EudraCT Number: 2010-020063-21

Full title of the trial: "A 20-week open-label study to assess the efficacy and safety of single doses of Ilaris® (Canakinumab, ACZ885) in patients with active, refractory urticarial vasculitis".

Publication title: Efficacy and safety of canakinumab in urticarial vasculitis: An open-label study

Publication: Journal of Allergy and Clinical Immunology JDDG, Volume 132, Number 3

Publisher: Elsevier

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DOI: 10.1016/j.jaci.2013.04.008

Efficacy and safety of canakinumab in urticarial vasculitis: An open-label study

To the Editor:

Urticarial vasculitis (UV) is a rare chronic disease characterized by persisting urticarial lesions combined with the histopathologic findings of leukocytoclastic vasculitis. UV lesions may induce burning or pain rather than pruritus and often resolve with purpura or hyperpigmentation. Also, systemic manifestations such as joint, pulmonary, gastrointestinal, and renal involvement can be found and seem to occur with a higher incidence in hypocomplementemic UV patients.[1]

UV's etiology remains unknown in most cases although connective tissue disorders, drugs, infections, and hematologic disorders may be associated with it. Treatment in limited disease includes antihistamines, nonsteroidal anti-inflammatory drugs, colchicine, and immunomodulators such as hydroxychloroquine or dapsone. In more severe and systemic disease, immunosuppressives such as corticosteroids, cyclosporine A, azathioprine, cyclophosphamide, or methotrexate can be effective but may cause side effects with long-term use.[1] None of these drugs is approved for UV, and management recommendations rely on a handful of case reports because clinical studies investigating the effects of treatment on the signs and symptoms of UV are lacking.

Recently, anakinra, a natural IL-1 receptor antagonist, completely abrogated the clinical symptoms in a patient with therapy-refractory UV.[2] IL-1 plays a key role in the pathogenesis of autoinflammatory diseases such as cryopyrin-associated periodic syndrome (CAPS).[3] Many clinical features of autoinflammatory diseases including urticarial skin lesions, arthralgias, and further systemic involvement are shared by UV. Also, serum cytokines of the IL-1 family are found to be upregulated in autoinflammatory syndromes[3] and have been proposed to also be involved in the pathogenesis of leukocytoclastic vasculitis.[4]

Canakinumab is a long-acting fully humanized monoclonal anti–IL-1β antibody approved for and highly effective in the treatment of CAPS. On the basis of the hypothesis that IL-1 also contributes to the vascular inflammation in UV, we investigated the effects of canakinumab on the clinical signs and symptoms, quality of life, inflammation markers, and cytokine levels in 10 patients with active UV.

Patients participated in this single-center investigator-initiated open-label pilot study between July 2010 and August 2011 and gave written informed consent at enrollment. The study was approved by the ethics committee of the State of Berlin (EudraCT number: 2010-020063-21) and was conducted according to the Declaration of Helsinki and the "Good Clinical Practice, Standard Operating Procedures of the Allergie-Centrum-Charité." Following a baseline period of 2 weeks, all patients were administered a single dose of 300 mg canakinumab subcutaneously (day 0) and assessed for efficacy and safety over a 16-week period at days 7, 14, 28, 56, 84, and 112.

The primary end point of our study was the change in mean UV activity score (UVAS) values from baseline (days –14 to 0) to days 15 to 28 obtained by patient daily self-assessment. The UVAS was developed as a modification of instruments previously validated for CAPS.[5] It consists of 5 subscales corresponding to the 5 key symptoms of UV: wheals, burning/pruritus, residual skin pigmentation, joint pain, and general symptoms (fatigue, exhaustion, chills, fever). Values for the subscale UVAS can range from 0 to 10 per day (0-10 for each symptom: 0 = none; 10 = very severe). Total UVAS values (0-10) were calculated by dividing the sum scores of all subscale values by 5.

Secondary end points included changes in the physician and patient global assessment of disease activity (10-point visual analog scale [VAS]) and changes in inflammation markers C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) during the 16 weeks following canakinumab treatment as compared to baseline. In addition, we monitored serum levels of the IL-1 pathway, namely, IL-1 receptor antagonist (IL-1Ra), and IL-6, using FlowCytomix Pro 2.4 according to the manufacturer's protocol (eBioscience, San Diego, Calif). These were compared with cytokine levels of 5 healthy controls. Also, changes in the patients' quality of life (QOL) assessed by the Dermatology Life Quality Index (DLQI) were evaluated. Furthermore, the safety and tolerability of canakinumab treatment were assessed by the incidence and outcome of adverse events (AEs), the routine clinical examination, and safety laboratory tests.

Details on the eligibility criteria, statistical analysis, individual patient characteristics as well as course of the study are presented in this article's Online Repository (including Table E1 and Fig E1) at www.jacionline.org.

Canakinumab single-dose treatment resulted in significant reductions in mean total UVAS from 4.0 ± 1.8 (range, 2.3-7.1) at baseline (days –14 to 0) to 2.4 ± 1.7 (range, 0.6-4.8) at days 15 to 28 ($P \leq .005$), which were maintained until the end of the study (Fig 1, *A*). On an individual basis, for 7 of 10 patients, this represented a more than 50% improvement in disease activity as assessed by the UVAS. Also, all UV subscales, except for burning/pruritus, demonstrated reductions in subscores that were significant at days 15 to 28 ($P \leq .05$) compared with baseline (Fig 1, *B-F*). The evaluation of global disease activity (VAS 0-10) showed a significant reduction in physician-based mean VAS levels at day 14 (3.8 ± 1.5; mean improvement of 41%, with 4 of 10 patients demonstrating a ≥50% improvement) compared with day 0 (6.6 ± 1.6, $P \leq .001$). Similarly, patient-reported mean VAS levels decreased from 6.8 ± 2.1 at day 0 to 4.2 ± 2.3 at day 14 ($P \leq .05$; mean improvement of 31%, with 5 of 10 patients demonstrating a ≥50% improvement) (Fig 2, *A*). Both physician and patient VAS levels remained low until the end of the study.

Inflammatory markers CRP and ESR were significantly reduced at day 7 (CRP 0.7 ± 1.1 mg/dL; ESR 15.1 ± 8.9 mm/h; for each, $P \leq .05$) compared with baseline day 0 mean levels (CRP 1.6 ± 2.2 mg/dL; ESR 25.6 ± 14.0 mm/h) (Fig 2, *B* and *C*). CRP and ESR levels remained low in 7 of 10 patients, with significant reductions in CRP levels at days 28 and 84 and in ESR levels on days 28, 56, and 112. Taken together, a complete clinical and laboratory remission (UVAS 0-1 for each subscale; CRP <0.5 mg/dL) was seen in 2 of 10 patients.

Baseline IL-1Ra serum levels ranged from 209 pg/mL to 3065 pg/mL (mean, 1340 ± 889 pg/mL). Baseline IL-6 serum levels showed a range from 6.0 pg/mL to 33.7 pg/mL (mean, 11.4 ± 8.8 pg/mL). In comparison, IL-1Ra and IL-6 levels in 5 healthy controls were below the detection level in all individuals. Following canakinumab treatment, there was a nonsignificant and transient decrease in mean IL-1Ra levels while mean IL-6 levels were found to be significantly reduced at day 7 than at day 0 ($P \leq .05$) and remained at low levels until the study end (see Fig E2 in this article's Online Repository at www.jacionline.org).

Health-related QOL assessment demonstrated a significant decrease in DLQI scores from 9.2 ± 2.9 (moderate QOL

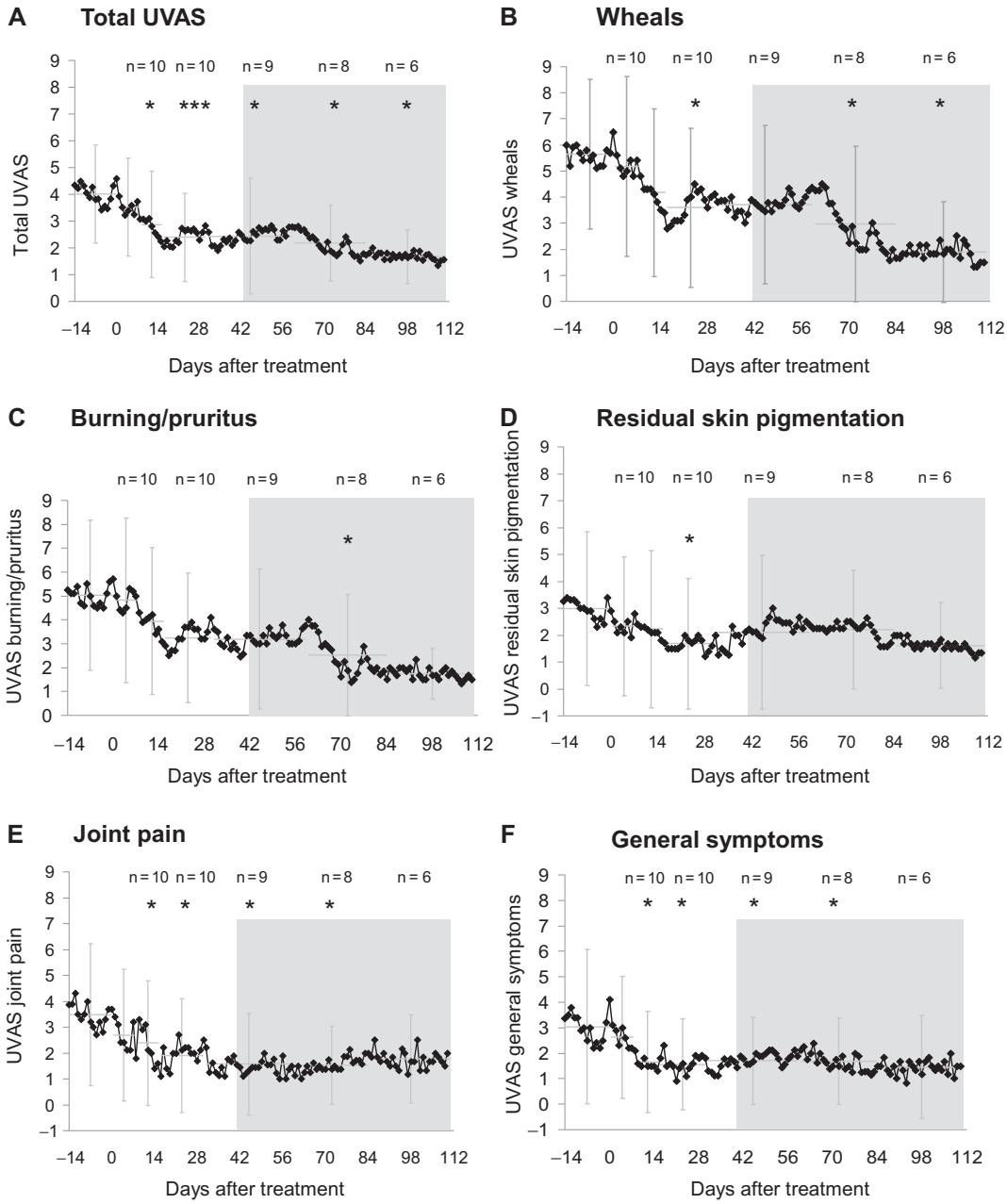

FIG 1. Mean patient-reported total **(A)** and subcategory **(B-F)** UVAS (range, 0-10) during the study period. The horizontal lines show mean values at baseline, days 0 to 7, days 8 to 14, days 15 to 28, days 29 to 56, days 57 to 84, and days 85 to 112. $*P \leq .05$ and $***P \leq .005$ relative to baseline (days –14 to 0).

impairment) at day 0 to 5.8 ± 5.0 (little QOL impairment) at day 14 ($P \leq .05$; mean improvement of 40%, with 5 of 10 patients demonstrating a ≥50% improvement) (see Fig E3 in this article's Online Repository at www.jacionline.org). In addition, a significant correlation of the changes (baseline vs days 15-28) in DLQI scores with the respective changes in total UVAS could be observed ($r = 0.643$; $P \leq .05$).

Canakinumab treatment was well tolerated without serious AEs reported. For further details regarding safety and tolerability, please refer to the Online Repository.

Our study is the first clinical trial in patients with UV and also the first one that studied the use of canakinumab in UV. By using the UVAS, a patient-reported disease activity score of 5 key UV symptoms, we could show a significant improvement in skin symptoms, joint pain, and general symptoms following canakinumab treatment. The clinical response was paralleled by significant reductions in all other outcome measures including physician and patient global assessment of disease activity, inflammation markers, QOL assessment, and cytokine levels. Given that standardized disease activity instruments in UV are lacking, our results support UVAS as a suitable instrument for measuring disease activity in this condition.

The high levels of cytokines IL-1Ra and IL-6 in our patients and their (at least for IL-6 significant) reduction following

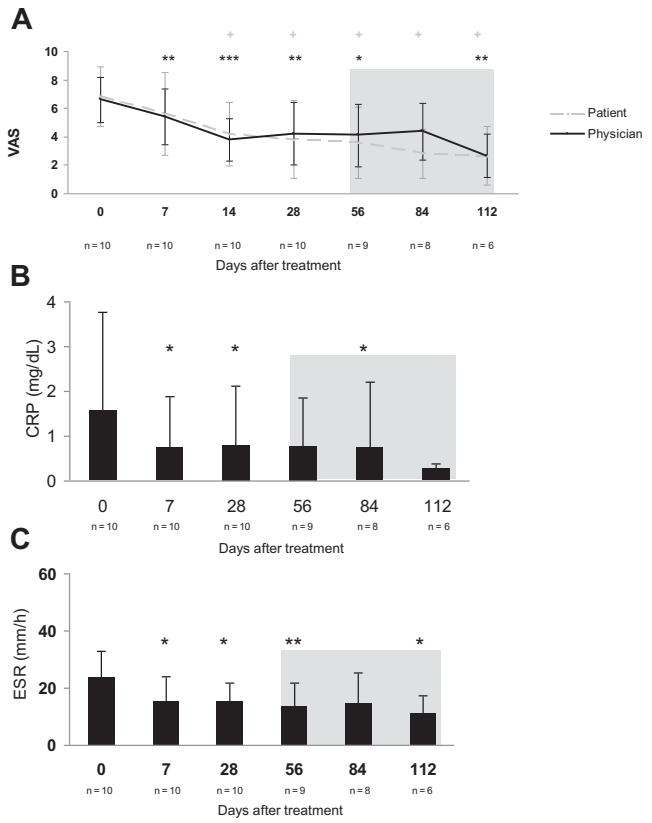

FIG 2. Physician- and patient-reported global assessment of mean disease activity (VAS 0-10) **(A)** and mean inflammation markers CRP (Ref. < 0.5 mg/dL) **(B)** and ESR (Ref. < 20 mm/h) **(C)** over the study period. *P* values are relative to baseline (day 0). $*^{,+}P \leq .05$, $**P \leq .01$ and $***P \leq .005$.

anti–IL-1 blockade are consistent with earlier studies in autoinflammatory syndromes[3] and support a pathogenic function for IL-1Ra and IL-6 in UV. However, given that canakinumab treatment did not result in complete symptom control in most patients, IL-1β is not likely the exclusive mediator of UV. Our results confirm and complement the findings of a 2012 case report showing elevated IL-6 levels and a favorable clinical response to anti–IL-6 treatment in a patient with UV associated with cutaneous lupus erythematosus.[6] It may be speculated that UV contains both autoimmune and autoinflammatory aspects similar to other inflammatory disorders such as Behçet's disease.[7] The reduction in IL-6 levels we observed after canakinumab treatment suggests that IL-6 acts downstream of IL-1β activation. Nevertheless, further mechanistic studies are needed to better characterize the role of cytokines in the pathogenesis of UV.

The assessment of QOL by the DLQI, a validated QOL instrument, revealed moderate to severe QOL impairment in all untreated patients. The mean DLQI levels reported for our study (9.2) were comparable with those seen in other chronic skin conditions including psoriasis (8.8), pruritus (10.3), and chronic urticaria (9.9).[8] The difference in mean DLQI scores (3.4) between baseline and day 14 after canakinumab administration exceeded the minimal important difference (2.24-3.10) reported for patients with chronic urticaria,[9] indicating a substantial and relevant QOL improvement in our patients. Also, the magnitude of DLQI improvement is consistent with that reported from other chronic skin diseases treated with biologics.[8]

Conventional UV treatments such as immunosuppressives can be associated with considerable side effects. In our study sample, single-dose canakinumab treatment showed only a few nonserious AEs. Canakinumab may, therefore, be a reasonable treatment alternative, especially in patients with comorbidities in whom immunosuppressive therapies are unwarranted.

A limitation of this trial is the open-label study design with only 10 patients receiving a single dose of canakinumab. This study design was chosen on the basis of (1) the little known evidence concerning the efficacy of anti–IL-1 treatment in UV, (2) the rarity of the disease with small available patient numbers, and (3) the incalculable risk of dropouts due to disease exacerbation in a placebo-controlled trial with many patients receiving immunosuppressives before entering the study. Repeated dosing efficacy or long-term safety of canakinumab was not studied. Also, there was only 1 patient with hypocomplementemic UV included in the study. This patient responded to anti–IL-1 treatment but demonstrated a greater disease activity and higher inflammation markers than did normocomplementemic patients, which is in line with previous reports.[1] Whether or not there are differences in treatment responses between normo- and hypocomplementemic UV patients needs to be investigated.

This study supports canakinumab as a potential effective treatment in UV. Given the relative longevity of efficacy observed with a single dose in this trial, canakinumab could be an ideal agent to evaluate disease-modifying qualities in longer trials. Our results also suggest that IL-1 contributes to the pathogenesis in UV. Anti–IL-1 blockade requires further evaluation including the analysis of long-term effects and safety of canakinumab in larger patient samples with UV.

We thank Marina Frömming, Hesna Gözlükaya, and Nikki Rooks for excellent technical assistance and Klaus Lenz for statistical support.

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This study was supported in part by a grant from Novartis Pharma GmbH.

Disclosure of potential conflict of interest: K. Krause has received one or more payments for lecturing from or is on the speakers' bureau for Novartis Pharma GmbH. M. Maurer has received one or more consulting fees or honoraria from Sobi, Novartis Pharma GmbH, and Regeneron. K. Weller has received one or more payments for lecturing from or is on the speakers' bureau for Novartis Pharma GmbH. T. Zuberbier has received one or more consulting fees or honoraria from Ansell, Bayer Schering, DST, Fujisawa, HAL, Henkel Kryolan, Leti, MSD, Novartis, Procter and Gamble, Sanofi-Aventis, Schering-Plough, Stallergenes, and UCB. The rest of the authors declare that they have no relevant conflicts of interest.

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Defective T_H17 development in human neonatal T cells involves reduced RORC2 mRNA content

To the Editor:

The neonatal immune system shows a different response on activation when compared with the adult system.[1] Several mechanisms contribute to this phenomenon, which involves both functioning of the innate system[2] and adaptive mechanisms of the immune system[3] of which the T_H2 bias has been investigated intensively. We previously showed an important role for human regulatory T (Treg) cells[4] in modulation of immune activation in the neonatal setting, which is induced by the interaction between antigen-presenting cells (APCs) and naive T cells. Especially programmed death-1 ligation by programmed death-L1 contributes significantly to the induction of Treg cells from human cord blood (CB)-derived precursors.[4]

T_H17 and Treg cells have a reciprocal development pathway.[5] Both cells play an important role in the induction and perpetuation of inflammatory responses during infection, and also in the pathogenesis of autoimmune and allergy-related diseases. On T-cell activation in the presence of TGF-β, both signature transcription factors for T_H17 and Treg-cell lineage are upregulated: retinoid acid–related orphan receptor (ROR) γT for T_H17 cells and forkhead box (FOXP) 3 for Treg cells. In the absence of proinflammatory cytokines, FOXP3 dominates RORγT function and prevents T_H17 development. Because of the propensity of Treg-cell induction in CB, we hypothesized there to be a regulatory mechanism in CB that inhibits T_H17 cell development in neonatal T cells derived from CB cells as compared with adult peripheral blood (APB) cells. Activation of $CD4^+CD25^-CD45RO^-$ T cells in the presence of APCs (see this article's Methods section in the Online Repository at www.jacionline.org) shows increased numbers of $FOXP3^+$ cells in the CB (shown to be functional Treg cells earlier[4]) than in the APB (Fig 1, *A* and *D*). IL-17 production, however, was not observed in the CB (Fig 1, *A* and *B*). Replacement of APCs by anti-CD28 antibody prevented T_H17 induction in the APB (see Fig E1, *A*, in the Online Repository at www.jacionline.org). The lack of IL-17, IL-21, IL-22, and GM-CSF (Fig 1, *C*) in the supernatants of CB cell cultures confirms that T_H17 phenotype is not induced in the CB after TCR stimulation. Other key cytokines, including IFN-γ and IL-13, were also reduced in CB cell cultures than in APB cells (Fig E1, *B*), confirming earlier work.[6] IL-21 and IL-22 in the APB were only partly derived from IL-17–producing cells (Fig E1, *C*).

T_H17 cells may derive from any naive T cell when activated in a conductive cytokine milieu, or from a defined precursor cell. In humans, $CD161^+CD4^+$ T cells are thought to be such precursors to the T_H17 cell lineage.[7] It has also been suggested that T_H17 cells more readily develop from $CD45RO^+$ memory T cells.[8] Therefore, we tested whether memory cell contamination within

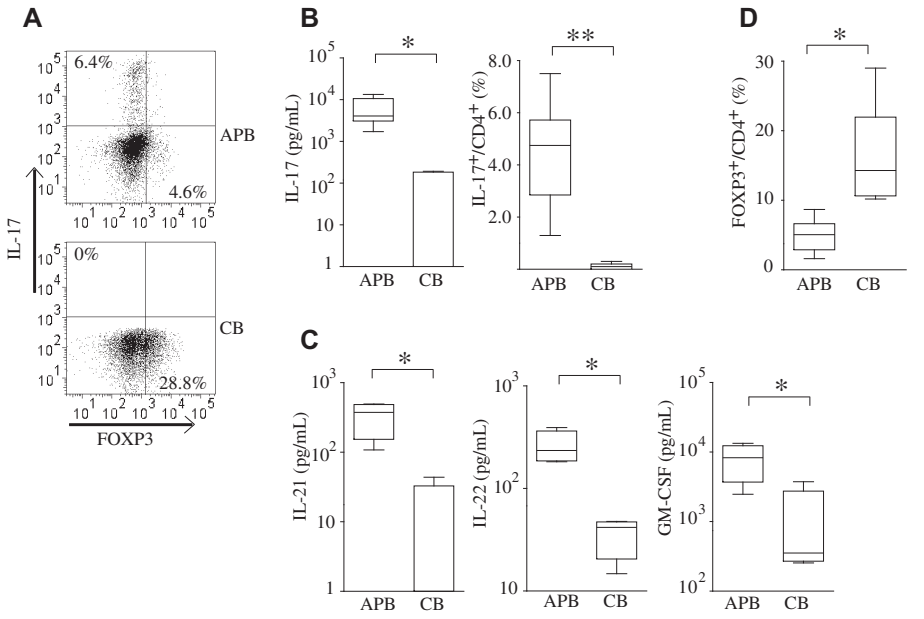

FIG 1. CB T cells are deficient in T_H17 development but do upregulate FOXP3. APB and CB-naive T cells were activated by plate-bound anti-CD3 in the presence of viable APC for 6 days. $IL\text{-}17^+$ and $FOXP3^+$ $CD4^+$ T-cell numbers were assessed by flow cytometry. **A,** Representative cytometry plots. **B,** Supernatant IL-17 concentration (n = 8) and percentage of $IL\text{-}17^+$ CD4 cells (n = 8 APB, n = 5 CB). **C,** Supernatant IL-21, IL-22, and GM-CSF (n = 4 APB, n = 5 CB). **D,** Percentage of $FOXP3^+$ $CD4^+$ cells (n = 8). $^*P < .05$ and $^{**}P < .01$, Mann-Whitney *U* test.

METHODS

Eligibility criteria

To be included in the study, patients had to fulfill the following diagnostic criteria of UV: (1) urticarial rash with individual lesions persisting for more than 24 hours and (2) UV confirmed by biopsy from lesional skin showing signs of leukocytoclasis (fragmentation of neutrophils with nuclear dust) and/or fibrinoid deposits in perivascular and interstitial locations.[E1] Participation in the study required active UV and insufficient response to treatment with antihistamines, nonsteroidal anti-inflammatory drugs, and/or immunomodulating or immunosuppressive drugs. Exclusion criteria included the absence of chronic infections such as tuberculosis, HIV, or hepatitis, malignancies within 5 years prior to enrolment, and pregnancy. Patients were also excluded if they suffered from further active systemic inflammatory diseases or were concurrently treated with other biologics, immunomodulating or immunosuppressive drugs including corticosteroids (>10 mg/d prednisolone equivalent).

Statistics

Descriptive statistics were used for demographic data and patient characteristics. For the analysis of clinical outcomes (UVAS, physician-based and patient-based global assessment) as well as inflammatory markers, cytokines, and DLQI, parametric tests (2-tailed *t* test) were applied. Correlation analyses were performed by using Pearson's correlation coefficient. A *P* value of less than .05 was considered to indicate statistical significance. Missing values were not replaced.

RESULTS

Safety and tolerability

There were no serious AEs reported, but a total of 9 nonserious AEs of mild to moderate severity were reported in 6 patients. These included 3 respiratory tract infections, 1 fever, and 5 laboratory abnormalities (transiently elevated liver enzymes and cholesterol levels, neutropenia). Apart from the mild neutropenia, which was possibly related to study drug administration, there was no suspected causal relationship for any other AE. The administration of canakinumab injections was well tolerated without reported injection site reactions.

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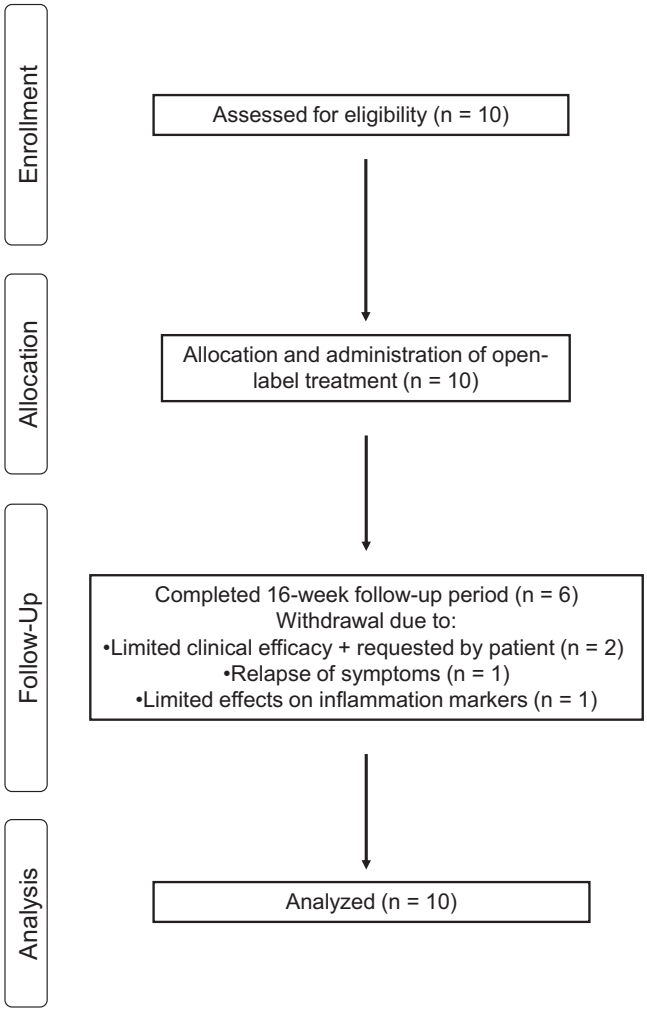

FIG E1. Consort study flowchart. A total of 6 patients completed all study visits. Four patients prematurely terminated the study. Reasons for discontinuation were a limited and decreasing clinical response to treatment paired with the patients' request for early termination (2 patients, weeks 8 and 12), early relapse of symptoms after initial good response (1 patient, week 4), and despite clinical improvement limited effects on inflammation markers (1 patient, week 12).

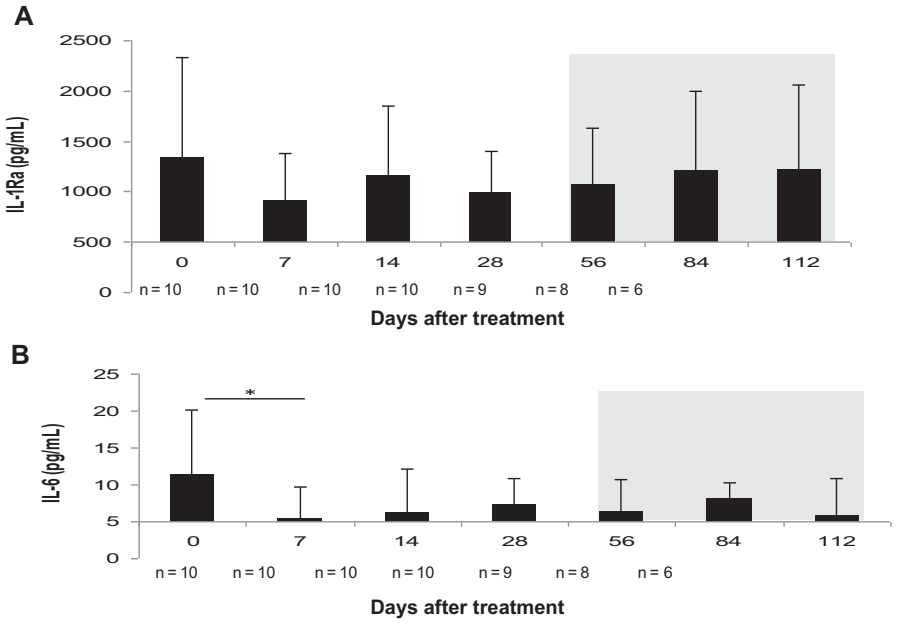

FIG E2. Mean levels of cytokines IL-1Ra **(A)** and IL-6 **(B)** over the study period. Reductions in IL-1Ra and IL-6 levels from baseline to day 7 correlate well ($r = 0.706$; $P \leq .05$). $*P \leq .05$.

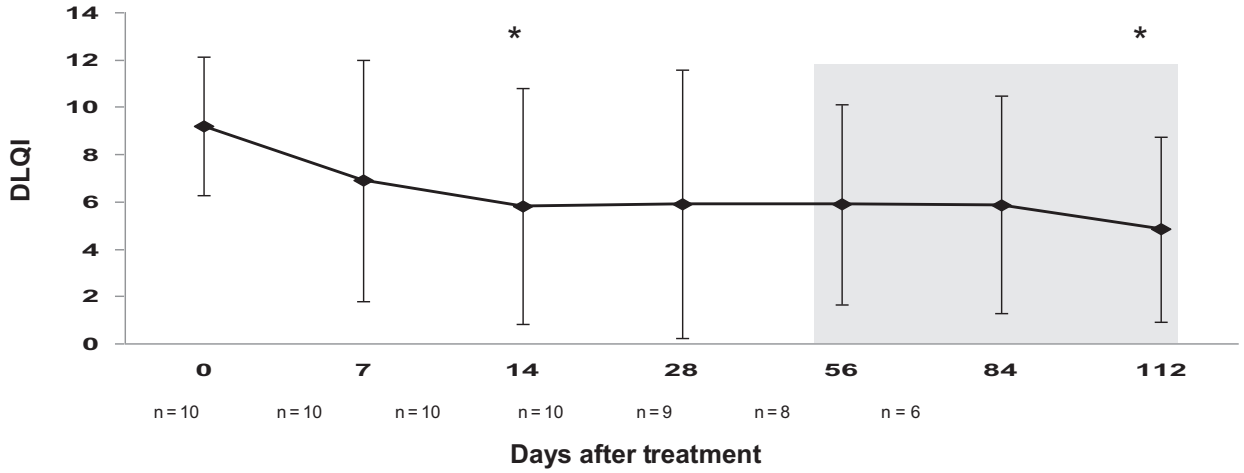

FIG E3. Mean QOL scores (DLQI) over the study period. The DLQI measures QOL impairment during the previous 7 days. It can range from a score of 0 (no QOL impairment) to 30 (very severe QOL impairment). DLQI subscores contain the subheadings *symptoms/feelings, daily activities, leisure, work/school, personal relationships,* and *treatment. P* values are relative to baseline (day 0). $*P \leq .05$.

TABLE E1. Individual patient characteristics

Patient no.	Sex	Age (y)	Disease duration (y)	Previous treatment	Hypocomplementemia (C3c↓ and/or C4↓)	Baseline CRP (mg/dL)/ESR (mm/h)
1	F	57	24	Antihistamines Dapsone	—	0.77/38
2	M	48	3	Antihistamines Corticosteroids Dapsone Hydroxychloroquine Ciclosporin	—	2.37/25
3	F	51	3	Antihistamines Corticosteroids	X	7.43/50
4	F	59	11	Dapsone Cyclophosphamide Hydroxychloroquine Corticosteroids Thalidomide	—	0.26/4
5	F	61	14	NSAIDs Corticosteroids Dapsone Hydroxychloroquine Chloroquine Thalidomide Azathioprine Cyclophosphamide	—	0.13/11
6	F	66	5	Antihistamines Corticosteroids Dapsone Azathioprine	—	0.22/30
7	F	41	1	Antihistamines NSAIDs	—	1.30/27
8	F	45	14	Antihistamines Corticosteroids	—	0.37/11
9	F	34	5	Antihistamines Corticosteroids	—	2.08/24
10	F	77	10	Antihistamines Corticosteroids Dapsone MTX	—	0.70/36

F, Female; *M*, male; *MTX*, methotrexate; *NSAIDs*, nonsteroidal anti-inflammatory drugs.