

Efficacy and safety of the interleukin-1 antagonist rilonacept in Schnitzler syndrome: an open-label study

K. Krause¹, K. Weller¹, R. Stefaniak¹, H. Wittkowski², S. Altrichter¹, F. Siebenhaar¹, T. Zuberbier¹ & M. Maurer¹

¹Department of Dermatology and Allergy, Allergie-Centrum-Charité, Charité – Universitätsmedizin Berlin, Berlin; ²Department of Pediatrics, Universitätsklinikum Münster, Münster, Germany

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Correspondence

Marcus Maurer, MD, Department of Dermatology and Allergy, Allergie-Centrum-Charité, Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany.
Tel.: + 49-30-450 518 043
Fax: + 49-30-450 518 972
E-mail: marcus.maurer@charite.de

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Abstract

Background: Schnitzler syndrome (SchS) is a rare disease with suspected autoinflammatory background that shares several clinical symptoms, including urticarial rash, fever episodes, arthralgia, and bone and muscle pain with cryopyrin-associated periodic syndromes (CAPS). Cryopyrin-associated periodic syndromes respond to treatment with interleukin-1 antagonists, and single case reports of Schnitzler syndrome have shown improvement following treatment with the interleukin-1 blocker anakinra. This study evaluated the effects of the interleukin-1 antagonist rilonacept on the clinical signs and symptoms of SchS.

Methods: Eight patients with SchS were included in this prospective, single-center, open-label study. After a 3-week baseline, patients received a subcutaneous loading dose of rilonacept 320 mg followed by weekly subcutaneous doses of 160 mg for up to 1 year. Efficacy was determined by patient-based daily health assessment forms, physician's global assessment (PGA), and measurement of inflammatory markers including C-reactive protein (CRP), serum amyloid A (SAA), and S100 calcium-binding protein A12 (S100A12).

Results: Treatment with rilonacept resulted in a rapid clinical response as demonstrated by significant reductions in daily health assessment scores and PGA scores compared with baseline levels ($P < 0.05$). These effects, which were accompanied by reductions in CRP and SAA, continued over the treatment duration. Rilonacept treatment was well tolerated. There were no treatment-related severe adverse events and no clinically significant changes in laboratory safety parameters.

Conclusion: Rilonacept was effective and well tolerated in patients with SchS and may represent a promising potential therapeutic option (NCT01045772 [ClinicalTrials.gov Identifier]; EudraCT #2006-004290-97).

Schnitzler syndrome (SchS) is a rare condition with slightly more than 100 cases identified. However, it is likely that SchS is underdiagnosed, especially because its clinical presentation

may overlap with common disorders such as chronic urticaria and patients commonly experience a delay in diagnosis that can exceed 5 years (1).

Patients with SchS are characterized by the hallmark symptoms of chronic urticarial rash and monoclonal gammopathy that is usually IgM but may also be IgG. These symptoms are required for a diagnosis along with the concurrent presence of at least two other characteristic symptoms including recurrent fever, arthralgia or arthritis, bone pain, lymphadenopathy, hepato- or splenomegaly, leukocytosis, elevated erythrocyte sedimentation rate, and abnormal bone morphology (1). However, a diagnosis of SchS can only be

Abbreviations

ADA Antidrug antibodies; AE adverse event; CAPS cryopyrin-associated periodic syndromes; DHAF Daily health assessment form; ETP extended treatment phase; hs-CRP high-sensitivity C-reactive protein; ITP initial treatment phase; MWS Muckle-Wells syndrome; PGA physician's global assessment; SAA serum amyloid A; SchAS Schnitzler syndrome activity score; SchS Schnitzler syndrome; S100A12 S100 calcium-binding protein A12.

made after exclusion of other diseases, most notably autoimmune, hereditary autoinflammatory, or hematologic disorders, chronic infections, as well as chronic spontaneous urticaria and urticarial vasculitis (1, 2). Long-term complications in patients with SchS involve lymphoproliferative disorders and type A amyloidosis (2, 3).

SchS shares several clinical symptoms with Muckle–Wells syndrome (MWS), including urticarial rash, fever episodes, arthralgia, bone and muscle pain, and risk of amyloidosis. Muckle–Wells syndrome is a rare inherited disease that is part of the cryopyrin-associated periodic syndromes (CAPS) spectrum of autoinflammatory disorders caused by mutations of the NLRP3 gene that result in overproduction of interleukin-1 (IL-1) (4, 5). In contrast to MWS and other CAPS, SchS develops late in life (mean age at onset is 51 years). Although specific mutations are not known in SchS, an NLRP3 mutation consistent with CAPS has recently been reported in a case of SchS (6). The quality-of-life has been suggested to be impaired in SchS (7); however, quantitative or comparative assessments of quality-of-life have not been published.

Treatment options for SchS are limited. Therapy has relied on glucocorticoids, nonsteroidal anti-inflammatory drugs, and immunosuppressants, all of which fail to provide long-term remission despite short-term improvement (7). Case reports have shown that daily subcutaneous injections of the IL-1 inhibitor anakinra are very effective within days in patients with SchS including those with long-standing failure of other therapies (8–13). As there are no approved treatments for SchS, anakinra has been used off-label.

Although the etiology of SchS is unknown and the pathophysiology of SchS has yet to be fully elucidated, a case report suggested that dysfunction of the inflammasome contributes to the underlying pathogenesis (14). The inflammasome is an intracellular multimeric protein complex that participates in the inflammatory response through caspase-1 activation leading to subsequent production of the pro-inflammatory mediator IL-1 β (15–17). This dysfunction supports the role of IL-1 in the disease process, not only suggesting similarity with MWS and other CAPS, but also providing an explanation for the effects of anakinra. Comparable to CAPS, peripheral blood monocytes of patients with SchS show elevated IL-1 production following lipopolysaccharide stimulation (18, 19). The clinical implication of these observations is that targeting IL-1 represents a rational approach to SchS treatment, similar to what has already been demonstrated for CAPS with the IL-1 inhibitors anakinra, canakinumab, and rilonacept (20–23). A specific role of IL-1 β in SchS was suggested by the successful treatment of three patients with canakinumab, a monoclonal antibody targeting IL-1 β (24).

Rilonacept is an IL-1 antagonist that is a recombinant fusion protein comprising the extracellular ligand-binding domains of human IL-1 type I receptor (IL-1RI) and IL-1 receptor accessory protein (IL-1RAcP), fused to the Fc portion of human IgG1 (25). As a soluble decoy receptor, it traps IL-1 α and IL-1 β with high affinity and is often referred to as IL-1 trap. It has been approved in the United States

(Food and Drug Administration) and Europe (European Medicines Agency) for the treatment of CAPS; administration is by once-weekly subcutaneous dosing.

Formal clinical studies for the treatment of SchS are lacking, mainly because few patients are available. The purpose of this study was to evaluate the safety and efficacy of rilonacept for the treatment of SchS.

Methods

Study design

This single-center, open-label study received approval from the study center's Institutional Review Board and was performed in accordance with the Declaration of Helsinki; all participants provided written informed consent at enrollment.

The study was designed to evaluate the safety of rilonacept in subjects with SchS or MWS, including treatment of up to 1 year, with a secondary objective of assessing the short- and long-term efficacy of rilonacept on clinical signs and symptoms. As there were only two patients with MWS, this analysis is limited to the patients with SchS. Upon enrollment, patients went through a 3-week baseline phase followed by a 4-week initial treatment phase (ITP). On day 0 (first day of the ITP), rilonacept was administered subcutaneously as a loading dose of 320 mg, with subsequent weekly subcutaneous doses of 160 mg for 4 weeks. During the extended treatment phase (ETP), which lasted an additional 48 weeks after ITP, rilonacept administration continued with weekly 160-mg doses. During the ETP, mandatory study visits for efficacy and safety evaluation occurred every 12 weeks, with additional safety visits at the study center or general practitioner at 6-week intervals.

Patient population

Patients were recruited between January and June 2009 from the Charité University Hospital (study center) patient pool and referrals from other German specialists; follow-up of enrolled patients was for 1 year. To be included, patients were required to be ≥ 18 years of age with symptomatic SchS. Patients were only enrolled in the study, if they fulfilled the diagnostic main criteria of chronic urticarial rash and monoclonal gammopathy, as well as at least two minor criteria consisting of recurrent fever, arthralgia or arthritis, bone pain, lymphadenopathy, hepato- or splenomegaly, leukocytosis, elevated erythrocyte sedimentation rate, and abnormal bone morphology as proposed by Lipsker et al. (1). Additional inclusion criteria were a willingness to complete all study-related procedures, attend all study visits, and consent to maintain adequate contraception for the study duration for men and women of childbearing potential. Key exclusion criteria were treatment with a live (attenuated) virus vaccine within 3 months prior to baseline; treatment with a tumor necrosis factor inhibitor or immunosuppressive within five half-lives prior to baseline; ongoing treatment with another anti-IL-1 blocker; the presence of active

systemic inflammatory conditions; evidence of active tuberculosis, HIV, hepatitis B or C, or malignancies within 5 years; and the presence of any medical condition that, in the investigator's opinion, would interfere with participation in the study or place the subject at risk.

Outcomes

The primary end points were safety and tolerability, assessed based on incidence of adverse events (AEs), clinical examination, and routine laboratory assessments.

Patient- and physician-reported outcomes as well as objective efficacy assessments including changes in inflammatory markers were evaluated as secondary end points.

Patient-reported changes in disease activity were captured during the ITP by calculating a Schnitzler Activity Score (SchAS) based on a Daily Health Assessment Form that was previously validated for CAPS (26). The SchAS enables patients to self-rate the severity of key disease-related symptoms and provides global assessment of disease activity; recall period is 24 h. The SchAS consists of five subscales, scored 0–10 (0 = none, 10 = very severe), corresponding to the five key symptoms of SchS. In the SchAS, bone/muscle pain is substituted for eye redness/pain used in the validated CAPS activity score, with the other symptom subscales remaining the same: urticarial rash, periodic fever, joint pain, and fatigue. Values for the total SchAS range from 0 to 50, with higher scores indicating greater severity. The mean daily scores were calculated by dividing the total score by five.

Patient-reported efficacy was assessed as the change in mean SchAS from baseline, derived from each patient's averaged 21-day baseline phase score (days –21 to day 0), to the mean of the last 21 days of the ITP (days 8–28), derived from the daily score for each patient averaged over this period.

Physician's global assessment (PGA) of disease activity was rated using a visual analog scale (0 = no disease activity to 10 = maximum disease activity) at screening and baseline, and at on-treatment weeks 4, 16, 28, 40, and 52. Physicians were blinded to the subject's SchAS scores at the time of PGA assessment. Changes from baseline were evaluated for all on-treatment PGA assessments.

Objective efficacy assessments included changes from baseline to week 4 in the inflammatory markers high-sensitivity C-reactive protein (hs-CRP) and serum amyloid A (SAA). When available, changes in these inflammatory markers were also evaluated during ETP (weeks 16, 28, 40 and 52). Additionally, changes in the S100 calcium-binding protein A12 (S100A12) were assessed. S100A12 is a pro-inflammatory protein produced in granulocytes that has been suggested to be a disease activity marker for several inflammatory and autoinflammatory conditions (27). Serum concentrations of S100A12 were measured using ELISA (28).

Serum samples were also evaluated for the presence of antidrug antibodies (ADA), and plasma samples were analyzed for rilonacept concentrations using a validated ELISA (29).

Patient response was characterized at the end of the ITP (week 4) and during the ETP (week 16). Complete responders

were defined as those having both a CRP < 1.0 mg/dl and a PGA reduction $\geq$ 50% at both time points relative to pooled screening and baseline values; partial responders were defined as CRP < 1.0 mg/dl and PGA reduction < 50% in the ITP and/or in the ETP relative to pooled screening and baseline; and nonresponders were defined as CRP $\geq$ 1.0 mg/dl and PGA unchanged or reduction < 50% at the two time points.

An exploratory analysis evaluated correlations between changes in inflammatory or disease markers (hs-CRP, SAA, and S100A12) and clinical assessments (PGA and SchAS scores) from baseline (day 0) to week 4 (end of ITP).

Statistical analysis

Descriptive statistics were used for continuous variables and for categorical data. Analysis of the inflammatory markers hs-CRP and SAA was based on log-transformed data using the parametric or nonparametric methods (e.g., Wilcoxon signed rank test) as warranted. Correlations between inflammatory markers and clinical outcomes (SchAS and PGA scores) were evaluated using the nonparametric Spearman's rank correlation.

Results

Demographics and patient disposition

Eight patients with SchS were enrolled, and the demographic characteristics of the individual patients with SchS are presented in Table 1. Figure 1 shows the study flowchart. Among the eight enrolled patients, seven were characterized by monoclonal IgM-kappa gammopathy (range, 146–1737 mg/dl), and one patient had monoclonal IgM-lambda gammopathy (417 mg/dl). One patient with IgM-kappa monoclonal gammopathy converted to polyclonal gammopathy during the study. Total gamma globulin levels did not change significantly.

Table 1 Demographic characteristics of individuals participating in the study

Patient number	Sex	Age, years	Gammopathy, type (mg/dl)*	Total gamma globulin level, % [†]	
				Baseline	End of study
1	Male	59	IgM-kappa (535)	11.2	11.0
2	Female	61	IgM-lambda (417)	13.0	12.4
3	Female	70	IgM-kappa (1737)	27.0	22.4
4	Male	45	IgM-kappa (1178) [‡]	16.8	16.6
5	Male	67	IgM-kappa (1086)	19.1	20.7
6	Male	68	IgM-kappa (146)	18.6	16.6
7	Female	51	IgM-kappa (370)	7.0	8.4
8	Female	59	IgM-kappa (370)	12.3	12.8

*Normal range 40–230 mg/dl.

[†]Normal range 10.5–19.5%.

[‡]Patient converted from monoclonal to polyclonal gammopathy during the course of the study.

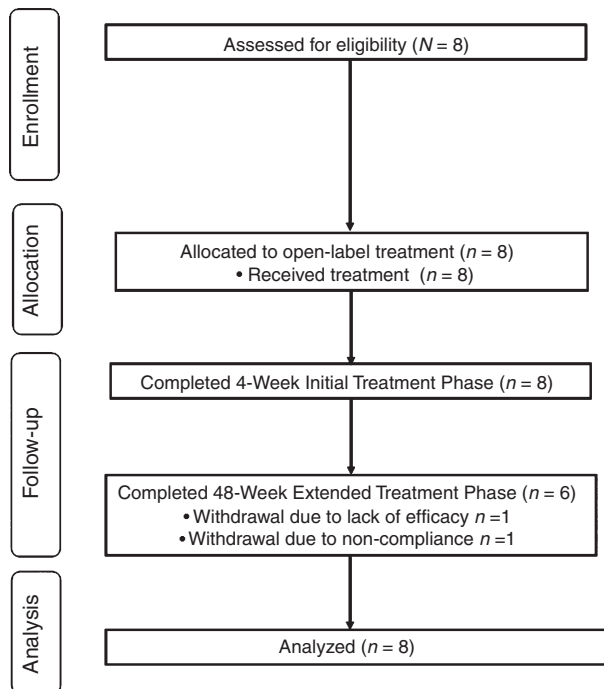


Figure 1 Consort flowchart.

All patients completed the ITP, and six patients completed the ETP. Reasons for discontinuation were complete lack of response in one patient who discontinued at study week 10 and one patient who was withdrawn at week 34 for noncompliance (discontinuation of study drug for several weeks). The latter one was classified as partial responder.

Safety and tolerability

A total of 13 AEs were reported; all were of mild ($n = 4$) or moderate ($n = 9$) severity, and none was considered related to study medication. Three AEs were infections, all in different patients, and included a common cold, otitis media, and a viral infection with diarrhea and fever. Five AEs were related to the skin and skin appendages: eczema, angioedema, transient diffuse hair loss, basal cell carcinoma, and actinic keratoses, the latter two in patients with a known history of these conditions. Other AEs included obstipation with abdominal pain, dental root inflammation, conjunctivitis, meniscus arthropathy, and osteoporosis in a patient with a long-standing history of systemic glucocorticoid intake. There were no serious AEs, and no significant changes in safety laboratory values were observed that could be considered of potential concern for specific organ toxicity by rilonacept. Once-weekly subcutaneous rilonacept injections were well tolerated without significant injection site reactions.

Clinical efficacy

Treatment with rilonacept resulted in significant reductions in total SchAS scores that were observed 8 days after treat-

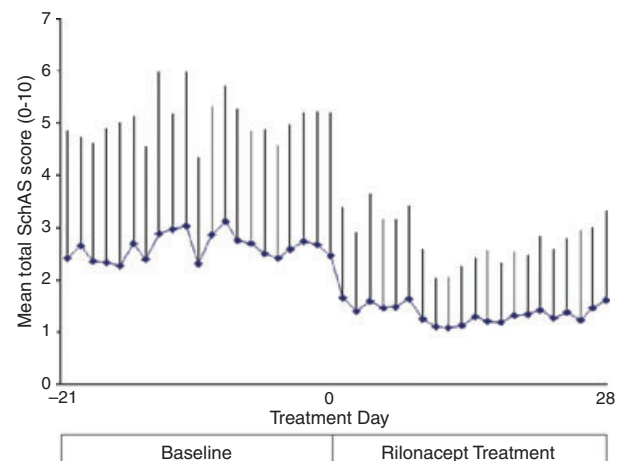


Figure 2 Mean patient-reported Schnitzler syndrome Activity Score (SchAS) as determined from the Daily Health Assessment Form (DHAf) during the baseline period (3 weeks) and the initial treatment period of 28 days. $P \leq 0.05$ for the final 3 weeks of treatment relative to the 3-week baseline period.

ment initiation and maintained throughout the ITP (Fig. 2). At day 28 (end of ITP; $n = 8$), the change in mean score from the pretreatment average (3.05 ± 2.38) to the average over the last 3 weeks of treatment (1.50 ± 1.53) was -1.55 ± 1.56 ($P = 0.0260$). Significant reductions from baseline at day 28 were also observed for the individual key symptoms of rash (-1.95 ± 2.02 ; $P = 0.0293$), joint pain (-1.75 ± 1.88 ; $P = 0.0336$), and bone/muscle pain (-1.63 ± 1.88 ; $P = 0.0442$) scores. However, the reductions in fever (-1.27 ± 1.73 ; $P = 0.0769$) and fatigue (-1.17 ± 1.66 ; $P = 0.0856$) were not statistically significant.

At the end of the ITP, the PGA showed significant improvements, with reduction from a mean score of 6.5 ± 1.69 at baseline to 3.5 ± 2.83 at 28 days ($P = 0.021$). These improvements were maintained at all ETP visits among the six patients who completed the ETP (Fig. 3).

On an individual patient level, four of the eight patients showed a rapid and complete response, with a marked reduction in rash observed as early as 24 h after initiating therapy

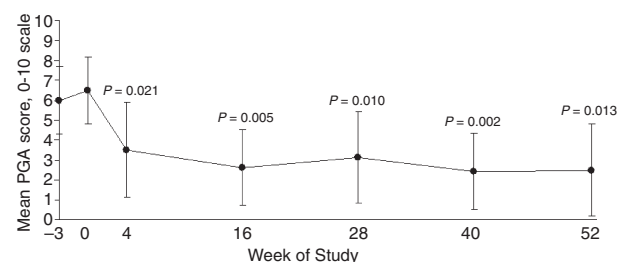


Figure 3 Change in physician's global assessment (PGA) of disease activity over the duration of treatment. P values are relative to baseline.

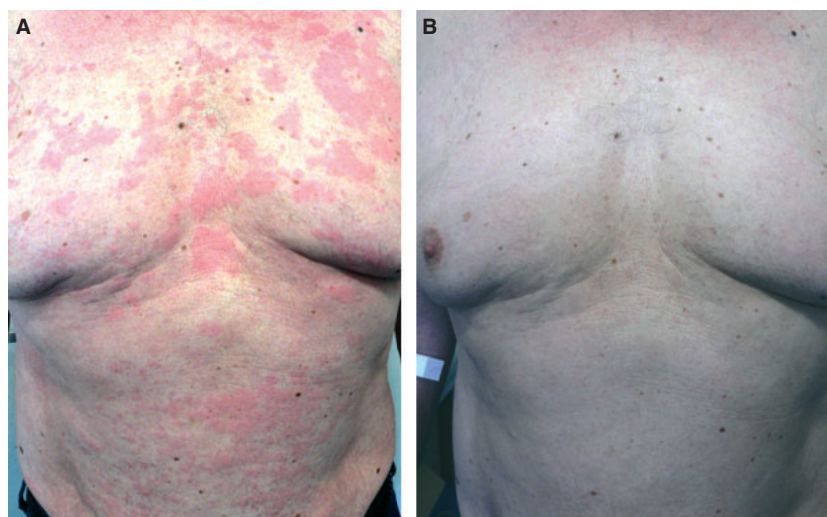


Figure 4 Representative resolution of urticaria after treatment with rilonacept. (A) Prior to treatment. (B) Same patient as in (A), 4 weeks after treatment initiation.

and complete resolution by the end of ITP (Fig. 4). These effects continued over the 1-year treatment duration. Three patients were classified as partial responders, and one patient was a nonresponder.

Markers of inflammation

By the end of the ITP at week 4, the inflammatory marker hs-CRP was reduced from baseline in all patients ($P = 0.076$) (Fig. 5A). Normalization of hs-CRP (<1 mg/dl) was observed at week 4 in all patients except for the nonresponder. At subsequent visits, serum concentrations of hs-CRP remained low and, relative to baseline, were observed to be significantly reduced at weeks 28, 40 and 52 ($P = 0.039$, $P = 0.036$, and $P = 0.040$, respectively). In patients with normalized hs-CRP values, these values were generally maintained for the study duration. For SAA, a trend in reduction from baseline was observed at week 4 ($P = 0.052$, Fig. 5B), and four patients (three responders and one partial responder) had normalized SAA values (<6 mg/l). Reductions in SAA levels were main-

tained without reaching clinical significance relative to baseline ($P = 0.079$).

Serum S100A12 concentrations (Fig. 6) showed nonsignificant reductions from baseline in four of the eight patients (three complete and one partial responders). Of the other four patients, one maintained high serum levels throughout the ITP (a nonresponder), and three had small to moderate increases in serum levels relative to baseline.

Over the study duration, the presence of ADA was detected in three patients, all partial responders, with titers ranging from 400 to 4000. Among the seven patients for whom plasma rilonacept values could be determined at week 4, the concentration in the nonresponder, 3900 ng/ml, was substantially lower than in the other patients, which ranged from 15 900 to 39 600 ng/ml.

Exploratory analysis

In the correlation analysis between inflammatory markers and clinical assessment, the mean decrease in hs-CRP and

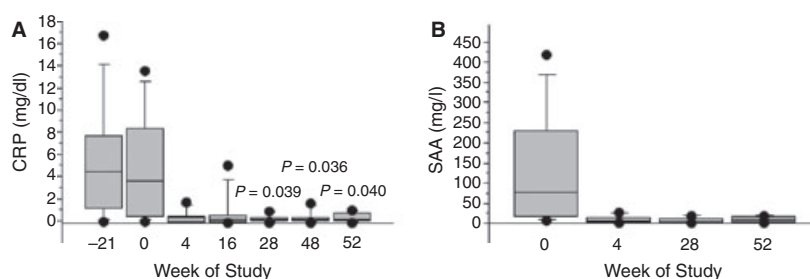


Figure 5 Change in inflammatory markers over the duration of treatment. (A) High-sensitivity C-reactive protein (hs-CRP); (B) serum amyloid A (SAA). P values are relative to baseline. The box and whisker plots show the median (horizontal line) with the inter-

quartile range (top and bottom of the box), the 10th and 90th percentiles (ends of the whiskers), and the minimum and maximum values (dots outside the whiskers).

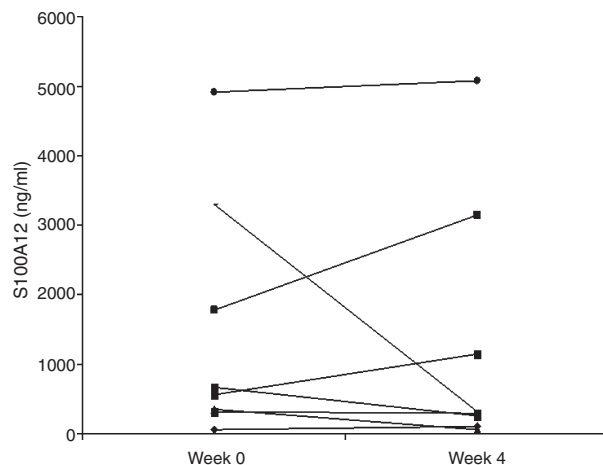


Figure 6 Change in individual patients in the disease activity marker S100 calcium-binding protein A12 (S100A12).

Table 2 Correlation between inflammatory markers and clinical outcomes

Marker	Spearman correlation coefficient, <i>r</i> (<i>P</i> -value)	
	PGA	DHAF score
hs-CRP	0.919 (0.003)	0.750 (0.052)
SAA	0.927 (0.001)	0.714 (0.047)
S100A12	0.732 (0.039)	0.381 (0.352)

PGA, physician's global assessment; DHAF, Daily Health Assessment Form; hs-CRP, high-sensitivity C-reactive protein; SAA, serum amyloid A; S100A12, S100 calcium-binding protein A12.

SAA was paralleled by a decrease in PGA. These changes not only showed strong and significant correlations ($P \leq 0.01$), but there were also correlations between these inflammatory markers and patient-reported disease activity as assessed using the SchAS (Table 2). The strongest correlation was between SAA and PGA ($r = 0.927$). While a strong correlation was also observed between levels of the S100A12 and PGA ($r = 0.732$, $P = 0.039$), there was no correlation with SchAS scores (Table 2).

Discussion

SchS is a very rare disease with few treatment options. It is therefore notable that the current study is the first clinical study on SchS, and also the first evaluation of rilonacept for SchS. Our results suggest that rilonacept may be a potential addition to the pharmacologic armamentarium available for long-term treatment of SchS; weekly subcutaneous doses of rilonacept for up to 1 year had a good safety and tolerability profile and provided rapid and sustained efficacy in reducing clinical symptoms and inflammatory markers. Importantly, complete or nearly complete remission appeared to be obtained in 4 (50%) of these patients. The patient who pre-

maturely discontinued because of the lack of treatment response was previously unresponsive to treatment with anakinra, another IL-1 antagonist. From a clinical point of view, the signs and symptoms presented by complete responders vs partial or nonresponders did not differ from each other.

Response to treatment is often correlated with pharmacokinetics of the medication and with the potential presence of ADAs in the case of biologic agents such as rilonacept; ADAs may affect long-term efficacy. In contrast to the complete responders who were negative for ADAs at all time points for which data were available, ADAs were detected in the three partial responders at multiple time points. Although the nonresponder was negative for ADA, the plasma concentration of rilonacept in this patient was substantially lower, 3900 ng/ml, than among the other patients, ranging from 15 900 to 39 600 ng/ml. While these data are suggestive of underlying mechanisms leading to nonresponse, further evaluation of the association between response and these parameters is warranted.

The clinical improvements observed with rilonacept in patients with SchS support a role of IL-1 in this disease as previously suggested by case reports with anakinra. However, it should also be noted that while daily subcutaneous administration is necessary with anakinra, the effects with rilonacept were achieved with weekly doses. Less frequent dosing is not only likely to be more acceptable to patients, but may also reduce side effects, notably injection site reactions. No treatment-related AEs except mild injection site reactions were reported among these patients with SchS treated with rilonacept, further supporting its safety and tolerability during long-term treatment of up to 1 year.

The correlations of hs-CRP and SAA with changes in PGA and SchAS suggest that these acute-phase reactants may be sensitive markers of disease activity in patients with SchS, although they have not been validated as predictors of either clinical improvement or safety. Nevertheless, these correlations are consistent with previous observations that serum levels of hs-CRP and SAA reflect clinical disease activity in patients with CAPS (20, 22). Two studies in patients with CAPS have also suggested that S100A12 follows disease activity (4, 21). While S100A12 correlated with PGA, supporting its potential as a marker of disease activity in SchS, there was poor correlation with SchAS. In particular, substantial increases in S100A12 levels at week 4 were observed in two partial responders and the nonresponder, while one of the complete responders had a dramatic decrease in S100A12; the other four patients had no or small changes just above the normal range (approximately 130 ng/ml).

There was also a wide range of paraprotein levels between individual patients, although quantitative paraprotein levels were not assessed on a regular basis within the study. However, total gamma globulin levels did not show significant changes over the course of the study, suggesting that rilonacept may not affect monoclonal gammopathy. This is consistent with observations in patients with SchS treated with anti-IL-6 therapy (30). Whether drugs targeting IL-1 provide long-term protection from lymphoproliferative disorders in SchS remains to be studied.

Several study limitations are worth noting, including the low number of patients, which may be especially relevant because the study is likely to be underpowered for detecting infrequent but clinically relevant safety issues despite long-term follow-up. However, the low number of patients is not surprising because the total number of known patients with SchS is slightly over 100. The low number of patients with SchS is also the basis for the limitation that this was an open-label study; to find sufficient patients for a randomized, placebo-controlled trial, a multicenter study would be needed.

Two limitations should be noted regarding the SchAS: The SchAS has not been validated, and there was substantial heterogeneity in SchAS among the patients. The presence and subjective severity of clinical symptoms varies considerably among patients with SchS, and this heterogeneity may have been exacerbated by the low number of patients. Nevertheless, rilonacept resulted in a reduction in SchAS from baseline that was statistically significant.

In conclusion, rilonacept was effective, well tolerated, and safe in the treatment of SchS for up to 1 year, resulting in reductions in clinical symptoms and inflammatory markers. Thus, treatment with rilonacept may represent a promising potential therapeutic option for these patients and warrants further evaluation.

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Author contributions

K. Krause substantially contributed to the conception and design of study, analyses and interpretation of data, drafted the article, and involved in final approval of the version to be published. K. Weller, H. Wittkowski, S. Altrichter, and F. Siebenhaar substantially contributed to acquisition of data and interpretation of data, critically revised the article for important intellectual content, and involved in final approval of the version to be published. R. Stefaniak, T. Zuberbier, and M. Maurer substantially contributed to the conception and design of study and interpretation of data, critically revised the article for important intellectual content, and involved in final approval of the version to be published.

Conflict of interest

Karoline Krause received a travel grant from Regeneron Pharmaceuticals; Helmut Wittkowski received grant from BMBF; Marcus Maurer received a travel grant from Regeneron Pharmaceuticals, grant from Novartis Pharma GmbH, honorarium or consulting fee from Novartis Pharma GmbH; and Karsten Weller, Richard Stefaniak, Sabine Altrichter, Frank Siebenhaar, and Torsten Zuberbier did not receive any funding.

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