ABSTRACT

Study title: Non-interventional study to review the changes of depression after first-year of tofacitinib (XELJANZ®) treatment in rheumatoid arthritis patients

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Rationale and background

Rheumatoid arthritis (RA) is a chronic auto-immune disease characterised by joint inflammation and destruction with subsequent disability and effects on one's mental health. Patients with rheumatoid arthritis are jeopardised not only by an increased risk of musculoskeletal complications, but also a higher risk of associated comorbidities (such as cardiovascular and infectious conditions, osteoporosis, and some types of malignancies) than the common population. This may be both due to RA therapies (corticosteroids, non-steroidal anti-inflammatory drugs) and the systemic inflammation associated with the underlying disease.

At the same time, rheumatoid arthritis patients exhibit an increased prevalence of mental diseases, particularly depression, anxiety, and sleep disorders. This may be partially explained by the presence of the physical impairment and psychological stressors. Nevertheless, activation of signal paths by proinflammatory cytokines such as TNF-α, INF- γ, IL-1, and IL-6, may also play its role.

Tofacitinib is an orally administered Janus kinase (JAK) inhibitor that inhibits the inflammatory reaction by reducing the production of proinflammatory cytokines. The safety and efficacy of tofacitinib in the treatment of RA was studied in 6 phase III randomised, double-blind multicentric trials. These trials showed that tofacitinib reduced the signs and symptoms of RA and improved the patients' qualify of life.

The effect of JAK inhibitor use in actual clinical practice on the prevalence and severity of associated mental diseases in RA patients is unknown.
This non-interventional study is designated as a post-authorization safety study (PASS) and is conducted voluntarily by Pfizer.

Research question and objectives

The purpose of the study is to evaluate changes in depression symptomatology after 12 months in RA patients with newly indicated tofacitinib treatment.

The primary objective of this study is to describe and evaluate the changes of depression level within 12 months from the start of tofacitinib therapy in patients with RA and at least minimal level of depression.

The secondary objectives of this study are to describe and evaluate the level and changes of pain, anxiety, and insomnia in patients with RA and at least minimal level of depression. Additionally, it will describe the safety and effectiveness of tofacitinib for the treatment of rheumatoid arthritis.

Study design

This is a 12-month, single arm, prospective cohort, non-interventional, multi-centre study according to Czech legal definitions (Law 378/2007 Sb.).

Data for the study will be obtained from clinical practice records and patients printed questionnaires and transcribed to an anonymous electronic case report form (eCRF).

Population and setting

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

1. Patients aged ≥18 years.

1. Moderate to severe activity of rheumatoid arthritis (DAS28 ≥3.2).

2. Patient for whom the physician decision has been made to initiate a treatment with tofacitinib.

3. Patient with at least minimal level of depression (CUDOS questionnaire ≥11 points).

4. Capable of understanding and signing a written informed consent form.

5. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study is a requirement for inclusion into this study.

Participants are **excluded** from the study if the following criterium applies:

1. Patients unwilling/unable to fill in printed patient questionnaires.

The data will be collected by physicians allowed (according to indication restriction of reimbursement) to prescribe tofacitinib and, at the same time are specialized in the treatment of rheumatoid arthritis in outpatient rheumatology clinics.

Variables

- Demographics (age, sex, height, weight, BMI, smoking status, alcohol consumption).

- Disease characteristics (date of diagnosis, EQ-5D, DAS28, CRP, ESR).

- Comorbidities.
- Prior and concomitant RA medication.
- Analgesics, antidepressants, anxiolytics, and hypnotics.
- Patient questionnaires rating depression (CUDOS), anxiety (CUXOS), insomnia (JSEQ), and patient assessment of arthritis pain (visual analogue scale (VAS)).
- Safety (serious/non-serious adverse drug event).

Data sources

Patient medical records and patient paper questionnaires.

Study size

The goal of the study is to test the change of the CUDOS score after 12 months of tofacitinib treatment – to assess the change in depression after the treatment. To have a sufficient 90% power at least 123 patients need to be analysed. Considering a 20% drop-out rate, 154 patients need to be recruited in total.

Data analysis

A descriptive and comparative statistical analysis will be completed. Data will be collected in form of continuous and categorical variables. For categorical variables, results will be expressed as counts and percentages. Continuous variables will be described as counts, means, standard deviations, median, minimum, and maximum values. All adverse events will be presented as absolute numbers, frequency, and line-listings.

Planned Milestones

Start of data collection: 01 Jun 2019

Registration in EU PAS register 30 April 2021

End of data collection (Last subject last visit (LSLV)) 22 Jan 2024

Final study report: 21 December 2024