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Original Article

Investigator-initiated, multi-center, single-arm, open-label study of the effectiveness of canakinumab in Japanese patients with Schnitzler syndrome

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AE, adverse event; ALP, alkaline phosphatase; CAPS, cryopyrin-associated periodic syndrome; CR, complete clinical response; CRP, C-reactive protein; DLQI, Dermatology Life Quality Index; IIT, investigator-initiated clinical trial; IL-1Ra, IL-1 receptor antagonist; JAK, Janus-associated kinase; NR, no clinical response;

ABSTRACT

Background: Schnitzler syndrome is an adult-onset autoinflammatory disease characterized by an urticaria-like rash and monoclonal gammopathy with fever and fatigue. Although some treatments have shown efficacy in clinical trials, no approved treatment exists. We aimed to assess canakinumab, an anti-IL-1β monoclonal antibody, in Japanese patients.

Methods: This phase II, multicenter, single-arm, open-label study enrolled five patients with active disease from four hospitals. Patients received a single subcutaneous dose of canakinumab 150 mg. The primary endpoint was the proportion of patients achieving a complete clinical response (CR), based on physician global assessment on Day 7. If a CR was not achieved on Day 7 or by 8 weeks post-treatment, the dose was increased to 300 mg. Dosing continued every 8 weeks until 24 weeks. The study also evaluated patient-reported disease activity and changes in acute inflammatory markers, including white blood cell count, neutrophil count, C-reactive protein concentration, and serum amyloid A level. Quality of life was assessed using the Dermatology Life Quality Index and the 36-item Short Form health survey. Safety was also evaluated.

Results: Sixty percent (3/5) of patients had a CR on Day 7. One of the remaining two patients had a CR 7 days after the dose was increased to 300 mg. All five patients, including those who did not achieve a CR, showed improvement in inflammatory markers and quality of life scores, and no new adverse events were detected.

Conclusions: In this trial, canakinumab showed a potential for usefulness in Japanese patients with Schnitzler syndrome.

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PGA, physician global assessment;
PR, partial clinical response;
PSL, prednisolone; QoL, quality of life;
SAA, Serum amyloid A; SchS, Schnitzler syndrome; SF-36, 36-item short form health survey; WBC, white blood cell

Introduction

Schnitzler syndrome (SchS) is an acquired autoinflammatory syndrome that typically occurs around age 50.[1] It was first reported by Lilian Schnitzler in 1972. Since then, fewer than 300 cases have been reported.[2,3] Based on the diagnostic criteria proposed by Lipsker *et al.*,[4] the Strasbourg criteria were developed by Schnitzler, Lipsker, and other experts.[3] They include two obligate criteria: chronic urticarial rash and monoclonal IgM, or rarely IgG, gammopathy. Minor criteria include recurrent fever, abnormal bone remodeling, a neutrophilic dermal infiltrate upon skin biopsy,[5,6] and leukocytosis and/or elevated C-reactive protein (CRP). Due to its rarity, the disease may not be well recognized, and many cases are likely to go undiagnosed. In our study, which summarized cases from Japan, it took an average of 3.3 years to reach a diagnosis.[7] Patients often experience severe quality of life (QoL) problems due to fever and fatigue. In addition, approximately 15 % of patients may develop malignant B-cell lymphomas, including Waldenström's macroglobulinemia.[8]

The clinical phenotype of SchS shares many similarities with cryopyrin-associated periodic syndrome (CAPS),[9] which is caused by a gain-of-function mutation in *NLRP3*. NLRP3 is an intracellular pattern recognition receptor. NLRP3 activation leads to the formation of inflammasomes and the activation of IL-1β, a cytokine that triggers inflammation.[10] Despite previous beliefs that SchS was linked to mutations in *NLRP3*, recent large cohort studies have not identified somatic or germline mutations associated with SchS.[11]

Currently, there is no approved therapy for SchS in any country. Along with the proposal of the Strasbourg diagnostic criteria, a treatment algorithm was also proposed.[3] For patients who do not experience significant changes in QoL and do not have persistent elevations in inflammatory markers, treatment options include follow-up, colchicine, and NSAIDs for flare-ups, joint pain, and bone pain. According to Lipsker *et al.*,[12] the efficacy of colchicine is only 25 %. However, due to its favorable benefit/risk ratio, colchicine is recommended as first-line treatment. Experts do not recommend systemic steroid use, particularly a prednisone (PSL)-equivalent dose exceeding 5 mg/day, due to concerns regarding side effects associated with long-term continuous use.[3] However, only a small percentage of patients fall into this category, and most cases of SchS are difficult to treat. In contrast, due to the similarity of clinical manifestations, treatment targeting IL-1, which is effective in CAPS,[13] has been effective.[14–16] Experts recommend the use of anakinra in patients with significant changes in QoL, and/or consistently elevated inflammatory markers.[3] Notably, if anakinra is ineffective, it is strongly recommended that the diagnosis be reconsidered.[3]

Canakinumab is a fully human IL-1β-specific mAb with the advantage of a long half-life; thus, it does not require frequent dosing compared to anakinra, which has a half-life of 4–6 h and requires daily subcutaneous injection. Canakinumab is approved for the treatment of CAPS, as well as Hyper-IgD syndrome/mevalonate kinase deficiency,[17] TNF receptor-associated periodic syndrome,[18] systemic juvenile idiopathic arthritis,[19,20] and colchicine-resistant familial Mediterranean fever.[21] For SchS, a 9-month open-label trial of canakinumab was first conducted in 8 patients, and efficacy was reported.[22] Subsequently, in a randomized, double-blind, placebo-controlled investigator-initiated clinical trial (IIT) conducted in Germany, 7 patients with SchS were assigned to receive canakinumab, and its efficacy and safety were shown,[23] including long-term study results.[24]

We conducted a multi-center, single-arm, open-label, phase II IIT of canakinumab in Japanese patients with SchS. Here, we report the results of Period I of that 24-week study.

Methods

Study design

This was a multicenter, open-label, single-arm, phase II study. The dosage, dosing interval, efficacy endpoint, and eligibility criteria were consistent with those of the preceding German IIT.[23,24] The trial consisted of a screening period, Period I (24 weeks), Period II (24 weeks), and Period III. Period I lasted from the first dose to 24 weeks. The evaluation of efficacy at 7 days after the first dose was the primary analysis. Period II spanned the time from 24 to 48 weeks after the first dose and evaluated the safety and efficacy of continued administration. Subsequently, Period III will continue until approval or discontinuation of development of canakinumab for SchS and will focus on long-term safety.

Assessments

The efficacy of canakinumab treatment was assessed using a physician global assessment (PGA) score that graded the 5 key symptoms of SchS (urticarial rash, fatigue, fever/chills, myalgia, and arthralgia/bone pain) on a 5-point Likert scale, with 0 indicating no disease activity and 4 indicating severe disease activity. The total PGA scores ranged from 0 to 20.

The modified SchS activity score[22] was used to evaluate the patient-assessed SchS disease score. Patients were requested to rate the severity of their overall symptoms on a scale from 0 (very good) to 10 (very bad) once per night, starting from the day before the first dose until 8 weeks, and then on the night before each subsequent visit.

Patients

The study enrolled patients aged 18 years or older who met the Strasbourg criteria[3] and had a PGA score of at least 8, a mean patient-assessed SchS disease score of at least 3, and at least one laboratory value (WBC count, neutrophil count, CRP concentration) that exceeded the institutional reference range. Participants were required to complete all study visits and procedures, have a negative pregnancy test result, and use effective contraception if they were of childbearing potential. Participants with active tuberculosis or chronic infections, a history of treatment with IL-1 blockers, or any malignancies were excluded. The use of certain drugs was prohibited from the time consent was obtained until the end of Period II. These drugs include immunosuppressants, molecular targeted therapeutics such as biological agents and Janus-associated kinase (JAK) inhibitors, colchicine, diphenyl sulfone, potassium iodide, methotrexate, alkylating agents, interferons, and steroids (PSL equivalent dose >5 mg/day). In addition to the above-

mentioned drugs, concomitant use of antihistamines and NSAIDs was prohibited until the primary endpoint assessment.

This IIT received approval from the ethics committees of each hospital (K085 at Kyoto University Hospital). Subsequently, a Clinical Trial Notification (2022-6745) was submitted and published in the Japan Registry of Clinical Trials (jRCT2051220139). Prior to any study-related procedures, all patients provided written informed consent.

Study endpoints

After screening, patients received a single subcutaneous injection of canakinumab 150 mg. At every clinic visit, blood samples were collected to determine acute-phase markers, including WBC count, neutrophil count, CRP concentration, serum amyloid A (SAA) level, concentrations of alkaline phosphatase (ALP) and ALP3, IgM concentration, and the free light-chain κ/λ ratio as an evaluation of monoclonality. Patients completed 2 questionnaires, the Dermatology Life Quality Index (DLQI) and the acute version of the 36-item Short Form health survey (SF-36), both of which have a recall period of 1 week.

The primary endpoint was the proportion of patients achieving a complete clinical response (CR) 1 week after canakinumab treatment. Secondary endpoints included the overall CR rate, changes in PGA score and patient-assessed SchS disease score, changes in acute-phase markers, and changes in QoL assessments. Additional secondary endpoints were related to the safety of canakinumab treatment, as assessed by physical examination, routine laboratory markers, vital signs, and adverse event (AE) reporting.

Study definitions

A CR was defined as no or minimal disease activity, indicated by a PGA score of 5 or less and no greater than 1 in any of the 5 constituent signs/symptoms. A partial clinical response (PR) was defined as mild to moderate disease activity with a PGA score of more than 5 and a reduction of 30 % or more compared to baseline. No clinical response (NR) was defined as high disease activity with PGA scores that remained stable, increased, or showed less than a 30 % reduction. A relapse or worsening of clinical symptoms was identified by a 50 % or greater increase in the PGA score compared to the score at initiation of canakinumab treatment.

Exploratory study

In addition to the IIT evaluations, plasma was stored at each blood collection point, and cytokines were measured using the human cytokine screening 48-Plex panels (BioPlex, Bio-Rad, Hercules, California). This study was approved by the Kyoto University Medical Ethics Committee Central IRB (R3704-3), and written consent was obtained from the participants.

Sample size and feasibility

The sample size was based on the number of affected patients in Japan. Prior to this IIT, we contacted the attending physicians of all 38 reported cases in Japan.[7] Only 7 cases were eligible for this IIT. We subsequently added two new cases and finally included five cases from four hospitals that met the criteria for conducting IIT. Statistical power studies were not applied, because no randomized trials were conducted in this population, and the variability of disease activity was unknown.

Results

Study population

Five patients were screened. All cases exhibited monoclonal gammopathy of IgM κ-type by immuno-electrophoresis (Supplementary Fig. 1), but lymphoid malignancies, such as myeloma, were ruled out by bone marrow biopsy.

They received an initial dose of canakinumab 150 mg between February and May 2023. Table 1 details each patient's diagnosis and includes lists of prior and concomitant medications. During the observation period, SCAN04 discontinued PSL (2.5 mg/day), which had been continuously administered before IIT enrollment, at the Week 16 visit. Additionally, SCAN01, SCAN02, and SCAN05 took one day of oral loxoprofen after Week 8. No other changes in concomitant medications were reported.

The mean age at consent was 60.0 ± 9.5 years (mean ± SD, 4 males and 1 female), with a mean height of 161.9 ± 4.9 cm and a mean weight of 58.6 ± 10.2 kg. No participant weighed less than 40 kg. Laboratory values at screening before canakinumab administration were as follows: WBC count, 14,080 ± 5520/μL (86.2 ± 4.9 % neutrophils), CRP concentration, 6.05 ± 4.19 mg/dL (normal <0.14 mg/dL) and SAA level, 356.5 ± 202.0 mg/L (normal <3.0 mg/L).

Clinical efficacy at the primary endpoint

The response rate at the primary endpoint was 60 % (3/5) one week after a single injection of canakinumab 150 mg (Fig. 1, 2A). SCAN01 and SCAN04, who did not achieve CR, had post-treatment PGA scores of 6 (Table 2). SCAN01 had scores of 2 for fever/chills and arthralgia/bone pain, while SCAN04 scored 2 for myalgia and arthralgia/bone pain. Both patients, however, had pre-treatment

Table 1
Patient background characteristics.

	Rash	IgM	Fever	Bone remodeling	Biopsy[†]	WBC (/μL)[‡]	CRP (mg/dL)[‡]	Strasbourg Criteria	Concomitant medications	Previously used drugs
SCAN01	+	IgM-κ	+	−	+	15,100	0.02	Definitive	PSL 5 mg	Tocilizumab, Loxoprofen, Bilastine
SCAN02	+	IgM-κ	+	−	+	5100	3.45	Definitive	−	Colchicine, Fexofenadine
SCAN03	+	IgM-κ	−	−	+	20,300	9.12	Definitive	−	Colchicine, Loxoprofen, Celecoxib, Acetaminophen, D-Chlorpheniramine, Fexofenadine, Bilastine, Montelukast, Famotidine
SCAN04	+	IgM-κ	+	NA	+	14,900	9.88	Definitive	PSL 2.5 mg[§]	Betamethasone, Colchicine, Loxoprofen, Diphenhydramine, Olopatadine, Glycyrrhetinic Acid
SCAN05	+	IgM-κ	+	+	+	15,000	7.76	Definitive	Betamethasone 0.5 mg	Colchicine, Rupatadine, d-Chlorpheniramine

PSL, prednisolone.
[†] A neutrophilic dermal infiltrate upon skin biopsy.
[‡] Value at screening after consent was obtained.
[§] Medication was continued prior to participation in the IIT and discontinued at the Week 16 visit.

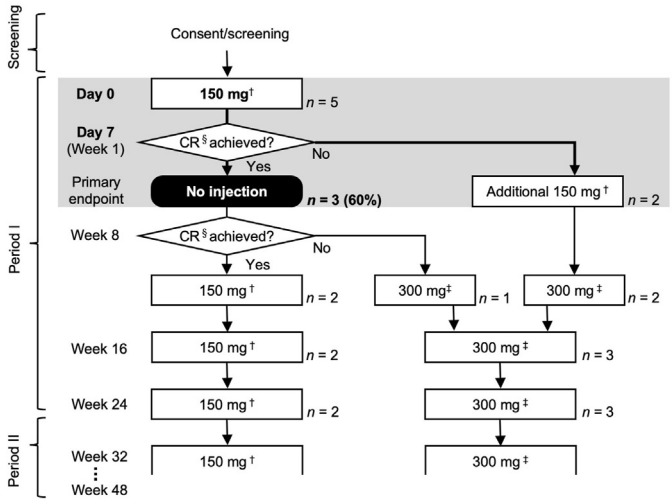

Fig. 1. Treatment diagram. Patients who met inclusion criteria at screening received a single dose of canakinumab 150 mg after post-consent pretreatment testing and investigation (5 patients). The primary endpoint was 1 week later (Day 7). Two patients who did not achieve a complete clinical response (CR) were given an additional dose of 150 mg. Two weeks after the first dose, the clinical response was again checked. At the time of the second dose, 8 weeks after the first dose, the two patients who had maintained a CR continued to receive 150 mg every 8 weeks. One patient who did not maintain a CR received 300 mg every 8 weeks from the second dose onward, as did the two patients who received an additional dose. The duration of Period I was 24 weeks.
† 2 mg/kg for body weight below 40 kg. ‡ 4 mg/kg for body weight below 40 kg. § CR, complete clinical response, defined by a physician global assessment (PGA) score of 5 or less and no greater than 1 in any of the 5 constituent signs/symptoms.

PGA score of 17, which improved after treatment with canakinumab.

Figures 2B and 2C displays SCAN01's urticaria-like rash before and after treatment. All five patients showed improvement, with SCAN01, SACN02, and SCAN03 achieving complete resolution of the rash one week post-treatment. The remaining two patients showed only slight residual skin rashes (Table 2). The initial disease activity level, determined by the total PGA score, was 15.0 ± 2.5 (Fig. 2D). After a single dose of canakinumab, the primary endpoint on Day 7 (Week 1) showed a reduction to 3.0 ± 2.8.

The patient-assessed SchS disease score dropped from 6.12 ± 1.88 before canakinumab administration to 4.32 ± 2.19 the night of administration, 2.40 ± 0.84 the following night, and 1.88 ± 0.88 on Day 3 (Fig. 2E). The scores continued to stay less than two points, with a primary endpoint assessment of 1.28 ± 0.99 on Day 7 (Week 1) post-dose (Fig. 2F).

Inflammation markers in the first week

The peripheral blood WBC count decreased from 17,200 ± 8517/μL pre-treatment to 7400 ± 2109/μL one week post-treatment, returning to normal levels (Fig. 2G). The neutrophil percentage also dropped from 85.2 ± 8.8 % (normal range: 40–74 %) to 59.5 ± 20.3 % (Fig. 2H), resulting in a decrease in neutrophil count from 15,029 ± 8577/μL to 4380 ± 1789/μL (Fig. 2I).

Serum CRP levels reduced from 7.24 ± 7.04 mg/dL pre-treatment to 0.23 ± 0.19 post-treatment (Fig. 2J). Similarly, SAA levels improved, dropping from 359.7 ± 319.4 mg/L to 4.0 ± 2.6 mg/L (Fig. 2K).

Serum ALP, an indicator of abnormal bone remodeling in SchS,[3] decreased slightly from 101.6 ± 63.5 U/L (normal range: 38–113 U/L) pre-treatment to 80.0 ± 32.6 U/L post-treatment (Fig. 2L). However, ALP3, a bone-derived fraction, remained stable at 26.9 ± 9.1 U/L post-treatment compared to 26.4 ± 10.2 U/L pre-treatment (Fig. 2M), suggesting that ALP values did not reflect bone lesions in this study.

QoL in the first week

The study assessed the impact of an urticaria-like rash on patients' QoL using DLQI. The DLQI consists of 10 questions with scores ranging from 0 (no impact) to 30 (very high impact),[25] where higher scores indicate lower QoL. The pre-treatment DLQI score was 14.2 ± 9.1, showing a high impact of skin symptoms on QoL (Fig. 3A). After one week of canakinumab treatment, this score reduced to 2.8 ± 3.6, reflecting minimal impact on QoL. Moreover, the DLQI evaluates 6 subscales: symptoms/feelings, daily activities, leisure, personal relationships, work/school, and treatment. All subscales, except for treatment, showed improvement one week after canakinumab treatment (Fig. 3B-G).

The SF-36 assesses overall health across eight domains, with scores ranging from 0 to 100, where higher scores indicate better health.[26] After one week of canakinumab treatment, improvement were seen across all domains (Fig. 3H-O).

Effects after week 1

SCAN01 and SCAN04, who failed to achieve CR at Week 1, received an additional 150 mg of canakinumab (Fig. 1). At Week 2, 60 % (3/5) of patients still achieved CR (Fig. 2A). Of those administered the additional dose, SCAN01 achieved CR, whereas SCAN04 did not. Meanwhile, SCAN05, who initially reached CR, regressed to PR at Week 2. The average PGA score across all five patients was 2.0 ± 1.2. SCAN04 and SCAN05, both failing to meet CR criteria due to arthralgia/bone pain (scored 2 points), had a low PGA score of 3 points. Despite these differences, all patients, both CR and PR, showed certain improvement from pre-treatment, with minimal variance in WBC count, neutrophil count, CRP concentration, and SAA values following 2 weeks of canakinumab treatment.

Figure 2E shows the patient-assessed SchS disease scores through Week 8. Despite slight variation in mean values (0.8–1.5), the subjective symptoms of SchS from 1 to 8 weeks post-treatment remained stable at a mean of 1.1 ± 0.2, indicating the drug's effect lasted 8 weeks.

SCAN03, who lost CR at Week 8, received 300 mg of canakinumab thereafter. Consequently, SCAN02 and SCAN05 continued with 150 mg every 8 weeks, while remaining three patients received 300 mg (Fig. 1). At Week 8, the mean PGA score was 3.0 ± 2.3, which decreased to 1.8 ± 2.5 at Week 16 (Fig. 2D). Sixty percent (3/5) achieved CR at both Week 8 and 16, while SCAN03 and SCAN04 remained at PR (Fig. 2A).

At Week 24, the mean PGA score increased to 3.6 ± 5.9, due to an abnormal rise in SCAN04's score (urticaria rash: 2, fatigue: 3, fever/chills: 3, myalgia: 3, arthralgia/bone pain: 3; total: 14) (Fig. 2D). This elevation can be attributed to two factors. First, the patient's physician was exposed to a COVID-19 case, preventing attendance, and the observation period was extended from the planned 8 weeks to an additional 3 weeks, resulting in an extended dosing interval. Second, PSL 2.5 mg/day, administered before IIT, was discontinued at Week 16. Consequently, 80 % (4/5) of the patients achieved CR at Week 24, while SCAN04 was classified as non-responsive (Fig. 2A).

The mean patient-assessed SchS disease score at Week 16 was 0.68 ± 1.10 and remained low at 0.72 ± 0.58 by Week 24, the last night of the Period I observation (Fig. 2F). This self-assessment score was unaffected by the 3-week extension of the observation period during the final PGA assessment. Additionally, as the inflammatory markers including WBC count (Fig. 2G), neutrophil

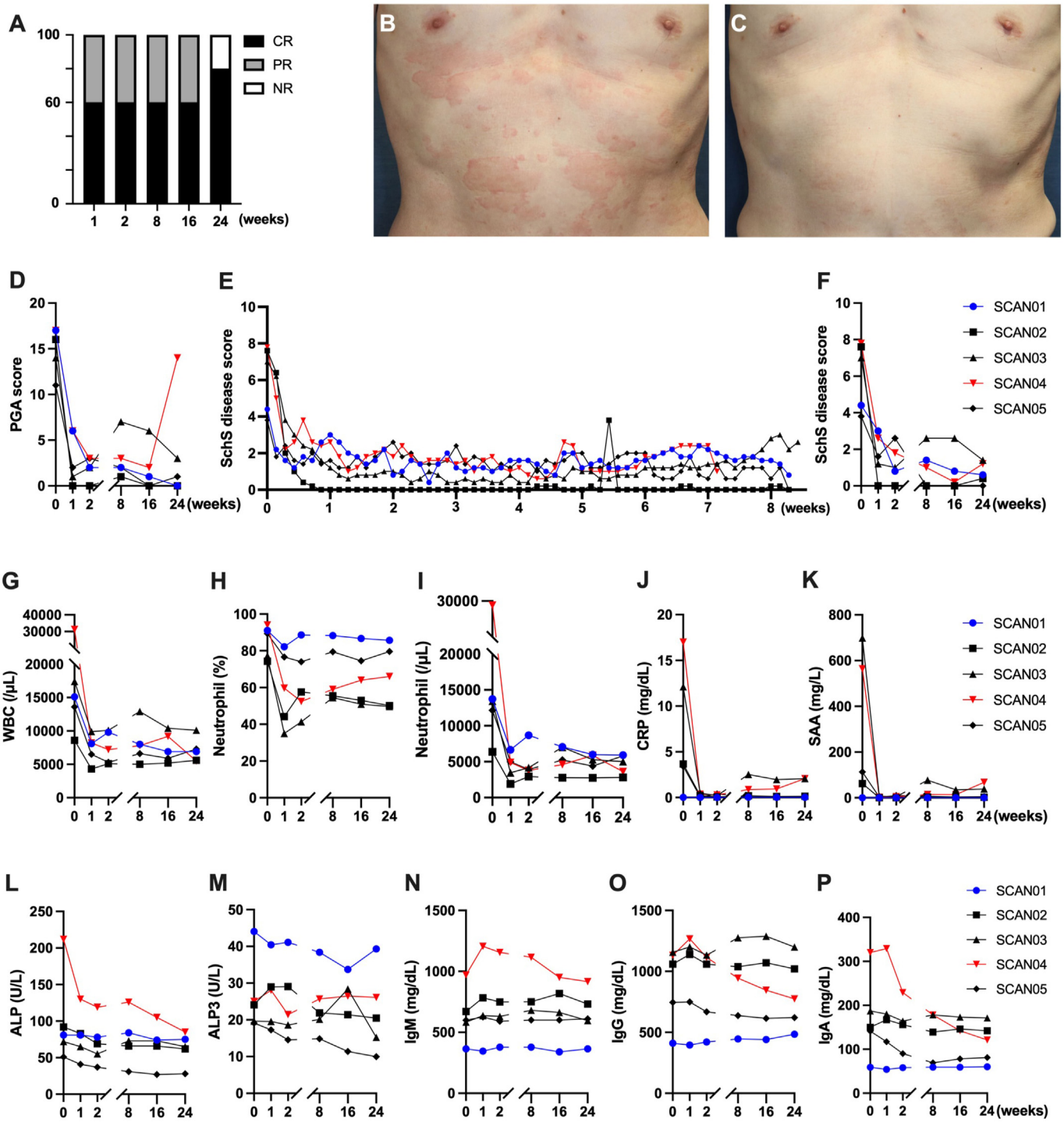

Fig. 2. Changes in disease activity of Schnitzler syndrome (SchS). **A,** Clinical Response rates. CR, complete clinical response defined by a physician global assessment (PGA) score of 5 or less and no greater than 1 in any of the 5 constituent signs/symptoms. PR, partial clinical response defined with a PGA score of more than 5 and a reduction of 30 % or more compared to baseline. NR, no clinical response. **B and C,** Urticaria-like rash of SCAN01 before and after a single injection of 150 mg canakinumab. **D,** Total PGA score graded the 5 key symptoms of SchS (urticarial rash, fatigue, fever/chills, myalgia, and arthralgia/bone pain) on a 5-point scale. The total PGA scores ranged from 0 to 20. **E and F,** SchS disease score rated by patients. Patients were requested to rate the severity of their overall symptoms on a scale from 0 (very good) to 10 (very bad) once per night, from the day before the first dose until 8 weeks **(E)**, and then on the night before each subsequent visit **(F)**. **G-P,** Changes in laboratory test. White blood cell (WBC) count, neutrophil percentage in WBC **(H)**, neutrophil count **(I)**, C-reactive protein (CRP) concentration **(J)**, serum amyloid A (SAA) levels **(K)**, alkaline phosphatase (ALP) levels **(L)**, ALP3 **(M)**, serum levels of IgM (normal range: male, 33–190 mg/dL, female, 46–260 mg/mL, N), IgG (normal range: 870–1700 mg/dL, **O**), and IgA (normal range: 110–410 mg/dL, **P**).

Table 2
PGA score before and 1 week after canakinumab administration.

	Urticarial rash		Fatigue		Fever/chills		Myalgia		Arthralgia/Bone pain		Total	
	Before	Week 1	Before	Week 1	Before	Week 1	Before	Week 1	Before	Week 1	Before	Week 1
SCAN01	4 →	0	3 →	1	3 →	2	3 →	1	4 →	2	17 →	6[†]
SCAN02	3 →	0	4 →	0	3 →	0	3 →	0	3 →	0	16 →	0
SCAN03	4 →	0	4 →	0	2 →	0	1 →	0	3 →	1	14 →	1
SCAN04	3 →	1	4 →	1	4 →	0	3 →	2	3 →	2	17 →	6[†]
SCAN05	4 →	1	3 →	1	2 →	0	1 →	0	1 →	0	11 →	2
Mean	3.6 →	0.4	3.6 →	0.6	2.8 →	0.4	2.2 →	0.6	2.8 →	1.0	15.0 →	3.0
SD	0.5	0.5	0.5	0.5	0.8	0.9	1.1	0.9	1.1	1.0	2.5	2.8

[†] Patient did not achieve complete clinical response (CR), which is defined as a physician global assessment (PGA) score of 5 or less and no greater than 1 in any of the 5 constituent signs/symptoms.

count (Fig. 2G), CRP concentration (Fig. 2J), and SAA level (Fig. 2K) were tested at the scheduled 8-week intervals, it was confirmed that their improvement was maintained.

Changes in serum IgM

SCAN04 showed a trend toward decreased serum IgM levels (Fig. 2N), along with reductions in IgG (Fig. 2O) and IgA (Fig. 2P) after two weeks of canakinumab treatment. However, in the other four patients, serum IgM levels remained stable throughout the 24 weeks of Period I.

The κ/λ ratio of free light chains, which has a shorter half-life than normal immunoglobulins, was monitored to detect potential progression to immunoglobulin-producing tumors. This ratio remained largely unchanged during the 24-week observation period (Supplementary Table 1).

AEs

AEs were reported in 60 % (3 patients) (Table 3). SCAN01 experienced an exacerbation of pre-existing xerosis, which resolved with topical steroids and moisturizers. SCAN04 suffered a right rib fracture from a fall. SCAN03 was diagnosed with nephrosclerosis, classified as a serious AE due to hospitalization. No therapeutic intervention was required, and the severity was classified as mild. SCAN03 also reported arthralgia, back pain, and urinary catheter site pain, all of which improved within two days with NSAIDs and were determined unrelated to canakinumab.

In contrast, SCAN03 reported fatigue after each of the four canakinumab doses in Period I, which was considered related to the drug (Table 3). The fatigue was mild, resolving without treatment the same day.

Additionally, SCAN04 experienced a 40 °C fever 11 weeks after the last dose. This fever was considered an exacerbation of SchS due to the extended dosing interval, rather than an AE, as the drug's effect had diminished.

Cytokine trends associated with canakinumab treatment

We measured cytokines and chemokines reported to be associated with SchS before and after canakinumab administration. IL-1Ra, known for its sensitivity to IL-1β, was detected at higher levels than IL-1β and followed similar trends (Supplementary Fig. 2A, B). However, no correlation were found between IL-1β, IL-1Ra, or CCL2 (Supplementary Fig. 2C) and WBC count, neutrophil count, acute inflammatory markers (such as CRP and SAA), PGA score, or patient-assessed SchS disease activity.

IL-6 was detected in two patients, SCAN01 and SCAN04, before canakinumab administration. SCAN01 had received tocilizumab up to 2 weeks before joining the IIT. After canakinumab treatment, IL-6 became undetectable in all five patients throughout the 24-week observation period (Supplementary Fig. 2D).

Discussion

During this 24-week Period I of a multi-center, single-arm, open-label IIT, canakinumab demonstrated substantial improvement in the clinical symptoms of SchS in Japanese patients. In this IIT, the primary endopoint was set for one week after a single dose of 150 mg canakinumab to compare the results with a previous German IIT and because the clinical effects of canakinumab reportedly appear within 6–24 h.[13,22] In the German IIT, a 20 % improvement in patient-rated SchS disease scores was observed within 24 h,[23] representing a rapid onset of action. In our study, patients reported a 30 % improvement in SchS disease scores (from 6.12 to 4.32) on the night of administration, which further improved to 70 % (1.88) within three days. The scores remained stable for the next 8 weeks (Fig. 2E). Based on these results, setting the primary endopoint one week after the first administration appears appropriate, especially considering the reduced burden on patients' visits.

The evaluation of clinical efficacy is based on the PGA score, which is assessed by the attending physician. This score combines the five key symptoms of SchS (urticarial rash, fatigue, fever/chills, myalgia, and arthralgia/bone pain). In a German IIT, the evaluation of each symptom was considered, but only fever/chills did not show statistically significant differences before and after canakinumab administration.[23] However, we do not believe that canakinumab is less effective against fever than other SchS symptoms. In the German IIT, only 3 out of 7 patients in the canakinumab group and 6 out of 13 in the placebo group had a fever prior to treatment, making it difficult to assess the improvement in fever after canakinumab administration. In our IIT, one patient (SCAN01) did not achieve CR at the primary endpoint, with fever/chills improving from 3 to 2 points, but this was insufficient for CR. However, the other four patients showed full improvement in fever (Table 2).

Patients with autoinflammatory diseases often experience significant QoL impairment. A previous German IIT[23] found baseline DLQI scores comparable to those in other chronic skin diseases, such as chronic urticaria[27] and urticarial vasculitis.[28] In contrast, a Japanese study on omalizumab[29] reported a baseline DLQI score of 8.4 ± 5.9 for urticaria, suggesting greater QoL impairment in SchS patients in this study. After one week of canakinumab treatment, QoL improved as assessed by the DLQI, which was reflected in the 'urticarial rash' scores on the PGA score (Table 2). International studies have shown that SchS mainly impacts physical health, while mental health is less affected.[23] The primary cause of reduced QoL is pain from myalgia and arthralgia/bone pain, linked to high PGA scores. However, studies conducted using the SF-36 on Japanese subjects have shown that, compared to Western population,

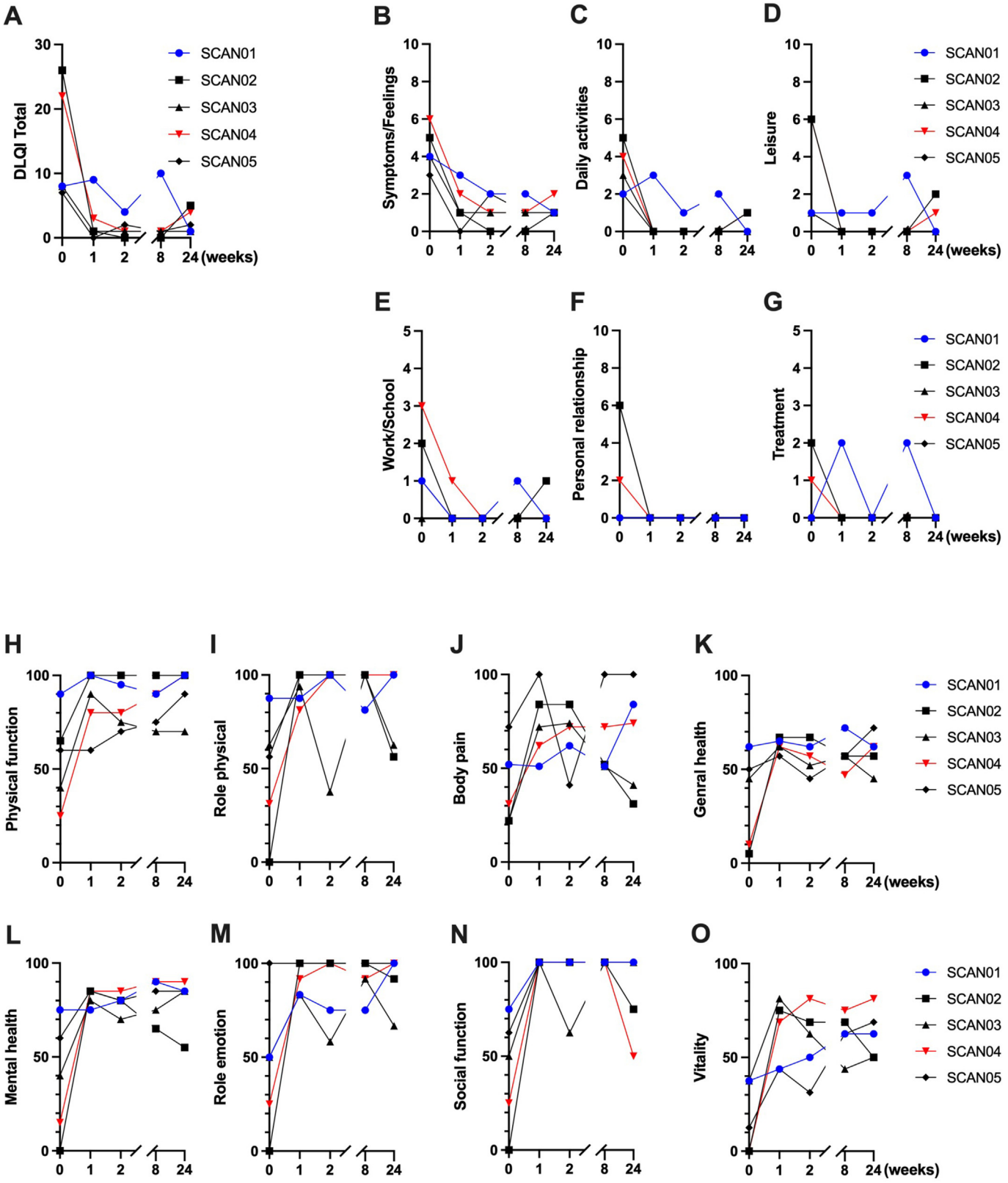

Fig. 3. Changes in quality of life (QoL) scores. **A,** Total score on the DLQI. **B-G,** Subscales of the DLQI. On the DLQI, a higher score indicates a lower QoL. **H–O,** SF-36 scores. Higher scores indicate better health.

Table 3
Adverse events.

	Event	Severity	Causality[†]	Treatment
SCAN01	Xerosis	Non-serious	No	Topical steroids and moisturizers
SCAN03	Fatigue	Non-serious	Yes	Untreated
	Nephrosclerosis	Serious	No	Untreated (hospitalized for renal biopsy)
	Right shoulder arthralgia	Non-serious	No	Topical use and oral administration of NSAIDs
	Back pain	Non-serious	No	Topical use and oral administration of NSAIDs
	Pain at the site of urinary catheter insertion	Non-serious	No	Oral administration of NSAIDs
SCAN04	Fall	Non-serious	No	Untreated
	Fracture of the right rib	Non-serious	No	Untreated

[†] Association between the adverse event and the use of canakinumab.

'physical pain' and 'vitality' have a greater impact on mental factors in Japanse people.[26] Our IIT revealed that Japanese SchS patients felt impairments in mental health-related domains, such as mental health, role emotional, social function, and vitality, prior to treatment. After one week of canakinumab treatment, all SF-36 domains, including those related to mental health, showed improvement (Fig. 3H-O).

Monoclonal IgM gammopathy is included in the obligate criteria for diagnosing SchS.[3] However, caution is needed when evaluating IgM levels. In a prior domestic survey conducted before this IIT,[7] some patients had serum IgM levels near the upper limit of normal at their first visit, with levels gradually increasing over the course of the disease. This phenomenon is not uncommon, even in patients receiving IL-1-targeted therapy.[30] The mechanism of SchS development remains unclear, along with the clinical significance of monoclonal IgM gammopathy and its potential risk of progression to hematologic tumors. However, during the 24-week Period I of this IIT, there were no indication that canakinumab affected IgM elevation or the free λ/κ ratio (Fig. 2N and Supplementary Table 1). Instead, the increases in IgM observed in the previous study[7] may reflect poorly controlled inflammation. Long-term observation, including safety evaluation, of this IIT is essential.

A previous German IIT of patients with SchS reported respiratory tract infections as the most frequent AEs,[23] consistent with earlier canakinumab studies in CAPS.[13,31] However, no respiratory tract infections were observed in our IIT. This study identified nephrosclerosis in SCAN03. The patient had CRP levels of around 2 mg/dL in 2010, and skin symptoms appeared in 2012. Mildly positive urinary protein was noted in 2022, followed by varying results, but the patient was under observation at the time of trial inclusion. Canakinumab dosage was increased to 300 mg at Week 8, and a renal biopsy was performed after elevated urinary protein levels were detected at Week 16. The patient had a pre-existing hypertension diagnosis and was on antihypertensive medication (telmisartan) before the IIT. Since nephrosclerosis has never been reported in SchS, and no amyloid deposition was found in the biopsy, we consider nephrosclerosis an incidental complication unrelated to disease progression or canakinumab. The study is ongoing in Period III, and safety monitoring continues.

Currently, there are no established biomarkers to assess SchS disease activity. Although IL-1β is a key inflammatory mediator in SchS, as evidenced by canakinumab's effectiveness, IL-1β is rarely detected in serum due to its short half-life and localized effects. Serum IL-1Ra levels are believed to reflect IL-1β status more accurately. A previous German IIT measured IL-1Ra levels and reported a correlation between changes in IL-1Ra levels and disease activity.[23] In our study, IL-1Ra plasma levels were about 50 times higher than IL-1β and showed similar trends, but did not correlate with clinical symptoms or other inflammatory markers (Supplementary Fig. 2). Additionally, plasma CCL2 levels did not correlate with clinical symptoms or inflammatory markers, which contrasts with previous studies suggesting CCL2,[32] also known as MCP-1, as a useful marker doe to its role as a potent chemoattractant for monocytes and macrophages.[33]

According to the treatment algorithm for SchS,[3] it is recommended to reduce the PSL-equivalent dose of oral corticosteroids to 5 mg or less per day. In this study, concomitant medications were limited to those at or below this dose. At the time of the initial canakinumab administration, SCAN01, SCAN04, and SCAN05 were on oral corticosteroids (Table 1), and their pre-treatment WBC and neutrophil counts may have been influenced by these steroids. However, since the steroid doses were unchanged before evaluating the primary endpoint, we believe they did not affect the canakinumab results.

In the treatment algorithm,[3] tocilizumab, which targets IL-6, is also being evaluated.[34,35] In an open-label trial involving 9 SchS patients,[34] tocilizumab initially reduced symptoms and inflammatory markers, but its efficacy diminished over time in most cases. In our cohort study,[7] which collected reports from Japan, six SchS patients, including SCAN01who participated in this IIT, were treated with tocilizumab. Two patients who had used tocilizumab for 1 and 3 years achieved a PGA score of zero, but some patients treated with tocilizumab in the previous study[7] experienced symptom recurrence after several years. SCAN01 was included in this IIT because symptoms were not fully controlled by tocilizumab treatment. His pre-treatment CRP and SAA levels were normal, likely due to the use of tocilizumab up to 2 weeks before the administration of canakinumab. The high plasma IL-6 level before canakinumab treatment could also be attributed to tocilizumab, which block the IL-6 receptor, but neither IL-6 nor its production. However, considering the half-life of tocilizumab, it is unlikely that tocilizumab affected the results of this trial. Additionally, IL-6 levels were undetectable one week after canakinumab administration (Supplementary Fig. 2D).

Limitations: This study is not placebo-controlled or double-blinded due to the limited number of cases in Japan. However, the effect of canakinumab was substantial. One patient classified as having NR at Week 24 was not observed by physician at the scheduled 8-week interval. However, we did not remove this case from the analysis because of the limited number of patients in this study.

In conclusion, our results demonstrate canakinumab has a potential usefulness in Japanese patients with SchS, reducing clinical symptoms and inflammation markers, as well as improving QoL. The 24-week study suggests that canakinumab treatment is both safe and well-tolerated.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2024.10.001.

Conflict of interest

NKam received canakinumab free of charge on behalf of this investigator-initiated clinical trial and consulting fees from Novartis. The rest of the authors have no conflict of interest.

Authors' contributions

NKam, HY, TJ, KI, TI, YA, and NKan designed the study. NKam wrote the manuscript. NKam, MY, KT, SK, YK, SN, and NI contributed to data collection. YI and SM performed the statistical analysis. All authors read and approved the final manuscript.

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