinal symptoms. As many as 430 genes are involved in PIDs, and 28 of these overlap with Behçet's. Prof Van Hagen concluded that Behçet's, PIDs and IBD share genes that harbour particular genetic variants, and that while Behçet's has predominantly autoinflammatory characteristics and fits in the PID classification, it is not a 'classical' PID with recurrent infections. However, various targeted treatments for PIDs might be worth investigating in Behçet's.

Andreas Altenburg (Germany) then discussed the epidemiology of Behçet's in Germany, presenting data from the German Behçet's registry which includes 900 patients. He began by saying that in follow-up of 79 patients with uveitis (137 affected eyes) between 1982 and 2006, 21% of affected developed functional blindness. Oral ulcers were by far the most common presenting symptom (83%), with genital ulcers being the most common second symptom (42%). Severe complications are rare, the most frequent being total blindness at 5.8%. The registry includes 77 patients with juvenile-onset Behçet's, of whom 24% showed the full symptom complex before the age of 16. The average time between the onset of the first and second symptom was 7 years. A family history of Behçet's is

present in 25% of patients with juvenile-onset disease compared with 7.3% of those with adult onset. Of people with Behçet's in Germany, 44% are of Turkish origin and 40% of German origin. A male predominance is seen among patients of Turkish origin but not in those of German origin. Patients of Turkish original have a higher proportion of positive family history and ocular lesions.

Luca Cantarini (Italy) spoke about the differential presentation of Behçet's in endemic and non-endemic areas, noting the marked epidemiological and clinical geographic variability. The highest prevalence is in Jordan with 660 cases per 100,000 population; Turkey has 420 cases per 100,000, but the prevalence is much lower in Western countries. The highest frequency of gastrointestinal involvement has been reported in Japan, while the pathergy reaction is much more common in the Middle East than in Western countries. A detailed analysis of 396 Behçet's patients attending three tertiary referral centres in Italy has recently been published. The median age at onset was 30 years, and 55% were female; however, the mean age of onset was lower in male patients. The slight preponderance of females contrasts with reports from Eastern countries. At onset, 91% of patients had oral ulcers, 26% had genital ulcers and 22% had uveitis. During the disease course, the proportions with genital ulcers and uveitis increased to 67% and 43%, while the percentage with gastrointestinal and vascular involvement increased from <5% to 34% and 24%, respectively. Major organ involvement was more common in male patients. In terms of treatment, 28% were receiving biologic therapy (mostly anti-TNFs) as monotherapy, with a further 15% receiving a biologic plus another immunosuppressant (most often azathioprine). Twenty-eight patients discontinued immunosuppressive therapy due to prolonged remission (at a mean age of 45).

In the next presentation, Farhad Shahram (Iran) returned to the subject of HLA-B51 and ERAP in Behçet's. He reminded the audience that there are multiple susceptibility genes for Behçet's, but the strongest association is with HLA-B51 and the strongest single marker outside the HLA region is ERAP-1. More than half of Behçet's patients in endemic areas are positive for B51, and the prevalence varies between phenotype clusters. This means that while B51 is not useful in the diagnosis of Behçet's, it is a factor in determining the phenotype. In Iran, B51 positivity in Behçet's patients is associated with a higher rate of positive pathergy reactions and of a family history of Behçet's. The frequency of B51 positivity in Japanese Behçet's patients has declined in recent years, along with an increase in gastrointestinal involvement and in the proportion of female patients. ERAP-1 is an enzyme in the endoplasmic reticulum, and one genetic variant is a risk factor for Behçet's in people positive for HLA-B51. ERAP-1 polymorphisms change the structure of the enzyme, altering B51 binding and modulating inflammatory processes; they have been found to be associated with uveitis, arthritis and neuro-Behçet's in various countries.

The session finished with presentation of two oral abstracts. Johannes Nowatzky (USA) continued the topic of HLA-B51 and ERAP-1, describing HLA class I-restricted processes that drive Behçet's in a genetically identifiable, susceptible subset of patients that may represent a disease endotype (O03). Amr Sawala (USA) showed that the increased genetic risk of Behçet's in males is largely explained by genetic loci within the HLA region (O04).

Challenges in diagnosis

Hasan Yazici (Turkey) began this short session with a presentation titled "What is not Behçet's disease?" He listed the strong elements (sensitive and/or specific) of the construct of Behçet's as oral ulcers, uveitis, major vascular disease, genital ulceration and parenchymal central nervous system disease. Uveitis in particular is a very strong and specific feature of Behçet's, and brainstem disease is >95% specific. Vessel wall thickness is a relatively new and strong element, but the histology needs to be understood in more detail. On the other hand, distinct phenotypical clusters, geographical variation in disease expression, differing end-organ response to different drugs and issues with IBD can be considered weak elements of the construct, suggesting that more than one disease mechanism is involved. Prof Yazici concluded that Behçet's is a very complex condition with weak and strong elements and clusters of disease expression. To understand it, more hypothesis-driven and deductive research is needed, with more emphasis on 'splitting' than on the more popular 'lumping' (a tendency to group conditions with some similarities together).

In his talk on recent advances in the diagnosis of Behçet's, Haner Direskeneli (Turkey) explained that Behçet's presents a diagnostic challenge as acute-phase responses (such as C-reactive protein) increase only in certain manifestations, autoantibodies are negative and there is no diagnostic tissue biopsy or genetic marker. In addition, the latest criteria have high sensitivity but low specificity, and many patients with probable Behçet's do not fulfil the criteria. The only available diagnostic test is the pathergy reaction, but this shows wide ethnic variation. The vascular involvement in Behçet's occurs mainly in the veins, and venous vessel wall thickness (VWT) is a potential indicator of Behçet's. This can be assessed using magnetic resonance imaging, and also potentially using ultrasound. Several studies have shown significantly greater VWT in male Behçet's patients compared with ankylosing spondylitis or healthy controls. In a larger study in 152 Behçet's patients, a similar number with other diseases including systemic vasculitis and deep vein thrombosis, and 51 healthy controls, femoral VWT was significantly higher in Behçet's than in all participants except those with antiphospholipid syndrome. The sensitivity for Behçet's was 91% and the specificity was 82%. No differences were seen according to age, gender, disease duration or corticosteroid treatment, and there was a trend towards higher VWT in patients with vascular disease. VWT was able to differentiate between Behçet's uveitis and non-Behçet's uveitis, as well as between complete and incomplete paediatric Behçet's. Prof Direskeneli concluded that venous inflammation may be a hallmark of Behçet's, and femoral VWT might be useful as a diagnostic test.

Treatment – what is new?

In his review of the year, Vedat Hamuryudan (Turkey) concentrated on TNF inhibitors and anticoagulants, noting that all the studies were retrospective rather than prospective trials. He began with a study of adalimumab plus conventional therapy versus conventional therapy alone for Behçet's retinal vasculitis. Treatment was effective in both groups, but adding adalimumab resulted in better efficacy; prognostic factors would be needed to determine which patients would benefit from the initial addition of adalimumab. Both adalimumab and infliximab can be tapered following remission; a new study of infliximab tapering showed 77% ocular remission after 3 years. A study comparing adalimumab and infliximab in non-infectious uveitis found a lower risk of relapse with infliximab; the response rate was better in the 27% of patients with Behçet's rather than idiopathic

uveitis. A similar study showed a better response to tocilizumab than TNF inhibitors, although only 17% of the patients had Behçet's. Finally, a study in 44 Behçet's patients showed that direct oral anticoagulants reduced the risk of relapse of venous thrombosis, and the effect was even greater when they were combined with an immunosuppressant.

Yusuf Yazici (USA) spoke about biologics and small molecules beyond anti-TNF agents. He noted the unmet need to study new drugs in different manifestations of Behçet's, adding that several small studies can be useful in the absence of larger clinical trials. For example, a few small studies suggest that ustekinumab (an IL-12/23 inhibitor) improves oral and genital ulcers and may be worth further study. A study of secukinumab (an IL-17A inhibitor) for uveitis did not meet its primary endpoint, so this drug may not be worth pursuing. Studies of the IL-1 inhibitors anakinra and canakinumab have not been successful, but gevokizumab shows some promise in ocular disease. The IL-6 inhibitor tocilizumab has shown some potential in improving ocular and vascular symptoms, but not gastrointestinal symptoms, while alemtuzumab (an anti-CD52 antibody) has some efficacy in hard-to-treat Behçet's but has a high adverse event rate. Apremilast (a small molecule PDE4 inhibitor) has been approved in the US for the treatment of oral ulcers; it has an acceptable safety profile and also has an effect on skin and joint symptoms. Dr Yazici concluded that it would be a good idea to test potential new therapies in small groups of homogeneous patients initially to see if a signal is detected before studying them in more diverse populations.

Next, Christos Zouboulis (Germany) introduced the European Reference Networks for Rare Diseases, which were initiated in 2017 with the aim of promoting cooperation in rare diseases. There are 24 groups, including one for rare and complex skin diseases (ERN Skin). This comprises nine thematic groups, most of which cover genetic diseases; Behçet's is included under "ALLOCATE SKIN", which covers cutaneous vasculitis, rare follicular diseases and complement diseases, and aims to improve healthcare and social support for patients with acquired immunological rare adult diseases of the skin. The group has patient representatives for each included disease and has developed a specific list of diagnostic technologies that will be certified or accredited to provide Europe-wide harmonisation of services. The next step is to develop an IT communication platform and work towards a single EU registry for each disease, which for Behçet's is being developed from the German registry. The group will also develop treatment guidelines for each disease (based on the German guideline for Behçet's), as well as e-health tools such as apps for patients and training resources for physicians and patients.

The session continued with a presentation by Masaki Takeuchi (Japan) of the Japanese guidelines for the treatment of ocular Behçet's. The overall guideline, published in 2020 and involving >70 specialists from multiple fields, comprises 153 clinical questions, each with a recommendation and a commentary. Of these, 37 relate to ocular involvement and were developed by 17 ophthalmic specialists. Each recommendation is evaluated according to level of evidence and level of agreement by the experts, and rated from A to D for strength of recommendation. For example, recommendation 7 states that colchicine is effective in suppressing ocular attacks and is recommended for use as a first-line drug for suppressing ocular attacks (strength C1). Recommendation 16 states that infliximab is effective in suppressing ocular attacks and is recommended for patients whose ocular attacks are difficult to treat with existing treatments (strength A). The guideline includes detailed algorithms for the prevention of ocular attacks.

To conclude the session, the last of the six selected oral abstracts were presented. Heera Lee (Korea) described the results of a study suggesting that the efficacy of apremilast in Behçet's might be related to inhibition of immunosenescence involving reduction of senescent cytotoxic T cells (O05). Robert Moots (UK) then presented the results of the BioBehçet's trial, which showed infliximab and interferon-alpha to be equally effective in reducing disease activity in Behçet's (O06).

Keynote lecture: The journey of TNF blockade

George Kollias (Greece) explained how TNF (tumour necrosis factor) acts on fibroblasts (mesenchymal cells in connective tissue) to orchestrate chronic inflammation. Fibroblasts are the first cells to react to the microbiota or stress (via TNF and other cytokines), producing pro-inflammatory molecules. TNF overexpression was shown to be a causal factor in the development of RA-like disease in mice in 1991, and treatment of RA with TNF inhibitors was first tested in 1993. In the mouse model, TNF-driven arthritis develops even in the absence of mature T and B cells, suggesting that the adaptive immune response is a secondary mechanism. The action of TNF on synovial fibroblasts was shown to be both sufficient and necessary for full TNF-driven destructive arthritis. The same applies to intestinal mesenchymal cells in the orchestration of Crohn's disease, and similar effects in other organs lead to the many comorbidities of such diseases. So mesenchymal cells targeted by TNF provide a common mechanistic principle to understand chronic inflammation and comorbidities. Tissue fibroblasts are heterogeneous, and Prof Kollias concluded that assigning biomarkers and function to fibroblast subpopulations may offer more specific and safer precision therapies for complex diseases such as Behçet's.

Special session – Towards a treat-to-target strategy

The final session of the in-person conference was a special session on treating to target in Behçet's. George Bertias (Greece) set the scene by describing how this has been approached in SLE, another complex, heterogeneous, relapsing–remitting disease. SLE was first treated with biologic drugs in 2011 and discussions about treating to target began in 2012, with learnings from RA. A literature search was conducted to determine the relationship between disease activity and outcomes in SLE, look for any definitions of low disease activity and remission, decide whether sustained reduction or remission of flares is an achievable goal, search for validated tools for assessment of irreversible damage, determine how well prevention of damage correlates with quality of life, and look for evidence on the benefits of different treatment strategies. Multiple 'targetable' factors affect the prognosis of SLE, leading to permanent organ damage with increased morbidity and mortality. In 2014, following expert discussions, an international taskforce published recommendations for treating to target in SLE. Further work was needed to establish definitions of low disease activity and remission, and to show that the ~50% of patients who can attain these have better outcomes.

Gonca Mumcu (Turkey) then spoke about measuring disease activity in Behçet's, stating that disease activity reflects the clinical manifestations at a specific time point. Measurement of disease activity is fundamental to clarify health status and inform individual treatment plans. Complete remission is defined in different ways and is difficult to achieve for most patients. Partial remission or sustained

low disease activity may be a more achievable goal, but the exact definitions are unclear. Consensus is needed on which metrics to use to measure disease activity. Activity indices used include laboratory tests and patient-reported outcomes. The main question is how to evaluate activity in a heterogeneous disease. Both disease-specific and organ-specific indices may be needed, along with patient-reported outcomes including fatigue and independence. Commonly used measures include the physician global assessment, patient global assessment, total clinical activity index and Behçet's syndrome activity score. Organ-specific measures include the oral ulcer severity score and genital ulcer severity score. The indices used need to be standardised so that results can be compared, and the most useful indices need to be determined so that real changes in activity can be detected by using a few relevant questions.

Next, Gülen Hatemi (Turkey) gave an update on the OMERACT initiative to standardise outcome measures in Behçet's. First she described the steps in developing a treat-to-target strategy as determining long-term goals, choosing a target, choosing how and when to assess the target, and deciding when to change treatment. An ideal target should reliably predict long-term damage and function, have a clear definition, be possible to assess reliably and be feasible in terms of cost and time required. Challenges in Behçet's include the fluctuating disease course and multi-organ involvement. The work done by OMERACT in the past 10 years has included a systematic review and discussions with experts and patients. It has identified a core set of mandatory domains that should be assessed for all clinical trials (e.g., overall disease activity and quality of life) and for mucocutaneous, ocular, musculoskeletal, vascular, gastrointestinal and nervous system involvement, as well as additional optional domains for some of these. One question is whether the outcome measures developed for clinical trials are good targets for a treat-to-target approach in Behçet's. There may be problems with using an overall disease activity index in a treat-to-target strategy, as it may lead to overtreatment in an attempt to eliminate all activity. Vascular leakage may be the most appropriate target in patients with uveitis, while recanalisation is a possible target for vascular disease as it predicts deep vein thrombosis (DVT) relapse. For gastrointestinal involvement, mucosal healing is a good indicator but requires regular endoscopies. While remission is the target for most manifestations, a state of minimal disease activity may be acceptable for mucocutaneous symptoms. The next step for OMERACT is to select the instruments for each domain and create a validated core set of outcome measures.

Jan van Laar (Netherlands) then considered therapeutic targets in Behçet's, saying that validated targets are lacking. Meta-analyses of clinical trials are not possible because of the heterogeneity of trial design, choice of intervention, and choice and timing of outcome measures. The EULAR 2018 recommendations for the management of Behçet's state that the goal of treatment is to promptly suppress inflammatory exacerbations and recurrences to prevent irreversible organ damage. In uveitis, the aim is to reduce short-term flares and long-term severe complications, to improve inflammatory activity, and to lower the risk of flares and visual impairment. Comparative studies of therapies for uveitis have used a wide range of outcome measures and definitions of success. Likewise, trials in mucocutaneous disease have used many different primary endpoints. For other manifestations, the primary outcome is clearer, such as prevention of recurrence of DVT. Rapid and sustained remission and prevention of relapses should be the target for ocular, gastrointestinal, vascular and nervous system involvement, while mucocutaneous and joint symptoms should be sufficiently controlled to achieve an acceptable quality of life.

The final presentation was on targeting remission and preventing damage in ocular Behçet's, by Bahram Bodaghi (France). Visual acuity is important, but it is not very informative on the level of ocular inflammation. However, grading of inflammation can only be done by specialists. Tools are available for non-invasive measurement of ocular inflammation, such as laser flare photometry. Fluorescein angiography is an important invasive tool for monitoring the blood vessels in the retina. Optical coherence tomography (OCT) is a useful non-invasive tool to examine the macula and optic disc, while OCT angiography is a newer method of assessing for vascular occlusion. The EULAR recommendations are still up to date and should be followed carefully. Systemic immunosuppressives should be used in patients with isolated anterior uveitis. For panuveitis, infliximab or adalimumab can induce remission, while tocilizumab may be more effective for macular oedema and may be able to replace interferon-alpha if it is not available. Achieving complete remission should be the main goal in treating ocular Behçet's, and treatment should not be delayed. Multimodal imaging and evaluation tools are the new standard for assessing remission.

Petros Sfikakis (Greece) led a discussion on implementing treat to target in treatment recommendations, noting that the 2018 EULAR recommendations make no mention of it. Treat to target is used in diabetes, hypertension, chronic obstructive pulmonary disease and RA, and has been shown to be better than usual care. There are several challenges to implementing it in Behçet's, including what the target should be. A review article by Gülen Hatemi published in January 2022 proposed different targets for different disease manifestations. Such an approach would require involvement of several specialties. The ultimate target is drug-free remission, which may be achievable with TNF inhibitors in some patients. The plan is to ask EULAR for support with setting up a task force to develop a treat-to-target strategy in Behçet's, but implementation of such a strategy will not be easy. Barriers will include access to care in some countries, lack of knowledge/belief on the part of physicians and logistical issues such as the need for frequent visits. Ocular Behçet's seems to be the most promising area to start with, and neuro-Behçet's has good examples to follow such as multiple sclerosis. There will also be a need to personalise targets to the individual and to have low-cost options, as is the case with diabetes. Finally, it is important to distinguish between targets and goals – the idea is to treat to target in order to achieve the goals.

Treatment aspects

Non-infectious uveitis: advances in treatment

This virtual-only session began with a presentation on TNF inhibitors by Rola Hamam (Lebanon). Infliximab has the longest history of use in Behçet's, as well as in other types of non-infectious uveitis, with around 82% of patients achieving clinical remission in a median time of 127 days. It has a good retention rate (89% at 1 year and 47% at 10 years) and is well tolerated. Infliximab has also been used intravitreally for active posterior uveitis in Behçet's, with control of inflammation in 35% and worsening in 20%. Adalimumab is approved for treating non-infectious uveitis in the US on the basis of multinational clinical trials. It has been shown to control ocular inflammation and allow discontinuation of corticosteroids in most patients. In a large observational study in 12 countries, 77% of patients with active uveitis were quiescent at 12 months, and 52% had discontinued steroids; quality of life was improved and economic burden was reduced in these patients. Intravitreal adalimumab was shown to control inflammation in 75% of patients. Golimumab has been shown to

be effective in reducing inflammation in small studies in non-infectious uveitis, while certolizumab has been shown to decrease recurrence. Etanercept is not effective in uveitis. In a meta-analysis of TNF inhibitors in Behçet's uveitis, the pooled remission rate was 68%, with a 60% rate of visual acuity improvement.

In her talk on IL-1 inhibitors, Katerina Laskari (Greece) reminded the audience that a minority of patients do not respond, or lose response, to TNF inhibitors. IL-1 seems to have a pathophysiological role in Behçet's, leading to trials of the IL-1 inhibitors canakinumab, anakinra and gevokizumab. Three studies of gevokizumab for ocular Behçet's have given contrasting results, with some indication of promising efficacy and a steroid-sparing effect, but no reduction in the risk of recurrence. A limited number of case reports and small case series with anakinra and canakinumab described successful treatment with these agents. A multicentre observational study of these two drugs in 19 patients showed decreases in ocular inflammatory flares, retinal vasculitis and steroid dosage. Another study in 30 Behçet's patients, 12 of them with uveitis, found a median time to response of 6 weeks for anakinra and 3 weeks for canakizumab; retention on therapy at 2 years was 32% for anakinra and 72% for canakizumab. Both drugs can be used as first-line or second-line therapy and have a good safety profile.

Claudia Fabiani (Italy) then spoke about IL-6, IL-23/IL-17 and JAK inhibitors. Like IL-1, IL-6 has a pathogenic role in Behçet's and two IL-6 inhibitors – tocilizumab and sarilumab – are available. Tocilizumab has been shown to be effective in refractory uveitis, with reduced steroid dose in 19/21 patients and steroid-free remission in 11 in one study and complete remission in 10/16 patients in another. A randomised controlled trial in 37 patients with non-infectious uveitis showed a significant reduction in central macular thickness and vitreous cell count after 6 months. A phase 2 study with sarilumab has also shown potential. Another potential pathway for targeting is JAK-STAT signalling. A pilot study of the JAK inhibitor tofacitinib in 13 patients with refractory Behçet's uveitis achieved treatment success in 10 cases, with corticosteroid withdrawal in all 10 and tofacitinib dose tapering in six. Further trials in non-infectious uveitis are ongoing. Finally, genes encoding the IL-17/IL-23 signalling pathway are associated with Behçet's. Some success has been reported with ustekinumab in a Behçet's patient and with secukinumab in non-Behçet's infectious uveitis. However, three randomised controlled trials of secukinumab in non-infectious uveitis (including Behçet's) did not meet their primary endpoint of reducing recurrence. In the absence of confirmatory clinical trials with newer agents in rare diseases, capturing data on their use in registries is important.

Adherence to treatment in Behçet's disease: a multifaceted issue

The last presentation in this session was by Rosaria Talarico (Italy) on the subject of adherence to treatment in Behçet's. Adherence is defined as the extent to which a person's behaviour (in terms of taking medications, following diets or executing other lifestyle changes) corresponds with agreed recommendations from a healthcare provider. Lack of adherence to medication leads to poorer health outcomes for the patient and economic loss for the healthcare system. For physicians, it can be difficult to distinguish between non-adherence and non-response. Adherence is influenced by multiple factors, including treatment efficacy and duration, administration routes, patient empowerment and the physician–patient relationship. Various patient-reported and objective methods are available for measuring adherence. Studies in 2018 and 2019 found adherence rates of 22–50% in Behçet's. A survey co-designed with a patients' association investigated characteristics of

non-adherent Behçet's patients. Less adherent patients were more likely to be in the third decade of life and to have been diagnosed for >5 years. A longer time since diagnosis increased the chances of being less adherent. This may be related to patients with a long history of Behçet's being more able to manage their disease and more prone to modifying their treatment without clinical consultation. Interventions to improve adherence include face-to-face counselling, educational programmes and patient empowerment. An international study called IMPACT_BD (IMProving AdherenCe to Treatment in Behçet's Disease) aims to explore the main reasons for non-adherence, create a specific tool to monitor adherence and plan specific actions to improve adherence in Behçet's. It is hoped that the results will identify individual and cultural barriers leading to non-adherence.

Some posters of interest

Among the posters presented during the conference, some might be of particular interest to patients. Diana Marinello presented a poster on BehçeTalk, an educational programme for patients, families and caregivers in Italy (P095). The programme was co-designed with patients and caregivers and offers educational webinars on different aspects of the disease, as well support groups for patients and caregivers coordinated by a psychologist with expertise in Behçet's. The programme received positive feedback from the patient community, reporting a significant benefit in their coping strategies and in better involving their caregivers and families in their journeys. A new edition of BehçeTalk in English will soon be launched to improve its accessibility.

Another poster from Italy, presented by Riccardo Laconi, looked at the impact of Behçet's on work activity and productivity (P098). Demographic and clinical data, as well as Work Productivity and Activity Impairment: General Health questionnaire results, were collected for 148 patients. Of 97 patients working for pay, 22 (28%) reported missing work in the previous week due to their health (absenteeism), with a mean proportion of missed working time of 34%. The only factor associated with absenteeism was ocular damage. More than a quarter of patients reported that their productivity while working was impaired due to their health problem (presenteeism). Ninety-nine (67%) patients complained of daily activity impairment, reporting that a third of their regular daily activities had been prevented due to their health problems. Factors significantly associated with patients' daily activity impairment were younger age at enrolment, higher disease activity and fibromyalgia.

Closing remarks

Closing the conference, Petros Sfikakis said that there had been 261 registered participants from 26 countries, a 10% increase from the Rotterdam conference in 2018, and 61 speakers from 24 countries. It was announced that the 20th ICBD will take place in Marrakesh, Morocco, in 2024.

Clare Griffith