Chronotherapy in Inflammatory Arthritis (ChronIA trial): a randomized controlled trial comparing the effectiveness of morning and evening dosing of tofacitinib extended-release

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This study has been transitioned to CTIS with ID 2024-517865-17-00 check the CTIS register for the current data. We hypothesize that the timing of treatment in IA, also known as chronotherapy, matters and that the efficacy of tofacitinib XR depends...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Synovial and bursal disorders
Study type	Interventional

Summary

ID

NL-OMON52175

Source
ToetsingOnline

Brief title
ChronIA trial

Condition

- Synovial and bursal disorders

Synonym
Inflammatory Arthirtis; Joint inflammatoin

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Pfizer B.V.

Intervention

Keyword: Chronotherapy, Effectiveness, Psoriatic arthritis, Rheumatoid arthritis

Outcome measures

Primary outcome

The primary outcome is the difference in self-reported disease activity, measured with the Routine Assessment of Patient Index Data 3 (RAPID-3), between morning and evening dosing of tofacitinib XR after 3 months of treatment.

Secondary outcome

For our secondary endpoints the effectiveness from a clinical, patient as well as a translational point of view, will be compared between morning and evening dosing of tofacitinib XR.

Clinical outcomes:

• In rheumatoid arthritis (RA) and psoriatic arthritis (PsA) patients disease activity (states) are respectively measured with the DAS and DAPSA. The DAS is a pooled index that involves the incorporation of a graded 53-joint count for tenderness (Ritchie Articular Index, RAI), a 44-joint count for swelling, an erythrocyte sedimentation rate (ESR) and general health (GH, measured with a VAS 0 - 100mm) into a formula to obtain a numerical indicator of disease activity. The DAS formula is 0.53938*(RAI) + 0.06465(SJC44) + 0.33ln(ESR) + 0.00722(GH). The DAPSA is also a pooled index, which is made up following 5

domains: (1) a 68-joint count for tenderness, (2) a 66-joint count for swelling, (3) a C-reactive protein (expressed in mg/dl),(4) a patient*s assessment of the disease activity (VAS, 0 - 10 cm) and (5) a patient*s assessment of pain severity (VAS, 0 - 10 cm). The numerical values for the aforementioned 5 domains are summed to provide the DAPSA score. Thresholds for remission and moderate-to-high disease activity are respectively <1.6 and <=4 and >=2.4 and >14.

Patient reported outcomes (PROs):

• Self-reported disease activity, measured with the Routine Assessment of Patient Index Data 3 (RAPID3). Thresholds for remission and moderate-to-high disease activity are respectively <3.1 and >=6.1 if the 0 - 30 scale is used.

• Morning stiffness (severity and duration), measured with a 10-point Likert scale, whereby higher scores reflect greater severity.

• General Health, measured with a visual analogue scale (VAS, 0 - 100 mm), whereby higher scores reflect greater severity.

• Fatigue, measured with the Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F). The FACIT-F consists of 13-items with a 7-day recall period. Items are scored on a 0 - 4 response scale with anchors ranging from *Not at all* to *Very much so*. All items are summed to create a single fatigue score with a range from 0 to 52 and higher scores represent less fatigue.

• Fatigue, measured with a visual analogue scale (VAS, 0 - 100 mm), whereby higher scores reflect greater severity.

• Pain, measured with a visual analogue scale (VAS, 0 - 100 mm), whereby higher

scores reflect greater severity.

• Pain, measured with the Generalized Pain Questionnaire (GPQ). The GPQ differentiates between pain presumably due to central nervous system hypersensitization and pain primarily due to local nociception or inflammation.

• Quality of sleep, measured with the sleep scale from the medical outcomes study (MOS-ss). The MOS-ss includes 12 items assessing sleep disturbance, sleep adequacy, somnolence, quantity of sleep, snoring, and awakening. A sleep problems index, grouping items from each of the former domains, is also available.

• Quality of sleep, measured with an actigraph. The wrist Actigraph, Condor ActTrust, registers motion by means of 3-axis accelerometry. In addition, it records sleep (Bed Time, Get Up Time, Time in Bed, Total Sleep Time -hours-, Onset Latency -minutes-, Sleep Efficiency -proportion-, wake after sleep onset and number of awakenings); environmental light and skin temperature. Information is downloaded with the Act Studio software (Condor Instruments, São Paulo, Brazil), which allows extracting, visualizing and exporting collected data.

• Functional ability, measured with the health assessment questionnaire (HAQ). Higher HAQ scores indicate poorer function.

• Quality of life, measured with the Dutch EuroQol questionnaire with 5 dimensions (EQ-5D) with 5 levels. Higher scores represent a higher quality of life.

• Worker productivity, measured with the Work Productivity and Activity Impairment (WPAI) questionnaire, which includes presentism and absenteeism.

WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.

• Treatment satisfaction, measured with a visual analogue scale (VAS, 0 - 100 mm), whereby higher scores correspond with more treatment satisfaction.

• Compliance, measured with the Medication Adherence Report Scale (MARS-5). The MARS-5 is a questionnaire in which the patient assesses how often he/she is non-complaint. Higher MARS-5 scores indicate higher levels of self-reported adherence. We will also add a question on administration time adherence with the same 5-point Likert scale as the MARS-5.

Translational outcomes:

• To explore if the expression of circadian clock genes change over time and whether these changes correlate with treatment response we will collect blood at the indicated time points and we will store it at -80C. Whole blood will be collected using Paxgene Blood RNA Tubes, Qiagen (Paxgene tubes). Total RNA will be isolated and transcriptomic analysis will be performed using RNAseq. to analyze the expression of the clock genes. In addition, inflammation markers will be measured using the Olink inflammation panel (92 proteins). Moreover, the phenotype of immune cells will be analyzed using multi-color flow cytometry on isolated PBMCs. For all three approaches (clock gene expression, biomarkers and immune cell phenotyping) the focus will be on comparing rheumatoid arthritis and psoriatica arthritis responders versus non-responders on morning versus evening dosing of tofacitinib XR.

• To investigate whether treatment with Tofacitinib XR leads to restoration of

eubiosis faecal samples will be collected in a tube including an integrated swab at baseline (T0) and 3 (T3) and 6 (T6) months after treatment. The participants are given instructions to store their sample in their own fridge immediately upon acquiring, preferably 24 hours prior to the visit. Samples are brought in by the patient at the moment of the visit. Food intake over the last 3 days prior to the time of collection will be monitored by a short survey. After arrival at the laboratory, the samples will be stored until analysis at -80°C. Bacterial DNA will be extracted from the faecal samples and the sequences of region V3-V4 of the 16S rRNA bacterial gene will be amplified using barcoded primers with Illumina adapters. Bacterial libraries are prepared according to 16S Metagenomic Sequencing Library Preparation protocol (Part # 15,044,223 Rev. B, Illumina, San Diego, CA, USA). Sequencing will be performed on an Illumina MiSeq platform using a MiSeq Reagent Kit v3 (600 cycles).

Study description

Background summary

Circadian rhythms control, under activity of biological clock genes, several daily processes which can be observed in our physiology and behaviour (i.e. secretion of hormones and cytokines and sleeping and eating). Disruption of the circadian rhythm may lead to immune dysregulation. For example, shift workers have a higher chance at developing rheumatoid arthritis (RA). In line with this, various inflammatory arthritis symptoms show a distinctive diurnal pattern, including pain and joint stiffness. However, in daily practice we often do not take advantage of these circadian rhythms, especially not with regard to treatment, also known as chronotherapy.

Perry et al previous showed that pro-inflammatory cytokines, i.e. tumour necrosis factor (TNF) and interleukin(IL)-6, levels are higher at night-time compared to healthy controls and that especially IL-6 an overnight variation had, which was also correlated with the severity of morning stiffness. This

altered daily variation of pro-inflammatory cytokines is provoked by a desynchronization of the circadian rhythm, which is caused by an altered expression of circadian clock genes. Moreover, this desynchronization of the circadian rhythm may lead to dysbiosis, but one can also reason vice versa. Kaneshiro et al recently demonstrated that biologicals modulate the expression of circadian clock genes in a positive manner, which might also lead to rebuilding microbiota. Subsequently, a balanced microbiota, or eubiosis, might lead to relief of symptoms.

Although aforementioned reasoning makes it plausible that the timing of treatment in inflammatory arthritis might improve the efficacy of the given drug, there are only a handful of trials that investigate this concept. In the past chronotherapy using NSAIDs, glucocorticoids and methotrexate was investigated, which showed a significant improvement in symptoms, including functional ability, morning stiffness and disease activity, but also a reduction in dosage without loss of efficacy. To our knowledge, studies looking into chronotherapy using biologicals and/or JAK inhibitors in inflammatory arthritis patients are non-existing, but there are a few studies in mice with collagen-induced arthritis. Yaekura et al, for example, showed that evening dosing of baricitinib enhances the efficacy.

Lastly, we want to emphasize that most clinical research in inflammatory arthritis on circadian rhythms and chronotherapy is exclusively done in rheumatoid arthritis.

Therefore, the aim of this project is to compare the effectiveness of tofacitinib extended release chronotherapy, morning versus evening dosing, in inflammatory arthritis, rheumatoid arthritis and psoriatic arthritis, patients from a patient*s, clinical as well as a translational point of view.

Study objective

This study has been transitioned to CTIS with ID 2024-517865-17-00 check the CTIS register for the current data.

We hypothesize that the timing of treatment in IA, also known as chronotherapy, matters and that the efficacy of tofacitinib XR depends on it.Therefore, the aims of this randomized controlled trial are:
1. To compare the clinical effectiveness of tofacitinib extended release (XR) chronotherapy for inflammatory arthritis by looking at the difference in the Routine Assessment of Patient Index Data 3 (RAPID-3) between morning and evening dosing of tofacitinib XR after 3 months of treatment. (primary outcome)
2. To evaluate if sleep quality and morning stiffness severity differs between morning and evening dosing of tofacitinib XR.
3. To compare patient-relevant outcome (PRO) domains; namely pain, fatigue, activity limitation, quality of life and worker productivity between both administration times.

4. To explore if the expression of circadian clock genes change over time and whether these changes correlate with treatment response.
5. To investigate whether treatment with Tofacitinib XR leads to restoration of eubiosis.
6. To explore whether aforementioned effects differ between rheumatoid arthritis and psoriatic arthritis patients and/or deteriorate or improve after switching from administration time.

Study design

The Chronotherapy in Inflammatory Arthritis (ChronIA) trial is an open-label, randomized controlled trial, which will be carried out in the Erasmus Medical Center and IJsselland Hospital. Patients will be randomized using minimization randomization stratified for diagnosis, by an independent call center. Trained research nurses will examine patients and calculate the DAS or DAPSA depending on the diagnosis.

Patients are randomized into morning or evening dosing of tofacitinib XR (11mg q.d.) for 3 months, which is followed by switching to the alternate regimen for the next 3 months. Patients will be instructed to take the tofacitinib XR at approximately 08:00 - 09:00 and 22:00 - 23:00 hours.

Concomitant treatment with csDMARD(s) and prednisone (or equivalent) at a dose <=7.5mg is allowed, but participants have to have been receiving a stable dose for >=8 weeks prior to randomization and this will be continued during the entire follow-up. It is, therefore, not allowed to change the csDMARD and/or glucocorticoid dosage, including the time of administration.

The prescribed medication within this trail are all approved and used according to label. Nevertheless, safety monitoring will be carried out according to Dutch guidelines, and includes laboratory tests at fixed intervals. The study drug will be stopped in accordance with the protocol if (serious) adverse events, using WHO*s adverse reaction terminology, are seen by the attending rheumatologist.

Patients will be assessed at baseline and after 1, 3 and 6 months of treatment. At each visit patients will fill out online questionnaires and are seen by the research nurse, who calculates the DAS or DAPSA depending on the diagnosis. Additional blood and faecal samples will be taken at baseline (T0), 1 month (T1; only blood), 3 months (T3) and 6 months (T6). Finally, patients will wear an actigraph unit, a wristwatch-like package, on the wrist 2-times for 2 weeks at home. The actigraph will be picked up by the patient in the hospital 2 weeks prior to the visit.

Intervention

See section study design

Study burden and risks

If successful, this study will define the optimal dosing time of tofacitinib XR and could be a step towards the implementation of chronotherapy on a regular basis in daily practice. Moreover, it may also help better address well-known problems such as morning stiffness and fatigue, which often persist after reaching low disease activity.

The prescribed medication, Tofacitinib XR, within this trail is approved and used according to label. Generic ('off the shelf') commercial supplies are to be used for Tofacitinib XR. Moreover, the medication protocol within this trial complies with current (inter)national guidelines. Nevertheless, safety monitoring will be carried out according to Dutch guidelines, and includes laboratory tests at fixed intervals.

Furthermore, study visits are planned as much as possible on the same day as the outpatient clinic visit. Questionnaires can be filled out online at home. The actigraph unit, a wristwatch-like package, is worn on the wrist 2-times for 2 weeks at home, but does need to be picked up at the hospital. Blood samples are taken after the study visit and we will try to combine them with the routine blood tests. Faecal samples are collected and stored at home 24 hours prior to the visit and are brought in by the patient. In our opinion, the knowledge we are expecting to gain from this study outweigh the study burden (number of study visits, time for filling out online questionnaires, wearing the actigraph and additional blood and faecal samples).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- RA or PsA, according to respectively the ACR/EULAR 2010 criteria for RA and CASPAR criteria
- Active disease, respectively defined as a DAS>2.4 or DAPSA>14
- Age >=18 years

Exclusion criteria

- Current or previous treatment of arthritis with tsDMARD(s)
- Prednisone (or equivalent) usage at a dose of >7.5mg
- Work in shifts
- (Relative) contraindications for study medication:
a. Evidence of ongoing infectious or malignant process obtained within 3 months prior to screening and evaluated by a qualified health care professional.
b. Pregnant or nursing (lactating) women.
c. Female participants of child bearing potential and male participants whose partner is of child bearing potential who are not willing to ensure that they or their partner use effective contraception during the trial and for 3 months thereafter as in standard practice.
d. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests (LFT) such as aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/ serum glutamic pyruvic transaminase (ALT/SGPT), alkaline phosphatase, or serum bilirubin. The Investigator should be guided by the following criteria: Any single parameter may not exceed 2 x upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more

as soon as possible, and in all cases, at least prior to enrolment/randomization, to rule out laboratory error.
e. History of renal trauma, glomerulonephritis, or subjects with one kidney only, or a glomerular filtration rate (GFR) <30 ml/min.
f. Other underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the Investigator immunocompromises the patient and/or places the patient at unacceptable risk for participation in an immunomodulatory therapy.
g. Use of powerful CYP3A4 inhibitors (e.g. ketoconazole, fluconazole, tacrolimus and ciclosporin)
- Unable to understand, speak and write in Dutch.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	28-06-2022
Enrollment:	84
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Xeljanz XR
Generic name:	Tofacitinib extended release
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	08-09-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-02-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-12-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-04-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-517865-17-00
EU-CTR	CTIS2024-517865-17-01
EudraCT	EUCTR2021-004131-84-NL
CCMO	NL78735.078.21