1.0 Abstract

Title

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Effectiveness of Adalimumab in moderate to severe Plaque Psoriasis Patients with distinct Co-morbidities

Complete Study Population (Austria, Greece, Israel, Portugal)

Keywords

Adalimumab, Psoriasis, co-morbidities

Rationale and Background

Plaque psoriasis is a chronic auto-inflammatory disease which primarily affects skin and nails. Although the disease itself has low attribute mortality, it can have a considerable impact on quality of life with significant co-morbid diseases and symptoms and psychological morbidity (Vena et al. (2010)). Patients with psoriasis have a risk for psoriatic arthritis of 30-40% (Harle et al., 2010), for depression of 21.7%, and 21.2% for hypertension. Estimated prevalence of obesity is 11.9%, for cardiovascular diseases 10.2%, for diabetes 8.5%, and for skin cancer and tumor 1.4% (Gottlieb and Dann, 2009; Kim et al., 2010; Mrowietz, 2010). Co-morbidities often become clinically manifest years after onset of psoriasis and tend to be more frequently seen in severe disease (Naldi and Mercuri, 2010).

In addition, psoriasis patients are more often prone to alcohol abuse and smoke tobacco more frequently than general population (Kirby et al., 2008, Armstrong et al., 2014). Disease severity also correlates with smoking and alcohol abuse (Gerdes et al., 2010).

The aim of this post-marketing observational study (PMOS) was the assessment of effectiveness of adalimumab in moderate to severe plaque psoriasis patients with distinct co-morbidities and impact of adalimumab on the quality of life (QoL) in routine clinical praxis over the period of 9 month.

The severity of psoriasis was established before and under treatment with adalimumab by calculation of the Psoriasis Area Severity Index (PASI) and the analysis of Dermatology Life Quality Index (DLQI) in patients with at least one co-morbid disease and/or symptom. In addition the prevalence of co-morbidities with regard to gender as well as different parameters of general life quality (SF-36) and life-quality for specific co-morbidities were evaluated**.**

Research Question and Objectives

Main objectives

The purpose of this study was to evaluate the effectiveness of adalimumab over a period of 9 months by analyzing the Psoriasis Area & Severity Index (PASI) in moderate to severe Plaque Psoriasis patients with distinct comorbidities.

Secondary objectives

Moreover the change of the psychological strain of the patients under the therapy with adalimumab should be analyzed by Dermatology Life Quality Index (DLQI) questionnaires and the prevalence of co-morbidities in consideration of gender should be described. The general Life-Quality and the Life-Quality for patients with comorbidities will be assessed by questionnaires. To compare the mean improvement in various Qualities of Life and to compare the percentage of patient's improvements, the minimum of clinical important differences (MCID) should be analyzed.

Study Design

This is a non-interventional, observational study conducted in a prospective, multi-country (Austria, Greece, Israel, Portugal), multicenter format.

Setting

The investigational sites were centers with a high level of experience in the treatment of Plaque Psoriasis patients and the conduct of non-interventional studies. 33 centers participated in the study.

Subjects and Study Size, Including Dropouts

In 33 centers 246 patients were recruited. From these 246 patients 153 (62%) patients were male and 93 (38%) were female.

72 (29.3%) patients stopped the study before the end time point projected by protocol. The most frequent reasons for early study termination were lack of efficacy (41.7 % overall), lost to follow-up (16.7 % overall) and adverse reactions (12.5 % overall).

Inclusion Criteria

1. Patients age > 18 years

2. Moderate to severe Plaque Psoriasis patients with at least one co-morbid disease and/or symptom such as hypertension, psoriasis arthritis (confirmed by a rheumatologist), obesity (defined as BMI >30), diabetes, metabolic syndrome (≥3 criteria of NCEP ATP III), depression (diagnosed by a medical specialist for psychology or neurology).

3. Adalimumab-naïve patients with moderate to severe Plaque Psoriasis after unsatisfactory response or non-tolerability or contraindication of systemic therapies such as cyclosporine, methotrexate or PUVA or after bDMARDs failure (e.g.: Infliximab, Etanercept or Ustekinumab)

4. Patients of each country must fulfill any local treatment recommendation for use of bDMARD in psoriasis in their respective country.

For Austria: Patients must fulfill Austrian Treatment Recommendations for use of BDMARD in Psoriasis (Chest X-ray and IGRA* interferon gamma release assay or PPD-skin test negative for tuberculosis)

5. Patient is willing to give informed consent anonymous data collection and their forwarding to AbbVie as well as to informed consent if required in different countries.

6. Patient must be able and willing to self-administer adalimumab injections or have a qualified person available to administer Humira® syringe or Humira® Pen injections.

Exclusion Criteria

1. Patients who meet contraindications as outlined in the latest version of the Humira syringe® SPC and Humira Pen® SPC.

2. Patients participating in another study program or clinical trial.

3. Patients who have been treated with Humira® before.

Variables and Data Sources

Patients were documented according to the following procedure:

- demographics (age, gender, race, disease duration, tobacco and alcohol use, results of Chest X-ray and a highly specific interferon-γ-release assay or "Purified protein derivative" (PPD)-test for Tb-screening),

- co-morbidities which do not constitute a contraindication for adalimumab as stated in the released Summary of Product Characteristics (SmPC) but may have an influence on anxiety assessment were collected for each patient,

- routine laboratory tests were performed according to physicians decision and availability of adequate test devices / laboratories. They were not performed for safety evaluation but part of effectiveness analysis.

- Complete Blood count and testing of C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) were requested if the evaluation of this marker was part of the routine tests.

For assessment of the area and severity of the disease of patients with psoriasis the Psoriasis Area & Severity Index (PASI) was applied.

The general life-quality and the life-quality for specific co-morbidities were assessed by questionnaires. Quality of life (QoL) was assessed with the application of SF36v2 for overall QoL and disease specific QoL was assessed by particular scores such as Dermatology Life Quality Index (DLQI) and Diabetes Quality of Life (DQOL). To assess the mean improvement in various parameters of quality of life and to calculate the percentage of patient's improvements, the minimum of clinical important differences (MCID) was analyzed.

Feelings of anxiety and depression were assessed by application of the Hospital Anxiety and Depression Scale (HADS).

The rheumatic status of the patients was assessed by application of the Health Assessment Questionnaire Disability Index (HAQ-DI)

Concomitant treatment with other medication or supplement at the start of adalimumab therapy was documented in the appropriate electronic case report form (eCRF).

All patient data entered by the investigational sites in the patient's electronic case report form (eCRF) was forwarded - without naming the patient - for evaluation to Data Management. In order to maintain patient confidentiality, instead of date of birth, the patient's age in year and gender was documented in the electronic case report form

(eCRF). The patients had to provide written authorization to the investigator to use and/or disclose personal and/or health data before entry into the study.

At the final patient visit the investigator had an opportunity to enter in the eCRF his final statement about the effectiveness and safety of the adalimumab treatment. Following categories could be entered: 1=excellent, 2=sufficient, 3=moderate, 4=unsatisfactory. In addition, final remarks about PASI and the Life Quality in general and the Life Quality of specific co-morbidities could be filled in by the investigator. Finally, there was a possibility to include the information about whether the therapy with adalimumab was continued after the study end and if not, what were the reasons for discontinuation.

Examinations, diagnostic measures, findings and observations routinely performed in patients included in this non-interventional observational study were entered by the investigator or staff according to the protocol in the electronic case report forms provided by AbbVie. Completed electronic case report forms (eCRF) visit modules were sent electronically immediately after completion to the Data Management.

Results

Demographics

In 33 centers 246 patients were recruited. 153 (62%) patients were male and 93 (38%) patients were female. Mean age was 48.8 years and mean duration of Psoriasis was 18.6 years. 91 (37%) patients were smokers at inclusion.

245 (99.6%) patients had co-morbidities which did not constitute a contraindication for the use of adalimumab. The most prevalent co-morbidity was psoriasis arthritis, with 114 patients (46.3%) being diagnosed for the disease. Metabolic syndrome was diagnosed for 72 patients (29.4%), and 64 patients (26.2%) were classified as obese or adipose. Diabetes was diagnosed for 31 patients (12.6%) and hypertension was found in 79 patients (32.1%).

72 (29.3%) patients terminated the study prematurely. Most frequent reason for early termination was “Lack of Efficacy” (n=30; 41.7%). All analyses were done on an “as observed” basis.

Pre-treatment

165 (67.3%) patients were biologics-naïve and the most frequent documented DMARD in this group was cyclosporine and methotrexate. In the non-naïve group (n=80 ; 32.7%) the most frequent documented bDMARD was Etanercept (n=58; 73.4%).

TB Screening

Chest x-ray was performed for 89.4% of the patients with five (2.3%) abnormal findings.

Interferon gamma test was performed on 50.6% of the patients with 12 (4.9%) positive and two (0.8%) indecisive findings. PPD skin test was performed on 58% of the patients with 27 (19%) positive findings.

Main Objective – Psoriasis Area & Severity Index (PASI)

PASI scores on average were statistically significantly reduced at each time point compared to visit 1 (WSR p-values < 0.001). PASI 75 was observed for 31.3% of the patients after 1 month, for 52.8% of the patients after 3 months, for 55.8% after 6 months and 57.5% after 9 months.

PASI 50 was observed for 72.5% of patients after 9 months.

43.7% of patients achieved PASI 90 after 9 months, and 30.4% of patients achieved PASI 100 after 9 months.

Secondary Objective – Dermatology Life Quality Index (DLQI)

DLQI scores on average were statistically significantly reduced at each time point compared to visit 1 (WSR p-values < 0.001).

Minimum clinically important difference (MCID) as reduction in DLQI of at least 5 points from the baseline score was observed for 47.4% of the patients after 1 month, for 58.5% of the patients after 3 months, for 64.3% after 6 months and for 65.3% after 9 months.

Secondary Objective - Hospital Anxiety and Depression Scale (HADS A; HADS D)

For HADS Anxiety MCID was observed for 22.4% of the patients after 1 month, for 29.9% of the patients after 3 months, for 38.0% after 6 months and for 38.1% after 9 months.

For HADS Depression score MCID was observed for 19.2% of the patients after 1 month, for 29.1% of the patients after 3 months, for 32.5% after 6 months and for 40.8% after 9 months.

Secondary Objective - Health Assessment Questionnaire Disability Index (HAQ-DI)

MCID was observed for 14% of the patients after 1 month, for 18.2% of the patients after 3 months, for 19.4% after 6 months and for 30.8% after 9 months.

Secondary Objective - Diabetes Quality of Life (DQOL)

MCID was observed for 10% of the patients after 1 month, for 33.3% of the patients after 3 months, for 31.3% after 6 months and for 31.6% after 9 months.

Secondary Objective - General perception of Health (SF36v2)

PF: MCID was observed for 22.5% of the patients after 1 month, for 32.6% of the patients after 3 months, for 35.8% after 6 months and for 41% after 9 months.

RP: MCID was observed for 11.7% of the patients after 1 month, for 21.4% of the patients after 3 months, for 24.2% after 6 months and for 26.8% after 9 months.

BP: MCID was observed for 22.4% of the patients after 1 month, for 28.3% of the patients after 3 months, for 28.3% after 6 months and for 40.6% after 9 months.

GH: MCID was observed for 28.4% of the patients after 1 month, for 35.1% of the patients after 3 months, for 37.9% after 6 months and for 43.9% after 9 months.

VT MCID was observed for 29.4% of the patients after 1 month, for 37% of the patients after 3 months, for 38.2% after 6 months and for 46.5% after 9 months.

SF: MCID was observed for 19% of the patients after 1 month, for 20.9% of the patients after 3 months, for 25% after 6 months and for 34% after 9 months.

RE: MCID was observed for 3.4% of the patients after 1 month, for 4.2% of the patients after 3 months, for 3.3% after 6 months and for 4.5% after 9 months.

MH: MCID was observed for 44.6% of the patients after 1 month, for 52.4% of the patients after 3 months, for 55.9% after 6 months and for 65.2% after 9 months.

PCS: MCID was observed for 38.3% of the patients after 1 month, for 52.9% of the patients after 3 months, for 48% after 6 months and for 55.2% after 9 months.

MCS: MCID was observed for 38.2% of the patients after 1 month, for 49.7% of the patients after 3 months, for 52.6% after 6 months and for 61.9% after 9 months.

Body Mass Index (BMI) and Waist circumference

BMI on average did not change statistically significantly compared to baseline at any visit (WSR p-values: V2 = 0.979; V3 = 0.721; V4 = 0.363; V5 = 0.094).

Waist circumference on average did not change statistically significantly compared to baseline at any time point (WSR p-values: V2 = 0.529; V3 = 0.679; V4 = 0.169; V5 = 0.688).

Final Statement

The final statement on effectiveness was in more than 70% of the assessments excellent or sufficient and on safety it was in more than 95% of the assessments excellent or sufficient.

Serious Adverse Events (SAE)

Overall 13 SAE were documented for 13 (5.3%) patients. Six SAE were assessed as "severe" (pneumonia - mycoplasma positive; ST elevation myocardial infarction (STEMI); ductales Adeno Carcinoma of left Mamma; massive redness and swelling at punction site; fracture of left humerus and left ulna; acute myocardial infarction) and three SAE were assessed as "probably related" to the study medication (Lymphocytosis; pneumonia - mycoplasma positive; Atrial fibrilation with rapid ventricular response). The patient with "ST elevation myocardial infarction" (STEMI) was a screening failure.

No deaths were reported during the study.

Discussion

In 33 centers 246 patients were recruited. 153 (62%) patients were male and 93 (38%) patients were female. This ratio is usual in psoriasis clinical studies, although according to most findings in the literature there is no difference in prevalence between genders (Parisi et al., 2013). Mean age was 48.8 years. 91 patients (37%) were smokers at inclusion. This prevalence of smokers among psoriasis patients is similar to that described in the literature (Armstrong et al., 2014).

174 patients (70.7%) finished the study per protocol and 72 (29.3%) patients terminated the study prematurely. The most frequent reason for early termination was "Lack of Efficacy" (n=30 / 41.7%). According to the literature data, approximately 70-80% of

patients stay on adalimumab in the first year of therapy (Gniadecki et al., 2015; Warren et al., 2015).

Mean duration of psoriasis was 18.6 years. 245 (99.6%) patients had co-morbidities which did not constitute a contraindication for the use of adalimumab.

Average PASI scores were statistically significantly reduced at each time point compared to visit 1 (WSR p-value < 0.001). PASI 75 was observed for 31.3% of the patients after 1 month, for 52.8% of the patients after 3 months and reached 55.8% after 6 months and 57.5% after 9 months. These findings correspond to the results of other clinical trials such as the REVEAL study (Menter et al., 2008), indicating that psoriasis patients with distinct co-morbidities in our study have similarly high response rates to adalimumab as patient population in other clinical trials with adalimumab.

Average DLQI scores were statistically significantly reduced at each time point compared to visit 1 (WSR p-value < 0.001).

Minimum clinically important difference (MCID) as reduction in DLQI of at least 5 points from the baseline score was observed for 47.4% of the patients after 1 month, for 58.5% of the patients after 3 months and reached 64.3% after 6 months and 65.3% after 9 months. The improvement of quality of life in our study population is similar to results from other adalimumab trial,such as the REVEAL study (Revicki et al, 2007).

Psoriasis patients are more prone to anxiety and depression (Kurd et al., 2010). For HADS Anxiety score MCID was observed for 22.4% of the patients after 1 month, for 29.9% of the patients after 3 months and reached 38.0% after 6 months and 38.1% after 9 months.

For HADS Depression score MCID was observed for 19.2% of the patients after 1 month, for 29.1% of the patients after 3 months and reached 32.5% after 6 months and 40.8% after 9 months.

Improvements of HADS scores upon treatment with an TNF inhibitor in chronic plaque psoriasis patients was previously described (Mrowietz et al., 2015).

Health Assessment Questionnaire Disability Index (HAQ-DI) is a tool which is used to assess physical function and functional loss of patients with rheumatologic disease. 114 patients (46.3%) participating in our study had a diagnosis of concomitant psoriatic arthritis. However, the MCID was calculated for the whole study population: 14.0% of the patients achieved MCID after 1 month, 18.2% of the patients after 3 months, 19.4% after 6 months and 30.8% after 9 months of therapy with adalimumab.

The proportion of patients achieving the MCID for HAQ-DI was lower in this study compared to the ADEPT study, where approximately half of patients reached the MCID (≥-0.3 points) after 12 weeks (Gladman et al, 2007). The ADEPT study was performed in PsA patients, whereas in this study 46.3% had a diagnosis of PsA, which might explain the difference in HAQ-DI results.

The General Perception of Health (SF36v2) improved upon adalimumab treatment. Overall, all of the eight health domains and psychometrically-based physical component summary (PCS) and mental component summary (MCS) scores raised statistically significantly at all visits compared to visit 1.Average BMI did not change statistically significantly compared to baseline at any visit (WSR p-values: V2 = 0.979; V3 = 0.721; V4 = 0.363; V5 = 0.094).

Average waist circumference did not change statistically significantly compared to baseline at any visit (WSR p-values: V2 = 0.529; V3 = 0.679; V4 = 0.169; V5 = 0.688).

Results described in the literature indicate that the therapy with TNF-α blockers could cause a significant weight gain (Gisondi et al., 2008, Saraceno et al., 2008, Tan et al., 2013). Our study could not confirm these findings.

The final statement of effectiveness rated more than 70% of the assessment as excellent or sufficient. The final statement of safety was in more than 95% of the assessment excellent or sufficient.

Serious Adverse Events (SAE)

Overall 13 SAE were documented for 13 (5.3%) patients. Six SAE were assessed as "*severe*" (*pneumonia – mycoplasma positive; ST elevation myocardial infarction (STEMI); ducales Adeno Carcinoma of left Mamma; massive redness and swelling at punction site; fracture of left humerus and left ulna; acute myocardial infarction*) and three SAE were assessed as "*probably related*" to the study medication (*Lymphocytosis; pneumonia – mycoplasma positive; Atrial fibrillation with rapid ventricular response*). The patient with "*ST elevation myocardial infarction*" was a screening failure.

Injection site reactions are common adverse events reported for adalimumab (Humira, SmPC). Serious infections were the most frequently reported serious adverse events across 13 clinical trials in psoriasis (1.7 event rates/100 patient years; Burmester et al., 2013). In the ongoing ESPRIT registry, 23.5 events of serious treatment-emergent adverse events per 100 patient years were reported within the first year of adalimumab treatment. 0.8 events of pneumonia per 100 patient years were reported within the first year of adalimumab exposure (Menter et al., 2015).

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