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Adalimumab improves patient-reported outcomes and reduces indirect costs in patients with moderate to severe Crohn's disease: Results from the CARE trial☆

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Abstract

Background and aims: Crohn's disease negatively affects patients' quality of life and ability to work. We investigated the impact of adalimumab on work productivity, daily activities, and quality of life in an open-label trial (N=945). The population comprised both infliximab-naïve and -exposed patients, including infliximab primary non-responders.
Methods: Patients received adalimumab induction therapy (160 mg/80 mg at Weeks 0/2), followed by adalimumab 40 mg every other week for up to 20 weeks (patients with flares/non-response could receive 40 mg weekly at/after Week 12). The Work Productivity and Activity Impairment Questionnaire and Short Inflammatory Bowel Disease Questionnaire were assessed. Indirect cost savings were estimated based on the average work productivity improvements at Week 20.

Abbreviations CARE, Crohn's treatment with adalimumab, patient response to a safety and efficacy study; CD, Crohn's disease; CRP, C-reactive protein; EIMs, extraintestinal manifestations; HBI, Harvey Bradshaw Index; HRQOL, health-related quality of life; MCID, minimum clinically important difference; PNR, primary non-responder; PRO, patient-reported outcome; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; TAI, total activity impairment; TNF, tumor necrosis factor; TWPI, total work productivity impairment; WPAI:CD, Work Productivity and Activity Impairment Questionnaire for CD.

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Results: Mean baseline scores indicated severe productivity impairment and poor quality of life. At Week 20, 60% of infliximab-naïve and 47% of infliximab primary non-responders achieved clinically important improvements (≥9 points) on the Short Inflammatory Bowel Disease Questionnaire, and 51% and 43%, respectively, achieved the minimum clinically important difference (improvement ≥7 percentage points) for total work productivity impairment (non-responder imputation). At Week 20, 64% of infliximab-naïve and 55% of infliximab primary non-responders achieved clinically important improvements in total activity impairment. Estimated 20-week total indirect productivity-related cost savings were €3070 per infliximab-naïve patient and €2059 per infliximab-exposed patient.
Conclusions: Adalimumab therapy significantly improved work productivity and disease-specific quality of life for patients with moderate to severe Crohn's disease. Patients who failed prior infliximab therapy and patients naïve to infliximab benefited from adalimumab, with potentially greater benefits for infliximab-naïve patients (NCT00409617).

1. Introduction

Crohn's disease (CD) is a chronic condition often diagnosed during early adulthood.[1] The symptoms of active CD, which include potentially debilitating abdominal pain and diarrhea as well as fever and weight loss, can have a substantial impact on patients' day-to-day activities, ability to work, and quality of life. Patients with moderately to severely active CD have low employment and high disability rates.[2] Employed patients can experience reduced productivity in the workplace (ie, presenteeism), and patients who are too ill to work or who require medical care for the treatment of active disease have increased time absent from work (ie, absenteeism).[3] In any given year, 15% to 25% of patients with CD require hospitalization for complications of the disease,[3] and estimates for surgical interventions during the life-long course of disease range from 57% to 80%.[5,6] In addition to symptoms of active disease, an estimated 35% of patients develop extraintestinal manifestations (EIMs), most commonly involving inflammation of the joints, skin, and eyes,[7] which can also contribute to disease-related burdens on productivity and quality of life.

The need for a better understanding of the potential economic and quality-of-life benefits associated with biologic therapies for CD has been recognized.[8] Studies in both the United States and Europe have demonstrated that the indirect costs caused by work loss and reduced productivity in the workplace constitute a significant percentage of the overall economic burden of CD.[2,3,9–12] This burden increases substantially with greater disease severity and exceeds that of direct medical costs in some cases.[9,11,12] Yu et al[11] found that estimated indirect costs accounted for 64% to 69% of the total costs of CD in Europe. Clinical remission in patients with CD is associated with lesser hospitalization and surgery rates and improvements in employment and health-related quality of life (HRQOL),[4] and data from clinical trials of anti–tumor necrosis factor (anti-TNF) agents have demonstrated a positive impact on work productivity.[13–16]

To further demonstrate the impact of adalimumab on patient-reported outcomes (PROs), we report quality-of-life and work-productivity results from CARE (Crohn's Treatment With Adalimumab: Patient Response to a Safety and Efficacy Study), an open-label trial of adalimumab for patients with moderate to severe CD that included both infliximab-naïve and infliximab-exposed patients. We also evaluated the impact of change in Harvey Bradshaw Index (HBI) score on PROs and quantified the indirect cost savings associated with improved work productivity. To date, CARE represents the largest prospective clinical trial in Europe to measure the effect of anti-TNF therapy on quality of life and work productivity in a setting that represents a reasonable reflection of real-world clinical practice.

2. Methods

Details of the study design and patient population and results for clinical efficacy, safety, fistula healing, and resolution of extraintestinal manifestations (EIMs) have been reported separately.[17]

2.1. Study design

CARE was a 20-week, multicenter (187 sites in 17 European countries), Phase IIIb, open-label trial of adalimumab 40 mg every other week (eow) in patients with moderate to severe CD. The study population comprised patients who were naïve to infliximab, patients who never responded clinically to infliximab (primary non-responders [PNRs]), and patients who failed infliximab for other reasons. Classification of patients with prior exposure to infliximab was determined by the investigator. The study was conducted from December 2006 to July 2008 (NCT00409617). The institutional review board or independent ethics committee at each participating site approved the protocol, and each patient provided written informed consent before any study-related procedures were performed. CARE was conducted in accordance with the protocol, International Conference on Harmonization Guidelines for Good Clinical Practice, the Declaration of Helsinki, and other regulations governing clinical study conduct. Compliance with local laws and customs was ensured by the investigators.

2.2. Patients

Men and women aged 18 to 75 years with a diagnosis of moderately to severely active CD (confirmed by endoscopy or radiologic evaluation) for more than 4 months were included. Moderate to severe CD was defined by a HBI ≥7 points at screening. Patients were to have failed conventional therapy

and could have received infliximab or any anti-TNF agent until 8 weeks before baseline. Adequate contraception was required for women of childbearing potential.

Prior treatment with adalimumab or previous participation in an adalimumab clinical study was not allowed. In addition, patients with ulcerative or indeterminate colitis, known obstructive strictures, abscess or suspicion of abscess, bowel resection within the past 6 months, ostomy, short bowel syndrome (as determined by the investigator), or active infection; history of cancer or lymphoproliferative disease (other than a successfully and completely treated cutaneous squamous cell or basal cell carcinoma or carcinoma in situ of the cervix) or *Listeria* infection; chronic or active hepatitis B, human immunodeficiency virus, or prior or active tuberculosis; central nervous system demyelinating disease; clinically significant drug or alcohol abuse (within the last year); receipt of an investigational chemical or biologic agent within 30 days or 5 half-lives (whichever is longer) prior to baseline; treatment with systemic antibiotics, antivirals, or antifungals within 3 weeks of baseline; pregnancy or lactation; poorly controlled medical condition; positive *Clostridium difficile* stool assay; significant deviations in prespecified laboratory parameters; use of cyclosporine, tacrolimus, or mycophenolate mofetil within 8 weeks of baseline; any prior exposure to natalizumab; and known hypersensitivity to the excipients of adalimumab were excluded.

Patients could continue concurrent CD-related medications at stable doses (eg, azathioprine, 6-mercaptopurine, methotrexate, corticosteroids, aminosalicylates, and/or antibiotics) per protocol. Modification of CD-related concomitant medications was allowed starting at Week 8.

2.3. Study procedures

A screening period of up to 2 weeks preceded the baseline assessments. All eligible patients received induction therapy with open-label adalimumab 160 mg subcutaneously at the baseline visit (Week 0) followed by 80 mg at Week 2. Starting at Week 4, all patients received adalimumab 40 mg eow. At or after Week 12, patients who experienced a disease flare (defined by a HBI increase ≥ 3 points and a total HBI ≥ 7 compared with Week 4) or who were not responding to study medication (non-response was defined as a decrease in HBI <3 compared with baseline) could have their dosage adjusted to adalimumab 40 mg weekly.

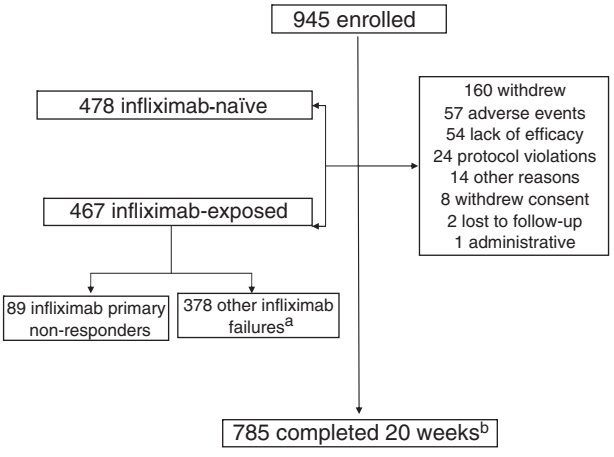

Figure 1 Patient disposition. [a]Other infliximab failures include loss of response, intolerance/adverse events, and other/missing reasons. [b]Dosage increase prior to Week 20 occurred in 14% of patients (10% for the anti-TNF-naïve group and 18% for the prior infliximab group).

2.4. Assessments

Patients were assessed at Weeks 0, 2, 4, 8, 12, and 20, and every 12 weeks thereafter. HRQOL was measured by the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) at each visit through Week 20, except for patients enrolled in Slovakia (no validated Slovak-language translation). The SIBDQ was developed as a short version of the Inflammatory Bowel Disease Questionnaire and is a simple, validated 10-item instrument that assesses HRQOL in patients with inflammatory bowel disease.[18] Total scores range from 10 to 70, with greater scores indicating better HRQOL. A 9-point change in the SIBDQ correlates with a 100-point change in Crohn's Disease Activity Index score,[18] and a 9-point SIBDQ improvement was considered the minimum clinically important difference (MCID) in this analysis.

Work productivity was assessed at each visit through Week 20 using the Work Productivity Activity Impairment Questionnaire for CD (WPAI:CD), a validated, 6-item, self-administered tool that assesses the impact of disease on work productivity and daily activities.[19,20] The WPAI:CD generates scores for 4 components: percentage of time work missed (absenteeism), percentage of impairment while working (presenteeism), percentage of overall work impairment (absenteeism and presenteeism combined), and percentage of activity impairment. Unemployed patients only answered questions relating to employment status and daily activities. WPAI:CD scores range from 0% (no impairment) to 100% (total loss of work productivity/activity), and the MCID is a 7 percentage point change.[21]

2.5. Statistical analysis

2.5.1. Subgroups

Data were summarized separately for infliximab-naïve patients and infliximab-exposed patients (including all reasons for discontinuation of infliximab). Among the infliximab-exposed patients, 2 subgroups were summarized: infliximab PNRs (ie, patients who never responded clinically to infliximab) and patients who discontinued infliximab therapy for other reasons (including loss of response for initial infliximab responders, intolerance or adverse events for initial infliximab responders, and missing/other reasons).

2.5.2. Changes in PROs

Absolute values for SIBDQ and WPAI:CD scores were calculated for all patients at baseline, Week 4, and Week 20 (observed values). Changes from baseline to Weeks 4 and 20 were analyzed for subgroups by prior infliximab exposure as well as by reason for infliximab discontinuation (paired Student *t*-tests). Descriptive analysis of all endpoints was

Table 1 Baseline demographics and clinical characteristics: by prior infliximab use.

	Infliximab-naïve (*N*=478)	Prior infliximab (*N*=467)	All adalimumab (*N*=945)
Women, *n* (%) [a]	266 (55.6)	302 (64.7)	568 (60.1)
Age (yrs), mean (SD)	34.8 (11.3)	35.8 (11.3)	35.3 (11.3)
White, *n* (%)	468 (97.9)	458 (98.1)	926 (98.0)
Body weight (kg), mean (SD)	68.8 (16.8)	67.1 (15.7)	67.9 (16.3)
Draining fistulas at baseline, *n* (%) [b]	63 (13.2)	108 (23.1)	171 (18.1)
HBI, median (range) [c]	9.0 (3–27)	10.0 (7–47)	10.0 (3–47)
Employed, *n* (%)	283 (59.2)	259 (55.5)	542 (57.4)
Current smoker, *n* (%)	202 (42.3)	197 (42.3)	399 (42.3)
Duration of CD (years) [c]			
Mean (SD)	8.6 (7.5)	10.6 (7.7)	9.6 (7.7)
Median (range)	6.3 (0.4–45.4)	9.1 (0.5–40.5)	7.8 (0.4–45.4)
CRP concentration (mg/dL)			
Mean (SD)	1.9 (2.9)	2.4 (5.3)	2.1 (4.3)
Median (range)	0.8 (0–33.8)	1.1 (0–98.5)	0.9 (0–98.5)
≥1.0, *n* (%)	211 (45.7)	231 (50.7)	442 (48.1)
Reason for infliximab discontinuation, *n* (%)			
PNR	NA	89 (19.1)	89 (9.4)
Other	NA	378 (80.9)	378 (40.0)
Loss or response	NA	170 (36.4)	170 (18.0)
Intolerance/adverse event	NA	110 (23.6)	110 (11.6)
Other/missing	NA	98 (21.0)	98 (10.4)
Concomitant medications, *n* (%)			
Aminosalicylates [d]	200 (41.8)	121 (25.9)	321 (34.0)
Corticosteroids and/or immunomodulators	363 (75.9)	343 (73.4)	706 (74.7)
Immunomodulators [e]	262 (54.8)	255 (54.6)	517 (54.7)
Corticosteroids [f,g]	219 (45.8)	182 (39.0)	401 (42.4) [h]
CD-related antibiotics [i]	23 (4.8)	24 (5.1)	47 (5.0)

CD, Crohn's disease; CRP, C-reactive protein; HBI, Harvey Bradshaw Index; PNR, primary non-responder; TNF, tumor necrosis factor.
[a] $p=0.005$ from Fisher's exact test to compare strata.
[b] $p<0.0001$ from Fisher's exact test to compare strata.
[c] $p<0.001$ from 1-way analysis of variance to compare strata.
[d] Includes balsalazide, mesalamine, olsalazine, and sulfasalazine.
[e] Includes azathioprine, mercaptopurine, methotrexate, and tioguanine.
[f] Includes prednisolone, methylprednisolone, budesonide, prednisone, and other.
[g] $p=0.035$ from Fisher's exact test to compare strata.
[h] Of the 544 patients who were not receiving corticosteroids at baseline, 7% initiated them from Week 8 to Week 20.
[i] Includes ciprofloxacin, metronidazole, and other.

prespecified in the protocol; all statistical analyses were performed *post hoc*. The percentages of patients who achieved the MCID on the SIBDQ and the WPAI:CD total work productivity impairment (TWPI) and WPAI:CD total activity impairment (TAI) scores were calculated at Weeks 4 and 20, using non-responder imputation for patients with missing data; if a patient had a missing SIBDQ or WPAI:CD value at certain time point, the patient was considered as not achieving the MCID for the respective outcome at that time point.

2.5.3. Relationship between HBI and PROs

A multiple linear regression model, with control for covariates including demographic characteristics, lifestyle (eg, tobacco use), and CD-related characteristics (eg, duration of disease; presence of fistulas; CD-related symptoms not directly included in the HBI, such as rectal bleeding, nausea, and vomiting; and concomitant drug use) was used to assess the relationship between HBI score and PRO outcomes at Week 20.

2.5.4. Cost analysis

To evaluate the potential economic benefit of adalimumab therapy during the 20-week study period, indirect cost savings from an employer's perspective were estimated by using the mean WPAI:CD improvements. Estimates of improvements in absenteeism, presenteeism, and TWPI at Week 20 were multiplied by €12,040, which represents the 20-week average gross earnings for full-time employees in the European Union (based on the EU average annual salary of €31,302.1 for 27 countries in 2006).[22] The cost analysis included only patients who were continuously employed throughout the study and had WPAI:CD data at baseline and Week 20. Patients who were unemployed at baseline

Table 2 Mean WPAI:CD and SIBDQ changes from baseline to Week 4 and Week 20: all adalimumab-treated patients (as-observed). [a]

	Baseline visit value		Change from baseline to Week 4		Change from baseline to Week 20	
Variable	*N*	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)
WPAI:CD component score [b]						
Absenteeism [c]	468	23.1 (34.4)	353	−9.6 (30.0)	328	−9.8 (31.7)
Presenteeism [c]	484	45.4 (27.2)	395	−17.3 (27.1)	360	−20.0 (30.9)
TWPI [c]	442	51.9 (29.0)	327	−18.4 (30.0)	302	−21.4 (33.6)
TAI	907	56.6 (25.8)	856	−21.3 (27.0)	747	−25.9 (29.7)
SIBDQ total score [d,e]	910	36.7 (10.3)	880	12.1 (22.0)	763	14.7 (12.9)

SIBDQ, Short Inflammatory Bowel Disease Questionnaire; TAI, total activity impairment; TWPI, total work productivity impairment; WPAI:CD, Work Productivity and Activity Impairment Questionnaire for CD.

[a] All changes from baseline at both time points exceeded the MCID for all WPAI:CD components (≥7 percentage points) and the SIBDQ (9-point improvement). All $p<0.001$.

[b] Decreases from baseline indicate improvement.

[c] WPAI:CD work-related items (absenteeism, presenteeism, and TWPI) were to be completed only by patients who were employed ($N=542$ of 920 without missing data for the employment question; every patient did not respond for all WPAI:CD components).

[d] Increases from baseline indicate improvement.

[e] SIBDQ was not evaluated in patients enrolled in Slovakia.

and patients who were employed at baseline but became unemployed during the study were not included.

3. Results

3.1. Baseline demographics and clinical characteristics

Of the 945 patients enrolled in the trial, 785 (83%) completed 20 weeks of adalimumab therapy (Fig. 1). Approximately half of the population had failed prior infliximab therapy ($n=467$), including 89 patients who were PNRs. Of the infliximab failures, 3 also had received etanercept and 42 certolizumab. Three patients in the infliximab-naïve cohort had received an anti-TNF agent other than infliximab before entering CARE. Adverse events (57 patients, 6.0%) and lack of efficacy (54 patients, 5.7%) were the most common reasons for discontinuation of adalimumab during the study. Patients were predominantly white (98.0%) and female (60.1%) and had a mean duration of CD of 9.6 years (Table 1). At baseline, the subgroup of patients with prior infliximab exposure tended to have longer disease durations, greater mean C-reactive protein concentrations, and lesser rates of concomitant aminosalicylate use. In addition, a greater percentage of infliximab-exposed patients had at least 1 draining fistula at baseline compared with infliximab-naïve patients.

3.2. Patient-reported outcomes: SIBDQ and WPAI:CD

Baseline SIBDQ and WPAI:CD scores indicated severe impairment of HRQOL and work productivity; mean TWPI was 51.9%

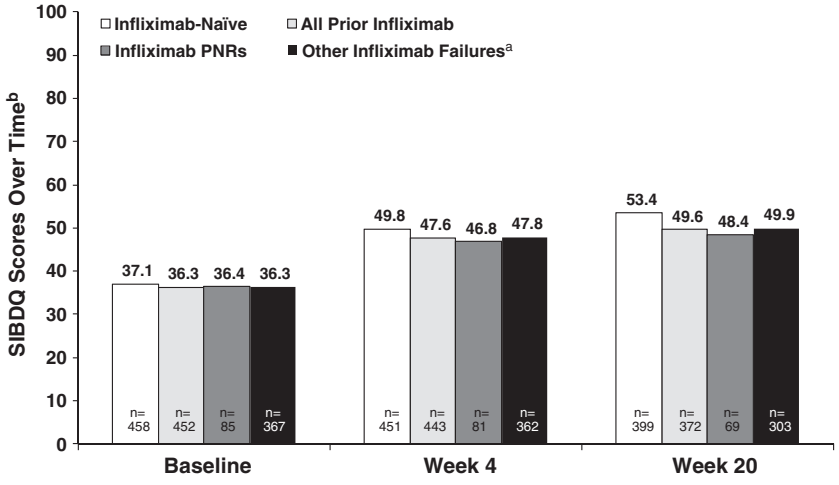

Figure 2 Mean Absolute Change in SIBDQ Scores From Baseline to Week 4 and Week 20. SIBDQ, Short Inflammatory Bowel Disease Questionnaire. [a]Includes loss of response, intolerance/adverse events, and other/missing. [b]$p<0.05$ vs. baseline for all comparisons. Greater changes indicate greater improvements in quality of life.

at baseline (Table 2). Clinically significant mean changes from baseline exceeded the MCID for all WPAI:CD components (improvement of $\geq$7 percentage points) and the SIBDQ (9-point improvement) at Week 4, and these improvements were sustained until Week 20 (Table 2). At Week 20, impairment of overall work productivity was reduced by

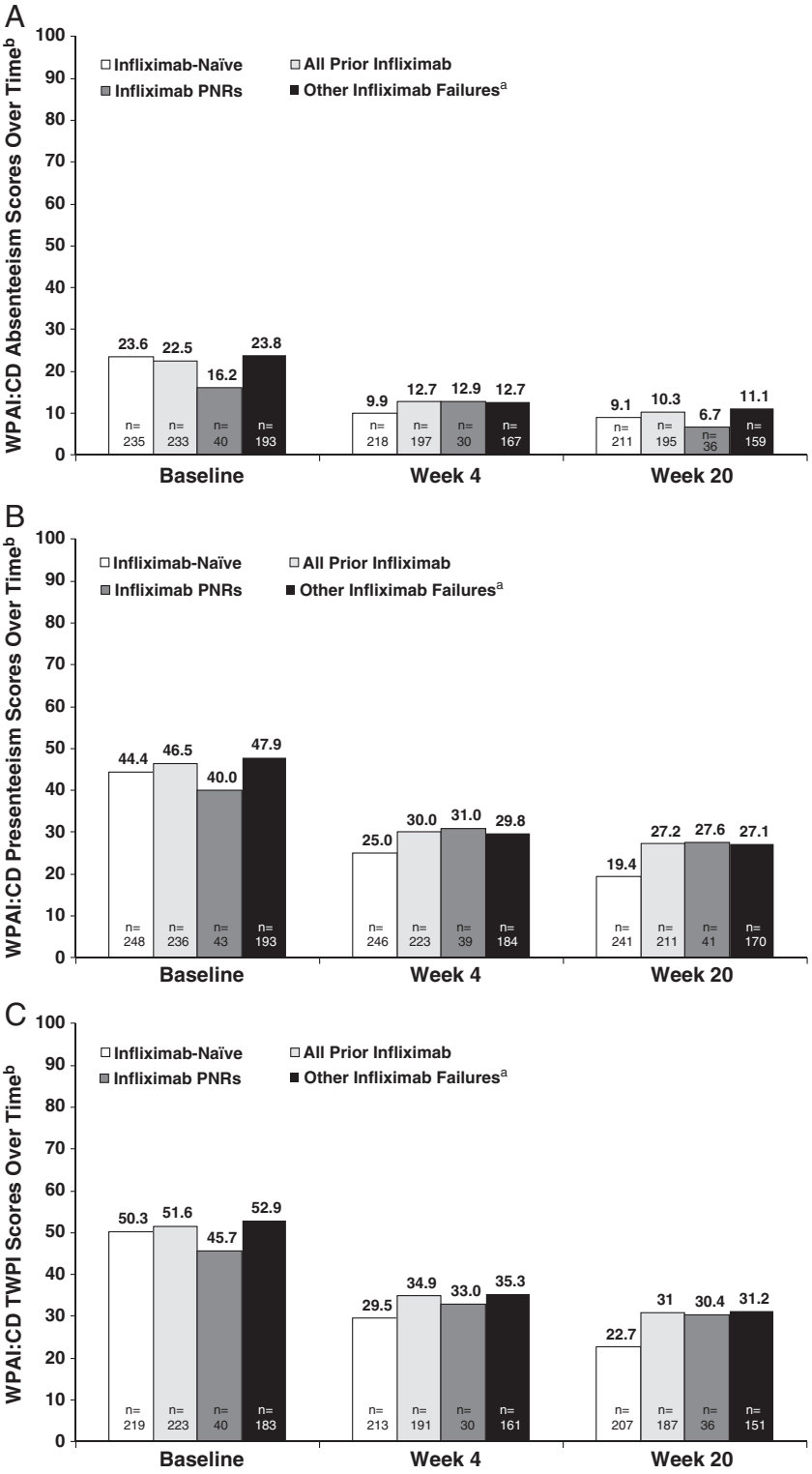

Figure 3 WPAI:CD Scores at Baseline, Week 4, and Week 20. (A) Absenteeism. (B) Presenteeism. (C) TWPI. (D) TAI. TAI, total activity impairment; PNR, primary non-responder; TWPI, total work productivity impairment; WPAI:CD, Work Productivity and Activity Impairment Questionnaire for CD. [a]Includes loss of response, intolerance/adverse events, and other/missing. [b]$p<0.05$ for mean absolute change from baseline, except for absenteeism at either time point for infliximab PNRs. Greater decreases in WPAI:CD component scores indicate lesser productivity/activity impairment.

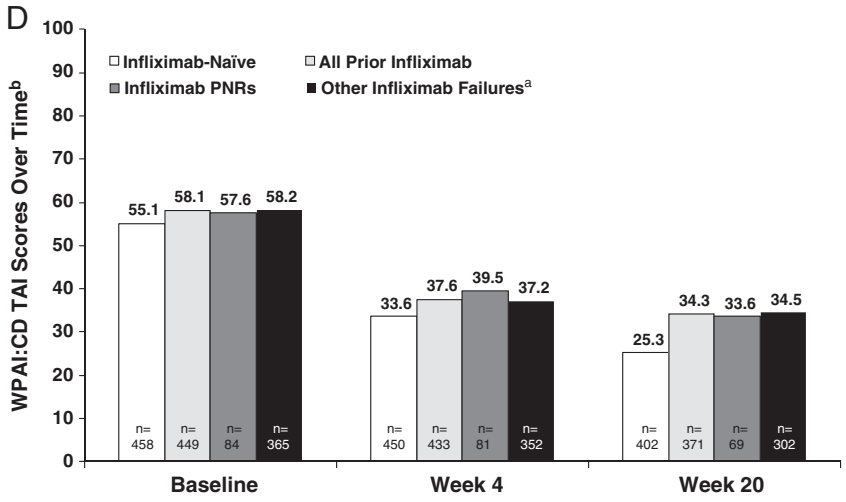

Figure 3 (*continued*).

21.4 points and impairment of daily non-work activities was reduced by 25.9 points (Table 2). By subgroup, SIBDQ improvements from baseline for infliximab-naïve patients and infliximab-exposed patients overall were both clinically and statistically significant at Weeks 4 and 20 (Fig. 2). Likewise WPAI:CD presenteeism, TWPI, and TAI showed clinically important decreases at Week 4 that were maintained at Week 20, even for infliximab PNRs (Fig. 3A–D); however, improvements in absenteeism for infliximab PNRs were not significant at either time point.

MCID response rates for TWPI in the infliximab-naïve group were 51% at both Week 4 and Week 20 (Fig. 4A). For infliximab PNRs, 33% met the MCID for TWPI at Week 4 and this percentage increased to 43% at Week 20. For TAI, MCID response rates were similar across subgroups at Week 4 (67%–68%) (Fig. 4B). The percentages of patients with clinically important TAI improvements decreased from Week 4 to Week 20 for all subgroups; infliximab-exposed patients had the lowest Week-20 TAI response rate (55%). With respect to disease-specific quality of life, the percentages of patients achieving the MCID at Week 20 ranged from 60% for the infliximab-naïve group to 47% for the infliximab PNR group (Fig. 4C).

3.3. Relationship between HBI and PROs

In a multiple linear regression model, 1 unit decrease in HBI from baseline to Week 20 was associated with a 1.8-point improvement in SIBDQ, a 3.4-point improvement in TAI, and a 3.8-point improvement in TWPI (Table 3).

3.4. Productivity-related indirect cost analysis

Estimated indirect cost savings during the study period, based on average WPAI:CD work productivity improvements at Week 20, are summarized for all adalimumab-treated patients and for the infliximab-naïve, infliximab-exposed, and infliximab PNR subgroups (Table 4). For all patients combined, TWPI improvements with adalimumab therapy (mean change of −21.4) translated into an estimated per-patient indirect cost savings of €2577, owing to reductions in CD-related work loss and productivity impairment. Results for absenteeism (mean change of −9.8) yielded an expected cost savings of €1180 from reduced work loss alone. By subgroup, estimated total indirect productivity-related cost savings were €3070 per infliximab-naïve patient compared with €2059 per patient who failed infliximab for any reason and €1336 per infliximab PNR.

4. Discussion

Reducing the negative impact of CD on patients' quality of life and reducing the overall economic burden associated with work disability and productivity impairment at work and in daily activities are increasingly important treatment goals. Unlike other studies that evaluated the effects of anti-TNF therapies on quality of life and productivity in patients with CD, which were randomized controlled clinical trials with more rigid inclusion/exclusion criteria,[4,13,14,16,23,24] CARE was designed to more closely approximate real-world clinical practice and provides the opportunity to assess patient-reported data from a large European cohort that included both infliximab-naïve and infliximab-exposed patients. Nevertheless, CARE did not have a control population and the results should be interpreted within that context.

Consistent with previous evaluations of PROs in patients with CD,[4,13–16,23,24] the CARE study population had poor HRQOL at baseline. With adalimumab therapy, significant improvements in disease-specific quality of life were observed for all subgroups analyzed. The mean changes in SIBDQ scores from baseline to Weeks 4 and 20 were both statistically significant and clinically important. Further, the improvement for infliximab-naïve patients was numerically greater than that for infliximab-exposed patients. The benefit observed in the infliximab PNR group suggests that adalimumab was effective regardless of prior experience with another anti-TNF agent. Recently published data from the WELCOME study demonstrated that certolizumab pegol was associated with improvements in WPAI:CD and Inflammatory

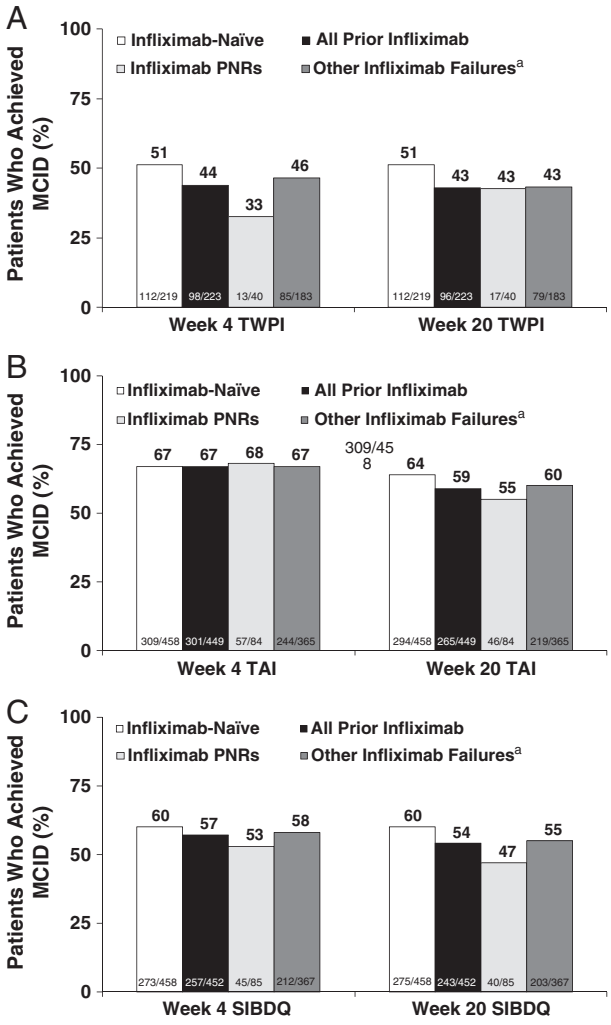

Figure 4 Percentages of patients achieving the MCID from baseline. (A) WPAI:CD TWPI. Included only employed patients who had no missing data at baseline. MCID defined as ≥7 percentage points. (B) WPAI:CD TAI. Included both employed and unemployed patients who had no missing data at baseline. MCID defined as improvement ≥7 percentage points. (C) SIBDQ. Included only patients who had no missing data at baseline. MCID defined as ≥9-point improvement. MCID, minimum clinically important difference; PNR, primary non-responder; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; TAI, total activity impairment; TWPI, total work productivity impairment; WPAI:CD, Work Productivity and Activity Impairment Questionnaire for CD. [a]Includes loss of response, intolerance/adverse events, and other/missing.

Bowel Disease Questionnaire scores in patients who had lost response or became intolerant of infliximab.[16] To our knowledge, however, the current study is the first to show such improvements in patients who never responded to infliximab.

The burden of disease-related work productivity loss translates to substantial costs to employers and society.[2,9–12] In the present study, patients' baseline work capacity was reduced by half, indicating extensive CD-related work productivity loss. Starting at Week 4 of adalimumab therapy, overall work productivity improved substantially for infliximab-naïve patients, infliximab PNRs, and patients who initially responded to infliximab and subsequently failed for other reasons; however, the mean changes from baseline were numerically less pronounced for the infliximab PNRs and these patients were the least likely to experience improvements absenteeism. The estimated 20-week indirect cost savings were greatest when adalimumab was administered as a first-line agent in infliximab-naïve patients. Nevertheless, substantial cost savings also were observed in the difficult-to-treat population of infliximab failures. Although the analysis included adalimumab-treated patients who were continuously employed throughout the study, the current cost analysis might underestimate the work-related indirect cost savings because the costs of unemployment were not factored in to the estimation. On the other hand, a limitation of the cost analysis was that medication costs for patients who required dosage increase to weekly therapy were not included; however, dosage increase prior to Week 20 occurred in only 14% of patients. The impact of productivity-related indirect costs should be taken into account when assessing the cost-effectiveness of treatment strategies for CD.

Table 3 Regression coefficients (β_1) for PRO scores at Week 20 related to a 1-point decrease in HBI from baseline. [a,b]

	SIBDQ	TAI	TWPI	Presenteeism	Absenteeism
β_1	−1.86 [c]	3.44 [c]	3.81 [c]	3.48 [c]	1.18 [d]

HBI, Harvey Bradshaw Index; PRO, patient-reported outcome; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; TAI, total activity impairment; TWPI, total work productivity impairment; WPAI:CD, Work Productivity and Activity Impairment Questionnaire for CD.

[a] Regression model: Week 20 PRO score = $\beta_0 + \beta_1 \times$ HBI reduction + other baseline covariates.

[b] Improvement is indicated by a negative parameter estimate for SIBDQ and a positive parameter estimate for WPAI:CD components (TAI, TWPI, absenteeism, and presenteeism).

[c] $p<0.0001$.

[d] $p<0.0005$.

The overall improvements in WPAI:CD components are consistent with other trials of anti-TNF agents.[13–16] One of the treatment goals in CD is to restore normal function in daily work-related and non-work activities, and data from CARE support the use of adalimumab in achieving this important goal. Significant reductions in the clinical symptoms of CD were demonstrated in CARE, in which 43% and 52% of patients achieved HBI remission (HBI <5) at Weeks 4 and 20, respectively.[17] Similar to studies that assessed the relationship between the Crohn's Disease Activity Index or the HBI and quality of life,[13,24,25] the improvements in quality of life and work productivity in the present study were closely associated with the benefits of adalimumab for intestinal symptoms, as measured by the HBI. The regression showed incremental benefits in quality of life and work productivity improvements with a 1-point reduction in HBI score from baseline. In addition, adalimumab therapy has been shown to lead to resolution of many commonly reported EIMs,[17]

Table 4 Estimated indirect cost savings based on average WPAI:CD work productivity improvements at Week 20.

WPAI:CD component	Estimated average 20-week cost savings in Euros (€) [a]			
	All adalimumab	Infliximab-naïve	All prior infliximab	Infliximab PNR
Absenteeism	1180	1469	867	494
Presenteeism	2408	2805	1975	1276
TWPI	2577	3070	2059	1336

PNR, primary non-responder; TNF, tumor necrosis factor; TWPI, total work productivity impairment; WPAI:CD, Work Productivity and Activity Impairment Questionnaire for CD.

[a] Estimated average cost savings per patient were calculated by multiplying the mean percentage improvement for the respective WPAI:CD component by €12,040, which represents the 20-week 2006 EU average annual gross income [(€31,302.1/52 weeks)×20 weeks = €12,040].[22]

and the relationship between EIMs and quality of life is a topic worthy of further exploration.

4.1. Summary

In summary, CARE provided data supporting disease-specific quality-of-life improvements and reductions in work productivity and daily activity impairment for patients receiving adalimumab in a large-scale, real-world, clinical cohort in Europe. Reductions in work productivity impairment with adalimumab may translate into substantial indirect cost savings per employed patient in the year following initiation of therapy. These benefits were observed in both anti-TNF failures, including PNRs, and infliximab-naïve patients, although the impact may be more pronounced for patients who were naïve to infliximab.

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