1.0 Abstract

Title

A Long-Term Non-Interventional Registry to Assess Safety and Effectiveness of Humira® (Adalimumab) in Subjects with Moderately to Severely Active Crohn's Disease (CD)

Keywords

Humira; adult; Crohn's disease; non-interventional; long-term safety

Rationale and Background

This registry, Registry P06-134, as well as the submission of this final report, is part of a postmarketing commitment from AbbVie to the United States (US) Food and Drug Administration and the European Medicines Agency. This postmarketing observational registry was designed to assess the long-term safety and effectiveness of Humira as used in routine clinical practice in adult patients with moderately to severely active CD who are candidates for anti-tumor necrosis factor therapy as recommended in the local product label. Each patient who consented to take part in the registry was to be followed for up to 6 years. Enrollment for this registry is complete. This final report provides cumulative, long-term safety and effectiveness data from the registry. The data collected in this registry are complementary to data from the preregistration studies of Humira in patients with moderately to severely active CD.

Objectives

The primary objective of this registry was to evaluate the long-term safety of Humira in adult patients with CD treated as recommended in the local product label. The secondary objective was to evaluate long-term effectiveness of Humira in adult patients with CD treated as recommended in the local product label.

The study was designed to rule out a doubling of the expected background rate of lymphoma in adult patients with CD treated with Humira in clinical practice.

Study Design

This is a multi-center, uncontrolled, observational registry of adult patients with moderately to severely active CD treated with Humira in a routine clinical practice setting.

Setting

Approximately 450 physicians were expected to participate in this registry by enrolling patients whom they had previously decided to treat with Humira. Of these 450 physicians, approximately 185 were to be included as investigators based on their participation in prior AbbVie-sponsored clinical development studies and 265 physicians were to be included based on their eligible patient population.

Patients and Study Size, Including Dropouts

Approximately 5,000 patients in the US, Canada, the European Union, South Africa, Australia, and New Zealand were to be enrolled. The sources for patients included:

- Patients who were newly prescribed Humira therapy; i.e., patients who had never been treated with Humira.
- Patients who were current participants in AbbVie sponsored investigational CD trials who were currently receiving Humira and for whom the treating physician made the decision to continue with Humira therapy beyond the duration of the investigational trial.
- Patients who were prior participants in AbbVie sponsored investigational CD trials and did not have dose interruptions since the last dose of Humira received in the trial and the Investigator provided source documentation of dosing information.
- Patients who were currently receiving Humira, as per the local product label, who did not have dose interruptions since the induction dose of Humira and the Investigator provided source documentation of dosing information.

A total of 5061 patients were enrolled in the registry. The data from 36 patients were excluded from the analyses due to non-compliance at a US site. Therefore, the data from 5025 patients were analyzed in this final report. Of note, among the 5025 patients, there were 34 patients with unsigned casebooks in spite of efforts to obtain physician signatures. A sensitivity analysis was performed in which the data from the 4991 patients with signed casebooks was compared with the data of the 5025 patients that included 34 patients with unsigned casebooks. The results of this comparison confirmed that the data from these 34 patients did not significantly alter the overall study results and conclusions.

Overall, a total of 3478/5025 patients (69.2%) in the all treated population discontinued Humira or the registry.

Variables and Data Sources

Included in this final report:

- Serious adverse events (SAEs) and adverse events (AEs) of special interest
- Effectiveness data including: Short Inflammatory Bowel Disease Questionnaire (SIBDQ), Work Productivity and Activity Impairment: Special Health Problem (WPAI:SHP), and Physician's Global Assessment of disease activity (PGA).

Final Registry Results

The database for Registry P06-134 was open and dynamic until database lock, which occurred shortly after the end of data collection on 04 February 2016. Therefore, if new information was received, the event details may have changed from the 7th interim report. In this final report, Medical Dictionary for Regulatory Activities (MedDRA) Version 18.1 Lowest Level MedDRA Queries were used without further adjudication.

This completed international registry was conducted in 5025 adult patients with CD who accumulated 16,680 patient-years (PYs) of exposure to Humira, not including the use of Humira prior to registry enrollment in clinical trials or by commercial prescription. The majority of patients (88%) were not prior participants in Humira clinical trials. Prior anti-tumor necrosis factor (TNF) or biologic use was present in 56.8% of patients. Most patients were Caucasian (96.4%), the mean age ± SD was 37.8 ± 12.7 years and 43.1% of patients had ≥ 10 years of disease duration. Participants were encouraged to remain in the registry during interruption or discontinuation of Humira therapy. Some patients who discontinued the registry were re-enrolled to continue their long-term observation, as outlined below.

At the request of the European Medicines Agency (EMA), the registry protocol was amended (Amendment 2; Section 9.1) to provide a process for gathering vital status data on patients who became lost to follow up or discontinued the registry prior to the full 6 years of observation time. The process included a revised consent form that allowed information gathering under these circumstances. Active registry participants were re-consented; patients who then discontinued the registry could be contacted by the site for this information. Re-consented patients who were then lost to follow-up had their information submitted by a third-party vendor (ProClinica) to the National Death Index (NDI) database, which has statistics and details on the deaths of US citizens. In addition, sites outside of the US were instructed to search national/regional vital registries when available and allowed by local regulations.

A number of patients discontinued the registry prior to the implementation of Amendment 2. Therefore, they could not give permission for vital status data collection. In an effort to include the data from these patients, AbbVie contacted the sites' Ethics Committees and requested approval to collect their vital status information. However, AbbVie did not request that the sites pursue information on (1) patients who had withdrawn consent because they did not want to be contacted or (2) patients who were lost to follow-up because the site had no information on how to reach them.

If the sites' Ethics Committee granted approval, the site personnel contacted discontinued patients, obtained consent, collected vital status data and entered it into the registry database. The results of vital status collection and the NDI search are included in Section 10.6.3.

The Humira registry exposure of 16,680 PYs exceeded the required 15,180 PYs needed to provide 90% power to rule out a doubling of the expected background lymphoma rate of 0.084 events (E)/100 PYs. The expected background lymphoma rate was based on a weighted average of background lymphoma rates of patients with and without prior thiopurine use. The final observed registry exposure-adjusted lymphoma rate was 0.060 E/100 PYs, which is lower than the expected background rate of 0.084 E/100 PYs. The upper bound of the 1-sided 95% confidence interval (CI) of the observed lymphoma rate was 0.102 E/100 PYs. Since the upper bound of the 1-sided 95% CI fell below 0.168 E/100 PYs (double the assumed background rate of 0.084 E/100 PYs), the registry reached the goal of ruling out a doubling of lymphoma risk in patients with CD treated with Humira.

A total of 36.9% (1853/5025) of patients reported at least 1 registry treatment-emergent (TE) serious adverse event (SAE). The registry exposure-adjusted SAE rate was 24.8 E/100 PYs.

Registry treatment-emergent adverse events (TEAEs) leading to permanent discontinuation of Humira were reported in 596 patients (11.9%, 4.6 E/100 PYs). Registry TEAEs leading to permanent discontinuation in 296 patients were considered to be possibly or probably related to Humira by the physician.

No patients reported Hepatosplenic T-cell lymphoma (HSTCL), glioblastoma, Merkel Cell carcinoma, Waldenström's macroglobulinemia, reactivation of hepatitis B, progressive multifocal leukoencephalopathy (PML), or Humira administration-related medication errors. Stevens-Johnson syndrome (SJS) and reversible posterior leukoencephalopathy syndrome (RPLS) were reported in 1 patient each as non-treatment-emergent events.

The observed TEAEs of special interest during the registry included:

- 855 patients (17.0%) reported infections (8.0 E/100 PYs).
- 556 patients (11.1%) reported serious infections (4.7 E/100 PYs).
- 1 patient (< 0.1%) reported a Legionella infection (< 0.1 E/100 PYs).
- 19 patients (0.4%) reported an opportunistic infection (0.1 E/100 PYs).
- 9 patients (0.2%) reported oral candidiasis (< 0.1 E/100 PYs).
- 17 patients (0.3%) reported tuberculosis (TB) (0.1 E/100 PYs). Of these, 10 patients (0.2%) reported active TB (< 0.1 E/100 PYs) and 7 patients (0.1%) reported latent TB (< 0.1 E/100 PYs).
- 4 patients (< 0.1%) reported parasitic infection (< 0.1 E/100 PYs).
- 6 patients (0.1%) reported diverticulitis (≤ 0.1 E/100 PYs).
- 116 patients (2.3%) reported malignancy (0.8 E/100 PYs).
- 11 patients (0.2%) reported melanoma (< 0.1 E/100 PYs).
- 10 patients (0.2%) reported lymphoma (< 0.1 E/100 PYs).
- 3 patients (< 0.1%) reported leukemia (< 0.1 E/100 PYs).
- 36 patients (0.7%) reported non-melanoma skin cancer (NMSC) (0.3 E/100 PYs).
- 60 patients (1.2%) reported malignancy other than lymphoma, HSTCL, NMSC, melanoma, and leukemia (0.4 E/100 PYs).
- 29 patients (0.6%) reported systemic lupus erythematosus and lupus-like reactions (0.2 E/100 PYs).
- 1 patient (< 0.1%) reported sarcoidosis (< 0.1 E/100 PYs).
- 30 patients (0.6%) reported allergic reactions (0.2 E/100 PYs); 9 patients reported serious allergic reactions.
- 11 patients (0.2%) reported vasculitis (4 non-cutaneous, 7 cutaneous) (< 0.1 E/100 PYs).
- 13 patients (0.3%) reported myocardial infarction (< 0.1 E/100 PYs).
- 11 patients (0.2%) reported cerebrovascular accident-related AEs (< 0.1 E/100 PYs).

- 3 patients (< 0.1%) reported congestive heart failure-related AEs (< 0.1 E/100 PYs).
- 13 patients (0.3%) reported pulmonary embolism-related AEs (< 0.1 E/100 PYs).
- 4 patients (< 0.1%) reported interstitial lung disease (< 0.1 E/100 PYs).
- 1 patient (< 0.1%) reported primary lateral sclerosis, which is a non-clinially definitive event of ALS but not a diagnosis.
- 27 patients (0.5%) reported intestinal perforation-related AEs (0.2 E/100 PYs).
- 475 patients (9.5%) reported an intestinal stricture-related AE (3.5 E/100 PYs).
- 17 patients (0.3%) reported pancreatitis (0.1 E/100 PYs).
- 92 patients (1.8%) reported worsening and/or new onset of psoriasis (0.6 E/100 PYs).
- 1 patient (< 0.1%) reported erythema multiforme (< 0.1 E/100 PYs).
- 8 patients (0.2%) reported demyelinating disorder-related AEs (< 0.1 E/100 PYs).
- 64 patients (1.3%) reported hematologic events (0.4 E/100 PYs).
- 13 patients (0.3%) reported liver failure or another liver event (< 0.1 E/100 PYs).
- 12 patients (0.2%) reported injection site reactions (0.1 E/100 PYs).

All evaluations of effectiveness showed improvement over time.

Discussion

This completed international registry was conducted in 5025 adult patients with CD who accumulated 16,680 PYs of exposure to Humira, not including the use of Humira prior to registry enrollment in clinical trials or by commercial prescription. Humira was well tolerated; the AEs reported were consistent with the established Humira safety profile. No patients reported HSTCL, glioblastoma, Merkel Cell carcinoma, Waldenström's macroglobulinemia, reactivation of hepatitis B, PML, or Humira administration-related medication errors. SJS and RPLS were reported in 1 patient each as non-treatment-emergent events.

The sample size of this study was calculated to rule out the doubling of the expected rate of lymphoma in patients with moderate to severe CD treated with Humira in clinical practice. The estimated registry background lymphoma rate was based on several assumptions. Firstly, patients with CD not treated with thiopurine were assumed to have a lymphoma rate similar to the general population of 0.0263 E/100 PYs for patients between 15 – 76 years of age according to the SEER 17 Registry database.[9] This rate was sex-adjusted to match the Crohn's disease population, which is approximately 60% female. Secondly, patients with thiopurine treatment would have a lymphoma rate approximately 4 times higher than patients not exposed to thiopurines (0.1052 E/100 PYs, which is 4 times 0.0263 E/100 PYs). Thirdly, 73% of the CD registry patients were assumed to have a history of thiopurine exposure while the remaining 27% of the patients would not have used thiopurines. The assumed background lymphoma rate for the registry population was therefore based on a weighted average of these two lymphoma rates; 0.084 E/100 PYs (73%*0.1052 E/100 PYs + 27%*0.0263 E/100 PYs = 0.084 E/100 PYs).

Calculations yielded that at least 15,180 PYs were required to provide a 90% power to rule out a doubling of the background lymphoma rate of 0.084 E/100 PYs at a 1-sided type I error rate of $\alpha = 5\%$ and the required sample size to gather this amount of PYs with a planned up to 6 years of follow-up per patient was determined by factoring in the estimated attrition rate from the registry. The final Humira registry exposure of 16,680 PYs exceeded the required 15,180 PYs. Furthermore, the final registry sex ratio (57.1% female) and prior thiopurine use (78.2%) were similar to the predicted 60% female and 73% thiopurine exposure used for the estimation of PYs required.

There were 10 treatment-emergent events of lymphoma during the registry. There were no non-treatment-emergent lymphoma events reported. Nine of the 10 patients had prior treatment with thiopurines; 3 of these 9 patients were receiving thiopurine at enrollment and were still being treated with thiopurine at diagnosis. Conversely, 6 of the 9 patients with lymphoma who had prior thiopurine use were not taking thiopurine during registry participation. The 10 lymphoma events were of 7 different types;

2 each of Hodgkin's lymphoma, Non-Hodgkin's lymphoma, and B-cell lymphoma; 1 each of T-cell lymphoma, follicle center lymphoma, metastatic lymphoma and mycosis fungoides. Using the most conservative registry exposure time (16,680 PYs) the registry-exposure adjusted lymphoma rate for these patients with CD was 0.060 E/100 PYs. The upper bound of the 1-sided 95% CI of this rate was 0.102 E/100 PYs, which was below 0.168 E/100 PYs (double the background rate of 0.084 E/100 PYs). Thus, a doubling of lymphoma risk in patients with CD treated with Humira was ruled out. The lymphoma rate adjusted for the overall Humira exposure, including registry and prior clinical trial exposure of 17,765 PYs, was 0.056 E/100 PYs.

A total of 69 deaths were reported; during registry participation 63 deaths occurred, of which 43 were treatment emergent and 20 were non-treatment emergent, and an additional 6 deaths were reported after patients had discontinued from the registry via above mentioned vital status data collection and National Death Index (NDI) search. The overall death rate during the registry (N = 63) was 0.38 E/100 PYs based on registry exposure of 16,680 PYs. The treatment-emergent mortality rate in the TREAT registry of infliximab treated patients with CD was 0.58 E/100 PYs based on 14,184 PYs of exposure,[10] which was higher than the rate observed in Registry P06-134, even though the 0.38 E/100 PYs rate from Registry P06-134 described above included deaths that were not treatment-emergent. The Standard Mortality Ratio (SMR) for treatment-emergent deaths in the registry was calculated based on the expected death rate in an age and sex matched adult general population. For details on the SMR calculation see the statistical analysis plan (SAP) Version 2.0 in Annex 4. The registry SMR of 0.88 with 95% CI [0.63, 1.18] was calculated from registry treatment-emergent deaths (N = 43) and the overall Humira exposure, including prior exposure in clinical trials (17,764.7 PYs). The SMR calculated based on treatment-emergent deaths and overall Humira exposure did not exceed 1.00, indicating that the observed death rate was consistent with the expected rate for an age and sex matched adult general population.

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