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LABORATORY OF BIOMATHEMATICS
MSC
RESEARCH METHOLOGY IN BIOMEDICINE
BIOSTATISTICS AND CLINICAL BIOINFORMATICS

PROTOCOL FOR AN OBSERVATIONAL STUDY FOR TOCILIZUMAB FOR TREATING RHERMATOID ARTHRITIS

ΠΡΩΤΟΚΟΛΛΟ ΓΙΑ ΜΙΑ ΜΕΛΕΤΗ ΠΑΡΑΤΗΡΗΣΗΣ ΓΙΑ ΤΟ TOCILIZUMAB ΓΙΑ ΤΗΝ ΘΕΡΑΠΕΙΑ ΑΣΘΕΝΩΝ ΜΕ ΡΕΥΜΑΤΟΕΙΔΗ ΑΡΘΡΟΙΤΙΔΑ

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FEBRUARY 2018

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Protocol for an observational study for Tocilizumab for treating rheumatoid arthritis

1. ABSTRACT

Objectives

Primary Objective

The primary objective for this study is as follows:

• To describe the clinical effectiveness and safety in patients suffering from rheumatoid arthritis (RA) who have been prescribed tocilizumab(TCZ), an interleukin -6 receptor inhibitor, in clinical practice. The main assessment time-point is Week 24 .

Secondary Objectives

The secondary objectives for this study are as follows:

• To compare tocilizumab effectiveness in two different subpopulations according to the previous pharmacological treatment.

• To observe quality of life (QoL) and safety outcomes.

• The clinical benefits as (TCZ) monotherapy.

Study Design

Description of Study

European, multicenter, prospective, non interventional observational study in RA patients treated with commercially available intravenous TCZ.

Number of Patients

Approximately 295 patients will be recruited in this observational study.

Target Population

Patients must meet the following criteria for study entry:

•Adult Patients, aged ≥18, suffering from moderate to severe RA.

• Also patients who have been prescribed a biologic therapy by his/her rheumatologist up to 6 weeks prior to the inclusion visit.

• Patients who have been given oral and written information about the study and agree their personal details to be used to computerized data.

Patients who meet the following criteria will be excluded from study entry:

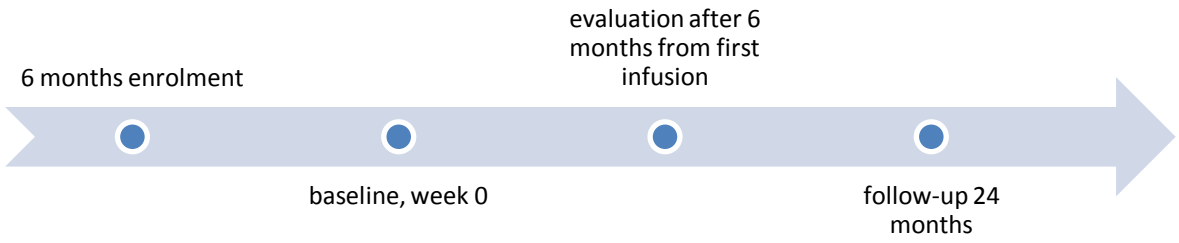
• Patients who suffer from severe ongoing infections and hypersensitivity to the active substance.

• Patients who are receiving or have received experimental DMARDs as part of a clinical trial studying RA treatment in the last 12 months

• Patients who have received any biologic therapy for more than 6 weeks prior to the inclusion visit and also women who are Pregnant or wishing to conceive.

Length of study

Approximately, enrolment will take place over a period of 6 months. Patients may be enrolled up to 6 weeks after commencing TCZ. The duration of observation for each patient will be 24 months.



Patient Reported Outcomes

Clinical outcomes will be evaluated by Health Assessment Questionnaire(HAQ) score and by 28-joint Disease Activity score(DAS28), Functional Assessment of Chronic Illness Therapy, visual analogue scale pain and morning stiffness where available.

Statistical Methods

The statistical analysis will be performed using SAS System software and were mainly descriptive. For continuous variables, descriptive statistics will be used. As far as the categorical variables counts of subjects and percentages will be performed. All patients receiving tocilizumab will be included in the analysis and, unless otherwise specified, missing data will not be imputed.

2. BACKGROUND

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterized by a progressive destruction of joints[1-2] which, depending on the severity, may be accompanied by systemic manifestations involving skin, blood vessels and internal organs which lead to progressive joint damage, functional disability and impaired quality of life. Is often associated with systemic manifestations such anemia, fatigue and osteoporosis [10].

In the absence of treatment, RA may cause a severe functional disability of the individual, an important reduction in QoL and an increase in mortality [2;4-8]. RA disease affects approximately a range between 0.5 and 1% of worldwide adult population [9] .Although the etiology of RA is unknown, it is considered to be multifactorial with the most important risk factors being, besides the genetic susceptibility, gender, age and smoking[1-2;5-8].It is worth mentioned that early diagnosis and implementation of adequate therapy are very important to reach clinical disease control.

Clinical diagnosis includes the determination of the rheumatoid factor (RF) classification criteria for RA, blood tests and physical exams. Recently, other specific antibodies were also assessed, including the

anti-citrullinated cyclic peptides (CCP) antibodies which arrear before the symptoms of the disease represents a useful therapeutic approach to RA [2;6].

Background on Tocilizumab

Tocilizumab is a humanized monoclonal antibody targeting the human IL-6 receptor [9] . It is a first-line biologic therapy and usually is used, after failure of two sDMARDs and as a subsequent-line biologic therapy after failure of TNFi in patients with severe RA (DAS28 >5.1) [11–13]. It is the first monoclonal antibody developed for RA treatment with this mechanism of action and has been recently approved by regulatory authorities in several regions and countries.

3. AIMS-OBJECTIVES

PRIMARY OBJECTIVE

The primary objective for this study is:

• To describe the clinical effectiveness and safety in patients suffering from rheumatoid arthritis (RA) who have been prescribed tocilizumab, an interleukin-6 receptor inhibitor, in clinical practice. The main assessment time-point is Week 24.

SECONDARY OBJECTIVES

The secondary objectives for this study are:

• To compare tocilizumab effectiveness in two different subpopulations according to the previous pharmacological treatment.

• To observe quality of life (QoL) and safety outcomes.

• The clinical benefits as tocilizumab monotherapy.

• To observe efficacy by RA patient types following initiation of first biologic therapy.

• To observe the additional effects of tocilizumab by assessing the score, if it is available:

Like the proportion of patients achieving remission at Week 24 ,

- according to the ACR/EULAR criteria definition and
- defined by Clinical Disease Activity Index (CDAI) score ≤2.8.
- and also defined by Simplified Disease Activity Index (SDAI) score ≤3.3.

- Proportion of patients achieving disease activity score remission and Low Disease Activity state at Week 24.

4. SETTINGS AND DESIGN

This is a global, observational, multi-center, non interventional study in RA patients, who are being treated with commercially available intravenous tocilizumab as a biologic therapy.

In accordance with the observational nature of the study, all procedures are consistent with normal clinical practice and no additional diagnostic or monitoring procedures which might modify the routine clinical practice have been applied to the patients. No study-specific medication will be administered and no other interventional procedures additional to those comprising routine clinical practice will be performed.

Approximately 295 patients will be recruited to this observational study. Around 59 centers in approximately 5 European countries will participate in the study. In case patients may have initiated treatment prior to study start-up, data collection may be partially retrospective. It is worth mentioned that patients who stop treatment with the prescribed tocilizumab for reasons of inefficacy or intolerance will continue to be observed for the planned period of 24 weeks.

Since the study is observational, visits are those pre-scheduled as part of usual clinical practice. These include:

• One enrolment visit may occur up to 6 weeks after the start of the biologic therapy, and in this case data collection will be retrospectively collected up to the time of enrolment.

• Usual follow-up visits according to the center's practice will take place during the study, observation period up to 24 weeks after the start of

the biologic therapy, with data collection planned at Week 0 baseline, at Week 12 and Week 24.

• Whereas the final visit, corresponding to that performed nearest to 24 weeks after starting first biologic therapy.

Furthermore data will be recorded at the enrolment visits, week 12 and 24 after the beginning of the therapy. Also additional tests for the recruited patients are not foreseen, and treatment-related information may be collected.

END OF STUDY

End of study is expected to be approximately 24 months, after enrollment of last patient in the study.

RATIONALE FOR TEST PRODUCT DOSAGE

As the objective of the study is to observe routine practice patterns of usage, the study protocol does not stipulate any specific dosing regimen. Dosage and duration of TCZ treatment were decided by the physician, according to the approved product information, the local treatment guidelines and the daily medical practice: The approved dosage, according to the Summary Product Characteristics (SmPC), is 8 mg/kg body weight, once every 4 weeks. The period of patient enrolment was 6 months. Any concomitant medication was recorded. When available, effectiveness and safety data were collected at baseline and 0, 2, 4, 6 and 12 months after the first TCZ infusion.

RATIONALE FOR PATIENT POPULATION AND ANALYSIS GROUPS

This study aims to evaluate in routine practice the relative comparative clinical effectiveness and safety outcomes of tocilizumab prescribed to patients starting their first biologic therapy. The patients will be observed for a period of 24 weeks from the start of the first biologic therapy, with attention to biologic treatment effectiveness and biologic treatment drug survival and safety outcomes.

5. OUTCOME MEASURES

CLINICAL EFFECTIVENESS MEASURES

The primary efficacy observation is the mean change in calculated DAS28-erythrocyte sedimentation rate (ESR) 12 weeks after start of biologic therapy at Week 0 (baseline). Furthermore the following efficacy parameters will be documented to enable description of the change over time at 0, 12 and 24 weeks as available.

• Tender joint count (TJC) and swollen joint count (SJC) based on 28 joint count, Creactive protein (CRP) also Physician Global Assessment and Patient Global Assessment of Disease Activity.

• All the above will be calculated by DAS28/CDAI/SDAI score based on 28 joint count. Furthermore the following information will be collected:

- Loss of efficacy or development of intolerance to biologic therapy.
- Rates and reasons for dose modifications .
- Rates, reasons, frequency and timing of permanent discontinuation of first biologic therapy and subsequent therapy introduced.

SAFETY OUTCOME MEASURES

The safety outcome measures for this study are as follows:

• Incidence of infusion reactions or injection site reactions during the study following the start of the therapy.

• Incidence of serious and non-serious AEs during the study as well as serious and non-serious AEs of special interest, including infections, during the study.

PATIENT REPORTED OUTCOME MEASURES

The patient reported outcome measures for this study are as follows:

- Health Assessment Questionnaire-Disability Index (HAQ-DI) score, Functional Assessment of Chronic Illness Therapy (FACIT), visual analogue scale (VAS) pain
- and morning stiffness where available.

6. MATERIALS AND METHODS

PATIENTS

The study population will include patients with moderate to severe RA, according to ACR classification criteria, of at least 24 weeks of evolution, in whom the treating physician has made the decision to commence treatment with TCZ within 6 weeks prior to the enrollment visit. Furthermore, patients must give their informed consent and must fulfill all inclusion criteria and exclusion criteria. Approximately 295 patients will be observed during this observational study.

INCLUSION CRITERIA

Patients must meet the following criteria for study entry:

•Adult Patients, aged ≥18, suffering from moderate to severe RA.

• Also patients who have been prescribed a biologic therapy by his/her rheumatologist up to 6 weeks prior to the inclusion visit.

• Patients who have been given oral and written information about the study and agree their personal details to be used to computerized data.

EXCLUSION CRITERIA

Patients who meet any of the following criteria will be excluded from study entry:

• Patients who suffer from severe ongoing infections and hypersensitivity to the active substance.

• Patients who are receiving or have received experimental DMARDs as part of a clinical trial studying RA treatment in the last 12 months

• Patients who have received any biologic therapy for more than 6 weeks prior to the inclusion visit and also women who are Pregnant or wishing to conceive.

• Patients whose first biologic therapy is given as part of a clinical trial studying RA treatment.

METHOD OF TREATMENT ASSIGNMENT

No study treatment will be administered, dosage and duration of TCZ treatment were decided by the physician and will be prescribed

according to the approved product information, local treatment guidelines and routine clinical practice. All procedures are consistent with normal clinical practice and no additional diagnostic or monitoring procedures which have been applied to the patients. The approved dosage, according to the SmPC, is 8 mg/kg body weight, once every 4 weeks. The period of patient enrolment was 6 months and concomitant medication was recorded.

DRUG AND PATIENT DISCONTINUATION

During the study the investigator has the right to discontinue a patient from the TCZ or draw away a patient from the study at any time. Also on the other hand patients have the right to voluntarily discontinue the TCZ or depart from the study at any time for any reason.

7. ASSESSMENT OF SAFETY

SAFETY PLAN

MANAGEMENT OF SPECIFIC ADVERSE EVENTS

During the study side effects were characterized early, and have been shown to be mechanistically linked to its mode of action and its effect on inflammation. In the case of TCZ: neutropenia, thrombocytopenia, elevation of liver enzymes as indicated by the results of liver function tests, lipid disorders and bronchitis ,are included[13,14,15].

Such adverse reactions, local prescribing information for TCZ offers recommendations for managing where the treatment dose and the concomitant medications might be temporarily adjusted TCZ dose decrease from 8 mg/kg to 4 mg/kg or tocilizumab transient interruption depending on the AE and clinical criterion.

SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist recording AEs, including serious adverse events (SAEs) and non-serious AEs of special interest also measurement of safety laboratory assessments, measurement of vital signs and other tests that are important to the safety evaluation of the study.

ADVERSE EVENTS

An adverse event (AE) can therefore be any unfavourable and unintended sign, including an abnormal laboratory finding, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can be any of the following cases:

• Any new disease or exacerbation of an existing disease that worsening in the character, frequency, or severity of a known condition.

• An intermittent medical condition like headache which was not recorded at Week 0 (baseline).

• Any deterioration in a laboratory value or other clinical test that is associated with symptoms or leads to discontinuation from the TCZ.

SERIOUS ADVERSE EVENTS

An SAE is any AE that meets any of the following criteria:

• Fatal and Life threatening although this does not include any AE that had it occurred in a more severe form or was allowed to continue might have caused death.

• Requires or prolongs inpatient hospitalization.

• Results in persistent or significant disability/incapacity.

• Significant medical event in the investigator's judgment.

NON-SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST

Non-serious AEs of special interest are required to be reported by the Investigator to the Sponsor within 1 working day after learning of the event. These can be the follow:

Infections, Myocardial infarction/acute coronary syndrome, GI perforation and related events, Anaphylaxis / Hypersensitivity reactions, Demyelinating disorders, Stroke, Bleeding events and Hepatic events.

The recording of AEs of special interest will follow the established procedures for AEs and SAEs in the study furthermore Guided questionnaires have been prepared for the AEs of special interest which will be sent to the investigators to obtain more detailed information.

8. FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

INVESTIGATOR AND SPONSOR FOLLOW-UP

In case the patient is lost follow up, or withdraws with consent, the investigator should follow each AE until the event has resolved to the Week 0 grade or better then the event is assessed as stable by the Investigator. Furthermore in time between the study, every SAEs considered to be related to tocilizumab should be reported. Also resolution of AEs should be reported in patient's medical record. In case the stabilization cannot be collected or returns to Week 0 an explanation should be recorded on the Adverse Event eCRF.

The sponsor may follow up by mail, fax, telephone or a traditional visit to obtain detail and outcome information in order to be considered if necessary to SAEs, non-serious AEs of special interest.

9. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The statistical analysis will be performed using SAS System software and were mainly descriptive .In addition, for continuous variables, descriptive statistics and modeling will be used to highlight interesting aspects of the data and to investigate the biologic treatment received at enrollment. As far as the categorical variables counts of subjects and percentages will be performed. Adverse events will be assigned a proffered term (PT) and will be categorized according to the medical dictionary for regulatory activities (MedDRA) .Also laboratory test will be summarized using descriptive statistics.

The main time-points of interest are Week 0, 12 and Week 24 post-baseline. The timing of assessment cannot be mandated, for that reason appropriate windows around these time points will be defined based on the date of each assessment as entered in the eCRF. All patients

receiving tocilizumab will be included in the analysis and, unless otherwise specified, missing data will not be imputed. Kaplan Meier analysis also will be performed on time to response, defined as the time in days from the start of observation to the first assessment of a DAS28>1.2.

ANALYSIS POPULATIONS

In the primary analysis population will be used for efficacy and safety analyses all recruited patients who received at least one dose of TCZ during the study. In case of other analysis populations, may be defined based on more restrictive criteria, such as fulfillment of eligibility criteria or a minimum duration of the observation period.

10. EFFICACY ANALYSES

PRIMARY EFFICACY VARIABLE

The primary efficacy observation of this study is the mean change in calculated DAS28- ESR 12 weeks after the start of biologic therapy at Week 0.

Descriptive summaries by biologic treatment group will be provided. Estimation of the primary analysis variable in the treatment group will be based on an analysis of covariance model including the baseline DAS28-ESR score as a covariate. The primary model may also include adjustment for other relevant baseline characteristics, such as the use of gender or RA duration. The evaluation of the TCZ will be explored using statistical models, such as analysis of covariance, that account for differences in the baseline characteristics of the groups. Kaplan Meier analysis also will be performed on time to response, defined as the time in days from the start of observation to the first assessment of a DAS28>1.2.

SECONDARY EFFICACY VARIABLES

The following efficacy parameters will be documented to enable description of the change over time at 0, 12 and 24 weeks:

• Mean change in DAS28-ESR 52 weeks after the start of biologic therapy at Week 0

• Mean change over time in TJC, SJC, ESR and CRP at 12 and 24 weeks after the start of biologic therapy and Mean change over time in CDAI and SDAI score at 12 and 24 weeks after the start of biologic therapy.

Secondary variables will be summarized. In addition selected continuous variables will be analyzed using descriptive statistics, number of cases, mean, standart deviation median minimum and maximum. The adverse events will be assigned a preferred term (PT) according to the MedDRA.

11. SAFETY ANALYSES

Safety parameters include:

• Incidence of infusion reactions or injection site reactions during the study following the start of the first biologic therapy.

• Incidence of serious and non-serious AEs during the study.

• Incidence of serious and non-serious AEs of special interest, including infections, during the study. Adverse events will be coded and categorized into body systems.

Adverse events will also be tabulated by severity and relationship to medication. Furthermore Serious AEs and AEs of special interest will be summarized separately. Laboratory tests will also summarized.

12. PATIENT-REPORTED OUTCOMES, QUALITY OF LIFE AND OTHER OBSERVATIONS

Where available, the following information will be captured:

• Disease activity based on DAS28, CDAI and SDAI.

- Health Assessment Questionnaire-Disability Index (HAQ-DI) score, Functional Assessment of Chronic Illness Therapy (FACIT), visual analogue scale (VAS) pain
- and morning stiffness where available.
- Loss of efficacy or development of intolerance to biologic therapy.

- Rates, reasons, frequency and timing of permanent discontinuation of first biologic therapy and subsequent therapy introduced.

INTERIM ANALYSIS

During the study interim analysis of baseline characteristics, efficacy and safety variables may be performed. But none of them will have confirmatory character.

13. DETERMINATION OF SAMPLE SIZE

The sample size was determined with reference to the final estimate of the proportion of RA patients achieving remission (DAS28<2.6) after a period of 6 months treating TCZ. An expected value of 31.5%was calculated, a result of other studies [17.18], and assuming that dosage of 8 mg/kg every 4 weeks for 6 months. The sample size turned out to be 236 patients, assuming to estimate this proportion by a one-side confidence interval (CI) 95% and choose as a distance from the lower limit a value of 5%. Considering a drop-out rate of 20%, the sample size was 295 patients.

14. ETHICAL CONSIDERATIONS

COMPLIANCE WITH LAWS AND REGULATIONS

The investigator of the study will ensure that this study is conducted in full conformance with the laws and regulations of the country in which the research is conducted. Also should make sure that the individual is protected to the greatest. The procedures should ensure that the sponsor and investigator abide by the principles of the ISPE GPP, the European Federation of Pharmaceutical Industries and Associations (EFPIA) Code on the Promotion of Prescription-only Medicines to, and Interactions With, Healthcare Professionals, and Volume 9A of The Rules Governing Medicinal Products in the EU. The study will also be carried out in keeping with local legal requirements. Further more Good Clinical Practice guidance is not applicable to this non-interventional study.

INFORMED CONSENT

To each patient will be provided a Informed Consent Form. If it is available a translation of the local language can be provided. The inform consent should be simple and understanding. In the end according to local requirements the final IRB/EC-approved Consent Forms must be provided to health authority submission purposes.

INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms and also any information which will be given to the patient and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated.The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments, also are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

CONFIDENTIALITY

In order confidentiality maintains, a coding system of each patient enrolled is applied. This means that every patient has a unique identification number. For each patient medical information are obtained confidential and may only be disclosed only by permission Informed Consent Form signed by the patient, unless permitted or required by law. After request, medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

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APPENDIX

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACR American College of Rheumatology

AE adverse event ALT alanine aminotransferase

CCP citrullinated cyclic peptides

CDAI Clinical Disease Activity Index

DAS28 disease activity score based on 28 joint count

DMARD disease-modifying anti-rheumatic drug

EC Ethics Committee (e)

CRF (electronic) Case Report Form

ESR erythrocyte sedimentation rate

EU European Union

EULAR European League Against Rheumatism

FACIT Functional Assessment of Chronic Illness Therapy

FDA Food and Drug Administration

Health Assessment Questionnaire-Disability Index

GI gastrointestinal

HDL high density lipoprotein

ICH International Conference on Harmonization

IL interleukin

IND Investigational New Drug (application)

IRB Institutional Review Board

LDL low density lipoprotein PRO patient-reported outcome

QoL quality of life

RA rheumatoid arthritis

RF rheumatoid factor

SAE serious adverse event

SAP statistical analysis plan

SDAI Simplified Disease Activity Index

SGPT serum glutamate pyruvate transaminase

SGOT serum glutamate oxaloacetic transaminase

SI serious infection SJC swollen joint count

TJC tender joint count

VAS visual analogue scale

DISEASE ACTIVITY SCORE (DAS28) DAS28

1. Tender-joint count of 28 joints, square-root transformed

2. Swollen-joint count of 28 joints, square-root transformed

3. Acute-phase inflammatory markers (ESR [mm/h] or CRP [mg/l]), log transformed

4. Patient's global assessment of disease activity (PGA) by visual analogue scale.

Calculation The DAS28 score is calculated according to the following formula:

DAS28(ESR) = 0.56 × SQRT(TJC28) + 0.28SQRT(SJC28) + 0.70 × ln(ESR) + 0.014 × GH
DAS28(CRP) = 0.56 × SQRT(TJC28) + 0.28SQRT(SJC28) + 0.36 × ln(CRP+1) + 0.014 × GH + 0.96
Total score, range 0.49–9.07

Scoring

• Disease remission < 2.6

• Low disease activity < 3.2 and ≥ 2.6

• Moderate disease activity ≥ 3.2 and ≤ 5.1

• High disease activity > 5.1