CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

TOCILIZUMAB (ACTEMRA – HOFFMANN-LA ROCHE LIMITED)
Indication: Giant cell arteritis

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that tocilizumab be reimbursed for the treatment of giant cell arteritis (GCA) in adult patients, if the following criteria and conditions are met:

Criteria
- At initiation of therapy, or with relapse, patients should be receiving prednisone.
- Duration of therapy with tocilizumab should be limited to 52 weeks per treatment course.

Conditions
- Patients should be under the care of a physician with experience in the diagnosis and management of GCA.
- A reduction in price.

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Reasons for the Recommendation

1. One double-blind, randomized controlled trial (RCT) in patients with new-onset or relapsing active GCA (GiACTA trial; N = 251) demonstrated that a statistically significantly higher proportion of patients (56% and 53%) in the tocilizumab weekly and biweekly groups (plus 26-week prednisone taper) achieved sustained remission at week 52 compared with 14% and 18% of those in the placebo plus 26-week prednisone taper and the placebo plus 52-week taper groups, respectively. Furthermore, the results for the cumulative prednisone dose and time to first flare also favoured treatment with tocilizumab versus placebo. No signal of increased harm associated with tocilizumab was identified in the GiACTA trial.
2. At the submitted price, CADTH Common Drug Review (CDR) estimated the adjusted incremental cost-utility ratio (ICUR) to be $187,389 per quality-adjusted life-year (QALY), based on a once-weekly dose of tocilizumab. A price reduction of at least 45% would be required to reduce the revised ICUR estimate to less than $100,000 per QALY and a price reduction of at least 65% would be required for an ICUR of approximately $50,000 per QALY. The costs attributed to the complications of prednisone therapy are highly uncertain.

Of Note

- CDEC noted that data from the GiACTA trial was limited to 52 weeks of therapy. A 104-week open-label extension phase of the trial was conducted to assess overall benefits and risks of therapy beyond 52 weeks. However, the results of this phase were not available at the time of this review. Patients who were in remission at the end of 52 weeks were followed for 104 weeks off the study drug, while those not in remission had the option to receive open-label tocilizumab 162 mg subcutaneous (SC) injections weekly for up to 104 weeks.
- CDEC noted that to be considered eligible for tocilizumab therapy, patients in the GiACTA trial were required to be receiving the equivalent of 20 mg to 60 mg of prednisone daily at baseline. Available treatment guidelines recommend the use of glucocorticoids upon suspicion of GCA. Therefore, tocilizumab should be used in conjunction with moderate- to high-dose corticosteroids when initiated for new-onset patients or patients who are experiencing a relapse.

Discussion Points

- CDEC noted that an important goal of therapy with tocilizumab is related to the benefit of preventing morbidities associated with chronic moderate- to high-dose glucocorticoids. The prednisone tapering protocols in the GiACTA trial had patients scheduled to be at a dose of 0 mg at week 26 (in the 26-week taper groups) and a daily dose of 5 mg, 6 mg, or 7 mg after 26 weeks in the 52-week taper group. Patients who experienced a disease flare or could not adhere to the tapering schedule due to ongoing disease activity stopped the protocol-defined tapering schedule and could receive escape prednisone. The proportion of patients who received escape prednisone was 23%, 33%, 74%, and 55% in the tocilizumab weekly, tocilizumab biweekly, placebo

(26-week taper), and placebo (52-week taper) groups, respectively. However, it is unknown how long these patients were on escape prednisone, and at what dosages. Given the uncertainty in the safety and efficacy of tocilizumab in patients still requiring moderate to high doses of prednisone in the long term, and in view of relevant side effects and patient-reported outcomes, CDEC noted that discontinuation of tocilizumab could be considered by week 26 if the daily dose of prednisone could not be tapered below a level that the patient and their physician considered appropriate.

- CDEC noted that data from the GiACTA trial suggested that most of the safety and efficacy outcomes associated with tocilizumab treatment were numerically similar for the groups given once-weekly or once-every-other-week injections, which would have implications for the costs and achieving a desirable ICUR/QALY. The Health Canada–approved product monograph states that every-other-week dosing of tocilizumab may be prescribed based on clinical considerations.
- CDEC noted that treatment for GCA is generally started immediately following clinical diagnosis. Diagnosis of GCA can be made by temporal artery biopsy or imaging (e.g., magnetic resonance angiography, computed tomography angiography, or positron emission tomography scan). However, the sensitivity and specificity of the imaging tests is not established for GCA and there are a number of factors that could lead to false-negative results with temporal artery biopsy (e.g., the use of corticosteroid therapy, skip lesions).
- CDEC noted that there is a spectrum of disease from polymyalgia rheumatica (PMR) to GCA, and the distinction is not always clear. According to the clinical expert consulted, there is a possibility that clinicians may attempt to use tocilizumab off-label for the treatment of PMR (and potentially other forms of large-vessel vasculitis).

Background

Tocilizumab is an anti-human interleukin-6 receptor monoclonal antibody that has a Health Canada–approved indication for treatment of GCA in adults. Tocilizumab is available as a single-use, pre-filled syringe containing 162 mg of tocilizumab in 0.9 mL of solution. The Health Canada–recommended dose for GCA is 162 mg given once every week as an SC injection, in combination with a tapering course of glucocorticoids. A dose of 162 mg given once every other week may be prescribed based on clinical considerations.

Submission History

Tocilizumab was previously reviewed by CDR for the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis and received the following reimbursement recommendations:

- CDEC recommends that subcutaneous tocilizumab be reimbursed for the treatment of patients with moderately to severely active rheumatoid arthritis who have an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs), tumour necrosis factor (TNF) antagonists, or both DMARDs and TNF antagonists (tocilizumab SC form). (See *Notice of CDEC Final Recommendation, February 19, 2015.*)
- CDEC recommends that tocilizumab be reimbursed for the treatment of patients with polyarticular juvenile idiopathic arthritis who have an inadequate response to one or more DMARDs. (See *Notice of CDEC Final Recommendation March 19, 2014.*)
- CDEC recommends that tocilizumab be reimbursed for the treatment of active systemic juvenile idiopathic arthritis in patients two years of age and older who have responded inadequately to nonsteroidal anti-inflammatory drugs and systemic corticosteroids (with or without methotrexate), due to intolerance or lack of efficacy. (See *Notice of CDEC Final Recommendation July 19, 2012.*)
- Canadian Expert Drug Advisory Committee (CEDAC) recommends that tocilizumab be reimbursed for adults with moderately to severely active rheumatoid arthritis who have failed to respond to an adequate trial of both DMARDs and a TNF-alpha inhibitor (tocilizumab intravenous formulation) (see *Notice of CEDAC Final Recommendation, November 17, 2010.*)

Summary of CDEC Considerations

The committee considered the following information prepared by CDR: a systematic review of RCTs of tocilizumab and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients with GCA, and patient group–submitted information about outcomes and issues important to patients.

Patient Input Information

One patient group, Arthritis Consumer Experts (ACE), provided input for this submission. Patient perspectives were obtained from one patient with GCA, and from ACE based on its work with patients, researchers, and members of the ACE Advisory Board. The following is a summary of key input from the perspective of the patient group:

- Patient experiences with GCA and corticosteroid therapy vary depending on how quickly and completely symptoms resolved. The patient group interviewed one patient with GCA who stated that her condition was currently controlled with prednisone and methotrexate and she was able to perform all of her daily activities. The patient experienced side effects from corticosteroid therapy that included insatiable appetite, face puffiness, and insomnia.
- ACE itself notes that long-term prednisone therapy increases the risk of cardiovascular disease, hypertension, and osteoporosis.

Clinical Trials

The systematic review included one 52-week double-blind randomized placebo-controlled trial of patients 50 years of age or older with GCA (GiACTA study). Patients enrolled were either newly diagnosed, or had relapsing disease, and were receiving treatment with 20 mg to 60 mg of prednisone daily (N = 251). Patients were randomized 2:1:1:1 to tocilizumab 162 mg SC weekly or every other week (both with a 26-week prednisone taper), placebo with 26-week prednisone taper, or placebo with 52-week prednisone taper. Study patients were predominantly female, white, and had a mean age per group that ranged from 67.8 to 69.5 years. The proportion of patients who withdrew from the study ranged from 10% to 18% per treatment group.

The available evidence was limited to a single placebo-controlled trial with a relatively small number of patients per treatment group (50 or 100).

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following: sustained remission, cumulative prednisone dose, time to disease flare, health-related quality of life, and harms.

- Sustained remission was defined as the absence of flare following induction of remission within 12 weeks of randomization and maintained from week 12 up to week 52. Remission was defined as the absence of flare and normalization of C-reactive protein (less than 1 mg/dL).
- Flare was determined by the investigator and defined as the recurrence of signs or symptoms of GCA and/or an erythrocyte sedimentation rate ≥ 30 mm per hour attributable to GCA.
- Cumulative prednisone dose was defined as the total of all scheduled taper, escape, or commercial prednisone doses the patient received since baseline. Totals were based on drug dispensing logs containing records of prednisone dispensed to, and returned by, patients.
- Short Form Health Survey 36 (SF-36) is a generic health assessment questionnaire that has been used in clinical trials to measure health-related quality of life. It consists of eight domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health) and provides two component summaries: the physical component summary (PCS) and the mental component summary (MCS). All domains and summary scores are measured on a scale of 0 to 100, with an increase in score indicating improvement in health status. In general use, a minimal clinically important difference of 2 to 4 points for each domain or 2 to 3 points for the MCS and PCS has been reported in the literature.
- The Patient's Global Assessment of disease activity was measured using a visual analogue scale (VAS). Patients in the GiACTA trial were asked, "On a scale of 0-100 where would you rate the overall effect your giant cell arteritis has on you at this time?"

The value of zero corresponded to “has no effect at all” and the value of 100 corresponded to “worst possible effect.” No information was found on the use of the Patient’s Global Assessment on a VAS in the GCA population.

- Harms included adverse events, serious adverse events, withdrawals due to adverse events, and notable harms.

The primary outcome in the trial was the proportion of patients in sustained remission at week 52 following induction and adherence to the protocol-defined prednisone taper regimen. The GiACTA study was not adequately powered or of sufficient duration to evaluate longer-term GCA- and prednisone-related morbidities such as fractures and cardiovascular events, which are important to patients.

Efficacy

Overall, 56% and 53% of patients in the tocilizumab weekly and biweekly groups (plus 26-week prednisone taper) were in sustained remission at week 52 compared with 14% and 18% of those in the placebo plus 26-week prednisone taper and the placebo plus 52-week taper groups, respectively. The proportion of patients with sustained remission at week 52 was statistically significantly higher for both tocilizumab regimens compared with placebo plus 26-week taper in the intention-to-treat (ITT) population, with an absolute difference of 42%; 99.5% confidence interval (CI), 18% to 66% ($P < 0.0001$) for the weekly tocilizumab regimen, and 39%; 99.5% CI, 12% to 66% ($P < 0.0001$) for the tocilizumab biweekly group.

The key secondary end point demonstrated the non-inferiority and superiority of both tocilizumab regimens compared with placebo plus 52-week taper in the ITT population, with an absolute increase in proportion of patients with sustained remission of 38%; 99.5% CI, 18% to 59% ($P < 0.0001$) for the weekly regimen, and 35%; 99.5% CI, 10% to 60% ($P = 0.0002$) for the tocilizumab biweekly group. For both tocilizumab dosage groups, the lower bound of the 99.5% CI for the difference in remission rates exceeded the –22.5% non-inferiority margin.

The median cumulative prednisone dose over the 52-week blinded treatment period (which included scheduled taper doses and all escape or commercial prednisone doses) was 1,862 mg in both tocilizumab groups, 3,296 mg in the placebo plus 26-week taper group, and 3,818 mg in the placebo plus 52-week taper group.

The time to first flare data suggested that flare may be delayed with weekly tocilizumab versus both placebo groups and for biweekly tocilizumab versus the placebo plus 26-week taper group, with hazard ratios ranging from 0.23 to 0.39, and 99% CIs that excluded the null. However, the cumulative prednisone dose and time to first flare were secondary outcomes that were outside the statistical testing hierarchy and should be interpreted as exploratory.

Few clinically important differences between tocilizumab and placebo groups were detected on health-related quality of life based on the SF-36 and Patient’s Global Assessment of disease activity VAS. However, the trial was not powered for patient-reported outcomes and the instruments used may not be responsive to change in GCA patients. All patient-reported outcomes were outside the statistical testing hierarchy and were limited by the extent of missing data.

Harms (Safety and Tolerability)

Most patients in the 52-week GiACTA study experienced one or more adverse events, including serious adverse events, which were reported in 14% to 15% of tocilizumab-treated patients and 22% to 26% of placebo-treated patients.

Infections or infestations were the most commonly reported system organ class group of adverse events (tocilizumab: 73% to 75%, placebo: 65% to 76%), of which 4% to 7% of patients in the tocilizumab groups and 4% to 12% in the placebo groups had infections that were considered serious.

The frequency of withdrawals due to adverse events was similar in the tocilizumab and placebo groups with a 26-week prednisone taper (11% to 12%), whereas no patients in the placebo plus 52-week taper stopped treatment due to adverse events.

Other than infection, the notable adverse events identified in this review’s protocol were generally infrequent or showed a similar frequency across treatment groups.

The trial duration was limited to 52 weeks, and thus does not provide information on longer-term adverse events. However, the safety profile of tocilizumab is generally known, as the drug is approved in Canada for rheumatoid arthritis and juvenile idiopathic arthritis.

Cost and Cost-Effectiveness

Tocilizumab is available as a solution for injection in a 162 mg, 0.9 mL syringe at a price of $358.90. At the recommended dose of 162 mg administered via subcutaneous injection weekly, the annual drug cost is $18,663 per patient.

The manufacturer submitted a cost-utility analysis comparing tocilizumab plus prednisone with prednisone alone in adult patients with GCA over a lifetime time horizon (20 years) from the perspective of the Canadian health care payer. A semi-Markov model was developed based on the GiACTA trial data and extrapolated to a second year (on tocilizumab treatment) and beyond. The model considered flare after treatment, as well as GCA or prednisone-related adverse events. The treatment effects and adverse events of tocilizumab plus prednisone and prednisone alone were taken from the GiACTA trial. Other inputs such as costs and utility values were obtained from published literature. In its base case, the manufacturer reported the ICUR for tocilizumab plus prednisone compared with prednisone alone was $82,496 per QALY (probabilistic analysis).

CDR identified several key limitations with the submitted analysis. First, clinical benefit was assumed to last for the patient's lifetime (20 years) after the treatment period of tocilizumab (two years), which according to the CDR clinical expert consulted for this review is likely to overestimate the benefit of tocilizumab. Furthermore, prednisone-related adverse events (e.g., fractures, diabetes mellitus) were estimated from observational data, which in the absence of measurement of outcomes adds uncertainty. In addition, the manufacturer assumed that all fractures (including vertebral) were treated as an in-patient, which may overestimate the prednisone-related adverse event costs. Further, there were also uncertainties concerning the assumption of the disutility associated with being on prednisone, as well as utility estimates from the GiACTA trial data. Last, the manufacturer assumed a 50% mortality rate for major stroke, which is much higher than observed in Canadian studies for a similar cohort.

CDR attempted to address these issues in a plausible CDR base case that assumes the same relative efficacy in flares after the treatment period of two years combining two separate analyses. The revised base case also corrected the cost of fractures to account for outpatient treatment of vertebral fractures. The ICUR for tocilizumab plus prednisone was $187,389 per QALY when compared with prednisone alone.

In further sensitivity and scenario analysis on the CDR base case, removing the prednisone disutility (from simply taking the medication) resulted in an ICUR of $187,689 per QALY. Varying the prednisone-related adverse events by ± 25% resulted in ICURs of $151,364 to $210,847 per QALY.

Based on the CDR revised base case a price reduction of at least 65% for tocilizumab would be required to reduce the ICUR to $50,000 per QALY.

CDEC Members

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

February 21, 2018 Meeting

Regrets:

One CDEC member did not attend.

Conflicts of Interest

None