Methotrexate: *CIRT*ified for preventing atherosclerotic events?

Akshat Pandey[1], Mohit Goyal[2]

Title Low-dose methotrexate for the prevention of atherosclerotic events

Authors Ridker PM, Everett BM, Pradhan A et al.; CIRT Investigators

Journal *N Engl J Med* 2019; 21: 380: 752–62.

Financial and Competing Interests: No conflict of interests declared

Correspondence to:
Akshat Pandey
Department of Clinical Immunology and Rheumatology
Apollo Hospitals
Indore (MP)
India

Email:
drakshat23@gmail.com

Summary

Ischemic heart disease (IHD) with angina and acute myocardial infarction (MI) as its leading manifestations is the cause of major morbidity and mortality in developed and low- and middle-income countries.[1] There are significant data underscoring the relationship between various biomarkers of inflammation and prospective cardiovascular risk, both in patients with coronary heart disease or heart failure as well as healthy individuals. These biomarkers play a pivotal role in the initiation and propagation of atherosclerosis as inflammation accompanies vasospasm, impaired coronary blood flow and myocardial ischemia.[2] Inflammation may also lead to restenosis after angioplasty.[3]

Activation of intrinsic mechanisms by the macrophages leads to release of inflammatory cytokines, such as interleukin-1 beta (IL-1β). The inflammation thus moves downstream and leads to release of the potent inflammatory cytokine interleukin-6 (IL-6). IL-1β is, therefore, a potential target to control inflammation and impedes atherosclerosis.[4]

Methotrexate (MTX) in low dose of 7.5–25 mg once every week is used in the treatment of many autoimmune rheumatic diseases. One of the many mechanisms by which MTX acts is by inhibition of purine biosynthesis, leading to the accumulation of enzyme aminoimidazolecarboxamidoadenosineribonucleotide (AICAR) and its metabolites. This in turn has a direct inhibitory effect on two key enzymes, adenosine deaminase and adenosine monophosphate deaminase, resulting in increased concentrations of adenosine and adenine nucleotides intracellularly. Adenosine inhibits tumour necrosis factor alpha (TNF-α) and has a significant effect on IL-6, IL-8, IL-10, IL-12 and macrophage inflammatory protein-1α.[5]

The recently concluded Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS), involving over 10,000 patients, studied the role of canakinumab, an anti-IL-1β monoclonal antibody, in patients with IHD who had persistently raised high sensitivity C-reactive protein (hsCRP) levels of 2 mg/l or more. The group on canakinumab at a dose of 150 mg every 3 months had significantly lower incidence of nonfatal MI, ischemic stroke and death related to cardiovascular events. A significant reduction in hsCRP was associated with a lower risk of recurrence of cardiovascular events and a significant reduction in cardiovascular mortality, at both the doses of canakinumab used.[4,6,7]

It has been observed in data from various studies that patients who received low-dose MTX for rheumatoid arthritis (RA) and psoriatic arthritis have been found to have fewer cardiovascular events compared to placebo.[8,9] An alternative thought, therefore, has been to try to lower the cardiovascular event rates by using low-dose MTX for inhibition of inflammation.

The Cardiovascular Inflammation Reduction Trial (CIRT) studied low-dose MTX in patients with previous MI or multivessel coronary disease who additionally had either type 2 diabetes or metabolic syndrome. This randomised, double-blind trial involving 4,786 patients compared MTX at doses of 15–20 mg weekly with placebo and the participants were followed up for a median of 2.3 years. The primary end point was a composite of nonfatal MI, nonfatal stroke or cardiovascular death, and hospitalisation for unstable angina was added before unblinding. Treatment with MTX did not result in significantly lower levels of IL-1β, IL-6 or C-reactive protein (CRP) levels. The final primary end point was comparable in both groups (201 patients in MTX group vs 207 in placebo). Incidence rates were 4.13 vs 4.31 per

[1]Department of Clinical Immunology and Rheumatology, Apollo Hospitals, Indore, India; [2]CARE Pain and Arthritis Centre, Goyal Hospital, Udaipur, India

Table 1 Main differentiating features of CANTOS and CIRT trials

	CANTOS	CIRT
Inclusion criteria	Patients with established ischemic heart disease who continued to have elevation of hsCRP in serum beyond 2 mg/l	Previous history of myocardial infarction or coronary disease who additionally had either type 2 diabetes or metabolic syndrome
Molecule	Canakinumab	Methotrexate
CRP	CANTOS limited enrollment to patients with persistently elevated hsCRP levels	CIRT did not screen for CRP level, instead required participants to have either diabetes or metabolic syndrome
Mechanism of controlling inflammation	Canakinumab targets IL-1β–IL-6 pathway	Methotrexate's adenosine-mediated anti-inflammatory effects
Conclusion	The reduction from baseline in IL-6 and CRP levels was greater in the group assigned to receive canakinumab	Ability of methotrexate to reduce CRP level is limited to situations in which inflammation levels are high
Complications	None with canakinumab	Resulted in non-basal-cell skin cancer, altered liver functions and leucopenia

CANTOS: Canakinumab Anti-inflammatory Thrombosis Outcomes Study; CIRT: Cardiovascular Inflammation Reduction Trial; CRP: C-reactive protein; hsCRP: high sensitivity C-reactive protein; IL-1β: interleukin-1 beta; IL-6: interleukin-6

100 person years, respectively, hazard ratio was 0.96. The original primary end point was also comparable (170 patients in MTX group vs 167 in the placebo group) with incidence rates of 3.46 vs 3.43 per 100 person years, respectively, and hazard ratio of 1.01. MTX was associated with a higher incidence of non-basal-cell skin cancers. Elevation in liver enzyme levels and reduction in white blood cells counts were also observed in patients on MTX.[10]

Opinion

MTX has been known to reduce the incidence of MI in patients with RA.[8,9] A cross-sectional study involving 4,363 patients with RA with no previous history of cardiovascular disease (CVD) from 15 countries showed that MTX use led to lower risks of all CVD events, MI and stroke.[11] In another cohort involving 6,707 veterans in the USA with RA, use of low-dose MTX resulted in reduction of CVD events.[12] MTX has a significant effect on reduction of TNF-α, CRP, IL-6 and on various other cytokines that play a role in the development of atherosclerosis.

The CIRT trial was conducted with the hypothesis that low-dose MTX can lead to reduction in inflammatory markers and consequently cardiovascular mortality. CANTOS had concluded that the incidence rates of the primary end points, i.e. nonfatal MI, ischemic stroke and death related to cardiovascular events, as well as secondary end points, i.e. primary end points with the additional requirement of revascularisation procedure at 4 years of follow up, were significantly lower for the group receiving canakinumab. A secondary analysis of CANTOS further concluded a significantly reduced risk of recurrence of cardiovascular events in the group attaining a hsCRP level <2 mg/l.[6,7] MTX in many aforementioned observational studies did lower vascular event rates in RA and psoriatic arthritis, the mechanism for which is poorly understood, but probably reflects its adenosine-mediated anti-inflammatory effects.[5] A possible reason for this observed benefit might be a higher level of inflammation in patients with RA and psoriatic arthritis and its successful reduction by MTX. The drug may not lead to a further reduction in levels of inflammatory cytokines in subjects with cardiovascular diseases but without inflammatory arthritides. Additionally, the CIRT trial did not have hsCRP levels as a criterion for inclusion, and lower baseline levels may have contributed to the inefficacy of MTX. Another plausible explanation for the failure of MTX could be the difference in the pathways targeted by the two drugs, as canakinumab targets the IL-1β–IL-6 pathway, while MTX does not. The key differences between the two studies are summarised in Table 1. We are of the opinion that the current evidence does not support the use of MTX in the reduction of atherosclerotic events in patients who do not have high inflammatory burden due to some autoimmune inflammatory conditions, such as rheumatoid or psoriatic arthritis.

References

1 Gaziano T, Reddy KS, Paccaud F et al. Chapter 33 Cardiovascular Disease. In: Jamison DT, Breman JG, Measham AR et al., editors. *Disease Control Priorities in Developing Countries*. 2nd edition. Washington (DC): The International Bank for Reconstruction and Development/The World Bank; 2006.

2 Libby P, Ridker PM, Hansson GK; Leducq Transatlantic Network on Atherothrombosis. Inflammation in atherosclerosis: from pathophysiology to practice. *J Am Coll Cardiol* 2009; 54: 2129–38.

3 Abbasi SH, Boroumand MA. Expanded network of inflammatory markers of atherogenesis: where are we now? *Open Cardiovasc Med J* 2010; 4: 38–44.

4 Misra DP, Agarwal V. CANTOS – is selective targeting of inflammation in atherosclerosis enough? *J R Coll Physicians Edinb* 2018; 48: 246–7.

5 Chan ES, Cronstein BN. Molecular action of methotrexate in inflammatory diseases. *Arthritis Res* 2002; 4: 266–73.

6 Ridker PM, MacFadyen JG, Everett BM et al. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomized controlled trial. *Lancet* 2018; 391: 319–28.

7 Ridker PM, Libby P, MacFadyen JG et al. Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS). *Eur Heart J* 2018; 39: 3499–507.

8 Choi HK, Hernán MA, Seeger JD et al. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. *Lancet* 2002; 359: 1173–7.

9 Westlake SL, Colebatch AN, Baird J et al. The effect of methotrexate on cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review. *Rheumatology (Oxford)* 2010; 49: 295–307.

10 Ridker PM, Everett BM, Pradhan A et al.; CIRT Investigators. Low-dose methotrexate for the prevention of atherosclerotic events. *N Engl J Med* 2019; 21; 380: 752–62.

11 Naranjo A, Sokka T, Descalzo MA et al.; QUEST-RA Group. Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. *Arthritis Res Ther* 2008; 10: R30.

12 Prodanovich S, Ma F, Taylor JR et al. Methotrexate reduces incidence of vascular diseases in veterans with psoriasis or rheumatoid arthritis. *J Am Acad Dermatol* 2005; 52: 262–7.