Contemporary Clinical Trials Communications 22 (2021) 100770

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: http://www.elsevier.com/locate/conctc

Prediction of response to Certolizumab-Pegol in rheumatoid arthritis (PreCePRA) by functional MRI of the brain – Study protocol for a randomized double-blind controlled study

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ARTICLE INFO

Keywords:
Rheumatoid arthritis
functional MRI
TNF inhibition
Neuroimaging

ABSTRACT

Background: Tumor necrosis factor inhibitors (TNFi) signify a major advance in the treatment of rheumatoid arthritis (RA). However, treatment success initially remains uncertain as approximately half of the patients do not respond adequately to TNFi. Thus, an unmet need exists to better predict therapeutic outcome of biologicals.

Objectives: We investigated whether brain activity associated with arthritis measured by functional magnetic resonance imaging (fMRI) of the brain can serve as a predictor of response to TNFi in RA patients.

Methods: PreCePRA is a multi-center, randomized, double-blind, placebo-controlled fMRI trial on patients with RA [1] [2]. Active RA patients failing csDMARDs therapy with a DAS28 > 3.2 and at least three tender and/or swollen joints underwent a brain BOLD (blood-oxygen-level dependent) fMRI scan upon joint compression at screening. Patients were then randomized into a 12-week double-blinded treatment phase with 200 mg Certolizumab Pegol (CZP) every two weeks (arm 1: fMRI BOLD signal activated volume > 2000 voxel, i.e. 2 cm^3; arm 2: fMRI BOLD signal activated volume < 2000 voxel) or placebo (arm 3). DAS28 low disease activity at 12 weeks was assigned as primary endpoint. A 12-week follow-up phase in which patients were switched from the placebo to the treatment arm followed the blinded phase. fMRI was carried out at screening as well as after 12 and 24 weeks of receiving CZP or placebo.

Conclusion: We hypothesize that high-level central nervous representation of pain in patients with rheumatoid arthritis predicts response to the TNFi CZP which we further investigate in the PreCePRA trial.

1. Background

1.1. Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory, autoimmune disorder of the synovium that causes severe morbidity and increased mortality. Early recognition and treatment with disease-modifying antirheumatic drugs is mandatory in achieving control of disease and prevention of joint dysfunction. However, in patients with longstanding and poorly controlled disease, joint manifestations such as erosions, rheumatoid nodules, and extraarticular manifestations are often present. Until now prognosis of RA studies have dominantly focused on physical joint function, disease activity and quality of life [3].

New therapeutic concepts have evolved over the recent decades and have led to significant improvement in the management of RA. One of the major effector in arthritis is TNF-alpha (TNFα) by stimulating the activation of the cytokine cascade. TNFα influences the disease state of patients with RA not only by eliciting activation of other pro-inflammatory cytokines but also by direct effects on nociceptors and the central nervous system (CNS). These modulatory effects have been shown by Schafers and colleagues [4]. The peripheral production of cytokines modifies CNS responses which in turn influence peripheral

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https://doi.org/10.1016/j.conctc.2021.100770
Received 28 July 2020; Received in revised form 9 March 2021; Accepted 5 April 2021
Available online 4 May 2021

arthritis via feedback-loops [5]. Atzeni et al. discussed that TNFα inhibitors (TNFi) do not only improve the signs and symptoms of RA, but also foster anti-inflammatory pathways, such as hormonal axes [6]. Recently, Hess and colleagues have shown that TNFi influence CNS activity shortly after treatment onset, even before the appearance of any discernible clinical anti-inflammatory effect [2].

Therefore, TNFi are considered a significant milestone in the treatment of RA. However, 30–40% of RA patients treated with biological DMARDs experience drug discontinuation because of either inefficacy or adverse events and most biologic-naïve RA patients fail to reach treatment targets on their first biologic therapy and subsequently have to switch to a different treatment [7,8]. Avoiding anti-TNF cycling would prevent disease progression and improve quality of life for RA patients who are primary non-responders to anti-TNFs. The development of an individualized approach to identify primary non-responders to anti-TNFs prior to treatment would allow significantly more patients to reach their treatment target and may increase treatment adherence of patients [8,9]. However, the search for predictors of response to TNFi has not been fruitful so far as no clinical and laboratory markers are known to predict TNFi response-to-treatment. Since treatment with TNFi is cost-intensive, a tailored use in patients responding best to therapy by avoiding unnecessary or even harmful exposure of patients unresponsive to therapy is vital. Our study explores the role of functional MRI of the brain as a predictor of TNFi response in patients with rheumatoid arthritis.

1.2. Study rationale

By using functional magnetic resonance imaging (fMRI) we have recently shown that TNFi elicit changes in brain function linked to the perception of pain in RA [2]. Functional MRI allows the detection of tiny changes in neuronal activity by measuring alterations of hemodynamics driven by neuronal activation, the so called BOLD (blood oxygenation level dependent) effect. TNFi rapidly reversed the widespread activation of brain regions involved in pain such as the thalamus and somatosensory cortex, as well as those involved in control of mood and emotions such as the limbic system. Moreover, a small phase I study of 10 patients with RA showed that high brain activity detected by fMRI before treatment predicts clinical response to Certolizumab Pegol (CZP) in combination with Methotrexate (MTX) after one month, suggesting that fMRI of the brain may be used as a tool to predict response to TNFi [1]. The rationale of this study is to validate the preliminary findings of this small study on a large cohort of patients.

2. Methods/design

2.1. Study objectives

2.1.1. Primary objectives

The primary outcome of interest is the proportion of patients who reach low disease activity measured by DAS28 (DAS28 $<$ 3.2) after 12 weeks of CZP study treatment according to their CNS activity measured by fMRI at the screening visit.

2.1.2. Secondary objectives

To compare clinical response to CZP to that of placebo in RA patients with high or low baseline CNS activity in the fMRI.

2.2. Investigational plan

2.2.1. Overall study design

This is a phase III, international, multi-centre, randomized, double-blind (first 12 weeks, followed by a 12-week single-blind), placebo-controlled, parallel-group, efficacy and safety study in RA patients. The study has 2 phases following a screening period of up to 4 weeks; a placebo controlled, three-arm, 12-week treatment phase for all randomized patients, followed by a 12 week treatment phase for responders and patients switching from the placebo arm, not reaching DAS28 remission (DAS28 $\leq$ 2.6), to the treatment arm.

2.2.2. Screening phase

Screening procedures including ultrasound as well as the first fMRI were performed within 4 weeks prior to the start of study medication at visit 2 (baseline). Subjects had to fulfil the 2010 RA classification criteria of the American College of Rheumatology (ACR) with a disease duration of at least 6 months.

2.2.3. Treatment phase

Subjects who met the inclusion criteria were randomized to CZP or placebo in a 2:1 ratio stratified by an fMRI voxel count of 2000, i.e. 2 cm^3, resulting in three study arms in a 1:1:1 ratio; namely high-voxel treatment group (arm A) low-voxel treatment group (arm B), and placebo group (arm C) (Fig. 1). They received either CZP in arm A and arm B or placebo in arm C after the initial fMRI examination. CZP was given according to the licensed label of CZP.

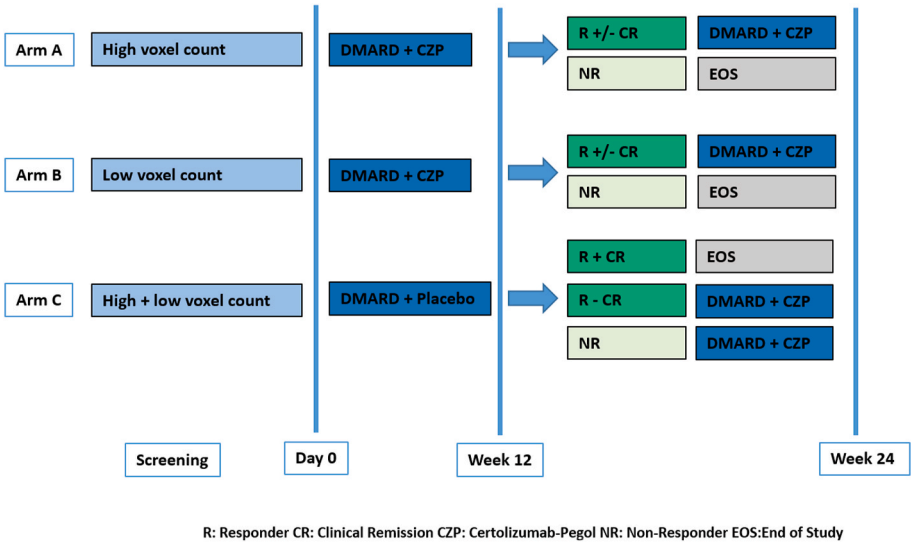

Fig. 1. Treatment diagram.

Clinical scores that constitute the study baseline were acquired at visit 2. All assessments including fMRI and ultrasound were performed at screening, week 12 and week 24.

2.2.4. Follow-up phase

Following the 12 week treatment phase, subjects were observed up to week 24 (visit 6) in order to analyse changes in clinical condition and safety.

2.2.5. Treatment diagram

Patients were randomized 2:1 into MTX plus CZP as TNFi or MTX plus placebo. Within the MTX plus TNFi treatment groups, patients were pre-stratified based on the results of the fMRI (high voxel or low voxel count). After 12 weeks, the clinical response (DAS28) was evaluated in all patients according to the label of CZP. Patients were classified as "responders" if there was a decline in DAS28 score of at least ≥1.2. vs. baseline and as “non-responders” if the decline was <1.2. Patients with DAS28 score <2.6 were considered in remission.

Non-responders from arms A and B (unless in remission) were withdrawn from the trial and treated according to local guidelines.

Responders and/or patients attaining remission from arms A and B continued to receive DMARDs (e.g. MTX) and CZP 200 mg every two weeks until week 24. Non-responders from arm C and responders from arm C who did not reach remission continued DMARDs (e.g. MTX) and switched from placebo to CZP with a loading dose of 400 mg at weeks 12, 14 and 16 and 200 mg every two weeks until week 24. Patients not achieving decrease in DAS28 thereafter were withdrawn from the study treatment and consequently treated according to respective local guidelines and observed until week 24.

2.3. Study endpoints

2.3.1. Primary endpoint

Proportion of patients who reach low disease activity according to the DAS28 (DAS28 < 3.2) at 12 weeks.

2.3.2. Secondary endpoints

- Remission defined as DAS28 < 2.6 at weeks 2, 12 and 24
- Low disease activity (defined as DAS 28 < 3.2) at 24 weeks
- DAS28 scores at 2, 12 and 24 weeks
- RAID score at 2, 12 and 24 weeks
- HAQ score at 2, 12 and 24 weeks
- SF-36 score at 2, 12 and 24 weeks
- Consistent changes in functional MRI scans over weeks 12 and 24
- Ultrasound OMERACT score at 2, 12 and 24 weeks
- Total volume of BOLD signal at screening, week 12 and 24 weeks
- Number of all adverse events, serious adverse events or suspected unexpected serious adverse reactions to study treatments
- Study treatment discontinuation due to any adverse event
- Hormone levels at 2, 12 and 24 weeks
- Cytokine levels at 2, 12 and 24 weeks

2.4. Efficacy and quality of life assessments during visits

2.4.1. fMRI

The non-invasive fMRI represents a specialized functional MRI scan of the brain, where local haemodynamic responses driven by neuronal activity in the brain can be measured. fMRI measures the blood-oxygen-level-dependent (BOLD) signal which allows localizing tiny changes in blood oxygenation status that reflect neuronal oxygen consumption, hence instantaneous neuronal activity. For instance, these BOLD signals can reflect the perception of inflammatory pain in the CNS during arthritis. Pain is the dominant symptom of RA and represents a potentially strong candidate for a relevant fMRI read-out to detect therapeutic response in RA. Direct effects of TNFi on pain have recently been demonstrated as reflected by reduced activation volume and decreased BOLD signal intensity of pain related brain regions in the fMRI [2]. Moreover, due to its non-invasive nature and lack of radiation exposure, BOLD fMRI can be repeated to characterize change over time. Functional MRI was performed at screening, at weeks 12 and 24.

2.4.2. Power-Doppler ultrasound

Power-Doppler ultrasound (PDUS) has emerged as an attractive imaging technique for the assessment and monitoring of synovial inflammation in RA. Standard validated methods are available for the quantitative analysis of synovitis in RA patients [10]. We used the OMERACT score evaluating wrists, MCPs 2–5, PIPs 2–5, knee joints and MTPs 2–5 for synovial hypertrophy (0–3), effusion (0–3) and power-doppler signal (0–3) [11]. Ultrasound examination was performed at screening, baseline and at weeks 2, 12 and 24.

2.4.3. DAS 28

DAS 28 is an RA disease activity score comprising 28 joints of shoulders, elbows, knees, wrists, MCPs and PIPs regarding tenderness and swelling. It is calculated using joint counts for swollen and tender joints, a marker of inflammation such as CRP or first-hour ESR, a VAS for global disease activity to be judged by the patient [12–15]. DAS28 was performed during all visits including screening and baseline.

2.4.4. Patient's and Physician's assessment of global disease activity (VAS)

The VAS (visual analog scale) for patients' self-assessment of global status (patient's global assessment of disease activity) and physician's global assessment of disease activity were planned during all visits including screening and baseline.

2.4.5. Duration of morning stiffness

At all visits the patients were asked for the average duration of stiffness in their hands upon arising in the morning.

2.4.6. Swollen and tender joint count (SJC/TJC)

An assessment of joints for swelling and for tenderness were completed at all visits including screening and baseline. Joints were assessed and classified as swollen/not swollen and tender/not tender by pressure and joint manipulation on physical examination.

2.4.7. Health assessment questionnaire (HAQ-DI) (Fig. 1)

The Stanford Health Assessment Questionnaire disability index was completed during all visits including screening and baseline. It is a patient reported questionnaire to assess difficulty during activities of daily living for RA and consists of 20 questions referring to eight component sets: dressing/grooming, arising, eating, walking, hygiene, grip, and activities [16,17].

2.4.8. RAID (rheumatoid arthritis impact of disease) (Fig. 2)

The RAID was completed during all visits including screening and inclusion visit. It is based on a patient reported questionnaire, for assessment and quantification of the impact of RA on person's life [18,19].

2.4.9. SF-36 (Fig. 3)

The SF-36 (Short Form 36) was completed during all visits including screening and inclusion visit. The SF-36 is one of the most frequently used questionnaires to assess health related quality of life [20].

2.5. Study sites

International participating clinics involved:

- Erlangen, Germany

- Berlin, Germany
- Frankfurt, Germany
- Freiburg, Germany
- Leipzig, Germany
- Coimbra, Portugal
- Belgrade, Serbia

2.6. Study duration

Recruitment period for each patient lasts 4 weeks followed by the treatment and follow-up period of 24 weeks in total.

2.7. Study population

2.7.1. Patient recruitment

Recruitment was planned in the outpatient and inpatient departments of the Medical Clinic 3, University Hospital Erlangen Germany, as well as in other participating centers. All materials involved were submitted to the respective local Ethics Committee (EC) for approval prior to use.

2.7.2. Screening and eligibility

All patients were to sign and date the most current IRB/IEC-approved written informed consent form (ICF) before any study specific assessments or procedures were performed. Patients had to fulfil all the inclusion criteria for participation in the study. At the screening visit, clinical and laboratory assessments were performed to determine patient eligibility based on inclusion/exclusion criteria. The following procedures and assessments were completed at the screening visit:

- Written informed consent
- Inclusion/Exclusion Criteria.
- Demographics and medical history.
- Review patient eligibility and ensure that all inclusion and exclusion criteria are met.
- Physical examination, including pulse rate, systolic and diastolic blood pressure, body temperature, body weight and physician's global assessment of disease status.
- ECG: a 12-lead ECG with formal readings.
- TB testing performed according to local guidelines.
- Rheumatoid factor and CCP-antibodies.
- Cytokines and Hormones of the hypothalamic-pituitary-adrenal/gonadal axis (IL-6, TNF, IFN-gamma, cortisol, ACTH und NPY).
- Hematology: Hematology includes complete blood count (RBC count, hemoglobin, heamatocrit, WBC count and differential, absolute WBC counts and platelet count).
- Blood chemistry/Serum chemistry (total protein, albumin, calcium, magnesium, phosphorous, glucose, uric acid, sodium, potassium, chloride, creatinine, liver profile (total bilirubin, alkaline phosphatase, AST [SGOT], ALT [SGPT], gamma-glutamyl transferase [GGT]), lactate dehydrogenase [LDH], LDL, HDL, total cholesterol, ESR, C-reactive Protein (CRP).
- Urinalysis (specific gravity, pH, glucose, protein, ketones, bilirubin).
- Hepatitis serology (according to national and international guidelines).

2.8. Inclusion criteria

Patient eligible for study participation had to fulfil the following requirements:

- Subjects must have a diagnosis of Rheumatoid Arthritis (RA), fulfilling the new ACR/EULAR classification criteria 2010 with disease duration for at least 24 weeks.
- Active RA with a DAS28 $\geq$ 3.2.
- $\geq$ 3 swollen and/or tender joints of the hands.
- Subjects must be DMARD-IR (inadequate responder).
- Must understand and voluntarily sign an informed consent form including written consent for data protection.
- Must be able to adhere to the study visit schedule and other protocol requirements.
- Must be aged $\geq$18 years at time of consent.
- Glucocorticoids treatment up to 10 mg prednisolone per day was allowed at study entry.
- At screening-visit patients should have been under stable dose DMARD therapy for at least three months (i.e. Methotrexate, MTX).

2.9. Exclusion criteria

- Individuals not able to understand and follow study protocol and not able to voluntarily sign informed consent.
- Individuals not willing to follow study protocol and sign informed consent.
- Patients treated with biological or investigational products before.
- Individuals with claustrophobia, tattoos containing metal, magnetic endoprotheses, surgery on bone in the previous 3 months, or any other condition prohibiting an MRI scan.
- Current treatment with MMF or preparations still in development.
- Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.
- A diagnosis of fibromyalgia, autoimmune or inflammatory disease other than RA; such as Psoriasis, Systemic Lupus Erythematosus, Progressive Systemic Sclerosis, Mixed Connective-Tissue Disease, Spondyloarthropathy, Behcet's disease, vasculitis, and autoimmune hepatitis.
- Participation in another phase 1–4 treatment study for RA.
- Patients younger than 18 years or are incapable to understand the aim, importance and consequences of the study.
- Pregnant or lactating female (women with childbearing potential have to use a highly effective contraceptive measure and continue its use for the time of exposure to the drug as required).
- Patients who possibly are dependent on the Principle Investigator or Investigator.
- Patients with serious or chronic infections within the previous 3 months.
- Opportunistic infections within the 6 months before screening.
- Cancer within the 5 years before screening (with the exception of treated and cured squamous or basal cell carcinoma of the skin).
- History of severe congestive heart failure.
- Current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, hematologic, gastrointestinal (a.e. diverticulitis), endocrine, pulmonary, cardiac, neurologic or cerebral disease.
- A history of organ transplantation (with the exception of corneal transplantation done more than 3 months before screening).
- Evidence of active tuberculosis.
- Evidence of chronic or active hepatitis B or C.

2.10. Statistical analysis and sample size calculation

Data will be analysed according to the Intent-to-treat (ITT) principle. Patients that are lost to follow-up will be treated according to the last observation carried forward principle, i.e. the data from the last completed visit will be used to impute missing values of subsequent visits of the same patient. If patients have shown response before loss to follow-up they will be considered as responders in the final data analysis. If there is no indication of response until loss to follow-up, patients

will be considered as non-responders. Issues of multiplicity will be accounted for by Bonferroni-Holm adjustment.

All relevant efficacy and safety outcomes will be evaluated in an explorative, descriptive manner, providing mean, minimum and maximum values, standard deviations and 95% confidence intervals for continuous variables and frequency analysis for categorical or binomial variables. If p-values will be calculated, they will be presented explicitly without referring to hypotheses but to study endpoints. All inferential tests will be two-sided if not stated otherwise. Comparisons between treatment arms will be performed applying cross-tabulation tests (i.e. Chi-square or Fisher's exact test) for proportions and *t*-test or Mann-Whitney-U-test for metric data, depending on whether the assumption of Gaussian distribution of sampling characteristics are met.

Safety data information on adverse events, severe adverse events or suspected unexpected serious adverse reactions or other reportable events regarding drug safety will be listed by the department responsible for pharmacovigilance.

The effect size of the primary outcome will be defined as differences in proportions with respect to low disease activity status.

In view of the primary outcome, the following proportions of patients are expected to attain low disease activity at the end of the first 12 weeks of study participation:

Arm A (high voxel count treated with Certolizumab Pegol): 80%
Arm B (low voxel count treated with Certolizumab Pegol): 40%
Arm C (high or low voxel count treated with placebo): 20%

Accordingly, the following effect sizes are:

Arm A vs. Arm B: d = 0.40
Arm A vs. Arm C: d = 0.60

Sample size calculation was based on the most conservative scenario i.e an effect size of 0.4, a type I error probability of 2.5%, and a type II error probability of 10%. According to the method suggested by Halperin et al. the sample size per subgroup would be 40. In order to maintain the level of the error probabilities, we additionally conservatively accounted for a proportion of 30% of possible missing values, due to losses to follow-up visits, non-compliance or adverse events. This leads to a total sample size of $N = 156$ subjects that will have to be allocated to the previously mentioned subgroups by randomization [21].

	Screening Phase	Treatment Phase		Follow-Up Phase		
Visit No.	1	2	3	4	5	6
Week	−4 to 0	Bas	2	12	14	24
Visit Window ± calendar days	0	0	±1	±1	±1	7
Written informed Consent	X					
Inclusion/Exclusion Criteria	X	X				
Demographics & medical history	X	X				
Hepatitis serology	X					
Randomization		X				
Vital signs (1)/weight (kg)	X	X	X	X	X	X
ECG	X	X				X
TBC testing (2)	X					
Ultrasound Scanning	X	X	X	X	X	X
FMRI	X			X		X
Hematology (3)	X	X	X	X	X	X
Physical exam (4)	X	X	X	X	X	X
Rheumatoid factor and CCP-antibodies	X					
Blood chemistry (5)	X	X	X	X	X	X
Hormones/Cytokines (IL-6, TNF, IFN-alpha, IFN-gamma, Cort, ACTH, NPY)	X	X	X	X	X	X
ESR	X	X	X	X	X	X
hsCRP	X	X	X	X	X	X
DAS28	X	X	X	X	X	X
RAID	X	X	X	X	X	X
HAQ-DI	X	X	X	X	X	X
SF-36	X	X	X	X	X	X
Safety evaluation		X	X	X	X	X
Concomitant medication since last visit		X	X	X	X	X

3. Discussion

The options for treating RA have increased over the last decades, however a considerable of patients do not respond adequately.

Rapid control of symptoms is intimately linked to the downregulation of pain in patients with RA. Inflammatory cytokines including TNFα, GMCSF, IL-6 and IL-17 stimulate peripheral nociceptive nerves and trigger pain in the context of inflammation [22,23]. Most cytokines associated with RA pathogenesis and pain are affected directly (via signaling through the Jak/STAT pathway) or indirectly (via enhancement by or a decrease in upstream or downstream signaling through the Jak/STAT pathway) [24]. However, effective targeting of effector cytokines could also interrupt the interaction between inflammation and pain responses explaining the rapid improvement of symptoms of arthritis observed in the context of cytokine inhibition. Furthermore, direct effects on nociception could complement the anti-inflammatory effect of cytokine inhibition allowing a more robust symptom control in the patients [25,26]. TNFα influence the disease state of patients with RA not only by eliciting activation of other pro-inflammatory cytokines but also by direct effects on nociceptors and the CNS [4]. Moreover, the peripheral production of cytokines modifies CNS responses which in turn influence peripheral arthritis via feedback-loops [5]. Atzeni et al. discussed that TNFi do not only improve the signs and symptoms of RA, but also foster anti-inflammatory pathways, such as the hormonal axes [6]. Recently, Hess and colleagues could show that TNFi influence CNS activity rapidly after treatment onset, even before anti-inflammatory effects could be observed [1,2].

Furthermore, it has been shown by Ogawa and colleagues that the peripheral nociceptor forms an excitatory synapse with second-order neurons in the dorsal horn of the spinal cord to initiate transmission in the CNS. These cytokine receptors, such as TNFR1, TNFR2, IL-1R, and IL-6R, are expressed by the second-order dorsal horn neurons. In fact, IL- 6, TNFα, and IL-1b enhance spontaneous post-synaptic current (sEPSCs) in the spinal cord by both increasing excitatory synaptic neurotransmission and suppressing inhibitory synaptic transmissions [27]. König et al., for instance, discuss that the induction of hypersensitivity of spinal nociceptive neurons by TNF-α depends significantly on IL-6/sIL-6R signaling acting downstream of TNF-α [28]. Taken together, these studies show that targeting peripheral inflammation by immunosuppressants will not necessarily affect persistent, chronic pain. Moreover, chronic pain mainfests itself in the CNS not only by functional but also anatomical changes [23]. However, modulating multiple pathways at the spinal level (e.g. TNFi, IL-6i or covering all of them by JAK inhibition) might be an effective way to prevent the development of chronic pain and to alleviate ongoing pain [27]. Successful treatment, as a predictive hypothesis, should lead to rapid retransformation of functional changes as already shown by Hess et al. and even to anatomical reconversion in the long term [2].

This study protocol describes a diagnostic strategy to better predict therapy success in RA patients treated with TNFi and could form the basis for new study strategies with new immunosuppressants. Therefore, PreCePra study is innovative in several aspects. Rather than pursuing treatment options following a try-and-error concept, this study explores outcome prediction of TNFi treatment by using fMRI of the brain, i.e. the final information integration system of the body. By using fully non-invasive BOLD fMRI we measure the network of brain structures in RA patients activated in response to nociceptive stimulation of the affected

joint before and at subsequent points in time after subcutaneous application of CZP. We also hope to achieve a better understanding of how chronic inflammation may alter physical or cognitive fatigue and how other rheumatic disorders and associated sickness behaviours will be influenced by immunosuppressants [29].

Other elemental aspects of this study include the prospective, sequential and simultaneous analysis of brain activity, clinical disease activity, joint imaging by ultrasound as well as laboratory data (biomarker, including the possibility for analyzing cytokines and hormones) and sociopsychological states (e.g. HAQ, RAID, SF36).

Another key outcome of the study will be to determine whether the response of a patient to a specific TNFi therapy can be predicted prior to that therapy by measuring individual BOLD activities in the brain before treatment. We hypothesize that measurable differences in brain activity between post-hoc responders and non-responders before the start of the therapy can predict treatment success.

In previous studies, we demonstrated that both mice with TNF-mediated arthritis and humans show enhanced brain activity in centers involved in pain perception and the control of emotions, while TNFi can rapidly down-regulate pathologically increased neuronal activity in the brain. We were able to show that there are specific differences in the connectivity of brain centers among TNFi responders and non-responders [1]. Hess et al. showed that neutralization of the proinflammatory cytokine TNFα rapidly affects CNS pain responses elicited by arthritis [2] and also Crohn's disease [30]. Therefore, TNFα inhibition has a direct impact on central pain processing by far preceding its anti-inflammatory peripheral effects [31]. To further investigate whether fMRI can also be used to differentiate between prospective responders and non-responders to TNFi, we undertook this follow-up study in a multi-center international patient cohort.

We anticipate that the PreCePRA study will allow us to better define the outcome of TNFi treatment in patients with RA before they are treated.

4. Conclusion

PreCePRA tests the hypothesis that functional MRI of the brain is able to predict treatment success of TNFi in RA patients. The objective of this paper is to describe the design of the trial and address major issues related to its development. The use of fMRI to predict treatment outcome is unique in the field of clinical RA trials and may be extended to other investigations respectively diseases. Successful achievement of the primary outcome in this trial would mark the first demonstration of an effective treatment prediction in a larger patient cohort to achieve a safer and better treatment for patients with RA.

Trial status

The date of the sponsor's authorisation by the Paul-Ehrlich-Institut (PEI) to conduct the PreCePRA-study was May 13th, 2013. The final ethical approval was on April 25th of 2013. The first study object was randomly assigned on September 3rd of 2013. Trial completed recruitment on January 1st of 2020.

The study was supported by UCB Biopharma SPRL, Brussels, Belgium, according to the items outlined in the IIS Contract.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2021.100770.

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