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Anti-inflammatory drug cuts risk of heart disease — and cancer

Results from Novartis's huge trial of the interleukin-1β blocker canakinumab could revitalize efforts to target inflammation in atherosclerosis, and have demonstrated unanticipated activity in lung cancer.

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After years of trying, researchers have finally shown that a targeted anti-inflammatory agent can guard against life-threatening plaque ruptures in heart attack survivors who remain at risk of further vascular events despite well-controlled lipid levels.

The highest dose of Novartis's canakinumab — an antibody that binds interleukin (IL)-1β — reduced the incidence of heart attack, stroke and death by 15% in the ~10,000-patient CANTOS trial, which was reported at the European Society of Cardiology Congress in August 2017 and published concurrently in the *New England Journal of Medicine*. Researchers expect that the finding will breathe new life into the quest for anti-inflammatory drugs for cardiovascular disease.

Nearly half of all patients with chronic atherosclerosis who are treated with statins still have residual inflammatory risk, as indicated by levels of C-reactive protein (CRP) in the bloodstream, and so could in theory benefit from such therapies. Now, "for the first time, CANTOS leaves us optimistic that we can reduce residual risk," says Michael Farkouh, a cardiologist at the Toronto General Hospital Research Institute in Canada, who was not involved in the trial.

"As proof of principle, it really opens up the field for evaluating other anti-inflammatory agents that are available for use in clinical practice but not for this indication," says Robert Rosenson, a cardiologist at the Icahn School of Medicine at Mount Sinai in New York City, who was also not involved in the study.

From the immediate clinical and commercial perspectives, however, the results are more of a mixed bag. Canakinumab, already approved for several rare autoimmune diseases, has a sticker price of US$16,000 per injection and was used quarterly in the CANTOS trial, likely making it too expensive to be prescribed widely as a preventive cardiovascular agent. Novartis could lower the price to reflect the larger market share on offer in a cardiovascular setting, but will still have to contend with the increased risk of infection associated with canakinumab that offsets its cardiovascular benefits. The firm remains optimistic about its ability to balance the benefit–risk–price trifecta, and plans to file the drug for supplementary approval for heart disease.

Fanning the flames

It has long been known that patients with high levels of CRP and other inflammatory markers are at increased risk of plaque ruptures and their artery-blocking consequences. But drug developers have struggled to translate this information into new treatment options.

Although trials that tested the impact of statins in patients with naturally low levels of low-density lipoprotein (LDL) cholesterol have shown that these therapies can lower CRP levels and reduce the rate of cardiovascular events, it was impossible to tell whether the clinical benefit arose from the inhibition of inflammation, from further cholesterol reduction or from both.

Compounding the problem, previous attempts to improve outcomes with novel agents aimed more pointedly at reducing inflammation have failed. These experimental disappointments include Anthera Pharmaceutical's secretory phospholipase inhibitor varespladib and GlaxoSmithKline's lipoprotein-associated phospholipase A2 inhibitor darapladib, which both block pro-inflammatory modifications to LDL cholesterol (*Nat. Rev. Drug Discov.* **13**, 481–482; 2014). Some researchers think these drugs may have failed because they act on targets that are not in the IL-1 to tumour necrosis factor (TNF)-α to IL-6 pathway that leads to CRP production in the liver.

CANTOS was the first major test of whether inhibiting one of the cytokines upstream of CRP synthesis could prevent atherosclerotic plaque disruption and thrombosis.

In targeting IL-1β — the main circulating form of IL-1 — canakinumab neutralizes this apical mediator of inflammation, which is produced when cholesterol crystals activate the NLRP3 inflammasome. IL-1β then induces expression of several secondary pro-inflammatory

messengers, including IL-6, a cytokine that triggers production of both CRP and itself and that has been implicated directly in atherosclerotic plaque development and destabilization.

Trials have shown that Roche's tocilizumab, an anti-IL-6 receptor antibody used mainly for rheumatoid arthritis, can reduce CRP levels in patients who have just experienced a heart attack. However, tocilizumab also increases LDL cholesterol levels, and the net cardiovascular effect seems to be negligible.

Ideally, canakinumab would be given only to patients with pathologically elevated IL-1β activity, but this cytokine cannot be reliably quantified in the bloodstream. So the CANTOS investigators recruited patients with elevated CRP levels instead, as a proxy measure. Problematically, "CRP is a relatively crude systemic biomarker that does not necessarily reflect the extent of IL-1β activity at pathologically important sites," says Robin Choudhury, a cardiologist at the University of Oxford, UK. "It's too far removed from the action and probably not a sufficiently precise way to select or stratify patients for this highly targeted therapy."

This could be seen in the CANTOS data. Even though all the study participants had high levels of CRP to begin with, a post-hoc analysis showed that only around half saw those levels change as a result of IL-1β inhibition over the course of the trial. And it was only this subgroup of patients that had a statistically significant reduction in cardiovascular events. Thus, although changes in CRP may be a good indicator of response, baseline CRP levels are not a great predictor of one. "We have no sophisticated way to tailor the therapy to the patients who might stand to benefit," Choudhury says.

The combination of an inability to find patients who are most likely to benefit, the high cost of an antibody and the risk of infection bodes poorly for the use of canakinumab in a cardiovascular setting. But cheap and safe generic drugs that can induce the same protective effects could fare better, even without predictive biomarkers. The leading contenders are low-dose methotrexate and colchicine, agents that have long been used to treat arthritis and gout, respectively.

Methotrexate has various anti-inflammatory properties, including the ability to inhibit the production of IL-6 and so would act just downstream of canakinumab. It is being evaluated in the CIRT trial of 7,000 people with type 2 diabetes or metabolic syndrome and a history of heart attacks or coronary blockages. If the drug succeeds in lowering cardiovascular risk in this study, "it will tell us that there are several ways of altering this IL-1 to IL-6 pathway," says principal investigator Paul Ridker, a cardiologist at the Brigham and Women's Hospital in Boston who also led CANTOS. "If it fails, we just have to go back and stay in the narrow-spectrum approach."

Results from CIRT will not be known for a couple years, but Jean-Claude Tardif, director of the Montreal Heart Institute Research Centre in Canada, says he wouldn't be surprised if less targeted, generic therapies actually prove more beneficial than canakinumab. "There are several pathways that could be involved in inflammation and atherosclerosis," he says, "and just blocking a single one like IL-1β might very well not be enough." Tardif is leading the 4,500-patient COLCOT study of colchicine in patients who have had a heart attack. Colchicine is thought of primarily as an anti-tubulin agent, but it also affects the function of the NLRP3 inflammasome and, thus, the IL-1–IL-6–CRP pathway.

COLCOT is scheduled to run through 2019, but that timeline could be shortened in light of the CANTOS results.

Even if residual inflammation can be tamped out, the CANTOS data suggest that many responders with chronic atherosclerosis will still die from cardiovascular disease. For Christian Gleißner, a cardiologist at the University Hospital Heidelberg in Germany, that means the research community still needs to look for other drug targets outside of the inflammatory cascade. "There may be something beyond LDLs and beyond inflammation that we're missing right now," he says.

Not just for heart health

CANTOS could also prompt more testing of anti-inflammatory drugs in oncology. In addition to looking at cardiovascular outcomes, the trial investigators catalogued all the cancers that occurred in the study — prompted by the known link between inflammation and tumour development. Their most eye-popping finding, reported in *The Lancet*, was that high-dose canakinumab lowered total cancer mortality by more than 50% compared with placebo, with the bulk of the survival benefit coming from the reduced incidence of lung cancer.

"This is elegant confirmation that inflammation in the tumour microenvironment clearly impacts upon outcomes, and that it's a modifiable target for cancer patients," Ridker says. "Every major pharmaceutical company in the world right now is looking into their armamentarium to see what they might have that inhibits this pathway," he adds. "The cancer finding, as much as the atherosclerosis finding, is going to drive that investigation."

The reason canakinumab showed its most pronounced effect on preventing lung cancer likely has to do with the particulars of the study population — 71% of whom were current or former smokers, a habit that induces lung inflammation. Give the drug to a different vulnerable population — miners exposed to asbestos at risk of mesothelioma, or people with chronic hepatitis infections who are prone to liver cancer — and the same benefit could hold true, predicts Ron Apte, a cancer immunologist at Ben-Gurion University of the Negev in Be'er Sheva, Israel.

That conjecture will need to be tested. And for Brendan Jenkins, a cancer immunologist at the Hudson Institute of Medical Research in Clayton, Australia, much more work is needed to understand which lung cancer patients are most likely to benefit from anti-IL-1 therapy. Is it just atherosclerotic patients? What cancer stages are affected by IL-1 blockade? Is activity dependent on mutations in *KRAS*, *EGFR* or other genes?

There is some precedent for targeting IL-1 in cancer patients. One phase II trial showed that multiple myeloma patients who received Swedish Orphan Biovitrum's IL-1 receptor antagonist anakinra had a longer progression-free survival relative to historical experience. XBiotech is also developing an IL-1α-targeted antibody for colorectal cancer, but earlier this year the European Medicines Agency rejected a request for marketing authorization of the antibody and the company terminated a phase III trial because of futility.

The CANTOS results could, however, lead to a surge of interest in cancer-focused research into this target, says oncologist Razelle Kurzrock, from the University of California, San Diego. "There's been an underlying rumble of interest in inflammation for a few years," she says. "I really hope that this does spur new interest, because it's a pretty fantastic finding."