BMJ Open

Long-term prognosis and quality of life in patients with early rheumatoid arthritis treated according to the 2015 ACR guideline (LELAND): protocol for a multicentre prospective observational study in Southern China

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ABSTRACT

Introduction Rheumatoid arthritis (RA) is a chronic systemic disease and one of the most disabling diseases for patients. The American College of Rheumatology (ACR) issued a new guideline in 2015 for the treatment of RA based on the treat-to-target strategy to achieve better outcomes. This study will focus on the real-world rates of remission and low disease activity of patients with early RA in China, who will be treated according to the 2015 ACR guideline. Additionally, factors influencing treat-to-target outcomes will be analysed, and long-term prognosis and quality of life will be assessed.

Method and analysis Two-hundred patients with early RA will be enrolled, treated and followed up once every 3 months for 48 months. These patients should fulfil the 2010 RA classification criteria of the ACR/European League Against Rheumatism with a disease course of no more than 6 months and should also fulfil other eligibility criteria. The patients will be treated following the 2015 ACR guideline. Their disease activity will be assessed, and they will be instructed to complete several questionnaires once every 3 months. The primary outcomes are the Disease Activity Score on 28 joints and Health Assessment Questionnaire Disability Index. The secondary outcome variables are the Simplified Disease Activity Index, Clinical Disease Activity Index and Routine Assessment of Patient Index Data 3 results, imaging data and personal medical costs. The data will be analysed using appropriate statistical analyses.

Ethics and dissemination This research was approved by the Nanfang Hospital Ethics Committee (NFEC-2017−192). The results of the study will be published in international peer-reviewed journals.

Trial registration number NCT03508713; Pre-results.

Strengths and limitations of this study

► This study will last for 4 years and will reflect the real-world rates of remission and low disease activity of patients with rheumatoid arthritis (RA) in China.

► In addition to the primary outcome variables, this study will collect many secondary outcome variables, such as economic analysis, and intends to identify relevant factors affecting disease activity and prognosis in a real-world setting.

► The follow-up protocol and medication changes will be performed according to the 2015 American College of Rheumatology guideline.

► This study is an investigation of real-world patients with early RA, and some confounders may induce a certain degree of bias.

► Two research centres located in Guangdong Province of China are participating in this study, and more samples and research centres may be added in the future based on the study results.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown cause. In genetically susceptible individuals, an external stimulus, such as cigarette smoking or infection, is theorised to trigger an autoimmune reaction, leading to synovial hypertrophy and chronic joint inflammation along with the potential for extra-articular manifestations.[1] In China, the disease incidence is 0.19%–0.41%, and females are four times more likely to develop RA than are males.[2 3] With the emergence of an ageing population in China, the number of patients with RA is increasing rapidly.[2 3] If these patients cannot be treated properly, half of them may become disabled, and their life spans may decrease 3–5 years, which will impose a heavy burden on the social medical system.[4–6]

Fortunately, the treat-to-target concept was put forward in 2010. According to the

2015 American College of Rheumatology (ACR) guideline, patients are in remission if their Disease Activity Score on 28 joints (DAS28) <2.6, whereas patients with a DAS28 ≥2.6 and <3.2 are in low disease activity (LDA), and the treatment target should ideally be remission or LDA, that is, a DAS28 <3.2.[7 8] Recently, due to tight control of treat-to-target therapy and the availability of several biological agents, rheumatologists have been able to treat patients with RA more appropriately and obtain better disease outcomes, with 50% of patients with RA maintaining LDA and approximately 15% achieving complete remission.[9–13] Tight control of treat-to-target therapy can effectively halt bone destruction, decrease the RA-induced disability rate and help patients with RA achieve a better quality of life.[11]

Recent research has shown that rapid progression of cartilage and bone damage occur during the early stage of RA[14 15] and thus tightly controlled treatment at the early stage has a better outcome than does treatment initiated at a later stage.[16] Therefore, clinicians should develop strategies to obtain better outcome, such as early diagnosis, early treatment and treat-to-target therapy. We searched for clinical trials of RA at http://www.chictr.org.cn/ and http://apps.who.int/trialsearch from 2010 to 2017 and found that those studies mainly focused on medications and had few observation indexes. Thus, they did not reflect the current state of real-world treat-to-target research.

Unfortunately, insufficient training of rheumatologists on RA and inadequate care of patients with RA have resulted in ≤10% of patients with RA in China achieving treat-to-target goals.[17] The rates of remission and LDA in patients with early RA treated following the 2015 ACR guideline, the factor or factors that influence the rates of remission and LDA, and the long-term prognosis and quality of life among patients with RA in China remain unclear. This study seeks to address these topics.

Rationale
In 2015, the ACR provided a guideline for RA treatment. Patients were classified into early RA and established RA and treated accordingly. Patients with early RA are treated as shown in figure 1.[7]

Patients with early RA who meet the treat-to-target targets will have a good long-term prognosis and quality of life compared with those who do not achieve these targets. However, these targets are not easy to achieve, and some factors may influence the rates of remission and LDA, such as disease activity (mild, moderate and severe), medications (traditional disease-modifying antirheumatic drugs (DMARDs) and biological agents), blood parameters (anti-cyclic citrullinated peptide antibody (CCP) and rheumatoid factor (RF)), ultrasonic and radiographic progression and economic factors.

Aims
To investigate the real-world rates of remission and LDA of patients with early RA treated following the 2015 ACR

guideline for the treatment of RA, the long-term prognosis and quality of life and the factors influencing the rates of remission and LDA.

METHODS
Study design
This multicentre prospective observational study will be conducted in Nanfang Hospital and Zhujiang Hospital of Southern Medical University and will recruit 200 patients with early RA. The participants will be followed up once every 3 months for 48 months to assess their disease activity and to survey their health-related quality of life and their work efficiency. The study will be conducted in full compliance with the articles of the Declaration of Helsinki. All analyses will be conducted by a statistician according to the prespecified statistical analysis plan.

Participants
The participants must meet the following criteria:
1. ≥18 years of age.
2. Fulfil the ACR/European League Against Rheumatism 2010 RA classification criteria.[18]
3. Disease course of less than 6 months.
4. Demonstrate complete understanding of the survey and have the ability to complete the questionnaires independently.
5. Willingness to enrol in the study and sign the consent form allowing the researchers to use their personal health information.

Exclusion criteria: Patients who meet one of the following conditions at baseline will be excluded:
1. Pregnant or lactating women or women who plan to become pregnant within the next 2 years.
2. Enrolment in another RA clinical study in the last 24 weeks.
3. Inability to report quality of life or medical resources.

Drop-out criteria: Participants can drop out of the study at any time. Participants will be removed from the study if they meet one of the following conditions:
1. The researchers believe that study removal will benefit the patient.
2. The participants refuse to answer the questionnaires or do not follow the follow-up time schedule included in the research protocol.

Sample size calculation
This study will recruit 200 patients with early RA whose disease courses are no more than 6 months. Considering a mean ΔHealth Assessment Questionnaire Disability Index (HAQ-DI) of −0.21, an SD of 0.5, a significance level of 0.05 in two-sided tests and a drop-out rate of 20%, the indicated sample size will result in 99% statistical power, suggesting that a ΔHAQ-DI <0 reflects a statistically significant improvement. Considering a mean ΔHAQ-DI of −0.5, an SD of 0.7, a significance level of 0.05 in two-sided tests
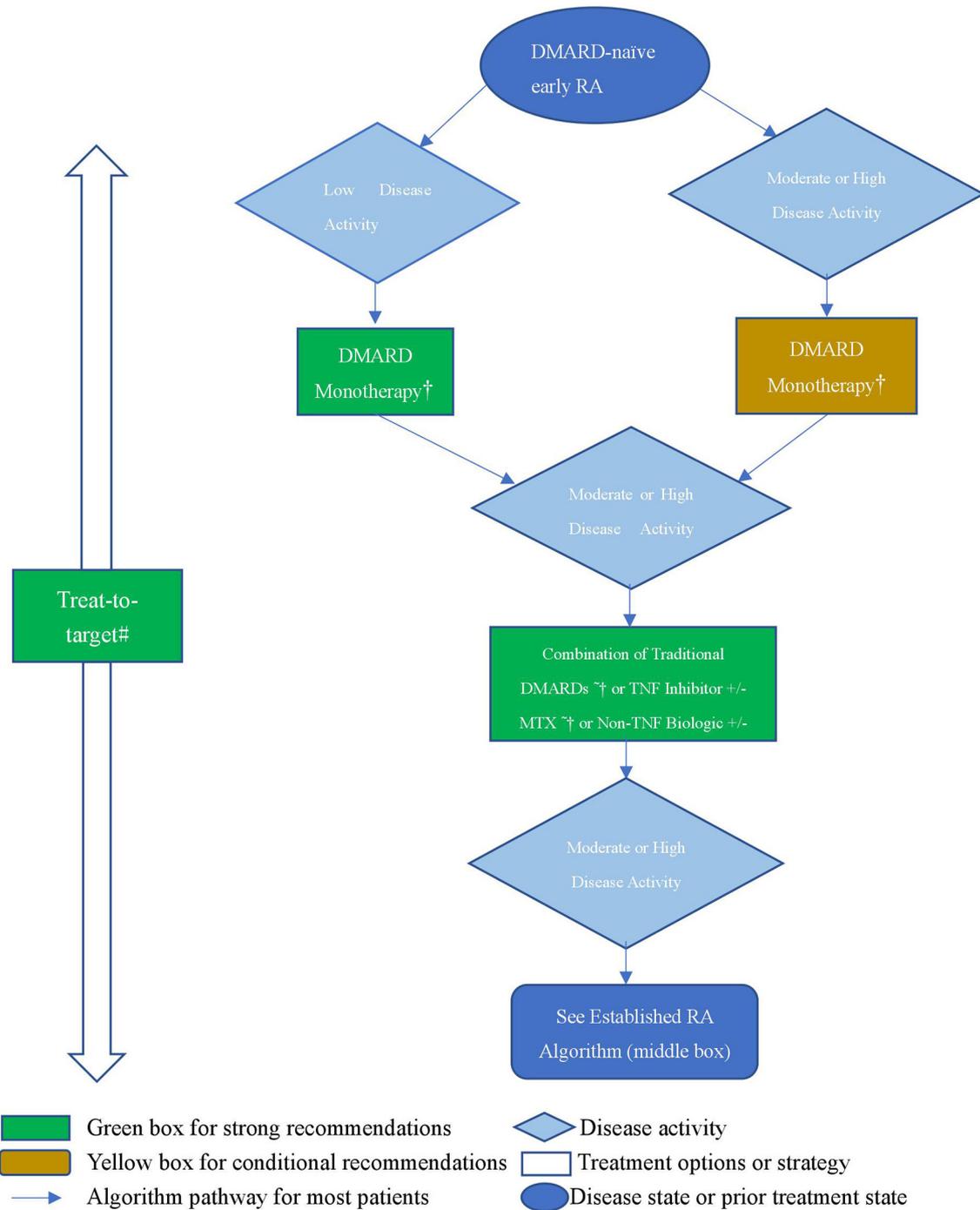
Figure 1 2015 ACR RA treatment recommendations. The 2015 ACR recommendations for the treatment of early RA,[7] which is defined as a disease duration <6 months. ˜Consider adding low-dose glucocorticoids (≤10 mg/day of prednisone or equivalent) in patients with moderate or high disease activity when starting disease-modifying ant-rheumatic drugs (DMARDs) and in patients with DMARD failure or biological failure. †Consider using short-term glucocorticoids (defined as <3 months of treatment) for RA disease flares. Glucocorticoids should be used at the lowest possible dose and for the shortest possible duration to provide the best benefit–risk ratio for patients. #The treatment target should ideally be low disease activity or remission. For the level of evidence supporting each recommendation, see the related section in the results. ACR, American College of Rheumatology; RA, rheumatoid arthritis; MTX, methotrexate; TNF, tumour necrosis factor.

and a drop-out rate of 20%, the indicated sample size will result in 99% statistical power, suggesting that a ΔHAQ-DI <0.22 reflects clinically significant improvement. For the Work Productivity and Activity Impairment Questionnaire (WPAI), which is the secondary endpoint analysis indicator, considering a significance level of 0.05 in two-sided tests, a drop-out rate of 20%, a mean score of 10 for loss of working time, an SD of 30 and a population unemployment rate of 50%, the indicated sample size will result in 83% statistical

Table 1 Summary of measures to be collected

Protocol	Baseline	Month 3	Month 6	Month 9	Every 3 months	Early termination or drop-out
Fill out by clinicians						
Inclusion or exclusion standard table	√					
Sign informed notice	√					
Patients' case history and demographic data	√					
Intercurrent diseases	√					
DAS28-ESR or DAS28-CRP	√	√	√	√	√	√
Adverse events		√	√	√	√	√
Pregnancy report	√	√	√	√	√	√
Clinical routine inspection	√	√	√	√	√	√
Filled out by subjects						
HAQ-DI	√	√	√	√	√	√
SF-36	√	√	√	√	√	√
EQ-5D	√	√	√	√	√	√
WPAI	√	√	√	√	√	√
HCRU	√	√	√	√	√	√
PGIC		√	√	√	√	√
SAS	√	√	√	√	√	√
SDS	√	√	√	√	√	√
Satisfaction questionnaires post-treatment	√	√	√	√	√	√

CRP, C reactive protein; DAS28, Disease Activity Score on 28 joints; EQ-5D, European Quality of Life-5 Dimensions; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; HCRU, healthcare resource utilisation; PGIC, Patient Global Impression Change; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; SF-36, Short Form 36 Health Survey Questionnaire; WPAI, Work Productivity and Activity Impairment Questionnaire.

power, suggesting that loss of working time is clinically significant.

Clinical examinations and blood samples

At baseline (pretreatment), the participants will be asked to register data for their case history, demographics and intercurrent diseases. The participants will follow the procedure shown in table 1.

The tender joint count and swollen joint count assessments include the proximal interphalangeal joint and metacarpophalangeal joints of the hands, wrists, elbows, shoulders and knees on both sides. Rest pain and morning stiffness will be scored by the patients according to the Visual Analogue Scale. The above clinical examinations will be assessed once every 3 months. Blood samples will be collected once every 3 months by a trained laboratory technician. Routine tests, including a routine blood test, hepatic and renal function, erythrocyte sedimentation rate, C reactive protein, RF, immunoglobulin and complement, will be tested once every 3 months. The CCP and antikeratin antibody will be tested once a year.

Outcomes

The primary outcome variables are DAS28 and HAQ-DI. The formulas for measurement of DSA28 refer to the relevant literature.[8]

The secondary outcome variables are the Simplified Disease Activity Index, Clinical Disease Activity Index and Routine Assessment of Patient Index Data 3 results, imaging data, including musculoskeletal ultrasound and modified Total Sharp Score (mTSS), European Quality of Life-5 Dimensions (EQ-5D), Short Form 36 Health Survey Questionnaire (SF-36), WPAI, Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS), healthcare resource utilisation, the Patient Global Impression Change and personal medical costs, including the costs of medicine and examinations. The above variables will be recorded at each follow-up. Other secondary outcome variables include changes in patient-reported outcomes (PROs) pretreatment and post-treatment, such as those related to the SF-36, EQ-5D and WPAI, and correlations between disease severity and PROs, between changes in disease severity and changes in PROs and between changes in disease

severity and imaging data, including musculoskeletal ultrasound and mTSS.

The exploratory outcome variables are changes in the subjects' satisfaction with the primary treatment throughout the follow-up and the factors influencing the rates of remission and LDA, such as the Disease Activity Index at baseline, treatment medications (eg, traditional DMARDs or biological agents), haematology indexes (eg, CCP and RF) and radiographic progression.

Statistical analyses

All statistics will be calculated independently with SPSS (V.20, SPSS). Continuous variables will be described by the mean, SD, minimum, maximum and median. Categorical variables will be described by numbers and percentages. Significant changes in parameters will be estimated by t-tests or variance analysis, and significant changes in non-parametric data will be assessed using the Wilcoxon symbol rank test. The data analysis will also include the severity levels, such as moderate and severe, and the quartiles of the disease course will be compared over time with a maximum of two other subgroups. The Cochran-Armitage trend test or other similar tests can also be used to compare different categories of subjects. Multiple regression analysis will be used to obtain mixed-effects models to statistically analyse the factors influencing the rates of remission and LDA, such as the initial Disease Activity Index, the choice of therapeutic drugs (eg, traditional DMARDs or biological agents), haematology indexes (eg, CCP and RF) and radiographic progression. To investigate the effect of duration of treatment target on patients with RA, the study will classify patients with RA into three groups according to their outcomes. The first outcome category is sustained remission, which includes patients who achieve 4 targets every year. The second category is intermittent remission, which includes patients who achieve 2–3 targets and the third category is active disease, which includes patients who achieve 0–1 targets. The HAQ-DI of these three groups from baseline to post-treatment will be analysed. Bivariate analysis will be performed between the clinical categories and the HAQ-DI. The ORs and their 95% CIs will be reported. In addition, the regression model will be used to identify the effect of each potential risk factor adjusted for other factors. Variables with $p < 0.05$ in the bivariate analysis will be included in the regression models. The adjusted ORs and 95% CIs will be reported. All p values are two tailed. A $p < 0.05$ is considered statistically significant.

Patient and public involvement

Neither patients nor the public were involved in the development of the research question, study design, outcome measures, recruitment and conduct of the study or the assessment of the burden of the intervention. We will make an allowance of ¥200 at each follow-up for transportation costs. The research results will be disseminated to the study participants on the subsequent visit.

DISCUSSION

This study aims to explore the real-world rates of remission and LDA of patients with early RA treated following the 2015 ACR guideline for the treatment of RA in Southern China. The trend of DSA28 and HAQ-DI from baseline to the end of the study may reflect the treatment effects and provide guidance for the treatment of patients with RA.

In this study, factors influencing the rates of remission and LDA, long-term prognosis and quality of life among patients will be observed. Multiple regression analysis will be adopted to obtain mixed-effects models to analyse these factors, including the initial Disease Activity Index, the medicine selection of traditional DMARDs or biological agents, haematology indexes, such as CCP and RF, and radiographic progression, such as mTSS. HAQ-DI and PROs related to SF-36, EQ-5D and WPAI will be analysed at every follow-up time point to determine trends in patients' disease changes. At the same time, correlations between disease severity and PROs and their changes will be explored, as well as the SDS and SAS.

China's society is experiencing rapid ageing. Approximately 5 million patients with RA have been diagnosed, although China has no more than 8000 rheumatologists. Influenced by traditional culture, most patients with RA are inclined to adopt traditional Chinese medicine as their first choice, and these patients have been lulled into thinking that traditional Chinese medicine can cure the disease with few side effects but that DMARDs only relieve symptoms with many side effects. Therefore, this research will benefit patients with RA in China by educating them on how to obtain appropriate and timely treatment and how to achieve a good prognosis.

This study has some limitations. Both research centres in this study are located in Guangdong Province, China, which may induce poor representativeness of the samples. The non-randomised study design inherits the risks of confounding; therefore, thorough statistical analysis and confounder adjustment are important.

ETHICS AND DISSEMINATION

This study mainly focuses on the real-world rates of remission and LDA, long-term prognosis and quality of life of patients with early RA treated following the 2015 ACR guideline for the treatment of RA. The study is an observational study with no patient interaction. All data will be processed under the rules of the government and law. All researchers will guarantee the anonymity of the patients and will not reveal patient names on forms or reports or in articles unless legally required. Only authorised individuals can access the patients' health information. All researchers handling data must follow specific training to address adverse events. The results will be published in international peer-reviewed journals.

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