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Comparison of serum biomarkers for the diagnosis of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis

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ABSTRACT

Our study aimed to compare the accuracy of serum biomarkers for the diagnosis of macrophage activation syndrome (MAS) complicating systemic juvenile idiopathic arthritis (s-JIA). Serum cytokine levels (neopterin, IL-18, and CXCL9 and soluble tumor necrosis factor receptor type I (sTNFR-I) and II) were determined by enzyme-linked immunosorbent assay in 78 patients with s-JIA, including 21 with MAS. Receiver operating characteristic curve analysis revealed area under the curve values and cut off values of neopterin, IL-18, CXCL9, sTNFR-II/I ratio and ferritin were 0.9465/19.5 nmol/l, 0.8895/69250 ng/ml, 0.9333/3130 pg/ml, 0.9395/3.796 and 0.8671/2560 ng/ml, respectively. Serum neopterin levels were significantly elevated in patients with MAS and those were correlated positively with disease activity. In conclusion, serum neopterin levels may be used as a promising indicator of disease activity in s-JIA and MAS and for evaluating it. It may also be a useful marker to diagnose the transition to MAS from active-phase s-JIA.

1. Introduction

Macrophage activation syndrome (MAS) is a severe life-threatening condition that complicates systemic juvenile idiopathic arthritis (s-JIA). Clinical features of MAS are characterized by fever, splenomegaly, haemorrhages; and involvement of liver, central nervous system, and kidney; and eventually, multiple organ failure [1]. Laboratory findings include decreases in haemoglobin and white blood cell and platelet counts, hypertransaminasaemia, hyperferritinaemia, and evidence of intravascular coagulation [1]. A proper diagnosis of MAS is essential to start appropriate therapeutic interventions and change unfavourable outcomes. However, it is often difficult to distinguish MAS from s-JIA flares, sepsis, or haemophagocytic lymphohistiocytosis (HLH), especially in the early stage of MAS. Differentiating MAS from these conditions is essential for selecting appropriate therapeutic interventions in a timely manner. However, there is no definite clinical or laboratory parameter that can effectively diagnose MAS.

The hallmark of MAS includes uncontrolled and dysfunctional immune responses involving continual activation and expansion of T lymphocytes and macrophages, which in turn lead to marked hypercytokinaemia [2]. Interleukin (IL)-1, IL-6, and IL-18 play important roles in s-JIA pathogenesis [3]. However, the role of interferon (IFN)-γ and tumor necrosis factor (TNF)-α becomes dominant over that of IL-6 and IL-1β as MAS develops [4,5]. IL-18 and IL-6 overproduction might be associated with MAS development through NK cell dysfunction [6,7]. Moreover, IFN-γ and TNF-α is a key cytokine in the pathogenesis of MAS as well as primary and other secondary HLH [8–13]. Recent reports have shown that serum levels of IFN-γ and IFN-γ-induced chemokines, soluble TNF receptor type II /I ratio (sTNFR-II/I) are markedly elevated in patients with MAS compared with those in patients with active-phase s-JIA without MAS [4,5,14].

Neopterin, a 2-amino-4-hydroxy-(1′,2,′3′-trihydroxypropyl)-pteridine, is produced by activated monocytes/macrophages from guanosine triphosphate (GTP) via GTP cyclohydrolase I [15]. The activity of this enzyme is greatly enhanced by IFN-γ and, to a lesser extent, by IFN-α, other cytokines, and endotoxins [15]. IFN-γ, which is released by activated helper T lymphocytes type 1 and natural killer cells, is the most potent inducer of neopterin production. However, measuring

Abbreviations: MAS, macrophage activation syndrome; s-JIA, systemic juvenile idiopathic arthritis; IL, interleukin; sTNFR, soluble tumor necrosis factor receptor; TNF, tumor necrosis factor; EBV-HLH, Epstein–Barr virus-induced haemophagocytic lymphohistiocytosis; KD, Kawasaki disease; HCs, healthy controls; IFN, interferon; PSL, prednisolone; PBMCs, peripheral blood mononuclear cells

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ORIGINAL ARTICLE

Development and exacerbation of pulmonary nontuberculous mycobacterial infection in patients with systemic autoimmune rheumatic diseases

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ABSTRACT

Objectives: To examine the development and exacerbation of pulmonary nontuberculous mycobacterial (NTM) infection in patients with systemic autoimmune rheumatic diseases (SARD).

Methods: We conducted a case–control study. Seventeen of 7013 patients with SARD fulfilling the criteria for pulmonary NTM infection were enrolled in the NTM group. The control group was matched for age, sex, and SARD at a ratio of 2:1.

Results: Eight patients with rheumatoid arthritis, four with systemic vasculitis, three with Sjögren's syndrome, and one each with dermatomyositis and systemic lupus erythematosus were included in the NTM group. *Mycobacterium avium* was detected in 12 (71%) patients, *M. chelonae* in 2, and *M. intracellulare*, *M. abscessus*, and *M. kansasii* in 1 patient each. Preexisting lung disease was more common in the NTM group than in the control group (88% versus 38%, $p = .0009$), particularly bronchiectasis (65% versus 29%, $p = .033$). The body mass index and serum albumin level were significantly lower in the NTM group than in the control group. Six patients (35%) experienced NTM exacerbation during observation. Clinical immune status at the time of NTM diagnosis, as indicated by the peripheral blood leukocyte/lymphocyte count and serum immunoglobulin G level, was unremarkable and comparable between patients with and without exacerbation, as were the treatments for SARD.

Conclusions: In patients with SARD, pulmonary NTM infection may develop and exacerbate without clinically apparent immunosuppression.

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Bronchiectasis; immunosuppression; nontuberculous mycobacterium; rheumatic diseases

Introduction

The advent of immunosuppressive drugs and biological agents has improved the treatment of systemic autoimmune rheumatic diseases (SARD), such as rheumatoid arthritis (RA) and systemic vasculitis. However, these innovations have been accompanied by serious concerns about the risk of opportunistic infections, including pneumocystis pneumonia and mycobacterial infection [1]. For example, the incidence of nontuberculous mycobacterial (NTM) infection in patients with RA is twice that in the general population, and in the US anti-tumor necrosis factor (TNF) therapy has been reported to increase the incidence of NTM by approximately 5-fold [2]. Japanese post-marketing surveillance of patients with RA receiving biological agents reported that the incidence of NTM infection was 0.1%–0.2%, which is comparable with that of tuberculosis (TB) [3–7]. Further, the incidence of NTM in Nagasaki, Japan, was estimated to be 11.0 and 10.1 per 100,000 in 2008 and 2009, respectively [8], and 14.7 per 100,000 in Japan in 2015 [9], while the national prevalence of NTM in Japan was 33–65/100,000 in 2005 [10].

The 2014 Japanese Respiratory Society guideline on the use of biological agents in NTM [11] states as follows: 'In principle, biological agents are contraindicated in patients with NTM disease. However, their use may be considered in cases of NTM caused by *Mycobacterium (M.) avium* complex (MAC), with a number of conditions being met, and in those with high disease activity of RA, but only after fully evaluating the benefit-risk balance'. This statement is based on the fact that, unlike TB, there are no preventive treatments for NTM.

Older age, a longer disease duration, pulmonary comorbidity such as TB, chronic obstructive pulmonary disease, interstitial lung disease and bronchiectasis, elevated C-reactive protein or erythrocyte sedimentation rate, and treatment with glucocorticoids or biological agents such as anti-TNF, have been identified as risk factors for development and exacerbation of NTM infection in patients with RA or other SARD [12–18]. However, the relative importance of focal (lung disease) and systemic (immune status) factors has not been elucidated to date.

The aim of this case-control study was to identify focal and systemic risk factors for development and exacerbation

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Original article

Predictive factors for sustained remission with stratification by myositis-specific autoantibodies in adult polymyositis/dermatomyositis

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Abstract

Objective. The aim of this study was to clarify predictive factors for sustained remission in adult patients with PM/DM, particularly focusing on stratification by myositis-specific autoantibodies (MSAs).

Methods. A total of 162 adult patients with PM/DM who were followed up for >1 year after diagnosis were retrospectively enrolled. MSAs were evaluated comprehensively in 102 patients whose sera were available. Sustained remission was defined as no evidence of disease activity (active skin rash, active myositis or active interstitial lung disease) for longer than a 6-month continuous period while undergoing myositis therapy or no medication. Clinical data were reviewed in patients' medical charts

Results. The sustained remission rate for all patients was 58% during the median follow-up period at 4 years. With regard to MSAs, the achievement rate of sustained remission among MSA-negative patients was significantly higher than that for patients with anti-aminoacyl-tRNA synthetase ($P = 0.004$), anti-melanoma differentiation-associated gene 5 ($P = 0.037$) or anti-transcriptional intermediary factor 1-γ ($P = 0.013$) antibodies. MSA-negative status (odds ratio 5.84, $P = 0.009$) and absence of severe muscle weakness requiring assistance at diagnosis (odds ratio 43.6, $P < 0.001$) were independent factors associated with sustained remission in multivariate analysis. Cumulative remission rates were significantly higher ($P < 0.001$) in patients with both the MSA-negative status and absence of severe muscle weakness at diagnosis than the others.

Conclusion. MSA-negative status and the absence of severe muscle weakness requiring assistance at diagnosis are independent predictive factors for sustained remission in adult PM/DM patients.

Key words: polymyositis, dermatomyositis, myositis-specific autoantibodies, prediction, treatment outcome, remission

CLINICAL SCIENCE

Rheumatology key messages

- Approximately half of the PM/DM patients achieved sustained remission after induction therapy.
- The absence of severe muscle weakness is strongly associated with sustained remission in PM/DM.
- Myositis-specific autoantibody-negative PM/DM patients have a better clinical outcome than those with other MSAs.

Introduction

PM/DM are idiopathic inflammatory myopathies that affect skeletal muscle, skin, and other organs such as the lungs, heart and joints [1]. The measurement of myositis-specific autoantibodies (MSAs) is highly useful to predict the clinical presentation, treatment response and prognosis in PM/DM [2, 3]. Prognostic factors for patients with PM/DM have been reported as follows: elderly age, male, amyopathic DM, dysphagia, interstitial lung disease (ILD), cardiac involvement and malignancy [3–5]. The MSAs strongly associated with a poor prognosis are anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibody and anti-transcriptional intermediary factor 1-γ (anti-TIF1-γ) antibody, because anti-MDA5 and anti-TIF1-γ are associated with fatal complications developing into rapidly progressive ILD (RP-ILD) and malignancy, respectively [6, 7]. Thus, PM/DM patients with these fatal complications must be managed appropriately to improve their prognosis.

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EPIDEMIOLOGICAL SCIENCE

First external validation of sensitivity and specificity of the European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria for idiopathic inflammatory myopathies with a Japanese cohort

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ABSTRACT

Objective To externally validate the performance of the new European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria set for idiopathic inflammatory myopathies (IIM) with a Japanese cohort.

Methods This study included 420 IIM and 402 non-IIM cases. Probability of having IIM in each patient was calculated using the collected data set. The cut-off probability was set at 55%, as recommended by EULAR/ACR. Patients classified as IIM by the criteria were further subclassified with classification trees.

Results When the probability cut-off was set at 55%, the sensitivity/specificity of the new criteria to diagnose IIM were 89.3%/91.0% in the total cohort, 88.1%/95.1% without muscle biopsy data and 90.4%/65.5% with biopsy data. The cohort included 12 overlap syndrome patients with biopsy data, who were included as non-IIM cases in accordance with traditional Japanese methods. When they were included in the IIM cases, the specificity in patients with biopsy increased to 74.4%. The sensitivity/specificity of the new criteria to diagnose polymyositis/dermatomyositis (PM/DM) plus juvenile and amyopathic DM in the Japanese cohort was 87.4%/92.4%, which were greater than those of the Tanimoto's criteria revised to enable classification of amyopathic DM (ADM) (71.2%/87.8%) and were comparable with those of Bohan & Peter's criteria to diagnose those diseases except for ADM (88.4%/88.3%).

Conclusions Our study externally validated high specificity of the new criteria for the first time, although with several limitations, including low percentage of child patients. The new criteria have higher sensitivity and/or specificity in classification of PM/DM than the previously reported criteria, demonstrating its usefulness for interethnic patients.

Key messages

What is already known about this subject?

► New classification criteria for idiopathic inflammatory myopathies were proposed on the basis of the data analyses by the International Myositis Classification Criteria Project. Examined for sensitivity validation with external cohorts, they were recently approved by European League Against Rheumatism and American College of Rheumatology.

What does this study add?

► Our study externally validated high specificity of the new criteria for the first time.

How might this impact on clinical practice or future developments?

► The new criteria have higher sensitivity and/or specificity in classification of polymyositis/dermatomyositis than the previously reported criteria, demonstrating its usefulness for interethnic patients. Setting probability cut-off at 55% in the new criteria together with use of the classification tree was acceptable for the Japanese cohort.

INTRODUCTION

Idiopathic inflammatory myopathies (IIM) are heterogeneous disorders characterised by muscle weakness and muscle inflammation and include polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM).[1] Immune-mediated necrotising myopathy (IMNM) could be an independent disease entity in IIM. Various classification criteria for IIM and its subgroups have been published since 1970.[2] Among them, the Bohan & Peter's criteria and Tanimoto's criteria for PM/DM have been commonly used in Japan.[3–5]

Bohan & Peter's criteria, described in 1975, include five variables. There are some limitations, however; IBM and muscular dystrophies with

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A comprehensive analysis of the clinical characteristics and laboratory features in 179 patients with autoimmune autonomic ganglionopathy

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ABSTRACT

The clinical importance of autoantibodies against the ganglionic acetylcholine receptor (gAChR) remains to be fully elucidated. We aimed to identify the clinical characteristics of autoimmune autonomic ganglionopathy (AAG) in patients with gAChR autoantibodies. For this cohort investigation, serum samples were obtained from patients with AAG between 2012 and 2018 in Japan. We measured the levels of autoantibodies against gAChRα3 and gAChRβ4 and evaluated clinical features, as well as assessing the laboratory investigation results among the included patients. A total of 179 patients tested positive for antibodies, including 116 gAChRα3-positive, 13 gAChRβ4-positive, and 50 double antibody-positive patients. Seropositive AAG patients exhibited widespread autonomic dysfunction. Extra-autonomic manifestations including sensory disturbance, central nervous system involvement, endocrine disorders, autoimmune diseases, and tumours were present in 118 patients (83%). We observed significant differences in the frequencies of several autonomic and extra-autonomic symptoms among the three groups. Our ^{123}I-metaiodobenzylguanidine myocardial scintigraphy analysis of the entire cohort revealed that the heart-to-mediastinum ratio had decreased by 80%. The present study is the first to demonstrate that patients with AAG who are seropositive for anti-gAChRβ4 autoantibodies exhibit unique autonomic and extra-autonomic signs. Decreased cardiac uptake occurred in most cases, indicating that ^{123}I- metaiodobenzylguanidine myocardial scintigraphy may be useful for monitoring AAG. Therefore, our findings indicate that gAChRα3 and gAChRβ4 autoantibodies cause functional changes in postganglionic fibres in the autonomic nervous system and extra-autonomic manifestations in seropositive patients with AAG.

1. Introduction

Autoimmune autonomic ganglionopathy (AAG) is a rare disease that presents with various autonomic symptoms. The ganglionic neuronal nicotinic acetylcholine receptor (gAChR) mediates fast synaptic transmission in all peripheral autonomic ganglia in the autonomic nervous system, comprising two α3 subunits and three β4 subunits [1,2]. However, the frequency of symptoms, extra-autonomic manifestations

Abbreviations: AAG, autoimmune autonomic ganglionopathy; Abs, autoantibodies; AChRs, acetylcholine receptors; AI, antibody index; CSF, cerebrospinal fluid; CVRR, coefficient of variation in R-R intervals; gAChR, ganglionic acetylcholine receptor; GI, gastrointestinal; GL, Gaussia luciferase; H/M, heart to mediastinum; IVIg, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; LIPS, luciferase immunoprecipitation system; MIBG, metaiodobenzylguanidine; nAChR, nicotinic acetylcholine receptor; PSL, prednisolone; RLU, relative luminescence unit; SD, standard deviations

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Multicenter Prospective Study of the Efficacy and Safety of Combined Immunosuppressive Therapy With High-Dose Glucocorticoid, Tacrolimus, and Cyclophosphamide in Interstitial Lung Diseases Accompanied by Anti–Melanoma Differentiation–Associated Gene 5–Positive Dermatomyositis

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Objective. Interstitial lung disease (ILD) accompanied by anti–melanoma differentiation–associated gene 5 (anti–MDA-5)–positive dermatomyositis (DM) is often rapidly progressive and associated with poor prognosis. Because there is no established treatment, we undertook this study to prospectively evaluate the efficacy and safety of a combined immunosuppressive regimen for anti–MDA-5–positive DM patients with ILD.

Methods. Adult Japanese patients with new-onset anti–MDA-5–positive DM with ILD (n = 29) were enrolled at multiple study centers from 2014 to 2017. They were treated with a regimen of high-dose glucocorticoids (GCs), tacrolimus, and intravenous cyclophosphamide (IV CYC). Plasmapheresis was used if a patient's condition worsened after the regimen started. The primary end point was 6-month survival, which was compared between this group of patients and a historical control group (n = 15) consisting of anti–MDA-5–positive DM patients with ILD who received step-up treatment (high-dose GC and stepwise addition of immunosuppressant). Secondary end points were 12-month survival rate, adverse events, and changes in laboratory data.

Results. The combined immunosuppressive regimen group showed significantly higher 6-month survival rates than the step-up treatment group (89% versus 33%; $P < 0.0001$). Over a period of 52 weeks, improvements in anti–MDA-5 titers, serum ferritin levels, vital capacity, and chest high-resolution computed tomography scores were observed. The combined immunosuppressive regimen group received IV CYC nearly 20 days earlier with shorter intervals and tended to receive plasmapheresis more often than patients undergoing step-up treatment. Cytomegalovirus reactivation was frequently observed over 52 weeks.

Conclusion. A combined immunosuppressive regimen is effective for anti–MDA-5–positive DM patients with ILD. Plasmapheresis can be used for additional effect in intractable disease. Patients should be carefully monitored for opportunistic infections during treatment.

INTRODUCTION

Idiopathic inflammatory myopathies (IIMs) are heterogeneous autoimmune diseases that affect skeletal muscle and various organs, including the skin, lungs, heart, and joints. IIMs have been categorized on the basis of clinical phenotype or histopathologic characteristics; however, recent studies have focused on the utility of myositis-specific autoantibodies (MSAs) for

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EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update

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ABSTRACT

Objectives To provide an update of the European League Against Rheumatism (EULAR) rheumatoid arthritis (RA) management recommendations to account for the most recent developments in the field.

Methods An international task force considered new evidence supporting or contradicting previous recommendations and novel therapies and strategic insights based on two systematic literature searches on efficacy and safety of disease-modifying antirheumatic drugs (DMARDs) since the last update (2016) until 2019. A predefined voting process was applied, current levels of evidence and strengths of recommendation were assigned and participants ultimately voted independently on their level of agreement with each of the items.

Results The task force agreed on 5 overarching principles and 12 recommendations concerning use of conventional synthetic (cs) DMARDs (methotrexate (MTX), leflunomide, sulfasalazine); glucocorticoids (GCs); biological (b) DMARDs (tumour necrosis factor inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), abatacept, rituximab, tocilizumab, sarilumab and biosimilar (bs) DMARDs) and targeted synthetic (ts) DMARDs (the Janus kinase (JAK) inhibitors tofacitinib, baricitinib, filgotinib, upadacitinib). Guidance on monotherapy, combination therapy, treatment strategies (treat-to-target) and tapering on sustained clinical remission is provided. Cost and sequencing of b/tsDMARDs are addressed. Initially, MTX plus GCs and upon insufficient response to this therapy within 3 to 6 months, stratification according to risk factors is recommended. With poor prognostic factors (presence of autoantibodies, high disease activity, early erosions or failure of two csDMARDs), any bDMARD or JAK inhibitor should be added to the csDMARD. If this fails, any other bDMARD (from another or the same class) or tsDMARD is recommended. On sustained remission, DMARDs may be tapered, but not be stopped. Levels of evidence and levels of agreement were mostly high.

Conclusions These updated EULAR recommendations provide consensus on the management of RA with respect to benefit, safety, preferences and cost.

The European League Against Rheumatism (EULAR) developed its first recommendations for the management of rheumatoid arthritis (RA) with synthetic and biological disease-modifying antirheumatic drugs (DMARDs) in 2010.[1] They summarised the state of the art and provided rheumatologists, patients, payers and other stakeholders with the evidence-based views of European experts on the optimal use and sequence of pharmaceutical therapies in patients with RA. Over the course of the decade, the development of new classification criteria for RA[2]; novel information on optimal clinical targets, such as the American College of Rheumatology (ACR)-EULAR remission definitions[3]; evolution of treatment algorithms and strategies[4 5] and the advent of new drugs[6 7] already necessitated two updates of the EULAR recommendations.[8 9] The ACR, the Asian-Pacific League of Associations for Rheumatology (APLAR) and the Pan-American League of Associations for Rheumatology (PANLAR) have published similar guidance documents, although using slightly different approaches.[10–12]

Today it is widely accepted that clinical remission is the main therapeutic target for patients with RA,

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ORIGINAL ARTICLE

Response to tocilizumab and work productivity in patients with rheumatoid arthritis: 2-year follow-up of FIRST ACT-SC study

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ABSTRACT

Objectives: We evaluated long-term control of rheumatoid arthritis (RA) in Japanese paid workers (PWs) and house workers (HWs) treated with subcutaneous tocilizumab (TCZ-SC) and explored factors affecting response to TCZ-SC regarding work productivity.

Methods: This study collected data from patients with RA in the TCZ-SC +/− conventional synthetic disease-modifying antirheumatic drugs group. Factors affecting the response to tocilizumab regarding work productivity were explored using logistic regression. Differences in quality-adjusted life years (QALYs) between with/without response were analysed by a linear regression.

Results: Data were analysed for 357/360 patients. Patients with a $\geq$75% improvement in activity impairment (AI) were considered responders. EuroQol-5 Dimension (EQ-5D), six-item Kessler psychological distress scale score (K6), Health Assessment Questionnaire Disability Index (HAQ-DI), and the patient's disease global health by visual analogue scale were significant contributors to TCZ-SC response based on improvements in AI. Work Functioning Impairment Scale, presenteeism, EQ-5D, K6, and HAQ-DI significantly contributed to the improvement of overall work impairment in PWs. Shorter disease duration also was related to TCZ-SC response based on AI improvements. Responders had significantly larger mean QALYs than non-responders (difference = 0.2614; $p < .001$).

Conclusions: These real-world clinical data support long-term work productivity control with TCZ-SC for biologic-naïve HWs and PWs with RA.

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KEYWORDS
Activity impairment; rheumatoid arthritis; patient-reported outcome; tocilizumab; work productivity

Introduction

Impaired musculoskeletal health and its profound impact on morbidity and mortality is a globally recognized problem [1]. Rheumatoid arthritis (RA) is a major cause of work disability, sickness absence from work, presenteeism, and loss of productivity in developed countries [2]. The decreased work productivity resulting from the persistent pain, impaired mobility and function, and reduced quality of life (QOL) of RA patients [3] has important personal, societal [1], and economic consequences [4]. The estimated prevalence of RA in Japan is reportedly between 0.6 and 1.0% [5]. A recent online survey of 500 RA Japanese patients reported that among this population, the percentages of absenteeism and presenteeism were 1 and 23%, respectively [6].

Tocilizumab (Actemra®, Chugai Pharmaceutical Co., Ltd.; TCZ) is a humanized monoclonal antibody targeting the interleukin-6 receptor [7]. The efficacy of TCZ as monotherapy and in combination with methotrexate has been reported in several trials overseas and in Japan [8–10]. We evaluated the effect of subcutaneous TCZ (TCZ-SC) based on improvements in work productivity and activity impairment (WPAI) among biologic-naïve Japanese house workers (HWs) and paid workers (PWs) with RA in real-world clinical practice in Japan in the FIRST ACT-SC study. Based on the interim results of this study up to 52 weeks [11], we

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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

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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

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ORIGINAL ARTICLE

2019 Diagnostic criteria for mixed connective tissue disease (MCTD): From the Japan research committee of the ministry of health, labor, and welfare for systemic autoimmune diseases

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ABSTRACT

Objective: To update and revise the diagnostic criteria for mixed connective tissue disease (MCTD) issued by the Japan Research Committee of the Ministry of Health, Labor, and Welfare (MHLW), a round table discussion by experts from rheumatology, dermatology, and pediatric medicine was conducted in multiple occasions.

Methods: The definition of MCTD, and items included in the diagnostic criteria were generated by consensus method and evaluation using clinical data of typical and borderline cases of MCTD, by applying to the diagnostic criteria for MCTD proposed in 1996 and 2004 by the Research Committee of MHLW.

Results: To the end, all committee members reached consensus. Then, the criteria were assessed in an independent validation cohort and tested against preexisting criteria. The revised criteria facilitate an understanding of the overall picture of this disease by describing the concept of MCTD, common manifestations, immunological manifestation and characteristic organ involvement. Conditions with characteristic organ involvement include pulmonary arterial hypertension, aseptic meningitis and trigeminal neuropathy. Even if the overlapping manifestations are absent, MCTD can be diagnosed based on the presence of the characteristic organ involvement. Furthermore, the criteria were validated for applicability in actual clinical cases, and public comments were solicited from the Japan College of Rheumatology and other associated societies.

Conclusion: After being reviewed through public comments, the revised diagnostic criteria have been finalized.

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KEYWORDS
Diagnosis; criteria; mixed connective tissue disease

Introduction

In 1972, Sharp et al. proposed mixed connective tissue disease (MCTD) as a disease entity characterized by overlapping clinical features of systemic lupus erythematosus (SLE), systemic sclerosis, and polymyositis, as well as high titers of serum anti-U1 ribonucleoprotein (U1-RNP) antibody [1]. Although MCTD was previously considered a subtype of systemic sclerosis, it has recently been recognized as an independent disease entity in terms of organ involvement because of its characteristic association with conditions such as pulmonary arterial hypertension, aseptic meningitis, and trigeminal neuropathy [2–9].

In 1986, the MCTD criteria was first proposed by Kasukawa et al., as representatives of the research committee for MCTD of the Ministry of Health and Welfare in Japan during an International Symposium on Mixed Connective Tissue Disease and Anti-nuclear Antibodies [6]. MCTD was designated as a specified disease by the Ministry of Health, Labor, and Welfare (MHLW) in Japan in 1993. At present, it is a designated intractable disease affecting 11,000

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Original article

Clinical characteristics of cancer-associated myositis complicated by interstitial lung disease: a large-scale multicentre cohort study

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Abstract

Objective. To clarify the incidence, risk factors, and impact of malignancy in patients with PM/DM-associated interstitial lung disease (ILD).

Methods. This study used data from 497 patients with PM/DM-associated ILD enrolled in a multicentre, retrospective and prospective cohort of incident cases. Cancer-associated myositis (CAM) was defined as malignancy diagnosed within 3 years before or after PM/DM diagnosis. Demographic and clinical information was recorded at the time of diagnosis, and data about the occurrence of mortality and malignancy was collected.

Results. CAM was identified in 32 patients with PM/DM-associated ILD (6.4%). Patients with CAM were older (64 *vs* 55 years, $P < 0.001$), presented with arthritis less frequently (24% *vs* 49%, $P = 0.01$), and showed a lower level of serum Krebs von den Lungen-6 (687 *vs* 820 IU/l, $P = 0.03$) than those without CAM. The distribution of myositis-specific autoantibodies, including anti-melanoma differentiation-associated gene 5, anti-aminoacyl tRNA synthetase, and anti-transcriptional intermediary factor 1-γ antibodies, did not differ between the groups. Survival analysis demonstrated that CAM patients had a poorer survival than non-CAM patients ($P = 0.006$), primarily due to excess deaths by concomitant malignancy, while mortality due to ILD-related respiratory failure was similar between the groups ($P = 0.51$).

Conclusion. Concomitant malignancy can occur in patients with PM/DM-associated ILD, and has significant impact on mortality. Older age, lack of arthritis, and a lower level of serum Krebs von den Lungen-6 at diagnosis are predictors of concomitant malignancy.

Key words: cancer-associated, myositis, interstitial lung diseases

CLINICAL SCIENCE

Rheumatology key messages

- Concomitant malignancy can occur in patients with PM/DM-associated ILD.
- Older age, lack of arthritis, and a lower KL-6 at diagnosis predict concomitant malignancy.
- Mortality due to ILD is comparable between CAM and non-CAM patients.

Introduction

PM and DM are a heterogeneous disease entity of idiopathic inflammatory myopathy that mainly affects skeletal muscle, skin, and lungs [1]. The first case of stomach cancer associated with DM was reported in 1916 by Stertz [2]. Since then, the association between PM/DM and cancer has been formally specified in the first classification of myositis by Bohan and Peter [3], and has been evidenced by a number of case reports, large cohorts,

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Original Research

Physical inactivity, prolonged sedentary behaviors, and use of visual display terminals as potential risk factors for dry eye disease: JPHC-NEXT study

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ABSTRACT

Purpose: This population-based, cross-sectional study was performed to assess the influence of life-style modalities, including physical activity, sedentary behaviors, and visual display terminal (VDT) use, on the prevalence of dry eye disease (DED).

Methods: The study included a total of 102,582 participants aged 40–74 years, from the Japan Public Health Center-based Prospective Study for the Next Generation, a large nationwide prospective ongoing Japanese cohort study. Logistic regression analyses were used to investigate the relationship of total and leisure-time physical activity, duration of sedentary behaviors, and VDT use (hours/day) with DED.

Results: Among 47,346 men and 55,236 women, 25,234 (8315 males and 16,919 females) cases of DED were documented. Total physical activity was significantly related to decreased DED in both sexes; for the highest vs. lowest total physical activity quartiles, the multivariable-adjusted odds ratios (ORs) for DED were 0.90 (95% confidence interval [CI], 0.84–0.97; $P_{trend} < 0.03$) and 0.91 (95% CI, 0.86–0.95; $P_{trend} < 0.001$) for men and women, respectively. Conversely, prolonged sedentary behaviors and VDT use had significantly higher prevalence of DED in both sexes ($P_{trend} < 0.001$). Notably, the favorable effect of total physical activity on decreased DED in women was more prevalent with prolonged VDT use (≥ 2 h/day) ($P_{interaction} < 0.01$). In men, the duration of VDT use or sitting was a significant modifier of the inverse relationship between leisure-time physical activity and DED ($P_{interaction} < 0.05$).

Conclusions: Physical inactivity, prolonged sedentary behaviors, and use of VDT were related to increased susceptibility to DED among middle-aged to older Japanese adults.

Abbreviations: ACSM, American College of Sports Medicine; AHA, American Heart Association; CI, confidence interval; DED, dry eye disease; DEWS, Dry Eye Workshop; IRB, Institutional Review Board; JPHC-NEXT Study, the Japan Public Health Center-based Prospective Study for the Next Generation; METs, metabolic equivalents of task score; OR, odds ratio; SD, standard deviation; TBUT, tear break-up time; TFOS, Tear Film and Ocular surface Society; VDT, visual display terminal

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LETTER TO THE EDITOR

2019 Updated diagnostic criteria and disease severity classification for TAFRO syndrome

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TAFRO syndrome, first reported in 2010, is a systemic inflammatory disorder manifesting as thrombocytopenia; anasarca, including pleural effusion and ascites; fever; reticulin myelofibrosis and/or renal insufficiency; and organomegaly, including hepatosplenomegaly and lymphadenopathy. The annual incidence rate of TAFRO syndrome in Japan has been estimated to be 0.9–4.9 per million individuals, and the nationwide prevalence to be 860–7240 cases [1], numbers which are larger than previously expected. Most patients with TAFRO syndrome manifest modest-to-mild systemic lymphadenopathy with characteristic histopathological features resembling those of Castleman disease. Some researchers, therefore, consider that TAFRO syndrome to be a subtype of idiopathic multicentric Castleman disease (iMCD) [2]. However, clinical features of TAFRO syndrome are quite different from those of classical Castleman disease [3], and we consider TAFRO syndrome to be a distinct clinical entity, although several pathological findings of lymph nodes resemble those in iMCD.

In 2015, we proposed diagnostic criteria and a disease severity classification for TAFRO syndrome [4], which have been widely accepted and cited. Almost simultaneously, another research group proposed diagnostic criteria for TAFRO syndrome with iMCD histology (TAFRO-iMCD) [2]. In the latter criteria, characteristic histopathological findings of lymph nodes are essential for diagnosis. We are aware that histological findings from lymph nodes are important for diagnosis, but lymph node biopsy from patients with TAFRO syndrome is sometimes difficult or nearly impossible, due to anasarca, bleeding tendency, and/or the smallness or unclear of the target lymph node. In addition, prompt diagnosis and initiation of treatment without delay are required to rescue such patients. Therefore, our diagnostic criteria include patients without histological confirmation of lymph nodes.

After our proposal of the diagnostic criteria and disease severity classification in 2015, we gained some additional insights and experiences that prompted us to update these criteria and classification. Recently, we retrospectively analyzed data from 220 patients stored in the database of the Multicenter Collaborative Retrospective Study for establishing the concept of TAFRO syndrome [3]. In that study, we compared clinical features of patients with iMCD, not otherwise specified (iMCD-NOS), TAFRO-iMCD, and TAFRO-without-proven-iMCD (TAFRO-w/op-iMCD). Our analysis clearly demonstrated that iMCD-NOS and TAFRO-iMCD are different clinical entities, whereas TAFRO-iMCD and TAFRO-w/op-iMCD, which were diagnosed without lymph node biopsy, could be considered the same clinical entity, requiring prompt diagnosis and intensive care [3]. In this retrospective study, we also found that patients with various diseases, including

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CLINICAL RESEARCH ARTICLE

MUSCLE&NERVE WILEY

Thigh muscle MRI findings in myopathy associated with anti-mitochondrial antibody

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Abstract

Introduction: Myopathy associated with anti-mitochondrial antibody (AMA) has recently been characterized as a distinct type of idiopathic inflammatory myopathy. The purpose of this study is to evaluate the pattern of involvement in thigh muscles in AMA myopathy using MRI.

Methods: Six patients with AMA myopathy were identified and their muscle MRI findings evaluated.

Results: On thigh muscle MRI, all six patients showed high signal intensity with short-tau inversion recovery that reflected disease activity mostly in the adductor magnus, called a "cuneiform sign." Fatty degeneration was also prominent in the adductor magnus, as well as the semimembranosus muscles.

Discussion: These characteristic changes on MRI contrast with those of other inflammatory myopathies. From these observations, we concluded that the localization pattern of the inflammatory changes in muscle MRI can contribute to the diagnosis of AMA myopathy.

KEYWORDS

granulomatous, myopathy, anti-mitochondrial antibody, idiopathic inflammatory myopathies, muscle MRI, myopathy, myositis

1 | INTRODUCTION

Myopathy associated with anti-mitochondrial antibody (AMA) has recently been characterized as a distinct type of idiopathic inflammatory myopathy (IIM).[1-5] The IIMs consist of heterogeneous subgroups of autoimmune diseases characterized by progressive muscle weakness and skeletal muscle inflammation. Polymyositis (PM), dermatomyositis (DM), inclusion body myositis (IBM), and immune-mediated necrotizing myopathy are the major subtypes of IIMs, and subtype-specific autoantibodies are a helpful diagnostic tool.[6] AMA and anti-mitochondrial M2 antibody (AMA-M2) were originally identified as specific autoantibodies for primary biliary cirrhosis (PBC).[7] Following the first report by Uhl et al in 1974,[2] the association of PBC with IIMs was reported in in case reports and small series.[1,5,8-10] These studies propose AMA myopathy as a distinct subgroup of IIMs. AMA myopathy is characterized by slowly progressive skeletal

Abbreviations: AMA, anti-mitochondrial antibody; AMA-M2, anti-mitochondrial M2 antibody; CK, creatine kinase; DM, dermatomyositis; HIS, high-intensity signal; IBM, inclusion body myositis; IIM, idiopathic inflammatory myopathy; PBC, primary biliary cirrhosis; PM, polymyositis; STIR, short-tau inversion recovery; TE, echo time; TR, repetition time; T1W, T1-weighted.

S.N. and S.U. contributed equally to this study.

OPEN ACCESS

TRANSLATIONAL SCIENCE

Antigen-driven selection of antibodies against SSA, SSB and the centromere 'complex', including a novel antigen, MIS12 complex, in human salivary glands

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ABSTRACT

Objectives Recent evidences have revealed that anti-SSA/SSB antibodies, the major autoantibodies in Sjögren's syndrome (SS), are produced in salivary glands. This study aims to clarify overall of autoantibody production at lesion site, including anti-centromere antibody (ACA)-positive SS.

Methods Antibodies of antibody-secreting cells in human salivary glands were produced as recombinant antibodies. The reactivity of these antibodies and their revertants were investigated by ELISA and newly developed antigen-binding beads assay, which can detect conformational epitopes. The target of uncharacterised antibodies was identified by immunoprecipitation and mass spectrometry. Autoantibody-secreting cells in salivary gland tissue were identified by immunohistochemistry using green fluorescent protein-autoantigen fusion proteins.

Results A total of 256 lesion antibodies were generated, and 69 autoantibodies including 24 ACAs were identified among them. Beads assay could detect more autoantibodies than ELISA, suggesting autoantibodies target to antigens with native conformation. After somatic hypermutations were reverted, autoantibodies drastically decreased antigen reactivity. We showed that MIS12 complex, a novel target of ACA, and CENP-C are major targets of ACA produced in salivary glands by examining cloned antibodies and immunohistochemistry, whereas few anti-CENP-B antibodies were detected. The target profiling of serum ACA from 269 patients with SS, systemic sclerosis (SSc), primary biliary cirrhosis (PBC) and healthy controls revealed that ACA-positive patients have antibodies against various sites of centromere complex regardless of disease.

Conclusion We showed direct evidences of antigen-driven maturation of anti-SSA/SSB antibody and ACA in SS lesion. ACA recognises centromere 'complex' rather than individual protein, and this feature is common among patients with SS, SSc and PBC.

Key messages

What is already known about this subject?
- The typical autoantibody of Sjögren's syndrome (SS), anti-SSA and anti-SSB antibody, is produced in salivary glands.
- Anti-centromere antibody (ACA) is the major autoantibody detected in limited-cutaneous systemic sclerosis and primary biliary cirrhosis (PBC) but it is also detected in a part of SS patients' serum.

What does this study add?
- In addition to anti-SSA/SSB antibody, ACA is also produced in the salivary glands of SS patients in an antigen-driven manner.
- Serum ACA of patients with SS, SSc and PBC are commonly targeted to various sites of the centromere 'complex', not to individual proteins.

How might this impact on clinical practice or future developments?
- This study highlights the significance of detail immunological analysis in local lesion for better understanding of disease-relevant autoantibody and classification of autoimmune diseases.

INTRODUCTION

Serum autoantibody tests are widely used in clinical practice because the type of autoantibody is related to clinical course, treatment response and prognosis.[1 2] Sjögren's syndrome (SS) is an autoimmune disease that is characterised by chronic lymphocyte infiltration into salivary and lacrimal glands, that results in destruction of glands and causes sicca syndrome.[3] Anti-SSA antibody, which is collective term for multiple antibodies reacting to the SSA52 (TRIM21) and SSA60 (TROVE2), and anti-SSB antibody are the most commonly detected autoantibody in SS, and actually, anti-SSA antibody are used as one of the classification criteria of SS.[4]

Other autoantibodies, including anti-centromere antibody (ACA), anti-α-fodrin antibody and anti-muscarinic receptor three antibody, are also reported in a part of SS patients.[5] ACA is the major autoantibody detected in limited-cutaneous systemic sclerosis (lcSSc)[6] and primary biliary cirrhosis (PBC),[7] and clinically used in the classification criteria for systemic sclerosis (SSc),[8] but not included in the classification criteria for SS. In practice, ACA is detected by anti-nuclear antibody (ANA) test as discrete-speckled pattern (corresponding to the centromere region of chromosome). ELISA of anti-CENP-B antibody is also used because this result is highly consistent with ACA by

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Safety and tolerability of anifrolumab, a monoclonal antibody targeting type I interferon receptor, in Japanese patients with systemic lupus erythematosus: A multicenter, phase 2, open-label study.

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Author information

Abstract

Objectives: This study evaluated the safety and tolerability of anifrolumab, a monoclonal antibody targeting the type I interferon (IFN) receptor, in Japanese patients with moderate-to-severe systemic lupus erythematosus (SLE).**Methods:** In this open-label, phase 2, dose-escalation study, patients received intravenous (IV) anifrolumab 100, 300, or 1000 mg every 4 weeks from days 29 to 337 (Stage 1). Patients who completed Stage 1 continued anifrolumab 300 mg every 4 weeks for 156 weeks (Stage 2). The primary objective was to evaluate the safety of anifrolumab for 48 weeks (Stage 1) and 156 weeks (Stage 2). The pharmacokinetics and pharmacodynamics of anifrolumab were also assessed.**Results:** Of 20 patients enrolled in Stage 1, 17 received IV anifrolumab 100 mg (n = 6), 300 mg (n = 5), or 1000 mg (n = 6). Adverse events (AE) and serious AE (SAE) incidences were similar between dose cohorts. SAEs occurred in 41% (Stage 1) and 33% (Stage 2) of patients; AEs leading to discontinuation occurred in 24% (Stage 1) and 22% (Stage 2) of patients. Anifrolumab had non-linear pharmacokinetics after the first and last dose and dose-dependently suppressed the IFN gene signature.**Conclusion:** Anifrolumab was well tolerated among Japanese patients with moderate-to-severe SLE.

KEYWORDS: Anifrolumab; dose escalation; intravenous; safety; systemic lupus erythematosus

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REVIEW ARTICLE

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

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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

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Developing classification criteria for skin-predominant dermatomyositis: the Delphi process

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Conflicts of interest
None declared.

See Appendix S1 for the full list of co-authors of the Skin Myositis Delphi Group.

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Summary

Background The European League Against Rheumatism/American College of Rheumatology classification criteria for inflammatory myopathies are able to classify patients with skin-predominant dermatomyositis (DM). However, approximately 25% of patients with skin-predominant DM do not meet two of the three hallmark skin signs and fail to meet the criteria.

Objectives To develop a set of skin-focused classification criteria that will distinguish cutaneous DM from mimickers and allow a more inclusive definition of skin-predominant disease.

Methods An extensive literature review was done to generate items for the Delphi process. Items were grouped into categories of distribution, morphology, symptoms, antibodies, histology and contextual factors. Using REDCap™, participants rated these items in terms of appropriateness and distinguishing ability from mimickers. The relevance score ranged from 1 to 100, and the median score determined a rank-ordered list. A prespecified median score cut-off was decided by the steering committee and the participants. There was a pre-Delphi and two rounds of actual Delphi.

Results There were 50 participating dermatologists and rheumatologists from North America, South America, Europe and Asia. After a cut-off score of 70 during the first round, 37 of the initial 54 items were retained and carried over to the next round. The cut-off was raised to 80 during round two and a list of 25 items was generated.

Conclusions This project is a key step in the development of prospectively validated classification criteria that will create a more inclusive population of patients with DM for clinical research.

What's already known about this topic?

- Proper classification of patients with skin-predominant dermatomyositis (DM) is indispensable in the appropriate conduct of clinical/translational research in the field.

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ORIGINAL ARTICLE

Pre-conception status, obstetric outcome and use of medications during pregnancy of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) in Japan: Multi-center retrospective descriptive study

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ABSTRACT

Objective: To describe the pre-conception status, pregnancy outcomes, and medication prevalence in systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Crohn's disease (CD), and ulcerative colitis (UC).

Methods: E-mail-based questionnaire survey for the Japan Maternal Fetal Intensive Care Unit Network hospitals inquiring prevalence and clinical features of SLE, RA, CD and UC complicated pregnancies for 2 years.

Results: The number of SLE, RA, CD and UC among 69,810 deliveries was 184, 139, 27 and 178, respectively. Less than half of pregnancies were planned. Assisted reproductive technology (ART) pregnancy rates were higher in SLE, RA and UC than in the general population (11.4, 23.0 and 7.4 vs 5.1%, $p < .001$ each). Preterm delivery, preeclampsia, and fetal growth restriction (FGR) were more frequent in SLE than in the general population (39.4 vs. 5.6% $p < .001$, 15.0 vs. 6.0% $p < .001$, 12.9 vs 4.2% $p < .001$). Prevalence of preterm delivery in RA and UC (27.5 vs. 5.6% $p < .001$, 11.3 vs. 5.6% $p < .05$) and FGR in CD (28.6 vs. 4.2% $p < .001$) was also higher than that in the general population.

Conclusion: SLE, RA, CD, and UC complicated pregnancies were at high risks of obstetric adverse outcome. High ART rates necessitate pre-conception counseling in SLE, RA, and UC pregnancies.

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Received 26 March 2019
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KEYWORDS
Crohn's disease; pregnancy; rheumatoid arthritis; systemic lupus erythematosus; ulcerative colitis

Introduction

Current treatment advances including the advent of anti-TNF inhibitors, CTLA4–immunoglobulin, and IL-6 receptor antagonists have enabled more women with rheumatoid arthritis (RA) or inflammatory bowel disease (IBD) to achieve remission, resulting in an increased number of births in these patient populations [1,2]. The incidence of adverse pregnancy outcomes is lower when disease is in remission than during active disease [3–7]. Therefore, guidelines and recommendations mention that the use of anti-TNF inhibitors during pregnancy should be considered if disease activity needs to be controlled [8,9]. Although antenatal use of anti-TNF inhibitors has been reported as having low teratologic risk, guidelines recommend discontinuation

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RESEARCH ARTICLE

Is TAFRO syndrome a subtype of idiopathic multicentric Castleman disease?

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Abstract

Castleman disease (CD) is a rare lymphoproliferative disorder that can be unicentric or multicentric. Multicentric CD (MCD) is further subdivided into human herpesvirus type-8-associated, POEMS syndrome-associated, and idiopathic (iMCD). TAFRO syndrome is a newly identified disorder of unknown etiology characterized by **t**hrombocytopenia, **a**nasarca, **f**ever, **r**eticulin myelofibrosis, renal dysfunction, and **o**rganomegaly. The TAFRO syndrome is sometimes regarded as a subtype of iMCD (TAFRO-iMCD), whereas iMCD without TAFRO syndrome is considered "not otherwise specified" (iMCD-NOS). However, a proportion of patients with TAFRO syndrome have been diagnosed without lymph node biopsies (TAFRO syndrome without proven iMCD; TAFRO-w/op-iMCD). To clarify the clinical features of iMCD-NOS, TAFRO-iMCD, and TAFRO-w/op-iMCD, we retrospectively analyzed 220 patients extracted from the database of the Multicenter Collaborative Retrospective Study for Establishing the Concept of TAFRO Syndrome. The patients included 87 with iMCD-NOS, 63 with TAFRO-iMCD, and 19 with TAFRO-w/op-iMCD. Patients in all three groups exhibited anemia, hypoalbuminemia, and elevated serum C-reactive protein and interleukin-6 levels. No significant differences in clinical, laboratory, and prognostic features were noted between the TAFRO-iMCD, and TAFRO-w/op-iMCD groups. However, the iMCD-NOS group exhibited polyclonal hyper-γ-globulinemia. The five-year survival rates of patients in the iMCD-NOS and TAFRO-involved groups were 100% and 66.5%, respectively (dropping markedly during the first few months in the latter). The iMCD-NOS and the TAFRO-iMCD samples typically showed plasma cell and mixed-type histologies, respectively. Thus, iMCD can be classified into two distinct subtypes, iMCD-NOS and TAFRO-iMCD. As such, TAFRO-iMCD and TAFRO-w/op-iMCD may be considered the same entity, requiring prompt diagnosis and intensive care.

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ORIGINAL ARTICLE

Clinical subsets of juvenile dermatomyositis classified by myositis-specific autoantibodies: Experience at a single center in Japan

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ABSTRACT

Objectives: This study investigated the association between myositis-specific autoantibodies (MSAs) and clinical subsets of juvenile dermatomyositis (JDM) in Japanese patients.

Methods: Twenty-one patients at a single center who developed initial or relapsed JDM from 2011 to 2016 were analyzed. Serum concentrations of MSAs against TIF1-γ, MDA5, NXP2, Mi-2, ARS, and SAE were measured by enzyme-linked immunosorbent assays. Clinical symptoms and laboratory data were obtained from clinical records. Clinical characteristics were compared in patients with autoantibodies against TIF1-γ, MDA5, and NXP2.

Results: Of the 21 patients, 20 (95.2%) were positive for one or more MSAs, including nine (42.9%), five (23.8%), six (28.6%), and one (4.8%) positive for anti-TIF1-γ, anti-MDA5, anti-NXP2, and anti-Mi-2 autoantibodies. No patient was positive for anti-ARS or anti-SAE autoantibodies. The frequency of diffuse cutaneous lesions was higher in patients with anti-TIF1-γ autoantibodies. Anti-MDA5 autoantibody-positive patients had features of interstitial lung disease on chest computed tomography. Severe muscle damage at disease onset was significantly associated with positivity for anti-NXP2 autoantibodies.

Conclusion: Similar to findings in Western countries, the clinical characteristics of JDM in Japanese may differ for each type of MSAs.

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KEYWORDS
Anti-MDA5; anti-NXP2; anti-TIF1-γ; juvenile dermatomyositis; myositis specific antibody

Introduction

Juvenile dermatomyositis (JDM) is a major subset of juvenile idiopathic inflammatory myopathy (JIIM), dominantly affecting both muscle and skin, and occasionally lung tissues. Various myositis-specific autoantibodies (MSAs) have been reported as specific disease markers of JDM [1–4]. In addition, recent studies have demonstrated associations among MSA and clinical phenotype in adult patients with dermatomyositis from various ethnicities [5,6]. Although such associations have also been demonstrated in children of Europe and the United States, reports of those in Asian patients are scarce [7].

In the present study, we analyzed the MSA profiles in children with JDM treated at a single center in Japan, as well as the clinical characteristics associated with each MSA.

Materials and methods

Patients

This study included patients with JDM who developed dermatomyositis at age <16 years and were evaluated at the time of onset or recurrence at Aichi Children's Health and Medical Center between January 2011 and December 2016. Patients diagnosed with JDM prior to 2001 were excluded. This study was approved by the ethics committee of Aichi Children's Health and Medical Center.

JDM was diagnosed as described [8], with patients subdivided into those with possible, probable, and definite JDM. Juvenile amyopathic dermatomyositis (ADM) was diagnosed as a typical skin rash but with no clinical evidence of proximal muscle weakness [9].

Data collection

Baseline clinical and laboratory data at diagnosis and during the study period were retrospectively obtained from medical records including fever, JDM-associated skin lesions, muscle weakness, and arthralgia or arthritis. Severe muscle weakness was defined as level 2 or lower on manual muscle testing or its equivalent. Rapidly progressive muscle weakness was defined as weakness that progressed to severe within 3 months after onset of any weakness. Muscle weakness during the disease course was evaluated by assessing dysphagia

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Mucosal Immunology

ARTICLE OPEN

JunB plays a crucial role in development of regulatory T cells by promoting IL-2 signaling

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The AP-1 transcription factor JunB plays crucial roles in multiple biological processes, including placental formation and bone homeostasis. We recently reported that JunB is essential for development of Th17 cells, and thus *Junb*-deficient mice are resistant to experimental autoimmune encephalomyelitis. However, the role of JunB in CD4$^+$ T cells under other inflammatory disease conditions is unknown. Here we show that mice lacking JunB in CD4$^+$ T cells (*Junb*$^{fl/fl}$*Cd4-Cre* mice) were more susceptible to dextran sulfate sodium (DSS)-induced colitis because of impaired development of regulatory T (Treg) cells. Production of interleukin (IL)-2 and expression of CD25, a high affinity IL-2 receptor component, were decreased in *Junb*-deficient CD4$^+$ T cells in vitro and in vivo. Naive CD4$^+$ T cells from *Junb*$^{fl/fl}$*Cd4-Cre* mice failed to differentiate into Treg cells in the absence of exogenously added IL-2 in vitro. A mixed bone marrow transfer experiment revealed that defective Treg development of *Junb*-deficient CD4$^+$ T cells was not rescued by co-transferred wild-type cells, indicating a significance of the cell-intrinsic defect. Injection of IL-2-anti-IL-2 antibody complexes induced expansion of Treg cells and alleviated DSS-induced colitis in *Junb*$^{fl/fl}$*Cd4-Cre* mice. Thus JunB plays a crucial role in the development of Treg cells by facilitating IL-2 signaling.

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INTRODUCTION

The AP-1 transcription factor JunB, which is encoded by the immediate early gene *Junb*, mediates multiple biological processes including placentation, suppression of myeloid cell proliferation, and maintenance of bone and skin homeostasis.[1–4] JunB is a basic leucine zipper (bZIP) protein and forms an AP-1 complex by dimerizing with other bZIP proteins, such as Fos or BATF family members. Recently we and other groups have reported that JunB is essential for the development of IL-17-producing helper T (Th17) cells, and thus *Junb*-deficient mice are completely resistant to experimental autoimmune encephalomyelitis (EAE).[5–7] In addition, the transfer of CD45RB^{hi}CD25$^-$CD4$^+$ T cells from *Junb*-deficient mice to *Rag1*-deficient mice fails to induce colitis,[6] suggesting that JunB is indispensable for pathogenicity of T cells in these autoimmune diseases. On the other hand, it is unclear whether JunB in CD4$^+$ T cells is involved in other inflammatory diseases such as those induced by innate immune cells.

Inflammatory bowel diseases (IBDs) are inflammatory disorders that are characterized by mucosal damage and intestinal inflammation.[8,9] Although the etiology of the IBDs is poorly understood, aberrant activation of immune cells against intestinal microbiota has been proposed to be a cause of the disease. In addition to the genetic and environmental factors, imbalance of the microbiota composition, called dysbiosis, is suggested to play a key role in the pathology of IBDs.[10] Ulcerative colitis (UC) and Crohn's disease (CD) are two major types of IBDs. The dextran sulfate sodium (DSS)-induced colitis is an experimental mouse model of human IBDs.[11,12] In this model, administration of DSS via drinking water causes epithelial barrier damages, which allow penetration of intestinal microbiota into injured mucosa to induce inflammation through infiltration of innate immune cells. DSS-induced colitis shares several aspects of clinical pathology with human UC such as confined symptoms at the colon. Because severe combined immunodeficient (SCID) mice are not resistant to DSS-induced colitis,[13] this disease model is considered to be evoked by innate immune cells. *Rag2*$^{-/-}$ mice are more susceptible to DSS-induced colitis, and the pathology is alleviated by transfer of wild-type CD4$^+$ T cells,[14] indicating a protective role for CD4$^+$ T cells in the DSS-induced colitis.

Regulatory T (Treg) cells, specified by expression of the transcription factor forkhead box P3 (Foxp3), play crucial roles in maintenance of homeostasis by limiting multiple immune responses.[15–17] It has been shown that Treg cells ameliorate DSS-induced colitis.[18,19] Development of Treg cells requires IL-2 signaling, as indicated by the fact that mice deficient in IL-2 or its receptor subunits exhibit a marked reduction in Treg cells, leading to lethal autoimmune disorders.[20] Among the three subunits

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RHEUMATOLOGY

Letter to the Editor (Case report)

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Pregnancy triggers the onset of anti-transcriptional intermediary factor 1γ antibody-positive dermatomyositis: a case series

Rheumatology key message

- The onset anti-TIF1γ antibody-positive DM might be triggered by pregnancy in young adult female patients.

Sir, DM is an idiopathic inflammatory myopathy that has been proved to be related to some types of myositis-specific autoantibodies. Several environmental risk factors for the development of DM have been reported. For instance, anti-transcriptional intermediary factor 1 (TIF1)γ antibody is closely associated with paraneoplastic DM in elderly patients [1], whereas a few previous case reports have suggested that pregnancy can trigger the onset of DM in some cases [2]. Akalin *et al.* [2] reported in their literature review that ∼40% and 10% of patients with histories of pregnancy developed DM during pregnancy and in post-partum periods, respectively. No study has investigated myositis-specific autoantibodies of pregnancy-associated DM.

A total of 62 patients who were diagnosed with myositis-specific autoantibody-associated DM in our department between January 2010 and November 2018 were enrolled in this retrospective case series study. The myositis-specific autoantibodies, including anti-aminoacyl-tRNA synthetases (ARS), anti-TIF1γ, anti-Mi2β, and anti-melanoma differentiation-associated gene 5 (MDA5) antibodies, were evaluated using established ELISA kits (MESACUP; Medical & Biological Laboratories, Tokyo, Japan). This study was exempted from approval by the medical ethics review committee of the University of Tsukuba Hospital (H27-207).

We identified 13 female cases of childbearing age (15–49 years) who developed DM, including 7 cases of anti-TIF1γ antibody-positive DM (patients 1–7 in Table 1), 4 cases of anti-ARS antibody-positive DM and 2 cases of anti-MDA5 antibody-positive DM. Three of the seven cases with anti-TIF1γ antibody-positive DM presented with onsets during the pregnancy/post-partum periods: a 32-year-old woman during the gestation period of her first child (patient 3), a 34-year-old woman 8 weeks after the birth of her second child (patient 4) and a 35-year-old woman within a few days after the birth of her first child (patient 5) (see Table 1). In contrast, a 48-year-old patient developed anti-TIF1γ antibody-positive paraneoplastic DM (patient 7), while three patients developed anti-TIF1γ antibody-positive DM without any correlations with pregnancy or malignancy (patients 1, 2 and 6; Table 1). The other six reproductive-age females, including four anti-ARS antibody-positive DM cases and two anti-MDA5 antibody-positive DM cases, also developed DM without any correlations with pregnancy.

It has been reported that in elderly patients with anti-TIF1γ antibody-positive paraneoplastic DM, disease activity was inhibited by cancer resection and malignant tumours presented a high expression of TIF1γ [3]. Another report showed that mutations and loss of heterozygosity in TIF1γ were detected in tumours of patients with DM and that TIF1γ was overexpressed in tumours, muscle tissues and the skin [4]. These findings suggest that overexpression of

Table 1 Female patients of childbearing age with development of DM

Patient	Age of onset, years	Autoantigen for myositis-specific autoantibody	Association with pregnancy period[a]	History of malignant tumour	Muscle weakness	Interstitial lung disease
1	25	TIF1γ	−	−	−	−
2	29	TIF1γ	−	−	−	−
3	32	TIF1γ	+	−	−	−
4	34	TIF1γ	+	−	−	−
5	35	TIF1γ	+	−	−	−
6	48	TIF1γ	−	−	+	−
7	48	TIF1γ	−	Breast cancer	+	−
8	38	ARS	−	−	−	+
9	47	ARS	−	−	−	+
10	47	ARS	−	−	+	+
11	49	ARS	−	−	+	−
12	44	MDA5	−	−	+	+
13	49	MDA5	−	−	−	+

[a]From pregnancy to post-partum period.
+: positive; −: negative.

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Article type : Brief Report

Brief Report

Finger joint cartilage evaluated by semi-quantitative ultrasound score in patients with rheumatoid arthritis

Running Title: US semi-quantitative cartilage score

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Japanese Dermatological Association
The Journal of Dermatology

Letters to the Editor

Drug-induced acute eosinophilic pneumonia due to hydroxychloroquine in a chilblain lupus patient

Dear Editor,

Gastrointestinal symptoms and retinopathy are among the adverse effects of hydroxychloroquine (HCQ) administration.[1] No reports have been published on acute eosinophilic pneumonia (AEP)[2] attributed to HCQ. We report a case of AEP associated with HCQ.

A 69-year-old woman had been suffering from chilblain lupus erythematosus (LE) for 14 years. She had scaly and hyperkeratotic erythema and erosions with crusts on her hands (Fig 1a), and these exacerbated every winter. Laboratory examinations, including those for complete blood cell count, liver and renal function, and urinalysis, showed no abnormalities. Antinuclear antibodies and other LE-associated autoantibodies were all negative. Histological examination of the erythema revealed hyperkeratosis and lymphocytic infiltrates in the perivascular and periadnexal areas. Lupus band tests revealed linear deposits of immunoglobulin (Ig)G at the basement membrane zone and granular deposits of IgG/IgA/IgM in the dermal papillae. These findings are consistent with chilblain LE. We treated the patient with a topical corticosteroid, but this was unsuccessful. Oral betamethasone (0.5 mg/day) had been introduced 3 years before. She had started taking oral HCQ (200 mg/day) in addition to betamethasone. Two weeks later, she developed rashes, stopped taking HCQ and was admitted to our hospital. She had erythema on the face, trunk and extremities (Fig 1b), and a few blisters on the left forearm. A skin biopsy specimen from the erythema on her right leg indicated edema in the superficial dermis and inflammatory cell infiltration around dermal capillaries (Fig 1c). Only a small number of eosinophils were seen. Remarkable leukocytosis (18 200/μL) with eosinophilia (7553/μL) was present. Chest computed tomography (CT) revealed patchy ground-glass opacities that were predominant in peripheral areas of the lung (Fig. 1d). HCQ was the only drug that the patient had newly received before the onset of the eruptions, although the drug-induced lymphocyte stimulation test by HCQ was

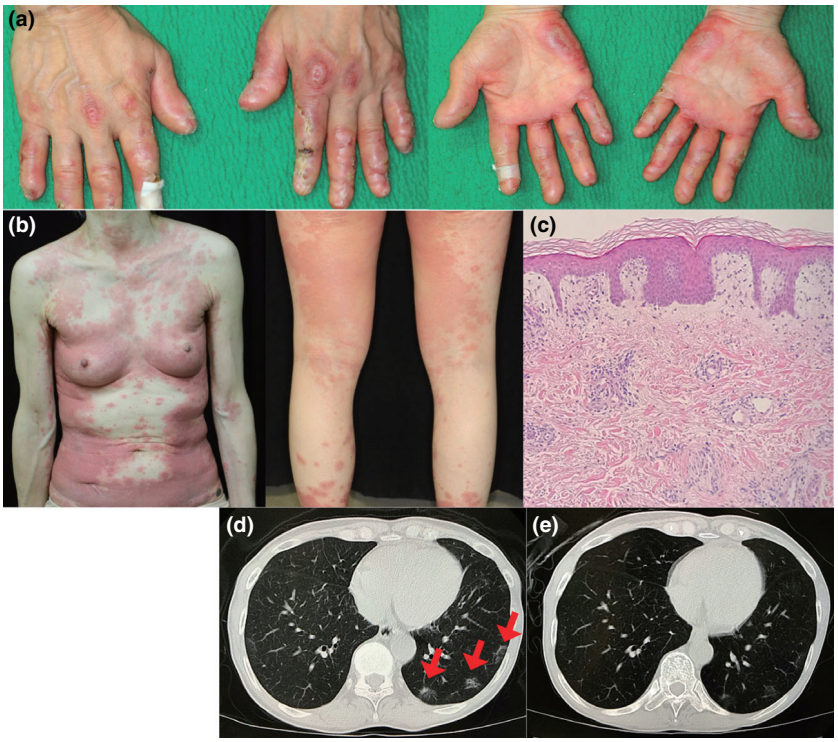

Figure 1. Skin manifestations and chest computed tomography (CT) findings. (a) Hyperkeratotic erythema and erosions with crusts are seen on the hands. (b) There is erythema on the chest, abdomen and extremities. (c) A skin biopsy specimen from the erythema on the right leg shows edema in the superficial dermis and inflammatory cell infiltration around dermal capillaries (hematoxylin–eosin, original magnification ×100). (d) CT before treatment shows patchy ground-glass opacities predominantly in peripheral areas of the lung. (e) The lung lesions significantly improved after the discontinuation of hydroxychloroquine and with oral prednisolone treatment 11 days after admission.

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Letter to the Editor

Clinical characteristics of anti-Ro52α and anti-Ro52β antibodies in dermatomyositis/polymyositis

The anti-Ro52 antibody is found in a number of autoimmune diseases, including Sjögren's syndrome (SS), systemic lupus erythematosus, systemic sclerosis and dermatomyositis (DM)/polymyositis (PM). It is most frequently found in SS (37.4–66.7%) and second-most frequently in DM/PM (26.3–31.2%) [1]. It is also one of the most common autoantibodies in inflammatory myopathies and is classified as a myositis-associated antibody (MAA), which is frequently found in PM/DM but not specific for this diagnosis [2,3]. There are two spliced forms of the Ro52 antigen: Ro52α and Ro52β. Ro52β was reported in 1995 as a splice variant of Ro52, in which exon4 of Ro52α is deleted. Ro52β was found to be expressed in the human heart [4]. We investigated the clinical and laboratory characteristics of DM/PM patients with anti-Ro52α/β antibodies in this study.

Two hundred twenty-eight Japanese patients were enrolled. Demographic and medical information was retrospectively collected from chart reviews or unified questionnaires. One hundred forty-nine patients fulfilled the criteria of Bohan and Peter for DM/PM [5], and the remaining 79 met the criteria for clinically amyopathic DM (CADM) [6]. Of the 228 patients, 82 patients had classical DM, 79 had CADM, 48 had cancer-associated DM, 8 had juvenile DM, 10 had PM and 1 had myositis overlap syndrome. Interstitial lung disease (ILD) was diagnosed by chest X-ray and/or high-resolution computed tomography of the lungs. Ethical approval for the study was obtained from the individual institutional review boards.

All sera were tested by anti-Ro52 (Ro52α) enzyme-linked immunosorbent assay (ELISA) kits (Orgentec®, Mainz, Germany). To measure antibodies to Ro52β, an in-house ELISA (iELISA) using biotinylated recombinant Ro52β protein, which was produced from the full-length cDNA clone of human Ro52β in pBluescript cDNA using the T7 Quick Coupled Transcription/Translation System (Promega®, Madison, WI, USA), was applied, and we followed the procedures in previously published protocols [7,8] except for using a serum dilution buffer containing 0.05% sodium dodecyl sulfate and 10% fetal bovine serum.

Myositis-specific autoantibodies (MSA), including anti-Mi-2, anti-TIF1γ, anti-MDA-5, anti-NXP-2, anti-TIF1β, anti-HMG-CoA, anti-SRP54, and anti-SAE1/2; and MAA, including anti-Ku70/80 and anti-PM/Scl-75/100, were tested by iELISA with biotinylated recombinant proteins [8]. When the results obtained by anti-aminoacyl-transfer RNA synthetase (anti-ARS) ELISA kits (MBL®, Nagoya, Japan) were positive, autoantibodies against the individual ARS, e.g., EJ, Jo-1, KS, PL-7 and PL-12, were tested by iELISA [8]. The results were analyzed by Fisher's exact test, Mann-Whitney U test, or log rank test, as appropriate, using SPSS version 22 (IBM, Armonk, NY, USA). P values less than 0.05 were considered significant.

Forty-five of the 228 patients were anti-Ro52α-positive (19.7%) (Table 1). Although 4 anti-Ro52α-positive and 23 anti-Ro52α-negative patients were excluded for insufficient data, 31 patients out of the 41 anti-Ro52α-positive patients (76%) had ILD ($P = 0.0024$). ILD was a significantly frequent complication in the anti-Ro52α-positive patients. In the 228 patients, anti-MDA5 was most frequently found, in 48 patients (20.9%), followed by anti-TIF1γ, anti-ARS, anti-Mi-2, anti-NXP2 and other antibodies. Nineteen patients out of the 33 anti-Ro52α-positive patients (58%) had anti-ARS antibodies. Anti-ARS antibodies were more frequently found in anti-Ro52α-positive patients than in anti-Ro52α-negative patients ($P < 0.0001$). The frequencies of anti-Ro52α-positive patients among patients with each subtype of anti-ARS autoantibody were as follows: 57% (8 patients out of 14 anti-Jo-1-positive patients) of the anti-Jo-1-positive patients, 66% (6/9) of the anti-EJ-positive patients, 60% (3/5) of the anti-PL-7-positive patients, 67% (2/3) of the anti-KS-positive patients, and 50% (1/2) of the anti-PL-12-positive patients.

Next, we tried to find the clinical features of the anti-Ro52α-positive patients in the three major MSAs (anti-ARS, anti-MDA5 and anti-TIF1γ)-positive groups (Supplementary Table S1). We analyzed age, sex, type of myositis, presence of ILD/cancer, peaks of serum creatine kinase (CK), and characteristic skin manifestations. No clinical features were associated with the presence/absence of anti-Ro52α, except for the significantly lower peak of serum CK in the anti-Ro52α-positive patients among the anti-MDA5-positive patients (122.8 ± 121.0 IU/ml in anti-Ro52α-positive patients vs. 268.7 ± 387.5 IU/ml in anti-Ro52α-negative patients, $P = 0.02$).

Autoantibodies to Ro52β were screened in sera from the 228 patients. Twenty-six patients (11.4%) were anti-Ro52β-positive, and all 26 of these patients were also anti-Ro52α-positive. The demographic and clinical features of the 19 anti-Ro52α single-positive patients and of the 26 both anti-Ro52α- and anti-Ro52β-positive patients are shown in Table 2. The average age of DM onset is significantly higher for the both anti-Ro52α- and anti-Ro52β-positive group ($P = 0.005$). The peak of serum CK is higher in the both anti-Ro52α- and anti-Ro52β-positive patients, but not significantly ($P = 0.069$). Interestingly, all 6 patients in whom no MSA/MAA was found other than anti-Ro52 were both anti-Ro52α- and anti-Ro52β-positive ($P = 0.03$).

Anti-Ro52 has been known to be associated with ILD and Raynaud's phenomenon, but some reports were controversial [1]. A juvenile myositis study showed that anti-Ro52 in DM/PM was frequently detected with anti-ARS and strongly associated with ILD

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Brief Communication

Macrophage activation syndrome in neonates born to mothers with adult-onset Still's disease: Perinatal effect of maternal IL-18

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ABSTRACT

Overproduction of interleukin (IL)-18 is closely related to the pathogenesis of adult-onset Still's disea and the development of macrophage activation syndrome (MAS), a life-threating complication of AOSD. We reported three cases of MAS occurring in infants born to mothers with AOSD. The infants developed MAS at age 13 and 8 days and at birth. Serum IL-18 levels were extremely elevated in all infants (147,000 pg/mL; 378,000 pg/mL; 95,000 pg/mL) as well as in their mothers (58,500 pg/mL; 367,000 pg/mL; 84,000 pg/mL). Physicians should be aware that infants born to mothers with AOSD are at a risk of developing MAS. S levels in mothers with AOSD and their infants should be monitored.

1. Introduction

Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder of unknown etiology characterized by spiking fever, skin rash, myalgia, sore throat, hepatomegaly, splenomegaly, lymphadenopathy and arthritis [1]. Bywaters first described AOSD in 1971, noting that this condition shared clinical similarities with systemic juvenile idiopathic arthritis (s-JIA), although the age of onset is > 16 years [1].

Macrophage activation syndrome (MAS) is a severe, potentially life-threatening complication of both s-JIA and AOSD [2,3]. MAS occurs in 7%–10% of patients with s-JIA and 12–17% of patients with AOSD [2,3]. The hallmark of MAS is an uncontrolled and dysfunctional immune response involving the continual activation and expansion of T lymphocytes and macrophages, leading to marked hypercytokinemia [3]. MAS is clinically characterized by fever, hepatosplenomegaly, lymphadenopathy, a profound decrease in all three blood cell lineages, liver function dysregulation, intravascular coagulation, and central nervous system dysfunction [3]. A characteristic feature is seen on bone-marrow examination that often reveals numerous morphologically benign macrophages exhibiting hemophagocytic activity [3].

Recent investigations into the pathophysiology of s-JIA/AOSD have focused on mediators of the innate immune system [4,5]. In particular, serum interleukin (IL)-18 levels correlate with disease activity and secondary complications in both diseases [6–10]. We previ ported that patients with AOSD and s-JIA share a common cytokine profile pattern involving a significant increase in IL-18 [10]. more, a recent study showed serum IL-18 levels can disting from hemophagocytic lymphohistiocytosis (HLH) as well as toinflammatory syndromes [11]. NK cell dysfunction is we consequence of familial HLH, a syndrome caused by genetic de impair granule-mediated cytotoxicity [12–16]. Decreased function was also reported in s-JIA and MAS [12–16]. High IL are associated with the transient NK cell dysfunction observe and MAS [12].

We previously reported that IL-18 can pass from the motl fetus, resulting in significantly increased serum IL-18 leve newborn [17]. Furthermore, serum IL-18 levels are persist vated in the infant for nearly one month after birth. At birth, had a significantly lower number of CD16+ $CD56^{dim}$ NK impaired cell function. This impaired NK cell function clos lated with serum IL-18 levels and recovered when these levels normalized. From these observations, we hypothesize that an infa a woman with AOSD may have increased serum IL-18 levels, and therefore, may be at risk of developing MAS/HLH. Here, we report

Abbreviations: MAS, macrophage activation syndrome; IL, interleukin; sTNFR, soluble tumour necrosis factor receptor; IFN, interferon; TNF, tumour necr NK, natural killer

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PAPER

Pregnancy outcomes in women with rheumatic diseases: a real-world observational study in Japan

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Objectives: We aimed to evaluate the obstetric complications and the risk factors for these events in pregnant women with rheumatic diseases (RDs). **Methods:** A single-center retrospective study of women with RDs at Hokkaido University Hospital between 2007 and 2016 was conducted. Clinical features and maternal and fetal outcomes were retrospectively collected. The rate of pregnancy complications was compared with the general obstetric population (GOP) in Japan. **Results:** Overall, 132 pregnancies in 95 women with RDs were recorded. Underlying RDs were systemic erythematosus (SLE) ($n=57$), antiphospholipid syndrome (APS) ($n=35$), rheumatoid arthritis ($n=9$), and other RDs ($n=31$). Antiphospholipid antibodies (aPL) were detected in 44 pregnancies (32%). Glucocorticoid was used in 82 pregnancies (62%), and tacrolimus in 20 pregnancies (15%). There were 24 disease flares (18%), but no RD-related death was documented. We recorded 112 live births, 6 abortions, 8 miscarriages, and 6 stillbirths. Pregnancies with RDs appeared to have frequent, emergency cesarean sections and preterm deliveries compared with GOP (30% vs 15% and 21% vs 14%, respectively). The median [interquartile range] birthweight in SLE and APS was lower than GOP (2591 [2231–2958] g and 2600 [2276–2920] g vs 2950 [2650–3250] g, respectively). In pregnancies with SLE, low complement levels presented the risk of maternal complications (odds ratio [95% CI]; 3.9 [1.0–14.9], $p=0.046$) and anti-DNA antibody positivity was significantly correlated with the risk of fetal complications (3.5 [1.1–11.2], $p=0.036$). In pregnancies with APS, maternal age over 35 years and duration of disease longer than 9 years (7.4 [1.3–40.8], $p=0.021$, and 11.16 [1.1–118.8], $p=0.046$, respectively) were significantly correlated with the risk of fetal complications. **Conclusion:** Pregnancies with RDs were at increased risk of having both maternal complications and adverse neonatal outcomes, indicating these pregnancies should be closely monitored. *Lupus* (2019) **28,** 1407–1416.

Key words: Rheumatic diseases; pregnancy; systemic lupus erythematosus; antiphospholipid syndrome; rheumatoid arthritis

Introduction

Rheumatic diseases (RDs) such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome (APS), systemic sclerosis (SSc), Sjögren's syndrome (SS) and polymyositis/dermatomyositis (PM/DM) occur among women of childbearing age.[1] Adverse events during pregnancy in RDs including disease flare, preterm delivery, fetal or neonatal death and fetal negative outcome, have been frequently reported,[2] leading some women to avoid pregnancy. On the other hand, recent advances in the treatment of RDs has significantly improved pregnancy management in RA and SLE, PM/DM, systemic vasculitis, SS, and Behçet's disease (BD).[3-8] However, risk factors in pregnancies with RDs remain controversial and there are no standard guidelines. To date, although numerous agents including immunosuppressants and biologics are available, the effects of these drugs on pregnancies are still uncertain. We hypothesized that women with RDs would have higher rates of pregnancy complications, obstetric interventions, and adverse infant outcomes even under these treatments.

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TRANSLATIONAL SCIENCE

Multi-dimensional analysis identified rheumatoid arthritis-driving pathway in human T cell

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ABSTRACT

Objectives Rheumatoid arthritis (RA) is an autoimmune disease accompanied by lymphocyte infiltration into joint synovium. While T cells are considered to be important for its pathogenesis, the features that are the most relevant to disease and how they change after treatment remain unclear. The aim of this study was to clarify the characteristics of T cells in RA, comprehensively.

Methods We enrolled a total of 311 patients with RA and 73 healthy participants, and carefully classified them by disease state, constructed multiple cohorts and analysed clinical samples from them in a stepwise manner. We performed immunophenotyping with multiple evaluation axes, and two independent transcriptome analyses complementary to each other.

Results We identified that 'effector memory-Tfh' subset was specifically expanded in the peripheral blood (PB) of patients with RA in correlation with disease activity, and reverted after treatment. Besides, we revealed distinct features of T cells in synovial fluid (SF) that the expression of Tfh/Tph-related genes and pro-inflammatory cytokines and chemokines, including *CXCL13*, were significantly enriched, whereas these phenotype were Th1-like. Finally, we identified specific pathways, such as mTORC1, IL-2-stat5, E2F, cell cycle and interferon-related genes, that were significantly enriched in SF, in particular, as well as PB of untreated patients with RA, and notably, these features reverted after treatment.

Conclusion Our multi-dimensional investigation identified disease relevant T-cell subsets and gene signatures deeply involved in pathogenesis of RA. These findings could aid in our understanding of essential roles of T cells in RA and will facilitate to development better diagnostic and therapeutic interventions.

Key messages

What is already known about this subject?

- Multiple observations from various studies and therapeutic reactivities suggest that T cells play an important role in the pathogenesis of rheumatoid arthritis (RA); however, the T-cell features that are most relevant to the disease and how they change in response to treatment remain unclear.

What does this study add?

- We found two disease-relevant subsets, effector memory-Tfh and effector memory T helper 17, by immunophenotyping using multi-axis evaluation.
- Disease-driving pathways, such as mTORC1, IL-2-stat5, cell cycle, E2F and interferon-related genes, and the list of differentially expressed genes including several pro-inflammatory cytokines and chemokines were identified by non-biased comprehensive gene expression analyses.

How might this impact on clinical practice or future developments?

- Our finding could deepen understanding of essential roles of T cells in RA, and will facilitate to develop better diagnostic and therapeutic interventions in future.

INTRODUCTION

Rheumatoid arthritis (RA) is a common autoimmune disorder characterised by lymphocyte infiltration and chronic inflammation of the synovial tissues and progressive joint disability.[1] Both genetic and environmental factors influence its pathogenesis, and the strongest contributor to disease heritability is the major histocompatibility complex (MHC) class II, which is involved in antigen presentation to $CD4^+$ T cells.[2] Genes associated with RA risk alleles outside the MHC locus are also preferentially expressed in $CD4^+$ T cells,[3 4] and multiple lines of evidence from both genetic and clinical research indicate a central role for autoreactive $CD4^+$ T cells in RA pathogenesis.[5] Emerging evidence also points to a role for $CD8^+$ T cells in RA.[6] A subset of $CD8^+$ T cells was found to be essential for ectopic germinal centre formation in the synovial membrane in RA,[7] and clonal expansion was observed for $CD8^+$ T cells but not for $CD4^+$ T cells in newly diagnosed patients with RA.[8]

Despite convincing evidence for T-cell involvement in RA pathogenesis, the specific cell subsets and states that drive the disease have been challenging to identify since T cells are highly heterogeneous, displaying diverse surface markers, developmental and activation states, and effector functions, which has led to multiple systems of classification. Functionally, $CD4^+$ T cells are classified into many subfractions, such as Th1, Th17, Treg,

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CLINICAL SCIENCE

Efficacy and safety of peficitinib (ASP015K) in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III randomised, double-blind, placebo-controlled trial (RAJ4) in Japan

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ABSTRACT

Objective To evaluate the efficacy and safety of the oral Janus kinase (JAK) inhibitor peficitinib versus placebo in Japanese patients with rheumatoid arthritis (RA).

Methods In this multicentre, double-blind, parallel-group, placebo-controlled phase III study, patients with RA and inadequate response to methotrexate (MTX) were randomised 1:1:1 to placebo, peficitinib 100 mg once daily or peficitinib 150 mg once daily with MTX for 52 weeks. Based on baseline randomisation, at week 12, non-responders receiving placebo were switched to peficitinib until the end of treatment; the remaining patients were switched to peficitinib at week 28. Primary efficacy variables were American College of Rheumatology (ACR)20 response rate at week 12/early termination (ET) and change from baseline in van der Heijde-modified total Sharp score (mTSS) at week 28/ET.

Results 519 patients were randomised and treated. Significantly more (p<0.001) peficitinib (58.6%, 100 mg; 64.4%, 150 mg) than placebo (21.8%) recipients achieved ACR20 response at week 12/ET. Significantly lower (p<0.001) mean changes from baseline in mTSS at week 28/ET occurred in peficitinib (1.62, 100 mg; 1.03, 150 mg) than placebo (3.37) recipients. Peficitinib was associated with haematological and biochemical parameter changes, and increased incidence of serious infections and herpes zoster-related disease. One death from suicide occurred in a patient in the placebo group after switching to peficitinib 100 mg.

Conclusions In Japanese patients with RA and inadequate response to MTX, peficitinib demonstrated significant superiority versus placebo in reducing RA symptoms and suppressing joint destruction. Peficitinib had an acceptable safety and tolerability profile, with no new safety signals compared with other JAK inhibitors.

Trial registration number NCT02305849.

Key messages

What is already known about this subject?

► Peficitinib inhibits the kinase activities of all Janus kinase (JAK) family members (pan-JAK inhibition) and was approved in Japan in 2019 as a once-daily rheumatoid arthritis (RA) therapy in both 100 and 150 mg/day regimens, with no dose adjustment for renal injury.

What does this study add?

► This study was a randomised, double-blind, phase III study conducted in patients who had an inadequate response to methotrexate (MTX). Patients from Japan were randomised to 52 weeks' treatment with peficitinib 100 or 150 mg/day, or placebo, in combination with MTX.

► Peficitinib demonstrated superiority over placebo at both doses in reducing RA symptoms and suppressing joint destruction, according to the primary efficacy variables of ACR response and van der Heijde-modified total Sharp score.

► The efficacy of peficitinib 150 mg/day was numerically superior to the 100 mg/day dose, with no apparent dose dependency from a safety perspective and similar safety signals, such as serious infections, herpes zoster and malignancies, to those of other JAK inhibitors.

How might this impact on clinical practice or future developments?

► Based on these results, peficitinib may be a valuable addition to the treatment options for RA, particularly for patients with RA who are unresponsive to conventional treatments.

INTRODUCTION

Despite the advances in the management of rheumatoid arthritis (RA),[1] a vast unmet need remains in relation to progressive disability, reduced quality of life, systemic comorbidities, premature death and high socioeconomic costs.[2–5] RA therapy includes conventional synthetic disease-modifying antirheumatic drugs (csDMARDs)[6 7] and biological disease-modifying antirheumatic drugs (DMARDs), mostly in combination with methotrexate (MTX), with the objective of achieving remission or low disease

Identification of U11snRNA as an endogenous agonist of TLR7-mediated immune pathogenesis

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Contributed by Tadatsugu Taniguchi, October 8, 2019 (sent for review September 9, 2019; reviewed by Jeffrey V. Ravetch and Akinori Takaoka)

The activation of innate immune receptors by pathogen-associated molecular patterns (PAMPs) is central to host defense against infections. On the other hand, these receptors are also activated by immunogenic damage-associated molecular patterns (DAMPs), typically released from dying cells, and the activation can evoke chronic inflammatory or autoimmune disorders. One of the best known receptors involved in the immune pathogenesis is Toll-like receptor 7 (TLR7), which recognizes RNA with single-stranded structure. However, the causative DAMP RNA(s) in the pathogenesis has yet to be identified. Here, we first developed a chemical compound, termed KN69, that suppresses autoimmunity in several established mouse models. A subsequent search for KN69-binding partners led to the identification of U11 small nuclear RNA (U11snRNA) as a candidate DAMP RNA involved in TLR7-induced autoimmunity. We then showed that U11snRNA robustly activated the TLR7 pathway in vitro and induced arthritis disease in vivo. We also found a correlation between high serum level of U11snRNA and autoimmune diseases in human subjects and established mouse models. Finally, by revealing the structural basis for U11snRNA's ability to activate TLR7, we developed more potent TLR7 agonists and TLR7 antagonists, which may offer new therapeutic approaches for autoimmunity or other immune-driven diseases. Thus, our study has revealed a hitherto unknown immune function of U11snRNA, providing insight into TLR7-mediated autoimmunity and its potential for further therapeutic applications.

U11snRNA | TLR7 | autoimmune diseases | DAMPs | type I IFN

Activated B and T lymphocytes with autoreactivity against a diverse array of self-derived molecules are central mediators of autoimmune disease pathophysiology. However, an essential role of innate immune responses in the initiation and maintenance of autoimmune disorders has increasingly come into focus. For example, the exuberant production of type I interferons (IFNs) and proinflammatory cytokines is linked to autoimmunity by either an inappropriate triggering of innate immune receptors or genetic mutations in the receptor pathways that govern the production of those cytokines (1–3). In general, when these cytokines are produced en masse and/or chronically, they contribute to a "break" in immune tolerance and to triggering the differentiation and expansion of self-reactive pathogenic T and B cells (1–3).

Among the innate immune receptors, genetic and functional data have implicated a causative role for nucleic acid-sensing receptors. Typically, RNA-sensing Toll-like receptor 7 (TLR7) and DNA-sensing TLR9 have been most extensively studied for their involvement in autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) (1–6). In this context, growing evidence indicates that, in addition to pathogen-derived nucleic acids, self-derived nucleic acids also activate those innate receptors, thereby contributing to autoimmunity (1–3, 7–10).

TLR7 has been well-described for its role in the detection of virus-derived single-stranded RNAs (ssRNAs) or other RNAs that contain ssRNA structures (1–3). In the context of autoimmunity, the chronic and/or excessive exposure of self-derived RNA to TLR7 is thought to be critical in driving disease (1–3). Deficiency

Significance

Immunogenic damage-associated molecular patterns (DAMPs), typically released from dying cells, can evoke chronic inflammatory or autoimmune disorders via their activation of innate immune receptors. Since an association of RNA-sensing Toll-like receptor 7 (TLR7) signaling with autoimmunity is well-documented, identification of a DAMP(s) that triggers TLR7 is critical to understanding the disease pathogenesis. By generating the synthetic compound KN69 that inhibits autoimmunity in mouse models, we identified U11 small nuclear RNA (U11snRNA) as a target of KN69 and strong activator of TLR7. We found a correlation between high serum level of U11snRNA and autoimmune diseases in human subjects and mouse models. Finally, we generated TLR7 agonists and TLR7 antagonists. Our study provides therapeutic insight into autoimmunity and other diseases.

Author contributions: H.N., N.E., and T.T. designed research; H.N., N.E., Y.N., T. Nishiyama, Y.T., R.K., A.M., K.M., T.N.-K., and T.I. performed research; T. Nishiyama, T.O., S.T., H.I., S.-i.I., T. Natsume, T.A., H.K., T.D., K.F., and K.Y. contributed new reagents/analytic tools; H.N., N.E., Y.N., T. Nishiyama, Y.T., J.N., R.K., A.M., K.M., T.O., T.N.-K., T.I., T.D., S.H., H.Y., and T.T. analyzed data; and H.N., N.E., J.N., S.H., H.Y., and T.T. wrote the paper.

Reviewers: J.V.R., Rockefeller University; and A.T., Hokkaido University.

Competing interest statement: T. Nishiyama, Y.T., S.T., H.I., and T.D. are employees of Kowa Company, Ltd., and N.E. is an employee of Astellas Pharma, Inc.

Data deposition: RNA-sequencing data reported in this paper have been deposited in the DNA Data Bank of Japan (BioProject ID code PRJDB8733).

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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

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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

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Antiphospholipid antibody-positive Sjögren's syndrome with leg ulcers

Dear Editor,

A review of 558 patients with primary Sjögren's syndrome (SS) found cutaneous involvement in 16% of these patients, with cutaneous vasculitis being the most frequent cutaneous symptom.[1] Anti-phosphatidylserine/prothrombin complex (aPS/PT) antibodies are included in antiphospholipid antibodies (APA)

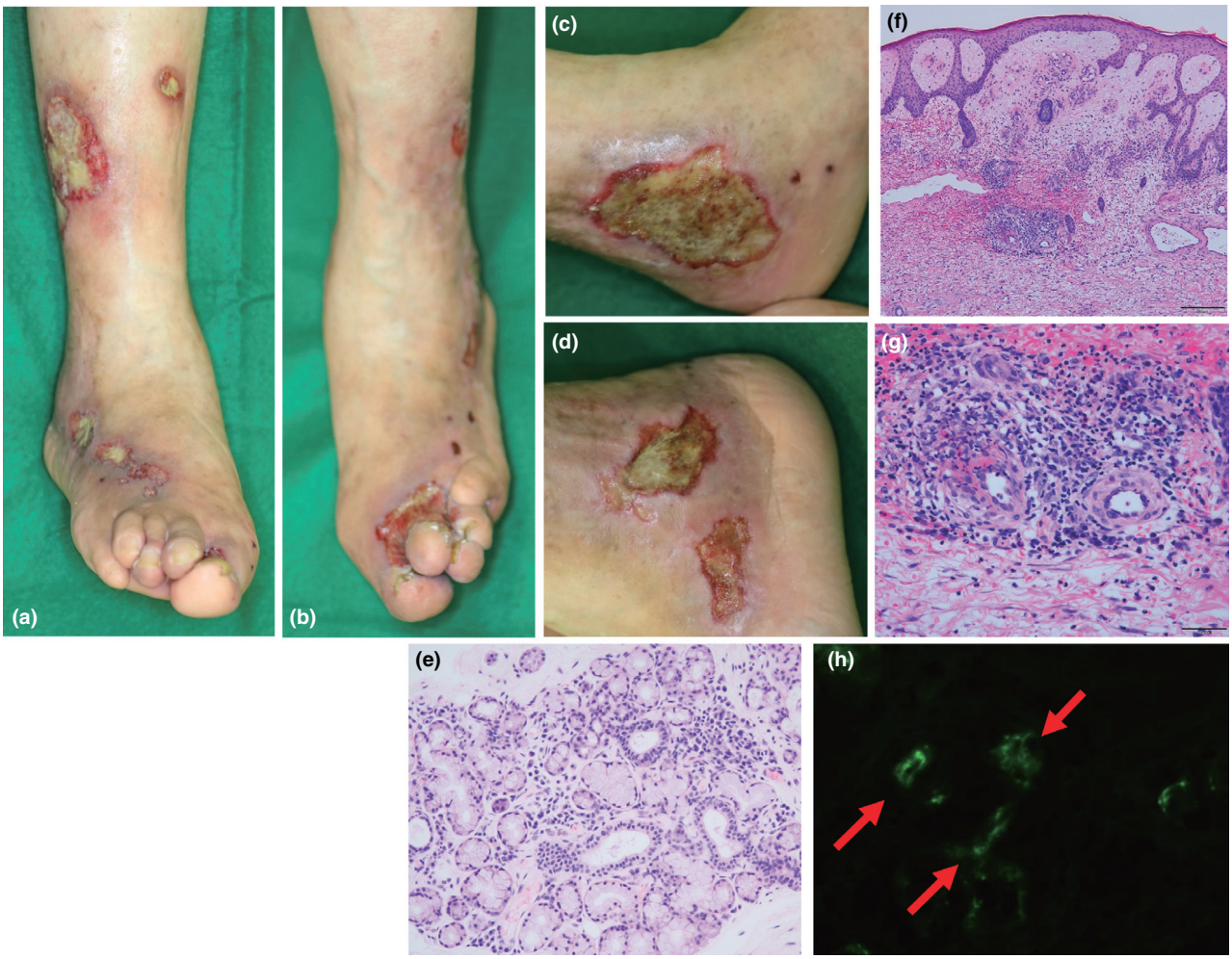

Figure 1. Clinical and histological features of the patient. (a–d) Multiple cutaneous ulcers are seen on the lower legs, ankles and feet. Deformities of the feet and toes and dilated varicose veins are seen. (e) The histopathology of the minor salivary gland in the lower lip shows infiltration of lymphocytes and plasma cells with interstitial fibrosis. (f,g) A biopsy specimen from the skin adjacent to the ulcer in the right leg shows hemorrhage in the upper dermis and infiltration of inflammatory cells consisting of lymphocytes, plasma cells and neutrophils with nuclear dust around the dermal blood vessels (bars: [e] 100 μ, [f] 100 μ, [g] 200 μ). (h) Immunofluorescence staining reveals C3 deposition (red arrows) on the vascular walls in the upper dermis.

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Systemic manifestations of primary Sjögren's syndrome out of the ESSDAI classification: prevalence and clinical relevance in a large international, multi-ethnic cohort of patients

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on behalf of the Sjögren Big Data Consortium

Affiliations: see page S-103.

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Key words: primary Sjögren's syndrome, ESSDAI, Raynaud's phenomenon, pleuritis, pericarditis, uveitis, congenital heart block, pulmonary arterial hypertension

Competing interests: see page S-104.

ABSTRACT

Objective. *To analyse the frequency and characterise the systemic presentation of primary Sjögren's syndrome (SS) out of the ESSDAI classification in a large international, multi-ethnic cohort of patients.*

Methods. *The Big Data Sjögren Project Consortium is an international, multicentre registry based on worldwide data-sharing and cooperative merging of pre-existing clinical SS databases from leading centres in clinical research in SS from the five continents. A list of 26 organ-by-organ systemic features not currently included in the ESSDAI classification was defined according to previous studies; these features were retrospectively recorded.*

Results. *Information about non-ESSDAI features was available in 6331 patients [5,917 female, mean age at diagnosis 52 years, mainly White (86.3%)]. A total of 1641 (26%) patients had at least one of the ESSDAI systemic features. Cardiovascular manifestations were the most frequent organ-specific group of non-ESSDAI features reported in our patients (17% of the total cohort), with Raynaud's phenomenon being reported in 15%. Patients with systemic disease due to non-ESSDAI features had a lower frequency of dry mouth (90.7% vs. 94.1%, p<0.001) and positive minor salivary gland biopsy (86.7% vs. 89%, p=0.033), a higher frequency of anti-Ro/SSA (74.7% vs. 68.7%, p<0.001), anti-La/SSB antibodies (44.5% vs. 40.4%, p=0.004), ANA (82.7% vs. 79.5%, p=0.006), low C3 levels (17.4% vs. 9.7%, p<0.001), low C4 levels (14.4% vs. 9.6%, p<0.001), and positive serum cryoglobulins (8.6% vs. 5.5%, p=0.001). Systemic activity measured by the ESSDAI, clinESSDAI and DAS was higher in patients with systemic disease out of the ESSDAI in comparison with those without these features (p<0.001 for all comparisons).*

Conclusion. *More than a quarter of patients with primary SS may have systemic manifestations not currently included in the ESSDAI classification, with a wide variety of cardiovascular, digestive, pulmonary, neurological, ocular, ENT (ear, nose, and throat), cutaneous and urological features that increase the scope of the systemic phenotype of the disease. However, the individual frequency of each of these non-ESSDAI features was very low, except for Raynaud's phenomenon.*

Introduction

Primary Sjögren's syndrome (SS) is a systemic autoimmune disease in which the immune system targets the exocrine glands (1). The disease affects women in more than 95% of reported cases, with a frequency ranging between 0.01 and 0.72% (2). The key clinical presentation of primary SjS is sicca syndrome, reported by more than 95% at the time of diagnosis (3), although patients may also develop a wide variety of systemic manifestations, which may even be the presenting manifestation (4).

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[ORIGINAL ARTICLE]

Hydroxychloroquine Improves the Disease Activity and Allows the Reduction of the Corticosteroid Dose Regardless of Background Treatment in Japanese Patients with Systemic Lupus Erythematosus

Hironari Hanaoka, Harunobu Iida, Tomofumi Kiyokawa,
Yukiko Takakuwa and Kimito Kawahata

Abstract:
Objective Hydroxychloroquine (HCQ) was not approved in Japan until 2015, and its therapeutic potential has not been explored in depth. We evaluated the additional therapeutic effect of HCQ in Japanese patients with systemic lupus erythematosus (SLE) on maintenance therapy.
Methods Patients with SLE who visited our hospital from 2015 to 2016 and were taking prednisolone (PSL) at <20 mg/day were retrospectively evaluated. All patients were divided into three groups according to their maintenance treatment regimen: PSL + immunosuppressant, PSL alone, and no treatment. We compared the changes in the SLE disease activity index (SLEDAI), PSL dose, and cumulative flare rate between patients who were and were not treated with HCQ.
Results Among the 165 patients evaluated, 35 (21.2%) were treated with HCQ. The mean period of observation did not differ markedly between patients who did and did not receive HCQ (p=0.3). The SLEDAI and PSL dose were significantly reduced in patients who received HCQ, regardless of their background treatment regimen. The cumulative flare rate was lower in patients who received HCQ than in those who did not in the PSL + immunosuppressant and no maintenance treatment groups (p=0.03 and 0.05, respectively).
Conclusion The addition of HCQ reduced the disease activity and allowed PSL dose reduction, regardless of background treatment, in Japanese patients with SLE.

Key words: systemic lupus erythematosus, hydroxychloroquine, SLEDAI

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Introduction

Hydroxychloroquine (HCQ) is an antimalarial drug that is recommended for patients with systemic lupus erythematosus (SLE) because of its beneficial effect on decreasing the risk of flares (1), diabetes mellitus (2), thrombotic events (3, 4), and dyslipidaemia (5). HCQ also reportedly reduces damage accrual (6) and improves the survival (7).

Many investigators have recently examined the association between the blood HCQ concentration and the clinical outcome (8-11). According to Mok et al., an increased concentration of HCQ is associated with a reduced number of flares in patients in clinical remission (8). Yeon et al. examined factors related to the blood HCQ concentration in SLE patients and concluded that taking an additional immunosuppressant other than a corticosteroid is associated with increased HCQ concentrations (9). Therefore, the therapeutic effect of HCQ may differ depending on the background treatment.

Given that HCQ was not approved in Japan until 2015, its therapeutic potential remains poorly understood in the Japanese population. In one study, a randomized trial showed that the mean cutaneous lupus erythematosus disease area and severity index (CLASI) were significantly improved in the HCQ group compared with the placebo group among

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Research letter

Antihelix/helix violaceous macules in Japanese patients with anti-melanoma differentiation-associated protein 5 (MDA5) antibody-associated dermatomyositis

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Dear Editor, The diagnosis of clinically amyopathic dermatomyositis (CADM) essentially depends on cutaneous manifestations. Early diagnosis of CADM associated with the anti-melanoma differentiation-associated protein-5 (MDA5) antibody is especially important because it includes a subset of patients highly at risk for rapidly progressive interstitial lung disease (RP-ILD) with potentially fatal outcomes.[1] Moreover, the recognition of distinctive rashes for anti-MDA5 antibody-positive DM can greatly aid in distinguishing from other DM subsets, as serological anti-MDA5 antibody testing is not yet widely accessible. These subsets include cutaneous ulcers, palmar violaceous papules/macules, alopecia and painful oral ulcers.[2–7] Here, we present another characteristic cutaneous manifestation: antihelix/helix violaceous macules.

A 57-year-old woman (case 1) was diagnosed with DM with heliotrope rash, Gottron papules, Gottron sign on the knees, seborrhoeic area erythema[8] on the forehead, V-neck sign, palmar violaceous macules/papules, and violaceous macules on the antihelices and helices (Fig. 1a) accompanied by ILD with a nonspecific interstitial pneumonia (NSIP) pattern. Muscle weakness of the limbs was observed. The patient tested positive for anti-MDA5 antibody in an enzyme-linked immunosorbent assay. The rash, myositis and ILD completely improved after administration of daily oral prednisolone (PSL; 40 mg) and tacrolimus (3 mg), biweekly intravenous cyclophosphamide (IVCY; 750 mg m^{-2}), and monthly intravenous immunoglobulins (IVIGs; 400 mg kg^{-1} per day for 5 days).

A 66-year-old man (case 2) was diagnosed with CADM with heliotrope rash, Gottron papules, Gottron sign on the elbows, palmar violaceous macules/papules, and violaceous macules on the antihelices and helices (Fig. 1b), accompanied by RP-ILD. The patient tested positive for anti-MDA5 antibody. He died from RP-ILD 1 month after treatment with daily oral PSL (70 mg) and tacrolimus (5 mg), biweekly IVCY, monthly IVIGs and methylprednisolone pulse therapy (1000 mg per day for 3 days).

A 69-year-old woman (case 3) had CADM with heliotrope rash, Gottron papules, palmar violaceous macules/papules, and violaceous macules on the antihelices and helices (Fig. 1c) accompanied by ILD (NSIP pattern). The patient tested positive for anti-MDA5 antibody. The rash and ILD completely improved after administration of daily oral PSL (50 mg) and tacrolimus (4 mg), biweekly IVCY, monthly IVIGs and methylprednisolone pulse therapy.

A 57-year-old woman (case 4) was diagnosed with DM with heliotrope rash, Gottron papules, seborrhoeic area erythema on the forehead and scalp, palmar violaceous macules/papules, and violaceous macules on the antihelices and helices (Fig. 1d), accompanied by ILD (NSIP pattern). Muscle weakness of the limbs was observed. The patient tested positive for anti-MDA5 antibody. The rash, myositis and ILD improved after administration of daily oral PSL (50 mg) and tacrolimus (3 mg), and monthly IVIGs; however, relapse marked by the rash and ILD occurred 1 year later.

A 59-year-old woman (case 5) was diagnosed with CADM and heliotrope rash, Gottron papules, Gottron sign on the

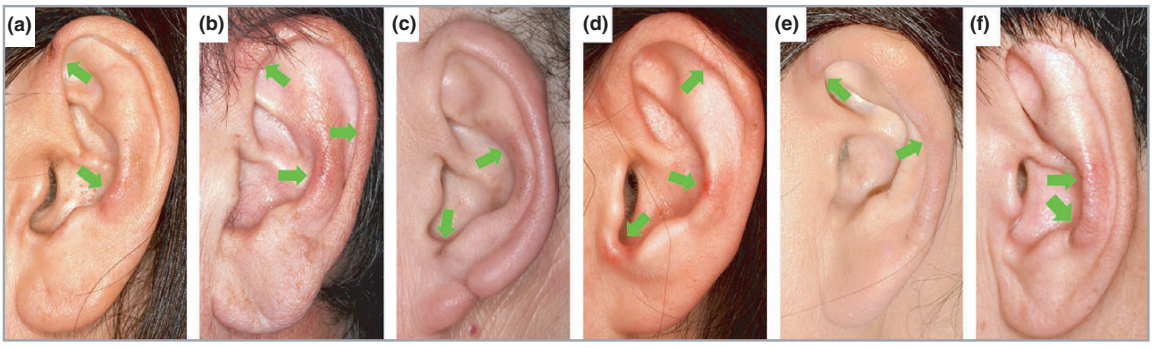

Fig 1. Antihelix/helix violaceous macules in cases 1 (a), 2 (b), 3 (c), 4 (d), 5 (e), and 6 (f).

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Original article

Serum matrix metalloproteinase levels in polymyositis/dermatomyositis patients with interstitial lung disease

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Abstract

Objective. We aimed to clarify the clinical significance of serum levels of MMPs in interstitial lung disease (ILD) complicated with PM/DM (PM/DM-ILD).

Methods. We retrospectively analysed serum levels of seven subsets of MMPs in 52 PM/DM-ILD patients diagnosed at Kyoto University Hospital or Tenri Hospital from January 2005 to December 2014. The patients were sub-grouped based on the presence of anti-amimoacyl-tRNA synthetase antibody (anti-ARS antibody), anti-melanoma differentiation-associated protein 5 antibody (anti-MDA5 antibody) or lack of the antibodies (ARS-ILD, MDA5-ILD and other-ILD groups, respectively) and independently analysed. Eighteen PM/DM patients without ILD and 55 healthy control were also analysed. Associations between serum levels of MMPs and clinical findings including mortality were analysed.

Results. Among the MMPs analysed, MMP-7 serum levels in the ARS-ILD group were significantly higher compared with those in any of the other groups of PM/DM patients or in healthy controls. On the other hand, in the MDA5-ILD group, serum MMP-7 levels >5.08 ng/ml were associated with worse overall survival both in univariate (P = 0.017; odds ratio 18.0; 95% CI 1.69, 192.00) and multivariate (P = 0.027; odds ratio 14.60; 95% CI 1.11, 192.00) analyses. Immunohistochemical analysis suggested that MMP-7 was expressed in type II alveolar epithelial cells adjacent to the fibrotic lesions.

Conclusion. Serum MMP-7 levels were higher in anti-ARS antibody-positive PM/DM-ILD patients, while higher serum MMP-7 levels among anti-MDA5 antibody-positive PM/DM-ILD patients were associated with a worse prognosis. Fibrotic processes may be associated with the elevation of serum MMP-7 levels.

Key words: polymyositis/dermatomyositis, interstitial lung disease, anti-MDA5 antibody, anti-ARS antibody, matrix metalloproteinase, fibrosis

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An extranodal histopathological analysis of idiopathic multicentric Castleman disease with and without TAFRO syndrome

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ABSTRACT

Thrombocytopenia, anasarca, fever, renal failure or reticulin fibrosis, and organomegaly (TAFRO) syndrome, a poor prognostic clinical condition showing similar histopathological findings to idiopathic multicentric Castleman disease (iMCD), has been reported in Japan. In our previous report, a clinicopathological analysis was performed on 70 nodal cases of iMCD with/without TAFRO. iMCD is classified into three types based on histopathology: (i) plasmacytic (PC), (ii) mixed, and (iii) hypervascular (hyperV). In this report, extranodal histopathological changes of iMCD with/without TAFRO were analyzed. Regarding the kidney pathology, we observed the proliferation of mesangial cells with positive staining of interleukin-6 (IL-6), consistent with membranoproliferative glomerulonephritis, in two cases of iMCD with TAFRO. The number of megakaryocytes per high-powered fields was not significantly different between iMCD cases with and without TAFRO. In conclusion, extranodal lesions of iMCD with/without TAFRO showed various interesting histopathological findings. These lesions may therefore be related to the clinical condition of TAFRO. Obtaining further knowledge about TAFRO will require the observation of nodal as well as extranodal lesions.

1. Introduction

Multicentric Castleman's disease (MCD) causes overproduction of interleukin-6 (IL-6) and shows various clinical conditions, such as fever, malaise, systemic lymphadenopathy, and multiple organ failure [1]. It also indicates various laboratory abnormalities, such as hypergammaglobulinemia, thrombocytosis, anemia, and elevation of C-reactive protein levels [1].

It is well-known that Human herpes virus^{-8} (HHV-8)-related MCD occur mainly in patients suffering from human immunodeficiency virus (HIV) infection. However, idiopathic MCD (iMCD) cases with HIV-negative and HHV-8-negative have been reported in Japan [2–4]. In addition, Fajgenbaum et al. [5] have recently described the presence of HIV-negative and HHV-8-negative iMCD in Western countries. They classified iMCD into three types based on histopathology: (i) plasmacytic (PC), (ii) mixed, and (iii) hypervascular (hyperV).

In 2010, the report from Takai et al. [6] showed three cases termed TAFRO syndrome displaying several common clinical symptoms, such as thrombocytopenia, anasarca, fever, renal failure or reticulin fibrosis, and organomegaly. The lymph node (LN) obtained from the TAFRO syndrome patients was histopathologically similar to hyaline-vascular type of CD, but they were clinically quite different from typical iMCD. Despite these findings, Fajgenbaum, et al. [5] later classified this characteristic syndrome as one phenotype type for MCD according to the histopathological similarity of LN lesions in iMCD.

In our previous report [7], a clinicopathological analysis was performed on 70 nodal cases of iMCD with/without TAFRO. The tissue of LN in PC-type histopathologically showed a characteristically atrophic lymphoid follicle (LF) and mild vascular proliferation at the germinal center (GC). Also, at the interfollicular area, a sheet-like infiltration of plasma cells was observed but vascular proliferation was very sparsely seen. In the mixed-type, atrophic to hyperplastic LF was formed, and

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ORIGINAL ARTICLE

Nintedanib for Systemic Sclerosis–Associated Interstitial Lung Disease

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ABSTRACT

BACKGROUND

Interstitial lung disease (ILD) is a common manifestation of systemic sclerosis and a leading cause of systemic sclerosis–related death. Nintedanib, a tyrosine kinase inhibitor, has been shown to have antifibrotic and antiinflammatory effects in preclinical models of systemic sclerosis and ILD.

METHODS

We conducted a randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of nintedanib in patients with ILD associated with systemic sclerosis. Patients who had systemic sclerosis with an onset of the first non-Raynaud's symptom within the past 7 years and a high-resolution computed tomographic scan that showed fibrosis affecting at least 10% of the lungs were randomly assigned, in a 1:1 ratio, to receive 150 mg of nintedanib, administered orally twice daily, or placebo. The primary end point was the annual rate of decline in forced vital capacity (FVC), assessed over a 52-week period. Key secondary end points were absolute changes from baseline in the modified Rodnan skin score and in the total score on the St. George's Respiratory Questionnaire (SGRQ) at week 52.

RESULTS

A total of 576 patients received at least one dose of nintedanib or placebo; 51.9% had diffuse cutaneous systemic sclerosis, and 48.4% were receiving mycophenolate at baseline. In the primary end-point analysis, the adjusted annual rate of change in FVC was −52.4 ml per year in the nintedanib group and −93.3 ml per year in the placebo group (difference, 41.0 ml per year; 95% confidence interval [CI], 2.9 to 79.0; P=0.04). Sensitivity analyses based on multiple imputation for missing data yielded P values for the primary end point ranging from 0.06 to 0.10. The change from baseline in the modified Rodnan skin score and the total score on the SGRQ at week 52 did not differ significantly between the trial groups, with differences of −0.21 (95% CI, −0.94 to 0.53; P=0.58) and 1.69 (95% CI, −0.73 to 4.12 [not adjusted for multiple comparisons]), respectively. Diarrhea, the most common adverse event, was reported in 75.7% of the patients in the nintedanib group and in 31.6% of those in the placebo group.

CONCLUSIONS

Among patients with ILD associated with systemic sclerosis, the annual rate of decline in FVC was lower with nintedanib than with placebo; no clinical benefit of nintedanib was observed for other manifestations of systemic sclerosis. The adverse-event profile of nintedanib observed in this trial was similar to that observed in patients with idiopathic pulmonary fibrosis; gastrointestinal adverse events, including diarrhea, were more common with nintedanib than with placebo. (Funded by Boehringer Ingelheim; SENSCIS ClinicalTrials.gov number, NCT02597933.)

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*A complete list of investigators in the SENSCIS trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Distler and Highland contributed equally to this article.

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ORIGINAL ARTICLE

The development of quality indicators for systemic lupus erythematosus using electronic health data: A modified RAND appropriateness method

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ABSTRACT

Objective: Quality indicators (QIs) are tools that standardize evaluations in terms of the minimum acceptable quality of care, presumably contributing for the better management of patients with systemic lupus erythematosus (SLE). This study aimed to develop QIs for SLE using electronic health data.

Methods: The modified RAND/UCLA Appropriateness Method was used to develop the QIs. First, a literature review was conducted. Second, the candidate QI items that were available to be evaluated using the electronic health data were extracted. Third, the appropriateness of the items was assessed via rating rounds and panelists' discussions.

Results: We found 3621 articles in the initial search. Finally, 34 studies were reviewed, from which 17 potential indicators were extracted as candidate QIs. Twelve indicators were selected as the final QI set through the process of appropriateness. The median appropriateness of these 12 indicators was at least 7.5, and all of them were without disagreement. The QI included assessment of disease activity, treatment of SLE, drug toxicity monitoring, treatment of glucocorticoid complications, and assessment of SLE complications.

Conclusion: We formulated 12 QIs for the assessment of patients with SLE based on electronic medical data. Our QI set would be a practical tool as a quality measure.

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KEYWORDS
Performance measures; quality indicators; quality measures; systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease of unknown cause. The frequency of related morbidities is said to be one in 1000–10,000 people. SLE can lead to significant organ damage involving the kidneys and central nervous system, ultimately causing serious conditions requiring multidisciplinary medical care.

The definition of practice quality is: 'Quality is the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge.' [1]. Tools used to increase the likelihood of desired health outcomes are clinical practice guidelines (CPGs). However, a routine practice sometimes deviates from the CPGs, and the gap between them is called the evidence practice gap. Quality indicators (QIs) can be used to quantify the evidence practice gap and evaluate certain therapeutic quality measures. Assessments of quality of care can improve patient

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ORIGINAL ARTICLE

High plasma mycophenolate acid concentration in the early phase of induction therapy predicts good renal outcome in lupus nephritis

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ABSTRACT

Objectives: To identify the prognostic predictive factor of complete renal response (CR) at week 12 by focusing on the plasma mycophenolic acid (MPA) concentration in induction therapy in lupus nephritis.

Methods: We prospectively enrolled patients with biopsy-proven LN class III/IV who were hospitalized between 2016 and 2017. As an induction therapy, mycophenolate mofetil was continuously introduced at 2000 mg/day. We measured the MPA plasma concentration at two time points depending on the induction therapy phase, early (week 4) or middle (week 12). The association between these concentrations and CR rate at week 12 was evaluated.

Results: Ten patients were enrolled. A significantly higher AUC_{0-12} between 0 and 12 h of MPA at the early phase was observed in the patients with CR at week 12 than in those without ($p = .03$). All the patients with high MPA-AUC_{0-12} (> 40 mg h/L) at the early phase achieved CR at week 12, but no such association was found at the middle phase. The multivariate analysis revealed that MPA-AUC0–12 was selected as an independent predictive factor of CR at week 12 (odds ratio: 1.12; 95% confidence interval: 1.01–1.45, $p = .02$).

Conclusion: The high AUC_{0-12} of MPA at the early phase of induction therapy may predict good renal response.

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KEYWORDS
Lupus nephritis; mycophenolate mofetil; mycophenolic acid; therapeutic drug monitoring

Introduction

Lupus nephritis (LN) is one of the most serious manifestations of systemic lupus erythematosus (SLE), affecting >50% of patients with SLE [1]. Mycophenolate mofetil (MMF) is recommended as an initial induction treatment for most cases of LN class III or IV [2,3]. MMF is an inactive prodrug that is converted to its active metabolite (mycophenolic acid [MPA]) by intestinal, liver and plasma esterases. Although the association between the area under the concentration-versus-time curve (AUC) of MPA and therapeutic efficacy has been well shown in renal transplantation [4], it has been poorly investigated in LN. Lertdumrongluk et al. recently reported the association between MPA-AUC and renal response at week 24 [5]. As we have shown previously [6], early renal response may predict good renal or systemic outcome; therefore, a predictive factor at the early phase of induction therapy, such as before week 24, has been required in clinical settings.

As MMF interacts with multiple factors, some advantages of measuring MPA concentration may be expected in LN as compared with renal transplantation. When glucuronic acid conjugation is promoted by prednisolone (PSL), MMF is converted to mycophenolic acid glucuronide (MPAG) as an inactive form. Thus, the AUC of MPA is reduced due to high-dose PSL [7]. Because hypoalbuminemia increases free MPA and clearance becomes larger, the AUC of MPA is reduced [8]. Because a glucuronic acid conjugated compound accumulates for the renal failure, the AUC of MPA is inversely correlated with a glomerular filtration rate [9]. Considering that these factors dramatically change in the induction phase of LN, the plasma concentration of MPA may also be changed by a fixed dose of MMF administration.

Here, we measured the AUC_{0-12} of MPA at different phases of the induction treatment, early and middle, and prospectively investigated which concentration predicted future renal response in LN class III or IV.

Materials and methods

Patients

We prospectively enrolled 10 Japanese patients with biopsy-proven LN class III or IV according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification, who were hospitalized at St. Marianna University Hospital between April 2016 and October 2017. All the patients completed the 6-month observation during the induction phase. Patients were enrolled if they fulfilled

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Performance of Candidate Serum Biomarkers for Systemic Sclerosis–Associated Interstitial Lung Disease

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Objective. Interstitial lung disease (ILD) in systemic sclerosis (SSc) runs a highly variable course, and prediction tools are highly desired. The aim of this study was to assess the diagnostic and prognostic performance of 4 candidate serum biomarkers for SSc-associated ILD.

Methods. Serum samples from a combined cohort of SSc patients (from Paris, France and Oslo, Norway; n = 427) were analyzed by enzyme-linked immunosorbent assay for concentrations of lung epithelial–derived surfactant protein D (SP-D), Krebs von den Lungen 6 glycoprotein (KL-6), CCL18, and OX40 ligand (OX40L). Lung fibrosis was measured by high-resolution computed tomography and pulmonary function tests. Associations of these candidate biomarkers with baseline disease involvement and prediction of disease progression over time (mean ± SD follow-up 3.2 ± 4.4 years) were investigated.

Results. In SSc patients at baseline, serum levels of KL-6 correlated with the forced vital capacity (FVC) (r = –0.317, $P < 0.001$), diffusing capacity for carbon monoxide (r = –0.335, $P < 0.001$), and extent of lung fibrosis (r = 0.551, $P < 0.001$). In multivariate analyses, serum levels of KL-6 and SP-D, but not CCL18 and OX40L, were associated with lung fibrosis (odds ratio [OR] 2.41, 95% confidence interval [95% CI] 1.43–4.07 [$P = 0.001$] and OR 3.15, 95% CI 1.81–5.48 [$P < 0.001$], respectively). In SSc patients with ILD at baseline, longitudinal, multivariate analyses showed that CCL18 serum levels were an independent predictor of a >10% decrease in the FVC (hazard ratio [HR] 2.90, 95% CI 1.25–6.73; $P = 0.014$) and de novo development of extensive disease (HR 3.71, 95% CI 1.02–13.52; $P = 0.048$). Matrix-based logistic regression models for the diagnosis and prognosis of SSc-associated ILD were constructed, and these models discriminated 3 groups of risk (mild, moderate, or high) for the diagnosis or worsening of lung fibrosis according to the serum levels of SP-D (for diagnosis) and serum levels of CCL18 (for progression of disease).

Conclusion. These results show that SP-D is a relevant diagnostic biomarker for SSc-associated ILD, whereas KL-6 could be used to assess the severity of lung fibrosis. CCL18 appears to be a potential predictive marker for progression of ILD in SSc.

INTRODUCTION

Interstitial lung disease (ILD) is common in systemic sclerosis (SSc), and despite recent advances in treatment, it remains the leading cause of death in patients with SSc (1–4). However, SSc-associated ILD is characterized by high heterogeneity: some patients have limited, nonprogressive fibrosis, while others will develop extensive fibrosis that rapidly progresses to respiratory failure (1,5). Until now, pulmonary function tests (PFTs) and high-resolution computed tomography (HRCT) have remained the mainstays not only for diagnosis, but also for prognosis of SSc-associated ILD, but there have been concerns regarding the potential for radiation exposure with HRCT (6,7).

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No potential conflicts of interest relevant to this article were reported.

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ORIGINAL ARTICLE

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A low perfusion-metabolic mismatch in ^{99m}Tl and ^{123}I-BMIPP scintigraphy predicts poor prognosis in systemic sclerosis patients with asymptomatic cardiac involvement

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Abstract

Aim: This study investigated the prognostic factors of cardiac death or cardiac failure using cardiac scintigraphy, echocardiography (UCG), and magnetic resonance imaging (MRI) in asymptomatic systemic sclerosis (SSc) patients.

Methods: We retrospectively evaluated SSc patients who had undergone cardiac scintigraphy using ^{99m}thallium (^{99m}Tl) and ^{123}I-β-methyl-P-iodophenyl-pentadecanoic acid (^{123}I-BMIPP), UCG, and cardiac MRI. We calculated the mismatch score in scintigraphy by subtracting the uptake of ^{123}I-BMIPP from that of ^{99m}Tl. Patients were divided into two groups according to whether they survived with no cardiac failure or subsequently proceeded to cardiac failure or death during the study period. We identified prognostic factors by analyzing ^{99m}Tl and ^{123}I-BMIPP uptake, mismatch scores, UCG findings, and cardiac delayed enhancement on MRI. We also evaluated pathological evidence of myocardial fibrosis.

Results: Of 33 SSc cases, 11 proceeded to cardiac failure or death. There was no significant difference in UCG or MRI findings between the two groups. Low mismatch score in cardiac scintigraphy was the only predictive factor of cardiac failure or death by multivariate analysis (odds ratio, 6.48; 95% confidence interval, 1.22-423.2; $P = 0.01$). When patients were grouped according to high or low mismatch scores based on a cut-off using receiver operating characteristics curve analysis, the cumulative incidence of cardiac failure or death was higher in the low mismatch group than in the high mismatch group ($P = 0.02$). The percentage of fibrosis was significantly higher in deceased cases compared to surviving cases.

Conclusions: Low mismatch score in cardiac scintigraphy was associated with cardiac death or cardiac failure in SSc patients.

KEYWORDS

cardiac involvement, cardiac scintigraphy, systemic sclerosis

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Pathogenic roles of anti-C1q antibodies in recurrent pregnancy loss

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ABSTRACT

Recurrent pregnancy loss (RPL) is often considered idiopathic, however excessive complement activation has been observed in pregnancy related manifestations. Anti-C1q antibodies (anti-C1q) are associated with the activation of complement pathway in lupus patients, while it remains unclear in RPL. Firstly, we showed that both the prevalence and titre of anti-C1q were significantly higher in unexplained RPL than in healthy parous individuals. Secondly, we established the murine model of anti-C1q induced pregnancy loss using a monoclonal anti-mouse C1q antibody, JL-1. In mice treated with JL-1, high ratio of pregnancy loss and fetal growth restriction were frequently observed and complement activation occurred. C5a receptor (C5aR) blockade cancelled these pathogenic changes in mice treated with JL-1. In conclusion, our study reveals an association between the prevalence of anti-C1q and RPL. Additionally, our murine model has indicated that anti-C1q can induce reproductive failure, which might be ameliorated by therapy targeting the C5-C5aR axis.

1. Introduction

Recurrent pregnancy loss (RPL) is a heterogeneous clinical condition characterized by the occurrence of two or more failed clinical pregnancies [1]. The causes of RPL include genetic alterations, female genital tract malformations, endocrine diseases and antiphospholipid antibodies. However, up to 50% of RPL cases are of unknown etiology, being termed unexplained RPL [2]. Among those unexplained RPL, autoimmunity would be one of the most plausible pathophysiology, although the autoantigens have not been clearly identified.

In pregnancy, maternal immune system tolerates the semi-allogenic fetus whose tissues are directly exposed to the maternal blood with the potential for attack by the maternal innate and acquired immune systems. Tolerance at the feto-maternal interface in mice is regulated by the local expression of complement regulating proteins, such as CD55 (decay-accelerating factor, DAF), CD59, CD46 (membrane cofactor protein, MCP) and complement receptor 1-like protein y (Crry) and/or some population of regulatory T cell (Treg) induced by exogenous antigens in the periphery [3–6]. Foetal loss occurs when these mechanisms are dysregulated. Excessive complement activation was observed in several murine models, such as the allogeneic murine model, lipopolysaccharide (LPS)-induced miscarriage model, and antibody-mediated foetal loss model [7–11]. The immune regulatory network at the feto-maternal interface is thought to play a key role in preventing infertility, RPL, preeclampsia, foetal growth restriction and premature birth.

Complement system is a component of innate immunity that not only neutralizes infectious agents but also promotes removal of immune complexes and apoptotic cells. In addition, the acquired immune system is collaborating with complement system via activated complement fragments, such as the anaphylatoxins C5a, C3a [12–16]. Plasma levels of complement components are increased and complement deposition in placental tissue is observed in healthy individuals as well as in complicated pregnancies [17–22]. C1q, the sub-component of the C1 protein, is a key molecule in innate immunity that triggers the activation of the classical pathway of the complement system. C1q plays a regulatory role in pregnancy maintenance such as in trophoblast migration, spiral artery remodeling and normal placentation, resulting in foetal survival [23]. Moreover, C1q at the feto-maternal interface is presumed to be involved in preventing pathogen entry through the placenta. Excessive complement activation induces foetal loss in the antibody-mediated pregnancy loss model, due to triggering of abnormal complement activation by antiphospholipid antibodies, which overwhelms the physiological complement regulatory proteins [10,24,25].

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JAMA | Original Investigation

Effect of Filgotinib vs Placebo on Clinical Response in Patients With Moderate to Severe Rheumatoid Arthritis Refractory to Disease-Modifying Antirheumatic Drug Therapy
The FINCH 2 Randomized Clinical Trial

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IMPORTANCE Patients with active rheumatoid arthritis (RA) despite treatment with biologic disease-modifying antirheumatic drug (bDMARD) therapy need treatment options.

OBJECTIVE To evaluate the effects of filgotinib vs placebo on the signs and symptoms of RA in a treatment-refractory population.

DESIGN, SETTING, AND PARTICIPANTS A 24-week, randomized, placebo-controlled, multinational phase 3 trial conducted from July 2016 to June 2018 at 114 sites internationally, randomizing 449 adult patients (and treating 448) with moderately to severely active RA and inadequate response/intolerance to 1 or more prior bDMARDs.

INTERVENTIONS Filgotinib, 200 mg (n = 148); filgotinib, 100 mg (n = 153); or placebo (n = 148) once daily; patients continued concomitant stable conventional synthetic DMARDs (csDMARDs).

MAIN OUTCOMES AND MEASURES The primary end point was the proportion of patients who achieved 20% improvement in the American College of Rheumatology criteria (ACR20) at week 12. Secondary outcomes included week 12 assessments of low disease activity (disease activity score in 28 joints–C-reactive protein [DAS28-CRP] ≤3.2) and change in Health Assessment Questionnaire–Disability Index, 36-Item Short-Form Health Survey Physical Component, and Functional Assessment of Chronic Illness Therapy–Fatigue scores, as well as week 24 assessment of remission (DAS28-CRP <2.6) and adverse events.

RESULTS Among 448 patients who were treated (mean [SD] age, 56 [12] years; 360 women [80.4%]; mean [SD] DAS28-CRP score, 5.9 [0.96]; 105 [23.4%] with ≥3 prior bDMARDs), 381 (85%) completed the study. At week 12, more patients receiving filgotinib, 200 mg (66.0%) or 100 mg (57.5%), achieved ACR20 response (placebo, 31.1%; difference vs placebo: 34.9% [95% CI, 23.5%-46.3%] and 26.4% [95% CI, 15.0%-37.9%], respectively; both $P < .001$), including among patients with prior exposure to 3 or more bDMARDs (70.3%, 58.8%, and 17.6%, respectively; difference vs placebo: 52.6% [95% CI, 30.3%-75.0%] for filgotinib, 200 mg, and 41.2% [95% CI, 17.3%-65.0%] for filgotinib, 100 mg; both $P < .001$). The most common adverse events were nasopharyngitis (10.2%) for filgotinib, 200 mg; headache, nasopharyngitis, and upper respiratory infection (5.9% each) for filgotinib, 100 mg; and RA (6.1%) for placebo. Four uncomplicated herpes zoster cases and 1 retinal vein occlusion were reported with filgotinib; there were no opportunistic infections, active tuberculosis, malignancies, gastrointestinal perforations, or deaths.

CONCLUSIONS AND RELEVANCE Among patients with active RA who had an inadequate response or intolerance to 1 or more bDMARDs, filgotinib, 100 mg daily or 200 mg daily, compared with placebo resulted in a significantly greater proportion achieving a clinical response at week 12. However, further research is needed to assess longer-term efficacy and safety.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02873936

Visual Abstract

Editorial page 309

Supplemental content

CME Quiz at jamanetwork.com/learning and CME Questions page 359

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patients were male; the majority (10; 67%) were non-Hispanic white with mean age 53 years. Six of the 9 participants who enrolled for 4 weeks continued for 12 weeks. There was no difference in the mean percent change in *GLI1* mRNA levels between itraconazole and placebo groups at 4 weeks (132% vs 19.0% from baseline; $P = .20$). There was no statistically significant difference in the percent change in tumor area between itraconazole and placebo at 4 weeks (0.04% vs −10.9% from baseline; $P = .40$) and 12 weeks (8.9% vs 26.5%; $P = .40$). In post hoc analysis, the itraconazole group showed reduced BCC tumor area in the subgroup of BCCs located on the back; however, given multiple testing for different anatomic locations, this difference was ultimately not statistically significant. Using liquid chromatography–mass spectrometry, intratumor itraconazole concentration was 133 µg/g of skin at 4 weeks and 96 µg/g at 12 weeks. There was no association between change in BCC tumor area and *GLI1* mRNA levels. Other major metabolites such as hydroxy-itraconazole were not measured given their weaker half maximal inhibitory concentrations (IC_{50}).

One patient had grade 1 liver function test abnormalities at weeks 4 and 12, but this patient had fatty liver disease. Plasma itraconazole levels were undetectable after 4 and 12 weeks, except for 1 patient with a plasma level of 4.12 ng/mL. Topical itraconazole caused only grade 1 to2 adverse effects: application site reaction (n = 4), pruritus (n = 4), lesion pain (n = 3), dysgeusia (n = 1), and xerosis (n = 1). These adverse effects resolved by the end of the study except in 2 patients who had persistent mild lesion pain, pruritus, and xerosis.

Discussion | Itraconazole, 0.7%, gel appears safe, is associated with intratumor drug concentrations after 4 weeks, and is not associated with systemic absorption. However, topical itraconazole failed to reduce *GLI1* mRNA levels and tumor area. Topical and oral itraconazole are associated with BCC shrinkage in mice,[4] but topical penetration in humans is more difficult owing to a thicker epidermis.

Conclusions | Itraconazole gel at the maximally soluble formulation of 0.7% did not reduce *GLI1* mRNA levels and BCC tumor size. However, this study does not rule out whether other formulations of itraconazole at higher concentrations may be more effective.

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Author Contributions: Dr Tang had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Kwon, Oro, Tang.
Acquisition, analysis, or interpretation of data: Sohn, Kwon, Bailey-Healy, Mirza, Sarin, Tang.
Drafting of the manuscript: Sohn, Bailey-Healy, Tang.
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Statistical analysis: Sohn, Mirza, Tang.
Obtained funding: Oro, Tang.
Administrative, technical, or material support: Bailey- Healy, Sarin, Oro, Tang.
Study supervision: Kwon, Oro, Tang.

Conflict of Interest Disclosures: Dr Tang is a director of and holds stock in PellePharm Inc and holds a provisional patent for topical itraconazole. No other disclosures were reported.

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Distinct Histopathologic Patterns of Finger Eruptions in Dermatomyositis Based on Myositis-Specific Autoantibody Profiles

A number of myositis-specific autoantibodies have been identified in patients with dermatomyositis (DM), including anti-aminoacyl-transfer RNA synthetase (ARS), antimelanoma differentiation-associated protein 5 (MDA5), and antitranscriptional intermediary factor 1 (TIF1)γ antibodies, each of which is respectively associated with characteristic cutaneous manifestations.[1,2] We analyzed the histologic findings of finger lesions based on these 3 myositis-specific autoantibodies.

Supplemental content

Methods | This retrospective observational study was performed on patients with DM diagnosed with typical rash and the presence of anti-ARS, anti-MDA5, and TIF1γ antibodies detected using enzyme-linked immunosorbent assay kits (Medical and Biological Labratories) in our dermatology departments from September 2007 to August 2018. We found 74 cases (30, 19, and 25 cases in the ARS, MDA5, and TIF1γ groups, respectively) where patients underwent skin biopsies of finger eruptions (eTable in the Supplement). The medical ethics review committee of each hospital exempted this study from ethical approval and waived the need for patient written informed consent because all data used were

CLINICAL SCIENCE

Outcomes of patients with systemic sclerosis treated with rituximab in contemporary practice: a prospective cohort study

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ABSTRACT

Objective To assess the safety and efficacy of rituximab in systemic sclerosis (SSc) in clinical practice.

Methods We performed a prospective study including patients with SSc from the European Scleroderma Trials and Research (EUSTAR) network treated with rituximab and matched with untreated patients with SSc. The main outcomes measures were adverse events, skin fibrosis improvement, lung fibrosis worsening and steroids use among propensity score-matched patients treated or not with rituximab.

Results 254 patients were treated with rituximab, in 58% for lung and in 32% for skin involvement. After a median follow-up of 2 years, about 70% of the patients had no side effect. Comparison of treated patients with 9575 propensity-score matched patients showed that patients treated with rituximab were more likely to have skin fibrosis improvement (22.7 vs 14.03 events per 100 person-years; OR: 2.79 [1.47–5.32]; p=0.002). Treated patients did not have significantly different rates of decrease in forced vital capacity (FVC)>10% (OR: 1.03 [0.55–1.94]; p=0.93) nor in carbon monoxide diffusing capacity (DLCO) decrease. Patients having received rituximab were more prone to stop or decrease steroids (OR: 2.34 [1.56–3.53], p<0.0001). Patients treated concomitantly with mycophenolate mofetil had a trend for better outcomes as compared with patients receiving rituximab alone (delta FVC: 5.22 [0.83–9.62]; p=0.019 as compared with controls vs 3 [0.66–5.35]; p=0.012).

Conclusion Rituximab use was associated with a good safety profile in this large SSc-cohort. Significant change was observed on skin fibrosis, but not on lung. However, the limitation is the observational design. The potential stabilisation of lung fibrosis by rituximab has to be addressed by a randomised trial.

Key messages

What is already known about this subject?

- Some efficacy of rituximab in systemic sclerosis (SSc) has been suggested by few small-sized uncontrolled studies. Large controlled studies were lacking.

What does this study add?

- Rituximab is safe in SSc.
- Treatment with rituximab improves skin fibrosis, which is a marker of disease activity and severity as compared with untreated control-patients.
- No significant change was observed on lung fibrosis in the whole cohort.
- Secondary analyses suggest that combination therapy with mycophenolate mofetil might be more effective for treating lung fibrosis.

How might this impact on clinical practice or future developments?

- A clue for the future to get a better impact on SSc outcomes might be combination therapy, which should be further studied.

INTRODUCTION

Systemic sclerosis (SSc) is an orphan disease that is characterised by fibrosis of the skin and internal organs, autoimmunity and vasculopathy.[1] SSc has the highest cause-specific mortality among connective tissue diseases.[2] Progressive interstitial lung disease (ILD) is the leading cause of death in SSc.[3] Despite the fatal burden associated with this condition, treatment options for SSc remain limited.[4] Preliminary case-reports and series have suggested that rituximab, a chimeric monoclonal antibody targeting B cells, could improve

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ORIGINAL ARTICLE

KL-6 is a long-term disease-activity biomarker for interstitial lung disease associated with polymyositis/dermatomyositis, but is not a short-term disease-activity biomarker

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ABSTRACT

Objectives: We aimed to evaluate the usefulness of serum KL-6 for interstitial lung disease (ILD) with polymyositis/dermatomyositis (PM/DM).

Methods: All consecutive and previously untreated adult patients with PM/DM who were admitted to our hospital from 2010 to 2015 were included. The associations between serum KL-6 levels and clinical information were retrospectively analyzed.

Results: Baseline serum KL-6 levels were significantly higher in patients with ILD than in those without ($n = 41$ and 15, respectively; $p < .001$). In the 14 patients whose ILD improved within 4 weeks post-treatment, their serum KL-6 levels did not significantly decrease at 2 weeks, 4 weeks, or 3 months post-treatment ($p = 1.00$, 1.00, and .83, respectively). Conversely, their serum KL-6 levels significantly decreased at 6, 9, and 12 months post-treatment ($p = .01$ in all comparisons). In the 12 patients whose ILD remained unchanged or deteriorated in 4 weeks post-treatment, only the difference between their serum KL-6 levels at 3 and 12 months was significant ($p = .003$).

Conclusions: The present study validated the serum KL-6 as a diagnostic marker for ILD in PM/DM. However, serum KL-6 is not a short-term disease-activity biomarker for ILD with PM/DM, but it is a long-term disease-activity biomarker.

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Dermatomyositis; interstitial lung disease; KL-6; polymyositis

Introduction

Polymyositis (PM) and dermatomyositis (DM) are characterized clinically by weakness and low skeletal muscle endurance [1–4]. In addition, a subset of patients with DM who have cutaneous lesions in the absence of muscle weakness are known as clinically amyopathic dermatomyositis (CADM) [2]. Interstitial lung disease (ILD) is a frequent pulmonary manifestation and an important cause of morbidity and mortality in patients with PM/DM [5–7]. Its prevalence varies from 19.9 to 86% in published reports [5]. The initial presentation and clinical course of ILD in PM/DM are heterogeneous, and its management is complex and requires close patient follow-up. Some patients are even asymptomatic, so ILD may be an incidental finding on a radiologic examination [5]. In contrast, rapidly progressive (RP)-ILD, mostly complicated with CADM and/or the presence of anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibodies, is a life-threatening complication [8,9]. Early and accurate diagnosis of ILD is critical to prevent the development from initial inflammatory activity (alveolitis) to end-stage disease with irreversible honeycombing and fibrosis [10].

High-resolution computed tomography (HRCT), bronchoscopic examination, and/or surgical lung biopsy are fundamental steps required to make a definite diagnosis of various ILDs [11]. Furthermore, serial pulmonary function tests (PFTs) are generally used to monitor disease activity and/or predict the prognosis in patients with ILDs. However, these tests are not always sensitive and are sometimes nonspecific [10]. Furthermore, PFTs are not always easily available, and repeated radiological examinations are limited in terms of radiation exposure [10,11]. Thus, identification of serum biomarkers would greatly benefit the management of ILD. For example, we have previously reported that high levels of serum ferritin are associated with the severity and prognosis of RP-ILD with PM/DM, particularly in patients harboring anti-MDA5 antibodies [8,12,13]. However, ferritin is not useful for the assessment of chronic or slowly-progressive ILD.

A high-molecular-weight glycoprotein, Krebs von den Lungen-6 (KL-6), which is classified as a human MUC1 mucin protein, is an established biomarker for ILD [11,14]. Serum KL-6 levels are elevated in 70–100% of patients with various ILDs, including idiopathic interstitial pneumonia, connective tissue disease-associated ILD, hypersensitivity pneumonia, radiation pneumonitis, drug-induced ILDs, acute respiratory distress syndrome, pulmonary sarcoidosis, and pulmonary alveolar proteinosis. As summarized in the review paper [11], the primary cellular source of KL-6 in the affected lungs of patients with ILDs is regenerating type

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ORIGINAL ARTICLE

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Hepatitis B virus reactivation with corticosteroid therapy in patients with adrenal insufficiency

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Abstract

Objective: Whether or not reactivation of hepatitis B virus (HBV) might occur during corticosteroid therapy in hepatitis B surface antigen (HBsAg)-negative patients with adrenal insufficiency was investigated.

Patients and Methods: We consecutively enrolled 66 patients with adrenal insufficiency undergoing physiological corticosteroid replacement therapy at Saitama Medical University Hospital between June 2013 and June 2014, and 220 patients with rheumatic disease receiving a pharmacologic dose of corticosteroids served as the positive control group. The latter group was separated into 101 patients treated only with corticosteroids, and 119 patients given corticosteroids plus immunosuppressants and/or disease-modifying antirheumatic drugs (DMARDs). HBsAg and antibody (Ab) levels against HBs, and hepatitis B core (HBc) were determined in all the patients. In patients with positive HBsAb and/or HBcAb, real-time PCR was performed for HBV-DNA. The incidence rates of conversion to HBV-DNA-positive status were evaluated.

Results: Hepatitis B virus reactivation occurred in six patients with rheumatic disease, three of whom were receiving a pharmacological dose of corticosteroids only, and three who were receiving corticosteroids with immunosuppressants and/or DMARDs. However, no reactivation occurred in patients receiving corticosteroid replacements for adrenal insufficiency. Maintenance and maximum corticosteroid doses administered to patients with rheumatic disease were significantly greater than those in patients with adrenal insufficiency.

Conclusion: These results suggest that, although corticosteroid replacement therapy for adrenal insufficiency might be safe with respect to HBV reactivation, attention should be paid to HBV reactivation during corticosteroid therapy in rheumatic disease patients, since the dose of corticosteroids administered is usually large, and since other immunosuppressants are co-administered.

KEYWORDS
adrenal insufficiency, corticosteroids, hepatitis B virus reactivation, rheumatic disease

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Clinical significance of serum CXCL9 levels as a biomarker for systemic juvenile idiopathic arthritis associated macrophage activation syndrome

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ABSTRACT

To clarify cytokines involved in the development of systemic juvenile idiopathic arthritis (s-JIA) associated macrophage activation syndrome (MAS) and to identify the serum biomarkers for the diagnosis of s-JIA associated MAS, we employed an antibody array that simultaneously detects 174 cytokines. Fifteen s-JIA patients including 5 patients receiving tocilizumab (TCZ) were analyzed. The levels of five cytokines were significantly elevated in MAS phase compared to those in the active phase of s-JIA. CXCL9 showed the most significant increase following the development of s-JIA associated MAS. Next, to confirm clinical significance of serum CXCL9 levels as a biomarker for s-JIA associated MAS, serum CXCL9 levels in 56 patients with s-JIA including 20 with MAS were analyzed. Results were compared with the clinical features of s-JIA associated MAS. Serum CXCL9 levels correlated positively with disease activity. Monitoring of serum CXCL9 is useful for the evaluation of disease activity in s-JIA associated MAS.

1. Introduction

Systemic juvenile idiopathic arthritis (s-JIA) is characterized by chronic arthritis accompanied by high fever and other systemic symptoms, including salmon-pink evanescent rash, hepatosplenomegaly, lymphadenopathy, and serositis [1]. It has been suggested that s-JIA is an auto-inflammatory condition and aberrant induction of proinflammatory cytokines, such as interleukin (IL)-6, IL-1β, and IL-18, may be involved in the pathogenesis of s-JIA and correlate with disease activity [2].

Macrophage activation syndrome (MAS) is a severe complication of s-JIA, which is clinically characterized by fever, hepatosplenomegaly, lymphadenopathy, profound depression of all three blood cell lines, impaired liver function, intravascular coagulation, and central nervous system dysfunction [3]. Examination of bone marrow shows a feature of numerous macrophages exhibiting hemophagocytosis. MAS is considered as a secondary hemophagocytic lymphohistiocytosis (HLH) because of its close resemblance to a group of HLH syndromes [4,5].

The hallmark of MAS is an uncontrolled and dysfunctional immune response, which leads to marked hypercytokinemia [6]. There is accumulating evidence regarding the role of IL-18 as a key driver of both s-JIA and potentially its association with s-JIA associated MAS [7–11]. Although IL-1 and IL-6 are key cytokines in the pathogenesis of s-JIA, IL-18 may play a central role in the pathogenesis of s-JIA associated MAS. However, the cytokines involved in the pathogenesis of s-JIA associated remain to be determined.

Tocilizumab (TCZ) – a humanized anti-IL-6 receptor monoclonal antibody – is an effective cytokine inhibitor for the treatment of s-JIA, with demonstrated clinical efficacy [12,13]. Studies have reported that clinical symptoms and laboratory abnormalities were milder in patients with s-JIA receiving TCZ than in those not receiving TCZ [14,15]. In particular, the concentration of serum C-reactive protein (CRP) did not increase during TCZ therapy, even in patients with MAS. Inhibition of IL-6 by TCZ may induce suppression of the production of inflammatory cytokines [14]. However, the cytokine cascades affected by TCZ in s-JIA associated MAS remain to be determined.

MAS is a potentially life-threatening disease. Therefore, prompt diagnosis is essential to initiate life-saving treatment. However, distinguishing s-JIA associated MAS from s-JIA flares, sepsis, or other secondary HLH may be challenging. Differentiation of s-JIA associated MAS from these conditions is essential for the selection of an appropriate therapeutic intervention in a timely fashion. However, currently,

Abbreviations: s-JIA, systemic juvenile idiopathic arthritis; MAS, macrophage activation syndrome; IL, interleukin; HLH, hemophagocytic lymphohistiocytosis; TCZ, tocilizumab; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; HC, healthy children; sTNFR, soluble tumor necrosis factor receptor; IFN, interferon

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Cluster of differentiation 30 expression in lacrimal gland and conjunctival tissues in patients with Sjögren's syndrome

Case series

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Abstract

Introduction: Sjögren's syndrome (SS) often causes lymphoproliferative disorders such as malignant lymphoma and macroglobrinemia. Approximately 5% of long-term follow-up SS patients develop malignant lymphoma. Recently, the tumor necrosis factor receptor superfamily cluster of differentiation 30 (CD30) has been thought to be implicated in malignant cells in organs affected by Hodgkin lymphoma or in a prognostic marker of diffuse large B cell lymphoma. In this study, we investigated CD30 expression in lacrimal gland and conjunctiva in patients with SS.

Methods: We examined lacrimal gland and conjunctival tissues for the diagnosis from 3 female SS patients with a median age of 51 and 3 female chronic graft-versus-host disease (cGVHD) patients with a median age of 41. Histological analysis of these tissues of the remaining samples was conducted by methods including immunohistochemistry and electron microscopy (#20090277). We analyzed the expression and localization of cluster of differentiation 4 (CD4), cluster of differentiation 8 (CD8), cluster of differentiation 20 (CD20), CD30, and Interferon-γ in tissue sections prepared from lacrimal glands and conjunctiva in 3 each of SS and cGVHD patients.

Results: There were more B cells and plasma cells in lobules of SS-affected lacrimal glands than in those of their cGVHD-affected counterparts. Interferon-γ was expressed on endothelia of capillaries in SS-affected lacrimal gland and conjunctival tissues whereas it was expressed on fibroblasts in their GVHD-affected equivalents. Furthermore, lacrimal glands and conjunctiva disordered by SS had a greater number of $CD30^+$ cells than those disordered by cGVHD.

Conclusion: Our results suggest that $CD30^+$ cells are increased in lacrimal glands and conjunctiva affected by SS and that a subset of SS patients are thereby at risk of development malignant lymphoma.

Abbreviations: ACR = American College of Rheumatology, ALCL = anaplastic large cell lymphoma, CD = cluster of differentiation, CHL = classical Hodgkin lymphoma, DLBCL = diffuse large B-cell lymphoma, EULAR = European League Against Rheumatism, GVHD = graft-versus-host disease, HE = Hematoxylin & Eosin, HL = Hodgikin lymphoma, IFN-γ = Interferron-γ, kd = kilodalton, MHC = major histocompatibility antigen, ML = malignant lymphoma, OCT = optical cutting temperature, RA = rheumatoid arthritis, SS = Sjögren's syndrome, TNFR = tumor necrosis factor receptor.

Keywords: cluster of differentiation 30, conjunctiva, lacrimal glands, malignant lymphoma, Sjögren's syndrome

1. Introduction

Sjögren's syndrome (SS) is characterized by inflammatory cell infiltration into lacrimal glands, salivary glands, and other exocrine glands, leading to dry eye, dry mouth, and extra-glandular syndrome.[1] SS is an autoimmune disease and a third of SS patients develop systemic complications including pulmonary, renal, neurological disorders, hematological, and musculoskeleton.[2] There are 2 types of SS—one is primary SS without

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Prognosis of dysphagia in dermatomyositis

Sirs,

Dysphagia is relatively common complication in dermatomyositis (DM), with 18–58% of patients reported to have this manifestation (1-4). Although risk factors of dysphagia in DM and polymyositis are reported to be age, male gender, anti-TIF1-γ antibody, muscle weakness, and malignancy (5, 6), there is very little published data on the prevalence, treatment outcomes and prognosis of dysphagia in patients with DM.

In this research, which features a cohort of patients with DM, our aims were to (i) reveal the appropriate treatment types and intervention timing for dysphagia recovery, and (ii) identify risk factors for non-recovery from dysphagia.

Serum samples were obtained from adult Japanese patients with DM followed at each medical centre from 2003 to 2016. Detailed medical histories of every patient were retrospectively gathered by unified questionnaire. Eighty-five patients fulfilled the "definite to probable" criterion of Bohan and Peter (7). Autoantibody detection and statistical methods were the same as in our previous study (8). This study was approved by the Ethics Committee of the Nagoya University Graduate School of Medicine and by the individual participating centres.

Of 85 DM patients, 57 (67%) were female. The mean age at DM diagnosis was 61.0±13.9 years. 30 patients were considered to have dysphagia as determined by subjective symptoms judged by their physician's evaluation (10 of 30), examination by otolaryngologists (14 of 30), or examination by speech therapists (5 of 30). The clinical and laboratory characteristics of the 85 DM patients with and without dysphagia are detailed in Supplementary Table S1.

Of the 30 DM patients with dysphagia, we analysed 29 patients' data, excluding one patient with insufficient data (Table I). Sixteen of the 29 patients showed recovery with dysphagia. Survival rates showed strong association with dysphagia recovery (p=0.000003), and high initial dose of prednisolone (PSL) seemed to influence the recovery rate (p=0.045). There was a significant negative correlation between cancer and dysphagia recovery (p=0.025). Other factors, such as age, sex, periods from onset to hospital visit or treatment, intravenous immunoglobulin (IVIG) or other immunosuppressive therapy use did not significantly correlate with dysphagia recovery.

Of the 29 dysphagia-complicated DM patients, 13 patients (33%) died during the follow-up period: 5 from cancer complications (38%), 3 from aspiration pneumonia, and 5 from various other causes. The mean follow-up duration was 15.1±15.5 months. Kaplan-Meier survival curves show the survival probability for patients with or without dysphagia recovery (Supplementary Fig. S1). The mortality rate is significantly higher in patients without recovery from dysphagia than in patients with recovery from dysphagia (p<0.000001).

Table I. Association between recovery from dysphagia and clinical/laboratory features.

	Improvement of dysphagia		p-value
	(+) n=16 (%)	(-) n=13 (%)	
Age	69.1 ± 7.3	72.5 ± 7.7	0.50
Sex (female)	7 (44)	6 (46)	1
Period (months)			
DM onset to dysphagia*	2.4 ± 2.5	1.6 ± 0.9	0.11
Visit to dysphagia**	0.6 ± 1.1	1.4 ± 2.6	0.77
Treatment to dysphagia***	-0.2 ± 0.9	0.8 ± 2.4	0.39
Visits up to death****	13	5. ± 5.2	0.39
Survival rate	15 (94)	1 (8)	<0.000001
Cancer	5 (31)	10 (76)	0.025
Anti-TIF1-γ	6 (38)	10 (76)	0.06
CK max	3010 ± 2721	2854 ± 3063	0.91
Initial dose of PSL (mg/day)	44.4 ± 19.2	29.2 ± 18.1	0.045
IVIG	3 (18)	0 (0)	0.25
Other medications*****	8 (50)	4 (30)	0.45

*DM onset to dysphagia: period (months) from DM onset to dysphagia onset, **Visit to dysphagia: period (months) from first hospital visit to dysphagia onset, ***Treatment to dysphagia: period (months) from treatment to dysphagia onset, ****Visits up to death: period (months) from first hospital visit up to death. *****Other medications: intravenous steroid pulse therapy, azathioprine, tacrolimus, methotrexate other than oral PSL and IVIG.
CK: creatine kinase; IVIG: Intravenous immunoglobulin; PSL: prednisolone

In the unrecovered group, 76.9% of patients (10 of 13) had cancer, and this factor may lead clinicians to choose mild immunosuppressive treatments. Medications other than oral PSL, including IVIG, were not significantly related to dysphagia recovery. All but 1 of the 15 surviving patients (93.7%) showed dysphagia recovery. These results suggest that dysphagia in DM might often be reversible without any specific medication.

A major limitation in our study is the lack of standardised dysphagia evaluation methods. Given this limitation, we were unable to compare and discuss the extent of dysphagia recovery between cases. Another limitation was that we did not collect the dates on which the clinician discovered the dysphagia recovery. Future prospective studies on dysphagia recovery and time course are necessary.

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REVIEW ARTICLE

Clinical practice guidance for juvenile idiopathic arthritis (JIA) 2018

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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,

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ORIGINAL ARTICLE

Add-on tocilizumab versus conventional treatment for systemic sclerosis, and cytokine analysis to identify an endotype to tocilizumab therapy

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ABSTRACT

Objectives: To evaluate the anti-interleukin (IL)-6 receptor antibody tocilizumab (TCZ) as a treatment of systemic sclerosis (SSc), a randomised parallel group study was conducted, and compared their results and baseline cytokine/chemokine profiles.

Methods: Patients were assigned to a TCZ add-on group (TCZ group, $n = 7$) and a conventional therapy group (Conv group, $n = 6$). TCZ (8 mg/kg/month) for 6 months, and the modified Rodnan total skin score (mRSS) were used to compare the efficacy. The association of medical history, baseline pulmonary function tests, blood cell counts, serum C-reactive protein (CRP) and 26 cytokines/chemokines and decrease in mRSS were analysed.

Results: The mean change in mRSS was larger in the TCZ group (6.3) than in the Conv group (3.4), but the difference was not statistically significant because of high variance in the TCZ group. Patients with shorter disease histories and higher CRP had larger decreases in mRSS, and the decrease in mRSS was negatively correlated with IL-13 and C–C motif chemokine ligand (CCL)5.

Conclusion: Although significant between-group differences were not observed, some patients had a decrease in mRSS. Short disease duration, high CRP, low IL-13 and low CCL5 may represent an SSc endotype responsive to TCZ therapy.

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KEYWORDS
Systemic sclerosis; tocilizumab; IL-6; IL-13; CCL5

Introduction

Systemic sclerosis (SSc) is a connective tissue disease that presents as sclerosis of the skin and visceral organs. Although there is no specific treatment, interleukin (IL)-6 is known to contribute to SSc pathogenesis. IL-6 was found to be present in the serum of SSc patients but not healthy controls [1], and IL-6 levels were higher in supernatants from cultures of skin tissue isolated from SSc patients than in isolates from healthy donors [2]. Sato et al. found a correlation between IL-6 levels and mRSS [3], and Kawaguchi et al. showed that production of type-1 procollagen by skin fibroblasts isolated from SSc patients was suppressed by anti-IL-6 antibody [4]. We previously demonstrated an *in vivo* effect of anti-IL-6 receptor antibody in a bleomycin-induced mouse SSc model [5] and reported the successful treatment of two SSc patients with tocilizumab (TCZ), a humanised anti-IL-6 receptor antibody [6].

TCZ is a monoclonal antibody against the IL-6 receptor, and it diminishes the cytokine effects of IL-6 by preventing receptor binding. The clinical effects of TCZ have been demonstrated in Castleman's disease and rheumatoid arthritis (RA). If IL-6 is involved in the pathogenesis of SSc, then TCZ should have a therapeutic effect in patients with the disease. We have reported decreases in skin scores in SSc patients treated with TCZ [6,7], but several randomised placebo control trials showed spontaneous remission in some SSc patients [8,9]. Therefore, to avoid the effect of spontaneous remission on the results, parallel group comparisons are needed to evaluate TCZ treatment. In a randomised placebo controlled (faSScinate) trial conducted in Europe and North America, the mean skin score of the TCZ group patients was lower than that in the placebo group, but the difference was not statistically significant [10]. We hypothesised that some patients respond well and some respond poorly to TCZ treatment. This randomised parallel group comparison study (UMIN0000055550) was designed to identify the characteristics of SSc patients suitable for TCZ therapy.

Methods

Patients and TCZ administration

The study protocol was approved by the institutional review boards of the Keio University Hospital, Tokyo Women's Medical University Hospital and Osaka University Hospital, and was registered as (UMIN0000055550) at the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR, https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000006582) as a randomised, open label, multicentre trial to assess humanised anti-IL-6

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Innovative Techniques and Technology

A novel and innovative paper-based analytical device for assessing tear lactoferrin of dry eye patients

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ARTICLE INFO

Keywords:
Microfluicic paper-based analytical device
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ABSTRACT

Purpose: To elucidate the correlation between lactoferrin concentration in the tear film and signs and symptoms of severe dry eye disease (DED) using a novel microfluidic paper-based analytical device (μPAD) and enzyme-linked immunosorbent assay (ELISA).
Methods: Twenty-four patients were recruited at the Keio University Hospital. Using a novel μPAD, lactoferrin concentrations were measured in 4 patients with GVHD-related DED, 3 patients with other types of DED and 2 controls (Group A). For validation by ELISA, 22 patients (7 patients from Group A) comprising 9 patients with GVHD-related DED, 6 patients with other types of DED and 7 controls were examined (Group B). The link between lactoferrin concentration and clinical data about the severity of aqueous tear deficient DED was also investigated by both μPAD and ELISA.
Results: The lactoferrin concentration in tear fluid of the DED patients was positively correlated between μPAD and ELISA ($p = 0.006$, $r = 0.886$). The tear fluid of the GVHD patients showed low or undetectable lactoferrin concentration. Analysis by ELISA demonstrated that lactoferrin concentrations in the tear film from the GVHD patients were significantly lower than those from the non-GVHD patients ($p = 0.010576$). ELISA revealed lactoferrin concentration correlated with the value of Schirmer test and tear film breakup time, whereas it was inversely correlated with OSDI, fluorescein and rose bengal scores.
Conclusions: The novel μPAD may pave the way for measuring lactoferrin concentration in tear fluid from DED patients. Our results suggested that lactoferrin concentration in tear fluid reflect the severity of DED.

1. Introduction

Tear film plays an indispensable role in maintaining corneal and conjunctival homeostasis by protecting against foreign body microbial invasion and preserving visual acuity [1]. Tear fluid is composed of a variety of proteins, enzymes, water, lipids, and electrolytes [1–3]. Lactoferrin as well as lysozyme, lipocalin, secretory IgA, phospholipase A, and secretory and membrane-associated mucins are important tear components that protect against invading pathogens [4]. Lactoferrin, a protein secreted from lacrimal gland acini, exerts a bactericidal, anti-tumor, and anti-viral/-fungal effect; exhibits immunomodulatory properties, and maintains homeostasis of ocular surface health [5]. Lactoferrin binds to iron in tear fluid; thus, bacteria cannot colonize the ocular surface due to the lack of this nutrient [4]. Lactoferrin levels in tear fluid are reduced in SS and non-SS dry eye patients [2,4,6–8].

The Tear Film Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) recently revised the definition of dry eye as “a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles” [9]. On the other hand, the Asia Dry Eye Society proposed a new consensus definition of dry eye disease as “a multifactorial disease characterized by unstable tear film causing a variety of symptoms and/or visual impairment, potentially accompanied by ocular surface damage” [10]. Both definitions indicate that an understanding of tear film, including tear dynamics and components, is essential for dry eye disease.

The diagnosis of dry eye disease is based on a combination of signs and symptoms. The ocular surface disease index (OSDI), fluorescein and rose bengal staining, and tear film breakup time (TFBUT) are used as

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ORIGINAL ARTICLE

National survey of Japanese patients with mevalonate kinase deficiency reveals distinctive genetic and clinical characteristics

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ABSTRACT

Objectives: Mevalonate kinase deficiency (MKD), a rare autosomal recessive autoinflammatory syndrome, is caused by disease-causing variants of the mevalonate kinase (MVK) gene. A national survey was undertaken to investigate clinical and genetic features of MKD patients in Japan.

Methods: The survey identified ten patients with MKD. Clinical information and laboratory data were collected from medical records and by direct interviews with patients, their families, and their attending physicians. Genetic analysis and measurement of MVK activity and urinary excretion of mevalonic acid were performed.

Results: None of the 10 patients harbored *MVK* disease-causing variants that are common in European patients. However, overall symptoms were in line with previous European reports. Continuous fever was observed in half of the patients. Elevated transaminase was observed in four of the 10 patients, two of whom fulfilled the diagnostic criteria for hemophagocytic lymphohistiocytosis. About half of the patients responded to temporary administration of glucocorticoids and NSAIDs; the others required biologics such as anti-IL-1 drugs.

Conclusion: This is the first national survey of MKD patients in a non-European country. Although clinical symptoms were similar to those reported in Europe, the incidence of continuous fever and elevated transaminase was higher, probably due to differences in disease-causing variants.

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KEYWORDS
Canakinumab; genotype-phenotype relationship; mevalonate kinase deficiency; national survey

Introduction

Mevalonate kinase deficiency (MKD) is a rare autosomal recessive autoinflammatory syndrome caused by disease-causing variants of the gene encoding mevalonate kinase (*MVK*), an enzyme involved in biosynthesis of cholesterol and isoprenoids [1]. The disease manifests as a continuous spectrum of clinical signs ranging from recurrent febrile attacks, known as hyperimmunoglobulinemia D syndrome (HIDS, MIM no. 260920), to a more severe form known as mevalonic aciduria (MA, MIM no. 610377), which is also associated with psychomotor retardation, facial dysmorphia, cataract, and failure to thrive [2]. Low MVK activity reduces production of cholesterol and non-sterol isoprenoids. A shortage of isoprenoids, mainly geranyl-geranyl groups, leads to decreased geranylgeranylation of RhoA and increased production of IL-1β [3,4]. Currently, treatment of MKD is based on the severity of the symptoms shown by each patient; mild cases require NSAIDs or glucocorticoids, whereas more severe cases require biologics or hematopoietic stem cell transplantation [5,6].

Large international surveys, mainly conducted in Europe, provide useful information about the clinical, genetic, and therapeutic characteristics of MKD [6,7]; however, no national surveys have been undertaken in non-European countries. Several MKD patients have been identified in Japan since 2009 [8], some of whom harbor novel disease-causing variants [9,10]. Therefore, we performed a national survey to investigate the clinical and genetic characteristics of Japanese pediatric MKD patients. We identified 10 patients who presented with disease of varying severity, experienced different complications, and showed different responses to treatment. The information reported herein provides clinical and genetic profiles of Asian patients with

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Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

Antifibrotic effects of 2-carba cyclic phosphatidic acid (2ccPA) in systemic sclerosis: contribution to the novel treatment

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Abstract

Background: Cyclic phosphatidic acid (cPA) has an inhibitory effect on the autotaxin (ATX)/lysophosphatidic acid (LPA) axis, which has been implicated to play an important role in the progression of fibrosis in systemic sclerosis (SSc). The purpose of this study is to assess the antifibrotic activity of cPA for the treatment of SSc using SSc skin fibroblasts and an animal model of bleomycin-induced skin fibrosis.

Methods: We used a chemically stable derivative of cPA (2ccPA). First, we investigated the effect of 2ccPA on extracellular matrix (ECM) expression in skin fibroblasts. Next, the effect of 2ccPA on the intracellular cAMP levels was determined to investigate the mechanisms of the antifibrotic activity of 2ccPA. Finally, we administered 2ccPA to bleomycin-induced SSc model mice to evaluate whether 2ccPA prevented the progression of skin fibrosis.

Results: 2ccPA decreased ECM expression in SSc skin fibroblasts and TGF-β1-treated healthy skin fibroblasts without LPA stimulation. 2ccPA increased the intracellular cAMP levels in skin fibroblasts, suggesting that the antifibrotic effect of 2ccPA was the consequence of the increase in the intracellular cAMP levels. Administration of 2ccPA also ameliorated the progression of bleomycin-induced skin fibrosis in mice.

Conclusions: Our data indicated that 2ccPA had inhibitory effects on the progression of skin fibrosis by abrogating ECM production from activated skin fibroblasts. These cells were repressed, at least in part, by increased intracellular cAMP levels. 2ccPA may be able to be used to treat fibrotic lesions in SSc.

Keywords: Fibrosis, Fibroblasts, Systemic sclerosis, Cyclic phosphatidic acid, Treatment

Background

Systemic sclerosis (SSc) is a systemic connective tissue disease with excessive fibrosis and vascular malformation based on autoimmunity [1–3]. Progressive fibrosis, which affects vital organs, such as the lungs and the gastrointestinal tract, is sometimes fatal or severely impairs quality of life [4]. Fibrosis of the skin, namely, scleroderma, is a major therapeutic target of SSc. Several molecules, such as transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF), have been reported to be closely associated with the progression of fibrosis [1–3, 5–7]. However, treatments including blocking agents of these molecules have not previously been established because of their limited therapeutic effects and/or severe adverse events [5–7].

An autotaxin (ATX)/lysophosphatidic acid (LPA) axis has emerged as a novel pathogenic factor in various diseases, including fibrosing disorder [8–10]. ATX is a secreted form of lysophospholipase D. One of the major properties of ATX is LPA production via cleavage of the choline group from lysophosphatidylcholine (LPC) [10]. LPA binds to six specific G protein-coupled receptors (GPCRs) (LPA_{1-6}) and intracellular PPARγ [11, 12]. LPA is known to regulate several cellular properties,

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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)

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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

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RHEUMATOLOGY

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Concise report

Antiphospholipid score is a novel risk factor for idiopathic osteonecrosis of the femoral head in patients with systemic lupus erythematosus

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Abstract

Objectives. Idiopathic osteonecrosis of the femoral head (ION) is a common complication of SLE associated with CS therapy. Although the pathogenesis of ION involves local bone ischaemia favoured by thrombophilia, the involvement of aPL in lupus ION remains to be elucidated. We have previously reported the aPL score (aPL-S) as a quantitative marker of aPL and the development of thrombotic events in autoimmune diseases. The aim of this study was to identify the impact of aPL on the development of ION using aPL-S.

Methods. This was a single-centre retrospective study comprising 88 consecutive SLE patients who underwent MRI of the hip joints from January 2000 to March 2017. Baseline characteristics, pharmacotherapy and total hip arthroplasty performed during follow-up were evaluated.

Results. The presence of ION was confirmed by MRI scan in 38 patients (43.1%). Male gender, positivity of any aPL, aPL-S, high aPL-S ($\geqslant$30) and high dose of CS were identified as risk factors for ION by univariate analysis. Multivariate analysis revealed high aPL-S (odds ratio 5.12, 95% CI 1.18–29.79) and use of high-dose CS (odds ratio 10.25, 95% CI 3.00–48.38) as independent variables. Kaplan–Meier analysis showed that patients with high aPL-S received total hip arthroplasty more frequently than those without aPL ($P = 0.010$).

Conclusion. We newly identified high aPL-S as an important risk factor for ION development in SLE, suggesting the involvement of aPL-induced coagulopathy in the pathophysiology of lupus ION.

Key words: systemic lupus erythematosus, antiphospholipid antibodies, antiphospholipid score, idiopathic osteonecrosis, magnetic resonance imaging

Rheumatology key messages

- High aPL score was newly identified as a risk factor for idiopathic osteonecrosis in SLE.
- Patients with high aPL score were at high risk of total hip arthroplasty.

Introduction

Idiopathic osteonecrosis of the femoral head (ION) remains a serious complication of SLE associated with CS therapy due to the lack of established prophylaxis. ION leads to a significant decrease in quality of life associated with pain and disability, with advanced cases requiring major surgical procedures such as total hip arthroplasty (THA). The diagnosis of ION can be made using radiographs, skeletal scintigraphy, CT and MRI. Among these, MRI may be used to detect a very early stage of ION with high specificity. A prospective MRI study has revealed that ION can be found in about 40% of SLE patients [1], which is much higher than in patients with other autoimmune or rheumatic diseases, suggesting the

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CLINICAL SCIENCE

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Original Research

Commensal microflora in human conjunctiva; characteristics of microflora in the patients with chronic ocular graft-versus-host disease

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ABSTRACT

Purpose: To investigate the transformation in the composition of ocular surface microflora. Evidence shows that microbial diversity correlates with autoimmune disorders. Chronic ocular graft-versus-host disease (GVHD) is the lethal complication after hematopoietic stem cell transplantation (HSCT) which influences patients' quality of life. It has a similar pathophysiology to autoimmune disorders but the relation of the microbial status especially in the ocular surface and chronic ocular GVHD is still unknown.

Methods: We prospectively harvested conjunctival microorganism with a cotton swab from following 3 groups, 32 eyes/20 ocular GVHD patients (9 males, 11 females), 28 eyes/20 nonGVHD cases (10 males, 10 females) which defined as post hematopoietic stem cell transplantation and without ocular GVHD, and 20 eyes/11 controls (7 males, 4 females). Conventional culture-based methods were performed to examine the microbial community.

Results: Ocular surface microbes in the GVHD patients was more complex in diversity compared with in the nonGVHD patients and the control. *Staphylococcus species, Alpha-haemo Streptococcus, Corynebacterium species, Propionibacterium Acnes, Aerobic gram-positive cocci, Haemophilus Influenzae,* and *Aerobic gram-positive rod* were observed in the GVHD patients, whereas only a few species detected in the other groups.

Conclusions: We found that ocular surface microbes in the GVHD patients is more diverse than that in the nonGVHD patients and the controls. These results suggest the alternation of microbes are involved in the pathogenic process of the chronic ocular GVHD. Further examination using state-of-the-art methods will be needed to gain greater insights into the diversity of microflora on the chronic GVHD-affected ocular surface.

1. Introduction

Commensal microflora co-evolves with their hosts on the ocular surface [1,2]. Host microflora contains a numerous capability of activating immunological cascades and exert pathologic effects. The status relates to several diseases such as infections and immune-mediated diseases [3,4]. Chronic graft-versus-host disease (GVHD) has similar pathophysiology, as it has been reported that one of the prominent features of chronic GVHD is an abnormality of immune system [5]. Chronic GVHD is the major complication of hematopoietic stem cell transplantation (HSCT) [6]. Recipients of HSCT are subjected to high-risk factors due to irradiation, immune suppressants, and high-dose corticosteroid treatments. Focusing on ophthalmologic evaluation in chronic GVHD, the main phenotype is dry eye syndrome (DED) [6–10]. It is defined as chronic ocular GVHD when the DED outbreaks after HSCT [11,12]. Fifty percent of recipients develop DED within 2 years after HSCT [7]. Several risks were reported in the past and development of chronic ocular GVHD leads to their poor prognosis [5]. In the advance of the Omics study, it makes possible to detect the details of the species using 16S rRNA sequencer [13]. Applying this advanced technique, several references are reported including significantly diversified microflora in Celiac disease patients' duodenal mucosa [14]. In addition, some references show dysbiosis relation in several immune-mediated disorders [15,16]. Furthermore, it is said that patients of chronic GVHD and their gut microflora establishes a close relationship, for example, loss of diversity in intestinal microbiota with simultaneous

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BRIEF REPORT

Low-dose rituximab as induction therapy for ANCA-associated vasculitis

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Abstract

Administration of four once-weekly doses of 375 mg/m^2 rituximab (RTX) is commonly used as remission induction therapy for ANCA-associated vasculitis (AAV). Low-dose RTX has been recently shown to produce closely similar results to conventional treatments in other autoimmune diseases. However, the therapeutic potential of this approach in AAV remains largely unknown. Here, we analyzed the efficacy and tolerability of high- and low-dose regimens of RTX in patients with AAV. We retrospectively examined AAV patients who met the classification algorithm of Watts et al. from 2006 to 2016. Patients were divided into high- (HD) and low-dose (LD) RTX groups. HD-RTX was the original regimen while LD-RTX consisted of two once-weekly doses of 375 mg/m^2. Cumulative complete remission (CR) rates for 1 year were compared, and serial changes in peripheral B cell counts and serious adverse events were monitored. Apart from a higher percentage of elderly patients in the LD group ($p < 0.01$), the 17 patients with HD-RTX and 11 patients with LD-RTX showed no significant differences in clinical characteristics, including Birmingham Vasculitis Activity Score (BVAS), Vasculitis Damage Index (VDI), and the initial dose of glucocorticoid. On 1-year observation, cumulative CR rates did not significantly differ ($p = 0.20$). Further, peripheral B cell counts and incidence of serious adverse events also did not differ. Cumulative CR rate did not significantly differ between LD and HD groups. Further study is warranted to confirm these results.

Keywords ANCA-associated vasculitis · High dose · Low dose · Rituximab

Introduction

Antineutrophil cytoplasmic autoantibody (ANCA)–associated vasculitis (AAV) is a group of heterogeneous systemic vasculitis diseases that include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). Since mortality is as high as 90% if untreated, aggressive initial immunosuppression is generally required for generalized AAV [1, 2]. Initial immunosuppressive therapy in GPA and MPA typically consists of glucocorticoids (GC) combined with either cyclophosphamide (CY) or rituximab (RTX) [3]. This strategy was based on the results of two randomized trials conducted in Europe and America [4, 5]. RTX is an effective alternative to CY for the initial treatment of patients who have newly diagnosed disease or relapsed disease following treatment with CY or other immunosuppressive therapy [4, 5]. The therapeutic dose of RTX for AAV was determined based on the regimen for CD20-positive B cell non-Hodgkin's lymphoma (four once-weekly doses of 375 mg/m^2), however, an appropriate dose for AAV has yet to be determined [6, 7]. Recently, low-dose RTX was shown to provide results which were closely similar to the successful results provided by conventional regimens in other autoimmune diseases, including rheumatoid arthritis (two doses of 500 mg), immune thrombocytopenia (100 mg weekly for 4 weeks), and kidney transplantation (single dose of 50–100 mg/m^2) [8–10]. Here, we comprehensively analyzed the efficacy and safety of high- and low-dose RTX regimens in patients with AAV.

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Autoantibody to transcriptional intermediary factor-1β as a myositis-specific antibody: clinical correlation with clinically amyopathic dermatomyositis or dermatomyositis with mild myopathy*

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Summary

Background Myositis-specific autoantibodies (MSAs) are associated with unique clinical subsets in polymyositis/dermatomyositis (PM/DM). Autoantibodies against transcriptional intermediary factor (TIF)-1γ and TIF-1α are known to be MSAs. Previously, we reported that TIF-1β is also targeted in patients with DM with or without concomitant anti-TIF-1α/γ antibodies.

Objectives To evaluate the clinical features of seven cases with anti-TIF-1β antibodies alone.

Methods Serum autoantibody profiles were determined, and protein and RNA immunoprecipitation studies were conducted. Western blotting was performed to confirm autoantibody reactivity against TIF-1β.

Results Anti-TIF-1β antibody was identified by immunoprecipitation assay in 24 cases. Among them, seven patients were positive for anti-TIF-1β antibody alone. Six of the seven patients were classified as having DM. Among the six cases of DM, two patients had no muscle weakness and normal creatine kinase (CK) levels, and were classified as having clinically amyopathic DM. Four patients had muscle weakness, but three of them had normal serum CK levels that responded well to systemic steroids. Characteristic features of DM included skin rashes, such as Gottron sign, periungual erythema, punctate haemorrhage on the perionychium and facial erythema including heliotrope, which were observed in 86%, 57%, 86% and 71% of our cases, respectively. One of the seven patients had appendiceal cancer. None of the patients had interstitial lung disease.

Conclusions Seven patients were confirmed to have anti-TIF-1β antibody without any other MSAs, including TIF-1α/γ antibodies, and six of them were diagnosed with DM. We suggest that anti-TIF-1β antibody is an MSA, and that it is associated with clinically amyopathic DM or DM with mild myopathy.

What's already known about this topic?

- Previously we reported that transcriptional intermediary factor (TIF)-1β is also targeted in patients with dermatomyositis with or without concomitant anti-TIF-1α/γ antibodies.
- Anti-TIF-1β antibody could be a myositis-specific autoantibody.

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None to declare.

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Differential expression of antibodies to NMDA receptor in anti-NMDA receptor encephalitis and in neuropsychiatric systemic lupus erythematosus

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ABSTRACT

Objective Anti-NMDA receptor encephalitis is the most prevalent autoimmune encephalitis having characteristic clinical features with autoantibodies against tetrameric transmembrane channels composed of combinations of NR1 subunits of NMDA receptors with NR2 subunits, which are detected by cell-based assay (anti-NR1/NR2). On the other hand, antibodies against the linear epitope in NR2 subunit (anti-NR2) have been shown to be expressed in patients with diffuse psychiatric/neuropsychological syndromes of neuropsychiatric SLE (diffuse NPSLE). However, it has not been explored whether anti-NR1/NR2 might be detected in NPSLE, nor has it been clear whether anti-NR2 might have cross-reactivity with anti-NR1/NR2. The current study was therefore performed to explore the prevalence of anti-NR1/NR2 in NPSLE.

Methods Serum specimens were obtained from 31 patients with NPSLE (22 with diffuse NPSLE and 9 with neurological syndromes or polyneuropathy) and from 18 normal healthy subjects. Anti-NR2 and anti-NR1/NR2 were measured by ELISA and cell-based assay, respectively. The positivity for anti-NR2 was defined by a value exceeding mean+2 SD of normal healthy subjects.

Results Anti-NR2 was positive in the sera of 19 of 31 patients with NPSLE (in 15 of 22 patients with diffuse NPSLE). By contrast, anti-NR1/NR2 was positive only in 2 of 31 patients with NPSLE (in 2 of 22 patients with diffuse SLE). The positivity for anti-NR1/NR2 was not correlated with anti-NR2 values.

Conclusions These results demonstrate that the prevalence of anti-NR1/NR2 is extremely low in NPSLE. Moreover, the data also confirm that anti-NR2 antibodies do not have cross-reactivity with anti-NR1/NR2.

INTRODUCTION

Neuropsychiatric manifestations in SLE are difficult complications that may cause substantial impairment of quality of life as well as disability.[1 2] Previous studies demonstrated that IgG antineuronal antibodies (anti-N) were specifically elevated in the cerebrospinal fluid (CSF) of patients with active neuropsychiatric SLE (NPSLE),[3 4] whereas the targets of these anti-N remained unclear for a long time. Of note, it was demonstrated that a subset of murine anti-DNA antibodies cross-reacted with a sequence within the N-methyl-D-aspartate (NMDA) receptor subunit NR2.[5 6] More importantly, recent studies have demonstrated that CSF anti-NMDA receptor NR2 antibodies (anti-NR2) are associated with diffuse psychiatric/neuropsychological syndromes of human NPSLE.[7–9]

On the other hand, a new category of encephalitis has been discovered in patients with ovarian teratoma, characterised by the sequential development of prodromal symptoms, prominent psychiatric manifestations, and seizures followed by catatonia, hypoventilation and involuntary orofacial-limb movements.[10–14] This autoimmune encephalitis has been found to be closely related to the antibodies against tetramerised NR1-NR2 subunits of NMDA receptors detected by cell-based assay (anti-NR1/NR2) mainly in CSF.[15] Thus, it has been called anti-NMDA receptor encephalitis.[15]

Since there is a close analogy of clinical characteristics between diffuse NPSLE and anti-NMDA receptor encephalitis, it is possible that a fraction of patients with diffuse NPSLE might express anti-NR1/NR2. However, it has not been explored whether anti-NR1/NR2 might be expressed in NPSLE, nor has it been clear whether anti-NR2 might have cross-reactivity with anti-NR1/NR2. The current study was therefore performed to explore the prevalence of anti-NR1/NR2 in NPSLE.

METHODS

Patients and samples

Thirty-one patients with SLE were included in the present study. All patients fulfilled the American College of Rheumatology (ACR) 1982 revised criteria for the classification of SLE.[16] Of the 31 patients with SLE, 22 showed diffuse psychiatric/neuropsychological syndromes (diffuse NPSLE) according to

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Kinetic visual acuity is correlated with functional visual acuity at higher speeds

Ikko Iehisa, Kazuno Negishi , Masahiko Ayaki , Kazuo Tsubota

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ABSTRACT

Objective To measure the kinetic visual acuity (KVA) which is the ability to identify approaching objects and the functional visual acuity (FVA) which is continuous VA during 1 min under binocular and monocular condition (non-dominant eye shielding) for healthy subjects, and related ocular parameters to explore their correlation and implication in aspect of integrated visual function.

Methods The mean age of the 28 participants was 38.6±8.9 years (range, 23–57 years; 6 women). A KVA metre (AS-4Fα) and FVA metre (AS-28) were used to measure KVA and FVA, respectively. Multiple regression analysis was conducted to explore correlations among the measured visual function and related parameters, including age, binocularity, best-corrected visual acuity, refraction and tear break-up time.

Results The results of binocular KVA were better than monocular KVA at all speeds. A strong correlation was found between monocular and binocular KVA. The results of binocular FVA were better than monocular FVA ($p<0.001$) and there was a correlation between monocular and binocular FVA ($R=0.638$, $p<0.001$), as well as the maintenance rate for FVA ($R=0.228$, $p=0.003$). A linear mixed-effects model revealed that binocularity for KVA prediction was significant at all speeds and FVA was also significant at 60 km/h ($p<0.05$).

Conclusion The current results suggest that both binocularity and FVA may contribute to KVA.

Trial registration number UMIN00032385

Key messages

What is already known about this subject?

- Previous investigations described binocular kinetic visual acuity (KVA) was superior to monocular KVA, however, there have been only a few investigations on other factors influencing differences in KVA.

What are the new findings?

- KVA was closely correlated with functional visual acuity (FVA) at higher speeds and this was stronger than the correlation between KVA and binocularity.

How might these results change the focus of research or clinical practice?

- Close correlation between KVA and FVA suggests that FVA could be a potential indicator for evaluating visual function in daily life to percept moving objects.

INTRODUCTION

A better understanding of binocular visual function is required in modern society. People with monocular vision may suffer impaired visual function as the superiority of binocularity is well established in visual acuity (VA), reading speed, depth perception and movement detection.[1–6] Binocular summation/binocularity is composed of probability summation and neural summation. When the light stimulates the photoreceptors in one eye, the corresponding photoreceptors in the contralateral eye are simultaneously stimulated. Thus, the probability of photoreceptor stimulation in the binocular conditions is higher with binocular than monocular viewing.[3] Other studies reported that binocular viewing lowers the contrast threshold by up to 40%[7 8] and the degree of summation is related to the complexity of the visual task.[9]

However, the functional role of binocularity has not been fully determined for daily activities. Common vision-threatening diseases that may cause monocular status include cataract, glaucoma and age-related macular degeneration, along with disorders of the central nervous system, such as cerebral infarction. A recent increase in the prevalence of the above-mentioned age-related eye diseases[10–13] may be associated with increased traffic fatalities involving the elderly as binocular or monocular diseases can affect the integrated visual function essential for traffic safety. It is an emerging issue in our ageing society.

Kinetic VA (KVA) is the ability to identify approaching objects, whereas the ability to identify objects moving horizontally or vertically is called dynamic VA.[14] There have been only a few investigations of KVA, and detailed studies have not been conducted on factors influencing differences in KVA ability. Rose[3] reported that the threshold of movement detection for binocular viewing is quite small compared with monocular viewing, and the threshold for monocular viewing is higher than that for binocular viewing out to distances of 15–20 m, beyond which they are the same. This finding indicates that binocularity may contribute more at higher speeds to recognise distant objects.

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$CD4^+CD25^+LAG3^+$ T Cells With a Feature of Th17 Cells Associated With Systemic Lupus Erythematosus Disease Activity

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Systemic lupus erythematosus (SLE) is an autoimmune disease that involves multiple immune cell subsets. We analyzed immune cell subsets in human peripheral blood mononuclear cells (PBMC) in order to identify the cells that are significantly associated with SLE disease activity and treatment. The frequencies of various subsets of $CD4^+$ T cells, B cells, monocytes and NK cells in PBMC were assessed in 30 healthy controls (HC), 30 rheumatoid arthritis (RA) patients and 26 SLE patients using flow cytometry. The correlations between subset frequencies in SLE and clinical traits including Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) were examined. Changes in subset frequencies after the treatment in SLE patients were investigated. We focused on $CD25^+LAG3^+$ T cells and investigated their characteristics, including cytokine secretion, mRNA expression and suppression capacity. We assessed correlations between $CD25^+LAG3^+$ T cells and SLEDAI by Spearman's rank correlation coefficient. $CD25^+LAG3^+$ T cells were significantly increased in SLE whereas there were few in RA and HC groups. $CD25^+LAG3^+$ T cell frequencies were significantly correlated with SLEDAI and were increased in patients with a high SLEDAI score (> 10). $CD25^+LAG3^+$ T cells produced both IL-17 and FOXP3, expressed mRNA of both *FOXP3* and *RORC* and lacked suppressive capacity. $CD25^+LAG3^+$ T cells were associated with disease activity of SLE. $CD25^+LAG3^+$ T cells had features of both $CD25^+FOXP3^+$ regulatory T cells ($CD25^+$ Treg) and Th17. $CD25^+LAG3^+$ T cells could be associated with the inflammatory pathophysiology of SLE.

Keywords: systematic lupus erythematosus, LAG3, regulatory T cells, Th17, SLEDAI

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease that is characterized by loss of tolerance, production of autoantibodies, immune complex deposition, and end organ damage. Multiple immune cell subsets are involved in the pathophysiology of SLE. SLE appears to be induced by persistent apoptotic debris (1) that primes neutrophils' NETosis (2), induces

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A Critical Role for Mucosal-Associated Invariant T Cells as Regulators and Therapeutic Targets in Systemic Lupus Erythematosus

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Mucosal-associated invariant T (MAIT) cells are a subset of innate-like lymphocytes that are restricted by major histocompatibility complex-related molecule 1 (MR1). In this study, we investigated the role of MAIT cells in the pathogenesis of lupus in FcγRIIb$^{-/-}$*Yaa* mice, a spontaneous animal model of lupus. Using two approaches of MAIT cell deficiency, MR1 knockout animals and a newly synthesized inhibitory MR1 ligand, we demonstrate that MAIT cells augment the disease course of lupus by enhancing autoantibody production and tissue inflammation. MR1 deficiency reduced germinal center responses and T cell responses in these mice. Suppression of MAIT cell activation by the inhibitory MR1 ligand reduced autoantibody production and lupus nephritis in FcγRIIb$^{-/-}$*Yaa* mice. MAIT cells directly enhanced autoantibody production by B cells *in vitro*. Our results indicate the contribution of MAIT cells to lupus pathology and the potential of these cells as novel therapeutic targets for autoimmune diseases such as lupus.

Keywords: MAIT cell, innate lymphocyte, MR1 ligand, lupus, T-B cell interaction

INTRODUCTION

Mucosal-associated invariant T (MAIT) cells are a subset of innate-like T lymphocytes restricted by major histocompatibility complex-related molecule 1 (MR1) (1) and display innate-like properties. The majority of MR1-restricted MAIT cells express the semi-invariant T cell receptor (TCR) α chain Vα7.2-Jα33 in humans and Vα19-Jα33 in mice. MAIT cells develop in the thymus and are selected by double positive thymocytes in a MR1 dependent manner (1–3). MAIT cells recognize non-peptide antigens presented by the non-polymorphic MR1 molecules that include microbially-derived vitamin B2 (riboflavin) derivatives with MAIT cell-activating activity and vitamin B9 (folic acid) derivatives that are non-activating (4). Similar to other innate lymphocytes, including invariant natural killer T (iNKT) cells, MAIT cells respond very rapidly upon activation by TCR signaling or cytokine stimulation in the absence of exogenous antigens (5–8). Activated MAIT cells

Case Report

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Osteomyelitis due to methicillin-resistant *Staphylococcus aureus* successfully treated by an oral combination of minocycline and trimethoprim–sulfamethoxazole

Kojiro Sato, Hiroaki Yazawa, Daisuke Ikuma, Takashi Maruyama, Hiroshi Kajiyama and Toshihide Mimura

Abstract

Most of the anti-methicillin-resistant *Staphylococcus aureus* drugs available in Japan are administered intravenously, except for linezolid, which can also be administered orally. Here, we report a lupus patient with methicillin-resistant *S. aureus*–induced osteomyelitis. Linezolid had to be stopped due to severe anemia. In an effort to treat her on an outpatient basis, we planned to use a combination of minocycline and trimethoprim–sulfamethoxazole that exhibited in vitro sensitivity against the methicillin-resistant *S. aureus* detected, and rifampicin is used against methicillin-resistant *S. aureus* in certain cases. The use of rifampicin increased the level of C-reactive protein even though the prednisolone dose used was doubled, so we gave up using it. The combined application of oral minocycline and trimethoprim–sulfamethoxazole, however, controlled the inflammation, and the patient was able to be discharged. Fourteen months later, we discontinued the administration of both drugs and there has been no relapse more than a year. This combination of antibiotics may be useful, especially when patients want to be treated on an outpatient basis.

Keywords

Methicillin-resistant *Staphylococcus aureus*, osteomyelitis, minocycline, trimethoprim–sulfamethoxazole, linezolid

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Introduction

The treatment of osteomyelitis, especially when it is caused by methicillin-resistant *Staphylococcus aureus* (MRSA) infection, can be highly challenging.[1] Linezolid (LZD) is the only oral anti-MRSA agent available in Japan. Thus, if LZD cannot be used due to its side effects, patients with osteomyelitis caused by MRSA may have to be kept in hospital for quite a long period of time. The transition from inpatient- to outpatient-basis treatment may require some trial-and-error process.

Case report

A 43-year-old woman afflicted with systemic lupus erythematosus (SLE) for over 22 years was referred to our department from the department of plastic surgery for further treatment. She was paraplegic due to lupus-related transverse myelitis below the level of thoracic vertebrae 6 (Th6), along with dysfunction of the bladder and bowel. She had been treated mainly at this hospital on an outpatient basis and been in remission with prednisolone (PSL) at a dose of 11 mg/day. In February 2014, an ischial decubitous ulcer was noticed. She was admitted to the department of plastic surgery of this hospital and an operation for the decubitus ulcer (i.e. debridement) was performed in June. MRSA (3+) and *Corynebacterium* species (1+) were detected in the wound. After the surgery, cefmetazole (1 g, twice daily) was administered for 5 days. During the hospitalization, she developed bilateral polyarthritis of finger and hand joints and was diagnosed with seronegative rheumatoid arthritis (RA) in July (Figure 1(a)). Salazosulfapyridine (SASP, 1 g/day) and

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(原著論文) Original Paper

Extension of Sinkhorn Method: Optimal Movement Estimation of Agents Moving at Constant Velocity

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keywords: bioimaging, optimal transport, tracking

Summary

In the field of bioimaging, an important part of analyzing the motion of objects is tracking. We propose a method that applies the Sinkhorn distance for solving the optimal transport problem to track objects. The advantage of this method is that it can flexibly incorporate various assumptions in tracking as a cost matrix. First, we extend the Sinkhorn distance from two dimensions to three dimensions. Using this three-dimensional distance, we compare the performance of two types of tracking technique, namely tracking that associates objects that are close to each other, which conventionally uses the nearest-neighbor method, and tracking that assumes that the object is moving at constant velocity, using three types of simulation data. The results suggest that when tracking objects moving at constant velocity, our method is superior to conventional nearest-neighbor tracking as long as the added noise is not excessively large. We show that the Sinkhorn method can be applied effectively to object tracking. Our simulation data analysis suggests that when objects are moving at constant velocity, our method, which sets acceleration as a cost, outperforms the traditional nearest-neighbor method in terms of tracking objects. To apply the proposed method to real bioimaging data, it is necessary to set an appropriate cost indicator based on the movement features.

1. Introduction

In the field of bioimaging, an important part of analyzing the motion of objects is tracking [Celler 13, Genovesio 06, Smal 08]. The tracking process can be described as follows. Images taken at fixed time intervals contain many objects. The goal is to identify which signals correspond to which object at the next time point. This task is important for bioimaging analysis, such as the analysis of microscopy videos, because it is indispensable for analyzing the motion of objects from image data taken at fixed time intervals. However, automatic tracking is difficult. Many types of algorithm have been proposed for this task [Chenouard 14, Kalaidzidis 09], including the nearest-neighbor method [Crocker 96], probabilistic data association [Kirubarajan 04], and multiple hypothesis tracking [Reid 79].

Nearest-neighbor algorithms, the most simple of tracking methods, are used for live-cell tracking in the field of bioimaging analysis [Mazzaferri 14]. These algorithms associate objects that are close to each other. Although this is a simple task, the performance of nearest-neighbor algorithms is inadequate when the objects are crowded together or their movement distance is long. These difficult conditions are common in bioimaging data. In this study, we extend the nearest-neighbor method. Because nearest-neighbor tracking can be considered as an optimal transport algorithm, we adopt the Sinkhorn method [Cuturi 13], an optimal transport algorithm, to modify nearest-neighbor tracking.

In this research, we apply the Sinkhorn method to object tracking. This allows us to perform tracking using various transport costs based on a model of object behavior. For tracking, we do not have to associate the nearest objects at two consecutive time points; we can associate objects so that their trajectories are smooth. A smooth trajectory means that changes in velocity are small, or that the ob-

IgG4-related disease in the Japanese population: a genome-wide association study

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Summary

Background IgG4-related disease is a newly recognised immunopathological entity that includes autoimmune pancreatitis, IgG4-related sialadenitis, and IgG4-related kidney disease. To understand the genetic landscape of IgG4-related disease, we did a genome-wide association study.

Methods We did a genome-wide association study of Japanese individuals, initially screening 857 patients with IgG4-related disease at 50 Japanese research institutions and DNA samples from 2082 healthy control participants from the Nagahama Prospective Genome Cohort for the Comprehensive Human Bioscience. From Oct 27, 2008, to July 22, 2014, we enrolled 835 patients and used data from 1789 healthy participants. Only patients with confirmed diagnosis of IgG4-related disease according to the international diagnostic criteria were included. Genotyping was done with the Infinium HumanOmni5Exome, HumanOmni2.5Exome, or HumanOmni2.5 Illumina arrays, and genomic distributions were compared between case and control samples for 958 440 single nucleotide polymorphisms. The *HLA* region was extensively analysed using imputation of *HLA* alleles and aminoacid residues. Fine mapping of the *FCGR2B* region was also done. Associations between clinical manifestations of disease and the genetic variations identified in these two genes were examined.

Findings We identified the *HLA-DRB1* ($p=1\cdot1\times10^{-11}$) and *FCGR2B* ($p=2\cdot0\times10^{-8}$) regions as susceptibility loci for IgG4-related disease. We also identified crucial aminoacid residues in the β domain of the peptide-binding groove of HLA-DRB1, in which the seventh aminoacid residue showed the strongest association signal with IgG4-related disease ($p=1\cdot7\times10^{-14}$), as has been reported with other autoimmune diseases. rs1340976 in *FCGR2B* showed an association with increased *FCGR2B* expression ($p=2\cdot7\times10^{-10}$) and was in weak linkage disequilibrium with rs1050501, a missense variant of *FCGR2B* previously associated with systemic lupus erythematosus. Furthermore, rs1340976 was associated with the number of swollen organs at diagnosis ($p=0\cdot011$) and IgG4 concentration at diagnosis ($p=0\cdot035$).

Interpretation Two susceptibility loci for IgG4-related disease were identified. Both *FCGR2B* and *HLA* loci might have important roles in IgG4-related disease development. Common molecular mechanisms might underlie IgG4-related disease and other immune-related disorders

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Introduction

IgG4-related disease is a newly recognised immunopathological entity that is characterised by swelling in the affected organs, increased serum concentrations of total IgG and IgG4, tissue infiltration of plasmacytes and eosinophils, tissue fibrosis, and a good response to corticosteroid therapy.[1] IgG4 is a subtype of immunoglobulin γ with specific features, including anti-inflammatory activity because of its much weaker binding to complement proteins and Fcγ receptors than IgG1. Another unique feature of IgG4 is its ability to become bispecific through exchange of one antigen-binding arm with that of another IgG4 molecule, which might interfere with the formation of immune complexes by other antibody isotypes, thus inhibiting inflammatory reactions.[2] Increased serum IgG4 concentrations were first reported in patients with autoimmune pancreatitis (IgG4-related pancreatitis),[3] and subsequently in various diseases affecting different organs, such as IgG4-related sialadenitis (Mikulicz's disease) or IgG4-related kidney disease.[4] Patients with IgG4-related disease are often positive for rheumatoid factor and have antinuclear antibodies with substantially decreased concentrations of specific autoantibodies, such as anti-SSA/Ro and anti-SSB/La, compared with patients with Sjögren's syndrome.[1] Autoantigens detected in patients with IgG4-related disease have been reported, including those

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Original Article

Epidemiological analysis of multicentric and unicentric Castleman disease and TAFRO syndrome in Japan

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Castleman disease is a polyclonal lymphoproliferative disease which is clinically classified into unicentric (UCD) and multicentric (MCD). TAFRO syndrome is a relatively new concept that partly overlaps with MCD. Due to their rarity, their incidence remains unknown. This study investigated the incidence and prevalence of UCD, MCD, and TAFRO syndrome in Japan using a fixed-point observation method based on their incidence in Ishikawa prefecture. The annual incidences of MCD, UCD, and TAFRO syndrome in Japan were 309-731, 71-542, and 110-502, respectively, yielding annual incidence rates per million individuals of 2.4-5.8, 0.6-4.3, and 0.9-4.9, respectively, and nationwide prevalence of 4,180-14,900, 1,350-10,300, and 860-7,240, respectively. In conclusion, MCD, UCD and TAFRO syndrome may not be as rare as previously estimated in Japan.

Key words: disease incidence, Statistical Research Committee of Japanese Society of Hematology, specific use survey, fixed-point observation method

INTRODUCTION

Castleman disease was initially described as a lymphoproliferative disorder causing mediastinal masses characterized by abnormal histopathology.[1] Castleman disease has since been subclassified clinically into unicentric (UCD) and multicentric Castleman disease (MCD),[2] and subclassified histopathologically into the hyaline-vascular type (HV), plasma-cell type (PC), mixed type, plasmablastic type, and hypervascular type.[3] MCD was recently subclassified into human herpes virus-8 (HHV-8)-associated, HHV-8-unassociated (idiopathic MCD [iMCD]), POEMS syndrome-associated, and others.[3]

A new clinical entity, TAFRO syndrome, characterized by thrombocytopenia, anasarca (edema, pleural effusion, and ascites), fever, reticulin myelofibrosis (or renal insufficiency), and organomegaly (hepatosplenomegaly and lymphadenopathy), was recently described.[4] Its diagnostic criteria and disease severity criteria, determined by the All Japan TAFRO Syndrome Research Group in the Research Program for Intractable Diseases of the Ministry of Health, Labour and Welfare (MHLW) of Japan,[5] were recently updated (https://www.facebook.com/CastlemanTAFRO). As the lymph nodes of individuals with TAFRO syndrome were characterized histopathologically as Castleman disease,[6] TAFRO syndrome has been categorized as part of iMCD.

Recently, clinical and basic studies on Castleman disease and TAFRO syndrome were started in Japan and the USA. We collected and analyzed data from more than 200 patients with iMCD, TAFRO syndrome, or conditions mimicking these disorders. Most patients with iMCD exhibit a chronic/indolent clinical course, characterized by polyclonal hypergammopathy, multiple lymphadenopathy, and thrombocytosis. In contrast, most patients with TAFRO syndrome have an acute or sub-acute onset and progressive clinical course, characterized by normal to reduced gammaglobulin levels, thrombocytopenia, small or unnoticeable lymph nodes, and severe pleural effusion, ascites, and anasarca. Lymph node

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