Journal of Crohn's and Colitis (2013) 7, 213–221

Available online at www.sciencedirect.com

SciVerse ScienceDirect

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

S. Schreiber [a,*], W. Reinisch [b,**], J.F. Colombel [c], W.J. Sandborn [d], D.W. Hommes [e], A.M. Robinson [f], B. Huang [f], K.G. Lomax [f], P.F. Pollack [f]

[a] *Department of Medicine I, University Hospital Schleswig-Holstein, Kiel, Christian-Albrechts University, Germany*
[b] *Gastroenterology and Hepatology, Medical University of Vienna, Vienna, Austria*
[c] *Hepatogastroenterology, Centre Hospitalier Universitaire de Lille, Lille, France*
[d] *Division of Gastroenterology, University of California San Diego, La Jolla, CA, USA*
[e] *Division of Digestive Diseases, University of California Los Angeles, CA, USA*
[f] *Abbott Laboratories, Abbott Park, IL, USA*

Received 15 December 2011; received in revised form 3 May 2012; accepted 19 May 2012

KEYWORDS
Adalimumab;
Clinical remission;
Early Crohn's disease;
Disease duration;
Safety

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

* Correspondence to: S. Schreiber, Christian-Albrechts University, University Hospital Schleswig-Holstein, Department of Internal Medicine I , Schittenhelmstrasse 12 , Kiel, 24105, Germany. Tel.: +49 431 597 1279.
** Correspondence to: W. Reinisch, Medical University of Vienna, Department Internal Medicine III, Waehringer Guertel 18–20, Vienna, A-1090, Austria. Tel.: +43 1 40 400 4741.
E-mail addresses: s.schreiber@mucosa.de (S. Schreiber), walter.reinisch@meduniwien.ac.at (W. Reinisch).

1873-9946/$ - see front matter
doi:10.1016/j.crohns.2012.05.015

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

meaningful analysis. The primary analysis group for this disease duration analysis was the intent-to-treat (ITT) population, defined as all randomised patients (regardless of response status at week 4) who received at least 1 dose of study drug.

Clinical assessments were performed at weeks 0, 2, 4, 6, 8, 12, 16, 20, 26, 32, 40, 48, and 56 of CHARM. Clinical remission (CDAI <150) and clinical response rates (CR-100 [CDAI decrease by ≥100 points compared with baseline] and CR-70) were summarised at weeks 26 and 56 for adalimumab- and placebo-treated patients in each disease duration subgroup. Patients who entered ADHERE were assessed at weeks 2, 4, 8, 12 (corresponding to weeks 58, 60, 64, and 68 from CHARM baseline) and every 12 weeks thereafter.

2.3. Statistical analysis

Baseline characteristics among the 3 disease duration subgroups were compared with Kruskal–Wallis tests for continuous variables and chi-square tests for categorical variables. Prior use of CD-related medications was compared using chi-square tests.

In the analyses of clinical remission/response, patients who dropped out, had missing data, or moved to open-label/weekly therapy during CHARM were considered non-remitters/non-responders from that point forward (non-responder imputation, or NRI). Within each disease duration subgroup, the percentages of patients achieving remission/response at weeks 26 and 56 of CHARM were compared between adalimumab (40 mg eow and 40 mg weekly groups combined) and placebo using Fisher's exact tests. All treatment comparisons used two-sided tests; statistical significance was set at $P<0.05$.

Logistic regression models were used to examine the potential predictive variables for achieving clinical remission at week 56 and for experiencing any treatment-emergent adverse event during double-blind treatment. The predictor variables included in the models were: age (continuous), baseline C-reactive protein (CRP; continuous), baseline CDAI (continuous), disease duration (continuous), tobacco use (former smoker, never smoked, current smoker), baseline immunosuppressant use (yes/no), baseline steroid use (yes/no), baseline aminosalicylate use (yes/no), previous anti-TNF therapy (yes/no), previous immunosuppressant use (yes/no), previous steroid use (yes/no), previous aminosalicylate use (yes/no), and baseline fistula (yes/no). Stepwise selection procedure was used to determine the factors to be included in the final model (with the criterion of P value 0.10 for entry and 0.05 for remaining in the model) in adalimumab-treated patients. To confirm the treatment effect of adalimumab on clinical remission after controlling for disease duration and other predictor variables, a logistic regression model with treatment as an additional factor was also conducted, including both adalimumab- and placebo-treated patients.

All-cause hospitalisation during the double-blind period (week 4 through week 56) of CHARM was analysed within each disease duration subgroup for placebo- or adalimumab-treated patients, using Kaplan–Meier methods to estimate one year hospitalisation-free survival rates and 95% confidence intervals (CI). Patients who did not have a hospitalisation during the double-blind period were censored at week 56; patients who discontinued during double-blind treatment were censored at the end of a 70-day follow-up period. Statistical comparisons for the differences in the time to hospitalisation between the adalimumab- and placebo-treated patients were based on the log-rank test.

All treatment comparisons used two-sided tests; statistical significance was set at $P<0.05$.

3. Results

3.1. Baseline demographics and clinical characteristics by disease duration

When stratified by duration of CD, the subgroup with disease duration <2 years included 93 patients (37 placebo, 56 adalimumab), the subgroup with disease duration 2 to <5 years included 148 patients (53 placebo, 95 adalimumab), and the subgroup with disease duration ≥5 years included 536 patients (170 placebo, 366 adalimumab). Significant differences in age, sex, baseline CDAI, and prior anti-TNF therapy use were observed across the disease duration subgroups (Tables 1 and 2). Patients with disease duration <2 years were younger, had lower baseline CDAI, and were less likely to have received prior anti-TNF therapy. Patients in the longest disease duration subgroup were more likely to have fistulae present at baseline than the shorter disease duration groups, although this difference was not statistically significant. Prior and concurrent use of steroids and immunosuppressants in the group with disease duration <2 years was similar to that in groups with longer durations of CD, and there were no significant differences in prior CD-related medication use between disease duration subgroups (Table 2).

3.2. Clinical remission

In the overall population, significantly greater percentages of adalimumab- versus placebo-treated patients in the ITT population achieved clinical remission at week 26 (33% versus 14%, respectively, Fig. 1A) and week 56 (30% versus 10%, respectively, Fig. 1B). Significantly greater percentages of adalimumab-treated patients in the subgroups with disease duration <2 years and ≥5 years achieved clinical remission at week 26 compared with the respective placebo-treated patients (Fig. 1A). The week-26 remission rate in placebo-treated patients with disease duration 2 to <5 years was high (23%); the remission rate for the adalimumab-treated patients in this subgroup was numerically greater (28%) but the difference did not reach statistical significance compared with placebo. Week-56 remission rates for adalimumab-treated patients in each disease duration subgroup were significantly greater than the corresponding rates in the placebo subgroups (Fig. 1B). At both week 26 and week 56, patients with disease duration <2 years had numerically greater remission rates compared with the 2 subgroups with longer durations of CD. A similar trend was observed in patients who responded to induction at week 4 (randomised responders, data not shown).

The long-term remission rates for were consistently higher for the short-duration subgroup from week 56 of CHARM through week 108 of ADHERE (corresponding to 3 years of therapy on adalimumab), Fig. 2.

Table 1 Baseline demographics and clinical characteristics by duration of disease: ITT population.

Variable	Disease duration <2 years (*N*=93)	Disease duration 2 to <5 years (*N*=148)	Disease duration ≥5 years (*N*=536)
Age (yrs), mean *	34.9	34.3	38.0
Women, *n* (%) *	59 (63.4)	105 (70.9)	318 (59.3)
White, *n* (%)	86 (92.5)	138 (93.2)	498 (92.9)
Baseline CRP (mg/dL)			
Mean	2.1	2.3	2.1
≥1.0, *n* (%)	43 (46.2)	72 (48.6)	247 (46.1)
Baseline CDAI, mean *	298.8	302.9	315.5
Baseline IBDQ total score, mean	122.5	125.3	122.0
Fistula at baseline, *n* (%)	11 (11.8)	19 (12.8)	87 (16.2)
Smoking status, n (%)			
Current	26 (28.0)	53 (35.8)	197 (36.8)
Prior	27 (29.0)	35 (23.6)	133 (24.8)
Never	82 (43.0)	60 (40.5)	206 (38.4)

CDAI, Crohn's disease activity index; CRP, C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; ITT, intent-to-treat; TNF, tumour necrosis factor.

* $P<0.05$ among the disease duration subgroups, using Kruskal–Wallis tests (continuous variables) or chi-square test (categorical variables).

3.3. Clinical response

The overall pattern of results for CR-100 rates by disease duration followed the same pattern as the results for clinical remission. CR-100 results at weeks 26 and 56 are provided in Figs. S1A and S1B, and CR-100 over time during ADHERE is provided in Fig. S2 (on-line supplement). CR-70 results at weeks 26 and 56 and over time in ADHERE were similar to the CR-100 results (data not shown).

3.4. Logistic regression

The logistic regression model confirmed disease duration as a significant predictive factor for clinical remission at week 56 (odds ratio [OR]/year=0.974, 95% CI=0.950, 1.000; $P=0.046$) in the final model; disease duration was not a statistically significant factor at Week 26 (Table 3). Baseline CRP, baseline CDAI, and previous anti-TNF use were significant predictive factors in the final model at both week 26 and week 56, and baseline aminosalicylate use was also a significant factor at week 56. In the logistic regression analysis that included both adalimumab- and placebo-treated patients and added treatment group as a factor, the positive treatment effect of adalimumab compared with placebo on clinical remission remained a significant factor at week 26 and week 56, after adjusting for disease duration and other factors.

3.5. Kaplan–Meier analysis of time to hospitalisation by disease duration

During the CHARM double-blind study period, 82 hospitalisations occurred: 7 in the <2 year subgroup (4/37 placebo, 4/56 adalimumab), 15 in the 2–5 year subgroup (7/53 placebo, 8/95 adalimumab), and 60 in the >5 year subgroup (27/170 placebo, 33/366 adalimumab). Within each subgroup, the risk of hospitalisation was numerically lower in the patients treated with adalimumab, compared with placebo-treated patients (Table 4); for the >5 year subgroup, $P=0.051$. The risk of hospitalisation was lowest in the shortest disease duration subgroup and greatest in the patients with longest disease duration.

3.6. Adverse events by disease duration

In adalimumab-treated patients, the overall rate of adverse events per 100 patient-years was greatest in patients with disease duration ≥5 years (Table 5), but the trend was not consistent for all adverse event categories. Placebo-treated patients in each disease duration subgroup tended to have greater rates of serious adverse events (including serious infections) and discontinuations due to adverse events compared with the respective adalimumab-treated groups. Rates of serious infections were low in all the groups, regardless of treatment; no adalimumab-treated patients in the early CD group (disease duration <2 years) developed a serious infection. There were no events of congestive heart failure or demyelinating disease and no deaths in any group. Long-term safety data for ADHERE have been reported previously.[23,24]

Logistic regression analysis identified baseline aminosalicylate use as the only significant predictive factor for experiencing any treatment-emergent adverse event in CHARM (OR=0.463, 95% CI=0.275, 0.779; $P=0.004$, for aminosalicylate use no versus yes).

4. Discussion

In this post hoc analysis of all randomised patients in CHARM, significantly higher clinical remission and response rates for adalimumab-treated patients with CD were observed and maintained from week 26 to week 56 versus placebo in each disease duration subgroup. The adalimumab-treated patients had a lower risk of hospitalisation than placebo-treated patients in all disease duration subgroups. Clinical remission and response rates were inversely related to disease duration for both adalimumab and placebo, except for the intermediate disease duration subgroup (2 to <5 years) at week 26. The logistic regression results in our analyses confirmed that after adjusting for other factors in the final model, shorter disease duration was significantly associated with a greater likelihood of sustaining clinical remission with adalimumab therapy. Adalimumab-treated patients in the <2-year subgroup consistently achieved the

Table 2 Prior and concurrent CD-related medication use: ITT population.

	Disease duration <2 years (*N*=93)	Disease duration 2 to <5 years (*N*=148)	Disease duration ≥5 years (*N*=536)
Concurrent medication, n (%)			
Corticosteroids only	18 (19.4)	37 (25.0)	159 (19.4)
Immunosuppressants only	30 (32.3)	46 (31.1)	135 (25.2)
Both corticosteroids and immunosuppressants	22 (23.7)	22 (14.9)	109 (20.3)
Neither corticosteroids nor immunosuppressants	23 (24.7)	43 (29.1)	188 (35.1)
Prior medication, n (%)			
Anti-TNF agent, *n* (%) *	25 (26.9)	60 (40.5)	305 (56.9)
Corticosteroids	75 (80.6)	119 (80.4)	461 (86.0)
Immunosuppressants	65 (69.9)	114 (77.0)	416 (77.6)
Aminosalicylates	59 (63.4)	101 (68.2)	343 (64.0)

CD, Crohn's disease; ITT, intent-to-treat.

* $P<0.05$ among the disease duration subgroups, using chi-square test.

greatest rates of remission and response through 3 years of therapy (1 year of CHARM and 2 years in ADHERE), and the risk of hospitalisation during the CHARM double-blind study period was the lowest in the shortest disease duration subgroup and greatest in the longest disease duration patients. These data indicate the potential benefits that might be derived from initiating biologic therapy early in the course of CD.

Our findings were similar to those observed with certolizumab pegol in patients who responded to induction therapy in the PRECiSE 2 study, in which rates of clinical remission and CR-100 at week 26 were significantly greater for certolizumab pegol versus placebo in the early and late disease duration subgroups, but statistical significance was not consistently observed in the intermediate subgroups.[14] Certolizumab-treated patients with CD for <1 year had significantly greater response rates versus patients with disease duration ≥5 years; the trend for clinical remission was similar but not statistically significant.

The association between disease duration and maintenance of clinical remission or response has been inconsistent in other studies. An analyses of predictors of response and remission with certolizumab pegol in patients who failed infliximab therapy in the WELCOME study found no association between disease duration and clinical remission at

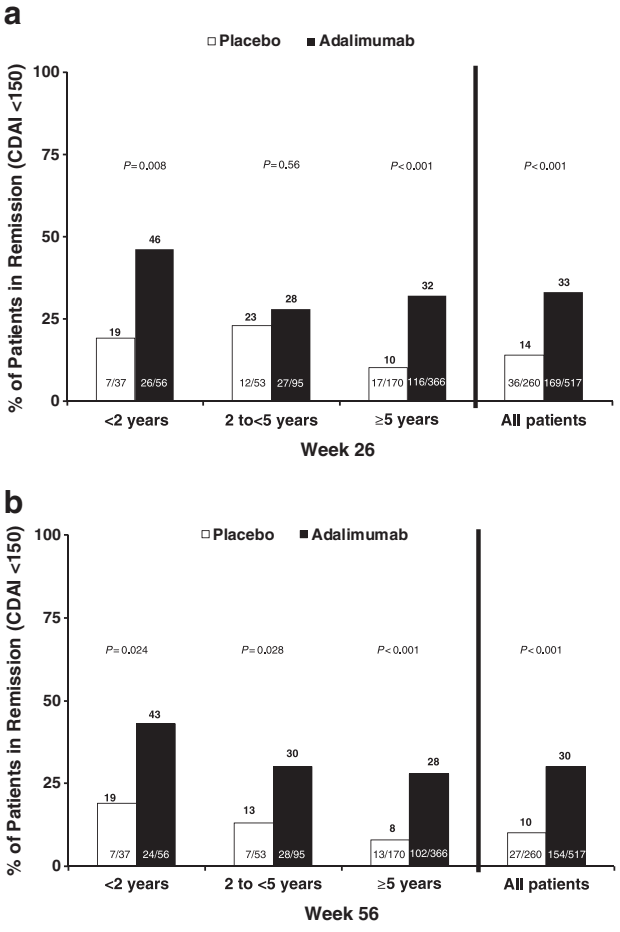

Figure 1 Clinical remission at week 26 (a) and week 56 (b) by disease duration: all patients randomised (ITT population). *P* values from Fisher's exact test.

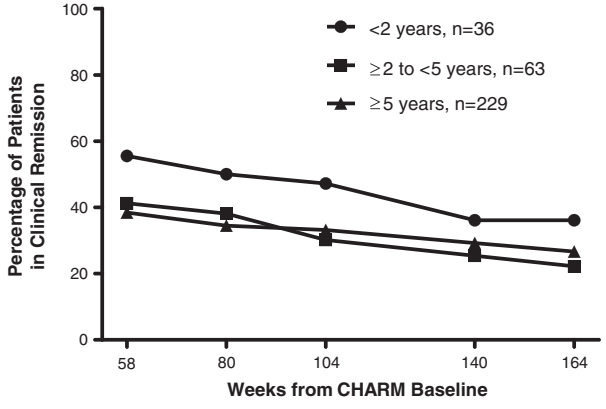

Figure 2 Clinical remission over time in ADHERE (NRI): all patients randomised to adalimumab treatment in CHARM who enrolled in ADHERE.

Table 3 Stepwise logistic regression for clinical remission (CDAI <150) at weeks 26 and 56: adalimumab-treated patients (ITT).

Variable [a]	Week 26			Week 56		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Baseline disease duration	Not significant			0.974	0.950, 1.000	0.046
Baseline CRP concentration	1.106	1.038, 1.179	0.002	1.122	1.049, 1.200	<0.001
Baseline CDAI	0.994	0.991, 0.998	0.001	0.995	0.992, 0.999	0.01
Prior anti-TNF use (no versus yes)	1.615	1.106, 2.358	0.013	1.605	1.078, 2.389	0.02
Baseline aminosalicylate use (no versus yes)	Not significant			0.629	0.411, 0.963	0.033

CDAI, Crohn's disease activity index; CI, confidence interval; CRP, C-reactive protein; ITT, intent-to-treat; TNF, tumour necrosis factor.

[a] Age, tobacco use, baseline immunosuppressant use, baseline steroid use, prior immunosuppressant use, prior steroid use, prior aminosalicylate use, and fistula at baseline were not significant factors at either time point.

week 26.[25] In the ENCORE trial, remission rates with natalizumab were consistently higher at weeks 8 and 12 for patients with disease duration ≤3 years than in the overall population, although in ENACT-2 remission rates at 6 and 12 months among natalizumab-treated patients were similar between those with disease duration ≤3 years and the overall population.[15]

Similar to other studies investigating predictors of remission or response, we identified additional factors typically associated with early CD, such as lower disease activity and lack of previous exposure to anti-TNF therapy, as significant prognostic factors.[14,25–27] Although baseline CRP concentrations were similar between patients with early and late CD in CHARM, higher baseline CRP concentrations were a significant factor in predicting maintenance of remission at week 26 and week 56. Anti-TNF agents target the inflammatory process, for which CRP is a biomarker; thus, an association between CRP concentration and therapeutic response is not unexpected.

Early CD has not been defined, *per se*; however, simply defining it based on time since diagnosis may not be adequate considering that evidence of stricturing or penetrating disease is present in 20% of newly diagnosed patients.[4] Also, many patients are symptomatic for years before they receive the formal diagnosis of CD.[4] Using rheumatoid arthritis as a model, Peyrin-Biroulet et al. [28] proposed a multidimensional definition of early CD that includes patients with clinical or biologic evidence of disease activity, normal bowel function, no bowel damage, no prior CD-related surgery, no prior use of immunosuppressants and biologic therapy, and disease duration ≤2 years. This definition has yet to be applied in clinical trials; however, the patients in the SONIC trial, all of whom were naïve to immunosuppressants and anti-TNF agents and had median disease duration of 2.3 years and median CRP concentrations of 1.1 mg/dL, could be generally considered to meet the proposed criteria for the early disease definition.[16] Although the primary objective of SONIC was to test the efficacy of infliximab plus azathioprine versus monotherapy with each agent at week 26 and the trial did not have a long-duration CD subgroup, the study also supports that early treatment with anti-TNF agents is safe and effective for patients with CD who did not respond to first-line therapy.

We noted increasing rates of overall adverse events with increasing duration of CD in adalimumab-treated patients, though the trend was not consistent for each type of adverse event recorded. Patients with longer duration of disease had higher CDAI, were older, and were slightly more likely to have fistulae. This group also had the highest rates of prior anti-TNF use. These findings suggest the longest disease duration subgroup in CHARM had more complicated disease than the shorter duration subgroups. The trend for more adverse events in the longest disease duration group is consistent with data reported from the TREAT registry,[29] in which baseline moderate to severe disease activity and disease duration were associated with increased risk of serious infections.

In our analyses, baseline aminosalicylates use was identified in the logistic regression as a significant predictor of remission at week 56. Aminosalicylate use was also associated with adverse events. The clinical significance of these findings is uncertain. Aminosalicylates are known to be ineffective as maintenance therapy for Crohn's disease,[30] and in other studies have been shown to be associated with increased risk of disease progression and surgery,[4] and with increased risk of hospitalisation.[31]

Table 4 Estimated hospitalisation-free rates during double-blind treatment in CHARM by disease duration: ITT population. Time to hospitalisation was assessed using Kaplan–Meier methods, with comparison between adalimumab- and placebo-treated patients using the log-rank test.

	Disease duration <2 years		Disease duration 2 to <5 years		Disease duration ≥5 years	
	Placebo *N*=37	Adalimumab *N*=56	Placebo *N*=53	Adalimumab *N*=95	Placebo *N*=170	Adalimumab *N*=366
Hospitalisation-free survival rate, % (95% CI)	81.5 (55.2, 93.2)	93.0 (78.5, 97.8)	83.6 (66.3, 92.5)	89.7 (79.7, 94.9)	72.9 (59.0, 82.8)	85.6 (80.0, 89.7) *

* *P*=0.051 versus placebo, using log-rank test.

Table 5 Adverse events per 100 patient-years by disease duration, double-blind treatment: ITT population.

	Disease duration <2 years events (E/100PY)		Disease duration 2 to <5 years events (E/100PY)		Disease duration ≥5 years events (E/100PY)	
	Placebo *N*=37 PY=17.0	Adalimumab *N*=56 PY=35.6	Placebo *N*=53 PY=21.4	Adalimumab *N*=95 PY=52.8	Placebo *N*=170 PY=53.9	Adalimumab *N*=366 PY=200.0
Any AE	180 (1058.8)	266 (747.2)	167 (780.4)	422 (799.2)	604 (1120.6)	1635 (817.5)
AEs leading to discontinuation	4 (23.5)	3 (8.4)	6 (28.0)	8 (15.2)	25 (46.4)	33 (16.5)
Any severe AE	18 (105.9)	18 (50.6)	8 (37.4)	30 (56.8)	67 (124.3)	74 (37.0)
Any SAE	4 (23.5)	5 (14.0)	9 (42.1)	12 (22.7)	34 (63.1)	44 (22.0)
Infectious AE	39 (229.4)	52 (146.1)	32 (149.5)	82 (155.3)	84 (155.8)	293 (146.5)
Infectious SAE	1 (5.9)	0	2 (9.3)	2 (3.8)	6 (11.1)	12 (6.0)
Injection-site pain	0	2 (5.6)	0	0	2 (3.7)	7 (3.5)
Opportunistic infection	0	0	1 (4.7) [a]	0	1 (1.9) [a]	6 (3.0) [a]
Malignant neoplasm	0	0	0	0	1 (1.9) [b]	0
Death	0	0	0	0	0	0

AE, adverse event; E, event; PY, patient-years; SAE, serious adverse event.

[a] All opportunistic infections were candidiasis or oral candidiasis.
[b] Breast cancer.

The safety of long-term therapy with anti-TNF agents remains a potential concern, particularly with earlier initiation of typically chronic therapy. Data on the use of chronic biologic therapy, with or without immunosuppressants, in patients with early CD are limited. No new safety concerns were identified in patients with disease duration <2 years treated with adalimumab for up to 56 weeks, and there were no serious infections in this subgroup. These results are consistent with the 26-week safety profile by disease duration reported for certolizumab pegol,[14] but it will be important to confirm these observations in prospective trials. When choosing therapies for patients with early disease, the risks associated with early use of anti-TNF therapy should be considered against the known risks associated with standard first-line agents, such as bone loss with corticosteroids.[32]

Limitations of the present analysis include that it was conducted post hoc, patients were not randomised on the basis of disease duration, the number of patients in the short disease duration subgroup was relatively small, and the impact of early therapy has yet to be conclusively demonstrated in prospective studies. Because of this, the results can be considered hypothesis-generating only. In addition, we could not examine the effect of adalimumab therapy in patients with short disease duration and stricturing or penetrating phenotypes and/or prior resections because Vienna classification and surgical history were not collected in CHARM.

In summary, the efficacy of adalimumab compared with placebo demonstrated in patients with early, moderate to severe CD is promising; nevertheless, the risk–benefit balance of early intervention with anti-TNF therapy must be considered on a patient-by-patient basis, because not all patients will follow a progressive and complicated disease course. However, the relatively high and sustained remission rates in patients with early CD, and the results of logistic regression showing disease duration as a predictive factor in adalimumab-treated patients, suggest potentially greater efficacy with early use of anti-TNF therapy with adalimumab. Future studies identifying predictors of best candidates for early intervention with anti-TNF agents are of critical importance for clinical practice.

Conflicts of Interest

S. Schreiber has served as a study investigator and consultant for Abbott Laboratories, Centocor, Schering-Plough and UCB, and has participated in continuing medical education events supported by unrestricted educational grants from Abbott Laboratories.

W. Reinisch has served as a speaker, a consultant and/or an advisory board member for Abbott Laboratories, Aesca, Astra Zeneca, Biogen IDEC, Cellerix, Chemocentryx, Centocor, Danone Austria, Elan, Ferring, Genentech, Lipid Therapeutics, Millenium, MSD, Novartis, Ocera, Otsuka, PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Schering-Plough, Shire, Therakos, UCB, Vifor, Yakult Austria, and 4SC.

J. F. Colombel has served as a consultant and an advisory board member for Abbott Laboratories, ActoGeniX NV, Albireo Pharma, Astra Zeneca, Bayer Schering Pharma, Biogen Idec, Boehringer-Ingelheim, Bristol-Myers Squibb, Cellerix, Centocor, Chemocentryx, Cosmo Technologies, Danone France, Elan, Genentech, Giuliani, Given Imaging, GlaxoSmithKline, Merck, Millennium, NeoVacs, Ocerra (previously named Renovia), Otsuka American, PDL Biopharma (previously named Protein Design Labs), Pfizer, Ribo Vacs Biotech, Schering-Plough, Shire, Synta, Teva and Petah Tikva, Therakos, UCB (previously named Celltech Therapeutics) and Wyeth, has received lecture fees from speaking at continuing medical education events indirectly sponsored by a commercial sponsor from Abbott Laboratories, Astra Zeneca, Centocor, Elan, Falk, Ferring, Given Imaging, Otsuka American, PDL, Schering-Plough, Shire and UCB, has received grant support from Astra-Zeneca, Danisco, Danone,

Dysphar, Ferring, Giuliani, Lesaffre, Mapi Naxis, Ocerra Therapeutics (previously named Renovia), Roquette, Schering-Plough and UCB, and owns stock in Intestinal Biotech Development.

W. J. Sandborn has served as a consultant for CentocorOrthoBiotech, Abbott Laboratories, UCB Pharma, and Merck (previously Schering Plough), and has received research funding from CentocorOrthoBiotech, Abbott Laboratories, and UCB Pharma.

D. W. Hommes has nothing to disclose.

B. Huang, A. M. Robinson, and P. F. Pollack are employees of Abbott and own Abbott stock.

K. G. Lomax is a former employee of Abbott and may own Abbott stock.

Acknowledgements

Declaration of funding interests: This study and all data analyses were funded in full by Abbott Laboratories, Abbott Park, IL. Medical writing services were provided by Cathryn M. Carter, MS, of Arbor Communications, Inc., Ann Arbor, MI, and funded by Abbott, and by Laurinda Cooker, PhD, of Abbott.

Author contributions: SS, WR, JFC, WJS, DWH: Conception and design, collection of data, interpretation of results, development of manuscript, approval of final manuscript version.

AMR, KGL, PFP: Conception and design, interpretation of results, development of manuscript, approval of final manuscript version.

BH: Conception and design, performance of statistical analyses, interpretation of results, development of manuscript, approval of final manuscript version.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.crohns.2012.05.015.

References

1. Cosnes J, Cattan S, Blain A, Beaugerie L, Carbonnel F, Parc R, et al. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis* 2002;**8**:244–50.
2. Louis E, Collard A, Oger AF, Degroote E, Aboul Nasr El, Yafi FA, et al. Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease. *Gut* 2001;**49**:777–82.
3. Pariente B, Cosnes J, Danese S, Sandborn WJ, Lewin M, Fletcher JG, et al. Development of the Crohn's disease digestive damage score, the Lemann score. *Inflamm Bowel Dis* 2011;**17**:1415–22.
4. Thia KT, Sandborn WJ, Harmsen WS, Zinsmeister AR, Loftus Jr EV. Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. *Gastroenterology* 2010;**139**:1147–55.
5. Peyrin-Biroulet L, Loftus Jr EV, Colombel JF, Sandborn WJ. Early Crohn disease: a proposed definition for use in disease-modification trials. *Gut* 2010;**59**:141–7.
6. Castiglione F, Rispo A, Di Girolamo E, Cozzolino A, Manguso F, Grassia R, et al. Antibiotic treatment of small bowel bacterial overgrowth in patients with Crohn's disease. *Aliment Pharmacol Ther* 2003;**18**:1107–12.
7. Hofmann AF. The syndrome of ileal disease and the broken enterohepatic circulation: cholerhetic enteropathy. *Gastroenterology* 1967;**52**:752–7.
8. Hofmann AF, Poley JR. Role of bile acid malabsorption in pathogenesis of diarrhea and steatorrhea in patients with ileal resection. I. Response to cholestyramine or replacement of dietary long chain triglyceride by medium chain triglyceride. *Gastroenterology* 1972;**62**:918–34.
9. Cosnes J, de Parades V, Carbonnel F, Beaugerie L, Ngo Y, Gendre JP, et al. Classification of the sequelae of bowel resection for Crohn's disease. *Br J Surg* 1994;**81**:1627–31.
10. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000;**343**:1586–93.
11. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 2006;**54**:26–37.
12. Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. *Arthritis Rheum* 2002;**46**:1443–50.
13. St Clair EW, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum* 2004;**50**:3432–43.
14. Schreiber S, Colombel JF, Bloomfield R, Nikolaus S, Scholmerich J, Panes J, et al. Increased response and remission rates in short-duration Crohn's disease with subcutaneous certolizumab pegol: an analysis of PRECiSE 2 randomized maintenance trial data. *Am J Gastroenterol* 2010;**105**:1574–82.
15. Schreiber S, Targan S. Efficacy of natalizumab in Crohn's patients with disease duration less than three years. *Gastroenterology* 2007;**132**:A509.
16. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010;**362**:1383–95.
17. D'Haens G, Baert F, van Assche G, Caenepeel P, Vergauwe P, Tuynman H, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet* 2008;**371**:660–7.
18. Schnitzler F, Fidder H, Ferrante M, Noman M, Arijs I, Van Assche G, et al. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. *Gut* 2009;**58**:492–500.
19. Vermeire S, Louis E, Carbonez A, Van Assche G, Noman M, Belaiche J, et al. Demographic and clinical parameters influencing the short-term outcome of anti-tumor necrosis factor (infliximab) treatment in Crohn's disease. *Am J Gastroenterol* 2002;**97**:2357–63.
20. D'Haens GR, Fedorak R, Lemann M, Feagan BG, Kamm MA, Cosnes J, et al. Endpoints for clinical trials evaluating disease modification and structural damage in adults with Crohn's disease. *Inflamm Bowel Dis* 2009;**15**:1599–604.
21. Van Assche G, Vermeire S, Rutgeerts P. The potential for disease modification in Crohn's disease. *Nat Rev Gastroenterol Hepatol* 2010;**7**:79–85.
22. Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007;**132**:52–65.
23. Panaccione R, Colombel JF, Sandborn WJ, Rutgeerts P, D'Haens GR, Robinson AM, et al. Adalimumab sustains clinical remission

and overall clinical benefit after 2 years of therapy for Crohn's disease. *Aliment Pharmacol Ther* 2010;**31**:1296–309.
24. Kamm MA, Hanauer SB, Panaccione R, Colombel JF, Sandborn WJ, Pollack PF, et al. Adalimumab sustains steroid-free remission after 3 years of therapy for Crohn's disease. *Aliment Pharmacol Ther* 2011;**34**:306–17.
25. Sandborn WJ, Abreu MT, D'Haens GR, Colombel J-F, Vermeire S, Mitchev K, et al. Predictors of response and remission to certolizumab pegol in patients with Crohn's disease: Data from the WELCOME Study. *Gastroenterology* 2010;**138**:S-164.
26. Hanauer S, Schreiber S, Thompsen O. Analysis of predictors of response maintenance to certolizumab pegol in patients with active Crohn's disease: data from PRECiSE 2. *J Crohns Colitis* 2008;**2**:6.
27. Hanauer SB, Panes J, Colombel JF, Bloomfield R, Schreiber S, Sandborn WJ. Clinical trial: impact of prior infliximab therapy on the clinical response to certolizumab pegol maintenance therapy for Crohn's disease. *Aliment Pharmacol Ther* 2010;**32**: 384–93.
28. Peyrin-Biroulet L, Loftus Jr EV, Colombel JF, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. *Am J Gastroenterol* 2010;**105**:289–97.
29. Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Chen DM, et al. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. *Clin Gastroenterol Hepatol* 2006;**4**:621–30.
30. Akobeng AK, Gardener E. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's disease. *Cochrane Database Syst Rev* 2005, Issue 1. Art. No.: CD003715. http://dx.doi.org/10.1002/14651858.CD003715.pub2.
31. Thomsen OO, Cortot A, Jewell D, Wright JP, Winter T, Veloso FT, et al. A comparison of budesonide and mesalamine for active Crohn's disease. International Budesonide-Mesalamine Study Group. *N Engl J Med* 1998;**339**:370–4.
32. Rutgeerts PJ. Review article: the limitations of corticosteroid therapy in Crohn's disease. *Aliment Pharmacol Ther* 2001;**15**: 1515–25.