Canakinumab for Atherosclerotic Cardiovascular Disease: Effectiveness and Value

Final Background and Scope

August 30, 2018

Background

Atherosclerotic cardiovascular disease (ASCVD) is the most common cause of death in the United States (US) and approximately one third of American adults have ASCVD.[1] Low density lipoprotein cholesterol (LDL) is a major modifiable risk factor for myocardial infarction (MI), stroke, and death from cardiovascular disease.[1] The use of statins to decrease LDL has contributed to the marked decline in death from ASCVD since 1950.[2] However, patients with ASCVD remain at high risk for additional ASCVD events despite optimal treatment with high-intensity statin therapy and anti-platelet agents. Recently, PCSK9 inhibitors have been shown to reduce events in patients with ASCVD, but additional therapies are needed.[3,4]

Inflammation is important in the formation of cholesterol deposits in arterial walls.[5] Inflammation, as measured by high-sensitivity C-reactive protein level (hsCRP), is a known risk factor for ASCVD events, but the benefits of anti-inflammatory drugs in reducing ASCVD events has been controversial. The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS), published in 2017, found that canakinumab, which uses a novel mechanism of action to reduce inflammation also reduces ASCVD events in patients with a prior MI and a hsCRP ≥ 2 mg/L.[6] Canakinumab is a monoclonal antibody to IL-1β, which appears to act through its effects on macrophages, smooth muscle, and endothelial cells.[5] It was initially approved as an orphan drug for several rare periodic fever syndromes and is very expensive. An FDA decision on an expanded indication for canakinumab that includes ASCVD is expected towards the end of 2018.

Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patient advocacy organizations, clinicians, researchers, and the manufacturer of the agent of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. A final scoping document will be posted following a three-week public comment period. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

The patients we spoke with were hopeful that canakinumab would provide an option for patients who are intolerant of statin therapy. They did not think that need to give the drug by subcutaneous injection would be a major burden to patients. They did express concerns about barriers to access for the drug including cost and insurance restrictions. Outcomes that mattered to patients included energy level and an improvement in the number of days that patients could be active.

Report Aim

This project will evaluate the health and economic outcomes of canakinumab for ASCVD. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions. In addition to the assessment of the effectiveness and cost-effectiveness of canakinumab in patients with a prior MI, we will look for subgroups of patients likely to have the greatest net benefit from canakinumab, recognizing both the background of other available CV therapies and the potential for harm from increased risk of infectious diseases.

Scope of Clinical Evidence Review

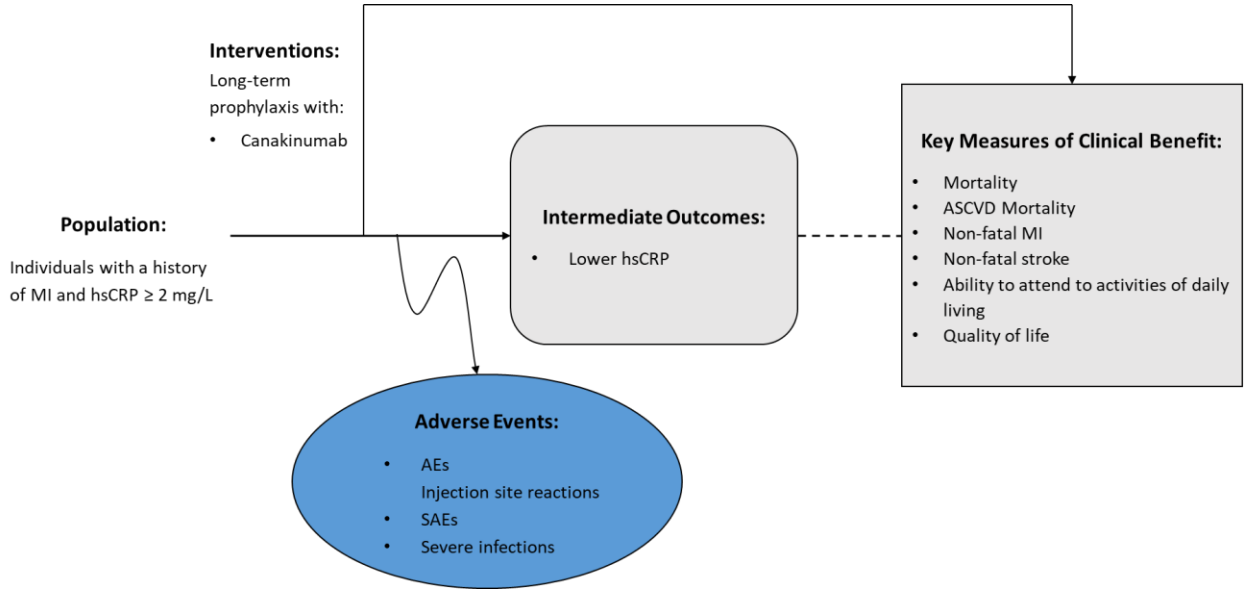
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the finalized scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Analytic Framework

The general analytic framework for assessment of therapies for ASCVD is depicted in Figure 1.1 on the following page.

Figure 1.1. Analytic Framework: Canakinumab for Atherosclerotic Cardiovascular Disease



AE: adverse event, SAE: serious adverse event, ASCVD: Atherosclerotic Cardiovascular Disease, MI: myocardial infraction, hsCRP: high-sensitivity C-reactive protein

The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes; those within the rounded boxes are intermediate outcomes (e.g., change in hsCRP), and those within the squared-off boxes are key measures of benefit (MI, stroke, death). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipse.[7]

Populations

The population of focus for the review is patients with a prior MI and a high sensitivity hsCRP ≥ 2 mg/L despite use of aggressive secondary prevention strategies.

Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which drugs to include. The full list of interventions is as follows:

- Canakinumab 150 mg SC every three months

Comparators

We intend to compare canakinumab to standard of care, which includes high intensity statin therapy and aspirin in patients able to tolerate those therapies. We do not expect to be able to assess the efficacy of canakinumab in patients who are receiving a PCSK9 inhibitor (a newer biologic therapy intended for additional cholesterol-lowering in those with suboptimal response to or intolerance of statins) in addition to statin therapy.

Outcomes

The outcomes of interest are described in the table below.

Table 1.2. Key Outcomes and Harms

Outcomes	Key Harms
Mortality	Infection/sepsis
Mortality from ASCVD	Significant adverse events
Non-fatal MI	Adverse events leading to discontinuation
Non-fatal Stroke	Injection site reactions
Unstable angina	
Revascularization	
Ability to attend to activities of daily living	
Quality of life	
Effects on other conditions (i.e., lung cancer, gout, osteoarthritis)	

Timing

Evidence on intervention effectiveness will be derived from studies of at least one year's duration and evidence on harms from studies of at least three month's duration.

Settings

All relevant settings will be considered, with a focus on outpatient settings in the US.

Other Benefits and Contextual Considerations

Our reviews seek to provide information on other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in the table below.

Table 1.1. Potential Other Benefits and Contextual Considerations

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to "the comparator," there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to "the comparator," there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop a simulation model to assess the lifetime cost-effectiveness of canakinumab relative to relevant comparator treatments among patients with ASCVD receiving optimal medical therapy including aspirin and a high-intensity statin. We will develop a *de novo* state-transition Markov model for this analysis, but key inputs will be informed by the published literature as well as our prior work on simulation modeling of ASCVD.[8-10]

The base-case analysis will include individuals with established ASCVD and a prior history of MI, with an elevated hsCRP (≥ 2 mg/L) despite optimal medical therapy. It will adopt a US health care sector perspective (i.e., it will include all direct health care costs regardless of payer but will not consider productivity losses due to morbidity or premature mortality) and a lifetime analytic horizon. All future costs and benefits will be discounted at 3% per year.[11] The drug currently has a price for its indications as an orphan anti-inflammatory drug for rare conditions; however, the pricing structure could differ for the cardiovascular indication.

The model will consist of health states including prior history of MI, prior history of stroke, prior history of both MI and stroke, death from cardiovascular causes, and death from non-cardiovascular causes (including sepsis and cancer). Key model inputs will include transition probabilities, quality-of-life values, and health care costs. Treatment effectiveness and rate of adverse events (AEs) will be derived from the evidence review described above. Health outcomes and costs will be dependent on time spent in each health state, clinical events, AEs, and direct medical costs. Quality of life weights will be applied to each health state, including quality of life decrements for each cardiovascular event and for serious adverse events.

Key clinical outcomes will be number of major adverse cardiovascular events (MACE) averted (defined as a composite of cardiovascular death, non-fatal MI, and non-fatal stroke), the number of patients who need to be treated for five years to avert one MACE (NNT_5), and quality-adjusted life years (QALYs) gained. Other clinical outcomes that may also be tracked include the number of cases of non-fatal MI, non-fatal stroke, cardiovascular death, and non-cardiovascular death. The key economic outcomes are direct health care costs (in 2018 US dollars), incremental cost-effectiveness ratios in 2018 US dollars per QALY gained, and the price at which the drug would be cost-effective at willingness-to-pay thresholds of $50,000, $100,000, and $150,000 per QALY.

In deterministic and probabilistic sensitivity analyses, we will examine the robustness of our findings to uncertainty in key input parameters. In discussion with key stakeholders, we may perform a scenario analysis in which we restrict the model to "responders only" (i.e., eligible patients who achieve an on-treatment hsCRP < 2 mg/L after three months of canakinumab therapy), recognizing that we may have limited randomized trial data on efficacy in this subgroup.[6,12-14] Data permitting, we will also perform a scenario analysis using a modified societal perspective where productivity losses and other indirect costs will be considered.

In separate analyses, we will explore the potential health system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the simulation model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found at: http://icer-review.org/wp-content/uploads/2018/05/ICER-value-framework-v1-21-18.pdf.

Identification of Low-Value Services

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/material/final-vaf-2017-

2019/). These services are ones that would not be directly affected by canakinumab (e.g., revascularization, hospitalization for MI), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of ASCVD beyond the potential offsets that arise from a new intervention. In their comments on the draft scope, stakeholders identified several types of low-value services, including the inappropriate use of percutaneous coronary interventions, routine ECG screening, and inappropriate medication prescriptions in elderly patients. ICER encourages all stakeholders to continue to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient. These will be reported in detail in the draft and final report.

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