Important New Evidence Service

In Partnership with The Centre for Medicines Optimisation at Keele University

ScriptSwitch™ Rapid Update 2 – October 2017

Cardiovascular disease: anti-inflammatory therapy with canakinumab for coronary artery disease

Canakinumab is a human monoclonal antibody targeting interleukin-1 beta which has anti-inflammatory effects and is licensed in the UK to treat a range of rheumatological disorders.

A multicentre randomised controlled trial (CANTOS) involving more than 10,000 people with previous myocardial infarction (MI) and an elevated level of high-sensitivity C-reactive protein found that canakinumab 150 mg every three months significantly lowered the incidence of recurrent cardiovascular events compared with placebo. However, there was no significant difference seen with other doses and no effect on all-cause mortality. The absolute clinical cardiovascular benefits demonstrated by canakinumab were modest (fewer than one event prevented per 100 person-years) and this needs to be balanced against the increased risk of infection (and death due to infection) observed in the study. Canakinumab costs around £10,000 per 150 mg vial, which will also need to be factored into any decision making about its use in those with a previous MI.

Reference: Ridker PM, Everett BM, Thuren T *et al.* Anti-inflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017; 377:1119-1131. DOI: 10.1056/NEJMoa1707914

What do we know already?

- Biomarkers of inflammation, such as high-sensitivity C-reactive protein and interleukin-6, are known to be associated with an increased risk of cardiovascular events, independent of the cholesterol level.
- Inflammatory reactions probably increase plaque instability, possibly resulting in plaque rupture, fissuring or erosion and initiating the thrombotic response, leading to myocardial damage or infarction (see associated editorial).
- Statins can reduce levels of cholesterol and markers of inflammation and their beneficial effects in patients relate to both of these actions, although, to date, no evidence has shown that reducing vascular inflammation in the absence of concomitant lipid-lowering reduces the rates of cardiovascular effects (Ridker *et al,* 2017).
- A previous phase 2 study of patients with diabetes at high vascular risk showed inhibition of interleukin-1 beta with canakinumab markedly reduced levels of interleukin-6 and high-sensitivity C-reactive protein without lowering LDL cholesterol.

What does this evidence add?

- This study found that canakinumab significantly reduced high-sensitivity C-reactive protein levels from baseline, in a dose-dependent manner, without reducing LDL cholesterol. The 150 mg dose significantly reduced the incidence of the primary endpoint (a composite of non-fatal MI, non-fatal stroke and cardiovascular death) compared with placebo (3.9 *vs.* 4.5 events per 100 person-years) but did not reduce all-cause mortality. The modest cardiovascular benefit was driven by a lower incidence of MI.
- Canakinumab was associated with a significantly higher incidence of fatal infection and a lower incidence of cancer death.
- The results from CANTOS will probably stimulate further research seeking to identify other anti-inflammatory pathways that might serve as targets for new drugs to reduce cardiovascular risk, and with an improved safety profile.

Study details

Participants:

- CANTOS was a randomised, double-blind, placebo-controlled trial conducted in 39 countries enrolling 10,061 patients with a history of MI and a blood level of high-sensitivity C-reactive protein of 2 mg or more per litre (median 4.2 mg per litre) despite aggressive use of secondary prevention strategies. Patients were excluded if they had a history of chronic or recurrent infection, previous cancer, were immunocompromised, had a history or high risk for tuberculosis or disease related to the human immunodeficiency virus, or ongoing use of other anti-inflammatory treatments.
- The mean age of participants was 61 years, 25.7% were women, 40% had diabetes and 23.5% were current smokers. Most participants had undergone previous revascularisation procedures (66.7% of the patients had undergone percutaneous coronary intervention and 14.0% coronary-artery bypass grafting). At baseline, antithrombotic agents were taken by 95% of patients, lipid-lowering agents by 93.4%, anti-ischaemia agents by 91.4% and inhibitors of the renin-angiotensin system by 79.7%.

Intervention and comparison:

- Patients were randomly assigned to one of three doses of canakinumab (50 mg, 150 mg or 300 mg) or placebo, administered subcutaneously every three months. Patients receiving the 300 mg dose initially had two injections two weeks apart after which they then received the dose every three months.
- According to a related editorial, after enrolment to CANTOS had begun, and based on financial considerations, the sponsor (without access to the data) modified the trial design to decrease the sample size from 17,200 to 10,000 participants. To compensate for the reduced number of participants, the follow-up period was then extended to allow the accumulation of an adequate number of events. It should be noted that longer follow-up periods in clinical trials of chronic diseases have the potential to magnify any treatment benefit observed.
- CANTOS began in April 2011 and was completed in March 2014; the last trial visit being in June 2017.

Outcomes and results:

- At 48 months, the median reduction from baseline in high-sensitivity C-reactive protein level was 26% greater for the 50 mg dose of canakinumab, 37% greater for the 150 mg group and 41% greater for the 300 mg group than in the placebo group (p < 0.001 for all doses *vs.* placebo). Canakinumab did not significantly reduce LDL cholesterol or HDL cholesterol levels from baseline.
- At a median follow-up of 3.7 years, the incidence rate for the primary endpoint of non-fatal MI, non-fatal stroke or cardiovascular death was 4.5 events per 100 person-years in the placebo group, 4.1 events per 100 person-years for the 50 mg dose of canakinumab, 3.9 events per 100 person-years in the 150 mg group and 3.9 events per 100 person-years in the 300 mg group. This modest effect only achieved significance for the 150 mg group (hazard ratio [HR] *vs.* placebo 0.85, 95% confidence interval [CI], 0.74 to 0.98, p = 0.02) and was driven by a lower incidence of MI.
- Considering results for the 150 mg dose only, the HR *vs.* placebo for the key secondary endpoint (the components of the primary endpoint plus hospitalisation for unstable angina that led to urgent revascularisation) was 0.83 (95% CI 0.73 to 0.95, p = 0.005).
- In an analysis where data for all three doses of canakinumab were combined, neutropenia was more common among patients assigned to receive canakinumab and significantly more deaths from infection occurred in patients receiving canakinumab versus placebo (incidence rate 0.31 *vs.* 0.18 events per 100 person-years, p = 0.02). Patients who died tended to be older and more likely to have diabetes. Thrombocytopaenia was more common among patients assigned to receive canakinumab but no significant difference in the incidence of haemorrhage was observed. There was a lower risk of cancer with canakinumab versus placebo.
- There were fewer reports of arthritis, gout and osteoarthritis with canakinumab compared with placebo, a finding that is consistent with known effects of interleukin-1β inhibition.
- All-cause mortality was not significantly different in the canakinumab groups compared with the placebo group (HR for all doses *vs.* placebo 0.94, 95% CI 0.83 to 1.06, p = 0.31).

Level of evidence:
Level 1 (good quality patient-oriented evidence) according to SORT criteria.

Study funding:
Novartis (manufacturer).