Efficacy and safety of canakinumab in Schnitzler syndrome: A multicenter randomized placebo-controlled study

Karoline Krause, MD,[a,b] Athanasios Tsianakas, MD,[c] Nicola Wagner, MD,[d] Jörg Fischer, MD,[e] Karsten Weller, MD,[a] Martin Metz, MD,[a] Martin K. Church, PhD,[a] and Marcus Maurer, MD[a,b] *Berlin, Münster, Darmstadt, and Tübingen, Germany*

Background: Schnitzler syndrome is an adult-onset autoinflammatory disease characterized by urticarial exanthema and monoclonal gammopathy accompanied by systemic symptoms such as fever, bone, and muscle pain. Up to now, approved treatment options are not available.
Objective: We assessed effects of the anti–IL-1β mAb canakinumab on the clinical signs and symptoms of Schnitzler syndrome.
Methods: In this phase II, randomized placebo-controlled multicenter study, 20 patients with active disease enrolled in 4 German study centers. Patients were randomly assigned to receive single subcutaneous canakinumab 150 mg or placebo injections for 7 days, followed by a 16-week open-label phase with canakinumab injections on confirmed relapse of symptoms. The primary end point was the proportion of patients with complete clinical response evaluated by physician global assessment at day 7. Key secondary end points included changes in patient-reported disease activity (Schnitzler activity score), inflammation markers (C-reactive protein and serum amyloid A), and quality-of-life assessments (Dermatology Life Quality Index and 36-item short form health survey).
Results: The proportion of patients with complete clinical response at day 7 was significantly higher ($P = .001$) in the canakinumab-treated group (n = 5 of 7) than in the placebo group (n = 0 of 13). Levels of inflammation markers C-reactive protein and serum amyloid A and quality-of-life scores were significantly reduced in canakinumab-treated but not in placebo-treated individuals. Positive effects continued up to 16 weeks. Adverse events were manageable and included respiratory tract infections, gastrointestinal symptoms, and hypertension.
Conclusions: In this first placebo-controlled study, canakinumab was effective in patients with Schnitzler syndrome, and thus canakinumab may be further evaluated as a therapeutic option for this rare disease. (J Allergy Clin Immunol 2017;139:1311-20.)

Key words: *Autoinflammatory, canakinumab, IL-1, Schnitzler syndrome, urticaria*

Schnitzler syndrome, first reported in 1972 by the French dermatologist Liliane Schnitzler,[1,2] is a multifactorial systemic inflammatory disorder with late onset, usually at around 50 years of age.[3] It is characterized by chronic urticarial rash and monoclonal gammopathy (typically IgM, less often IgG).[4] Symptoms frequently associated with Schnitzler syndrome are recurrent fever attacks, bone and muscle pain, arthralgia, and lymphadenopathy.[5] Schnitzler syndrome is ultrarare, with fewer than 300 cases reported in the literature.[4,6] However, it is likely that many cases presenting with therapy-refractory chronic urticarial eruptions are undiagnosed. Patients usually suffer from severe quality-of-life impairment and may develop malignant B-cell lymphoma such as Waldenström macroglobulinemia in around 15% of cases.[7]

Schnitzler syndrome is held to be a paradigm of an acquired and late-onset autoinflammatory disease, a group of diseases characterized by inflammasome activation and IL-1–driven morbidity and mortality. This notion is based on several independent lines of evidence. First, the clinical phenotype shares many similarities with cryopyrin-associated periodic syndrome (CAPS), a member of the monogenic systemic autoinflammatory disorder group. Second, patients with Schnitzler syndrome exhibit changes in the expression of inflammasome components that are typical for autoinflammatory disorders including apoptosis-associated speck-like protein containing a caspase recruitment domain and the P2X7 receptor.[8] Third, IL-1β secretion from PBMCs of patients with Schnitzler syndrome is increased.[9]

Approved treatment options are completely lacking in Schnitzler syndrome. The use of systemic corticosteroids, other immunosuppressives, and nonsteroidal antiphlogistics has demonstrated poor efficacy.[4] Recently, anti–IL-1–targeting therapies, in case reports on anakinra treatment and 2 open-label studies with rilonacept and canakinumab, have been shown to be very effective in reducing the clinical symptoms

From [a]the Department of Dermatology and Allergy and [b]Autoinflammation Reference Center Charité, Charité – Universitätsmedizin Berlin, Berlin; [c]the Department of Dermatology, Universitätsklinikum Münster, Münster; and [d]the Department of Dermatology, Klinikum Darmstadt, Darmstadt, and [e]the Department of Dermatology and Allergy, Universitätsklinik Tübingen, Tübingen.

This study was financially supported by Novartis Pharma GmbH and intramural grants.
Disclosure of potential conflict of interest: K. Krause has received grants from Regeneron and Novartis; has consultant arrangements with Novartis; and has received payment for lectures from Roche and Novartis. K. Weller has received grants, payment for lectures, and travel support from Novartis; has worked on different projects funded by Novartis during the past 3 years outside the submitted work; has a board membership and consultant arrangements with Novartis; and has received honoraria for educational lectures from Dr R. Pfleger, Essex Pharma (now MSD), Uriach, UCB, Novartis, Shire, Viropharma, and Moxie. In addition, he received honoraria for consulting from Novartis and he is or was involved in clinical research projects of Dr R. Pfleger, Essex Pharma (now MSD), Faes, Uriach, Novartis, Shire, and Viropharma. M. Metz has received payment for lectures from Bayer, Dr R. Pfleger, GlaxoSmithKline, Moxie, Nerre, Novartis, Roche, and Sanofi. M. Maurer has received grants from Novartis and Regeneron and has received a consulting fee or honorarium and travel support from Novartis. The rest of the authors declare that they have no relevant conflicts of interest.
Received for publication March 3, 2016; revised July 13, 2016; accepted for publication July 21, 2016.
Available online September 19, 2016.
Corresponding author: Karoline Krause, MD, Dept of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Charitéplatz 1, D-10117 Berlin, Germany. E-mail: karoline.krause@charite.de.
The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections
0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2016.07.041

Abbreviations used
CAPS: Cryopyrin-associated periodic syndrome
CRP: C-reactive protein
DLQI: Dermatology Life Quality Index
IL-1Ra: IL-1 receptor antagonist
PGA: Physician global assessment
SAA: Serum amyloid A
SF-36: 36-item short form health survey

and inflammation in Schnitzler syndrome.[9-13] Canakinumab is a fully human IL-1β–specific mAb approved for the treatment of CAPS,[14] systemic juvenile idiopathic arthritis,[15] and therapy-refractory gout.[16] Here, we report the efficacy and safety of canakinumab in the first randomized, double-blind, placebo-controlled study in patients with Schnitzler syndrome.

METHODS

Study design

This investigator-initiated study of canakinumab in 20 patients with active Schnitzler syndrome was conducted in 4 German study centers and consisted of 3 parts, 2 of which have been completed. The first part was an initial 7-day double-blind, placebo-controlled study of a single subcutaneous dose of canakinumab 150 mg. The second part was a 16-week open-label follow-up to establish the optimal dose of canakinumab, 150 or 300 mg, and to assess adverse responses. The third part, a 4-year open-label extension to monitor long-term efficacy, quality of life, and unwanted effects, is ongoing.

For part 1 of the study, after screening for 7 to 28 days, patients were assigned randomly (1:1) to receive a single subcutaneous injection of canakinumab 150 mg or placebo at day 0. No stratification was applied. Central block randomization was used to form the allocation list for the 2 treatment groups. Patients, investigators, and site personnel were blinded to the treatment assignment. To preserve blinding, canakinumab and placebo were visually indistinguishable and packaged identically. Changes in clinical symptoms, inflammation markers, quality of life, and adverse events were assessed for the next 7 days. Following treatment response evaluation at day 7, patients were unblinded and moved to the open-label phase.

In the 16-week open-label follow-up phase of the study, all patients were treated with canakinumab injections depending on relapse or worsening of symptoms. Patients with complete clinical response (as defined below) to canakinumab 150 mg and normalized C-reactive protein (CRP) levels continued with canakinumab 150-mg injections when needed. Partial responders to canakinumab 150 mg with or without CRP above the upper limit of normal (≥0.5 mg/dL) were given canakinumab 300 mg on relapse/worsening of the disease. At all decision steps, nonresponders left the study.

Patients

For inclusion, patients had to fulfil the diagnostic criteria established by Lipsker et al[5] in 2001. These consist of monoclonal gammopathy and chronic urticarial rash combined with at least 2 of the following symptoms: fatigue, recurrent fever, myalgia, arthralgia or arthritis, lymphadenopathy, hepato-/splenomegaly, leukocytosis and/or elevated erythrocyte sedimentation rate, and abnormal bone morphology.[5] Only adult patients (≥18 years) with a physician global assessment (PGA) score of 8 or more (range, 0-20) and CRP level above the upper limit of normal at visit 2 (day 0) were eligible to participate in the study. Further inclusion criteria were the willingness to complete all study visits and study-related procedures, a negative pregnancy test result, and effective contraceptive methods for women of childbearing potential. Exclusion criteria included active tuberculosis and other chronic infections, ongoing treatment with IL-1 blockers, other biologics or immunosuppressives, and the presence of malignancies within the last 5 years.

The study was approved by a central institutional review board and the ethics committee of each study center (EudraCT no. 2010-024156-28) and followed Good Clinical Practice guidelines and the Declaration of Helsinki. The ClinicalTrials.gov identifier is NCT01390350. All patients gave written informed consent before any study-related procedures.

Assessments

The PGA was the primary instrument used to assess the efficacy of canakinumab treatment. For the PGA, the 5 key symptoms of Schnitzler syndrome (urticarial rash, fatigue, fever/chills, myalgia, and arthralgia/bone pain) were each graded on a 5-point Likert scale, with 0 = no, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe disease activity. The total PGA scores ranged between 0 and 20. Patient-reported disease activity was assessed using a modified Schnitzler activity score[10] in which patients were asked to grade the severity of their total symptoms daily on a scale ranging from 0 (very good) to 10 (very bad).

At every clinic visit, serum samples were collected to determine acute-phase reactants CRP and serum amyloid A (SAA) levels and patients completed 2 questionnaires—the Dermatology Life Quality Index (DLQI), a skin disease–specific quality-of-life questionnaire, and the 36-item short form health survey (SF-36), a generic health-related quality-of-life instrument—both of which have a recall period of 1 week. *Post hoc* assessments included blood levels of the inflammatory marker S100A12 protein and IL-1 receptor antagonist (IL-1Ra), evaluated at days 0, 7, and 120.

Study end points

The primary end point was the rate of complete clinical responders in the canakinumab-treated group as compared with the placebo group on day 7 of the double-blind phase of the study. Secondary end points included the overall clinical response rate, changes in physician (PGA) and patient-reported (Schnitzler activity score) assessments of disease activity, changes in acute-phase reactants (CRP and SAA), and changes in quality-of-life assessments (DLQI and SF-36). Further secondary end points were safety of canakinumab treatment assessed by physical examination, routine laboratory markers, vital signs, and adverse event reporting. *Post hoc* analyses included changes in S100A12 levels and cytokine (IL-1Ra) levels during the study.

Study definitions

A complete clinical response was defined as no or minimal disease activity, that is, a PGA score of 5 or less and no greater than 1 in any of the 5 constituent signs/symptoms. *A partial clinical response* was defined as mild to moderate disease activity with a PGA score of more than 5 and PGA reduction of 30% or more as compared with baseline. *No clinical response* was defined as high disease activity with PGA scores that were increased, stable, or showed less than 30% reduction. Relapse or worsening of clinical symptoms was identified by a 50% or more increase in the PGA score as compared with the PGA score 7 to 14 days after canakinumab initiation.

Statistical analysis

This trial was a pilot study intended to provide information on the efficacy, safety, and tolerability of canakinumab in patients with Schnitzler syndrome, an ultrarare disease. The sample size reflects the known number of affected patients in Germany. Because of the absence of randomized trials in this population and the unknown variability of disease activity, statistical power considerations were not applicable.

The difference between the rates of complete clinical responders in the 2 treatment groups (the primary end point) was calculated using Fisher exact test with a 2-tailed significance level of 5%. In the placebo-controlled treatment phase, the differences within treatment groups for PGA Likert scales and blood values were calculated by using Wilcoxon signed rank test. For patient-reported outcomes, an independent-samples *t* test was applied to test for differences in overall Schnitzler activity scores between the canakinumab-treated and placebo groups and a paired *t* test was used to test for differences in quality-of-life measurements within treatment groups. The

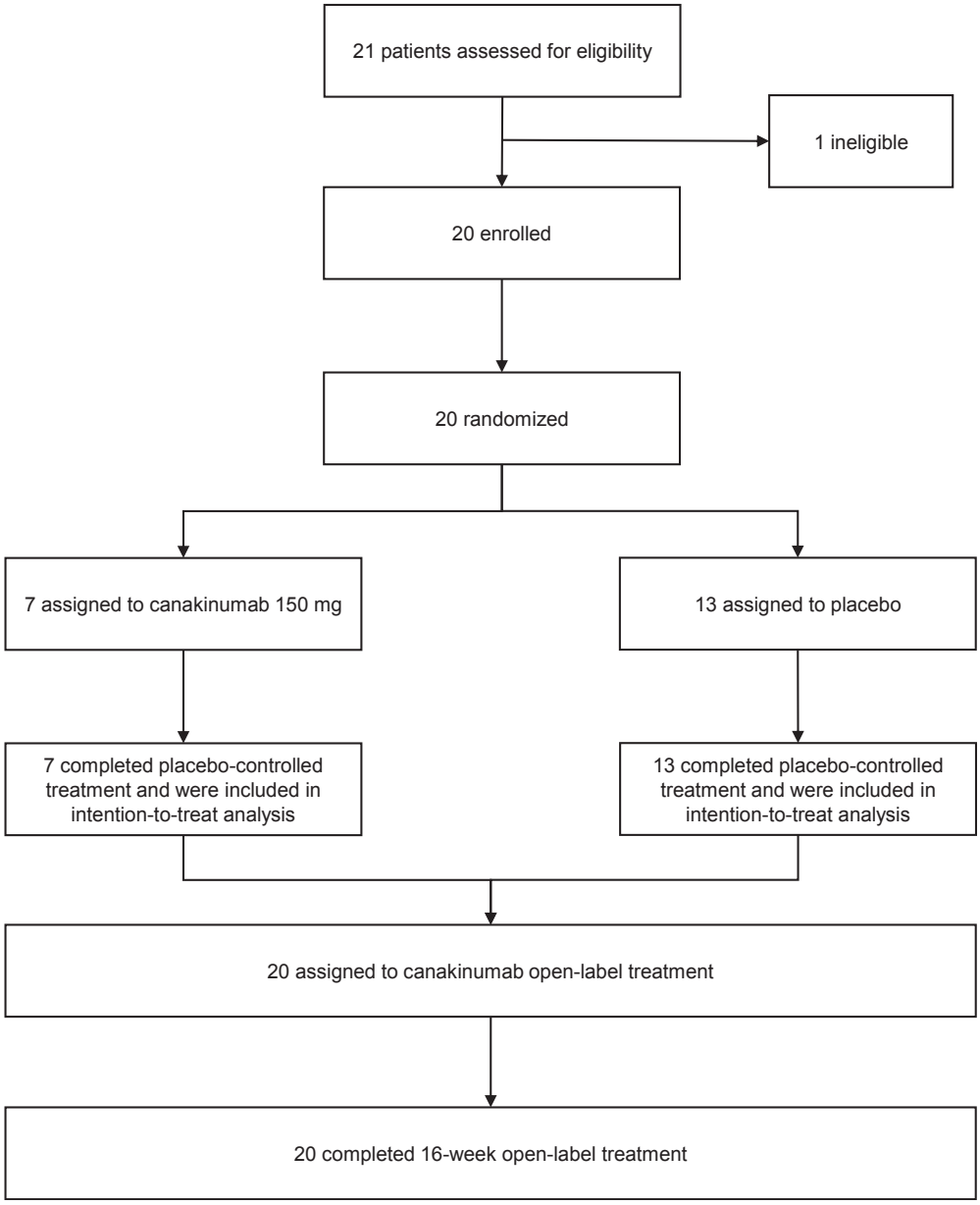

FIG 1. Subject disposition showing the number of screened, randomized, and completed patients.

Mann-Whitney *U* test was applied to assess differences in changes in clinical scores, inflammation markers, and quality of life between the canakinumab-treated group and the placebo group. All differences between day 0 and day 120 were analyzed by Wilcoxon signed rank test. Correlation was assessed using Spearman rank correlation. Data are presented either as median with range or mean ± SEM. A *P* value of .05 or less was considered to indicate statistically significant differences. Per protocol, the full analysis and safety set included all subjects with Schnitzler syndrome who received at least 1 dose of study medication. All analyses were performed with IBM SPSS version 22 (IBM Corporation, Armonk, NY).

RESULTS

Study population

Twenty-one patients were screened, and 20 of them underwent randomization and received at least 1 dose of study drug between July 23, 2011, and August 17, 2012 (Fig 1). Of these, 7 were assigned to the canakinumab-treated group and 13 were assigned to the placebo group. This difference in group sizes was caused by an inadvertent imbalance in study drug distribution between the study centers due to an error in the ratio of placebo versus canakinumab in a subset of study medication that one of the study centers was provided with, which resulted in higher than intended numbers of patients treated with placebo during the double-blind, controlled phase of the study. All randomized patients received at least 1 treatment, completed the double-blind and open-label phase of the study, and were included in the primary end-point analysis and safety analysis.

The percentage of women was slightly higher in the canakinumab group (57%) than in the placebo group (38%). At baseline, markers of systemic inflammation (CRP and SAA) were elevated in both groups, with somewhat higher median CRP values in the canakinumab group. Other baseline demographic

TABLE I. Baseline demographic, clinical, and laboratory characteristics across the study groups

Characteristic	Canakinumab	Placebo
Age* (y)	62 (54-71)	64 (28-74)
Sex (n)	F/M: 4/3	F/M: 5/8
Disease duration* (y)	5.5 (3-13.5)	6.3 (1.5-22)
Clinical symptoms, n		
Urticarial rash	7 of 7	13 of 13
Fatigue	6 of 7	13 of 13
Fever	3 of 7	6 of 13
Myalgia	7 of 7	11 of 13
Arthralgia/bone pain	7 of 7	13 of 13
Paraproteins, n		
IgM kappa	5 of 7	9 of 13
IgM lambda	0 of 7	1 of 13
IgG kappa	1 of 7	1 of 13
IgG lambda	0 of 7	2 of 13
IgA lambda	1 of 7	0 of 13
CRP* (mg/dL) (reference, <0.5 mg/dL)	9.3 (1.4-25.4)	3.1 (0.7-13.9)
SAA* (mg/L) (reference, <6 mg/L)	428 (69-857)	160 (2-1,310)
S100A12* (ng/mL) (reference, <200 ng/mL)	969 (151-1,797)	626 (151-3,036)
IL-1Ra* (pg/mL) (reference, <500 pg/mL)	1026 (262-5,189)	1846 (1,093-10,027)

F, Female; *M*, male.
*Data are expressed as median with range.

and clinical characteristics were similar across the study groups (Table I). All patients were white and the median disease duration was 5.5 years (range, 2-22 years). Ten of 20 patients had previously been checked for NLRP3 mutations to exclude late-onset CAPS in the diagnostic workup. Except for a heterozygous Q703K polymorphism in 2 patients, which was reported in up to 5% of the general population,[17] no relevant mutations were found. Quantitative baseline paraprotein levels ranged from 318 to 2400 mg/dL for IgM (reference, 40-230 mg/dL) and 776 to 1662 mg/dL for IgG (reference, 700-1600 mg/dL). Eight of 20 patients (3 of them in the canakinumab group and 5 of them in the placebo group) had previously received anakinra and had stopped treatment at least 3 days before day 0. All of them had benefited from anakinra treatment including 1 patient with IgA variant paraprotein. Concomitant medication included on-demand nonsteroidal anti-inflammatory drugs in most patients and low-dose oral corticosteroids (≤10 mg of prednisolone equivalent) in single patients.

Clinical efficacy

On day 7, the rate of complete clinical response (primary end point), that is, no or minimal disease activity, was significantly higher in the canakinumab-treated group (n = 5 of 7 patients) than in the placebo group (n = 0 of 13 patients) ($P = .001$; Fig 2, *A*). Baseline disease activity, as determined by total PGA, was comparable in the canakinumab-treated group (median, 14; range, 8-20) and in the placebo group (median, 15; range, 8-20). At the end of the double-blind treatment phase (day 7), disease activity was significantly reduced from baseline (day 0) in the canakinumab-treated group ($P = .018$; Fig 2, *B* and *C*), but not in the placebo group. The difference in median changes in PGA total scores (canakinumab −11 vs placebo 0) was significant between treatment groups ($P < .0001$; Table II). Patient-assessed disease activity (overall Schnitzler activity score) also showed a marked decline during the first 7 days of treatment (canakinumab –5.5 vs placebo −1.9). In the canakinumab-treated group, disease activity scores were reduced by 20% within 24 hours, and significant differences between the 2 groups were achieved as early as on day 3 of treatment ($P < .05$; Fig 2, *D*).

Effects on inflammation markers and IL-1Ra

Baseline inflammation markers displayed high interindividual differences. Median serum levels of CRP and SAA in the canakinumab-treated group fell from 9.3 mg/dL at day 0 to 0.6 mg/dL at day 7 ($P = .031$) and from 428 mg/L to 13 mg/L ($P = .031$), respectively, but increased in the placebo group from 3.1 mg/dL to 5.0 mg/dL for CRP ($P = .685$) and 160 mg/L to 211 mg/L for SAA ($P = .733$) (Fig 3, *A* and *B*). Median S100A12 levels were reduced from 969 ng/mL to 189 ng/mL ($P = .016$) in canakinumab-treated patients, but did not change significantly with placebo ($P = .734$) after the first week of treatment (Fig 3, *C*). Median serum levels of IL-1Ra, a biomarker of autoinflammatory disorders, were increased before treatment, and fell from 1026 pg/mL at baseline to 562 pg/mL at day 7 in the canakinumab-treated group ($P = .016$), but did not decline in the placebo group ($P = .641$) (Fig 3, *D*). The changes in CRP, SAA, and IL-1Ra levels were significantly different between treatment groups (Table II).

Effects on quality of life

Quality of life was considerably impaired at baseline and similar in both treatment groups. Within the first week, canakinumab significantly reduced mean DLQI sum scores from moderate (8.2 ± 2.4) to mild impairment (2.8 ± 1.7; $P = .003$) and improved SF-36 mean physical component summary scores from moderate impairment (32.8 ± 4.6) to normal values (46.6 ± 3.0; $P = .008$) (Fig 4). There were no significant changes in quality-of-life impairment in placebo-treated patients (DLQI, $P = .270$; SF-36 physical component, $P = .787$). Between treatment groups, the changes for both, the DLQI sum scores and the physical component summary of the SF-36, were highly significantly different ($P < .0001$; Table II).

Open-label phase

During the open-label phase of the study, all the patients who switched to canakinumab therapy improved and the patients who stayed on canakimumab treatment improved further. Seven to 14 days after canakinumab initiation, 15 of 20 patients were complete clinical responders and the remaining 5 were partial responders. At day 120, disease activity scores (PGA), inflammation markers, and quality-of-life scores (DLQI and SF-36) were all significantly reduced as compared with baseline (Table III). Canakinumab doses during the open-label phase were based on individual clinical and laboratory responses. Eight patients with complete clinical response and normalized CRP levels 7 days after treatment initiation continued with canakinumab 150-mg doses. Twelve patients received canakinumab 300-mg doses because of slightly elevated inflammation markers and/or remaining mild to moderate disease activity after

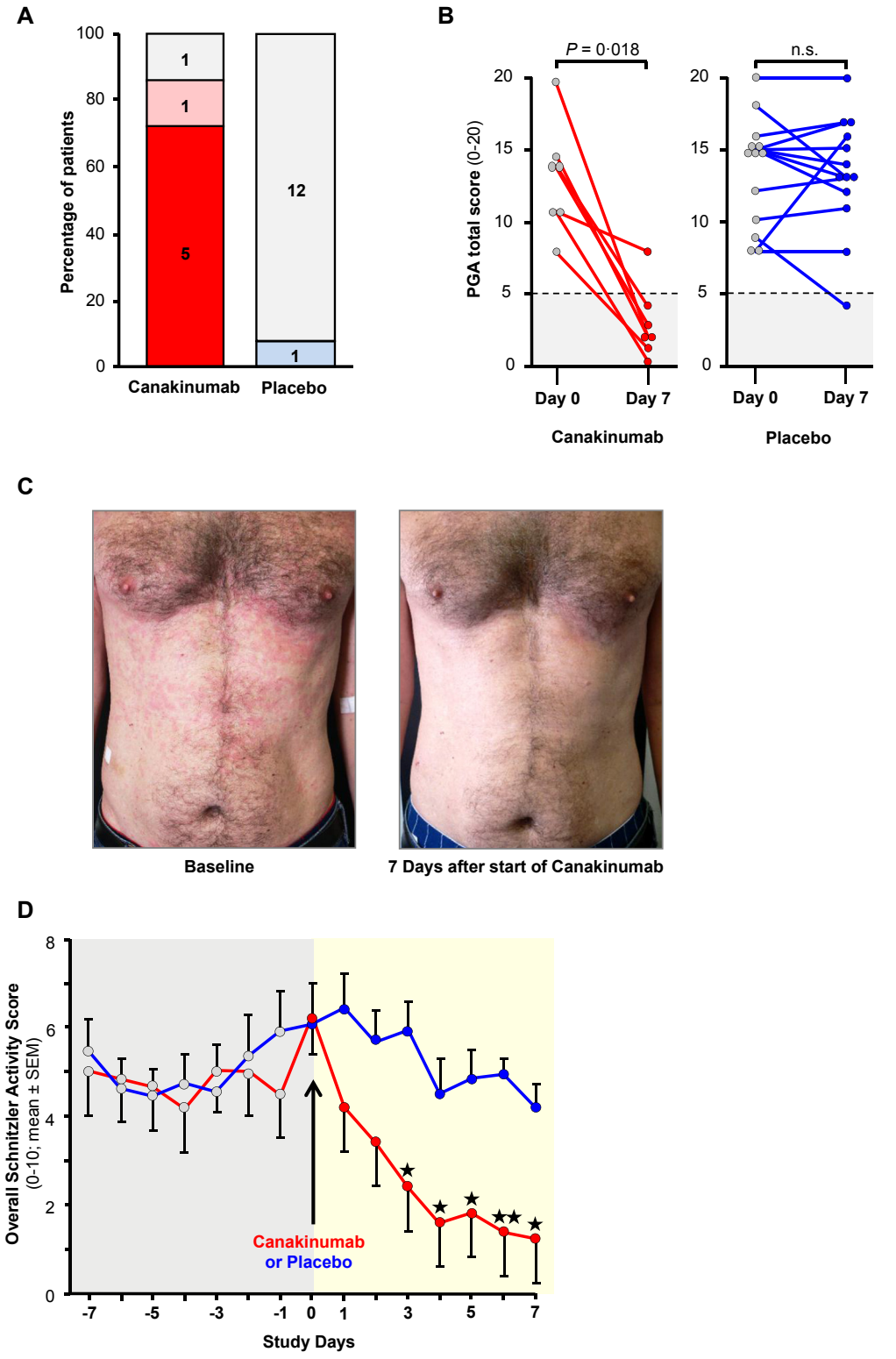

FIG 2. Changes in disease activity. **A,** Responder rates at day 7. *Red*, complete responders; *pink*, partial responders to canakinumab; *light blue*, partial responders to placebo; *gray*, nonresponders. Absolute patient numbers are indicated in the bars. **B,** PGA. The *light gray* areas indicate minimal disease activity. **C,** Representative patient images. **D,** The overall Schnitzler activity score for 7 days before and 7 days after treatment with canakinumab 150 mg or placebo. Asterisks indicate a significant (*$P \leq .05$; **$P \leq .01$) difference from placebo. Changes in overall Schnitzler activity scores correlated with changes in total PGA scores ($r = 0.595$; $P = .012$). *n.s.*, Nonsignificant.

TABLE II. Changes in disease activity, quality-of-life impairment, inflammation markers, and IL-1 receptor antagonist levels in canakinumab-treated and placebo-treated patients from baseline to day 7, the end of the double-blind treatment phase

Parameter	Canakinumab	Placebo	*P* value
PGA scores			
Total (0-20)	−11 (−18 to −3)	0 (−8 to 5)	**<.0001**
Urticarial rash (0-4)	−3 (−4 to −1)	0 (−2 to 2)	**<.0001**
Fatigue (0-4)	−2 (−4 to 0)	0 (−3 to 1)	**.015**
Fever/chills (0-4)	0 (−4 to 0)	0 (−1 to 2)	.065
Myalgia (0-4)	−3 (−4 to 0)	0 (−2 to 3)	**.001**
Arthralgia/bone pain (0-4)	−3 (−4 to 0)	0 (−2 to 1)	**.004**
Acute-phase reactants			
CRP (mg/dL) (Ref., <0.5 mg/dL)	−7.99 (−24.28 to −0.49)	0.08 (−3.65 to 6.26)	**.002**
SAA (mg/L) (Ref., <6 mg/L)	−389.65 (−817.1 to −64.6)	−13.4 (−1003 to 4238)	**.032**
S100A12 (ng/mL) (Ref., <200 ng/mL)	−723 (−837 to −119)	290 (−911 to 973)	.055
IL-1Ra (pg/mL) (Ref., <500 pg/mL)	−645 (−4282 to −33)	294 (−8028 to 1607)	**.037**
DLQI sum scores (0-30)	−5 (−10 to 1)	0.5 (−3 to 8)	**.0001**
SF-36 scores (0-100)			
Physical component sum	13 (3 to 32)	−1 (−9 to 5)	**.0001**
Physical function	10 (0 to 90)	0 (−25 to 20)	**.032**
Role physical	50 (0 to 100)	0 (−50 to 25)	**.001**
Bodily pain	32.5 (10 to 68)	0 (−23 to 30)	**.003**
General health	10 (5 to 25)	−5 (−30 to 10)	**.001**
Mental component sum	1 (−8 to 24)	−1 (−14 to 8)	.351
Mental health	12 (0 to 36)	0 (−32 to 20)	**.014**
Role emotional	0 (0 to 100)	0 (−100 to 33)	.392
Social function	12.5 (0 to 75)	0 (−50 to 25)	.208
Vitality	15 (10 to 30)	0 (−35 to 20)	**.001**

Ref., Reference.
Data are expressed as median with range. Significant *P* values are in boldface.

canakinumab 150-mg initiation. The duration of clinical improvement after canakinumab administration showed major interindividual and some intraindividual differences. In total, 14 of 20 patients experienced relapse of clinical symptoms and received 1 to 3 further canakinumab injections within the first 16 weeks of the study (Fig 5). Disease relapse or recurrence of subclinical inflammation also accounted for moderately elevated inflammation markers in single patients at day 120. There was no significant difference in the duration of clinical improvement between the canakinumab 150-mg and 300-mg dose groups. The monoclonal gammopathy persisted in all participants, and no significant changes in paraprotein levels occurred during the study period. From baseline to day 120, median IgM levels marginally increased from 560 mg/dL to 634 mg/dL and median IgG levels slightly decreased from 1219 mg/dL to 1094 mg/dL.

Adverse events

There were 31 adverse events in 17 patients, 6 during the screening period, none in the placebo-controlled phase, and 25 during the open-label part including 3 serious adverse events (2 hypertensive episodes in one patient with concomitant oral corticosteroid medication and severe lumbago with hospitalization in another patient). The other 22 adverse events during canakinumab open-label treatment were mild or moderate and included infections (eg, respiratory [n = 10] and urinary tract [n = 2]), gastrointestinal complaints (n = 3), nonspecific pain (n = 2), skin symptoms (pruritus [n = 1] and methicillin-resistant *Staphylococcus aureus* colonization [n = 1]), osteochondrosis (n = 1), asthma (n = 1), and weight gain (n = 1). No significant changes in safety laboratory parameters were observed, and canakinumab injections were well tolerated without noticeable injection-site reactions.

DISCUSSION

In this 4-month placebo-controlled study, canakinumab significantly improved the clinical signs and symptoms of Schnitzler syndrome, reduced inflammation markers, and improved quality of life. By using the PGA score that combines the 5 key symptoms of Schnitzler syndrome, that is, urticarial rash, fatigue, fever/chills, myalgia, and arthralgia/bone pain, we demonstrated that all patients benefited from canakinumab treatment, and all clinical symptoms except fever were significantly improved after the first week of therapy. The absence of significant changes in fever scores may be explained by its episodic nature; only 9 of 20 patients had fever at day 0. Canakinumab's rapid onset of action with 20% improvement in overall Schnitzler activity scores within 24 hours confirms earlier observations in CAPS and Schnitzler syndrome that clinical effects of canakinumab treatment first appeared after 6 to 24 hours.[11,14]

In autoinflammatory diseases, continuous inflammation is known to be associated with an increased risk of permanent tissue damage such as amyloidosis.[18] The significant reduction in CRP and SAA levels in all canakinumab-treated patients within 7 days and normalization of median CRP levels at day 120 indicate effective control of inflammation and support previous reports in patients with CAPS.[14,19]

Phagocyte-specific S100 proteins A8/9 and A12 are known to be sensitive markers of disease activity and inflammation in

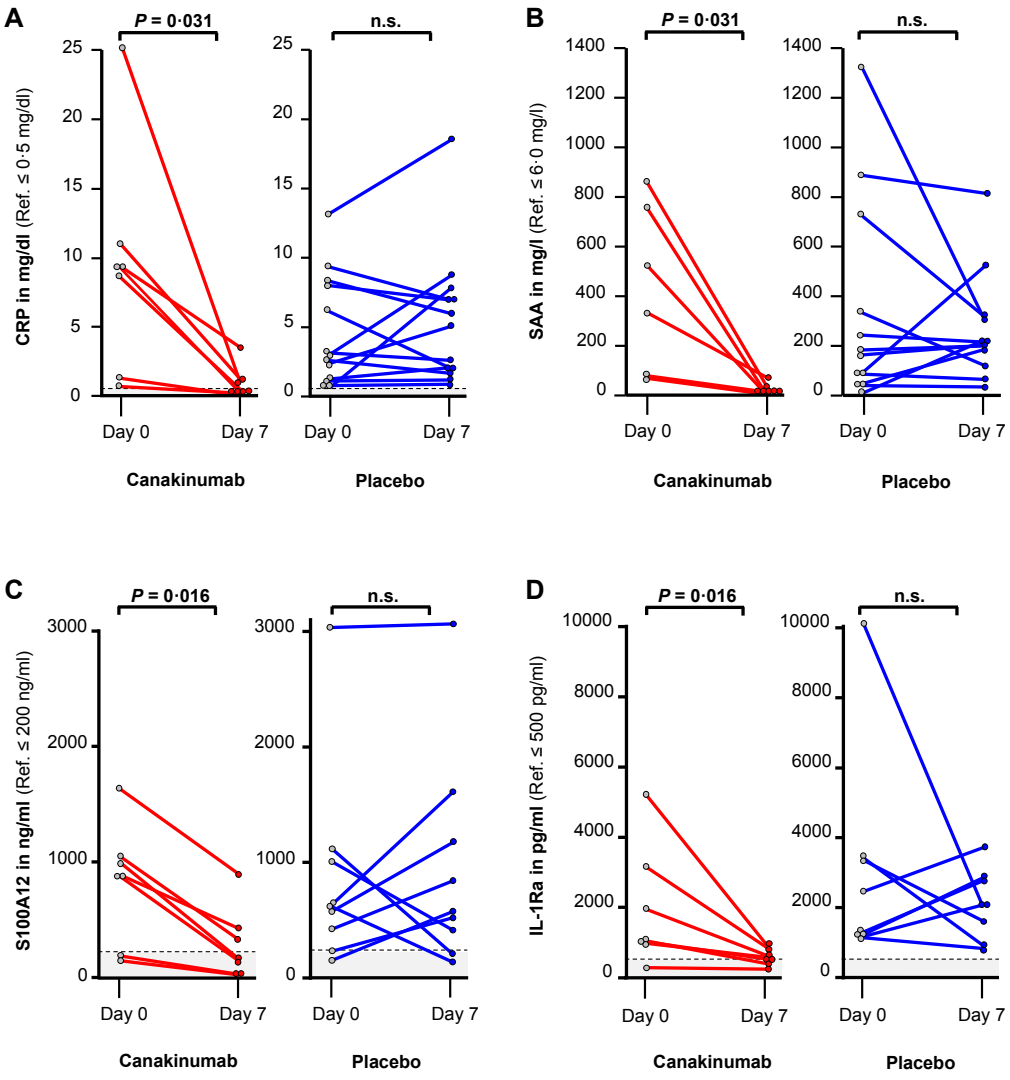

FIG 3. Changes in inflammation markers and IL-1Ra levels. **A,** CRP levels. **B,** SAA levels. **C,** S100A12 levels. **D,** IL-1Ra levels. The *light gray* areas indicate normal values. Changes in CRP, SAA, and IL-1Ra levels correlated with changes in total PGA scores (CRP: $r = 0.748$, $P < .0001$; SAA: $r = 0.585$, $P = .011$; IL-1Ra: $r = 0.600$, $P = .018$). Changes in S100A12 values followed changes in PGA urticarial rash scores ($r = 0.556$, $P = .025$) but not PGA total scores. *n.s.,* Nonsignificant.

autoinflammatory disorders including Schnitzler syndrome.[20-22] In our patient cohort, S100A12 baseline values ranged between those reported for CAPS (ca 150-700 ng/mL) and systemic juvenile idiopathic arthritis (ca 7000 ng/mL).[23] The changes in S100A12 levels significantly correlated with changes in PGA urticarial rash scores but not with PGA total scores or CRP and SAA levels. Because urticarial rash is among the first symptoms in disease exacerbations of Schnitzler syndrome and S100A12 is a known danger molecule and chemoattractant to mast cells,[24] our results suggest that S100A12 proteins may play a crucial role in the early flare reaction by activating skin mast cells that are known to induce the IL-1β–mediated urticarial rash in Schnitzler syndrome and CAPS.[25,26]

As of now, no biomarkers are established to assess patients with Schnitzler syndrome for changes in disease activity in response to treatment. IL-1β is the key inflammatory mediator in Schnitzler syndrome. Its secretion from PBMCs is increased in patients with Schnitzler syndrome and is inhibited *ex vivo* and *in vivo* by IL-1 blockade.[9,27] Because IL-1β in the serum is virtually undetectable, we measured serum levels of IL-1Ra, which is produced at steady-state levels with the IL-1 receptor and inhibits the proinflammatory cytokines IL-1α and IL-1β by nonproductively binding to the IL-1 receptor. Following IL-1β neutralization in patients with CAPS, IL-1Ra serum levels were shown to be downregulated within a few days.[28] In our study, changes in IL-1Ra levels and disease activity in response to canakinumab correlated well, suggesting that IL-1Ra may be a good biomarker for monitoring disease activity in patients with Schnitzler syndrome. Possibly, the high clinical disease activity in single patients with only modest elevations in CRP and SAA levels may be explained by excessive IL-1Ra levels.

Patients with autoinflammatory conditions including Schnitzler syndrome often suffer from considerable quality-of-life

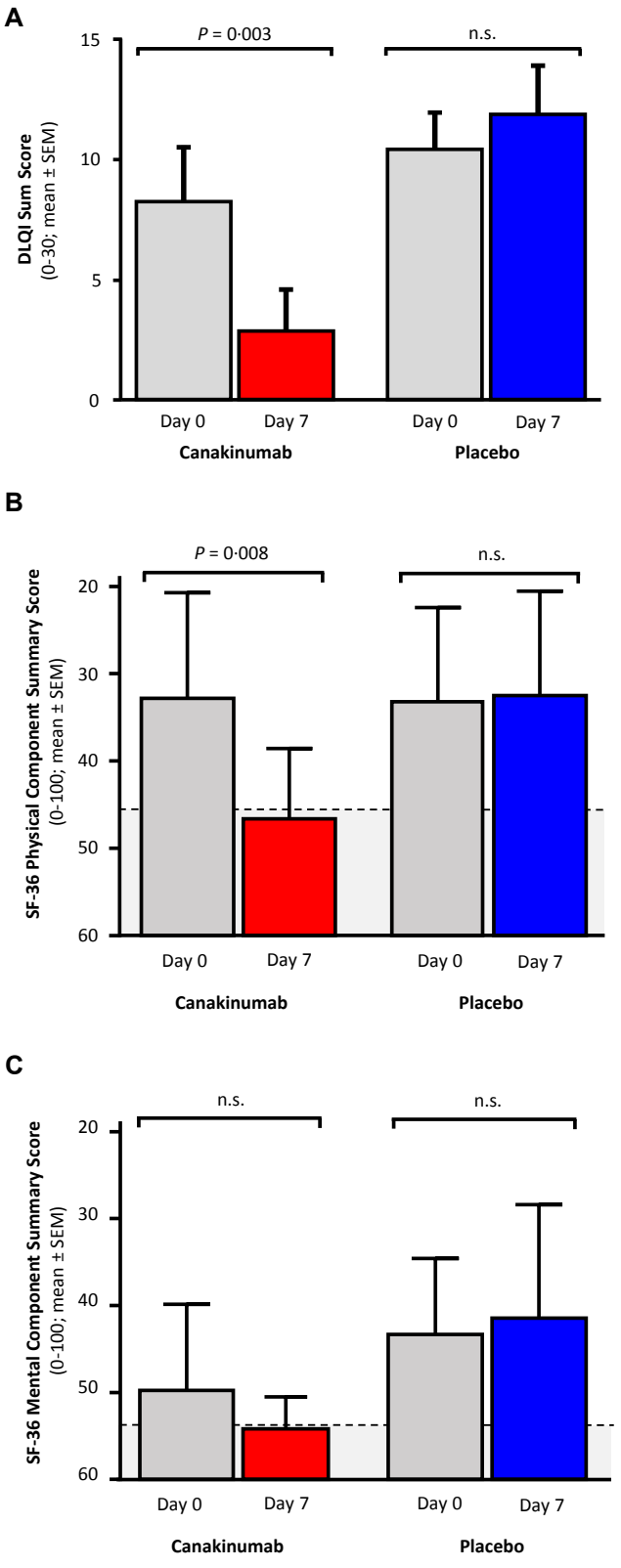

FIG 4. Changes in quality-of-life scores. **A,** DLQI scores. **B,** SF-36 physical component summary scores. **C,** SF-36 mental component summary scores. The *light gray* areas indicate reference values (physical component, 44.81; mental component, 53.18) of an age-matched (61-70 years) German healthy population. Changes in DLQI sum scores and SF-36 physical component summary scores correlated with changes in PGA total scores (DLQI: $r = 0.487$, $P = .034$; SF-36 physical component summary: $r = 0.780$, $P < .0001$). *n.s.*, Nonsignificant.

impairment. In our patients, baseline DLQI scores were comparable to those reported for other chronic skin disorders including chronic urticaria (9.9)[29] and urticarial vasculitis (9.2).[30] Interestingly and in line with previous results from patients with Schnitzler syndrome,[11] the assessment of SF-36 baseline scores revealed physical health to be clearly compromised but mental health to be less affected. Analysis of SF-36 subdomains shows pain to be a major inducer of quality-of-life impairment, which is mirrored by high PGA scores for the key symptoms myalgia and arthralgia/bone pain. Also, the great improvement in physical health–related quality-of-life scores and the almost complete restoration of skin-related quality of life at day 120 underscores the efficacy of canakinumab treatment.

Some intraindividual differences in time to relapse after canakinumab administration may be explained by seasonal variations with more pronounced symptoms during winter or infections triggering disease activity. In accordance with earlier findings,[11] we observed considerable interindividual variability in the duration of clinical improvement that was not closely linked to disease activity scores or inflammation markers.

Respiratory tract infections were the most frequent adverse events in our study, which is in line with the results of earlier canakinumab studies in patients with CAPS.[14,19] Although respiratory tract infections are very common in the general population, it cannot be excluded that these infections may have been facilitated by the anti–IL-1 treatment. Thus, patients on IL-1 blockade should be closely monitored for potential infections and adequately treated to prevent complications. This also includes common vaccinations such as influenza and pneumococcal infections, which are recommended before start of long-term anti–IL-1 treatment. The 3 serious adverse events, 2 hypertensive episodes in one patient with Schnitzler syndrome with concomitant oral corticosteroid use and known hypertensive disease as well as severe lumbago with subsequent hospitalization in another patient, were not considered to be drug related. Still, because hypertension is very common in the elderly population, it will be important to closely monitor the effect of canakinumab on blood pressure and possible drug interactions in future clinical trials. This study has several strengths and limitations. The latter include the number of patients enrolled in this trial. However, this is by far the biggest clinical trial in patients with Schnitzler syndrome, an ultrarare disease. In addition, the placebo-controlled phase of 7 days was short, but to withhold effective treatment for longer than this would have been unethical, and patients in the canakinumab-treated group showed marked and significant improvement during this first week of treatment. The imbalance in randomization with 7 canakinumab-treated and 13 placebo-treated patients is another limitation, but is unlikely to affect the study results because all patients responded well to canakinumab open-label treatment. Also, our results are preliminary in the sense of treatment duration and have to be interpreted with care because the open-label treatment phase of this study is still ongoing. Therefore, long-term efficacy and safety are further monitored, and detailed results will be reported on study completion. The major strength of this study is its placebo-controlled design, making it the first and as of yet only randomized controlled trial in patients with Schnitzler syndrome. This primary multicenter study confirms the marked efficacy of previous case reports and small open-label studies on IL-1

TABLE III. Clinical and laboratory efficacy during open-label canakinumab treatment

Parameter	Baseline (day 0)	Canakinumab open-label (day 120)	*P* value
PGA total scores	14.5 (8-20)	3.5 (0-9)	**<.0001**
Acute-phase reactants			
CRP (mg/dL) (Ref., <0.5 mg/dL)	6.09 (0.7-25.4)	0.3 (0.04-6.24)	**<.0001**
SAA (mg/L) (Ref., <6 mg/L)	180 (1.9-1,310)	13.3 (4.6-409)	**.001**
S100A12 (ng/mL) (Ref., <200 ng/mL)	901 (151-3,036)	113 (20-3,470)	**.041**
IL-1Ra (pg/mL) (Ref., <500 pg/mL)	1592 (262-10,027)	583 (283-1,401)	**.001**
DLQI sum scores (0-30)	8.5 (1-21)	1 (0-25)	**.006**
SF-36 scores (0-100)			
Physical component summary	28.8 (33.7)	47.0 (42.7)	**.003**
Mental component summary	47.0 (31.62)	50.7 (34.7)	.058

Data are expressed as median with range. Significant *P* values are in boldface.

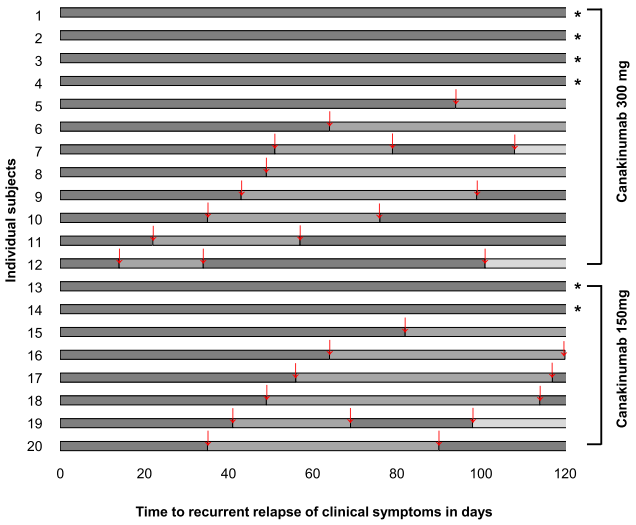

FIG 5. Individual duration of clinical improvement following canakinumab administration during open-label treatment. *Red arrows* indicate individual time points of relapsing symptoms and subsequent canakinumab treatment. *Asterisks* indicate ongoing clinical improvement beyond day 120.

blockade in this condition,[10,11,31] which facilitates the treatment of patients with Schnitzler syndrome and encourages the use of canakinumab or other IL-1–targeting treatments in this disease. In comparison to anakinra (4-6 hours) and rilonacept (67 hours to 7 days), canakinumab has a longer half-life (21-28 days) and exclusively binds to IL-1β, the key inflammatory mediator in Schnitzler syndrome, but not to IL-1α or the IL-1 receptor. Besides the advantage of less frequent dosing with canakinumab, injection- site reactions (which were absent in our study) are less often reported as compared with anakinra and rilonacept.[32] In conclusion, our study results show good efficacy of canakinumab treatment against placebo in reducing the clinical symptoms, inflammation markers, and enhancing quality of life in patients with symptomatic Schnitzler syndrome. Over the limited 4-month duration of this study, canakinumab treatment appeared to be safe and well tolerated. Treatment of greater patient numbers and long-term administration are necessary to further evaluate the efficacy and safety of canakinumab treatment in Schnitzler syndrome.

We thank Hesna Gözlükaya, Marina Frömming, and Evelin Hagen for excellent technical assistance and Dr Gladitz Statistikservice for statistical support.

Clinical implications: Currently, there is no approved treatment for Schnitzler syndrome. Our study results implicate that continuous canakinumab treatment effectively controls the symptoms and the inflammation that underlies this disabling disease.

REFERENCES

1. Schnitzler L. Lesions urticariennes chroniques permanentes (erytheme petaloıde?) Cas cliniques no.46B [Abstract]. Journee Dermatologique d'Angers; 1972.
2. Schnitzler LSB, Boasson M, Gardais J, Tourmen A. Urticaire chronique, lésions osseuses, macroglobulinémie IgM: maladie de Waldenström? Bull Soc Fr Dermatol Syphiligr 1974;81:363.
3. de Koning HD, Bodar EJ, van der Meer JW, Simon A. Schnitzler Syndrome Study Group. Schnitzler syndrome: beyond the case reports: review and follow-up of 94 patients with an emphasis on prognosis and treatment. Semin Arthritis Rheum 2007;37:137-48.
4. Simon A, Asli B, Braun-Falco M, De Koning H, Fermand JP, Grattan C, et al. Schnitzler's syndrome: diagnosis, treatment, and follow-up. Allergy 2013;68: 562-8.
5. Lipsker D, Veran Y, Grunenberger F, Cribier B, Heid E, Grosshans E. The Schnitzler syndrome: four new cases and review of the literature. Medicine (Baltimore) 2001;80:37-44.
6. de Koning HD. Schnitzler's syndrome: lessons from 281 cases. Clin Transl Allergy 2014;4:41.
7. Rizzi R, Curci P, Rinaldi E, Rinaldi F, Cimmino A, Ricco R, et al. Schnitzler's syndrome: monoclonal gammopathy associated with chronic urticaria. Acta Haematol 2008;120:1-4.
8. Pizzirani C, Falzoni S, Govoni M, La Corte R, Donadei S, Di Virgilio F, et al. Dysfunctional inflammasome in Schnitzler's syndrome. Rheumatology (Oxford) 2009;48:1304-8.
9. Ryan JG, de Koning HD, Beck LA, Booty MG, Kastner DL, Simon A. IL-1 blockade in Schnitzler syndrome: ex vivo findings correlate with clinical remission. J Allergy Clin Immunol 2008;121:260-2.
10. Krause K, Weller K, Stefaniak R, Wittkowski H, Altrichter S, Siebenhaar F, et al. Efficacy and safety of the interleukin-1 antagonist rilonacept in Schnitzler syndrome: an open-label study. Allergy 2012;67:943-50.
11. de Koning HD, Schalkwijk J, van der Ven-Jongekrijg J, Stoffels M, van der Meer JW, Simon A. Sustained efficacy of the monoclonal anti-interleukin-1 beta antibody canakinumab in a 9-month trial in Schnitzler's syndrome. Ann Rheum Dis 2013;72:1634-8.
12. Martinez-Taboada VM, Fontalba A, Blanco R, Fernandez-Luna JL. Successful treatment of refractory Schnitzler syndrome with anakinra: comment on the article by Hawkins et al. Arthritis Rheum 2005;52:2226-7.
13. Besada E, Nossent H. Dramatic response to IL1-RA treatment in longstanding multidrug resistant Schnitzler's syndrome: a case report and literature review. Clin Rheumatol 2010;29:567-71.
14. Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, Leslie KS, Hachulla E, Quartier P, et al. Use of canakinumab in the cryopyrin-associated periodic syndrome. N Engl J Med 2009;360:2416-25.
15. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Horneff G, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. N Engl J Med 2012;367:2396-406.
16. Schlesinger N, Alten RE, Bardin T, Schumacher HR, Bloch M, Gimona A, et al. Canakinumab for acute gouty arthritis in patients with limited treatment options:

results from two randomised, multicentre, active-controlled, double-blind trials and their initial extensions. Ann Rheum Dis 2012;71:1839-48.
17. Hoffman HM, Gregory SG, Mueller JL, Tresierras M, Broide DH, Wanderer AA, et al. Fine structure mapping of CIAS1: identification of an ancestral haplotype and a common FCAS mutation, L353P. Hum Genet 2003;112:209-16.
18. Lachmann HJ, Goodman HJ, Gilbertson JA, Gallimore JR, Sabin CA, Gillmore JD, et al. Natural history and outcome in systemic AA amyloidosis. N Engl J Med 2007;356:2361-71.
19. Kuemmerle-Deschner JB, Hachulla E, Cartwright R, Hawkins PN, Tran TA, Bader-Meunier B, et al. Two-year results from an open-label, multicentre, phase III study evaluating the safety and efficacy of canakinumab in patients with cryopyrin-associated periodic syndrome across different severity phenotypes. Ann Rheum Dis 2011;70:2095-102.
20. Wittkowski H, Kuemmerle-Deschner JB, Austermann J, Holzinger D, Goldbach-Mansky R, Gramlich K, et al. MRP8 and MRP14, phagocyte-specific danger signals, are sensitive biomarkers of disease activity in cryopyrin-associated periodic syndromes. Ann Rheum Dis 2011;70:2075-81.
21. Kallinich T, Wittkowski H, Keitzer R, Roth J, Foell D. Neutrophil-derived S100A12 as novel biomarker of inflammation in familial Mediterranean fever. Ann Rheum Dis 2010;69:677-82.
22. de Koning HD, Schalkwijk J, Stoffels M, Jongekrijg J, Jacobs JF, Verwiel E, et al. The role of interleukin-1 beta in the pathophysiology of Schnitzler's syndrome. Arthritis Res Ther 2015;17:187.
23. Wittkowski H, Frosch M, Wulffraat N, Goldbach-Mansky R, Kallinich T, Kuemmerle-Deschner J, et al. S100A12 is a novel molecular marker differentiating systemic-onset juvenile idiopathic arthritis from other causes of fever of unknown origin. Arthritis Rheum 2008;58:3924-31.
24. Yang Z, Yan WX, Cai H, Tedla N, Armishaw C, Di Girolamo N, et al. S100A12 provokes mast cell activation: a potential amplification pathway in asthma and innate immunity. J Allergy Clin Immunol 2007;119:106-14.
25. Nakamura Y, Kambe N, Saito M, Nishikomori R, Kim YG, Murakami M, et al. Mast cells mediate neutrophil recruitment and vascular leakage through the NLRP3 inflammasome in histamine-independent urticaria. J Exp Med 2009;206:1037-46.
26. de Koning HD, van Vlijmen-Willems IM, Rodijk-Olthuis D, van der Meer JW, Zeeuwen PL, Simon A, et al. Mast-cell interleukin-1beta, neutrophil interleukin-17 and epidermal antimicrobial proteins in the neutrophilic urticarial dermatosis in Schnitzler's syndrome. Br J Dermatol 2015;173:448-56.
27. Launay D, Dutoit-Lefevre V, Faure E, Robineau O, Hauspie C, Sobanski V, et al. Effect of in vitro and in vivo anakinra on cytokines production in Schnitzler syndrome. PLoS One 2013;8:e59327.
28. Lachmann HJ, Lowe P, Felix SD, Rordorf C, Leslie K, Madhoo S, et al. In vivo regulation of interleukin 1beta in patients with cryopyrin-associated periodic syndromes. J Exp Med 2009;206:1029-36.
29. Lewis V, Finlay AY. 10 years experience of the Dermatology Life Quality Index (DLQI). J Investig Dermatol Symp Proc 2004;9:169-80.
30. Krause K, Mahamed A, Weller K, Metz M, Zuberbier T, Maurer M. Efficacy and safety of canakinumab in urticarial vasculitis: an open-label study. J Allergy Clin Immunol 2013;132:751-4.e5.
31. Neel A, Henry B, Barbarot S, Masseau A, Perrin F, Bernier C, et al. Long-term effectiveness and safety of interleukin-1 receptor antagonist (anakinra) in Schnitzler's syndrome: a French multicenter study. Autoimmun Rev 2014;13:1035-41.
32. Dinarello CA, Simon A, van der Meer JW. Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. Nat Rev Drug Discov 2012;11:633-52.