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Comparing the effectiveness of our tailor-made management approach for rheumatoid arthritis with routine care from a clinical, patient, as well as economic point of view

Submission date
09/06/2020

Recruitment status
No longer recruiting

Registration date
27/10/2020

Overall study status
Completed

Last Edited
12/12/2023

Condition category
Musculoskeletal Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Rheumatoid arthritis is a long-term condition that causes pain, swelling and stiffness in the joints. The condition usually affects the hands, feet and wrists. There may be periods where symptoms become worse, known as flare-ups or flares.
Current management recommendations still adopt a 'one-size-fits-all' treatment approach, where ideally individualized treatment, or personalized medicine, is preferred. The prerequisite for precision medicine is the ability to classify individuals into groups that differ in their response to a specific treatment, which for RA still needs to be unravelled. However, we do believe that it is nowadays possible to individualize RA management by taking into account the presence of autoantibodies and the quick response to treatments such as glucocorticoids and targeted synthetic (ts)DMARDs.
Therefore, the aim of this project is to compare the effectiveness of our tailor-made management approach with routine care from a clinical, patient's as well as an economic point of view. In addition, we will investigate if our tailor-made management approach can be improved by adding biomarkers.

Who can participate?
Newly diagnosed, DMARD-naive, adult rheumatoid arthritis patients, according to the ACR /EULAR 2010 classification criteria

What does the study involve?
Patients will be assessed every 3 months with additional visits in month 1, 2 and 4.
Our tailor-made management approach is superior to routine care if treatment goals are attained faster without the use of more b- or tsDMARDs. The primary outcome for the cost-effectiveness analysis will be the incremental cost-effectiveness ratio (ICER), which is the ratio of the difference in costs to incremental benefits between both management approaches.

Patients are randomized into routine care or our tailor-made approach.
Both management approaches use a treat-to-target strategy, aiming for low disease activity. In routine care medication can be intensified every 3 months, reflecting current daily practice.

What are the possible benefits and risks of participating?
All patients will receive active treatment for their recently diagnosed rheumatoid arthritis. Although all prescribed medication within this trial is approved and used according to label, patients can still experience side effects. Common side effects, which depend on the given medication, are pneumonia, sinusitis, pharyngitis, headache, abdominal pain, nausea, vomiting, anemia, leucopenia, neutropenia, elevated liver enzymes and injection site reactions.

Where is the study run from?
Erasmus Medical Center, Rotterdam (The Netherlands)

When is the study starting and how long is it expected to run for?
December 2019 to December 2024

Who is funding the study?
Galapagos N.V. (Belgium)

Who is the main contact?
Dr. P.H.P. de Jong (p.h.p.dejong@erasmusmc.nl)

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2020-002802-21

IRAS number

ClinicalTrials.gov number

Nil known

Secondary identifying numbers
PRIMERA001

Study information

Scientific Title
PeRsonalIzed MEdicine in Rheumatoid Arthritis (PRIMERA trial): a multicenter, single-blinded, randomized controlled trial comparing usual care with a tailor-made approach

Acronym
PRIMERA

Study objectives
We hypothesize that treatment of RA can be individualized by taking into account the presence of autoantibodies and quick response to glucocorticoids and tsDMARDs. Therefore, the aims of this trial are:
1. To compare clinical effectiveness between our tailor-made management approach and routine care in newly diagnosed, DMARD naive, rheumatoid arthritis patients, by looking at:
a. Proportion of patients using a b- or tsDMARD after 9 months of treatment.
b. Disease Activity Score (DAS) over time
Noteworthy is the fact that our tailor-made management approach is only superior to routine care if treatment goals are attained faster without the use of more b- or tsDMARDs
2. To evaluate the cost-effectiveness of our tailor-made treatment approach versus routine care, by using the incremental cost-effectiveness ratio (ICER) as outcome, which is the ratio of the difference in costs to incremental benefits between both management approaches
3. To evaluate if patient participation, satisfaction and compliance is increased with our tailor-made management approach compared to routine care
4. To explore whether our tailor-made management approach can be more individualized by adding biomarker(s)

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approval pending, Medisch Ethische Toetsings Commissie (METC) Erasmus Medical Center (Dr. Molenwaterplein 40, Rotterdam, 3015 GD, The Netherlands)

Study design
Multicenter single-blinded randomized controlled clinical trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet.

Health condition(s) or problem(s) studied
Rheumatoid arthritis

Interventions
In this trial the effectiveness of a tailor-made management approach is compared to routine care, from a clinical, patients as well as an economic point of view, in patients with rheumatoid arthritis (RA).

Patients are randomized into routine care or our tailor-made approach using minimisation randomization stratified for center, by an independent call center.

In routine care patients are initially treated with methotrexate(MTX) and glucocorticoids(GCs) once intramuscularly (im). The initial therapy of patients randomized to our tailor-made approach depends on the presence of autoantibodies. Patients without auto-antibodies will receive hydroxychloroquine(HCQ)+GCs im, while patients with auto-antibodies start with MTX+GCs im.

Both management approaches use a treat-to-target strategy, aiming for low disease activity (DAS<2.4). If DAS ≥2.4 treatment is intensified until the aforementioned target is reached. In routine care medication can be intensified every 3 months, reflecting current daily practice. The intensifications steps are in following order: (1) Triple DMARD therapy (TDT), consisting of MTX, sulfasalazine (SASP) and HCQ; (2) MTX + Filgotinib (FIL); (3) MTX + TNF inhibitor (TNFi); and (4) MTX + 2nd TNFi. In our tailor-made approach besides the possible 3 monthly treatment intensification, medication alterations can also occur after 1 month and 4months, depending on the response to respectively GCs im and filgotinib (FIL). A good response to GCs im and FIL after respectively 1 and 4 months is defined as a DAS <2.4 OR ΔDAS >0.6. The intensifications steps in the tailor-made management approach are the same as routine care.

The prescribed medication within this trial are all approved and used according to label. DMARD dosages are MTX 25 mg/week orally (week 1 15mg/week; week 2 20mg/week and week 3 and thereafter 25mg/week),SASP 2 g/day (week 1 500mg bid; week 2 500mg tid; and week 3 and thereafter 1000mg bid) and HCQ 400 mg/day. GCs are givenonce intramuscularly with either methylprednisolone 120mg or triamcinolone acetonide 80mg. Filgotinib is a once-daily oral therapy of 200mg. The TNFi, including adalimumab 40mg/2 weeks s.c; etanercept 50mg/week s.c; certolizumab pegol 200mg/2 weeks s.c(after loading doses of 400mg/2 weeks at week 0, 2 and 4).; golimumab 50mg/4 weeks s.c.; and infliximab 3-5mg/kg at week 0, 2and 6 and 8 weekly thereafter, is free of choice for the treating rheumatologist. Concurrent treatment with NSAIDs and intra-articular GC injections (maximum of 2 per 3 months) will be allowed during follow-up.

Intervention Type
Drug

Phase
Phase III/IV

Drug/device/biological/vaccine name(s)

csDMARDs 1. Methotrexate 2. Sulfasalazine 3. Hydroxychloroquine tsDMARDs 4. Filgotinib bDMARDs 5. Etanercept 6. Adalimumab 7. Certolizumab pegol 8. Golimumab 9. Infliximab Others: 10. Glucocorticoids 11. NSAIDs (i.e. naproxen, diclofenac, ibuprofen)

Primary outcome measure

1. Clinical effectiveness:
1.1. Proportion of patients using a b- or tsDMARD after 10 months of treatment measured using patient records
1.2. Disease activity, measured with the disease activity score (DAS) every 3 months with additional visits at months 1,2 and 4. (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, 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)

2. Cost-effectiveness:
2.1. Quality Adjusted Life Years (QALYs). QALYs are determined by calculating the area under the curve of dutch EuroQol questionnaire with 5 dimensions (EQ-5D) every 3 months with additional visits at months 1, 2 and 4
2.2. Total costs divided into direct and indirect costs:
2.2.1. Direct costs: Medication costs are calculated from doses reported in the patients' case records, valued according to the Dutch college of health insurance. Medical consumption, including duration of hospitalizations and admission diagnosis, are recorded every 3 months with the iMTA medical consumption questionnaire. We will use the Dutch average length of stay by diagnosis if the duration of hospitalization is unknown.
2.2.2. Worker productivity is measured with the WorkProductivity and Activity Impairment (WPAI) questionnaire at ???, which includes presenteeism and absenteeism. WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.

Secondary outcome measures

Patients will be assessed every 3 months with additional visits at months 1, 2 and 4. At each visit patients will fill out all abovementioned questionnaires online and are seen by the research nurse, who calculates the DAS. Additional blood samples will be taken at baseline and 1 month and only at 2, 3 and 4 months if DAS ≥2.4 at the previous visit.

1. Clinical outcomes:
1.1. Disease activity (states) at 10 months, measured with the DAS
1.2. Biomarker(s) (levels). Blood will be collected at the indicated time points and inflammation markers will be measured using the Olink inflammation panel (92 proteins). In addition, immune pathway analysis will be performed on whole blood using RNAseq analysis

2. Patient-reported outcomes (PROs):
2.1. Self-reported disease activity, measured with the Routine Assessment of Patient Index Data 3 (RAPID3)
2.2. Morning stiffness (severity and duration), measured with a 10-point Likert scale
2.3. General Health, measured with a visual analogue scale (VAS, 0 – 100 mm
2.4. Fatigue, measured with a visual analogue scale (VAS, 0 – 100 mm)
2.5. Pain, measured with a visual analogue scale (VAS, 0 – 100 mm)
2.6. Functional ability, measured with the health assessment questionnaire (HAQ)
2.7. Quality of life, measured with the 36-Item Short Form Health Survey(SF-36) and dutch

EuroQol questionnaire with 5 dimensions (EQ-5D) with 5 levels
2.6. Patient satisfaction measured with the Treatment SatisfactionQuestionnaire for Medication (TSQM) and VAS
2.7. Compliance measured with the Medication Adherence Report Scale (MARS-5)
2.8. Patient participation measured with the 9-Item Shared Decision Making Questionnaire (SDM-Q9)
2.7. Patient participation and autonomy measured using the Impact on Participation and Autonomy questionnaire (IPAQ)

3. Societal outcomes
3.1. Worker productivity, measured with the Work Productivity and Activity Impairment (WPAI) questionnaire

Overall study start date
09/12/2019

Completion date
01/12/2024

Eligibility

Key inclusion criteria
1. Newly diagnosed, DMARD-naive RA patients, according to 2010 criteria
2. Between 18 and 80 years of age
3. Female participants of child bearing potential and male participants whose partner is of child bearing potential must be willing to ensure that they or their partner use effective contraception during the trial and for 3 months thereafter as in standard practice

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
300

Key exclusion criteria
1. Current or previous treatment of arthritis with DMARDs
2. Glucocorticoids (GCs) in the 3 months prior to randomization
3. (Relative) contraindications for study medication:
3.1. Evidence of ongoing infectious or malignant process obtained within 3 months prior to screening and evaluated by a qualified health care professional
3.2. Pregnant or nursing (lactating) women

3.3. 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.
3.4. 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 enrollment/randomization, to rule out laboratory error
3.5. History of renal trauma, glomerulonephritis, or subjects with one kidney only, or a glomerular filtration rate (GFR) < 30 ml/min.
3.6. 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
4. Unable to understand, speak and write in Dutch

Date of first enrolment
01/12/2020

Date of final enrolment
01/07/2022

Locations

Countries of recruitment
Netherlands

Study participating centre
Erasmus Medical Center
Dr. Molewaterplein 40
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Study participating centre
Leiden University Medical Center
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Study participating centre

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Study participating centre
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Netherlands
4818 CK

Study participating centre
IJsselland Hospital
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Sponsor information

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Sponsor type
Hospital/treatment centre

Website
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ROR
https://ror.org/018906e22

Funder(s)

Funder type
Industry

Funder Name
Galapagos N.V.

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal.

Intention to publish date
01/07/2025

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date