Real-world safety and effectiveness of canakinumab in patients with cryopyrin-associated periodic fever syndrome: a long-term observational study in Japan

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Abstract

Objective

A post-marketing all-patient surveillance program was conducted to evaluate the safety and effectiveness of canakinumab, a monoclonal anti-interleukin-1β antibody, in patients in Japan with cryopyrin-associated periodic fever syndrome (CAPS), including familial cold auto-inflammatory syndrome, Muckle-Wells syndrome, and neonatal onset multisystem inflammatory disease.

Methods

All patients with CAPS who received canakinumab treatment after drug approval in Japan were registered in this non-interventional, observational study. The observation period per patient was two years. Patients newly treated with canakinumab (New patients; NP) and those continuously treated with canakinumab following clinical trials (Roll-over patients; RP) were included. Data collection of clinical symptoms affecting physical function and prognosis was not mandated but assessed where available. Here, the interim results are reported.

Results

Of 87 patients in the safety set, the proportion of patients with any adverse drug reactions (ADRs) and any serious ADRs was 31.03% and 3.45%, respectively. The most common ADRs reported under system organ class were infections and infestations (20.69%). Of 84 patients in the effectiveness set, 75.76% and 83.33% of NP and RP, respectively, were responders at Week 24, achieving complete response without relapse. Responder rates were maintained up to Week 104. Clinical symptoms affecting physical function and prognosis remained unchanged in over half of those patients.

Conclusion

Interim results provided the safety profile of canakinumab in a real-world setting, and identified no new safety concerns. Treatment with canakinumab has suggested sustained remission in the majority of patients in the real-world setting.

Key words

canakinumab, cryopyrin-associated periodic syndrome, familial cold auto-inflammatory syndrome, interleukin-1β, Muckle-Wells syndrome, neonatal onset multisystem inflammatory disease, observational study, rare diseases, auto-inflammatory diseases, Japan

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Introduction

Cryopyrin-associated periodic syndrome (CAPS) is a rare autosomal dominant auto-inflammatory disease that includes a group of 3 overlapping inflammatory disorders, ranging in severity (1): familial cold auto-inflammatory syndrome (FCAS), which is the mildest form, Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease/chronic infantile neurologic cutaneous articular syndrome (NOMID/CINCA, hereafter referred to as NOMID), which is the most severe form. NOMID is the rarest form of CAPS, but has the greatest patient burden (2-4). Common clinical characteristics of CAPS include fever, urticarial rash, ocular manifestations such as conjunctivitis, and articular involvement. However, fever and rash patterns, AA amyloidosis risk, and other features differ between CAPS subtypes (5, 6). All CAPS-related symptoms can have a profound impact on patients' quality of life, which can be further affected by diagnostic delays and inappropriate treatment (7-9). The prevalence of CAPS is estimated to be 1-2 cases per million in the United States (10) and 1 per 360,000 in France (11). In Japan, the estimated number of CAPS patients is 100 across the overall population (12).

CAPS is associated with mutations in the nucleotide-binding domain leucine-rich repeat containing (NLR) family pyrin domain containing 3 (*NLRP3*) genes encoding the cryopyrin protein, leading to excess production of interleukin-1 beta (IL-1β) and subsequent inflammation (13, 14).

Canakinumab is a fully human anti-IL-1β monoclonal antibody that selectively binds to IL-1β, thereby blocking its signalling and was first proven to be efficacious in the treatment of CAPS patients, the majority of whom were of Caucasian origin (15). In 2009, canakinumab (150 mg subcutaneously [SC] every 8 weeks [q8w]) was approved in Europe for the treatment of patients with FCAS, MWS, and NOMID in adults, adolescents, and children aged ≥2 years (16), and in the United States for the treatment of FCAS and MWS patients (adults and children, aged ≥4 years) (17). In Japan, canakinumab (2 mg/kg [150 mg maximum] to 8 mg/kg [600 mg maximum]) demonstrated early and sustained efficacy with a consistent safety profile in a pivotal Phase 3 study of CAPS patients (18, 19) and was approved for all three phenotypes with no age restriction in 2011 (20). As a condition of approval, the Japanese health authority required that a post-marketing surveillance program was conducted for all patients who received canakinumab to investigate its long-term safety and effectiveness. Moreover, it was deemed important to collect data on patients, such as those aged <2 years, whose clinical information is limited to date. It was for these reasons that this observational study to evaluate the safety and effectiveness of the prolonged use of canakinumab in patients with CAPS under routine care was initiated. Based on data from patients who started canakinumab between September 26, 2011 (drug approval date in Japan) and June 30, 2019, the interim results are reported here.

Methods

Study design

This is an ongoing, open-label, multicentre observational study in accordance with good post-marketing study practice (GPSP; 21). All patients in Japan who were diagnosed with FCAS, MWS, or NOMID and received canakinumab after the drug approval date were registered in this all-patient surveillance, in which informed consent was not mandated because it was not necessary as per GPSP ordinance. The observation period per patient was 2 years (104 weeks), and surveillance forms were collected at 6 months, 1 year, and 2 years. The planned study period was from the marketed date of canakinumab in Japan (December 7, 2011) to the completion date of re-examination (September 25, 2021).

Patients

New patients (NP) were defined as those who were newly treated with canakinumab following its approval. Roll-over patients (RP) were defined as those who started treatment with canakinumab in the previous clinical

trial NCT00991146 from 2009 (18, 19), and continued treatment with canakinumab following approval. The observation period started from the first canakinumab administration for NP or the switch to marketed canakinumab for RP.

Canakinumab therapy

Canakinumab was administered in accordance with the drug label: SC administration q8w for 2 mg/kg for body weight ≤40 kg, or 150 mg for body weight >40 kg; the dosage could be increased if adequate clinical effects are not observed (up to 8 mg/kg for body weight ≤40 kg and 600 mg for patients weighing >40 kg). If a relapse occurs within 8 weeks of administration of maximum dosage, the dosing interval may be shortened to every 4 weeks.

Study assessments

Survey items, recorded by the investigators, in registration and survey forms included patient characteristics, history of prior therapies, administration status of canakinumab/concomitant therapies, presence/absence of treatment suspension, and pregnancy. Safety assessment included the incidence of adverse drug reactions (ADRs), defined as adverse events (AEs) for which any causal relationship with canakinumab cannot be excluded.

This study focused particularly on the safety information of priority investigation items, specified by Pharmaceuticals and Medical Devices Agency (PMDA) based on the clinical trial data; infection (including opportunistic infections), tuberculosis, severe injection-site reactions, malignancies, demyelinating disorder, neutropenia, hypercholesterolaemia, hepatic dysfunctions, shock, and anaphylaxis.

Effectiveness assessments included the following: absence/presence of relapse after complete response, physician's global assessment (PGA) of auto-inflammatory disease activity, C-reactive protein (CRP), or serum amyloid A (SAA) levels, and physician's assessment of clinical symptoms affecting physical function and prognosis. PGA and each of the following symptoms were assessed using a 5-point scale (absent, minimal, mild, moderate, or severe): skin disease, arthralgia, myalgia, headache/migraine, conjunctivitis, fatigue or malaise, and other symptoms related or unrelated to CAPS.

Complete response was defined as the PGA of auto-inflammatory disease activity of absent or minimal, with assessment of skin disease of absent or minimal (clinical remission), and serological response of CRP <1 mg/dL (10 mg/L) or SAA <10 mg/L (serological remission). Patients who achieved a complete response were included in the assessment of relapse. Relapse was defined as having both clinical relapse (PGA ≥ "mild", or PGA = "minimal" plus assessment of skin disease ≥ "mild") and serological relapse (CRP>3 mg/dL or SAA>30 mg/L). Responders were defined as patients who achieved a complete response and remained relapse free (with or without a relapsing-remitting pattern) at subsequent assessment points; the proportion of responders was defined as the responder rate.

The clinical symptoms affecting physical function and prognosis were assessed when available but were not mandated; auditory dysfunction, visual disturbance, renal impairment and joint dysfunction were assessed using a 5-point scale, and central nervous system disorder was assessed as the absence/presence.

Statistical analysis

The safety analysis set and effectiveness analysis set included all patients who had received at least one dose of canakinumab during the study period and whose data were fixed. Descriptive statistics were used to summarise demographics, effectiveness, and safety. The number of patients with ADRs and their incidences were aggregated by system organ class.

The relationship between patient background factors, including CAPS phenotype, age categories, disease duration, *NLRP3* mutation, prior exposure to biologics, and ADRs or effectiveness was analysed in the safety or effectiveness analysis set, respectively. A Fisher's exact test was used if the factors were nominal, while the Mann-Whitney U-test was used for ordinal values groups (exception: a Fisher's

Table I. Demographics and baseline characteristics of patients (safety analysis set).

Characteristics	All patients (N=87)	By phenotype		
		FCAS (n=11)	MWS (n=51)	NOMID (n=25)
Sex, n (%)				
Male	44 (50.57)	6 (54.55)	22 (43.14)	16 (64.0)
Age, years, median (range)	19.0 (0–65)	18.0 (2–59)	28.0 (0–64)	16.0 (0–65)
Age categories				
<2 years	7 (8.05)	0	2 (3.92)	5 (20.0)
≥2 – <15 years	26 (29.89)	5 (45.45)	14 (27.45)	7 (28.0)
≥15 – <45 years	40 (45.98)	4 (36.36)	24 (47.06)	12 (48.0)
≥45 – <65 years	13 (14.94)	2 (18.18)	11 (21.57)	0
≥65 years	1 (1.15)	0	0	1 (4.0)
Weight at the first dose (kg) (mean ± SD)	37.88 ± 18.25	34.29 ± 17.84	43.52 ± 17.13	27.49 ± 16.26
Weight categories, n (%)				
≤40 kg	37 (42.53)	5 (45.45)	14 (27.45)	18 (72.0)
>40 kg	50 (57.47)	6 (54.55)	37 (72.55)	7 (28.0)
NLRP3 gene mutation, n (%)	77 (88.51)	10 (90.91)	46 (90.20)	21 (84.0)
Previous treatment, n (%)	64 (73.56)	7 (63.64)	34 (66.67)	23 (92.00)
Previous biologics use, n (%)	33 (37.93)	0	17 (33.33)	16 (64.00)
Prior exposure to infliximab, n (%)	3 (3.45)	0	3 (5.88)	0
Prior exposure to tocilizumab, n (%)	7 (8.05)	0	5 (9.80)	2 (8.00)
Prior exposure to anakinra, n (%)	16 (18.39)	0	8 (15.69)	8 (32.00)
Prior exposure to canakinumab, n (%)	19 (21.84)	0	7 (13.73)	12 (48.00)
Concomitant drug, n (%)	72 (82.76)	8 (72.73)	40 (78.43)	24 (96.00)

FCAS: familial cold auto-inflammatory syndrome; MWS: Muckle–Wells syndrome; N: total number of patients; n: number of patients; NOMID: neonatal onset multisystem inflammatory disease; SD: standard deviation.

exact test was used when the analysis resulted in a 2×2 contingency). The level of significance was 0.05 in two-tailed hypothesis tests.

Results

Patient demographics

A total of 87 patients (NP, n=68; RP, n=19) and 84 patients (NP, n=66; RP, n=18) were included in the safety and effectiveness analysis sets, respectively. In the safety analysis set, the proportion of male and female patients were balanced (male, 50.57%; female, 49.43%; Table I). The median age at enrolment was 19.0 (range: 0-65) years. An *NLRP3* gene mutation was reported in 77 (88.51%) patients. The majority of patients had MWS (58.62%, n=51), followed by NOMID (28.74%, n=25), and FCAS (12.64%, n=11). There were seven patients (NOMID, n=5; MWS, n=2) aged <2 years, all of whom were <1 year old.

Among the CAPS phenotypes, the proportion of patients in the age range ≥2 and <15 years was higher (45.45%, n=5) in the FCAS group compared with MWS (27.45%, n=14) and NOMID (28.0%, n=7). More patients with MWS (47.06%, n=24) and NOMID (60.0%, n=15) had complications at baseline. Most NOMID patients (96.00%, n=24) were receiving concomitant medications. Medical history and complications of patients at baseline are shown in Supplementary Table S1.

Prior exposure to biologics

Prior to the survey, 64 patients (73.56%) had received previous treatment for CAPS and of these, 33 (37.93%) had prior exposure to biologics. The majority of these 33 patients had participated in previous clinical trials and 19 patients had prior exposure to canakinumab. Sixteen patients had previously received anakinra treatment, although anakinra is not approved in Japan. The most common reasons for discontinuation of biologics were "switching to a marketed product" (n=17, canakinumab), inadequate response (n=1, infliximab; n=5, tocilizumab), and others (n=7, anakinra). No FCAS patients had prior exposure to biologics.

Table II. Canakinumab exposure (safety analysis set).

	All patients (N=87)	By phenotype		
		FCAS (n=11)	MWS (n=51)	NOMID (n=25)
Duration of treatment with canakinumab, days, median (range)*	701.0 (163–729)	699.0 (351–723)	701.0 (163–729)	701.0 (327–729)
0 – <25 weeks	1 (1.15)	0	1 (1.96)	0
≥25 – <49 weeks	3 (3.45)	0	2 (3.92)	1 (4.00)
≥49 – <75 weeks	7 (8.05)	2 (18.18)	2 (3.92)	3 (12.00)
≥75 – <105 weeks	76 (87.36)	9 (81.82)	46 (90.20)	21 (84.00)
Dose increase, n (%)				
Absent	43 (49.43)	8 (72.73)	27 (52.94)	8 (32.00)
Present	44 (50.57)	3 (27.27)	24 (47.06)	17 (68.00)
Final dose ≤40 kg¥, n (%)	N=33	N=4	N=11	N=18
<2 mg/kg	5 (15.15)	1 (25.00)	3 (27.27)	1 (5.56)
≥2 mg/kg – <4 mg/kg	6 (18.18)	0	2 (18.18)	4 (22.22)
≥4 mg/kg – <6 mg/kg	5 (15.15)	2 (50.00)	2 (18.18)	1 (5.56)
≥6 mg/kg – <8 mg/kg	11 (33.33)	1 (25.00)	2 (18.18)	8 (44.44)
≥8 mg/kg	6 (18.18)	0	2 (18.18)	4 (22.22)
Final dose >40 kg¥, n (%)	N=54	N=7	N=40	N=7
≥150 mg – <300 mg	33 (61.11)	7 (100.00)	24 (60.00)	2 (28.57)
≥300 mg – <450 mg	16 (29.63)	0	13 (32.50)	3 (42.86)
≥450 mg – <600 mg	4 (7.41)	0	2 (5.00)	2 (28.57)
≥600 mg	1 (1.85)	0	1 (2.50)	0

A case with multiple reasons for study drug interruption was counted as one case in each reason.
*Summary statistics of the duration of treatment with canakinumab were calculated based on the number of days; ¥ The latest doses and weights recorded in the survey forms.
FCAS: familial cold auto-inflammatory syndrome; MWS: Muckle-Wells syndrome; N: total number of patients; n: number of patients; NOMID: neonatal onset multisystem inflammatory disease.

Canakinumab exposure

In the safety set, the median duration of canakinumab treatment was 701 (range: 163–729) days. During the observation period, 50.57% (n=44) of patients were treated with increased doses. The most common final dose, or the most recent dose recorded in the survey forms, of canakinumab was ≥150 to <300 mg (61.11%, n=33) in patients whose body weight was >40 kg, and ≥6 to <8 mg/kg (33.33%, n=11) in patients whose body weight was ≤40 kg (Table II). The main reason for a dose increase was "no clinical effectiveness" (n=32), "relapse" (n=10), "unknown" (n=4), and other reasons (n=10), including "symptoms worsened in winter" and "to return to the original dosing interval/dose".

Among the CAPS phenotypes, the median duration of canakinumab treatment was 699.0 (351–723) days, 701.0 (163–729) days, and 701.0 (327–729) days, in FCAS, MWS, and NOMID patients, respectively (Table II). A dose increase was performed for 68.00% (n=17) of NOMID patients compared with 27.27% (n=3) and 47.06% (n=24) of FCAS and MWS patients, respectively. The final dose of canakinumab according to patients' body weight (≤40 kg or >40kg) showed that, in FCAS, the dose was increased to ≥4 to <6 mg/kg (50.0%, n=2) and ≥6 to <8 mg/kg (25.0%, n=1) in the ≤40 kg group. In MWS, 60.00% (n=24) patients in the >40 kg group received ≥150 to <300 mg. In NOMID, 22.22% (n=4) of patients received the highest dose of ≥8 mg/kg in the ≤40 kg group while no patients received ≥600 mg in >40 kg group.

Of 87 patients, three (3.45%) discontinued canakinumab. The reasons for discontinuation included "onset of AEs" (n=1), "inadequate response" (n=1), and "stopped visiting hospital" (n=1). Treatment with canakinumab was interrupted and restarted in 10 (11.49%) patients due to onset of AEs (n=2) and other reasons (n=9). No case

Table III. Incidence of adverse drug reactions by system organ class (safety analysis set)*.

System organ class	All patients, (N=87) n (%)	By phenotype		
		FCAS (n=11) n (%)	MWS (n=51) n (%)	NOMID (n=25) n (%)
Total	27 (31.03)	2 (18.18)	16 (31.37)	9 (36.00)
Infections and infestations	18 (20.69)	1 (9.09)	11 (21.57)	6 (24.00)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (1.15)	–	1 (1.96)	–
Blood and lymphatic system disorders	1 (1.15)	1 (9.09)	–	–
Metabolism and nutrition disorders	1 (1.15)	–	–	1 (4.00)
Psychiatric disorders	1 (1.15)	–	–	1 (4.00)
Nervous system disorders	2 (2.30)	–	1 (1.96)	1 (4.00)
Eye disorders	1 (1.15)	–	–	1 (4.00)
Respiratory, thoracic and mediastinal disorders	6 (6.90)	–	3 (5.88)	3 (12.00)
Gastrointestinal disorders	5 (5.75)	1 (9.09)	1 (1.96)	3 (12.00)
Hepatobiliary disorders	2 (2.30)	–	1 (1.96)	1 (4.00)
Skin and subcutaneous tissue disorders	1 (1.15)	–	1 (1.96)	–
Musculoskeletal and connective tissue disorders	1 (1.15)	–	–	1 (4.00)
Congenital, familial and genetic disorders	1 (1.15)	–	1 (1.96)	–
General disorders and administration site conditions	2 (2.30)	–	1 (1.96)	1 (4.00)
Laboratory test	5 (5.75)	–	2 (3.92)	3 (12.00)

*If the same event occurs more than once in a patient, the event shall be counted as one case.
FCAS: familial cold auto-inflammatory syndrome; MWS: Muckle-Wells syndrome; N: total number of patients; n: number of patients with adverse drug reactions; NOMID: neonatal onset multisystem inflammatory disease.

of pregnancy was reported during the observation period.

Safety

- ADRs

The proportion of patients with any ADR was 31.03% (n=27) in the safety analysis set, with infections and infestations (20.69%) being the most common. ADRs were reported in 33.82% and 21.05% of NP and RP, respectively. Among the CAPS phenotypes, ADRs were reported in 18.18% of FCAS patients, 31.37% of MWS patients, and 36.00% of NOMID patients (Table III, Supplementary Table S2).

- Serious ADRs

Serious ADRs, reported in 3.45% (n=3) of the safety analysis set, included pneumonia and neutropenia in one FCAS patient (a 3-year-old, female), respiratory syncytial virus bronchiolitis and pyrexia in one NOMID patient (a <1-year-old, male), and malignancy (rhabdomyosarcoma) in one MWS patient (a 7-year-old female).

Pneumonia was seen 726 days after initial treatment and recovered 14 days after onset. Neutropenia was seen 732 days after initial treatment and was reported as resolved four days after onset. Respiratory syncytial virus bronchiolitis was seen 20 days after initial treatment and was reported as recovering 6 days after onset. Pyrexia, which was seen 75 days after initial treatment, developed after the second pneumococcal vaccination and was reported as recovering 6 days after onset. Pyrexia also developed with two other pneumococcal vaccinations, but both ADRs were reported as non-serious. Canakinumab treatment continued after ADR/serious ADR onset in all of these cases during the observation period.

Rhabdomyosarcoma was spontaneously reported by the investigator during the follow-up period. The outcomes and relationships to canakinumab of rhabdomyosarcoma were reported as unknown, and canakinumab treatment continued after ADRs.

One NOMID patient (a <1-year-old, male) died 372 days after initial canakinumab treatment. The AEs reported in this patient included pneumonia, atelectasis, asthma, bronchitis, circulatory collapse, cardiac ventricular thrombosis, sepsis, and subdural haematoma; all AEs were considered unrelated to canakinumab by the investigator.

According to the spontaneous report, the patient had complications of transposition of the great arteries, intramural coronary artery, ventricular septal defect, aortic constriction, patent ductus arteriosus, patent foramen ovale, and pulmonary hypertension, for which he had underwent balloon atrial septostomy, aortic reconstruction surgery, and pulmonary artery strangulation surgery prior to starting canakinumab. After starting canakinumab, he underwent a repair surgery for intraventricular blood flow conversion. After surgery, he developed systemic circulatory failure, right ventricular outflow tract thrombus, sepsis, and acute subdural haematoma. Subsequently, he underwent another right ventricular outflow tract reconstructive surgery and again developed sepsis, which led to death. The investigator reported that the cardiac failure and sepsis developed from the underlying medical conditions and were not suspected to be related to canakinumab.

- Incidence of ADRs as priority investigation items

Safety information of the following priority investigation items was analysed: infection, tuberculosis, severe injection-site reactions, malignancies, demyelinating disorder, neutropenia, hypercholesterolaemia, hepatic dysfunctions, shock, and anaphylaxis. Infection (including opportunistic infection) ADRs were reported in 18 (20.69%) patients. Serious ADRs of infections (pneumonia and respiratory syncytial virus bronchiolitis), malignancy (rhabdomyosarcoma), and neutropenia were described in the above section. Severe injection-site reaction (n=1), reported in one MWS patient, was considered non-serious and resolved two days after onset. Hepatic dysfunction was reported in five patients, which were considered to be non-serious. Of the five cases, two were reported as "recovered/resolved", one as "recovering/resolving", and two as "not recovered/not resolved". No patients experienced tuberculosis, demyelinating disease, shock, anaphylaxis, or hypercholesterolaemia during the observation period.

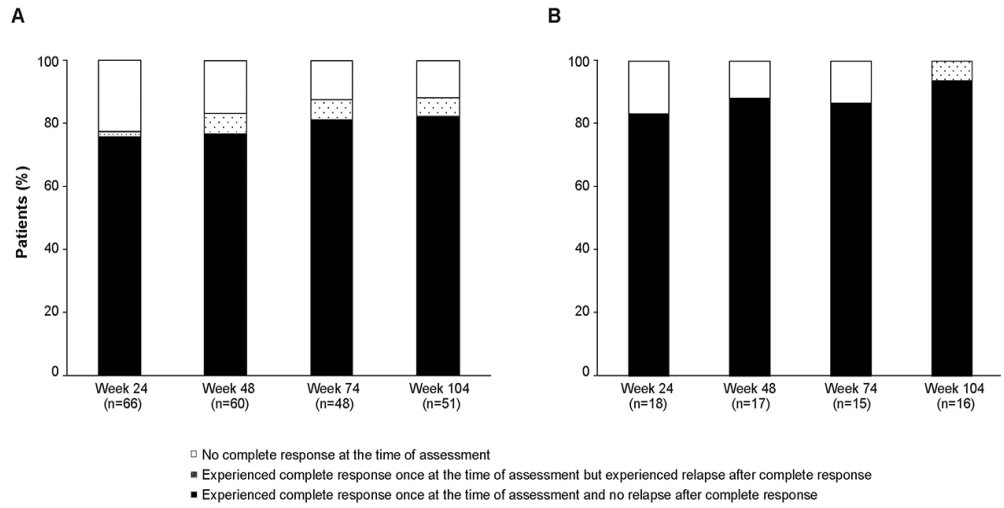

Fig. 1. Responder rate (effectiveness analysis set).
A: new patients;
B: roll-over patients.
n: number of cases which had evaluation during each corresponding period (Week 24: Day 168±28, Week 48: Day 336±28, Week 74: Day 518±28, or Week 104: Day 728±28).

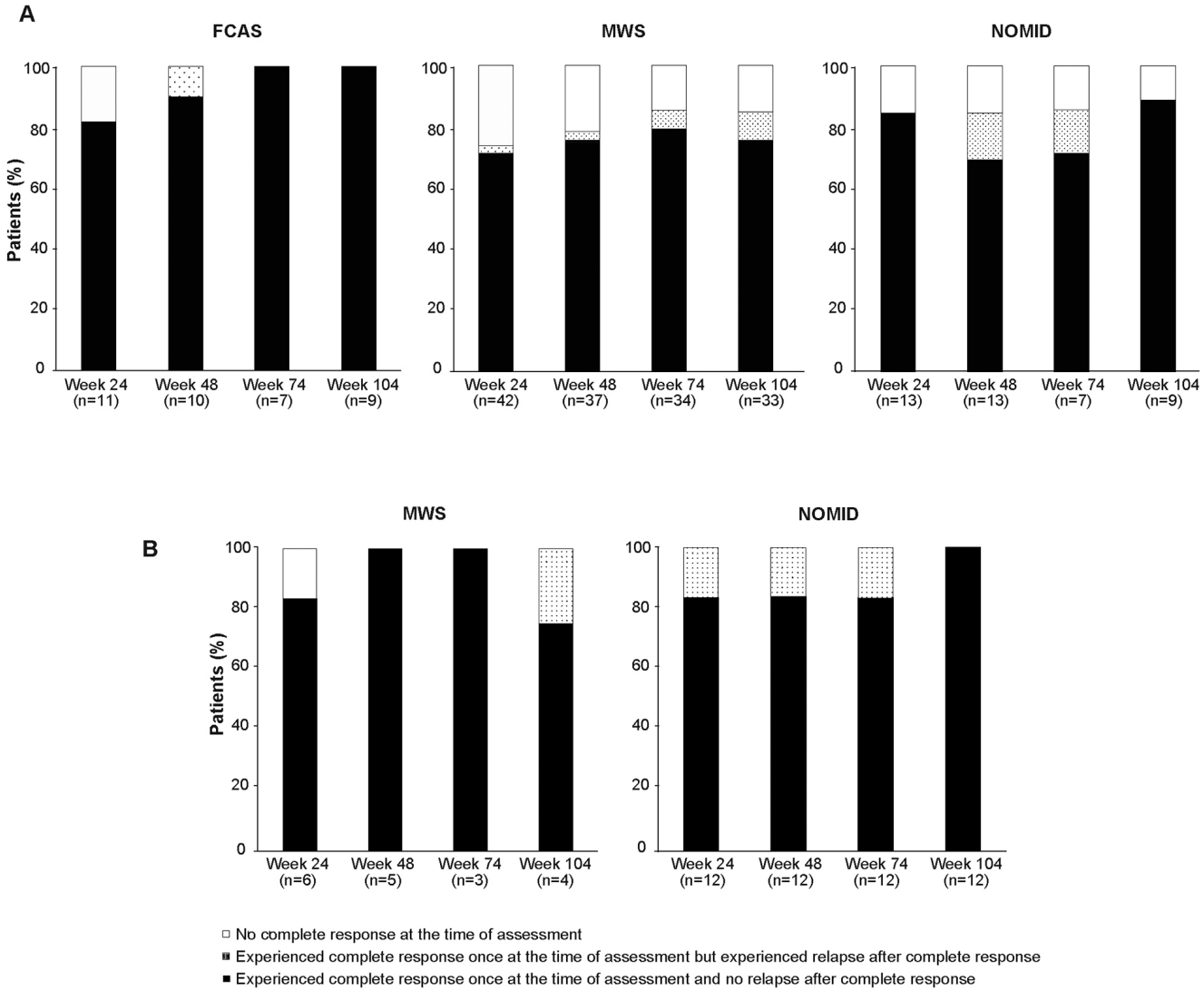

Fig. 2. Responder rate by phenotypes (effectiveness analysis set). **A**: new patients (by phenotype); **B**: roll-over patients (by phenotype).
n: number of cases which had evaluation during each corresponding period (Week 24: Day 168±28, Week 48: Day 336±28, Week 74: Day 518±28, or Week 104: Day 728 ±28).
FCAS: familial cold auto-inflammatory syndrome; MWS: Muckle-Wells syndrome; n, number of patients; NOMID: neonatal onset multisystem inflammatory disease.

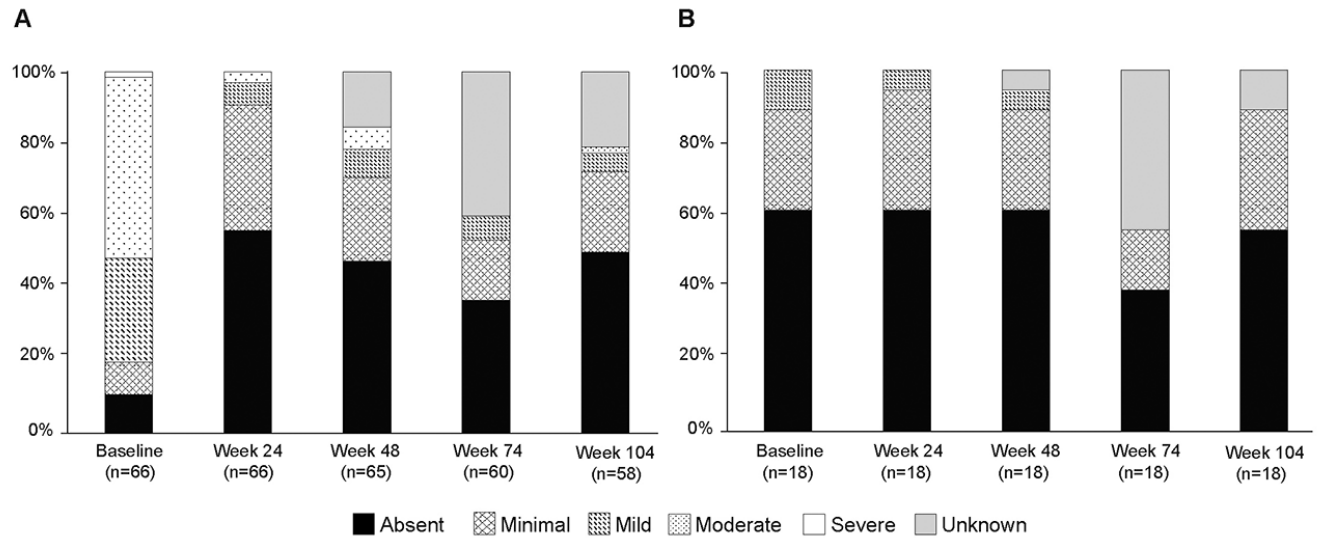

Fig. 3. Physician's global assessment for activity of auto-inflammatory disease in NP and RP (effectiveness analysis set).
A: new patients; **B**: roll-over patients.
n, number of cases which had evaluation during each corresponding period (Week 24: Day 168±28, Week 48: Day 336±28, Week 74: Day 518±28, or Week 104: Day 728±28). NP: new patients; RP: roll-over patients.

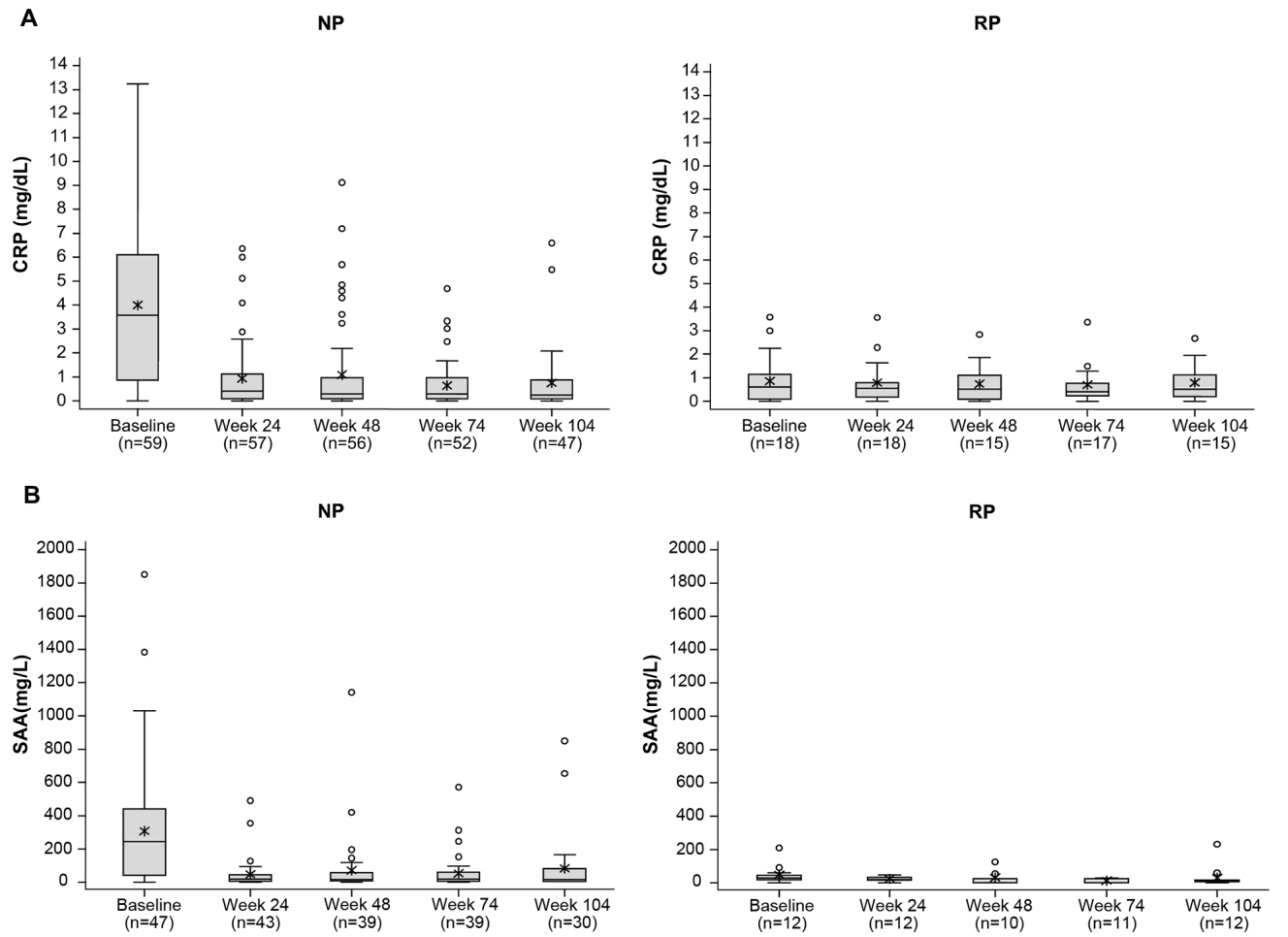

Fig. 4. Changes in CRP and SAA levels over time in NP and RP (effectiveness analysis set).
A: Change in CRP levels over time; **B**: Change in SAA levels over time.
n: number of patients which had the test values during each corresponding period (Week 24: Day 168±28, Week 48: Day 336±28, Week 74: Day 518±28, or Week 104: Day 728±28); open circle, outliers; asterisk, mean.
CRP: C-reactive protein; NP: new patients; RP: roll-over patients; SAA: serum amyloid A.

Table IV. Physician's assessment of clinical symptoms (auditory and joint dysfunction, effectiveness analysis set).

A: Auditory disorder

NP

Week 24 \ Baseline	Absent	Minimal	Mild	Moderate	Severe	Unknown/ unlisted	total
Absent	**12**		1			3	16
Minimal		**1**	2			1	4
Mild			**2**			1	3
Moderate				**7**			7
Severe					**5**		5
Unknown/ unlisted	8		5	1	2		31
Total	20	1	10	8	7	20	66

Week 104 \ Baseline	Absent	Minimal	Mild	Moderate	Severe	Unknown/ unlisted	total
Absent	**5**		1			5	11
Minimal		**1**	3	1			5
Mild			**1**				1
Moderate			1	**4**			5
Severe					5		5
Unknown/ unlisted	11		4	3	2	11	31
Total	16	1	10	8	7	16	58

RP

Week 24 \ Baseline	Absent	Minimal	Mild	Moderate	Severe	Unknown/ unlisted	total
Absent						1	1
Minimal							
Mild			**2**	1			3
Moderate				**3**			3
Severe					**2**		2
Unknown/ unlisted						9	9
Total			2	4	2	10	18

Week 104 \ Baseline	Absent	Minimal	Mild	Moderate	Severe	Unknown/ unlisted	total
Absent						4	4
Minimal						1	1
Mild				1			1
Moderate				**1**			1
Severe			1		1		2
Unknown/ unlisted			1	2	1	5	9
Total			2	4	2	10	18

B: Joint dysfunction

NP

Week 24 \ Baseline	Absent	Minimal	Mild	Moderate	Severe	Unknown/ unlisted	Total
Absent	**17**	4	2			1	24
Minimal		**2**	2				4
Mild				1			1
Moderate				**2**			2
Severe							
Unknown/ unlisted	1	1	2			31	35
Total	18	7	6	3		32	66

Week 104 \ Baseline	Absent	Minimal	Mild	Moderate	Severe	Unknown/ unlisted	Total
Absent	**10**	1	1			9	21
Minimal		**2**	1			1	4
Mild		1		1			2
Moderate				**1**			1
Severe							
Unknown/ unlisted	7	2	4	1		16	30
Total	17	6	6	3		26	58

RP

Week 24 \ Baseline	Absent	Minimal	Mild	Moderate	Severe	Unknown/ unlisted	Total
Absent	**5**						5
Minimal							
Mild		1		1			2
Moderate							
Severe					2		2
Unknown/ unlisted		1				8	9
Total	5	2		1	2	8	18

Week 104 \ Baseline	Absent	Minimal	Mild	Moderate	Severe	Unknown/ unlisted	Total
Absent	**1**						3
Minimal	1			1			2
Mild		2					2
Moderate							
Severe					2		2
Unknown/ unlisted	3					6	9
Total	5	2		1	2	8	18

Colour codes: dark grey, improvement; black, no change; light grey, worsening; white, unknown/unlisted.
Cases with the evaluations at baseline and Week 24 (Day 168+28), Week 104 (Day 728+28) after starting treatment were included.
NP: new patients; RP: roll-over patients.

- Incidence of ADRs by patient demographic characteristics

In order to identify the safety risk factors, the proportion of patients with ADRs was compared with patient background factors. No statistically significant differences were observed in the correlation with ADR incidence among all background factors except for prior use of infliximab (p=0.0276, data not shown).

Effectiveness

- Responder rate

In the effectiveness analysis set, the proportion of NP who remained relapse-free at Weeks 24, 48, 74, and 104 after achieving complete response before the corresponding week were 75.76%, 76.67%, 81.25%, and 82.35%, respectively (Fig. 1A). Among the CAPS phenotypes, the responder rates at Weeks 24 and 104 were 81.82% and 100.00% in FCAS NP, 71.43% and 75.76% in MWS NP, 84.62% and 88.89% in NOMID NP, respectively (Fig. 2A, 2B). In children (aged <15 years), the responder rates were 76.00%, 72.73%, 88.24%, and 81.25% at Weeks 24, 48, 74, and 104, respectively; 85.71% (6/7 patients) of children aged ≤2 years were reported as responders at Week 24.

The responder rates in RP were 83.33%, 88.24%, 86.67%, and 93.75% at Weeks 24, 48, 74, and 104, respectively (Fig. 1B). In children (aged <15 years), the responder rate was 100% at every time point and no children aged <2 years were included in the RP group. The responder rates by patient background factor were analysed for both NP and RP. No statistically significant differences were observed in responder rates among all background factors (data not shown).

- Physician's global assessment

The proportion of NP with a PGA of auto-inflammatory disease activity assessment indicating "absent" or "minimal" activity increased from 10.61% and 9.09% at the start of canakinumab dosing to 56.06% and 34.85% at Week 24, respectively (Fig. 3A). No patient had disease activity assessed as "severe" at Weeks 48, 74, and 104. A similar trend was observed in RP (Fig. 3B).

- CRP/SAA levels

The mean ± standard deviation (SD) levels of CRP at baseline were 3.96±3.33 mg/dL and 0.91±1.04 mg/dL in NP (n=66) and RP (n=18), respectively. At Week 24, the mean CRP levels decreased to 0.93±1.41 and 0.83±0.90 mg/dL in NP and RP, respectively. In both patient groups, the mean CRP levels remained stable from Weeks 24–104 (Fig. 4A).

At Week 24, SAA levels decreased from 309.29±361.97 mg/L and 39.73±54.171 mg/L at baseline to 45.10±90.27 mg/L and 18.32±9.616 mg/L in NP and RP, respectively. The SAA levels increased at Weeks 48, 74, and 104, but remained lower compared with the start of canakinumab initiation in NP. The levels were continuously lower than at baseline after Week 24 to 104 in RP (Fig. 4B).

- Clinical symptoms affecting physical function and prognosis

The presence/absence and severity of auditory and joint dysfunction, was assessed. According to the available post-treatment data, the symptoms remained unchanged in more than half of patients (Table IV and Supplementary Table S3). At Week 104, 22 NP with auditory dysfunction were assessed, where five reported an improvement; 16 reported no change, while one showed worsening of the symptoms. The severity of auditory function in the 5 patients who reported improvement was mild or moderate at baseline. Among the 16 patients who showed no change, 5 had no auditory disorder at baseline. In total, 18 NP were assessed for joint dysfunction at Week 104; 4 patients reported an improvement, 13 reported no change, 10 of whom had no joint dysfunction at baseline, and one showed worsening of symptoms (Table IV-B). Among 10 NP with available visual disturbance data, two patients had worsening at Week 104; one patient presented no symptoms at baseline but assessed symptoms as moderate at Week 104, another patient was assessed as moderate at baseline, which changed to severe at Week 104 (Supplementary Table S3-A). Most patients (38/40) showed no renal impairment at either baseline or at Week 104. In the 2 patients who presented renal impairment at baseline (1 with mild, 1 with severe), the clinical assessment was unchanged at Week 104 (Supplementary Table S3-B). Majority of NP (36/43) showed no central nervous disorder at baseline or at Week 104. Among 7 patients who had central nervous disorder at baseline, the symptom was absent in one patient at Week 104 whereas it persisted in the remaining 6 patients (Supplementary Table S3-C). Much less information was available in RP, where each case presented variable outcomes at Week 104 (Table IV and Supplementary Table S3).

Discussion

This interim observational study showed the safety and effectiveness of canakinumab for 2 years in the treatment of patients with CAPS in Japan across phenotypes of different severity, providing an insight for the long-term use of canakinumab in the real world. This is the first study to demonstrate the safety and effectiveness of canakinumab that included patients aged <2 years and FCAS patients, who had not been included in the previous Phase 3 clinical trials (18, 19).

The majority of patients in the safety analysis set remained under treatment with canakinumab during the survey. Patients with more severe forms of CAPS (MWS and NOMID) displayed a trend of increased canakinumab exposure compared with the milder form (FCAS), while the responder rates were similar among phenotypes. These results are in line with findings from a previous study (22) and reflect more persistent auto-inflammatory symptoms in those with severe forms of the disease. Frequent, stepwise dose up-titration was also required in MWS and NOMID patients regardless of patient body weight. Therefore, CAPS phenotype might be a key factor for physicians to determine and manage canakinumab dosage since those with severe phenotypes are likely to require higher doses to maintain optimal response.

In this study, no new safety concerns were observed, regardless of differences in canakinumab exposure in each CAPS phenotype and the safety profile

was consistent with previous canakinumab studies in CAPS (18, 19, 22) as well as other indications (23). One death was reported during the study period, which was considered unrelated to the study drug. The most common ADRs and serious ADRs were infections. There was no significant difference in the incidence of ADRs among special age groups, such as the paediatric and elderly populations. Considering that numerically higher ADRs were reported in patients with NOMID than MWS or FCAS, a careful management of ADRs might be necessary, especially in NOMID patients.

No patient background factors, except for prior use of infliximab, were found to be statistically significant for correlation with the incidence of ADR. The result should be interpreted with caution because the cases with prior use of infliximab were limited (3.45%, n=3). Although no case of pregnancy was reported during the observation period, one MWS patient became pregnant three years after initiating canakinumab treatment. This patient continued the treatment until 34 weeks' gestation and restarted canakinumab one day after the delivery (24). In this case, foetal growth was normal and the infant showed no abnormalities at birth.

Among 84 cases in the effectiveness analysis set, the responder rate was 75.86% in 66 NP and 83.3% in 18 RP at Week 24.

Rates of responders and auto-inflammatory disease activity, as assessed by PGA, were similar among CAPS phenotypes over the course of canakinumab treatment. Patients who had continued canakinumab treatment, since the previous clinical trial started from 2009, showed well-controlled disease activity. Approximately, 93.75% of RP did not experience any episodes of relapse up to 104 weeks from the start of this study, indicating a sustained beneficial effect of canakinumab. These results are in line with previous studies, which demonstrated sustained efficacy of canakinumab (19). No patient background factors assessed in this interim analysis were observed to be statistically significant for correlation with effectiveness, indicating the effectiveness of canakinumab in patients aged <2 years and FCAS patients.

Clinical symptoms affecting physical function and prognosis remained unchanged with canakinumab treatment in more than half of the patients. The majority of those patients' assessment was absent at baseline and other timepoints, indicating that they had been free from those symptoms during canakinumab treatment, whereas some had manifestations at baseline but experienced no progression or improvement afterwards. It should be noted that, due to the observational nature of this study, these results are derived from a limited number of patient assessments, as it was not mandatory for participating physicians to perform clinical assessments of treatment response. In addition, this interim analysis did not include assessment of correlation of the improvement of clinical symptoms and disease duration. A previous report has shown that early canakinumab therapy led to improved hearing ability, relief of symptoms, and normalisation of laboratory parameters in Japanese patients with CAPS (25). Analysis to determine how disease duration and phenotypes can affect canakinumab effectiveness on clinical symptoms is warranted to further support the beneficial effect of earlier diagnosis and appropriate treatment on preventing irreversible dysfunction.

The study has limitations with regard to its small sample size, due to the low incidence of CAPS, and the open-label observational study design.

In conclusion, the present data provide preliminary evidence of prolonged use of canakinumab in controlling auto-inflammatory disease activity. Canakinumab was well tolerated in patients with all CAPS phenotypes in Japan with an acceptable safety profile in real-world settings. Further investigation is required to determine the optimal treatment strategy with canakinumab and to better control clinical symptoms of CAPS patients.

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