



Canadian Agency for
Drugs and Technologies
in Health

COMMON DRUG REVIEW

Summary of CEDAC Discussion

Adalimumab (Humira[®] – Abbott Laboratories Ltd.) Resubmission #3 for Crohn's Disease

Canadian Expert Drug Advisory Committee (CEDAC) Members Participating

(in person or by teleconference): Dr. Braden Manns (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Michael Evans, Dr. Malcolm Man-Son-Hing, Dr. Laurie Mallery, Ms. Nancy McColl, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Robert Peterson, Dr. Dale Quest, Dr. Kelly Zarnke.

Regrets

None

Conflicts of Interest

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

Description

Adalimumab is a recombinant human immunoglobulin monoclonal antibody specific to tumour necrosis factor (TNF). Adalimumab is indicated for the reduction of signs and symptoms, and for the induction and maintenance of remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy, including corticosteroids and immunosuppressants. It is also indicated for reducing signs and symptoms, and inducing clinical remission in patients who have lost response to or are intolerant to infliximab.

Discussion of Clinical and Pharmacoeconomic Reviews

CEDAC considered a systematic review of published and unpublished clinical studies prepared by CDR, and a CDR review of a pharmacoeconomic evaluation supplied by the manufacturer. An overview of these reviews is available on the CADTH web site (www.cadth.ca).

A presentation by CEDAC members, and the discussion that ensued, addressed the following points:

Therapeutic Rationale and Need

The incidence of Crohn's disease in Canada was reported as approximately 4,600 cases in the year 2000, and the prevalence as approximately 81,000 cases. Crohn's is a chronic, incurable,

Common Drug Review

relapsing condition. The goals of therapy are to induce and then maintain remission, with minimal corticosteroid use. North American guidelines suggest the use of biologics, such as adalimumab or infliximab, for those who have failed conventional treatments. There are limited treatment options for patients who have lost response to infliximab, or in those who have contraindications to its use.

Clinical Trials

Four double-blind randomized placebo-controlled trials of patients with moderate to severe Crohn's disease were evaluated. Two were four-week induction studies: CLASSIC I (n=299) and GAIN (n=325). The CLASSIC I trial enrolled anti-TNF naïve patients and the GAIN trial exclusively enrolled patients who had lost response to or were intolerant to infliximab. Two trials were one-year maintenance studies: CLASSIC II (n=55, an extension study of CLASSIC I that randomized patients in remission); and CHARM, which following a four-week open-label induction period, randomized responders and nonresponders with a separate evaluation of each (n=499, the randomized responder population).

Comparators or Other Available Treatment Options

No active comparator trials met the review criteria. The lack of a direct comparison with infliximab was highlighted in CEDAC's discussion. Concomitant use of corticosteroids and immunosuppressants was permitted in the four trials.

Outcomes

The primary outcome measure was the Crohn's Disease Activity Index (CDAI), which is a common tool used for the assessment of clinical response in Crohn's disease clinical trials. Although a minimal clinically important change in the CDAI scale has not been defined, the Food and Drug Administration and the European Medicines Agency have stated that a decrease of 100 points is considered a meaningful reduction. Remission has been defined as a total CDAI score <150. Rates of corticosteroid reduction and discontinuation are also considered important outcomes; however, in the absence of comparative trials, it is unclear if anti-TNF agents are safer than corticosteroids. Quality of life was measured by the Inflammatory Bowel Disease Questionnaire (IBDQ) and the SF-36 physical and mental component summary measures, which are validated tools.

Effectiveness

In both induction trials adalimumab demonstrated a statistically significant improvement in remission rates (CDAI <150) compared to placebo with a number needed to treat (NNT) of between four and seven. IBDQ was also statistically improved, although the clinical importance of a mean difference of 14 points on a 224-point scale is unclear as no studies have defined the minimal change of score that represents clinical significance. In the maintenance trials, the randomized population of CLASSIC II trial did not demonstrate superiority compared with placebo at week 56 in CDAI response or remission rates, IBDQ, or corticosteroid discontinuation rates. (Note: the CEDAC discussion was based on the CDR review, which included unpublished data submitted by the manufacturer. The remission rates differed in the

published data regarding the CLASSIC II trial.) In the CHARM trial, adalimumab demonstrated superiority compared with placebo in remission rates (NNT= 4), IBDQ, and corticosteroid discontinuation rates. There was no difference between groups in SF-36, a measure of general quality of life, in CHARM.

Safety and Tolerability (harms)

In the one year followup of the two maintenance studies, there were fewer serious adverse events with adalimumab compared to placebo, overall adverse event rates were similar, and there were slightly more infectious adverse events with adalimumab. The product monograph warns about the potential for serious adverse events due to infections or malignancies. The issue of long-term harms of anti-TNF agents was highlighted in the CEDAC discussion as a concern.

Cost and Pharmacoeconomic Evaluation

Adalimumab, at a cost of \$20,700 in the first year and \$18,000 for subsequent years of treatment, is much more costly than standard therapy (sulfasalazine, immunosuppressants, and corticosteroids); however, it is less costly than infliximab, which is \$29,000 in the first year and \$22,000 per year thereafter. Cost comparisons, however, do not take into account the potential for dose escalation of both adalimumab and infliximab.

Other Discussion Points

- There is no reliable evidence to support the continued use of adalimumab beyond four weeks in nonresponders.
- A limitation in the design of the maintenance trial was noted: both the adalimumab and placebo treatment arms in the CHARM trial were exposed to adalimumab before randomization, thereby limiting valid conclusions regarding the potential harms of adalimumab versus placebo. Also, only 38% of responders randomized in the CHARM trial completed 56 weeks of double-blind therapy, and this limits the conclusions that can be drawn.
- Concern was expressed regarding the potential for dose escalation with adalimumab and the lack of randomized controlled trial data evaluating the relative benefit and harm of increasing the dose to more than 40 mg every two weeks.
- The status of public drug plans regarding the funding of escalating doses was reviewed.
- The issue of sequential use of anti-TNF agents where there is a loss of response or intolerance, and the associated high cost was discussed.
- Induction of antibodies could potentially neutralize the drug's beneficial effects over time or lead to the development of intolerance (hypersensitivity). The clinical relevance of anti-adalimumab antibodies, detected during the drug's use for Crohn's disease or for other indications, has not been determined.
- The ability to administer adalimumab by the subcutaneous route offers the advantage of home administration by the patient, compared with the need for intravenous infusions for infliximab.
- The need to address the use of adalimumab in children was raised for future consideration.
- The need for a class review of anti-TNF agents for Crohn's disease was discussed.

CEDAC Recommendation

CEDAC recommends that adalimumab be listed for moderate to severely active Crohn's disease in patients who are refractory to or have contraindications to an adequate course of 5-aminosalicylic acid, corticosteroids, and other immunosuppressive therapy. Eligible patients should receive an induction dose of 160 mg followed by 80 mg two weeks later. Clinical

response to adalimumab should be assessed four weeks after the first induction dose, using criteria such as a 100-point reduction in the CDAI. Ongoing coverage for adalimumab maintenance therapy should only be provided for responders, as noted above, and for a dose not exceeding 40 mg every two weeks.

Reasons for the Recommendation

- Adalimumab has been demonstrated to be superior at inducing and maintaining remission, compared with standard therapy, and it has been shown to improve measures of quality of life when used during the induction and maintenance phases of therapy.
- Patients who do not respond to the induction phase of treatment with adalimumab appear to derive little benefit from further therapy with adalimumab.
- The annual cost of adalimumab is \$20,700 in the first year and \$18,000 for subsequent years of treatment, which is significantly greater than that of standard therapy (corticosteroids, sulfasalazine, and immunosuppressants), but less than the cost of infliximab (\$29,000 in the first year and \$22,000 thereafter). The manufacturer submitted an economic evaluation that reported adalimumab was cost saving when compared with infliximab, and was associated with an incremental cost per quality-adjusted life year gained of \$113,000 when compared to standard therapy during a 56-week time horizon. Although the incremental cost per quality-adjusted life year gained is in excess of traditional standards, infliximab is currently funded by most public drugs plans for use in Crohn's disease.
- Given that there are no randomized controlled trials that evaluate the impact of increasing the maintenance dose of adalimumab beyond 40 mg every two weeks, and that there are significant safety concerns associated with the use of all anti-TNF agents, CEDAC was not supportive of escalating doses beyond 40 mg every two weeks.

The Summary of CEDAC Discussion

This document contains a summary of the relevant discussion by CEDAC members in making the formulary listing recommendation for participating public drug plans regarding this drug. This summary is not a complete record of the proceedings of the CEDAC meeting at which the drug was considered.

The information in this summary should not be used as a substitute for clinical judgment in the care of a particular patient, nor is it intended to replace professional advice. CADTH is not liable for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada, the federal government, any provincial or territorial government, or any pharmaceutical manufacturer.