Calcineurin inhibitors for adult-onset Still's disease: a multicentre retrospective cohort study

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ABSTRACT

Objective. *To clarify the efficacy and safety of calcineurin inhibitors (CNI) for treating adult-onset Still's disease (AOSD).*

Methods. *This multicentre historical cohort study enrolled the consecutive patients with AOSD according to Yamaguchi classification criteria. The endpoints were set as the time from the initiation of treatment to events, the persistency rate of CNI and safety. Based on the recurrent event data analysis, these endpoints were evaluated for each event. We divided the events into two groups according to the treatment that included CNI or conventional therapy without CNI.*

Results. *One hundred and seventy-eight patients with 247 events were analysed. CNI were predominantly used in 72 events with a recurrent history, typical skin rash, high ferritin levels, and/or severe complications such as macrophage activation syndrome, disseminated intravascular coagulation, serositis, meningitis. CNI led to a significantly longer event-free survival (hazard ratio: 0.57, 95% confidential interval: 0.32–0.99) after adjustment of concomitant medications. Subgroup analysis showed that CNI were effective for AOSD patients with high ALT level (hazard ratio: 0.11, 95% confidential interval: 0.02–0.59) and severe complications (hazard ratio: 0.11, 95% confidential interval: 0.01-0.94). The persistency rate of CNI was 71% at 5th year. Adverse events occurred more frequently in the CNI group (18% vs. 8%, p=0.02); however, CNI did not involve in increased risk of adverse events, including nephrotoxicity, after adjustment (p=0.23).*

Conclusion. *Our retrospective analysis suggested that CNI could be an effective and safe option for treating AOSD.*

Introduction

Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder characterised by high spiking fever, transient salmon-pink rash and non-erosive polyarthritis (1). Although its aetiology has been unknown, predominant Th1 cytokines and activated macrophages are mainly involved in the pathophysiology of AOSD. Th1 immune response increases the production of IL-2, which subsequently activates T cells and macrophages (2). Activated macrophages initiate an inflammatory cascade composed of IL-1, IL-6 and TNF-α. Overproduction of these cytokines, coined as "cytokine-storm", causes the symptoms found in patients with AOSD. This pathophysiological hypothesis provides us the possible therapeutic cytokine targets (3). Because of rarity and severity of the disease, the standard care of AOSD has not been established. AOSD is generally responsive to corticosteroid (CS) therapy, whereas CS monotherapy frequently fails to induce/maintain remission in patients with AOSD. In such refractory cases, methotrexate (MTX) and/or biologics including TNF-α, IL-1, or IL-6 inhibitors are used (4). MTX has relatively high consensus but with low evidence level as a treating option for refractory AOSD. Some randomised controlled trials, retrospective observational studies and/or case series have provided us the evidence on the efficacy and safety of biologics (5-10). In particular, IL-1 and IL-6 inhibitors are widely used with good effect for CS-dependent / MTX-registrant AOSD. However, more treatment options are required for AOSD with intolerant or insensitive to MTX and/or biologics. Calcineurin inhibitors (CNI) down-regulate T cell activation through inhibiting IL-2 transcription and signal transduction. CNI also suppress IL-18/IFN-γ pathway essential for ac-

tivating macrophages and initiating an inflammatory cascade. Therefore, CNI are reasonable therapeutic medication for AOSD as multiple cytokine suppressors, considering that T cells and subsequently activated macrophages play a key role in AOSD. Nevertheless, only a few case series have indicated effects of CNI on patients with AOSD (11-13). To clarify the efficacy and the safety of CNI for AOSD, we conducted a multicentre historical cohort study.

Patients and methods

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines and approved by Hokkaido University Hospital ethics committee (approval no.: 017-0445).

Study design

This is a historical cohort study. The cohort comprised the consecutive patients with AOSD in accordance with Yamaguchi classification criteria (14), who were attending the medical institutions between January 2000 and December 2017. The patients were initially treated with CS. In CS-resistant/dependent cases, MTX, biologics and/or CNI were concomitantly used by each clinician's judgement. Severe complications were defined as macrophage activation syndrome (MAS), disseminated intravascular coagulation (DIC), serositis and meningitis. All data were extracted from the medical records. The primary endpoint was event-free survival which was the time from the initiation of treatment to event defined as death of any causes or major relapse of AOSD. Major relapse was defined as reappearance of symptoms and/or laboratory data abnormalities to require a change of therapeutic regimen with an increase of CS dose. Secondary endpoints were the persistency rate of CNI and safety. Based on the recurrent event data analysis, the endpoints were evaluated for each event. We divided the events into two groups according to the treatment that included CNI (CNI+) or conventional therapy without CNI (CNI-).

Statistical analysis

Categorical variables described as counts and/or percentages were compared with chi-square test. Continuous variables were expressed as the median and quartile. If continuous variables were categorised, the cut-off values were set in reference to upper quartile of the dataset and clinical significance. Event rate and the persistency rate of CNI were estimated by Kaplan-Meier method. Event-free survival were assessed using Cox proportional hazards model for recurrent time-to-event outcomes. In our historical cohort, the demography and severity of AOSD patients was thought to be allocated at random between CNI+ and CNI- group because the treatment regimens were independently used by each clinician's judgement. When we evaluate the efficacy and safety of CNI, concomitant medications can strongly affect the outcome as potential confounding factors. Thus, we adjusted concomitant medications, such as methotrexate, biologics, dose of CS and steroid pulse, in multivariate analysis. We performed the same analysis in subgroups based on the patients' demography, symptom and laboratory data. When the *p*-value was below 0.05 and 95% confident interval (CI) of hazard ratio did not cross the one, the result showed sta-

Table I. Patients' characteristics (n=178).

Female, n	125 (70%)
Age at onset, years	Median: 42, quartile: 30-64
Clinical symptoms	
High spike fever, n	171 (96%)
Arthralgia or arthritis, n	131 (74%)
Typical skin rash, n	112 (63%)
Sore throat, n	70 (39%)
Lymphadenopathy, n	66 (37%)
Hepatosplenomegaly, n	65 (37%)
Leukocytosis, n	98 (55%)
Abnormal liver function, n	96 (54%)
Disseminated intravascular coagulation, n	12 (7%)
Macrophage activation syndrome, n	19 (11%)
Serositis, n	17 (10%)
Meningitis, n	2 (1%)
Comorbidity	
Overall, n	47 (26%)
Diabetes, n	24 (13%)
Hypertension, n	18 (10%)
Dyslipidemia, n	4 (2%)
Heart disease, n	4 (2%)
Chronic kidney disease, n	2 (1%)
Atopic dermatitis, n	2 (1%)
Others, n	6 (3%)

Table II. Treatment for adult-onset Still's disease in our cohort (247 events).

Initial dose of PSL, mg/day	Median: 30, quartile: 24-40
Pulse steroid therapy, n	72 (29%)
Conventional therapy	
PSL monotherapy, n	88 (36%)
PSL + MTX, n	60 (24%)
PSL + TNFi, n	2 (1%)
PSL + IL-6i, n	7 (3%)
PSL + MTX + TNFi, n	4 (2%)
PSL + MTX + IL-6i, n	15 (6%)
Therapeutic regimen including calcineurin inhibitors	
PSL + CNI, n	28 (11%)
PSL + CNI + MTX, n	22 (9%)
PSL + CNI + TNFi, n	4 (2%)
PSL + CNI + IL-6i, n	6 (2%)
PSL + CNI + MTX + TNFi, n	6 (2%)
PSL + CNI + MTX + IL-6i, n	5 (2%)

PSL: prednisolone; MTX: methotrexate; TNFi: tumour necrosis factor inhibitors; IL-6i: interleukin 6 inhibitors; CNI: calcineurin inhibitors.

Table III. Patients' background in therapeutic regimen including calcineurin inhibitors (CNI+) group *versus* conventional therapy without calcineurin inhibitors (CNI-) group.

	CNI+ (71 events)	CNI- (176 events)	*p*-value
Female, %	76.1	70.0	.33
Age at initiation of treatment, years	42 (30-63)	43 (30-66)	
≥ 60 year-old, %	28.2	39.2	.10
Comorbidity, %	**18.3**	**30.7**	**.04**
Recurrent history, %	**52.1**	**35.8**	**.02**
Clinical symptoms			
High spike fever, %	94.4	90.3	.30
Arthralgia or arthritis, %	80.3	72.7	.21
Typical skin rash, %	**73.2**	**54.6**	**< .01**
Sore throat, %	32.4	35.2	.67
Lymphadenopathy, %	25.4	31.8	.32
Hepatosplenomegaly, %	31.0	30.7	.96
Severe complications*, %	**30.0**	**16.0**	**.02**
Laboratory findings			
WBC, /μL	14100 (9400-20600)	11500 (7400-15400)	
Leukocytosis, %	60.6	48.3	.08
CRP, mg/dL	7.9 (2.9-15.5)	7.7 (4.2-13.2)	
≥10.0 mg/dL, %	45.1	35.4	.16
ALT, IU/L	42 (20-125)	36 (19-84)	
≥80 IU/L, %	30.0	26.4	.57
LDH, IU/L	380 (260-670)	330 (230-560)	
≥500 IU/L, %	37.7	28.4	.16
Ferritin, ng/mL	2600 (300-8000)	1000 (300-4500)	
≥5000 ng/mL, %	**37.1**	**23.3**	**.03**
Treatment			
Initial dose of PSL, mg/day	40 (30-50)	30 (20-40)	
≥40 mg/day, %	55.0	45.1	.16
Pulse steroid therapy, %	**47.9**	**21.6**	**< .01**
Methotrexate, %	46.5	44.9	.82
TNF inhibitors, %	**14.1**	**3.4**	**< .01**
IL-6 inhibitors, %	15.5	12.5	.54

Continuous variables were expressed as median (quartile).
*Severe complications include macrophage activation syndrome, disseminated intravascular coagulation, serositis and meningitis.
PSL: prednisolone; TNF: tumour necrosis factor; IL-6: interleukin 6.

Table IV. Adverse events in therapeutic regimen including calcineurin inhibitors (CNI+) group *vs*. conventional therapy without calcineurin inhibitors (CNI-) group.

	CNI+ (71 events)	CNI- (176 events)
Overall, n (%)	**13 (18%)**	**14 (8%)**
Hospitalisation, n (%)	**7 (10%)**	**7 (4%)**
Life-threatening, n (%)	**2 (3%)**	**3 (2%)**
Respiratory infection	4	2
Herpes zoster	3	1
Cytomegalovirus reactivation	1	2
Urinary tract infection	0	2
Gastrointestinal perforation	0	2
Drug eruption	2	0
Septic shock	1	1
Gastrointestinal infection	1	0
Varicella	1	0
Cellulitis	0	1
Malignant lymphoma	0	1
Femoral head necrosis	0	1
Abnormal liver dysfunction	0	1

tistical significance. All analyses were performed using the JMP Pro software (v. 12.0; SAS Institute Inc., Cary, NC, USA).

Results

Patients' background

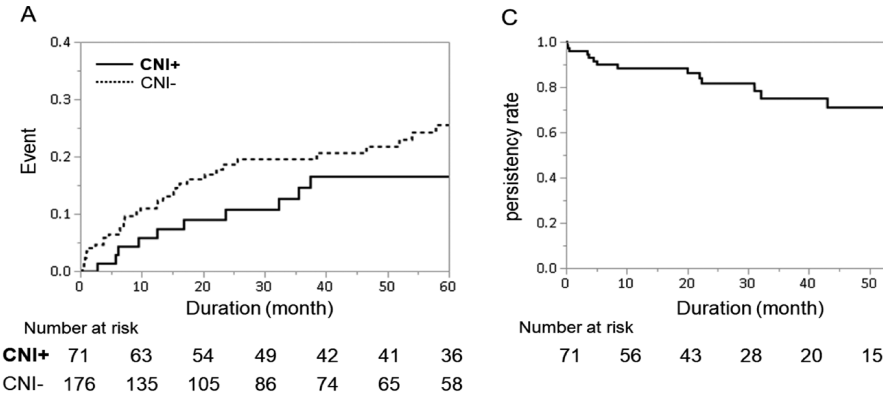
One hundred and seventy-eight patients (125 female and 53 male) were enrolled in this study. Median age at onset was 42 year-old, and median follow-up period was 36 months (interquartile range was 13–129 months). Fever was the most frequent symptom found in 96% of the patients, followed by an arthralgia in 74% and skin rash in 63%. As severe complications, MAS, DIC, serositis and meningitis were found in 11%, 7%, 10% and 1%, respectively (Table I). We analysed 247 events consisted of 147 initial and 100 recurrent events in 178 patients. Median initial dose of prednisolone (PSL) was 30 mg/day, and pulse steroid therapy was given for 72 events in 61 patients. Seventy-one events in 56 patients were treated with therapeutic regimen including CNI (cyclosporine: 11, tacrolimus: 60), and 176 events in 138 patients were treated with the conventional therapy excluding CNI (Table II). CNI were predominantly used in AOSD patients with a recurrent history, meaning that CNI were mainly selected in recurrent cases as retreatment regimen. Typical skin rash, high ferritin levels and/or severe complications were frequent in the CNI+ group. Pulse steroid therapy and TNF-inhibitors were used more frequently in the CNI+ group as concomitant medications. Comorbidities, including diabetes and hypertension, were less frequent in the CNI+ group (Table III).

Event-free survival

The CNI+ group had longer event-free survival than the CNI group (83% *vs*. 75% at the 5th year) (Fig. 1A). After adjustment of the concomitant medications, the hazard ratio (HR) of CNI- was 0.57, and the 95% CI was 0.32-0.99 (Fig. 1-B). Subgroup analysis showed that CNI were effective for AOSD patients with high ALT level (HR: 0.11, 95% CI: 0.02–0.59) and severe complications (HR: 0.11, 95% CI: 0.01–0.94) (Fig. 2).

Safety

The persistency rate of CNI was 71% at the 5th year (Fig. 1-C). Eight patients discontinued CNI because of inadequate efficacy and five patients did due to adverse events. Overall adverse events occurred more frequently in the



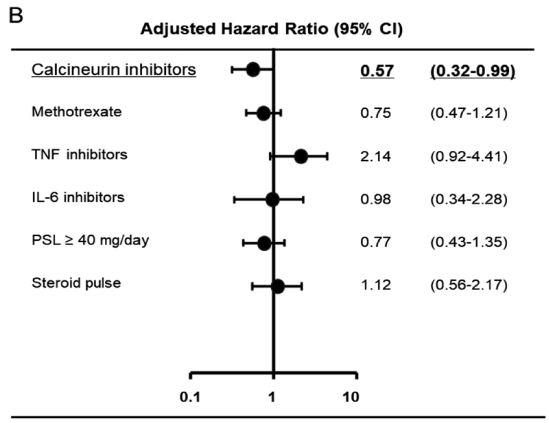


Fig. 1. **(A)** Event-free survival curve in patients with adult-onset Still's disease (AOSD) between the treatment that included calcineurin inhibitors (CNI+) or conventional therapy without CNI (CNI-). **(B)** The forest plots show hazard ratios and their 95% confident intervals (CI) of each indicated medication for event defined as death of any causes or relapse of AOSD. When the 95% CI do not cross the one, the result indicates statistical significance shown in bold. **(C)** Kaplan-Meier curve about the persistency rate of CNI. TNF, tumour necrosis factor; IL-6, interleukin 6; PSL, prednisolone.

Table V. Association between adverse events and medications.

	Multivariate	
	Odds ratio	95% confidential interval
Overall adverse events		
Calcineurin inhibitors	1.75	0.70-4.33
Methotrexate	**2.86**	**1.17-7.58**
TNF inhibitors	**4.40**	**1.11-16.16**
IL-6 inhibitors	**3.76**	**1.31-10.45**
PSL ≥ 40 mg/day	1.15	0.38-3.42
Pulse steroid therapy	**2.95**	**1.02-8.90**

TNF: tumour necrosis factor; IL-6: interleukin 6; PSL: prednisolone.

CNI+ group than in the CNI- group (18% *vs*. 8%, p=0.02); however, hospitalisation (10% *vs*. 4%, p=0.07) and life-threatening adverse events (3% *vs*. 2%, p=0.57) did not significantly increase in the CNI+ group (Table IV). Moreover, after adjustment of the concomitant medications, CNI did not involve in increased risk of adverse events (p=0.23). Multivariate analysis showed that adverse events related to other concomitant medications rather than CNI (Table V). One patient had a fatal course due to septic shock. The patient had several recurrent history and had been treated with combination therapy of high-dose CS, CNI and TNF inhibitors.

Discussion

This is the first study to evaluate the efficacy and safety of CNI in one of the largest cohort of AOSD patients. CNI led the AOSD patients to a significantly longer event-free survival in our cohort after adjustment of the concomitant medications, although our patients in the CNI+ group had significantly greater proportion of a recurrent history, high ferritin level and severe complications, suggesting that disease severity was considered to be higher. Subgroup analysis showed that CNI might be useful in severe AOSD patient with high ALT level, MAS, DIC, serositis and/or meningitis. Regarding AOSD patients, serum ALT level reflects macrophage activation in liver, and DIC in AOSD generally develops as a part of MAS (15, 16). Serositis has been reported to be a prognostic factor of AOSD in Asian population (17, 18). CNI might be effective to such severe cases with hyper-activation of macrophages *via* suppressing T cell activation and IL-2 hyper-secretion as the main target of treatment in AOSD (19-21). Previous studies have indicated that CNI, especially cyclosporine, are effective for treating MAS in systemic juvenile idiopathic arthritis, the juvenile form of AOSD (22, 23).

CNI also had acceptable safety profile for treating AOSD. CNI have several unique side effects, such as nephrotoxicity, hyperkalemia, hyperglycemia, gastrointestinal symptoms (24). These side effects were, however, uncommon during the observation period in this retrospective cohort. That would be because the dose of CNI was strictly adjusted based on the trough concentration as the standard daily clinical practice in our cohort. Although the adverse events, mainly infectious complications, occurred more frequently in the CNI+ group, CNI did not involve in increased risk of the adverse events after adjustment of other concomitant medications. The CNI+ group included severe AOSD patients treated with a multi-agent combination regimen. Hospitalisation and life-threatening adverse events did not significantly increase in the CNI+ group. However, we encountered a fatal septic shock due to multiple combination therapy including CNI. In our cohort, CNI showed the effectiveness for treating AOSD in

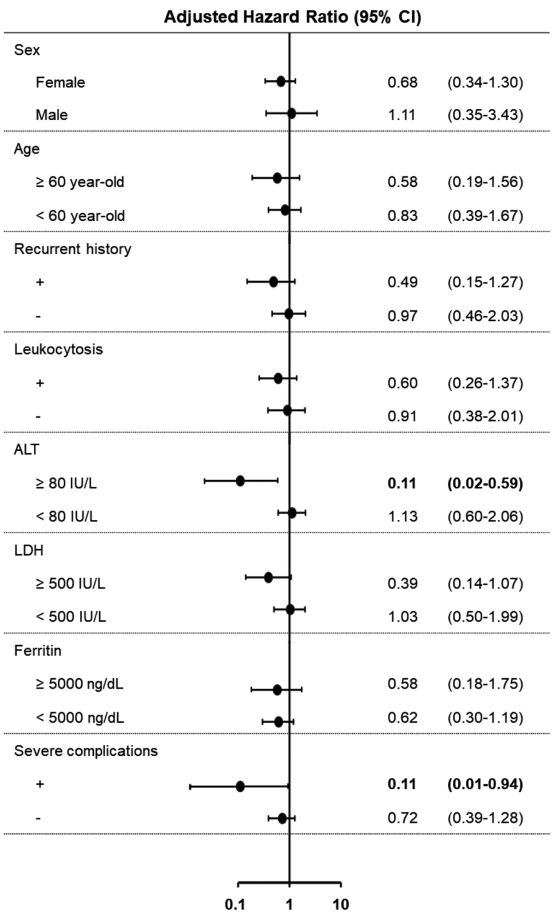


Fig. 2. Subgroup analysis. The forest plots show hazard ratios and their 95% confident intervals (CI) of calcineurin inhibitors for event defined as death of any causes or relapse of AOSD. When the 95% CI do not cross the one, the result indicates statistical significance shown in bold. Severe complications mean macrophage activation syndrome, disseminated intravascular coagulation, serositis and meningitis.

terms of extending event-free survival and acceptable safety, resulting in good persistency rate of CNI at 5th year.

We acknowledge that this study has several limitations. First, the retrospective study design connotes high selection bias. In particular, concomitant medications and disease severity were biased between the groups. We adjusted only concomitant medications as the most relevant confounding factors. Disease severity was unadjusted because it was higher in the CNI+ group. The fact might underestimate the real effect of CNI, but never give us misinterpretation about the effect of CNI. Second, the database in our cohort depends on the medical records. Thus, we could not evaluated the information not written in the medical records, especially mild and trivial adverse events. Third, the study included only Japanese population, and our cohort lacked users of anakinra, an IL-1 inhibitor, unavailable in Japan. In conclusion, we suggest that CNI could be an effective and safe option for refractory AOSD through the multicentre historical cohort study. Randomised controlled trials is encouraged to validate our results and to establish strong evidence on management of AOSD.

Competing interests

I. Yokota has received a speaker's fee from Chugai Pharmaceutical Co., Ltd. and Japan Tabaco Inc. T. Atsumi has received honoraria from Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co., Ltd., Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., Pfizer Inc., AbbVie Inc., Eisai Co. Ltd., Daiichi Sankyo Co.; consultancies from AstraZeneca plc., Medical & Biological Laboratories Co. Ltd., Pfizer Inc., AbbVie Inc., Ono Pharmaceutical Co. Ltd., Novartis Pharma K.K., and research funding from Astellas Pharma Inc., Takeda Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co. Ltd., Daiichi Sankyo Co. Ltd., Otsuka Pharmaceutical Co. Ltd., Pfizer Inc. and Alexion Inc. The other co-authors have declared no competing interests.

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