NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Long Term Adherence and Efficacy of Etanercept in SpA Iraqi Patients: 7 Year Data From Local Registry
Protocol number	B1801414
Protocol version identifier	3.0
Date	28 July 2021
Active substance	Etanercept
Medicinal product	Etanercept
Research question and objectives	Patients' adherence to biological treatment is one of the key factors for better response. The objective of this study is to evaluate the long-term adherence of SpA patients on Enbrel and the difference in efficacy between adherent and nonadherent groups.
Author	PPD – MD, M.Sc. PPD Pfizer Inc – Iraq
This document contains confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing this document, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.	

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
AE	Adverse Event
ANA	Antinuclear Antibody
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
GGP	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
MTX	Methotrexate
NA	Not Applicable
NIS	Non-interventional Study
NSAIDs	Nonsteroidal Anti-inflammatory Drugs

Abbreviation	**Definition**
RA	Rheumatoid Arthritis
SpA	*Apondyloarhtopathies*

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. ABSTRACT

See ANNEX 1.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	28 July 2021	Section 4 Abstract	Added back in to accept link	Administrative
		Throughout Document	Spelling errors	Administrative
		Section 6. Milestones	Updated to align with Study Report	Administrative

6. MILESTONES

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

7. RATIONALE AND BACKGROUND

Spondyloarthropathy or spondyloarthrosis refers to any joint disease of the vertebral column. As such, it is a class or category of diseases rather than a single, specific entity.[1]

Non-vertebral signs and symptoms of degenerative or other not-directly-infected inflammation, in the manner of spondyloarthropathies, include asymmetric peripheral arthritis (which is distinct from rheumatoid arthritis), arthritis of the toe interphalangeal joints, sausage digits, Achilles tendinitis, plantar fasciitis, costochondritis, iritis, and mucocutaneous lesions. However, lower back pain is the most common clinical presentation of the causes of spondyloarthropathies; this back pain is unique because it decreases with activity.[2] *Spondyloarthropathies* have an increased incidence of HLA-B27, as well as negative rheumatoid factor and ANA.

Ankylosing spondylitis (AS) is a type of arthritis in which there is long-term inflammation of the joints of the spine. Typically, the joints where the spine joins the pelvis are also affected. Occasionally, other joints such as the shoulders or hips are involved. Eye and bowel problems may also occur. Back pain is a characteristic symptom of AS, and it often comes and goes. Stiffness of the affected joints generally worsens over time.[3]

Between 0.1% and 1.8% of people are affected with AS world wide.[4] Onset is typically in young adults. Males are more often affected than females.[4]

There is no cure for ankylosing spondylitis. Treatments may improve symptoms and prevent worsening. Treatments may include medication, exercise, and surgery. Medications used include NSAIDs, steroids, DMARDs such as sulfasalazine, and biologic agents.[5]

8. RESEARCH QUESTION AND OBJECTIVES

The objective of this study was to evaluate the 1 and 7 years (long-term) adherence of SpA patients on Enbrel and the difference in efficacy between adherent and nonadherent groups.

9. RESEARCH METHODS

9.1. Study Design

- **Retrospective analysis** of patients with SpA that received etanercept from Baghdad Teaching Hospital (Rheumatology Center) from May 2012 through August 2019.
- **Primary objective:** 1 and 7 years adherence of SpA patients on Enbrel.
- **Secondary objective:** The difference in efficacy between the adherent group of patients (who continued Enbrel treatment) and the nonadherent group.

9.2. Setting

Patients and Methods

Data was collected from the Baghdad Teaching Hospital rheumatology registry. It captured all patients who have been treated with biologic therapies managed in the rheumatology department. The decision to initiate and maintain the treatment was guided by the American College of Rheumatology (ACR) recommendations.

Study population

Patients included in the study met the American College of Rheumatology/European League Against Rheumatism (EULAR) 2019 criteria for SpA[6], with at least 1 year of follow-up after starting their first biologic therapy. Exclusion criteria: patients previously or currently treated with other biological treatments.

Hypothesis

There was a small percentage of patients who adhered to Enbrel over 7 years, and there was no difference between the adherent and the nonadherent group in efficacy.

9.2.1. Inclusion Criteria

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

1. Diagnosed SpA patients.
2. 18 years of age and older.
3. Did not receive previous other biological treatments.
4. Patients have at least 1 year on Enbrel.

9.2.2. Exclusion Criteria

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

1. Had previously used another biological treatments.

2. Use of etanercept for less than 1 year duration.

9.3. Data Sources

Patients were identified from the rheumatology patient registry with a SpA diagnosis and information was obtained on patient demographics (age, gender), education-level (years), present smoking status, disease duration (years), current MTX and steroid therapy (yes/no), baseline BASDAI, and BASFI and last assessment of baseline BASDAI and BASFI.

Primary Outcomes: was the percentage of patients that have 7 year adherence on Enbrel.

9.4. Study Size

There was no pre-identified study-size sample. Patients that met the criteria were entered into the study.

9.5. Data Management

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

9.6. 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 dichotomous and polychotomous variables when performing descriptive analysis of categorical data. Means, medians, standard deviations, and interquartile range as appropriate will be provided for continuous variables when performing descriptive analysis of continuous data. Patients will be assessed for first-year adherence (first-year adherence is defined as patients having at least 7 consecutive visits in one year of Enbrel treatment), then the 7-year adherence will be assessed and the percentage of patients that achieve 7-year adherence will be calculated. The difference between adherent and nonadherent groups in baseline visit and last visit BASDAI and BASFI will be assessed for both groups.

The bivariate analysis will be conducted to determine if there is any association between the outcome and the exposure (the covariates). Unadjusted comparisons between groups of covariates and outcomes 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 will be generated. The baseline variables considered demographic data, disease duration (years), methotrexate (yes/no), current steroid therapy (yes/no), present smoking (yes/no).

The difference in efficacy between adherent and nonadherent groups by using change from the baseline in BASDAI and BASFI at the last visit will be determined. P-value <0.05 will be considered statistically significant, without multiplicity adjustment for this post-hoc analysis.

9.7. Quality Control

NA.

9.8. Limitations of the Research Methods

No missing data that could lead to bias was an identified limitation in this study.

9.9. Other Aspects

NA.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

10.2. This study involved data that exist in an anonymized, structured format and do not contain the patient's personal information.Patient Consent

As this retrospective study involved anonymized, structured data, which according to applicable legal requirements did not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer was not required.

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

Not required.

10.4. Ethical Conduct of the Study

The study was conducted in accordance with legal and regulatory requirements, as well as, with scientific purpose, value, and rigor, and followed 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).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involved data that exist as structured data from the time of study-start.

In these data sources, individual patient data were not retrieved, or validated and was 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) could not be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

There was no event of any prohibition or restriction imposed (eg, clinical hold) by any applicable competent authority in any area of the world. Nor was the investigator aware of any new information that might have influenced the evaluation of the benefits and risks of a Pfizer product.

13. REFERENCES

1. Proft, Fabian, and Denis Poddubnyy. “Ankylosing Spondylitis and Axial Spondyloarthritis: Recent Insights and Impact of New Classification Criteria.” Therapeutic Advances in Musculoskeletal Disease, June 2018, pp. 129–139.

2. Garcia-Montoya, Leticia et al. “Recent advances in ankylosing spondylitis: understanding the disease and management.” F1000Research vol. 7 F1000 Faculty Rev-1512. 21 Sep. 2018.

3. Jürgen Braun, Axial spondyloarthritis including ankylosing spondylitis, Rheumatology, Volume 57, Issue suppl_6, November 2018, Pages vi1–vi3.

4. Dubash, Sayam, et al. “New Advances in the Understanding and Treatment of Axial Spondyloarthritis: From Chance to Choice.” Therapeutic Advances in Chronic Disease, Mar. 2018, pp. 77–87.

5. 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.

14. LIST OF TABLES

NA.

15. LIST OF FIGURES

NA.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	Section 4	21 June 2021	*Long Term Adherence and Efficacy of Etanercept in SpA Iraqi Patients: 7 Year Data From Local Registry*

Document Approval Record

Document Name:	B1801414 Non Interventional Protocol Amendment 2 (clean) version 3 , 28 July 2021
Document Title:	B1801414 Non Interventional Protocol Amendment 2 (clean) version 3 , 28 July 2021

Signed By:	Date(GMT)	Signing Capacity
PPD	05-Aug-2021 13:29:44	Author Approval