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Subgroup analysis of the placebo-controlled CHARM trial: Increased remission rates through 3 years for adalimumab-treated patients with early Crohn's disease

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Abstract

Background and aims: We examined the impact of disease duration on clinical outcomes and safety in a post hoc analysis of a remission maintenance trial with adalimumab in patients with moderate to severe CD.
Methods: Patients in the CHARM trial were divided into 3 disease duration categories: <2 (n=93), 2 to <5 (n=148), and ≥5 years (n=536). Clinical remission and response rates at weeks 26 and 56 were compared between adalimumab and placebo subgroups, and assessed through 3 years of adalimumab treatment in the ADHERE follow-on trial. Logistic regression assessed the effect of disease duration and other factors on remission and safety.
Results: At week 56, clinical remission rates were significantly greater for adalimumab-treated versus placebo-treated patients in all 3 duration subgroups (19% versus 43% for <2 years; P=0.024; 13% versus 30% for 2 to <5 years; P=0.028; 8% versus 28% for ≥5 years, P<0.001). Logistic regression identified shorter duration as a significant predictor for higher remission rate in adalimumab-treated patients. Patients with disease duration <2 years maintained higher remission

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rates than patients with longer disease duration through 3 years of treatment. The incidence of serious adverse events in adalimumab-treated patients was lowest with disease duration <2 years. *Conclusions:* Adalimumab was superior to placebo for maintaining clinical remission in patients with moderately to severely active CD after 1 year of treatment regardless of disease duration. Clinical remission rates through 3 years of treatment were highest in the shortest disease duration subgroup in adalimumab-treated patients, with a trend to fewer side effects.

1. Introduction

The clinical course of Crohn's disease (CD) typically follows a pattern of relapsing and remitting symptoms; however, progression to structural bowel damage (i.e., strictures and/or fistulae) can occur even during phases in which the disease appears to be well controlled.[1–4] A majority of adults with CD will develop strictures and fistulae, which represent serious complications of the disease and often lead to hospitaliation and surgery.[4] Surgery for CD is not curative, and active CD recurs in 44% to 55% of patients within 10 years post-surgery.[5]

Chronic inflammation is associated with accumulation of tissue damage, usually manifesting as disease complications, such as stricture and fistula, which may be irreversible, and surgical resection, which is definitely irreversible.[1–4] Problems related to tissue damage include bacterial overgrowth (resulting from strictures, internal fistulae, and/or surgical resection of the ileocecal valve),[6] bile salt diarrhoea (resulting from surgical resection of the terminal ileum),[7,8] and steatorrhea (resulting from surgical resection of small bowel).[8,9] Symptoms such as these are not directly related to inflammation, add to clinical symptoms in patients with CD,[9] and may lead to reduced responsiveness to therapeutic interventions that target the inflammatory cascade.[3] Anti-tumour necrosis factor (anti-TNF) agents have demonstrated pronounced efficacy in patients with early rheumatoid arthritis (RA).[10–13] Subgroup analyses from prospective randomised controlled trials support the idea that patients with shorter duration of CD achieve greater clinical benefit compared with patients treated later.[14,15] In addition, high steroid-free clinical remission rates were demonstrated in two trials of infliximab in immunosuppressant- and anti-TNF-naïve patients who were characterised by a relatively short-duration CD.[16,17] In contrast, post hoc analyses of two observational, single-centre patient cohorts treated with infliximab failed to find a relationship between disease duration and clinical outcome.[18,19]

The focus of treatment goals for CD is evolving from symptomatic control to disease modification, which entails controlling intestinal inflammation early in the disease course to prevent subsequent tissue damage.[5,20,21] The objective of the current analysis was to compare clinical remission and response rates for patients with early versus late CD, and assess disease duration as a predictor of clinical remission with adalimumab treatment in patients with moderately to severely active CD in the placebo-controlled CHARM (Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance) trial,[22] and the follow-on open-label extension ADHERE trial.[23]

2. Methods

2.1. Study design

Data for this post hoc subanalysis were from CHARM (www.clinicaltrials.gov, NCT00077779), a 56-week, randomised, double-blind, placebo-controlled, multicentre maintenance trial of adalimumab in patients with moderately to severely active CD. Data for long-term remission and response rates were drawn from ADHERE (www.clinicaltrials.gov, NCT00195715), the open-label extension of the CHARM trial. Details of the study design, inclusion/exclusion criteria, and primary efficacy and safety results have been published previously.[22–24]

Briefly, patients between 18 and 75 years old with a confirmed diagnosis of CD for more than 4 months and a Crohn's Disease Activity Index (CDAI) score between 220 and 450 were eligible. Patients were to have discontinued any previous anti-TNF therapy at least 12 weeks prior to enrolment. Concomitant CD-related medications were to be maintained at stable doses, except for corticosteroids, which could be tapered starting at week 8 in CR-70 responders (decrease in CDAI of ≥70 points compared with baseline).

All patients received open-label induction therapy with adalimumab 80/40 mg at weeks 0/2. Patients were stratified by previous exposure to anti-TNF agents and CR-70 responder status at week 4 and randomised to receive adalimumab 40 mg every other week (eow), adalimumab 40 mg weekly, or placebo for the 52-week blinded phase. At or after week 12, patients who experienced a lack of response or a disease flare could receive open-label adalimumab 40 mg eow and subsequently adalimumab 40 mg weekly for continued non-response or recurrent flare.

After the blinded phase, patients could enter the open-label extension ADHERE. Patients who completed CHARM on blinded therapy received open-label adalimumab 40 mg eow in ADHERE, and those already receiving open-label adalimumab therapy continued the same dose. During ADHERE, increasing adalimumab dosing from eow to weekly was allowed for patients who experienced disease flare or non-response. The present study analysed data from patients in ADHERE who had been randomised to adalimumab groups in CHARM.

2.2. Patient sample and clinical assessments

For this analysis, patients were divided into 3 subgroups based on duration of disease since diagnosis at baseline: <2 years, 2 to <5 years, and ≥5 years. These disease duration categories allowed a sufficient distribution of patients in each group for a