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Anakinra for the treatment of acute gout flares: a randomized, double-blind, placebo-controlled, active-comparator, non-inferiority trial

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Abstract

Objectives. To evaluate the efficacy and safety of anakinra in treating acute gout flares in a randomized, double-blind, placebo-controlled, active comparator, non-inferiority (NI) trial.

Methods. Patients with a crystal-proven acute gout flare were randomized (1: 1) to treatment with anakinra or treatment as usual (free choice: either colchicine, naproxen or prednisone). The primary end point was the change in pain between baseline and the averaged pain score on days 2–4 measured on a five-point rating scale. NI of anakinra would be established if the upper bound of the 95% CI of the numeric difference in changed pain scores between treatment groups did not exceed the NI limit of 0.4 in favour of treatment as usual, in the per-protocol (PP) and intention-to-treat (ITT) populations, assessed in an analysis of covariance model. Secondary outcomes included safety assessments, improvement in pain, swelling, tenderness and treatment response after 5 days, assessed using linear mixed models and binary logistic regression models.

Results. Forty-three patients received anakinra and 45 treatment as usual. Anakinra was non-inferior (mean difference; 95% CI) to treatment as usual in both the PP (–0.13; –0.44, 0.18) and ITT (–0.18; –0.44, 0.08) populations. No unexpected or uncommon (serious) adverse events were observed in either treatment arm. Analyses of secondary outcomes showed that patients in both groups reported similar significant reductions in their gout symptoms.

Conclusion. Efficacy of anakinra was shown to be non-inferior to treatment as usual for the treatment of acute gout flares, suggesting that anakinra is an effective treatment alternative for acute gout flares.

Trial registration. Het Nederlands Trial Register, www.trialregister.nl, NTR5234

Key words: gout, interleukin-1, anakinra, efficacy, safety

Rheumatology key messages

- A five-day treatment of anakinra was non-inferior to registered treatment as usual in treating acute gout flares.
- Results suggest anakinra is an effective treatment alternative for the treatment of acute gout flares.

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Introduction

Gout is a common form of auto-inflammatory arthritis, caused by the deposition of MSU crystals within the soft tissue of synovial joints [1]. Acute gout flares are characterized by distinct inflammatory symptoms (e.g. pain, erythema, swelling), and may cause physical disability, as well as decreased quality of life [2, 3]. Therefore, rapid reduction of auto-inflammation to achieve prompt symptom control is a main goal in managing acute gout.

Colchicine, NSAIDs and glucocorticosteroids are recommended first-line treatment agents for acute gout [4–8]. Unfortunately, comorbidities that may result in contraindications to these medications are common in

gout [9, 10]. Moreover, some patients are intolerant of, or fail to respond to these medications [11]. For such patients, potent treatment alternatives are needed. The 2016 updated EULAR guidelines recommend considering treatment with an IL-1 inhibitor in patients having frequent flares and in those who are difficult to treat using conventional therapies [5].

Canakinumab is currently the only IL-1 inhibitor that has been registered in Europe for the treatment of gout. However, its high costs per treatment may discourage prescribers in daily practice. An alternative might be the IL-1 receptor antagonist anakinra [12]. Although anakinra has been applied in rheumatoid arthritis for many years, trials on its efficacy and safety in acute gout are lacking, having only been investigated in case reports, a few retrospective studies and a small open-label study [13–29]. Therefore, we evaluated the efficacy and safety of anakinra for the treatment of acute gout flares, compared with treatment as usual, in a randomized, controlled, non-inferiority (NI) trial.

Methods

Study design and patient population

This randomized, double-blind, double-dummy, active comparator placebo-controlled trial, was conducted at the rheumatology departments of seven hospitals in the Netherlands, between 2016 and 2018. The study was approved by an Ethical Review Board (METC Twente, Enschede, the Netherlands), the institutional review board or ethics committee of each participating centre, and performed in accordance with the principles outlined in the Declaration of Helsinki and Dutch legislation.

Eligible subjects were recruited and screened by the attending rheumatologist and an instructed specialized rheumatology nurse at the outpatient clinics. All adult ($\geqslant$18 years) patients, with a diagnosis of an acute flare of gouty arthritis, confirmed by microscopic identification of intracellular MSU crystals in the primary joint were eligible for participation. The primary joint was defined as the joint that was most affected by acute gouty arthritis, according to the rheumatologist. Patients with current use of urate lowering therapy (ULT), as well as those experiencing only no to mild gout-related pain, were not included. Other non-inclusion criteria included concurrent use of other IL-1 inhibitors; known history of allergy or sensitivity to latex; absolute contraindication for all available types of ULT; absolute contraindication to anakinra (e.g. neutropenia and severe renal impairment defined as a creatinine clearance rate $<$ 30 ml/min); absolute contraindication for all three conventional treatment options; presence of liver disease that according to the treating rheumatologist precluded participation in the study; an active or recurrent bacterial, fungal or viral infection; use of tumour necrosis factor inhibitors; pregnancy or lactation; women who planned on becoming pregnant during the study period, and insufficient command of the Dutch language. Following screening, all patients were given a maximum of 24 h to decide on participation in the study and to provide written informed consent prior to randomization and study initiation at baseline.

Randomization, treatment and dosing

The attending rheumatologist, together with the patient, decided on the treatment as usual (colchicine, naproxen or prednisone) that would suit the patient best. Subsequently, patients were randomly allocated (1: 1) to either a five-day treatment with anakinra (subcutaneous injection 100 mg once daily) plus oral placebo up to three times daily (colchicine), two times daily (naproxen) or one time daily (prednisone); or to a treatment with oral standard of care in line with the assigned standard treatment by the caregiver (0.5 mg up to three times daily for colchicine; 500 mg up to twice daily for naproxen; 35 mg once daily for 5 days for prednisone) plus subcutaneous injection placebo once daily for 5 days. For treatment as usual, the dosages and duration were in line with national acute gout treatment guidelines [4]. The placebo injections and placebo pills were identical in appearance to the anakinra injections and treatment as usual pills, respectively. Considering the short duration of anakinra treatment given to patients, no pre-study screening for latent tuberculosis was done. The randomization allocation sequence list was generated using a computer randomization application, based on atmospheric noise. Patients, caregivers, local pharmacies, and trial investigators had no knowledge of the allocation sequence during the entire course of the study. Study medication was stored at the hospital pharmacy and released in sequential order to patients. Patients received instructions on the use of study medication from a blinded study nurse, and the first dosages of study medication, both oral pills and injection, were taken by patients under supervision of a blinded study nurse during the baseline visit. During the first 7 days of the study, no prescription-based, rescue medication was available to patients, but the use of over-the-counter pain-relieving agents (NSAIDs and aspirin) was allowed. Patients also initiated ULT at baseline with allopurinol, febuxostat or benzbromarone, at the discretion of the treating rheumatologist.

Study assessments

For this study, the OMERACT recommendations for acute gout were followed [30]. Starting at baseline (day 1), patients were asked to fill in a gout flare diary for seven consecutive days, wherein levels of pain (1 = none; 2 = mild; 3 = moderate; 4 = a lot; 5 = extreme), tenderness (1 = none; 2 = slightly; 3 = fairly; 4 = very; 5 = extremely) and swelling (1 = none; 2 = somewhat; 3 = fairly; 4 = very; 5 = extremely) of the primary joint were recorded using five-point rating scales. Patients were also asked to report their level of pain in the primary joint (0 = absolutely no pain, 10 = unbearable pain) and their global assessment of overall wellbeing (0 = very bad, 10 = very good) on a 10-point numeric rating scale (NRS), and their level of treatment response on an eight-point rating scale (1 = completely disappeared; 2 = very much improved; 3 = much improved; 4 = somewhat improved; 5 = unchanged; 6 = slightly worse; 7 = much

worse; 8 = very much worse). Finally, experienced side-effects and the intake of any other painkillers and/or anti-inflammatory medication were to be reported in the flare diary daily.

Physical examination, medical history and gout status were assessed at baseline, and patients returned for a clinic visit at day 7. Laboratory measurements (serum uric acid, CRP) were performed at baseline and at day 7. Any (serious) adverse events ((S)AE)) were reported and evaluated at day 7.

Study endpoints

The primary end point, i.e. ΔPain, was defined as the mean change in patient-reported pain in the most affected joint, from baseline to the average of pain scores at days 2–4 on the five-point rating scale [31, 32]. We reasoned a priori that anakinra could be a useful treatment alternative for gout patients with contraindications to the standard treatment options, even when not proven more effective than treatment as usual, if it could be demonstrated that anakinra has an effect greater than the effect of imputed placebo [33]; and that any potential inferiority of anakinra compared with treatment as usual would not be clinically meaningful. Therefore, a NI design was adopted with a NI margin of 0.4 points on the five-point rating scale. A difference of 0.4 points in favour of treatment as usual is slightly more stringent compared with previous NI studies in gout known to us, that have used 0.5 as a NI margin for ΔPain [31, 34, 35]. It is also more stringent than other studies assessing change in pain as a primary outcome, for which 10% of the scale (e.g. 10 mm on a 100-mm visual analogue scale (VAS)) is frequently used as an upper limit of acceptable difference [36, 37]. Moreover, in the only available study that allowed for a placebo effect to be estimated for ΔPain, the difference between groups in ΔPain was found to be at least 0.4 points in favour of NSAID compared with placebo (i.e. 95% CI was 0.4–1.0) [32]. Therefore, assuming a placebo effect of similar magnitude, the effect of anakinra in the current trial can be considered greater than imputed placebo when the upper bound of the 95% CI for the ΔPain (anakinra-treatment as usual) does not exceed 0.4 points in favour of treatment as usual [32]. A priori power calculation showed that, if there would be no difference in ΔPain between the groups, 87 patients per treatment arm would need to be included to have an 80% chance of demonstrating NI with a chance of a type 1 error of 5% or less.

Secondary outcomes included the improvement of primary joint pain (NRS scores), tenderness, swelling, treatment response and patient global assessment (PGA) of wellbeing across days 1–5. The number of patients achieving $\geqslant$ 50% decrease in NRS pain scores following baseline on days 2–5 were also compared between treatment arms. Other outcomes included the number and type of AE that occurred during the first 7 days of the study, as well as the decrease in CRP levels after 7 days. Finally, use of concomitant pain-relieving agents, both prescription-based and over the counter medication, during days 1–7 were determined.

Statistical analysis

The primary study end point was assessed using an analysis of covariance (ANCOVA) model, with treatment received as a fixed effect, and baseline pain scores measured on the five-point rating scale as a covariate. Subsequently, we obtained a 95% CI for the baseline pain adjusted marginal mean difference in ΔPain between the treatment groups. We tested whether the upper bound of the CI of the numeric difference in changed pain scores between anakinra and treatment as usual would not exceed the NI margin of 0.4 in favour of treatment as usual (H0: $\Delta Pain_{Anakinra} - \Delta Pain_{TreatmentAsUsual} > 0.4$ *vs* Ha: $\Delta Pain_{Anakinra} - \Delta Pain_{TreatmentAsUsual} \leqslant 0.4$). If this criterion was met in both the per-protocol (PP) and intention-to-treat (ITT) populations, NI of anakinra compared with treatment as usual would be concluded. The ITT analysis was performed on all patients who were randomized to a treatment at baseline and received at least one dose of study medication. The PP population contained patients who had no missing data for $\geqslant$ 1 of the assessments needed for the primary outcome, and who did not take any interfering concomitant pain-relieving medications during days 1–4 of the study. This included any prescription-based pain-relieving medication (e.g. opioid formulations, intake of colchicine while the patient was prescribed naproxen), but over the counter pain-relieving agents were allowed.

Analysis of secondary endpoints were performed in the ITT population, using linear mixed effects models, with time, treatment arm, and the interaction between time and treatment arm as fixed effects. For each outcome analysed, the covariance matrix was chosen that had the best fit according to the Bayesian information criterion. All statistical tests were performed at the Bonferroni corrected 0.05 level. The difference between treatment groups in achieving $\geqslant$ 50% decrease in NRS pain scores in the days following baseline was assessed using binary logistic regression analysis.

For the analyses of the ITT population, plausible values for missing observations of the seven-day flare diary and CRP values were generated using multiple imputation by chained equations. Percentages of missing data were determined for variables needed for the primary efficacy analyses. Data from the seven-day flare diary was used as input for the imputation models, as well as treatment received, age, gender and log-transformed CRP values. Following the imputation process, the latter were transformed back to normal CRP values. In total, 20 datasets were generated, and the observed and imputed distributions were visually compared for similarity. Reporting guidelines for handling analysis affected by missing data were followed [38].

Characteristics of the study population were summarized using means and standard deviations, or median and first and third quartiles for continuous outcomes. Categorical variables were summarized using frequency counts and percentages, and compared using Pearson's χ^2 statistics, as appropriate, for secondary outcomes. Other secondary outcomes were compared using t-tests

or a non-parametric equivalent, as appropriate. *P*-values <0.05 were considered statistically significant. All analyses were done using IBM statistics SPSS version 22. The Reporting of NI and Equivalence Randomized Trials extension of the CONSORT 2010 statement was followed in reporting this study [39].

Results

Patient characteristics

Eighty-eight patients were enrolled in the study, and all patients (100%) completed the seven-day follow-up. Of these, 43 patients (48.9%) were randomized to a treatment with anakinra and 45 (51.1%) to treatment as usual (Fig. 1). Patient baseline characteristics are listed in Table 1. The majority of patients in both groups (>90%) were male and more than half of the patients had monoarticular gout. Of the patients in the treatment as usual arm, 18 received a treatment with colchicine, and 13 and 14 patients received a treatment with naproxen and prednisone, respectively.

Efficacy assessment

Pain scores measured on the five-point rating scale decreased to a similar extent in both groups over days 1–4. For the PP population, results of the univariate ANCOVA for the primary outcome showed that the estimated marginal mean difference between treatment arms, –0.132 points on the five-point rating scale, was in favour of anakinra, and that the upper bound of the 95% CI of this difference (–0.44, 0.18) did not surpass the NI margin of 0.4 (Fig. 2). In the ITT population, plausible values for missing data of the five-point rating scale pain scores at baseline, day 2, day 3, and day 4 post baseline were generated for 12 (13.6%), 6 (6.8%), 3 (3.4%) and 5 (5.7%) cases, respectively. Here, the primary analysis yielded similar results, with an estimated marginal mean difference of –0.178 (95% CI –0.44, 0.08) (Fig. 2). Because in both of these analyses the upper bound of the 95% CI did not surpass the 0.4 NI margin, the null hypothesis that treatment with anakinra is less effective than treatment as usual for treating acute gout flares by at least 0.4 points on the five-point rating scale, was rejected. We concluded that the pain-relieving effect of anakinra in patients with gout was greater than the estimated effect of placebo, and that efficacy of anakinra was non-inferior to treatment as usual.

Secondary outcomes

For all the secondary outcomes assessed using the linear mixed effects model, the pattern of change was similar for the anakinra and treatment as usual group over 5 days, with significant improvements over time, but no significant between-group effects, or group-by-time interactions (Fig. 3; results for PGA not shown). These findings provide no evidence for a differential effect on any outcome. For PGA, the mean ± standard error (S.E.) scores increased from 4.4 ± 0.34 to 6.7 ± 0.31 in the conventional treatment arm, and from 4.9 ± 0.38 to 7.31 ± 0.32 in the anakinra treatment group. After 2 days, more patients in the anakinra treatment group achieved $\geqslant$ 50% decrease in NRS

Fig. 1 Flow diagram of patient selection

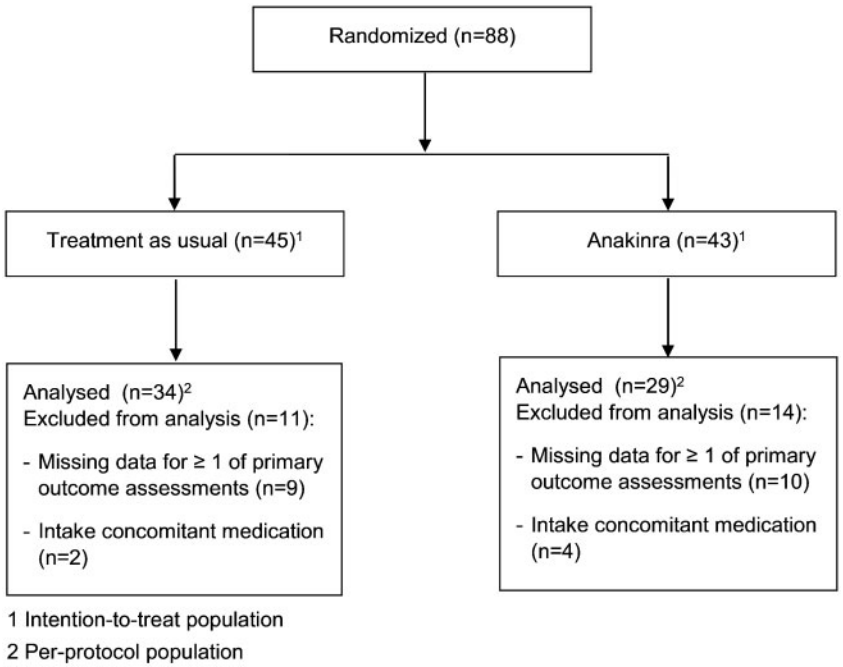
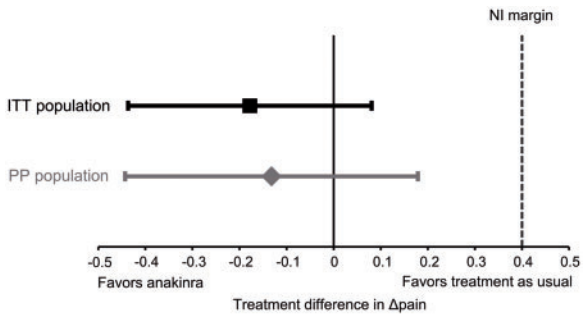


Table 1 Baseline demographic and clinical characteristics

	Score range of measure	Treatment as usual[a] ($n = 45$)	Anakinra ($n = 43$)
Age, years, mean ± S.D.	—	59.9 ± 12.7	63.4 ± 12.9
Male sex	—	42 (93.3)	41 (95.3)
BMI, kg/m^2, mean ± S.D.	—	28.6 ± 4.0	29.5 ± 4.2
Systolic blood pressure, mm Hg, mean ± S.D.	0–999	141.5 ± 24.2	145.1 ± 21.6
Diastolic blood pressure mm Hg, mean ± S.D.	0–999	85.7 ± 14.6	84.8 ± 14.6
SUA, mmol/L, median (Q1, Q3)	0–9	0.52 (0.45, 0.64)	0.50 (0.42, 0.57)
CRP, mg/L, median (Q1, Q3)	0–999	14.0 (6.0, 30.5)	15.0 (5.5, 32.0)
Comorbidities[b]			
Hypertension	—	17 (65)	10 (37)
Cardiovascular disease	—	11 (42)	18 (67)
Diabetes Mellitus	—	5 (19)	3 (11)
Renal disorders	—	1 (4)	4 (15)
Musculoskeletal disease[c]	—	4 (15)	6 (22)
Gout classification[d]			
Monoarticular	—	30 (66.7)	23 (53.5)
Oligoarticular	—	11 (24.4)	17 (39.5)
Polyarticular	—	4 (8.9)	3 (7.0)

Data are presented as *n* (%) unless stated otherwise. [a]In the treatment as usual group, 18 patients received colchicine, 13 naproxen and 14 prednisone. [b]Number and percentages based on available data from patients in the anakinra arm ($n = 27$) and treatment as usual arm ($n = 26$). [c]Diseases other than gout. [d]Monoarticular implies one joint has been affected by gout; oligoarticular > 1 but < 5 joints have been affected by gout; polyarticular $\geqslant 5$ joints have been affected by gout. SUA: serum urate acid.

Fig. 2 The 95% CI for the estimated marginal mean difference in ΔPain between the treatment groups



ΔPain is the mean change in patient-reported pain from baseline to the average of pain scores at days 2–4 on the five-point rating scale. NI: non-inferiority.

pain scores (odds ratio (OR) 1.41, 95% CI 0.53, 3.73) compared with the treatment as usual arm, although not statistically significant. Also, on days 3–5, OR were in favour for anakinra. However, only on day 3 was this difference statistically significant (Supplementary Table S1, available at *Rheumatology* online).

Both treatment groups showed a reduction in their CRP values after 7 days from baseline. The mean ± SE reduction in the treatment as usual arm was 13.9 ± 7.1 after 7 days, which was not significantly different to the reduction observed in the anakinra treatment arm of 11.1 ± 7.5.

During the first 7 days following baseline, more patients in the anakinra group ($n = 20$, 46.5%) compared with the treatment as usual arm ($n = 16$, 35.6%), took some form of pain-relieving medication, over the counter or prescription-based, aside from their study medication. However, this difference was not statistically significant between the groups.

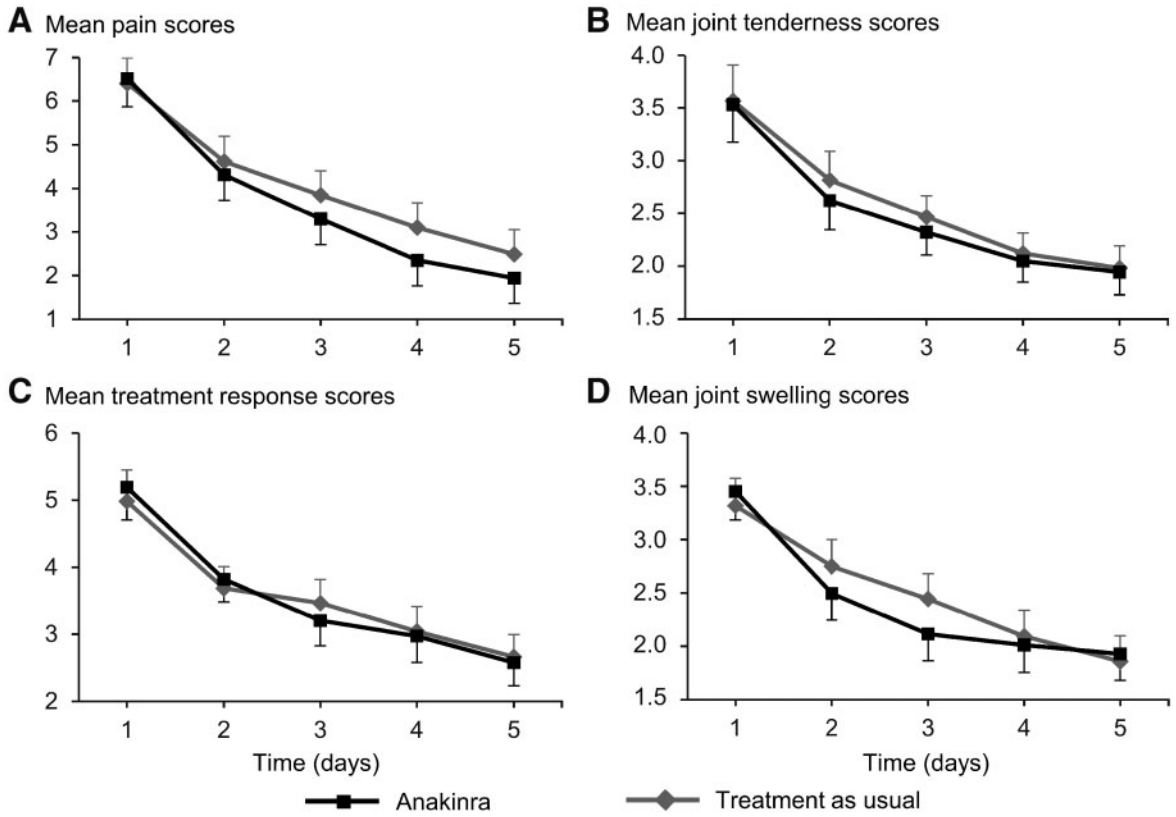
Safety assessment

Out of the 88 patients, 36 (40.9%) patients reported an AE during the first 7 days post baseline, of which more than half ($n = 21$, 58.3%) were patients in the treatment as usual arm (Table 2). Interestingly, three injection site reactions were reported in the treatment as usual group with the placebo injections, compared with none in the anakinra treatment group. One patient in the treatment as usual group reported to have viral gastroenteritis (stomach flu), and one patient in the anakinra group had a respiratory tract infection (severe cold). No SAE were reported during the 7 days following baseline.

Discussion

In this study we set out to determine the clinical efficacy and safety of anakinra for the treatment of acute, crystal-proven, gout flares in a randomized, active-comparator, NI trial. A daily subcutaneous injection of anakinra was compared with oral treatments administered according to the standard of care, using optimal dosages as recommended in gout guidelines. As far as we know, this is the

FIG. 3 Mean scores on days 1–5 (bars represent one-sided 95% CI) of the secondary outcomes (panel **A**–**D**)



first double-blind, randomized controlled trial to evaluate the use of anakinra in an acute gouty arthritis population.

The results presented here show at least NI of anakinra compared with conventional therapies for the treatment of acute gout flares, supported by the additional finding that patients in both treatment arms achieved a significant reduction of their gout-related symptoms over the course of one week. Additionally, evaluation of the reported AE did not reveal any severe, uncommon or unexpected safety outcomes. These findings suggest that anakinra might be a viable treatment option for gout flares.

To date, various non-randomized, uncontrolled, observational studies have reported on the clinical efficacy of anakinra for treating gout, mostly reporting promising outcomes on the numbers or percentages of patients who responded well to anakinra within the first days of treatment [15–25, 40–43]. However, the absence of a control group in these studies hampers the interpretation of such results, as the observed improved clinical status of patients might merely reflect the self-limiting natural course of acute gout [44]. In our present study, anakinra was compared with treatment in accordance with current gout management guidelines, using several anti-inflammatory agents with previously established effectiveness in treating gout flares [5, 45]. The results showed that the efficacy of anakinra in treating gout flares was consistently numerically superior to standard of care treatment across the primary and secondary study outcomes. However, the direct comparison of anakinra with standard of care does not by itself allow for conclusions about the effectiveness of either treatment in gout, as no placebo arm was included. By relating the results to a NI margin that was estimated using the imputed placebo method, our results indirectly support the efficacy of anakinra in gout. However, this conclusion is based on the assumption that the relative effectiveness of standard of care treatment compared with placebo would have been the same as the relative effectiveness of NSAID compared with placebo that was observed in the study used for estimating the NI margin [32, 46, 47].

Data from our study builds on previous clinical trials that have reported varying efficacies of IL-1 inhibitors in gout patients. Terkeltaub *et al.* [32] reported on rilonacept, in which treatment with rilonacept plus NSAID did not significantly improve pain levels compared with NSAID monotherapy, and rilonacept monotherapy was shown to be inferior to NSAID monotherapy over a 72-h follow-up period. This difference in efficacy compared with our study might be attributed to differences in study designs, but also to pharmacokinetic differences between the IL-1

Table 2 Number and percentage (%) of adverse events occurring per treatment arm during the 7 days following baseline

	Treatment as usual ($n = 45$)	Anakinra ($n = 43$)
Total number of SAE[a] reported	0 (0)	0 (0)
Number of cases having an AE[b]	21 (46.7)	15 (34.9)
Total number of AE reported	49 (57.0)	37 (43.0)
Type of AE reported[c]		
Musculoskeletal pain	4 (8.2)	6 (16.2)
Musculoskeletal stiffness, swelling, spasms	4 (8.2)	5 (13.5)
Injection site reaction	3 (6.1)	0 (0.0)
Infections[d]	1 (2.0)	1 (2.7)
Vomiting	0 (0.0)	1 (2.7)
Diarrhea	9 (18.4)	3 (8.1)
Nausea	5 (10.2)	3 (8.1)
Other GI disorders	3 (6.1)	0 (0.0)
Headache	4 (8.2)	2 (5.4)
Dizziness	4 (8.2)	0 (0.0)
Fatigue	1 (2.0)	2 (5.4)
Pruritus (itchiness)	0 (0.0)	3 (8.1)
Paresthesia or tremor	1 (2.0)	2 (5.4)
Other AE	10 (20.4)	9 (24.3)

[a]Defined as any medical occurrence or event that was life threatening at the time of event, resulted in death, resulted in persistent or significant disability, led to hospitalization or prolongation of existing hospitalization, led to a congenital anomaly or birth defect. [b]Given as percentage of total patients within group. [c]Given as percentage of total number of AE reported within group. [d]Type of infection reported in the treatment as usual group was gastroenteritis viral, and in the anakinra group a respiratory tract infection. SAE: serious adverse event; AE: adverse event; GI: gastrointestinal.

inhibiting drugs. The authors reflect that rilonacept reaches its maximum plasma concentration after 48–72 h, which could potentially have led to insufficient drug concentrations during the period of the primary outcome assessment. For anakinra, maximum plasma concentrations are reached within 3–7 h . This rapid increase in drug plasma concentrations may explain why the results in our study seem more promising 72 h after baseline, than those seen with rilonacept. Canakinumab is currently the only IL-1 inhibitor for which effectiveness during an acute gout exacerbation has been demonstrated in a randomized study [36, 48]. Schlesinger *et al.* [49] reported that a single subcutaneous injection of canakinumab 150 mg was superior to a single intramuscular injection of triamcinolone acetonide 40 mg, in relieving pain after 72 h. The mean VAS (0–100 mm) pain score at that moment was 25 mm for the canakinumab arm. Although it is difficult to compare these outcomes with our results, because of differences in study design and populations, results from our study reveal similar pain scores after 72 h in the anakinra group on a 0–10 NRS (i.e. score = 2.4).

Considering the high costs of canakinumab treatment, anakinra therefore seems to be a cost-effective alternative for gout patients seen in daily practice who are difficult to treat with conventional therapies, in case they meet the local reimbursement criteria. Importantly, anakinra could possibly allow a larger proportion of the difficult to treat gout population to be treated with an IL-1 inhibitor, including patients having comorbidities as diabetes mellitus, renal disorders or cardiovascular disease. In this respect it should be noted that patients with severe renal impairment were excluded from participation in our study. However, favourable outcomes have previously been described in a retrospective case-series of 31 patients with either a renal transplantation or stage 4 or stage 5 chronic kidney disease, that signs and symptoms of gout flares subsided after admission of treatment with anakinra [50]. Moreover, a current ongoing feasibility study, designed as a double-blind, double-dummy, randomized controlled trial, will contribute to developing a definite clinical trial wherein the efficacy and tolerability of anakinra to corticosteroids in patients with chronic kidney disease will be compared [29].

The multicentre, randomized, placebo-controlled, double-blinded nature of our study, as well as the inclusion of only patients with MSU crystal-proven gout, the diagnostic gold-standard, are strengths of our study. However, the present study was not without limitations. First, the total number of patients included was lower than initially calculated in the power analyses for the primary efficacy analyses. However, in contrast to the a priori power calculation that assumed no difference between the treatment arms in ΔPain, we found a difference in favour of anakinra in both the PP and ITT analyses, with on average 0.155 points on a five-point rating scale. Therefore, and having the other assumptions remain constant, a smaller sample size would have sufficed to demonstrate NI of anakinra compared with imputed placebo. Within the limitations of a small clinical trial, relatively few data on the safety of anakinra in gout was obtained. However, the long-term treatment experience of anakinra in rheumatoid arthritis already provides a sound safety profile. Nevertheless, additional short-term safety data for anakinra in gout is desired. Finally, the study was carried out in a hospital-based setting, possibly making our results less generalizable to a primary care setting, in which other types of acute gout patients may be treated.

In conclusion, in our study anakinra was shown to be non-inferior to registered treatment as usual for the treatment of acute gout flares. Our results suggest that anakinra is an effective treatment alternative for the treatment of acute gout flares.

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Supplementary data

Supplementary data are available at *Rheumatology* online. Anonymized, patient level data are available from Dr M.A.H. Oude Voshaar (a.h.oudevoshaar@utwente.nl) upon request, subject to submission of a suitable study protocol and data analysis plan.

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