1.0 Abstract

Title

Post-marketing Observational Study to Evaluate the Effectiveness and Patient-Reported Outcome of Adalimumab in Patients with Moderate to Severe Plaque Psoriasis in China (ADAPT)

Keywords

Adalimumab, Plaque Psoriasis, Effectiveness and Patient-Reported Outcome

Rationale and Background

Psoriasis is an immune-mediated chronic, recurrent, inflammatory, and systemic disease induced by a combination of genetics and environment, with typical clinical manifestations of scaly erythema or plaques, being localized or widely distributed, non-infectious, difficult to treat, and often lifelong. The etiology of psoriasis involves various factors such as genetics, immunity, and environment, and it cause excessive proliferation of keratinocytes or inflammation of joint synoviocytes and chondrocytes through immune responses mainly mediated by T lymphocytes and involving a variety of immune cells. The treatment regimen of psoriasis should be determined according to the patient's symptoms, mild topical treatment is the main treatment, systemic treatment can be used for moderate to severe cases, and targeted biological agents can be appropriately selected for patients with poor response to traditional systemic drug therapy. The treatment of psoriasis is based on controlling symptoms and improving the quality of life of patients.

Adalimumab as a fully human monoclonal antibody against TNF-α, has received approval in China for treatment of chronic plaque psoriasis, the efficacy and safety of adalimumab in Psoriasis have been well evaluated in Study M13-606 with strict inclusion criteria as well as exclusion criteria. Therefore, the effectiveness and safety in a wider psoriasis patient population in real-world clinical practice would be a major concern in China after launch. To examine these questions, this open-label, multicenter, observational study in China was designed to demonstrate Adalimumab's effectiveness in psoriasis patients, as prescribed according to the local product label. The results from this study are expected to help better understand the effects of Adalimumab use in real-world practice, and generate more comprehensive local data to support the government’s initiative to establish cost-

efficacy/cost-effectiveness evaluation to innovative medicines in China as we can provide information based in real world data generated in Chinese patients in China.

Research Question and Objectives

To evaluate the effectiveness, safety, patient-reported outcomes and healthcare resource utilization of Adalimumab for the treatment of moderate to severe plaque psoriasis in daily clinical practice in China.

Study Design

This study was designed as a prospective, observational study to assess the effectiveness, safety and patient reported outcomes or healthcare resource utilization of Adalimumab in patients with moderate to severe plaque psoriasis in China.

Patients with moderate to severe plaque psoriasis, for whom Adalimumab treatment had already been decided as per local label, were recruited from within the clinical settings of each dermatologist participating in the study. It was planned to enroll approximately 181 patients diagnosed with moderate to severe plaque psoriasis from 15 sites who met the inclusion criteria and none of the exclusion criteria into this study.

To determine efficacy, the patients were assessed for their psoriasis area and severity index (PASI) 50, PASI 75, PASI 90, PASI 100, dermatology life quality index (DLQI), and physician's global assessment (PGA) (0/1) responses, based on the data collected at baseline and through clinic visits at Week 3, 12, 24, and 36 after the start of treatment with Adalimumab. Study visits in the first 12 weeks as well as after the 12 weeks were defined as the nearest clinic visit ±2 weeks of the study-defined time point. In addition, patient-reported outcomes (PROs) related to work activities and health, including the DLQI and European Quality of Life - 5 Dimensions (EQ-5D), and healthcare resource utilization (HCRU) were also evaluated at baseline, Week 3, 12, 24, and 36. HCRU includes medication, hospitalization, length of hospital stay, physician consultation, etc.

Setting

This study took place in China with multiple sites. The study sites were identified and selected by AbbVie. The study population comprised of male and/or female adult patients who attended a routine clinical visit and met all of the inclusion criteria and none of the exclusion criteria. Overall, eligible 181 patients with clinically diagnosed as moderate to severe plaque psoriasis were planned to be enrolled in the study across around 15 sites.

The recruiting investigators enrolled potentially eligible patients from consecutive visits within their clinic based on the inclusion and exclusion criteria. It was the responsibility of each physician to ask every patient who met the inclusion criteria of the study to participate to avoid selection bias, and if investigators held different types of clinics (e.g. routine visit clinics versus emergency clinics), only patients visiting their routine clinics would be selected. Site personnel should thoroughly assess the eligibility criteria and evidence of this should be stored with the source documentation at site.

Where there was any deviation from the inclusion/exclusion criteria, the patient should be excluded from the study.

A total of 11 clinical study sites in China were included in this study, with the site ID and names specified below.

Site ID	Site Name
01	Rui Jin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine
03	Shenzhen Hospital of Southern Medical University
04	First Affiliated Hospital of Shantou University Medical College
05	Shenyang Seventh People's Hospital
07	Shanghai Tenth People's Hospital
10	Dermatology Hospital of Southern Medical University (Guangdong Provincial Dermatology Hospital)
13	Sir Run Run Shaw Hospital Affiliated to Zhejiang University School of Medicine
16	Shandong Provincial Hospital of Dermatology
19	The Second Affiliated Hospital Zhejiang University School of Medicine
20	Institute of Dermatology, Anhui Medical University
23	Traditional Chinese Medicine Hospital of Xinjiang Uygur Autonomous Region

Patients and Study Size, Including Dropouts

Based on the results from the Chinese Phase III trial, the PASI 75 response rate was about 77.8% at Week 12 in Adalimumab arm (the dropout was considered for estimation). In order to achieve a precision of 14% in the final confidence interval (CI) for the PASI 75 response rate, a sample size of 136 would be required if a response rate of 77.8% was to be estimated as the assumed true point, i.e., +/- 7% for the point estimate of 77.8%. The sample size was expanded to 181 to maintain the same precision considering a 25% drop-out rate.

A total of about 181 eligible patients were planned to be enrolled in this study from 15 sites in China, and a total of 153 eligible patients were actually enrolled in 11 sites. Of all patients enrolled, 97 patients (63.4%) completed the trial, 56 patients (36.6%) prematurely discontinued from the study.

Variables and Data Sources

Variables

Primary Variable

- Proportion of patients with at least 75% reduction in PASI score from baseline at Week 12.

Key Secondary Variable

- Change from baseline in DLQI at Week 12.

Other Secondary Variables

- Proportion of patients achieving PASI 50/75/90/100 response at Week 3, 12, 24 and 36.

- Change from baseline in PASI score at Week 3, 12, 24 and 36.

- Percent of patients achieving minimal clinically important difference (MCID) of the DLQI in change from baseline to Week 3, 12, 24 and 36.

- Proportion of patients achieving PGA 0/1 at Week 3,12, 24 and 36.

- Adverse events of special interest (AESIs) and serious adverse events (SAEs).

Exploratory Variables

- Change from baseline in EQ-5D at Week 3, 12, 24 and 36.

- HCRU at baseline, Week 3, 12, 24 and 36.

- Change in PASI score at Week 36 after the initiation of Adalimumab, in those patients continuing on Adalimumab, compared with those patients not continuing on Adalimumab.

- Change in DLQI at Week 36 after the initiation of Adalimumab, in those patients continuing on Adalimumab, compared with those patients not continuing on Adalimumab.

Data Sources

The main data sources for this study were case report forms (CRFs) and patients' questionnaires. Data collected during the study included, but were not limited to patients' demographics, clinical history, comorbidities, reported adverse events and concomitant medications. The questionnaires including DLQI, EQ-5D, and HCRU were utilized to collect data directly from enrolling patients, as applicable.

This was a non-interventional, observational study. Unlike clinical trials, the available data from this study were limited and there was a possibility of missing data.

Results

Analysis of Primary Endpoint

The results of the primary analysis showed that of the 151 patients in the full analysis set (FAS), 90 patients achieved PASI 75 response at Week 12, with a response rate of 59.6%; the results of the sensitivity analysis showed that of the 150 patients in the per protocol set (PPS), 90 patients achieved PASI 75 response at Week 12, with a response rate of 60.0%.

Analysis of Secondary Endpoints

PASI Analysis

The mean (±standard deviation [SD]) PASI score and change from baseline for patients at Visits 2-5 (i.e., Week 3, 12, 24, and 36) were -9.42±9.916, -14.92±13.151, -15.88±13.134, and -15.86±13.204, respectively, with statistically significant differences achieved.

At Visits 2-5 (i.e., Week 3, 12, 24, and 36), the number of patients who achieved PASI 50 and the response rates were 65 (43.0%), 114 (75.5%), 91 (60.3%), and 83 (55.0%), respectively; the number of patients who achieved PASI 75 and the response rates were 30 (19.9%), 90 (59.6%), 79 (52.3%), and 74 (49.0%), respectively; the number of patients who achieved PASI 90 and the response rates were 11 (7.3%), 57 (37.7%), 58 (38.4%), and 59 (39.1%), respectively; the number of patients who achieved PASI 100 and the response rates were 4 (2.6%), 12 (7.9%), 19 (12.6%), and 23 (15.2%), respectively.

DLQI Score

The mean (±SD) of change from baseline in DLQI score at Visit 2-5 (i.e., Week 3, 12, 24 and 36) were -4.6±5.52, -7.4±6.95, -8.4±6.96 and -8.4±6.82, respectively, with statistically significant differences achieved.

The number of patients achieving MCID and response rate at Visits 2-5 (i.e., Week 3, 12, 24, and 36) were 65 (43.0%), 88 (58.3%), 72 (47.7%), and 71 (47.0%), respectively.

PGA Response

The number of patients who achieved PGA (0/1) at Visits 2-5 and the response rates were 7 (4.6%), 64 (42.4%), 61 (40.4%), and 62 (41.1%), respectively.

Adalimumab Treatment Utilization

Of the 151 patients enrolled and administered in this study, 79 patients (52.3%) were administered continuously, 27 patients (17.9%) were administered intermittently, and 45 patients (29.8%) were permanently discontinued.

Exploratory Analysis

The exploratory analyses were based on treatment utilization.

Comparison of changes in PASI and DLQI scores between continuous treatment and intermittent treatment

The mean (±SD) change from baseline in PASI at Week 36 for patients receiving continuous Adalimumab (continuous treatment) and those not receiving continuous Adalimumab (intermittent treatment) were -17.62±13.846 and -15.98±14.364, respectively, and no statistically significant difference was achieved. The mean (±SD) change from baseline in DLQI at Week 36 for patients receiving continuous Adalimumab (continuous treatment) and those not receiving continuous Adalimumab (intermittent treatment) were -9.0±6.79 and -9.3±6.51, respectively, and no statistically significant difference was achieved.

EQ-5D-3L score

The mean (±SD) change from baseline at Visits 2-5 were -0.11±0.301, -0.20±0.303, -0.24±0.259, and -0.24±0.264, respectively, with a statistically significant difference achieved.

Analysis of prognostic factors for PASI 75 response at Week 12

Analysis of PASI 75 response at Week 12 and associated prognostic factors showed that only a positive and statistically significant correlation between psoriasis body surface area and PASI 75 response at Week 12.

Safety Analysis

Of the 151 patients included in the safety set (SS) in this study, 20 patients (13.2%) experienced 27 adverse events (AEs), with an incidence of 22.02 (100 patients-years), all of which were treatment-emergent adverse events (TEAEs); 4 patients (2.6%) experienced 5 SAEs, with an incidence of 4.40 (100 patients-years); 1 patient (0.7%) experienced 2 AESIs, with incidence of 1.10 (100 patients-years); no patient experienced AEs leading to death.

Of the AEs reasonably related to the AbbVie product, 8 patients (5.3%) experienced 15 AEs, with an incidence of 8.81 (100 patients-years), all of which were TEAEs; 2 patients (1.3%) experienced 3 SAEs, with an incidence of 2.20 (100 patients-years); 1 patient (0.7%) experienced 2 AESIs, with an incidence of 1.10 (100 patients-years); no patients experienced AEs leading to death.

By the last visit, 2 patients experienced 3 AEs with outcome of not recovered, 4 patients experienced 7 AEs with outcome of recovering, 1 patient experienced 1 AE with outcome of unknown, and the remaining AEs had recovered.

Discussion

With regard to efficacy, Adalimumab can significantly improve the psoriasis after treatment for 3 weeks, thereby improving the health status and quality of life of patients, and the improvement effect is better after treatment for 12 weeks. In addition, continuous and intermittent treatment had no significant effect on the efficacy of Adalimumab. Analysis of relevant prognostic factors found that psoriasis body surface area was associated with Adalimumab response.

With regard to safety, the incidence of AEs in this study was low, and the most commonly reported adverse reaction (ADR) to Adalimumab was folliculitis. The safety results were consistent with previous studies, and no new safety signals were identified. It is shown that Adalimumab has a good safety profile.

Marketing Authorization Holder(s)

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