NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Clinical Outcomes of Early Versus Delayed Management of Iraqi Patients With ankylosing spondylitis (AS) With Etanercept
Protocol number	B1801415
Protocol version identifier	3.0
Date	29 July 2021
Active substance	Etanercept
Medicinal product	Etanercept
Research question and objectives	Many publications found that the early initiation of biological treatment had positive impact on patients' response to the treatment regimen, and with this Real World Data (RWD), our objective is to evaluate the impact of early initiation of etanercept on patient-response compared to delayed introduction of biological treatment.
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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
AE	Adverse Event
Anti-CCP	Anti-Cyclic Citrullinated Peptide
AS	Ankylosing Spondylitis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
DMARDs	Disease-Modifying Antirheumatic Drugs
EULAR	European League Against Rheumatism
GEP	Good Epidemiological Practice
GPP	Guidelines for Good Pharmacoepidemiology Practices
HLA-B27	Human Leukocyte Antigen B27
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
N/A	Not Applicable
NI	Non-Interventional
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
RA	Rheumatoid Arthritis

Abbreviation	Definition
RWD	Real World Data

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
PPD, MD, M.Sc.	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	08 July 2021	Section 5. Milestones	Updated to align with Study Report	Administrative
2	29 July 2021	Throughout document	Spelling errors	Administrative
		Section 5 Milestones	Updated to align with Study Report	Administrative

5. MILESTONES

Milestone	Planned date
Start of data collection	01 August 2020
End of data collection	01 October 2020
Final study report	01 September 2021

6. RATIONALE AND BACKGROUND

In the past 1–2 decades, treatment paradigms in Ankylosing Spondylitis (AS) have shifted dramatically from initial treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), followed by the cautiously progressive addition of disease-modifying antirheumatic drugs (DMARDs), to the current treatment approach of the aggressive initiation of DMARD therapy soon after the diagnosis of AS has been made. This change in AS 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 AS 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 AS has on these outcomes is essential.

Accurate diagnosis of early AS begins with clear definitions of AS, as there is considerable variability in the literature regarding the time frame defining early AS.[1] Previous intervention studies in early AS have included early AS as disease duration from 3 months to 3 years; however, with the knowledge of improved outcomes with earlier treatment in AS, it becomes clear that a shorter time interval for classification of early rheumatoid arthritis (RA) is clinically significant. Due to the wide range of definitions of early AS presented in the literature, it is difficult to characterize the specific time frame that defines early AS.

Multiple studies have evaluated the benefits of early treatment of AS, including several that have evaluated the impact of early DMARD treatment on successful response to therapy. In particular, a meta-analysis of ~1,400 AS 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.

7. RESEARCH QUESTION AND OBJECTIVES

The objective of this study is to evaluate 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 AS that received etanercept from Baghdad teaching hospital (Rheumatology center) from August 2012 until March 2020 (inclusion and exclusion criteria will apply for selecting patients).

- **Primary objective:** determine the clinical impact of early referral for management in patients with AS compared to delayed management.

- **Secondary objective:** determine the influence of early referral on the response to biological treatment.

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 met the American College of Rheumatology/The European League Against Rheumatism (EULAR) 2019 criteria for AS, 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

There is no difference in response between early and delayed referral to biological treatment.

8.2.1. Inclusion Criteria

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

1. Diagnosed AS patients.

2. ≥18 years old.

3. Did not receive previous biological treatment for any reason.

8.2.2. Exclusion Criteria

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

1. Patients previously or currently treated with other biological therapies.
2. Use of etanercept for less than 1-year duration.

8.3. Data Sources

Patients will be identified from the rheumatology patient registry with rheumatoid arthritis and will obtain information on patient demographics (age, gender), education level (years), present smoking status, disease duration (years), current steroid therapy (yes/no), baseline bath ankylosing spondylitis disease activity index (BASDAI), Bath Ankylosing spondylitis functional index (BASFI), human leukocyte antigen B27 (HLA-B27), anticitrullinated protein antibody (anti-CCP) status.

Primary Outcomes: Disease activity Index BASFI and BASDAI from the last follow-up visit.

8.4. Study Size

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

8.5. Data Management

The study data is structured data and will be exported into an excel spreadsheet. The rheumatology center in Baghdad Teaching Hospital will analyze the data and provide it with results based on the defined primary and secondary endpoints.

8.6. Data Analysis

All covariates will be summarized to get information about frequency distribution and mean, median or standard deviation. Numbers and percentages will be provided for categorical variables when performing descriptive analysis. Means, medians, standard deviations, or interquartile range as appropriate will be provided for continuous variables when performing descriptive analysis of continuous data.

Patients will be divided according to the mean of disease duration groups (below and above mean) and unadjusted comparisons between groups of the covariates and they will be evaluated using appropriate tests: chi-squared test will be used for categorical variables, t-test will be used for continuous variables, and the Kruskal-Wallis test for non-parametric variables; p-values willl be generated.

We will determine the effect of early referral on the biologic treatment response patients with AS a multivariate analysis by using a stepwise linear regression model. The response variable is defined as BASFI and BASDAI at last visit. The baseline variables are considered demographic data, disease duration (years), methotrexate (yes/no), Current steroid therapy (yes/no), baseline BASFI, BASDAI, HLA-B27 positive (yes/no), anti-CCP (yes/no), present smoking (yes/no).

We will determine the effect of early response by using the difference in change between the baseline of BASDAI and BASFI and last follow-up. P-value <0.05 will be considered statistically significant.

8.7. Quality Control

Not Applicable (N/A).

8.8. Limitations of the Research Methods

Missing data that could lead to bias is a limitation in this study.

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 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 the 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. Davide Simone, M Hussein Al Mossawi, Paul Bowness, Progress in our understanding of the pathogenesis of ankylosing spondylitis, Rheumatology, Volume 57, Issue suppl_6, November 2018, Pages vi4–vi9.

13. LIST OF TABLES

Not Applicable (N/A).

14. LIST OF FIGURES

Not Applicable (N/A).

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

Document Approval Record

Document Name:	B1801415 Amendment 2 (clean) 29 July 2021
Document Title:	B1801415 Amendment 2 (clean) 29 July 2021

Signed By:	Date(GMT)	Signing Capacity
PPD	05-Aug-2021 13:04:26	Author Approval