



Effect of interleukin-1 β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial

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Summary

Background Inflammation in the tumour microenvironment mediated by interleukin 1 β is hypothesised to have a major role in cancer invasiveness, progression, and metastases. We did an additional analysis in the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS), a randomised trial of the role of interleukin-1 β inhibition in atherosclerosis, with the aim of establishing whether inhibition of a major product of the Nod-like receptor protein 3 (NLRP3) inflammasome with canakinumab might alter cancer incidence.

Methods We did a randomised, double-blind, placebo-controlled trial of canakinumab in 10 061 patients with atherosclerosis who had had a myocardial infarction, were free of previously diagnosed cancer, and had concentrations of high-sensitivity C-reactive protein (hsCRP) of 2 mg/L or greater. To assess dose–response effects, patients were randomly assigned by computer-generated codes to three canakinumab doses (50 mg, 150 mg, and 300 mg, subcutaneously every 3 months) or placebo. Participants were followed up for incident cancer diagnoses, which were adjudicated by an oncology endpoint committee masked to drug or dose allocation. Analysis was by intention to treat. The trial is registered with ClinicalTrials.gov, NCT01327846. The trial is closed (the last patient visit was in June, 2017).

Findings Baseline concentrations of hsCRP (median 6·0 mg/L vs 4·2 mg/L; $p<0\cdot0001$) and interleukin 6 (3·2 vs 2·6 ng/L; $p<0\cdot0001$) were significantly higher among participants subsequently diagnosed with lung cancer than among those not diagnosed with cancer. During median follow-up of 3·7 years, compared with placebo, canakinumab was associated with dose-dependent reductions in concentrations of hsCRP of 26–41% and of interleukin 6 of 25–43% ($p<0\cdot0001$ for all comparisons). Total cancer mortality ($n=196$) was significantly lower in the pooled canakinumab group than in the placebo group ($p=0\cdot0007$ for trend across groups), but was significantly lower than placebo only in the 300 mg group individually (hazard ratio [HR] 0·49 [95% CI 0·31–0·75]; $p=0\cdot0009$). Incident lung cancer ($n=129$) was significantly less frequent in the 150 mg (HR 0·61 [95% CI 0·39–0·97]; $p=0\cdot034$) and 300 mg groups (HR 0·33 [95% CI 0·18–0·59]; $p<0\cdot0001$; $p<0\cdot0001$ for trend across groups). Lung cancer mortality was significantly less common in the canakinumab 300 mg group than in the placebo group (HR 0·23 [95% CI 0·10–0·54]; $p=0\cdot0002$) and in the pooled canakinumab population than in the placebo group ($p=0\cdot0002$ for trend across groups). Fatal infections or sepsis were significantly more common in the canakinumab groups than in the placebo group. All-cause mortality did not differ significantly between the canakinumab and placebo groups (HR 0·94 [95% CI 0·83–1·06]; $p=0\cdot31$).

Interpretation Our hypothesis-generating data suggest the possibility that anti-inflammatory therapy with canakinumab targeting the interleukin-1 β innate immunity pathway could significantly reduce incident lung cancer and lung cancer mortality. Replication of these data in formal settings of cancer screening and treatment is required.

Funding Novartis Pharmaceuticals.

Introduction

Many malignancies arise in areas of chronic inflammation,^{1,2} and inadequate resolution of inflammation could have a major role in tumour invasion, progression, and metastases.^{3–5} Inflammation is of particular pathophysiological relevance in lung cancer, in that chronic bronchitis, triggered by asbestos, silica, smoking, and other external inhaled toxins, results in a persistent inflammatory response.^{6,7} Inflammatory activation in the lung is partly mediated through activation of the Nod-like receptor protein 3 (NLRP3) inflammasome, with consequent local generation of active interleukin 1 β ,

a process that can lead to both chronic fibrosis and cancer.^{8,9} In mice, inflammasome activation and pro-interleukin-1 β processing accelerates tumour invasiveness, growth, and metastatic spread.³ For example, in interleukin 1 β ^{−/−} mice, neither local tumours nor lung metastases developed after localised or intravenous inoculation with melanoma cell lines, which suggests that interleukin 1 β participates in the invasiveness of already existing malignancies.¹⁰ Thus, inhibition of interleukin 1 β might have an adjunctive role in the treatment of cancers that have at least a partial inflammatory basis.^{11–14}

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Research in context

Evidence before this study

During protocol development in 2010, and intermittently through trial completion in 2017, we searched MEDLINE with the terms “inflammation”, “cancer”, “lung cancer”, “canakinumab”, “interleukin-1 β ”, and “anakinra” for articles published in English. We also included major review articles from noted experts. We identified previous evidence from animal models suggesting a potential role for interleukin-1 β inhibition in cancer invasiveness, growth, and metastasis, but little data from human studies.

Added value of this study

CANTOS provides the first evidence from a randomised trial in human beings that inhibition of interleukin 1 β with the

monoclonal antibody canakinumab is associated with reduced incidences of fatal cancer, lung cancer, and fatal lung cancer. Our data should be interpreted in the context that the primary aim of the trial was to investigate cardiac events rather than cancer events (the trial also showed a significant reduction in cardiovascular events with canakinumab compared with placebo).

Implications of all the available evidence

Our exploratory data should be replicated and extended in settings directly related to early cancer screening and initial treatment of cancers, particularly lung cancer.

The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) was a randomised, double-blind, placebo-controlled trial of 10 061 patients who were stable after a myocardial infarction. It was designed primarily to assess whether canakinumab, a human monoclonal antibody targeting interleukin 1 β , can prevent recurrent vascular events among men and women who have a persistent proinflammatory response defined by the presence of high-sensitivity C-reactive protein (hsCRP) concentrations of 2 mg/L or higher.^{15,16} The primary endpoints were non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death.¹⁷ By design, however, all participants had to be free of previously diagnosed cancer (other than basal cell skin carcinoma) at trial entry and were followed up prospectively for incident medical events for 3–5 years. Individuals with increased hsCRP concentrations have increased risk of several inflammatory cancers, most prominently lung cancer.^{18–20} Furthermore, patients with atherosclerosis commonly smoke, which is a major risk factor for cancer. By enrolling such patients, CANTOS afforded the additional opportunity to address in a high-risk population and within the context of a prospective, randomised, placebo-controlled trial whether interleukin-1 β inhibition with canakinumab could be associated with reduced incidence of site-specific cancers.

Methods

Trial population

We did a secondary analysis of the randomised controlled CANTOS trial to assess the effect of interleukin-1 β inhibition with canakinumab on incident cancer. Screening for inclusion in CANTOS began on April 11, 2011. People were eligible for enrolment if they had a history of myocardial infarction and blood concentrations of hsCRP of 2 mg/L or higher at entry despite use of aggressive secondary prevention strategies. People with a history of chronic or recurrent infections, previous malignancy other than basal cell skin carcinoma, a suspected or known immunocompromised state, or a history of (or at

high risk for) tuberculosis or HIV-related disease, and those using systemic anti-inflammatory treatments were excluded. Detailed inclusion and exclusion criteria are in the appendix. The trial protocol was approved at participating centres by the responsible institutional review board or ethics committee, as applicable in the 39 countries involved. All participants provided written consent to participate in the trial, which was overseen by an independent data and safety monitoring committee.

Randomisation

On the basis of results from our phase 2b study,¹⁶ we initially selected an anchor dose for canakinumab of 150 mg subcutaneously every 3 months. A higher dose of 300 mg given twice during a 2-week period and then every 3 months was also initially selected to address concerns about interleukin-1 β autoinduction. Thus, patients were randomly assigned (1:1:1) to standard care plus placebo, standard care plus canakinumab 150 mg, or standard care plus canakinumab 300 mg. Randomisation was by computer-generated code. However, health authorities requested broader dose–response data, and thus a lower dose arm (canakinumab 50 mg subcutaneously every 3 months) was added to the trial. The protocol was thus amended, and a formal four-arm structure was approved in July, 2011, although adoption date varied by region and site.

To accommodate this structural change, the proportions of individuals allocated to placebo and to the 50 mg dose were increased. Thus, the treatment allocation ratios were altered from 1:1:1 for the first 741 participants recruited to 2:1:4:1:3:1:3 (placebo: 50 mg canakinumab: 150 mg canakinumab: 300 mg canakinumab) for the remaining 9320 participants. Furthermore, on Dec 10, 2013, the executive committee accepted a request from the sponsor to reduce the study sample size from 17 200 to 10 000 for reasons related to portfolio and budgetary optimisation, but also to extend study duration by about 1 year to maintain specified power. Trial

enrolment was completed in March, 2014, and the last patient visit was in June, 2017.

The CANTOS protocol specified that full blood counts, lipid panels, hsCRP, and renal and hepatic function should be measured in all randomly assigned participants at baseline and 3, 6, 9, 12, 24, 36, and 48 months after randomisation. Interleukin 6 concentrations were measured 3 months and 12 months after randomisation.

Procedures

As prespecified in the trial safety monitoring plan, medical records were sought for all incident cancers reported during follow-up. These records were reviewed and classified by an endpoints panel of oncologists who were masked to study drug allocation. Fatal cancers were also independently classified by the trial endpoint committee. Cancers adjudicated by the cancer endpoint committee were used in the primary analysis, and sensitivity analyses were done with any reported cancers.

Statistical analysis

We compared baseline characteristics between randomly assigned participants in all treatment groups combined who remained cancer free and those who developed cancer at any time during follow-up with the χ^2 test for categorical variables and Wilcoxon rank sum tests for continuous variables. We used Cox proportional hazards

models to estimate hazard ratios (HRs) comparing each active dose with placebo, with separate models for each active dose versus placebo, and for overall cancer, fatal and non-fatal cancer, and site-specific cancer. Additionally, we did tests for trend with a proportional hazards model with scores of 0, 1, 3, and 6 proportional to dose to estimate HRs across ascending dose groups. In other proportional hazards models, we calculated HRs for the pooled group of all individuals assigned to canakinumab versus those assigned to placebo. In analyses of cancers by site, participants with a cancer at another site continued to be followed for incident cancer. All analyses were by intention to treat. Additional analyses were done comparing cancer rates in the placebo group to cancer rates in the pooled canakinumab groups among those with concentrations of hsCRP or interleukin 6 at 3 months higher than, or equal to or lower than, the study median. The trial is registered at ClinicalTrials.gov, NCT01327846.

Role of the funding source

This trial was sponsored by Novartis Pharmaceuticals. Employees of the sponsor were involved in design of the trial protocol, and the sponsor was responsible for data collection. The corresponding author had full access to all study data and was responsible for the decision to submit for publication.

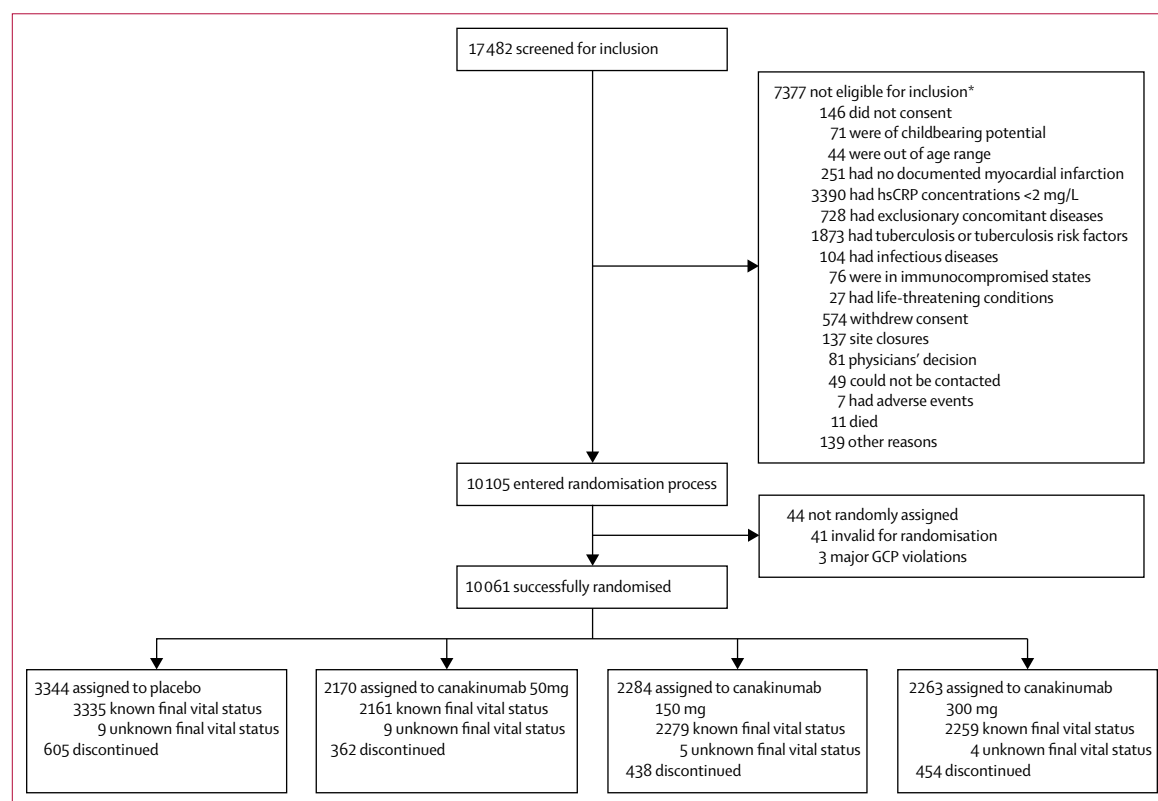


Figure 1: Trial profile

hsCRP=high-sensitivity C-reactive protein. GCP=good clinical practice. *Some participants had more than one exclusionary characteristic.

	No incident cancers		Incident non-lung cancers		Incident lung cancers	
	Placebo (n=3113)	Canakinumab (n=6286)	Placebo (n=179)	Canakinumab (n=377)	Placebo (n=61)	Canakinumab (n=68)
Age, years	61.0 (54.0–68.0)	61.0 (54.0–68.0)	67.0 (61.0–73.0)	66.0 (60.0–72.0)	66.0 (61.0–72.0)	64.0 (60.0–71.0)
Female sex	818 (26%)	1621 (26%)	40 (22%)	85 (23%)	9 (15%)	18 (26%)
Smoking status						
Current smoker	695 (22%)	1485 (24%)	46 (26%)	93 (25%)	28 (46%)	29 (43%)
Past smoker	1493 (48%)	2921 (46%)	99 (55%)	184 (49%)	31 (51%)	37 (54%)
Never smoker	925 (30%)	1880 (30%)	34 (19%)	100 (27%)	2 (3%)	2 (3%)
Body-mass index (kg/m ²)	29.8 (26.6–33.9)	29.8 (26.5–33.8)	29.0 (26.0–32.8)	30.1 (26.7–34.3)	28.3 (24.9–33.2)	29.7 (26.1–34.0)
Waist circumference (cm)	104.0 (96.0–114.0)	104.1 (96.0–114.0)	103.0 (95.3–112.5)	106.0 (97.0–116.8)	106.0 (95.5–118.0)	110.0 (96.5–119.8)
Alcohol use (>one drink per day)	125 (4%)	242 (4%)	10 (6%)	17 (5%)	2 (3%)	2 (3%)
Hypertension	2453 (79%)	5006 (80%)	152 (85%)	320 (85%)	48 (79%)	50 (74%)
Diabetes	1236 (40%)	2510 (40%)	73 (41%)	167 (44%)	28 (46%)	26 (38%)
Daily exercise	543 (17%)	1058 (17%)	35 (20%)	68 (18%)	7 (11%)	7 (10%)
hsCRP (mg/L)	4.1 (2.8–6.8)	4.2 (2.8–7.1)	4.3 (3.0–7.9)	4.4 (2.9–7.4)	6.8 (3.4–12.4)	6.0 (3.5–11.5)
Interleukin 6 (ng/L)	2.6 (1.8–4.0)	2.6 (1.8–4.1)	3.0 (1.9–4.2)	2.6 (1.9–3.9)	3.4 (2.3–6.8)	3.1 (2.5–5.2)
Total cholesterol (mmol/L)	4.2 (3.6–4.9)	4.1 (3.5–4.9)	3.9 (3.3–4.7)	4.0 (3.4–4.7)	4.1 (3.3–4.8)	4.1 (3.4–5.0)
LDL cholesterol (mmol/L)	2.2 (1.7–2.8)	2.1 (1.6–2.8)	2.0 (1.6–2.6)	2.0 (1.6–2.6)	2.0 (1.5–2.6)	2.1 (1.6–2.9)
HDL cholesterol (mmol/L)	1.1 (1.0–1.4)	1.1 (1.0–1.4)	1.2 (1.0–1.4)	1.2 (1.0–1.4)	1.2 (0.9–1.4)	1.1 (0.9–1.3)
Triglycerides (mmol/L)	1.6 (1.1–2.2)	1.6 (1.2–2.2)	1.4 (1.1–2.0)	1.5 (1.1–2.0)	1.6 (1.2–2.6)	1.5 (1.1–2.1)
Estimated GFR (mL/min per 1.73 m ²)	79.0 (65.0–93.0)	79.0 (65.0–93.0)	75.0 (60.0–93.0)	74.0 (58.0–87.0)	72.0 (62.0–89.0)	77.5 (60.0–92.5)

Continuous data are reported as median (IQR), dichotomous data are reported as n (%). 23 participants developed both non-lung cancer and lung cancer during trial follow-up. hsCRP=high-sensitivity C-reactive protein. GFR=glomerular filtration rate.

Table 1: Baseline clinical characteristics of participants who did and did not develop incident cancers during follow-up

Results

Of 17482 patients screened for CANTOS, 10061 were randomly assigned, 3344 to placebo, 2170 to the canakinumab 50 mg group, 2284 to the canakinumab 150mg group, and 2263 to the canakinumab 300 mg group (figure 1). The most common reasons for pre-randomisation exclusion were hsCRP concentration of less than 2 mg/L, active tuberculosis or tuberculosis

risk factors, and exclusionary concomitant disorders (figure 1). Baseline clinical characteristics and cancer risk factors were well matched between groups (appendix). 2366 participants (24%) were current smokers, and 4753 (47%) were past smokers, and the median hsCRP concentration was 4.2 mg/L.

Compared with participants who were not diagnosed with cancer, those who developed incident lung cancers were older ($p<0.0001$) and more likely to be current smokers ($p<0.0001$; table 1). Median hsCRP (6.0 mg/L vs 4.2 mg/L; $p<0.0001$; table 1) and interleukin 6 concentrations (3.2 ng/L vs 2.6 ng/L; $p<0.0001$; table 1) were significantly higher at baseline in people who were diagnosed with lung cancer during follow-up than in those who remained free of any cancer diagnosis.

During trial follow-up, compared with placebo, canakinumab was associated with dose-dependent reductions in hsCRP of 26–41% ($p<0.0001$ for all groups) and interleukin 6 of 25–43% ($p<0.0001$ for all groups).¹⁷ Canakinumab had no effect on LDL or HDL cholesterol.¹⁷

During the median 3.7 year follow-up period, total cancer mortality was lower in the combined canakinumab groups than in the placebo group ($p=0.0158$). For this endpoint ($n=196$), compared with placebo, HRs were 0.86 (95% CI 0.59–1.24; $p=0.42$) for the 50 mg group, 0.78 (95% CI 0.54–1.13; $p=0.19$) for the 150 mg group, and 0.49 (95% CI 0.31–0.75; $p=0.0009$) for the 300 mg group (table 2). The incidence rate of cancer mortality per 100 person-years was 0.64 in the placebo group, 0.55 in the 50 mg group, 0.50 in the 150 mg, and 0.31 in the 300 mg group ($p=0.0007$ for trend across active dose groups compared with placebo; figure 2A, table 2).

Lung cancer accounted for 26% of all cancers and 47% of all cancer deaths in the placebo group, but only 16% of all cancers and 34% of cancer deaths in the canakinumab groups. For incident lung cancer ($n=129$), compared with placebo, HRs were 0.74 (95% CI 0.47–1.17; $p=0.20$) for the 50 mg group, 0.61 (95% CI 0.39–0.97; $p=0.034$) in the 150 mg group, and 0.33 (95% CI 0.18–0.59; $p<0.0001$) for the 300 mg group (figure 2B, table 2). The incidence rate of lung cancer per 100 person-years was 0.49 in the placebo group, 0.35 in the 50 mg group, 0.30 in the 150 mg group, and 0.16 in the 300 mg group ($p<0.0001$ for trend across active dose groups compared with placebo; figure 2B, table 2). Lung cancer mortality ($n=77$) was significantly less common in the canakinumab 300 mg group than in the placebo group (HR 0.23 [95% CI 0.10–0.54]; $p=0.0002$; figure 2C, table 2). The incidence rate of lung cancer mortality per 100 person-years was 0.30 in the placebo group, 0.20 in the 50 mg group, 0.19 in the 150 mg group, and 0.07 in the 300 mg group ($p=0.0002$ for trend across active dose groups compared with placebo; figure 2C, table 2).

Stratification by smoking suggested that the effect of canakinumab on lung cancer was slightly stronger in current than in past smokers (HR 0.50 [$p=0.005$]

	Placebo (n=3344)	Canakinumab 50 mg (n=2170)	Canakinumab 150 mg (n=2284)	Canakinumab 300 mg (n=2263)	All doses (n=6717)	p value (for trend across doses)
Any cancer (all)						
Incident rate (n)	1.88 (231)	1.85 (144)	1.69 (143)	1.72 (144)	1.75 (431)	0.31
HR (95% CI)	1 (ref)	0.99 (0.80–1.22)	0.90 (0.73–1.11)	0.91 (0.74–1.12)	0.93 (0.79–1.09)	..
p	Ref	0.91	0.31	0.38	0.38	..
Any cancer (fatal)						
Incidence rate (n)	0.64 (81)	0.55 (44)	0.50 (44)	0.31 (27)	0.45 (115)	0.0007
HR (95% CI)	1 (ref)	0.86 (0.59–1.24)	0.78 (0.54–1.13)	0.49 (0.31–0.75)	0.71 (0.53–0.94)	..
p	Ref	0.42	0.19	0.0009	0.0158	..
Lung cancer (all)						
Incidence rate (n)	0.49 (61)	0.35 (28)	0.30 (26)	0.16 (14)	0.27 (68)	<0.0001
HR (95% CI)	1 (ref)	0.74 (0.47–1.17)	0.61 (0.39–0.97)	0.33 (0.18–0.59)	0.55 (0.39–0.78)	..
p	Ref	0.20	0.0337	<0.0001	0.0007	..
Lung cancer (fatal)						
Incidence rate (n)	0.30 (38)	0.20 (16)	0.19 (17)	0.07 (6)	0.15 (39)	0.0002
HR (95% CI)	1 (ref)	0.67 (0.37–1.20)	0.64 (0.36–1.14)	0.23 (0.10–0.54)	0.51 (0.33–0.80)	..
p	Ref	0.18	0.13	0.0002	0.0026	..
Non-lung cancer (all)						
Incidence rate (n)	1.46 (179)	1.55 (121)	1.44 (122)	1.60 (134)	1.53 (377)	0.54
HR (95% CI)	1 (ref)	1.08 (0.85–1.36)	0.99 (0.78–1.24)	1.10 (0.88–1.37)	1.05 (0.88–1.26)	..
p	Ref	0.54	0.91	0.42	0.58	..
Non-lung cancer (fatal)						
Incidence rate (n)	0.39 (49)	0.38 (30)	0.34 (30)	0.24 (21)	0.32 (81)	0.06
HR (95% CI)	1 (ref)	0.96 (0.61–1.51)	0.88 (0.56–1.39)	0.63 (0.38–1.04)	0.82 (0.58–1.17)	..
p	Ref	0.86	0.60	0.07	0.28	..

HR=hazard ratio.

Table 2: Incidence rates (per 100 person-years) and HRs for all incident cancers, lung cancers, and non-lung cancers

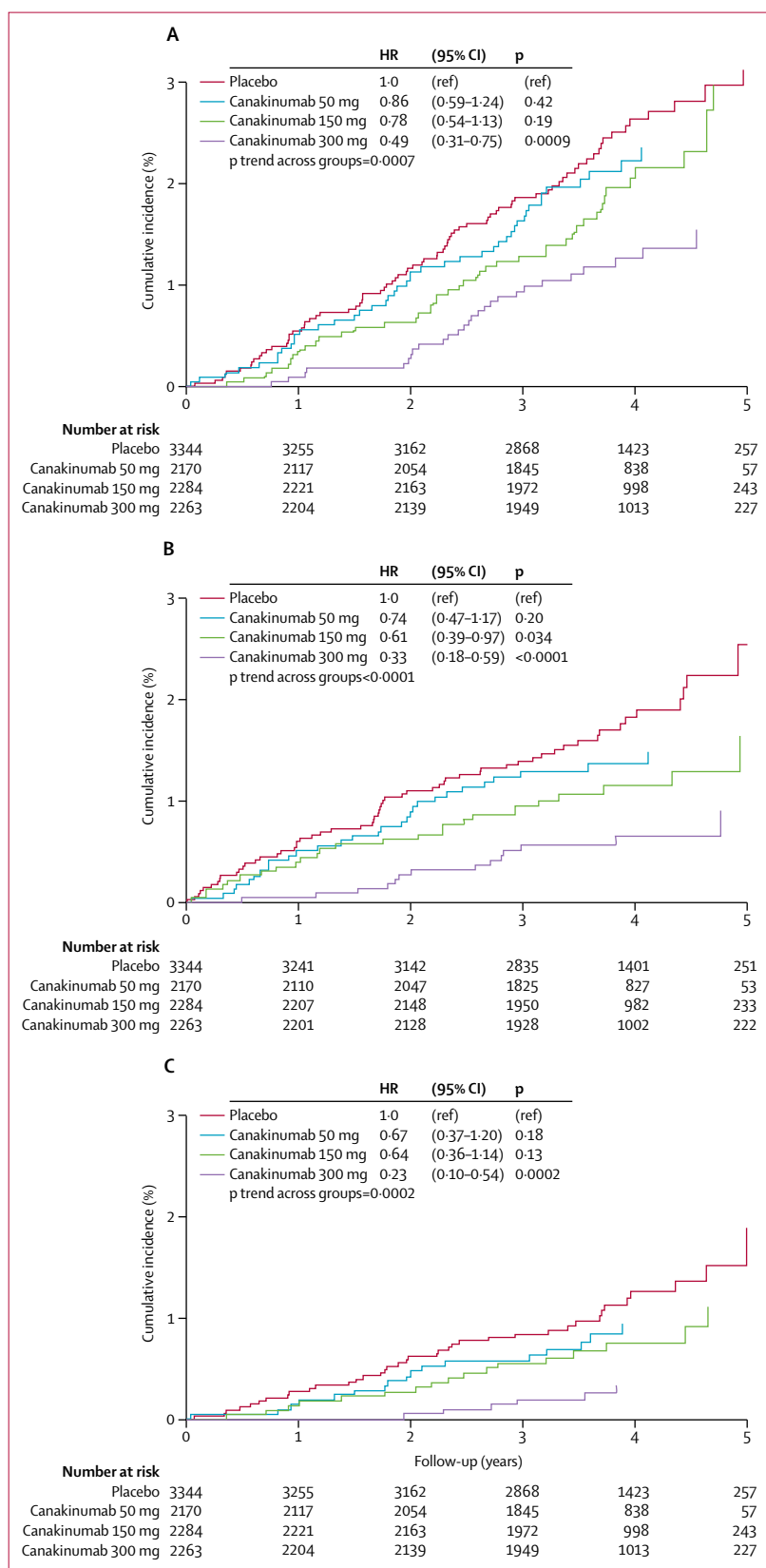
vs HR 0.61 [$p=0.006$]). This effect was more prominent in the 300 mg group (HR 0.25 [$p=0.002$] vs HR 0.44 [$p=0.025$]; appendix).

The incidences of lung cancer of unspecified type, histologically defined lung adenocarcinoma, and histologically defined poorly differentiated large cell cancer were significantly lower in the combined canakinumab group than in the placebo group (combined incidence rate per 100 person-years was 0.41 in the placebo group, 0.33 in the 50 mg group, 0.27 in the 150 mg group, and 0.12 in the 300 mg group [$p<0.0001$ for trend across dose groups compared with placebo]; appendix). There were too few cases for meaningful assessment of the effects of canakinumab on the incidence of small-cell lung cancers or squamous cell carcinomas (appendix).

In analyses of combined canakinumab doses, compared with placebo, the HR for lung cancer among participants on canakinumab who had hsCRP concentrations at 3 months less than the median value of 1.8 mg/L was 0.29 (95% CI 0.17–0.51; $p<0.0001$). The incidence of lung cancer did not differ significantly between participants in the placebo group and those in the canakinumab group

whose serum hsCRP concentrations were higher than the median of 1.8 mg/L at 3 months (HR 0.83 [95% CI 0.56–1.22]; $p=0.34$). Similar effects were noted for median interleukin 6 concentrations at 3 months. For canakinumab-treated participants with 3-month interleukin 6 concentrations less than 1.64 ng/L, the HR for lung cancer was 0.24 (95% CI 0.12–0.50; $p<0.0001$). For canakinumab-treated participants with 3-month interleukin 6 concentrations higher than 1.64 ng/L, no benefit was noted for lung cancer (HR 1.0 [95% CI 0.62–1.60]; $p=0.997$).

Compared with placebo, canakinumab was not associated with significant reductions in incident cancers at other sites (appendix). The incidence of basal cell carcinoma per 100 person-years was higher in combined canakinumab groups than in the placebo group, but this difference was not significant (incident rate 0.26 vs 0.18; $p=0.16$). Although previous non-basal-cell malignancy was an exclusion criterion, review of enrolment records suggested that 76 (1%) of the 10061 participants potentially had previous cancers. Post-hoc exclusion of these individuals had no effect on our results. Results



from sensitivity analyses based on any reported cancers were almost identical to analyses based on cancers adjudicated by the oncology endpoint committee (appendix).

Grade 1 thrombocytopenia and neutropenia were rare, but more common in the canakinumab groups than in the placebo group (table 3). We noted no differences in the frequency of grade 3 or 4 episodes between groups (table 3). A significantly higher proportion of fatal events attributed to infection or sepsis per 100 person-years was noted in the three canakinumab groups combined than in the placebo group (incidence rate 0.31 vs 0.18; $p=0.023$; table 4). Participants who died from infection tended to be older and more likely to have diabetes than those who did not.¹⁷ Incidence of non-cardiovascular mortality (HR 0.97 [95% CI 0.79–1.19]; $p=0.80$) and all-cause mortality (HR 0.94 [95% CI 0.83–1.06]; $p=0.31$) did not differ significantly between the placebo and canakinumab groups. Serious tuberculosis infections were rare and occurred at similar frequencies in the canakinumab and placebo groups (0.06%).¹⁷ Injection-site reactions occurred with similar frequencies in the canakinumab and placebo groups (table 4). Canakinumab was associated with significant reductions in adverse reports of arthritis, gout, and osteoarthritis compared with placebo (table 4). Before the final visit, study drug was discontinued with similar frequency in the placebo and canakinumab groups (figure 1). Compared with placebo, non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death were reduced by 15% in the 150 mg and 300 mg canakinumab groups.¹⁷ This risk reduction was 17% for the prespecified secondary cardiovascular endpoint that included non-fatal myocardial infarction, non-fatal stroke, hospital admission for unstable angina requiring urgent revascularisation, and cardiovascular death.¹⁷

Discussion

Our exploratory data from the randomised, double-blind, placebo-controlled CANTOS trial suggest that inhibition of interleukin 1 β with canakinumab over a median period of 3.7 years was associated with a reduction in the occurrence of fatal and non-fatal lung cancers among patients with atherosclerosis who had increased hsCRP concentrations and who did not have previous diagnoses of cancer. Effects were dose dependent, with relative hazard reductions of 67% ($p<0.0001$) for total lung cancer and 77% ($p=0.0002$) for fatal lung cancer in participants allocated to the canakinumab 300 mg dose. Patients with increased concentrations of the inflammatory biomarkers hsCRP and interleukin 6 had the highest risk for incident lung cancer. Smokers and

Figure 2: Cumulative incidence of all fatal cancer (A), lung cancer (B), and fatal lung cancer (C) among CANTOS participants
CANTOS=Canakinumab Anti-inflammatory Thrombosis Outcomes Study.
HR=hazard ratio.

	Placebo (n=3344)	Canakinumab 50 mg (n=2170)	Canakinumab 150 mg (n=2284)	Canakinumab 300 mg (n=2263)	All doses (n=6717)	p value (for trend across doses)	p value (for combined dose groups)
Platelets (per mm³)							
Thrombocytopenia reported as adverse event*	53 (0.43)	44 (0.56)	46 (0.54)	60 (0.71)	150 (0.60)	0.0218	0.0308
Healthy platelet count	2731 (91.1)	1741 (88.9)	1777 (87.5)	1698 (84.0)	5216 (86.8)	<0.0001	<0.0001
Grade 1 thrombocytopenia (75 000 to <150 000)	259 (8.6)	214 (10.9)	252 (12.4)	316 (15.6)	782 (13.0)
Grade 2 thrombocytopenia (50 000 to <75 000)	6 (0.20)	3 (0.15)	1 (0.05)	6 (0.30)	10 (0.17)
Grade 3 thrombocytopenia (25 000 to <50 000)	1 (0.03)	0 (0.00)	2 (0.10)	2 (0.10)	4 (0.07)
Leucocytes (per mm³)							
Leucopenia reported as adverse event*	30 (0.24)	24 (0.30)	32 (0.37)	44 (0.52)	100 (0.40)	0.0021	0.0128
High leucocyte count (>15 000)	11 (0.37)	9 (0.46)	9 (0.44)	2 (0.10)	20 (0.33)	0.09	0.56
Normal leucocyte count (3000 to <15 000)	2980 (99.3)	1944 (99.2)	2016 (99.0)	2018 (99.5)	5978 (99.2)
Low leucocyte count (<3000)	9 (0.30)	7 (0.36)	11 (0.54)	9 (0.44)	27 (0.45)
Neutrophils (per mm³)							
Neutropenia reported as adverse event	7 (0.06)	4 (0.05)	6 (0.07)	15 (0.18)	25 (0.10)	0.0140	0.17
Healthy neutrophil count	2954 (99.4)	1917 (99.4)	1991 (99.1)	1983 (99.2)	5891 (99.2)	0.33	0.72
Grade 1 neutropenia (1500 to <1600)	5 (0.17)	4 (0.21)	4 (0.20)	6 (0.30)	14 (0.24)
Grade 2 neutropenia (1000 to <1500)	10 (0.34)	6 (0.31)	12 (0.60)	10 (0.50)	28 (0.47)
Grade 3 neutropenia (500 to <1000)	3 (0.10)	2 (0.10)	2 (0.10)	1 (0.05)	5 (0.08)
Erythrocytes (× 10¹²)							
Anaemia reported as adverse event	171 (1.40)	66 (0.84)	102 (1.21)	110 (1.31)	278 (1.13)	0.89	0.0257
High erythrocyte count (>6.8)	2 (0.07)	1 (0.05)	0 (0.00)	3 (0.15)	4 (0.07)	0.31	0.62
Normal erythrocyte count (3.3–6.8)	2993 (99.7)	1954 (99.7)	2031 (99.8)	2017 (99.4)	6002 (99.6)
Low erythrocyte count (<3.3)	6 (0.20)	5 (0.26)	5 (0.25)	9 (0.44)	19 (0.32)

Adverse events were collected throughout the study and are reported as number of events (incidence rate per 100 person-years). Data for platelet, leucocyte, neutrophil, and erythrocyte counts are at 12 months. *Standardised Medical Dictionary for Regulatory Activities queries.

Table 3: Changes to platelet, leucocyte, neutrophil, and erythrocyte counts after 12 months of treatment

those who achieved the greatest reductions in hsCRP or interleukin 6 seemed to gain the most benefit. By contrast, canakinumab did not significantly affect the frequency of site-specific cancers other than lung cancer. However, total cancer mortality was more than 50% lower in the canakinumab 300 mg group than in the placebo group ($p=0.0009$).

CANTOS was a trial¹⁷ of inflammation reduction done in patients with increased hsCRP concentrations who had had myocardial infarction, and in whom the rates of current or past smoking were high. These characteristics put the CANTOS population at higher-than-average risk of lung cancer, and afforded us the additional opportunity to address the effect of inhibition of interleukin 1 β on cancer. However, by design, we do not have data for individuals free of atherosclerotic disease or with low blood concentrations of hsCRP.

Canakinumab seems unlikely to have had direct effects on oncogenesis and the development of new lung cancers (although this possibility cannot be ruled out). Patients

who developed lung cancer during follow-up were on average 65 years old at study entry, and more than 90% were current or former smokers. Furthermore, the median follow-up time was unlikely to have been adequate to show a reduction in new cancers. A more biologically plausible explanation is that canakinumab reduced the rate of progression, invasiveness, and metastatic spread of lung cancers that were prevalent but undiagnosed at trial entry. In this regard, our clinical data are consistent with previous experimental work suggesting that cytokines such as interleukin 1 β can promote angiogenesis and tumour growth and that interleukin 1 β is essential to tumour invasiveness in already existing malignant cells.^{1–5,10} In mice, high concentrations of interleukin 1 β within the tumour microenvironment were associated with more virulent phenotypes,¹⁴ and secreted interleukin 1 β derived from this microenvironment (or directly from malignant cells) promoted tumour invasiveness and, in some cases, induced tumour-mediated suppression.^{2,3,10,21}

	Placebo (n=3344)	Canakinumab 50 mg (n=2170)	Canakinumab 150 mg (n=2284)	Canakinumab 300 mg (n=2263)	All doses (n=6717)	p value (for trend across doses)	p value (for combined dose groups)
Any serious adverse event	12.0 (1202)	11.4 (741)	11.7 (812)	12.3 (836)	11.8 (2389)	0.43	0.79
Infection							
Any serious infection	2.86 (342)	3.03 (230)	3.13 (258)	3.25 (265)	3.14 (753)	0.12	0.14
Cellulitis	0.24 (30)	0.24 (19)	0.37 (32)	0.41 (35)	0.34 (86)	0.0213	0.09
Pneumonia	0.90 (112)	0.94 (74)	0.94 (80)	0.99 (84)	0.95 (238)	0.56	0.62
Urinary tract infection	0.22 (27)	0.18 (14)	0.24 (21)	0.20 (17)	0.21 (52)	0.84	0.87
Opportunistic infections*	0.18 (23)	0.16 (13)	0.15 (13)	0.20 (17)	0.17 (43)	0.97	0.78
Pseudomembranous colitis†	0.03 (4)	0.13 (10)	0.05 (4)	0.12 (10)	0.10 (24)	0.13	0.0302
Fatal infections or sepsis	0.18 (23)	0.31 (25)	0.28 (24)	0.34 (29)	0.31 (78)	0.09	0.0228
Other adverse events							
Injection-site reaction*	0.23 (29)	0.27 (21)	0.28 (24)	0.30 (26)	0.28 (71)	0.49	0.36
Arthritis†	3.32 (385)	2.15 (164)	2.17 (180)	2.47 (201)	2.26 (545)	0.0020	<0.0001
Osteoarthritis	1.67 (202)	1.21 (94)	1.12 (95)	1.30 (109)	1.21 (298)	0.0393	0.0005
Gout	0.80 (99)	0.43 (34)	0.35 (30)	0.37 (32)	0.38 (96)	<0.0001	<0.0001
Drug-induced liver injury*	0.18 (23)	0.15 (12)	0.13 (11)	0.05 (4)	0.11 (27)	0.0039	0.0541
Any haemorrhage†	4.01 (462)	3.33 (249)	4.15 (327)	3.82 (301)	3.78 (877)	0.94	0.31
Hepatic safety data							
Alanine aminotransferase >three times ULN	46 (1%)	42 (2%)	44 (2%)	45 (2%)	131 (2%)	0.19	0.0580
Aspartate aminotransferase >three times ULN	36 (1%)	32 (1%)	35 (2%)	34 (2%)	101 (2%)	0.30	0.11
Alkaline phosphatase >three times ULN	15 (<1%)	11 (1%)	10 (<1%)	12 (1%)	33 (<1%)	0.67	0.82
Bilirubin >two times ULN	26 (1%)	21 (1%)	15 (1%)	15 (1%)	51 (1%)	0.34	0.83

Data are incident rate per 100 person-years (n), or n (%). ULN=upper limit of normal. *Sponsor categorisation of adverse events of special interest. †Standardised Medical Dictionary for Regulatory Activities queries.

Table 4: Incidence rates (per 100 person-years) of serious adverse events and selected on-treatment safety laboratory data

Since the time of Virchow, inflammation has been linked to cancer. As Balkwill and Mantovani have written, “if genetic damage is ‘the match that lights the fire’ of cancer, some types of inflammation may provide the ‘fuel that feeds the flames’”.²² This hypothesis helps to partly explain why the chronic use of aspirin and other non-steroidal anti-inflammatory drugs is associated with reduced mortality from colorectal cancer and lung adenocarcinomas.^{23,24} However, whereas those drugs need to be used for more than a decade to affect cancer incidence, we noted potential beneficial effects of canakinumab on the incidence of lung cancer and lung cancer mortality in a much shorter timeframe.

The apparent specificity of canakinumab in our data for lung cancer and canakinumab's augmented effect among current smokers is of interest because inflammasome-mediated production of interleukin 1 β is triggered by several inhaled environmental toxins that are known to induce local pulmonary inflammation and cancer.^{8,9} Furthermore, genetic polymorphism in the genes coding for interleukin 1 β and for naturally occurring interleukin-1-receptor antagonists are both associated with lung-cancer risk.^{25–28} Although obesity is commonly linked to both cancer and inflammation, lung cancer is not typically

thought to be an obesity-related cancer,²⁹ and our data were consistent with previous findings.

The randomised design of our trial means that prevalent cancers undiagnosed at trial entry and cancer risk factors were probably equally distributed among treatment groups. CANTOS, however, was not formally designed as a cancer detection or treatment trial, and thus the findings reported here will need to be carefully replicated in different settings. Most importantly, we think that our data warrant prospective assessment of canakinumab as a potential therapy for early lung cancers or after imaging-based lung-cancer screening, perhaps in combination with debulking procedures, radiation, and other immunomodulating treatments. There is precedent for such an interleukin-1-targeted cytokine approach for other cancer types. For example, the interleukin-1-receptor antagonist anakinra was reported to moderately reduce the progression of smouldering or indolent myeloma in a case series of 47 patients.³⁰ In a second case series³¹ of 52 patients with diverse metastatic cancers, a human antibody targeting interleukin 1 α was well tolerated and associated with moderate improvement in lean body mass, appetite, and pain.³¹ Our data also warrant consideration of trials of canakinumab for lung cancer prevention and treatment based on genetic

screening within loci associated with inflammatory cytokine function, including interleukins 1 and 6.^{25–28,32,33} These concepts further merit investigation of alternative agents targeting NLRP3 function or that inhibit downstream signalling through interleukin 6.

Canakinumab moderately reduces absolute neutrophil counts—an effect noted in our data. Reductions in platelet counts were minimal and not associated with haemorrhagic events, and we noted no important hepatic toxicity. The beneficial effects of canakinumab on arthritis, gout, and osteoarthritis are consistent with well described effects of interleukin 1 in these disorders. The major toxicity of canakinumab in CANTOS was a significant increase in fatal infection and sepsis in the pooled group of participants assigned to any active dose of canakinumab compared with placebo. This adverse effect was balanced, however, by the reduction in cancer mortality such that no increase in non-cardiovascular or all-cause mortality was noted. If our data are replicated in future studies, participants treated with canakinumab should be carefully monitored for early signs and symptoms of serious infection in a manner similar to that done for individuals taking other immunomodulating biologics.

As part of our safety monitoring plan, all cancer endpoints in CANTOS were adjudicated by a committee of oncologists blinded to treatment allocation. Our data nonetheless require replication, because lung cancer was not a formally prespecified study endpoint. Chance is a possible explanation for our findings, but is unlikely in view of the biological mechanisms and highly significant associations reported. The randomised nature of our trial also greatly reduces, but does not eliminate, the potential for confounding. Differential surveillance can induce bias, but careful monitoring of study participants showed little differences between groups in visit attendance, dropouts, and loss to follow-up. Canakinumab treatment is unlikely to have delayed detection of lung cancer, but if it did, the direction of this bias is uncertain and would be unlikely to explain differences in mortality. Bias from competing risks should be considered, because of the increased incidence of death from infection or sepsis. However, review of fatality records showed no clear pattern of infections or evidence of a link with cancer, and the total number of deaths from infection or sepsis was not large. Finally, we found no relation between canakinumab allocation and incident cases of chronic obstructive pulmonary disease, another potential confounding disorder.

Contributors

PMR was the trial's principal investigator and trial chairman, ran all investigator meetings, oversaw all daily trial activities, and wrote and edited the primary Article. JGM was the primary trial programmer and did all initial and subsequent analyses. TT assisted with trial logistics. BME chaired the Clinical Endpoints Committee and made logistic contributions. PL assisted in all investigator meetings and executive committee meetings. RJG was the academic trial statistician, designed and did the primary statistical analyses, and was the statistical liaison to the Data and Safety Monitoring Board. All authors additionally assisted in study design and data interpretation, and provided comments on the final Article.

Declaration of interests

PMR and RJG received research grant support from Novartis Pharmaceuticals to conduct the trial. PMR has served as a consultant to Novartis Pharmaceuticals and is listed as a co-inventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes that have been licensed to AstraZeneca and Siemens. TT is an employee of, and holds stock in, Novartis Pharmaceuticals. All other authors declare no competing interests.

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