NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	The impact of RF, and anti-CCP on RA patients in response to Etanercept
Protocol number	B1801417
Protocol version identifier	3.0
Date	27 July 2021
Active substance	etanercept
Medicinal product	etanercept
Research question and objectives	The RF and anti-CCP are found to be positive in 70% and 65% of RA patients respectively. Researchers have found that RF and anti-CCP have an impact on RA response. The objective is to evaluate the impact of RF and ACCP on RA patients in response to Enbrel from the local data.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
AE	Adverse Event
anti-CCP	Anti-Cyclic Citrullinated Peptide
CDAI	Clinical Disease Activity Index
DAS28	Disease Activity Score 28
DMARD	Disease -Modifying Antirheumatic Drug
EULAR	The European League Against Rheumatism
GEP	Good Epidemiological Practice
GGP	Guidelines for Good Pharmacoepidemiology Practices
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MTX	Methotrexate
NA	Not Applicable
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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

4. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	22 June 2021	Section 5. Milestones	Updated to align with Study Report	Administrative
2	27 July 2021	Throughout the document	Spelling errors	Administrative

5. MILESTONES

Milestone	Planned date	Actual Date
Start of data collection	01 July 2020	01 July 2020
End of data collection	01 August 2020	01 August 2020
Final study report	30 June 2021	29 June 2021

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.[1,3]

Rheumatoid factor (RF) has long been a component of the diagnostic criteria for rheumatoid arthritis and although it positive in 70% of RA patients. RF is well studied and its associations with a more severe disease course have been extensively described in Western countries. In more recent years, anti-CCP was positive in 65%-80% of RA patients. The anti-CCP status provides important prognostic information in RA. Also, Rönnelid et al *s*howed that anti-CCP seropositive patients had more active disease during follow-up than seronegative patients.[2]

Given the optionality of biological treatment for RA patients, identifying a predictor for response will required more attention from rheumatologists for such patients.[4]

7. RESEARCH QUESTION AND OBJECTIVES

The objective of this study is to evaluate the impact of RF and anti-CCP positivity on RA patients.

8. RESEARCH METHODS

8.1. Study Design

- **Retrospective analysis** of patients with RA that received etanercept from Baghdad Teaching Hospital (Rheumatology center) from May 2012 until August 2019 (inclusion and exclusion criteria will apply for selecting patients).

- **Primary objective:** Determine the clinical impact of RF and anti-CCP for management (etanercept) in patients with RA compared to negative RF and anti-CCP in RA patients.

8.2. Setting

Patients and Methods

Data will be 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 American College of Rheumatology (ACR) recommendations.

Study population

Patients will be included in the study if they meet the American College of Rheumatology/The European League Against Rheumatism (EULAR) 2010 criteria for Rheumatoid Arthritis,[5] with at least 1 year of follow-up after starting their first biologic therapy. This includes patients who were in monotherapy or in combo-therapy with concomitant conventional DMARDs.

Hypothesis

Our hypothesis is that there is no difference in response between seropositive and seronegative RA patients to Enbrel.

8.2.1. Inclusion Criteria

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

1. Diagnosed RA patients.
2. ≥18 years of age.
3. Did not receive previous another 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 of etanercept for less than 1 year.

8.3. Data Sources

Patients will be identified from the rheumatology patient registry with rheumatoid arthritis and obtained information on patient demographics (age, gender), education level (years), present smoking status, disease duration (years), current MTX and steroid therapy (yes/no), baseline Disease Activity Score 28(DAS28) and Clinical Disease Activity Index (CDAI), RF status, anti-CCP status. Primary Outcomes: DAS28 and CDAI in last follow-up visit.

8.4. Study Size

There is no pre-identified study size sample. All patients that meet the criteria will be entered into the study.

8.5. Data Management

The structured data is exported into an Excel spreadsheet and then transferred to the SPSS (version 23) database for statistical analysis.

8.6. Data Analysis

Categorical covariates will be described by frequency distribution while continuous covariates will be expressed in terms of their mean and standard deviation or median and interquartile range as appropriate. Patients will be divided for seropositive RA and seronegative RA (according to anti-CCP status). The unadjusted comparisons between groups of the covariates and the outcomes will be evaluated using chi2 tests for categorical data, while for continuous data, the Student's t-test will be used for normally distributed variables and the Kruskall-Wallis test for non-parametric data.

The effect of biologic treatment response in patients with sero-positive RA will be determined with a multivariate analysis by using a stepwise linear regression model. 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), and present smoking (yes/no).

The effect of response will be determined by using change from baseline in DAS28 and CDAI at the last visit. A p-value of <0.05 is considered statistically significant, without multiplicity adjustment, for this post-hoc analysis.

8.7. Quality Control

NA.

8.8. Limitations of the Research Methods

Missing data that could lead to bias is an identified limitation of this study.

8.9. Other Aspects

NA.

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 retrospective 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 will be 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

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2. Rönnelid J, et al. Longitudinal analysis of citrullinated protein/peptide antibodies (anti-CP) during 5 year follow up in early rheumatoid arthritis: anti-CP status predicts worse disease activity and greater radiological progression. Ann Rheum Dis 2005;64:1744–9.

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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.

5. Neogi T, Aletaha D, Silman AJ, et al. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: phase 2 methodological report, Arthritis Rheum, 2010, vol. 62 (pg. 2582 - 91).

13. LIST OF TABLES

NA.

14. LIST OF FIGURES

NA.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

Document Approval Record

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