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

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This study has been transitioned to CTIS with ID 2024-511530-12-01 check the CTIS register for the current data. We hypothesize that treatment of RA can be individualized by taking into account the presence of autoantibodies and quick response to...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON49359

Source
ToetsingOnline

Brief title
PRIMERA

Condition

- Autoimmune disorders
- Synovial and bursal disorders

Synonym
Rheumatoid Arthritis; Symmetrical (small) joint inflammation with or without auto-antibodies

Research involving
Human

Sponsors and support

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

Intervention

Keyword: (Cost-)effectiveness, Personalized medicine, Rheumatoid Arthritis, Treatment strategies

Outcome measures

Primary outcome

The primary outcomes for the clinical effectiveness consists of 2 parts, namely the difference in (1) proportion of patients using a b- or tsDMARD after 10 months of treatment and (2) disease activity, measured with the disease activity score (DAS) over time. 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). Thresholds for remission and moderate-to-high disease activity for DAS are respectively <1.6 and >=2.4. Our tailor-made management approach is superior to routine care if treatment goals (DAS<2.4) 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.

For the cost-effectiveness analysis we will calculate the Quality Adjusted Life Years (QALYs) and total costs. QALYs express the impact of the disease on patients* health over time. Living in perfect health corresponds to a QALY of 1, a QALY of 0 reflects death. QALYs are determined by calculating the area under the curve of dutch EuroQol questionnaire with 5 dimensions (EQ-5D) with 5 levels.

Costs are divided in direct and indirect costs. We will analyse direct and indirect costs from a societal perspective. Direct costs are the costs of treatment and medical consumption, whereas indirect costs are costs due to loss of productivity (i.e. presenteeism and absenteeism).

Medication costs are calculated from doses reported in the patients* case records, valued according to the Dutch college of health insurances. Medical consumption, including duration of hospitalizations and admission diagnosis are recorded every three 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.

Indirect costs include not fully functioning, sick leave and reduction in work time. Worker productivity is measured with the Work Productivity and Activity Impairment (WPAI) questionnaire, which includes presenteeism and absenteeism. WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.

Secondary outcome

For our secondary endpoints the effectiveness after 10 months and over time, from a clinical, patient and societal perspective, will be compared between our

tailor-made management approach and routine care.

Clinical outcomes:

• Disease activity (states) at 10 months, measured with the DAS. 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). Thresholds for remission and moderate-to-high disease activity for DAS are respectively <1.6 and >=2.4.
• To investigate whether (changes in) biomarker(s) (levels) can adequately predict treatment response. For this, blood (sera, plasma and whole blood) will be collected at the indicated time points and stored at -80C. 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. Total RNA will be isolated and transcriptomic analysis will be performed using RNA-seq. Moreover, the phenotype of immune cells will be analysed using multi-color flow cytometry on isolated PBMCs. For all three approaches (biomarkers, immune pathway analysis and immune cell phenotyping) the focus will be on comparing ACPA negative with positive and treatment responders with non-responders.

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 <1.1 and >=2 if the 0 - 10 scale is used.

• Morning stiffness (severity and duration), measured with a 10-point Likert scale

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

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

• Pain, measured with Generalized Pain Questionnaire(GPQ) and PainDetect. The GPQ differentiates between pain presumably due to central nervous system hypersensitization and pain primarily due to local nociception or inflammation. The PainDETECT is designed to identify neuropathic pain components and its score ranges between 1 and 38. A score <13 and >18 respectively reflects the absence and presence of a neuropathic pain component.

• 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.

• Patient satisfaction, compliance and patient participation is respectively measured with the the Treatment Satisfaction Questionnaire for Medication (TSQM) and VAS, the Medication Adherence Report Scale (MARS-5) and the 9-Item Shared Decision Making Questionnaire (SDM-Q9). The TSQM measure treatment

satisfaction and covers 4 domains, namely effectiveness, side effects, convenience and global satisfaction. Higher TSQM scores correspond with more treatment satisfaction. The MARS-5 is a questionnaire in which the patient assess how often he/she is non-complaint. Higher MARS-5 scores indicate higher levels of self-reported adherence. The SDM-Q9 measures the patient perception of the extent of SDM.39 Higher SDM-Q9 scores indicate higher levels of perceived SDM.

• The Impact on Participation and Autonomy questionnaire (IPAQ) focuses on autonomy and participation of patients with chronic conditions. The IPAQ covers 5 domains, namely (1) autonomy indoors, (2) autonomy outdoors, (3) family roles, (4) social relationships and (5) paid work and education and in each domain the scores are averaged. Higher IPAQ-domain scores correspond with lower participation or more problems experienced.

Societal outcomes:

• 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.

Study description

Background summary

Clinical and radiographic outcomes in RA have improved enormously due to early detection of the disease, early initiation of *intensive* therapy and a

treat-to-target approach. The emphasis on early diagnosis and treatment has led to the development of the 2010 ACR/EULAR classification criteria for RA. With the introduction of these new classification criteria, the heterogeneity of the RA disease spectrum has become more visible.
Despite the heterogeneity of RA current management recommendations still adopt an *one-size-fits-all* approach, where ideally individualized treatment, or personalized medicine, is preferred. The prerequisite for precision medicine is the ability to classify individuals into subpopulations that differ in their response to a specific treatment, which for RA still needs to be unraveled. 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 glucocorticoids and targeted synthetic (ts)DMARDs.

First, the presence of autoantibodies, anti-citrullinated protein antibody and/or rheumatoid factor, is associated with a worse prognosis. Even current treatment recommendations advise to consider more aggressive therapy for RA patients with autoantibodies compared to RA patients without autoantibodies, also known as seronegative RA, when they fail on their conventional synthetic (cs)DMARD strategy. Moreover, literature suggests that these different disease subsets could be treated differently, with less intensive treatment regimens for seronegative RA patients. Recently, we demonstrated that seronegative RA patients can be treated with hydroxychloroquine with similar efficacy to methotrexate (MTX).

Secondly, delayed treatment responses increase the risk of erosive disease and functional impairment and also significantly influences the quality of life for RA patients. However, the optimal effect of csDMARDs is at least 6-12 weeks, which implies that the right choice of the initial csDMARD strategy has an important role in how fast treatment goals are attained. We previously showed that treatment goals are attained faster with a combination of csDMARDs compared to MTX monotherapy. However, treating physicians try to avoid problems as over-treatment and accompanying (serious) adverse events. Therefore, it would be helpful to be able to predict the initial treatment response as early as possible, with the purpose that rheumatologist can initiate less aggressive treatment and intensify it without delay when necessary. The early glucocorticoid response, measured within 1 month, is a useful tool for recognising RA patients who will probably fail on their initial csDMARD strategy and is, therefore, the key for aforementioned approach.

Finally, if the treatment target is not achieved with csDMARD(s) a biological (b-) or tsDMARD should be added. In daily practice TNFinhibitors are often the first choice, because of experience, long-term safety data and costs. However, the time to maximum response is longer for TNF inhibitors compared to the recently available tsDMARDs. To illustrate, the time to maximum ACR50 response is 8 weeks for filgotinib, compared to 24 weeks for adalimumab, the most prescribed TNF inhibitor. If we apply same reasoning as previous paragraph, an early inadequate tsDMARD response, measured within 8 weeks, is an indication to

switch to a bDMARD.

Although our elucidate tailor-made management approach is based upon 3 substantiated concepts, they have never been combined to one approach. Nor has it shown its benefit over routine care. 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.

Study objective

This study has been transitioned to CTIS with ID 2024-511530-12-01 check the CTIS register for the current data.

We hypothesize that treatment of RA can be individualized by taking into account the presence of autoantibodies and quick response to glucocorticoids and JAK inhibitors. Therefore, the aims of this randomized controlled 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 biological or targeted synthetic DMARD 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 biological or targeted synthetic DMARDs.

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 satisfaction, compliance and patient participation 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).

Study design

The PeRsonalIzed MEdicine in RA (PRIMERA) trial is a multicenter, single-blinded randomized controlled trial, which will be carried out in multiple hospitals in the southwestern part of the Netherlands. Patients will

be randomized using minimisation randomization stratified for center, by an independant call center. Trained research nurses, blinded to the allocated treatment arm throughout the study, will examine patients and calculate the Disease Activity Score (DAS).

Patients are randomized into routine care or our tailor-made approach. 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 4 months, 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.

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 given once 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, 2 and 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.

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 or the dosage lowered in accordance with the protocol if (serious) adverse events, using WHO*s adverse reaction terminology, are seen by the attending rheumatologist. MTX can be given subcutaneously if patients experience gastrointestinal complaints. If MTX is stopped for safety reasons,

it will be substituted by leflunomide (20mg/day).

Patients will be assessed every 3 months with additional visits at months 1,2 and 4. At each visit patients will fill out online questionnaires and are seen by the research nurse, who calculates the DAS. Additional blood samples will be taken at baseline (T0), 1 (T1) and 3 (T3) months and only at 2 (T2), and 4 (T4) months if DAS>=2.4 at the previous visit.

Intervention

See section study design.

Study burden and risks

If successful, this study will define a more tailor-made management approach for RA and could be a step towards personalized medicine. Problems as over-treatment and accompanying (serious) adverse events are then circumvented by this tailor-made management approach, while disease control is attained even faster without the use of more b- or tsDMARDs.
Within this trial all prescribed drugs are used according to label.
Furthermore, study visits are planned as much as possible on the same day as the outpatient clinic visit and questionnaires can be filled out online at home. Blood samples are taken after the study visit and we will try to combine them with the routine blood tests. Therefore, 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 and additional blood 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

- Newly diagnosed, DMARD-naive RA patients, according to 2010 criteria
- Age >=18 years

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:
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 enrollment/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.

4. 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:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-04-2021
Enrollment:	300
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Etanercept
Generic name:	Etanercept
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Filgotinib

Generic name:	Filgotinib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Hydroxychloroquine
Generic name:	Hydroxychloroquine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Methotrexate
Generic name:	Methotrexate
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Sulfasalazine
Generic name:	Sulfasalazine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	20-10-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-12-2020
Application type:	First submission
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	CTIS2024-511530-12-01
EudraCT	EUCTR2020-002802-21-NL
ISRCTN	ISRCTN16170070
CCMO	NL70492.078.20