EXTENDED REPORT

Sustained efficacy of the monoclonal anti-interleukin-1 beta antibody canakinumab in a 9-month trial in Schnitzler's syndrome

Heleen D de Koning,[1,2,3,4,5] Joost Schalkwijk,[1,2,3] Johanna van der Ven-Jongekrijg,[3,4] Monique Stoffels,[3,4,5] Jos W M van der Meer,[3,4,5] Anna Simon[3,4,5]

Handling editor Tore K Kvien

▶ Additional supplementary data are published online. To view these files please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2012-202192).

[1]Department of Dermatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
[2]Department of Dermatology, Nijmegen Centre for Molecular Life Sciences (NCMLS), Nijmegen, The Netherlands
[3]Department of Dermatology, Nijmegen Institute for Infection, Inflammation and Immunity (N4i), Nijmegen, The Netherlands
[4]Department of General Internal Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
[5]Department of General Internal Medicine, N4i Centre for Immunodeficiency and Autoinflammation, Nijmegen, The Netherlands

Correspondence to
Dr Heleen Dian de Koning, Department of Dermatology, Radboud University Nijmegen Medical Centre, PO Box 9101, Nijmegen 6500 HB, The Netherlands; h.dekoning@derma.umcn.nl

Accepted 23 September 2012
Published Online First 19 October 2012

To cite: de Koning HD, Schalkwijk J, van der Ven-Jongekrijg J, *et al*. *Ann Rheum Dis* 2013;**72**:1634–1638.

ABSTRACT

Objectives Schnitzler's syndrome is a chronic disabling autoinflammatory disorder, characterised by chronic urticaria, paraproteinemia and systemic inflammation. The interleukin (IL) 1 receptor antagonist anakinra is a very effective treatment, but requires daily injection and blocks both IL-1α and IL-1β. Canakinumab is a selective human monoclonal anti-IL-1β antibody with a long half-life. We investigated the long-term efficacy and safety of canakinumab in Schnitzler's syndrome.

Methods In an open-label, single-treatment arm trial, eight patients with Schnitzler's syndrome received monthly injections with 150 mg canakinumab subcutaneously for 6 months, followed by a 3-month observation period. Primary outcome was complete or clinical remission at day 14. Secondary outcome measures included inflammatory markers, quality of life, time to relapse, safety and tolerability.

Results After stopping anakinra, patients developed moderate to severe clinical symptoms. Canakinumab induced complete or clinical remission at day 14 in all eight patients. Median C-reactive protein concentrations decreased from 169 mg/l at baseline to less than 10 mg/l on day 14 and remained low or undetectable. One patient discontinued participation on day 39 because of return of symptoms while all others remained in complete or clinical remission during the 6-month treatment period. Relapse after last canakinumab dose occurred within 3 months in four patients. For two patients, remission continued several months post-study. Five patients reported at least one adverse event, predominantly mild upper respiratory tract infections. One patient died in a traffic accident.

Conclusions In this 9-month study, monthly 150 mg canakinumab injection was an effective and well-tolerated treatment for Schnitzler's syndrome. Our data demonstrate that IL-1β plays a pivotal role in this disease.

ClinicalTrials.gov NCT01276522.

INTRODUCTION

Schnitzler's syndrome is a chronic disabling autoinflammatory disorder, characterised by chronic urticaria, paraproteinemia and systemic inflammation. Patients are affected to different degrees by fever, bone pain and arthralgias or arthritis, and are at risk of developing a lymphoproliferative disorder and AA amyloidosis in the long term.[1–3] Over 160 cases have been reported to date, but the actual prevalence is probably much higher. The aetiology of Schnitzler's syndrome is unknown. Numerous immunosuppressive therapies have failed, but the interleukin (IL) 1 receptor antagonist anakinra was found to be effective in over 45 cases to date, implying a pivotal pathophysiological role of IL-1, either IL-1α, IL-1β, or both.[4–8] The short half-life of anakinra requires daily subcutaneous injections, which occasionally lead to strong local injection-site reactions, which raised the need for a longer-acting agent. Canakinumab is a fully human selective monoclonal anti-IL-1β antibody with a half-life of approximately 28 days. It is effective in cryopyrin-associated periodic syndrome (CAPS), a rare hereditary autoinflammatory disorder caused by IL-1β-activating NLRP3 mutations.[9 10] Phenotypical similarities to CAPS and in-vitro findings in Schnitzler's syndrome patient cells suggest that IL-1β, not IL-1α, is also the principal pathophysiological cytokine in Schnitzler's syndrome.[11] We have previously reported short-term successful treatment with canakinumab in three patients with Schnitzler's syndrome, and one case of long-term remission was recently reported.[12 13] Here we report efficacy and safety data of a 9-month trial of the long-acting monoclonal anti-IL-1β antibody canakinumab in eight patients with Schnitzler's syndrome.

METHODS

Design overview

The design was an open-label, single-arm 9-month trial comprising 6 months of 150 mg canakinumab subcutaneous injections every 4 weeks and 3 months of follow-up (ClinicalTrials.gov registration number: NCT01276522). Dose adjustment to 300 mg was possible in the case of incomplete response at day 7. The study was approved by the local medical ethical board and patients' informed consent was obtained according to the principles of the Declaration of Helsinki.

Patients and intervention

The trial took place in a single academic centre. Patients were eligible if they had active Schnitzler's syndrome as defined by the adapted Lipsker criteria,[1 2] responded well to anakinra therapy, and fulfilled the other inclusion and exclusion criteria (see supplementary table S1, available online only). After discontinuation of anakinra treatment and the return of symptoms of Schnitzler's syndrome, patients entered the study to receive their first dose of 150 mg canakinumab subcutaneously. Patients were then evaluated 3, 7, 14 and 28 days later and

subsequently every 4 weeks, and received a canakinumab injection every 4 weeks for a total of 6 months. After the last injection, patients were followed until disease relapse or until 3 months passed. Upon disease relapse, the patients were restarted on anakinra.

Outcome measures

The primary outcome measure was complete or clinical remission at day 14 of the trial (definitions are outlined in supplementary table S2, available online only). Complete remission was defined as absent or minimal clinical disease activity with normal C-reactive protein (CRP), and clinical remission as absent or minimal disease activity and a greater than 75% improvement of CRP concentration from baseline, although still above 10 mg/l. Secondary outcome measures included prevention of disease relapse during the trial; change in inflammatory markers (CRP and serum amyloid A; SAA), physician global assessment (PGA) and patient global assessment (PaGA) of disease activity (respectively, scale 0 (absent), 1 (minimal), 2 (mild), 3 (moderate) to 4 (severe)), quality of life (QoL) using the RAND-36 questionnaire;[14] time to disease relapse after the last canakinumab dose; safety and tolerability. Paraprotein levels were measured throughout the trial.

Statistical analysis

The difference in QoL measurements (RAND-36 data) between under anakinra treatment and without treatment (baseline), under canakinumab treatment day 14 versus baseline and under anakinra treatment versus canakinumab treatment day 14 was tested with a paired Student's t test. Also serum concentrations of CRP and SAA at baseline versus day 7 after the first canakinumab injection were tested with a paired Student's t test; $p<0.05$ was regarded as statistically significant.

RESULTS

Patients

All patients with Schnitzler's syndrome known to us in The Netherlands at the start of the trial (nine in total) were invited and screened for participation. One patient preferred not to discontinue anakinra treatment for personal reasons, but the others provided informed consent and were eligible. Therefore, eight patients aged 51–75 years (mean 64 years) with classic (IgM) or variant (IgG) type Schnitzler's syndrome were included in the trial. Baseline patient characteristics are shown in table 1.

Within 35 to 96 h (median 43 h) after stopping anakinra, the patients gradually developed general malaise, non-pruritic to burning urticaria, fever and arthralgia, as before the initiation of anakinra. At the baseline visit 4–6 days after discontinuing anakinra, they presented with disseminated urticaria and arthralgia. Five patients had frank arthritis in one to seven joints. Baseline SAA (median 974 mg/l, range 72–2390 mg/l) and CRP (median 169 mg/l, range 18–333 mg/l) concentrations were elevated, and seven patients had neutrophilic leucocytosis.

Primary outcome and disease activity

After the first subcutaneous injection of 150 mg canakinumab, symptoms in all patients started to abate within 6–16 h, and all were asymptomatic after 2–7 days. By day 14, all eight patients met the primary outcome by achieving complete or clinical remission. Six patients were in complete remission and two in clinical remission due to slightly elevated CRP levels (18 and 28 mg/l) (figure 1A).

PGA and PaGA were almost identical during the trial, and showed moderate to severe disease activity at baseline (mean 3.5, on a scale from 0 (absent) to 4 (severe activity)), which improved to minimal or no disease activity at day 7 (mean 0.8) (figure 1B and see supplementary figure S1, available online only). There was rapid resolution (median duration 18 h, range 10–48 h) of the typical urticarial rash after the first canakinumab administration as illustrated in figure 1C. During the ensuing months, disease activity remained mild or absent in all patients except for patient 8, as described below (figure 1A,B).

Serum CRP and SAA concentrations dropped dramatically within the first week (at day 7: CRP median 13 mg/l ($p=0.004$), range <5–46 mg/l; SAA median 9 mg/l ($p=0.009$), range 1–103 mg/l) and remained low or undetectable during the ensuing months (eg, after 6 months: CRP median <5 mg/l, range < 5–20 mg/l; SAA median 5 mg/l, range 1–25 mg/l) (figure 2). Paraprotein levels were stable throughout the trial and fluctuated less than 1 mg/l compared to the measurement before the trial.

After an initial clinical remission and drop in CRP from 333 mg/l at baseline to 18 mg/l at day 14, patient 8 started experiencing symptoms at day 18 and had a clear clinical and biochemical relapse at day 27. The second canakinumab dose of 150 mg at that time again induced clinical remission, but symptoms reappeared at day 37. The patient chose to discontinue with the trial at day 39; return to anakinra treatment was successful in controlling disease activity.

Table 1 Baseline patient characteristics (after discontinuation of anakinra)

Patient	1	2	3	4*	5	6	7	8
Sex	M	F	M	M	M	M	F	M
Age (years)	66	67	51	63	67	75	63	59
Disease duration (years)	14	2,5	6	20	10	17	25	9
Anakinra use (years)	4.5	0.25	2.5	6	7	6.5	7	2
Paraprotein subtype	IgMκ & λ	IgGκ	IgMκ	IgGκ	IgMκ	IgMκ	IgGκ†	IgGκ†
PGA‡	3	4	3	3	3	4	4	4
CRP level (mg/L)	202	147	190	16	60	250	95	333
SAA level (mg/L)	1380	867	1840	72	109	1080	502	2390
Neutrophils (*10^9/ml)	11.1	7.5	12.1	4.9	10.4	8.3	15.6	11.3

*This patient required antihistamines for concomitant cold-induced urticaria during both anakinra and canakinumab treatment. The other patients did not use any concomitant anti-inflammatory drugs.
†Previously an unquantifiably low IgGκ paraprotein was found, but this is currently undetectable.
‡Five-point score of disease activity from 0 (absent) to 4 (severe).
CRP, C-reactive protein; PGA, physician global assessment; SAA, serum amyloid A.

QoL assessment

At each visit, QoL was assessed with the RAND-36 questionnaire. At baseline during active disease, patient QoL had substantially decreased in all dimensions compared to QoL under anakinra treatment when their disease was inactive (figure 3 and supplementary tables S3 and S4, available online only). Pain and role impairment due to a physical problem were the most affected dimensions, whereas mental health remained relatively stable. On starting canakinumab treatment, patient QoL rapidly improved during the first week and remained stable during the whole trial (see supplementary figure S2 and table S3, available online only). In the dimensions role impairment due to a physical problem and vitality, patients scored their QoL slightly, but statistically significantly better during canakinumab (day 14) than during anakinra treatment (see supplementary table S4, available online only).

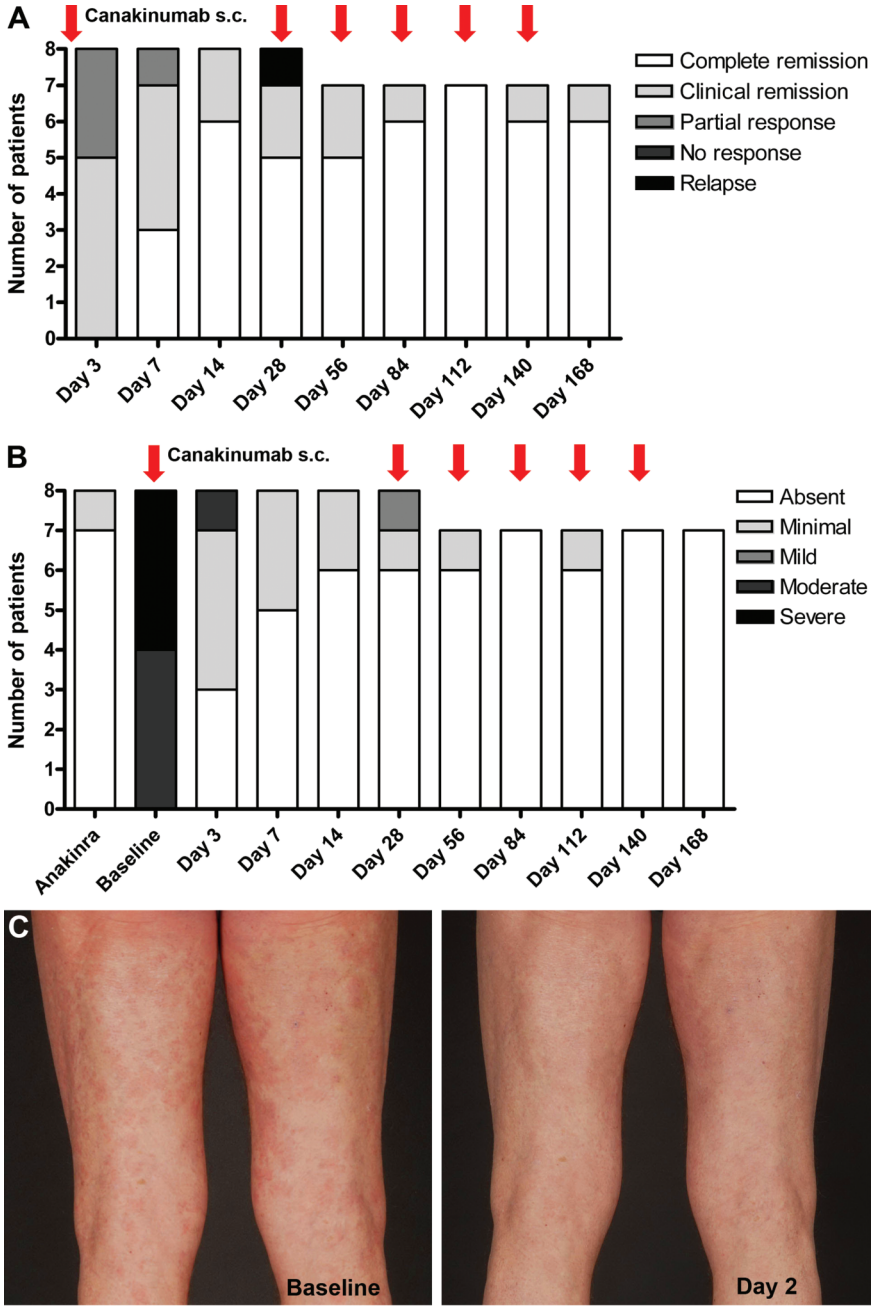

Figure 1 Trial outcome and clinical assessments. (A) Outcome during the trial in days after the first injection of canakinumab. Arrows indicate subcutaneous injection with 150 mg canakinumab. The single relapse at day 28 was seen in patient 8. (B) Physician global assessment of disease activity scores. Arrows indicate subcutaneous injection with 150 mg canakinumab. (C) Urticarial rash on thighs of patient 6 at baseline; urticaria had almost vanished 2 days after the first canakinumab injection.

Relapse of disease activity after last dose of canakinumab

Within the 3-month follow-up, four patients relapsed (for definition see supplementary table S2, available online only) and one died in a traffic accident while asymptomatic. In two patients, remission continued until 7 and 8 months after the last injection (figure 4). Of the six patients who completed the trial, median time to relapse was 72 days after the last canakinumab dose (range 40–234 days). All were restarted on anakinra, which quickly induced disease remission. Disease activity at relapse (figure 4) was much milder than at study entry when they had discontinued anakinra and relapsed, as evidenced by the lower PGA and PaGA scores (figure 1B and supplementary figure 1), lower CRP levels (figure 2), and less pronounced drop in the QoL, as shown for the most severely affected dimensions in supplementary figure S2 (available online only).

Adverse events

During the whole trial, blood pressure, weight, kidney function and liver enzymes remained unaffected. Twenty-two adverse events were reported by five patients and were predominantly upper respiratory tract infections. All but rhinitis, pharyngitis, light-headedness and vertigo (each N=2) were reported in one patient only. One death due to a traffic accident occurred during the follow-up phase, 45 days after the last injection of canakinumab (trial day 185). There was no apparent relationship with the study drug. All adverse events are listed in table 2.

DISCUSSION

This study shows that monthly subcutaneous injection with 150 mg canakinumab is an effective treatment in patients with Schnitzler's syndrome and that IL-1β, not IL-1α, causes the systemic inflammation. All patients met the criteria for the primary

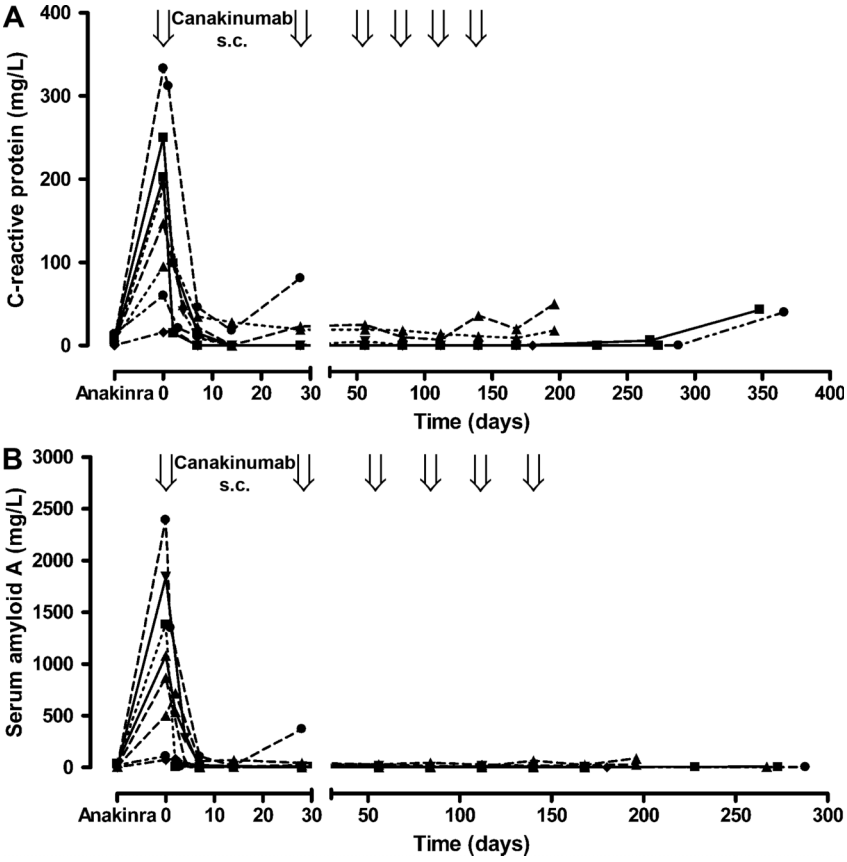

Figure 2 Sustained suppression of systemic inflammation. (A) Serum C-reactive protein (CRP) and (B) serum amyloid A (SAA) levels as a measure of systemic inflammation during the trial and during follow-up. Each line represents one patient. At day 10, CRP and SAA levels under anakinra are shown. Upper limit of normal is 10 mg/l.

outcome measure—clinical or complete remission of disease activity at day 14.

One patient relapsed after initial clinical remission. In view of his severe inflammation at baseline, initial response to canakinumab and relatively high body mass index, we hypothesise that he might have benefitted from higher dosing.

The time to relapse after the end of the trial varied greatly among the patients. For two patients, canakinumab induced a long-term remission of this unremitting disease. Seemingly, a vicious circle of inflammation had been interrupted (IL-1β induces its own production) with canakinumab treatment, but the reason why this created such long-term remission in these particular patients remains elusive. They both had had Schnitzler's syndrome for many years, and their disease activity at baseline was intermediate compared to the other patients.

The monthly dosing regimen was based on the report that in 24.1% of 109 CAPS patients who were injected bimonthly, an increase in dose or frequency was required.[15] Based on our data, in some patients less frequent dosing may suffice, while others require more frequent or higher dosing. Pharmacokinetic

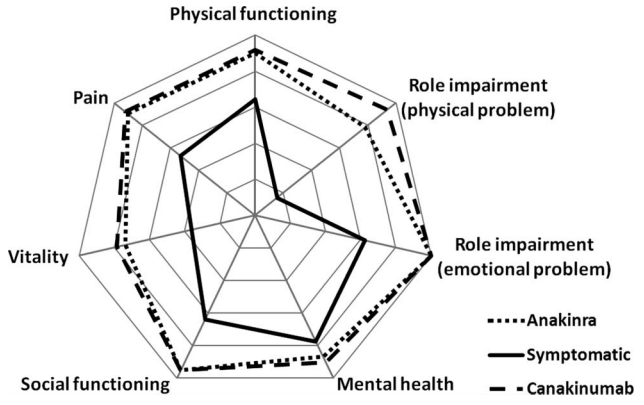

Figure 3 Quality of life (QoL) assessment. Spidergram depicting seven dimensions of the RAND-36 QoL questionnaire. Data are normalised to a scale of 0 (the worst) to 100 (excellent QoL) and the lines indicate the mean scores during anakinra treatment, symptomatic episode upon stopping anakinra, and at day 14 after the first canakinumab injection.

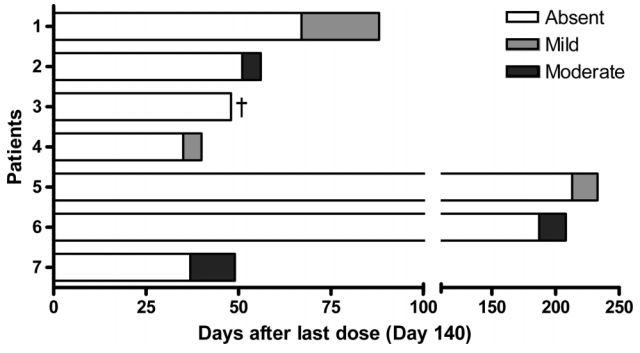

Figure 4 Time to relapse. The duration in days after the last canakinumab dose until relapse is shown for the seven patients who finished the 6-month treatment part of the trial. Four patients (patients 1, 2, 4 and 7) relapsed within the 3-month follow-up period during the trial, whereas two patients (patients 5 and 6) relapsed several months later. The cross indicates the patient who died in a traffic accident during the follow-up phase. The duration from the beginning of symptoms to clear relapse (objectified by a physician) is indicate by light grey (physician global assessment (PGA) grade 2, mild disease activity at relapse visit) and dark grey (PGA grade 3, moderate disease activity) bar endings.

Table 2 Adverse events

	No of patients with adverseevents (total N=5)
Serious adverse event	
Death in traffic accident	1
Adverse events	
Infections	
Rhinitis	2
Pharyngitis	2
Sinusitis (*Haemophilus parainfluenzae*)	1
Herpes labialis	1
Injection site reaction	1
Other	
Light-headedness	2
Hot flushes	1
Headache	1
Fatigue	1
Palpitations	1
Tinnitus	1
Vertigo	2
Anterior uveitis	1
Diarrhoea	1
Transient INR rise under anticoagulation	1
Numb feeling foot soles	1
Transient increase hair loss	1
Jaw luxation	1

INR, international normalised ratio.

studies with larger patient numbers may yield the optimal regimen. One option may be to use a higher dose or more frequent dosing for a short period of time ('loading dose') to induce a strong response followed by a lower or less frequent dosing regimen at some point to maintain that response.

Apart from a fatal traffic accident that was unrelated to the study drug, adverse events were mild and were predominantly viral upper airway infections.

To date, anakinra was the only therapy reported to be highly effective in almost all patients with Schnitzler's syndrome, but its daily injections raised the need for a more patient-friendly alternative.[4–6] Eight patients recently responded well to rilonacept, which requires weekly administration and is more expensive than canakinumab, which in turn is more expensive than anakinra.[16] Both anakinra and rilonacept block IL-1α and IL-1β, but canakinumab specifically blocks IL-1β. Consequently, this study indicates that IL-1β is the key cytokine responsible for inflammation in Schnitzler's syndrome. Therefore, the neutrophilic urticaria is also instigated by IL-1β, which is scarce in skin under normal conditions, and not by IL-1α, which is ubiquitous intracellularly in keratinocytes. IL-6 inhibition was recently also found to be effective in three patients with Schnitzler's syndrome.[17] The patients in that study were the first in which IL-1 inhibition was reported to be ineffective, which is interesting from a pathophysiological point of view and could indicate that these patients constitute a distinct subset.

The serum paraprotein concentrations were not affected by canakinumab treatment in this trial. This mirrors the absence of an effect on paraprotein concentration by anakinra, even after years of treatment (personal observation). Long-term follow-up is needed to evaluate whether IL-1 inhibition has any effect on the progression to lymphoproliferative disorders, to which patients with Schnitzler's syndrome are at risk.[1]

To conclude, in this trial, monthly 150 mg subcutaneous canakinumab was effective and well tolerated in Schnitzler's syndrome. The study demonstrated that IL-1β is pivotal in the pathophysiology of this debilitating disease.

Acknowledgements The authors would like to thank Dr E. Ton and Dr J. Tekstra, Department of Rheumatology, University Medical Centre Utrecht, The Netherlands, for referring two patients for the trial.

Contributors HDdK, JS, JWMvdM and AS were involved in the study design; HDdK, JvdV-J and MS collected the data; all authors were involved in data analysis and figure design; HDdK wrote the paper and all others commented on it.

Funding This is an investigator-initiated study, primarily funded by the Radboud University Nijmegen Medical Centre and a VIDI grant of The Netherlands Organisation for Scientific Research. Novartis supplied canakinumab free of charge and provided some financial research support.

Competing interests Novartis provided research support, including the canakinumab vials, to AS and HDdK. AS and JWMvdM received consulting fees from Novartis. The other authors have no conflicts of interest to declare.

Ethics approval The study was approved by the local medical ethical board in Arnhem-Nijmegen.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 de Koning HD, Bodar EJ, van der Meer JW, *et al*. Schnitzler syndrome: beyond the case reports: review and follow-up of 94 patients with an emphasis on prognosis and treatment. *SeminArthritis Rheum* 2007;37:137–48.
2 Lipsker D, Veran Y, Grunenberger F, *et al*. The Schnitzler syndrome. Four new cases and review of the literature. *Medicine* 2001;80:37–44.
3 Schnitzler L. Lesions urticariennes chroniques permanentes (Érythème pétaloïde). *J Dermatol Angers* 1972.
4 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.
5 de Koning HD, Bodar EJ, Simon A, *et al*. Beneficial response to anakinra and thalidomide in Schnitzler's syndrome. *Ann Rheum Dis* 2006;65:542–4.
6 Schuster C, Kranke B, Aberer E, *et al*. Schnitzler syndrome: response to anakinra in two cases and a review of the literature. *Int J Dermatol* 2009;48:1190–4.
7 Dybowski F, Sepp N, Bergerhausen HJ, *et al*. Successful use of anakinra to treat refractory Schnitzler's syndrome. *ClinExp Rheumatol* 2008;26:354–7.
8 Gran JT, Midtvedt O, Haug S, *et al*. Treatment of Schnitzler's syndrome with anakinra: report of three cases and review of the literature. *ScandJ Rheumatol* 2011;40:74–9.
9 Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, *et al*. Use of canakinumab in the cryopyrin-associated periodic syndrome. *N Engl J Med* 2009;360:2416–25.
10 Lachmann HJ, Lowe P, Felix SD, *et al*. In vivo regulation of interleukin 1beta in patients with cryopyrin-associated periodic syndromes. *J Exp Med* 2009;206:1029–36.
11 Ryan JG, de Koning HD, Beck LA, *et al*. IL-1 blockade in Schnitzler syndrome: ex vivo findings correlate with clinical remission. *J Allergy Clin Immunol* 2008;121:260–2.
12 de Koning HD, Schalkwijk J, van der Meer JW, *et al*. Successful canakinumab treatment identifies IL-1beta as a pivotal mediator in Schnitzler syndrome. *JAllergy Clin Immunol* 2011;128:1352–4.
13 Vanderschueren S, Knockaert D. Canakinumab in Schnitzler syndrome. *Semin Arthritis Rheum*. Published Online First: 17 Aug 2012. doi:10.1016/j.semarthrit.2012.06.003
14 Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. *Ann Med* 2001;33:350–7.
15 Kuemmerle-Deschner JB, Ramos E, Blank N, *et al*. Canakinumab (ACZ885, a fully human IgG1 anti-IL-1beta mAb) induces sustained remission in pediatric patients with cryopyrin-associated periodic syndrome (CAPS). *Arthritis Res Ther* 2011;13:R34.
16 Krause K, Weller K, Stefaniak R, *et al*. Efficacy and safety of the interleukin-1 antagonist rilonacept in Schnitzler syndrome: an open-label study. *Allergy* 2012;67:943–50.
17 Krause K, Feist E, Fiene M, *et al*. Complete remission in 3 of 3 anti-IL-6-treated patients with Schnitzler syndrome. *J Allergy Clin Immunol* 2012;129:848–50.

Sustained efficacy of the monoclonal anti-interleukin-1 beta antibody canakinumab in a 9-month trial in Schnitzler's syndrome

Heleen D de Koning, Joost Schalkwijk, Johanna van der Ven-Jongekrijg, Monique Stoffels, Jos W M van der Meer and Anna Simon

Ann Rheum Dis 2013 72: 1634-1638 originally published online October 19, 2012
doi: 10.1136/annrheumdis-2012-202192