

The 14th International Conference on Behçet's Disease
Queen Mary University, London, 8–10 July 2010

The 14th International Conference on Behçet's Disease was attended by around 300 delegates. Twenty-five abstracts were presented orally and more than 150 as posters. There were also a number of presentations from outside speakers and ISBD invited speakers.

Immunology

Professor Adrian Hayday from Cancer Research UK spoke about the lymphoid stress-surveillance (LSS) response, a new idea in immunology and inflammation. The epithelial tissues, which are the site of many important inflammatory diseases including Behçet's disease (BD), appear to be more than just a physical barrier to challenges such as infections. Endothelial cells, in response to stress, can produce stress antigens that elicit a T-cell response resulting in the release of pro-inflammatory cytokines and also in feedback to the epithelium to initiate wound healing. This LSS response seems to be important in viral infections and affects downstream adaptive immunity; it represents a potential local target for immune intervention.

Dr Bahram Bodaghi from France then outlined a new therapeutic strategy targeting regulatory T cells (Tregs) in non-infectious uveitis, which is a major complication of BD. Tregs are a component of the immune system that suppress immune responses of other cells, maintaining tolerance to self-antigens. Intravitreal injection of pre-activated Tregs has been shown to reduce uveitis in mice for up to 3 weeks, and the number of Tregs has been found to be low in patients with active uveitis. A clinical trial is now ongoing in which Tregs from BD patients with severe bilateral uveitis are purified, expanded, activated and reinjected into one eye. The purity of the Tregs is important, as contamination is a safety concern.

Among the new research presented, a group from Korea found that serum levels of the protein S100A12 (EN-RAGE), a marker of chronic subclinical inflammation, are increased in patients with BD compared with healthy controls.¹ The level was correlated with disease activity and decreased after treatment, and the researchers suggested that it may be a better marker of disease activity than interleukin-8. Researchers from Istanbul and London used whole-genome microarray analysis to look at profiles of cytokine expression in patients with BD and familial Mediterranean fever. They found overexpression of various genes, including Janus kinase 1 (JAK1) in monocytes from BD patients, concluding that activation of JAK1 through various cytokines such as IL2, IL6, IL15 and interferon- γ may be the dominant signalling pathway driving inflammation in BD.² A US research group using a novel mouse model characterised by arthritis and uveitis found that deficiency of interferon- γ was protective in the joints but was associated with severe anterior uveitis with marked

posterior involvement akin to the ocular disease in BD.³ This suggests that interferon- γ has different roles in eye and joint disease in BD.

Vasculitis

To start the session on vasculitis, Dr Justin Mason from Hammersmith Hospital spoke about the use of imaging in large vessel vasculitis, showing how new developments and the use of combinations of modalities can be used to improve diagnosis, localise inflammation and monitor treatment. Professor Hasan Yazici from Istanbul then gave a presentation on the vasculitis of BD subtitled “What do we know and not know?”. Vasculitis is seen in the erythema nodosum (EN) lesions of BD but not in other types of EN, but it is only seen in 50% of EN cases in BD. Central nervous system lesions show some vasculitis but mainly inflammation, while pyoderma gangrenosum is characterised by inflammation without vasculitis. Arterial disease seems to have a later age of onset than venous or pulmonary disease, and different mechanisms may be involved. Patients with eye involvement seem to have fewer vascular events, but this may be because they receive more immunosuppressive treatment. Endothelial dysfunction leads to atherosclerosis, but angina and myocardial infarction are not increased in BD. Recurrent vascular events are not very common, and anticoagulants are probably not needed. Professor Yazici concluded that many manifestations of BD are not explained by vasculitis and that more attention should be given to the non-vasculitis aspects of BD.

A London group reviewed vascular involvement in the 657 patients referred for assessment to a tertiary BD clinic between 1994 and 2009. Sixty-two of the patients had a history of thrombosis, and 55 (89%) had been treated with warfarin before referral.⁴ This is contrary to EULAR recommendations, which state that vascular involvement in BD should be treated with corticosteroids and immunosuppressive agents rather than anticoagulation therapy. However, thrombosis was the event that led to diagnosis of BD in 39 of the patients, and anticoagulation may be appropriate in the UK in the light of diagnostic uncertainty and the risk of pulmonary embolism.

Researchers in Turkey looked at the incidence of pulmonary hypertension in BD patients with and without pulmonary artery involvement (PAI) and healthy controls. Pulmonary hypertension was present in 5/30 BD patients with PAI compared with 2/26 of those with vascular disease but no PAI, 0/21 patients without vascular disease and 0/21 healthy controls.⁵ This indicates that BD may involve small/micro pulmonary vessels as well as large pulmonary arteries. Another Turkish group analysed pulmonary perfusion scintigraphy findings in BD patients with vascular involvement, pulmonary symptoms or abnormal chest X-ray/thorax CT. They found a significant association between perfusion defects on scintigraphy and arterial aneurism or any vascular involvement, but no association with any other manifestation of BD or with pulmonary embolism.⁶ These findings suggest that many BD patients may have unrecognised small vessel and/or parenchymal lesions, but

pulmonary scintigraphy is not a useful screening tool in patients without vascular involvement.

Regional inflammation

Dr Dennis McGonigle from Leeds spoke about BD classification as an intermediate between adaptive and innate mediated immune disease. Autoimmunity is a long-standing concept with a mechanism involving B cells and T cells. Most autoimmune disorders (such as systemic lupus erythematosus, rheumatoid arthritis and type 1 diabetes) are polygenic. It was later recognised that some diseases did not involve adaptive immunity, and the concept of autoinflammatory disorders was developed. These are diseases of innate immunity, and BD was included on the list. The mechanism is a self-directed inflammation that is not autoimmune in origin and involves local tissue factors. For a disease to be classified as autoimmune, the presence of autoantibodies before disease onset needs to be demonstrated. There is a spectrum of diseases, with BD fitting into the innate/intermediate zone along with conditions such as ankylosing spondylitis and psoriatic arthritis. The genotype has consequences for the phenotype, with HLA types acting as modifiers for the extent and severity of several of these diseases.

Dr Ahmet Gül from Istanbul gave a presentation entitled “Multiple faces of inflammation in Behçet’s disease”. There are subsets of BD patients, with a large group having only mucocutaneous manifestations; other subsets include patients with vascular disease, eye disease and papulopustular skin and joint involvement. BD is characterised by recurrent inflammatory attacks, which are self-limiting and usually leave no scars, although occasional permanent tissue damage does occur. The innate immune system is usually involved, with pro-inflammatory cytokines such as IL1 and TNF α , but the adaptive immune system may also be involved. There is ongoing low grade inflammation between attacks, and triggering factors may include systemic or local infection, physical trauma and psychological stress. The interface between the body and the environment is important. BD seems to result from a genetic tendency for an increased inflammatory response (HLA-B52, MICA, IL10) and an interaction with environmental triggers leading to episodic attacks.

Researchers from Istanbul presented the SHIELD study, in which BD patients with uveitis are being treated with AIN457, an inhibitor of IL17A. IL17 is a key cytokine in immune-mediated inflammatory diseases and has broad pro-inflammatory effects. AIN457, a monoclonal antibody, has been used in more than 1400 patients with a variety of diseases, including rheumatoid arthritis, Crohn’s disease and multiple sclerosis, with no safety problems emerging. In this 24-week trial, more than 100 patients will be randomised to a high or low dose of AIN457 or placebo. The aim is to control uveitis and prevent recurrences and to reduce the need for concomitant medications. The results are expected at the end of 2010.⁷ A group from Iran presented the results of 15 years’ follow-up of 597 ocular BD patients treated with methotrexate and prednisolone (tapered). Visual acuity stabilised or improved over

this period in 62% of treated eyes, with mean visual acuity increasing significantly from 5.1 to 5.5. The best results were in patients with posterior uveitis and no clinical evidence of retinal vasculitis.⁸

Turkish researchers compared the symptoms and the clinical, endoscopic and histological findings in 36 patients with gastrointestinal BD and 72 with Crohn's disease (CD). They found that the age at diagnosis was lower in BD and surgery was needed more often and at a younger age. The location of gastrointestinal involvement was similar in the two groups, with focal single ulceration being more common in BD. Diarrhoea was more common in patients with CD, but BD patients were more likely to have gross rectal bleeding and perforations.⁹

Age-related BD

Professor Michael Beresford gave a presentation on the UK Paediatric Rheumatology Clinical Studies Group (PRCSG). Rare disease in children pose a particular problem in that the evidence base for any treatment is very small. Diseases such as the vasculitides, systemic lupus erythematosus and scleroderma are complex conditions characterised by a lack of biomarkers and robust outcome measures. There have been recent international collaborations on juvenile idiopathic arthritis, and a large clinical trial of etanercept studied about 2,000 children. Other trials have been done, but few biologic treatments have been licensed in children. The UK PRCSG has linked existing registries and collaborations and formed topic groups that can collaborate with international organisations and the pharmaceutical industry to identify key clinical research priorities and global themes, research tools and methods. Clinical research should be the norm in paediatric rheumatology, so that more clinical trials can be run and biologic treatments licensed. Registries monitor the long-term safety and efficacy of biologics in all paediatric rheumatology patients.

Dr Isabelle Kone-Paut from France spoke about the diagnostic problems and treatment peculiarities in paediatric BD. She said that patients very rarely fulfil the complete criteria for BD before the age of 16, with insidious onset and atypical presentations being common; it can be very difficult to exclude all the other possible causes of the symptoms seen. A family history is more common in paediatric patients than in adults. An international cohort study that has been running for a year is aiming to define paediatric BD more accurately. So far, 110 children aged under 16 from 11 countries have been included with suspected BD. Common symptoms in addition to oral ulcers include genital ulcers, pathergy, pustular lesions and uveitis. Genital ulcers are more common in girls and ocular symptoms in boys. So far, BD has been confirmed in 30 patients; the only symptoms significantly associated with confirmed BD are genital ulcers ($P=0.03$) and skin lesions ($p=0.0001$). The study needs to enrol more patients. Treatment is generally as for adults, but paying particular attention to the toxicity of drugs such as steroids and immunosuppressants. The time of transition to adult services is very important, with a need for continuity in follow-up.

An analysis of registry data in Germany found that male patients and those of Turkish origin had a younger age of onset and a more rapid disease course compared with female patients and those of German origin. Turkish origin patients were also more likely to be positive for HLA-B51, and this factor was associated with more mucocutaneous and ocular symptoms.¹⁰ A Japanese study looked at eye disease in juvenile BD patients. Of 136 paediatric patients attending a BD clinic between 1980 and 2006, 76 (56%) had ocular symptoms; in 70 of these children, eye disease was present at the initial visit. The ocular involvement was bilateral in 66 patients and was more common in boys than girls. Eye disease in paediatric BD patients seems to have a more favourable outcome than in adults.¹¹

As BD is most active during the working years, a Turkish group studied work disability in BD patients. They used a standard questionnaire to survey 300 consecutive patients attending a BD clinic. Of the 149 patients who were eligible for work, 29 (19%) were unemployed; all but one had been employed before diagnosis. The general unemployment rate in Turkey at this time was 14%. The type of organ involvement in BD did not significantly predict employment status, but unemployed patients were more likely to be taking immunosuppressants.¹²

Genetics

Dr Oliver Brand gave a talk entitled “Genetics of complex diseases: lessons from Graves’ disease”. This condition involves overactivity of the thyroid gland and affects 2–3% of Western populations, with a strong female preponderance (about 80%). About 80% of risk for the disease can be attributed to genetics. Several different genes are known to be implicated, including HLA class I and II, IL2R and CTLA4, but many others may be involved. The only Graves’ disease-specific association is with TSHR, a gene on chromosome 14. It is thought that a variant of the A subunit of the TSH receptor results in autoantibody production.

Next, Dr Eun-Bong Lee from Korea presented an overview of candidate gene analysis in BD. The pathogenesis of BD is complex, resulting in many candidate genes. The strongest association, with HLA-B51, has been known since the late 1970s. This molecule is involved in antigen presentation. HLA-B57 and A26 are also associated with BD, but their functional role is not known. Of other major histocompatibility complex genes, the most consistently associated with BD is MICA009. TNF α is also associated to a lesser degree. Among inflammation-related genes, IL1 α is associated in Turkish populations. IL6 and IL8 show an association in some populations, as do IL10, 12, 17 and 18. Intercellular adhesion molecule (ICAM)-1 shows marginal association. Of adaptive immunity-related genes, CTLA-4 has uncertain association and an unclear role. Of innate immunity-related genes, toll-like receptor (TLR)-2 is not associated with BD, while TLR-4 has been found to be slightly associated in Turkish and Japanese populations. Several genes involved in endothelial cell function have shown some marginal associations in certain populations, including E-NOS,

ACE and VEGF. It is apparent that the interaction of a number of genes contributes to the development of BD.

The results of two genome-wide association studies (GWAS) were presented. In one, more than 500,000 single nucleotide polymorphisms (SNPs) from 612 Japanese BD patients and 740 controls were compared. Two significant associations with BD were found outside the HLA region, in genes for IL10 and IL23R-IL12RB2. These associations were replicated in Turkish and Korean populations.¹³ The other GWAS used more than 300,000 SNPs from 1215 BD patients and 1278 controls in Turkey. In addition to the known association with HLA-B51, evidence was found for a second, independent susceptibility locus in the MCH class I region. This study also found significant associations with the gene for IL10, a powerful anti-inflammatory cytokine, and with a variant located in the non-coding region between two genes encoding receptor subunits of the pro-inflammatory cytokines IL23 and IL12. The disease-associated IL10 variant was associated with diminished mRNA expression and low protein production by cells obtained from healthy blood donors, suggesting novel therapeutic targets for BD.¹⁴

In other genetic research, an Iranian group reported no significant associations between polymorphisms in the methylenetetrahydrofolate reductase (MTHFR) gene in BD patients with thrombosis.¹⁵ The relevance of this is that MTHFR is an enzyme that breaks down homocysteine, and increased plasma homocysteine level has been associated with a tendency to induce thrombosis in patients with BD. A Turkish study found that the frequency of monozygotic (identical) twins in BD did not differ from the general population, while dizygotic twins were seen less frequently in BD. The concordances for BD were higher in monozygotic than dizygotic twin pairs, suggesting a genetic predisposition.¹⁶

Treatment of BD

Across the various sessions of the conference, there were several reports of studies of biologic therapies. In an international case series, 17/18 neuro-BD patients treated with infliximab has a favourable outcome.¹⁷ A prospective study of 20 patients in Italy found infliximab therapy to be safe and effective in preventing uveitis relapses, maintaining baseline visual acuity in all the patients after a mean follow-up of 3.5 years.¹⁸ Two different Japanese studies found improved visual acuity and reduced attack frequency in patients with ocular BD treated with infliximab,^{19,20} while another found favourable outcomes with the same drug in intestinal BD.²¹ Infliximab is the most commonly used TNF inhibitor in BD, but not all patients respond and some lose efficacy or have adverse reactions. Italian researchers reported on the use of adalimumab in patients unsuccessfully treated with infliximab. Of 17 patients who discontinued infliximab, remission was achieved with adalimumab in nine cases and partial remission in another three.²² A Dutch group reported good long-term results (over 5 years) with adalimumab in BD patients with a variety of symptoms refractory to traditional immunosuppressants,²³ while Tunisian researchers reported good

medium-term results with etanercept in five BD patients with ocular symptoms.²⁴ A systematic review of TNF inhibitors found them to be promising agents especially for resistant ocular, gastrointestinal and central nervous system involvement.²⁵

In addition, a group from Cambridge, UK, reported a complete remission rate of 74% among 20 patients treated since 1998 with alemtuzumab (CAMPATH-1H), a T-cell depleting anti-CD52 agent. Re-treatment was effective in patients who relapsed.²⁶ Turkish researchers reported preliminary results using XOMA 052, an IL1 β -regulating agent, to treat resistant uveitis in seven BD patients; a rapid onset of effect was seen.²⁷

There were also several reports of interferon- α treatment in BD. An analysis of the records of 121 Turkish BD patients with uveitis treated with interferon found a decrease in recurrent attacks and improved visual acuity.²⁸ Also in Turkey, a prospective study of interferon treatment in 37 patients with refractory uveitis showed remission in the majority of patients, sustained over 2 years.²⁹ However, a randomized trial of interferon versus cyclosporine in 52 Turkish BD patients with uveitis found that cyclosporine was more effective in preventing attacks.³⁰

Debates

Two debates took place during the conference. The subject of the first debate was “Autoimmunity versus autoinflammation”. Professor Haner Disrekeneli said that the term autoinflammation was first used in 1999 to describe seemingly unprovoked inflammation in the absence of high-titre autoantibodies or antigen-specific T lymphocytes. The innate immune system plays a role. Inflammasomes are activated by antigens, leading to activation of IL1. Characteristics that point to BD being autoinflammatory include the treatment responses and the fact that mortality is higher in the early years. Dr Graham Wallace said that autoimmunity is characterised by out of control hypersensitivity and loss of tolerance to stimulants. Cells involved in the adaptive immune response, such as Th1 cells, may have an important role in BD. Autoantibodies to enolase and co-stimulation molecules are found in BD, and several single nucleotide polymorphisms related to autoimmunity are associated with BD. It was agreed in the ensuing discussion that BD probably has elements of both autoinflammation and autoimmunity. There is a lot of overlap between the innate and adaptive immune systems, and different subsets of BD patients may have more of one component. The concept that BD is not simply an autoimmune disease led the way to new treatment options.

The second debate was entitled “Geographical differences in BD”. Professor Shigeaki Ohno said that the BD seen in Chinese patients is very similar to that in Japan, while cases in Iran and throughout the Middle East and around the Mediterranean are also typical. HLA-B51 is also prevalent in the same areas. However, northern European patients have different polymorphisms compared with Japanese patients. It seems likely that the disease started in the Middle East and then moved eastwards and

northwestwards, with different polymorphisms appearing. Professor Ohno went on to say that BD in Japan seems to be changing, with a consistent decrease in the number of new cases in the past 15–20 years. By contrast, the incidence appears to have remained constant in Turkey and is still increasing in Korea. The disease also seems to be becoming milder in Japan, and this coincides with an increase in allergic conditions. Professor Miles Stanford described the results of a systematic review of population-based studies, which found no evidence for different phenotypes in different ethnic groups. One study found no differences between Jewish and Arab patients, while another found that Japanese patients tended to be older than British patients, with no other differences. German patients had delayed recognition of BD compared with Turkish patients in Germany, with no other major differences. Any differences found largely arise from methodological flaws such as referral bias and lack of consistent diagnostic criteria.

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