ORIGINAL ARTICLE

Canakinumab for the Treatment of Autoinflammatory Recurrent Fever Syndromes

F. De Benedetti, M. Gattorno, J. Anton, E. Ben-Chetrit, J. Frenkel, H.M. Hoffman, I. Koné-Paut, H.J. Lachmann, S. Ozen, A. Simon, A. Zeft, I. Calvo Penades, M. Moutschen, P. Quartier, O. Kasapcopur, A. Shcherbina, M. Hofer, P.J. Hashkes, J. Van der Hilst, R. Hara, S. Bujan-Rivas, T. Constantin, A. Gul, A. Livneh, P. Brogan, M. Cattalini, L. Obici, K. Lheritier, A. Speziale, and G. Junge

ABSTRACT

BACKGROUND

Familial Mediterranean fever, mevalonate kinase deficiency (also known as the hyperimmunoglobulinemia D syndrome), and the tumor necrosis factor receptor–associated periodic syndrome (TRAPS) are monogenic autoinflammatory diseases characterized by recurrent fever flares.

METHODS

We randomly assigned patients with genetically confirmed colchicine-resistant familial Mediterranean fever, mevalonate kinase deficiency, or TRAPS at the time of a flare to receive 150 mg of canakinumab subcutaneously or placebo every 4 weeks. Patients who did not have a resolution of their flare received an add-on injection of 150 mg of canakinumab. The primary outcome was complete response (resolution of flare and no flare until week 16). In the subsequent phase up to week 40, patients who had a complete response underwent a second randomization to receive canakinumab or placebo every 8 weeks. Patients who underwent a second randomization and had a subsequent flare and all other patients received open-label canakinumab.

RESULTS

At week 16, significantly more patients receiving canakinumab had a complete response than those receiving placebo: 61% vs. 6% of patients with colchicine-resistant familial Mediterranean fever ($P<0.001$), 35% versus 6% of those with mevalonate kinase deficiency ($P=0.003$), and 45% versus 8% of those with TRAPS ($P=0.006$). The inclusion of patients whose dose was increased to 300 mg every 4 weeks yielded a complete response in 71% of those with colchicine-resistant familial Mediterranean fever, 57% of those with mevalonate kinase deficiency, and 73% of those with TRAPS. After week 16, an extended dosing regimen (every 8 weeks) maintained disease control in 46% of patients with colchicine-resistant familial Mediterranean fever, 23% of those with mevalonate kinase deficiency, and 53% of those with TRAPS. Among patients who received canakinumab, the most frequently reported adverse events were infections (173.3, 313.5, and 148.0 per 100 patient-years among patients with colchicine-resistant familial Mediterranean fever, those with mevalonate kinase deficiency, and those with TRAPS, respectively), with a few being serious infections (6.6, 13.7, and 0.0 per 100 patient-years).

CONCLUSIONS

In this trial, canakinumab was effective in controlling and preventing flares in patients with colchicine-resistant familial Mediterranean fever, mevalonate kinase deficiency, and TRAPS. (Funded by Novartis; CLUSTER ClinicalTrials.gov number, NCT02059291.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. De Benedetti at the Division of Rheumatology, Ospedale Pediatrico Bambino Gesù, Piazza S. Onofrio 4, 00186 Rome, Italy, or at fabrizio.debenedetti@opbg.net.

A list of the principal investigators for CLUSTER is provided in the Supplementary Appendix, available at NEJM.org.

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Familial mediterranean fever, mevalonate kinase deficiency (also known as the hyperimmunoglobulinemia D syndrome), and the tumor necrosis factor receptor–associated periodic syndrome (TRAPS) are monogenic autoinflammatory diseases that are characterized by recurrent fever episodes, with variable skin, joint, and serosal involvement.[1-3] Flares last several days or weeks and affect functional capacity and quality of life.[4-6] Amyloid A (inflammatory) amyloidosis is a long-term complication.[7] Colchicine is the standard treatment for familial Mediterranean fever. However, it is ineffective or associated with unacceptable side effects in 5 to 10% of patients.[8] No standard treatments are available for mevalonate kinase deficiency or TRAPS.

Evidence of excessive interleukin-1β production in familial Mediterranean fever, mevalonate kinase deficiency, and TRAPS suggests that interleukin-1β is a common mediator in these diseases, although molecular mechanisms differ. Mutations of *MEFV* cause abnormal activation of the pyrin inflammasome.[9,10] Mevalonate kinase deficiency leads to constitutive activation of the pyrin inflammasome and to toll-like receptor–induced inflammatory responses.[9,11-13] In TRAPS, accumulation of mutant TNFR1 protein within the endoplasmic reticulum and abnormal autophagy cause interleukin-1β production.[14-17] Small studies have suggested that interleukin-1 inhibition improves clinical and laboratory features in colchicine-resistant familial Mediterranean fever,[18-22] mevalonate kinase deficiency,[23] and TRAPS.[24,25] The phase 3 Canakinumab Pivotal Umbrella Study in Three Hereditary Periodic Fevers (CLUSTER) was conducted to evaluate the efficacy and safety of canakinumab, an anti–interleukin-1β monoclonal antibody, in patients with colchicine-resistant familial Mediterranean fever, mevalonate kinase deficiency, and TRAPS.

METHODS

TRIAL DESIGN

This trial consisted of one cohort per disease (colchicine-resistant familial Mediterranean fever, mevalonate kinase deficiency, and TRAPS). Each cohort followed the same design (Fig. 1). A screening period defined eligibility (epoch 1 of the trial). Patients with a flare, referred to as a baseline flare, were randomly assigned (at the beginning of epoch 2), in a 1:1 ratio, to receive subcutaneous canakinumab (150 mg, or 2 mg per kilogram of body weight for patients weighing ≤40 kg) or placebo every 4 weeks. A flare was defined as a C-reactive protein (CRP) level of more than 10 mg per liter and a physician's global assessment (PGA) score of 2 or higher. To determine the score, physicians assessed global disease activity, taking into account fever and clinical signs and symptoms associated with each disease (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org) and using a 5-point scale, with scores of 0 (none), 1 (minimal), 2 (mild), 3 (moderate), and 4 (severe).

All the patients were eligible for a blinded dose increase if they had a persistent baseline flare between days 8 and 14 (PGA score of ≥2, or CRP level of >10 mg per liter with <40% reduction from baseline) or a lack of resolution at day 15 (resolution was defined as a PGA score of <2 plus a CRP level of ≤10 mg per liter or a reduction by ≥70% from baseline) (Fig. 1). The blinded dose increase consisted of one add-on injection of 150 mg of canakinumab every 4 weeks.

After day 29, patients were eligible for an open-label increase in the dose if they had a flare (PGA score of ≥2 and CRP level of ≥30 mg per liter). Patients receiving placebo could receive 150 mg of canakinumab every 4 weeks. If they still had a PGA score of 2 or higher and a CRP level of 30 mg or more per liter, they could receive 300 mg, or 4 mg per kilogram for patients weighing 40 kg or more, at their next visit. Patients receiving 150 mg of canakinumab every 4 weeks could receive 300 mg every 4 weeks.

When entering epoch 3, patients assigned to canakinumab who met the primary outcome in epoch 2 underwent a second randomization, in a 1:1 ratio, to receive 150 mg of canakinumab or placebo every 8 weeks. The other patients continued open-label canakinumab. Among patients assigned to placebo every 8 weeks in the second randomization, those who had a flare within 8 weeks switched to open-label canakinumab at a dose of 150 mg every 4 weeks, and those who had a flare after more than 8 weeks switched to canakinumab at a dose of 150 mg every 8 weeks. Patients assigned to canakinumab every 8 weeks in the second randomization who had another flare switched back to every 4 weeks at any time. Any patient who had a flare could receive the maximum dose of 300 mg every 4 weeks.

Approval by the institutional review board or

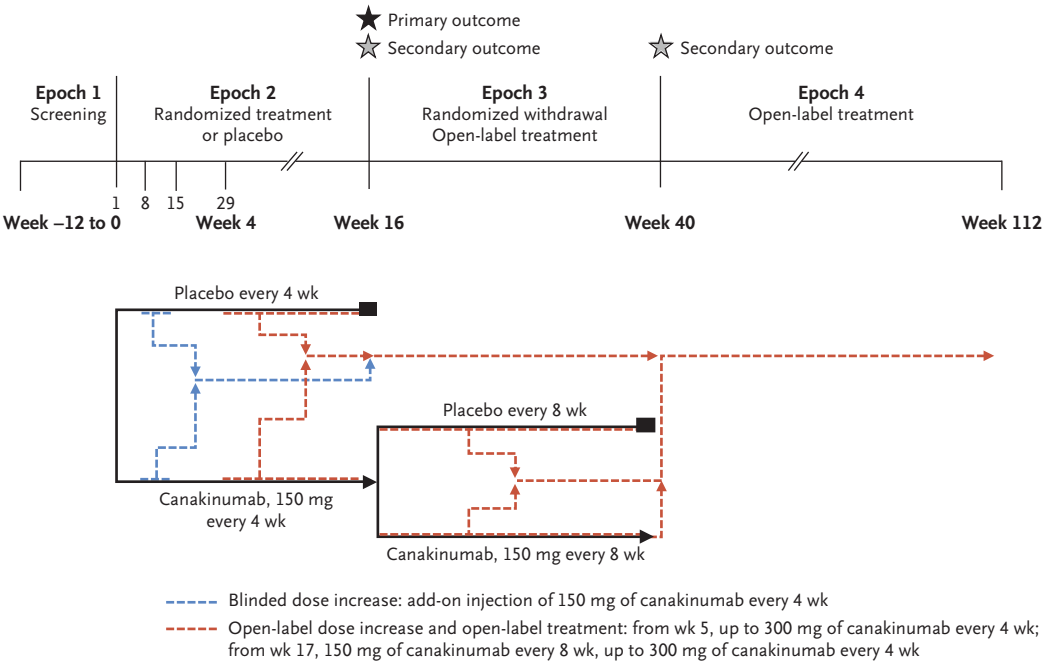

Figure 1. Trial Design Followed by Each Disease Cohort.

The trial design included a screening period of up to 12 weeks (epoch 1), a randomized, double-blind, placebo-controlled period of 16 weeks (epoch 2), a randomized withdrawal and open-label period of 24 weeks (epoch 3), and an open-label extension period of 72 weeks. The primary outcome of complete response (black star) was evaluated at week 16 (end of epoch 2). The secondary outcomes (gray star) of a score on the physician's global assessment of disease activity of less than 2 (on a scale from 0 [none] to 4 [severe]), a C-reactive protein level of 10 mg or less per liter, and a serum amyloid A level of 10 mg or less per liter were evaluated at week 16. The secondary outcome (gray star) of the proportion of patients receiving placebo or canakinumab every 8 weeks (second randomization) who did not have a flare was evaluated at week 40.

independent ethics committee was obtained at each center. Written informed consent was provided by patients or guardians, as appropriate. The trial was designed by the first, third-to-last, and last authors and the sponsor (Novartis). The sponsor was responsible for all data gathering, processing, and management as well as statistical analysis and result reporting. The first author was responsible for drafting the manuscript with assistance from the second and last three authors plus medical writers who were paid by Novartis. All the authors vouch for the completeness and accuracy of the data and the analysis and for the adherence of the trial to the protocol (available at NEJM.org). All the authors contributed to revising the manuscript and made the decision to submit the manuscript for publication.

PATIENTS

Eligible patients were 2 years of age or older. Inclusion criteria for patients with colchicine-resistant familial Mediterranean fever were fulfillment of Tel-Hashomer diagnostic criteria[26] (Table S2 in the Supplementary Appendix), at least one known *MEFV* exon 10 mutation,[27] and historical data documenting at least one fever episode per month despite a standard dose of colchicine (1.5 to 3.0 mg per day or equivalent pediatric-adjusted regimen) or at least one fever episode per month with unacceptable side effects to colchicine. Colchicine was continued at a stable dose that was not associated with unacceptable side effects. Inclusion criteria for patients with mevalonate kinase deficiency were a genetic[27] or enzymatic diagnosis of mevalonate kinase deficiency and historical data documenting at least three fever episodes in a 6-month period. Inclusion criteria for patients with TRAPS were *TNFRSF1A* mutation[27] and chronic or recurrent disease (recurrent disease was defined as >6 fever episodes per year). If patients were currently receiving biologic therapy, historical data for the previous 12 months were obtained.

Historical data on the number of fever episodes were obtained from medical records. A total of 18 patients with TRAPS who were participating in an open-label study[6] entered open-label treatment in epoch 3.

OUTCOMES

Clinical and laboratory assessments were performed at days 1, 15, and 29 and every 28 days thereafter. The number of days with a temperature that was higher than 38°C was recorded in an electronic diary. The primary outcome was the proportion of patients who had a complete response, defined as resolution of the baseline flare at day 15 (PGA score of <2 plus CRP level of ≤10 mg per liter or a reduction by ≥70% from baseline) and no new flare (PGA score of ≥2 and CRP level of ≥30 mg per liter) until week 16. The secondary outcomes were the proportion of patients who had a PGA score of less than 2, a CRP level of 10 mg or less per liter, or a serum amyloid A (SAA) level of 10 mg or less per liter at week 16 and, in epoch 3, the proportion of patients receiving canakinumab or placebo every 8 weeks who had no flare. All outcomes were common to the three cohorts.

STATISTICAL ANALYSIS

Baseline demographic and clinical characteristics were summarized with descriptive statistics. In an intention-to-treat approach, patients with a dose that was increased during epoch 2 were considered not to have had a complete response for primary and secondary outcomes. Data from each cohort were analyzed separately. The frequencies of patients who had a complete response are reported with differences in risk. P values, which were calculated with the use of Fisher's exact test, are shown at a two-sided 5% level. Primary and secondary objectives were tested in a hierarchical testing procedure to control the overall type I error (Table S3 in the Supplementary Appendix). Exploratory analyses were conducted including patients who were assigned to canakinumab and who received a blinded dose increase to 300 mg every 4 weeks. Safety data include exposure up to week 40 for all randomly assigned patients and epoch 3 data for the patients with TRAPS who had been recruited in an open-label study[6] (and the subsequent multiple patient program implemented to ensure treatment continuity) and continued to receive canakinumab in epoch 3.

RESULTS

TRIAL POPULATION

A total of 63 patients with colchicine-resistant familial Mediterranean fever, 72 with mevalonate kinase deficiency, and 46 with TRAPS underwent randomization. Patients had genetically confirmed disease (Table S4 in the Supplementary Appendix) and a severe disease course (Table 1). The majority of patients with colchicine-resistant familial Mediterranean fever were receiving colchicine. In epoch 3, a total of 19 patients with colchicine-resistant familial Mediterranean fever, 13 with mevalonate kinase deficiency, and 9 with TRAPS underwent a second randomization. A total of 40 patients with colchicine-resistant familial Mediterranean fever, 53 with mevalonate kinase deficiency, and 33 with TRAPS continued open-label treatment (Fig. S1 in the Supplementary Appendix). A total of 18 patients with TRAPS participating in an ongoing open-label study continued to receive canakinumab in epoch 3.[6] A total of 6 patients (5 receiving placebo and 1 receiving canakinumab) withdrew during epoch 2, and 9 patients (all receiving canakinumab) withdrew during epoch 3. Of the 15 patients who withdrew, 4 withdrew owing to adverse events, of whom 3 were receiving canakinumab (Fig. S1 in the Supplementary Appendix).

EFFICACY

More patients assigned to canakinumab than to placebo had a resolution of the baseline flare at day 15 (Fig. 2A, and Table S5 in the Supplementary Appendix). At week 16, for all diseases, significantly more patients receiving canakinumab than those receiving placebo met the primary outcome of complete response: 61% versus 6% of those with colchicine-resistant familial Mediterranean fever (P<0.001), 35% versus 6% of those with mevalonate kinase deficiency (P=0.003), and 45% versus 8% of those with TRAPS (P=0.006) (Fig. 2B). In an exploratory analysis involving patients assigned to canakinumab, inclusion of those who received a blinded dose increase to 300 mg every 4 weeks led to a complete response in 71% of those with colchicine-resistant familial Mediterranean fever, 57% of those with mevalonate kinase deficiency, and 73% of those with TRAPS (P<0.001 vs. corresponding placebo for the three comparisons) (Table S6 in the Supplementary Appendix). The proportion of patients

Table 1. Baseline Characteristics of the Patients.*

Characteristic	crFMF		MKD		TRAPS	
	Canakinumab (N=31)	Placebo (N=32)	Canakinumab (N=37)	Placebo (N=35)	Canakinumab (N=22)	Placebo (N=24)
Age						
Mean — yr	22.5±15.0	21.8±13.4	13.0±8.5	13.9±11.6	21.0±19.2	23.6±18.3
Distribution — no. (%)						
≥2 to <12 yr	9 (29)	4 (12)	18 (49)	19 (54)	9 (41)	8 (33)
≥12 to <18 yr	5 (16)	11 (34)	10 (27)	7 (20)	5 (23)	5 (21)
≥18 yr	17 (55)	17 (53)	9 (24)	9 (26)	8 (36)	11 (46)
Female sex — no. (%)	14 (45)	15 (47)	24 (65)	19 (54)	10 (45)	13 (54)
Duration of disease — yr	17.1±11.2	15.1±8.7	11.6±6.1	12.8±11.5	14.9±16.3	12.4±14.1
Fever episodes/yr before the trial	27.9±30.3	20.5±13.2	15.0±6.2	14.0±7.2	9.2±4.7	10.9±7.5
Previous use of biologic agent — no. (%)†	7 (23)	8 (25)	9 (24)	4 (11)	8 (36)	8 (33)
Concomitant colchicine — no. (%)	29 (94)	26 (81)	NA	NA	NA	NA
PGA score — no. (%)‡						
0 or 1	0	0	0	0	0	0
2	3 (10)	6 (19)	10 (27)	7 (20)	9 (41)	11 (46)
3	17 (55)	19 (59)	22 (59)	21 (60)	11 (50)	11 (46)
4	11 (35)	7 (22)	5 (14)	7 (20)	2 (9)	2 (8)
C-reactive protein — mg/liter	164±135	118±113	163±142	182±154	183±195	133±128
Serum amyloid A — mg/liter	1685±2570	865±1018	3191±3173	2960±2677	2074±2734	2558±3880

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. The term crFMF denotes colchicine-resistant familial Mediterranean fever, MKD mevalonate kinase deficiency, NA not applicable, and TRAPS the tumor necrosis factor receptor–associated periodic syndrome.
† A patient could have received one or more biologic agents.
‡ Scores on the physician's global assessment (PGA) of disease activity range from 0 (none) to 4 (severe).

who had a complete response was higher with canakinumab than with placebo in all age groups (Table S7 in the Supplementary Appendix).

For secondary outcomes, significantly more patients in the canakinumab group than in the placebo group had a PGA score of less than 2 (65% vs. 9% of those with colchicine-resistant familial Mediterranean fever [P<0.001], 46% vs. 6% of those with mevalonate kinase deficiency [P=0.001], and 45% vs. 4% of those with TRAPS [P=0.006]) and a CRP level of 10 mg or less per liter (68% vs. 6% of those with colchicine-resistant familial Mediterranean fever [P<0.001], 41% vs. 6% of those with mevalonate kinase deficiency [P=0.002], and 36% vs. 8% of those with TRAPS [P=0.03]) (Fig. 2C, and Table S8 in the Supplementary Appendix). For an SAA level of 10 mg or less per liter, canakinumab was significantly superior only in the TRAPS cohort (27% vs. 0%, P=0.047). No further statistical comparison was performed as per the hierarchical testing procedure (Table S3 in the Supplementary Appendix).

In epoch 3, among patients who underwent a second randomization to canakinumab or placebo every 8 weeks, a lower proportion of those receiving canakinumab than those receiving placebo had flares in all three cohorts (overall, 6 of 19 patients [32%] vs. 16 of 22 [73%]) (Table S9 in the Supplementary Appendix). Among patients who had a complete response in epoch 2, all the patients with colchicine-resistant familial Mediterranean fever, 82% of those with mevalonate kinase deficiency, and 83% of those with TRAPS maintained an absence of flares up to week 40 (Fig. S2 in the Supplementary Appendix). In patients who did not have a complete response, the mean number of days with a temperature that

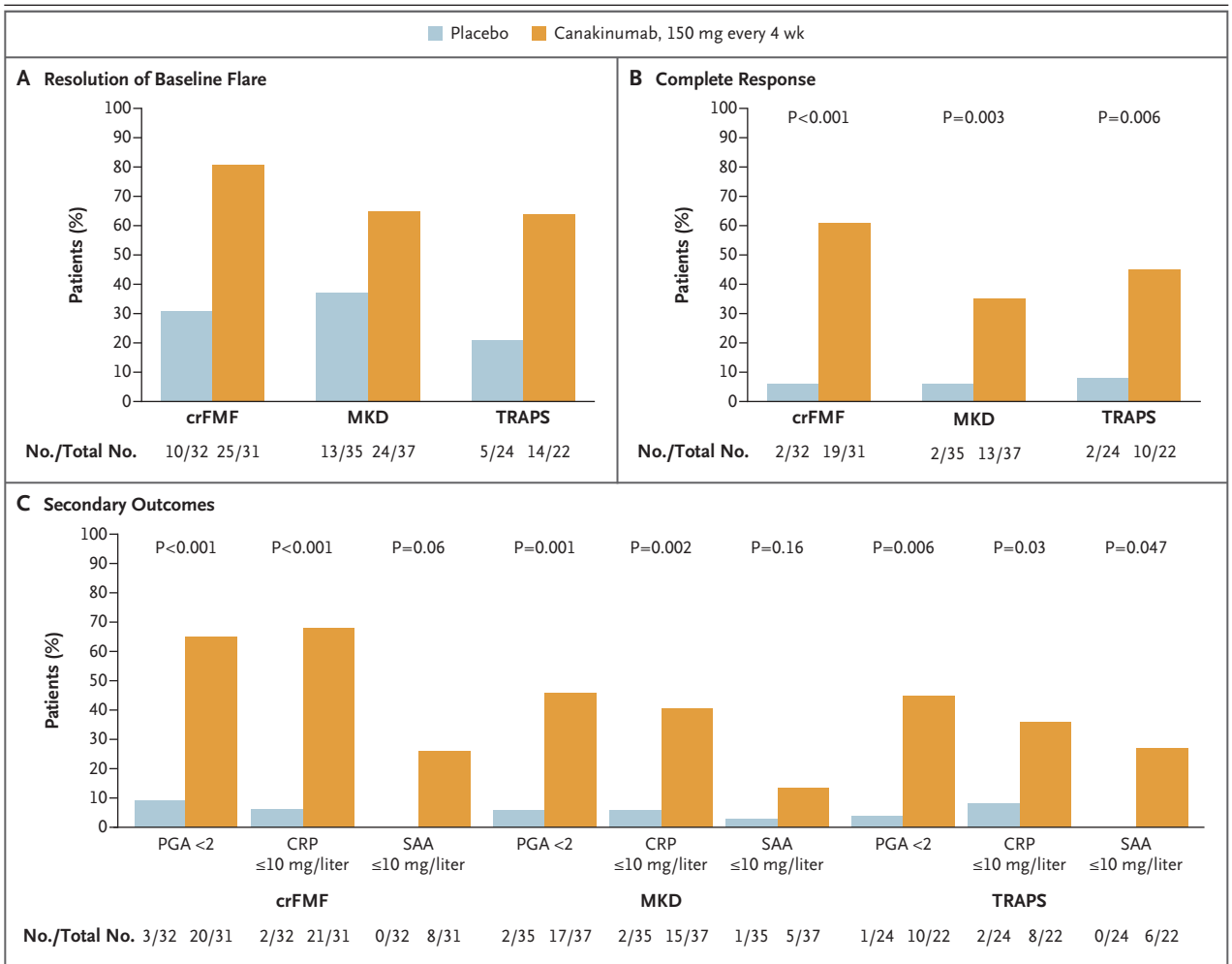

Figure 2. Resolution of Baseline Flare and Response Rate for Primary and Secondary Outcomes at the End of Epoch 2 (Week 16).

Panel A shows the rates of patients assigned to placebo or to 150 mg of canakinumab every 4 weeks who had a resolution of their baseline flare by day 15 (defined as a physician's global assessment [PGA] score of <2 plus a C-reactive protein [CRP] level of ≤10 mg per liter or a reduction by ≥70% from baseline). The PGA measures disease severity, taking into account fever and clinical signs and symptoms associated with each disease (see Table S1 in the Supplementary Appendix), with the use of a 5-point scale with scores of 0 (none), 1 (minimal), 2 (mild), 3 (moderate), and 4 (severe). Panel B shows the rates of patients assigned to placebo or to 150 mg of canakinumab every 4 weeks who met the primary outcome of complete response, defined as the resolution of the baseline flare by day 15 (defined as in Panel A) and no new flare (defined as a PGA score of ≥2 and a CRP level of ≥30 mg per liter) until week 16. Panel C shows the rates of patients assigned to placebo or to 150 mg of canakinumab every 4 weeks who met the secondary outcomes of a PGA score of less than 2, a CRP level of 10 mg or less per liter, and a serum amyloid A (SAA) level of 10 mg or less per liter. The term crFMF denotes colchicine-resistant familial Mediterranean fever, MKD mevalonate kinase deficiency, and TRAPS the tumor necrosis factor receptor–associated periodic syndrome.

was higher than 38°C (from baseline to week 40, normalized to 1 year) was 11.3 in those with colchicine-resistant familial Mediterranean fever, 19.8 in those with mevalonate kinase deficiency, and 23.1 in those with TRAPS. In patients who did not have a complete response, although the mean number of fever episodes in the 12 months before baseline was 32.5 in patients with colchicine-resistant familial Mediterranean fever, 14.7 in those with mevalonate kinase deficiency, and 10.1 in those with TRAPS, the mean number of flares (from baseline to week 40, normalized to 1 year) was 1.2, 2.0, and 1.2, respectively (Fig. 3).

An extended dosing interval of canakinumab every 8 weeks was sufficient to maintain disease control in 46% of patients with colchicine-resis-

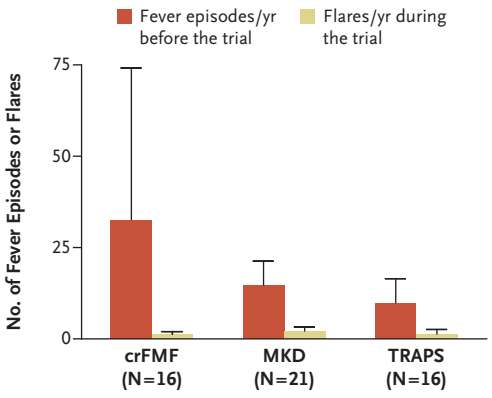

Figure 3. Effect of Canakinumab in Patients Who Did Not Have a Complete Response.

Shown are the number of fever episodes in the 12 months before baseline, as recorded in the clinical history of the patients, and the number of flares during the trial (from baseline to week 40, normalized to 1 year) in patients who did not meet the primary outcome of a complete response at week 16. A flare was defined as a PGA score of 2 or higher and a CRP level of 30 mg or more per liter. Values are expressed as means and standard deviations (T bars).

tant familial Mediterranean fever, 23% of those with mevalonate kinase deficiency, and 53% of those with TRAPS (Fig. S3 in the Supplementary Appendix). An increase in the dose to 300 mg every 4 weeks was required in 10% of patients with colchicine-resistant familial Mediterranean fever, 29% of those with mevalonate kinase deficiency, and 8% of those with TRAPS (Fig. S3 in the Supplementary Appendix). At week 40, levels of SAA had decreased in all cohorts, with a median of 20.0, 14.5, and 10.5 mg per liter in patients with colchicine-resistant familial Mediterranean fever, those with mevalonate kinase deficiency, and those with TRAPS, respectively, with approximately 25% of patients having levels of more than 50 mg per liter and more than half having levels of less than 20 mg per liter (Fig. S4 in the Supplementary Appendix).

SAFETY

No opportunistic infections, cases of tuberculosis, or deaths occurred. During epoch 2, the number of adverse events and serious adverse events was higher in patients receiving canakinumab than in those receiving placebo (Table 2, and Table S10 in the Supplementary Appendix). Overall, the most frequently reported adverse events were infections (particularly respiratory infections), abdominal pain, headaches, and injection-site reactions (Table 2, and Tables S10 and S11 in the Supplementary Appendix). The rate of serious adverse events per 100 patient-years with placebo versus canakinumab was 97.4 versus 42.7 among patients with colchicine-resistant familial Mediterranean fever, 135.5 versus 57.6 among those with mevalonate kinase deficiency, and 50.0 versus 24.8 among those with TRAPS. The cumulative rates of adverse events and serious adverse events during epochs 2 and 3 did not increase as compared with the rates during epoch 2 alone.

Twelve infections were serious. All resolved without sequelae. Two serious infections occurred in patients receiving placebo: pneumonia in a patient with colchicine-resistant familial Mediterranean fever, and infectious diarrhea in a patient with mevalonate kinase deficiency (rate of serious infection in the combined placebo groups, 24.9 per 100 patient-years). Three serious infections (one each of cellulitis, pelvic abscess, and pharyngotonsillitis) were reported in two patients with colchicine-resistant familial Mediterranean fever receiving canakinumab, and seven serious infections (three cases of pneumonia and one each of pharyngitis, laryngitis, gastroenteritis, and conjunctivitis) were reported in six patients with mevalonate kinase deficiency receiving canakinumab (rate of serious infection in all cohorts receiving canakinumab, 7.4 per 100 patient-years).

Adverse events led to discontinuation of canakinumab in two patients with mevalonate kinase deficiency during epoch 2 (one patient had a disease flare, and one had an event of pericarditis) and in two patients with TRAPS during epoch 3 (one patient had grade 2 neutropenia, which was considered by the investigator to be related to canakinumab and which resolved in 5 days, and one had a mild reduction in the glomerular filtration rate, which was considered to be unrelated to the canakinumab). During epoch 2, two patients receiving canakinumab (one with mevalonate kinase deficiency and one with TRAPS) had grade 3 neutropenia, which resolved. No additional grade 3 neutropenia was reported during epoch 3.

DISCUSSION

In this trial, canakinumab was efficacious in controlling and preventing flares in colchicine-resis-

Table 2. Adverse Events and Exposure-Adjusted Rates of Adverse Events.*

Variable	Epoch 2				Cumulative Epochs 2 and 3		
	Combined Placebo†	Canakinumab			Canakinumab		
		crFMF	*MKD*	*TRAPS*	*crFMF*	*MKD*	*TRAPS*
Exposure — patient-yr	8.0	16.4	19.1	12.1	45.6	51.0	39.2
Adverse events — no. of events (rate/100 patient-yr)							
Including fever and disease flare	136 (1693.0)	134 (816.7)	251 (1313.6)	112 (925.7)	332 (728.2)	613 (1201.2)	265 (676.2)
Excluding fever and disease flare	114 (1419.6)	126 (768.2)	243 (1272.2)	111 (917.3)	306 (671.0)	591 (1158.8)	261 (665.8)
Including infections only	19 (236.5)	28 (170.6)	72 (376.8)	26 (214.9)	79 (173.3)	160 (313.5)	58 (148.0)
Most common noninfectious adverse events — no. of events (rate/100 patient-yr)							
Abdominal pain	9 (112.0)	6 (36.6)	6 (31.4)	4 (33.1)	12 (26.3)	15 (29.4)	10 (25.5)
Headache	7 (87.1)	5 (30.5)	12 (62.8)	2 (16.5)	13 (28.5)	25 (49.0)	11 (28.1)
Diarrhea	4 (49.8)	7 (42.7)	10 (52.3)	2 (16.5)	9 (19.7)	20 (39.2)	8 (20.4)
Arthralgia	2 (24.9)	2 (12.2)	9 (47.1)	1 (8.3)	7 (15.4)	20 (39.2)	9 (23.0)
Injection-site reaction	1 (12.4)	13 (79.2)	8 (41.9)	8 (66.1)	20 (43.9)	17 (33.3)	11 (28.1)
Serious adverse events — no. of events (rate/100 patient-yr)							
Including disease flare	8 (99.6)	7 (42.7)	11 (57.6)	3 (24.8)	17 (37.3)	20 (39.2)	5 (12.8)
Excluding disease flare	6 (74.7)	7 (42.7)	8 (41.9)	3 (24.8)	14 (30.7)	14 (27.4)	5 (12.8)
Including infections only	2 (24.9)	1 (6.1)	4 (20.9)	0	3 (6.6)	7 (13.7)	0

* An event that occurred in any patient after receiving at least one dose of canakinumab is listed under canakinumab. See Table S10 in the Supplementary Appendix for a complete list of serious adverse events. Adverse events with at least 20 occurrences are listed; see Table S11 in the Supplementary Appendix for a complete list.
† The combined placebo group includes the patients in all three cohorts who were randomly assigned to placebo at baseline.

The New England Journal of Medicine

tant familial Mediterranean fever, mevalonate kinase deficiency, and TRAPS and produced rapid and sustained improvement in children and adults with severe disease documented by a high number of fever episodes in disease history. Our results corroborate open-label observations with interleukin-1 inhibitors in these diseases[18-25] and the results of two small, controlled trials of other interleukin-1 inhibitors (rilonacept[28] [also known as interleukin-1 trap] and anakinra[29]) in colchicine-resistant familial Mediterranean fever.

The design of our trial was chosen to address the rarity of the diseases, the wide age range, and the need for a randomized, controlled trial, while exploiting the hypothesis of a key common mediator. It also allowed the creation of a larger safety database than could have been generated for one disease. In diseases characterized by acute recurrences, we used, as a clinically meaningful efficacy measure, a complete response that included resolution of the baseline flare and maintenance of the absence of flares over a period of 16 weeks.

Because the trial included three diseases with different frequencies and durations of fever episodes and different clinical presentations (e.g., frequent serositis in familial Mediterranean fever but not in TRAPS or mevalonate kinase deficiency), we chose a definition of flare that was based on the PGA score, a comprehensive clinical measure of severity, and the CRP level, a biochemical measure of inflammation. The same definition of flare was used in the controlled trial of canakinumab in cryopyrinopathies.[30] Indeed, the PGA is part of several outcome measures for rheumatic diseases and is routinely used in clinical practice and trials, including open-label studies of canakinumab in colchicine-resistant familial Mediterranean fever, mevalonate kinase deficiency, and TRAPS.[6,18,23] Although it reduces the effect of the experience of the patient or the patient's parent on assessment of severity, it solves the problem that the results of patient or parent assessment may not be comparable among adults, adolescents, and parents responding on behalf of children.[31]

Few patients receiving placebo had a complete response; this supports the appropriateness of the primary outcome. In patients assigned to canakinumab, including those who received a blinded dose increase to 300 mg every 4 weeks, a complete response occurred in 71% of patients with colchicine-resistant familial Mediterranean fever, 57% of those with mevalonate kinase deficiency, and 73% of those with TRAPS. Among patients who had a complete response, all the patients with colchicine-resistant familial Mediterranean fever and more than 80% of patients with mevalonate kinase deficiency or TRAPS had no flare as of week 40, findings that indicate that responses were durable.

Patients benefited from canakinumab even without having had a complete response. Patients who did not have a complete response had a lower number of days of fever per year (11 in patients with colchicine-resistant familial Mediterranean fever, 20 in those with mevalonate kinase deficiency, and 23 in those with TRAPS) than reported in the literature: 33.2 for familial Mediterranean fever,[32] 33.6 to 48 for mevalonate kinase deficiency,[1,32] and 64.3 to 83.1 for TRAPS.[2,32] In all cohorts, the number of flares per year during the trial was less than 2 in patients who did not have a complete response. The apparent discrepancy between the number of flares and the number of days of fever might be explained by low PGA scores or by an increase in the CRP level to less than 30 mg per liter, suggesting reduced severity of episodes. In patients who did not have a complete response, the number of flares per year during the trial was also remarkably lower than the number of fever episodes in the 12 months before baseline (ranging from 32 in patients with colchicine-resistant familial Mediterranean fever to 10 in those with TRAPS). Information about flares, defined according to trial criteria, was collected prospectively, whereas information on episodes of fever before baseline was collected retrospectively. Although several patients had SAA levels that did not reach a normal range, at week 40 the majority of the patients had SAA levels of less than 20 mg per liter, levels that are associated with decreased progression of amyloid A amyloidosis.[33]

During epoch 3, an extended dosing regimen (every 8 weeks) was evaluated to gain information about the maintenance dose of canakinumab. With this regimen, an absence of flares was maintained in approximately half the patients with colchicine-resistant familial Mediterranean fever and TRAPS; approximately one third of the patients in these two cohorts switched to a regimen equivalent to the starting dose of 150 mg every 4 weeks. In contrast, findings from the

blinded dose increase in epoch 2 and dose adjustment in epoch 3 suggest that a higher dose of canakinumab may be needed to control and prevent disease flares in patients with mevalonate kinase deficiency.

No deaths, opportunistic infections, or cancers were reported. In all three cohorts, infections were more numerous in the canakinumab group than in the placebo group. The rate of infectious events and serious infectious events did not increase during epoch 3. The rate of serious infections in the three cohorts receiving canakinumab (7.4 per 100 patient-years) appears to be similar to that observed among patients with cryopyrinopathies who received canakinumab (5.6 per 100 patient-years).[34,35] Infections appeared to be more frequent among patients with mevalonate kinase deficiency than among those with colchicine-resistant familial Mediterranean fever or TRAPS; this is possibly related to the younger age of this cohort. Although most infections were not serious and all of them resolved without sequelae, vigilance for suspected infections is required. Adverse events led to discontinuation of canakinumab in four patients: two patients had events related to a lack of efficacy, one had grade 2 neutropenia, and one had a mild reduction in the glomerular filtration rate, which was considered to be unrelated to the drug. Two additional episodes of grade 3 neutropenia were reported in two patients receiving canakinumab; both resolved spontaneously with no concurrent infections.

In conclusion, CLUSTER, which used a novel approach of grouping separate diseases with different genetic causes on the basis of a common targetable pathogenic mediator, provided evidence of a pathogenic role of interleukin-1β in colchicine-resistant familial Mediterranean fever, mevalonate kinase deficiency, and TRAPS. It also showed that the inhibition of interleukin-1β was efficacious in controlling and preventing flares in patients with these diseases.

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APPENDIX

The authors' full names and academic degrees are as follows: Fabrizio De Benedetti, M.D., Ph.D., Marco Gattorno, M.D., Jordi Anton, M.D., Ph.D., Eldad Ben-Chetrit, M.D., Joost Frenkel, M.D., Ph.D., Hal M. Hoffman, M.D., Isabelle Koné-Paut, M.D., Ph.D., Helen J. Lachmann, M.D., Seza Ozen, M.D., Anna Simon, M.D., Ph.D., Andrew Zeft, M.D., Inmaculada Calvo Penades, M.D., Ph.D., Michel Moutschen, M.D., Ph.D., Pierre Quartier, M.D., Ozgur Kasapcopur, M.D., Anna Shcherbina, M.D., Ph.D., Michael Hofer, M.D., Ph.D., Philip J. Hashkes, M.D., Jeroen Van der Hilst, M.D., Ph.D., Ryoki Hara, M.D., Ph.D., Segundo Bujan-Rivas, M.D., Tamas Constantin, M.D., Ph.D., Ahmet Gul, M.D., Avi Livneh, M.D., Paul Brogan, M.D., Ph.D., Marco Cattalini, M.D., Laura Obici, M.D., Karine Lheritier, Ph.D., Antonio Speziale, M.D., and Guido Junge, M.D.

From the Division of Rheumatology, Ospedale Pediatrico Bambino Gesù, Rome (F.D.B.), Clinica Pediatrica e Reumatologia, Unità Operativa Semplice Dipartimentale di Malattie Autoinfiammatorie e Immunodeficienze, IRCCS, Istituto G. Gaslini, Genoa (M.G.), the

Pediatric Clinic, University of Brescia and Spedali Civili, Brescia (M.C.), and the Amyloidosis Research and Treatment Center, Biotechnology Research Laboratories, Fondazione IRCCS Policlinico San Matteo, Pavia (L.O.) — all in Italy; the Division of Pediatric Rheumatology, Hospital Sant Joan de Déu, Universitat de Barcelona (J.A.), and the Internal Medicine Department, Autoimmune and Systemic Diseases Unit, Hospital Vall d'Hebron (S.B.-R.), Barcelona, and the Pediatric Rheumatology Unit, Hospital Universitario y Politécnico La Fe, Valencia (I.C.P.) — all in Spain; the Rheumatology Unit, Hadassah–Hebrew University Hospital (E.B.-C.), and the Pediatric Rheumatology Unit, Shaare Zedek Medical Center (P.J.H.), Jerusalem, and Heller Institute of Medical Research and Medicine Faculty, Sheba Medical Center, Tel-Hashomer and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv (A.L.) — all in Israel; the Division of Pediatrics, University Medical Center Utrecht, Utrecht (J.F.), and the Radboud Expertise Center for Immunodeficiency and Autoinflammation, Department of Internal Medicine, Radboud University Medical Center, Nijmegen (A. Simon) — both in the Netherlands; the Departments of Pediatrics and Medicine, University of California at San Diego and Rady Children's Hospital San Diego, San Diego (H.M.H.); the Department of Pediatric Rheumatology, Centre de Référence des Maladies Auto-inflammatoires et de l'Amylose Inflammatoire, Centre Hospitalier Universitaire (CHU) de Bicêtre, Assistance Publique–Hopitaux de Paris (APHP), Université de Paris Sud (I.K.-P.), and Paris-Descartes University, Imagine Institute, Unité d'Immuno-Hématologie et Rhumatologie Pédiatrique, Hôpital Necker–Enfants Malades, APHP (P.Q.), Paris; the National Amyloidosis Centre, University College London Division of Medicine, Royal Free Campus (H.J.L.), and University College London, Great Ormond Street Institute of Child Health, and Great Ormond Street Hospital for Children NHS Foundation Trust (P.B.), London; the Department of Pediatrics, Hacettepe University, Ankara (S.O.), and the Department of Pediatric Rheumatology, Cerrahpasa Medical School (O.K.), and Istanbul Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology (A.G.), Istanbul University, Istanbul — all in Turkey; the Department of Pediatrics, Division of Pediatric Rheumatology, Cleveland Clinic, Cleveland (A.Z.); the Department of Infectious Diseases and General Internal Medicine, CHU Sart-Tilman, University of Liège, Liege (M.M.), and the Department of Infectious Diseases and Immunity, Jessa Hospital, University of Hasselt, Hasselt (J.V.H.) — both in Belgium; the Department of Clinical Immunology, Center for Pediatric Hematology, Oncology, and Immunology, Moscow (A. Shcherbina); Pediatric Rheumatology of Western Switzerland, University of Lausanne, Lausanne, (M.H.), and Novartis, Basel (K.L., A. Speziale, G.J.) — both in Switzerland; the Department of Pediatrics, Yokohama City University Graduate School of Medicine, Yokohama, Japan (R.H.); and the Department of Pediatrics, Semmelweis Egyetem, Budapest, Hungary (T.C.).

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