Impact of interleukin-1β antibody (canakinumab) on glycaemic indicators in patients with type 2 diabetes mellitus: Results of secondary endpoints from a randomized, placebo-controlled trial

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Received 7 May 2013; received in revised form 3 July 2013; accepted 5 July 2013

Abstract

Aims/hypothesis. – This study was conducted to determine the optimal monthly subcutaneous dose of canakinumab (a human monoclonal anti-human IL-1β antibody) needed to improve glucose control in metformin-treated patients with type 2 diabetes mellitus (T2DM).

Methods. – This was a parallel-group, randomized, double-blind, multicentre, placebo-controlled study designed to assess the effect on HbA1c and the safety/tolerability of four monthly doses of canakinumab (5, 15, 50, or 150 mg) as an add-on to metformin over 4 months.

Results. – Patients (n = 551; mean age 54.1 years; mean baseline HbA1c 7.4%) were randomized and treated in a double-blind fashion to canakinumab 5 mg (n = 93), 15 mg (n = 95), 50 mg (n = 92), 150 mg (n = 92) or placebo (n = 179) monthly. There was no dose response detected between active canakinumab doses, but all doses numerically lowered HbA1c (primary endpoint) from baseline between 0.19% and 0.31% (placebo-unadjusted), with maximal effect noted in the 50 mg dose of canakinumab (−0.18% difference vs placebo; multiplicity-adjusted, P = 0.13902) as reported earlier (Ridker et al., 2012). No other glycaemic control parameters (FGP, fasting insulin, plasma glucose AUC0–4h, 2-h PPG, peak glucose, C-peptide AUC0–4h, peak C-peptide, insulin AUC0–4h, peak insulin, ISRo–2h, HOMA-β and HOMA-IR) showed any meaningful changes by canakinumab therapy. Canakinumab treatment was safe and well tolerated. There were no relevant differences in adverse events between the canakinumab and placebo groups.

Conclusions/interpretation. – A 4-month course of monthly canakinumab (50 mg) produced a numerical reduction of HbA1c in T2DM patients on metformin, potentially by improving beta-cell function. The safety and tolerability profile of canakinumab was consistent with prior trials.

Trial registration. – Registry: http://www.ClinicalTrials.gov, Registration No.: NCT00900146

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Keywords: Canakinumab; Diabetes mellitus; Interleukin-1β; Metformin; Monoclonal antibody

Résumé

Incidence de l’anticorps anti-interleukine-1β (canakinumab) sur les indicateurs de glycémie chez les patients atteints de diabète de type 2 : résultats des critères d’évaluation secondaires d’un essai à répartition aléatoire et contrôlé par placebo.

Objectifs/hypothèse. – Cette étude a été menée pour déterminer la dose mensuelle optimale de canakinumab (un anticorps monoclonal humain dirigé contre l’IL-1β) administrée par voie sous-cutanée, nécessaire pour améliorer la maîtrise de la glycémie chez les patients atteints de diabète de type 2 traités par la metformine.

Méthodes. – Il s’agissait d’une étude multicentrique, avec répartition aléatoire, à double insu, contrôlée par placebo et menée en groupes parallèles conçus pour évaluer l’effet sur le taux d’HbA1c et l’innocuité/tolérabilité de quatre doses mensuelles de canakinumab (à 5, 15, 50 ou 150 mg) ajoutées à la metformine pendant quatre mois.

Résultats. – Les patients (n = 551; âge moyen de 54,1 ans; taux d’HbA1c initial moyen de 7,4%) ont été répartis aléatoirement et traités, en double insu, par le canakinumab à 5 mg (n = 93), 15 mg (n = 95), 50 mg (n = 92), 150 mg (n = 92) ou le placebo (n = 179) une fois par mois. On n’a découvert aucune relation dose–effet entre les doses actives de canakinumab, mais toutes les doses ont diminué le taux d’HbA1c sur le plan numérique (critère d’évaluation principal) par rapport au départ, soit entre 0,19 % et 0,31 % (non ajustée en fonction du placebo). L’effet maximal

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http://dx.doi.org/10.1016/j.diabet.2013.07.003
a été observé avec la dose de canakinumab à 50 mg (différence de −0,18 % p/t au placebo ; ajustée en fonction des doses multiples, P = 0,13902) comme il a été signalé dans une étude antérieure (Ridker et al., 2012). Aucun autre paramètre de maîtrise de la glycémie (la GPl, insulin e à jeun, l’ASC 0–4h de la glycémie, la GPP à 2 h, les pics de glycémie, l’ASC 0–2h du taux de peptide C, les pics de peptide C, l’ASC 0–3h de l’insuline, les pico s d’insul ine, le taux de sécrétion d’insuline/2h, le modèle d’évaluation de l’homéostasie de la fonction des cellules β et le modèle d’évaluation de l’homéostasie de la résistance à l’insuline) n’a montré de variation importante en raison du traitement par le canakinumab. Le traitement par le canakinumab a été sécuritaire et bien toléré. Aucune différence pertinente en termes d’événements indésirables n’a été signalée entre les groupes traités par le canakinumab et le groupe placebo.

**Conclusions/Interprétation.** Un traitement mensuel par le canakinumab (50 mg) d’une durée de quatre mois a entraîné une réduction numérique du taux de HbA1c chez les patients atteints de diabète de type 2 traités par la metformine, possiblement en améliorant la fonction des cellules bêta. Le profil d’innocuité et de tolérabilité du canakinumab correspondait avec celui déterminé lors d’essais précédents.

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**Mots clés :** Canakinumab ; Diabète sucré ; Interleukine-1β ; Metformine ; Anticorps monoclonal

1. Introduction

Despite the rising prevalence of type 2 diabetes mellitus (T2DM) and the increasing availability of new anti-diabetic therapies, glycaemic control remains suboptimal in a significant proportion of the affected population [1]. This underscores the need to identify and target physiological and cellular pathways involved in the pathogenesis of the disease, which are not otherwise addressed by current therapeutic agents.

Indeed, the available therapies focus mainly on the management of hyperglycaemia and, with the possible exceptions of thiazolidinediones and exenatide, have little or no effect in preventing the decline of pancreatic beta-cell function [2–5]. Various studies suggest that inflammatory responses play a role in the loss of pancreatic beta-cell function [6–10], and preclinical data have implicated the importance of IL-1β in this mechanistic pathway [7,11–13]. In addition, all body tissues, pancreatic beta cells have the greatest density of IL-1β receptors [14,15]. Furthermore, IL-1β activity and/or expression may be increased in the pancreatic beta cells of T2DM patients [10,16,17]. Subsequent preclinical and clinical trials have demonstrated that blocking the IL-1β activity, either via an IL-1 receptor antagonist or with a neutralizing IL-1β antibody, can enhance pancreatic beta-cell secretory function and, thereby, reduce HbA1c in T2DM patients [14,17–20].

Canakinumab (ACZ885) is a human monoclonal anti-human-IL-1β antibody of the IgG1/k isotype that reduces inflammation, thereby, potentially preserving/improving pancreatic beta-cell function. It has been approved for treating cryopyrin-associated periodic syndromes (CAPS), an IL-1β-driven inflammatory disease [21,22]. It is also being investigated for refractory gout, rheumatoid arthritis and systemic juvenile idiopathic arthritis (SJIA) [23–25]. Canakinumab binds to human IL-1β and, blocks the interaction of this cytokine with its receptors. This results in neutralized bioactivity of IL-1β but does not prevent the binding of the natural inhibitor, IL-1Ra, nor of IL-1α [22].

This study was conducted to determine the optimal dose, and evaluate the efficacy and safety, of canakinumab when dosed once a month subcutaneously in T2DM patients on metformin therapy, including patients at early stage of the disease. Outcomes of inflammatory biomarkers (C-reactive protein, interleukin-6 and fibrinogen), lipid levels, and primary endpoint (HbA1c) results in dose selection Period II of this trial were published in a recent article by Ridker et al. [26]. Here we describe the glucose-related secondary and exploratory parameters in detail, and the safety results in the entire trial, including the extension Period III.

2. Methods

This dose-finding study evaluating monthly canakinumab administration in metformin-treated T2DM patients was conducted at 108 centres in 14 countries (Argentina, Belgium, Germany, Great Britain, Hong Kong, Hungary, India, Japan, Peru, Romania, South Africa, South Korea, Turkey, and the United States). The study was carried out in accordance to the Declaration of Helsinki and with appropriate ethics review board approvals. All patients signed an informed consent form before randomization.

2.1. Patient eligibility

The study population included patients aged 18–74 years diagnosed with T2DM (either a fasting plasma glucose [FPG] ≥7.0 mmol/L or an oral glucose tolerance test [OGTT] test 2-h plasma glucose [PG] ≥11.1 mmol/L) prior to screening. Subjects were also required to satisfy any one of the following criteria sets:

- drug naïve to oral anti-diabetic drug (OAD) therapy, with an HbA1c of 7.5%–11.0%, and be eligible for metformin monotherapy;
- on stable metformin monotherapy for at least 3 months at screening, have an HbA1c of 7.0%–9.0%, and take metformin as their first and only OAD;
- or taking an alpha-glucosidase inhibitor (AGI) as their first and only OAD, have the AGI stopped and be washed out from the AGI for at least 1 week prior to run-in, have an HbA1c of 7.0%–9.0%, and be eligible for metformin monotherapy.

Finally, subjects were required to have a morning FPG result less than10.0 mmol/L, one month prior to randomization and to be on a daily dose of metformin greater than or equal to 1000 mg.

Key exclusion criteria included type 1 diabetes, secondary forms of diabetes, significant laboratory abnormalities, active pulmonary disease, fungal diseases, active/recurrent hepatitis B.

or C infections and immunocompromised conditions. Patients with a history of malignancy within the past 5 years, a history of cardiovascular events within the last 6 months, those with recent/current use of other investigational drugs, those received live vaccinations within 3 months before randomization or live vaccinations planned during the trial up to 3 months following the last dose of study drug were also excluded.

### 2.2. Study design and treatments

This was a phase IIb, parallel-group, randomized, double-blind, multicentre, placebo-controlled study consisting of three periods: a 3-week screening followed by an 8-week open-label placebo run-in period (Period I), a 16-week dose-finding period (Period II), and a variable-duration extension period (Period III).

During the run-in period (Period I), patients were treated with two subcutaneous open-label injections of placebo. Furthermore, metformin was introduced to drug-naïve patients or patients who had recently stopped taking AGIs or optimized for patients already on metformin. Each patient was titrated to his/her maximum-tolerated dose. For the dose-finding period (Period II), patients continued metformin treatment and were randomized to one of four canakinumab doses (5, 15, 50, or 150 mg) or placebo in a 1:1:1:1:2 ratio, respectively, for the 4-month treatment period. Patients had their canakinumab dose injected at every monthly visit during this period. Patients with morning FPG greater than 11.1 mmol/L in consecutive visits were treated with a daily injection of insulin glargine as add-on therapy.

The extension period (Period III) began after patients completed their 4-month visit. Patients continued their randomized treatment and made brief visits to the clinic every month. Those patients with HbA1c greater than 7.5% on consecutive visits were treated with a daily injection of insulin glargine as add-on therapy. Other than the study drug, metformin at a maximally tolerated dose greater than or equal to 1000 mg/day, rescue medication (insulin glargine during Periods II or III, prandial insulin [rapid-acting analogue/regular human insulin] during Period III), and medication required to treat adverse events (AEs), no other drug was permitted from randomization until the end of all evaluations. Medications other than those for treating hyperglycaemia were allowed if doses were stabilized before the beginning of the study.

### 2.3. Study endpoints

The primary efficacy variable was change in HbA1c from baseline to end of Period II. Secondary efficacy variables included but were not limited to FPG, fasting insulin, AUC0–4h and peak values of C-peptide, glucose and insulin following a mixed-meal tolerance test (MMTT), insulin secretion rate (ISR) based on glucose following the MMTT, mean and peak values based on glucose meter data, HOMA-β, HOMA for insulin resistance (HOMA2-IR), HbA1c (rescue-free) responder analysis of patients with HbA1c less than 7% at Month 4, and changes in high sensitivity C-reactive protein (hsCRP) and fasting lipid profiles.

The standard liquid MMTT was performed at randomization and at the end of treatment. Patients were required to fast overnight and were also prohibited from taking any anti-diabetic medication beforehand. During the study visit, patients completed the liquid MMTT (Nestle Boost® Plus [360 calories and 45 g total carbohydrates] or equivalent) within 5 minutes, with measurement of the following variables prior to and after meal: glucose, insulin, and C-peptide at sampling times −20, −10, −1, 10, 20, 30, 60, 90, 120, 150, 180, and 240 minutes.

Hypoglycaemic events were also recorded and reported as AEs if they met the criteria to be reported as serious AEs (SAEs) including: coma or seizure, need for hospitalization, PG less than 3.1 mmol/L, or if a PG was not taken but the patient had prompt recovery on treatment and third-party assistance was required.

Safety assessments included physical examination, vital signs, haematology/chemistry, urinalysis, and electrocardiogram at screening, randomization, and end of 4 months, with monitoring and recording of all AEs at each study visit along with their severity, duration, and correlation to study drug. SAEs were monitored from the time the patient signed the informed consent form until 90 days after the patient had stopped study participation.

### 2.4. Statistical analysis

The primary objective of the study, dose-finding, was based on change from baseline in HbA1c at Month 4 in the full analysis set (FAS) which included all randomized except mis-randomized patients (not qualified for randomization but were inadvertently randomized and did not receive study drug). An analysis of covariance (ANCOVA) followed by two-sided step-down Dunnett’s test for multiple comparisons was used for the comparison of each active dose vs placebo. The ANCOVA model included treatment and metformin dose category (<1500 mg and ≥1500 mg daily) as the classification variables and baseline as the covariate. Nominal 95.01% CI for the estimated difference between each active dose and placebo was also determined based on the ANCOVA model. The overall alpha level was 0.05 but due to the interim analysis, the step-down Dunnett’s test was conducted to a significance level of 0.0499 (two-sided). The last observation carried forward (LOCF) method was used for patients without month 4 HbA1c measurement for any reason, as well as for patients who required rescue medication or used any glucose-lowering agents other than metformin. The study, at a planned sample size of n = 100 for each dose group and n = 200 for the placebo group, had 80% power to demonstrate that at least one active dose was significantly different from placebo by 0.41% based on an assumed standard deviation of 1%.

An unblinded interim analysis at 0.0001 level was performed when 152 patients had completed month 3 to allow an expedited evaluation of the risk-benefit profile of this compound in T2DM patients. Only personnel without direct contact with sites had access to unblinded interim analysis data.

The secondary variables were also analyzed using ANCOVA followed by step-down Dunnett’s test on change from baseline. Safety assessment was based primarily on the frequency of AEs, laboratory abnormalities, and SAEs data from Periods II and III.
that were pooled for analysis. The safety set (SAF) included all patients who received at least one dose of study medication.

3. Results

3.1. Patients and study medications

Disposition of patients is shown in Fig. S1 (see supplementary material associated with this article online). A total of 556 patients were randomized at the start of Period II. Recruitment began in April 2009 and follow-up was completed in November 2010. A summary of this data was presented as a figure in the Ridker et al. article [26].

A total of 524 (94.2%) randomized patients completed Period II of the study. Slightly higher percentages of patients receiving canakinumab completed the study than placebo group. There were no clinically meaningful differences between treatments with respect to reasons given for discontinuing from the study. Five patients were mis-randomized and did not receive study drug. One patient was not included because information regarding the study completion page was missing (Fig. S1, see supplementary material associated with this article online). However, visit information was available for this patient and, therefore, this patient was included in all other data analyses. Demographic, baseline disease characteristics, and medication parameters of the FAS during Period II were generally similar between the treatment and placebo groups and were published by Ridker et al. [26]. Mean values for age, duration of diabetes, and BMI at baseline were 54.1 years, 3.7 years, and 29.8 kg/m² respectively. The percentage of males was slightly lower than females in the canakinumab 50 mg group (48.9 vs 51.1% respectively) and higher than females in the canakinumab 150 mg group (62.0 vs 38.0% respectively). The percentage of patients using statins in the canakinumab 15 mg group was higher than that for the total population at baseline (35.8% vs 28.3% respectively).

3.2. Efficacy

The primary efficacy analysis showed no significant dose response in patients receiving canakinumab doses, although the reduction in HbA1c in the 5 mg dose group was less than that in the 15, 50 and 150 mg groups, as reported by Ridker et al. [26]. The responder rates of patients (HbA1c <7%) at Month 4 in the FAS were 13/64 (20.3%) in canakinumab 5 mg, 19/64 (29.7%) in canakinumab 15 mg, 16/62 (25.8%) in canakinumab 50 mg, 22/68 (32.4%) in canakinumab 150 mg and 34/137 (24.8%) in the placebo group. An HbA1c (rescue-free) responder analysis of patients showed no statistically significant differences for any canakinumab dose group vs placebo. The difference from baseline to month 4 (LOCF) in FPG, fasting insulin, PG AUC0-4h, post meal-challenge glucose (2-h postprandial and peak levels), C-peptide AUC0-4h, post meal-challenge peak C-peptide, ISR, and mean/peak glucose values, based on 7-point PG data, HOMA-β and HOMA2-IR, did not reveal any consistent significant improvement with any canakinumab dose group vs placebo (Table 1). In the 150 mg treatment group, some comparisons vs placebo was associated with unadjusted \( P < 0.05 \): change from baseline in PG AUC0-4h (1.618 vs −0.851 mmol/L), 2-h PPG (0.262 vs −0.347 mmol/L), and peak glucose (0.381 vs −0.339 mmol/L).

When compared with placebo-treated patients, canakinumab did not show significant changes in LDL-C, HDL-C, or non-HDL over the study period. Median triglyceride levels did rise approximately 10% at Month 4 vs 2.5% rise in placebo-treated patients, \( P < 0.05 \) only in the 50 and 150 mg groups as reported by Ridker et al. [26].

After completing Period II, most patients entered an extension Period III where they continued to receive monthly injections of the study drug. Hba1c and FPG were the only measurements of glycaemic control that were measured during Period III. There was a minimal change in Hba1c from end of Period II to the last visit completed in Period III (Fig. S2, see supplementary material associated with this article online). There was no apparent difference in FPG between canakinumab doses and placebo during Period III. No liquid MMTT was performed during the Period III.

3.3. Safety

Safety results presented herein are based on events/assessments during the combined study periods (Periods II and III). Of the 551 patients receiving Period II study drug, 518 received Period III study treatment. Patients received up to 17 monthly injections of study drug during Periods II and III, with a median of six monthly injections. Treatment-emergent AEs (TEAEs) were reported by half the patients (286 patients, 51.9%) and TEAEs leading to permanent discontinuation occurred in four subjects (Table 2). According to the MedDRA primary system organ class (SOC), the most frequently reported AEs (≥5% overall treatment groups) were infections and infestations (132 patients, 24.0%), musculoskeletal and connective tissue disorders (64 patients, 11.6%), gastrointestinal disorders (43 patients, 7.8%), investigations (41 patients, 7.4%), skin and subcutaneous tissue disorders (32 patients, 5.8%), and nervous system disorders (30 patients, 5.4%). There were three injection site reactions reported (1 in the 50 mg canakinumab dose group, 2 in the placebo group) associated with more than 3600 injections during Periods II and III. These three cases of injection site reactions were transient and were not associated with significant erythema or swelling. Anti-canakinumab antibodies were not detected in any of the patients for which injection site reactions were reported.

There was no apparent dose dependency but incidence of infections was higher in the canakinumab 50 mg group when compared with other canakinumab groups and placebo (Table 2), and the majority of infections were mild to moderate. Renal and urinary tract disorders were more frequently reported in the canakinumab groups than in the placebo group: nephrolithiasis (5 patients), calculus ureteric (2 patients), crystalluria (2 patients), dysuria (2 patients), calculus urinary (1 patient), hydronephrosis (1 patient), leukocyturia (1 patient), pollakiuria (1 patient), renal cyst (1 patient), renal failure acute (1 patient) and renal mass (1 patient). By preferred term, the
most frequently reported AEs during Periods II and Period III were nasopharyngitis (37 patients, 6.7%) and urinary tract infection (28 patients, 5.1%). Nasopharyngitis was reported by similar percentages of patients receiving canakinumab (range, 4.2%–9.8%) and placebo (8.4%), and was not dose related. Urinary tract infection was reported by a slightly higher percentage of patients in the placebo group (6.1%) than canakinumab treatment groups (range, 3.2%–5.4%). There were no clinically meaningful differences between canakinumab treatments with respect to percentages of patients reporting cardiovascular and cerebrovascular events. TEAEs related to malignant events were reported by one (1.1%) patient (basal cell carcinoma) in the canakinumab 150 mg group. As expected, mean white blood cell counts and neutrophil counts were lower on canakinumab treatment when compared with placebo but these differences were not thought to be clinically meaningful because the decrease in neutrophil counts did not result in clinically significant persistent CTC grade 3 or, worse neutropenia. Direct platelet counts at Month 4 were lower in patients on canakinumab treatment than on placebo, but this was not thought to be clinically meaningful because the decrease in platelets did not result in any clinically significant CTC grade 3 or worse thrombocytopenia.

Table 1
Secondary efficacy endpoints least squares mean change from baseline.

<table>
<thead>
<tr>
<th>Parameter, 4-month rescue-free, utilizing LOCF</th>
<th>Canakinumab 5 mg</th>
<th>Canakinumab 15 mg</th>
<th>Canakinumab 50 mg</th>
<th>Canakinumab 150 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG (mmol/L)</td>
<td>n = 89, 93, 98, 90, 172</td>
<td>0.25 (0.162)</td>
<td>-0.19 (0.159)</td>
<td>-0.29 (0.162)</td>
<td>0.19 (0.160)</td>
</tr>
<tr>
<td>Fasting insulin (pmol/L)</td>
<td>n = 75, 81, 73, 83, 143</td>
<td>4.3 (4.74)</td>
<td>7.2 (4.57)</td>
<td>7.0 (4.67)</td>
<td>4.4 (4.47)</td>
</tr>
<tr>
<td>Plasma glucose AUC0–2h (pmol/L)</td>
<td>n = 79, 83, 82, 84, 147</td>
<td>-0.999 (0.8094)</td>
<td>-1.012 (0.7917)</td>
<td>2.103 (0.7928)</td>
<td>1.618 (0.7791)*</td>
</tr>
<tr>
<td>2-h FPG (mmol/L)</td>
<td>n = 79, 85, 83, 84, 151</td>
<td>-0.427 (0.2537)</td>
<td>-0.239 (0.2457)</td>
<td>-0.777 (0.2471)</td>
<td>0.262 (0.2445)*</td>
</tr>
<tr>
<td>Peak glucose (mmol/L)</td>
<td>n = 81, 85, 83, 87, 152</td>
<td>-0.386 (0.2302)</td>
<td>-0.380 (0.2257)</td>
<td>-0.565 (0.2770)</td>
<td>0.381 (0.2208)*</td>
</tr>
<tr>
<td>C-peptide AUC0–4h (mmol/L)</td>
<td>n = 81, 87, 83, 86, 153</td>
<td>-0.399 (0.1444)</td>
<td>-0.388 (0.1394)</td>
<td>-0.834 (0.1425)</td>
<td>-0.610 (0.1396)</td>
</tr>
<tr>
<td>7-point SMPG (mmol/L)</td>
<td>n = 81, 85, 82, 86, 152</td>
<td>-0.357 (0.1626)</td>
<td>-0.218 (0.1589)</td>
<td>-0.275 (0.1614)</td>
<td>-0.040 (0.1569)</td>
</tr>
<tr>
<td>Peak 7-point SMPG (mmol/L)</td>
<td>n = 81, 85, 82, 86, 152</td>
<td>-0.549 (0.2669)</td>
<td>-0.129 (0.2610)</td>
<td>-0.421 (0.2653)</td>
<td>-0.333 (0.2578)</td>
</tr>
<tr>
<td>HOMA-β</td>
<td>n = 75, 79, 77, 83, 143</td>
<td>-1.067 (6.0549)</td>
<td>2.259 (5.9304)</td>
<td>8.215 (5.9727)</td>
<td>6.217 (5.7307)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>n = 75, 71, 87, 83, 143</td>
<td>0.245 (3.107)</td>
<td>0.517 (0.2990)</td>
<td>0.255 (0.3054)</td>
<td>0.252 (0.2925)</td>
</tr>
</tbody>
</table>

FPG: fasting plasma glucose; ISR: insulin secretion rate; PE: point estimate; PPG: postprandial glucose; SMPG: self-measured plasma glucose; LOCF: last observation carried forward.

Point estimates, standard errors (SE), confidence intervals (CI) and P-values are calculated from an analysis of covariance of the change from baseline in parameter with treatment and metformin dose group as main effects and parameter baseline value as a covariate.

*Two-sided P-value versus placebo less than 0.05. n: number of patients with values at both baseline and endpoint (including all other main effects and covariates).
Table 2
Treatment-emergent adverse events during Periods II and III by treatment group (safety set).

<table>
<thead>
<tr>
<th></th>
<th>Canakinumab</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 mg n=93</td>
<td>15 mg n=95</td>
<td>50 mg n=92</td>
</tr>
<tr>
<td>Deaths, other serious/clinically significant adverse events or related discontinuations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEs leading to death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SAEs</td>
<td>3 (3.2)</td>
<td>1 (1.1)</td>
<td>5 (5.4)</td>
</tr>
<tr>
<td>AEs leading to permanent study treatment discontinuation</td>
<td>0</td>
<td>1 (1.1)</td>
<td>0</td>
</tr>
<tr>
<td>Other clinically significant AEs</td>
<td>19 (20.4)</td>
<td>26 (27.4)</td>
<td>28 (30.4)</td>
</tr>
<tr>
<td>CCV events</td>
<td>1 (1.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Immunogenicity/Allergenicity</td>
<td>0</td>
<td>1 (1.1)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>19 (20.4)</td>
<td>25 (26.3)</td>
<td>27 (29.3)</td>
</tr>
<tr>
<td>Malignant events</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SAEs leading to permanent study treatment discontinuation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MedDRA Primary SOC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>43 (46.2)</td>
<td>49 (51.6)</td>
<td>53 (57.6)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>19 (20.4)</td>
<td>25 (26.3)</td>
<td>27 (29.3)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>7 (7.5)</td>
<td>14 (14.7)</td>
<td>10 (10.9)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>7 (7.5)</td>
<td>5 (5.3)</td>
<td>11 (12.0)</td>
</tr>
<tr>
<td>Investigations*</td>
<td>5 (5.4)</td>
<td>5 (5.3)</td>
<td>9 (9.8)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>4 (4.3)</td>
<td>5 (5.3)</td>
<td>6 (6.5)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>6 (6.5)</td>
<td>2 (2.1)</td>
<td>5 (5.4)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>6 (6.5)</td>
<td>3 (3.2)</td>
<td>4 (4.3)</td>
</tr>
<tr>
<td>Injury, poisoning, and procedural complications</td>
<td>3 (3.2)</td>
<td>4 (4.2)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>1 (1.1)</td>
<td>6 (6.3)</td>
<td>3 (3.3)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>3 (3.2)</td>
<td>4 (4.2)</td>
<td>3 (3.3)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>2 (2.2)</td>
<td>2 (2.1)</td>
<td>3 (3.3)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>4 (4.3)</td>
<td>1 (1.1)</td>
<td>5 (5.4)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>1 (1.1)</td>
<td>4 (4.2)</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>3 (3.2)</td>
<td>3 (3.2)</td>
<td>5 (5.4)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>3 (3.2)</td>
<td>2 (2.1)</td>
<td>5 (5.4)</td>
</tr>
</tbody>
</table>

AE: adverse event; CCV: cardiovascular and cerebrovascular; SAE: serious adverse event; SOC: system organ class. AEs concerning CCV events are identified using the SMQ: “myocardial infarction”, “central nervous system haemorrhages and cerebrovascular conditions”, and PT: “foetal cerebrovascular disorder”, “in-stent coronary artery restenosis”, “coronary artery restenosis”, “sudden cardiac death”, and “cardiac death.” Adverse events concerning immunogenicity/allergenicity events are identified using the narrow SMQ: “anaphylactic reaction”, “angioedema”, and “severe cutaneous adverse reactions”. Adverse events concerning malignant events are identified using the narrow SMQ: “malignant or unspecified tumors”.

Patients with multiple events within one category/a primary SOC are counted only once in the relevant category. Primary SOCs are sorted by descending frequency of total group. Hypoglycaemic events are included. * includes mostly laboratory or ECG abnormalities.

These elevations in liver function test (LFT) were variable in duration, but none of the elevations fulfilled the criteria for Hy’s Law. These elevations were not associated with clinical symptoms of liver disease and no patient discontinued study drug due to elevation in LFT.

There were no clinically meaningful differences between treatments with respect to SAEs. According to the primary SOC, the most frequent SAEs reported by at least two patients were infections and infestations (7 patients, 1.3%), renal and urinary disorders (5 patients, 0.9%), cardiac disorders (4 patients, 0.7%), gastrointestinal disorders, hepatobiliary disorders, metabolism and nutrition disorders, and musculoskeletal and connective tissue disorders (2 patients, 0.4% for each). One patient discontinued from the study during Period III because of an adverse event (angina pectoris). There were no deaths in this study.

Safety results for patients at the end of Period II, as reported in the Ridker et al. article [26], were similar to the results presented here, which include Periods II and III.

4. Discussion

The present study demonstrated that a 4-month course of monthly canakinumab resulted in a numerical HbA1c reduction in early stage T2DM patients receiving metformin therapy. The clinical significance of the improvement in HbA1c may have been less pronounced because of the relatively good glycaemic control at baseline (average HbA1c 7.4%). Specifically, a 30 mg dose of monthly canakinumab for 4 months resulted in a 0.19% placebo-adjusted decrement in HbA1c. This confirms that blocking IL-1β-mediated inflammation with canakinumab resulted in small improvements in glycaemic control. Coinciding with this were increases in peak insulin levels in most of the canakinumab groups, and these differences were also not associated with statistical significance (P < 0.05) vs placebo. The mean change from baseline to 4 months for fasting insulin increased for all canakinumab treatment groups, but the peak insulin level only increased for the 5, 15 and 50 mg groups, although not
significantly. The ISR\textsubscript{0–2h} was not significantly different compared with the placebo group and the C-peptide AUC\textsubscript{0–4h} was not different in the canakinumab-treated patients compared with the placebo group, suggesting a positive trend while not statistically significant change in beta-cell function.

The small number of reported SAEs and discontinuations due to AEs in canakinumab treatment groups supports the short term safety and tolerability of canakinumab in T2DM patients. The most commonly reported preferred terms in this study were nasopharyngitis and urinary tract infection, and an increased risk of mild-to-moderate infections was a previously identified risk of canakinumab therapy. There were three injection site reactions reported (1 in the 50 mg canakinumab dose group, 2 in the placebo group) associated with greater than 3600 injections during Periods II and III. Overall the safety and tolerability profile noted in the study is consistent with the known safety experience of canakinumab in other trials with different patient population [22]. The safety data was not based on 4 months only but a median of 6 months up to 17 months treatment.

There were several strengths to this study, including its double-blind, randomized, placebo-controlled design. Furthermore, the dosage of the background metformin for each patient was titrated to their individual maximum-tolerated dose during the run-in period. This allowed for a uniform study group, in terms of background therapy and stable glycaemic control, to be randomized to the canakinumab therapy or placebo. The inclusion criterion of a morning FPG less than 10.0 mmol/L during the run-in period further ensured that patients were reasonably controlled before randomization and minimized the risk of requiring rescue medication during the 4-month dose-finding period (no subject took meal time insulin as rescue medication and 9 subjects took insulin glargine as rescue medication during Period II: canakinumab 5 mg 3 patients [3.2%], canakinumab 15 mg 2 patients [2.1%), canakinumab 50 mg 1 patient [1.1%] and canakinumab 150 mg 0 patients [0%]). However, the small number of patients requiring insulin prevents an evaluation in relation to the dose administered. And during Period III 27 patients took insulin glargine as rescue medication: canakinumab 5 mg (6), canakinumab 15 mg (4), canakinumab 50 mg (2), canakinumab 150 mg (3) and placebo (12). Finally, patients were randomized to one of the four canakinumab doses or placebo in a ratio of 1:1:1:1:2, respectively. The larger placebo group maximized statistical power and, therefore, minimized the number of patients needed to be exposed to canakinumab.

The most notable limitation of this study was the short duration of the trial, which precludes any long-term efficacy or safety conclusions of canakinumab in T2DM patients. Further, although this study included diabetic patients with either a short duration of disease, as demonstrated by the years of treatment, or patients naïve to OAD; these patients presumably have had a progressive decline in beta-cell capacity for longer time prior to diagnosis and beta-cell functionality that may or may not be restored after IL-1β blockade by canakinumab. The question of whether canakinumab may be more useful in preventing onset of T2DM through the prevention of loss of beta-cell function may be addressed in the upcoming Canakinumab ANti-Inflammatory Thrombosis Outcomes Study (CANTOS), which will evaluate whether IL-1β inhibition as compared with placebo can reduce rates of recurrent cardiovascular events as primary endpoint and the rate of new onset diabetes among stable post-myocardial infarction patients who remain at high vascular risk as one of the secondary endpoints [27].

Disclosure of interest

V.W. is a full-time employee of Novartis Pharma and holds stock ownership therein. C.P.H. and T.T. are employees of Novartis Pharmaceuticals Corporation. T.T. is also a stockholder.

Acknowledgements

This study was supported by Novartis Pharmaceuticals Corporation. Editorial assistance was provided by Peloton Advantage, LLC, supported by Novartis Pharmaceuticals Corporation.

A preliminary report of this study was presented at the European Association for the Study of Diabetes (EASD) meeting in 2011.

Appendix A. Supplementary materials

Supplementary materials (Figs. S1 and S2) associated with this article can be found at http://dx.doi.org/10.1016/j.diabet.2013.07.003.

References


