Arthritis prevention in the pre-clinical phase of RA with abatacept (the APIPPRA study): a multi-centre, randomised, double blind, parallel group placebo-controlled clinical trial Protocol

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Abstract

Trial design: We present a study protocol for a multi-centre, randomised, double blind, parallel group, placebo-controlled trial that seeks to test the feasibility, acceptability and effectiveness of a 52-week period of treatment with the first-in-class costimulatory blocker abatacept for preventing or delaying the onset of inflammatory arthritis. Methods: The study aimed to recruit 206 male or female subjects from the secondary care hospital setting across the UK and the Netherlands. Participants aged 18 or over who report inflammatory sounding joint pain (clinically suspicious arthralgia) and who are found to be positive for serum autoantibodies associated with RA were eligible for enrolment. All study subjects were randomised to receive weekly injections of investigational medicinal product (IMP), either abatacept or placebo treatment over a 52-week period. Participants were then followed up for a further 52 weeks. The primary endpoint was defined as the time to development of ≥ 3 swollen joints, or to the fulfilment of the 2010 ACR/EULAR classification criteria for RA using swollen but not tender joints, whichever endpoint was met first. In either case, swollen joints were confirmed by ultrasonography. Participants, care givers, and those assessing the outcomes were all blinded to group assignment. Clinical assessors and ultrasonographers were also blinded to each other's assessments for the duration of the study. Conclusions: There is limited experience of the design and implementation of trials for the prevention of inflammatory joint diseases. We discuss the rationale behind choice and duration of treatment, the challenges associated with defining the "at risk" state, and offer pragmatic solutions in the protocol to enrolling subjects at risk of RA. Trial registration: Current Controlled Trials, ID: ISRCTN46017566. Registered on 04 July 2014.

Background

Rheumatoid arthritis is a common chronic inflammatory immune-mediated disease of joints afflicting more than 500,000 subjects in the UK (1, 2). If not adequately treated the condition leads to destruction of synovial joints and significant disability. RA is costly to individuals and their families; one third of patients with arthritis stop work within 2 years of onset because of the deterioration in quality of life associated with their disease (3). In the UK, RA is costly to the economy, estimated to be in the region of £5 billion per year, through direct costs to the NHS and associated healthcare

providers, and indirect costs associated with early mortality and loss of productivity (4).

The introduction of therapeutic strategies that focus on early, intensive treatment with conventional synthetic and biological disease modifying anti-rheumatic drugs (DMARDs) has transformed the treatment of RA. Clinical trials have demonstrated that this approach leads to higher proportions of patients achieving periods of sustained clinical remission. This is associated with improved function and slowing or even prevention of joint damage over time. Indeed, intensive “treat-to-target” strategies in patients with very early RA can subsequently lead to extended periods of drug free remission in a subset of patients (5). If the pre-clinical phase of disease could be defined with accuracy, targeting therapy to those at highest risk of developing disease would have the potential to prevent or at the very least delay the onset of RA. Were such an approach to be successful, the disabling symptoms and signs of arthritis and the potential risks of unemployment could be prevented. Furthermore, the development of potentially life-threatening co-morbidities associated with chronic inflammatory diseases, such as cardiovascular disease and infection, could be substantially reduced.

The combination of serum antibodies to citrullinated protein antigens (ACPA) and joint pain (termed arthralgia), in the absence of clinically detectable synovitis, is considered to most accurately define subjects at high risk of progressing to RA (6-8). Data from longitudinal observational cohorts indicate that ~ 40% of high risk subjects progress to clinically apparent arthritis within 18 months (9). The combination of IgM rheumatoid factor (RF) and high serum ACPA levels define those at highest risk; recent unpublished data indicate that the risk of developing disease in subjects with high titre ACPA in the absence of RF may be comparable to ACPA+RF+ subjects (9). It follows from this that ACPA+RF+ or ACPA+RF- arthralgia individuals would provide a valid target population for therapeutic intervention aimed at prevention of the syndrome we recognise as RA.

Abatacept is a fusion protein composed of the Fc region of the immunoglobulin IgG1 fused to the extracellular domain of CTLA-4 (10). Specifically, abatacept, a first-in-class costimulatory blocker, is a biologic DMARD (disease-modifying antirheumatic drug) that targets immune reactions early in the chain of events leading to inflammation in RA. It functions by interrupting the interaction between T-

cells and antigen presenting cells, attenuating the costimulatory signals required for T cell activation, differentiation and effector responses (11). This results in downstream immunomodulatory effects on other inflammatory cells of the immune system.

In patients with established RA, administration of abatacept is associated with statistically significant and clinically meaningful improvements in the signs and symptoms, physical function and health-related quality of life. It inhibits structural damage in a broad spectrum of patients (12, 13), including early as well as established disease (14), as well as patients with an inadequate response to TNF blockade (15). Interestingly, disease activity scores have been shown to continue to improve beyond 12 months, indicating that the beneficial effects of co-stimulatory blockade are not only sustained but accumulate over extended periods of time.

In the ADJUST study, abatacept demonstrated good efficacy in patients with very early RA, including ACPA+ patients with undifferentiated arthritis, delaying onset of RA when compared to placebo, and promoting sustained remission rates and reduced radiographic progression, even after therapy is withdrawn (16). More recent phase III studies have confirmed the efficacy of weekly subcutaneous (SC) injections of abatacept (17). Clinical efficacy as measured by ACR 20 and HAQ response was similar between SC abatacept and IV abatacept. Clinical trials and post marketing surveillance suggest that the drug has an acceptable safety profile, with particular respect to infection.

While abatacept has a very favourable safety profile, suggesting that this approach might be acceptable to individuals during the pre-clinical phase of RA, there were no published studies at the time of APIPPRA study protocol development investigating the acceptability of targeted treatment strategies during the pre-clinical phase of RA. Understanding the factors that influence the acceptability of this therapeutic approach, and the willingness of at risk subjects to participate in interventional studies will therefore be fundamental to trial methodology and the success of preventative, personalised medicine in the future.

Methods And Design

Study Objectives

The principal objective of the study is to determine whether rheumatoid arthritis (RA) can be

prevented or delayed if targeted immunotherapy is administered to subjects in whom autoantibody screening indicates a high risk of developing disease. Specifically, this study will test the hypothesis that the onset of arthritis in an “at risk" group can be prevented or delayed by weekly injections of abatacept for a period of 52 weeks.

The specific aims of study are to:

1. Evaluate the feasibility, efficacy and acceptability of abatacept therapy in subjects at high risk of developing RA, and

2. Characterise immune and inflammatory responses associated with ACPA before, during and after therapy with abatacept.

Trial Design

The APIPPRA trial is a randomised, placebo controlled, double-blind multicentre trial undertaken at 31 specialist rheumatology clinics across the UK and the Netherlands. The trial was designed to ascertain the effectiveness of abatacept in ACPA+RF+ or ACPAhighRF- subjects with arthralgia who are deemed to be at high risk of developing rheumatoid arthritis (RA). Eligible subjects will be randomly allocated to receive weekly injections of either abatacept or placebo treatment over a 52 week period. This provides the best chance of establishing whether differences observed between the two groups are due to the treatment. The study design is shown in Figure 1.

Study population

The APIPPRA study will recruit study subjects who are at high risk of developing RA who show no clinical evidence of joint swelling. Participants may be recruited using a range of ethically approved methods, including during rheumatology out-patient clinics, following referral to recruiting centres from other rheumatology out-patient clinics, referrals from GP practices through the routine referral pathway or patient identification centre (PIC) pathway, or through existing research databases and registries. Subjects may be identified by pre-screening of laboratory results for RF and ACPA.

Eligibility criteria

Inclusion Criteria

1. Male or female subjects, aged ≥ 18 years.

2. Arthralgia, defined as non-traumatic joint pain localised to synovial joints including, but not necessarily confined to, hands, wrists or feet, and in the opinion of the supervising rheumatologist considered to be inflammatory in nature.

3. Positive for serum rheumatoid factor (RF) and antibodies to citrullinated protein antigens (ACPA) as defined by local clinical laboratory testing. Subjects who are RF negative, but who carry high levels of serum ACPA (defined as being ≥ 3 x upper limit of normal [ULN] for the assay) may be included.

4. Able and willing to give written informed consent and comply with the requirements of the study protocol.

Exclusion Criteria

Target disease exceptions

1. Previous diagnosis of RA or other form of inflammatory arthritis including, but not limited to Systemic Lupus Erythematosus (SLE), psoriatic arthritis, ankylosing spondylitis, gout or pyrophosphate arthropathy, and including current treatment with DMARDs or biological therapy.

2. Arthralgia that, in the opinion of the supervising physician, is poorly localised e.g. pelvic or shoulder girdle pain, that is confined to the axial skeleton or entheses, or pain which the physician considers to be due to osteoarthritis or fibromyalgia or related to other autoimmune conditions such as type I diabetes, coeliac or autoimmune thyroid disease.

3. Clinically apparent inflammatory arthritis, as assessed by a rheumatologist, characterised by soft tissue swelling of one or more synovial joints. Subclinical synovitis, as detected by imaging modalities such as ultrasonography or MRI, is NOT an exclusion criterion.

4. A history of oral or parenteral use of corticosteroids within the last 12 weeks used to treat the current episode of musculoskeletal symptoms.

5. Co-morbidities requiring chronic treatment with immunosuppressive or immune modulating therapy.

6. Subjects who have at any time received treatment with any investigational drug within 28 days of the first dose of study drug.

7. A history of acute allergic reactions to biological therapy or immunoglobulins

Medical history and concurrent diseases

1. Subjects who are incapable of completing study-related assessments or give informed consent.

2. Subjects with current symptoms of severe, progressive, or uncontrolled renal, hepatic, hematologic, gastrointestinal, pulmonary, cardiac, neurologic, or cerebral disease, whether or not related to RA and which, in the opinion of the investigator, might place a subject at unacceptable risk for participation in the study.

3. Subjects with a history of cancer in the last 5 years, other than non-melanoma skin cell cancers cured by local resection or carcinoma in situ.

4. Subjects with tuberculosis (TB), including those at high risk of TB, chronic viral infections, recent serious bacterial infections, subjects receiving live vaccinations within 3 months of the anticipated first dose of study medication, or those with chronic illnesses that would, in the opinion of the investigator, put the participant at risk.

5. Subjects who currently abuse drugs or alcohol.

6. Subjects who are pregnant or breastfeeding, or women of child bearing potential not willing to use adequate contraception during the period of IMP dosing and for up to 14 weeks after the last dose of study drug.

7. Male subjects not willing to use adequate contraception during the period of IMP dosing and for up to 14 weeks after the last dose of study drug.

Physical and laboratory tests at screening

Subjects must not test positive for:

1. Latent tuberculous infection according to the interferon gamma release assay. Subjects who are positive and who have been treated for ≥ 4 weeks may be selected.

2. Antibodies to hepatitis B surface antigen.

3. Hepatitis C antibody if the presence of hepatitis C virus was also shown with polymerase chain reaction or recombinant immunoblot assay.

4. HIV.

Subjects with any of the following laboratory values or other test results that in the opinion of the

Principal Investigator, might place a subject at unacceptable risk for participation in the study:

1. Haemoglobin < 85 g/L

2. WBC <3 x 109/L

3. Platelets < 100 x 109/L

4. Serum creatinine > 2 times the ULN

5. Serum ALT or AST > 2 times the ULN

Trial intervention

Investigational medicinal product/placebo schedule and administration

Abatacept will be administered by subcutaneous injection at a dose of 125 mg/injection (125 mg/mL). Placebo is supplied as identically labelled injections containing a sterile saline solution for subcutaneous administration. Investigational medicinal product (IMP) is supplied as kits of four pre-filled syringes with coded label. Given that there are no guidelines or therapies licensed for treating subjects at risk of RA, and that close monitoring of signs and symptoms until the development of swollen joints is standard of care, the use of placebo was deemed to be acceptable in this clinical trial.

Treatment period (weeks 0-52)

Following randomisation, participants will start their dosing regimen at the baseline visit. Abatacept (or placebo) will be injected weekly at the recommended dosage of 125 mg/ml for 52 weeks. Participants are trained to self-administer study drug subcutaneously (for the first injection) using the single-dose prefilled syringe according to local practices for the administration of biological therapy as part of standard care. Participants will be given 3 months' worth of study medication at baseline and at each subsequent 3 monthly scheduled visits during the first 12 months. Participants will also be given information about the study drug, such as the Arthritis Research UK (now Versus Arthritis) Drug Information leaflet, according to local practise. Subjects will also be given a study medication diary card to record their weekly injections.

In the event of missed doses, participants should not take their medication unless it is within ± 3 days of the scheduled medication dosing date. In addition to the 3 monthly visits, there will be brief

telephone consultations, once a month, to check that study subjects are administering their weekly injections, and to ask if there have been any changes in their symptoms.

Follow up period (weeks 53-104):

Once participants have completed the 52-week course of IMP/placebo, they will be seen in the outpatient clinic every 3 months for similar assessments (see Table 1; Schedule of blood and urine sampling) to those in year 1, to monitor the impact of the treatment phase. This follow up period is especially important because if at any time participants develop new joint pains or swelling, they will be assessed promptly and treated appropriately, in a similar way that clinical staff would assess any new patient presenting with similar symptoms.

Concomitant Medication

For the duration of the trial the investigator or another healthcare professional (for example GP) may prescribe simple analgesics or non-steroidal anti-inflammatory drugs considered necessary for the treatment of the participant's joint symptoms. Treatments for concurrent non-rheumatic disorders will be given as needed provided that they are not expected to interfere with the evaluation of the study medication. The following drugs, however, are not permitted before the onset of clinically apparent synovitis (primary endpoint):

· Oral or parenteral glucocorticoids; short courses (< 2 weeks) of oral or parenteral steroids will be permitted for the treatment of significant, non-rheumatic, concurrent illnesses, including but not confined to asthma and chronic obstructive pulmonary disease.

· Disease modifying anti-rheumatic drugs.

· Any other biological agent for the treatment of RA.

· Any other medicinal product that may, in the supervising physician's opinion, influence underlying disease activity through effects on immune and/or inflammatory responses (with the exception of NSAIDs).

Treatment of study subjects reaching primary endpoint

For those study subjects achieving the primary endpoint – the development of clinically apparent synovitis or RA – the use of corticosteroids and disease modifying anti-rheumatic drugs will be

permitted, the choice of therapy being left to the discretion of the supervising physician. All subjects remain in the study and complete follow up assessments according to the schedule of visits (see Table 1, Trial Flowchart), including full documentation of treatment for their inflammatory arthritis.

Treatment Stopping Rules

The trial may be prematurely discontinued by the Sponsor or Chief Investigator on the basis of new safety information or recommendations given by the Data Monitoring & Ethics Committee to the Trial Steering Committee. If the trial is prematurely discontinued, active participants will be informed, final data will be collected, and no further participant data will be collected thereafter. The Research Ethics Committee will be informed within 15 days of the early termination of the trial.

Study assessments

Following screening, all participants will undergo baseline study visits and then 3 monthly follow up visits for the duration of the trial. Clinical assessors will be blinded to joint assessments by ultrasonography.

Participants will follow the visit schedule summarised in Table 1 unless participants consider that they are experiencing a worsening of symptoms, or have developed swelling of joints, in which case participants will be seen within two weeks. In addition to attending the 3 monthly assessments, they will be telephoned by their Research Nurse or designated staff involved in the study every month (during the treatment period) to check that study subjects are adhering to their study medication and managing their symptoms. Details of assessments and flexibility at scheduled visits are shown in Table 1.

The baseline assessment should be performed no later than four weeks after the screening assessment. For all subsequent assessments, if participants cannot attend on the due date, a two-week window either side of the assessment due date will be permitted

Unscheduled visit assessments

These assessments will be undertaken for subjects experiencing worsening of symptoms or swelling of joints between scheduled visits. Study subjects will be seen promptly, and usually within 2 weeks of new signs and symptoms developing.

1. Physical examination

2. Disease Activity (includes Extended joint counts 68/66, DAS28, SDAI, CDAI, Pain VAS and Physician and patient global assessments (VAS))

3. ACR/EULAR remission, as defined (18)

4. Acute Phase reactants - ESR and C-reactive protein

5. Patient Questionnaires as listed above at baseline visit.

6. Confirmation of clinically apparent synovitis by ultrasonography

7. Blood for biomarkers (this will replace the subsequent scheduled blood draw when the date of the unscheduled visit precedes the next scheduled visit by ≤ 4 weeks)

8. Urine for biomarkers (this will replace the subsequent scheduled urine collection when the date of the unscheduled visit precedes the next scheduled visit by ≤ 4 weeks)

Ultrasonography

Participants will also undergo imaging by ultrasonography. This part of the APIPPRA study will be undertaken in those recruiting centres that provide this service as part of routine clinical care, and/or where there are personnel trained in musculoskeletal ultrasound using imaging equipment approved by the APIPPRA study investigators (e.g. probes with a frequency of at least 12mHz and acceptable power Doppler sensitivity). All participating ultrasonographers were mandated to undertake study specific training.

Scans will be performed at baseline, 6, 12, 18 and 24 months (and at any point between where the supervising physician believes that the study subject has achieved the primary endpoint). At each scanning visit, designated sonographers will scan a core set of joints including, but not confined to, dorsal views of the wrists, metacarpophalangeal (MCP1-3), proximal interphalangeal (PIP2,3), and metatarsophalangeal (MTP2-5) joints. Grading of grayscale and power Doppler measurements will be documented by applying semi-quantitative scales dictated by atlases provided to each participating centre. The scanning process will be scheduled before treatment is initiated for the baseline scan, and within 2 weeks either side of scheduled 6, 12, 18 and 24 month visits, if scans cannot be accommodated at the same time as scheduled visits.

In addition to the above assessments, ultrasound evaluation will be performed to confirm whether the study subject has met the primary outcome, and will include the core set of joints, as above, as well as imaging of any additional symptomatic joints. Ultrasound assessments and scores will be added to the eCRF upon completion of the imaging study and scores will be blinded to the supervising PI or clinical assessor. Anonymised copies of images will be either stored on CDs and securely mailed or sent electronically to a secure email address in a central unit so that scores can be reviewed to ensure consistency of assessments across centres.

X-ray Imaging

All X-ray images will be uploaded onto a dedicated, password protected web-based system and will be scored centrally.

Routine Clinical Laboratory Tests

Study subjects will undergo routine blood monitoring to screen for biological therapy related toxicity at all assessments, or according to local practice if more frequent.

Routine blood monitoring beyond the 12 month study visit will be taken only if clinically indicated, and left to the discretion of the supervising physician

Exploratory Laboratory Tests

These assays will be undertaken by the study investigators or designated collaborators either within or outside of the UK, as agreed and designated by the APIPPRA study investigators. Samples of blood and urine will be transported from recruiting sites across the UK and the Netherlands to pre-designated laboratories based in academic centres for processing and storage. Subsequently, all samples will be shipped from processing hubs in batches to the UK Biocentre for long term storage prior to distribution to the relevant research laboratory for subsequent biomarker analysis as outlined below.

The schedule of blood and urine sampling is summarised in Table 2.

Study endpoints

Primary endpoint

The primary endpoint of this study is the time to development of clinical synovitis or RA defined by

one of the following methods, whichever is met first:

1. The time to development of clinically apparent synovitis in ≥ 3 joints, as determined by two independent assessors with experience in clinical assessment of RA.

2. The time to development of RA according to the ACR/EULAR 2010 classification criteria (19), where joint involvement is defined as joint swelling. The ACR/EULAR 2010 classification criteria for RA redefines previous paradigms of RA by focusing on features at earlier stages of disease that best discriminate those features associated with persistent and/or erosive disease from those that do not. They were defined by consensus with the aim of identifying a disease state for which starting disease modifying therapy was deemed appropriate.

For either endpoint joint swelling will be confirmed by ultrasonography (Figure 2). If the primary endpoint is not confirmed, study participants continue IMP.

Secondary endpoints

The secondary endpoints of this study are:

1. The development of RA according to the ACR/EULAR 2010 criteria where joint involvement based on ultrasound assessments will be included.

2. Assessments of disease activity and progression over time, including:

· DAS28 (tender and swollen joint counts, patient global visual analogue score (VAS), ESR) and Extended Joint Count 68/66

· Simple Disease Activity Score (SDAI) and Clinical Disease Activity Score (CDAI)

· Pain VAS

· Lifestyle Factors Questionnaire, Health Assessment Questionnaire (HAQ), Modified Illness Perception Questionnaire (Modified IPQ) and Euro-Quality of Life Questionnaire (EQ-5D)

· Hospital Anxiety and Depression Scale (HADS)

· Work Instability Scale (RA-WIS)

· Functional Assessment of Chronic Illness Therapy- Fatigue Questionnaire (FACIT-F)

· Symptoms in Persons At Risk of Rheumatoid Arthritis (SPARRA) questionnaire.

3. The proportion of participants requiring DMARD therapy, and the time to commencing DMARD

therapy, including oral or parenteral corticosteroids.

4. Progression of radiographic changes in X-rays of the hands and feet scored by van der Heijde Sharpe Modified Scores or using the Larsen score.

5. Changes in scores of synovitis and vascularity defined by ultrasonography and power Doppler over time.

6. Adverse events.

7. A Perceptions of Trial Participation Questionnaire was also included to gain insights into the acceptability of this therapeutic approach.

Exploratory endpoints

1. Changes in serum ACPA levels over time.

2. ACPA isotype and antigenic fine specificity over time.

3. Signatures of immune and inflammatory responses as defined through analysis of serum, peripheral blood cell subsets, peripheral blood RNA expression profiling and urine.

The focus of the proposed biomarker analysis is two-fold. Firstly, autoantibody profiles, immune cell phenotyping and gene expression signatures will be interrogated to identify novel signatures associated with a high risk state. This could be used to stratify patients for future prevention studies. Secondly, we will use similar assays to better understand the mechanisms whereby study subjects respond to abatacept.

Statistical considerations

Randomisation procedure, blinding and data management

If the participant is willing to participate in the trial, informed consent will be obtained at the start of the screening visit. Screening assessment data will be entered by sites onto a web-based InferMed MACRO Electronic Data Capture (EDC) system hosted on a dedicated secure web site by King's College London, using only the participant's initials and date of birth as identifiers. The EDC system will automatically assign a unique participant identification number (PIN) to each participant as they are registered onto the EDC system. Participants who consent to screening but who are subsequently found to be ineligible will also be recorded in the EDC system, for CONSORT reporting purposes.

These procedures will operate in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines for good clinical practice (GCP), meeting the requirements of the Medicines and Healthcare products Regulatory Agency (MHRA).

Once participants are confirmed eligible, authorised study site staff will access the web-based randomisation system and enter the PIN, initials and date of birth of the participant along with details of any characteristics to be used in the randomisation algorithm. Staff at individual centres and the sponsor will be unaware of the allocation sequence.

Participants will be randomised to IMP (abatacept) and placebo groups using the method of stratified randomisation with randomly permuted blocks within strata defined by gender, country (UK, Netherlands) and smoking status (never, previous and current). Once randomised, the system will automatically recognise what active and placebo kit numbers are available in the site pharmacy and will select 4 blinded treatment kit numbers from the appropriate trial arm and this will be allocated to the participant. At each follow up visit, site staff will again access the randomisation system and allocate new treatment kits for the participant. All participants and staff involved in the conduct of the study will be blind to treatment allocation throughout the trial.

Assessment of Safety

All subjects who receive study drugs will be evaluated for safety. Safety outcomes include adverse events, clinically significant changes in vital signs, laboratory test abnormalities, and clinical tolerability of the drug. The investigator will determine the severity of each adverse event as mild, moderate, severe, or very severe. Laboratory findings that the investigator feels are clinically relevant will be recorded as adverse events. In addition, the investigator will determine the relationship of the adverse event to the administration of the study drug. Any occurrence of a serious adverse event (SAE) from time of consent forward, up to and including follow-up visits will be reported.

Sample Size

Using time to development of arthritis as the primary outcome, or development of RA within 24 months of follow-up, according to 2010 ACR/EULAR criteria, a total of 52 study subjects need to

present with this endpoint from 206 randomised, based on the following information. It is anticipated conservatively that 40% of participants on placebo will develop arthritis. A sample size of 172 subjects would be needed to provide 80% power, to detect a 50% relative reduction to 20% in the abatacept arm (a hazard ratio of 0.437), based on a two-sided log rank test at the 5% level of significance, without loss to follow-up of any of the required 52 events. Therefore 206 subjects (103 per arm) will be randomised to allow for loss of events due to dropout, applying a conservative 20% inflation for dropout.

Similar effect sizes are detectable for binary outcomes and for other time-to-event and proportion outcomes such as the development of RA according to ACR/EULAR 2010 criteria alone. For continuous secondary outcomes, such as disease activity score measures, a medium effect size difference in means (of size 0.5 of a Standard Deviation) between the arms, based on the two-sided unpaired t-test at the 5% significance level can be detected with 85% to 90% power if 146 to 172 subjects are followed up. In view of the number of required secondary outcomes, with 172 participants followed up, there is also 80% power to detect medium sized effects in secondary outcomes (0.52 of a SD) using a secondly applied significance level of 1%. Analyses incorporating baseline adjustment and/or repeated measures data will provide increased precision.

In view of the large number of secondary outcomes, and that the sample size was not set to detect powered effects specifically on the scale of these secondary measures, the use of a 1% level of significance goes only partway towards addressing that multiple testing increases the chance that significant secondary findings are false. The results from secondary outcome analyses will be interpreted cautiously, and in relation to the estimated confidence limits on the actual scale of the measures. Significance tests will be used sparingly and restricted where possible to addressing the stated hypotheses. Results that are significant in isolation will be interpreted less strongly than set of results that are mutually supportive, or which support the corresponding primary outcome, or which are supported in previous research findings.

Withdrawal of Subjects

Participants will be free to withdraw at any time. Participants who do withdraw from IMP will be invited

to return for milestone assessments (at months 3, 6, 9 and 12, or at months 15, 18, 21 and 24, depending on the phase of the study) so that data may be collected and changes in their disease can be assessed; it will be made clear to them that this is entirely at their own discretion.

Subjects will discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

1. Withdrawal of informed consent (subject's decision to withdraw for any reason).

2. Any clinical adverse event, laboratory abnormality, or intercurrent illness which, in the opinion of the Principal Investigator, indicates that continued participation in the study is not in the best interest of the subject.

3. In the Principal Investigator's opinion, the need to administer concomitant medication not permitted by the trial protocol.

4. Pregnancy.

All subjects who discontinue should comply with protocol-specified follow-up procedures. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely. If a subject withdraws before completing the study, the reason for withdrawal will be documented appropriately.

Statistical analysis

The primary analysis approach will be an intention to treat strategy including sensitivity analysis for missing data (20), sensitivity analysis for low compliance (21), and sensitivity analysis for use of forbidden rescue medication or potential informative dropout (described in the detailed statistical analysis plan).

For each time to event outcome, including the primary outcome, Kaplan Meier survival curves will be estimated. A Cox stratified proportional hazards regression model, accounting for the randomisation stratifiers in the form of nominal categorical variables, will be used to compare randomised arms and obtain an estimated hazard ratio for the treatment effect with 95% confidence interval. Participant follow-up is on a three-monthly basis, with additional monthly phone calls when participants will be able to additionally report on their progress. Days will be the unit of time within the model in order to

fully capture the inevitable variation in the time from baseline to monthly contacts and to ascertained outcome events. Each participant who drops out will be included in the analysis and will be assumed not to have the event and be censored at the point of dropout. Time will also be censored for those reaching 24 months follow-up without an event. Those with an event will not contribute any further time after the event. For the primary outcome, sensitivity analysis will be carried out. This includes an analysis assuming that those who have dropped out for reasons connected with disease severity are alternatively deemed to have had the event, and an analysis assuming this alternative for those having experienced two affected joints.

For each binary outcome, a stratified difference in proportions using the Cochran-Mantel-Haenszel method will be used to compare arms accounting for the randomisation stratifiers in their nominal categorical form. For each continuous outcome, including DAS28, differences in the mean of the outcome between arms will be estimated using a linear mixed effects regression model of the repeated measures of the outcome across follow-up. ‘Visit’ will be included in the model as a continuous covariate with full polynomial terms equivalent to including ‘Visit’ as a categorical factor. Outcome data will be included from the regular visits and from times of measurement, including at ultrasound visits. The model will have a heterogeneous variance first-order autoregressive covariance structure, where measurements at the non-regular visits are included in the variance part of the model at the nearest visit, and are included in the mean part of the model in proportion to how the measurement was timed between two visits. The ‘visit’ covariate will be located with an origin at 24-months, so that the model with the interactions of the ‘time’ terms with the other included main effect covariates of study arm, the randomisation stratifiers, and the baseline of the outcome and its missing indicator, will directly provide the estimate of the study arm effect and its standard error. The missing indicator method (21) will be used to enable those participants having any outcome data, but with missing baseline data, to contribute to the estimate.

Descriptive statistics will be reported for measures of acceptability, feasibility and safety. Percentage measures will be reported with exact 95% confidence intervals. There is no plan to have stopping rules. It is anticipated that the Data Monitoring Committee will request interim data on safety and will

advise on further data required for monitoring, and on trial statistician blinding status. A detailed statistical analysis plan will be developed from the study protocol prior to the availability of follow-up data for approval by the independent Trial Steering Committee (TSC). The primary analysis will follow the intention to treat (ITT) principle, that is, participants will be analysed in the groups to which they were randomised irrespective of treatment received, utilising all available follow up data from all randomised participants, with a per protocol analysis of compliers only, as defined in the statistical analysis plan. Alterations to the statistical analysis plan will require re-approval from TSC.

Trial oversight

A independent Data Monitoring Committee (DMC) will assess the trial's progress, occurrence of adverse events and all other aspects. It will comprise a committee Chair, the APIPPRA study trial statisticians, one independent statistician, and at least two independent members with experience in RA trials. The DMC will also be responsible for monitoring evidence of harm and for reviewing decisions relating to all aspects of safety reporting. They will meet prior to initiation of the study and at approximately 6 monthly intervals, or at more frequent intervals as deemed appropriate, for the duration of the study. The statistical analytical plan will be used to guide decision making.

The Trial Steering Committee (TSC) was formed to provide oversight of this trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The Trial Steering Committee will agree the trial protocol and any protocol amendments and will provide advice to the investigators on all aspects of the study. The TSC will include an independent Chair, the Chief Investigator and core study team, an independent statistician, at least two clinicians with experience in RA trials who are not otherwise involved in the study, and an experienced patient expert as patient representative. The TSC is main decision-making body and will be responsible for trial conduct and scientific direction and will ensure that the study objectives are achieved in a timely fashion and within budget.

Data Management

InferMed MACRO Electronic Data Capture will be used in this study. KCTU has extensive experience of this system. Password management and data exports will be controlled by the KCTU. No outcome

data will be exported without the explicit consent of the trial statistician. Changes to the EDC system once the study has begun will be minimised and will only be undertaken with the full agreement of the trial statistician, CI and KCTU where it is essential to the successful conduct of the study.

Direct Access to Source Data and Documents

Site Investigator(s) will permit trial-related monitoring, audits, and regulatory inspections (where appropriate) by providing the Sponsors, Regulators with direct access to source data and other documents (for example, hospital case notes, electronic patient records, completed forms and questionnaires, and the investigator site file). All reasonable precautions to maintain the confidentiality of participants' identities and protect the integrity of the data will be taken.

Quality Assurance

This trial will be monitored to ensure compliance with the trial protocol, Good Clinical Practice and all applicable regulations, and to protect scientific integrity. Study management staff will undertake routine quality control checks of the data. This will include additional central and site-based data checking to ensure the data quality is accurate. Data queries will be raised, responded and closed within the EDC system. Range and validation checks will be programmed into the EDC system to minimise transcription errors. Source data verification checks undertaken at site will be documented to ensure the final dataset has not been amended after checks have been completed. Checks of randomisation data will be undertaken periodically to identify any errors. Prior to database lock, all SAEs reported via fax or email will be cross-checked with the EDC system to ensure all are present in the analysis dataset. Any data issues identified by the trial statistician during preparation of DMC reports will be reported to the trial coordinator and systematically rectified across the dataset, either through central or site data checks.

Discussion

This study protocol describes a secondary prevention strategy for a common immune mediated inflammatory disease targeting a phase of the disease process for which there is currently no recognised treatment. The trial will recruit one of the largest populations of "at risk" subjects to a randomised clinical trial described to date.

The APIPPRA study, designed by clinicians, experienced trialists and patients, is unusual in several respects. Rather than testing the acceptability and efficacy of an unlicensed IMP in a population of patients with established disease, this study will explore the effects of a licensed biologic disease modifying anti-rheumatic drug in a population of otherwise healthy individuals deemed to be at risk of developing RA (22). When the study was first conceived the phenotype of at risk subjects was only beginning to emerge. In 2012 a European League Against Rheumatism (EULAR) working group published recommendations describing the natural history of RA, highlighting how each phase of the disease corresponded to distinct clinical and laboratory characteristics (23). These recommendations were informed in part by longitudinal observational studies of at risk subjects. These and many other studies have been pivotal to stratifying those at highest risk (22, 24-27), in whom therapeutic intervention is considered to be appropriate, and have provided a framework for estimating progression rates, and for computing sample size calculations for our study.

The armamentarium for treating patients with established RA has grown substantially over the last two decades, and this, together with intensive, target driven treatment strategies (1, 5, 28), has had a major impact on disease outcomes with remission rates approaching 40% within 6 months of commencing therapy. There is growing appreciation, however, that the efficacy of interventions may depend on the specific phase of the disease (reviewed in 29). For example, it remains to be determined whether targeting inflammatory cytokines during the preclinical phase of RA at a time when the inflammatory burden of disease is minimal would be as beneficial as immunomodulatory drugs. Clinical trials of corticosteroids, for example, have not demonstrated durable clinical outcomes in the at-risk population (30-32). Costimulatory blockade with abatacept targets one of the earliest phases of the disease process – attenuating *de novo* activation of self-reactive T cells by antigen presenting cells. Abatacept has proven efficacy in early and established RA, but the drug has never been tested in subjects prior to the onset of clinically apparent arthritis. Nonetheless, the presence of disease-associated autoantibodies in serum indicates that the autoimmune process has already started and so we hypothesise that interrupting these immune reactions with abatacept is a biologically plausible approach. Furthermore, there are currently no other licensed therapies available

with a comparable safety profile that target adaptive immunity. Finally, the duration of IMP exposure used in the APIPPRA study is largely empirical. Clinical trials of abatacept in patients with recent onset type I diabetes, however, have documented durable outcomes beyond the period of therapy, suggesting that immune modulation might be more profound, or sustained, if used at the earliest detectable point in the disease course (33). Whether costimulatory blockade induces immunological tolerance, on the other hand, requires further investigation.

The primary endpoint of the APIPPRA trial is the time to the development of clinically swollen joints or fulfilment of the 2010 ACR/EULAR classification criteria for RA, whichever endpoint is met first. Three swollen joints were chosen for the first primary outcome since this was the median number of swollen joints identified from cohorts of at risk subjects at the time of development of clinically apparent arthritis (9). In routine practice, this is very often the point in the disease course when physicians see patients with inflammatory arthritis for the first time. The validity of the 2010 ACR/EULAR classification criteria for RA is underpinned by an intention to treat with disease modifying drugs (19), and so including these criteria as a co-primary outcome (by achieving a score of ≧ 6) reduces the risk of exposing study subjects to placebo, or to IMP that has proven inadequate to suppress signs and symptoms, at a time when standard therapy for new onset RA would be deemed appropriate by the supervising physician. Clinical assessments are notoriously subjective, especially when inflammatory joint disease is in the very earliest stages. To define primary endpoints with precision we opted to confirm the presence of synovitis in clinically swollen joints by ultrasonography. For these imaging assessments, and for the duration of the study, clinical assessors and ultrasonographers are blinded to each other’s joint scores to limit bias. For consistency of scoring, all ultrasonographers undergo study specific training, and have access to a reference Atlas of images for all joints to be assessed.

A key outcome of the APIPPRA study will be to determine whether intervention at this phase of the disease is considered to be acceptable to the high risk subject. To this end we have included as part of study assessments questionnaires that probe in more detail people’s perception of risk. We anticipate that the APIPPRA study will allow us to better define the at-risk state, based on data we acquire from

questionnaires that probe deeper into clinical phenotypes, from the monitoring of images of symptomatic joints by ultrasound over time, and from immune phenotypes acquired from analysis of biological samples. This information can then be exploited in future studies to identify those most likely to progress over pre-defined time periods on the one hand, while minimising exposure of individuals to an intervention that may never need.

Trial Status

The APIPPRA study trial received ethical approval on 13th March 2014. The first study subject was randomised in January 2015 and the trial is likely to complete recruitment by the end of December 2018.

Protocol version

The protocol published here is version 3.2 dated 22nd March 2018.

Declarations

Ethics approval and consent to participate

This clinical trial has been approved by the London – Westminster National Research Ethics Service (NRES) Committee (reference 14/LO/0100), the Health Research Authority (HRA) (reference 135429) and the Medicines and Healthcare products Regulatory Agency (MHRA) for clinical trial authorisation (reference 28482/0012/001-0001). The ethics committee approved all amendments and study extensions. Ethical approval has also been obtained from the University Hospital Executive Boards in the Netherlands relevant to all participating sites. Informed written consent will be obtained from all participants prior to recruitment to the study.

Consent for publication

Not Applicable

Availability of data and material

Further information regarding the logistics of RA prevention study operations are available from the authors upon reasonable request.

Competing interests

M.A-L., M.J., S.A., A.B., C.C., J.H.J., A.F., B.A.F., P.H., C.J., H.L., D. van S., D.S., A.J.W., J.V., J.K., C.M., and A.T.P. declare no competing interests relating to this study.

I.N.B., C.D.B, M-A. D'A., P.E., T.W.J.H., J.D.I., I.B.M., A.O., A.G.P., K.R., P.C.T., and A.P.C. have received honoraria, speaker fees and/or research funding from Bristol Myers-Squibb, or have received honoraria, speaker fees and/or research funding from other Pharmaceutical companies.

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Author's contributions

M.J., S.A., I.N.B., C.D.B., C.C., P.E., J.H.G., B.A.F., J.D.I., T.W.J.H., P.H., I.B.M., A.G.P., A.O., D.S., P.C.T., J.K. and C.M. contributed to study design and reviewed the manuscript. A.B. and C.J. convened the patient focus group to inform study design and patient facing documents. K.R., D. van S., H.L. and A.J.W. designed study questionnaires, contributed to study design and reviewed the manuscript. A.F. and M-A. D'A. designed the ultrasound imaging protocol, prepared the atlas, coordinated all aspects of ultrasound training sessions and reviewed the manuscript. A.T.P., and J.C.V. prepared the statistical analytical plan and oversaw sample size calculations. A.P.C. conceived the study and wrote the manuscript with M.A-L and coordinated the submission.

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List Of Abbreviations

ACPA; Anti-Citrullinated Peptide Antibody

ACR;American College of Rheumatology

AE; Adverse Event

Anti-CCP; Anti-Cyclic Citrullinated Peptides

APIPPRA; Arthritis Prevention In the Pre-clinical Phase of RA with Abatacept

AST; Aspartate Aminotransferase

BMS; Bristol-Myers Squibb

BP; Blood Pressure

CDAI; Clinical Disease Activity Index

Cmax; Maximum Concentration of A Drug In The Body After Dosing

CONSORT; Consolidated Standards of Reporting Trials

CPA; Citrullinated Potein Antigens

CRP; C-Reactive Protein

CTLA-4; Cytotoxic T-Lymphocyte Antigen 4

DAS; Disease Activity Score

DMARDs; Disease Modifying Anti Rheumatic Drugs

DMC; Data Monitoring Committee

DNA; Deoxyribonucleic Acid

eCRF; Electronic Case Report Form

EDC; Electronic Data Capture

EQ-5D; Euro-Quality of Life Questionnaire

ESR; Erythrocyte Sedimentation Rate

EULAR; European League Against Rheumatism

FACIT-F; Functional Assessment of Chronic Illness Therapy-Fatigue

FAS; Full Analysis Set

GCP; Good Clinical Practice

HADS; Hospital Anxiety and Depression Scale

HAQ; Health Assessment Questionnaire

HRUS; High Resolution Ultrasound

HIV; Human Immunodeficiency Virus

HTA; Human Tissue Authority

IB; Investigators Brochure

ICH; International Conference on Harmonisation

IEC; Independent Ethics Committee

Ig; Immunoglobulin

IgG; Immunoglobulin G

IM; Immunogenicity

IMP; Investigational Medicinal Product

IRE; Initial Rate of Enhancement

ISR; Investigator Sponsored Research

ITT; Intention To Treat

IV; Intravenous

KCTU; King’s Clinical Trials Unit

KHP-CTO; King’s Health Partners Clinical Trials Office

MCP; Metacarphophalangeal

MHRA; Medicines and Healthcare Products Regulatory Agency

MRI; Magnetic Resonance Imaging

mRNA; Messenger Ribonucleic Acid

MTP2-5; Metatarsophalangeal

MTX; Methotrexate

Modified IPQ-R; Modified Ilness Perception Questionnaire

NSAID; Non-Steroidal Anti-Inflammatory Drugs

PBMC; Peripheral Blood Mononuclear Cells

PDUS; Power Doppler Ultrasound

RA; Rheumatoid Arthritis

REC; Research Ethics Committee

RF; Rheumatoid Factor

RNA; Ribonucleic Acid

SAE; Serious Adverse Event

SAP; Statistical Analysis Plan

SC; Sub Cutaneous

SD; Standard Deviation

SDAI; Simple Disease Activity Index

SmPC; Summary of Product Characteristics

SOP; Standard Operating Procedures

SPARRA; Symptoms in Persons at Risk of Rheumatoid Arthritis Questionnaire

SUSAR; Suspected Unexpected Serious Adverse Event

T1D; Type 1 Diabetes

TB; Tuberculosis

TSC; Trial Steering Committee

UA; Undifferentiated Arthritis

ULN; Upper Limit of Normal

US; Ultrasound

VAS; Visual Analog Scale

WBC; White Blood Cell

RA-WIS; Rheumatoid Arthritis Work Instability Scale

WOCBP; Women of Child-Bearing Potential

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Tables

Due to technical limitations, all tables for this manuscript have been included in the supplementary files section.

Figures

Figure 1

Study design and flowchart

Figure 2

Primary endpoint roadmap

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

Table 1.pdf
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SPIRIT_Fillable-checklist-APIPPRA_v2.docx
Appendix 3_additional information Final.docx