

The TACERA study; Towards A Cure for Early Rheumatoid Arrthritis

PROTOCOL TITLE: The TACERA study; a longitudinal observational study of patients with early rheumatoid arthritis.

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Appendix II: Formulae for computing disease activity scores

1.0. Background & Rationale

Early diagnosis and treatment is crucial for preventing disease progression in patients with rheumatoid arthritis (RA). Indeed, prompt therapy and tight control have been proven in clinical trials of RA to alter the long-term course of disease towards a more benign outcome by limiting structural damage and long term disability (1). Nonetheless, clinical remission is only achieved in a minority of subjects, and in spite of recent therapeutic advances, drug-free remission remains a rare event (2,3). This may be due to many factors. For example, there are no validated instruments for reliably predicting how patients will respond to therapy. Nor is it possible to predict which patients will respond more favourably to one particular drug or drug combination, compared to another. Secondly, our understanding of low disease activity states in patients with RA is limited (4,5). As a consequence we lack the clinical and laboratory tools to identify those patients in clinical remission who would tolerate drug tapering or withdrawal. The ability to target remission-inducing therapies to individual patients very early in the disease course would be a major advance. Accurate prediction of disease resolution would also prevent unnecessary exposure of patients to potentially toxic therapies. Indeed, by identifying biomarkers that reflect a state of true biological/sub-clinical remission it would be possible to withdraw medication safely, and to achieve drug-free remission in a substantial proportion of patients.

Under this backdrop, we conceptualize that it will be possible to (i) apply a combination of clinical and laboratory parameters to predict clinical responses to disease modifying drugs in patients with recent onset RA; (ii) use laboratory parameters to monitor biological responses to therapy; and (iii) define a true biological remission state in patients with early RA. Such an approach to therapeutic decision-making means that patients receive the drug combinations most likely to induce and sustain remission.

1.1. Working hypothesis

Our working hypothesis is that a suite of immunological assays (hereafter termed “the immunological toolkit”) can be used to accurately predict clinical responses to therapy at a molecular and cellular level. We also propose that immune based assays can be adapted to define an immune signature associated with a state of sustained clinical remission in patients with early RA. This study protocol seeks to recruit a large cohort of patients with early RA. Biological samples will be acquired from study subjects and used to develop the immunological toolkit, through the identification of baseline biomarker signatures (prior to starting therapy), and by documenting the changes in the immune system in response to therapeutic intervention.

Several principles underpin this study:

1. RA is associated with detectable perturbations of the immune system at very early stages of disease.
2. Clinical remission is associated with a biological state that has similarities to a healthy immune system.
3. The healthy immune system is associated with a distinct immunological fingerprint defined by serum, cellular and/or molecular signatures in peripheral blood.
4. Restoration of this state of immune health may be induced with therapies that target these perturbations.

1.2. Study Design

In order to develop such an immunological toolkit, we will establish a longitudinal observational cohort of patients with early RA. These patients will be followed up for a period of at least 18 months, during which time biological samples will be collected at pre-defined time points.

1.3. Choice of design

We have opted for a UK-wide longitudinal observational study, in which early RA patients will receive intensive treatment using synthetic and biological disease modifying anti-rheumatic drugs (DMARDs). This prospective study is therefore aimed at collecting data relating to “real life” management for this disease using national guidelines to inform therapy decisions. Samples derived from the cohort will be used to develop the immunological toolkit. The clinical and laboratory data collected will be used to define predictors of clinical response, and to further refine definitions of the remission state with particular emphasis on immune biomarkers. By collecting samples before and after therapy adjustments it will be possible to document changes in immune signatures in response to therapy, and ultimately to define how these changes relate to clinical outcomes. While the focus of this study will be the initial 18 months following diagnosis, longer term data on clinical outcomes will be collected where resources permit.

1.4. Study population

We plan to recruit patients with early inflammatory arthritis with symptom duration less than 6 months, who fulfill the 1987 American College of Rheumatology (6) and/or the 2010 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) Classification Criteria for Rheumatoid Arthritis (7). All study subjects will be DMARD naïve and will not have previously received corticosteroids for the current episode of inflammatory arthritis. We plan to study patients who carry rheumatoid factor (RF) and antibodies to citrullinated protein antigens (ACPA) in their serum. It is accepted that this subgroup represents a subset of genetically and phenotypically distinct patients when compared to those with seronegative disease, since ACPA+ disease is associated with different disease pathogenesis, natural history and response to treatment (8,9). In particular, these patients are more likely to accrue joint damage (10), therefore improving the likelihood of our being able to study biomarkers of tissue damage over time.

1.5. Justification for the study

There are many published longitudinal studies and inception cohorts of patients with RA that have collated detailed clinical information over time, including, but not confined to, patients recruited to clinical trials.

Examples of such studies undertaken in the UK include:

- (a) *British Society for Rheumatology Biologics Registry (BSRBR)*: This registry was launched in October 2001 with the aim of examining the outcome and long term safety of TNF inhibitors in patients with RA, with specific focus on serious infection, malignancy and cardiovascular morbidity, and collecting data on sufficient patients to capture rare, unexpected adverse events (11). The target population was 4000 patients treated with each biologic agent followed for 5 years. No biological samples were collected at initiation of the registry, but genomic DNA has been acquired subsequently in the BRAGGS study for pharmacogenomic as well as genome wide association studies (12).
- (b) *Early Rheumatoid Arthritis Network (ERAN)*: ERAN, evolved from its precursor ERAS, is a prospective observational cohort of 1153 newly

diagnosed RA patients established to monitor outcomes of patients with early RA treated according to local standards of practice with conventional DMARDs (13). Standardized data sets including demographic, comorbidity, disease activity and outcome measures have been collected prospectively, and at regular intervals thereafter, but no biological samples have been collected.

- (c) *Norfolk Arthritis Register (NOAR)*: NOAR is an early inflammatory arthritis inception cohort (14). From 1990, general practitioners and local rheumatologists have referred all adults (aged ≥ 16) with two or more swollen joints, lasting for 4 weeks or more. With the principal aim of studying the natural history of RA, longitudinal data from this cohort ($n = 4000$) have been used to examine the prevalence and predictors of remission, functional disability, radiological outcome, cardiovascular mortality and comorbidity, and the development of non-Hodgkin's lymphoma. Serum and genomic DNA, but not peripheral blood mononuclear cells (PBMC), have been acquired from all participants and stored.

These large cohorts were established with very specific goals in mind, such as monitoring for disease outcome, drug toxicity, identification of risk factors or genome wide genetic analysis, and so extensive sampling of biological material for immunological analysis was not included. Accordingly, there is no information about the immune status of these subjects prior to or subsequent to introducing therapy.

More recent studies have sought to identify molecular and cellular signatures associated with disease activity states or response to therapy in a range of clinical settings. Examples of such studies include:

- (a) Burgoyne and colleagues demonstrated that in a subset of RA patients in clinical remission persistence of an atypical population of peripheral blood T cells, termed inflammation related cells (IRC) defined by flow cytometry, predicted disease flare at 18 months (OR 6.4; $p < 0.001$) (15).
- (b) Saleem and colleagues recently demonstrated increased proportions of naïve CD4+ T cells and reduced numbers IRC in RA patients in sustained remission (16). Paradoxically, the % of CD62L^{neg}, Foxp3⁺ regulatory T cells was higher in those patients who flared after discontinuing TNF inhibitors.
- (c) Haupl and colleagues studied female RA patients during and after pregnancy to study molecular signatures associated with disease remission and postpartum relapse (17). While only subtle differences could be documented during pregnancy, postpartum flare was associated with cell subset specific signatures associated with activation of the innate immune system.
- (d) The group of Tak and Verweij demonstrated a negative correlation between a type I IFN gene signature in peripheral blood mononuclear cells and the response to rituximab (18). The same group were unable to detect a specific gene expression signature in synovial tissue that was associated with subsequent clinical response to infliximab (19).
- (e) In a study of renal transplant patients, investigators from the Immune Tolerance Network identified a B cell signature associated with drug free, stable graft tolerance. This included a panel of genes associated with B cell differentiation, and elevated numbers of peripheral blood naïve and transitional B cells (20).

These data highlight the potential value of defining immune signatures in the clinical setting. However, because of their relatively small sample size, they also emphasise the need for a more systematic and unbiased approach to defining molecular and cellular signatures associated with distinct disease activity states in much larger cohorts of patients.

1.6. Choice of therapy

One of the major goals of this study is to define predictors of clinical remission, as well as developing a set of biomarkers that describe a biological state of remission. To this end, patients will be treated intensively with synthetic and biological DMARDs, using as a treatment schedule the national clinical guidelines for the management of RA in adults, commissioned by the National Collaborating Centre for Chronic Conditions, funded by the National Institute for Health and Clinical Excellence (NICE), and published by the Royal College of Physicians in February, 2009 (21). The treatment goal will be disease remission. Therapy adjustments, made at the discretion of the supervising physician, will be informed by monitoring of disease activity using the validated composite disease activity score for 28 joints (DAS28); this general approach is also known as “Treat to Target” (22). This schedule may include the use of combination DMARDs, including, but not confined to, methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, azathioprine or gold, with corticosteroids for the first 6 months, with therapy adjustments aiming for DAS28 < 2.6. By 6 months (or later, depending on treatment response), those patients with persistent disease activity will be offered TNF inhibitors in combination with DMARDs in the event of an inadequate response to at least two DMARDs (DAS28>5.1). An alternative biological agent will be considered in those patients in whom a TNF inhibitor is contraindicated or not tolerated. At or after 12 months rituximab, tocilizumab or abatacept will be considered for those with an inadequate response to TNF inhibitors. Therapy choices will be made in line with NICE guidelines (21). Those patients with adequate or partial responses to combination DMARDs or TNF inhibitor will continue to be monitored for the duration of the study.

1.7. Impact of the study on the management of patients in the future

The current study will benefit participants since they will be treated intensively according to best practice guidelines, and their responses monitored closely. Disease remission will be the goal. Study participants are unlikely to benefit directly from the biomarker studies in the short term, since the clinical outcomes of study subjects will be used to develop the immunological toolkit. However, those patients achieving low disease activity states (including clinical remission defined by the new ACR/EULAR criteria; ref 23), and who also demonstrate immunological signatures commensurate with biological remission may be suitable for drug tapering or withdrawal. This would reduce unnecessary drug exposure and reduce health care costs. In the longer term, the development of serum, cellular and molecular markers (the “toolkit”) that inform therapy choices from the outset, predict remission and define biological remission states would be a major advance for patients with RA, with treatments being individually tailored to the patient.

2.0. Study Objectives and Design

2.1. Study Objectives

Primary objective:

- 1) To establish a cohort of newly diagnosed patients with RA to develop an immunological toolkit, a suite of molecular and cell-based assays. The toolkit will be developed through in depth laboratory analysis of biological samples and clinical data collected at pre-defined time points.

Secondary objectives:

To use the results from the immunological analysis to develop algorithms for:

- 1) Stratifying patient subgroups with respect to prognosis based on immune signatures.
- 2) Predicting responses to specific therapies.
- 3) Defining how changes in immune signatures over time relate to clinical outcomes.
- 4) Defining true biological/subclinical remission state or states.
- 5) Correlating biological signatures with clinical as well as patient-reported health outcomes.

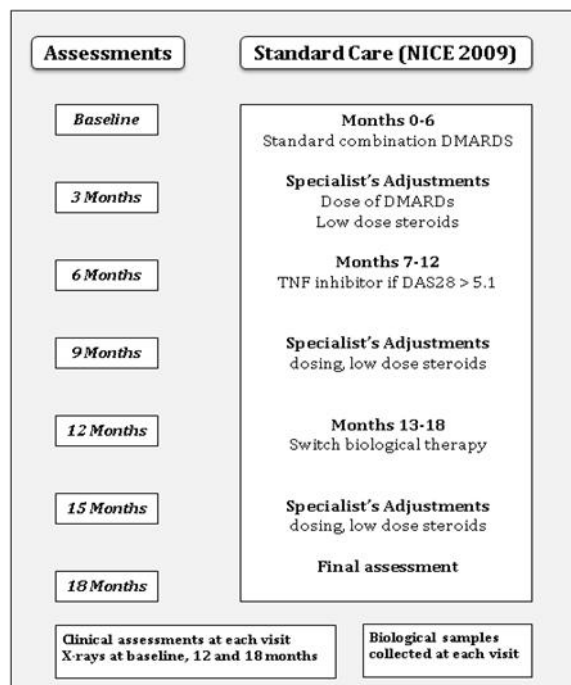
2.2. Study design

The TACERA study is a UK longitudinal observational cohort of 410 patients with early seropositive RA treated according to NICE guidelines.

2.3. Target population

Patients presenting to early arthritis or general rheumatology clinics with signs and symptoms of inflammatory polyarthritis of ≤ 6 months duration will be recruited to the study if they fulfill classification criteria for RA (6,7) and there is considered to be a clear intention on the part of the supervising rheumatologist to commence therapy with DMARDs. All patients will be positive for RF and ACPA, as defined by routine clinical laboratory testing, and will have had no prior exposure to DMARDs, or to corticosteroids for the current episode of arthritis.

2.4. Study summary flowchart



2.5. Study summary of clinical and laboratory assessments

Assessment ^a	Screening ^b	Baseline Month 0 ^b	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18 ^c
		<i>Day 0</i>	<i>Day 91</i>	<i>Day 182</i>	<i>Day 273</i>	<i>Day 364</i>	<i>Day 448</i>	<i>Day 532</i>
			<i>Week 13</i>	<i>Week 26</i>	<i>Week 39</i>	<i>Week 52</i>	<i>Week 64</i>	<i>Week 76</i>
Informed consent	X							
Inclusion criteria checks ^d	X							
Exclusion criteria checks ^d	X							
Routine blood (FBC, creatinine, LFTs)	X		X	X	X	X	X	X
RF/ACPA	X ^e							
X-rays (chest)		X ^f						
X-rays (hands & feet)		X ^e				X ^g		X ^h
Extended 66/68-Joint Count		X	X	X	X	X	X	X
Physician and patient global assessments		X	X	X	X	X	X	X
Acute phase reactants ESR, CRP	X	X ^e	X	X	X	X	X	X
DAS28, SDAI, CDAI Calculations (automatic EDC calculation)		X	X	X	X	X	X	X
ACR/EULAR remission criteria check		X	X	X	X	X	X	X
Pain VAS		X	X	X	X	X	X	X
Lifestyle Factors Questionnaire		X	X	X	X	X	X	X
HAQ		X	X	X	X	X	X	X
IPQ-R-RA		X		X		X		X
EQ5D		X		X		X		X
SF-36		X		X		X		X
FACIT-F		X		X		X		X
MAPLe-RA		X		X		X		X
RA medication review		X	X	X	X	X	X	X
Compliance checks			X	X	X	X	X	X
Adverse event review			X	X	X	X	X	X
Blood for biomarkers ⁱ		X	X	X	X	X	X	X
Urine for biomarkers ⁱ		X	X	X	X	X	X	X
Ultrasonography of hands and wrists (optional)		X		X		X		X
Final Status Report								X

Notes:

^a Flexibility of +/- 2 weeks either side of visit will be allowed.

^b Screening and baseline assessments may be undertaken at the same visit according to local departmental and/or patient preference.

^c Withdrawal Assessment will be consistent with the 18month assessment except x-rays of hands and feet should be taken within 6 months of the date of assessment. However, if the patient withdraws at month 6, baseline x-rays may be used.

^d Inclusion and exclusion criteria are listed in section 4.0 below.

^e Serology (ESR and CRP for calculating DAS28 scores and completing remission criteria) and x-rays of hands and feet will not be necessary at screening or baseline visits if these have already been undertaken at the initial outpatient visit (however, results for ESR and CRP must not be >2 weeks old and should be re-taken if so). Formulae for computing disease activity scores are listed in Appendix II. X-rays of hands and feet must be taken within 3 months of the date of assessment.

^f Chest x-ray will be taken as part of routine clinical evaluation prior to starting therapy for RA

^g X-rays of hands and feet must be taken within 3 months of the date of assessment unless the patient has withdrawn. If withdrawal is after month 6 and prior to month 12 x-rays taken at the withdrawal assessment should be used for the 12 month assessment.

^h X-rays of hands and feet must be taken within 3 months of the date of assessment unless the patient has withdrawn. X-rays dated up to 6 months prior to the date of the assessment may be used in the case of withdrawn patients.

ⁱ See table below for schedule of sampling for exploratory biomarkers.

Patients may be called by telephone to check for any medication adherence issues and adverse events during the initial period of therapy, according to local practice, or until dosing schedules have been stabilised. Details collected as part of telephone monitoring should be reported in the patient's medical notes and then added to the electronic Case Report Form (eCRF) at the next study assessment. All Adverse Events will be reported in the eCRF.

2.6. Summary biological sampling schedule

Biological sample	Baseline 0	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18
Serum	18ml*	18ml	18ml	18ml	18ml	18ml	18ml
Plasma	6ml		6ml		6ml		6ml
PBMC (store)	30ml	30ml	30ml	30ml	30ml	30ml	30ml
Whole blood for flow cytometry	20ml		20ml		20ml		20ml
Separation of cell subsets for RNA	40ml		40ml		40ml		40ml
RNA	5ml	5ml	5ml	5ml	5ml	5ml	5ml
DNA		8ml					
Routine drug monitoring		10ml	10ml	10ml	10ml	10ml	10ml
Total volume of Blood draw	119ml	71ml	129ml	63ml	129ml	63ml	129ml
Urine**	20ml	20ml	20ml	20ml	20ml	20ml	20ml

* reflects volume of whole blood draw into sample specific tubes

** up to 20 mls will be collected

Total blood draw for duration of study will be 703ml over 18 months. In addition to blood, urine will be collected at each visit.

Contingency Plan in the Event of Lost or Damaged Samples

In the unlikely event that blood and urine samples are lost or damaged on route, or there are unacceptable delays in reaching the processing site, the research nurse will contact the patient to explain what has happened and see if they would be happy

to provide another sample. If so, the patient will sign an additional consent form to provide this replacement sample within a time frame that is acceptable to the patient, but likely to be within 2 weeks.

3.0. Study medication

The TACERA study is a longitudinal observational inception cohort in which therapeutic interventions are made at the discretion of the supervising rheumatologist; consequently study medications are considered to be licensed, non-investigational medicinal products (NIMPS). The prescribing of non-licensed medication to study participants, or recruitment to other trials of investigational medicinal products or devices will not be permitted. Any intervention that may impact on a patient's treatment or disease activity will also not be permitted. Other interventions for diagnostic or prognostic purposes e.g. ultrasound guided synovial biopsy, observational studies or questionnaire based studies will be permitted. If in doubt, the Study Co-ordinator or Chief Investigator should be contacted for advice.

3.1. DMARDs

All study participants will receive DMARDs prescribed at study entry at standard doses as detailed in Appendix I. The exact choice of DMARD will be left to the discretion of the supervising rheumatologist. However, it is recommended that patients follow a standard treatment regimen, according to the most recent NICE guidelines available at the time, unless there are contra-indications. A patient's DMARD combination can be adjusted by the Principal Investigator because of toxicity to an existing DMARD, in which case the patient should be switched to an alternative DMARD.

Patients will have their DMARD monitoring performed as part of standard care according to local practice. The study's safety monitoring has been designed to fit with routine clinical practice (i.e. patients will have their blood monitoring performed according to local practice, which will include a monitoring bleed when they attend for study assessments).

3.2. Biological therapies

Those study subjects with inadequate clinical responses to conventional synthetic DMARDs (DAS28 > 5.1) at 6 months (or earlier if synthetic DMARDs are contra-indicated) will be offered biological therapy at doses recommended in the Summary of Product Characteristics (SmPC). The first choice will be a TNF inhibitor, unless contra-indicated; subsequent choices will be guided by the latest NICE guidelines. Pre-biologic drug safety screening protocols will be followed according to local guidelines.

3.3. Dosing regimen

Doses of DMARDs may be adjusted according to clinical assessments up to and including dosing as recommended (see Appendix 1/SmPC/local guidelines or electronic medicines compendium for recommended doses).

3.4. Folic acid

Patients taking methotrexate should receive folic acid (e.g. at least 5mg/wk) as is standard practice to limit adverse events.

3.5. Concomitant medication

During the 18 month study period the investigator (supervising rheumatologist) or another healthcare professional (for example GP) may prescribe the following medication considered necessary for the treatment of the patient's rheumatoid arthritis:

- Oral glucocorticoids: these may be taken with study medication at doses deemed appropriate for patients with RA.
- Intramuscular corticosteroids are permitted, but only from study entry.
- Non-steroidal anti-inflammatory drugs: these may be used as required.
- Intra-muscular steroids can be given on the advice of treating rheumatologists.
- Intra-articular steroids will be given on the advice of treating rheumatologists. Injections should be at 10-80mg methylprednisolone or equivalent (depending on the joint to be injected).
- The frequency and number of intra-muscular and intra-articular injections will be left to the discrimination of the supervising physician.

All interventions will be recorded in the eCRF. Treatments for concurrent non-rheumatic disorders will be prescribed as required.

3.6. Drug Accountability

Drug accountability will not be required as part of this observational study. All prescribed RA medications may be dispensed at study initiation by hospital pharmacies, according to local practice. However, initial prescriptions may be photocopied and included in the patient's record folder to assist in verification of medications that have been prescribed to patients. All subsequent prescriptions, which may be dispensed in primary care, will be tracked at study visits by recording periods off study medication (e.g. for adverse events, intercurrent infections) and by noting any other medication compliance issues, such as missed doses, in the eCRF.

3.7. Adherence to Prescribed RA Medications

Adherence to medications will be assessed during study visits at local rheumatology departments every three months and by telephone calls between visits, where appropriate (see section 2.5 above). Any drug adherence issues reported by the participant or by other medical professionals will be reported in the patient's medical notes and in the eCRF.

4.0. Selection and Withdrawal of Study Subjects

4.1. Inclusion criteria

- Patients should fulfill either 1987 ACR or 2010 ACR/EULAR classification criteria for diagnosis of early RA (6,7).
- Positive for serum rheumatoid factor and anti-citrullinated protein autoantibodies (ACPA).
- Within 6 months of symptom onset.
- Supervising rheumatologist considers that starting therapy with DMARDs is appropriate.
- At least 18 years of age.
- Able and willing to give informed consent to provide clinical data and blood samples at defined time points for the duration of the study.

4.2. Exclusion criteria

- Previous treatment with DMARDs or biologics.
- Corticosteroid treatment for the current episode of inflammatory arthritis within the last 6 months (patients with a previous episode of inflammatory arthritis treated with corticosteroids more than 6 months before screening will be permitted providing this episode was not ongoing).
- Use of intramuscular steroid injections between the first clinic attendance (when the diagnosis of RA is made) and study entry.
- Significant comorbidities (e.g. severe congestive heart failure, renal, hepatic, malignant disease), as judged by the supervising physician.
- Pregnant or wishing to conceive.
- Participating in trials of investigational medicinal products or devices, or other interventions (e.g. exercise) which may have an impact on the patient's treatment, immune status or disease activity.

4.3. Identification and Selection of Participants

Patients will be recruited from rheumatology outpatient clinics in the UK using ethically approved advertisements (e.g. which may be posted in outpatient departments or clinics), letters, or via patient support groups or related organizations, as appropriate.

Routine full clinical evaluation during the first outpatient visit will determine suitability for recruitment to the study. Standard clinical practice includes the evaluation of the disease activity score for 28 joints (DAS28; based on swollen and tender joint counts, patient global assessment and ESR, or CRP for those centres who do not measure ESR, ref 24); blood samples for full blood count (FBC), liver function tests (LFTs), ESR, CRP, rheumatoid factor and anti-citrullinated peptide antibodies (ACPA); and X-rays of chest, hands and feet. Results from these tests may be incorporated subsequently into screening and/or baseline assessments.

Patients identified by rheumatologists and clinic nurses at participating centres will be approached by their rheumatologist or nurse and given an explanation of the programme. If the patient is interested in participating, they will be given a patient information sheet/brochure to read. The patient will then be contacted by telephone at least 24 hours after receiving the patient information sheet to see if they are interested in participating in the observational study. Depending on local practice, there will be the option for a telephone discussion with patients interested in participating or attending a visit to discuss the study and if the patient is happy to be screened on the same day then this will take place. If a patient does not wish to participate they will be reassured that their routine care will not be affected and a routine follow up appointment will be made.

Details of all patients approached to participate in the study will be documented on the study screening logs. We estimate that up to 30-40 Centres may need to be established in order to recruit 410 patients over the 24 month period of recruitment.

4.4. Withdrawal of Patients

Patients may withdraw from the study at any time. Patients wishing to withdraw will be asked to complete a withdrawal assessment and reasons for withdrawal will be documented (see note ^c in the study summary for details of assessment).

Due to the nature of the study we envisage 2 main reasons why patients may wish to withdraw:

- Unwillingness to provide biological samples for immunoanalysis every 3 months or at all
- Unwillingness to attend every 3 months to complete all clinical evaluations and questionnaires

Therefore, withdrawn patients will be invited to consider attending less frequent assessments, to enable continued data collection and biological sampling.

5.0. Study Procedures

Patients will follow the visit schedule summarised in section 2.4. All data will be collected in electronic case report forms (eCRF) accessed through MHRA approved web-based electronic data capture (EDC) systems, which comply with the research governance framework. Additional visits, particularly during the first 3-6 months, may be scheduled at the discretion of the supervising rheumatologist in order to facilitate dose escalation, ensure treatment compliance, and to monitor for drug toxicity. Those patients who consider that they are experiencing a flare will be seen urgently (e.g. within one week). Patients should then attend their next study assessment as usual and any additional interventions recorded in the eCRF. In addition to attending the 3 monthly assessments, patients may be contacted by their Research Nurse by telephone between visits, if necessary, to check how well their disease is being controlled by their medication.

The baseline assessment should be performed no later than 2 weeks after the screening assessment, if not scheduled on the same day.

For assessments 3, 6, 9, 12, 15 and 18, a two week window either side of the assessment due date will be permitted if patients cannot attend their assessment on the due date.

5.1. Screening and Baseline Visit (Day 0)

Screening and baseline visits should ideally be scheduled no more than 4 weeks after the diagnosis has been confirmed. However, it is anticipated that the majority of subjects will be able to start treatment within a week of the diagnosis being made. They may be undertaken on the same day, or separately, according to physician and patient preference. Following written consent, results obtained during the initial outpatient visit may be used as part of the screening and/or baseline data collection to avoid unnecessary duplication, providing the assessment(s) is within 2 weeks of when the samples were taken. If the Screening and/or Baseline assessments are carried out after more than 2 weeks the relevant blood samples will need to be taken again. The baseline visit should be scheduled within 2 weeks of the screening visit, if done separately. Patients who do not fulfill entry criteria will be excluded from the study and continue with standard care. Consenting patients who fulfill study criteria will complete the following clinical and functional assessments, recorded in the eCRF:

Screening visit:

1. Written informed consent (obtained by physician or nurse deemed to be suitably trained)
2. Inclusion/exclusion criteria review (including medical and drug history).
3. Confirmation of rheumatoid arthritis according to either 1987 ACR or 2010 ACR/EULAR classification criteria.

4. Assignment of patient study number.
5. Clinical laboratory tests, including full blood count, creatinine, liver function tests, ESR, CRP, rheumatoid factor, and anti-citrullinated peptide antibodies (ACPA), if not already performed and recorded in the medical case notes at first outpatient visit (or if tests performed more than 2 weeks before the date of the screening assessment).

Baseline visit:

1. Demography (patient's date of birth, race, sex).
2. Height and weight.
3. Lifestyle factors questionnaire
4. Clinical assessments of arthritis: swollen and tender joint counts (66/68 joints), patient global assessment (100mm VAS), physician global assessment (100mm VAS), pain score (100mm VAS).
5. Patient self assessed function and quality of life measures: Health Assessment Questionnaire (HAQ), SF-36, EQ5D, FACIT-F and MAPLe-RA.
6. Self-assessed psychosocial measures: Illness perception questionnaire (IPQ-R-RA).
7. Comorbidities and associated medication.
8. Extra-articular features of RA.
9. X-rays of hands, feet and chest (chest x-ray will be taken as part of routine care).
10. Prior medication for arthritis: NSAIDs, analgesics.
11. Starting medication for RA: this includes the initial medication prescribed for RA (DMARDs, corticosteroids) as well as concomitant medication (NSAIDs and analgesics).
12. Biological samples (serum, peripheral blood mononuclear cells, whole blood DNA and RNA, and urine). These will be transported to the clinical laboratory and designated research laboratories for processing, storage, and/or analysis.
13. Those patients who will receive high resolution ultrasonography (HRUS) of hands and wrists as part of routine clinical care will have the results recorded in the eCRF.

5.2. Follow up Assessments (Months 3, 6, 9, 12, 15, and 18)

1. Clinical assessments of arthritis: swollen and tender joint counts (66/68 joints), patient global assessment (100mm VAS), physician global assessment (100mm VAS), pain score (100mm VAS).
2. Clinical laboratory tests (for completion of DAS and routine monitoring).
3. Lifestyle factors questionnaire
4. Patient self assessed function and quality of life measures: HAQ (at all assessments); SF-36, EQ5D, FACIT-F and MAPLe-RA (at 6, 12 and 18 months only).
5. Self-assessed psychosocial measures: IPQ-R-RA (at 6, 12 and 18 months only)
6. Comorbidities and associated medication.
7. Extra-articular features of RA documented, as appropriate.
8. RA Medication Review (including changes in medication, medication adherence and concomitant medication).
9. Adverse events.
10. X-rays of hands and feet (at 12 and 18 months only).
11. Biological samples (for serum, peripheral blood mononuclear cells, whole blood DNA and RNA, and urine). These will be transported to the clinical laboratory and designated research laboratories for processing, storage, and/or analysis.
12. Record details of HRUS studies, as appropriate (at 6 and 12 months. An 18 month scan will be optional).

5.3. Telephone consultations

Study subjects may be contacted by telephone between study visits by the research nurse to discuss the control of their arthritis by their RA medication, and any other issues relating to the study.

5.4. Routine clinical laboratory tests

Patients will undergo routine blood monitoring for DMARDs and biological therapy related toxicity at all assessments, or according to local practice if more frequent.

5.5. Ultrasound study

Participants will be invited to undergo ultrasound based imaging. This part of the TACERA study will be undertaken in those recruiting centres that provide this service as part of routine clinical care, and where there are personnel trained in musculoskeletal ultrasound using imaging equipment approved by the TACERA study investigators (e.g. probes with a frequency of 12MHz and acceptable power Doppler sensitivity). Machines will be calibrated centrally with study specific presets before the start of the project.

Scans will be performed at baseline, 6 and 12 months. An 18 month scan will be optional. At each scanning visit, designated sonographers will scan a range of joints including bilateral wrist, metacarpophalangeal (MCP1-5), proximal interphalangeal (PIP1-5), knee, ankle and metatarsophalangeal (MTP2-5) joints with associated tendon sheaths (MCP, wrist, ankle). Grading of grayscale and power Doppler measurements will be documented by applying semi-quantitative scales dictated by atlases. The scanning process should take no longer than 20-30 minutes, and should be scheduled before treatment is initiated for the baseline scan, and within 2 weeks of scheduled 6 and 12 month visits, if scans cannot be accommodated at the same time as scheduled visits.

5.6. Exploratory laboratory tests

These assays will be undertaken by the study investigators or designated collaborators either within or outside of the UK, as prioritised by the Programme Steering Group. The following blood samples will be taken at the same time as the blood draw used for routine monitoring for drug toxicity at each visit (full blood count, renal and liver function tests). Protocols established for each assay have been refined to use the minimal blood volumes possible to complete the studies.

Serum/plasma: samples will be analysed for extended autoantibody serotyping, measurement of inflammatory mediators including, but not confined to, cytokines, chemokines and growth factors, factors associated with cartilage and bone catabolism, and serum factors associated with comorbidities such as high and low density lipoproteins. Plasma samples will also undergo metabolomic analysis. Serum volumes reflect the need to use autologous serum for in vitro functional lymphocyte assays.

Whole blood: cells will be used to generate whole blood RNA for gene expression (microarray) profiling and for profiling of microRNA using gene chip high density platforms or by quantitative PCR. Multi-parametric flow cytometric analysis will be undertaken on whole blood to quantify cell subsets. Cell subsets will be purified from whole blood for gene expression and microRNA profiling. These assays will be undertaken using fresh cells and volumes have been calculated to accommodate the

amount of blood required to complete detailed immune phenotyping by multi-parametric flow cytometric analysis.

Peripheral blood mononuclear cells (PBMC): cells will be isolated and frozen for subsequent immune phenotyping by multi-parameter flow cytometric analysis, for *in vitro* functional assays, and for preparation of RNA. Cell subsets will be purified from PBMC for (microarray) gene expression profiling. To keep blood volumes to a minimum, PBMC for cell subset purification and analysis will only be undertaken at baseline and at 6 monthly visits.

RNA (microRNA and messenger RNA): RNA extracted from whole blood, from whole PBMC or from PBMC subsets will be used for gene expression profiling to define signatures of dysregulated immune responses, biomarker signatures that predict those subjects that will achieve remission, clinical responses to specific therapy (synthetic or biologic DMARDs), and to stratify sub-groups of patients based on specific gene signatures.

DNA: DNA will be extracted from whole blood or PBMC for extensive genotyping for allelic variants associated with disease susceptibility and disease progression.

Urine: urine will be subjected to biomarker analysis using a range of technologies including, but not confined to, metabolomics to identify unique small molecules and metabolites associated with inflammatory disease activity and target tissue (e.g. bone and cartilage) damage.

This information will be used to select a final 'immunological toolkit' of flow cytometric and *in vitro* functional assays to:

1. Provide a novel classifier of immune functional status for RA patients ('molecular DAS' and 'molecular damage score') at the outset of disease.
2. Be able to accurately measure, at a molecular and cellular level, the effects of therapeutic interventions on the immune system in RA, and to show how these correlate with 'downstream' inflammation and damage.
3. Identify immune signals at an early time point in disease that predict prognosis and guide therapy, thereby tailoring therapy to risk of progression and damage.
4. Identify, via immune markers, the most appropriate therapy for a particular patient at a given time (personalised medicine).
5. Provide immune markers that inform drug dosage adjustment and, critically, drug tapering or discontinuation in patients who are in true immunological remission.

6.0. Outcome Measures

6.1. Primary Outcome Measures

Disease remission at 6 months will be the primary outcome and this will be measured using both the long established DAS28 criterion (DAS28 score <2.6) and the new ACR/EULAR remission criteria (ref 23, see Appendix II):

- Swollen joint count ≤ 1
- Tender joint count ≤ 1
- CRP ≤ 1 (mg/dl)
- Patient global ≤ 1 (on a 1 to 10 scale)

or a Simplified Disease Activity Index (SDAI) ≤ 3.3

6.2. Secondary Outcome Measures

Extended 66/68-Joint Count

DAS28, Simple Disease Activity Score (SDAI) and Clinical Disease Activity Score (CDAI), and components thereof (see Appendix II)

Health Assessment Questionnaire (HAQ) scores

EQ5D scores

SF-36

Radiographic progression of hands and feet X-rays scored by Larsen's or van der Heijde Sharpe Modified Scores

Disease remission (as defined above) at 12 and 18 months

Immune signatures derived from the analysis of biological samples

7.0. Safety Reporting

7.1. Specification, Timing and Recording of Safety Parameters

As part of the study protocol, patients will attend clinic every 3 months for safety monitoring, which will follow national guidelines for DMARDs and biological therapies, with blood counts and liver function tests plus renal function (creatinine), blood pressure measurements and urinalysis where appropriate. Patients may undergo additional visits to participating centres or their GP, as per local guidelines, especially during treatment initiation and dose escalation. Patients will be carefully monitored to ensure there is no evidence of infections, in line with current routine practice; no special specific monitoring for infections will be employed for DMARDs as is current national practice for these medications. Screening for infection will be included for biologics, according to local guidelines.

7.2. Pharmacovigilance

7.2.1. Responsibilities

The sponsor (KCL) has delegated responsibility for pharmacovigilance to the Chief Investigator. The Principal Investigator at each site is responsible for reviewing all AEs, and recording them appropriately in the eCRF.

7.2.2. Procedures for Recording and Reporting Adverse Events

Any adverse event considered as 'Serious' will be reported within 24 hours of knowledge to the Chief Investigator. It will be assessed for 'Causality' in relationship to RA medication and 'Expectedness' by both the Principal and Chief Investigators.

Serious adverse events (SAEs) and serious adverse reactions (SARs) will be reported annually to Ethics and all participating sites.

Any SAE found to be both unexpected and related to RA medications will be reported to Ethics by the Chief Investigator within 15 days of receiving the initial report. The Study Co-ordination Team will at the same time report through the yellow card scheme.

For the purpose of this observational study those events or reactions listed in the Summary of Product Characteristic for Methotrexate, other DMARDs and TNF-inhibitors in the most current version of the British National Formulary will not be considered as unexpected.

7.3. Adjusting Patient Medication during Study Period

For patients developing toxicity to an existing DMARD, the dose may be tapered, or the patient may be switched to an alternative DMARD or considered for biological therapy, as deemed appropriate, according to the most recent NICE guidelines. The decision to stop RA medications will be made by the supervising rheumatologist/Principal Investigator. All patients switching therapy will remain in the study and data collected and recorded for the duration of the study, according to the study protocol. All changes to medication must be recorded in the eCRF.

8.0. Statistics

8.1. Sample Size

Peduzzi *et al* recommend 10 patient outcomes per variable are needed in regression analyses (25), and so studying 150 patients in remission would allow us to include 15 clinical, imaging and laboratory variables in the evaluation of the remission state. Recent RCTs in early RA using combination DMARDs or biologics and DMARDs report that an average of 35-40% (mean 38%) of patients achieve remission by 12 months. However, it is not known how this translates to patients treated using intensive combinations as recommended by NICE. Estimating the frequency of remission at a likely level of 40% with 95% confidence interval and a margin of error of $\pm 5\%$ will require us to enrol 410 patients with early RA, allowing for 10% loss to follow up. This should provide ~150 RA patients who achieve remission as the comparator for active, drug naïve RA in clinical and immunological studies.

8.2. Analysis

Clinical remission will be defined using the co-primary outcome criteria described above. Descriptive analysis will define the frequency of clinical responses over time. The role of extended clinical assessments, ESR/CRP, RF/ACPA, HRUS/power Doppler (PD) and atypical immune profiles in identifying and predicting clinical response (focusing on remission) compared with DAS28, SDAI and CDAI will be evaluated using multivariate regression analyses adjusted for age, gender and region. The effects of demographic data and standard disease assessments will also be examined. Individual variables and combined indices will be evaluated at single time points and as “time integrated” variables; time to remission will also be considered as an outcome in the analysis and appropriate survival analysis techniques employed. Issues of multiple testing, validation, correct functional forms, highly correlated biomarkers will be addressed by using false discovery rates, utilising training and testing data-sets, by considering transformations, fractional polynomials and additive models, and by adopting multivariate analysis techniques

(e.g. factor analysis and dimension reduction techniques). Tree-based models may also be considered in defining extended (clinical and subclinical) remission criteria based on imaging and immunological biomarkers. Specifically, we will focus on comparing these parameters according to 1) non-progression of radiological scores over 12 and 18 months and 2) absence of Power Doppler evidence of synovitis at time of remission, in Centres where this facility is available. In addition, mixed effects, marginal and multi-state models will be considered when analysing longitudinal outcome data. Moreover, statistical methods, such as multiple imputation, linear increments, pattern-mixture models and selection models will be adopted to handle potentially missing data.

9.0. Study Steering and Data Monitoring Committee

A Study Steering Committee will be formed to provide oversight of this observational study and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The Study Steering Committee will agree the study protocol and any protocol amendments and provide advice to the investigators on all aspects of the study. The Study Steering Committee will have an independent chair, at least one other independent member and patient representatives in addition to three members of UK RA Consortium, including industry partners, and members of the Study Management team. The committee will meet every 6-12 months during the study. An important function will be to monitor recruitment rates to ensure timely completion of timelines and milestones of the study.

Members of the Study Steering Committee will serve on the Data Monitoring Committee. It will function to monitor the quality of data collected and to determine that the acquisition and storage of biological samples has been undertaken according to study SOPs.

10.0. Direct Access to Source Data and Documents

The study team will be provided access to all medical records for source data verification. These will include the centre/hospital case notes, pathology results, electronic patient records, radiology, completed forms and questionnaires, as well as the investigator site file. All reasonable precautions to maintain the confidentiality of subjects' identities and protect the integrity of the data will be taken within the constraints of the applicable regulatory requirement(s). Data source verification will be undertaken at participating centres by designated members of the clinical trials team (KMS-CTU).

11.0. Ethics & Regulatory Approvals

This longitudinal observational study will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework.

This protocol and all related documents will be submitted for review to a Research Ethics Committee (REC). Any amendments to approved documents or newly created documents will likewise be submitted for approval. The study will be submitted for

consideration for adoption on to the National Institutes for Health Research musculoskeletal portfolio.

Annual progress and safety reports and a final report at conclusion of the study will be submitted to the REC within the timelines defined in the Regulations.

12.0. Quality Assurance

Monitoring of this study to protect scientific integrity will be performed by King's Musculoskeletal Clinical Trials Unit (KMS CTU) to ensure compliance with the study protocol, Good Clinical Practice and all applicable regulations. Monitoring of source data will follow approved KMS CTU Working Practices/Standard Operating Procedures.

13.0. Data Handling

The Chief Investigator will act as custodian for the observational study data. The following guidelines will be strictly adhered to:

- (1) Patient data will be pseudo-anonymised and stored within the study's EDC system. The EDC system's data will be stored on high capacity servers stored in climate controlled, fire sensitive, alarmed and secure access locked rooms.
- (2) The eCRF/EDC will be accessible via web-based secure application, built on Microsoft.NET platform. Web-based application is accessible via internet via Secure Hypertext Transfer Protocol (HTTPS). Usernames and passwords will be used to authenticate each individual user. Different data accessibility levels will be used to allow individual users to see the data at their accessibility level.
- (3) Only designated, suitably trained clinical and designated research staff will be given access to the data. The Unit will only release passwords to personnel designated on the study's signature and delegation log as requiring login details to enter data. Central password lists will not be stored external to the system. Only staff with global administrator status, which must be authorised by the Chief Investigator, CTU Directors and Programme Director, have privileges to view other staff passwords.
- (4) EDC data will also be backed up by printing onto paper every three months.
- (5) All study data will be stored and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the Joint Clinical Trials Office Archiving SOP.
- (6) The data may be transferred to a central database platform (or warehouse) that incorporates biological data (e.g. transcriptomics) to facilitate data sharing and extended analysis. Since study subjects may be recruited subsequent research studies beyond the 18 month study period, and since data generated in the TACERA study may be relevant to such studies, patients can be identified by their NHS number. However, patient's names will not be recorded.

14.0. Publication Policy

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals. The Study Steering Committee, together with Chief Investigator and Principal Investigators will ensure that on completion of the study, the results are analysed, written up, reported and disseminated. Study findings will be submitted to a peer-reviewed journal, irrespective of the results of the study. The outcomes of the study will also be disseminated to appropriate patient groups through national patient organizations, as appropriate.

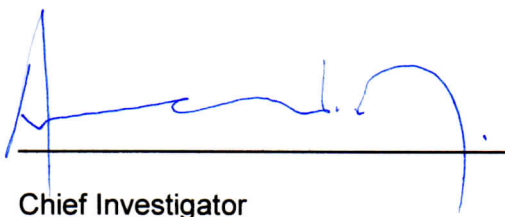
15.0. Financial Aspects

The study is funded by a grant from The Medical Research Council, UK.

As this is a non-commercial research study eligible for adoption onto the National Institute for Health Research (NIHR) Clinical Research Network Portfolio database, NHS Support Costs, including the additional patient-related costs associated with the research (costs which would end once the R&D activity in question has stopped) for example extra patient tests, extra in-patient days, and extra nursing attention, will be met by NHS R&D Support Funding (Clinical Local Research Network (CLRN) funding). [Ref: DoH ReSeT document].

Likewise, treatment costs (patient care costs incurred by the NHS which would continue to be incurred if the patient care service in question continued to be provided after the R&D activity had stopped) and excess treatment costs (the difference between the total Treatment Costs incurred by the research activity and the costs of the standard treatment) are the responsibility of the NHS and are funded through normal arrangements for commissioning patient care.


16.0. Signatures



Chief Investigator

28/11/12

Date



Print name:

17.0. REFERENCES

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18.0. Appendices

APPENDIX I: DMARD standard doses

DMARD	Standard Dose Range
Methotrexate	7.5-25mg per week (5mg increments)
Leflunomide	10-20mg daily. Start at 10mg, should not be increased if used in combination with methotrexate
Sulfasalazine	500mg-3g daily (start at 500mg, increase in 500mg increments)
Hydroxychloroquine	200-400mg daily (option to start at 200mg, increase in one increment within two weeks of starting therapy)
Ciclosporin	2-3.5mg/kg (increase incrementally depending on creatinine levels)
Gold injections	N/A, but start with test dose, then 50mg/week for 20 weeks, then 50mg per month
Penicillamine	125 to 250mg daily for the first month. Increase by the same amount every four to 12 weeks until remission occurs. The usual maintenance dose is 500 to 750mg daily. Up to 1500mg daily may be required
Azathioprine	1 to 3 mg/kg daily, and should be adjusted, within these limits

APPENDIX II: Formulae for computing disease activity scores

DAS28-ESR

$$0.56 \sqrt{\text{TJC}} + 0.28 \sqrt{\text{SJC}} + 0.14\text{PG} + 0.7\text{LN}(\text{ESR})$$

DAS28-CRP

$$0.56 \sqrt{\text{TJC}} + 0.28 \sqrt{\text{SJC}} + 0.14\text{PG} + 0.36\text{LN}(\text{CRP} + 1) + 0.96$$

SDAI

$$\text{TJC} + \text{SJC} + \text{MDG} + \text{PG} + \text{CRP}$$

CDAI

$$\text{TJC} + \text{SJC} + \text{MDG} + \text{PG}$$