NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Correlation of Anti-CCP with Disease Activity and its Impact on Biological Response in PsA in Iraqi Patients
Protocol number	B1801418
Protocol version identifier	Version 4.0
Date	27 July 2021
Active substance	Etanercept
Medicinal product	Etanercept
Research question and objectives	Determine the clinical impact of ACCP positivity for management (etanercept) in patients with PsA compared to negative ACCP patients.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACCP	Anti-Cyclic Citrullinated Peptide
ACR	American College of Rheumatology
AE	Adverse Event
anti-CCP	Anti-Citrullinated Protein Antibody
DAPSA	Disease Activity in Psoriatic Arthritis
DMARDs	Disease-Modifying Antirheumatic Drugs
EULAR	European League Against Rheumatism
GEP	Good Epidemiological Practice
GPP	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
PsA	Psoriatic Arthritis
RA	Rheumatoid Arthritis
SAP	Statistical Analysis Plan (if applicable)

Abbreviation	Definition
SPSS	Statistical Package for the Social Science (Software)
TNF	Tumor Necrosis Factor

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	22 June 2021	Section 5	Updated to align with Study Report	Administrative
2	15 July 2021	8.6	Clarified tools used for data analysis	Administrative
3	26 July 2021	Throughout document	Spelling errors	Administrative
4	27 July 2021	Throughout 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

Psoriatic arthritis is a chronic, systemic inflammatory arthritis that occurs in 6 to 42% of patients with psoriasis, affecting the peripheral joints, tendons, ligaments, and the axial skeleton. Current treatment guidelines for psoriatic arthritis recommends conventional synthetic disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, as initial therapy, followed by biologic DMARDs (tumor necrosis factor [TNF] inhibitors, interleukin- 12 and interleukin-23 inhibitors, and interleukin-17 inhibitors) or apremilast in patients who had an inadequate response to conventional synthetic DMARDs.[1]

The presence of anti-CCP antibodies in PsA and the prevalence was between 5.6 and 15.7% giving the optionality of biological treatment for RA patients, identifying a predictor for response will acquire more attention to rheumatologists for such patients.[1,2]

Psoriatic arthritis is a severe form of arthritis in which deformities and joint damage develop in many patients. Bone erosions are observed in 47% of patients within the first 2 years, despite the use of traditional disease-modifying medications in more than half the patients. Furthermore, presence of ACCP in PsA patients consider one of bad prognostic factors for PsA Patients.[3]

7. RESEARCH QUESTION AND OBJECTIVES

ACCP have been associated with lower response in PsA patients with positive ACCP. The objective is to evaluate the effect of ACCP on PsA patients and effect on their response to biological treatment.

8. RESEARCH METHODS

8.1. Study Design

- **Retrospective analysis** of patients with PsA 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 ACCP positivity for management (etanercept) in patients with PsA compared to negative ACCP patients.

- **Primary objective:** Determine the clinical impact of ACCP positivity for management (etanercept) in patients with PsA compared to negative ACCP patients.

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 American College of Rheumatology (ACR) recommendations.[4]

Study population

Patients will be included in the study if they meet the ACR/European League Against Rheumatism (EULAR) 2010 criteria for PsA[3,4] with at least 1 year of follow-up after starting their first biologic therapy. This includes patients who were in monotherapy or in combination therapy with concomitant conventional DMARDs.

Hypothesis

Our hypothesis is that there is no difference in response between sero-positive and sero-negative PsA patients to treatment with Enbrel.

8.2.1. Inclusion Criteria

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

1. Diagnosed PsA patients.
2. ≥18 years of age.
3. Have not received previous biological treatment.

8.2.2. Exclusion Criteria

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

1. Previous use of other biological treatments.
2. Etanercept use for less than 1-year duration.

8.3. Data Sources

Patients with PsA will be identified in the rheumatology registry. Patient demographic information (age, gender), education level (years), present smoking status, disease duration (years), current MTX and steroid therapy (yes/no), baseline DAPSA (Disease Activity in Psoriatic Arthritis), anti-citrullinated protein antibody (ACCP) status will be obtained. Primary Outcomes: DAPSA in first and last follow up visit.

8.4. Study Size

There is no pre-identified study size. 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 database (version 23) for statistical analysis.

8.6. Data Analysis

Categorical covariates will be described by frequency distribution while continuous covariates expressed in terms of their mean and standard deviation or median and interquartile range as appropriate. Patients will be divided for sero-positive PsA and sero-negative PsA (according to ACCP status) the 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 sero-positive on the biologic treatment response patients with PsA a multivariate analysis by using a stepwise linear regression model. The response variable is defined as disease activity index (either DAPSA, DAS-28 ESR, or DAS-28 CRP) at last visit. The baseline variables considered demographic data, disease duration (years), methotrexate (yes/no), current steroid therapy (yes/no), baseline disease activity index, anti-CCP (yes/no), psoriasis presentation and present smoking (yes/no).

We determined the effect of response by using change from baseline in disease activity index at the last visit. P value <0.05 is considered statistically significant, without multiplicity adjustment, for this post-hoc analysis.

8.7. Quality Control

Not Applicable (NA).

8.8. Limitations of the Research Methods

The missing data that could lead to bias is an identified limitation in this study.

8.9. Other Aspects

Not Applicable (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 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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3. Gossec L, et al. Ann Rheum Dis 2016;75:499–510. doi:10.1136/annrheumdis-2015-208337.

4. Coates, L.C.et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. Arthritis & Rheumatology, 2016. 68: 1060-1071.

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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