1.0 Abstract

Title

Impact of adalimumab on patient-reported outcomes (PROs) in Canadian patients with moderate-to-severe ulcerative colitis (UCanADA): a prospective observational cohort study

Keywords

Adalimumab, patient-reported outcome measures, real-life effectiveness, ulcerative colitis

Rationale and Background

The efficacy and safety of adalimumab have been demonstrated in pivotal trials but there remains a need to assess more holistically how the clinical results achieved translate into concrete improvements in key aspects of the daily lives of UC patients, such as symptoms, quality of life (QoL) and disability. Although some PROs from existing studies may have items capturing some of these aspects, no data is currently available for adalimumab in UC specifically on psychological distress/depression, disability, fatigue, pain or sleep quality in real-life setting.

It is expected that PROs will become increasingly important in the regulatory assessments of treatments in UC. There is limited information on a range of diverse humanistic outcomes in patients treated with biologic therapy within the same study setting. Therefore, there is a need to fully characterize 1) the impact of these treatments on the burden of UC, and 2) the humanistic outcomes that may be positively impacted by adalimumab treatment over more than 6 months.

Furthermore, the reimbursement landscape of biologic therapy for UC in Canada remains particularly difficult, with very limited reimbursement of biologic therapy. Few biologics are recognized as first-line therapy for UC, there is no public reimbursement available for other biologics, and biosimilars are increasingly

recognized as first-line therapies over biologics. A Canadian-specific study and subsequent availability of local data on a substantial cohort of moderate-to-severe UC patients allow for the generation of a rich database which may be leveraged for resubmissions and to facilitate future payer discussions of new products coming to the market. New data is also a prerequisite to re-approach certain Canadian decision-making bodies following negative reimbursement decisions.

The overarching goal for the UCanADA study is to assess the real-life effectiveness of adalimumab on PRO measures, while taking the opportunity to use the IBD Disability Index to assess the impact of adalimumab on key components of patients' functioning when affected with moderate-to-severe UC.

Research Question and Objectives

Primary objective:

- Evaluate the real-life effect on psychological distress/depression symptoms using change from baseline in the Patient Health Questionnaire (PHQ-9) following initiation of adalimumab in moderate-to-severe UC patients and after 1 year of treatment

Secondary objectives:

- Evaluate the real-life impact of adalimumab on disability using the IBD Disability Index (IBD-DI) in Canadian UC patients

- Assess the sensitivity to change of the IBD-DI in adalimumab-treated UC patients

- Evaluate the real-life effect of adalimumab on other PRO measures in moderate-to-severe UC patients, such as: fatigue, health-related quality of life, sleep impairment, and work productivity

- Evaluate the real-life effect on psychological distress/depression symptoms using change from baseline in PHQ-9 at week 8

- Determine the proportion of patients with PHQ-9 ≥10 at weeks 8 and 52

- Determine the real-life response and remission rates in moderate-to-severe UC patients treated with adalimumab at weeks 8 and 52

- Determine the correlation between effectiveness (clinical response and remission) rates and PRO measures

- Investigate the correlation between objective signs of disease activity (Fecal Calprotectin [FCal], endoscopy) and PRO measures

- Determine the correlation between Physician's Global Assessment (PGA) and PRO measures

- Determine if there is a difference in outcomes between bio-naïve and bio-experienced patients

Study Design

UCanADA was a single arm, 1-year multicenter Canadian post-marketing observational study (PMOS) utilizing a prospective cohort design to assess the real-life effectiveness of adalimumab on PRO measures in moderate-to-severe UC patients. The study was planned to have a 3.5-year enrolment period (approximately), with a 1-year observational period for a total duration of approximately 4.5 years. Assessments were performed during patients' routine care visit schedule, which was at the initiation of adalimumab (baseline), after induction (approximately 8 weeks), and 52 weeks after baseline. Additional optional assessments between weeks 8 and 52 were collected at least once but no more than two times during this period.

Setting

Patient historical data up to 6-month prior to baseline visit were collected. Although there were no study-specific requirements given the observational nature of the study, data were to be collected at approximately 8 and 52 weeks after baseline, coinciding with the patient's routine care visit schedule.

It was anticipated that some patients would be seen more frequently, in which case the site reviewed the patient's medical chart at the time of the visit where data was collected, to determine what, if any, information collected during the other routine care visits was appropriate for and needed to be entered into the case report form (CRF). Additional optional assessments between weeks 8 and 52 were collected at least once but no more than two times during this period.

Study patients were followed for up to 52 weeks. All study data were recorded in the patient's source documentation and collected on the appropriate CRF. Patient-reported outcome (PRO) instruments were evaluated using self-administered questionnaires. The variables to be collected during the study were listed in the CRF.

Patients and Study Size, Including Dropouts

Potential patients were assessed for their eligibility to participate in the study using the inclusion and exclusion criteria as follows.

To be eligible for study entry, each patient must have met all of the following inclusion criteria:

1. Provide voluntary written informed consent (patient authorization) for participation in the study, allowing use of their data for the study, and permission for contact by study personnel.

2. A male or female of ≥ 18 years of age.

3. A confirmed diagnosis of ulcerative colitis.

4. Objective evidence of moderate-to-severe disease activity, described by:

   a. a Mayo endoscopic subscore of 2 or 3 from endoscopic investigation in the previous 3-months closest to the baseline visit, OR

   b. a Mayo rectal bleeding subscore ≥ 2 and a fecal calprotectin value greater than 250 ug/gr.

5. Been prescribed adalimumab as part of their treatment by their treating physician.

6. If previously treated with vedolizumab or any anti-TNF agent (except adalimumab), an appropriate washout period has taken place per routine practice.

To be eligible for study entry, each patient must have not met any of the following exclusion criteria:

1. Previously received adalimumab.

2. Previously used infliximab or any anti-TNF agent and did not clinically respond at any time ("primary non-responder") unless they experienced a treatment limiting reaction.

3. History of subtotal colectomy with ileorectostomy or colectomy with ileoanal pouch, Kock pouch, or ileostomy for UC or planned bowel surgery.

4. Current diagnosis of indeterminate colitis, ulcerative proctitis only, or with a current diagnosis and/or have a history of Crohn's disease.

5. Other TNF immune-modulated disease.

6. Significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, cardiovascular, or hepatic disease that in the opinion of the investigator would adversely affect his/her participating in this study.

7. A female patient that is pregnant or breast-feeding.

8. Currently participating in another prospective study including controlled clinical trials.

One hundred patients, who provided written consent, were enrolled and formed the final study population. The enrolment period (i.e., time elapsed between first and last patient enrolled) was approximately 3.5 years. In total for the final analysis, 98 patients were included in the safety population, 94 patients were included in the intent-to-treat (ITT) population, and 48 patients were included in the completers population.

Variables and Data Sources

Primary variable:

- Change from baseline in depressive symptoms at week 52 as measured by the PHQ-9.

Secondary variables:

- Change from baseline in depressive symptoms at week 8 as measured by the PHQ-9.

- Change from baseline in the proportion of patients with PHQ-9 $\geq$ 10 at weeks 8 and 52.

- Change from baseline in the IBD Disability Index at weeks 8 and 52.

- Change from baseline in the EuroQol 5-Dimensions, 5 Levels (EQ-5D-5L) and EQ5D Visual Analogue Scale (EQ VAS) at weeks 8 and 52.

- Change from baseline in the Short Quality of Life in Inflammatory Bowel Disease Questionnaire (SIBDQ) at weeks 8 and 52.

- Change from baseline in the Functional Assessment Chronic Illness Therapy-Fatigue (FACIT-F) at weeks 8 and 52.

- Change from baseline in the Medical Outcomes Study Sleep (MOS Sleep) Scale at weeks 8 and 52.

- Change from baseline in the Work Productivity and Activity Impairment (WPAI) and Valuation of Lost Productivity (VOLP) at weeks 8 and 52.

Secondary clinical endpoint variables:

- Response and remission rates as assessed by the Simple Clinical Colitis Activity Index (SCCAI).

- Change from baseline in fecal calprotectin levels.

- Endoscopic improvement (Mayo endoscopic subscore) and/or improvement of Mayo rectal bleeding subscore (RBS) (as available) from baseline.

- Proportion of patients with complications, including hospitalization and surgery, at 52 weeks.

- Proportion of patients on steroids at 52 weeks.

- Change from baseline in PGA.

Safety variables: Adverse events (AEs), clinical laboratory results, and physical examinations.

Given that the primary objective of this study was not to assess any safety parameters, only spontaneously reported serious adverse events (SAEs), non-serious event of malignancy in patients 30 years of age and younger, AE leading to discontinuation of prescribed treatment under observation, unusual failure in efficacy and pregnancies were reported and collected.

Baseline information pertaining to socio-demographic, clinical, and environmental variables were collected based on the review of the patient at the baseline visit.

As this is a prospective cohort study, the data was collected throughout the study by use of the Case Report Form (CRF). The clinical information was filled by the investigator/clinical personnel. A section of the CRF was filled by the patients in order to collect the PRO information. This document was available in paper format for the sites to record the information mentioned above.

Results

One hundred patients were included in this final analysis, with 94 (94%) patients included in the efficacy population (also identified as the ITT population), 48 (48%) patients included in the completers' population, and 98 (98%) patients included in the safety population.

The primary endpoint – the proportion of patients who achieved a change from baseline, defined as an improvement in total severity score relative to baseline, in the PHQ-9 measure at week 52 – was 61.5% (40/65 patients; 95% CI: 49.7%, 73.4%) for the ITT population and 65.9% (29/44 patients; 95% CI: 51.9%, 79.9%) for completers.

The secondary endpoints that showed improvement from baseline were:

- Clinical endpoints: The proportion of patients who achieved a clinical response at Week 52, as measured by the SCCAI was 65.7% (44/73 patients) in the ITT population (85.4% [35/47 patients] in completers). Clinical remission at Week

52 was achieved in 47.8% (32/73) of patients in the ITT population and 73.2% (30/47 patients) in the completers population.

- Regarding the PRO instruments, significant improvements from baseline to Week 52 were shown for the IBD disability index, EQ-5D-5L, SIBDQ, FACIT-F, MOS Sleep and the WPAI.

- The odds of improving depressive symptoms for those achieving a clinical remission at Week 52 was 7.94 higher compared to those not achieving a clinical remission. (OR 7.94; CI: 1.42, 44.41; p=0.018).

The primary objective of this study was not to assess safety parameters. The key safety data collected were as follows:

- The median time in trial was 328.5 days (range: 3 – 663 days), and the median treatment duration was 323.0 days (range: 1 – 590 days) for the ITT population. For the completers population, the median time in trial was 395.0 days (range: 229 – 663 days), and the median treatment duration was 375.0 days (range: 216 – 590 days). No great variance was observed between the ITT population and safety population.

- No deaths were reported during the study.

- Only one report of basal cell cancer in a 63-year old male. There were no reports of malignancy in patients 30 years of age and younger during the study (as per protocol safety variable).

- Two (2.0%) patients experienced serious treatment-related adverse events that were assessed by the Investigator to be reasonably possibly related to adalimumab: 1 (1.0%) patient experienced two events of severe oesophagitis that led to hospitalization and prolongation of hospitalization, and one event of severe aggravated colitis that led to hospitalization; 1 (1.0%) patient experienced severe injection site pain.

- The proportion of patients with a C-reactive protein level within the normal range increased over time.

- Mean changes from baseline to each analysis visits in physical examination values were clinically unremarkable.

Discussion

UCanADA was a 1-year multicentre Canadian PMOS utilizing a prospective cohort design to assess real-life effectiveness of adalimumab on psychological distress/depression symptoms, disability, other PRO measures, and to determine correlations between PRO measures and objective signs of disease activity and response and remission rates in moderate-to-severe UC patients. This final CSR includes analyses initially planned in Protocol P15-325.

Marketing Authorisation Holder(s)

AbbVie Corporation

Names and Affiliations of Study Investigators

The study investigators were from 23 Canadian centers, as listed below.

Investigator	Affiliation