CONCISE REPORT

Formative research in clinical trial development: attitudes of patients with arthritis in enhancing prevention trials

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In preparation for randomised controlled trials (RCTs) of disease-modifying antirheumatic drugs in patients with early inflammatory arthritis (EIA), formative research was conducted to enhance the design of such trials. The objectives of this research were to (1) determine patients' educational needs as they relate to the necessary elements of informed consent; and (2) assess patients' interest in enrolling in a hypothetical prevention trial. In-depth interviews were conducted with nine patients. Seven patients were women and all but one white. The mean age was 48 years. During the 4-month enrolment period, only three patients with EIA were identified; six patients with longer duration of symptoms were also interviewed. Most patients were able to express the primary aim of a hypothetical prevention trial presented. Factors cited by patients favouring enrolment were potential for direct medical benefit and knowledge that they would be withdrawn from the trial if they developed symptoms. Factors cited by patients against enrolment were the inclusion of a placebo and general uncertainty regarding treatment required by the RCT design. Pending larger-scale empirical projects to explore patients' attitudes about prevention trials, small-scale formative research in advance of such trials ought to be conducted.

Recent scientific advances have suggested the possibility of conducting primary and secondary prevention trials in an effort to attenuate the morbidity and mortality associated with rheumatoid arthritis. In preparation for randomised controlled trials (RCTs) of disease-modifying antirheumatic drugs (DMARDs) in patients with early inflammatory arthritis (EIA), formative research was conducted to enhance the design of such trials. The term formative research derives from the social marketing literature. This type of research, which involves direct patient interviews, is used before the introduction of a new product to better understand the characteristics and needs of the intended consumer.[1 2] Recently, it has been recommended that health researchers use formative research to prepare for prevention trials,[3] especially for those that raise particularly difficult ethical or social issues, and to facilitate implementation of the trials.

To assess the value of DMARD treatment in patients with EIA, investigators have proposed targeting patients as early as possible in the course of disease and determining whether disease persistence and resulting complications can be prevented.[4–6] Depending on the time after symptom onset, some, or even many, patients enrolling could have self-limited disease that would remit in the absence of DMARDs.[7–12] On the other hand, a study of such patients could include a control group that did not receive DMARDs, raising ethical issues about undertreatment of a potentially serious disease.

Given such issues raised by clinical trials in patients with EIA, we decided to conduct formative research in which we presented patients with a trial design based on a comparison of a DMARD alone versus placebo alone versus a DMARD in combination with a tumour necrosis factor blocker in patients with <3 months of signs and symptoms of inflammatory arthritis. Our results provide guidance for such a trial, including designing recruitment procedures and developing appropriate informed consent procedures.

MATERIALS AND METHODS

In-depth interviews were conducted to determine how patients with arthritis would respond to the idea of enrolling in a prevention trial where uncertainty may exist about their diagnosis, symptoms may be minimal, the interventions have known toxicities and the likelihood of efficacy is undetermined. Patients eligible are those with EIA. An initial draft of the interview guide and a hypothetical rheumatoid arthritis prevention trial summary were developed by the authors and then vetted with practising rheumatologists. The guide included the following domains: diagnosis, experience with the healthcare system, current treatment, expectations regarding disease progression, general health history, general attitudes about health and general attitudes about research. Once these domains were discussed, the hypothetical trial was presented. After the presentation, patients were asked about their understanding of the trial, encouraged to ask questions and then asked about their willingness to consider enrolment in the proposed prevention trial. The project was approved by the Johns Hopkins Medical Institutions Institutional Review Board.

Recruitment of patients was facilitated by rheumatologists who referred interested patients. Informed consent was obtained from each patient and one of the authors (HAT) conducted all the in-person interviews. Interviews were audiotaped, transcribed verbatim and then verified against the audiotape. A brief summary was prepared at the conclusion of each interview. Each transcript was reviewed and coded, and a thematic summary was prepared. A summary of common themes was then assembled.

A total of 10 patients were approached over a 14-week period late in 2004. Nine agreed to be interviewed; one patient refused, stating unwillingness to participate before the winter holidays. Interviews were conducted in the patients' home (n = 8), in an empty clinic examination room (n = 1) or in the interviewer's office (n = 1), and lasted from 30 to 100 min.

RESULTS

Basic demographics

Seven patients were women and eight were white. The mean age was 48 (range 35–71) years. Two patients were joined by their spouses during the interview.

Abbreviations: DMARD, disease-modifying antirheumatic drug; EIA, early inflammatory arthritis; RCT, randomised controlled trial

Diagnostic history

The referring rheumatologists had difficulty in identifying and recruiting patients who had EIA, as many of the potentially eligible patients had already had symptoms for several months before presenting for their first rheumatology evaluation. As a result, we interviewed three patients with EIA and six patients with longer duration of symptoms who fulfilled the diagnostic criteria for rheumatoid arthritis. Three had received a definitive diagnosis of rheumatoid arthritis in the past 12 months, one 18 months ago and two reported being told by their doctor that they had rheumatoid arthritis but had not yet received a definitive diagnosis.

Attitudes about research

All patients had a generally positive attitude towards the research enterprise and understood that research is required for scientific advancement. Nevertheless, almost half indicated that they would be reluctant to enrol in any clinical research protocol. All but one reported having been approached to enrol in some kind of research protocol in the past, and one reported past enrolment.

Understanding of the proposed study

Most patients were able to express the primary aim of the hypothetical trial presented. When asked which benefits they could recall, some patients indicated that arthritis would be put into remission. During the presentation of the hypothetical trial, the potential risk of being exposed to potentially toxic drugs was described. When asked, most patients could recall this risk. A risk identified by some patients was the possibility of being randomised to a placebo.

Willingness to enrol

The patients were classified into three categories: those who were unwilling to consider enrolment (n = 4); those who reported they would need more information and/or more time to make a decision about enrolment (n = 4); and those who would be willing to enrol (n = 1). Although each patient had a unique response to the question about their willingness to enrol, a number of themes emerged from the responses.

Factors considered in favour of enrollment

Two common themes emerged from those who would be willing to enrolor who needed more information or time to consider enrolment (n = 5). Firstly, the most important motivator was the possibility of direct medical benefit. Four of those with more advanced disease (one of whom indicated that she would be hesitant to enrol herself) reported that they would encourage anyone eligible for the trial to enrol. For these patients, the benefits of enrolment clearly outweighed the drug-related risks. Patients with less severe disease were reassured by the fact that the drugs on the study were the same as they would receive if they progressed to rheumatoid arthritis. Secondly, willingness to consider enrolment was influenced by the understanding that if patients enrolled and experienced symptoms, they would be taken off the trial and treated.

Factors considered against enrolment

Themes common to those who were unwilling to enrol or needed more information or time to consider enrolment (n = 8) varied. Some patients reported that they were hesitant (or, in one case, unwilling) to enrol in an RCT that included a placebo. This hesitancy seemed strongest for those who had progressed to rheumatoid arthritis; these patients were currently being treated for what was in some cases severe pain and swelling, and seemed unable to imagine being in a trial where they may receive nothing. Secondly, some reported hesitancy to enrol in an RCT because of uncertainty about exactly which agent they would receive. Although such patients may be reassured that none of the drugs would be experimental, on the other hand, ignorance of which drugs they would receive could be reason enough to not enrol.

DISCUSSION

This formative research provides useful insights into the design of prevention trials in rheumatoid arthritis, although the findings should be interpreted with limitations in mind. All patients came from a single site and were referred by the same rheumatologists. In addition, the referring rheumatologists were in the midst of recruiting for an early rheumatoid arthritis treatment trial. Patients who had been previously approached to enrol in the early rheumatoid arthritis treatment trial had recently heard about the option of enrolment in a trial and therefore may have been better able to understand the hypothetical proposed prevention trial presented.

A number of patients had a negative response to the placebo arm in the trial. Previous research has documented negative attitudes about placebos as a reason why some potential patients refuse enrolment in clinical trials.[13–15] Thus, the use of the true placebo arm in rheumatoid arthritis prevention trials should be reconsidered. Although the absence of the placebo arm may reduce the scientific value of the study, it may make the study more acceptable to potential patients. Alternatively, the fact that patients on the placebo arm will receive the standard of care for their relative stage in disease progression (eg, non-steroidal anti-inflammatory drugs, steroids and pain relief as necessary) could be described in more detail.

The most promising finding of this research was that none of the patients with EIA dismissed the idea of enrolment out of hand. All three indicated that they would be willing to consider enrolment but would require additional information and/or time to make a decision. It is important to note that, during the 4-month recruitment period, only one patient in the sample was identified early enough to be considered eligible for the hypothetical rheumatoid arthritis prevention trial. The failure to identify patients early enough in their disease progression to participate in the interview study could identify a challenging barrier to recruitment efforts for proposed prevention trials.

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