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Long-term safety and efficacy of adalimumab in Japanese patients with moderate to severe Crohn's disease☆

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Abstract

Background and aims: Adalimumab has been shown to be effective and well tolerated in patients with Crohn's disease. This analysis reports the results of a cohort of Japanese patients with moderate to severe Crohn's disease who were evaluated for up to 3 years to assess the long-term use of adalimumab.
Methods: The study consisted of a double-blind part and an open-label part. Patients were included either in the 52-week double-blind, placebo-controlled part of the study followed by a 96-week open-label extension or in the open-label part from the beginning or in the event of a flare. Patients were treated with adalimumab and evaluated for up to 148 weeks as 3 data cohorts: the all-adalimumab cohort (patients receiving ≥1 injection of adalimumab), the 148-week follow-up subcohort (patients who completed 148 weeks of follow-up after the first adalimumab dose), and the dose-escalation subcohort (patients receiving adalimumab doses that increased to 80 mg every other week).

Abbreviations: 6-MP, 6-mercaptopurine; AAA, antibodies against adalimumab; ADA, adalimumab; AE, adverse event; AZA, azathioprine; CD, Crohn's disease; CDAI, CD activity index; CR, clinical response; CR-70, CR, decrease in CDAI score of ≥70; CR-100, CR, decrease in CDAI score of ≥100; eow, every other week; IOIBD, International Organization of Inflammatory Bowel Disease; IBDQ, Inflammatory Bowel Disease Questionnaire; LOCF, last observation carried forward; PY, patient years; QOL, quality of life; SD, standard deviation; SF-36, Short Form 36 Health Survey; TNF-α, tumor necrosis factor-alpha.

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Results: In the all-adalimumab cohort (n = 79), clinical remission rates were approximately 30% after 36 weeks of exposure to adalimumab and for the remainder of the study (35%, 33%, and 28% for weeks 48, 108, and 144, respectively). An improvement in quality of life was also maintained over the same period. In the dose-escalation subcohort (n = 40), the clinical remission rate was 75% (6/8) 48 weeks after dose escalation. Adalimumab was tolerated, and no deaths were reported.

Conclusions: Adalimumab is effective for maintaining long-term clinical remission in Japanese patients with moderate to severe Crohn's disease (NCT00445432).

1. Introduction

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract associated with transmural inflammation, which may lead to bowel damage and progressive disability.[1] Overexpression of the inflammatory cytokine tumor necrosis factor-alpha (TNF-α) is a hallmark of CD pathogenesis, with elevated levels of TNF-α present in the colonic mucosa,[2] blood,[3] and stool.[4] Therefore, recent advances in the treatment of CD have focused on the development of biologic agents targeted at neutralizing TNF-α function.[5] Monoclonal antibodies targeting TNF-α, such as infliximab and adalimumab, have demonstrated efficacy in the induction and maintenance of remission in patients with moderate to severe CD.[6,7] Infliximab was the first TNF-α chimerical monoclonal antibody introduced for the treatment of CD. Although infliximab is highly effective in many patients with CD, some patients are unable to continue on long-term infliximab maintenance therapy because of hypersensitivity reactions or loss of response.[8–10]

Adalimumab (Humira®, AbbVie Inc., North Chicago, IL) is a fully human, recombinant, subcutaneously administered immunoglobulin G1 monoclonal antibody that binds with high affinity and specificity to TNF-α. Adalimumab is effective for inducing and maintaining remission in patients with moderate to severe CD at an induction dose of 160/80 mg (Week 0/Week 2) and at a maintenance dose of 40 mg every other week (eow).[7,11,12] In addition, adalimumab is effective at inducing clinical remission in patients who have lost response to or are intolerant to infliximab therapy.[13] An open-label extension trial of adalimumab in Western patients has shown maintenance of remission through 4 years.[14]

Recently, the efficacy of adalimumab was demonstrated in the treatment of CD in Japanese patients during a 4-week induction trial followed by a 52-week maintenance trial,[15] and adalimumab was approved for the treatment of CD in Japan on this basis. In the present maintenance trial, the long-term safety and efficacy of adalimumab treatment for maintaining clinical remission as well as its effect on quality of life (QOL) in Japanese patients with moderate to severe CD were assessed.

2. Materials and methods

2.1. Study design

The reported cohort is from a maintenance trial (NCT00445432) that followed a preceding induction trial (NCT00445939) and evaluated the efficacy and safety of adalimumab in Japanese patients with moderate to severe CD in a randomized, double-blind, placebo-controlled design.[15] The study methods and entry criteria have been previously described.[15] Briefly, patients who were older than 15 years but younger than 75 had been diagnosed with CD for longer than 4 months (diagnosis was confirmed by endoscopic or radiologic evaluation), and patients who had a CD activity index (CDAI) of 220 to 450 were included in the induction trial and rolled over into the maintenance trial. Patients who achieved a clinical response (CR), defined as a decrease in CDAI of $\geq$70 points versus baseline (CR-70), at the end of the 4-week induction trial entered the randomized portion of the maintenance trial (for a total of 52 weeks; 40 mg adalimumab or placebo eow). All the patients who did not achieve CR-70 (nonresponders) at the end of the 4-week induction trial entered the open-label arm of the maintenance trial later on. In addition, patients from the randomized, double-blind portion of the maintenance trial who experienced a flare were also moved to the open-label arm of the maintenance trial. Flare was defined as a recurrence of active disease, i.e., an increase of $\geq$70 points in CDAI compared with baseline in the maintenance trial and a CDAI >220.[15] Patients in the open-label arm of the maintenance study were given 40 mg adalimumab eow and could increase their dose to 80 mg eow in the event of nonresponse or a flare. After 1 year in the maintenance study, all patients could continue in the extension portion of the maintenance trial and receive open-label adalimumab at a dose of 40 mg eow or 80 mg eow for patients in the open-label arm who had previously been dose escalated to 80 mg eow (Fig. 1).

This study was approved by the institutional review boards of each study site and was conducted according to the principles of the Helsinki Declaration of 1975. Patients, or a parent or legal guardian if the patient was younger than 20 years old, provided written informed consent prior to study participation.

2.2. Clinical assessments

The CDAI and the International Organization of Inflammatory Bowel Disease (IOIBD) scores were assessed every 4 weeks until Week 52x and every 12 weeks afterwards. The Inflammatory Bowel Disease Questionnaire (IBDQ) score and the Short Form 36 Health Survey (SF-36) summary score were assessed at Weeks 8x, 24x, 52x, and every 24 weeks afterwards.

Samples for measurements of adalimumab plasma levels and antibodies against adalimumab (AAAs) were collected every 4 weeks until Week 24x, at Weeks 36x and 52x, and