

2012 International Conference

The 15th International Congress on Behçet's Disease was held at the Conference Centre in Yokohama, Japan, on 13–15 July 2012. It proved to be an excellent meeting, with many presentations describing novel or confirmatory results that increased our understanding of this complex disease.



Genetics of Behçet's disease

The sessions started with presentations on the genetic basis of Behçet's disease (BD). Following on from the recent genome-wide analysis (GWAS) studies presented at the 14th Congress in London, Remmers (USA) and Gul (Turkey) discussed further studies using this data. Using a process called imputation, where changes in gene structure are implied from GWAS data, and sophisticated statistics, they identified polymorphisms in new genes associated with the immune response, some of which were protective. Of particular interest was a gene called ERAP that trims protein sequences to fit into molecules such as HLA-B51, which is associated with BD. This was particularly linked in patients with eye disease. Kappen (Netherlands) discussed a GWAS finding of a novel polymorphism on chromosome 18. These results show that a mixed cohort can still be used for GWAS. Takeuchi (Japan) reminded us that it is not only HLA-B51 that is linked with BD on chromosome 6 by showing that HLA-A26 was associated in patients with complete BD (Japanese

classification). Moreover, the previous GWAS showed that a single nucleotide polymorphism (SNP) for IL-10 was associated with various manifestations, and 22 Japanese patients who were required to go on to infliximab were IL-10 positive. These results show that while HLA-B51 is still the major genetic factor in BD, other genes also play a role in BD.

Cytokines are molecules that signal between cells involved in the immune response and can be classified as pro-inflammatory (IL-17, IFN α) or anti-inflammatory (IL-10). Yasuoka (Japan) showed that plasma IL-17 levels were raised in samples from BD patients. Interestingly, the cells producing IL-17 were raised in both active and inactive BD but were greater in inactive disease. It was suggested that this is due to IL-17 producing cells (Th17) being in tissues rather than blood during active disease, but this has to be proven. In paediatric BD patients, there was a normal frequency of T-regulatory cells, which damp down inflammation, and depletion experiments showed that these cells were functional. However, there was also an increase in Th17 after stimulation, and in blood there was increased IFN α and IL-17. This suggests that there is no functional defect in regulatory cells in paediatric BD, but that there may be an increase in pro-inflammatory responses regardless (Tran, France).



Disease processes and markers

Session 2 focused on potential processes and markers of disease in patients with BD.

Bergmeier (UK) discussed brush biopsies of the mouth lining and showed that molecules involved in recognition of bacteria and viruses had a different form in patients. This could be involved in the development of persistent mouth ulcers. In a second study from the same group, a protein that controls cytokine production (called SOCS3) was decreased in blood cells from patients with BD, both quiescent and relapsed. However, there was more SOCS3 in neutrophils in relapsed BD patients. Cho (Korea) used the latest spectroscopic analysis and identified hnRNP/B1 as a possible antibody target in BD, as there were greater levels of antibodies against this molecule in patients. Moreover, hnRNP/B1 expression increased in culture medium in response to BD serum or bacterial stimulation, and in oral and genital ulcers. hnRNP release may reflect vascular damage or a pathological immune response inducing inflammation.

In recent years, another level of control of gene expression has been identified. Small molecules called miRNA bind to and inhibit gene expression in most cell types. Yang (China) selected five immunologically relevant miRNAs to analyse in BD. miR155 was decreased in blood cells from patients with active BD. Studies on blood cells in the laboratory showed that increasing or decreasing miR155 had a functional effect. As manipulation of miRNA is being tested in several disease states, this suggests a potentially important new avenue of research. Iwabuchi (Japan) presented data showing that plasma levels of osteopontin were increased in both BD and Vogt–Koyanagi–Harada syndrome patients with uveitis. To investigate this in mice, they induced eye disease and blocked osteopontin in these animals. The results showed reduced disease scores in animals, probably due to suppressed production of IFN α and TNF by sensitised T cells. Kitachi (Japan) analysed levels of advanced glycation end-products (AGE), which are a product of inflammatory responses and may exacerbate the situation. They appear to have an effect on experimental allergic uveitis, as disease was milder when AGE was inhibited by drugs.

The results of this session tell us that many pathways are activated by the inflammatory response in patients with BD, but also identify potential targets for new drug regimens that could modulate this response.

Drug treatments

With regards to current treatment, several talks discussed the use of anti-TNF drugs (infliximab, etc). Mizuki (Japan) described the standard regimen in Japan of infliximab every 8 weeks, but found that many patients still had a relapse of uveitis before the next injection. Therefore, they are now looking to dose more often than every 8 weeks. He showed that infliximab generally led to fewer ocular attacks and better maintenance of vision. These results were supported by Lecesse (Italy), who showed that after 12 months on infliximab 90% of patients had partial or complete remission of uveitis, but also other manifestations. Takamoto (Japan) found that the frequency of ocular attacks was reduced and visual acuity improved. Adverse effects were low and not problematic. Interestingly, one patient dropped out of the study as they could not last the 2-hour infusion time without a cigarette! Inoue showed that the therapeutic response was not related to baseline TNF levels in BD patients, which is different from other diseases such as rheumatoid arthritis. Interestingly, from these reports, males are much more likely to require anti-TNF treatment than females. Discussion followed as to when infliximab therapy could be stopped or reduced in well patients. The consensus was to reduce time to next infusion from 8 to 12 weeks and see how patients respond. The point was also made that good outcome measures need to be established for all aspects of BD to get maximum benefit from all these studies. However, it is clear that infliximab and other anti-TNF drugs are a major advance for patients with BD who are failing on standard treatment, particularly those with uveitis as discussed in a recent editorial in the *British Journal of Ophthalmology*.

The other major new drug treatment of the past few years is interferon- 2α (IFN 2α). Yacildag (Turkey) described use of IFN 2α in patients not responding to conventional therapy. It was made clear that other systemic immunomodulatory drugs should be discontinued at this time as an intact immune response is needed for full effect of IFN 2α . About 50% of patients went into remission, 30% had mild anterior uveitis attacks and 20% did not respond. In discussion, it was suggested that IFN 2α is preferable to infliximab because it uses the patient's immune system, inducing IL-10, and this may be relevant to long-term remission seen with this drug. In Turkey, IFN 2α is preferred and infliximab is only used on patients who fail on it. Sahin (Turkey) discussed the downside of IFN 2α treatment: 15% had psychiatric problems, including one attempted suicide, and four patients developed thyroid disease. However, this was the only group of patients discussed in which IFN 2α was used with other

immunosuppressant drugs, and caution was advised from the floor. The fatigue element associated with this drug was supported by others, however, and can be very severe.

Some novel therapies were discussed. Anti-vascular endothelial growth factor, which is used for age-related macular degeneration, led to increases levels of TGF β , an anti-inflammatory cytokine, but other cytokines were not affected. Davatchi (Iran) presented data on long-term follow-up in the use of cytotoxic drugs for BD, including ciclosporin and methotrexate either alone or in combination: 785 of patients with posterior uveitis improved. A question from the floor was concerned about the cancer risk of long-term use of these drugs, but this was not an issue in these patients. Sharquie (Iraq) discussed the use of isotretinoin, a vitamin A derivative, in patients with BD. It is used in acne, psoriasis and lupus. Good effects were seen in skin lesions, but results on oral and genital ulcers were minimal, and there was no effect on joint disease.

This session showed that the new biologic drugs are a major boost to treatment of BD, but they do not work in all patients and can have serious side-effects. Novel therapies are still being tested and showing some effect on disease.



Other topics

Session 4 addressed vascular disease in BD. Tascilar (Turkey) confirmed in a large retrospective study that venous involvement is a major cause of aneurysm in BD: 93% had a deep vein thrombosis in lower or upper limbs, 2.6% had a central nervous system event, 6.8%

a pulmonary aneurysm, 1.4% aortic, 3.7% peripheral or carotid, and 2.3% other.

Interestingly, different vascular events had different ages of onset. Imaging venous wall thickness is not easy due to blood flow through the vessel. Dorian Haskard (UK) presented a new method in which the patient remains prone for 15 minutes in an MRI machine to eliminate skeletal muscle movement and multiple images are taken of the same site. While it is not straightforward for the patient to remain still for so long, the results are promising.

There was evidence of increased vein wall abnormalities in patients with BD compared with normal healthy controls. Gul (Turkey) discussed abdominal aortic aneurysms in 11 patients (10 males) studied using CT and MRI scans. The presenting symptoms were mainly abdominal or lower back pain. Most patients were given endovascular stents, and most had complete resolution, but this took up to a year suggesting that perivascular inflammation was still present after stenting.

Kone-Paut (France) brought the community up to date with the paediatric BD register. There are 206 patients so far from 22 centres in 12 countries. The male to female ratio is 1:1. The mean age of first symptom is 8.8 years and the mean follow-up 5.5 years. This is a project that should be supported by all, and any suspected paediatric BD should be entered.

The final session discussed oral health and gastrointestinal (GI) lesions in BD. Mumcu (Turkey) suggested that oral hygiene and food intake may affect salivary flora. The researchers followed patients for 5 years and found that use of oral health services was associated with a decreased oral ulcer rate and better periodontal health. In Turkey, socioeconomic status is important in oral hygiene. Professor Ohno (Japan) from the floor said that the decrease in BD in Japan was probably due to better oral hygiene.

Naganuma (Japan) showed that GI disease in BD appeared as deep, round ulcers in an ileocaecal area that is very different from Crohn's disease, although both affect the ileocaecal area. Pain and diarrhoea are the main symptoms. Data for controlling GI BD is lacking. Azathioprine decreases relapse after surgery, with infliximab used for patients who do not respond. Younger age is an independent risk factor for relapse. Deep ulcer and apparent GI symptoms at 8 weeks are predictive factors for infliximab use. Watanabe (Japan) and Siato (Japan) produced similar results for Japan. Hatemi (Turkey) described similar levels of GI BD, but also showed that ocular involvement was generally lower in GI BD patients, a point that was agreed by the Japanese.

There were four very good lunchtime seminars from leaders in different fields of disease whose work clearly had importance for BD. A special lecture was given by Dr Daniel Kastener (USA), who explained the great advances being made by genetic studies and the potential use of these findings. In particular, he presented a set of proteins that he believes are fundamental in BD and suggested targeting one of them, the cytokine IL-23, in future studies. His lively, entertaining and thought-provoking presentation was a highpoint of the Congress. Finally, Professor Dilsen (Turkey) gave a historical retrospective of BD and the ISBD Congress. As one of the few people left who actually met Hulushi Behçet, and who has attended every Congress, he presented an excellent overview of our meetings to discuss this complex disease.

In conclusion, the 15th International Congress on Behçet's disease was excellent, with new and interesting data being presented in the wonderful city of Yokohama. Great praise must be given to Professor Yoshi Ishigatsubo and his team for organising both the scientific and social sessions for the delegates and the concurrent Patients' Conference. Next stop Paris for the 16th Congress.

Dr Graham Wallace