Pharmacokinetic and Pharmacodynamic Characteristics of Single-dose Canakinumab in Patients With Type 2 Diabetes Mellitus

Adele Noe, PhD[1]; Campbell Howard, MD[2]; Tom Thuren, MD, PhD[2]; Ann Taylor, MD[3]; and Andrej Skerjanec, PhD[1]

[1]Novartis Pharma AG, Basel, Switzerland; [2]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey; and [3]Novartis Institutes for BioMedical Research, Cambridge, Massachusetts

ABSTRACT

Purpose: Interleukin (IL)-1β, an inflammatory molecule, contributes to the development of atherothrombosis and worsening of islet β-cell function. Canakinumab, a human monoclonal antibody, targets IL-1β–dependent inflammation and reduces the vascular inflammatory biomarker, high-sensitivity C-reactive protein (hsCRP), and other inflammatory cardiovascular biomarkers. Here, we aimed to assess the pharmacokinetic (PK) and pharmacodynamic characteristics, including the effect on hsCRP, of canakinumab in patients with type 2 diabetes mellitus (T2DM) after a 2-hour single-dose intravenous infusion.

Methods: This multicenter, randomized, double-blind, placebo-controlled, dose-escalation study was conducted in patients with T2DM (diagnosed ≥6 months before screening) on a stable daily dose of metformin. Patients were randomly assigned to receive a single intravenous dose of canakinumab 0.03, 0.1, 0.3, 1.5, or 10 mg/kg or placebo. The study was initially designed with 1 small cohort (15 patients, 0.3 mg/kg) on a stable dose of metformin ≥500 mg/d for an initial tolerability evaluation; all other patients were on a stable dose of ≥850 mg/d of metformin. The PK profile was assessed at 0 and 2 hours and at days 2, 14, 28, 56, 84, and 168. Changes in hsCRP and hemoglobin (Hb) A_{1c} levels were assessed at weeks 4, 8, 12, and 24.

Findings: Of the 231 enrolled patients, 222 completed the study. Median hsCRP values at screening ranged from 1.8 to 3.2 mg/L, and the median daily dose of metformin ranged from 1000 to 2000 mg. Exposure to canakinumab was dose proportional. The mean half-life ranged from 17 to 26 days, and mean systemic clearance ranged from 0.094 to 0.128 mL/h/kg. Dose-related reductions in hsCRP were significantly greater with canakinumab compared with those with placebo at week 4 (−0.2 mg/L, −0.5 mg/L, −1.5 mg/L, and −1.7 mg/L with the 0.1-, 0.3-, 1.5-, and 10-mg/kg doses, respectively; all, $P < 0.05$). Significant reductions in hsCRP were maintained up to week 12 with the 2 highest doses of canakinumab (−0.8 mg/L with 1.5 mg/kg and −1.3 mg/L with 10 mg/kg; both, $P < 0.05$). A placebo-adjusted decrease in HbA1c of 0.31% at week 12 was reported with canakinumab 10 mg/kg ($P = 0.038$), and a reduction of 0.23% at week 4 was found with canakinumab 1.5 mg/kg ($P = 0.011$).

Implications: The findings from this study suggest that IL-1β blockade after single-dose administration of canakinumab at 1.5 and 10 mg/kg provided sustained suppression of hsCRP levels for 12 weeks in patients with T2DM. ClinicalTrials.gov identifier: NCT00900146. (*Clin Ther.* 2014;36:1625–1637) © 2014 The Authors. Published by Elsevier HS Journals, Inc.

Key words: canakinumab, high-sensitivity C-reactive protein, interleukin-1β, pharmacodynamics, pharmacokinetics, type 2 diabetes mellitus.

INTRODUCTION

Chronic poor glycemic control leads to the development of cardiovascular complications in patients with type 2 diabetes mellitus (T2DM).[1] Most clinical studies use morbidity and all-cause mortality as parameters to assess cardiovascular outcomes in

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patients with T2DM. However, the use of surrogate biomarkers such as high-sensitivity C-reactive protein (hsCRP), interleukin (IL)-6, and fibrinogen can provide a clearer understanding of the early inflammatory changes at the subclinical level in response to the drug effect, thus providing additive value in the assessment of cardiovascular risk in patients with T2DM. Although hsCRP is not a validated biomarker for cardiovascular disease as yet, a meta-analysis conducted by the Emerging Risk Factors Collaboration Centre[2] reported that each 1-SD increase in hsCRP was associated with an increase in vascular risk at least as great as that associated with an SD increase in either blood pressure or cholesterol. Furthermore, in multiple statin trials, hsCRP predicted vascular risk as accurately as did on-treatment levels of low-density lipoprotein cholesterol (LDL-C).[3–7] Findings from previously reported prospective cohort studies suggest that patients with hsCRP of ≥ 2 mg/L were at high risk for cardiovascular diseases. PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy)[4] and A-to-Z (Aggrastat-to-Zocor Trial)[5] used a cutoff criterion of hsCRP <2 mg/L and reported a clinically meaningful relationship between the reduction in hsCRP and a concurrent decrease in the risk for cardiovascular disease. Similarly, in a subgroup analysis from the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial, Ridker et al[7] reported that reductions in both LDL-C to <70 mg/dL and hsCRP to <2 mg/L were independently associated with a lower cardiovascular-events rate in healthy individuals with healthy cholesterol levels. Moreover, the JUPITER study reported that a reduction in hsCRP to <1.0 mg/L was associated with further reductions in events rates independent of the achieved LDL-C levels.

Canakinumab, a human immunoglobulin (Ig) G1 monoclonal anti–IL-1β antibody of the IgG1/k isotype, competitively prevents IL-1β binding to IL-1 receptors. Canakinumab targets the IL-1β–dependent inflammation pathway, thereby reducing the levels of hsCRP and other inflammatory cardiovascular biomarkers.[8] IL-1β plays an important role in the pathophysiology of autoinflammatory diseases such as cryopyrin-associated periodic syndromes, specifically Muckle-Wells syndrome and familial cold autoinflammatory syndrome, systemic juvenile idiopathic arthritis, adult and juvenile rheumatoid arthritis, and gouty arthritis.[9] Furthermore, IL-1β blockade has been shown to improve β-cell function and to prevent or delay the destruction of β cells and worsening of diabetes in patients with T2DM.[10] However, there is limited evidence regarding the use of canakinumab in patients with T2DM. This article describes the pharmacokinetic (PK) and pharmacodynamic (PD) data from a study that assessed the efficacy and tolerability of canakinumab in patients with T2DM. PD data include the measurements of hsCRP as well as total IL-1β (free and canakinumab–IL-1β complex) serum concentrations, which are surrogate markers of drug activity. We also report the change in hemoglobin (Hb) A_{1c} levels and tolerability in patients with T2DM.

PATIENTS AND METHODS

Study Design

This multicenter, randomized, double-blind, placebo-controlled, single-dose study of canakinumab versus placebo was conducted in patients with T2DM on a stable daily dose of metformin. The study was conducted at 15 centers across Germany, the United States, and Russia. The study was conducted according to the ethical principles of the Declaration of Helsinki. The study protocol and all amendments were reviewed and approved by an independent ethics committee or institutional review board. Written informed consent was requested from all eligible patients before randomization. This study is registered with EUDRACT No. 2007-003729-26 and ClinicalTrials.gov Identifier NCT00900146.

In this study, 5 dose levels of canakinumab versus placebo were evaluated in 4 cohorts. This study was initially designed with 1 small cohort (cohort 1, 15 patients randomized 2:1 to active treatment:placebo) for an initial tolerability evaluation using a single intravenous dose (2-hour infusion) of canakinumab 0.3 mg/kg, followed by a cohort of 90 patients (cohort 2, 90 patients randomized 1:1 to active treatment: placebo) who received a single intravenous dose of canakinumab 10 mg/kg or placebo. Subsequently, on the basis of the 1-month postdose data from cohort 2, the study continued with the evaluation of the response to lower doses. In cohort 3, 96 patients were randomized to receive either 0.1, 0.3, or 1.5 mg/kg of canakinumab or placebo (1:1:1:1 randomization). In cohort 4 ($n = 30$), patients were randomized (2:1,

active treatment:placebo) to receive either canakinumab 0.03 mg/kg or placebo.

Patients in cohort 1 were on a stable dose of 500 mg/d of metformin, whereas all other patients were on a stable dose of ≥850 mg/d of metformin. Metformin was the only oral antidiabetic agent allowed in this study.

Inclusion and Exclusion Criteria

Men and women aged 18 to 70 years with a confirmed diagnosis of T2DM for at least 6 months, stable body weight (±5 kg) within 3 months before screening, a body mass index of 25 to 40 kg/m^2, HbA_{1c} levels between 7% and 9.5% inclusive, and on stable dose of metformin monotherapy for at least 3 months before the screening visit were eligible to participate in this study. The key exclusion criteria included a history of type 1 diabetes or secondary types of diabetes; complications of diabetes (ketoacidosis); severe diabetic nephropathy or renal disease with impaired glomerular filtration rate; any active infection or laboratory evidence of neutropenia (neutrophil count below the normal range); myocardial infarction, unstable angina, or congestive heart failure (New York Heart Association functional class III or IV) in the preceding 6 months; and treatment with any other antidiabetic agent, except metformin monotherapy. Patients with any of the following laboratory abnormalities at baseline were excluded: alanine aminotransferase or aspartate aminotransferase >2 times the upper limit of normal, serum creatinine ≥1.5 times the upper limit of normal, proteinuria ≥1 g/d, and/or hsCRP ≥10 mg/L.

Assessments

PK Measurements

Blood samples were collected just before drug administration (0 hour), at 2 hours, and on days 2, 14, 28, 56, 84, and 168 after administration to measure serum canakinumab concentrations and to assess the PK parameters. Serum canakinumab concentrations were measured using competitive ELISA, with a lower limit of quantification (LLOQ) of 100 ng/mL. PK parameters including CL of drug from the serum, V_d during the terminal elimination phase, $t_{½}$, C_{max}, and T_{max} were characterized using noncompartmental analysis by WinNonlin Professional version 5.2 (Pharsight Corporation, Mountain View, California).

PD Measurements

IL-1β

Total IL-1β (sum of free and canakinumab bound) was determined in the serum at 0 and 2 hours and on days 2, 14, 28, 56, 84, and 168 after administration using a commercially available sandwich ELISA method (Quantikine HS kit; R&D Systems Inc, Minneapolis, Minnesota), with an LLOQ of 0.5 pg/mL. The drug CL and ligand production and elimination CL were estimated by nonlinear mixed-effects modeling (NONMEM; Icon plc, Dublin, Ireland) using the drug-ligand–binding model described previously by Chakraborty et al.[9]

hsCRP

At baseline, hsCRP was measured at a local laboratory, together with a central laboratory, to enable the timely inclusion of patients into the study. HsCRP levels were assessed at baseline and at weeks 4, 8, 12, and 24 by immunonephelometry using the BNII System nephelometer (Siemens Healthcare Diagnostics Inc, Deerfield, Illinois) at the central laboratory. The hsCRP concentrations were determined with an intra-assay precision of 2.3% to 4.4%, an inter-assay precision of 2.1% to 5.7%, and an LLOQ of 0.020 mg/dL.

HbA_{1c}

The screening HbA_{1c} sample for inclusionary purposes was analyzed at a local laboratory in each of the cohorts to enable the timely enrollment of patients. However, samples were sent to a central laboratory for uniformity of assessment and ranges during the study. HbA_{1c} levels were assessed at baseline and at weeks 4, 12, 18, and 24.

Tolerability Assessments

Tolerability assessments consisted of collecting all adverse events (AEs) and serious AEs and assessing their severity and relationship to the study drug. The regular monitoring of hematology, blood chemistry, and urinalysis were performed at local laboratories. Vital signs, 12-lead ECG, physical condition, and weight were also assessed.

Statistical Analysis

The primary efficacy variable included PD effect of canakinumab on HbA_{1c} levels (cohorts 2, 3, and 4). The secondary variables included assessments of PK

and PD biomarkers, total serum canakinumab–IL-1β complex concentrations, and hsCRP levels. Tolerability was assessed throughout the study.

The tolerability of the initial dose of canakinumab was assessed in 15 patients with T2DM in cohort 1. This sample size ensured 83% power to detect an absolute difference of 60% in adverse event (AE) rate between the active and placebo groups at an α level of 0.10 using a 1-sided Fisher exact test. The remaining cohorts were the basis for the assessments of efficacy and PD effect of canakinumab in patients with T2DM. In the largest cohort of this study (cohort 2), 90 patients were randomized 1:1 to receive either placebo or canakinumab 10 mg/kg with a 90% likelihood of detection of a significant difference (each at an α level of 0.025) in HbA_{1c} in canakinumab-treated patients at week 4. A minimum sample size of 40 completing patients per treatment group would provide 75% power to detect a 0.5% underlying difference (absolute difference) in HbA_{1c} between treatments, which is generally considered as the lower limit of clinical relevance in HbA_{1c} reduction. Blinded partial HbA_{1c} data from cohort 2 suggested that the variability at week 4 was considerably lower than was the original statistical assumption and was ~0.5% (absolute unit). On the basis of the revised assumption of variability, the sample size of 20 per treatment group in cohort 3 would ensure 80% power to detect a significant difference in change from baseline in HbA_{1c} between one of the active groups and placebo at a 1-sided α level of 0.05, if the true difference were 0.4% or greater. In cohort 4, 30 patients would need to be enrolled to ensure that at least 27 patients would complete the trial. At sample sizes of 18 and 9 completing patients in the 0.03-mg/kg dose and placebo groups, respectively, cohort 4 had 80% probability of detecting a significant difference in change from baseline in HbA_{1c} between the active-treatment and placebo groups at a 1-sided α level of 0.05, if the true difference were 0.6% or greater. The primary goal of cohort 4 was, however, to characterize the effect of a very low dose instead of hypothesis testing. All statistical evaluations were performed using SAS statistical software (SAS Institute Inc, Cary, North Carolina).

All randomized patients who received the study drug were included in the tolerability analysis. All randomized patients who received the study drug and had data available from at least 1 postbaseline assessment were included in the PD data analysis as the intent-to-treat population. The per-protocol population included patients who completed the study up to day 28 without a major protocol deviation. All patients with evaluable PK data were included in the PK data analysis.

Canakinumab PK parameters were determined by the noncompartmental and compartmental modeling methods using a PK binding model, and further details are described elsewhere by Chakraborty et al.[9] PK parameters were analyzed using descriptive statistics such as mean, SD, and %CV, and minimum and maximum. hsCRP and biomarkers (IL-1β) were logarithm-transformed (base e) before analysis to normalize the skewed data. The difference between each dose level of canakinumab and placebo was back-transformed to give point estimates. The hsCRP levels were analyzed using the ANCOVA model, with treatment as a fixed effect and baseline as a covariate at 95% CIs. The corresponding *P* values are also presented. The changes in HbA_{1c} from baseline to weeks 4, 12, 18, and 24 were assessed separately using repeated-measures analysis, with treatment as a fixed effect and day as a repeated factor within the patient. Safety data were summarized using descriptive statistics by treatment cohort and dose. Because the sample size of cohort 2 was clearly greater than those of the other cohorts, an exploratory analysis was performed in this cohort to estimate the number of patients with hsCRP of ≥ 2 mg/L at baseline, and the corresponding patients who achieved hsCRP <2 mg/L at weeks 4 and 12 postdose both in the 10-mg/kg and the placebo groups, using noninferential statistics.

RESULTS

Patient Disposition and Baseline Characteristics

A total of 231 patients with T2DM were enrolled, of whom 222 (cohort 1, 10 active treatment and 5 placebo; cohort 2, 44 active treatment and 45 placebo; cohort 3, 68 active treatment and 24 placebo, and cohort 4, 18 active treatment and 8 placebo) completed the study. The major reasons for study discontinuation were withdrawal of consent (3 patients) and loss to follow-up (2 patients) (Table I).

Patients' demographic and clinical characteristics at baseline were comparable across the treatment groups (Table II). The mean ages of the groups ranged between 52 and 57 years, and >90% were white. Some imbalances between the cohorts with respect to sex and duration of T2DM were noted. The 0.3-mg/

Table I. Patient disposition in this study of the pharmacokinetic properties of canakinumab.

Disposition	Cohort 1		Cohort 2		Cohort 3			Cohort 4	
	Canakinumab 0.3 mg/kg (n = 10)	Placebo (n = 5)	Canakinumab 10 mg/kg (n = 45)	Placebo (n = 45)	Canakinumab 0.1 mg/kg (n = 25)	Canakinumab 0.3 mg/kg (n = 24)	Canakinumab 1.5 mg/kg (n = 23)	Placebo (n = 24)	Canakinumab 0.03 mg/kg (n = 20)	Placebo (n = 10)
Completed	10 (100)	5 (100)	44 (97.8)	45 (100)	24 (96.0)	22 (91.7)	22 (95.7)	24 (100)	18 (90.0)	8 (80.0)
Discontinued	0	0	1 (2.2)	0	1 (4.0)	2 (8.3)	1 (4.3)	0	2 (10.0)	2 (20.0)
Abnormal laboratory value(s)	0	0	0	0	0	0	0	0	1 (5.0)	0
Administrative problems	0	0	0	0	0	0	1 (4.3)	0	0	0
Lost to follow-up	0	0	0	0	0	0	0	0	1 (5.0)	1 (10.0)
Protocol deviation	0	0	1 (2.2)	0	1 (4.0)	0	0	0	0	0
Patient withdrew consent	0	0	0	0	0	2 (8.3)	0	0	0	1 (10.0)

kg dose group in cohort 3 had a higher percentage of female patients (70.8%). The median duration of T2DM was shorter in the 1.5- and 0.03-mg/kg dose groups (3.0 and 3.8 years, respectively) and was longest (9.6 years) in the placebo group in cohort 1. Median hsCRP values at screening ranged from 1.8 (0.1 mg/kg, cohort 3) to 3.2 mg/L (0.03 mg/kg, cohort 4). The median daily doses of metformin ranged from 1000 to 2000 mg (mean daily dose, 1060.0–1788.9 mg).

Pharmacokinetic Properties

Exposure to canakinumab was dose proportional; systemic CLs across groups were comparable. There was no indication of accelerated CL from the terminal phases of the concentration compared with the time profiles that would suggest the formation of antibody against canakinumab. Serum concentrations of canakinumab at various time points after single-dose intravenous administration are presented in Figure 1.

After single-dose intravenous injection, canakinumab reached a C_{max} of 0.9 to 244 μg/mL at a median time (T_{max}) of 2 to 4 hours. The mean CL rate ranged from 0.094 to 0.128 mL/h/kg across all doses, and the mean apparent V_d ranged from 38 to 88 mL/kg in patients with T2DM. With the exception of the lowest-dose cohort (0.03 mg/kg) (216 hours), the mean $t_{½}$ of canakinumab ranged from 413 hours (17 days) to 612 hours (26 days). PK parameters calculated using noncompartmental analyses are summarized in Table III.

Pharmacodynamic Properties

IL-1β

Total canakinumab and total IL-1β concentration data were available from 145 patients in the active-treatment groups. The total IL-1β concentrations in serum were increased after single-dose intravenous administration in patients with T2DM (Figure 2), reflecting binding of canakinumab to serum IL-1β and slow CL of the IL-1β–antibody complex. The mean (range) drug CL, free ligand CL, and ligand production rates were 0.26 (0.1–1.45) L/day, 10.02 (7.65–15.01) L/day, and 6.84 (3.52–16.88) ng/day, respectively. As expected, the free ligand CLs were greater than were the antibody CLs.

Table II. Baseline demographic and clinical characteristics of the patients in this study of the pharmacokinetic properties of canakinumab (randomized set).

Characteristic	Cohort 1		Cohort 2		Cohort 3			Cohort 4	Cohorts 3 and 4
	Canakinumab 0.3 mg/kg (n = 10)	Placebo (n = 5)	Canakinumab 10 mg/kg (n = 45)	Placebo (n = 45)	Canakinumab 0.1 mg/kg (n = 25)	Canakinumab 0.3 mg/kg (n = 24)	Canakinumab 1.5 mg/kg (n = 23)	Canakinumab 0.03 mg/kg (n = 20)	Placebo (n = 34)
Demographic									
Age, y									
Mean	53.0	52.0	57.1	57.5	53.9	55.0	55.1	53.9	55.1
Range	43–67	45–63	30–70	35–69	40–69	39–69	34–68	32–67	38–68
Sex, no. (%)									
Female	6 (60.0)	3 (60.0)	21 (46.7)	14 (31.1)	13 (52.0)	17 (70.8)	14 (60.9)	10 (50.0)	18 (52.9)
Male	4 (40.0)	2 (40.0)	24 (53.3)	31 (68.9)	12 (48.0)	7 (29.2)	9 (39.1)	10 (50.0)	16 (47.1)
White race, no. (%)	9 (90.0)	4 (80.0)	42 (93.3)	43 (95.6)	23 (92.0)	23 (95.8)	22 (95.7)	19 (95.0)	31 (91.2)
Clinical									
BMI, kg/m^2									
Mean	31.2	30.7	30.7	30.8	32.6	31.6	32.5	30.4	32.8
Range	26–40	27–35	25–39	25–39	26–41	25–39	26–38	26–37	27–40
Group, no. (%)									
<30 kg/m^2	5 (50.0)	2 (40.0)	21 (46.7)	17 (37.8)	6 (24.0)	10 (41.7)	7 (30.4)	9 (45.0)	16 (47.1)
≥ 30 kg/m^2	5 (50.0)	3 (60.0)	24 (53.3)	28 (62.2)	19 (76.0)	14 (58.3)	16 (69.6)	11 (55.0)	18 (52.9)
Duration of T2DM, y									
Median	5.4	9.6	7.3	5.1	5.6	7.3	3.0	3.8	5.6
Range	1.6–27.0	4.6–13.0	0.7–24.0	0.3–21.0	1.4–13.6	1.2–20.8	0.7–15.3	0.6–13.9	0.8–21.9
HbA_{1c}, mean, %	8.0	7.1	7.9	7.8	7.6	7.4	7.7	7.6	7.7
hsCRP, mg/L									
Median	No data collected	No data collected	2.3	2.0	1.8	2.0	2.4	3.2	2.5
Range	—	—	0.25–9.81	0.48–8.85	0.31–6.46	0.42–8.66	0.86–13.80	0.56–9.61	0.20–8.83
Metformin dose, mg/d									
Median	1000	1000	1500	1000	1700	1850	1700	1500	2000
Range	500–2000	500–1700	850–3000	850–2550	1000–3000	1000–3000	850–3000	1000–2000	1000–3000

BMI, body mass index; HbA_{1c} hemoglobin A_{1c}; hsCRP, high-sensitivity C-reactive protein; T2DM, type 2 diabetes mellitus.

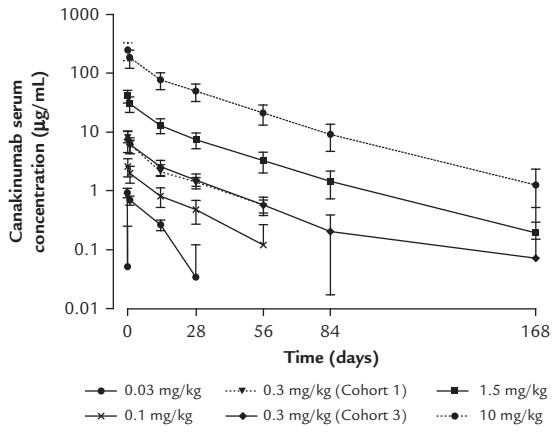

Figure 1. Mean (SD) serum concentrations of canakinumab at various time points after single-dose intravenous administration in patients with type 2 diabetes mellitus (pharmacokinetic data set).

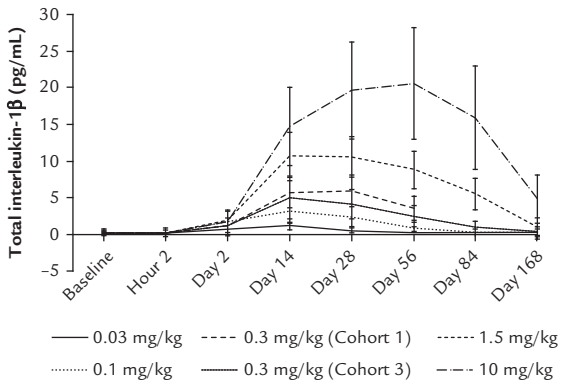

Figure 2. Total IL-1β canakinumab concentration–time profiles in patients with type 2 diabetes mellitus after single-dose intravenous administration (intent-to-treat population). Data are given as mean (SD).

hsCRP

The time course of the median change in hsCRP levels over 24 weeks is presented in Figure 3A. A significant dose-related reduction in hsCRP was observed at week 4, with greater reductions with higher canakinumab doses compared with placebo (−41%, −45%, −70%, and −74% with 0.1, 0.3, 1.5, and 10 mg/kg, respectively; all, $P < 0.05$) (Figure 3B). The corresponding median changes in hsCRP values from baseline to week 4 were −0.2, −0.5, −1.5, and −1.7 mg/L, respectively. The reduction in hsCRP was maintained up to week 12 with the 2 highest doses of canakinumab (−49% with 1.5 mg/kg and −60% with 10 mg/kg; both, $P < 0.05$), and the corresponding median changes in hsCRP levels from baseline were −0.8 and −1.3 mg/L, respectively.

At baseline, 60% (27/45) patients and 46.7% (21/45) patients had hsCRP values of ≥2 mg/L in the 10-mg/kg and placebo groups, respectively (Table IV). After single-dose administration of 10 mg/kg canakinumab, 21 of the 27 patients (77.8%) with a baseline hsCRP ≥2 mg/L achieved hsCRP <2 mg/L compared with 3 of 21 patients (14.3%) in the placebo group at week 4. This reduction in hsCRP to <2 mg/L was

Table III. Summary of key pharmacokinetic (PK) parameters of canakinumab (PK data set). Data are given as means (%CV) unless otherwise specified.

	Cohort 1	Cohort 2	Cohort 3			Cohort 4
Parameter	Canakinumab 0.3 mg/kg (n = 9)	Canakinumab 10 mg/kg (n = 44)	Canakinumab 0.1 mg/kg (n = 24)	Canakinumab 0.3 mg/kg (n = 19)	Canakinumab 1.5 mg/kg (n = 23)	Canakinumab 0.03 mg/kg (n = 17)
C_{max}, µg/mL	8.4 (23)	244 (33)	2.6 (29)	8.2 (18)	41.0 (24)	0.9 (25)
T_{max}, median, h	4	4	4	4	4	2
V_d, mL/kg	71 (16)	85 (24)	61 (39)	66 (25)	88 (92)	38 (19)
CL, mL/h/kg	0.094 (13)	0.099 (29)	0.116 (70)	0.095 (28)	0.116 (121)	0.128 (23)
$t_{½}$, h	521 (13)	612 (21)	413 (36)	494 (26)	572 (19)	216 (40)

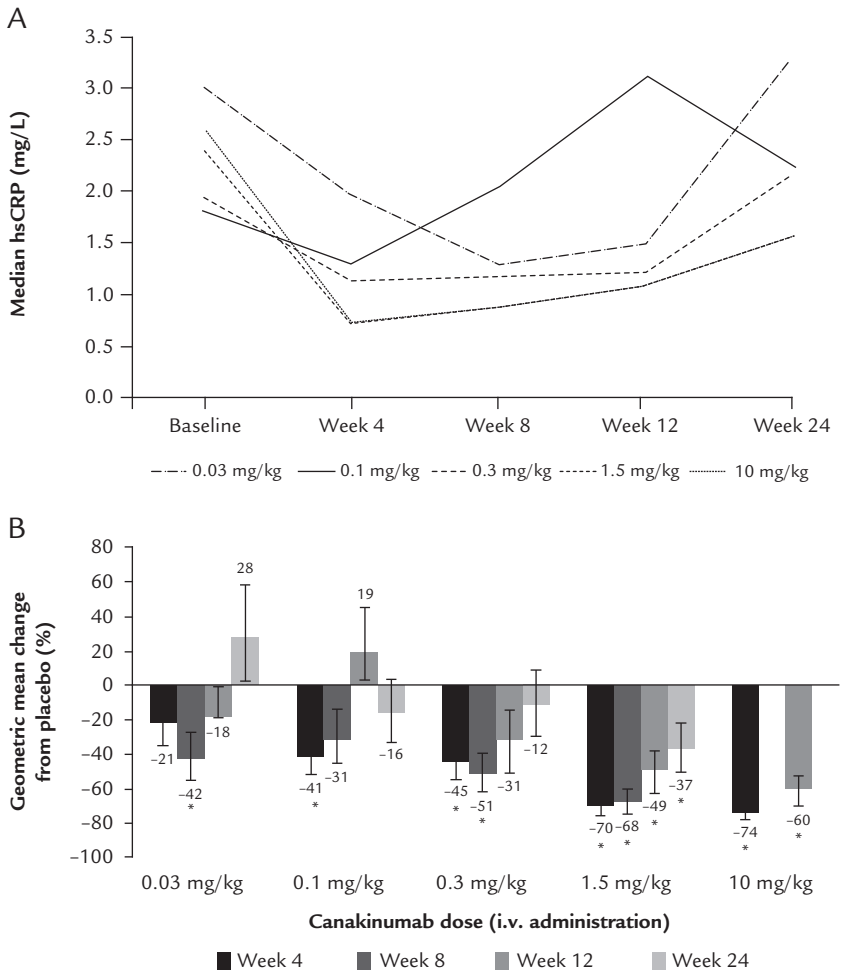

Figure 3. A, Time course of median high-sensitivity C-reactive protein (hsCRP) levels after single-dose administration of canakinumab (ITT population). B, Mean (SD) changes in hsCRP after single-dose administration of canakinumab (ITT population). *$P < 0.05$ versus placebo. Data on the 10-mg/kg dose were available only for weeks 4 and 12. ITT, intent-to-treat population using the last observation carried forward.

maintained in 17 of 27 patients (63.0%) treated with 10 mg/kg of canakinumab at week 12.

Change in HbA_{1c} Levels

Single-dose administration of canakinumab 10 mg/kg was associated with a placebo-adjusted decrease in HbA_{1c} of 0.31% ($P = 0.038$) at week 12. Single-dose administration of canakinumab 1.5 mg/kg was associated with a statistically significant, albeit clinically irrelevant, reduction in HbA_{1c} compared with placebo (–0.23%; $P = 0.011$) at week 4. In general, numerically moderate but statistically nonsignificant decreases from baseline to weeks 4 and 12 in HbA_{1c} were seen in all patients after single-dose intravenous administration of 5 different doses of canakinumab. The adjusted mean changes from baseline in HbA_{1c}, by treatment and visit, are presented in Table V.

Tolerability

Overall, the incidences of reported AEs were similar between the active-treatment and placebo groups. Patients reporting any AE were 1 (10%) with 0.3 mg/kg versus 2 (40%) with placebo in cohort 1; 18 (40.0%) with 10 mg/kg versus 14 (31.1%) with

Table IV. Rates of patients achieving hsCRP <2 mg/L with canakinumab versus placebo. Data are given as number (%) of patients.

Time Point	Canakinumab 10 mg/kg (n = 45)	Placebo (n = 45)
Baseline		
≥2 mg/L	27 (60.0)	21 (46.7)
<2 mg/L	18 (40.0)	24 (53.3)
Week 4 (hsCRP <2 mg/L)	21/27 (77.8)	3/21 (14.3)
Week 12* (hsCRP <2 mg/L)	17/27 (63.0)	3/21 (14.3)

*At week 12 in canakinumab 10 mg/kg group, data for one patient was missing.

placebo in cohort 2; 8 (32.0%) with 0.1 mg/kg, 6 (25.0%) with 0.3 mg/kg, 4 (17.4%) with 1.5 mg/kg, and 7 (29.2%) with placebo in cohort 3; and 10 (50.0%) with 0.03 mg/kg versus 2 (20.0%) with placebo in cohort 4. In cohort 1, 1 patient in the active-treatment group had influenza and 2 patients each in the placebo group had ocular hyperemia and headache. In cohort 2, the most common AEs reported were infections and infestations (nasopharyngitis and cystitis), gastrointestinal disorders (diarrhea), nervous system disorders (headache), and investigation (increased blood triglycerides and increased lipase). The most frequently reported events in cohorts 3 and 4 were infections and infestations (nasopharyngitis, bronchitis, and urinary tract infection); respiratory, thoracic, and mediastinal disorders (nasal congestion); gastrointestinal disorders (diarrhea and nausea); cardiac disorders (ventricular extra systoles); nervous system disorders (headache and dizziness), and skin and subcutaneous tissue disorders (rash). The incidence of AEs did not seem to be dose related and was similar to that in the placebo group. Most AEs were mild in intensity and were considered not related to the study drug. No apparent trend was observed over the dose range of single-dose administration of canakinumab. In the study, 3 patients reported serious AEs: 1 patient who received canakinumab 10 mg/kg experienced an intestinal polyp, and 2 patients in the placebo group in cohort 2 reported myocardial infarctions.

DISCUSSION

The results from this multicenter, double-blind, placebo-controlled, single-dose administration of canakinumab or placebo in patients with T2DM on a stable dose of metformin (median dose range, 1000–2000 mg/d) suggest that there were no tolerability issues with canakinumab. The clearance of canakinumab was time and dose independent, and canakinumab use was associated with a dose-dependent reduction in hsCRP levels at week 4, which was sustained for 12 weeks in the higher-dose groups (1.5 and 10 mg/kg). Both canakinumab 1.5 and 10 mg/kg doses showed a numerically moderate, albeit clinically irrelevant, reduction in HbA_{1c} in patients with T2DM receiving metformin (baseline HbA_{1c}, 7.4%–7.9%).

Canakinumab displayed the typical PK properties of an IgG1-type antibody, that is, low CL and low V_d, resulting in a long mean $t_{½}$ ranging from 17 to 26 days across doses, which is consistent with the 21-day terminal elimination half-life determined for a typical IgG1 antibody.[9] The mean $t_{½}$ was longer with the 1.5 and 10 mg/kg doses. Systemic CLs across dose groups were comparable, suggesting that within the administered dose range, the PK profile was dose proportional. There was no evidence of accelerated CL from the terminal phases of the concentration–time profiles that would suggest the formation of antibody against canakinumab. The results from this study are consistent with the previously reported data in healthy volunteers.[9]

Canakinumab binding to endogenous IL-1β neutralizes the bioactive effect of IL-1β, thereby resulting in the formation of a canakinumab–IL-1β complex.[9] The CL rate of the canakinumab-IL-1β complex was lower than that of the free ligand (IL-1β), leading to an increase in the total serum IL-1β concentration, suggesting the binding of IL-1β by canakinumab. This

Table V. Changes from baseline in hemoglobin A_{1c} with canakinumab versus placebo (intent-to-treat population). Data are given as %.

	Cohort 2		Cohorts 3 and 4				
Study Week	Canakinumab 10 mg/kg	Placebo	Canakinumab 0.03 mg/kg	Canakinumab 0.1 mg/kg	Canakinumab 0.3 mg/kg	Canakinumab 1.5 mg/kg	Placebo
Week 4							
No. of patients	45	45	20	25	23	23	34
Baseline	7.88 (0.101)	7.84 (0.122)	7.61 (0.176)	7.62 (0.171)	7.44 (0.106)	7.68 (0.157)	7.72 (0.162)
Δ vs baseline, adjusted mean (SE)	−0.38 (0.057)	−0.26 (0.057)	−0.13 (0.073)	−0.25 (0.065)	−0.30 (0.069)	−0.47 (0.068)	−0.24 (0.056)
Δ vs placebo							
Mean (SE)	−0.12 (0.080)	—	0.10 (0.092)	−0.01 (0.086)	−0.06 (0.089)	−0.23 (0.088)	—
95% CI	−0.28 to 0.04	—	−0.08 to 0.29	−0.18 to 0.16	−0.24 to 0.11	−0.40 to −0.05	—
P	0.142	—	0.258	0.890	0.487	0.011	—
Week 12							
No. of patients	44	42	20	25	23	23	33
Baseline	7.87 (0.103)	7.87 (0.127)	7.61 (0.176)	7.62 (0.171)	7.41 (0.105)	7.68 (0.157)	7.69 (0.165)
Δ vs baseline, adjusted mean (SE)	−0.46 (0.102)	−0.15 (0.105)	−0.15 (0.132)	−0.04 (0.118)	−0.43 (0.124)	−0.59 (0.124)	−0.32 (0.103)
Δ vs placebo							
Mean (SE)	−0.31 (0.147)	—	0.17 (0.168)	0.28 (0.157)	−0.11 (0.162)	−0.27 (0.161)	—
95% CI	−0.60 to −0.02	—	−0.16 to 0.50	−0.03 to 0.60	−0.43 to 0.21	−0.59 to 0.05	—
P	0.038	—	0.309	0.073	0.507	0.097	—
Week 18							
No. of patients	45	45	20	21	22	23	33
Baseline	7.88 (0.101)	7.84 (0.122)	7.61 (0.176)	7.39 (0.144)	7.47 (0.108)	7.68 (0.157)	7.75 (0.164)
Δ vs baseline, adjusted mean (SE)	−0.29 (0.101)	−0.02 (0.101)	−0.11 (0.128)	−0.08 (0.126)	−0.22 (0.123)	−0.40 (0.120)	−0.19 (0.101)
Δ vs placebo							
Mean (SE)	−0.27 (0.142)	—	0.08 (0.163)	0.11 (0.162)	−0.03 (0.159)	−0.21 (0.156)	—
95% CI	−0.55 to 0.02	—	−0.24 to 0.40	−0.21 to 0.43	−0.34 to 0.29	−0.52 to 0.10	—
P	0.066	—	0.630	0.512	0.862	0.179	—
Week 24							
No. of patients	43	45	20	24	20	21	33
Baseline	7.89 (0.104)	7.84 (0.122)	7.61 (0.176)	7.57 (0.172)	7.40 (0.111)	7.70 (0.168)	7.74 (0.167)
Δ vs baseline, adjusted mean (SE)	−0.26 (0.121)	−0.01 (0.118)	0.32 (0.177)	0.27 (0.162)	−0.18 (0.178)	−0.39 (0.173)	−0.12 (0.138)
Δ vs placebo							
Mean (SE)	−0.25 (0.169)	—	0.44 (0.225)	0.40 (0.213)	−0.06 (0.226)	−0.26 (0.221)	—
95% CI	−0.58 to 0.09	—	0.00 to 0.89	−0.02 to 0.82	−0.51 to 0.39	−0.70 to 0.18	—
P	0.149	—	0.052	0.065	0.796	0.238	—

apparent binding may have led to the blockage of downstream events of IL-1β signaling, including IL-1β production, IL-1β pathway–related gene activation (ie, elevation of acute phase proteins such as serum amyloid A and hsCRP), and mobilization of neutrophils and platelets from bone marrow. Similar results were observed in other populations (cryopyrin-associated periodic syndromes, gouty arthritis, rheumatoid arthritis, and healthy subjects).[9]

Inflammation plays a role in the development and progression of atherosclerosis and β-cell dysfunction. HsCRP, an acute-phase inflammatory biomarker, has the potential to identify individuals at high risk for both first and recurrent vascular events even in the absence of hyperlipidemia and other major vascular risk factors.[11] In a recent study, hsCRP was found to be a vascular-events predictor at least as strong as blood pressure and cholesterol levels.[2] In the present study, the antiinflammatory activity of canakinumab was evaluated by measuring the reduction in hsCRP levels over 24 weeks. The baseline median hsCRP levels of patients enrolled in this study ranged from 1.8 to 3.2 mg/L. Treatment with canakinumab across different doses was associated with statistically significant reductions in hsCRP of –0.2 to –1.7 mg/L versus baseline at the first time point at which hsCRP was measured (week 4) (all, $P < 0.05$). These reductions were sustained for 12 weeks in patients who received canakinumab 1.5 and 10 mg/kg (–0.8 and –1.3 mg/L, respectively, vs a baseline median ~2.4 mg/L). Furthermore, results from an exploratory analysis suggested that a single dose of 10 mg/kg canakinumab was associated with reductions in hsCRP to a clinically relevant value of <2.0 mg/L at weeks 4 and 12. This evidence is promising and suggests that long-term therapy with canakinumab may reduce cardiovascular risk. However, further studies with canakinumab needs to be investigated to affirm the sustained reduction in hsCRP levels in chronic diseases.

Few studies have evaluated the relationship between hsCRP and HbA_{1c} levels in patients with T2DM.[12,13] In this study, a statistically significant, albeit clinically irrelevant, reductions in HbA_{1c} were sustained for 12 weeks in patients who received canakinumab 10 mg/kg, for 4 weeks in patients who received the 1.5-mg/kg dose. The mean HbA_{1c} values at baseline in the 4 cohorts ranged between 7.1% and 8.0%, with no apparent correlation with hsCRP levels (baseline median hsCRP of 1.8–3.2 mg/L), probably due to the relatively satisfactory glycemic control. This single-dose study was designed to describe the PK properties of canakinumab and was not powered to ascertain the clinical correlation between hsCRP and HbA_{1c} levels.

A single injection of canakinumab across evaluated doses was found to be well tolerated in patients with T2DM. The AEs reported were similar between the canakinumab and placebo groups. The safety profile, including the incidence of infection, was consistent with those from other published clinical trials of canakinumab in patients with cryopyrin-associated periodic syndromes, rheumatoid arthritis, and gouty arthritis.[14–18]

The prolonged effect canakinumab on ablating the acute-phase inflammatory response suggests that quarterly dosing is feasible. Whether this regimen, once applied chronically in diseases in which modulation of hsCRP response may predict efficacy, translates into a clinically meaningful response is being evaluated in other trials. CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study) is an ongoing study exploring the efficacy of quarterly dosing of canakinumab to test the hypothesis of inflammation as a cause of atherothrombosis.

CANTOS is the first randomized trial aimed to determine whether the long-term inhibition of IL-1β with canakinumab (50, 150, or 300 mg administered subcutaneously every 3 months) compared with placebo reduces the rates of recurrent cardiovascular events, defined as nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death, among stable patients who have had a myocardial infarction and who remain at elevated cardiovascular risk due to increased hsCRP (≥2 mg/L) despite usual care, including statin therapy.[11] The prolonged effects on reducing hsCRP levels for 12 weeks with no significant adverse findings support the feasibility of the ongoing CANTOS trial. If positive, CANTOS will not only affirm the inflammatory hypothesis of atherothrombosis but also provide an entirely novel cytokine-based therapy for the secondary prevention of cardiovascular disease.[11]

CONCLUSIONS

The PK and PD properties of canakinumab, an anti-IL-1β monoclonal antibody, in patients with T2DM were consistent with the results reported previously in other populations such as cryopyrin-associated

periodic syndromes, rheumatoid arthritis, gouty arthritis, and healthy subjects.[9] A single dose of canakinumab 1.5 and 10 mg/kg was associated with a strong and sustained suppression of hsCRP levels and a moderate but sustained reduction in HbA_{1c} in patients with T2DM for 12 weeks.

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Drs. Noe and Skerjanec were primarily responsible for the development of the study design, data collection, data analysis, and data interpretation. Dr. Skerjanec contributed to the analysis of the PK/PD data. Dr. Taylor assisted in the development of the study design, changes in study design as the cohort data emerged, and approval of the final protocol. Drs. Howard and Thuren contributed in reviewing the study results and interpreting the data. All of the authors were involved in the development, review, and approval of the final manuscript for publication.

CONFLICTS OF INTEREST

This study was funded by Novartis Pharmaceuticals, Inc, the developers of canakinumab. All of the authors are employees of, and own stock options in Novartis. The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

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Address correspondence to: Adele Noe, PhD, Novartis Pharma AG, Postfach, CH-4002 Basel, Switzerland. E-mail: adele.noe@novartis.com