



2.0 Synopsis

Tumor necrosis factor (TNF) is a pro-inflammatory cytokine that plays an important role in many inflammatory disorders such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), Crohn's disease (CD), ankylosing spondylitis (AS) and psoriasis (Ps) among others. Adalimumab (Humira®) is the first and only fully human monoclonal antibody available in Mexico. Several studies suggest that patients who do not respond to or cannot tolerate either infliximab^{1,2,3,4,5,6,7,8,9} or etanercept^{11,12} may respond to adalimumab achieving a good clinical response¹⁰.

Infliximab is a chimeric monoclonal antibody (75% murine and 25% human) that loses efficacy over time (in some patients). Currently, 62% of patients receiving infliximab need an increased dose adjustment after 15 months of treatment¹³.

RA is a chronic progressive disease that generally requires continuous treatment, and thus when infliximab or etanercept treatment is stopped the disease may flare up. As far as we know, four studies have described the efficacy of adalimumab in patients with RA who previously discontinued infliximab or etanercept treatment^{5,10,11,12}. Therefore, the proposed study will contribute to confirm current knowledge, in Mexican population, about the effectiveness of adalimumab in patients with RA who had previously discontinued other TNF-blocker treatments due to lack of efficacy or intolerability, in daily clinical practice.

This is a 24 week, prospective, open label, single-arm, post marketing observational study, in adult patients with active RA who are discontinuing previous biologic treatment due to lack of efficacy, intolerability or incomplete response, with either infliximab or etanercept. The objectives of the study were:



Primary Objective

To assess the effectiveness of the treatment with adalimumab in patients with rheumatoid arthritis (RA) that have failed or presented an incomplete response to current treatment with either infliximab or etanercept.

Secondary Objective

Evaluate the compliance and clinical tolerability with adalimumab.

Inclusion Criteria

The following patients were included in this study:

- Patients ≥ 18 and < 75 years of age that met the American College of Rheumatology (ACR) criteria for RA.
- Patients with active RA defined as:
 - (a) ≥ 3 tender joints and ≥ 3 swollen joints, or
 - (b) DAS 28 score > 3.1
- Patients who were discontinuing treatment with either infliximab or etanercept due to:
 - (a) Lack of efficacy, or
 - (b) Incomplete response.
- Patients that, in the opinion of the physician, could result benefited with the locally approved treatment scheme of adalimumab.
- Those patients who switched from infliximab or etanercept to adalimumab in the last 60 days could be included in the study.

Exclusion Criteria

- Patients who had active infections.



- Patients with latent tuberculosis (TB). For this protocol, evidence of latent TB infection was defined as a positive tuberculin skin test (induration size of 5 mm or greater at 48 to 72 hr after placement of tuberculin test), and/or any suggested data in the clinical history or chest x-ray.
- Patients participating in another study or clinical trial
- Any condition that, according to the criteria of the participating physician, represented an obstacle for study conduct and/or represented a potential unacceptable risk for patients.

Variables and scales of measurements

Effectiveness was defined as a decrease of at least 1.2 points in 28 joint count Disease Activity Score (DAS28) at week 24 of treatment (visit 5). The main effectiveness variable was the DAS28. The data needed in order to obtain the DAS28 were condensed on pages 7, 12, 18 and 24, from the Case Report Form (CRF), which correspond to visits 2, 3, 4 and 5 respectively for each patient.

These variables are the following:

- The number of tender joints, from a total of 28 joints.
- The number of swollen joints, from a total of 28 joints.
- Samples of the swollen markers: the C Reactive Protein (CRP), and/or the Erythrocyte Sedimentation Rate (ESR) measured in mm/hour.
- The patient's General Health (GH) or global disease activity measured on a Visual Analogue Scale (VAS) of 100mm.
- Evaluation of the patient's pain measured on a Visual Analogue Scale (VAS) of 100mm.

$$\text{DAS 28 FORMULA} = (0.56\sqrt{\text{TJC28}}) + (0.28\sqrt{\text{SJC28}}) + (0.70\text{LN}(\text{ESR})) + (0.014\text{VAS})$$



Compliance was evaluated by analyzing the total number of doses of adalimumab omitted by subjects during the study period. Tolerability was evaluated by analyzing the number of patients that interrupted or discontinued their treatment with adalimumab by week 24 (visit 5).

Duration of the Study

Observations for each patient were made during their treatment with adalimumab for a period of 6 months. A follow-up visit was performed every two months. Five outpatient follow-up appointments occurred. During visit 1 the following information was recorded: patient demographics, informed consent, clinical history, vital signs, physical test, potential TB test, chest x-ray, previous treatments for RA, type of biological therapy used and reasons for its discontinuation. This visit occurred between day -7 and day 0. Visit 2 was the baseline visit, in which the first dose of adalimumab was administered and the patient was taught how to self administer it. Visits 3 and 4 were the follow up visits and they occurred in week 8 and 16, respectively. Visit 5 was the final visit and it occurred in week 24.

Design, Analysis and Interpretation of the Information

This was an observational, prospective, longitudinal, single arm, post marketing (PMOS), multicenter study, involving adult patients with active RA who discontinued their treatment with infliximab or etanercept due to lack of efficacy, intolerability, or to an incomplete response. The size of the sample in this study was based on practical considerations, such as: the duration of the study, the population of Mexican patients with active RA who have been previously exposed to biological therapy with anti-TNF agents, their attendance to the participating sites, and their acceptance into the study. It was estimated that 120 patients and



20 sites would be enrolled in the study; eventually, 82 patients and 11 sites have participated.

The data were analyzed using the statistical package [REDACTED]. Descriptive summaries were obtained for the variables of interest. For the categorical variables, the number and percentage was calculated for each category, frequency tables were also obtained, as well as bar and pie charts. For the cross-tabulation of categorical variables, a frequency table was obtained, a bar chart and an Independence test Chi-square when it applied. For the continuous variables, the mean, standard deviation, maximum and minimum, range, standardized skewness and standardized kurtosis were calculated, and in some cases the median when it was needed. Frequency table, histogram, and Box-and-Whisker plot, were obtained for each of the variables. To evaluate the normality of the data, the standardized skewness, standardized kurtosis, histogram, and a normal probability plot were calculated. For the comparison of related groups, the paired t-test, the non-parametric sign test and signed-rank test were used, depending on whether the data was normally distributed or not. P values ≤ 0.05 were considered as statistically significant.

MAIN RESULTS

Demographic data. Eighty-two patients were enrolled. From these, 83.54% were women (66/79). In three cases, gender was not reported (3.65%) and the mean and standard deviation for age (in years) was 48.34 ± 11.56 . Sixty-three percent of patients were under etanercept treatment. The most frequent reason for changing from the previous biological treatment was related to incomplete response (63%). Only 71 patients had complete data in DAS28 for basal and final visits.



Primary objective: Basal DAS28 value was 6.04 ± 1.17 (mean \pm SD, n=82). At follow-up visits, values were 4.63 ± 1.77 (n=80) and 4.05 ± 1.74 (n=79), respectively. Final DAS28 was 3.68 ± 1.47 (n=71). Main change in DAS28 from basal to final visit was 2.26 ± 1.58 (n=71), with a paired-t test value of $p < 0.001$. Patients who showed a reduction of ≥ 1.2 in DAS28 from basal to final visit represented 70.4% of the sample (50/71).

Secondary objectives: *Tender Joint Count:* At basal visit, 13.05 ± 7.29 (n=82) tender joints were observed. Follow-up visits reported 7.16 ± 6.37 (n=80) and 5.44 ± 5.76 (n=80) at weeks 8 and 16, respectively. At final visit, only 4.23 ± 5.32 (n=71) were observed. *Swollen Joint Count.* At basal visit, mean swollen joints was 9.56 ± 5.97 (n=82). Follow-up visits reported 4.48 ± 4.68 (n=80) and 3.15 ± 4.67 (n=80) at weeks 8 and 16, respectively. At final visit, only 2.52 ± 4.10 (n=71) swollen joints were observed. *Severity of Pain in a 100 mm Visual Analog Scale (VAS):* At basal visit, VAS was 62.88 ± 22.31 mm (n=82). Follow-up visits reported 39.69 ± 25.40 (n=80) and 32.35 ± 26.02 mm (n=80) at weeks 8 and 16, respectively. At final visit, only a VAS of 28.70 ± 23.32 mm (n=71) was observed. *Compliance:* At the end of the study period a total of only 12 doses were omitted. By week 8, one patient missed one dose, and 3 patients missed two doses; by week 16, one patient missed two doses, and another one missed three doses. Therefore, patient compliance was considered high (97.81% and 98.40% for visits 3 and 4, respectively). *Tolerability:* From the 82 patients who entered the study, 6 (7.32%) reported the discontinuation of adalimumab. Nonetheless, only one patient (1.22%) discontinued it prematurely (before week 24) due to a serious adverse event. The rest of them (5 patients, 6.09%) discontinued treatment after week 24 (visit 5); that is after the observation period concluded. Of these 5 patients, 2 (2.44%) temporarily interrupted treatment since they were



asymptomatic and on their own decision, stopped adalimumab administration. Three (3.66%) discontinued it definitively because of treatment failure.

Adverse Events: Seven patients reported 14 adverse events. Only one serious adverse event was reported (rectal bleeding and vomiting).

Overall conclusion: Adalimumab 40 mg every other week by subcutaneous route showed effectiveness, tolerability and good compliance at 24 week follow-up in patients that were switched from other biologic therapy due to inadequate response or intolerability.