by bone marrow aspiration and, if possible, exclusion of malignancy or deep infection using ^{18}F-FDG-PET. If available diagnostic tools are restricted to establishment of blood values, the following data are gathered together: an elevation of inflammatory markers such as CRP and ESR, a matrix metalloproteinase-3 (MMP-3) value that informs on synovitis as well as cartilage destruction, determination of HO-1, ferritin, and cytokines including IL-6 and IL-18, and NK cell activity.

Macrophage activation syndrome

Clinical features of macrophage activation syndrome

Macrophage activation syndrome is not a disease entity in itself but a pathological condition associated with systemic JIA as reported by Stephan in 1993 [50]. This first report already described a high level of urinary TNF-α. This pathological condition runs a short course but cannot be diagnosed by a single laboratory value or at a single time point. Laboratory data must be gathered over time and include platelet counts/white blood cell counts, D-dimer/FDP-E (fibrin degradation product in the blood), aspartate transaminase/lactate dehydrogenase, ferritin/β2-microglobulin, total cholesterol/triglycerides, and others. Fluctuations of such laboratory data are very common in this pathological condition and also among cases of hemophagocytic lymphohistiocytosis or familial (hereditary) hemophagocytic syndrome, as well as systemic inflammatory response syndrome. Hemophagocytic events are common findings among the above-mentioned pathological conditions. These findings can be reasonably explained by excessive production of inflammatory cytokines common to these syndromes, contributing to inflammatory pathogenesis by being produced and released in a certain order [51].

It was also reported that NK cells as well as $CD8^+$T cells had abnormally low perforin levels [52,53] in this pathological condition. Macrophages and dendritic cells infiltrating organs are activated to produce/release an uncontrolled large amount of inflammatory cytokines while vascular endothelial cells are activated and disrupted, and tissue and cellular apoptosis/necrosis progresses. It should, therefore, be assumed as an underlying etiology that NK cells and $CD8^+$ T cells have ceased to function properly. Stephan et al. suggested that transition from systemic JIA to macrophage activation syndrome can be triggered by virus infection or a change of medication [47], which remains to be confirmed.

Endothelial cell activation/disruption and activation of the coagulation and fibrinolytic system

In systemic inflammation, overproduced inflammatory cytokines circulate in the blood. Consequently, endothelial cells are activated by these inflammatory cytokines that are released by activated monocytes-macrophages and, in turn, endothelial cells themselves release cytokines such as IL-1β, IL-8, monocyte chemo-attractant protein-1 (MCP-1), and chemokines. Such interactive activation of macrophages and endothelial cells has recently attracted much attention [54]. Because certain cytokines, especially IFN-γ, upregulate the expression of HLA class-I molecules on the endothelial cells membrane, H and L chains are increasingly translated. As a result, a large amount of L chains that fail to assemble with H chains are excreted in the urine as β2-microglobulin [55].

Endothelial cells activated by inflammatory cytokines also express elevated levels of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and E-selectin, which direct activated neutrophils as well as cytotoxic mononuclear cells to sites of inflammation [56]. Endothelial cells continuously trap these activated cells via adhesion molecule/ligand interactions; some then release lysosomes, proteases, and reactive oxygen species into their immediate surroundings, resulting in destruction of the endothelial cells compromising endothelial integrity. They may be further damaged by tissue factor (TF) release. Because of vascular endothelial cells' ability to adjust permeability plays a vital role in homeostasis, it is important to attempt to repair them immediately [57]. Such damaged endothelial cells themselves and activated macrophages release TFs, which in turn activate coagulation factor VII as well as the extrinsic pathway [58]. Platelets adhere to and via von Willbrand factor agglutinate collagen exposed on damaged endothelial cells. Collagen activates coagulation factor XII as well as the intrinsic pathway. Injured vascular walls then become covered by fibrin nets and thrombi are formed, promoted by the activated extrinsic and intrinsic pathways, and platelet adhesion and aggregation, and eventually leading to blockage of plasma flow into tissues [59,60].

The fibrinolytic system is also activated to excise fibrins formed on endothelial cells, increasing the amount of FDP-E/D-dimer, a fibrin degradation product, in the blood. Levels of FDP-E/D-dimer reflect the extent of vascular endothelial cell damage. Endothelial cells thus activate the fibrinolytic system via inflammation [61]. If this activation goes beyond the bounds of physiological homeostasis, PT/APTT collapses and may progress to the development of disseminated intravascular coagulation (DIC).

Tissue/cell injury by TNF-α

TNF-α functions as an inflammatory cytokine and also as the next most important apoptosis inducer after Fas/Fas-ligand interactions [62]. If TNF-α is produced to a degree that overwhelms the neutralizing capacity of TNFRI, a soluble receptor, it binds to its specific receptors on the cell membrane, stimulates the intracellular signal transduction pathway and promotes the mitochondrial permeability transition [35]. Cytochrome C released from mitochondria then activates enzymes of the caspase family, one of which, caspase-3, is finally activated in cells to randomly cleave DNA, leading to cellular apoptosis/necrosis. On the other hand, since serum ferritin production by the reticuloendothelial system is controlled by TNF-α [36], the serum ferritin level, reflecting the amount of systemic TNF-α, provides a rough idea of the degree of TNF-α activation in the clinical setting.

As vascular endothelial cells become more badly damaged and the coagulation and fibrinolysis systems are activated to repair them, activation of coagulation may come to predominate. Dysregulated coagulation control involving antithrombin, activated protein C/protein S, and thrombomodulin results in the systemic pre-DIC state transitioning to the DIC state. This manifests itself as prolonged PT/APTT and the tendency to bleed. Because lipoprotein lipase activity is under the control of TNF-α [63], persistent high levels of TNF-α in the circulation can lead to abnormal lipid metabolism. Eventually, multiple organ failure via a series of events occurs in the following order: an elevation of the serum triglyceride level, a reduction of the serum total cholesterol level, renal failure as reflected by an increase of serum creatinine, liver dysfunction as evidenced by increased levels of alanine transaminase/total bilirubin, and pancreatic insufficiency represented by an elevation of serum amylase and lipase levels.

Treatment

Systemic JIA

In the past, there was no alternative but to treat this disease using long-term administration of high-dose corticosteroids to suppress severe systemic inflammation. This regimen greatly affected the quality of life of these children due to the following side effects: obesity, growth retardation, osteoporosis, compression fractures of the vertebrae, femur head necrosis, and steroid diabetes. TNF-α blocking agents, known to be effective for rheumatoid arthritis and

articular JIA, were tried but unfortunately they were found to have limited efficacy. In contrast, an IL-1 receptor antagonist (IL-1Ra), anakinra, was reported to be effective [64].

It was reported in the 1990s that IL-6 was the major factor involved in the pathogenesis of systemic JIA. It was shown blood IL-6 levels peaked one hour before fever onset and that reduction of the fever paralleled decreased IL-6 level [65]. An anti-IL-6 receptor monoclonal antibody, tocilizumab, was developed in Japan. After it was first administered to pediatric patients on a compassionate use basis, it proved to have impressive efficacy in phases II and III clinical trials [66,67] as discussed later and was the first in the world to gain regulatory agency approval.

Macrophage activation syndrome

Previously, the prognosis of patients with macrophage activation syndrome was extremely poor as in virus-associated hemophagocytic syndrome and septic systemic inflammatory syndrome. However, the pathophysiological mechanisms in macrophage activation syndrome have gradually become apparent, and clinical manifestations and the fluctuating laboratory parameters can be explained by the presence of excessive amounts of inflammatory cytokines [9]. Thus, macrophage activation syndrome can be managed at this time by the following approaches: alleviation of activated macrophages and dendritic cells by corticosteroids in addition to anticoagulant therapy; inhibition of the mitochondrial permeability transition by cyclosporine to deal with tissue/cellular injury caused by inflammatory cytokines; and plasma exchange to reduce excessive inflammatory cytokines [49]. These treatments are life-saving for most patients in our hospital.

Tocilizumab therapy (anti-IL-6 therapy)

IL-6 alone is not sufficient to cause inflammation, but when complexed with the soluble IL-6 receptor or the membrane-bound IL-6 receptor, gp130, is triggered to transduce inflammatory signals [68]. Consequently, tocilizumab blocks the IL-6 binding site and inhibits signaling by binding to both soluble and membrane-bound IL-6 receptors [69].

Tocilizumab has such a strong anti-inflammatory effect that a dose of 8 mg/kg already decreases fever within hours administration and alleviates malaise and anorexia. About one week after treatment initiation, the CRP level returns almost to normal, and arthritis starts to improve in a couple of weeks [66]. The IL-6 level may rise temporarily because of the lack of soluble IL-6 receptors in addition to the smoldering inflammation, but is generally reduced to undetectable levels in 3–6 months. Biweekly administration of tocilizumab, if repeated for a period of several months to several years, achieves an improvement rate of around 90% as evaluated by ACR Pedi 70 [67]. Briefly, it can be safely said that IL-6 has a leading role in systemic inflammation of systemic JIA, as evidenced by an anti-IL-6 receptor monoclonal antibody effectively depressing inflammation through blocking IL-6 signaling [70]. Recently, the efficacy and tolerability of tocilizumab for systemic JIA patients has been confirmed by De Benedetti and the European group [71].

Conclusions on systemic JIA

Blockade of signaling by the single cytokine IL-6 can abrogate inflammation in systemic JIA, which documents that IL-6 has a leading role in this disease. In vitro studies of CRP or SAA using hepatic cell cultures revealed the requirement for cooperation between IL-6 and IL-1β, implicating IL-1β as well as IL-6 in the pathogenesis of inflammation in systemic JIA. The efficacy of anakinra [64], and more recently canakinumab [72] is consistent with such a role for IL-1β.

Macrophage activation syndrome is a pathological condition which progresses from systemic JIA due to dysregulation of multiple inflammatory cytokines including TNF-α and IFN-γ. This results in cell/tissue damages and disruption of endothelial cells. However, the sequence and quantity of each cytokine remain to be investigated, and, more importantly, mechanisms regulating the production of each cytokine and their mutual effects are completely unknown. Hopefully, a way to comprehensively block the production of inflammatory cytokines will be developed in future, possibly an NF-kB blocking agent, or a way to block the augmentative loop of inflammatory response or to restore the negative feedback loop will be established [73,74].

Cryopyrin-associated periodic syndrome and IL-1β

Clinical manifestations and changes of laboratory data

Patients with cryopyrin-associated periodic syndrome (CAPS) present with periodic fever, urticaria-like skin rash, inflammation of the central nervous system and joint symptoms. They present with a variety of clinical symptoms such as amyloidosis because of the inflammation sustained over a prolonged course [75].

CAPS is divided into the following three categories according to the severity of the clinical symptoms [76,77]: familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), and chronic infantile neurological cutaneous and articular syndrome (CINCA; also known as neonatal-onset multisystem inflammatory disease [NOMID]). Each is caused by the same gene mutation, *CIAS1* [75].

FCAS

FCAS is regarded as the mildest form of CAPS [81]. It has an onset immediately after birth or before 6 months of age in 95% of cases. The onset is precipitated by exposure to low temperatures for 2–3 h. Clinical manifestations include urticaria-like skin rash that appears first in the limbs, spreading over the trunk. The skin rash is not urticaria itself but represents perivascular neutrophilic invasion in the skin as observed histologically. Concurrently, it is accompanied by fever, arthralgia, conjunctivitis, digestive symptoms, severe thirst, sweating, and headache. The complication of amyloidosis is rarely seen (2–4% of cases).

MWS

MWS is of intermediate severity among the categories of CAPS and its onset is at a later age than FCAS. It develops in adults as well as children, but with a preponderance in adolescence. It is characterized by a sudden onset of fever, accompanied by skin rash, arthritis/arthralgia, muscle pain, headache, conjunctivitis, episcleritis, uveitis, and other symptoms. A paroxysm of fever lasts for nearly three days. Fifty to seventy percent of patients eventually suffer hearing impairment or deafness, and progression to amyloidosis occurs in 25% of cases [75]. The *NLRP3 (CIAS1)* mutation is detected in 65–70% of cases.

NOMID

NOMID is also called CINCA and is the most severe form of CAPS [76,77]. About half of CINCA cases are born premature or have very low birth weight, with disease onset at birth or within several weeks. Fever and urticaria-like skin rash appear almost every day. Chronic aseptic meningitis causes repetitive irritability, vomiting, and headache. As the patient grows, neurological disorders, including hydrocephalus, developmental disorder, mental retardation, and hearing disorder progress.

Ophthalmologic findings include conjunctivitis, uveitis, optic pupillitis, and visual disturbance. Skeletal/cartilaginous

dysgenesis brings severe arthropathy before about 2 years of age. Excessively hypertrophied/ossified bone/cartilage of the distal end of the femur can be felt like a hard mass. X-rays show remarkable ossification, flaring, and abnormality as well as deformity of the epiphyseal nucleus of the distal end of the femur [78]. The patient is not able to walk due both to joint deformity and pain. The body shape is affected by disorders of the joints at different sites, resulting in short stature, prominent forehead, microcephaly, saddle nose, clubbed fingers, and wrinkled skin. NOMID has the poorest CAPS prognosis and around 20% of patients die before 20 years while the remainder progress to amyloidosis [79]. The gene mutation responsible for CAPS is detected in 50–60% of cases.

CIAS-1 gene mutation and pathological conditions caused by IL-1β

CAPS is caused by the *CIAS-1* gene mutation resulting in changed cryopyrin protein in NLRP3 (which forms a core protein of the inflammasome complex that controls production as well as release of IL-1β) [76,77]. Physiologically, the NLRP3 protein, when stimulated by PAMPs and DAMPs, forms an inflammasome complex associating pro-caspase-1 and ASC proteins. Stimuli mediated via TLRs results in pro-IL-1β and pro-IL-18 production, that is, precursors of IL-1β and IL-18, respectively [80]. Casapase-1 activated by the inflammasome then cleaves pro-IL-1β and pro-IL-18 to produce mature secreted forms of IL-1β and IL-18. IL-1β secreted from cells binds to IL-1 receptors and causes inflammation [80]. Such extracellular secretion of IL-1β requires $P2X_7$ receptor activation by ATP, a second stimulatory molecule [81]. Gene mutation-induced alteration of the NLRP3 protein maintains the inflammasome in an active state for IL-1β production and secretion, in a gain-of-function fashion [75]. In CAPS, the excessive amount of IL-1β produced and secreted is implicated in the pathogenesis of chronic inflammation.

In 2009, a clinical trial of the anti-IL-1β monoclonal antibody canakinumab [82] was started in Japan to treat 19 CAPS patients (MWS: 7 patients and NOMID: 11 patients) in whom the *CIAS1* gene mutation had been confirmed [83]. Eleven of these patients were aged 2–16 years and nine were over 16 years with the oldest being 48 years of age. Therapeutic efficacy was evaluated by improvement of clinical symptoms and the inflammatory markers CRP and SAA. Complete remission was assessed from the point of view of both clinical and serological remission: clinical remission was assessed by comprehensive scoring of autoinflammatory disease activity and dermatological symptomatology, and serological as CRP < 1 mg/dL and SAA < 10 μg/mL.

The initial canakinumab administration achieved a complete remission in 89.5% (17/19 cases) within 4 weeks and with a further remission by 24 weeks. A dramatic effect was thus seen in 95% of the patients, especially the improvement of skin symptoms, headache, conjunctivitis, and lassitude. Central nervous system disorders went into remission in 33.3% patients (4/12 cases) 8 days after starting therapy, and in 75% at the end of the clinical trial. In all cases, the CRP and SAA levels were decreased within 14 days of administration. However, 18 patients (95%) experienced at least one adverse event during the treatment course. Nasopharyngitis (36.8%), gastroenteritis (31.6%), upper respiratory tract infection (15.8%), and nasal discharge (15.8%) were most frequently observed. Additionally, diffuse vasculitis and pneumonia were seen in one patient. This clinical trial has confirmed a previous European trial [84].

Conclusions on CAPS

Systemic inflammation subsides after anti-IL-1β monoclonal antibody administration in CAPS, showing that IL-1β is the leading cytokine in the pathogenesis of CAPS. Thus, it has been demonstrated that the idea of inflammasomopathy is not misplaced when considering mechanisms of CAPS development [85].

Although there are protein abnormalities in the inflammasome in CAPS, questions arise as to why fever is periodic not sustained, and the major question of what triggers inflammasome activation. Can we not develop any therapeutic method to eliminate triggering factors? This will probably become the major task for the future.

Single-cytokine blocking therapy and its prospects

Inflammation is caused by inflammatory cytokines. These cytokines may be implicated in the pathogenesis of certain diseases if produced and released in excess, although they are engaged in essential biological defense mechanisms under normal circumstances. Typical diseases of excess inflammatory cytokine production are Kawasaki disease, systemic JIA and CAPS. In these diseases, different patterns of inflammatory cytokines are produced by known mechanisms of interactive stimulation. Each disease entity seems to have one specific *leading cytokine* in the clinical setting. We showed that we could end inflammation by blocking the appropriate leading cytokine in these diseases: first, in Kawasaki disease, an acute inflammatory disease, and where

Table 1. Differences between inflammation/inflammatory diseases and immune system/autoimmune diseases.

	Inflammation/inflammatory diseases	Immune system/autoimmune diseases
Pathogenic basis	Innate immunity	Adaptive immunity
Competent cells	Dendritic cells	CD4 + T cells:Th1/Th2/Th17/Treg
	Monocyte/macrophage	CD8 + T cells, B cells, macrophage
Activators	PAMPs/DAMPs	Antigen
Receptors	TLR/MDA5/RIG-I/NLR	TCR
Gene products	type I IFN	Antibodies
	Inflammatory cytokines	
Diseases due to Gene mutation	Congenital innate immuno-deficiency: deficiencies of NEMO/MyD88/IkBα/IRAK4	Primary immunodeficiency: CVID/agamma-globulinemia/ WAS/SCID/HIES etc.
Representative	Periodic fever syndrome: FMF/PFAPA/TRAPS/MVK/CAPS Systemic JIA, CRMO, Behcet D.	Autoimmune diseases: SLE, MCTD, SjS, J-SSc, etc.
Therapy	Removal of inflammatory cytokine	Immunosuppressive therapy, depletion of B cells
	Suppression of activated macrophages/dendritic cells	

PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; TCR, T cell receptor; TLR, toll-like receptor; MDA-5, melanoma differentiation-associated gene-5; RIG-I, retinoic acid-inducible gene-I; NLR, Nod-like receptor; IFN, interferon; CVID, common variable immunodeficiency; NEMO, NF-kB essential modulator; FMF, familial Mediterranean fever; PFAPA, periodic fever, aphthous, stomatitis, pharyngitis and cervical adenitis; TRAPS, tumor necrosis factor receptor-associated periodic syndrome; MVK, mevalonate kinase deficiency; CAPS, cryopyrin-associated periodic syndrome; SLE, systemic lupus erythematosus; MCTD, mixed connective tissue disease; SjS, Sjogren syndrome; J-SSc, juvenile systemic sclerosis; JIA, juvenile idiopathic arthritis; CRMO, chronic recurrent multifocal osteomyelitis.

TNF-α appears to be the leading cytokine for systemic inflammation and coronary arterial vasculitis; second, in systemic JIA, in which an excessive amount of IL-6 is implicated in the pathogenesis; third, in CAPS which is caused by overproduction of IL-1β due to a single-gene mutation. Currently, inflammatory cytokine blocking therapy using appropriate monoclonal antibodies specific for the leading cytokine is proving effective. However, such therapy can deal only with the cytokine already as it is produced and secreted, without addressing the causative factors responsible for this. There must be regulatory mechanisms in the innate immune system controlling the expression level as well as the order of expression of individual cytokines. It is therefore important to determine negative feedback mechanisms or downregulatory mechanisms for already-activated inflammation and inflammatory cytokine production. In the long run, establishment of techniques to control the regulatory system would make disease management easier from the clinical view point (Table1).

Conclusion

Inflammation is the manifestation of important innate immune mechanisms, different from the classic adaptive immune system. Consequently, since inflammatory disease involving innate immunity cannot be effectively treated with immunosuppressants, the major therapeutic strategy is to control inflammatory cytokines. Clarification of the dysregulated mechanisms responsible for excessive inflammatory cytokine production at the cellular level remains a task for the future.

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Conflict of interest

Shumpei Yokota and Takako Miyamae hold a patent for tocilizumab and receives royalties for Actemra.

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Original article

Clinical and laboratory features of fatal rapidly progressive interstitial lung disease associated with juvenile dermatomyositis

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Abstract

Objective. Rapidly progressive interstitial lung disease (RP-ILD) is a rare but potentially fatal complication of JDM. The aim of this study was to establish markers for the prediction and early diagnosis of RP-ILD associated with JDM.

Methods. The clinical records of 54 patients with JDM were retrospectively reviewed: 10 had RP-ILD (7 died, 3 survived), 19 had chronic ILD and 24 were without ILD. Routine tests included a high-resolution CT (HRCT) scan of the chest and measurement of serum levels of creatine phosphokinase, ferritin and Krebs von den Lungen-6 (KL-6). Anti-melanoma differentiation-associated gene 5 (MDA5) antibodies and IL-18 levels were measured by ELISA.

Results. No differences were found in the ratio of juvenile clinically amyopathic DM between the three groups. Initial chest HRCT scan findings were variable and could not distinguish between RP-ILD and chronic ILD. Anti-MDA5 antibodies were positive in all 8 patients with RP-ILD and 10 of 14 with chronic ILD, but none of the patients without ILD. Serum levels of anti-MDA5 antibody, ferritin, KL-6 and IL-18 were significantly higher in the RP-ILD group than in the chronic ILD and non-ILD groups. Serum levels of IL-18 positively correlated with serum KL-6 ($R = 0.66$, $P < 0.001$).

Conclusion. High serum levels of IL-18, KL-6, ferritin and anti-MDA5 antibodies (e.g. >200 units by ELISA) are associated with RP-ILD. These can be used as an indication for early intensive treatment. Both alveolar macrophages and autoimmunity to MDA5 are possibly involved in the development of RP-ILD associated with JDM.

Key words: juvenile dermatomyositis, interstitial lung disease, interleukin-18, anti-melanoma differentiation-associated gene 5, KL-6, ferritin.

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Introduction

JDM is a rare inflammatory disease characterized by typical skin rashes and muscle weakness. It affects 2–3/million children/yr, however, the frequency differs between ethnic groups [1–3]. Prior to the 1960s, more than one-third of patients died of the disease [4]. Advances in treatment with corticosteroids and immunosuppressants have reduced the mortality rate of JDM to 1–5% [5, 6]. Interstitial lung disease (ILD) is observed in up to 50% of adult DM cases and is a major cause of death when rapidly progressive ILD (RP-ILD) develops in association with clinically amyopathic DM (CADM) [7]. Nevertheless, radiologically confirmed ILD complicates only 2–14% of JDM cases [8, 9]. In a recent Japanese nationwide physician questionnaire-based survey of severe paediatric rheumatic diseases from 2005 to 2009, 13 deaths in patients with JDM were reported; there were >3 deaths in patients with SLE during the same period [10]. Complete clinical records and sera were available in 6 of the 13 JDM patients who died. Surprisingly, all six deaths were attributed to ILD. The Japanese survey demonstrates that RP-ILD is a major cause of death related to JDM in Japan. This prompted this study to establish markers for the prediction and early diagnosis of RP-ILD associated with JDM.

We have reported that the serum Krebs von den Lungen-6 (KL-6) level is a useful marker of ILD associated with JDM [11]. Furthermore, similar to adult cases, anti-CADM-140/melanoma differentiation-associated gene 5 (MDA5) autoantibodies are possible diagnostic markers of JDM-associated ILD [12–14]. Recent studies on adult DM-associated ILD have demonstrated elevated serum levels of both ferritin and IL-18, which is produced by macrophages and dendritic cells (DCs) and activates Th1 response [15–18]. However, cytokine profiles have not been reported in JDM-associated ILD, possibly because of the rarity of the complication. In the present Japanese nationwide collaborative study, we focused on the clinical, radiological and laboratory features of patients with JDM-associated RP-ILD and compared them with those of JDM patients without RP-ILD.

Patients and methods

Definition

Classic JDM was diagnosed according to Bohan and Peter [1]. As this was a retrospective study, muscle weakness was determined by the assessing physician and was not based on validated muscle assessment such as manual muscle test. Juvenile CADM (JCADM) was diagnosed according to modified Gerami *et al.* [19] criteria: hypomyopathic DM was defined as patients with classical cutaneous manifestations of DM and no proximal muscle weakness but with evidence of myositis on laboratory, electrophysiological and/or radiological testing; amyopathic DM patients had no clinical or laboratory evidence of myositis. Gerami *et al.* [19] originally defined JCADM as patients fulfilling the above conditions for ⩾6 months after onset without systemic treatment. However, in the present study we classified all patients without weakness at the commencement of treatment as having CADM, because most of the patients with ILD require early treatment with systemic corticosteroids and immunosuppressants, usually within 6 months after the onset of JDM. The diagnosis of ILD was made by using high-resolution CT (HRCT) scan of the chest and was confirmed by both a radiologist and a paediatric rheumatologist at each institute. RP-ILD was defined as the progression of dyspnoea or HRCT findings within 3 months after the onset of respiratory symptoms or at the time of diagnosis of JDM.

Patients

In the nationwide survey of severe paediatric rheumatic diseases, paediatricians in inpatient health care facilities in Japan were asked about the number of patients with rheumatic disease who had visited the clinic in 2009 and the number of deaths between 2005 and 2009. All the patients were Japanese. Nine institutes reported 13 deaths of children with classic JDM or JCADM. Furthermore, respondents were asked to answer questions about data based on the patients' medical charts. Among the 13 deaths in children with JDM, complete clinical records and sera were available in six patients and were retrospectively analysed. One patient died of *Pneumocystis jirovecii* pneumonia and was excluded. The other five patients died from RP-ILD [10, 21–24]. The number of cases of RP-ILD was increased by including two patients who died of JDM-associated RP-ILD before 2004 and by including three surviving cases with RP-ILD available from the authors' institutes [14, 25]. As a result, 10 patients (7 deceased and 3 survivors) were included in this category. Twenty patients with ILD associated with JDM (followed up by the authors) did not show a rapidly progressive course. One patient was excluded, leaving 19 patients in this chronic ILD group. The excluded patient had chronic ILD and severe myositis complicated by macrophage activation syndrome (MAS); the associated macrophage activation was presumed to be the cause of markedly elevated levels of IL-18 [20]. The clinical features of seven patients with ILD have been previously reported [14, 20–25]. Twenty-four patients with JDM without ILD on chest CT scan from Shinshu University Hospital, Aichi Children's Health and Medical Center and Hokkaido University Hospital were included in the non-ILD group.

Biochemical and serological analyses

Sera were collected from the patients at diagnosis of ILD or, in the case of patients without ILD, at diagnosis of JDM and stored at −20°C until use. Routine laboratory tests included measurement of serum levels of creatine phosphokinase (CK), ferritin and a marker for ILD, KL-6. Anti-MDA5 antibody levels were measured by both ELISA and immunoprecipitation as previously described [13]. Serum IL-18 levels were measured by ELISA according to the manufacturer's protocol (MBL, Nagoya, Japan).

Statistical analyses

The data were analysed by Tukey–Kramer's multiple comparison tests, Fisher's exact tests with Bonferroni adjustment and Pearson's product–moment correlation coefficient using JMP 10.0 for Windows (SAS Institute, Cary, NC, USA)

Ethics

The ethics committee of Shinshu University approved the present study. Written consent was obtained from the parents of the patients according to the Declaration of Helsinki.

Results

Clinical and radiological features of JDM-associated RP-ILD

The clinical and laboratory findings of 10 children with RP-ILD are shown in Table 1. Eight patients showed apparent muscle weakness, although the other two patients were classified as having JCADM. Nine of the 10 patients had characteristic skin findings and high fever (temperature >38°C). Gottron's papules were the most common skin lesion, followed by malar erythema and erythema of the knees and elbows. In contrast, heliotrope rash and ulcerative lesions were rarely observed. Respiratory symptoms such as dry cough, dyspnoea and fine crackles were observed in five, four and six patients, respectively, at diagnosis of ILD. The remaining patients had no respiratory symptoms or signs of ILD at diagnosis. Seven of the 10 patients with RP-ILD died of respiratory failure 1–4 months after the diagnosis of ILD.

HRCT findings of RP-ILD

Lung HRCT scan findings at the time of diagnosis of ILD are summarized in Table 1. Subpleural curvilinear shadow was the most predominant finding. Although localized ground glass opacity (GGO) was observed in six patients, GGOs developed during the disease course in all patients who died of ILD. Three patients (patients 3, 4 and 6) had consolidation around bronchovascular bundles (CABBs) accompanying extensive GGOs. Four patients (patients 1, 4, 6 and 7) developed an air leak such as pneumomediastinum and pneumothorax during the course of the disease. Although patient 1 had only bilateral pleural effusion on the initial HRCT, both elevated serum KL-6 levels and increased gallium-67 uptake on scintigraphy of the lungs were noted. One month later, chest HRCT demonstrated marked consolidation at the base of both lungs [22]. In all cases of death, the final diagnosis leading to death was acute interstitial pneumonia with acute and progressive respiratory failure accompanied by GGOs on HRCT. The clinical diagnosis was consistent with diffuse alveolar damage (DAD) patterns on autopsy or biopsy.

Comparison of the clinical features of the chronic ILD and non-ILD groups

The clinical features of the three groups are summarized in Table 2. The age of onset was significantly higher in the chronic ILD group than in the non-ILD group. No differences were found in the ratio of JCADM among the three groups. Seven of the 10 patients with RP-ILD died despite intensive treatment with methylprednisolone pulse therapy in combination with CSA and/or i.v. CYC, whereas none of the patients in the chronic ILD and non-ILD groups died.

Comparison of the laboratory features of the chronic ILD and non-ILD groups

The laboratory findings of the three groups are summarized in Table 2. Although serum CK levels were significantly higher in the non-ILD group than in the chronic ILD group, there was no significant difference between the RP-ILD and non-ILD groups. Serum KL-6 levels were significantly higher in the RP-ILD group than in either the chronic ILD or the non-ILD group. Serum ferritin levels in both the RP-ILD and chronic ILD groups were higher than those in the non-ILD group.

All 8 patients with RP-ILD and 10 of 14 patients with chronic ILD were positive for anti-MDA5 antibodies, but none of the 22 patients without ILD were positive for the antibodies. Titres of anti-MDA5 antibodies were significantly higher in the RP-ILD group than in either the chronic ILD or the non-ILD group (Table 2 and Fig. 1).

Serum IL-18 levels were significantly higher in the RP-ILD group than in the chronic ILD or non-ILD group (Table 2 and Fig. 2). Serum IL-18 levels correlated well with serum KL-6 levels ($R = 0.66$) but not with ferritin levels (Fig. 3 and data not shown). A patient with severe myositis, MAS and chronic ILD, who was excluded from statistical analyses, showed high serum levels of IL-18 (3265 pg/ml), ferritin (2235 ng/ml) and KL-6 (2096 U/ml), but only mild elevation of anti-MDA5 antibody levels (9.5 units) [20].

Sera were serially tested in two patients with RP-ILD who survived and two patients with chronic ILD who were positive for anti-MDA5 antibody. Serum levels of anti-MDA5 antibodies and IL-18 returned to below the cut-off values or to undetectable levels at remission of ILD (data not shown).

Discussion

Although previous studies have reported multiple organ involvement such as muscle weakness, aspiration pneumonia, myocarditis, peptic ulcer and sepsis as causes of death in JDM, the prognosis has improved through recent advances in the management of the disease [5, 26]. The Japanese nationwide survey demonstrated RP-ILD as a remaining major cause of death in JDM. The UK and Ireland national registry from 2000 to 2005 indicated only one death in patients with JDM [27]. A recent study in the USA that enrolled 329 patients with JDM recorded only eight deaths from 1999 to 2011, three of which were due to ILD [28]. Given the higher prevalence of adult CADM-associated RP-ILD in Asian countries, Japanese children with JDM may also be predisposed to RP-ILD compared with other ethnicities [7, 29]. In our previous nationwide survey we analysed the number of patients

TABLE 1 Clinical course of 10 children with JDM or JCADM-associated rapidly progressive ILD

Sex	Male	Female	Female	Male	Female	Female	Male	Female	Female	Male
Diagnosis	JDM	JCADM	JDM	JDM	JDM	JCADM	JDM	JDM	JDM	JDM
Age of JDM onset, years	9	4	4	10	6	4	7	1	13	7
Fever (>38°C)	+	+	+	+	+	+	+	+	+	−
Gottron's sign	+	+	+	−+	+	+	+	+	+	+
Malar rashes	+	+	+	−	+	+	+	+	+	+
Heliotrope rashes	−	−	−	−	−	+	+	+	+	+
Skin ulceration	−	−	−	−	−	−	+	+	−	−
Dry cough or dyspnoea at diagnosis of ILD	−	+	−	+	+	+	+	−	−	−
Interval between onset of JDM and diagnosis of ILD, months	5	3	1	1	5	6	2	5	1	1
Initial CT scan	PE	SCS	CABB, GGO, TB, SCS	CABB, GGO, SCS	SCS	CABB, GGO, TB, SCS	GGO	CABB, SCS	GGO, SCS	GGO, SCS
Outcome	Died	Died	Died	Died	Died	Died	Died	Alive	Alive	Alive
Autopsy	DAD	DAD	DAD	DAD[a]	DAD	ND	DAD			
Interval between diagnosis of ILD and death, months	4	4	1	3	2	1	2			
Interval between onset of respiratory symptoms and death, months	4	2	1	7 weeks	6.5	5	2			
Reference	[22]		[23]				[20]		[20]	

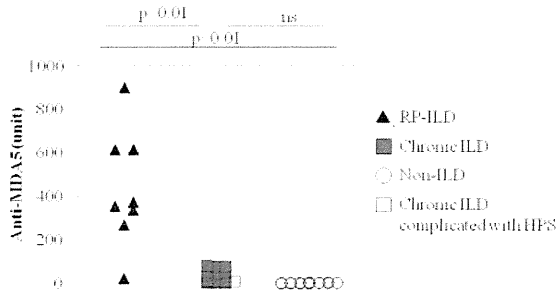
[a]Surgical lung biopsy. CABB: consolidation around bronchovascular bundles; DAD: diffuse alveolar damage; GGO: ground-glass opacity; JCADM: juvenile clinically amyopathic dermatomyositis; ND: not done; PE: pleural effusion; RP-ILD: rapidly progressive interstitial lung disease; SCS: subpleural curvilinear shadow; TB: traction bronchiectasis.

TABLE 2 Comparison of clinical and laboratory features

				P-value			
	RP-ILD ($n=10$)	Chronic-ILD ($n=19$)	Non-ILD ($n=24$)	*a*	*b*	*c*	Statistical analysis
Age, mean (S.D.), years	6.3 (3.5)	9.0 (3.6)	6.0 (3.3)	0.119	0.073	0.979	Tukey-Kramer test[b]
Sex, male/female	4/6	7/12	11/13	0.466	0.390	0.636	Fisher's exact test[a]
JCADM, *n*	2	2	3	0.337	0.613	0.367	Fisher's exact test[a]
Mortality, % (*n* dead/ *n* alive)	70.0 (7/3)	0.0 (0/19)	0.0 (0/24)	<0.001	0.390	<0.001	Fisher's exact test[a]
CK, mean (S.D.), IU/l	403.1 (604.2)	473.7 (1304.8)	1790.3 (3202.1)	0.999	0.012	0.043	Tukey-Kramer test[b]
KL-6, mean (S.D.), U/ml	2045.6 (881.5)	718.3 (699.0)	283.1 (113.3)	<0.001	0.001	<0.001	Tukey-Kramer test[b]
Anti-MDA5, mean (S.D.), units	387.9 (288.9) ($n=8$)	33.3 (30.1) ($n=14$)	2.4 (1.7) ($n=22$)	<0.001	0.734	<0.001	Tukey-Kramer test
Anti-MDA5 positive cases (cut-off value 8.0 units), %	100 ($n=8$)	71.4 ($n=14$)	0.0 ($n=22$)	0.327	<0.001	<0.001	Fisher's exact test[a]
IL-18, mean (S.D.), pg/ml	1447.0 (941.4) ($n=8$)	470.0 (341.6) ($n=19$)	570.1 (474.0) ($n=24$)	<0.001	0.904	<0.001	Tukey-Kramer test
Ferritin, mean (S.D.), ng/ml	355.4 (136.8) ($n=8$)	222.8 (129.3) ($n=19$)	131.2 (160.4) ($n=24$)	0.119	0.018	<0.001	Tukey-Kramer test[b]

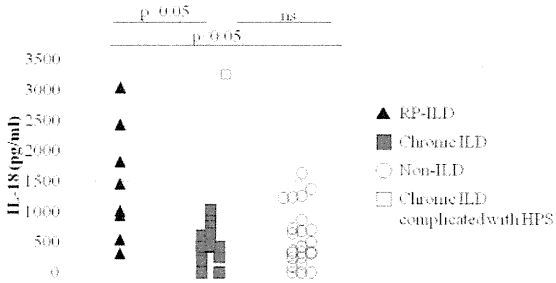
[a]To identify the difference among three groups, Fisher's exact test with Bonferroni adjustment was performed. $P<0.016$ was considered significant. [b]Tukey-Kramer test after log transformation. *a*: RP-ILD *vs* chronic-ILD; *b*: chronic-ILD *vs* non-ILD; *c*: RP-ILD *vs* non-ILD; CK: creatine phosphokinase; ILD: interstitial lung disease; JCADM: juvenile clinically amyopathic DM; KL-6: Krebs von Lungen-6; MDA5: differentiation-associated gene 5; ns: not significant; RP-ILD: rapidly progressive ILD.

Fig. 1 Chart of serum anti-MDA5 concentration



Serum anti-MDA5 antibody titres were significantly higher in RP-ILD than inchronic ILD or non-ILD with $P < 0.05$ (Tukey–Kramer test). One patient with chronic ILD (open square) is excluded from the statistical analysis. ns: not significant; ILD: interstitial lung disease; RP-ILD: rapidly progressive interstitial lung disease; HPS: haemophagocytic syndrome.

Fig. 2 Chart of serum IL-18 concentration

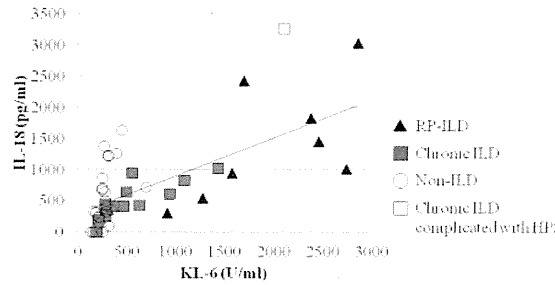


Serum IL-18 levels were significantly higher in RP-ILD than in chronic ILD or non-ILD with $P < 0.05$ (Tukey–Kramer test). One patient with chronic ILD (open square) is excluded from the statistical analysis. ns: not significant; ILD: interstitial lung disease; RP-ILD: rapidly progressive interstitial lung disease; HPS: haemophagocytic syndrome.

with rheumatic diseases who visited hospitals in 2009 and the number and causes of deaths between 2005 and 2009. Furthermore, we included five additional patients with RP-ILD who had presented to our hospital before the study period. A cohort study that captured all JDM cases nationwide is needed to determine the actual prevalence of ILD and the mortality rate of Japanese patients with JDM.

In the present study we could not identify any characteristic clinical features specific to JDM associated with RP-ILD. HRCT showed diffuse GGOs in all the deceased patients, which was consistent with a DAD pattern on autopsy. However, initial HRCT findings were variable and indistinguishable from those of survivors with RP-ILD or chronic ILD. Final radiological and pathological findings may represent merely the end stage of the disease,

Fig. 3 Correlation between KL-6 and IL-18



The closed triangle, closed square and open circle plots show RP-ILD, chronic ILD and non-ILD groups respectively. The coefficient of determination for total data was 0.66 ($P < 0.001$) indicating strong correlation between KL6 and IL18 (Pearson product–moment correlation coefficient). One patient with chronic ILD (open square) is excluded from the statistical analysis. ILD: interstitial lung disease; RP-ILD: rapidly progressive interstitial lung disease; HPS: haemophagocytic syndrome.

regardless of the original clinicopathological entities of ILD. Two of the four patients with pneumomediastinum and pneumothorax (patients 6 and 7, respectively) showed ulcerative lesions of their skin. Vasculopathy associated with JDM could have caused ulceration of both skin and airway walls, as suggested in adult cases [30].

We have reported that anti-MDA5 antibody is a useful disease marker of JDM-associated ILD [14]. The present study also demonstrated that higher levels of the antibody (e.g. >200 units by ELISA) were found in all but one of the RP-ILD group (patient 1), whereas the chronic ILD group had lower titres (<100 units). In addition, the titre of anti-MDA5 antibody declined to below the cut-off value (data not shown). Thus the antibody may help to differentiate RP-ILD from chronic ILD and may help in monitoring the response to treatment in JDM-associated RP-ILD. A similar correlation of the antibody titre with the activity of ILD has recently been reported in adult DM [31]. The antibody was originally reported as a disease marker of CADM-associated RP-ILD but is also detected in some adult cases of DM with chronic ILD on the basis of sensitive immunoblot analyses [12, 13, 32]. Given that anti-MDA5 antibodies were detected regardless of the severity of muscular lesions in our series, the antibodies are possibly related to ILD itself rather than JCADM. On the other hand, anti-MDA5 antibodies are associated with symmetrical arthritis, myositis and ILD, but not with CADM-associated RP-ILD in the USA [33]. Thus the clinical significance of the antibodies may differ between ethnic groups.

In addition to anti-MDA5 antibody, serum levels of ferritin, KL-6 and IL-18 were associated with RP-ILD, although the highest serum level of IL-18 was detected in a patient with severe myositis complicated by MAS and

chronic ILD. IL-18 is produced by both macrophages and DCs in the muscle tissues of patients with DM; IL-18 attracts plasmacytoid DCs that produce type 1 IFNs and correlates with disease activity in adult DM/PM patients without ILD [16, 17]. Extremely high levels of ferritin and IL-18 are reported in systemic JIA-associated MAS [34]. In addition, the association of elevated serum IL-18 levels with RP-ILD, as demonstrated in the present study, has also been reported in adult DM-associated ILD [35–37]. Activated alveolar macrophages are consistently found in bronchoalveolar lavage fluid from patients with DM-associated ILD [15]. Together, macrophages or DCs in the muscle, bone marrow and lungs are likely to play critical roles in myositis, MAS and JDM-associated ILD, respectively. Thus high levels of IL-18 or ferritin may not necessarily reflect the presence of RP-ILD in patients with severe myositis or MAS.

Studies of bronchoalveolar lavage fluid have also demonstrated restricted Vβ gene usage of T cell receptors and the presence of $CD8^+HLA\text{-}DR^+$ T cells in DM-associated ILD [38, 39]. Because IL-18 stimulates Th1 cells [18], T cells activated by alveolar macrophage-derived IL-18 could contribute to tissue destruction of the lung in an antigen-specific manner. Furthermore, since autoantigens identified by reactivity with autoantibodies also stimulate self-reactive T cells [40], MDA5 could be a target antigen of the T cells in DM/JDM-associated RP-ILD.

Of note, there was strong correlation between serum levels of IL-18 and KL-6. KL-6 is produced by type II pneumonocytes and bronchiolar epithelial cells, particularly during their regeneration. Furthermore, KL-6 functions as a chemoattractant for fibroblasts and is generally considered a biomarker of ILD that reflects the severity of the disease [41–43]. Given that the correlation between KL-6 and IL-18 is not initially observed in adult DM-associated ILD [44], remodelling of the lung may occur at an earlier phase of RP-ILD in JDM rather than in adulthood.

All three survivors with RP-ILD were found to have ILD on the basis of elevated KL-6 levels and HRCT findings and were treated with methylprednisolone pulse therapy in combination with CSA and/or monthly i.v. CYC before the development of respiratory symptoms. Thus screening for ILD using chest HRCT scan and routine monitoring of KL-6 levels is recommended for all patients with JDM regardless of respiratory symptoms. We have reported the efficacy of CSA in combination with methylprednisolone pulse therapy for JDM-associated ILD [21]. Early combination therapy with corticosteroid, CSA and i.v. CYC may further reduce the mortality of RP-ILD as reported in adult cases [45].

In conclusion, our results suggest the involvement of both autoimmunity and alveolar macrophages in the development of RP-ILD. Initial CT findings are often indistinguishable between RP-ILD and chronic ILD associated with JDM, however, early development of diffuse GGOs may predict poor outcome. Elevated serum levels of IL-18, KL-6, ferritin and anti-MDA5 antibody (>200 units by ELISA) are associated with RP-ILD in JDM and are indications for early intensive treatment.

Rheumatology key messages

- Rapidly progressive interstitial lung disease is a major cause of death in Japanese patients with JDM and needs early attention.
- Elevated serum IL-18, KL-6, ferritin and MDA5 antibodies are associated with RP-ILD.
- Both autoimmune processes and alveolar macrophages could be involved in the development of JDM-associated RP-ILD.

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ORIGINAL ARTICLE

Mycophenolate mofetil as maintenance therapy for childhood-onset systemic lupus erythematosus patients with severe lupus nephritis

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Abstract

Objectives. We evaluated histological changes occurring in renal biopsy specimens, between the time before initial induction therapy and after 12 months' maintenance therapy, as well as changes in laboratory parameters, SLE disease activity (SLEDAI), and dosage of corticosteroid (CS) in childhood-onset systemic lupus erythematosus (SLE) patients treated with mycophenolate mofetil (MMF).

Methods. A retrospective analysis was performed on nine patients diagnosed with childhood-onset SLE and lupus nephritis. They were treated with pulsed mPSL and intravenous cyclophosphamide as induction therapy and MMF (500–1500 mg/day) plus CS as maintenance therapy. Renal biopsy was performed before the initial induction therapy and after 12 months' maintenance therapy.

Results. Pathological findings at second biopsy were improved in eight of nine patients (89%). The findings of SLEDAI, urinalysis, and blood tests also showed improvement. CS doses could be tapered satisfactorily. Adverse events were observed in two patients. No patients treated with MMF experienced any disease flares during maintenance therapy.

Conclusions. MMF as maintenance therapy might be useful in that not only the histological findings of lupus nephritis were improved, but also CS doses could be beneficially tapered. Nonetheless, this is a retrospective report of only nine cases and further prospective multicenter studies are necessary.

Keywords

Childhood-onset systemic lupus erythematosus, Lupus nephritis, Mycophenolate mofetil, Intravenous cyclophosphamide

History

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Introduction

Childhood-onset systemic lupus erythematosus (c-SLE) and lupus nephritis are more severe and have a worse prognosis than in adults [1,2]. Renal outcome in adults has improved over the last few decades following the introduction of intravenous cyclophosphamide (IVCY) in the 1980s, and mycophenolate mofetil (MMF) in the 1990s in Western countries [3,4]. However, a precise comparison of one immunosuppressant with another has not yet been carried out in the pediatric field.

SLE is a chronic inflammatory disease caused by autoantibody-derived immune complex deposits in the vascular beds of target tissues and organs including glomeruli and the renal microvasculature, resulting in systemic inflammation and lupus nephritis [5,6]. To suppress the autoimmune reaction, high-dose corticosteroids (CS) are the mainstay of therapy from the onset of disease but must be continued long-term to treat repeated flares as CS doses are tapered and then increased again through the decades. The unavoidable administration of high-dose CS for c-SLE has many serious disadvantages in children, causing side effects such as obesity, Cushing syndrome-like symptoms, growth impairment, and osteoporosis [7]. In the 1980s, IVCY was successfully introduced as the standard of care for c-SLE itself as well as severe lupus nephritis [8].

Because the systemic disease SLE affects many internal organs and causes many problems including lupus nephritis, anti-inflammatory and immunosuppressive treatments such as pulsed methylprednisolone (mPSL) and IVCY (1-year course) are initiated as soon as possible after disease onset, depending on the severity, especially for lupus nephritis [9,10]. Until 2006, oral azathioprine (AZA) together with CS was used as standard post-induction maintenance therapy in our institute. More recently, MMF has emerged as a potential alternative maintenance therapy; we have employed MMF with CS treatment as maintenance therapy since 2006.

The main purpose of the present study was to evaluate MMF plus CS regarding efficacy assessed as histological changes in renal biopsies taken before the initial induction therapy and after 12 months' maintenance therapy, and to relate these results to laboratory parameters and disease activity.

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Subjects and methods

Since 2006, we experienced 17 cases of c-SLE. In all cases, renal biopsies were taken from all 17 patients, because of the high probability of lupus nephritis, regardless of whether or not proteinuria was present [11,12]. A retrospective analysis was performed on nine patients diagnosed with severe c-SLE in our institute. Patients eligible for inclusion had to fulfill the American College of Rheumatology criteria for the diagnosis of SLE at < 16 years of age at the time of disease onset [13]. Patients with drug-induced lupus, discoid lupus, or mixed connective tissue disease were excluded.

The nine c-SLE patients with biopsy-proven lupus nephritis who had received induction treatment with pulsed mPSL and IVCY were treated with oral MMF and CS as maintenance therapy regardless of proteinuria [11,12]. MMF was started after the pulsed mPSL phase.

Renal biopsies were obtained twice; first before the initial induction therapy and the second after 12 months' maintenance therapy (Figure 1). The histological findings of the biopsy specimens were examined and compared according to the INS/RPS classification criteria as follows: class I, mesangial immune deposits without mesangial hypercellularity; class II, mesangial immune deposits with mesangial hypercellularity; class III, focal proliferative glomerulonephritis; class IV, diffuse proliferative glomerulonephritis; and class V, membranous nephropathy [14].

All nine patients had severe lupus nephritis class III–V at the initial biopsy (class III: two patients, class IV: seven, class V: two, class V + III: one, class V + IV: one) (Table 1).

For induction therapy, pulses of mPSL were given at 30 mg/kg/day or a maximum dose of 1 g/day for 3 consecutive days, 2 cycles. IVCY was given at 500 mg/m^2 or a maximum dose of 1 g/day, once a month for the first 6 months and once every 2–3 months during the following 6 months (total 8–9 cycles/year). For maintenance therapy, MMF was used at 500–1500 mg/day (10.8–41.6 mg/kg/day), (mean 25.7 ± 8.1 mg/kg/day). The initial CS doses were 0.5 mg/kg/day, being gradually tapered depending on the improvement of clinical manifestations and laboratory parameters (Figure 1).

We evaluated determinants related to the efficacy of the maintenance therapy including disease activity (SLEIDAI), laboratory parameters such as serum albumin, creatinine, serum complement titer, anti-dsDNA antibody titer, and the amount of urinary protein. CS doses for maintenance therapy were also evaluated.

Reappearance of clinical symptoms, or flares reflected in laboratory data (an elevation of anti-dsDNA antibody titer, decreased serum complement components C3 < 50 mg/dl, C4 < 10 mg/dl, and increased urinary protein) were regarded as indicating clinical relapse.

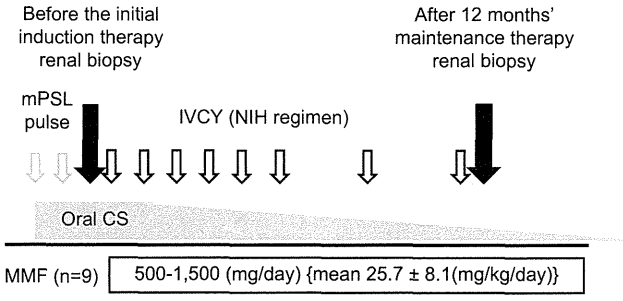

Figure 1. Protocol of induction and maintenance therapy. For induction therapy, pulses of mPSL were given at 30 mg/kg/day or a maximum dose of 1 g/day for 3 consecutive days, 2 cycles. IVCY was given at 500 mg/m^2 or a maximum dose of 1 g/day, once a month for the first 6 months and once every 2–3 months during the following 6 months (total 8–9 cycles/year). For maintenance therapy, MMF was used at 500–1500 mg/day (10.8–41.6 mg/kg/day).

Table 1. Histological findings of the biopsy specimens.

	Patient with c-SLE treatment with MMF	
Renal biopsy (INS/RPS classification)	Before the initial induction therapy (cases)	After 12 months' maintenance therapy (cases)
I	0	2
II	0	4
III	2	3
IV	7	0
V	2	3
Total	9	9
	V + III; I	V + II; I
	V + IV; I	V + III; I

Results

Patients' demographics and clinical characteristics

Table 1 shows the patients' demographics and characteristics in this study. The age at disease onset was 9–15 years (median, 11.5 years). The ratio of females to males was 8:1.

Histological findings of serial renal biopsy

All nine patients had class III or IV nephritis (one had class V + III, and one had class V + IV) (Tables 1 and 2). The frequency of severe mesangial proliferative lesions including class III and class IV thus extended to all patients, suggesting that the c-SLE cases in this study were at highest risk of progression to end-stage renal disease [15]. Proteinuria was detected in six patients at initial examination, and all of the patients eligible for this study had severe hypocomplementemia.

After induction therapy with pulsed mPSL and IVCY, all nine patients were treated with MMF and CS. All completed 12 months' maintenance therapy. The definition of histological improvement was based on decreased levels of disease classification. Eight of these nine patients (89%) showed improvement of histology, with one patient originally class III improving to class II, four from class IV to class I or II, and one from class IV to III. While class IV mesangial proliferative nephritis was improved to class II in the remaining patient, class V membranous nephropathy subsequently progressed (Figures 2 and 3). Initially, there were two patients with class V lesions, one with class III and another with class IV. After 12 months' maintenance therapy, the second renal biopsy of both patients revealed improved membranous depositions. Moreover, one patient with class V + IV histology also had mesangial proliferative lesions which improved to class III. One patient who had class V + III histology remained the same at class III mesangial proliferation.

Table 2. Histological findings of the biopsy specimens in each case.

	INS/RPS classification		
Case	Before the initial induction therapy	After 12 months' maintenance therapy	Improvement
1	IV	II + V	Good
2	IV	I	Good
3	IV + V	III + V	Good
4	IV	II	Good
5	III	II	Good
6	IV	I	Good
7	IV	II	Good
8	IV	III	Good
9	III + V	III + V	Poor

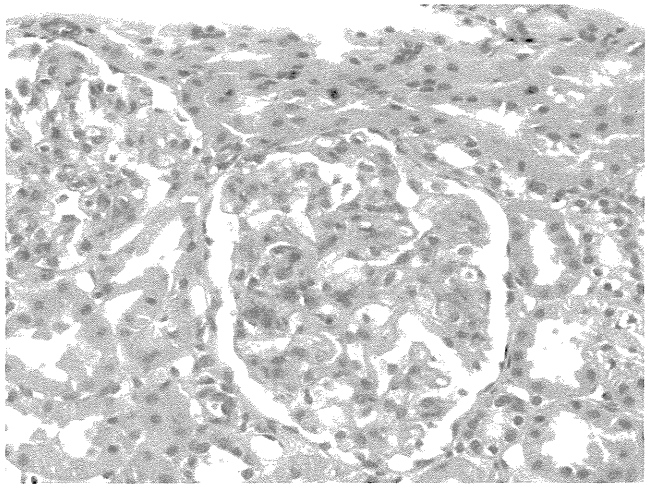

Figure 2. Histology before the initial induction therapy in case 6. This histology demonstrated a moderate mesangial proliferation and wire-loop in segmental areas, and large numbers of dense deposits in the subendothelial site, as seen by electron microscopy.

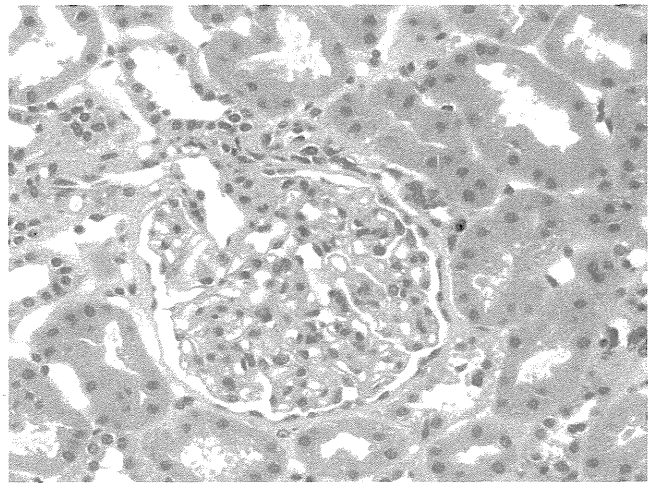

Figure 3. Histology after 12 months' maintenance therapy in case 6. Histological classification was changed from class IV to class I. Mesangial proliferation and wire-loop are no longer seen. The dense deposit decreased even in electron microscopy.

Evaluation of disease activity

Disease activity in c-SLE assessed by SLEDAI before the initial induction therapy was 16.2, which improved to 2.0 after 12 months' maintenance therapy (Table 3, Figure 4).

Evaluation by urinalysis and serology

Table 3 and Figure 5 show laboratory data from urinalysis and serological investigations before the initial induction therapy and after 12 months' maintenance therapy. Compared to the data of the initial assessment, improvements were seen with decreased levels of serum C3, C4, albumin, Cr, and urinary total protein/creatinine (TP/Cr) ratio, and less anti-dsDNA antibody.

CS doses and disease flares

During the maintenance course, CS was tapered. The doses were compared before and 12 months after treatment (Table 3, Figure 4). Furthermore, no patients treated with MMF experienced any disease flares during maintenance therapy.

Adverse events

Adverse events during maintenance therapy were observed in two patients .Herpes zoster was observed in two patients and MMF administration was resumed after a course of acyclovir.

Patient outcome

None of the patients with severe lupus nephritis developed malignancies or died during the observation period.

Discussion

Because a controlled trial is difficult to carry out in the pediatric field due to the small number of c-SLE patients with severe lupus nephritis in Japan, in the present study the efficacy and adverse events of maintenance therapy were retrospectively investigated during short-term treatment eras in a single institution. Remission induction of c-SLE with severe lupus nephritis was by means of mPSL pulse therapy and IVCY [9,10]. The evaluation of those patients that received a combination of CS and MMF more recently as maintenance therapy was reported [16–19] and can be compared with an earlier group receiving a combination of CS and AZA as maintenance therapy [9,17,19]. Satisfactory improvements in renal biopsy histology, disease activity, laboratory data, and corticosteroid-reducing effects in patients that completed 12 months' treatment were observed. Thus, in this retrospective study, the histology of the second biopsy specimen was significantly improved, although two patients with class V lesions (one class V + III and the other class V + IV) had little reduction of membranous deposits in spite of marked reduction of mesangial nephritis.

There were great improvements in the disease activity scores (SLEDAI). Patients had marked improvements in laboratory data (urinary protein, complement (C3, C4), urinary TP/Cr ratio, and anti-dsDNA antibody titer) after 12 months' maintenance therapy,

Table 3. Evaluation of disease activity, urinalysis and serology and CS doses.

		Before the initial induction therapy	After 12 months' maintenance therapy
Alb (g/dl)	(Mean ± SD) (Range)	3.51 ± 0.54 (2.9–4.3)	4.32 ± 0.35 (3.6–4.8)
Cr (mg/dl)	(Mean ± SD) (Range)	0.51 ± 0.27 (0.27–1.18)	0.52 ± 0.09 (0.36–0.65)
C3 (mg/dl)	(Mean ± SD) (Range)	38.3 ± 19.8 (15–72)	89.6 ± 17.2 (66–117)
C4 (mg/dl)	(Mean ± SD) (Range)	2.9 ± 1.4 (1–6)	16.4 ± 5.9 (9–26)
dsDNA (Ill/ml)	(Mean ± SD) (Range)	534.9 ± 648.7 (30–1780)	22.1 ± 19.8 (5–70)
SLEDAI	(Mean ± SD) (Range)	16.2 ± 6.1 (9–26)	2.0 ± 1.9 (0–4)
Urine TP/Cre ratio	(Mean ± SD) (Range)	1.76 ± 1.49 (0.02–3.15)	0.02 ± 0.00 (0.02–0.03)
CS (mg/day)	(Mean ± SD) (Range)	26.7 ± 12.7 (15–60)	8.6 ± 2.4 (6–13)
CS (mg/kg/day)	(Mean ± SD) (Range)	0.68 ± 0.29 (0.38–1.30)	0.19 ± 0.06 (0.13–0.29)

Alb albumin, *Cr* creatinine, *dsDNA* anti-double stranded DNA antibody, *SLEDAI* SLE Disease Activity Index, *CS* corticosteroid.

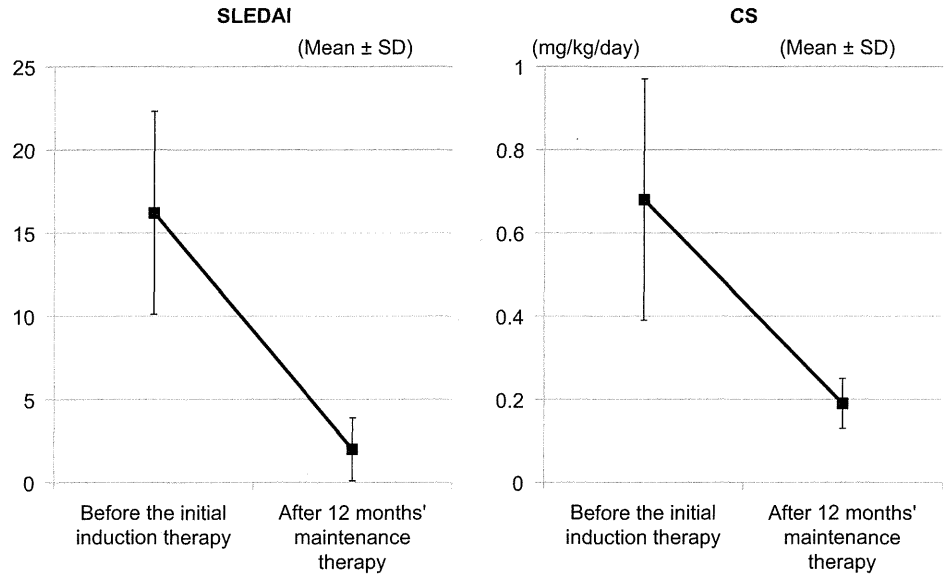

Figure 4. Evaluation of disease activity and CS doses. SLEDAI in the MMF group at the initial visit was 16.2, which improved to 2.0 after 12 months' maintenance therapy. The CS doses in the MMF were compared before and 12 months after treatment. A significant reduction was noted 12 months later.

suggesting that MMF with CS might be effective as a maintenance regimen.

Between 2000 and 2006, we had used AZA as maintenance therapy for c-SLE in 11 patients, of which 4 had flares with a marked decline of serum complement levels, requiring repeated mPSL pulse treatment. In contrast, after 2006, we have used MMF as maintenance therapy in nine cases, with no flares or severe side effects. No patients died or developed malignancies during this study. Regarding adverse events, two patients had herpes zoster, but responded to anti-virals immediately.

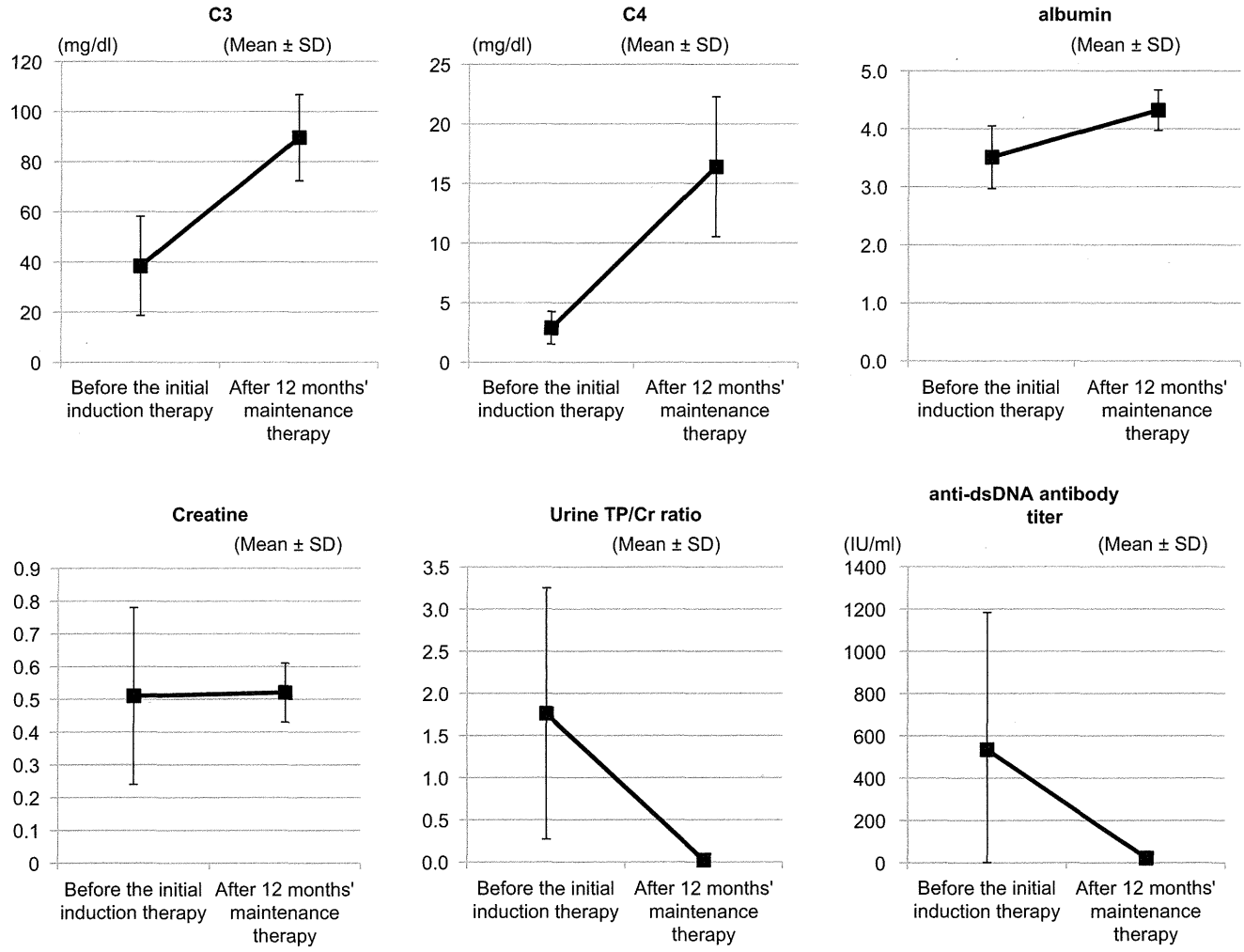

Figure 5. Evaluation of urinalysis and serology. Compared to the data of the initial assessment, patients showed an improvement, with decreased levels of serum C3, C4, albumin, Cr, and urinary total protein/creatinine (TP/Cr) ratio, and less anti-dsDNA antibody.

These data substantiate others' experience in both children and adults, and support the notion that MMF might also be of especial benefit to children because greater tapering of PSL in patients receiving MMF is possible, resulting in a requirement for lower CS doses than with AZA and less flares [16–19]. Lower doses of CS facilitate normal growth and less progression of osteoporosis, the major inevitable side effects of CS use in children.

MMF exerts its effects after being converted to the active metabolite mycophenolate in the blood, and inhibits the purine synthesis pathway, suppresses production of guanosine nucleotides, and interferes with DNA synthesis [20]. A number of studies have reported its efficacy for inhibition of SLE disease activity, alleviation of lupus nephritis, and long-term survival in adults [16,17,19,21]. In particular, it has been proposed as an alternative to IVCY for induction therapy and comparative studies have been carried out in the United States [22,23].

In summary, pulsed mPSL therapy and IVCY for remission induction followed by a combination of MMF and CS as maintenance therapy might be a better combination for c-SLE patients with severe lupus nephritis. It is important to treat c-SLE patients with lupus nephritis with a combination of CS and immunosuppressants for both remission-induction and maintenance in order to achieve anti-inflammatory and immunosuppressive control, reduce adverse events caused by both CS and immunosuppressants, and to prevent flares. In children with severe lupus nephritis, the present study showed that it might be possible to decrease severe renal damage while still reducing the dose of CS when using MMF instead of AZA as part of the maintenance therapy.

However, a number of issues remain to be resolved, such as how to determine the optimal duration of MMF administration, how to find the better way to taper CS doses, and how to replace IVCY with MMF.

There are several limitations to our study. First, it is a retrospective study. Second, it was only possible to include nine patients. Third, the study was carried out at a single institute. Thus, further investigations with more patients and a nation-wide prospective study will be needed.

Conflict of interest

None.

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ORIGINAL ARTICLE

Surveillance for the use of mycophenolate mofetil for adult patients with lupus nephritis in Japan

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Abstract

Objectives. Mycophenolate mofetil (MMF) is used as one of the standard induction/maintenance protocols for lupus nephritis (LN). However, MMF has not been approved for treating LN in any country, resulting in worldwide off-label use of this immunosuppressant. In order to clarify the real-world use of MMF as a treatment for LN in Japan, Japan College of Rheumatology surveyed the use of MMF in daily clinical practice.

Methods. Adult patients with LN who visited enrolled hospitals from October 2008 to September 2013 were surveyed for the initial, maximum, and maintenance doses of MMF. The safety and efficacy of MMF were retrospectively evaluated.

Results. One hundred and thirty-seven LN patients including 116 females were enrolled. The median of initial, maximum, and maintenance doses of MMF were 1.0 g/day, 1.5 g/day, and 1.0 g/day, respectively. Sixty-one adverse events were reported in 39 patients during the follow-up period. Median urine protein level decreased from 1.89 g/gCr to 0.21 g/gCr, meanC3 level increased from 66.4 mg/dl to 80.3 mg/dl, and median anti-DNA antibody titer decreased from 40.6 IU/ml to 10.6 IU/ml.

Conclusion. MMF was commonly used for the treatment of adult LN patients with acceptable efficacy and safety in Japan.

Keywords

Induction therapy, Mycophenolate mofetil, Mycophenolic acid, Proliferative lupus nephritis, Systemic lupus erythematosus

History

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Introduction

Systemic lupus erythematosus (SLE) is a prototype of systemic autoimmune diseases that predominantly affects females in their childbearing ages. Glomerulonephritis complicated with SLE—lupus nephritis (LN)—is one of the most important organ involvements in this disease, being critical for the prognosis of the affected patients [1]. Treatment for LN has been dependent on the long-term use of glucocorticoids (GCs) [2] until cyclophosphamide (CY) was introduced in the 1970s. Treatment of proliferative LN with oral CY at a dose of 2 mg/kg/day resulted in a preferable renal outcome [3], but unwanted side effects, such as alopecia, bone marrow suppression, opportunistic infections, hemorrhagic urocystitis, secondary malignancies, and/or premature menopause, induced the development of intermittent, intravenous administration of CY (IVCY). Since 1986 when Austin et al. [4] reported the efficacy and safety of high-dose IVCY, mainstream of the treatment for proliferative LN has been IVCY with GCs. According to a systematic review on randomized control trials for diffuse proliferative LN [5], IVCY plus GCs retained renal function but had no impact on overall mortality compared with corticosteroids alone. Further, the risk of ovarian failure increased significantly. Azathioprine (AZP) plus GCs reduced the risk for all-cause mortality but had no impact on renal function. Requirement for the smallest effective dose and shortest duration of the treatment by IVCY induced low-dose IVCY called "Euro-lupus regimen" [6]. Although IVCY still remains the mainstream of the induction treatment for proliferative LN, development of other immunosuppressant(s) with better safety profile has been awaited. Although the effect of tacrolimus as an induction therapy has been demonstrated in a relatively small population of the patients [7], its use as an induction therapy for active LN has not arrived consensus due to insufficient randomized control trials in different races/regions.

Mycophenolate mofetil (MMF) is an immunosuppressant originally used for the rejection of transplanted organs. Ginzler et al. [8] compared the effectiveness of high-dose IVCY with MMF for the treatment of proliferative LN. The rate of achieving complete remission was higher and the incidence of severe infections was lower in those treated with MMF. Aspreva Lupus Management Study (ALMS) group randomized patients from around the world

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