NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Clinical Outcomes of Early Versus Delayed Management of Iraqi Patients With Rheumatoid Arthritis With Etanercept
Protocol number	B1801411
Protocol version identifier	1
Date	04 November 2019
Active substance	etanercept
Medicinal product	etanercept
Research question and objectives	Many publications found that the early initiation of biological treatment had good impact on patient response to treatment, and with this RWD (Real World Data) our objective is to see the impact of early initiation of etanercept on patient response compared to delayed introduction of biological treatment.
Author	PPD – MD, M.Sc. Pfizer Inc. – Iraq

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
CCP	Cyclic Citrullinated Peptide
CDAI	Clinical Disease Activity Index
DAS28	Disease Activity Score
DMARDs	Disease Modified Anti Rheumatic Drugs
ENCePP	European Network of Cneters for pharmacoepidemiology and pharmacovigilance
EULAR	The European League Against Rheumatism
N/A	Non Applicable
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
RA	Rheumatoid Arthritis
RDW	Real World Data
RF	Rheumatoid Factor

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
PPD	Medical Advisor	Pfizer Inc. – Iraq	PPD

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Milestone	Planned date
Start of data collection	01 November 2018
End of data collection	01 December2018
Final study report	01 February 2019

This protocol was written post the conduct and completion of analysis.

6. RATIONALE AND BACKGROUND

In the past 1–2 decades, treatment paradigms in rheumatoid arthritis (RA) have shifted dramatically from initial treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), followed by cautiously progressive addition of disease-modifying antirheumatic drugs (DMARDs), to the current treatment approach of aggressive initiation of DMARD therapy soon after the diagnosis of RA has been made. This change in RA management results from increasing data supporting improved prognosis and outcomes with the initiation of DMARD therapy early in the course of symptomatic disease. Since the goals in RA management include not only disease remission, but also improved functional status, which is strongly associated with radiographic joint damage, an understanding of the impact that the initiation of appropriate treatment during early RA has on these outcomes is essential.

Accurate diagnosis of early RA begins with clear definitions of RA, as there is considerable variability in the literature regarding the time frame defining early RA.[1] Previous intervention studies in early RA have included early RA as disease duration from 3 months to 3 years; however, with the knowledge of improved outcomes with earlier treatment in RA, it becomes clear that a shorter time interval for classification of early RA is clinically significant. Due to the wide range of definitions of early RA presented in the literature, it is difficult to characterize the specific time frame that defines early RA. However, it is now generally accepted that early RA is the onset of symptoms of joint (typically polyarticular) pain, stiffness, or swelling within the past 3 months,[2,3] although in practical terms it may be difficult for rheumatologists to evaluate patients within that 3-month time frame, due to a variety of factors, including delay in referral of patients with early symptoms of inflammatory arthritis (IA) or delays in patients seeking medical attention for their symptoms.

Multiple studies have evaluated the benefits of early treatment of RA, including several that have evaluated the impact of early DMARD treatment on successful response to therapy. In particular, a meta-analysis of ~1,400 RA patients from 14 randomized controlled trials identified that one of the strongest predictors of response to therapy was a shorter disease duration at the time of treatment initiation.[4]

7. RESEARCH QUESTION AND OBJECTIVES

The objective of this study is to see the impact of early initiation of etanercept on patient response compared to delayed introduction of biological treatment.

8. RESEARCH METHODS

8.1. Study Design

- **Retrospective analysis** of patients with RA that received etanercept from Baghdad teaching hospital (Rheumatology center) from 2012 until 2018 (inclusion and exclusion criteria will apply for selecting patients).

- **Primary aim:** determine the impact of early referral for management in patients with RA compared to delayed management.

- **Secondary aims:** Determine the influence of early referral on the response to biological treatment.

8.2. Setting

Patients and Methods

Data collected from the Baghdad teaching hospital registry. The rheumatology patient registry is a prospective longitudinal multicenter cohort initiated in 2012. It captures all patients treated with biologic therapies managed in the rheumatology department. The decision to initiate and maintain the treatment is guided by the ACR (American College of Rheumatology) recommendations.

Study population

Patients included in the study if they met the American College of Rheumatology/EULAR (The European League Against Rheumatism) 2012 criteria for Rheumatoid Arthritis, with at least 1 year of follow up after starting their first biologic therapy.

Exclusion criteria: patients previously or currently treated with other biological therapies.

Hypothesis

Our initial hypothesis is that there is no difference in response between early and delayed referral to biological treatment.

8.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Diagnosed RA patients.

2. 18 years old and above.

3. Did not receive pervious biological treatment.

8.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1. Had previous biological treatment.

2. Use etanercept for less than 1 year.

8.3. Data Sources

We identified patients in rheumatology registry with rheumatoid arthritis and obtained information on patient demographics (age, gender), education level (years), present smoking status, disease duration (years), current steroid therapy (yes/no), baseline DAS28 (Disease Activity Index 28) & CDAI (Clinical Disease Activity Index) RF (Rheumatoid factor) status, anticitrullinated protein antibody (anti-CCP) status. Primary Outcomes: Disease activity Index (DAS28) and CDAI in last follow up visit.

8.4. Study Size

There is no pre identified study size. All patients that met the criteria entered for study.

8.5. Data Management

The data structured and exported in excel sheet.

8.6. Data Analysis

Categorical covariates described by frequency distribution while continuous covariates expressed in terms of their mean and standard deviation or median and interquartile range as appropriate. Patients were divided according to the mean of disease duration groups (below and above mean) and unadjusted comparisons between groups of the covariates and the outcomes are evaluated using chi2 tests for categorical data, while for continuous data, we used the student's t-test for normally distributed variables and the Kruskall-Wallis test for non-parametric data.

We determined the effect of early referral on the biologic treatment response patients with RA a multivariate analysis by using a stepwise linear regression models. The response variable is defined as DAS28 and CDAI at last visit. The baseline variables considered demographic data, disease duration (years), methotrexate (yes/no), Current steroid therapy (yes/no), baseline DAS28 and CDAI, RF positive (yes/no), anti-CCP (yes/no), present smoking (yes/no).

We determined the effect of early response by using the difference between the base line DAS28 and CDAI. P value <0.05 considered statistically significant.

8.7. Quality Control

N/A.

8.8. Limitations of the Research Methods

The limitation of this project could be the missing data that could lead to some bias.

8.9. Other Aspects

Not Applicable (N/A).

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information

This study involves data that exist in anonymized structured format and contain no patient personal information.

9.2. Patient Consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

9.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

Not required.

9.4. Ethical Conduct of the Study

The study conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), and Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

12. REFERENCES

1. A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: how to guide individual treatment decisions. van der Helm-van Mil AH, le Cessie S, van Dongen H, Breedveld FC, Toes RE, Huizinga TW . Arthritis Rheum. 2007 Feb; 56(2):433-40.

2. Attitudes to early rheumatoid arthritis: changing patterns. Results of a survey. Aletaha D, Eberl G, Nell VP, Machold KP, Smolen JS. Ann Rheum Dis. 2004 Oct; 63(10):1269-75.

3. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, Moreland LW, O'Dell J, Winthrop KL, Beukelman T, Bridges SL Jr, Chatham WW, Paulus HE, Suarez-Almazor M, Bombardier C, Dougados M, Khanna D, King CM, Leong AL, Matteson EL, Schousboe JT, Moynihan E, Kolba KS, Jain A, Volkmann ER, Agrawal H, Bae S, Mudano AS, Patkar NM, Saag KG. Arthritis Care Res (Hoboken). 2012 May; 64(5):625-39.

4. Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration. Anderson JJ, Wells G, Verhoeven AC, Felson DT. Arthritis Rheum. 2000 Jan; 43(1):22-9.

13. LIST OF TABLES

N/A.

14. LIST OF FIGURES

N/A.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP (EUROPEAN NETWORK OF CNETERS FOR PHARMACOEPIDEMIOLOGY AND PHARMACOVIGILANCE) CHECKLIST FOR STUDY PROTOCOLS

Not required.

ANNEX 3. ADDITIONAL INFORMATION

N/A.