Efficacy and safety of adalimumab in Canadian patients with moderate to severe Crohn’s disease: Results of the Adalimumab in Canadian Subjects with Moderate to Severe Crohn’s Disease (ACCESS) trial

Remo Panaccione MD, Edward V Loftus Jr MD, David Binion MD, Kevin McHugh PhD, Shamsul Alam PhD, Naijun Chen MS, Benoît Guérette PhD, Parvez Mulani PhD, Jingdong Chao PhD

OBJECTIVE: To evaluate open-label adalimumab therapy for clinical effectiveness, fistula healing, patient-reported outcomes and safety in Canadian patients with moderate to severe Crohn’s disease (CD) who were either naive to or previously exposed to anti tumour necrosis factor (anti-TNF) therapy.

METHODS: Patients with moderate to severe CD (CD activity index [CDAI] score of greater than 220, or Harvey-Bradshaw index [HBI] of 7 or greater) were eligible. Patients received open-label adalimumab as induction (160 mg and 80 mg subcutaneously [sc]) at weeks 0 and 2, respectively and maintenance (40 mg sc every other week) therapy. At or after eight weeks, patients with flare or nonresponse could have their dosage increased to 40 mg sc weekly. Patients were followed for a minimum of six months or until adalimumab was commercially available in Canada.

RESULTS: Of the 304 patients enrolled, 160 were infliximab experienced, while 144 were anti-TNF naive. HBI remission (HBI score of 4 or lower) at week 24 was achieved by 53% of anti-TNF-naive and 36% of infliximab-experienced patients (P<0.01; P<0.001 for both groups for all visits versus baseline). Fistula healing rates at week 12 were 48% for anti-TNF-naive patients, and 26% for infliximab-experienced patients. At week 24, fistula healing rates were significantly greater for the anti-TNF-naive group (60% versus 28%; P<0.01). Improvements in quality of life and work productivity were sustained from week 4 to week 24 for all patients. Serious infections occurred in 2% of patients.

CONCLUSIONS: Adalimumab therapy induced and sustained steroid-free remission in both infliximab-experienced and anti-TNF-naive patients with moderate to severe CD. Clinically meaningful rates of fistula healing were also observed. Improvements in patient-reported outcomes were sustained throughout the 24-week study period.

Key Words: Adalimumab; Crohn’s disease; Fistula; Quality of life; Steroid-free remission; Work productivity

Crohn’s disease (CD) is a chronic inflammatory bowel disorder in which patients with active disease often experience debilitating abdominal pain, diarrhoea and fatigue. The incidence and prevalence rates of CD in Canada are among the highest in the world. In a comprehensive study of five Canadian provinces, Bernstein et al (1) estimated that the incidence rate and prevalence (1998 to 2000) were 13.4 cases per 100,000 person-years, and 233.7 per 100,000 population, respectively. With onset often during early adulthood (1,2), CD can have a lifelong impact on patients’ lives and their ability to work. Complications such as abscesses, fistulas, small bowel obstructions and infections can lead to CD-related hospitalization and/or surgery, which contribute to both the direct and indirect costs of the disease.

1University of Calgary, Calgary, Alberta; 2Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota; 3University of Pittsburgh, Pittsburgh, Pennsylvania, USA; 4Abbott Laboratories, Montreal, Quebec; 5Abbott Laboratories, Abbott Park, Illinois, USA; 6Abbott Laboratories, Rungis, France

Correspondence: Dr Remo Panaccione, Division of Gastroenterology, Department of Medicine, University of Calgary, Room 6D28, Teaching, Research and Wellness Building, 3280 Hospital Drive Northwest, Calgary, Alberta T2N 1N4. Telephone 403-592-5025, fax 403-592-5050, e-mail rpanacc@ucalgary.ca

Can J Gastroenterol Vol 25 No 8 August 2011 ©2011 Pulsus Group Inc. All rights reserved 419
Indirect costs attributed to work loss and reduced productivity constitute a significant percentage of the overall economic burden of CD (3,4). Ultimately, CD can result in work disability, particularly for patients who require hospitalization or experience severe pain (5-7). Daily functioning, emotional and social well-being, and overall quality of life (QoL) are also negatively affected in patients with CD (8-10), even during periods of inactive disease (11). Patients with active CD tend to experience greater levels of distress, health anxiety and perceived stress, less social support and poorer disease-specific QoL relative to patients with inactive disease (10).

Antitumor necrosis factor (anti-TNF) agents represent an important treatment option for managing clinical symptoms and disease activity in patients with moderate to severe CD; however, research regarding the impact of anti-TNF therapy on work productivity and QoL is limited. In CD, adalimumab, a fully human monoclonal antibody specific to TNF, is effective for inducing and maintaining remission in patients with moderate to severe disease who are naïve to or experienced with anti-TNF therapy (12-15). Here, we report the results of the open-label Adalimumab in Canadian Subjects with ModErate to Severe Crohn's Disease (ACCESS) trial, including the safety and clinical benefits of adalimumab therapy for inducing and maintaining steroid-free remission, maintaining fistula healing, and improving QoL and work productivity in Canadian patients with moderate to severe CD. The trial offers the opportunity to compare clinical outcomes for anti-TNF-naïve and infliximab-experienced patients in a real-world, clinical practice setting.

METHODS

Study design and patients

ACCESS was a phase III, multicentre, open-label study of patients with moderate to severe CD conducted at 42 sites in Canada from January 27, 2007, to January 10, 2008 (www.clinicaltrials.gov, NCT00427921). Patients who were either naïve to anti-TNF therapy or who failed infliximab therapy were eligible to participate in the study. Infliximab-experienced patients included primary nonresponders, those who lost response and those who developed intolerance as defined by the investigator.

Patients received open-label induction therapy of adalimumab 160 mg and 80 mg subcutaneously (sc) at baseline and week 2, respectively, followed by 40 mg sc every-other-week (eow) open-label maintenance dosing from week 4 onward. If flare or nonresponse (as determined by the investigator) occurred while the patient was receiving 40 mg sc eow, the regimen could be changed to 40 mg sc weekly at or after week 8. Patients were to remain in the study for a minimum of 24 weeks. Study enrollment was halted shortly after adalimumab was approved for CD in Canada on July 5, 2007. Adalimumab was provided to study participants until appropriate insurance coverage was secured. For individuals losing insurance coverage, compassionate drug coverage was, and continues to be, provided as required.

Main inclusion/exclusion criteria

Patients 18 years of age or older with a diagnosis of CD confirmed by radiology or endoscopy for at least four months before screening with moderately to severely active CD (CD activity index [CDAI] score of greater than 220, or Harvey-Bradshaw index [HBI] score of 7 or greater) were eligible for enrollment. Patients were required to demonstrate failure to previous therapies, which included 5-aminosalicylic acid, corticosteroids and immunosuppressants (IMMs) such as azathioprine, 6-mercaptopyrurine and methotrexate. Infliximab-experienced patients were required to have undergone a minimum eight-week washout period (before baseline). Concomitant treatment with 5-aminosalicylates, corticosteroids and IMMs was permitted.

Exclusion criteria were as follows: persistent chronic or active non-CD-related infections that required treatment with intravenous antibiotics, antivirals or antifungals within 30 days before baseline; or oral antibiotics, antivirals or antifungals within 14 days before baseline. Patients with any of the following were also excluded: history of malignancy, other than a successfully treated nonmetastatic cutaneous squamous or basal cell carcinoma and/or localized carcinoma in situ of the cervix; history of Listeria infection, HIV or any immunodeficiency syndrome, demyelinating disease, chronic viral hepatitis or untreated tuberculosis; poorly controlled medical conditions including uncontrolled diabetes with documented history of recurrent infections, unstable ischemic heart disease, congestive heart failure, recent cerebrovascular accidents and any other condition, which in the opinion of the investigator or the sponsor, would have put the patient at risk by participating in the study; current treatment with total parenteral nutrition; any previous exposure to natalizumab; treatment with any investigational agent in the past 30 days or five half-lives before screening (whichever was longer); history of clinically significant drug or alcohol abuse in the past year; and known hypersensitivity to the excipients of adalimumab. Pregnant or breastfeeding women and women who were considering becoming pregnant during the study were not eligible.

Assessments

The primary objective was to expand the safety database of adalimumab for the treatment of Canadian patients with moderately to severely active CD. Assessment of changes in patient-reported outcomes from baseline was a secondary objective. Efficacy assessments were performed at baseline, week 4, week 12 and week 24, and at 12-week intervals thereafter until study termination. End points included clinical remission and response as measured by the HBI, QoL as measured by the Short Inflammatory Bowel Disease Questionnaire (SIBDQ), and work productivity as measured by the Work Productivity and Activity Impairment Questionnaire (WPAI). Fistula healing was also evaluated.

Clinical assessments: The HBI is a simple tool that measures CD activity by assessing general well-being, degree of abdominal pain, frequency of diarrhea, presence of abdominal mass and the presence of complications of CD. HBI remission was defined as an HBI score of 4 or lower, while HBI response was defined as a point decrease of 3 or greater in the patient's baseline HBI score. Steroid-free remission, defined as HBI remission in the absence of concomitant steroid use, was also assessed for all patients who were receiving steroids at baseline. In addition, sustained steroid-free remission was defined as being in HBI remission and steroid free for at least 90 days. The impact of baseline IMM use was assessed by evaluating HBI remission for patients with and without IMM use at baseline. HBI remission and response rates were also calculated for patients who required dose intensification to weekly therapy, infliximab primary nonresponders and patients with elevated levels of C-reactive protein (CRP) (10 mg/L or greater at baseline). The number of draining cutaneous abdominal and perianal fistulas (on gentle compression) was counted during each physical examination. Complete fistula healing, defined as complete closure of all fistulas that were draining at baseline, was assessed for all patients with at least one draining fistula at baseline.

Patient-reported outcomes: The SIBDQ, a simple validated, 10-item instrument, was used to assess the impact of disease on health-related QoL (HRQoL) (16). The SIBDQ gauges HRQoL in four domains: systemic, social, emotional and bowel. Questions concern patients' symptoms resulting from CD, as well as general mood and feelings, experienced during the two weeks before the visit. Total SIBDQ scores range from 10 to 70, with higher scores indicating better HRQoL.

The WPAI is a validated, self-administered, six-item instrument that assesses the impact of disease on productivity (17). As adapted for CD (18), the WPAI measures four components related to a patient's ability to work and perform regular activities of daily life: absenteeism (ie, CD-related work time missed), presenteeism (ie, CD-related work productivity loss), total work productivity impairment (TWPI) (ie, a composite of absenteeism and presenteeism) and total activity impairment (TAI) (ie, impairment of daily nonwork activities). Unemployed patients answered only select WPAI questions related to employment status and ability to perform daily activities other than work.
Safety assessments
Safety was assessed at each visit through the evaluation of adverse events (serious and nonserious), laboratory parameters, physical examination results and vital sign measurements. In addition, adverse events were assessed (via telephone call) approximately 70 days after discontinuation of the study drug.

Statistical analysis
Effectiveness and safety data were analyzed using the intention-to-treat population, which comprised all patients who received at least one injection of adalimumab. Results were stratified according to previous exposure to infliximab (ie, anti-TNF-naive and infliximab-experienced patients).

Demographics and baseline clinical characteristics were summarized for each subgroup, and differences between anti-TNF-naive and infliximab-experienced patients were compared using Student’s t tests for continuous variables and χ² tests for categorical variables.

Clinical remission, steroid-free remission, clinical response and fistula healing were analyzed using nonresponder imputation (NRI) analysis, in which patients with missing data for the end point in question were considered to be treatment failures. McNemar tests were used to compare differences between the anti-TNF-naive and infliximab-experienced groups.

Mean SIBDQ total scores for each visit versus baseline were calculated using last observation carried forward and analyzed by paired Student’s t tests. A nine-point change in total anti-TNF-naive score is correlated with a 10-point change in CDAI score (16). The impact of adalimumab on productivity was determined by comparing WPAI end points at scheduled visits versus baseline using paired Student’s t tests (last observation carried forward analysis). WPAI scores were calculated as a percentage of overall impairment, with 0% indicating no CD-related impairment and 100% corresponding to total loss of work productivity/activity. The minimum clinically important difference (MCID) was defined as an absolute change of 7% or greater in the WPAI component score (19).

Ethics
The present study was conducted in accordance with the protocol, the International Conference on Harmonization guidelines, Good Clinical Practice guidelines and the Declaration of Helsinki. Independent ethics committees/institutional review boards provided approval for each of the centres participating in the trial. Each patient provided written informed consent before any study-related procedures were performed.

RESULTS

Patient sample
Demographics and clinical characteristics: Patient demographics and clinical characteristics of the 304 patients enrolled in ACCESS are summarized in Table 1. More than one-half of the population were female, baseline HBI scores were consistent with moderate to severe CD (mean = 12), and approximately one-half of all patients were receiving steroids and/or IMMs at baseline. Approximately 50% of patients were infliximab experienced (n=160).

The infliximab-experienced and anti-TNF-naive subgroups were similar in terms of CD severity and baseline CRP concentration (Table 1). Infliximab-experienced patients experienced a significantly greater median duration of CD (12.2 versus 7.4 years) and less aminosalicylate use (12% versus 32%) compared with anti-TNF-naive patients (both P<0.0001). At least one draining fistula was present in 27% of infliximab-experienced patients versus 17% of anti-TNF-naive patients (P<0.05). Baseline TWPI and TAI scores indicated substantial CD-related impairment for both subgroups. Likewise, baseline SIBDQ scores indicated that the study population experienced a relatively poor QoL.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Baseline demographics and clinical characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab experienced (n=160)</td>
<td>Anti-TNF-naive (n=144)</td>
</tr>
<tr>
<td>Female, %</td>
<td>55.0</td>
</tr>
<tr>
<td>Age, years, mean ± SD</td>
<td>37±12</td>
</tr>
<tr>
<td>HBI, mean ± SD</td>
<td>13±6</td>
</tr>
<tr>
<td>At least 1 draining fistula†, %</td>
<td>26.9</td>
</tr>
<tr>
<td>Steroid use, %</td>
<td>44.4</td>
</tr>
<tr>
<td>Immunosuppressant use, %</td>
<td>50.0</td>
</tr>
<tr>
<td>Aminosalicylate use, %</td>
<td>11.9</td>
</tr>
<tr>
<td>Disease duration, years, median</td>
<td>12.2</td>
</tr>
<tr>
<td>CRP, mg/L, mean ± SD</td>
<td>20±30</td>
</tr>
<tr>
<td>SIBDQ, mean ± SD</td>
<td>36±10</td>
</tr>
<tr>
<td>Employed at baseline, %</td>
<td>60.6</td>
</tr>
<tr>
<td>WPAI component scores‡, mean ± SD</td>
<td>60.6</td>
</tr>
</tbody>
</table>

*P values comparing infliximab-experienced versus antitumour necrosis factor (anti-TNF) groups (t tests were used for continuous variables except disease duration, while χ² tests were used for categorical variables. Disease duration was not normally distributed and, therefore, Wilcoxon’s signed-rank test was used); †The denominators for patients with at least one draining fistula at baseline were based on nonmissing data (one patient in the anti-TNF-naive group had missing baseline fistula count data); ‡Mean absenteeism, presenteeism and total work productivity impairment (TWPI) scores were determined for employed patients at baseline, whereas mean total activity impairment (TAI) scores were calculated using data from both employed and unemployed patients. CRP C-reactive protein; HBI Harvey-Bradshaw index; SIBDQ Short Inflammatory Bowel Disease Questionnaire; WPAI Work Productivity and Activity Impairment Questionnaire

Patient disposition
Nineteen per cent (31 of 160 patients) of infliximab-experienced patients discontinued the study compared with 13% (19 of 144 patients) of anti-TNF-naive patients (Figure 1). For both groups, adverse events were the most common reason for withdrawing from the study (14 patients [10%] anti-TNF naive, 19 patients [12%] infliximab experienced). CD and bowel obstruction were the most common adverse events in patients who withdrew from the study.

Effectiveness
HBI remission and response: Adalimumab therapy significantly improved HBI scores, with a mean change from baseline to week 24 of −6.4±5.03 (95% CI −6.96 to −5.75) for all patients. For all adalimumab-treated patients, the HBI remission rate increased from 27% at week 4 to 44% at week 24 (Figure 2A). For both anti-TNF-naive and infliximab-experienced subgroups, clinical remission rates at each visit from weeks 4 to 24 of adalimumab therapy were significantly higher compared with baseline. Starting at week 8, remission rates were significantly higher for anti-TNF-naive patients than for infliximab-experienced patients. At week 24, 53% of anti-TNF-naive and 36% of infliximab-experienced patients achieved clinical remission (P<0.01). For HBI response among all adalimumab-treated patients,
The table presents data comparing the effectiveness of adalimumab therapy in anti-TNF-naive and infliximab-experienced patients. The primary outcome measure was clinical remission (HBI score of 4 or lower) and steroid-free remission (HBI score of 4 or lower and off steroids for at least 90 days). The table shows that adalimumab was effective for inducing clinical remission and steroid-free remission in both groups, with higher remission rates observed at week 24 compared with week 4.

The table also highlights the importance of baseline immunosuppressant use, with higher remission rates observed in patients with no baseline immunosuppressant use. The use of adalimumab was associated with substantial improvements in work productivity and ability to perform daily nonwork activities, with clinically significant improvements observed in the overall population (mean visit values of 36 at baseline and 46 at week 4). These improvements were sustained through week 24.

The table further details the gastrointestinal and abdominal symptoms in patients treated with adalimumab, including the proportion of patients with no draining fistulas and anal ulcers at baseline and week 24. The table shows that adalimumab treatment led to a decrease in gastrointestinal and abdominal symptoms, with a greater proportion of patients achieving clinical remission and steroid-free remission at week 24 compared with week 4.

The table concludes with a summary of the patient-reported outcomes, including improvements in health-related quality of life (HRQoL) and symptoms specific to inflammatory bowel disease (IBD). The table shows that adalimumab treatment was associated with significant improvements in HRQoL, with clinically important improvements observed in the overall population (mean visit values of 36 at baseline and 46 at week 4). These improvements were sustained through week 24.
MCID, was observed at each time point for both the anti-TNF-naive and infliximab-experienced subgroups (all P<0.0001); the greatest changes in presenteeism were observed at week 24 (~25.5 points and ~25.7 points compared with baseline, respectively). At the final visit, 69% of patients (74% anti-TNF naive and 64% of infliximab-experienced) were employed compared with 64% at baseline (68% anti-TNF naive, 60% infliximab experienced). TAI scores improved by 69% of patients (74% anti-TNF naive and 64% infliximab-experienced) were employed compared with 64% at baseline (68% anti-TNF naive, 60% infliximab experienced). TAI scores improved by 3 to 4 times the MCID throughout the study, indicating less impairment in daily nonwork activities for both anti-TNF-naive and infliximab-experienced groups.

Safety

Adverse events: Overall, 80% of patients experienced at least one adverse event during the study (Table 2). Anti-TNF-naive patients experienced more obstructions of the small intestine compared with infliximab-experienced patients (eight patients [5.6%] and one patient [0.7%], respectively), which contributed to the greater rate of serious adverse events in the anti-TNF-naive group (17.4% versus 11.9%, respectively). Eight patients experienced serious infections: two in the infliximab-experienced group and six in the anti-TNF-naive group. For all except one patient with Legionella pneumonia and one patient with acute appendicitis in the anti-TNF-naive group, all serious infections involved abscesses. Four patients developed opportunistic infections, all of which were nonserious oral candidiasis. One infliximab-experienced patient, a 33-year-old man with a history of smoking, azathioprine use, stricture with small bowel resection and tuberculosis were reported.

DISCUSSION

The goals of therapy when treating a patient with CD should include the rapid induction of remission, steroid sparing and improvement in QoL. In addition, increased work productivity is important both to individuals and to society. Patients with fistulas experience a significant impact on QoL; therefore, fistula healing is paramount. QoL improvements should include increasing work productivity, ability to perform daily activities and emotional well-being. Previous controlled trials have shown adalimumab to be effective for inducing sustained...
remission and steroid-free remission (13), maintaining complete fistula closure (20) and improving HRQoL (21) in patients with moderately to severely active CD.

Results from the present open-label study, which was designed to reflect a real-world clinical practice setting in Canadian patients eligible to receive anti-TNF therapy for CD, are supportive of previous findings in both anti-TNF-naive and infliximab-experienced patients. Rates of clinical remission, steroid-free remission and fistula healing in ACCESS were similar to those observed at week 26 in the placebo-controlled, 56-week Crohn’s Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM) (13), in which 40% (32%) anti-TNF experienced and 47% anti-TNF naive) of randomized responders treated with adalimumab 40 mg eow were in remission. However, it is important to note that clinical remission in CHARM was defined as a CDAI score of less than 150, whereas in ACCESS, remission was defined as an HBI of 4 or lower. The week-26 fistula healing rate for the combined biotherapy-naive and infliximab-experienced population in CHARM was 30%, and 19% of patients receiving adalimumab eow therapy achieved sustained steroid-free remission at week 26 (13). When stratified according to baseline IMM use, week-26 remission rates in CHARM were 39% for patients with IMM use and 42% for those without IMM use (13).

Results from ACCESS were also consistent with those observed in Crohn’s Treatment with Adalimumab: Patient Response to a Safety and Efficacy Study, a study with a similar design conducted in Europe (22). In CARE, HBI remission rates at week 20 of open-label adalimumab therapy were 61% for anti-TNF-naive patients and 42% for infliximab-experienced patients; fistula healing rates were 33% and 22%, respectively; and remission rates at week 20 were similar regardless of baseline IMM use (55% with IMM use versus 49% without IMM use). Although clinical outcomes for anti-TNF-naive patients tended to be better than those for infliximab-experienced patients, patients who failed infliximab therapy achieved clinically significant improvements with subsequent adalimumab therapy (36% in HBI remission and 19% with complete fistula healing at week 20 [NRI analysis]). Approximately one-half of patients in ACCESS had failed treatment with infliximab; thus, this study supports the effectiveness of adalimumab in this difficult-to-treat population.

Patients in ACCESS had substantial HRQoL and productivity impairments at baseline, and adalimumab maintenance therapy was equally effective for improving patient-reported outcomes, as measured by the SIBDQ and WPAI, in both biologic-naive and infliximab-experienced patients. These results are consistent with those from other trials that investigated the impact of biologic therapy on HRQoL in patients with CD (21,23,24).

Recent estimates of the economic burden of CD in terms of direct medical costs and indirect costs to society (eg, work loss and workforce nonparticipation) in Canada are available in a report from the Crohn’s and Colitis Foundation of Canada (25). Total indirect costs of inflammatory bowel disease (IBD) are estimated to account for more than $1 billion of the estimated $1.8 billion total IBD-related costs, with the indirect costs of CD specifically accounting for $595 million (2008 $CAD) (25). Long-term work loss, out-of-pocket expenses and short-term work loss (eg, absenteeism) comprised the majority of these indirect costs. For patients with IBD, labour force nonparticipation was estimated to be 3% to 13% greater than that for the general public, and the burden of long-term work loss costs exceeded more than $1 billion of the estimated $1.8 billion total IBD-related costs, with the indirect costs of CD specifically accounting for $595 million (2008 $CAD) (25). Long-term work loss, out-of-pocket expenses and short-term work loss (eg, absenteeism) comprised the majority of these indirect costs. For patients with IBD, labour force nonparticipation was estimated to be 3% to 13% greater than that for the general public, and the burden of long-term work loss costs exceeded $746 million per year (2008 $CAD). Indirect medical costs of short-term work loss in Canadian patients with IBD were estimated to be approximately $138 million per year (2008 $CAD). These costs reflect that an estimated 43% of patients with IBD require disease-related time off from work (7.2 days per employed person with IBD per year).

Our analysis of work productivity, which used the recently validated CD-specific version of the WPAI (18), indicates that adalimumab can provide sustained improvement in overall work productivity for patients with moderately to severely active CD. Productivity outside of work was also substantially improved. A recent analysis from the Manitoba IBD Cohort Study reported that although employment rates for patients with IBD were similar to those for the community controls, patients with IBD reduced their daily and work activities and missed more work days (26). Furthermore, IBD-related sick leave has

## TABLE 2
Overview of adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Infliximab experienced (n=160) (PYs=60.7)</th>
<th>Anti-TNF naive (n=144) (PYs=62.8)</th>
<th>All adalimumab (n=304) (PYs=132.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (%)</td>
<td>Events (E/100 – PYs)</td>
<td>Positive (%)</td>
<td>Events (E/100 – PYs)</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>125 (78.1)</td>
<td>511 (733.1)</td>
<td>117 (81.3)</td>
</tr>
<tr>
<td>At least possibly related to study drug</td>
<td>79 (49.4)</td>
<td>172 (246.8)</td>
<td>65 (45.1)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>19 (11.9)</td>
<td>30 (43.0)</td>
<td>25 (17.4)</td>
</tr>
<tr>
<td>Leading to discontinuation of study drug</td>
<td>19 (11.9)</td>
<td>26 (37.3)</td>
<td>14 (9.7)</td>
</tr>
<tr>
<td>Fatal adverse event*</td>
<td>1 (0.6)</td>
<td>2 (2.9)</td>
<td>0</td>
</tr>
</tbody>
</table>

### Adverse events of interest

- **Infection**
  - 45 (28.1)
  - 73 (104.7)
  - 45 (31.3)
  - 63 (100.3)
  - 90 (29.6)
  - 136 (102.6)

- **Serious infection**
  - 2 (1.3)¶
  - 3 (4.3)
  - 6 (4.2)¶
  - 6 (9.6)
  - 8 (2.6)
  - 9 (6.8)

- **Injection-site reaction**
  - 35 (21.9)
  - 53 (76.0)
  - 22 (15.3)
  - 36 (57.3)
  - 57 (18.8)
  - 89 (67.2)

- **Hepatic disorder**
  - 2 (1.3)
  - 2 (2.9)
  - 3 (2.1)
  - 4 (6.4)
  - 5 (1.6)
  - 6 (4.5)

- **Opportunistic infection§**
  - 1 (0.6)
  - 1 (1.4)
  - 3 (2.1)
  - 3 (4.8)
  - 4 (1.3)
  - 4 (3.0)

- **Tuberculosis**
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0

- **Malignancy**
  - 0
  - 0
  - 1 (0.7)¶
  - 1 (1.6)
  - 1 (0.3)
  - 1 (0.8)

- **Lymphoma**
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0

- **Nonmelanoma skin cancer**
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0

- **Allergic-like reaction**
  - 2 (1.3)
  - 2 (2.9)
  - 0
  - 0
  - 2 (0.7)
  - 2 (1.5)

- **Congestive heart failure**
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0

- **Demyelinating disorder**
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0

- **Lupus-like syndrome**
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0

*One death (abdominal pain) was reported during the study. The patient died on day 56 (13 days after the final dose of adalimumab); ¶Abdominal abscess (n=1) and intra-abdominal pelvic abscess (n=1) in the infliximab-experienced group; §Intra-abdominal abscess (n=2), Legionella pneumonia (n=1), perianal abscess (n=1), right-sided ischiorectal abscess (n=1) and acute appendicitis (n=1) in the antitumour necrosis factor (TNF)-naive group; ¶All opportunistic infections were oral candidiasis; §Metastatic lung adenocarcinoma. E Events; PYs Patient years
been shown to have a greater negative impact on HRQoL than that of unemployment and work disability (27). These findings are important in the context of the potential for work and overall productivity improvements to offset a portion of any increases in direct medical costs for biologic therapies as well as to reduce work loss and workforce nonparticipation costs incurred by employers and patients.

Limitations of the present study include the relatively short 24-week duration, the open-label and uncontrolled design, and the fact that strict inclusion/exclusion criteria were not used. In addition, infliximab failure was determined by the investigator rather than by prespecified clinical criteria. Although the current study enrolled patients who were primary nonresponders to infliximab, the small sample size (approximately 15% of the study population) limited the ability to draw meaningful conclusions in this population.

SUMMARY

Adalimumab therapy induced and sustained steroid-free remission and led to clinically meaningful rates of fistula healing for both anti-TNF-naive and infliximab-experienced patients with moderate to severe CD. In addition, adalimumab therapy significantly improved HRQoL, increased work productivity, and decreased daily nonwork activity impairment. Improvements in all measures of disease activity and patient-reported outcomes were maintained throughout the 24-week study period. The overall safety profile in ACCESS was consistent with a recently published, comprehensive safety analysis of six adalimumab trials in patients with moderate to severe CD (28).

FINANCIAL DISCLOSURES: Dr Panaccione has served as consultant for Biogen Idec, Abbott, Ferring, Merck, Schering-Plough, Shire, Centocor Ortho Biotech, Elan, GlaxoSmithKline, UCB, Proctor and Gamble, and Bristol Myers Squibb; has served on the speaker’s bureau for Abbott, Axcan, Centocor Ortho Biotech, Elan, Schering-Plough, Shire, Prometheus, and Proctor and Gamble; has served on the advisory board for Abbott, Ferring, Schering-Plough, Shire, Elan, and Proctor and Gamble; and has received research/educational support from Abbott, Ferring, Axcan, Jansen, Schering-Plough, Centocor, Millennium, Elan, Proctor and Gamble, and Bristol Myers Squibb. Dr Lofus has consulted for Abbott, Centocor Ortho Biotech, Procter & Gamble and UCB, and received research support from Abbott, ActoGenX, Otsuka America, and UCB. Dr Binion has received grant support from Biogen, Centocor, Elan, National Institutes of Health, and Proctor & Gamble; and served on advisory boards for Abbott and UCB. Drs McHugh, Guérette, Mulani, and Chao, and Mr Chen are employees of Abbott Laboratories. Dr Alam was an employee of Abbott Laboratories when this research was conducted. Drs Mulani and Chao own Abbott stock.

ACKNOWLEDGEMENT: The ACCESS study and all data analyses were funded by Abbott Laboratories, Abbott Park, Illinois, USA. The authors thank Jimmy Baloukas from clinical operations at the Canadian Affiliate for project management. Cathryn M Carter MS, of Arbor Communications Inc, provided medical writing services in the development and revision of the manuscript; this support was funded by Abbott.

REFERENCES

Submit your manuscripts at http://www.hindawi.com