1.0 Abstract

Title

A Prospective, Multi-Center Study in Rheumatoid Arthritis Patients on Adalimumab to Evaluate its Effect on Synovitis Using Ultrasonography in an Egyptian Population

Keywords

Synovitis

Rheumatoid Arthritis.

Rationale and Background

Rheumatoid arthritis (RA) is an autoimmune disease characterized by symmetrical joint involvement, inflammation, synovial lining hyperplasia, and formation of invasive granulation tissue or pannus. Progression of RA pathogenesis is associated with impaired joint function resulting from immune-mediated destruction of bone and cartilage. Considerable patient-to-patient variation exists in the number of affected joints, the levels of autoantibody titers and serum cytokines, and the rate of joint destruction. Disease heterogeneity is further evident upon histological examination of synovial tissues, where a spectrum of cellular compositions are found, ranging from diffuse leukocytic infiltration to well-organized, lymphocyte-containing follicle-like structures. RA is also heterogeneous in response to treatment. [1]

Patients with RA may not respond to treatment with disease-modifying anti-rheumatic drugs (DMARDs) alone. In patients who have failed DMARD therapy for RA, clinical studies have demonstrated the effectiveness of drugs directed against tumor necrosis factor (TNF) as monotherapy or when used in combination with DMARDs. Adalimumab (ADA) is a fully human anti-TNF monoclonal antibody for the treatment of moderate to severe RA. Initial clinical trials of ADA in patients with RA demonstrated a good safety profile, with improvements in disease signs and

symptoms and functional ability, achievement of clinical remission and inhibition of radiographic disease progression.

The Research in Active Rheumatoid Arthritis (ReAct) phase 3b study was initiated in 2002 to assess the safety and effectiveness of ADA in RA patients who had failed treatment with at least one traditional DMARD. ADA was well tolerated and effective, alone or with DMARDs, in 6,610 patients with active RA over mean treatment duration of 233 days.[2]

The aim of this study was to assess the effectiveness of Adalimumab on reducing synovitis assessed by ultrasonography in RA patients in Egypt, as this is an important marker of inflammation and such data is not yet fully available in such a population. The study collected B-mode ultrasonography data from RA patients who were on Adalimumab and had not been treated with any other anti-TNF therapy in the past.

Research Question and Objectives

The purpose of this study was to evaluate the changes in synovitis of Egyptian rheumatoid arthritis patients who were on Adalimumab.

The study investigated the rate of RA progression via changes in B-mode ultrasonography assessment score over time as well as changes in the number of joints with erosion over time.

The primary endpoint

The average change in synovitis measured by B-modal Ultrasonography assessment score after 13 weeks of treatment with Adalimumab.

Ultrasonography assessment scoring followed OMERACT scoring criteria and as described in Hammer et al (11). Presence of synovitis and joint fluid was scored on a scale from 0 to 3 (0=none,1=minor,2=moderate,3=major presence). The sum of scores of all 12 joints were taken as the ultrasonography assessment score (giving a

score range of 0 – 36). The 12 joints to be assessed were elbow, wrist, second Metacarpophalangeal joint (MCP), third MCP, knee and ankle, all on both sides.

The secondary endpoints

- The mean change in ultrasonography assessment score from Screening through Week12.
- The mean number of joints with detected erosions between Screening and Week 12
- Percentage of patients who achieved an ACR20 (American College of Rheumatology score) response at Week 12.
- The mean change in Health Assessment Questionnaire (HAQ) score at Week 12.

Study Design

This study was Prospective Observational, Multicenter Study conducted in 3 investigational sites. The planned number of sites was 5; however only 3 sites recruited patients while two sites [redacted] didn't enroll any patients. Patients were treated with Adalimumab in accordance with physicians' usual clinical care practices and local marketing authorization requirements with regards to dose, population, and indication.

During the study patients were observed over a period of maximum 13 weeks of treatment with Adalimumab during which a maximum of 5 visits were performed.

Setting

A total of 5 visits were conducted: Baseline (Visit 1), Visit 2, 3, 4 and 5 (week 13 is the final visit (visit 5) or might be before week 13 in case of occurrence of one of the reasons listed in the reasons for patient's withdrawal, which were mentioned below). The difference between the baseline visit and the second visit was approximately 2-3 weeks, with window of one week.

Subjects and Study Size, Including Dropouts

A sample size of 60 patients was targeted.

The study was terminated due to low recruitment: 2 sites didn't recruit any patients and one site recruited one patient. This was due to difficult reimbursement issues in Egypt; most of the patients pay out of pocket for their medication. This made recruitment difficult for investigators especially since the process to get financial support for patients from Ministry of Health was not guaranteed and became lengthy and complicated procedure after the political unrest during 2012-2013.

Total number of enrolled subjects wasixteen patients from three investigational sites, one patient was enrolled in site number one ([redacted]), thirteen patients were enrolled in site number two ([redacted]) and two patients were enrolled in site number four ([redacted]).

Criteria

Inclusion Criteria:

- A patient will be enrolled in this study if he/she fulfills ALL of the following criteria:
- Male or Female patients ≥ 18 years of age with diagnosis of RA
- Patient is eligible to start adalimumab therapy according to the local product label and prescription guidelines

- Patient is naïve to all biologics e.g. anti-CD4 and anti-TNF treatments at the start of the study
- Patient has no history of inflammatory arthritis other than rheumatoid arthritis
- Patient has no history of lymphoma or leukemia or other malignancies
- Has negative result of tuberculosis (TB) screening test or is receiving TB prophylaxis as per local guidelines, Provided written Authorization to the investigator to use and/or disclose personal and/or health data, or Informed Consent if requested by the Local Regulations

Exclusion Criteria:

- Patients that are not diagnosed with rheumatoid arthritis as judged by the American College of Rheumatology criteria
- Patient is currently diagnosed with any condition other than rheumatoid arthritis that may affect radiography progression
- Susceptibility to infections including TB, as judged by the investigator
- Patient is carrier of Hepatitis B virus
- Patient is a pregnant or lactating female at the time of screening

Variables and Data Sources

Baseline Visit 1 (week 1)

At Baseline visit patients signed informed consent and were evaluated for:

1-Inclusion / Exclusion criteria

2- Demography (Age, gender, duration since rheumatoid arthritis diagnosis)

3-Previous concomitant medications within 30 days prior to the start of the study including DMARD Therapy

4-Medical history

5-T.B. prescreening investigations results.

6-ACR core set

7- Rheumatoid Factor –if available

8- C-reactive protein, if available.

9- Erythrocytic sedimentation rate. (ESR), if available.

10-Ultrasonography assessment score including score for each examined joint (on a scale from 0 – 3 for each joint) and the sum of all 12 joint scores (on a scale from 0 – 36).

11- Number of joints with detected synovitis and/or erosion ultrasonography.

Follow Up Visits

Visits 2, 3, 4 and 5 were follow-up visits during which the following information were recorded if collected as per standard of care:

1-Concomitant medications including DMARD Therapy

2-Serious adverse events (SAE), if any.

3-Adalimumab Dosage

4-Tender joint count

5-Swollen joint count

6-Rheumatoid Factor – if available

7-Ultrasonography assessment score including score for each examined joint (on a scale from 0 – 3 for each joint) and the sum of all 12 joint scores (on a scale from 0 – 36).

8-Number of joints with detected synovitis and/or erosion via ultrasonography

9-C-reactive protein.

In addition, at visit 5, the following data was recorded if collected as per standard of care:

10-ACR core set

- TJC/SJC
- Patient's assessment of pain (on a scale from 0 to 100 where 0 means no pain and 100 means severe pain)

- Patient's assessment of disease activity (on a scale from 0 to 100 where 0 means no disease activity and 100 means extreme disease activity)
- Physician's assessment of disease activity (on a scale from 0 to 100 where 0 means no disease activity and 100 means extreme disease activity)
- HAQ score (on a scale from 0 to 3, where 0 means no difficulty and 3 means unable to perform activity)

Results

Sixteen patients with rheumatoid arthritis were enrolled to study the effect of Adalimumab on synovitis using ultrasonography among an Egyptian population. The mean age was 36 ±9.3 years, nine patients were males (56.25%) and seven were females (43.75%) and all the 16 subjects were Caucasian. The means weight, height and BMI were 80.6 ±19.6 kg, 167.3 ± 12.8 cm and 9.2 ±8.5 kg/m^2, respectively.

The baseline characteristics of the 16 patients who were suffering from RA for a mean duration of 3.7 ±3.9 years revealed that; the mean tender joint and swollen joint counts were 35.4 ± 16.26 tender joint out of 68 joints and 17.6 ±9.8 swollen joints out of 66 joints, respectively. The baseline patients' assessment (on scale from 0 to 100) for both pain and disease activates were 57.7 ±12.2 points and 56.4 ±12.2 points, respectively. On the other hand, the baseline physicians' assessment for disease activity was 48.6 ±15.5 points. Regarding the baseline lab values, the mean values of CRP, ESR and RF were 68.25 ± 42.5 mg/L, 72.9 ± 21.6 mm/hr and 139.81± 48.9 U/mL, respectively. The mean baseline health assessment questionnaire (HAQ) was 1.19 ±0.65 points while the mean final sum scores (all the 20 items on a scale of 0-3) was 23.88±12.95 points.

Regarding the baseline ultrasonography assessment, the mean synovitis score was 16.56±5.56 joints (of 12 joints on 3 point scale). On the other hand, the mean number

of joints with detected synovitis and/or erosion was 9.38±1.89 joints (of the total 12 joints).

The analysis of the data collected from the 16 enrolled patients (lower than planned) showed that there was considerable improvement on synovitis among patients with active rheumatoid arthritis as assessed by Ultrasonography after 13 weeks of well-tolerated 40 mg Adalimumab treatment as per the following percentages: ultrasonography assessment score (OMERACT scoring criteria) by 57%. Number of joints with detected erosions by 35%, Tender Joint Counts by 75%, Swollen Joint Counts by 72%, and Rheumatoid-Factor (RF) levels by 71%.

94% of patients achieved ≥ 20% improvement in both tender & swollen joint counts.

There were no AE or SAE reported for the enrolled patients however there was one discontinued patient due to lost to follow up after improvement.(Zero score for both tender and swollen joints)

Discussion

The objective of this study was to evaluate the changes in synovitis of Egyptian rheumatoid arthritis patients after therapy with Adalimumab. Sixteen patients were recruited. Although the results are not conclusive due to the small sample size, there were significant improvements in clinical outcomes and synovitis detected by ultrasounds. Adalimumab was generally well-tolerated. Further research needs to be conducted in order to confirm the findings of this study.

Marketing Authorisation Holder(s)

AbbVie UK

Names and Affiliations of Principal Investigators

[redacted]