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REVIEW ARTICLE

Clinical practice guidance for juvenile dermatomyositis (JDM) 2018-Update

Ichiro Kobayashi[a], Shinji Akioka[b], Norimoto Kobayashi[c], Naomi Iwata[d], Shunichiro Takezaki[e], Haruna Nakaseko[d], Satoshi Sato[f], Yutaka Nishida[g], Tomo Nozawa[h], Yuichi Yamasaki[i], Kazuko Yamazaki[j], Satoru Arai[k], Ichizo Nishino[l] and Masaaki Mori[m]

[a]Center for Pediatric Allergy and Rheumatology, KKR Sapporo Medical Center, Sapporo, Japan; [b]Department of Pediatrics, Kyoto Prefectural University of Medicine, Kyoto, Japan; [c]Department of Pediatrics, Shinshu University School of Medicine, Matsumoto, Japan; [d]Department of Infection and Immunology, Aichi Children's Health and Medical Center, Obu, Japan; [e]Department of Pediatrics, Hokkaido University Hospital, Sapporo, Japan; [f]Division of Infectious Disease and Immunology, Saitama Children's Medical Center, Omiya, Japan; [g]Department of Pediatrics, School of Medicine, Gunma University, Maebashi, Japan; [h]Department of Pediatrics, School of Medicine, Yokohama City University, Yokohama, Japan; [i]Department of Pediatrics, Kagoshima University Hospital, Kagoshima, Japan; [j]Department of Pediatrics, Saitama Medical Center, Saitama Medical University, Kawagoe, Japan; [k]Department of Dermatology, St. Luke's International Hospital, Tokyo, Japan; [l]Department of Neuromuscular Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Tokyo, Japan; [m]Lifetime Clinical Immunology, Tokyo Medical and Dental University, Tokyo, Japan

ABSTRACT

Juvenile dermatomyositis is the most common type of juvenile idiopathic inflammatory myopathy mainly affecting the skin and proximal muscles. We have published the Japanese version of 'Clinical practice guidance for juvenile dermatomyositis (JDM) 2018 'consisting of a review of articles in the field and evidence-informed consensus-based experts' opinion on the treatment strategy in collaboration with The Pediatric Rheumatology Association of Japan and The Japan College of Rheumatology under the financial support by 'Research on rare and intractable diseases, Health and Labor Sciences Research Grants'. This article is a digest version of the Japanese guidance.

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KEYWORDS
Diagnosis; pathophysiology; management; interstitial lung disease; myositis-specific autoantibodies

1. Introduction

Juvenile idiopathic inflammatory myopathy is an umbrella entity comprising juvenile dermatomyositis (JDM), juvenile polymyositis (JPM), immune-mediated necrotizing myopathy (IMNM), inclusion body myositis (IBM), and connective tissue disease-associated myositis, which develops before the age of 18 [1]. JDM is the most common form of juvenile idiopathic inflammatory myopathies (JIIMs) currently affecting 1.7 per 100,000 children in Japan [2]. Recently, Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) has published consensus-based recommendation for the management of JDM [3]. However, there are several differences in the frequency of complications and drug use between Europe or United States and Japan such as the frequency of anti-melanoma differentiation-association gene 5 (MDA5) antibody-positive rapidly progressive (RP)-interstitial lung disease (ILD) and the available route of methotrexate (MTX) administration, respectively [4–6]. These facts prompted us to develop clinical practice guidance for JDM suitable for patients in Japan. The Scientific Research Group for Pediatric Rheumatic Diseases (SRGPRD) was organized to standardize the diagnosis, evaluation of severity, and management of pediatric rheumatic diseases under the support by the Japanese Ministry of Health, Labor and Welfare. The JDM Research Group of SRGPRD consisting of 13 pediatric rheumatologists, a dermatologist and a pathologist has published the Japanese version of the guidance in collaboration with The Pediatric Rheumatology Association of Japan (PRAJ) and The Japan College of Rheumatology (JCR). Because evidence on the management of JDM is limited, this guidance mainly consists of narrative review of articles in the field and evidence-informed consensus-based experts' opinion on the treatment strategy. Articles were searched for the consensus-based part in MEDLINE and PubMed in 2017. Articles after the publication of the original Japanese version were hand-searched. Each section was reviewed and approved by all the JDM research group member. Final version of the manuscript was confirmed after public comments and approved by the steering committee of both PRAJ and JCR. The present English version summarizes the Japanese version with an update consisting of several recently published articles.

2. Definition

JDM is a symmetrical inflammatory myositis predominantly affecting proximal muscles with characteristic skin lesions [7]. However, some cases lack muscle weakness despite skin lesions characteristic of JDM and this is currently called juvenile clinically amyopathic dermatomyositis (JCADM) [8]. JCADM comprises juvenile amyopathic dermatomyositis

CONTACT Ichiro Kobayashi ichikoba@kkr-smc.com Center for Pediatric Allergy and Rheumatology, KKR Sapporo Medical Center, 3-40, Hiragishi 1-6, Toyohira-ku, Sapporo 062-0931 Japan

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ORIGINAL ARTICLE

Disease activity, treatment and long-term prognosis of adult juvenile idiopathic arthritis patients compared with rheumatoid arthritis patients

Takumi Matsumoto[a,b], Toshihiro Matsui[a,c], Fumio Hirano[a,b], Shigeto Tohma[c,d] and Masaaki Mori[a]

[a]Department of Lifetime Clinical Immunology, Graduate School of Medical and Dental Science, Tokyo Medical and Dental University (TMDU), Tokyo, Japan; [b]Department of Rheumatology, Graduate School of Medical and Dental Science, Tokyo Medical and Dental University (TMDU), Tokyo, Japan; [c]Department of Rheumatology, Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagamihara National Hospital, Kanagawa, Japan; [d]Department of Rheumatology, National Hospital Organization Tokyo National Hospital, Tokyo, Japan

ABSTRACT

Objective: To evaluate the difference between adult juvenile idiopathic arthritis (JIA, starting at <16 years) and rheumatoid arthritis (RA).

Methods: Data on 128 adult JIA patients were from the National Database of Rheumatic Diseases in Japan (NinJa), 2014, divided into 4 groups by period of disease onset (Group 1: 2000–2013, $n = 32$; Group 2: 1981–1999, $n = 32$; Group 3: 1966–1980, $n = 31$; Group 4: ~1965, $n = 33$). Disease activity, treatment and long-term prognosis of adult JIA patients were compared with RA patients matched for sex- and disease duration in each era.

Results: In Groups 1 and 2, adult JIA patients had significantly lower clinical disease activity indices (CDAI) (Group 1: adult JIA 1.5 [0.4–6.9]-vs-RA 5.3 [2.5–10.3], $p = .001$, Group 2: 2.6 [0.6–9.0]-vs-6.9 [3.5–11.0], $p = .001$, shown as median [quartile range], p-value, respectively), and had higher CDAI remission rates than RA patients (Group 1: 54.8%-vs-28.2%, $p = .002$, Group 2: 51.7%-vs-17.0%, $p < .001$). More adult JIA than RA patients in Group 1 used biologics (62.5%-vs-24.7%, $p < .001$). However, there were no adult JIA-vs-RA differences in joint destruction and physical function in any group.

Conclusions: Adult rheumatologists must recognize that adult JIA patients are different from RA patients even when disease duration is the same.

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KEYWORDS
Transition; adult Juvenile idiopathic arthritis (JIA); rheumatoid arthritis (RA)

Introduction

Juvenile idiopathic arthritis (JIA) is the most common form of arthritis in children. JIA is of unknown aetiology, beginning before the 16th birthday and persisting for at least 6 weeks [1]. Recently, treatment of JIA has been improved by employing biological therapies, as in rheumatoid arthritis (RA). Advances in pediatric medicine have resulted in increased numbers of adult patients who had childhood-onset chronic disease [2]. However, long-term follow-up data in other countries showed that JIA is still ongoing in 34–50% of JIA patients after they reach adulthood [3,4]. Therefore, a seamless transition in medical care from adolescence to adulthood (i.e. transitional care) is important [5,6]. However, adult rheumatologists who take over the care of adult JIA patients commonly have little knowledge of the pathogenesis, treatment and characteristics of JIA [7]. Moreover, it is unclear whether adult JIA patients should be treated similarly to RA patients [8]. To provide appropriate medical care, we should establish evidence-based management strategies for adult JIA.

In the pre-biologics era, only one study comparing the prognosis of JIA and RA has been published [9]. That study, which dealt with disease subtypes and the presence of antibody, indicated that oligoarticular JIA had the best outcome according to radiographic changes, whereas seropositive RA had the worst [9]. However, little evidence is available with regard to the difference in prognosis between adult JIA and RA in the biologics era. Although the long-term prognosis of JIA still requires elucidation, to the best of our knowledge, there are no large databases on adult JIA patients in Japan which could be explored for this purpose. For this reason, here we extracted data on adult JIA patients (defined as onset at <16 years of age) who were registered in the RA database as 'oligoarticular JIA (oligoarthritis) or polyarticular JIA (polyarthritis)'. We then compared their current status and prognosis with RA patients (defined as starting at ≧16 years of age) who had the same disease duration.

The National Database of Rheumatic Diseases in Japan (NinJa) was established in 2002 to reveal trends and problems associated with RA [10]. Nationwide, attending physicians in multiple centres register patients diagnosed with RA in this database, which includes disease activity, drug use, physical function, joint outcome and other data which are collected annually. Adult JIA patients (oligoarthritis or

CONTACT Takumi Matsumoto matsumoto.rheu@tmd.ac.jp Department of Lifetime Clinical Immunology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku Tokyo 113-8519, Japan

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Pediatric Rheumatology

RESEARCH ARTICLE Open Access

Tocilizumab modifies clinical and laboratory features of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis

Masaki Shimizu[1*], Mao Mizuta[1], Nami Okamoto[2], Takahiro Yasumi[3], Naomi Iwata[4], Hiroaki Umebayashi[5], Yuka Okura[6], Noriko Kinjo[7], Tomohiro Kubota[8], Yasuo Nakagishi[9], Kenichi Nishimura[10], Mariko Mohri[11], Masato Yashiro[12], Junko Yasumura[13], Hiroyuki Wakiguchi[14] and Masaaki Mori[11]

Abstract

Background: This study aimed to determine the influence of tocilizumab (TCZ) in modifying the clinical and laboratory features of macrophage activation syndrome (MAS) complicating systemic juvenile idiopathic arthritis (s-JIA). Furthermore, we assessed the performance of the 2016 MAS classification criteria for patients with s-JIA-associated MAS while treated with TCZ.

Methods: A panel of 15 pediatric rheumatologists conducted a combination of expert consensus and analysis of real patient data. Clinical and laboratory features of s-JIA-associated MAS in 12 TCZ-treated patients and 18 untreated patients were evaluated. Possible MAS was defined as having characteristic laboratory features but lack of clinical features of MAS, or atypical MAS, or early treatment that prevented full-blown MAS.

Results: Clinically, the TCZ-treated patients with s-JIA-associated MAS were less likely febrile and had significantly lower ferritin, triglyceride, and CRP levels than the untreated patients with s-JIA-associated MAS. Other laboratory features of MAS including lower platelet counts and lower fibrinogen were more pronounced in TCZ-treated patients. The TCZ-treated patients with s-JIA-associated MAS were less likely to be classified as MAS based on the MAS classification criteria (25% vs 83.3%, $p < 0.01$). This is ascribed to the absence of fever or insufficient ferritin elevation, compared with the untreated patients.

Conclusion: TCZ could modify the clinical and laboratory features of s-JIA-associated MAS. When evaluating the s-JIA patients while treated with TCZ, it is not applicable to use MAS classification criteria. Care must be taken to not underdiagnose MAS based on the MAS classification criteria.

Keywords: Macrophage activation syndrome, Systemic juvenile idiopathic arthritis, Tocilizumab, Classification criteria

Background

Macrophage activation syndrome (MAS) is a severe, potentially life-threatening complication of rheumatic diseases, which is clinically characterized by fever, hepatosplenomegaly, lymphadenopathy, profound depression of all three blood cell lines, deranged liver function, intravascular coagulation, and central nervous system dysfunction. The hallmark of MAS is an uncontrolled and dysfunctional immune response with excessive activation and expansion of T lymphocytes and macrophages exhibiting hemophagocytic activity, which leads to overproduction of numerous proinflammatory mediators, thereby eliciting a cytokine storm. MAS is complicated with many rheumatic diseases. However, MAS is most commonly seen in systemic juvenile idiopathic arthritis (s-JIA) and occurs in approximately 10% patients with s-JIA [1]. Furthermore, subclinical or occult MAS may occur in as many as 30–40% patients with active s-JIA [2].

s-JIA is a severe systemic inflammatory disorder of unknown etiology characterized by arthritis and systemic features such as spiking fever, skin rash, generalized

* Correspondence: shimizum@staff.kanazawa-u.ac.jp
[1]Department of Pediatrics, Graduate School of Medical Sciences, Kanazawa University, 13-1 Takaramachi, Kanazawa 920-8641, Japan
Full list of author information is available at the end of the article

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Pediatric Rheumatology

RESEARCH ARTICLE Open Access

Clinical features and characteristics of uveitis associated with juvenile idiopathic arthritis in Japan: first report of the pediatric rheumatology association of Japan (PRAJ)

Junko Yasumura[1*], Masato Yashiro[2], Nami Okamoto[3], Kosuke Shabana[3], Hiroaki Umebayashi[4], Naomi Iwata[5], Yuka Okura[6], Tomohiro Kubota[7], Masaki Shimizu[8], Minako Tomiita[9], Yasuo Nakagishi[10], Kenichi Nishimura[11], Ryoki Hara[11], Mao Mizuta[8], Takahiro Yasumi[12], Fumiya Yamaide[13], Hiroyuki Wakiguchi[14], Masao Kobayashi[1] and Masaaki Mori[15]

Abstract

Background: Although there are many reports on Juvenile Idiopathic arthritis-associated uveitis (JIA-U) from various countries, especially from Europe and North America, there are few reports from Asia. Our aim was to investigate the epidemiology, characteristics and predictors of JIA-U in Japan.

Methods: Data were retrospectively collected on 726 patients with JIA from medical records as of April 2016 at 15 medical centers specialized in pediatric rheumatic diseases. Of these, patients with uveitis were further investigated for the specific characteristics of this manifestation.

Results: The prevalence of uveitis was 6.1% in the 726 JIA patients examined. Incidence of uveitis was significantly higher in patients with an earlier arthritis onset (2.6-vs.-5.8 years, $P < 0.0001$), oligoarthritis (16.1%-vs.-1.6%, $P < 0.001$), or anti-nuclear antibodies. On the contrary, it was significantly less common in patients with rheumatoid factor or anti-cyclic citrullinated peptide antibodies. A history of using methotrexate (MTX), infliximab or adalimumab was also associated with uveitis occurrence. The median age at uveitis diagnosis was 5 years, and the median time from arthritis onset to uveitis diagnosis was 2 years. The occurrence of anterior and bilateral uveitis was 79.3 and 53.7%, respectively. There were no symptoms at uveitis diagnosis in 58.5% of cases. Complications arising between the time of uveitis diagnosis and the last observation increased from 31.7 to 56.1%; in particular, cataract was increased 3-fold. While no patients lost their vision, 61.9% did not recover normal vision (≥ 1.0), and in many cases active uveitis persisted, especially in males. In addition to steroid eye drops (97.6%) and MTX (15.4%), biological agents were used for treating the uveitis in 41.5% of patients.

Conclusions: The epidemiology, characteristics and predictors of JIA-U in Japan are described here for the first time. Although the prevalence of JIA-U in Japan is lower than in predominantly Caucasian cohorts, as reported from North America and Europe, the epidemiology, characteristics and predictors were found to be similar.

Keywords: Juvenile idiopathic arthritis, Uveitis, Epidemiology, Asian

* Correspondence: junko-ma562@hiroshima-u.ac.jp
[1]Department of Pediatrics, Hiroshima University Graduate School of Biomedical and Health Sciences, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan
Full list of author information is available at the end of the article

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REVIEW ARTICLE

Clinical practice guidance for juvenile idiopathic arthritis (JIA) 2018

Nami Okamoto[a], Shumpei Yokota[b], Syuji Takei[c], Yuka Okura[d], Tomohiro Kubota[c], Masaki Shimizu[e], Tomo Nozawa[f], Naomi Iwata[g], Hiroaki Umebayashi[h], Noriko Kinjo[i], Tomoko Kunishima[i], Junko Yasumura[j] and Masaaki Mori[k]

[a]Department of Pediatrics, Faculty of Medicine, Osaka Medical College, Takatsuki, Japan; [b]Laboratory of Pediatric Research, Institute of Tokyo Medical School, Tokyo, Japan; [c]Department of Pediatrics, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan; [d]Department of Pediatrics, KKR Sapporo Medical Center, Sapporo, Japan; [e]Department of Pediatrics, Graduate School of Medical Sciences, Kanazawa University, Kanazawa, Japan; [f]Department of Pediatrics, Yokohama City University Graduate School of Medicine, Yokohama, Japan; [g]Department of Infection and Immunology, Aichi Children's Health and Medical Center, Obu, Japan; [h]Department of General Pediatrics, Miyagi Children's Hospital, Sendai, Japan; [i]Department of Child Health and Welfare (Pediatrics), Graduate School of Medicine, University of the Ryukyus, Nishihara, Japan; [j]Department of Pediatrics, Hiroshima University Graduate School of Biomedical & Health Sciences, Hiroshima, Japan; [k]Department of Lifetime Clinical Immunology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan

ABSTRACT

Juvenile idiopathic arthritis (JIA) is the most common disease in pediatric rheumatism. There is no specific symptom or examination finding for JIA, and the diagnosis is made by exclusion and differentiation. Because non-pediatric rheumatologists are sometimes involved in medical care, 'proposal for JIA guidance on diagnosis and treatment for primary care pediatricians and non-pediatric rheumatologists' was first published in 2007. In these 10 years, a number of new findings on pathophysiology and treatment of JIA have been published; therefore, we propose this guidance of 2018th edition aiming at updating and standardization of JIA medical care in Japan. This edition included the management of uveitis, macrophage activation syndrome, infectious diseases before and during treatment. Moreover, details of biologics are also described. Although this guidance is tailored to adaptation of examinations and drugs, we do not purpose to limit the physicians' discretion in clinical practice. This guidance should be viewed as recommendations and be individualized according to the condition of the patient. We hope that medical care for JIA will advance and more patients will get benefit based on this guidance. Then, further revisions are needed due to changes in future conditions.

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KEYWORDS
Juvenile idiopathic arthritis; clinical practice guidance; algorism of treatment; macrophage activation syndrome; uveitis; biologics

1. General considerations and classification of pediatric patients with chronic arthritis

Juvenile idiopathic arthritis (JIA) is defined as chronic arthritis of unknown etiology beginning before the 16th birthday and persisting for at least 6 weeks when other known conditions are excluded.

The current classification of JIA was proposed by the Pediatric Standing Committee of the International League of Associations for Rheumatology (ILAR) [1], which published an initial revision in 1997 [2] and subsequently a second revision in 2001 [3]. This classification includes seven categories of JIA (Table 1) which mainly fall into two types according to the differences in clinical symptoms and pathophysiology, namely systemic arthritis (systemic JIA) and the other six JIA categories. The latter consist of oligoarthritis, rheumatoid factor-negative polyarthritis, rheumatoid factor-positive polyarthritis, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis, and are often considered as 'articular-type JIA' in clinical practice in Japan. We therefore use this term in this guide. Within systemic arthritis, we can clearly differentiate a form where only arthritis remains after systemic inflammation subsides (fever, eruption, hepatosplenomegaly, serositis, etc.) from articular-type JIA. Here, we will use the term 'systemic arthritis with active arthritis (and without active systemic features)' in the present guide, according to the '2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis' [4].

Recently, the term 'spondyloarthritis (SpA)' has been widely used in children. The main manifestations of this disease are axial arthritis (such as spondylitis and sacroiliitis), peripheral arthritis, and enthesitis of tendons and ligaments [5]. This is an umbrella disease which includes ankylosing spondylitis [6], psoriatic arthritis [7], arthritis of inflammatory bowel disease and reactive arthritis. Enthesitis-related arthritis, psoriatic arthritis, children with some undifferentiated arthritis in JIA categories are equivalent to SpA [5]. Because the categories which are excluded from the JIA classification (e.g. arthritis of inflammatory bowel disease) could be also diagnosed using SpA criteria,

CONTACT Nami Okamoto ped029@osaka-med.ac.jp Department of Pediatrics, Osaka Medical College, 2-7 Daigaku-machi, Takatsuki, Osaka, Japan
Collaborating Associations: Pediatric Rheumatology Association of Japan (PRAJ), Japan College of Rheumatology (JCR)

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Association of *NCF1* polymorphism with systemic lupus erythematosus and systemic sclerosis but not with ANCA-associated vasculitis in a Japanese population

Nozomi Yokoyama[1,2], Aya Kawasaki[1,2*], Takashi Matsushita[3], Hiroshi Furukawa[1,2,4,5], Yuya Kondo[6], Fumio Hirano[7,8], Ken-ei Sada[9], Isao Matsumoto[6], Makio Kusaoi[10], Hirofumi Amano[10], Shouhei Nagaoka[11], Keigo Setoguchi[12], Tatsuo Nagai[13], Kota Shimada[4,14], Shoji Sugii[14], Atsushi Hashimoto[4], Toshihiro Matsui[4], Akira Okamoto[15], Noriyuki Chiba[16], Eiichi Suematsu[17], Shigeru Ohno[18], Masao Katayama[19], Kiyoshi Migita[20], Hajime Kono[21], Minoru Hasegawa[22], Shigeto Kobayashi[23], Hidehiro Yamada[24,25], Kenji Nagasaka[26], Takahiko Sugihara[7,8,27], Kunihiro Yamagata[28], Shoichi Ozaki[24], Naoto Tamura[10], Yoshinari Takasaki[10,23], Hiroshi Hashimoto[29], Hirofumi Makino[30], Yoshihiro Arimura[31], Masayoshi Harigai[32], Shinichi Sato[33], Takayuki Sumida[6], Shigeto Tohma[4,5], Kazuhiko Takehara[3] & Naoyuki Tsuchiya[1,2*]

Genome-wide association studies of systemic lupus erythematosus (SLE) in Chinese and Korean populations demonstrated strong association of single nucleotide polymorphisms (SNPs) located in the

[1]University of Tsukuba, Faculty of Medicine, Molecular and Genetic Epidemiology Laboratory, Tsukuba, Japan. [2]University of Tsukuba, Graduate School of Comprehensive Human Sciences, Master's Program in Medical Sciences, Tsukuba, Japan. [3]Kanazawa University, Graduate School of Medical Sciences, Department of Dermatology, Kanazawa, Japan. [4]National Hospital Organization Sagamihara National Hospital, Clinical Research Center for Allergy and Rheumatology, Sagamihara, Japan. [5]National Hospital Organization Tokyo National Hospital, Kiyose, Japan. [6]University of Tsukuba, Faculty of Medicine, Department of Internal Medicine, Tsukuba, Japan. [7]Tokyo Medical and Dental University, Graduate School of Medical and Dental Sciences, Department of Rheumatology, Tokyo, Japan. [8]Tokyo Medical and Dental University, Graduate School of Medical and Dental Sciences, Department of Lifetime Clinical Immunology, Tokyo, Japan. [9]Okayama University, Graduate School of Medicine, Density and Pharmaceutical Sciences, Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama, Japan. [10]Juntendo University, School of Medicine, Department of Internal Medicine and Rheumatology, Tokyo, Japan. [11]Yokohama Minami Kyosai Hospital, Yokohama, Japan. [12]Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan. [13]Kitasato University, Department of Rheumatology and Infectious Diseases, Sagamihara, Japan. [14]Tokyo Metropolitan Tama Medical Center, Fuchu, Japan. [15]Himeji Medical Center, National Hospital Organization, Himeji, Japan. [16]Morioka Medical Center, National Hospital Organization, Morioka, Japan. [17]Kyushu Medical Center, National Hospital Organization, Fukuoka, Japan. [18]Yokohama City University Medical Center, Yokohama, Japan. [19]Nagoya Medical Center, National Hospital Organization, Nagoya, Japan. [20]Fukushima Medical University, School of Medicine, Fukushima, Japan. [21]Teikyo University School of Medicine, Department of Internal Medicine, Tokyo, Japan. [22]University of Fukui, Department of Dermatology, Fukui, Japan. [23]Juntendo University Koshigaya Hospital, Koshigaya, Japan. [24]St. Marianna University, School of Medicine, Department of Internal Medicine, Kawasaki, Japan. [25]Center for Rheumatic Diseases, Seirei Yokohama Hospital, Yokohama, Japan. [26]Ome Municipal General Hospital, Ome, Japan. [27]Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan. [28]University of Tsukuba, Faculty of Medicine, Department of Nephrology, Tsukuba, Japan. [29]Juntendo University School of Medicine, Tokyo, Japan. [30]Okayama University Hospital, Okayama, Japan. [31]Kyorin University School of Medicine, First Department of Internal Medicine, Mitaka, Japan. [32]Department of Rheumatology, School of Medicine, Tokyo Women's Medical University, Tokyo, Japan. [33]The University of Tokyo, Department of Dermatology, Tokyo, Japan. *email: a-kawasaki@umin.net; tsuchiya-tky@umin.net