Canadian Recommendations for Clinical Trials of Pharmacologic Interventions in Rheumatoid Arthritis: Inclusion Criteria and Study Design

JACOB KARSH, EDWARD C. KEYSTONE, BOULOS HARAOUI, J. CARTER THORNE, JANET E. POPE, VIVIAN P. BYKERK, WALTER P. MAKSYMOWYCH, MICHEL ZUMMER, WILLIAM G. BENSEN, MAJED M. KRAISHI, and members of the Canadian Rheumatology Research Consortium

ABSTRACT. Objective. Current clinical trial designs for pharmacologic interventions in rheumatoid arthritis (RA) do not reflect the innovations in RA diagnosis, treatment, and care in countries where new drugs are most often used. The objective of this project was to recommend revised entry criteria and other study design features for RA clinical trials.

Methods. Recommendations were developed using a modified nominal group consensus method. Canadian Rheumatology Research Consortium (CRRC) members were polled to rank the greatest challenges to clinical trial recruitment in their practices. Initial recommendations were developed by an expert panel of rheumatology trialists and other experts. A scoping study methodology was then used to examine the evidence available to support or refute each initial recommendation. The potential influence of CRRC recommendations on primary outcomes in future trials was examined. Recommendations were finalized using a consensus process.

Results. Recommendations for clinical trial inclusion criteria addressed measures of disease activity [Disease Activity Score 28 using erythrocyte sedimentation rate (DAS28-ESR) > 3.2 PLUS ≥ 3 tender joints using 28-joint count (TJC28) PLUS ≥ 3 swollen joint (SJC28) OR C-reactive protein (CRP) or ESR > upper limit of normal PLUS ≥ 3 TJC28 PLUS ≥ 3 SJC28], functional classification, disease classification and duration, and concomitant RA treatments. Additional recommendations regarding study design addressed rescue strategies and longterm extension.

Conclusion. There is an urgent need to modify clinical trial inclusion criteria and other study design features to better reflect the current characteristics of people living with RA in the countries where the new drugs will be used. (First Release July 15 2011; J Rheumatol 2011;38:2095–2104; doi:10.3899/jrheum.110188)

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RHEUMATOID ARTHRITIS        CLINICAL TRIALS       METHODOLOGY       ELIGIBILITY

The randomized controlled trial (RCT) is the standard for drug evaluation used by regulatory agencies and bodies deciding on drug reimbursement, such as the Canadian Agency for Drugs and Technologies in Health (CADTH) and the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom. Coincident with the reliance on well-executed RCT has been a considerable decline in recruitment in established sites with clinical trial experience and a shift to sites in countries with less developed medical research infrastructure. Concerns regarding the randomized controlled trial (RCT) are not new, and randomized trials will continue to be the cornerstone of clinical evaluation. However, there is an urgent need to modify the clinical trial inclusion criteria and other study design features to better reflect the current characteristics of people living with RA in the countries where the new drugs will be used.
ing research proficiency in sites with less clinical trial expertise are reflected in the variability in efficacy results and placebo response rates that have been observed globally. Additional challenges include the ability to collect informed consent from illiterate and vulnerable populations, and the ethics of testing drugs that will not be available to the host nation once the study is completed. Because of these factors there is an increasing concern that the globalization of clinical trials may impede the development of new therapies, not only in rheumatology, but across many diseases.

In rheumatology, substantial variation in the incidence of infectious adverse events has been observed from country to country, and this has influenced the withdrawal of new drugs. There is also evidence demonstrating that differences in baseline characteristics of patients with rheumatoid arthritis (RA) globally are related to the economic wealth of countries. As a result, RA populations in developing countries have a much higher level of RA disease activity than those in wealthier countries. This disparity calls into question the generalizability of research findings from studies where most participants have been recruited from developing countries, a point that is not lost on regulatory agencies or payers.

The globalization of clinical trials was in response to several factors including increasing costs and bureaucratic challenges in North America and Western Europe. Trial design is also affected by ethical and methodological requirements in countries that adhere to the International Conference on Harmonization guidelines for clinical trials of pharmaceuticals for human use. However, the need remains to test new therapies for RA. This can be facilitated by changing trial inclusion and exclusion criteria to better reflect the characteristics of RA populations in the countries where the drugs will most often be used.

The Canadian Rheumatology Research Consortium (CRRC) is a network of rheumatology trialists and other experts from across Canada. CRRC members have seen unprecedented changes in the clinical trials arena over the past decade. Earlier diagnosis and access to biologics in North America and Europe, coupled with the common use of higher doses of methotrexate (MTX), limits patient eligibility for trials. In addition, markers of disease activity for many patients have decreased overall, yet inclusion criteria for many trials continue to require high numbers of tender and swollen joints and high eligibility limits for laboratory values. This creates a critical situation by greatly reducing the number of Canadian patients enrolled in the studies that will be used to provide evidence to inform the availability and access to therapies and guide overall rheumatology care in Canada.

In the context of this dynamic international environment, the CRRC undertook a study to inform recommendations for the entry criteria and other design considerations to be used in clinical trials in RA.

**MATERIALS AND METHODS**

The CRRC recommendations were developed using a modified nominal group consensus method. CRRC members were polled using a questionnaire to rank the greatest challenges to clinical trial recruitment in their practices. A followup questionnaire was administered (with a very limited response period) to collect additional information about problematic trial eligibility criteria. Initial recommendations were developed by an expert panel of rheumatology trialists and other experts affiliated with the CRRC. A scoping study methodology was then used to examine the evidence available to support or refute each initial recommendation. Key steps are outlined in Table 1. The potential effects of CRRC recommendations on primary outcomes in future trials were considered. We examined the primary outcome variables from RCT using similar inclusion criteria to determine if there was any significant influence on expected short-term and longterm outcomes for American College of Rheumatology (ACR) response, European League Against Rheumatism (EULAR) response, and radiographic progression. Recommendations were finalized using a consensus process.

**RESULTS**

There are 63 CRRC members representing 38 distinct clinical sites. Twenty-eight sites (74%) completed the initial questionnaire, which addressed overall challenges to clinical trial recruitment. Fifteen of 63 (24%) CRRC members completed a followup questionnaire specifically targeting trial entry criteria. The low response rate is attributed to the limited response window, as it was circulated just prior to the 1-day workshop. Ten Canadian rheumatologists participated on the expert panel and prepared preliminary recommendations, reviewed current literature, and participated in the final consensus process. Resulting recommendations for study inclusion criteria addressed measures of disease activity and previous and concomitant RA treatments. Additional recommendations regarding study design features that may affect patient recruitment were also identified. Issues related to the limitations of traditional and current clinical trial design and RA outcomes and endpoints were the subject of much discussion and are the focus of a current CRRC scoping study. Along with the specific recommendations to improve trial recruitment, evidence-informed discussion points have been reported where appropriate.

**Inclusion and exclusion criteria.**

**Confirmed diagnosis of RA.** Recommendation: (future) clinical trials should use the 2010 ACR and EULAR classification criteria for RA.

The ACR and EULAR have collaborated to devise new RA classification criteria to replace the existing RA classification criteria. The 2010 RA classification criteria will not affect the inclusion of patients with established RA but may be important for studies of interventions for early RA to ensure the homogeneity of study populations. New analyses with these criteria have demonstrated that increased numbers of patients qualify as RA and this will enhance recruitment, and given weighting on seropositivity, will likely increase specificity of disease at entry.

**Disease activity.** Recommendation: (At the least) moderate disease at baseline defined by a Disease Activity Score 28 using erythrocyte sedimentation rate (DAS28-ESR) > 3.2
PLUS 3 or more tender joints using the 28-joint count (≥ 3 TJC28) PLUS 3 or more swollen joints using the 28-joint count (≥ 3 SJC28), OR, (b) C-reactive protein (CRP) greater than upper limit of normal (> ULN) according to the centralized reference laboratory or ESR > ULN using a licensed independent laboratory PLUS ≥ 3 TJC28 PLUS ≥ 3 SJC28.

Entry criteria for RA RCT have traditionally included a specific number of tender joints (TJ) and swollen joints (SJ) using the 68/66 joint count and specified levels for acute-phase reactants (APR). Recent changes include the move to the 28-joint count as used by the DAS24 and a baseline DAS28 to set the disease activity entry criterion25,26,27. Kingsley, et al28 have demonstrated that the DAS28 may better identify trial-ready patients in clinical cohorts. The use of specific cutoff criteria for ESR and/or CRP is being reconsidered. There is mounting evidence that APR levels...
may not be elevated in many patients, normal ranges may be declining in those who are diagnosed and treated early with conventional disease-modifying antirheumatic drugs (DMARD), and levels may not change at all in some patients despite the effectiveness of treatment. The new EULAR/ACR revised RA classification criteria do not contain specific laboratory values, but instead use normal and abnormal ratings as determined by local laboratory standards. The terminology “elevated ESR or CRP” without a value specified is starting to be used in RCT and takes into account the differences in laboratory reference rates. The CRP can be processed in a centralized laboratory, which is particularly important for international RCT. To improve reliability, we recommend that ESR be done in the office of the investigator, rather than be read by a licensed local independent laboratory. Differences in DAS28 classifications using ESR vs CRP have recently been examined. The DAS28 using CRP has not been validated for use in RCT. There is sufficient evidence from recent clinical trials that using a CRP ≥ 1 mg/dl or ≥ ULN and ESR ≥ ULN has not affected the ability to achieve a significant clinical or radiographic outcome.

Another challenge to trial recruitment in recent years is the significant reduction of actively inflamed joints seen in patients in usual care. In a cross-sectional analysis of 3 RA cohorts at 3 timepoints, contemporary cohorts had smaller numbers of tender and swollen joints. In Canada, the Canadian Early Arthritis Cohort (CATCH) is a recently established cohort of adults with early RA. In a recent analysis of 886 patients in CATCH, the median TJC28 and SJC28 was 2 at 12 weeks from consult (when patients would first be approached for RCT), and after therapy initiation (CATCH investigators, personal communication). A sub-analysis was recently completed to examine cohort eligibility for 312 CATCH patients receiving MTX, assessed at 6 months after initiation of treatment. The authors report that reducing joint criteria from 6 to 4 of 28 joints (in combination with elevated APR vs absolute cutoff criteria) resulted in a 25% increase in eligible patients; 40% of these subjects would be trial-eligible.

Concomitant RA medications at baseline. Recommendations: (a) Phase I: stable MTX or monotherapy without MTX background; (b) Phase II: stable MTX or MTX plus hydroxychloroquine; and (c) Phase III to IV: stable DMARD (monotherapy or combination).

There are 3 distinct cohorts of patients with RA available for clinical trials: patients who are naive to DMARD therapy, DMARD-inadequate responders and biologic-inadequate responders.

Some trials, particularly those in very early RA, will continue to require patients to be DMARD-naive and/or not receiving any DMARD at baseline. Methotrexate (MTX) add-on trials. Recommendations: Duration of MTX at baseline: (a) For a 3-month primary endpoint: 12 weeks of stable MTX. (b) For a 6-month primary endpoint: 8 weeks of stable MTX.

MTX monotherapy, or in combination with other DMARD, is now often the standard of care. Because patients can improve taking MTX over 3 to 6 months, the
Other DMARD add-on trials. Recommendation: If DMARD other than MTX are allowed to continue, the patient should have been taking each DMARD for at least 12 weeks and receiving a stable dose within local treatment guidelines for at least 4 weeks prior to initiation of study drug.

Patients taking a stable single or multiple DMARD should be allowed entry into trials unless there is a concern that there could be an unwanted drug interaction with a specific DMARD and the study medication. There are some people who cannot tolerate MTX or have contraindications to its use and they are often excluded from RA trials. In a real-world Canadian RCT only 70% of patients were currently taking MTX when a biologic was initiated. Newer trials have allowed the inclusion of other or combination stable DMARD as concomitant therapies and have demonstrated the efficacy of other DMARD in the optimal treatment of RA, in addition to MTX and biologics. Katchamart, et al recently completed a systematic review of RCT comparing MTX monotherapy vs MTX combined with other nonbiologic DMARD in adult RA populations. Nineteen trials, totaling 2025 patients, were reviewed. Ma, et al completed a metaanalysis of RCT to determine how combination DMARD therapies (including some biologics) plus MTX affect clinical and radiological outcomes compared to MTX therapy alone in early active RA. Fifteen RCT, totaling 4200 randomized patients, were included in the review. The CRRC supports the use of stable combination DMARD as opposed to discontinuing all DMARD except MTX. However, stratification for MTX alone vs other DMARD alone or in combination should occur to correct for potentially different response rates and toxicities between the underlying treatment groups. We recommend against the use of combination MTX and leflunomide in a clinical trial due to the increased risk of side effects and the recent finding from the Canadian RA treatment guidelines team that it has no added benefit relative to other DMARD combinations.

Oral corticosteroids at baseline. Recommendation: If low-dose oral corticosteroids are allowed, the patient must be on stable dosing for at least 4 weeks prior to initiation of study drug. “Low-dose” is considered < 10 mg/day.

Low-dose oral corticosteroids have been proven an effective therapy in the treatment of signs and symptoms of RA and may also improve radiographic outcomes. RA RCT allow the use of stable low-dose oral corticosteroids as a concomitant therapy. Hoes, et al have recently reviewed RCT of glucocorticoid cotherapy with DMARD in RA, and summarized the evidence to support low to medium doses (well under 10 mg/day). If a remission criterion stricter than the DAS remission is to be a study outcome, especially in trials of early RA, a mechanism will be required to taper and discontinue steroids. Stratification by use of steroids at baseline should likely be performed as the treatment effect could be different (as well as the severity of subjects taking steroids).

Exclusion criteria. Studies have suggested that the majority of exclusion criteria are not directly related to drug safety, but they impair trial recruitment and generalizability. In most trials, patients with significant comorbidities, older age, and past cancer have been excluded. It is important to balance safety with generalizability of the data from an ideal population to the real world. Only exclusion criteria that address the safety of a product should be considered, but not necessarily past treatments or remote (cured) cancers.

Study design. Rescue therapy. Recommendations: (a) rescue to the active drug should be allowed if the trial continues longer than 12 weeks, with criteria for rescue defined as failure of the patient to improve TJC and SJC by 20% or more or a DAS28 response less than 1.2. Failure to achieve an ACR20 criteria response should not be used as a rescue criterion; (b) change to active agent in Phase II and III trials.

Improvements in overall outcomes for patients over the past decade may be as attributable to the strategy of treatment as to the agent used. Rescue of participants with an inadequate response to their current regimen within an RCT is increasingly being included as a standard component of study design. However, the timing of rescue, and how it is measured, may affect withdrawal rates from trials, and these results may be misinterpreted by those conducting systematic reviews and guideline development. For example, in 2 RCT of certolizumab pegol the majority of participants receiving placebo (62.8% and 79.5%) were rescued at Week 16. Of significance, the criteria for rescue likely accounted for the high withdrawal rate in these 2 studies. Thus, instead of the criterion of failing to achieve a 20% improvement in the TJC and SJC, participants failing to achieve an ACR20 response were rescued. Upon further analysis, the primary reason for failing to achieve the ACR20 response related to patient-reported outcomes, not physician or laboratory outcomes (E.C. Keystone, personal communication). This result is consistent with other studies of ACR20 nonresponders. It is also important to note that if there is rescue therapy at 12 weeks, then the maximal ACR response scores could be blunted, as even with fast-acting agents ACR70 improvements usually occur beyond 12 weeks.

Despite the significant outlay of time and resources to
In recent years, RCT in rheumatology have become increasingly complicated. At the same time, participant recruitment at established rheumatology research sites is increasingly difficult. This situation has created an urgent impetus to modify traditional RCT design. This crisis has been addressed in the literature\textsuperscript{26,49,50,56,73,74,93,95,107,108,109,110,111,112,113,114,115,116,117,118,119}. However, there has been little effect of this body of work on RCT designed and sponsored by the pharmaceutical industry and required by regulators and payers.

The changes that we have outlined should increase the pool of appropriate trial participants by taking into consideration the baseline clinical characteristics of current patients with RA. There is now adequate literature to support these changes based on more recent studies that have generated similar clinical outcomes compared to more standard designs. More studies with these designs are needed to demonstrate comparable radiographic outcomes.

Of significance, the characteristics of patients entering trials with current designs generate results that do not reflect those of clinical practice in the real world\textsuperscript{26,49,50,112,113,114,115,116,117,118,119}. Thus, the lower disease activity of patients in practice may not result in treatment responses (as determined by ACR or EULAR DAS responses) as high as those in clinical trials, but do improve the proportion of patients achieving a low disease state or remission. It is time to adapt clinical trial outcomes to reflect disease states achieved, rather than treatment responses. The use of less stringent inclusion criteria in trials in concert with changes in primary outcomes would go a long way toward improving the generalizability of clinical trials to clinical practice in countries with established rheumatology infrastructure, while at the same time improving the participation of countries where therapies are most utilized.

We also proposed changes in trial design that would enhance the interpretation of the results. Among them is assuring stability of background DMARD to avoid a high placebo response rate, and utilizing higher doses and parenterally administered MTX to identify true MTX inadequate responders. We discussed the challenges of rescue strategies. Such strategies are important to enhance patient
acceptance of participation in a study but may have had unforeseen consequences of inappropriately high withdrawal rates leading to difficulties in the interpretation of results. In particular, short duration on placebo makes the interpretation of radiographic data very difficult and the timing of radiographic endpoints and the interpretation of their clinical significance may need to be reevaluated. It is a useful reminder that the original US Food and Drug Administration guidance document to industry for the acceptance of an indication for prevention of radiographic progression suggested placebo-controlled trials of 2 to 5 years.

We have not addressed many other barriers to clinical trial recruitment such as changing procedures to make trials more attractive to patients. CRRC members have reported that patients who are approached about enrolling in a clinical trial are often frightened by highly legalistic consent forms and inordinate time commitments (CRRC, personal communication). Increasing the number of centers doing trials could improve recruitment, but becoming a successful trialist can be a daunting and expensive task. Nevertheless, if the expertise in conducting clinical trials that has developed over the past 2 decades in established sites is to remain engaged, changes have to be considered. There are many important therapeutic questions remaining to be answered. A move to innovative trial designs is currently being discussed to address a similar crisis in cancer research.

There is an urgent need to modify RCT inclusion criteria and other study design features such as primary outcomes to better reflect the current characteristics of people living with RA in the countries where the new drugs will be used. Regulators, scientists, and others involved must address this crisis before we lose our capacity to participate in clinical trials that are relevant to the optimal treatment of our patients.

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