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A Randomized, Phase II Study Evaluating the Efficacy and Safety of Anakinra in the Treatment of Gout Flares

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Objective. To evaluate the efficacy and safety of anakinra compared to triamcinolone in the treatment of gout flares.

Methods. Patients for whom nonsteroidal antiinflammatory drugs and colchicine were not suitable treatments were enrolled in this multicenter, randomized, double-blind study with follow-up for up to 2 years. The study was designed to assess superiority of anakinra (100 or 200 mg/day for 5 days) over triamcinolone (40 mg in a single injection) for the primary end point of changed patient-assessed pain intensity in the most affected joint (scored on a visual analog scale of 0–100) from baseline to 24–72 hours. Secondary outcome measures included: safety, immunogenicity, and patient- and physician-assessed global response.

Results. One hundred sixty-five patients were randomized to receive anakinra (n = 110) or triamcinolone (n = 55). The median age was 55 years (range 25–83), 87% were men, the mean disease duration was 8.7 years, and the mean number of self-reported flares during the prior year was 4.5. A total of 301 flares were treated (214 with anakinra; 87 with triamcinolone). Anakinra in both doses and triamcinolone provided clinically meaningful reduction in patient-assessed pain intensity in the first and subsequent flares. For the first flare, the mean decline in pain intensity from baseline to 24–72 hours for total anakinra and triamcinolone was –41.2 and –39.4, respectively ($P = 0.688$). Anakinra performed better than triamcinolone for most secondary end points. There were no unexpected safety findings. The presence of antidrug antibodies was not associated with adverse events or altered pain reduction.

Conclusion. Anakinra was not superior to triamcinolone for the primary end point, but had comparable efficacy in pain reduction and was favored for most secondary end points. Anakinra is an effective option for gout flares when conventional therapy is unsuitable.

INTRODUCTION

Antiinflammatory agents used for treatment of gout flares include nonsteroidal antiinflammatory drugs (NSAIDs), colchicine, and glucocorticoids (1,2). However, many patients with gout have underlying comorbidities, including hypertension, chronic kidney disease, heart disease, gastroesophageal disease, and diabetes, that render them unsuitable for one or more of these treatments (3–7). Thus, there is an unmet need for effective gout flare treatment for patients who have contraindications to, do not tolerate, or whose disease is refractory to existing therapies.

Based on biologic activities in gouty inflammation and clinical data on the interleukin-1β (IL-1β)–specific monoclonal antibody canakinumab (8–13), IL–1β is an established target in the

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treatment of gout flares (1,6,7,14–17). However, according to European Medicines Agency and American College of Rheumatology (ACR) guidelines, IL-1 inhibition is clinically appropriate for only a small proportion of gout flares (18,19). Anakinra is a recombinant form of the constitutively expressed soluble IL-1 receptor antagonist (IL-1Ra) that limits the activity of IL-1α and IL-1β by competitively inhibiting their binding to IL-1R type I, thereby suppressing inflammation. The notion that IL-1 inhibition with anakinra is efficacious for gout flares is supported by results of a recent randomized, double-blind noninferiority trial comparing anakinra to free choice of prednisone, naproxen, or colchicine (20) and multiple case series and retrospective studies, most commonly using anakinra 100 mg/day administered subcutaneously for 3–5 days. Most studies included patients with intolerance or inadequate response to conventional antiinflammatory therapies. In addition, the IL-1β and IL-1α inhibitory IgG1 Fc-linked fusion protein rilonacept, a soluble IL-1R inhibitor shown to be effective in gout flare prophylaxis (21–24), was not associated with different pain relief, relative to indomethacin, over the first 72 hours of gout flares (25).

In the current study we investigated the efficacy and safety of anakinra at 2 different doses compared to intramuscular triamcinolone acetonide in the treatment of gout flares. This is the first reported adequately powered randomized controlled clinical trial evaluating anakinra and additionally testing 2 anakinra dosing regimens. We tested the specific hypothesis that anakinra would be superior to intramuscular triamcinolone for patient-assessed pain intensity in gout flare.

PATIENTS AND METHODS

Patients. To be eligible for the trial, patients had to be ≥18 years of age, have gout according to the ACR/European League Against Rheumatism (EULAR) 2015 classification criteria (26), have had ≥1 self-reported gout flare within 12 months prior to randomization, and have had onset of an ongoing flare (characterized by baseline pain intensity in the index joint of ≥50 on a 0–100 visual analog scale [VAS] and defined by tenderness and swelling in the index joint of ≥1 on a 0–4-point Likert scale) within 4 days prior to randomization. In addition, patients had to have had ≥1 episode of intolerance or nonresponsiveness to NSAIDs and colchicine or have had these treatments judged to be contraindicated or not appropriate. Signs of nonresponsiveness to NSAIDs and colchicine were prespecified and included lost efficacy over time, failure to treat acute gout pain, inadequate/unsatisfactory pain relief, or incapacity to achieve/maintain adequate dose regimen of these agents. Patients taking specified pain relief medications or biologic agents prior to randomization were excluded. Other exclusions were the presence of a contraindication to triamcinolone treatment or the presence of rheumatoid arthritis (RA), polyarticular gouty arthritis (involving >4 joints), infectious/septic arthritis, or any other acute inflammatory arthritis. Further details are provided in Supplementary Methods, Study Protocol (on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41699/abstract).

Study design. The Anakinra in Gout (anaGO) study (NCT03002974) was a randomized, double-blind, double-dummy, active-control, multicenter trial designed to assess superiority of anakinra over triamcinolone in the treatment of patient-assessed pain intensity. The study had 3 periods: a prescreening period, a double-blind treatment period for the first flare in the study, and an extension period for subsequent flares. Before treatment of the first flare, patients were randomized 1:1:1 to receive anakinra 100 mg, anakinra 200 mg, or triamcinolone 40 mg (approved for treatment of gout flares) (Figure 1). An interactive web response system was used for the randomization. The randomization was stratified by urate-lowering therapy (ULT) use (yes/no) and body mass index (BMI) (<30.0 or ≥30.0 kg/m^2). Randomization was in blocks, and equal numbers of patients were allocated to each group. Anakinra/placebo was administered subcutaneously once daily for

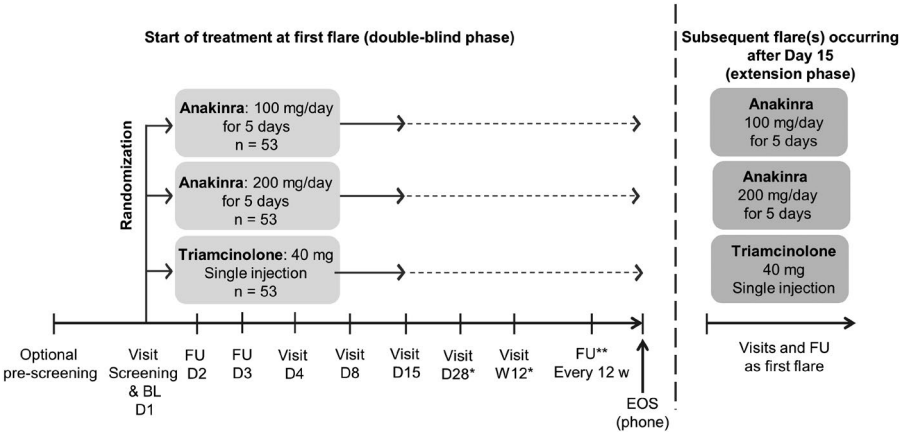

Figure 1. The anaGO clinical study design. * Visit takes place only if no subsequent flare has occurred. ** Telephone call every 12 weeks after the latest flare has occurred and been treated with study drug. BL = baseline; D = day; W = week; FU = follow-up by phone; EOS = end of study.

5 days, and triamcinolone as a single intramuscular injection on day 1. In accordance with the double-dummy design, the patients received 1 intramuscular injection and 2 subcutaneous injections on day 1 and 2 subcutaneous injections on days 2–5.

Treatments were initiated on the day of randomization (visit 1) and were supervised or given by the investigator (or delegated study staff) at the outpatient clinic, emergency department, or hospital. If a patient was treated at an outpatient clinic or was discharged from the hospital before the end of the 5-day drug administration period, the daily subcutaneous injections were administered at home by the patients themselves or a caregiver. The treatment and follow-up of the patients' flare was double-blinded, i.e., blinded for the patients, the investigators, and any other study personnel involved with the study conduct or evaluation at the investigational sites, contract research organization, and sponsor.

The extension period continued until 52 weeks after randomization of the last patient, but no longer than 2 years for each patient. Protocolized treatment for subsequent flares was the same as for the first flare, and the blinding was maintained for the patients and for personnel at the investigational sites and the contract research organization until the final database lock.

Ethics approval was provided by the following institutional review boards: Western Institutional, University of Michigan Medical School, Duke Medicine Institutional Review Board for Clinical Investigations, and Advarra (previously Quorum Review). The study was conducted in compliance with International Council for Harmonisation Guidelines for Good Clinical Practice and in accordance with the latest revision of the Declaration of Helsinki. All patients provided written informed consent prior to study admission.

Outcome measures. Study objectives and end points are listed in Supplementary Tables 1 and 2 (on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41699/abstract). The primary end point was the change in patient-assessed pain intensity from baseline to 24–72 hours (average of assessments at 24, 48 and 72 hours). Patients scored pain intensity in the joint most affected at baseline (the index joint) on a VAS ranging from 0 (no pain) to 100 (unbearable pain), using an e-diary. Allowed rescue medication was paracetamol/acetaminophen and/or codeine, short-acting tramadol, and topical ice/cold packs. If relief was insufficient, prednisone or prednisolone was permitted. In addition, physician and patient assessment of global response to treatment, physician assessment of clinical signs (index joint tenderness, swelling, and erythema), change in serum concentrations of inflammation markers (C-reactive protein [CRP] and serum amyloid A [SAA]), safety variables, serum concentration of IL-1Ra, and occurrence of antidrug antibodies and neutralizing antibodies were assessed at baseline and after a flare.

Statistical analysis. The population used for the primary analysis comprised all randomized patients grouped according to randomized treatment and stratum, regardless of whether any dose of study drug was administered. Sample size calculation was based on the change in VAS-scored pain intensity from baseline to 24–72 hours. A sample size of 106 patients receiving anakinra and 53 receiving triamcinolone ensured a power of 80% to reject the null hypothesis of no difference between anakinra and triamcinolone, assuming a true difference of 12 on mean change in pain intensity and a standard deviation of 25 when using a 2-sided test with a significance level of 5%.

The main efficacy analyses were performed 15 days from the onset of the first flare in all patients. The primary end point was estimated using a mixed-model repeated-measures analysis with the measurements at the individual time points as responses and with treatment, ULT use, BMI, visit, and treatment × visit interaction as fixed effects, and center as a random effect.

Secondary time-to-event end points were analyzed using a stratified log rank test, with ULT use and BMI as stratification factors. Secondary continuous end points were evaluated by analysis of covariance including factors for treatment, ULT use and BMI, and the baseline value as covariate. Secondary binary end points were evaluated using a logistic regression model with treatment, ULT use, and BMI as explanatory variables.

Adverse events. Adverse events (AEs) were reported from the time of the first treatment to day 28. In case of a subsequent flare, AE reporting started again. All AEs were followed up until resolution or until the patient's study participation ended. Serious AEs (SAEs) were reported from the time of signing the informed consent to week 12, and thereafter only if a causal relationship to the treatment was suspected.

RESULTS

Patient characteristics. Two hundred twenty-seven patients were screened, and 165 were randomized to a treatment group: 110 to receive anakinra (at 100 mg in 56 patients and 200 mg in 54 patients) and 55 to receive triamcinolone. For 4 patients, no data on the primary efficacy analysis were recorded; for 3 patients (1 in the anakinra 200 mg group, 2 in the triamcinolone group) data on VAS-scored pain up to 72 hours were missing due to technical issues with the diary device, and 1 patient was randomized in error and did not receive anakinra 200 mg (Figure 2).

The median age of the patients was 55 years (range 25–83), 87% were men, 72% were White, the mean ± SD disease duration was 8.7 ± 8.0 years, and the mean ± SD number of self-reported flares during the past year was 4.5 ± 2.5. Approximately 45% of the patients in both anakinra groups and the triamcinolone group were receiving ULT at baseline. Almost half of the patients had >3 of the predefined comorbidities at baseline (50.0% and 43.6% in the anakinra [total] and triamcinolone groups, respectively). Type 2

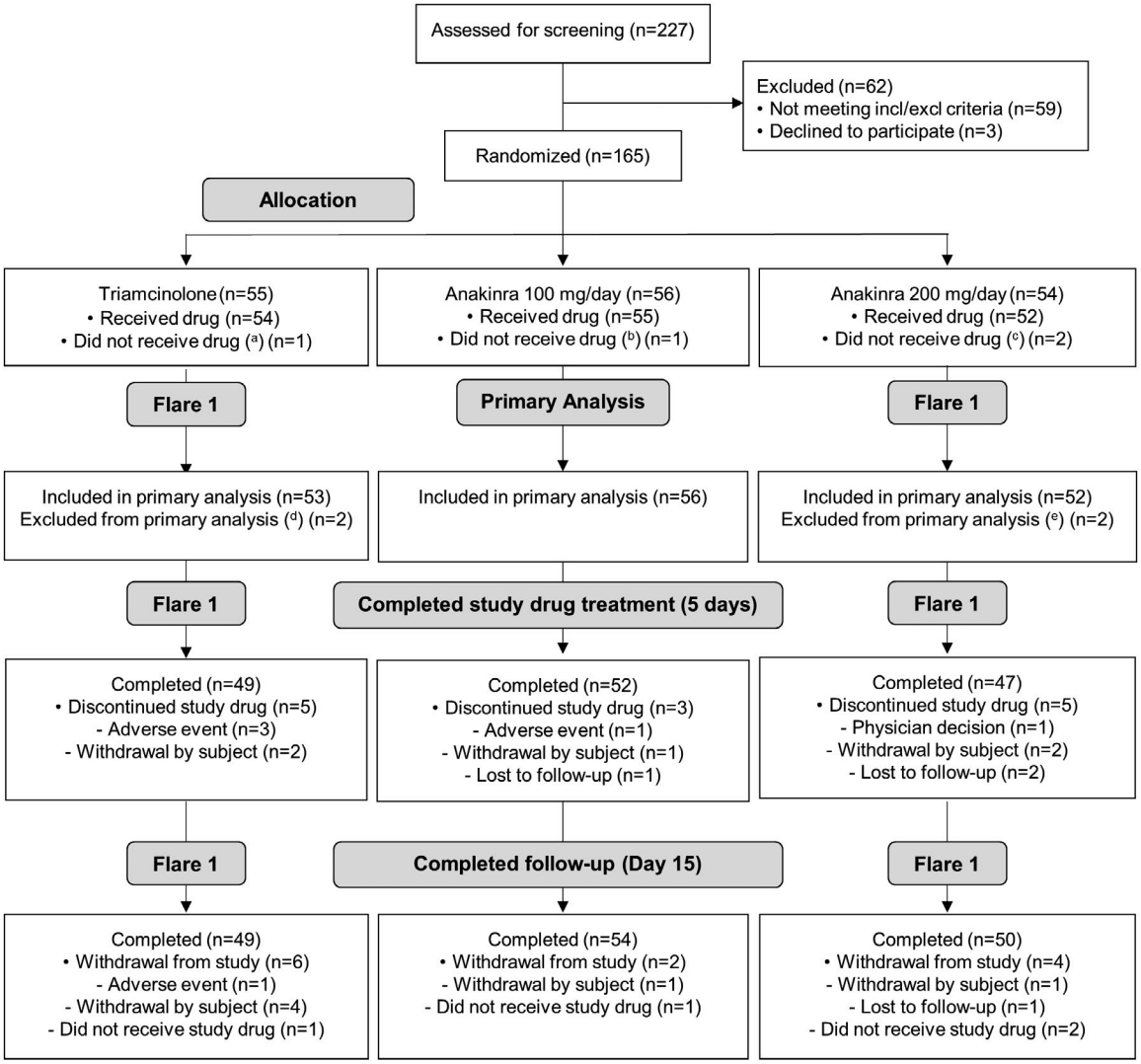

Figure 2. Flow diagram showing the distribution of the patients through the first gout flare. Details are given according to the Consolidated Standards of Reporting Trials (CONSORT) statement for reporting randomized controlled trials. [a] Withdrawal by subject. [b] Randomized in error. [c] Withdrawal by subject (n = 1) and randomized in error (n = 1). [d] Missing visual analog scale (VAS) score for pain up to 72 hours due to technical issues with the diary device. [e] Randomized in error and did not receive investigational medicinal product (n = 1) and missing VAS score for pain up to 72 hours due to technical issues with the diary device (n = 1). incl/excl = inclusion/exclusion.

diabetes mellitus was more common in the anakinra (total) group than in the triamcinolone group (32 patients [29.1%] versus 9 patients [16.4%]), whereas the frequency of obesity was comparable (BMI ≥30 kg/m^2 in 76.4% of the patients in the triamcinolone group and 73.6% in the anakinra group).

NSAID or colchicine treatment was considered unsuitable for the patients in the study as judged by the study investigators. The most common reason was lack of efficacy (Supplementary Table 3, on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41699/abstract).

The study started in December 2016 and recruitment continued until May 2018. The patients were followed up until August 2019, when the study ended. Patient demographic and baseline clinical characteristics were similar between groups (Table 1).

Patient-assessed pain intensity. The mean change from baseline to 24–72 hours in patient-assessed pain intensity for the first flare was –41.2 in the total anakinra group (95% confidence interval [95% CI] –46.3, –36.2) and –39.4 in the triamcinolone group (95% CI –46.8, –32.0). The mean change in pain intensity was similar in the anakinra 100 mg group (–41.8 [95% CI –48.9, –34.8]) and the anakinra 200 mg group (–40.7 [95% CI –47.9, –33.4]). The difference in mean change between the total anakinra and triamcinolone groups was not statistically significant (–1.8 [95% CI –10.8, 7.1]; P = 0.688) (Table 2). The mean ± SD time from pain onset to treatment start for the first flare in the study was 2.0 ± 1.0 days in the triamcinolone group and 2.2 ± 0.9 days in the anakinra (total) group.

Table 1. Demographic and baseline clinical characteristics of the gout patients studied*

	Triamcinolone (n = 55)	Anakinra total (n = 110)	Anakinra 100 mg/day (n = 56)	Anakinra 200 mg/day (n = 54)
Age, median (range) years	56.0 (30–83)	54.0 (25–79)	53.5 (25–79)	54.0 (27–78)
Male sex	48 (87.3)	95 (86.4)	48 (85.7)	47 (87.0)
Race				
White	39 (70.9)	80 (72.7)	38 (67.9)	42 (77.8)
Black	15 (27.3)	27 (24.5)	15 (26.8)	12 (22.2)
Asian	1 (1.8)	3 (2.7)	3 (5.4)	0
eGFR, ml/minute/1.73 m^2				
≥90	9 (16.4)	34 (30.9)	22 (39.3)	12 (22.2)
≥60–<90	31 (56.4)	54 (49.1)	23 (41.1)	31 (57.4)
≥30–<60	11 (20.0)	15 (13.6)	7 (12.5)	8 (14.8)
≥15–<30	1 (1.8)	0	0	0
Missing	3 (5.5)	7 (6.4)	4 ± 7.1	3 (5.6)
Disease duration, mean ± SD years	7.7 ± 7.6	9.2 ± 8.3	9.7 (8.8)	8.6 ± 7.7
No. of self-reported flares during the last year, mean ± SD	4.4 ± 2.0	4.5 ± 2.7	4.6 ± 3.4	4.4 ± 1.7
No. of affected joints at randomization				
1	46 (83.6)	82 (74.5)	43 (76.8)	39 (72.2)
2–4	9 (16.4)	24 (21.8)	11 (19.6)	13 (24.1)
Not reported	0	4 (3.6)	2 (3.6)	2 (3.7)
Tophi present	21 (38.2)	38 (34.5)	17 (30.4)	21 (38.9)
ULT use at randomization	23 (41.8)	50 (45.5)	28 (50.0)	22 (40.7)
No. of comorbidities				
0	0	2 (1.8)	1 (1.8)	1 (1.9)
1	2 (3.6)	9 (8.2)	7 (12.5)	2 (3.7)
2	10 (18.2)	19 (17.3)	8 (14.3)	11 (20.4)
3	16 (29.1)	19 (17.3)	13 (23.2)	6 (11.1)
>3	24 (43.6)	55 (50.0)	25 (44.6)	30 (55.6)
Not reported	3 (5.5)	6 (5.5)	2 (3.6)	4 (7.4)

* Except where indicated otherwise, values are the number (%). eGFR = estimated glomerular filtration rate; ULT = urate-lowering therapy.

Patient-assessed mean pain intensity was measured on a Likert scale, in addition to a VAS. By both parameters, pain intensity for the first flare at 6, 12, 18, 24, 36, 48, and 72 hours and on days 5, 6, 7, and 8 was similar in the anakinra and triamcinolone groups (Supplementary Figure 1, on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41699/abstract).

Time to effect of treatment. The median time to pain resolution for the first flare was 120.5 hours in the total anakinra group and 167.5 hours in the triamcinolone group (hazard ratio [HR] 1.29 [95% CI 0.9, 1.9]). The median time to response was 46.7 hours in the total anakinra group and 47.6 hours in the triamcinolone group (HR 1.19 [95% CI 0.8, 1.7]). The median time to onset of effect for the first flare was 17.8 hours in the total anakinra group and 22.3 hours in the triamcinolone group (HR 1.11 [95% CI –0.8, 1.6]) (Supplementary Table 4, http://onlinelibrary.wiley.com/doi/10.1002/art.41699/abstract). Differences between the treatment groups were not statistically significant. Resolution of pain was achieved in 36 patients (65.5%) in the triamcinolone group and 70 (63.6%) in the anakinra (total) group by day 15. During the time interval between the first study drug administration and day 15, 49 patients in the total anakinra group (44.5%) and 26 in the triamcinolone group (47.3%) received rescue medication. Since <50% of the patients took rescue medication, the overall median time to first intake of rescue medication could not be calculated.

Patient and physician assessments. The differences between treatment groups showed improvement in favor of anakinra for most of the secondary end points (Table 3). The mean patient assessment of global response to treatment was significantly better in the total anakinra group compared to the triamcinolone group on day 8 (–0.63 [95% CI –1.03, –0.22]) and day 15 (–0.44 [95% CI–0.86, –0.02]). The mean physician assessment of global response to treatment was also significantly better in anakinra-treated patients on day 8 (–0.40 [95% CI –0.78, –0.02]). In addition, the mean physician assessment of tenderness and swelling was significantly better in the total anakinra group compared to the triamcinolone group at 72 hours (–0.47 [95% CI –0.73, –0.20] and –0.31 [95% CI –0.56, –0.05], respectively), and was also better for swelling on day 8 (–0.33 [95% CI –0.55, –0.11]). Furthermore, significantly less presence of erythema was

Table 2. Estimated change in patient-assessed pain intensity (VAS) in the index joint from baseline to 24–72 hours in flares 1–3*

	Triamcinolone (n = 55)	Anakinra total (n = 110)	Anakinra 100 mg (n = 56)	Anakinra 200 mg (n = 54)
Flare 1				
No. of patients	53	108	56	52
VAS score at baseline, mean (95% CI)	77.9 (73.0, 82.8)	75.5 (71.4, 79.5)	75.6 (70.9, 80.3)	75.4 (70.7, 80.0)
VAS score at 24–72 hours, mean (95% CI)	38.5 (30.6, 46.4)	34.2 (28.4, 40.1)	33.8 (26.2, 41.3)	34.7 (27.1, 42.3)
Change from baseline, mean (95% CI)	−39.4 (−46.8, −32.0)	−41.2 (−46.3, −36.2)	−41.8 (−48.9, −34.8)	−40.7 (−47.9, −33.4)
Difference in mean change vs. triamcinolone (95% CI)	Referent	−1.8 (−10.8, −7.1)	−2.4 (−12.6, 7.8)	−1.2 (−11.6, 9.1)
P	–	0.688	0.643	0.812
Flare 2				
No. of patients	17	42	22	20
VAS score at baseline, mean (95% CI)	78.7 (69.2, 88.3)	74.8 (67.4, 82.2)	80.6 (71.8, 89.4)	69.0 (60.2, 77.8)
VAS score at 24–72 hours, mean (95% CI)	47.6 (35.1, 60.1)	40.9 (31.7, 50.1)	45.3 (34.3, 56.3)	36.5 (24.3, 48.7)
Change from baseline, mean (95% CI)	−31.1 (−44.6, −17.6)	−33.9 (−42.5, −25.4)	−35.3 (−46.7, −23.9)	−32.5 (−45.3, −19.7)
Difference in mean change vs. triamcinolone (95% CI)	Referent	−2.8 (−18.8, 13.2)	−4.2 (−21.9, 13.5)	−1.4 (−20.0, 17.2)
P	–	0.724	0.631	0.879
Flare 3				
No. of patients	5	26	13	13
VAS score at baseline, mean (95% CI)	80.4 (67.5, 93.2)	76.6 (70.7, 82.4)	79.2 (71.7, 86.8)	73.9 (65.9, 81.9)
VAS score at 24–72 hours, mean (95% CI)	29.2 (11.2, 47.3)	44.8 (36.7, 53.0)	38.9 (28.1, 49.6)	50.8 (39.1, 62.4)
Change from baseline, mean (95% CI)	−51.2 (−68.8, −33.5)	−31.8 (−39.7, −23.9)	−40.4 (−51.3, −29.5)	−23.1 (−34.6, −11.7)
Difference in mean change vs. triamcinolone (95% CI)	Referent	19.4 (0.1, 38.7)	10.8 (−10.0, 31.5)	28.0 (7.0, 49.1)
P	–	0.049	0.297	0.011

* VAS = visual analog scale (0–100); 95% CI = 95% confidence interval.

reported in the total anakinra group compared to the triamcinolone group at 72 hours (odds ratio 0.47 [95% CI 0.23, 0.95]).

Inflammation markers. Anakinra-treated patients had significantly reduced CRP levels at 72 hours and on day 8, compared to those in the triamcinolone group (mean difference –0.93 [95% CI –1.58, –0.29] and –0.55 [95% CI –1.05, –0.04], respectively). On day 15, however, CRP levels were significantly reduced in the triamcinolone group compared to the total anakinra group (mean difference 0.78 [95% CI 0.16, 1.40]) (Supplementary Figure 2A, http://onlinelibrary.wiley.com/doi/10.1002/art.41699/abstract). SAA levels were also significantly reduced in anakinra-treated patients compared to those treated with triamcinolone at 72 hours (mean difference –60.65 [95% CI –106.24, –15.06]) and on day 8 (–26.66 [95% CI –49.72, –3.61]), whereas no difference between the treatment groups was found on day 15 (Supplementary Figure 2B).

Extension phase. The median time of study participation for all patients was 62.4 weeks (range 0.1–119.6) and was similar in all treatment groups (Supplementary Table 5, on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41699/abstract). One hundred sixty-one patients were treated for 1 flare (n = 55, 52, and 54 in the anakinra 100 mg group, anakinra 200 mg group, and triamcinolone group, respectively) and 61 for 2 flares (n = 23, 21, and 17, respectively). More than twice as many patients were treated for 3 flares in the anakinra groups compared to the triamcinolone group (n = 13 in the anakinra 100 mg and 200 mg groups, n = 5 in the triamcinolone group). One patient (anakinra group) was treated for 9 flares. Overall, 301 flares were treated in the study (214 with anakinra and 87 with triamcinolone).

Reduction in pain intensity for the second and third flares was similar to that observed for the first flare. For the second flare, the mean change in pain was –33.9 with anakinra and –31.1 with triamcinolone. For the third flare the mean change in pain was –31.8 with anakinra and –51.2 with triamcinolone. The difference between anakinra and triamcinolone treatment in the mean change in pain intensity for the second flare did not reach statistical significance ($P = 0.724$), while the mean change for the third flare significantly favored triamcinolone ($P = 0.049$), although the number of subjects contributing to this finding was small (26 anakinra-treated patients and 5 triamcinolone-treated patients) (Table 2). This difference was not due to neutralizing antibodies to anakinra, since no patients in the anakinra groups had neutralizing antibodies when experiencing the third flare (Supplementary Figure 3, http://onlinelibrary.wiley.com/doi/10.1002/art.41699/abstract). Changes in pain were not analyzed for the fourth to ninth flares due to the small number of patients. Overall, anakinra showed numerically better improvement for most of the secondary end points (Table 3).

Safety. The incidence of treatment-emergent AEs during all flares was similar in the anakinra and triamcinolone groups (Table 4). There were no unexpected safety findings. Hypertriglyceridemia

Table 3. Secondary end points, global assessments, and signs of inflammation: anakinra versus triamcinolone*

Secondary end point	Day 4	Day 8	Day 15
Patient assessment of global response to treatment			
Flare 1	+	+†	+†
Flare 2	+	+	+
Flare 3	+	+	+
Physician assessment of global response to treatment			
Flare 1	+	+†	+
Flare 2	+	+	+
Flare 3	+	+	+
Physician assessment of tenderness			
Flare 1	+†	+	–
Flare 2	+	–	+
Flare 3	+	–	–
Physician assessment of swelling			
Flare 1	+†	+†	+
Flare 2	+	–	–
Flare 3	+	+	+
Physician assessment of erythema			
Flare 1	+†	–	–
Flare 2	+	–	+
Flare 3	+	+	–

* + indicates outcome in favor of anakinra; – indicates outcome in favor of triamcinolone.
† $P < 0.05$ (statistical testing was only performed at flare 1).

(5 patients), neutropenia (4 patients), and various types of injection site reactions (erythema, pruritus, or swelling) were the most frequently reported AEs in the anakinra groups. Hypertriglyceridemia, a common finding in patients with gout, occurred at a similar frequency in all treatment groups. Headache (2 patients) was most common in the triamcinolone group. The majority of AEs were mild. In the anakinra group, severe AEs were observed in 8 patients (7.5%), and SAEs occurred in 5 patients (4.7%). SAEs in the anakinra group were gastric ulcer, anemia, seizure, respiratory failure, cardiogenic shock, acute respiratory failure, coronary artery disease, and sickle cell anemia. All SAEs were judged to be not causally related to anakinra. No severe AEs or SAEs were observed in the triamcinolone group. The pattern and frequency of AEs did not appear to change during treatment of repeated flares.

Immunogenicity. One hundred seven anakinra-treated patients were tested for antidrug antibodies; 19 (17.8%) had antidrug antibodies in low titers at some time point, and 4 (3.7%) had neutralizing antibodies (Supplementary Figure 3, http://onlinelibrary.wiley.com/doi/10.1002/art.41699/abstract). Seven patients (6.5%) already tested positive for antidrug antibodies at baseline, which was similar to the percentage among healthy individuals during method validation. Of the 12 anakinra treatment–induced antidrug antibody–positive patients (11.2%), 6 had repeated positive findings on antidrug antibody tests at subsequent flares 2–8. Two triamcinolone-treated patients were positive for anakinra antidrug antibodies at baseline. Of the 12 patients with treatment-induced antidrug antibodies, 7 (58.3%) tested positive for cross-reactivity with "endogenous-like" recombinant IL-1Ra (IL-Ra antidrug antibodies) and 3 (25.0%) were positive for neutralizing antibodies. The incidence of neutralizing antibodies was similar to that previously observed with anakinra given for other indications and in other treatment regimens. The frequency of antidrug antibody occurrence did not appear to change across the repeated flares, with overall low antidrug antibody and neutralizing antibody titers. No antidrug antibody–associated AEs were observed, and there was no apparent impact of antidrug antibodies on serum anakinra levels, serum levels of CRP or SAA, or pain in the index joint through day 8.

DISCUSSION

In this study we evaluated the efficacy, safety, and dosing of anakinra for gout flares in patients for whom conventional antiinflammatory therapy is not suitable. Anakinra was not superior to triamcinolone with regard to the primary outcome measure, but outperformed triamcinolone on most of the individual secondary outcome measures. Results obtained with anakinra at 100 mg/day for 5 days were comparable to those obtained with a dosage

Table 4. Treatment-emergent adverse events (TEAEs) during the study*

	Triamcinolone (n = 54)	Anakinra total (n = 107)	Anakinra 100 mg/day (n = 55)	Anakinra 200 mg/day (n = 52)
TEAEs	22 (40.7)	50 (46.7)	21 (38.2)	29 (55.8)
Severe TEAEs	0	8 (7.5)	5 (9.1)	3 (5.8)
Nonserious TEAEs	22 (40.7)	48 (44.9)	19 (34.5)	29 (55.8)
Serious TEAEs	0	5 (4.7)	4 (7.3)	1 (1.9)
Related TEAEs	2 (3.7)	22 (20.6)	8 (14.5)	14 (26.9)
Fatal TEAEs	0	0	0	0
TEAEs leading to study withdrawal	2 (3.7)	1 (0.9)	0	1 (1.9)
TEAE leading to drug discontinuation	3 (5.6)	3 (2.8)	1 (1.8)	2 (3.8)

* Values are the number (%) of patients.

of 200 mg/day; therefore, the lower dose appears to be the clinically appropriate choice for treatment of a gout flare. Gout is a recurrent disease that frequently requires episodic re-treatment. The study extension period in the present work added to background evidence that anakinra is safe for recurrent episodic use (1,6,7,14–17).

The most common reason NSAID treatment was deemed inappropriate among the study participants was lack of efficacy. Since NSAIDs typically are effective in the treatment of gout flares, it is conceivable that gout was relatively refractory in many of the patients. This notion was supported by resolution of pain in only 65.5% (with triamcinolone) and 63.6% (with anakinra) on day 15.

Strengths of this study included a design that mimicked real-world treatment scenarios, which included patients who had comorbidities and were receiving ULT before or during the study. A superiority study design was selected to comply with US regulatory agency guidance at the time, which specified that trials intended to provide evidence of efficacy of an analgesic should be designed as superiority trials and that the comparator could be a lower dose of the investigational drug, placebo, or an active comparator. However, for the purpose of fully informing clinicians, a noninferiority design would have been more appropriate. A prime example is a recent randomized trial with a noninferiority design, in which anakinra was observed to be noninferior to the free choice of usual prednisone, naproxen, or colchicine treatment for gout flares (20).

The use of biologics raises the issue of immunogenicity and the potential development of antidrug antibodies, the occurrence of which can be linked to altered pharmacokinetics, increased risk of AEs, and reduced efficacy. Previous immunogenicity data on anakinra-treated patients with severe cryopyrin-associated periodic syndrome (CAPS) or RA have not indicated an association between antidrug antibodies and significant safety concerns (27–29). However, in CAPS and RA anakinra was administered regularly, rather than intermittently as in the present study. Overall, in this study the frequency of antidrug antibody positivity in the anakinra treatment groups was low and did not increase after repeated treatments. Furthermore, anakinra appeared to be generally well tolerated, with a safety profile similar to those previously recorded in studies of anakinra treatment for other indications and during postmarketing use.

The terminal half-life of anakinra ranges from 4 to 6 hours, which is considerably shorter than that of triamcinolone. Moreover, the effect of triamcinolone can be much longer than its half-life in plasma would suggest (delayed effect), such that the extended effect is not directly linked to plasma half-life. As seen from the serially tested levels of the inflammation markers CRP and SAA, anakinra had a more immediate short-term onset of effect but shorter duration of effect compared to triamcinolone.

Although anakinra was not superior to triamcinolone, it may be an alternative therapy for patients who cannot tolerate the approved therapies, or whose symptoms fail to respond to such therapies, as recommended in the current ACR/EULAR guideline. In contrast to glucocorticoids and/or NSAIDs, anakinra has not been reported to exacerbate diabetes or promote hypertension, renal failure, sodium retention, gastric ulcerogenesis, or myocardial infarction (30). Moreover, colchicine must be dosed with caution in patients with chronic kidney disease, those taking potent CYP3A4 or P-glycoprotein inhibitors, or those who are on a sustained colchicine regimen for gout flare prophylaxis or have recently received colchicine to treat a gout flare.

There were some limitations to this study. Since anakinra and triamcinolone reduced pain to similar extents in this trial, we speculate that a possible ceiling effect was reached for alleviation of gout flare–related pain by the antiinflammatory agents. As such, pain response as the primary end point might be seen as a limitation, particularly since secondary end points favored anakinra. Clearly, pain is an important and relevant end point in gout and, unlike multiple other clinical response parameters, is endorsed by the Outcome Measures in Rheumatology group as a validated outcome measure for acute gout flare (31). However, there has been recent attention to the need to better evaluate other clinical aspects of gout flares that are of importance to the patient such as tenderness, swelling, and immobility, including by a composite end point. One composite end point instrument in development, the Gout Attack Intensity Score, lacked a floor or ceiling effect with the use of patient-reported symptoms for discriminating responders from nonresponders (32) when data from the trial of anakinra compared to free choice usual care (20) were analyzed. Finally, investigation of the comparative effectiveness of anakinra and other IL-1 inhibitors for gout flare was beyond the scope of the present study. Unlike 5-day dosing of anakinra in this study, a single 150 mg dose of canakinumab was superior to the same 40 mg intramuscular triamcinolone acetonide comparator used here, by ~11 mm on a 0–100 mm VAS, for pain relief for acute gout flare at 72 hours (9). While it is inappropriate to directly compare studies post hoc, the study designs, study populations, and adherence to therapy appeared not to differ extensively, and there is therefore no obvious explanation for the disparate results. It is not possible to perform a robust quantitative comparison of the primary outcome measure of VAS pain responses in our anaGO study versus trials of the IL-1β blocking agent canakinumab for acute gout flares. Future head-to-head studies will be needed to directly test differences in the therapeutic effects of distinct biologic IL-1 antagonists for acute gout flare, and to discern the clinical immunopharmacologic bases for such differences.

In conclusion, anakinra was not superior to triamcinolone in this study but showed a substantial and similar reduction in patient-assessed pain, and most secondary outcomes favored anakinra. Consistent with current treatment guidelines, anakinra can be considered as an effective option in the treatment of gout flares when conventional therapy is unsuitable.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Saag had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Saag, Ohlman, Osterling Koskinen, Åkerblad, Wikén, So, Pillinger, Terkeltaub.

Acquisition of data. Saag, Khanna, Keenan.

Analysis and interpretation of data. Saag, Khanna, Keenan, Ohlman, Osterling Koskinen, Sparve, Åkerblad, Wikén, So, Pillinger, Terkeltaub.

ROLE OF THE STUDY SPONSOR

Sobi, with input from the authors, designed the study. The study investigators collected the data. Results were analyzed by Sobi and interpreted by Sobi and all authors. Sobi provided writing assistance for the manuscript and reviewed and approved the manuscript prior to submission. The authors had the final decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Sobi.

REFERENCES

1. Khanna D, Khanna PP, Fitzgerald JD, Singh MK, Bae S, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res (Hoboken) 2012;64:1447–61.
2. Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castaneda J, et al. 2018 updated European League Against Rheumatism evidence-based recommendations for the diagnosis of gout. Ann Rheum Dis 2020;79:31–8.
3. Chen K, Fields T, Mancuso CA, Bass AR, Vasanth L. Anakinra's efficacy is variable in refractory gout: report of ten cases. Semin Arthritis Rheum 2010;40:210–4.
4. Gratton SB, Scalapino KJ, Fye KH. Case of anakinra as a steroid-sparing agent for gout inflammation. Arthritis Rheum 2009;61:1268–70.
5. Keenan RT, O'Brien WR, Lee KH, Crittenden DB, Fisher MC, Goldfarb DS, et al. Prevalence of contraindications and prescription of pharmacologic therapies for gout. Am J Med 2011;124:155–63.
6. Thueringer JT, Doll NK, Gertner E. Anakinra for the treatment of acute severe gout in critically ill patients. Semin Arthritis Rheum 2015;45:81–5.
7. Tran AP, Edelman J. Interleukin-1 inhibition by anakinra in refractory chronic tophaceous gout. Int J Rheum Dis 2011;14:e33–7.
8. Hirsch JD, Gnanasakthy A, Lale R, Choi K, Sarkin AJ. Efficacy of canakinumab vs. triamcinolone acetonide according to multiple gouty arthritis-related health outcomes measures. Int J Clin Pract 2014;68:1503–7.
9. Schlesinger N, Alten RE, Bardin T, Schumacher HR, Bloch M, Gimona A, et al. Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomised, multicentre, active-controlled, double-blind trials and their initial extensions. Ann Rheum Dis 2012;71:1839–48.
10. Schlesinger N, De Meulemeester M, Pikhlak A, Yucel AE, Richard D, Murphy V, et al. Canakinumab relieves symptoms of acute flares and improves health-related quality of life in patients with difficult-to-treat gouty arthritis by suppressing inflammation: results of a randomized, dose-ranging study. Arthritis Res Ther 2011;13:R53.
11. Schlesinger N, Mysler E, Lin HY, De Meulemeester M, Rovensky J, Arulmani U, et al. Canakinumab reduces the risk of acute gouty arthritis flares during initiation of allopurinol treatment: results of a double-blind, randomised study. Ann Rheum Dis 2011;70:1264–71.
12. So A, De Meulemeester M, Pikhlak A, Yucel AE, Richard D, Murphy V, et al. Canakinumab for the treatment of acute flares in difficult-to-treat gouty arthritis: results of a multicenter, phase II, dose-ranging study. Arthritis Rheum 2010;62:3064–76.
13. Solomon DH, Glynn RJ, MacFadyen JG, Libby P, Thuren T, Everett BM, et al. Relationship of interleukin-1β blockade with incident gout and serum uric acid levels: exploratory analysis of a randomized controlled trial. Ann Intern Med 2018;169:535–42.
14. Aouba A, Deshayes S, Frenzel L, Decottignies A, Pressiat C, Bienvenu B, et al. Efficacy of anakinra for various types of crystal-induced arthritis in complex hospitalized patients: a case series and review of the literature. Mediators Inflamm 2015;2015:792173.
15. Ghosh P, Cho M, Rawat G, Simkin PA, Gardner GC. Treatment of acute gouty arthritis in complex hospitalized patients with anakinra. Arthritis Care Res (Hoboken) 2013;65:1381–4.
16. Ottaviani S, Molto A, Ea HK, Neveu S, Gill G, Brunier L, et al. Efficacy of anakinra in gouty arthritis: a retrospective study of 40 cases. Arthritis Res Ther 2013;15:R123.
17. So A, De Smedt T, Revaz S, Tschopp J. A pilot study of IL-1 inhibition by anakinra in acute gout. Arthritis Res Ther 2007;9:R28.
18. Pascart T, Norberciak L, Ea HK, Graf S, Guggenbuhl P, Liote F. Difficult-to-treat gout flares: eligibility for interleukin-1 inhibition in private practice is uncommon according to current EMA approval. Rheumatology (Oxford) 2019;58:2181–7.
19. FitzGerald JD, Dalbeth N, Mikuls T, Brignardello-Petersen R, Guyatt G, Abeles AM, et al. 2020 American College of Rheumatology guideline for the management of gout. Arthritis Rheumatol 2020;72:879–95.
20. Janssen CA, Oude Voshaar MA, Vonkeman HE, Jansen T, Janssen M, Kok MR, et al. Anakinra for the treatment of acute gout flares: a randomized, double-blind, placebo-controlled, active-comparator, non-inferiority trial. Rheumatology (Oxford) 2019;58:1344–52.
21. Mitha E, Schumacher HR, Fouche L, Luo SF, Weinstein SP, Yancopoulos GD, et al. Rilonacept for gout flare prevention during initiation of uric acid-lowering therapy: results from the PRESURGE-2 international, phase 3, randomized, placebo-controlled trial. Rheumatology (Oxford) 2013;52:1285–92.
22. Schumacher HR Jr, Evans RR, Saag KG, Clower J, Jennings W, Weinstein SP, et al. Rilonacept (interleukin-1 trap) for prevention of gout flares during initiation of uric acid–lowering therapy: results from a phase III randomized, double-blind, placebo-controlled, confirmatory efficacy study. Arthritis Care Res (Hoboken) 2012;64:1462–70.
23. Schumacher HR Jr, Sundy JS, Terkeltaub R, Knapp HR, Mellis SJ, Stahl N, et al. Rilonacept (interleukin-1 trap) in the prevention of acute gout flares during initiation of urate-lowering therapy: results of a phase II randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2012;64:876–84.
24. Terkeltaub R, Sundy JS, Schumacher HR, Murphy F, Bookbinder S, Biedermann S, et al. The interleukin 1 inhibitor rilonacept in treatment of chronic gouty arthritis: results of a placebo-controlled, monosequence crossover, non-randomised, single-blind pilot study. Ann Rheum Dis 2009;68:1613–7.
25. Terkeltaub RA, Schumacher HR, Carter JD, Baraf HS, Evans RR, Wang J, et al. Rilonacept in the treatment of acute gouty arthritis: a randomized, controlled clinical trial using indomethacin as the active comparator. Arthritis Res Ther 2013;15:R25.

26. Neogi T, Jansen TL, Dalbeth N, Fransen J, Schumacher HR, Berendsen D, et al. 2015 gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative [published erratum appears in Arthritis Rheumatol 2016;68:515]. Arthritis Rheumatol 2015;67:2557–68.
27. Cohen S, Hurd E, Cush J, Schiff M, Weinblatt ME, Moreland LW, et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four–week, multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002;46:614–24.
28. Fleischmann RM, Tesser J, Schiff MH, Schechtman J, Burmester GR, Bennett R, et al. Safety of extended treatment with anakinra in patients with rheumatoid arthritis. Ann Rheum Dis 2006;65:1006–12.
29. Wiken M, Hallen B, Kullenberg T, Koskinen LO. Development and effect of antibodies to anakinra during treatment of severe CAPS: sub-analysis of a long-term safety and efficacy study. Clin Rheumatol 2018;37:3381–6.
30. Kineret (anakinra) prescribing information. Stockholm (Sweden): Sobi; 2001. URL: https://wwwaccessdatafdagov/drugsatfda_docs/label/2012/103950s5136lblpdf.
31. Singh JA, Taylor WJ, Dalbeth N, Simon LS, Sundy J, Grainger R, et al. OMERACT endorsement of measures of outcome for studies of acute gout. J Rheumatol 2014;41:569–73.
32. Janssen CA, Voshaar MA, Klooster PM, Vonkeman HE, van de Laar M. Development and validation of a patient-reported gout attack intensity score for use in gout clinical studies. Rheumatology (Oxford) 2019;58:1928–34.

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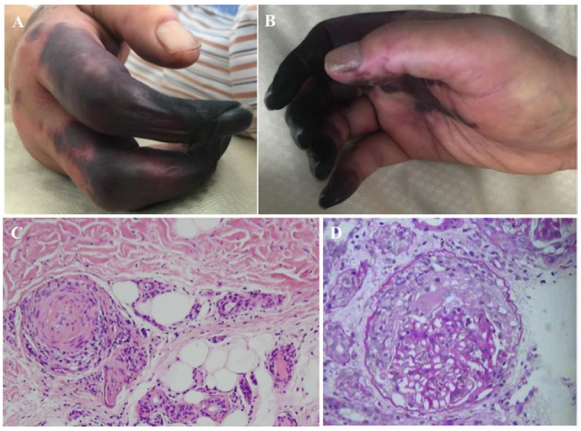
Clinical Images: Acute digital necrosis due to interferon-α–induced antineutrophil cytoplasmic antibody–associated vasculitis



The patient, a 69-year-old woman with a history of human T lymphotropic virus type I–associated myelopathy that had been treated with interferon-α (IFNα), presented with a three-week history of high fever and rapidly progressing discoloration and pain in the digits. Physical examination revealed black discoloration of the right second and fifth distal fingers (**A** and **B**) and left second through fifth distal fingers as well as purpuric lesions on several fingers. There were no sclerodactyly or telangiectasias to suggest scleroderma. The bilateral radial artery pulses were palpable. There had been no response to antiplatelet, anticoagulant, or vasodilator therapy. The biochemical profile showed elevated C-reactive protein (CRP) (21.72 mg/dl [normal <0.3]) and creatinine (2.50 mg/dl [normal <0.6]) and presence of myeloperoxidase (MPO)–antineutrophil cytoplasmic antibodies (ANCA) (98.8 IU/ml [normal <0.5]); prior to IFN therapy MPO-ANCA had been absent. Test results for antinuclear antibodies, antiphospholipid antibodies, cryoglobulins, and cold agglutinins were negative. Transesophageal echocardiography showed no vegetations in the cardiac valves. Biopsy of the digital lesions and kidney after initiation of steroid therapy demonstrated leukocytoclastic vasculitis in a small artery (**C**) and crescentic glomerulonephritis (**D**), respectively. The patient was clinically diagnosed as having IFN-induced ANCA-associated vasculitis (AAV). Treatment with oral prednisolone at 60 mg/day was initiated, and oral azathioprine at 100 mg/day was later added. After treatment, her symptoms improved, and CRP, creatinine, and ANCA levels normalized. Parts of the patient's necrotic fingers were amputated, but the other digits recovered completely. IFN-induced vasculitis is extremely rare; however, acute digital necrosis could be an initial manifestation of IFN-induced AAV (1,2). In patients with acute digital necrosis after treatment with IFN, AAV should be considered as a cause.

1. Grau RG. Drug-induced vasculitis: new insights and a changing lineup of suspects. Curr Rheumatol Rep 2015;17:71.
2. Derksen WJ, Erkan D, Potter HG, Lockshin MD. Interferon induced digital artery vasculitis. J Rheumatol 2005;32:191–2.

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