The 1st Annual Meeting of Japan Society of Behçet's Disease

The 8th Japan-Korea Joint Meeting on Behçet's Disease

Date: December 1st, 2017

Venue: PACIFICO YOKOHAMA Conference center, Room 418

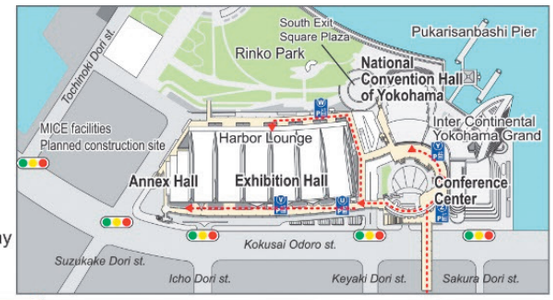
PACIFICO Yokohama Access & Area Map

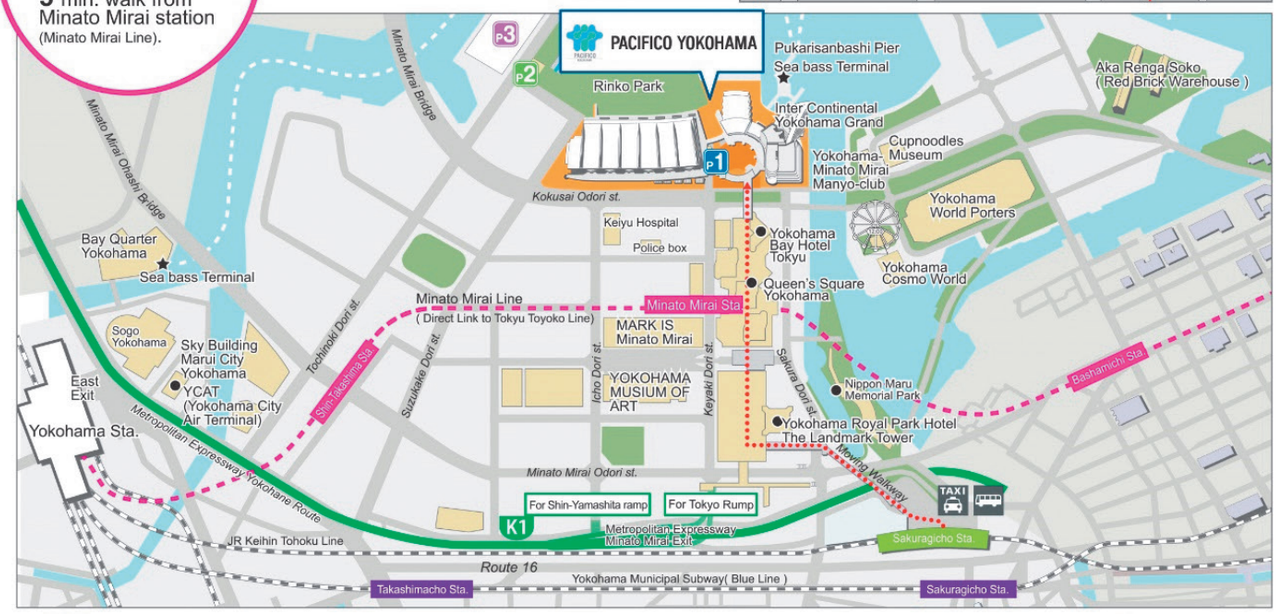
1-1-1 Minato Mirai, Nishi-ku, Yokohama 220-0012, Japan Information: TEL +81-45-221-2155

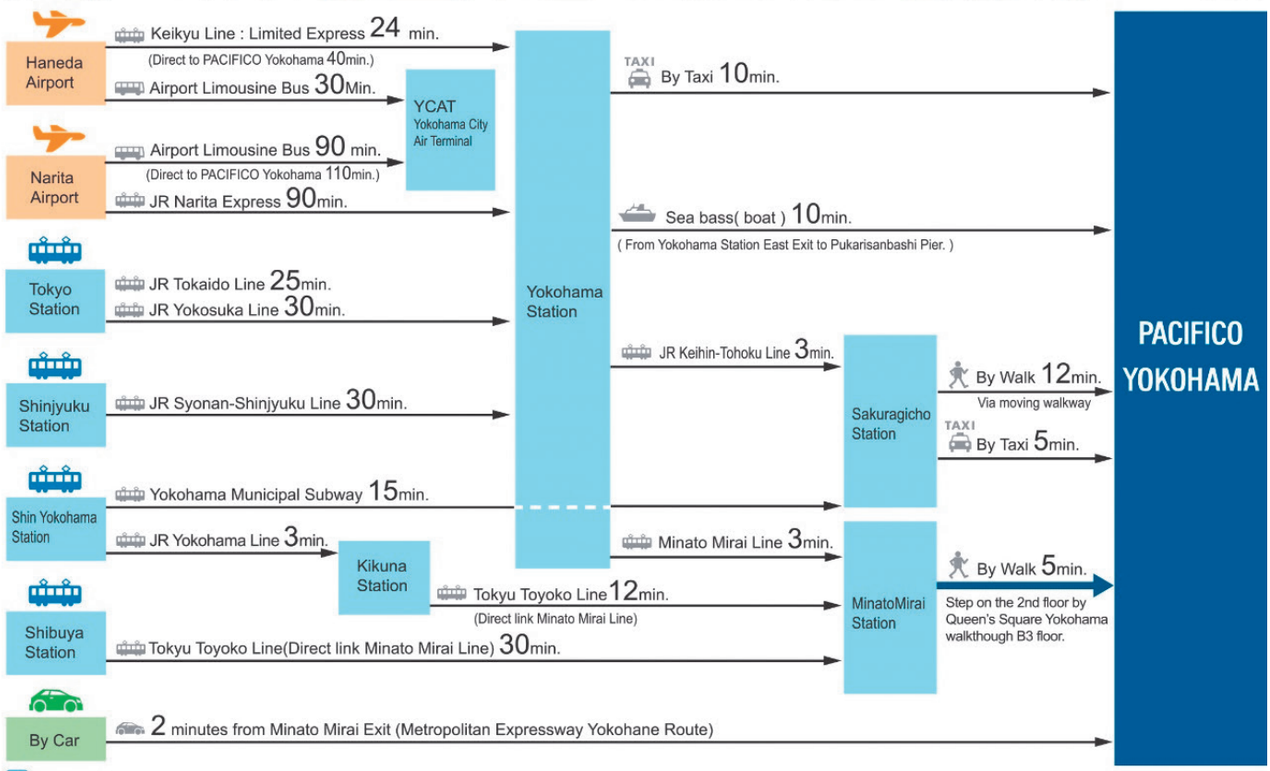
Easy access from all over the world.

30 min. from Tokyo by train.
5 min. walk from Minato Mirai station (Minato Mirai Line).

30 min. from Tokyo International Airport (Haneda).
100 min. from Narita International Airport.
20 min. from JR Shin Yokohama Station.
2 min. from Minato Mirai Exit (Metropolitan Expressway Yokohane Route) .







P1 Minato Mirai Public Parking Lot ￥270/30min. 7:00 to 24:00 *You can take your car out anytime 24hr.

P2 Rinko Park Parking Lot ￥250/30min. 8:00 to 21:00

P3 Bus / Large Vehicle Parking Lot ￥500/30min. 24 hours open *Enter and exit between 7:00 and 22:00. Advanced reservations required

Notes:
- Actual travel times required depend on the facilities you are going to visit. An early arrival is recommended.
- Transfer times are not included.
- Actual travel times required also depend on the road conditions and which terminal you will use.

Jan.1, 2017

Program

13:00 – 13:05

Opening Remarks

Nobuhisa Mizuki (Yokohama City University, Department of Ophthalmology)

The 8th Japan-Korea Joint Meeting on Behçet's Disease

13:05 – 14:05

Chair: Nobuhisa Mizuki (Yokohama City University, Department of Ophthalmology)

・Jae Hee Cheon (Yonsei University College of Medicine, Department of Internal Medicine)

・Eun-So Lee (Ajou University School of Medicine, Department of Dermatology)

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14:05 – 15:25

Basic Research

Chair: Mitsuhiro Takeno (Nippon Medical School, Department of Allergy and Rheumatology)

・Yohei Kirino (Yokohama City University, Department of Stem Cell and Immune Regulation)

・Masaki Takeuchi (Yokohama City University, Department of Ophthalmology)

・Noboru Suzuki (St. Marianna University School of Medicine, Department of Immunology and Medicine)

・Kazuya Iwabuchi (Kitasato University School of Medicine, Department of Immunology)

15:25 – 15:40

Coffee Break

15:40 – 17:00

Clinical Investigation 1

Chair: Yoshiaki Ishigatsubo (Yokohama City University School of Medicine)

・Hirotoshi Kikuchi (Teikyo University, Department of Internal Medicine)

・Koichiro Nakamura (Saitama Medical University, Department of Dermatology)

・Kenichi Yamaguchi (St.Luke's International Hospital, Immuno-Rheumatology Center)

・Mitsuhiro Takeno (Nippon Medical School, Department of Allergy and Rheumatology)

17:00 – 17:40

Clinical Investigation 2

Chair: Kenichi Namba (Hokkaido University, Department of Ophthalmology)

・Nobuyoshi Kitaichi (Health Sciences University of Hokkaido, Department of Ophthalmology)

・Toshikatsu Kaburaki (University of Tokyo, Department of Ophthalmology)

17:40 – 17:45

Closing Remarks

Nobuhisa Mizuki (Yokohama City University, Department of Ophthalmology)

18:00 –

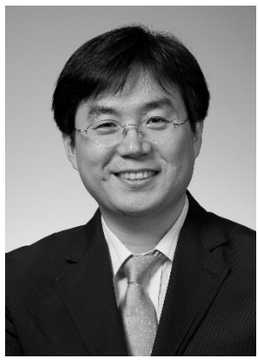
Opinion exchange meeting

at the Bnquet room of Intercontinental Yokohama Grand Hotel, Le Grand (30F)

The 8th Japan-Korea Joint Meeting on Behçet's Disease

Intestinal Behçet's Disease: Diagnosis, Treatment, and Prognosis

Prof. Jae Hee Cheon (Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea)



Education

M.D. – Seoul National University College of Medicine, Seoul, Korea, 1996, Medicine

M.S. - Seoul National University College of Medicine, Seoul, Korea, 2001, Internal Medicine

Ph.D. - Seoul National University College of Medicine, Seoul, Korea, 2006, Internal Medicine

Postgraduate Training

1996-1997 Intern, Seoul National University Hospital

1997-2000 Medical Residency, Internal Medicine, Seoul National University Hospital

2001-2003 Military service

2003 -2004 Public Health Care Doctor, National Cancer Center, Ilsan, Korea

2004-2005 Clinical and Research Fellow, Internal Medicine, Seoul National University Hospital

Academic appointments

2006-2007.2 Instructor of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea

2007.3-2011.2 Assistant Professor, Yonsei University College of Medicine, Seoul, Korea

2011.3-2016.2 Associate Professor, Yonsei University College of Medicine, Seoul, Korea

2011.8-present, Visiting scientist, Mucosal Immunology Section, International Vaccine Institute, Seoul, Korea

2016.3-present, Professor, Yonsei University College of Medicine, Seoul, Korea

Editorial Boards and Councils

Assistant Editor of Gut and Liver

Editorial Board member of Journal of Gastroenterology and Hepatology

Editorial Board member of Digestive Diseases and Sciences

Editorial Board member of the Korean Journal of Gastroenterology

Editorial Board Member of the Korean Society of Helicobacter and Upper GI Diseases Research

Contributing Associate Editors-in-Chief, World Journal of Gastroenterology

Associate Editor of Yonsei Medical Journal

Associate Editor of Clinical Endoscopy

Associate Editor of Intestinal Research

Editorial Board member of Intestinal inflammatory diseases

Board of directors of Korean Society for Behçet's disease

Board of directors of The Korean Association of Immunologists

Behçet's disease (BD) is a chronic multi-systemic immune-mediated disorder characterized by recurrent oral and/or genital ulcers, arthritis, skin manifestations, and ocular, vascular, neurological, or intestinal involvements. If gastrointestinal symptoms are present and typical ulcerative lesions are documented by objective measures in patients with BD, it is termed "intestinal BD". In BD, gastrointestinal involvement often leads to severe complications such as perforation or massive bleeding, and is one of the major causes of morbidity and mortality. Therefore, intestinal BD should not be considered a mild disease simply on the grounds that a large proportion of patients have a mild clinical course. The most significant drawback with intestinal BD is that although some studies have been conducted, the information currently available concerning intestinal BD is quite limited because of the rarity of the disease, and the management of intestinal BD is still heavily dependent on expert opinions and standardized medical treatments are yet to be established. Thus, intestinal BD is a disease with many issues to be resolved. It is often difficult to make a correct diagnosis, provide proper treatment, and monitor therapeutic response for intestinal BD. To overcome those challenges, specific diagnostic guidelines, a disease activity index, and treatment algorithms are newly developed. Intestinal BD patients with a severe clinical course require more frequent corticosteroid therapy, immunomodulator therapy, and multiple intestinal resections than those with a mild clinical course, which suggests that patients with a severe clinical course suffer more from the disease than those with a mild clinical course. This necessitates the introduction of new therapeutic modalities. Recent papers have reported that anti-TNF-α agents are promising. In the future, a more effective medical therapy will be established.

The role of immunosenescence in autoimmune/autoinflammatory pathogenesis of Behçet's disease

Prof. Eun-So Lee (Department of Dermatology, Ajou University School of Medicine, Suwon, Korea)

Education

1984 Bachelor of Medicine, Yonsei University College of Medicine

1987 Master of Medicine, Dermatology, Yonsei University College of Medicine

1990 Ph. D., Dermatology, Yonsei University College of Medicine

Employment

1988 ~ 1990 Research Fellow, Department of Dermatology, Yonsei University College of Medicine.

1992 ~ 1994 Instructor, Department of Dermatology, Ajou University School of Medicine.

1994 ~ 1998 Assistant Professor, Department of Dermatology, Ajou University School of Medicine.

1998 ~ 2003 Associate Professor, Department of Dermatology, Ajou University School of Medicine.

2003 ~ present Professor, Department of Dermatology, Ajou University School of Medicine.

2003 ~ 2011 Chairman, Department of Dermatology, Ajou University School of Medicine.

2005 ~ 2006 Head, Division of Medicine, Ajou University School of Medicine

2010 ~ 2014 Director, Center for Medical Information, Ajou University School of Medicine

Training Courses

1984 ~ 1985 Intern, Yonsei Medical Center, Severance Hospital.

1985 ~ 1988 Resident, Yonsei Medical Center, Severance Hospital.

1990.4 ~ 1992.2 Visiting Fellow, Dermatology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA.

1996. 11 ~ 1997.1 Visiting Researcher, Department of Dermatology, VA Hospital, UCSF, San Francisco, CA, USA.

Scientific or Professional Societies (committee member)

2009 ~ present Archives of Dermatological Research, overseas editor

2013 ~ present Annals of Dermatology, Editor-in-chief

2014 ~ present International Society for Behcet's Disease, Council Member

2015~ present Journal of the Korean Medical Association, Associate Editor

2016 ~ present Korean Society for Behcet's Disease, member of board of directors

2016 ~ present British Journal of Dermatology, International Editorial Board

2017 ~ present Korean Association of Medical Journal Editors, Vice-president

Behçet's disease (BD) is a chronic inflammatory disease characterized by recurrent mucocutaneous, ocular, and skin lesions. Immunosenescence is associated with increased susceptibility to infection and chronic low grade inflammation. This study aimed to investigate the differences in the frequencies of immunosenescent cells in the peripheral blood mononuclear cells (PBMCs) of patients with BD. PBMCs were isolated from age-matched patients with active BD (n = 19), inactive BD (n = 20), disease controls (DCs, n = 15) and healthy controls (HCs, n = 15). The frequencies of senescent CD4+ T cells (CD3+ CD4+ CD27- CD28- cells), CD8+ T cells (CD3+ CD8+ CD27- CD28- cells) and B cells (CD19+ CD27- IgD- cells) were analyzed using flow cytometry. Senescence-associated ß galactosidase activity was also measured in CD8+ T cells using flow cytometry with 5-dodecanoylaminofluorescein di-ß-D-galactopyranoside. Frequencies of senescent CD4+ and CD19+ cells were not significantly different between the groups. The frequency of senescent CD8+ T cells was significantly higher in active BD than in DCs and HCs. C-reactive protein and erythrocyte sedimentation rate levels, which indicate disease activity, did not correlate with increased frequencies of immunosenescent cells. Steroid treatment, specific organ involvement, and HLA-B51 status did not have a significant influence on the frequencies of immunosenescent cells. Frequencies of senescence-associated ß galactosidase+ CD8+ T cells were significantly higher in active BD and inactive BD compared to DCs and HCs.

In conclusion, senescent CD8+ T cells (comprising CD3+ CD8+ CD27- CD28- cells) were increased in the peripheral blood of BD patients. This increase was more pronounced in patients with active BD compared to those with inactive BD. Functional or senescence-inducing studies are needed to further elucidate the role of immunosenescence in the pathogenesis of BD.

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Basic Research

Beyond genome-wide association study of Behçet's disease

Yohei Kirino[1], Hiroto Nakano[1], Yutaro Soejima[1], Mitsuhiro Takeno[2], Masaki Takeuchi[3], Akira Meguro[3], Nobuhisa Mizuki[3], Hideaki Nakajima[1]

1. Yokohama City University Graduate School of Medicine, Department of Stem Cell and Immune Regulation
2. Nippon Medical School Graduate School of Medicine, Department of Allergy and Rheumatology
3. Yokohama City University Graduate School of Medicine, Department of Ophthalmology and Visual Science

Genome-wide association studies (GWAS) of Behçet's disease (BD) successfully identified multiple loci associated with the disease. However, actual mechanisms of identified loci in BD pathogenesis remain unclear. Moreover, clinical application of genetic findings in individual patients is challenging. To seek beyond GWAS era, we are now investigating several clinical questions. First, to identify the functions of established BD loci, expression quantitative loci (eQTL) effects of several genes in various leukocyte subsets are ongoing. For example, we recently identified eQTL of *CCR1* and *IL10* loci in polarized macrophages generated *in vitro*. IL-10 gene expression difference was observed only in M2 macrophages, whereas those of *CCR1* were seen in M1 macrophages. As expected from genetic data, M1 macrophage predominant inflammation was found in erythema nodosum of BD patients. Finally, M1 macrophages cultured in M2 condition resulted in the conversion of M1 macrophages into M2-like phenotype such as secretion of IL-10. These results support the idea that functional analysis of identified loci is necessary for the future clinical application of GWAS findings in BD. Second, genetic analysis of familial Behcet's cases is ongoing. We have now collected 7 BD families in which whole exome sequencing is currently under examination. I will discuss the opportunities and issues we have faced in the post-GWAS era in Behçet's disease.

Largest genetic analysis for Behçet's disease by dense genotyping of immune-related loci

Masaki Takeuchi[1,2], Akira Meguro[1], Yohei Kirino[3], Shigeaki Ohno[4], Yoshiaki Ishigatsubo[3], Ahmet Gül[5], Daniel L. Kastner[2] and Elaine F. Remmers[2] ,and Nobuhisa Mizuki1
1Dept. of Ophthalmology, Yokohama City Univ.; 2Inflammatory Disease Section, NHGRI, NIH; 3Dept. of Internal Med., Yokohama City Univ.; 5Translational Immunology Section, NIAMS, NIH; 4Dept. of Ophthalmology, Hokkaido Univ.; 5Dept. of Internal Med., Istanbul Fac. of Med., Istanbul Univ.

Objective: To densely genotype loci associated with immune-related diseases to identify novel susceptibility loci for Behçet's disease.
Methods: 1900 Turkish Behçet's disease patients and 1779 controls were genotyped using the Immunochip. For novel loci with the association test $P<5\times10^{-5}$, additional SNPs in the region were imputed. For replication, the lead SNP in each novel locus with $P<5\times10^{-5}$ was genotyped in 982 cases and 826 controls from Iran. We also replicated with imputed previous GWAS data from 608 Japanese cases and 737 controls. $P<5\times10^{-8}$ was considered the threshold for genome-wide significance.
Results: We identified 4 novel loci, *IL1A-IL1B*, *ADO-EGR2*, *IRF8,* and *CEBPB-PTPN1* in the Turkish case-control collection. Genotyping Iranian samples replicated associations of three loci, *ADO-EGR2*, *IRF8* and *CEBPB-PTPN1.* Comprehensive meta-analysis of the regional imputed genotype data of Turks and Japanese replicated two loci, *ADO-EGR2* and *IRF8*, and revealed two additional novel loci, *RIPK2* and *LACC1*. The disease associated allele of rs4402765, the lead marker of the *IL1A-IL1B* locus, was associated with both decreased IL-1α and increased IL-1ß protein production. Homozygosity for ancestry specific *FUT2* non-secretor genotypes, p.Trp143Ter (Turks and Iranians) and p.Ile139Phe (Japanese), showed strong disease association.
Conclusion: Here, we identified 6 novel loci (*IL1A-IL1B*, *RIPK2*, *ADO-EGR2*, *LACC1*, *IRF8*, and *CEBPB-PTPN1*) for Behçet's disease. Our findings that the disease-associated allele of *IL1A-IL1B* is associated with less IL-1α and more IL-1ß production, and that functionally defective structural *FUT2* variants are associated with disease risk suggest that dysregulated barrier function and host response to microbes may contribute to Behçet's disease susceptibility.

Characteristic Alteration of gut microbiota in patients with Behcet's disease

Jun Shimizu[1], Noboru Suzuki[1]
1. Department of Immunology and Medicine, St. Marianna University School of Medicine, Kawasaki, Japan.

Purpose: We have presented evidence that the frequency of helper T (Th)17 cells increased and the cells had already been activated in vivo in patients with Behcet's disease (BD). Recently, some researchers clarified the relationships among several gut bacteria, skewed Th17 cell function and local inflammation in autoimmune disease models. We conducted fecal metagenomic analysis (gut microbe composition and gene function analyses) of BD patients and compared the data with those of normal individuals (NI)
Methods: We explored fecal microbiota of 12 patients with BD and 27 NI by sequencing of 16S rRNA gene. We compared the relative abundance of bacterial taxa with fecal secretary IgA (sIgA) concentrations and a BD disease activity index in BD patients.
Results: The sequencing data showed that the species Eggerthella lenta, Lactobacillus iners, and Bifidobacterium bifidum increased significantly in BD. The species Megamonas hypermegale and Butyrivibrio species significantly increased in NI. Fecal sIgA concentrations increased significantly in BD patients compared with those in NI. None of the relative abundance of bacterial taxa correlated with fecal sIgA concentrations or the BD activity index of patients with BD.
Conclusions: Lactic acid producing bacteria, such as Bifidobacterium and Lactobacillus, were suggested to decrease short chain fatty acid production of microbes belonging to the class Clostridia, including Megamonas hypermegale and Butyrivibrio species. Short-chain fatty acids induced regulatory type T cells effectively in the intestine of mice. We suggest that low short chain fatty acid concentrations in the BD intestine may have a relationship with the skewed Th cell differentiation of BD.

NKT cell-based intervention to the development of experimental autoimmune uveoretinitis in mice

Masashi Satoh[1], Taiki Katoh[1], Nobuyoshi Kitaichi[2], Masaru Taniguchi[3], Luc Van Kaer[4], Kazuya Iwabuchi[1]

1. Department of Immunology, Kitasato University School of Medicine, Sagamihara, Japan
2. Department of Ophthalmology, Health Science University of Hokkaido, Sapporo, Japan
3. Immune Regulation Lab, Riken Center for Integrative Medical Sciences, Yokohama, Japan
4. Department of Microbiology and Immunology, Vanderbilt University School of Medicine, Nashville, TN, USA

Purpose: Severity of experimental autoimmune uveoretinitis (EAU) model in mice is aggravated in mice that lack natural killer T (NKT) cells. This implies that NKT cells may function as a regulator for ocular autoimmunity. To utilize the finding for the amelioration of EAU by activating NKT cells in wild type mice, we administered 2 kinds of NKT cell ligands in different timing during induction of the disease. We also apply the treatment to a recurrent uveitis model to control EAU after onset.

Methods: To induce EAU in mice, we immunized C57BL/6 mouse (B6; female, 6 wk) with emulsified 1:1 mixture of complete Freund's adjuvant (CFA) and a solution containing 200 μg of the 1st~20th peptide residue of human interphotoreceptor retinoid binding protein ($hIRBP_{1-20}$). B6 mice were administered with pertussis toxin (0.1 μg/head on day 0 of immunization) as an additional adjuvant. One of NKT cell ligands (2 μg of α-glactosylceramide, α-GC or α-carbaGC = RCAI-56 / head) and vehicle was administered at day 0 (immunization) or at day 10 (onset) to a group of immunized mice and the histopathological scores at day 21 were compared for evaluation. Recurrent EAU was induced with an administration of staphylococcal enterotoxin B (SEB; 12.5~200 μg/head) at day 24 when the inflammation started to be resolved as previously described by Kohno H *et al.* (Exp Eye Res 2009), and treated with NKT-cell ligands or vehicle on the day of induction.

Results: Immunized mice when administered RCAI-56 on induction but not at onset exhibited significantly lower scores than those of mice received vehicle. RCAI-56 stimulated NKT cells to produce IFN-g after 6 h of administration that led reduced production of TNF-α, IFN-γ, IL-17, and IL-22 from Ag-stimulated T cells. RCAI-56 also suppressed the recruitment of autoreactive T cells in the eyes. Above results indicated that NKT cells suppressed the induction of Th17 cells and infiltration of IRBP-specific T cells into the eyes, thus reducing ocular inflammation (Satoh M *et al.* Exp Eye Res 2016). Administration of SEB at day 24 indeed exhibited EAU recurrence (Kohno *ibid*). Evaluation for the effects of NKT-cell ligands is now underway.

Conclusions: NKT cell-based intervention could be utilized for the control of ocular inflammation, although the timing of administration of NKT-cell ligands is very important. Intervention through NKT cell activation may also be applicable to the recurrent model of EAU and it may contribute to the control of inflammation at remission phase of uveoretinitis.

clinical investigation 1

Recommendations for the Management of Neuro-Behçet's Disease by the Japanese National Research Committee for Behçet's Disease

Hirotoshi Kikuchi[1], Tetsuji Sawada[2], Masato Okada[3], Mitsuhiro Takeno[4], Masataka Kuwana[4], Yoshiaki Ishigatsubo[5], Izumi Kawachi[6], Hideki Mochizuki[7], Susumu Kusunoki[8], Shunsei Hirohata[9]

1. Department of Internal Medicine, Teikyo University School of Medicine
2. Department of Internal Medicine 3, Tokyo Medical University School of Medicine
3. Immuno-Rheumatology Center, St. Luke's International Hospital
4. Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine
5. Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine
6. Department of Neurology, Niigata University Medical and Dental Hospital, Niigata
7. Department of Neurology, Osaka University Graduate School of Medicine
8. Department of Neurology, Kinki University School of Medicine
9. Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine

Purpose: Diagnostic criteria were generated in 2013 based on a multicenter clinical survey performed by the Behçet's Disease (BD) Research Committee of the Ministry of Health, Labor and Welfare of the Japanese Government. Although 'Guidelines for Treatment of neuro-Behçet's disease (NBD)' was also proposed based on the survey, it is still preliminary. The aim of the current study is to develop evidence-based recommendations for the management of NBD supplemented by expert opinions where necessary.

Methods: First, clinical questions (CQs) on NBD were extracted from a literature search for problem areas and related keywords, and draft CQs and a flow chart were prepared. The expert committee, a task force of the research subcommittee for NBD, consisted of 7 board-certified rheumatologists (one was also a board-certified neurologist) and 3 board-certified neurologists. A total of 15 initial CQs were generated. These yielded the final recommendations developed from 3 blind Delphi rounds, in which the rate of agreement scores on CQs (range 1[strongly disagree]-5[strongly agree]) was determined though voting by the whole committee.

Results: Thirteen recommendations were developed for the management of NBD (general 1, acute type (ANBD) 7, chronic progressive type (CPNBD) 5). The strength of each recommendation was established based on the evidence level as well as rate of agreement. There was excellent concordance between the level of agreement of rheumatologists and that of neurologists. Based on these recommendations, a flow chart was established for the management for ANBD and CPNBD.

Conclusions: The recommendations generated in this study are mainly based not only on expert opinions but on the results of uncontrolled evidence from open trials and retrospective cohort

studies. Nevertheless, such guidelines that can be used for international studies would be needed, for which verification by further properly designed controlled clinical trials is required.

Clinical epidemiology of skin symptoms in Behçet's diseases in Japan

1. Koichiro Nakamura (Department of Dermatology, Saitama Medical University)
2. Michiko Kurosawa (Department of Epidemiology and Environmental Health, Juntendo University)
3. Fumio Kaneko (Institute of Dermato-Immunology and Allergy, Southern Tohoku Research Institute for Neuroscience)

Purpose and Methods: In order to clarify the prevalence of skin symptoms in Behçet's diseases during different time, we analyzed epidemiology based from clinical survey individual votes by the Ministry of Health, Labor and Welfare. Patients with Behçet's disease were enrolled as newly intractable diseases designated by the Ministry .

Results: The symptom ratio of oral aphthosis, skin symptoms and genital ulcer were decreased during 40 years since 1972 in both men and women. This tendency was observed more prominent in men rather than women. Concerning the correlation of specific type and skin symptoms, the symptom ration of patients with oral aphthosis was low in intestinal type and neural type. In patients with skin symptom alone, the symptom ratio was also low in intestinal type and neural type. Concerning the ratio with combination of four major symptoms, the symptom ratio was highest in group with all four symptoms in the data of 1972, however this ratio was decreased in 2010. The symptom ratio was observed high in group with skin symptoms with aphthosis, genital ulcers without ocular symptoms, following groups with both skin symptoms and aphthosis. The age of onset was observed highest in group with skin symptom alone or aphthosis alone. The age of onset was observed lowest in group with skin symptoms, ocular symptom and genital ulcer. The employment rate among 20 to 59 years old was 73.3% in men and 63.7% in women in patients, which was lower than average data in Japan.

Conclusion: The data show dynamic change of skin symptoms during 40 years according to the clinical epidemiology designed as intractable diseases.

The sensitivity of BD criteria made for adult patients were low in pediatric BD patients.

Ken-ichi Yamaguchi（St.Luke's International Hospital, Immuno-Rheumatology Center）、Shuichi Ito（Yokohama City University Hospital, Department of Pediatrics）、Satoshi Fujikawa（Fujikawa Pediatric Clinic. St.Luke's International Hospital, Immuno-Rheumatology Center）

Purpose： To diagnose pediatric patients as Behçet's disease (BD) is challenging. Sensitivity of BD criteria which was made for adult patients are not high enough for Japanese pediatric BD patients. The aim of this study is to clarify whether the similar trend exists in other country.
Methods： We compared the sensitivity of Japanese Ministry of Health Labor and Welfare criteria (MHLW criteria) in Indian pediatric BD patients and Japanese pediatric BD patients. Indian patients were reported in European Paediatric Rheumatology Congress 2014[1)], and Japanese patients were
collected by questionnaire survey of Pediatric Rheumatology Association of Japan (PRAJ).
Results： In thirteen pediatric BD patients from India, 23% were classified as incomplete BD, 54% were possible. No patient were met to complete BD. In 51 pediatric BD patient from Japan, 2% were classified as complete BD, 58% were incomplete and 40% were possible. Sensitivity of MHLW criteria was 23% in Indian pediatric BD patients and 60% in Japanese pediatric BD patients.
Conclusion： The sensitivity of BD criteria made for adult patients were low in pediatric BD patients, especially children in other countries.

Reference

1) Pandiarajan Vignesh et al. Pediatric-Onset Behçet's disease：An Experience from a Tertiary-care Centre In North India. PReS 2017

Draft of recommendations for the management of vasculo-Behçet's disease in Japan

Takeno M[1,2], Nagafuchi H[2,3], Ishibashi H[2,4], Ogino H[2,5], Maeda H[2,6], Kikuchi H[2,7], Ishigatsubo Y[2,8]

1 Nippon Medical School, 2 Behçet's Disease Research Committee, MHWL, Japan, 3 St Marianna University, 4 Aichi Medical University, 5 Tokyo Medical University, 6 Nihon University, 7 Teikyo University, 8 Yokohama City University

Purpose: Vascular involvement is one of the most serious manifestations of Behçet's disease (BD). This study aimed to establish clinical guidelines of vasculo-BD in Japan.

Methods: The working group including 4 rheumatologists and 3 cardiovascular surgeons determined clinical questions (CQ) concerning the management of vasculo-BD. Drafts of statements for individual clinical questions were generated based on literature, retrospective analysis of clinical data in 105 Japanese patients, and expert opinions. After a total of 15 panelists assessed the agreement of the individual statements on a five-point scale with critical comments, the statements were revised or eliminated. We had three rounds of the process to reach consensus in the remaining all statements.

Results: Among 18 original CQ, the consensus was obtained in 17 statements including 7 for diagnosis, 1 for assessment of clinical activity and 9 for treatment. Despite the absence of high-grade evidence for each statement, the mean agreement rates were ranged from 4.00 to 4.89 (4.56±0.28). In brief, the vascular lesions should be evaluated by imaging modalities including contrast CT, MRI/MRA, ultrasonography, and PET/CT. Immunosuppressive therapy using corticosteroids and immunosuppressants is the first line therapy for acute deep vein thrombosis and active arterial lesions. Unlike the 2008 EULAR recommendations, anticoagulation with warfarin or direct oral anticoagulants is recommended for thrombosis, because few patients develop fatal pulmonary hemorrhage in Japan. Anti-TNF-mAb can be optional for refractory cases, irrespective of clinical phenotypes. Surgical treatment should be considered for impending aneurysm rupture and involvement of the aortic valve under concurrent immunosuppression. Endovascular therapy can be alternative.

Conclusions: We generated the draft of recommendations for the management of vasculo-BD for the Japanese patients.

clinical investigation 2

Prevalence of allergic disorders in Behcet's disease – A nationwide survey

Nobuyoshi Kitaichi[1,2], Kenichi Namba[2], Shigeaki Ohno[2]

1. Department of Ophthalmology, Health Sciences University of Hokkaido, Sapporo, Japan
2. Department of Ophthalmology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo Japan

ABSTRACT

Behçet's disease is a systemic inflammatory disorder polarized to the Th1 and Th17 immune systems. Allergic diseases are polarized to the Th2 immune system. The aim of the present study is to investigate the prevalence of allergic diseases in patients with Behçet's disease as a nationwide questionnaire survey in Japan.

Patients & Methods: The study involved a large-scale interview survey of Japanese patients with Behçet' s disease at 21 institutes of ophthalmology, and 353 patients (255 males and 98 females) were recruited. We analysed the history of allergic diseases such as atopic dermatitis (AD), allergic rhinitis (AR), bronchial asthma (BA), and drug and/or food allergies (FA).

Results: Oral aphthous ulcers, ocular lesions, skin lesions, genital ulcers, arthritis, neurological lesions, intestinal lesions, deep vein thrombosis and epididymitis were reported in 95.8%, 98.6%, 72.5%, 44.8%, 13.9%, 6.8%, 6.2%, 3.7% and 1.4% of the patients, respectively. It was also reported that 73 patients (20.7%) had histories of allergic diseases. This percentage was significantly lower than that in a survey that Japanese government conducted for healthy population (47.6%) (odds ratio = 0.29, 95% confidence interval = 0.22-0.38, $p = 4.9\times10^{-22}$). AD (5 cases, 1.4%), AR (36 cases, 10.2%), and BA (19 cases, 5.4%) among the patients were significantly fewer than those of healthy population ($p = 4.9\times10^{-14}$, $p = 3.3\times10^{-22}$, $p = 0.006$, respectively)

Conclusions: Prevalence of allergic diseases in patients with Behçet's disease was investigated. The history of allergic diseases in Behçet's patients is lower than that in the Japanese population.

Behçet Disease Ocular Attack Score 24 (BOS24); a novel disease activity score for ocular Behçet disease

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Purpose: To review the published articles about Behçet Disease ocular attack score 24 (BOS24).
Methods: We had reported the novel ocular disease activity score system for Behçet disease uveitis, BOS24, in 2014. Using the MEDLINE, the reports about BOS24 were searched. Five clinical reports concerning BOS24 have been reported since October 2017. Of which, 4 articles were summarized and reviewed.
Results: The original article (Kaburaki T, Jpn J Ophthalmol 2014) introduced the definition and the methods for scoring using BOS24 scoring system. BOS24 scores were highly correlated with the physician's impression of disease severity. Moreover, the article demonstrated that infliximab treatment was significantly reduced the average BOS24 scores for individual ocular attacks, notably in the scores for posterior retina and fovea. Another our article demonstrated that the worsening of visual acuities during 5 years follow-up was significantly correlated with the accumulated scores of BOS24 during the 5 years in Behçet disease uveitis (Tanaka R, Br J Ophthalmol 2016). A recent case series study demonstrated that HLA-A26 positive cases were more severe disease course under infliximab therapy compared to HLA-B51 positive cases (Kuroyanagi K, Jpn J Ophthalmol 2016). The most recent study demonstrated that central foveal thickness showed significant correlations with visual acuity, BOS24 score, total fluorescein angiography score and total indocyanine green angiography score (Onal S, Retina 2017, in press).
Conclusions: These studies might indicate that BOS24 could be the useful parameters for the evaluation of ocular disease activities in Behçet disease uveitis.