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PII: S2213-2198(20)30826-6

DOI: <https://doi.org/10.1016/j.jaip.2020.07.058>

Reference: JAIP 3056

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 2 May 2020

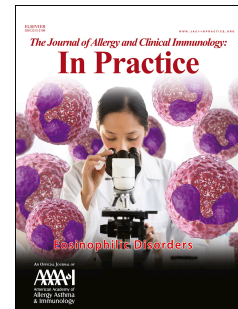
Revised Date: 17 July 2020

Accepted Date: 23 July 2020

Please cite this article as: Maul JT, Distler M, Kolios A, Maul LV, Guillet C, Graf N, Imhof L, Lang C, Navarini AA, Schmid-Grendelmeier P, Canakinumab Lacks Efficacy in Treating Adult Patients with Moderate to Severe Chronic Spontaneous Urticaria in a Phase II Randomized Double-blind Placebo-controlled Single Centre Study, *The Journal of Allergy and Clinical Immunology: In Practice* (2020), doi: <https://doi.org/10.1016/j.jaip.2020.07.058>.

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Canakinumab Lacks Efficacy in Treating Adult Patients with Moderate to Severe Chronic Spontaneous Urticaria in a Phase II Randomized Double-blind Placebo-controlled Single Centre Study

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Conflict of interest:

- Maul JT is an employee of USZ and holds a “Filling the GAP” scholarship. J-T Maul has served as advisor and/or received speaking fees and/or participated in clinical trials sponsored by AbbVie, Ammirall, Amgen, BMS, Celgene, Eli Lilly, LEO Pharma, Janssen-Cilag, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi, UCB.
- Distler M has no conflicts of interest
- Kolios A has served as an investigator, speaker, and/or advisor for AbbVie, Abbott, Janssen, Eli Lilly, MSD, Pfizer, Celgene, Novartis, Actelion, Leo, Amgen, and Alk-Abello; Dr. Kolios does not hold any shares or other financial interest in any related pharmaceutical company.
- Maul LV has served as advisor and/or received speaking fees and/or participated in clinical trials sponsored by Amgen, BMS, Celgene, Eli Lilly, MSD, Novartis, Pierre Fabre, Roche, Sanofi.
- Guillet C has no conflicts of interest
- Graf N has no conflicts of interest
- Imhof L is Advisory board member for Galderma
- Lang C has no conflicts of interest
- Navarini AA is funded by the Promedica and Bruno-Bloch Foundation, as well as Hochspezialisierte Medizin 2 of the Kanton Zürich, Switzerland. He is also on the advisory board of AbbVie, Pfizer, Novartis, Celgene, MSD, Galderma.
- Schmid-Grendelmeier P has investigator, speaker or advisor for Novartis Pharma. In addition, he has received honoraria as speaker and/or advisor from AbbVie, AstraZeneca, Bühlmann Labs, CSL, GSK, Leo, Roche, Takeda and Thermo Fisher Diagnostics.

Acknowledgment of funding: Supported by Novartis Pharma Switzerland

Abstract:**Background:**

Chronic spontaneous urticaria (CSU) is a common disease with a significant proportion of patients that do not respond to standard therapy with antihistamines and optionally corticosteroids/immunosuppressants.

Objective:

The IL-1 β antagonist canakinumab is effective in cryopyrin associated periodic syndromes (CAPS) associated with urticarial symptoms and urticarial vasculitis, so it was suspected that it could also be effective in patients with CSU.

Methods:

The effect of canakinumab was investigated in 20 patients with moderate to severe CSU in a 1:1 randomization to either canakinumab or placebo in a double-blind single-dose crossover design. The verum group received 150 mg canakinumab subcutaneously once at baseline. Patients who had received placebo were able to switch to canakinumab at week 4 if they did not improve. Primary endpoint was clinical UAS7 improvement at week 4 compared to baseline.

Secondary endpoints were the clinical UAS7 improvement at week 8 and the clinical improvement measured by the physician score and DLQI at week 1, 2, 4, and 8.

Results:

At week 4 two patients with canakinumab and three with placebo met the primary endpoint so that canakinumab failed the significant superiority to the placebo ($p=1.0$). An inclusion of the patients who switched to canakinumab after four weeks did not alter the result. There was also no significant difference between the verum and placebo groups for all secondary endpoints. The therapy was well tolerated, and mild AEs were equally distributed between verum and placebo.

Conclusion:

Due to this clinical trial with 20 patients, it must be assumed that canakinumab has no effect on lesions of CSU. In conclusion, this suggests that IL1 β may not play a crucial role in pathology of CSU patients, unlike e.g. in hereditary fevers or urticarial

vasculitis, where targeting IL 1 is a main treatment option. However, the good tolerability of canakinumab could be confirmed.

Highlights box

1. What is already known about this topic? Canakinumab works in urticarial due to autoinflammatory syndrome and urticarial vasculitis.

2. What does this article add to our knowledge? Canakinumab does NOT work in chronic spontaneous urticarial.

3. How does this study impact current management guidelines? IL-1 antagonists such as canakinumab should not be recommended in CSU guidelines.

Key words: Urticaria, therapy outcome, canakinumab, IL-1 β antagonist

LIST OF ABBREVIATIONS

AE	Adverse Event
AE-QoL	angioedema quality of life questionnaire
CAPS	cryopyrin-associated periodic syndrome
CSU	Chronic idiopathic urticaria/ Spontaneous urticaria
CU-Q2oL	Chronic Urticaria Quality of Life Questionnaire
DLQI	Dermatology Life Quality Index
DPU	delayed pressure urticaria
MWS	Muckle Wells syndrome
UAS	urticaria activity score
UCT	urticaria control test
TRS	Therapeutic Response Score
URTICANA	Urticaria and Canakinumab

1. Introduction

Chronic idiopathic urticaria (CSU) is a common disease affecting 0.5-1% of the population throughout the whole lifespan (1, 2). Spontaneous urticaria (CSU) is defined by pale or reddened irregular wheals (hives), angioedema or both for ≥ 6 weeks, with or without an identifiable trigger (3). The standard therapy of H1-antagonists often used in combination with leukotriene antagonists is sufficient to control the disease of most patients. If the symptoms persist for 2 weeks, the dosage of modern second-generation antihistamines is increased up to four-fold of the regular dosage. The third-line treatment includes the therapeutic escalation with omalizumab, cyclosporine A and montelukast. Systemic corticosteroids may be used for up to ten days at any time if exacerbation demands it (3).

However, not all patients with CSU are responsive to antihistamines and in some refractory cases, immunosuppressive therapy is equally ineffective or the patients cannot tolerate the pronounced side effects (4-8). Omalizumab, a therapeutic monoclonal anti-IgE antibody, is also a therapeutic option for the treatment of chronic spontaneous urticarial and allergic asthma. The clinical onset of efficacy of omalizumab within 4 weeks is an effective therapeutic alternative in many cases but also not always sufficiently effective (9).

There is growing evidence that the inflammasome and IL-1 β play a role in the pathogenesis of neutrophilic diseases like the cryopyrin-associated periodic syndrome (CAPS). In mice, mast cells carrying the NLRP3 mutation secrete IL-1 β and promote neutrophil recruitment and vascular leakage in the skin, both histological characteristics of the urticarial rash in CAPS (10).

The IL-1 β antagonist canakinumab is approved for cryopyrin-associated periodic syndrome (CAPS), a group of inherited disorders caused by mutations of the NLRP3-

gene (NACHT, LRR and PYD domains-containing protein 3) leading to inflammasome activation (11, 12), which includes Muckle–Wells syndrome (MWS) and others, where their one cutaneous leading symptom is urticaria. Cutaneous histopathological features are similar to chronic idiopathic urticaria (13). Most patients with MWS respond well to canakinumab concerning their cutaneous involvement.

The pathological similarities between the urticarial rash in the MWS and CSU suggest that canakinumab might be also efficacious in refractory CSU cases. This study is designed to evaluate the therapeutic effect of canakinumab in patients with CSU.

The burden of CSU is essential and affects not only the patient itself but also their families and furthermore the healthcare system. The use of patient-reported outcome measures such as the urticaria activity score (UAS), the angioedema activity score (AAS), the chronic urticaria quality of life questionnaire (CU-Q2oL), the angioedema quality of life questionnaire (AE-QoL) and the urticaria control test (UCT) in studies and clinical practice has helped to better define the effects and impact of CSU on patients (14, 15).

2. Methods

a. Patients

Twenty adult patients (age ≥ 18 years) with clinically and investigator-initiated confirmed CSU were enrolled in this monocentric prospective randomized double-blind placebo-controlled trial. All fulfilled the inclusion criteria (Appendix S1; see Supporting Information) and signed an informed consent. Adult patients with CSU participated in this monocentric prospective randomized double-blind placebo-controlled single dose trial at the University Hospital Zurich between 2012 and 2015. The study was approved by the local ethic committees of Zurich and was conducted according to the Declaration of Helsinki. The study is registered at ClinicalTrials.gov NCT01635127.

b. CSU Assessments

The UAS7 is used to assess the CSU symptoms such as number of wheals and intensity of itch during 7 consecutive days. Therefore, patients keep a diary which contains the daily medication. From this data the UAS7 was calculated at each visit to determine the disease activity and the response to treatment. The UAS7 (16) is the sum of the daily UAS (Urticaria activity) scores over 7 days (scale 0-42). The daily UAS is a composite score (scale, 0-6) calculated as the sum of the daily scores for severity of itch (0, none; 1, mild; 2, moderate; and 3, severe) and number of hives (0, none; 1, 1-6 hives; 2, 7-12 hives; and 3, >12 hives).

Additionally, a Likert-type Physician Severity Score Assessment (17) with a scale from 0 to 3 (0 corresponds to absent urticaria, 1 mild, 2 moderate and 3 severe), a Therapeutic Response Score (TRS) and a Dermatology Life Quality Index (DLQI) were collected at each visit.

c. Study procedures

Patients started with a run-in-period of one week collecting the UAS7- and a daily medication score (antihistamines and corticosteroids). After one-week period patients have been 1:1 randomized to either one shot 150 mg canakinumab or placebo s.c. at baseline (visit 2) (Fig.1., Tab.E2). At weekly visits, the scores mentioned above were recorded over four weeks. In the absence of response, (defined as reduction of the UAS7 score of at least 20% of the initial value, and/or reduction of the Likert-type Physician Severity Score Assessment of at least 1 point), there was the possibility of unblinding the patients after four weeks. Patients who were randomized to the placebo group were then switched to the canakinumab arm. The scores from these patients were collected weekly for four weeks. Patients who have been on canakinumab already had one last visit eight weeks after medication was given.

Primary endpoint of the study was clinical improvement at week 4 defined as a reduction in UAS7 $\geq 50\%$.

Secondary endpoints were clinical remission at week 4, defined as UAS7 = 0, reduction of the Likert-type Physician Severity Score Assessment by at least 1 point compared to baseline and clinical improvement in the DLQI compared to baseline.

>>>> Please insert Fig. 1 here <<<<<<<<

d. Statistical analysis

The difference of clinical remission and improvement (e.g. including the UAS7) between the two treatment groups was tested with a chi-square test or a Fisher's

exact test if number of expected frequencies was <5 in at least one cell. The difference in clinical improvement by DLQI was compared with an exact Mann-Whitney U test.

The results of randomized canakinumab (baseline to week 4) and the open label canakinumab after switch from placebo (week 4 to week 8) were pooled and tested against placebo (baseline to week 4). Moreover, an exact McNemar's test was performed for patients who switched to canakinumab to compare week 0-4 with week 4-8.

Values of canakinumab from baseline to week 1, 2 and 4 and from week 4 to week 5, 6 and 8 were also pooled and tested against placebo from baseline to week 1, 2, and 4. Moreover, an exact McNemar's test or an exact Wilcoxon test, respectively, was performed for patients who switched to canakinumab to compare week 1, 2 and 4 to week 5, 6 and 8.

In all tests p values of $p < 0.05$ were considered significant.

3. Results

a. Study population

A total of 29 patients with moderate to severe CSU were screened, whereof nine were screening failures (see appendix) in most cases due to lack of symptoms with an UAS7 < 21 (see below) or a positive Quantiferon test. However, 20 patients were included in the clinical trial. These were randomized 1:1 either to the canakinumab (n=10) or the placebo group (n=10). All patients completed the study and were followed up until week 8. A total of 6 patients violated the inclusion criteria (UAS7 ≤ 21 at run-in) but have also been included in all analyses. Patient demographics are shown in **Error! Reference source not found..**

In the canakinumab group the mean age was 42.2 +/- 17.89, the mean disease duration 2.73 years +/- 2.62 and there were more female than male patients (6:4) included.

b. Primary endpoint

The primary endpoint of this trial failed as no effect of canakinumab on CSU could be detected. An improvement in UAS7 at week 4 defined as reduction in UAS7 ≥ 50% was seen in two patients in the canakinumab and three patients in the placebo group (p=1.00) (Fig. 2.). This result did not change when patients who switched from placebo to canakinumab were included. Including the pooled data, four patients on canakinumab and three patients on placebo met the primary endpoint (p=1.00).

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c. Secondary endpoint

The secondary endpoints were also failed as there was no significant clinical improvement in the UAS7 or Likert-type Physician Severity Score Assessment at week 1, 2, 4 or 8 comparing the canakinumab and the placebo group. Also, the inclusion of patients who switched from placebo to canakinumab at week four did not alter the results (see appendix).

Furthermore, there was no significant clinical improvement in the DLQI, another secondary endpoint measure, comparing the treatment groups in week 1, 2, 4 or 8. The difference to baseline DLQI was 0.00 ($p = 0.752$) at week 1 in both arms, and in the pooled analysis 1.00 in the canakinumab group versus 0.00 in placebo ($p = 0.757$) (Fig. 3). At week 2 there was a difference of -1.00 in the canakinumab group compared to 0.00 in the placebo group ($p = 0.795$), and in the pooled analysis 2.00 in the canakinumab group compared to 0.00 in the placebo group ($p = 0.760$). At week 4, the difference was 1.00 in the verum group versus 0.50 in the placebo group ($p = 0.616$), in the pooled analysis 0.00 in patients on canakinumab versus 0.50 in patients on placebo ($p = 0.846$), in week 8 was the difference 1.00 in patients on canakinumab versus 0.00 in patients on placebo ($p = 0.558$).

Furthermore, there was no significant clinical improvement in the DLQI, another secondary endpoint measure, comparing the treatment groups in week 1, 2, 4 or 8. The difference to baseline DLQI in week 1, 2, 4 is 0, -1 and 1 in the canakinumab group versus 0, 0 and 0.5 in the placebo group. The difference in the pooled analysis is 1, 2, 0 in the canakinumab group and 0, 0, 0.5 in placebo group, respectively.

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264 **d. Adverse Events**

265 Canakinumab treatment was well tolerated without serious adverse events (AEs)
266 reported. There was also no significant difference between canakinumab and
267 placebo concerning safety. All adverse events were classified as mild and unrelated
268 to study medication. There also no difference between both arms concerning type or
269 distribution of the adverse events. Overall, serious adverse events, deaths or
270 pregnancies did not occur.

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4. Discussion

The management of CSU unresponsive to conventional therapy is challenging even though antihistamines can be used in an up to fourfold dose as first- and second-line treatment. The escalation with omalizumab, cyclosporine, montelukast and systemic steroids is widely considered to be the third-line therapy as cases unresponsive to this regimen are common. Other very promising substances for CSU are currently investigated or already in clinical use. Among others there are new treatment options for patients with CSU include IgG1 anti-IgE monoclonal antibodies (ligelizumab), chemoattractant receptor-homologous molecule expressed on TH2 cells antagonists (AZD1981), Bruton tyrosine kinase inhibitors (fenebrutinib), anti-siglec-8 monoclonal antibody (AK002), and topical spleen tyrosine kinase inhibitors (18).

Anakinra, an IL-1 receptor antagonist has been shown to be effective in a limited number of cases of delayed pressure urticaria (DPU), but also in Schnitzler's syndrome and CAPS (19). However, no reports about effectiveness in CSU without vasculitis are available or ongoing to our knowledge.

Furthermore, TNF-antagonist working in similar pathways were also shown to improve some special forms of urticaria in case series, namely in DPU (20).

Canakinumab is a fully humanized monoclonal anti-IL-1 β antibody approved for the treatment of CAPS (12, 21, 22) which has no cross-reactivity with other IL-1 family members (23). Therapeutic effects had also been shown in systemic juvenile idiopathic arthritis and therapy-refractory gout (24), Schnitzler syndrome (22), pyoderma gangrenosum (25) and in urticarial vasculitis (26).

Due to the clinical similarities in these diseases such as skin manifestations, it has been suggested that canakinumab may also have an effect on the symptoms of CSU.

Our study is the first in human clinical trial to investigate the efficacy of canakinumab in patients with CSU. Unfortunately, canakinumab was not efficacious to significantly reduce disease activity in CSU patients including objective and subjective measures. Consequently, the primary as well as the secondary endpoint were not reached. Moreover, none of all measured urticaria activity parameters was significantly different between canakinumab and placebo or even indicated a trend. Taken both study arms together, only one placebo patient experienced complete remission which can be interpreted as a spontaneous remission. However, canakinumab was generally well tolerated and no serious adverse events were observed. A limitation of this trial is the open label study design with only 20 patients receiving a single dose of canakinumab.

In contrast, the vasculitis study supports canakinumab as a potential medication to treat urticarial vasculitis. In that clinical trial, canakinumab was also given as a single dose which resulted in a long-lasting efficacy for up to 112 days (26).

Due to the clear lack of efficacy in all measured parameters, it can be assumed that canakinumab has no effect on CSU lesions. Although our study with a total number of 20 patients was rather small.

We would like to highlight the importance of treating CSU patient's refractory to conventional therapies with molecules with proven efficacy, especially when the high cost therapies are not supported on evidence-based studies.

In about 30-40% of cases with chronic urticarial symptoms where other organs such as gastro-intestinal, cardiovascular or neurological tract are involved, it might be that drugs like canakinumab have additional beneficial effects. However, such effects were not part of our study.

In conclusion, our investigator-initiated study suggests that IL-1 β does not play a crucial role in the pathology of the majority of CSU patients, unlike e.g. in hereditary fevers or urticaria vasculitis (26), where influencing IL1 is a key target in the therapy. The good tolerability of canakinumab could be confirmed again. Conclusively, our study advocates against the use of canakinumab in therapy-refractory cases of CSU without other associated symptoms due to lack of efficacy. However, in cases of urticarial vasculitis or signs of auto inflammatory diseases it might be an option worth to consider.

330

331 **Acknowledgments**

332 We would like to thank all patients for their voluntary participation in this study.

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Figure legends:

Fig.1. Flowchart of Methods: study enrolment. Patient inclusion and exclusion flow diagram of the URTICANA trial. Analyzing placebo versus canakinumab in patients with USU.

Fig. 2: UAS7 difference to baseline. Boxplots show median, first and third quartile, upper/lower whisker extends from the hinge to the largest/smallest value no further than $1.5 * IQR$ from the hinge, and dots indicate outliers.

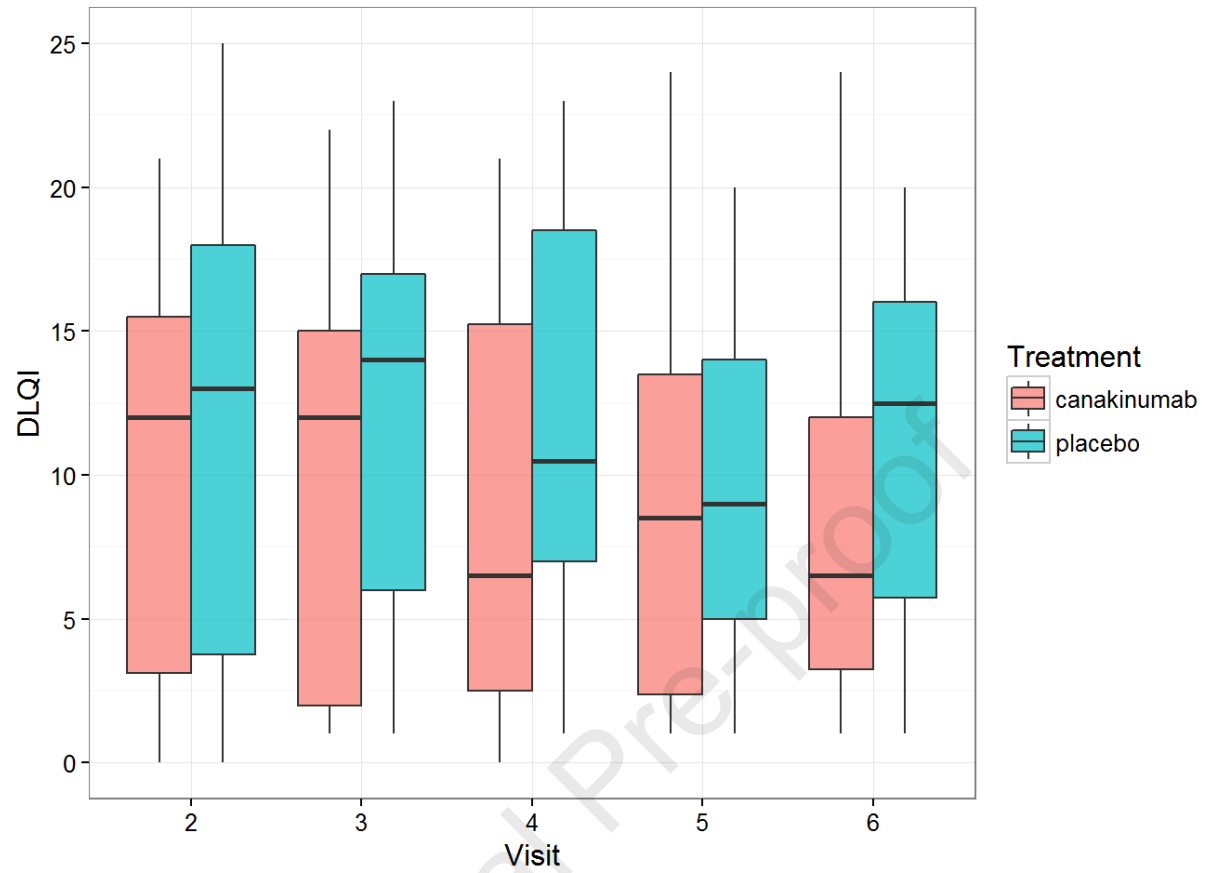
Fig. 3: DLQI difference to baseline, Boxplots show median, first and third quartile, upper/lower whisker extends from the hinge to the largest/smallest value no further than $1.5 * IQR$ from the hinge, and dots indicate outliers

414 **Table legend:**

415 Table 1: Demographics

	canakinumab	placebo
N	10	10
sex = female (%)	6 (60.0)	6 (60.0)
Age in y (mean (sd))	42.20 (17.89)	38.70 (9.56)
Disease duration in y (mean (sd))	2.73 (2.62)	9.45 (6.45)

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URTICANA

