THE RA BIODAM STUDY. Prospective Validation of Soluble Biomarkers as Predictors of Structural Damage in Rheumatoid Arthritis.

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To conduct a pivotal study to determine the independent predictive validity of several soluble biomarkers (e.g. MMP3, CTX-II, CTX-1, OPG, RANKL) considered to be high priority candidates for predicting structural damage in RA according to the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Joint disorders
Study type	Observational non invasive

Summary

ID

NL-OMON35219

Source
ToetsingOnline

Brief title
THE RA BIODAM STUDY

Condition

- Joint disorders

Synonym
rheumatism, rheumatoid arthritis

Research involving
Human

Sponsors and support

Primary sponsor: CaRE Arthritis

Source(s) of monetary or material Support: CaRe Arthritis

Intervention

Keyword: DMARDs, prognosis, rheumatoid arthritis, treatment strategy

Outcome measures

Primary outcome

Radiographic joint progression according to the modified Sharp/Van der Heijde score (SHS) (range of 0-448) assessed on radiographs of the hands and feet obtained at baseline and after 6 months of follow up on standard DMARD therapy or combination DMARD/anti-TNF therapy.

Secondary outcome

1. Radiographic progression according to the SHS after 1 year of follow up on standard DMARD or combination DMARD/anti-TNF therapy.

2. Radiographic progression according to the SHS after 2 years of follow up on standard DMARD or combination DMARD/anti-TNF therapy.

3. Radiographic progression as assessed by only the SHS erosion score (range 0-280).

4. 3-month change in biomarker level from baseline following the introduction of standard DMARD therapy.

5. 3-month change in biomarker level from baseline following the introduction of methotrexate monotherapy.

6. 3-month change in biomarker level from the start of a change in standard DMARD therapy.

7. 3-month change in biomarker level from the start of treatment with combination DMARD/anti-TNFα therapy.

8. 6-month change in biomarker level from baseline following the

introduction of standard DMARD therapy.

9. 6-month change in biomarker level from the start of a change in standard

DMARD therapy.

10. 6-month change in biomarker level from the start of treatment with

combination DMARD/anti-TNFα therapy.

11. Corresponding changes in DAS44, swollen joint count, tender joint count,

patient pain NRS, patient global NRS, physician global NRS,

HAQ, ESR, CRP, Hb, Platelet count, IgM-RF etc.

Study description

Background summary

There is consensus in the rheumatological community on a fundamental research and clinical imperative: the identification and validation of biomarkers that reflect structural damage endpoints in clinical trials and in clinical practice. The severity of disease is generally measured using clinical outcomes that remain difficult to quantify and whose predictive validity for structural damage endpoints tends to be poor. Traditional inflammation parameters, ESR and CRP,lack specificity and correlate poorly with damage at the individual patient level. Plain radiography remains the gold standard though it does not allow detection of early joint damage
and does not identify patients at particular risk of joint damage. The poor prognosis associated with early and destructive RA, and the benefit of aggressive treatment strategies, has led to an emphasis on early diagnosis and aggressive treatment regimens incorporating a TNF inhibitor.
A major problem related to the management of RA patients is the early identification of patients that are at risk of developing severe and destructive disease. Identification of soluble biomarkers that are predictive of radiographic progression would be extremely valuable to both clinical research and clinical practice:
1. It would allow for the selection of patients at high risk for radiographic progression in clinical trials reducing sample size requirement and duration of study.
2. It would allow for the identification of patients in clinical practice at

high risk for disease progression and therefore requiring aggressive intervention early in the disease course.
3. It would optimize ongoing management of patients during the course of disease by providing an *early-warning signal* to clinicians that more aggressive treatment is warranted to minimize the development of structural joint damage.
If active and agressive rheumatic disease could be identified early in the disease course through the simple measurement of feasible biomarkers this would support the early introduction of anti-TNFαtherapy as opposed to the delay incurred by the use of standard DMARD agents.
The proposed study will therefore assess the predictive validity of standard clinical and laboratory variables that are used to evaluate disease severity as well as high priority candidate soluble biomarkers. The data collected in the present study will also be used to derive risk
assessment and prognostic tools based on clinical and biological parameters, particularly for patients on standard DMARD therapies. In addition, results from this trial will be used to evaluate the impact of different treatments strategies on various biomarkers.
The results from the present study will have significant implications not only for individual patients but also from the societal perspective since it will enhance the overall understanding and application of different treatment approaches. Moreover, by proposing risk assessment and
prognostic tools, the current study will facilitate the appropriate and timely use of expensive biological drug therapies for those patients where the benefits will clearly outweigh the risks.

Study objective

To conduct a pivotal study to determine the independent predictive validity of several soluble biomarkers (e.g. MMP3, CTX-II, CTX-1, OPG, RANKL) considered to be high priority candidates for predicting structural damage in RA according to the criteria developed by the OMERACT Biomarker working group in patients receiving standard DMARD and anti-TNF therapy.

Study design

This OMERACT study is an observational study. The study design will facilitate capture of the following essential data components:

A. Change in biomarker following change/institution of standard DMARD therapy or following addition of anti-TNFalpha therapy.
1. increased dose of methotrexate by >=10 mg weekly to a maximum dose of 25mg weekly.
2. add-on of alternative DMARD.
3. switch to alternative DMARD.
4. add-on of anti-TNFalpha therapy.

B. Change in biomarker in relation to change in co-variates/predictors during the study.
Disease activity will be monitored systematically every 3 months by the DAS44. Changes in standard DMARD and/or anti-TNFalpha therapy will be implemented according to 2010 EULAR recommendations which state a target of remission (DAS44 <1.6) for patients receiving standard DMARD therapy in the setting of early disease and a target of low disease activity state (LDAS;DAS44 <=2.4) for patients receiving anti-TNFalpha therapy in the setting of established disease. Biomarker samples will be collected every 3 months and prior to change in DMARD and/or anti-TNFalpha therapy (specific criteria, see protocol).

C.Change in biomarker in relation to radiographic damage endpoint. Radiography will be conducted every 6 months (baseline, 6, 12, 18, 24 months).

Study burden and risks

Patients are treated according to international guidelines. No specific risks are associated with participation in this study. During 2 years patients will spend 8-9 hours at the study. Blood samples will be taken and X-rays every 6 months. Questionnaires will be carried out at almost every visit. The measurements will not cause an extra risk to the patients.

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

• 18 years of age or older;
• RA according to the 2010 Rheumatoid Arthritis Classification Criteria;
• Joint symptoms for >= 3 months prior to screening;
• DAS44 > 2.4;
• About to start DMARD therapy (methotrexate, salazopyrin, hydroxychloroquine, chloroquine, leflunomide) or
- increased dose of methotrexate by >=10 mg weekly to a maximum dose of 25mg weekly (if already receiving >15mg will require add-on DMARD/anti-TNF or switch to alternative DMARD),
- add-on of alternative DMARD,
- switch to alternative DMARD,
- start of first anti-TNFα agent (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab);
• If already on DMARD therapy this has been stable for the 3 months prior to the baseline visit;
• If already on systemic steroid, dose must be stable (prednisone <= 7.5mg/day) for 1 month prior to the baseline visit;
• Agreed to participate in the study by signing an informed consent;
• Patient will be available for follow up for a minimum of 24 months from the baseline visit.

Exclusion criteria

• Intra-articular steroid injection within 4 weeks prior to the baseline visit;
• Prior treatment with anti-TNFα or other biological agent (rituximab, abatacept, tocilizumab);
• Malignancy within past 5 years (other than basal cell carcinoma that has been adequately treated or excised, squamous cell cancer of the skin, and cervical carcinoma in situ);
• A serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level >= 3 times the upper limit of normal;
• A serum creatinine level >150 µmoles/liter or an estimated creatinine clearance <75 ml/minute;
• Concurrent pregnancy or breast feeding, wishes to conceive during the study period, or inadequate contraception;
• Alcohol and/or drug abuse as determined by investigator;
• History of:

a. Significant renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, neurological or dermatological disease;
b. Significant cardiac disease, myocardial infarction within 6 months of screening, unstable angina, congestive heart failure (New York Heart Association [NYHA] Class III-IV), known arrhythmias of ventricular etiology;
c. Serious infection (defined as requiring parenteral antibiotics or hospitalization) within 3 months prior to the baseline visit;
d. Active tuberculosis or history of tuberculosis without documented curative treatment
• For patients starting anti-TNF therapy, a positive TB screening test and no record of effective prophylaxis according to local expert recommendations;
• Significant trauma or major surgery within 3 months prior to the baseline visit, or known planned surgery during the next year;
• Known infection with Human Immunodeficiency Virus (HIV), Hepatitis B or Hepatitis C;
• Any clinically significant active infection including herpes lesions;
• Hematopoetic disorder:
a. Hgb <= 10g/dL or Hct <= 32%;
b. Absolute WBC count <= 3.0 × 109/L (3000/mm3);
c. Neutrophil count <= 1.2 × 109/L (1200/mm3);
d. Platelet count <= 100 × 109/L (100,000/mm3);
• Patient with any condition that would prevent participation in the study and completion of the study procedures, including language limitation;
• Patient is not willing to sign an informed consent.

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-03-2012
Enrollment:	70

Type:	Actual

Ethics review

Approved WMO Date:	19-12-2011
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)

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
CCMO	NL38200.096.11