Canadian Agency for Drugs and Technologies in Health

COMMON DRUG REVIEW

CEDAC FINAL RECOMMENDATION

TOCILIZUMAB
(Actemra – Hoffmann-La Roche Limited)
Indication: Rheumatoid Arthritis

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that tocilizumab be listed for adults with moderate-to-severely active rheumatoid arthritis (RA) who have failed to respond to an adequate trial of both disease-modifying antirheumatic drugs (DMARDs) and a tumour necrosis factor (TNF)-alpha inhibitor.

Tocilizumab is to be started at 4 mg/kg every four weeks in combination with methotrexate or other DMARDs; tocilizumab monotherapy may be used in cases where methotrexate is inappropriate or not tolerated. Response to tocilizumab should be assessed after 16 weeks of treatment and therapy be continued only if there is a clinical response.

Reasons for the Recommendation:

1. The recommendation, requiring both DMARD and TNF-alpha inhibitor inadequate response, is consistent with the Health Canada-approved indication that does not recommend general use of tocilizumab in patients with inadequate DMARD response alone. One double-blind randomized controlled trial in patients with an inadequate response to both DMARDs and TNF-alpha inhibitors, exhibited a modest response, based on the American College of Rheumatology (ACR) response criteria and the Health Assessment Questionnaire Disability Index (HAQ-DI) when tocilizumab was added to methotrexate. In the above trial, the modest clinical response was demonstrated at week 16, after which response cannot be reliably assessed because of permission of early escape.

2. The differences in measures of clinical response between tocilizumab 4 mg/kg and 8 mg/kg were small and of uncertain clinical significance.

Of Note:

1. DMARD and TNF-alpha inhibitor failure, as referred to in the recommendation above, is to be according to jurisdictional definitions.

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2. There is no definitive evidence that tocilizumab modifies radiographic progression. Only one trial, in patients with an inadequate response to DMARDs only, examined radiographic progression. The Committee expressed doubt regarding the validity of the findings because of the large amount of missing and imputed data at 52 weeks.
3. The available evidence is limited because of the short duration for which findings are considered valid. Further, none of the trials compared tocilizumab with other biologics or with optimized DMARD regimens.
4. Clinical response in the trials was defined by minimum criteria, such as a 20% improvement based on the ACR response criteria (ACR 20) or a 1.2-point improvement on the Disease Activity Score on 28 joints (DAS 28). The Committee expressed concern that these criteria may not be sufficiently clinically important in the short term and that the predictive value of these disease activity measures for long-term disease progression and morbidity is unknown.
5. The Committee expressed concern over the frequent observations of elevated liver transaminases, and the rare, but apparently increased risk, for gastrointestinal perforation with tocilizumab compared with TNF-alpha inhibitors.

Background:
Tocilizumab is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass. It is approved by Health Canada for reducing signs and symptoms in adult patients with moderate-to-severely active RA who have inadequate response to one or more DMARDs and/or TNF-alpha inhibitors. However, the product monograph further states that general use in DMARD inadequate responders is not recommended at this time, but that use in this patient population should be on a case-by-case basis.

Tocilizumab should be given in combination with methotrexate or other DMARDs. It may also be given as monotherapy in cases of intolerance to methotrexate, or where treatment with methotrexate is not appropriate. When used in combination with DMARDs or as monotherapy, the recommended starting dose is 4 mg/kg every four weeks; an increase to 8 mg/kg is permitted based on clinical response. Doses exceeding 800 mg per infusion are not recommended in the product monograph. It is available as a 20 mg/mL solution for intravenous infusion in single-dose vials of 4 mL (80 mg), 10 mL (200 mg) and 20 mL (400 mg).

Summary of CEDAC Considerations:
The Committee considered the following information: a systematic review of double-blind randomized controlled trials (RCTs) of tocilizumab, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Clinical Trials
The systematic review included six manufacturer-sponsored, double-blind, RCTs in patients with moderate-to-severely active RA (OPTION, LITHE, TOWARD, CHARISMA, SATORI, and RADIATE). Five trials (OPTION, LITHE, TOWARD, CHARISMA, and SATORI) enrolled patients

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with an inadequate response to DMARDs, most commonly methotrexate. One trial, RADIATE, enrolled patients with an inadequate response to both DMARDs (methotrexate) and to TNF-alpha inhibitors.

Trials enrolling patients with inadequate response to DMARDs:

- OPTION (N = 623) and LITHE (N = 1,196) were 24-week and 52-week trials respectively, which compared tocilizumab 4 mg/kg and 8 mg/kg every four weeks with placebo, all were as add-on to continued methotrexate treatment.
- TOWARD (N = 1,220) was a 24-week trial that compared tocilizumab 8 mg/kg every four weeks with placebo, both as add-on to continued DMARD treatment.
- CHARISMA (N = 359) was a 16-week trial that compared tocilizumab 4 mg/kg and 8 mg/kg every four weeks with placebo, all were as add-on to continued methotrexate treatment. This study also compared the switch to monotherapy with tocilizumab 4 mg/kg and 8 mg/kg every four weeks with a group receiving methotrexate monotherapy.
- SATORI (N = 127) was a 24-week trial that compared the switch to monotherapy with tocilizumab 8 mg/kg every four weeks with a group receiving methotrexate monotherapy.

Trials enrolling patients with inadequate response to DMARDs and TNF-alpha inhibitors:

- RADIATE (N = 499) was a 24-week trial that compared tocilizumab 4 mg/kg and 8 mg/kg every four weeks with placebo, all were as add-on to continued methotrexate treatment.

Completion rates were > 80% in all trials; however, four trials (OPTION, LITHE, TOWARD, and RADIATE) allowed patients to receive escape therapy if clinical response was inadequate by week 16. Use of escape therapy, resulting in considerable loss of data (post-escape results set to missing), may have biased results beyond 16 weeks; post-escape results were not reported.

Outcomes

The primary and co-primary outcomes in the trials were the proportion of patients with an ACR 20 response at week 24 (in all studies except CHARISMA, which measured ACR 20 response at 16 weeks) and the changes in the total Genant-modified Sharp score (GmSS) and the HAQ-DI at week 52 in the LITHE trial.

The ACR response criteria include the following components: swollen joint counts; tender joint counts; patient global assessment of disease activity; physician global assessment of disease activity; patient assessment of pain; physical function as assessed by the HAQ, HAQ-DI, or modified HAQ; and either C-reactive protein levels or erythrocyte sedimentation rates. Patients are considered ACR 20 responders if they have a 20% improvement from baseline in swollen and tender joint counts, plus a 20% improvement in three of the five other components.

The total GmSS measures radiographic progression in the hands and feet, based on both erosion and joint space narrowing. The total GmSS ranges from zero (no radiographic damage) to 290 (worst radiographic damage), which is the sum of the joint space narrowing (zero to 145) and erosion (zero to 145) scores.

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The HAQ-DI is a measure of physical functional status, which assessed the difficulty experienced by patients in dressing, arising, eating, walking, maintaining hygiene, reaching, gripping, and other common activities. Each function contributes equally to the total score that ranges between zero and three, with higher scores indicating greater disability. The mean clinically important difference is generally considered to be between 0.2 and 0.25 for patients with RA.

Other outcomes were also defined a priori in the CDR systematic review. Of these outcomes the Committee discussed the following: quality of life (based on the 36-item short-form [SF-36] health survey), fatigue, serious adverse events, adverse events, and incidence of infection.

Outcomes of importance to patient groups included: slowing of disease progression, relief of symptoms, pain, ability to perform daily activities (including continuing or returning to work), quality of life, improved sleep patterns, and restored libido. The majority of important symptoms identified by patient groups are included in the SF-36 and HAQ-DI. No data related to restored libido or improved sleep patterns were captured in trials included in the systematic review.

Results

Efficacy or Effectiveness

Tocilizumab versus placebo, as add-on to methotrexate or DMARD, in DMARD-inadequate responders

- Based on CADTH-pooled, 24-week data from OPTION, LITHE, and TOWARD, the proportion of patients achieving ACR 20, ACR 50, and ACR 70 at 24 weeks was statistically significantly greater for both doses of tocilizumab compared with placebo. Examination of pre-escape (week 16) data resulted in the same conclusions.
- In the LITHE trial, statistically significant differences in radiographic progression at 52 weeks between both doses of tocilizumab and placebo favoured tocilizumab (less progression); however, there was doubt regarding the validity of the findings, because of the large amount of imputed data, particularly in the comparator group.
- Based on CADTH-pooled, pre-escape (week 16) data from OPTION, LITHE, and TOWARD, short-term improvements in physical function (HAQ-DI) and fatigue (Functional Assessment of Chronic Illness Therapy – Fatigue [FACIT-F]) were statistically and clinically significantly greater for tocilizumab (both doses) compared with placebo.
- Based on CADTH-pooled, 24-week data from OPTION, LITHE and TOWARD, improvements in the physical component score of the SF-36 were statistically greater for tocilizumab (both doses) compared with placebo; however, differences were of only minimal clinical importance. Improvements in the mental component score of the SF-36 were of lesser magnitude and clinical importance than those of the physical component. Regardless, the SF-36 findings were of uncertain validity, as changes from baseline were reported only at week 24, at which point there was considerable missing data, which was unequally distributed across treatment groups.
- The Committee considered the DAS 28 data to be limited by the use of observed-case analyses.

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Tocilizumab versus placebo, as add-on to methotrexate, in DMARD and TNF-alpha inhibitor inadequate responders

- In the RADIATE trial, the proportion of patients achieving ACR 20 and ACR 50 at 24 weeks was statistically significantly greater for both doses of tocilizumab compared with placebo. Only the higher dose of tocilizumab (8 mg/kg) resulted in a statistically greater proportion of patients achieving ACR 70 compared with placebo at 24 weeks. Examination of pre-escape (week 16) data resulted in the same conclusions.
- Based on pre-escape (week 16) data from the RADIATE trial, short-term improvements in physical function (HAQ-DI) and fatigue symptoms (FACIT-F) were statistically and clinically significantly greater for tocilizumab (both doses) compared with placebo.
- In the RADIATE trial, 24-week improvements in the physical component score of the SF-36 were statistically greater for tocilizumab (both doses) compared with placebo; between-treatment differences were of only minimal clinical importance. Improvements in the mental component score of the SF-36 were not statistically different between tocilizumab and placebo. Regardless, the SF-36 findings were of uncertain validity, as changes from baseline were reported only at week 24, at which point there was considerable missing data, which was unequally distributed across treatment groups.
- The Committee considered the DAS 28 data to be limited by the use of observed-case analyses.

Harms (Safety and Tolerability)

- Pooled data up to 24 weeks found that the addition of tocilizumab (both 4 mg/kg and 8 mg/kg) to methotrexate or DMARDs resulted in a higher frequency of adverse events and withdrawal due to adverse events compared with placebo. However, the comparison of the frequency of adverse events was complicated by differences in exposure times between treatment groups.
- Neutropenia and infections (both total and serious) were more frequent in patients treated with tocilizumab relative to comparator.
- Increases in laboratory parameters, such as transaminases and serum lipids, were more commonly observed for tocilizumab-treated patients versus placebo. These changes did not appear to be associated with clinical adverse events, such as hepatitis or cardiovascular events, during the clinical trials.

Cost and Cost-Effectiveness

- The manufacturer submitted a cost-minimization analysis of tocilizumab compared with abatacept, adalimumab, etanercept, infliximab, and rituximab in patients with moderate-to-severely active RA who have inadequate response to one or more DMARDs and/or TNF-alpha inhibitors. The annual cost of tocilizumab is dependent on dose and patient weight ($11,348 to $17,472 for a 75 kg individual receiving 4 mg to 8 mg per kg every four weeks, up to a cost of $23,296 at the maximum dose of 800 mg per infusion for patients whose body weight is more than 100 kg) and is similar to the annual cost of other biologics: abatacept ($18,619 to $24,825), adalimumab ($18,388), etanercept ($18,942 to $20,486), golimumab ($17,364), rituximab ($9,348 to $28,314).

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Patient Input Information:

- Three national patient groups representing patients with arthritis submitted input for this review.
- Patients consider it very important for people with arthritis to have access to all treatment options, as individuals respond differently to medications available. They further indicated that tocilizumab may fill a need for patients who have not responded well or who have experienced no significant change with currently available medications.
- Issues with current therapies were mentioned, including special authority programs that cause delays in accessing treatment, and the difficulty in coordinating daily or weekly injections.
- Patients expect tocilizumab to slow or arrest disease progression and relieve daily symptoms, including pain, thereby improving quality of life. Pain was included in composite outcomes in the trials (e.g., ACR response), rather than a specific outcome of interest. As noted above, quality of life data from included trials, as measured by the SF-36, was of questionable validity.

Other Discussion Points:

- The incidence of gastrointestinal perforation appeared to be higher with tocilizumab compared with TNF-alpha inhibitors.
- The benefit and harm of tocilizumab relative to other biologic drugs is not directly known. Based on a CADTH mixed treatment comparison meta-analysis, it appears that tocilizumab is associated with similar rates of ACR 50 and ACR 70 response compared with TNF-alpha inhibitors in patients with inadequate response to DMARDs.
- Four of the six included trials, including the 52-week LITHE trial, featured an early-escape option for patients at 16 weeks. This study design severely limits placebo-controlled evidence of benefit and harm for this drug.
- ACR measures are a composite outcome of several biochemical and patient-reported outcomes. The correlation of ACR responses with long-term morbidity, including disease progression, is unknown.

CEDAC Members Participating:

Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, and Dr. Lindsay Nicolle.

Regrets:

Dr. Yvonne Shevchuk

Conflicts of Interest:

CEDAC members reported no conflicts of interest related to this submission.

About this Document:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

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CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and is used in CEDAC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

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