Arthritis Research UK Epidemiology Unit

Qualitative research proposal to explore factors influencing acceptable risk thresholds used to recommend particular treatment options for rheumatoid arthritis.

Empowering People through Informed Choice in Rheumatoid Arthritis (EPIC-RA)

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Table of Contents

Protocol

Title

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Summary

Rheumatoid arthritis (RA) is a common chronic inflammatory disease, which causes joint damage, pain, disability and reduced life expectancy. Methotrexate is usually the first choice of treatment for patients with RA as recommended by the National Institute for Health and Care Excellence (NICE). It is often used in combination with other disease modifying anti-rheumatic (DMARDs). However, if the joint inflammation fails to respond or the patient is unable to tolerate the treatment (due to the development of side effects), then patients may be prescribed biological therapies. Biological therapies are protein-based drugs that mimic naturally occurring molecules in the body and have been developed to block inflammatory pathways. Studies have consistently shown that these biological therapies improve disease outcome in patients and are more effective than DMARDs alone in many patients. There are a number of biologic drugs available, which can be grouped according to their mode of action: anti-TNF drugs are the most commonly prescribed biologic and target the tumour necrosis factor inflammatory pathway; rituximab results in depletion of B cells; tocilizumab targets the interleukin 6 pathway whilst abatacept acts on T cells to control inflammation. However, up to 40% patients will not respond adequately to each drug and it is not possible currently to know which drug will work best in an individual patient, each is used on a 'trial and error' basis until the drug that controls inflammation is found. As these drugs can be associated with severe side effects, methods to select the right drug for the right patient first time are needed.

There is, therefore a need to identify biomarkers that can predict response to a particular therapy so that patients can be recommended the appropriate treatment early in their disease progression. As biologic drugs are very expensive (£10,000 per patient per year), it would also be of huge economic benefit to be able to select the best treatment sooner in order to avoid unnecessary wastage of scare resources and to improve quality of life for patients

There are currently no predictors to identify which patients will respond best to which therapies. Therefore, a Medical Research Council/Arthritis Research UK funded consortium for stratified medicine (MATURA – MAximising Therapeutic Utility in RA) is developing diagnostic techniques and predictive markers to try and remedy this.

The markers identified are likely to provide a better estimate of the likelihood of responding to a particular treatment or the risk of not responding. However, very little has been done from the point of view of people with RA and we wish to explore what thresholds for recommending / not recommending a particular treatment would be acceptable to people with RA and to understand whether this is balanced by concerns about the test (for example whether it is a blood test or a more invasive test requiring a biopsy of the joint). Before designing the main study, we require some qualitative research to explore concerns of people with RA about testing to select therapy, in order to inform the design to the main study and ensure we capture all possible influences.

The aim of this project will be to organise 2-4 focus groups (of between 4-6 people) of members of the public who have rheumatoid arthritis and identify their opinions surrounding novel tests for biomarkers that would predict their response to a particular treatment and the risk thresholds that would be used to inform the selection or recommendation of treatments. The predictor tests could involve blood sampling and/or biopsies of the joint tissue. Note: these groups would not be undergoing any testing itself, just providing views.

We would like to ultimately engage with a wider audience of people with RA (via charity led organisations, for example, NRAS, EULAR (PARE), NOWGEN) and the current research will inform a future study questionnaire/survey to involve people with RA in determining the thresholds that should be used by clinicians to recommend/not recommend a particular therapy.

This public and patient involvement and engagement within the MATURA programme of work will ensure that the predictive markers identified through that research can be translated more quickly to the clinic because stakeholders will have been fully involved in deciding the thresholds for treatment recommendation. The current qualitative research proposal will inform the design of a subsequent discrete choice questionnaire that will be used to canvass opinions from a wide range of stakeholders using quantitative research methods.

Research Questions

To identify the factors that influence the opinions of people with RA to novel tests that could inform treatment recommendation decisions.

Objectives

To develop a framework that will identify the factors considered by people with RA when it comes to undertaking novel tests that aim to predict how they will respond to a particular therapy and inform the risk thresholds used to select therapy.

Background

RA is a chronic disease which affects 1% of the population (1). It causes joint destruction, disability (30% of patients stop work within 5 years of diagnosis) (2) and reduced life expectancy (3). The cost to individuals and their families, the NHS and society is high. The annual cost of RA (including health costs and lost working days) is approximately £1.3 billion (4).

The use of disease modifying anti-rheumatic drugs (DMARDs) and biological therapies leads to greatly improved disease outcomes (5-6). Recent guidance from the National Institute for Health and Clinical Excellence (NICE) (http://guidance.nice.org.uk/CG79) highlights the importance of early aggressive therapy and advocates the use of DMARDs in combination from the outset of the management of RA.

Methotrexate is typically prescribed as the first choice disease modifying anti-rheumatic drug (DMARD) to treat RA. However, patients who fail to respond to methotrexate can be prescribed another DMARD, or a biologic drug, which modulates the immune system and/or inflammatory pathways to alleviate disease. By two years, up to 45% of patients are non-responders to methotrexate (7). Furthermore, significant non-response rates have been reported for the

alternative RA treatments for example, up to 25% of patients given anti-TNF have shown non-response to the drug by 6 months of treatment (8), and 40% of patients given rituximab are non-responders by 6 months (9). Patients who fail to respond to their initial treatment have been shown to have worse long-term outcomes in terms of having greater disability and joint damage. Therefore, there is a great need to ensure that patients are given the right treatment earlier in their disease so that their disease outcome can be improved.

There is now research being conducted aimed at identifying blood-based and tissue-based biomarkers that predict response to treatment. Specifically, the MATURA consortium (MAximising Therapeutic Utility for Rheumatoid Arthritis) is an MRC/Arthritis Research UK funded initiative aimed to identify markers that can better inform treatment decisions to improve response rates by targeting the appropriate treatment to the right patient. However, we can find no evidence in the literature from a person with RA's point of view regarding markers of treatment response and what risk thresholds they would find acceptable in deciding whether specific treatments should be recommended or not.

This opportunity to carry out qualitative research amongst people with RA would inform the MATURA research programme. It would be beneficial to ascertain the views and opinions of people with inflammatory disease regarding the potential for different tests for biomarkers and the acceptable threshold which clinicians could use to recommend/not recommend treatment. (i.e. the acceptable risk/benefit ratio) within their inclination towards trying these novel tests.

Methods

A qualitative methodology approach will be used for this project. Public user involvement will be integral throughout. Members of the public with rheumatoid arthritis will be identified with the help of charity organisations such as the National Rheumatoid Arthritis Society (NRAS), Arthritis UK (ARUK), Manchester Research User Group (RUG), Queen Mary Trials Advisory Group (QMTAG), MATURA Patient Advisory Group (MPAG). These organisations would be sent the study information and then act as gatekeepers for recruitment to the study, We would request that they email suitable people to take part in a focus group. Others may be contacted via snowballing from the initial sources.

People with RA will be contacted via email or letter to invite them to a focus group. If they show an interest in taking part in the focus group, an information sheet will be sent to them. Time will be allowed for questions before they are asked to give consent. A neutral environment will be chosen for the focus group. This will either be a room on university campus (University of Manchester and University of Birmingham). Potentially, a room in the Nowgen Centre, Manchester may also be available.

Up to 6 people with inflammatory disease will be recruited for each focus group. There will be initially 2 focus groups. Further focus groups will be organised until there is a saturation of opinions. By working initially with the MATURA Patient User Group (MPAG), a topic guide will be developed by the research team which will then be used to explore the views of participants about medicines and diagnostic thresholds for treatment recommendation. Participants will have the study explained to them and then, if happy, asked to sign a consent form. Full confidentiality and data protection will be upheld.

A semi-structured topic guide will contain open-ended questions, example scenarios and prompt questions to be used by the researcher (who will be a rheumatology health professional with in depth knowledge of the common treatments used in controlling RA and will also have a wealth of experience in qualitative research methods and conducting research) to guide discussion within the focus group. A maximum variety approach will be used to capture a broad social and demographic subject range and interviews will continue to theoretical saturation. We would request a range of suggestions of people to contact from RA organisations to include a mixture of age, gender, ethnicity to try and get the views of as wide a range as possible. All interviews will be digitally recorded.

An active approach will be used when discussing with participants, which will allow the researcher to identify issues surrounding novel tests. A permissive environment will be provided for participants to talk freely about the issues related to treatment response and their opinions. As such, it will be made clear prior to the start of the focus group that all information discussed will and must remain confidential.

We will use a qualitative methodology to explore participants' opinions towards novel tests for biomarkers and ideas regarding invasiveness of these diagnostic procedures. During the focus groups, we will explore approaches that participants feel comfortable with in terms of methods of testing, how important it is for them to have these early predictors of treatment response and what thresholds they would like clinicians to use when recommending that a particular drug is or is not used.

Audio transcripts will be translated, data will be coded and analysed using thematical saturation framework. We will look for patterns in participants' opinions and develop themes to underpin our understanding of diagnostic testing. Recordings may be sent off site to a professional transcription company, these will be anonymised and no participant details will be exported.

Inclusion Criteria

- Have Rheumatoid Arthritis- it is important to identify opinions of people within one disease group for this initial pilot to get the best data possible before expanding to wider rheumatology and arthritis communities.
- Must be at least 18 years of age and able to provide informed consent.
- Are willing and able to participate.
- Are native English speakers – we need to get the most from a small group before expanding to the wider RA community.

Sample size

There will be approximately 4-6 participants for each focus group. The literature in qualitative research suggests a minimal of 2-3 groups to be sufficient, however additional focus groups will be recruited if saturation is not reached.

Data analysis

The transcribed data (one transcript per focus group) will be analysed by using thematic analysis. This process will involve looking at the different patterns and reflecting on the patterns to seek similarities between emerging themes. Each transcript will be coded (labels) to capture the essence of the participants' narratives. By creating several labels, a structure of codes will be developed to understand the meaning of the data. The coding will be staged. During the coding the researcher will look for demographic, factual and /or conceptual meaning. For example, "how certain would you like to be that a treatment will work if it is going to be recommended?", "how would you feel if it then didn't work?" or "how do they feel they are responding to treatment?". The researcher will allow for spontaneous themes to emerge.

Time scale

It is estimated that recruitment of people with rheumatoid arthritis disease from charity run groups, along with running the focus groups would take no more than 1 year.

Project management group

Professor Anne Barton
Dr Kanta Kumar
Deborah Maskell (Study Coordinator)

Other people involved: Dr Lis Cordingley
Mrs Zoe Ide (lay member of MATURA Patient Advisory Group)
Dr Nisha Nair (post doc RA for MATURA)

Impact

This study will be the first to systematically explore the level of acceptance to novel tests that predict the likelihood of responding to a drug. It will further inform the design of a subsequent qualitative study to determine the thresholds that patients with RA would like clinicians to use to guide therapy selection.

This initial piece of qualitative work will help to inform a patient discrete choice questionnaire/survey that would be expanded to the wider arthritis/rheumatic community and generate innovative data on patient reaction to the research being undertaken by the MATURA consortium.

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