Long-term efficacy of canakinumab in the treatment of Schnitzler syndrome

To the Editor:

Schnitzler syndrome (SchS) is a rare inflammatory disorder characterized by chronic urticarial rash, bone and joint inflammation, and recurrent fever; there have been only around 300 reported cases worldwide.[1] Aberrant NLRP3 inflammasome signaling and cytokine pathway dysregulation play a crucial role in SchS pathophysiology,[2] along with elevated levels of proinflammatory IL-1ß.[3] Systemic symptoms can severely affect quality of life (QoL), but no approved treatment for SchS exists. Because of its rarity, the therapeutic evidence comes mainly from small case reports and case series rather than from controlled trials; thus, patients with SchS urgently require effective new therapies.

Good clinical responses have been achieved with the IL-1 blockers anakinra[4] and rilonacept.[5] Canakinumab, a mAb targeting IL-1β, is approved for the treatment of cryopyrin-associated periodic syndrome (CAPS) and Still's disease; both conditions share similar clinical features with SchS. Previously, we reported the efficacy of canakinumab in SchS from a 4-month randomized placebo-controlled trial involving 20 patients.[6] Herein we report results from the 4-year extension

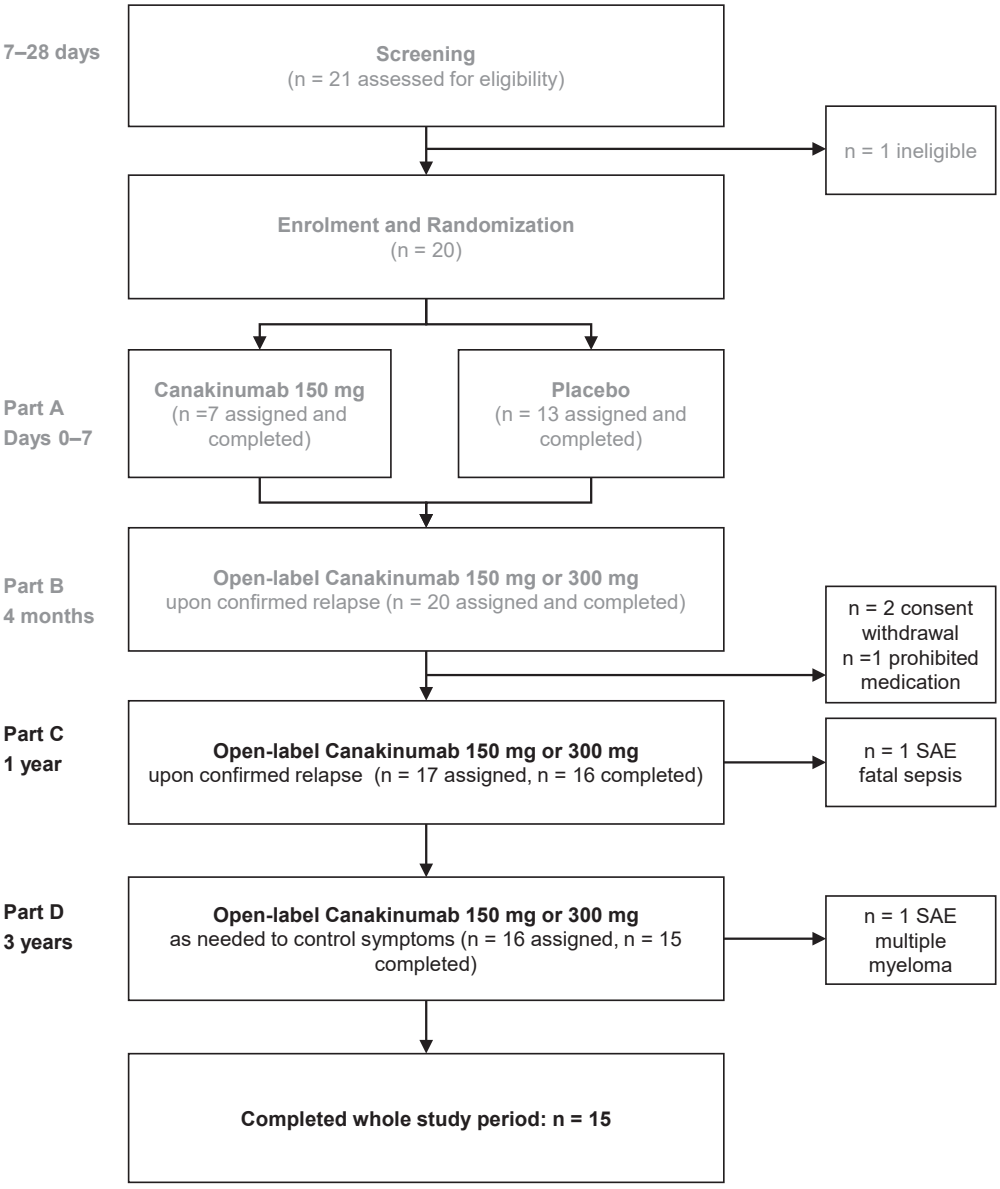

FIG 1. Patient disposition showing the number of patients screened, number randomized, and those who completed parts A to D of this 4-year study. Results from parts A and B (*text in light gray*) have been published previously.[6]

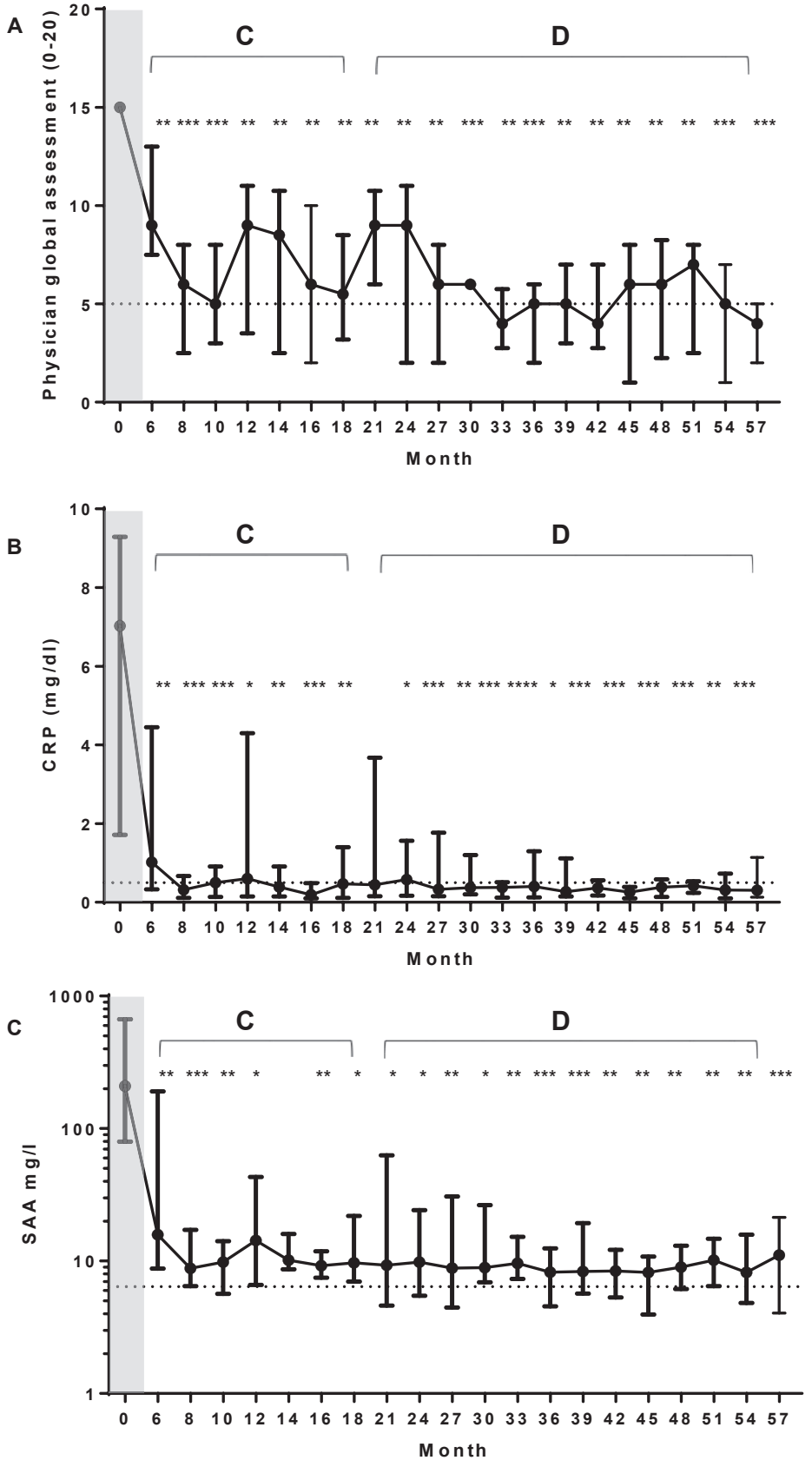

FIG 2. Total PGA scores (**A**), CRP levels (**B**), SAA levels (**C**), DLQI (**D**), SF-36 physical component scores (**E**), and mental component scores (**F**) from baseline to 57 months in patients with SchS treated with canakinumab, 150 mg or 300 mg. Significance assessed by the Wilcoxon matched-pairs signed rank test. Asterisks indicate significant differences (*$P \leq .05$; **$P \leq .01$;***$P \leq .001$; ****$P \leq .0001$) versus baseline. Data are shown as interquartile ranges for all visits. *Gray-shaded areas* reflect study parts A and B.

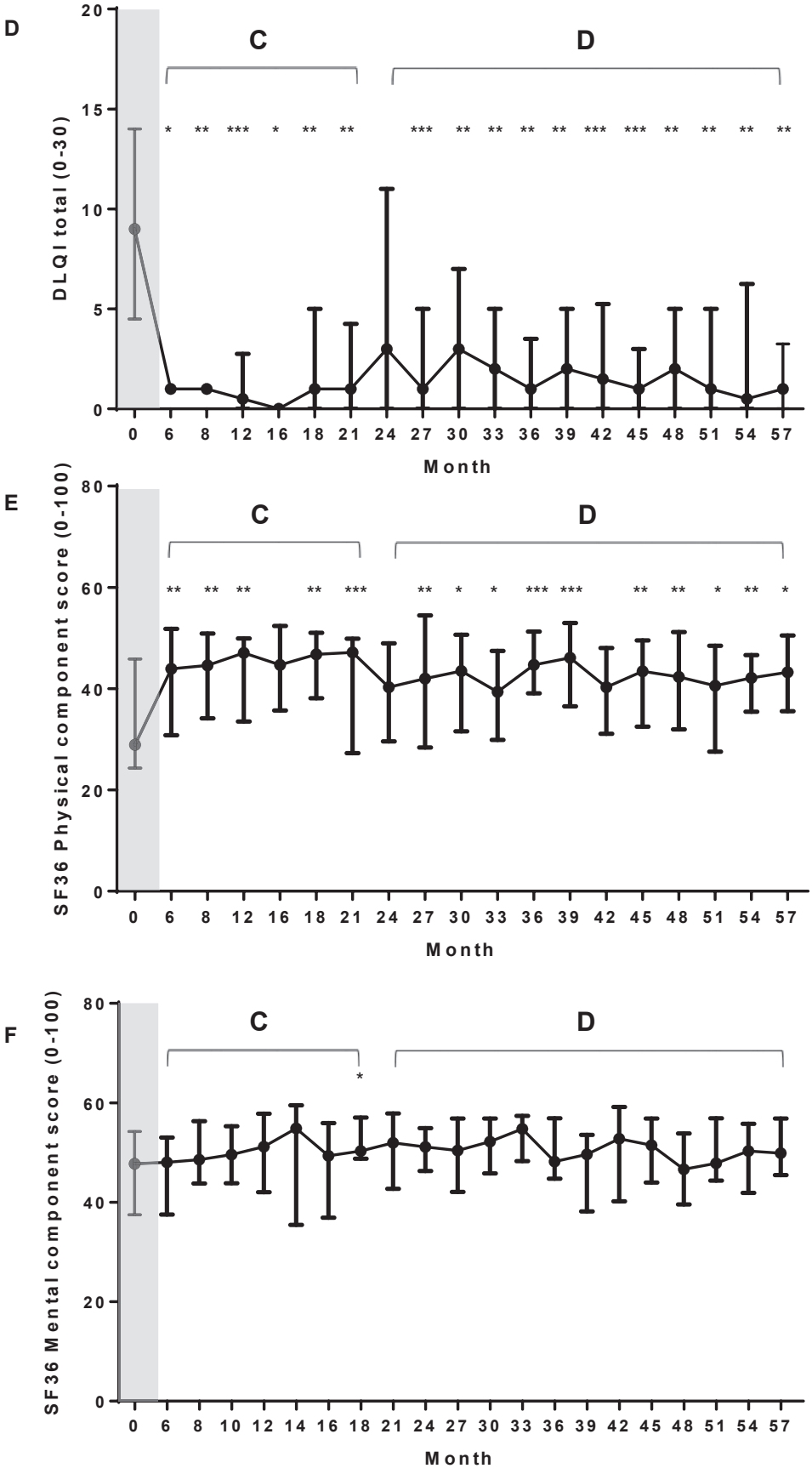

FIG 2. *(Continued).*

phase of this trial (ClinicalTrials.gov identifier NCT01390350; EudraCT no. 2010-024156-28).

In this investigator-initiated phase II study, canakinumab-responding patients who completed Part A (0-7 days) and Part B (16 weeks) entered the open-label extension phase to monitor long-term efficacy, QoL, and safety. During Part C of the study (1 year), patients were taking canakinumab in a dose of either 150 mg or 300 mg depending on their previous individual responses in parts A and B. Patients who were initially assessed as complete clinical responders to canakinumab, 150 mg, in parts A and B (no or minimal disease activity in Physician Global Assessment (PGA) scores within 7 days of the first injection) and normalized C-reactive protein (CRP) level, continued with this dose when needed (on confirmed relapse of symptoms) in Part C. Patients with an initial partial clinical response to canakinumab, 150 mg (mild-to-moderate disease activity in PGA scores within 7 days of the first injection), with or without CRP level above the reference value (≥0.5mg/dL) were administered canakinumab, 300 mg, when needed (on confirmed relapse of symptoms) in Part C. Confirmed relapse of symptoms was defined as at least a 50% increase in the total PGA score as compared with the total PGA score 7 to 14 days after initiation of canakinumab administration. In Part D (3 years), canakinumab was given as needed depending on the previous responses in Part C (individual mean dosing intervals) to ensure a constant low disease activity and low levels of inflammatory markers. Relapse of symptoms was not required for canakinumab dosing during Part D (Fig 1). Outcomes were measured in all patients who received canakinumab treatment, and the results were assessed versus baseline levels (by using the Wilcoxon matched-pairs signed rank test). Long-term efficacy was evaluated by using total PGA scores (grading 0-20 of 5 key SchS symptoms: urticarial rash, fatigue, fever/chills, myalgia, and arthralgia/bone pain)[6] on a 5-point Likert scale, and single subscores (grading 0-4). Changes in the serum levels of the inflammatory markers CRP and serum amyloid A (SAA) were measured. Also, health-related QoL was assessed by using the Dermatology Life Quality Index (a skin disease–specific QoL questionnaire) and a generic health-related QoL instrument (the 36-Item Short Form Health Survey [SF-36]), both with recall periods of 1 week.

Adverse events (AEs [Medical Dictionary for Regulatory Activities terminology]) and the results of routine safety laboratory assessments were recorded, and physicians performed physical examinations and electrocardiograms. The Spearman rank correlation coefficient was used to analyze individual dosing intervals with mean disease activity, inflammatory markers, and QoL.

A total of 17 patients (8 female and 9 male with a median age of 64 years [range 51-76 years]) entered the open-label extension study from July 2012 to February 2013; 15 of them completed the full 4 years. The long-term clinical efficacy of canakinumab was high, with most patients experiencing no, minimal, or mild disease activity, as demonstrated by significantly lower total PGA scores at all visits from 6 months (PGA score of 9) to 57 months (PGA score of 4) versus their baseline scores (PGA score of 14.5 [$P = .0063$-$.0005$]; Fig 2, *A* and see Table E1 [in this article's Online Repository at www.jacionline.org]). Individual reductions in total PGA scores over time are shown in Fig E1 (in the Online Repository available at www.jacionline.org). Patients achieved significant improvements versus their baseline scores on specific SchS symptoms (urticarial rash, fatigue, and arthralgia/bone pain) after 6 months of canakinumab treatment. Fever and myalgia had significantly improved by 36 months (Table E1). During Part D, in which patients injected canakinumab as needed, clinical efficacy was highest.

The numbers of complete clinical responders at 6, 12, 36, and 57 months were 2, 3, 5, and 6, respectively. No patient experienced a substantial loss of efficacy over time; 1 patient escalated the dosage from 150 mg to 300 mg of canakinumab at the end of the second study year (Part D) because of increased musculoskeletal complaints, as assessed by PGA subscores for myalgia and arthralgia/bone pain (3-4 of a maximum of 4) at subsequent visits during months 12 to 24. Symptom relapse was rare, occurring mainly after treatment interruption or infection. Clinical responses mirrored significant decreases and normalization in CRP level, which was stable throughout the study ($P = .04$-$.0001$); the median baseline CRP level (6.09 mg/dL) decreased by 6 months (1.02 mg/dL), remaining within the reference level (≤0.5 mg/dL) at most visits (Fig 2, *B*). In 5 patients, CRP levels decreased but remained above the reference values. Two of these patients displayed suboptimal clinical responses and discontinued the study on account of serious AEs (sepsis with a fatal outcome and multiple myeloma). SAA levels decreased significantly from baseline (180 mg/L) throughout the study (15.8 mg/L at 6 months and 11.1 mg/L at 57 months [$P = .03$-$.0005$]; Fig 2, *C*). The median paraprotein level changed from 566 mg/dL at baseline to 866 mg/dL at month 57. In 9 patients (8 with IgMκ and 1 with IgGκ) of the 11 for whom complete data were available, paraprotein levels increased slightly, and in 2 patients with IgMκ, immunoglobulin levels decreased.

Patients' QoL improved significantly throughout the study; the median baseline Dermatology Life Quality Index score of 9 (moderate QoL impairment) decreased to 1 (no QoL impairment) after 6 months of canakinumab treatment and remained low throughout the study ($P = .01$-$.0005$; Fig 2, *D*). The median SF-36 physical component increased significantly from 28.3 at baseline to 43.9 at 6 months and 43.2 by 57 months ($P = .03$-$.002$; Fig 2, *E*). In contrast, SF-36 mental component scores were barely affected (Fig 2, *F*).

On the basis of their responses to the previous 4-month treatment, 8 patients received canakinumab, 150 mg, and 9 patients received canakinumab, 300 mg (see Fig E2 in this article's Online Repository at www.jacionline.org). The median dosing intervals were 62 days and 63 days for canakinumab, in doses of 150 mg (n = 8) and 300 mg (n = 9), respectively. Dosing intervals were associated with scores of the PGA and SF-36 physical domains; lower disease activity (measured by total and individual PGA scores) allowed for prolonged dosing intervals (measured by injection intervals in days, as follows: total PGA, $r = –0.7549$ and $P = .0007$; myalgia, $r = –0.7627$ and $P = .0006$; arthralgia/bone pain, $r = –0.7264$ and $P = .0013$; and fatigue, $r = –0.5212$ and $P = .03$). Longer canakinumab injection intervals also correlated with improved SF36 physical component scores ($r = 0.531$ and $P = .03$).

Of the 176 AEs that occurred, 169 were mild or moderate. Respiratory tract infections (n = 42 in 14 patients) and urinary tract infections (n = 12 in 5 patients) were the most common. A total of 7 serious AEs occurred, including a case of multiple myeloma (the patient withdrew from the study) (see Tables E2 and E3 in this article's Online Repository at www.jacionline.org). Two suspected unexpected serious adverse reactions

occurred. In 1 case of sepsis, a causative relationship with canakinumab was suspected. In that case, a 72-year-old patient with comorbid heart failure who was undergoing concomitant therapy with prednisone developed sinusitis with fever and anemia after 8 months of taking canakinumab, 300 mg; his dosing interval was shortened from 56 to 28 days owing to increased disease activity. Despite extensive diagnostic and therapeutic measures, he died 10 weeks later because of sepsis with atypical mycobacteriosis. A second patient (aged 68 years) experienced pneumonia with transient hemiplegia. Canakinumab treatment was paused and restarted after complete recovery. In that case, a causative relationship with canakinumab was considered possible.

Here we have reported the first long-term, multicenter study to investigate the use of canakinumab to treat patients with SchS. The majority of patients in this study experienced no, minimal, or mild disease activity during their treatment, as reflected by significant improvements in PGA scores over time and normalized levels of the inflammatory markers CRP and SAA.

We used PGA scores to assess the key symptoms of SchS. Patients achieved significant improvements versus their baseline scores for most symptoms after 6 months of canakinumab treatment. Fever and myalgia took longer to improve (36 months), likely because of the intermittent nature of fever and its median baseline score of 0. These 2 symptoms were the first to return when the effects of canakinumab dissipated.

The higher disease activity and inflammatory marker levels at months 6 and 12 as compared with at months 36 to 57 are explained by the study design, which required relapse of clinical symptoms for canakinumab treatment during the first year (Part C). The median dosing interval of 62 to 63 days is comparable to the 8-week dosing regimen used for CAPS. As in our study, canakinumab dosing intervals in patients with CAPS are adjusted depending on clinical severity.[7] de Koning et al[8] used a different dosing interval, namely, 150 mg of canakinumab every 4 weeks over 9 months in 8 patients with SchS; although most patients experienced good clinical and laboratory responses, the 150-mg dose was insufficient to control symptoms in 1 individual. Considerable interindividual heterogeneity has been observed in the time to relapse after canakinumab administration, ranging from 40 to 234 days (median 72 days) after the last canakinumab injection.[8] Here, we demonstrated a broad range in dosing intervals from 28 days to at least 1 year (3 patients taking canakinumab, 150 mg, were symptom-free for at least 12 months). The time to relapse inversely correlated with disease activity, which is in line with observations in patients with CAPS, whereby more severely affected patients required more frequent dosing.[7] Patients with SchS whose disease is less severe may have lower IL-1ß levels; thus, IL-1ß downregulation and clinical remission induced by canakinumab may last longer. On the basis of our results, we recommend a dosing regimen of 150 mg of canakinumab every 8 weeks. If clinical response is unsatisfactory after 7 to 14 days, an additional 150 mg can be administered, with a 300-mg maintenance dose every 8 weeks. Injection intervals can be individualized in complete responders.

The age group of our SchS study (median age 64 years) was similar to that in the Canakinumab Anti-inflammatory Outcomes Study (mean age 61.1 years), which included more than 10,000 patients with previous myocardial infarction treated with long-term administration of canakinumab.[9] In our study, 176 AEs occurred, of which 169 were mild or moderate. In line with the findings for the elderly population in the Canakinumab Anti-inflammatory Outcomes Study, respiratory tract infections were the most common. However, respiratory infections are prevalent in the general population, especially when considered over 4 years. IL-1 blockade can interfere with patients' immune responses to bacteria, increasing the risk of opportunistic infections, which could explain the 2 suspected unexpected serious adverse reactions. During a long-term multicenter study with the IL-1 receptor antagonist anakinra in SchS, 2 fatal infections were reported.[4] Thus, it is essential to monitor, vaccinate, and screen patients appropriately to mitigate the risk of complications. Despite a considerable number of infections during our study, AE frequencies did not differ between the 300-mg and 150-mg canakinumab doses.

SchS is rare; thus, recruiting large numbers of patients is challenging. This study was limited by low patient numbers, making significance levels difficult to establish. Some patients missed visits, compounding the already-small numbers and potentially affecting the robustness of the data. Further, more extensive studies are required to extend and confirm our observations.

In conclusion, this first long-term, multicenter study confirms that canakinumab treatment effectively reduces the clinical signs and symptoms of SchS, decreases inflammatory marker levels, and improves overall QoL, with sustained effects over 4 years.

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Antibody-coated microbiota in nasopharynx of healthy individuals and IVIg-treated patients with hypogammaglobulinemia

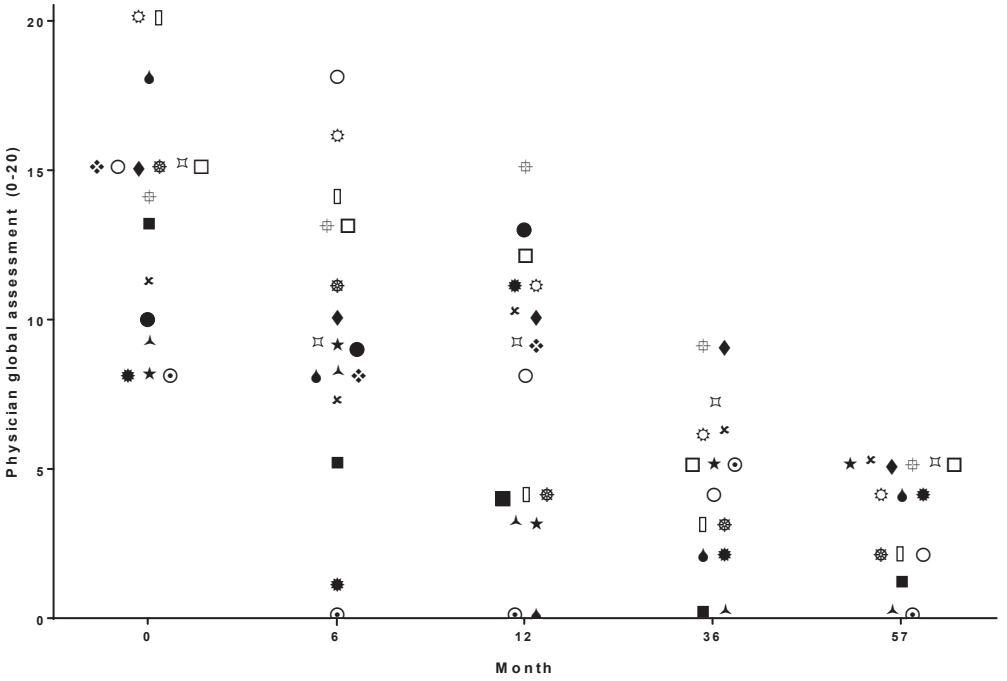
To the Editor:

Respiratory diseases are important causes of death, which collectively account for more than 1 in 10 of all deaths worldwide (World Health Organization). Pathobionts, potential pathogenic bacteria that under normal circumstances are present as harmless microorganisms, can be found embedded in the nasopharyngeal commensal microbiota. Interestingly, the composition of the upper airway microbiome seems very similar to that of the lung, and pathobionts present in the nasopharynx can be a primary source of lower respiratory tract infections.[1] Several elements participate in the respiratory mucosal barrier against invasive pathobionts, including the commensal microbiota and glands that secrete and create an antimicrobial mucus barrier containing antimicrobial peptides, immunoglobulins (Ig), and other soluble factors. Secretory IgA (sIgA) and secretory IgM are transported through nasopharynx epithelial cells by polymeric immunoglobulin receptor, and IgG is transported by neonatal Fc receptor FcR. Transepithelial transport of IgD has not been documented, but IgD is found in nasopharynx secretions,[2] perhaps deriving from paracellular diffusion through cell junctions.

sIgA is the predominant antibody isotype in human nasopharyngeal secretions, and it is assumed that most sIgA targets the resident commensal microbiota, inhibiting their penetration via agglutination within the mucus layer and thereby reinforcing commensalism and increasing microbiota diversity.[3] High-affinity sIgA appears to neutralize microbial toxins and invasive pathogens in the absence of complement fixation.[3] Interestingly, Fadlallah et al[4] reported recently that patients with selective IgA deficiency (SIgADef) display mild dysbiosis, with expansion of some pathobiont species in their feces as compared with in healthy controls, although these patients are not abnormally susceptible to intestinal infections. On the other hand, recurrent pulmonary infections constitute the most prevalent comorbidity in patients with SIgADef,[4] suggesting that sIgA may have tissue-specific roles in immune defense, especially in the respiratory tract. A better understanding of the Igs coating nasopharynx microbiota in healthy individuals could provide an important basis for the prevention of respiratory illnesses in some cases of humoral immunodeficiency.

To better understand the role for IgA (and other Ig isotypes) in regulating nasopharyngeal microbial communities, we analyzed nasopharyngeal samples to detect Ig-bound microbes and subsequently performed 16S ribosomal RNA (rRNA) sequencing to determine the type of bacteria targeted by each Ig isotype. We stained nasopharyngeal samples with anti-human IgA, IgM, IgD, and IgG antibodies and measured the Ig-bound populations by using a flow cytometer–based assay.[5] The gating strategy for Ig staining of human nasopharynx microbiota is shown in Fig E1 (see this article's Online Repository at www.jacionline.org for Fig E1 and for a Methods section that provides a description of all methods used in this study). On average, a majority of the nasopharynx microbiota appear targeted by sIgA in healthy subjects (see Fig E1, *A*), although the frequency of $sIgA^+$ microbes is highly variable between individuals (see Fig E1, *B*). Next, we performed flow sorting of IgA-bound nasopharyngeal microbiota, followed by 16S rRNA sequencing on a fraction of samples (n = 4) (see Fig E2, *A* in this article's Online Repository at www.jacionline.org). β-diversity shows the extent of difference in microbiota community composition from that in different environments or conditions. The β-diversity, based on Bray-Curtis distance matrix and subjected to principal coordinate analysis, suggests that bacteria derived from IgA^+ and IgA^- fractions cluster distinctly; however, the results of permutational multivariate ANOVA of the 2 fractions were not significantly different (see Fig E2, *A* and *B*). The α-diversity and the Shannon diversity index (a combined measure of evenness and number of bacteria) was slightly decreased in 16S rRNA sequences derived from the IgA^- fraction (see Fig E2, *C*). However, both the IgA^+ and IgA^- fractions exhibited equal distributions of rare and abundant genera, and thus, IgA appears to target nasopharyngeal commensals irrespective of their frequency (see Fig E2, *D*). These results suggest that under homeostatic conditions, sIgA binds to a broad repertoire of bacteria present in nasopharyngeal microbiota, including both commensals and pathobionts.[3]

Most patients with SIgADef have a mild clinical phenotype,[4] which may result from the ability of other Ig isotypes to functionally replace IgA. Increased IgD^+IgM^- B-cell populations and increased soluble IgD levels have been described in healthy human upper respiratory mucosa.[2] Therefore, even if IgM and IgD have the same V region and the same antigen specificity, nasopharynx and respiratory B cells apparently switch from IgM to secrete IgD, suggesting some functional advantage of the latter. The IgD hinge region linking is longer and more flexible than that of IgM, thereby facilitating IgD binding to antigens at lower concentrations and in immune complexes.[2] Still, secretory IgM binds some residual bacteria in the nasopharynx (see Fig E1), suggesting that IgM may participate in microbiota agglutination in the steady state. On the other hand, we found that the vast majority (86%) of the microorganisms constituting the nasopharynx microbiota are targeted by secreted IgD in healthy individuals (see Fig, E1). We observed that up to 60% of the microorganisms constituting the nasopharynx microbiota were double-$SIgA^+IgD^+$–coated (Fig 1, *A* and *B*). We performed flow sorting to isolate IgD-bound microbiota and 16S rRNA sequencing to identify the microbes specifically targeted by IgD (Fig 1, *C*). The IgD^+SIgA^- fraction showed a higher



Patient number and symbol:

1	✹	10	□
2	⊙	11	★
3	⅄	12	♦
4	❁	13	☼
5	❖	14	×
6	♦	15	▯
7	○	16	⌑
8	⌗	17	●
9	■		

FIG E1. Individual total Physician Global Assessment (PGA) scores of 17 patients with SchS over the 4-year study period.

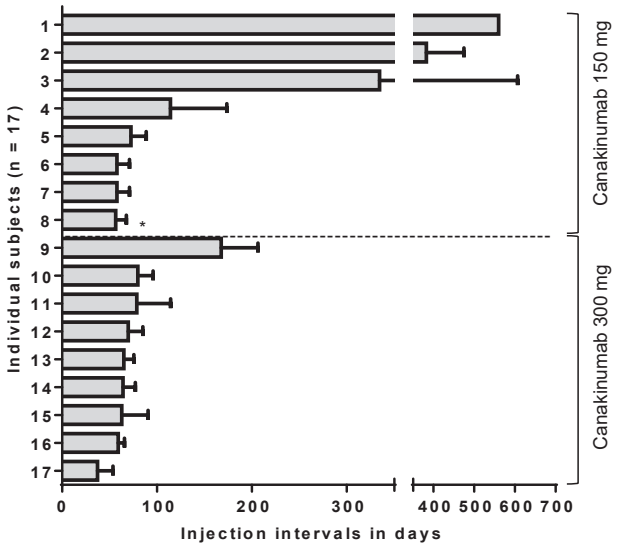


FIG E2. Individual dosing regimens of 17 patients with SchS who were being treated with either 150 mg or 300 mg of canakinumab during the open-label extension. Bars indicate the mean number of days between treatment injections. *Patient was switched from a canakinumab dose of 150 mg to a dose of 300 mg in the second study year because of increased musculoskeletal complaints.

TABLE E1. PGA total scores and subscores during the study

Physician global assessment	Baseline (Part A)	Month 6 (Part C)		Month 12 (Part C)		Month 36 (Part D)		Month 57 (Part D)	
	Median (range)	Median (range)	*P* value*	Median (range)	*P* value*	Median (range)	*P* value*	Median (range)	*P* value*
Total (0-20)	14.5 (8-20)	9 (1-18)	**.0014**	9 (0-15)	**.0016**	5 (0-9)	**.0007**	4 (0-5)	**.0007**
Urticarial rash (0-4)	4 (0-4)	2 (0-4)	**.0122**	1 (0-4)	**.0034**	0 (0-3)	**.0006**	0 (0-2)	**.0007**
Fatigue (0-4)	3 (0-4)	2 (0-4)	**.0033**	3 (0-4)	**.008**	1 (0-3)	**.0032**	1 (0-2)	**.0009**
Fever (0-4)	0 (0-4)	0 (0-3)	.276	0 (0-3)	.1779	0 (0)	**.0218**	0 (0)	**.0218**
Myalgia (0-4)	3 (0-4)	2 (0-4)	.2792	2 (0-4)	.1209	1 (0-3)	**.0058**	1 (0-2)	**.0024**
Arthralgia/ bone pain (0-4)	3.5 (1-4)	3 (0-4)	**.0046**	2 (0-3)	**.0025**	1 (0-3)	**.0022**	1 (0-3)	**.0019**

Boldface indicates statistical significance.
*Compared with baseline.

TABLE E2. Characteristics of AEs that were reported more than once in the 17 patients with at least 1 AE

Type of AE	No. of patients	No. of events
Cardiovascular		
Hypertension	4	6
Dysrhythmia	4	5
Gastrointestinal		
Gastrointestinal infection	3	5
Epigastric pain	3	3
Elevated liver enzyme levels	2	2
Colon adenoma	1	2
Diarrhea	2	2
Musculoskeletal and connective tissue		
Lumbago	3	3
Arthrosis/arthritis	5	6
Joint or bone pain	3	4
Muscular pain/cramps	3	3
Spinal disk herniation	2	2
Respiratory		
Respiratory tract infection	14	42
Eye, ear, nose, throat		
Conjunctivitis	2	2
Tinnitus	2	2
Sinusitis	1	2
Urogenital		
Urinary tract infections	5	12
Prostate hyperplasia	2	2
Chronic inflammation in prostate biopsy	1	2
Skin		
Eczema	4	5
Skin carcinoma	2	2
Atypical nevus (excision)	2	2
Tinea	2	2
Oral		
Dental root inflammation	2	2
Gingivitis	1	2
Other		
Night sweating	2	2
Vertigo	2	3

TABLE E3. Characteristics of serious AEs that were reported in the 6 patients with at least 1 SAE

Type of serious AE and patient outcome	Relationship with study drug	No. of events	Canakinumab dose (mg)
Pneumonia with consecutive paraplegia; recovered	Suspected	1	150
Sepsis due to atypical mycobacteriosis; fatal outcome	Suspected	1	300
Worsening of inguinal hernia; recovered	Not suspected	1	150
Multiple myeloma; left the study	Not suspected	1	150
Choledocholithiasis; recovered	Not suspected	1	300
Leiomyoma; recovered	Not suspected	1	300
Craniocerebral trauma due to assault; recovered	Not suspected	1	150