1.0 Abstract

Title

Canadian Humira Post Marketing Observational Epidemiological Study: Assessing Effectiveness in Ankylosing Spondylitis (COMPLETE – AS)

Keywords

Adalimumab; Effectiveness; Ankylosing Spondylitis; Post-Marketing Observational Study

Rationale and Background

Adalimumab (ADA) has been approved in Canada for the treatment of moderate to severe AS who are candidates for systemic therapy and have not responded or are intolerant to traditional disease modifying anti-rheumatic drugs (DMARDs). COMPLETE-AS was an observational study among biologic-naïve Canadian adults with active AS who were treated with ADA or non-steroidal anti-inflammatory drugs (NSAIDs/DMARDs). The study aimed to assess the real-life effectives of ADA in the management of AS compared to NSAIDs/DMARDs.

Research Question and Objectives

The primary objective was to compare the real – life effectiveness of adalimumab to NSAIDs and traditional non biologic DMARDs in the management, specifically the rates of occurrence or flare-up/exacerbation, of extra-articular manifestations of AS.

The secondary objectives were:

1. To describe the incidence, profile and predictors of extra-articular manifestations in Canadian AS patients.

2. To compare the real-life effectiveness of adalimumab to NSAIDs and non-biologic DMARDs in the prevention of the incidence and flare-up of extra-articular manifestations of AS.

3. To describe the profile and regional variation in terms of demographics, disease parameters, comorbidities, concomitant medication use, treatment, screening and management of extra-articular manifestations of Canadian patients with AS.

4. To describe the population-based burden of illness of AS and extra-articular manifestations in Canada in terms of quality of life, health care utilization, work productivity, health care costs, depression and psychological impairment.

5. To compare the effect of adalimumab, NSAIDs and non-biologic DMARDs and adalimumab on AS, associated extra-articular manifestations, related burden of illness in terms of quality of life, health care utilization, work productivity, health care costs, depression and psychological impairment in Canada.

6. To provide an ongoing assessment of the real – life safety and tolerability of adalimumab, NSAIDs and non-biologic DMARDs used in the management of AS under routine care in Canada.

Study Design

This was an observational study utilizing a prospective cohort design. Patients were enrolled at the time their AS treatment was changed for any reason and followed up for 24 months with recommended visits occurring at 3, 6, 12, 18, and 24 months after baseline visit.

Setting

Patients were enrolled from rheumatologist practices across Canada. Selection of physicians was done so that they were a random representation of the Canadian population and reflected the distribution of rheumatologists. A total of 56 sites were included from British Columbia, Alberta, Manitoba, New Brunswick, Newfoundland and Labrador, Nova Scotia, Ontario, and Quebec .

Subjects and Study Size, Including Dropouts

A total of 722 patients were enrolled in the study, specifically 213 (29.5%) in the NSAID/DMARD treatment group and 509 (70.5%) in the ADA treatment group. The safety population, defined as all patients who received at least one dose of study medication, consisted of 715 patients (212 [99.5% of patients enrolled in the NSAID/DMARD treatment group] and 503 [98.8% of patients enrolled in the ADA treatment group] in each treatment group, respectively). The ITT population, defined as all patients who received at least one dose of study medication and met all inclusion/exclusion criteria, consisted of 639 patients (187 [87.8%] and 452 [88.8%], respectively). Overall, 424 (66.4%) completed the study, whereby the main reasons for discontinuation were lost to follow-up for 114 (53.0% of discontinued patients) patients and consent withdrawal for 39 (18.1%) patients. Attrition was different between treatment groups, with 59.9% of NSAID/DMARD-treated patients completing the study compared to 69.0% of ADA-treated patients.

Variables and Data Sources

Variables assessed in this study included occurrence or flare-up/exacerbation of extra articular manifestations (EAMs), including uveitis, inflammatory bowel disease, psoriasis, and enthesitis of the heel, Bath AS Disease Activity Index (BASDAI), Bath AS Functional Assay (BASFI), Medical Outcome Study Short Form 12 (SF-12), Healthcare Resource Utilization (HCRU), Working Limitations Questionnaire (WLQ), Beck’s Depression Inventory (BDI), psoriasis and arthritis screening questionnaire

(PASQ), duration of morning stiffness, medical history, concomitant medications, and treatment compliance.

Results

Over the course of the study, ADA-treated patients had significantly lower rates of occurrence or flare-up/exacerbation of uveitis [RR (95% CI): 0.4 (0.2-0.6)] and enthesitis [0.4 (0.3-0.7)] compared to NSAID/DMARD-treated patients, but similar rates for IBD and PsO. In terms of EAM incidence, ADA-treated patients also had a significantly lower incidence of enthesitis [OR (95% CI): of 0.5 (0.3-0.9)], however the incidences of IBD, uveitis, and PsO were comparable with NSAID/DMARD-treated patients. In addition, ADA-treated patients had significantly lower risk of first occurrence for uveitis [HR (95% CI): 0.2 (0.0-0.8)] and enthesitis [0.5 (0.3-1.0)] compared to NSAID/DMARD-treated patients, but comparable risk for IBD and PsO first occurrence.

ADA-treated patients experienced significantly greater improvements in BASDAI and BASFI scores upon adjusting for potential confounders, and were also at higher odds of achieving most therapeutic thresholds, including BASDAI50 [OR (95% CI): 1.7 (1.2-2.3)], BASDAI<4 [1.8 (1.2-2.7)], minimal clinically important improvement (MCII) for BASDAI [1.9 (1.3-2.9)], and MCII for BASFI [1.6 (1.1-2.2)]. Furthermore, ADA-treated patients had a faster response to treatment, specifically with HRs (95% CI) as follows: 1.8 (1.1-2.8) for BASDAI50, 1.7 (1.6-3.6) for BASDAI<4, and 1.5 (1.0-2.3) for MCII for BASDAI. The time to achieving BASFI<3.8, MCII for BASFI, and MCII for SF-12 during the study, however, were statistically comparable between groups.

In terms of treatment retention, the Kaplan-Meier estimated mean time to initiating a bDMARD among NSAID/DMARD-treated patients was significantly shorter compared to the time to switching bDMARD among ADA-treated patients (25.2 vs. 32.8 months).

Regarding safety/tolerability, the overall incidence of AEs and SAEs was generally low although higher among ADA-treated patients compared to NSAID/DMARD-treated patients, specifically 0.9% vs. 9.9%, respectively for AEs and 0.9% vs. 8.2% for SAEs.

Discussion

ADA was more effective compared to NSAID/DMARDs at improving disease activity and functional status among patients with AS in a real-world setting and had improved treatment retention. Furthermore, ADA-treated patients were less likely to have occurrence or flare-up/exacerbation of uveitis and enthesitis. Finally, ADA was generally well tolerated and demonstrated a safety profile similar to that previously reported in the literature and the product monograph.

Marketing Authorisation Holder(s)

AbbVie Corporation

Names and Affiliations of Principal Investigators

A list of principal investigators and affiliations are presented in Appendix- Annex 3.