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Original Article

Cost-Effectiveness of Canakinumab From a Canadian Perspective for Recurrent Cardiovascular Events

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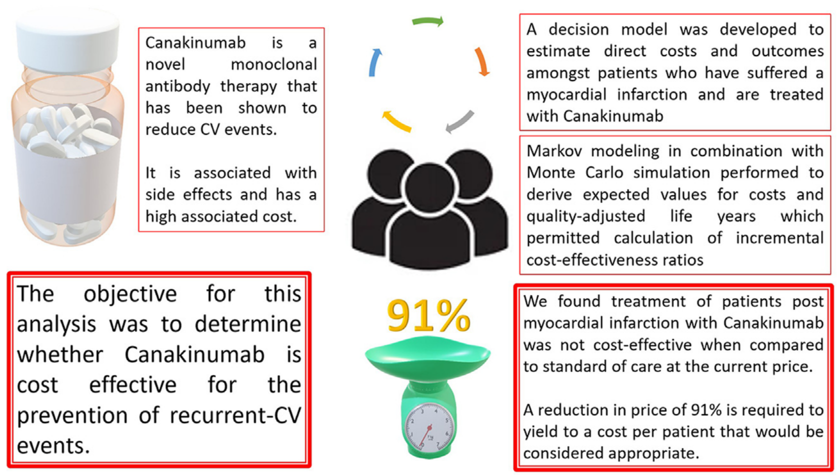

ABSTRACT

Background: Cardiovascular (CV) disease is a condition with high levels of morbidity and mortality. Canakinumab is a novel monoclonal antibody therapy that has been shown to reduce CV events but is associated with side effects and high cost. The main objective for this analysis is to determine whether canakinumab use is cost-effective for the prevention of recurrent CV events.

Methods: A decision model was developed to estimate the direct costs and outcomes among patients who have suffered a myocardial infarction and are treated with canakinumab. A lifetime study horizon

RÉSUMÉ

Introduction : La maladie cardiovasculaire (CV) est une affection à forts taux de morbidité et de mortalité. Le canakinumab est un nouveau traitement par anticorps monoclonaux qui s'est avéré diminuer les événements CV, mais qui est associé à des effets secondaires et des coûts élevés. Le principal objectif de la présente analyse est de déterminer si l'utilisation du canakinumab est rentable dans la prévention des événements CV récidivants.

Méthodes : Nous avons élaboré un modèle de prise de décision pour estimer les coûts directs et les résultats chez les patients qui ont

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Ethics Statement: Analysis is based on a mathematical model populated with available published data. The analysis corresponds to the Canadian Guidelines for Economic Evaluation.

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See page 447 for disclosure information.

The atherosclerotic disease process is responsible for a whole host of vascular complications and is a leading cause of morbidity and mortality in Canada and worldwide.[1,2] Inflammation is a key mediator that contributes to the progression of atherosclerosis and its complications, such as myocardial infarction (MI), stroke, and cardiovascular (CV) death; it also represents a potentially transformative therapeutic target.[3,4] While the compelling evidence on the role of

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was used to analyze the base-case costs and utilities from the perspective of the Canadian publicly funded healthcare system. Markov modeling was used in combination with Monte Carlo simulation to derive expected values for costs and quality-adjusted life years (QALYs), permitting the calculation of incremental cost-effectiveness ratios.

Results: Canakinumab was associated with higher average lifetime costs per patient ($457,982 vs $82,565) and higher average QALYs per patient (14.90 vs 14.20), compared with standard of care. Thus, the incremental cost per QALY gained for canakinumab treatment vs standard-of-care therapy was $535,365. The probability that canakinumab treatment is cost-effective was 0%. Results were consistent over a range of scenario analyses.

Conclusions: Treatment of patients post−myocardial infarction with canakinumab is not cost-effective, compared with standard-of-care therapy at the current price. Based on currently accepted willingness-to-pay thresholds in Canada, a reduction in price of 91% is required to yield a cost per patient that would be considered appropriate.

souffert d'un infarctus du myocarde et qui sont traités par canakinumab. Nous avons utilisé un horizon d'étude sur la vie entière pour l'analyse coût-utilité de référence selon la perspective du système de soins de santé du Canada financé par l'État. La modélisation de Markov qui a été utilisée en combinaison avec la simulation Monte Carlo pour obtenir les valeurs attendues des coûts et des années de vie ajustées en fonction de la qualité (AVAQ) a permis le calcul des ratios coûts-efficacité différentiels.

Résultats : Le canakinumab a été associé à des coûts moyens sur la vie entière plus élevés par patient (457 982 $ *vs* 82 565 $) et une AVAQ moyenne plus élevée par patient (14,90 *vs* 14,20) que le traitement selon la norme de soins. Par conséquent, le coût différentiel par AVAQ obtenu avec le traitement par canakinumab *vs* le traitement selon la norme de soins était de 535 365 $. La probabilité que le traitement par canakinumab soit rentable était de 0 %. Les résultats étaient cohérents dans un éventail d'analyses de scénarios.

Conclusions : Le traitement des patients après un infarctus du myocarde par canakinumab n'est pas rentable comparativement au traitement selon la norme de soins au prix actuel. Selon les seuils de propension à payer actuellement acceptés au Canada, une réduction du prix de 91 % est requise pour obtenir un coût par patient qui serait considéré comme approprié.

inflammation in atherosclerosis continues to mount, defining effective anti-inflammatory treatments to reduce events has been elusive, until recently. Glucocorticoids used in inflammatory diseases increase CV events.[5] Large trials in the area have been disappointing and have failed to show CV outcome benefits from therapies that target specific inflammation pathways, including the following: low-density lipoprotein oxidation[6]; secretory and lipoprotein-associated phospholipase A2 (sPLA2 and LpPLA2) [7-9]; and P38 mitogen-activated protein (MAP) kinase inhibitors[10,11] methotrexate[12] and P-selectin.[13]

The recent **C**anakinumab **An**ti-Inflammatory **T**hrombosis **O**utcomes **S**tudy (CANTOS) trial demonstrated that targeted inflammation therapy can impact CV outcomes.[4] In 10,061 patients who were more than 30 days post-MI, with elevated blood inflammatory markers (high-sensitivity C-reactive protein [hs-CRP] $>$ 2 mg/L), the interleukin (IL)-1β monoclonal antibody canakinumab reduced the primary composite end point of nonfatal MI, nonfatal stroke, or CV death (hazard ratio [HR] 0.85; 95% confidence interval [CI] : 0.74-0.98; $P = 0.021$ for the 150-mg dose), and the secondary composite endpoint, which included hospitalization for unstable angina (HR 0.83; 95% CI: 0.73-0.95; $P = 0.005$).[4]

Canakinumab represents a potential novel therapeutic agent in the treatment of atherosclerotic CV disease and its devastating sequelae. However, canakinumab is certainly not a silver bullet; its use was associated with an increased risk for potentially lethal adverse events (ie, fatal sepsis; 0.31 vs 0.18 events × 100 person-years; $P = 0.02$).[4] Further, as a biologic therapy approved for use in juvenile arthritis, it carries high costs to both patients and the healthcare system. The main objective for this analysis is to assess the cost-effectiveness associated with using canakinumab for the prevention of recurrent CV events.

Methods

Decision problem

The specific decision problem that this study addresses is whether a Canadian healthcare payer should reimburse for treatment with canakinumab for the reduction of recurrent CV events in adult patients in Canada with a prior myocardial infarction and high residual inflammatory burden. To address this decision problem, a cost-utility analysis was performed to compare canakinumab therapy to current standard-of-care therapies (ie, those that do not include anti-inflammatory therapy), from the perspective of the Canadian public healthcare payer over a lifetime horizon (specifically from the perspective of the Ontario Ministry of Health & Long-Term Care).

Model overview

A probabilistic Markov cohort model was used to derive the estimated direct costs and health outcomes (life years and quality-adjusted life years [QALYs]) among patients who have suffered an MI and have a residual high-inflammatory burden and are treated with canakinumab. The dosing of canakinumab 150 mg subcutaneously administered every 3 months was used as the treatment dose of choice, per the results of the CANTOS study.[4] We used a lifetime study horizon (400 cycles, equating to 33.33 years) to analyze the base-case costs and utilities from the perspective of the Canadian publicly funded healthcare system, and we incorporated certain model assumptions that were based on previously published literature.[14] The net present value of future costs and QALYs was determined using a 1.5% discount rate, per guidelines outlined by the Canadian Agency for Drugs and Technologies in Health (CADTH).[15] A Markov model combined with probabilistic analysis allowed estimation of costs (2021 Canadian dollars [CADs]) and QALYs, which then allowed for the calculation of incremental cost-effectiveness ratios (ICERs). In the reference case,

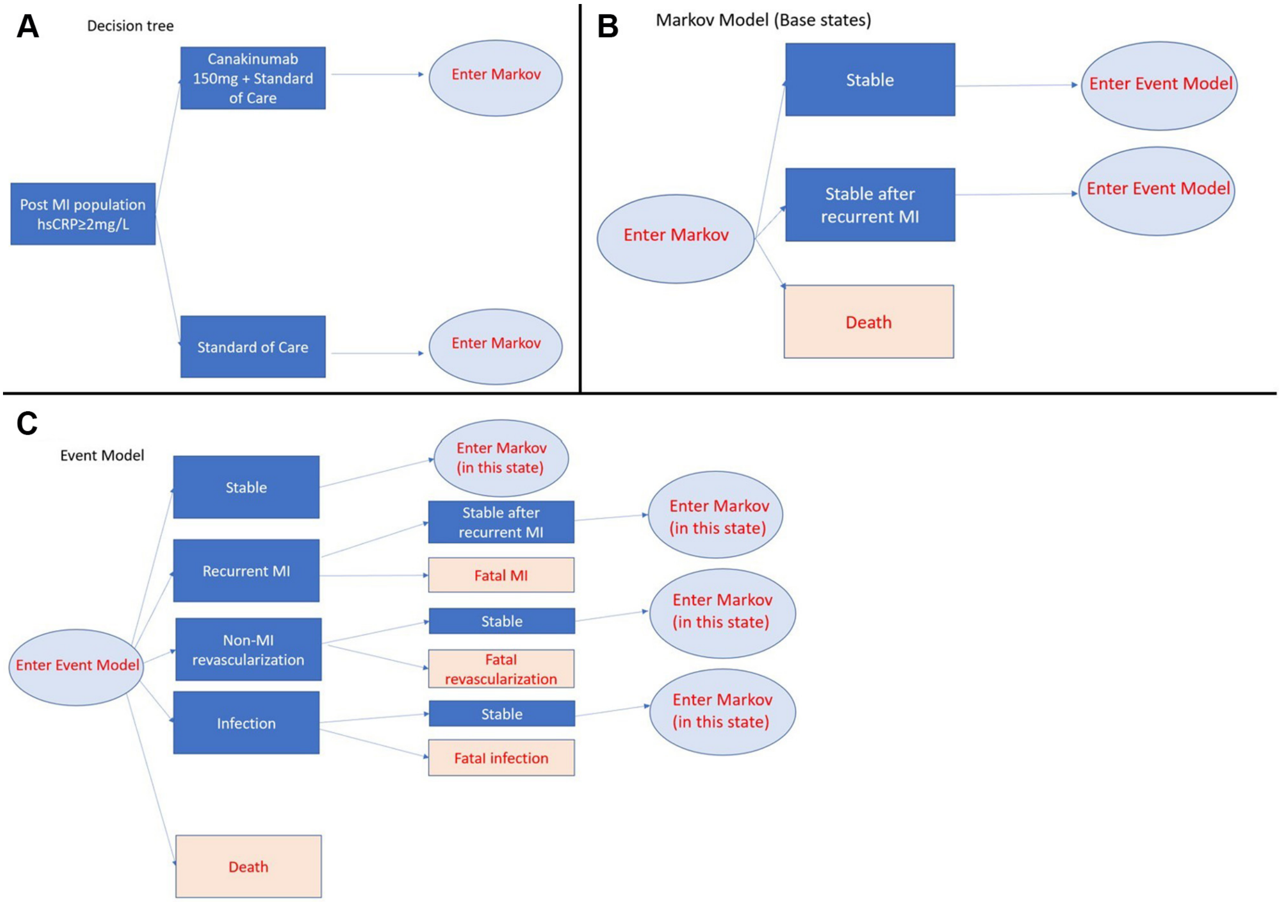

Figure 1. Markov model. (**A**) A survivor of myocardial infarction (MI) can be assigned to treatment with canakinumab 150 mg subcutaneously daily and standard-of-care treatment, or standard-of-care treatment alone. (**B, C**) Within each cycle, a survivor of MI can then either remain stable, suffer a recurrent MI (in which case they then enter the recurrent MI state), have a coronary revascularization procedure performed, suffer an infection, or remain in the death state. hsCRP, high-sensitivity C-reactive protein.

uncertainty regarding the value of each parameter was incorporated within the probabilistic analysis. Methodological uncertainty was explored by comparing the reference case results to those from non-reference case analyses using discount rates of 0% and 3%, per CADTH directives.[15] The impact on cost-effectiveness of uncertainty regarding the estimated parameters for costs and outcomes for the intervention was assessed by estimating the probability that canakinumab was cost-effective for alternative threshold values for a QALY.

Decision model

We developed a Markov model to follow a hypothetical cohort of patients who had suffered an MI and had residual inflammation (Fig. 1). Base states in the model included a stable state, a stable state after recurrent MI, and a death state. With each cycle, patients entered the event model ,which included the event states of: stable, recurrent MI, non-MI revascularization, infection, and death. We did not include stroke as a state in our model, as no reduction of stroke rate occurred in the CANTOS trial.[16] Patients could either recover or experience death with each of these events, and patients would then return to the appropriate base state following the event. The model allowed estimation of cycle-specific estimates of costs and QALYs, allowing for estimation of lifetime costs and QALYs.

Patient population

The cohort of patients was assumed to mirror the patient population within the CANTOS trial evaluating the impact of canakinumab on CV outcomes.[4] The mean age of participants was 60 years, and patients had a history of MI and a blood level of hsCRP of $\geq$ 2 mg per litre despite the use of aggressive secondary prevention strategies (ie, standard of care, which did not include anti-inflammatory therapy, but did include treatment with antiplatelet agents, statins, beta-blockers, and angiotensin-converting enzyme inhibitors; this treatment regimen is similar to that in the CANTOS trial and to what is done in clinical practice). Patients were excluded if they had a history of chronic or recurrent infections, previous cancer (other than basal-cell skin carcinoma), suspected or known immunocompromised state, history of tuberculosis, or ongoing use of alternative anti-inflammatory treatments.

Model inputs

Canakinumab treatment was evaluated against current standard-of-care therapies post-MI. In current practice, post-MI

Table 1. Distributions for probabilistic analysis

	Expected value	Probability distribution
Event probabilities		
Recurrent MI (standard care)	0.087	Beta (292, 3052)
Non-MI revascularization (standard care)	0.126	Beta (421, 2923)
Infection (standard care)	0.102	Beta (342, 3002)
Infection (canakinumab)	0.113	Beta (258, 2026)
Death post-revascularization	0.01	Beta (840, 128422)
Fatal MI	0.04	Beta (31, 759)
Fatal infection (standard care)	0.07	Beta (23, 207)
Fatal Infection (canakinumab)	0.09	Beta (24, 241)
Non-CV death (standard care)	0.042	Beta (140, 3204)
Hazard ratio (canakinumab vs standard care)		
Recurrent MI (canakinumab)	0.76	Lognormal (0.76, 0.62)
Non-MI revascularization (canakinumab)	0.68	Lognormal (0.68, 0.58)
Non-CV death (canakinumab)	0.97	Lognormal (0.97, 0.74)
Derived monthly transition probabilities		
Standard care		
Recurrent MI	0.00202	
Non-MI revascularization	0.00300	
Infection	0.00238	
Non-CV death	0.00092	
Canakinumab		
Recurrent MI	0.00154	
Non-MI revascularization	0.00204	
Infection	0.00260	
Non-CV death	0.00090	

CV, cardiovascular; MI, myocardial infarction.

care does not include anti-inflammatory therapies to reduce the risk of recurrent CV events. However, the recent CANTOS trial did indeed reveal outcome benefit to patients treated with canakinumab following an MI. However, this therapy has several perceivable disadvantages, in particular, an increased risk of infection. Per the drug regimen used in this trial, all patients received standard-of-care therapies, and the patients receiving canakinumab received 150 mg subcutaneously every 3 months.

Survival probabilities associated with standard-of-care therapy, as well as those with canakinumab treatment, are summarized in Table 1, and they were derived from the CANTOS study in which 10,061 patients were randomly assigned to either placebo or canakinumab. The uncertainty around these probabilities was incorporated into the probabilistic analysis.

In the base-case analysis, we assume that patients continue treatment beyond the 4-year time horizon of the clinical trial and that the benefit of treatment is maintained long term. Scenario analysis addressed the impact of these assumptions. In a scenario analysis, we adopted a 48-month time horizon, which allowed estimation of the proportion of the forecasted QALY gains for canakinumab that are generated after the period covered by the CANTOS trial. This analysis, which examines the impact of extrapolation, is recommended within the CADTH guidelines.[15] Per CADTH guidelines, in a further scenario analysis, we assumed a decline in treatment effect with the effect demonstrated within the clinical trial being maintained for the first 48 months followed by a linear decline in treatment effect until, at 96 months, there was no continued effect. Additionally, we assessed the impact of treatment discontinuation by assuming that after 48 months, patients would discontinue treatment with canakinumab at a rate of 10% per annum, with no continued effect after discontinuation. Finally, we assessed the cost-effectiveness

Table 2. Cost and utility data

Cost/Utility	Base-case estimate	Probability distribution
Monthly costs, $		
Standard care	238[21]	Gamma (18221.67, 0.01)
Canakinumab	5333	Fixed
Cost for event, $		
MI	25,028[17]	Gamma (10652.67, 1.92)
Revascularization	40,100[18]	Gamma (16, 1985.66)
Nonfatal infection admission	14,715[20]	Gamma (16, 661.56)
Fatal-infection admission	49,158[20]	Gamma (7261.44, 4.24)
Utilities		
Stable standard care	0.868[22]	Beta (3531.89, 537.11)
Stable recurrent MI	0.734[23]	Beta (14.68, 5.32)
Utility toll for MI/revascularization/ infection admission	−0.0986*	Beta (1385, 12657)

MI, myocardial infarction.

* Per expert opinion.

under a scenario in which canakinumab was 100% effective at reducing MIs and revascularizations, with no risk of infection.

The costs associated with each treatment strategy are summarized in Table 2. The monthly costs associated with canakinumab administration strategies and the costs of CV events, complications, and admissions were obtained from the literature and converted to 2021 CADs based on the Bank of Canada inflation calculator.[17-20] Similarly, we applied costs for standard-of-care treatment for coronary heart disease from published literature[21] and again converted it to 2021 CADs based on the Bank of Canada inflation calculator. Given the lack of available contemporaneous Canadian cost data for fatal MI and revascularization admissions, we elected to utilize the conservative estimate of assigning them the same cost as a nonfatal MI or revascularization procedure.

Utility values were derived from a variety of sources. Utility values associated with the base state of post-MI status was taken from an analysis and comparison of the **Moni**toring Trends and Determinants in **Ca**rdiovascular Disease / **Ko**operative Gesundheitsforschung in der **R**egion **A**ugsburg [Cooperative Health Research in the Region of Augsburg] (MONICA/KORA) registry to the general population.[22] Utility values for the recurrent MI state were obtained from research that investigated the stability of time-tradeoff utilities in survivors of MI.[23] Finally, disutility values associated with adverse outcomes were determined from expert opinion.[24]

Several additional model assumptions were included. First, the assumption was made that the consequences, not the probabilities, of adverse events in terms of costs and quality life effects were consistent across the treatments. This assumption could certainly lead to an underestimation of the cost estimates, as well as potential underestimation (or overestimation) of the disutility associated with these adverse events. However, we felt the assumption was reasonable to make, in order to reflect the average cost and disutility associated with the adverse events in our model. Second, based on literature from the CANTOS trial, we assumed that the 150-mg dose of canakinumab was the optimal dose for all patients.[4] A final limitation is the lack of contemporaneous cost data.

Model outputs and analysis

Markov modeling was used to calculate mean total healthcare costs and total QALYs gained for each strategy. Mean costs and utility values for each strategy for each cycle were estimated based on a probability-weighted sum for the weights for each state within the model. Cycle-specific estimates were then summed and discounted over the lifetime horizon to provide estimates of total costs and QALYs. Probabilistic analysis using Monte Carlo simulation with 5000 replications was performed to account for uncertainty in the input values, providing an estimate of the expected values for costs and QALYs. Cost-effectiveness was assessed by estimating the incremental cost per QALY gained against a base willingness-to-pay threshold of $50,000/QALY, with scenario analysis considering thresholds of $30,000 and $100,000.

Probabilistic scenario analyses were conducted to assess the impact of alternative modelling assumptions on the results of our analysis. Analyses related to alternative discount rates (0% and 3%) and alternative assumptions with respect to the continuance of treatment effect beyond the trial time horizon and discontinuation with treatment were also performed.

Model validity

Face validity was confirmed with experts in the field. Internal validation was conducted by the senior health economist reviewing the model structure and coding. The validity of our model was tested by comparing event rates from the CANTOS trial with the risk from our simulated canakinumab and standard-of-care cohorts at 3.7 years of elapsed follow-up time (the median follow-up time from the CANTOS trial). To assess the external validity of our model, we compared events in the standard-of-care arm from the **Col**chicine **C**ardiovascular **O**utcomes **T**rial (COLCOT) trial (a similar study population, albeit with slightly different study primary outcomes of CV death, spontaneous MI, or ischemic stroke) to results obtained from our standard-of-care model cohort (with outcomes of death or MI) at 22.6 months of follow-up (which was the median follow-up time from this trial).

Results

With respect to validity of our model, cumulative mortality estimates from our model were within the 95% CIs of the CANTOS trial estimates at 3.7 years of follow-up for both the standard-of-care and canakinumab groups. The mortality estimate for the canakinumab cohort was 9.5% in our model vs 9.6% (95% CI, 8.4%-10.8%) in the CANTOS trial. Event estimates from the standard-of-care group in our model were also comparable to those from the COLCOT standard-of-care group at 22.6 months of follow-up. The standard-of-care group total event estimate was 9.6% in our model, and was 9.6% in the COLCOT trial.

Results of our probabilistic analysis revealed that, compared to standard-of-care therapy, treatment with canakinumab was associated with greater discounted life expectancy (17.72 years vs 16.99 years), reduced lifetime incidence of MIs and revascularization, but with an increased incidence of infection (Table 3). Treatment with canakinumab was associated with higher healthcare costs than was standard of care ($457,982 vs $82,565; Table 4). The incremental costs of canakinumab use ($375,417) are almost exclusively due to the lifetime costs of canakinumab ($379,943), which are partially offset by the reductions in MIs and revascularizations. Cumulative QALYs were 14.90 in the canakinumab group, and 14.20 in the standard-of-care group, respectively. The corresponding ICER for canakinumab therapy was $535,365 (Table 4).

At a willingness-to pay threshold for a QALY of $50,000, canakinumab use had a 0% probability of being cost-effective (ie, the ICER was greater than $50,000 in all 5000 simulations), with this finding holding for threshold values up to $179,000. To achieve an ICER of $50,000 per QALY, the costs of canakinumab use have to be reduced by 91%, to $1477 per 150-mg injection. For willingness-to-pay thresholds of $30,000 and $100,000 per QALY, the necessary price reductions were 94% and 82%, respectively.

Scenario analyses relating to discount rates demonstrated consistency with our primary analysis (Table 4). In the

Table 3. Disaggregated results

Measure	Event	Canakinumab	Standard care	Difference
Incidence	Recurrent MI—nonfatal	0.387	0.484	−0.097 (−0.173, −0.008)
	Recurrent MI —fatal	0.016	0.020	−0.004 (−0.008, 0)
	Revascularization—nonfatal	0.531	0.717	−0.187 (−0.283, −0.082)
	Revascularization—fatal	0.003	0.029	−0.026 (−0.037, −0.016)
	Infection—nonfatal	0.616	0.533	0.083 (−0.019, 0.186)
	Infection—fatal	0.061	0.059	0.003 (−0.032, 0.038)
Costs, $	No new event	50,572	48,533	2039 (−1176, 5083)
	Canakinumab	379,943	N/A	379,943 (351,874, 407,106)
	Recurrent MI—nonfatal	6455	8115	−1,659 (−2913, −180)
	Recurrent MI—fatal	262	330	−67 (−130, −7)
	Revascularization—nonfatal	13,794	18,730	−4,935 (−8958, −1937)
	Revascularization—fatal	90	759	−669 (−1190, −322)
	Infection—nonfatal	5318	4617	701 (−158, 1,783)
	Infection—fatal	1547	1482	65 (−819, 941)
	Total costs	457,982	82,565	375,417 (342,599, 406,810)
QALYs		14.90	14.20	0.701 (−0.247, 1.593)
Life years		17.70	16.99	0.712 (−0.408, 1.771)

Figures in parenthesis are the 95% credible interval for the differences.
MI, myocardial infarction; QALY, quality-adjusted life years.

scenario analysis with a reduced time horizon of 48 months, estimated incremental QALY gains were only 0.03, suggesting that less than 4% of the forecasted QALY gains from canakinumab treatment occur during the initial time period representative of the CANTOS trial. Analyses incorporating waning of treatment effect with canakinumab and discontinuation of treatment with conakinumab revealed much higher ICERS than those in the base case (Table 4). Of note, in the scenario analysis whereby canakinumab was assumed to be 100% effective, the estimated ICER was still $265,622.

Discussion

As inflammation is now recognized as playing an important role in the pathogenesis of atherosclerotic cardiovascular events,[25,26] much attention has been focused in recent years on trying to identify potential anti-inflammatory agents that could be used to target this pathway to reduce CV risk for patients. A number of prospective randomized studies have been performed in recent years, with varying results. The monoclonal antibody canakinumab recently demonstrated benefit for the reduction of CV events in patients who have suffered a previous MI and who have a high residual inflammatory burden, in the CANTOS trial.[4] However, in the current analysis, cankinumab treatment did not demonstrate cost-effectiveness in the Canadian public healthcare context, owing largely to the high cost associated with the medication.

In the CANTOS trial, canakinumab was the first drug to show benefit in terms of CV event reduction by acting solely on an inflammatory pathway.[4] Canakinumab is not without side effects, however. Its beneficial actions are a direct result of its ability to modulate the immune system. However, this immune system modulation has negative consequences too. While Il-1β is not an immunosuppressant, and does not

Table 4. Cost-effectiveness results for base analysis and scenario analyses

Treatment group	Lifetime costs, $	Lifetime QALYs	ICER: canakinumab vs standard care, $
Base case			
Standard care	82,565	14.20	
Canakinumab	457,982	14.90	535,365
Discount rate: 0%			
Standard care	100,457	17.22	
Canakinumab	560,099	18.17	480,408
Discount rate: 3%			
Standard care	62,239	11.94	
Canakinumab	383.057	12.49	576,118
48-month time horizon			
Standard care	17,734	3.14	9,214,677
Canakinumab	251,288	3.17	
Gradual decline of treatment effect			
Standard care	82,527	14.19	
Canakinumab	452,108	14.47	1,334,400
Allowance for discontinuation with treatment			
Standard care	82,658	14.20	
Canakinumab	686,574	14.43	2,553,491
Canakinumab is 100% effective at reducing incidence of MI, revascularization, and infection			
Standard care	82,566	14,19	
Canakinumab	434,807	15.52	265,622

ICER, incremental cost per QALY gained; MI, myocardial infarction; QALY, quality-adjusted life year.

increase the risk of opportunistic infections or malignancy, it has been shown to increase the risk of fatal infections.[27] This increased risk is thought to be likely the result of a blunting of the inflammatory cascade that is a normal part of the body's reaction to infection.[27] Another major drawback to canakinumab use is its cost. The cost of canakinumab is $16,000 per 150-mg vial—an annual cost of approximately $64,000 per patient, assuming a dosing regimen similar to that used in the CANTOS trial.[4] Thus, although use of the current medications for secondary prevention in patients who have suffered an MI is well established, the question of whether canakinumab use should enter this domain has certainly not been resolved. The cost-effectiveness of the drug certainly will need to be considered in this clinical decision making, particularly in publicly funded healthcare systems. In this cost-effectiveness analysis, we evaluated the cost-effectiveness of canakinumab use against that of the current standard-of-care therapies for the secondary prevention of CV events, in the context of the Ontario public healthcare system. Our results demonstrate that, in comparison with standard of care, canakinumab treatment is currently not a cost-effective strategy in this area.

The predominant driver of higher costs was the drug costs. In one scenario analysis, for which we assumed that canakinumab was 100% effective at reducing events, the ICER was still in excess of $250,000, suggesting that regardless of the assumption of effectiveness, canakinumab use would not be cost-effective at the current price.

By conducting probabilistic analysis, we were able to incorporate a wide range of uncertainty into our model, thereby improving the robustness of our results. As evidenced by our study, the probability is negligible that canakinumab is cost-effective using our prespecified willingness-to-pay threshold of $50,000/QALY, and this conclusion remains consistent with much higher willingness-to-pay thresholds.

The major limitation of our study is that the efficacy of canakinumab was based on a single randomized controlled trial. However, at this point in time, this single trial encompasses almost the entire body of Phase 3 evidence on the subject, and currently comprises what is available for decision makers. The results of this analysis strongly suggest that regardless of relative effectiveness, canakinumab use is unlikely to be cost-effective in this context at its current price. Our base-case analysis adopted assumptions related to continuance with treatment and to treatment effect that were favourable toward canakinumab use. Given the lack of available contemporaneous Canadian cost data for fatal MI and revascularization admissions, we elected to utilize the conservative estimate of assigning the same cost to them as that of a nonfatal MI or revascularization procedure admission. Again, these assumptions favoured canakinumab use and would not alter the final conclusions of our analyses. Scenario analyses suggest that canakinumab use may be significantly less cost-effective than in our base case. The patients in the standard-of-care arm in the CANTOS trial were indeed receiving excellent care, with close to 80% or more of patients receiving anti-lipid, antithrombotic, antianginal, and ace-inhibitor therapies. A common misbelief is that patients being followed closely in a trial setting generally receive superior care; however, research has shown that, in fact, this is not the case.[28] However, if we were to assume that this assumption was indeed true, and that patients in a real-world setting receiving standard of care actually receive inferior care compared to the standard-of-care arm in the CANTOS trial, our model is overly conservative with respect to the estimate of benefit for canakinumab treatment. Excellent care compared to poorer care is likely cost-effective (as it is reimbursed within the Canadian healthcare system), and therefore our model is possibly underestimating the cost-effectiveness of canakinumab therapy vs current care; however, this being said, this underestimation is unlikely to change the conclusion of our study given that the high proposed cost of the drug is driving the results.

Use of anti-inflammatory medications for the reduction of CV events in high-risk patients seems to be a promising future direction in secondary prevention. Several medications for this purpose have been investigated, with some showing promise. However, as evidenced by this study, in future research, consideration needs to be given to therapeutics that are effective from both clinical and economic perspectives. In general, on some occasions, exceptions are made in the Canadian healthcare system to reimbursement for medications and therapeutic options that do not meet a willingness-to-pay threshold. Certainly, weighing the safety, efficacy, and efficiency of a drug is important, but care and consideration can also be given in considering the question of whether a novel therapy fills an unmet need for a patient demographic. In the case of canakinumab, although it is the first anti-inflammatory therapy to show benefit in this patient population, it is certainly not the last, and already, other anti-inflammatory drugs, in the time since the CANTOS trial, have shown CV benefit at a fraction of the cost.[29]

Conclusion

Treatment with canakinumab for secondary prevention of CV events is not cost-effective in the Canadian healthcare system. A substantial price reduction of 91% would need to occur before it could be considered a potentially cost-effective use of scarce healthcare resources. Future investigations of anti-inflammatory drugs, such as biologics, targeted at atherosclerosis must consider the balance of effectiveness vs economic impact on patients and the healthcare system.

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