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Long-term prognosis and quality of life in early rheumatoid arthritis patients treated by the 2015 ACR Guideline (LELAND): Protocol for a multicentre prospective observational study in southern China

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Long-term prognosis and quality of life in early rheumatoid arthritis patients treated by 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 in clinical practice. Recent research has shown that rapid progression of cartilage and bone damage can occur in the early stage of RA, and clinicians must develop strategies to prevent further deterioration, such as early diagnosis, early treatment and treat-to-target therapy. While only half of RA patients worldwide achieve low disease activity, only approximately 10% of RA patients exhibit low disease activity in China according to data released two years ago.

In 2015, the American College of Rheumatology (ACR) issued a new guideline for the treatment of RA to achieve better outcomes. Most published research has primarily focused on the medications used for RA treatment, and many investigations did not follow the 2015 ACR Guideline strictly and had few observational targets. Consequently, these studies do not reflect the real-world treat-to-target rate of RA.

This study will focus on the real-world treat-to-target rate of early RA patients, who will be treated according to the 2015 ACR Guideline. Additionally, the factors influencing the treat-to-target outcomes will be analysed, and long-term prognosis and quality of life will be assessed.

Method and analysis: 200 early RA patients will be enrolled, treated and followed up for 48 months. The patients should fulfil the 1987 ACR classification criteria for RA or the 2010 Rheumatoid arthritis classification criteria of the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR), with a disease course of no more than 6 months, and meet other conditions. They will be evaluated to determine their illness state and instructed to complete several questionnaires every 3 months.

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.

Keywords: Rheumatoid Arthritis (RA), treat-to-target, real-world, 2015 ACR Guideline.

STRENGTHS AND LIMITATIONS OF THIS STUDY

Early diagnosis and treatment of RA can improve patients' prognosis and quality of life. Therefore, treat-to-target therapy at an early stage is very important.[1] There are many problems in current clinical practice, such as failure to follow the 2015 ACR Guideline for the Treatment of RA. Consequently, only approximately 10% of RA patients in China achieve treat-to-target goals, which is significantly lower than the corresponding proportion of patients worldwide. Observing real-world data on early RA patients in China is very important. Most published research mainly focuses on the medications used for RA treatment, and many studies did not follow the 2015 ACR Guideline strictly and included few observational targets. Consequently, they could not reflect the real-world treat-to-target rate of RA or disease development and prognosis.

Two hundred early RA patients will be enrolled, treated and followed up for 48 months. The study will determine their long-term prognosis and evaluate their quality of life, without adding an economic burden. At the same time, the research will explore the reasons why Chinese early RA patients have a much lower treat-to-target rate and may provide some feasible solutions to improve it.

We do not deny that there are some limitations of the research, such as the number of enrolled patients, which will only be 200, and the inclusion of research centres mainly located in

Guangdong Province of China.

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 theorized to trigger an autoimmune reaction, leading to synovial hypertrophy and chronic joint inflammation along with the potential for extra-articular manifestations.[2] In China, the disease incidence is 0.3-0.4%, and females are 2 times more likely to develop RA than males. With the emergence of an ageing population in China, the number of RA patients is increasing rapidly. If they cannot be treated properly, half of these patients may become disabled, and their life span may decrease 3-5 years, which will impose a heavy burden on the social medical system.[3-5]

Fortunately, in recent years, due to tight control of treat-to-target therapy, increasingly more biological agents are becoming available, and rheumatologists can treat RA patients more appropriately and expect better outcomes, with 50% of RA patients maintaining low disease activity and approximately 15% of RA patients achieving complete remission and even stopping treatment.[6-10] Tight control of treat-to-target therapy can effectively stop bone destruction, lower the RA-induced disability rate and help RA patients achieve a better quality of life.[8]

Recent research has shown that rapid progression of cartilage and bone damage can occur at the early stage of RA,[11, 12] and evidence indicates that early, tightly controlled treatment results in greater improvement than therapy initiated at a later stage.[13] Therefore, clinicians should develop strategies to prevent further deterioration, such as early diagnosis, early treatment and treat-to-target therapy. In 2015, the ACR published a guideline for the treatment of RA.[14] We searched for clinical trials on RA at http://www.chictr.org.cn/ and http://apps.who.int/trialsearch from 2010 to 2017 and found that most published studies did not follow the 2015 ACR Guideline

for the Treatment of RA, mainly focused on medications, and had few observational targets; therefore, they did not reflect the real-world treat-to-target rate or disease progression and prognosis. Unfortunately, insufficient training of rheumatologists on RA and inadequate care for RA patients have resulted in ≤10% of RA patients achieving treatment targets in China.[15]

The remission rate in early RA patients treated according to the 2015 ACR Guideline in China, the factor or factors that influence the treat-to-target rate, and the long-term prognosis and quality of life among RA patients remain unclear. This study seeks to address these topics.

Rationale and hypothesis

In 2015, the American College of Rheumatology provided a guideline for the treatment of RA, and patients were classified into early RA patients and established RA patients and were treated accordingly. Early RA patients are treated as shown in Figure 1.[14] RA patients who achieve treat-to-target goals have a DAS28≤3. 2, a simplified disease activity index (SDAI)≤11, clinical disease activity index (CDAI)≤10 and routine assessment of patient index data (RAPID-3)≤2.[14, 16] The formulas for the measurement tools are as follows.[16, 17]

DAS28-CRP=0.56*sqrt(28TJC) +0.28*sqrt(28SJC) +0.36*Ln(CRP+1) +0.014*PGA+0.96,

DAS28-ESR=0.56*sqrt(28TJC) +0.28*sqrt(28SJC) +0.70*Ln(ESR) +0.014*PGA,

CDAI=28TJC+28SJC+PGA+EGA (TJC: tender joint count; SJC: swollen joint count; PGA: patient's global assessment of disease activity; EGA: evaluator's global assessment of disease activity).

SDAI=28TJC+28SJC+PGA+EGA+CRP (mg/dl),

RAPID-3=(FN+PN+PTGL)/3 (only patients' reported outcomes. FN: functional score, 0-10; PN:

pain score on the VAS, 0-10; PTGL: patient's global assessment of disease activity).[18]

Early RA patients who achieve the indicated targets will have a good long-term prognosis and good quality life compared with patients who do not achieve these targets. However, these targets are not easy to achieve, and some factors may influence the target rate, such as disease activity (mild, moderate, and severe), treatment medications (traditional DMARDs and biological agents), blood parameters (anti-cyclic citrullinated peptide antibody (CCP) and rheumatoid factor (RF)), and ultrasonic and radiographic progression.

Objectives

To investigate the real-world treat-to-target rate of early RA patients treated following the 2015 ACR Guideline for the Treatment of RA, the long-term prognosis and quality of life, and the factors influencing the target rate.

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 early RA patients. The follow-up will be 48 months. The real-world treat-to-target rate and the factors that influence this rate will be explored, as well as the long-term prognosis, quality of life and personal medical costs. The participants will be followed up once every 3 months to survey their work efficiency and health-related quality of life. All doctors who collect data will be trained to follow specific

standards, and a specialized expert will be assigned to assemble and analyse the data.

Participants

Participants will be recruited from two centres: Nanfang Hospital and Zhujiang Hospital of Southern Medical University. The participants must meet the following criteria:

(A) ≥18 years of age,

(B) fulfilment of the 1987 ACR classification criteria for rheumatoid arthritis[19] or the ACR/EULAR 2010 Rheumatoid arthritis classification criteria,[20]

(C) disease course of less than 6 months,

(D) ability to complete questionnaires independently, and

(E) complete comprehension of the survey and willingness to participate in the study, sign the consent form, and allow the researchers to use personal health information.

Exclusion criteria: Patients who meet one of the following conditions at baseline will be excluded:

(F) pregnant or lactating women or women who plan to become pregnant in the next 2 years,

(G) enrolment in another RA clinical study in the last 24 weeks, or

(H) confirmed 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:

(I) the researchers believe that study removal will benefit the patient, or

(J) failure to follow the study protocol.

Variables and outcome measures

The participants will follow the procedure shown in Table 1. The primary outcome variables are the real-world treat-to-target rate and changes in the DAS28 and Health Assessment Questionnaire Disability Index (HAQ-DI).

The secondary outcome variables are the results of the SDAI, CDAI, and RAPID-3; imaging data, including musculoskeletal ultrasound and modified total Sharp score (mTSS); HAQ-DI; The Work Productivity and Activity Impairment Questionnaire (WPAI); European Quality of Life-5 Dimensions (EQ-5D); Short Form 36 Health Survey Questionnaire (SF-36); self-rating anxiety scale (SAS); self-rating depression scale (SDS); health care resource utilization (HCRU); and the patient global impression change (PGIC), which will be completed by the participants at each follow-up.

Additional secondary outcome variables are as follows: changes in patient-reported outcomes (PROs) pre- and post-treatment, such as those related to the SF-36, EQ-5D and WPAI, and correlations between disease severity and PROs, correlations between changes in disease severity and changes in PROs, and correlations between changes in disease severity and imaging data, including musculoskeletal ultrasound and mTSS.

The exploratory outcome variables are changes in subjects' satisfaction with the primary treatment throughout the follow-up and the factors influencing the target rate, such as the disease activity index at baseline, treatment medications (e.g., traditional DMARDs or biological agents), haematology indexes (e.g., CCP and RF), and radiographic progression.

Clinical examinations and blood samples

TJC and SJC joints assessed include the proximal interphalangeal (PIP) 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. Blood samples will be collected every 3 months by a trained laboratory technician. Routine tests, including hepatic and renal function, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), immune globulin and complement, anti-cyclic citrullinated peptide antibody (CCP) and anti-Keratin antibody (AKA), will be tested once a year.

Sample size considerations and statistical analyses

This survey will be conducted at Nanfang Hospital and Zhujiang Hospital of Southern Medical University and will recruit 200 early RA patients whose disease courses are no more than 6 months. Considering a mean △HAQ-DI of -0.21, a standard deviation 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 △HAQ-DI<0 reflects a statistically significant improvement. Considering a mean △HAQ-DI of -0.5, a standard deviation of 0.7, 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 △HAQ-DI<-0.22 reflects clinically significant improvement. For WPAI, the secondary end point 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, a standard deviation of 30, and a population unemployment rate of 50%, the indicated sample size will result in 83% statistical power, suggesting that loss of working time is clinically significant.

All statistical tests will be two-sided. A P-value ≤0.05 will indicate a statistically significant outcome that will be included in the descriptive statistical analysis. Key parameters will also be

included in the descriptive statistical analysis. Continuous variables will be described by the mean, standard deviation, 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 nonparametric data will be assessed using the Wilcoxon symbol rank test. The data analysis will also include severity levels, such as moderate and severe, and the quartiles of the disease course will be compared over time in 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 target rate, such as the initial disease activity index, the choice of therapy drugs (e.g., traditional DMARDs or biological agents), haematology indexes (e.g., CCP and RF), and radiographic progression.

Patient and Public Involvement

Neither patients nor public were involved in the development of the research question, study design, outcome measures, recruitment to and conduct of the study or assessment of the burden of the intervention. Thanking for the patients' support, we will allowance the study participant 200 RMB at each follow-up as transportation costs. The research result will be disseminated to study participants on subsequent visit.

DISCUSSION

This study aims to explore the real-world treat-to-target rate of early RA patients treated following

the 2015 ACR Guideline for the Treatment of RA in southern China. The RA patients who achieve treat-to-target goals will have a DAS28≤3.2, SDAI≤11, CDAI≤10 and RAPID-3≤2. The study classifies RA patients into three groups according to outcome. 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 trend of the HAQ-DI from baseline to the end of the study may reflect treatment effects and provide guidance for treating RA patients.

In the research, the factors influencing the treat-to-target rate, 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 choice of traditional DMARDs or biological agents, haematology indexes such as CCP and RF, and radiographic progression. Changes in the HAQ-DI and PROs related to the SF-36, EQ-5D and WPAI will be analysed at every follow-up point to determine the trend of 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 ageing population is increasing rapidly, and increasingly more people have been diagnosed with RA. An estimated 5 million RA patients, but no more than 8000 rheumatologists, are present in China. Most RA patients are inclined to explore traditional Chinese medicine as their first choice of treatment due to the myth that traditional Chinese medicine can cure the disease, while DMARDs only relieve symptoms. Therefore, this research will benefit RA patients in China in terms of the provision of appropriate and timely treatment and medication selection.

ETHICS AND DISSEMINATION

This study mainly aims to determine the real-world treat-to-target rate, long-term prognosis and quality of life among early RA patients treated following the development of the 2015 American College of Rheumatology Guideline for the Treatment of RA. It is an observational study with no patient interaction. All data will be processed under the rules of 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 authorized individuals can access the patients' health information. All researchers handling data must follow specific training for addressing adverse events. The study has been approved by the Nanfang Hospital Ethics Committee (identification number NFEC-2017-192). The results will be published in international peer-reviewed journals.

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CONTRIBUTORS

Min Yang, Jinjun Zhao responsible for all phases from setup to the end of this study, including

data collection, analysis and interpret the manuscript. Min Yang, Jinjun Zhao and Taihe Zhan participated in the drafting of the protocol and applied for ethics committee approval. Min Yang, Jinjun Zhao, Taihe Zhan, Qin Huang, Hao Ren, Qinghong Yu, Jing Wu, Jingli Lin, Shengli An and Junqing Zhu all participated in the design of the study. All authors have checked and approved the protocol to be published.

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COMPETING INTERESTS

None.

ETHICS APPROVAL

The study has been approved by the Nanfang Hospital ethics committee.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

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FIGURE LEGENDS

Figure 1. 2015 American College of Rheumatology recommendations for the treatment of early RA,[14] 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 antirheumatic drugs (DMARDs) and in patients with DMARD failure or biologic 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. #: 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. MTX: methotrexate. TNF: tumour necrosis factor.

Table1 Summary of measures to be collected:

Protocol		baseline	Month 3	Month 6	Month 9	Every 3 month…	early termination or drop out
Fill by clinicians	Inclusion or exclusion standard table	√					
	Sign informed notice	√					
	Patients' case history and demographics data	√					
	Intercurrent disease	√					
	DAS28(ESR) or DAS28(CRP)	√	√	√	√	√	√
	Adverse event		√	√	√	√	√
	Pregnancy report	√	√	√	√	√	√
	Clinical routine	√	√	√	√	√	√

	inspection						
Filled by subjects	EQ-5D	√	√	√	√	√	√
	SF-36	√	√	√	√	√	√
	HAQ-DI	√	√	√	√	√	√
	WPAI	√	√	√	√	√	√
	HCRU	√	√	√	√	√	√
	PGIC		√	√	√	√	√
	SAS	√	√	√	√	√	√
	SDS	√	√	√	√	√	√
	Satisfaction questionnaires post-treatment	√	√	√	√	√	√

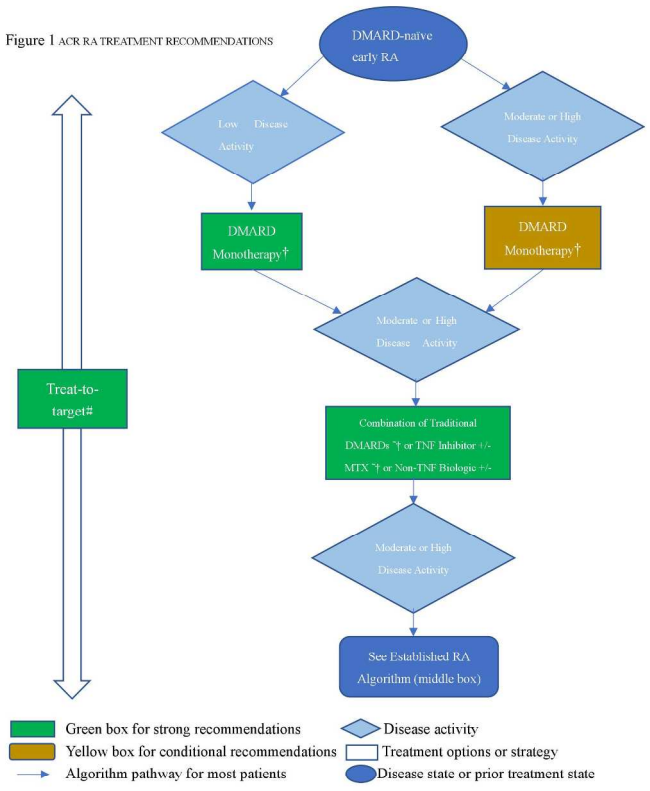

Figure 1. 2015 American College of Rheumatology recommendations for the treatment of early RA

210x297mm (300 x 300 DPI)

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Long-term prognosis and quality of life in early rheumatoid arthritis patients 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 treat-to-target rate of early RA patients 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 early RA patients will be enrolled, treated and followed up once every 3 months for 48 months. These patients should fulfil the 2010 rheumatoid arthritis classification criteria of the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 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 DAS28 and Health Assessment Questionnaire Disability Index (HAQ-DI). The secondary outcome variables are SDAI, CDAI and RAPID-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.

Keywords: rheumatoid arthritis (RA), treat-to-target, real-world, 2015 ACR Guideline.

STRENGTHS AND LIMITATIONS OF THIS STUDY

1) This study will last for 4 years and will reflect the real-world treat-to-target rate of RA patients in China.

2) 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.

3) The follow-up protocol and medication changes will be performed according to the 2015 ACR Guideline.

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

5) 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 theorized 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 4 times more likely to develop RA than are males.[2, 3] With the emergence of an ageing population in China, the number of RA patients 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. A RA patient with a DSA28≤3.2 indicates that he/she has achieved the treat-to-target goal. The real-world treat-to-target rate is the proportion of patients who achieve the treat-to-target goal out of the total number of RA patients. Recently, due to tight control of treat-to-target therapy and the availability of several biological agents, rheumatologists have been able to treat RA patients more appropriately and obtain better disease outcomes, with 50% of RA patients maintaining low disease activity and approximately 15% achieving complete remission.[7-11] Tight control of treat-to-target therapy can effectively halt bone destruction, decrease the RA-induced disability rate and help RA patients achieve a better quality of life.[9]

Recent research has shown that rapid progression of cartilage and bone damage occur during the early stage of RA[12, 13] and thus tightly controlled treatment at the early stage has a better outcome than does treatment initiated at a later stage.[14] 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 RA patients have resulted in ≤10% of RA patients in China achieving treat-to-target goals.[15] The treat-to-target rate in early RA patients treated following the 2015 ACR Guideline, the factor or factors that influence the treat-to-target rate and the long-term prognosis and quality of life among RA patients in China remain unclear. This study seeks to address these topics.

Rationale

In 2015, the American College of Rheumatology provided a guideline for RA treatment. Patients were classified into early RA patients and established RA patients and treated accordingly. Early RA patients are treated as shown in Figure 1.[16]

Early RA patients 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 target rate, such as disease activity (mild, moderate and severe), medications (traditional 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 treat-to-target rate of early RA patients treated following the 2015

ACR Guideline for the Treatment of RA, the long-term prognosis and quality of life and the factors influencing the treat-to-target rate.

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 early RA patients. 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/EULAR 2010 Rheumatoid arthritis classification criteria,[17]
3. disease course of less than 6 months,
4. demonstrate complete understanding of the survey and have the ability to complete the questionnaires independently and
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 and

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 and

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 early RA patients whose disease courses are no more than 6 months. Considering a mean Δ Health Assessment Questionnaire Disability Index (HAQ-DI) of -0.21, a standard deviation 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, a standard deviation of 0.7, 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<-0.22 reflects clinically significant improvement. For the WPAI, which is the secondary end point 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, a standard deviation of 30 and a population unemployment rate of 50%, the indicated sample size will result in 83% statistical power, suggesting that loss of working time is clinically significant.

Clinical examinations and blood samples

At baseline (pre-treatment), 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 (TJC) and swollen joint count (SJC) assessments include the proximal interphalangeal (PIP) 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 (ESR), C-reactive protein (CRP), rheumatoid factor (RF), immunoglobulin and complement will be tested once every 3 months. The anti-cyclic citrullinated peptide antibody (CCP) and anti-keratin antibody (AKA) 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.[18]

The secondary outcome variables are SDAI, CDAI and RAPID-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), The Work Productivity and Activity Impairment Questionnaire (WPAI), self-rating anxiety scale (SAS), self-rating depression scale (SDS), health care resource utilization (HCRU), the patient global impression change (PGIC) 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) pre- 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 treat-to-target rate, such as the disease activity index at baseline, treatment medications (e.g., traditional DMARDs or biological agents), haematology indexes (e.g., CCP and RF) and radiographic progression.

Statistical analyses

All statistics will be calculated independently with SPSS (V.20, SPSS Inc., Chicago, IL, USA). Continuous variables will be described by the mean, standard deviation, 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 nonparametric 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 target rate, such as the initial disease activity index, the choice of therapeutic drugs (e.g., traditional DMARDs or biological agents), haematology indexes (e.g., CCP and RF) and radiographic progression. The study will classify RA patients 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 odds ratios (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 odds ratios (AORs) 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 RMB 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 treat-to-target rate of early RA patients 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 RA patients.

In this study, factors influencing the treat-to-target rate, 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 aging. Approximately 5 million RA patients have been diagnosed, although China has no more than 8000 rheumatologists. Influenced by traditional culture, most RA patients 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 RA patients 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 treat-to-target rate, long-term prognosis and quality of life of early RA patients treated following the 2015 American College of Rheumatology 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 authorized individuals can access the patients' health information. All researchers handling data must follow specific training to address adverse events. The study

has been approved by the Nanfang Hospital Ethics Committee (identification number NFEC-2017-192). The results will be published in international peer-reviewed journals.

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CONTRIBUTORS

Min Yang and Jinjun Zhao are responsible for all phases from setup to the end of this study, including data collection, analysis and interpretation of the manuscript. Min Yang, Jinjun Zhao and Taihe Zhan participated in the drafting of the protocol and applied for ethics committee approval. Min Yang, Jinjun Zhao, Taihe Zhan and Junqing Zhu participated in revising the manuscript. Min Yang, Jinjun Zhao, Taihe Zhan, Junqing Zhu, Meida Fan, Qin Huang, Hao Ren, Qinghong Yu, Jing Wu, Jingli Lin, Qingqing Ouyang and Shengli An all participated in the study design. All authors have checked and approved the protocol to be published.

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COMPETING INTERESTS

None.

ETHICS APPROVAL

The study has been approved by the Nanfang Hospital ethics committee.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

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FIGURE LEGENDS

Figure 1. 2015 ACR RA Treatment Recommendations

The 2015 American College of Rheumatology recommendations for the treatment of early RA,[16] 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 antirheumatic drugs (DMARDs) and in patients with DMARD failure or biologic 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. MTX: methotrexate. TNF: tumour necrosis factor.

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	√	√	√	√	√	√

Note: DAS, disease activity score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; HAQ-DI, Health Assessment Questionnaire Disability Index; SF-36, Short Form 36 Health Survey Questionnaire; EQ-5D, European Quality of Life-5 Dimensions; WPAI, Activity Impairment Questionnaire; HCRU, Health Care Resource Utilization; PGIC, Patient Global Impression Change; SAS, self-rating anxiety scale; SDS, self-rating depression scale.

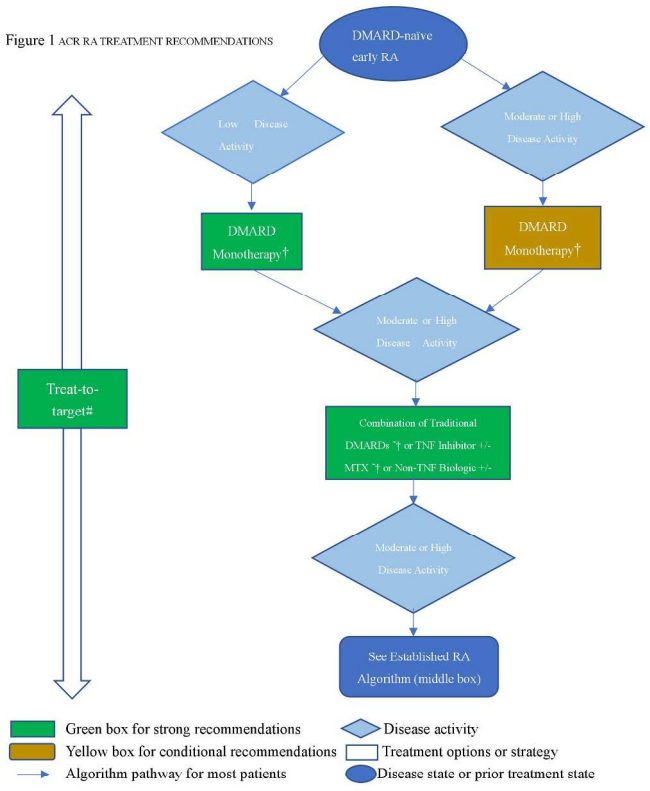

Figure 1. 2015 American College of Rheumatology recommendations for the treatment of early RA

210x297mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	**Title**: a multicentre prospective observational study
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	This study will focus on the real-world treat-to-target rate of early RA patients, treated according to the 2015 ACR Guideline. Additionally, factors influencing the treat-to-target outcomes will be analysed, and long-term prognosis and quality of life will be assessed. Two hundred early RA patients will be enrolled, treated and followed up once every 3 months for 48 months. Those patients should fulfil the 2010 Rheumatoid arthritis classification criteria of the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR), with a disease course of no more than 6 months and 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 DAS28 and Health Assessment Questionnaire Disability Index (HAQ-DI). The secondary outcome variables are SDAI, CDAI and RAPID-3 results,

				imaging data and personal medical costs. The data will be analysed using appropriate statistical analyses.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5	lines 55-95 of the manuscript.
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6	To investigate the real-world treat-to-target rate of early RA patients treated following the 2015 ACR Guideline for the Treatment of RA, the long-term prognosis and quality of life, and the factors influencing the target rate.
Methods				
Study design	4	Present key elements of study design early in the paper	6	lines 102-107 of the manuscript.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8	This multicentre prospective observational study will be conducted in full compliance with the articles of the Declaration of Helsinki. It will be conducted in Nanfang Hospital and Zhujiang Hospital of Southern Medical University and will recruit 200 early RA patients treated according to the 2015 ACR Guideline. 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.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of	6-7	The participants must meet the following criteria: 1. ≥18 years of age, 2. fulfil the ACR/EULAR 2010 Rheumatoid arthritis classification

	participants		criteria,[17] 3. disease course of less than 6 months, 4. demonstrate complete understanding of the survey and have the ability to complete the questionnaires independently and 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 and 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 and 2. the participants refuse to answer the questionnaires or do not follow the follow-up time schedule included in the research protocol.
	(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per	N/A	N/A

		case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8,9	Paragraph under section heading, **Outcomes**.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9	Paragraph under section heading, **Clinical examinations and blood samples** and **Outcomes**.
Bias	9	Describe any efforts to address potential sources of bias	6,11	All analyses will be conducted by a statistician, according to the prespecified statistical analysis plan. statistical analysis and confounder adjustment are taken. All researchers handling data must follow specific training to address adverse events.
Study size	10	Explain how the study size was arrived at	7	Paragraph under section heading, **Sample size calculation**

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,9,10	Paragraphs in the **Sample size calculation** and **statistical analyses**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9,10	Paragraphs in the **Statistical analyses**
		(*b*) Describe any methods used to examine subgroups and interactions	9,10	Paragraphs in the **Statistical analyses**
		(*c*) Explain how missing data were addressed	None	The patients missing data will not be included in the analysis
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	None	The patients missing data will not be included in the analysis
		(*e*) Describe any sensitivity analyses	9,10	Paragraphs in the **Statistical analyses**
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A	N/A
		(b) Give reasons for non-participation at each stage	N/A	N/A
		(c) Consider use of a flow diagram	N/A	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A	N/A
		(b) Indicate number of participants with missing data for each variable of interest	N/A	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A	N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A	N/A
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A	N/A
		(*b*) Report category boundaries when continuous variables were categorized	N/A	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time	N/A	N/A

	period

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A	N/A
Discussion				
Key results	18	Summarise key results with reference to study objectives	10	the real-world treat-to-target rate of early RA patients
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11	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
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10,11	**DISCUSSION** (paragraphs 1,2,4).
Generalisability	21	Discuss the generalisability (external validity) of the study results	11	**DISCUSSION** (paragraph 3).
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12	Provided. Southern Medical University

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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

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Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Rheumatology
Keywords:	Rheumatoid Arthritis (RA), treat-to-target, real-world, 2015 ACR Guideline

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

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[†]These authors contributed equally in this study.

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 (LDA) of early RA patients 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 early RA patients 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 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 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 (DAS28) and Health Assessment Questionnaire Disability Index (HAQ-DI). The secondary outcome variables are the Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI) and Routine Assessment of Patient Index Data (RAPID-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.

Keywords: rheumatoid arthritis (RA), treat-to-target, real-world, 2015 ACR Guideline.

STRENGTHS AND LIMITATIONS OF THIS STUDY

1) This study will last for 4 years and will reflect the real-world rates of remission and LDA of RA patients in China.

2) 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.

3) The follow-up protocol and medication changes will be performed according to the 2015 ACR Guideline.

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

5) 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 theorized 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 4 times more likely to develop RA than are males.[2, 3] With the emergence of an ageing population in China, the number of RA patients 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 RA patients more appropriately and obtain better disease outcomes, with 50% of RA patients 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 RA patients 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 RA patients have resulted in ≤10% of RA patients in China achieving treat-to-target goals.[17] The rates of remission and LDA in early RA patients 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 RA patients 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 patients and established RA patients and treated accordingly. Early RA patients are treated as shown in Figure 1.[7]

Early RA patients 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 anti-rheumatic 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 early RA patients 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 early RA patients. 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 (ACR/EULAR) 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 and

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 and

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 and

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 early RA patients whose disease courses are no more than 6 months. Considering a mean Δ Health Assessment Questionnaire Disability Index (HAQ-DI) of -0.21, a standard deviation 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, a standard deviation of 0.7, 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<-0.22 reflects clinically significant improvement. For the Work Productivity and Activity Impairment Questionnaire (WPAI), which is the secondary end point 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, a standard deviation of 30 and a population unemployment rate of 50%, the indicated sample size will result in 83% statistical power, suggesting that loss of working time is

clinically significant.

Clinical examinations and blood samples

At baseline (pre-treatment), 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 (TJC) and swollen joint count (SJC) assessments include the proximal interphalangeal (PIP) 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 (ESR), C-reactive protein (CRP), RF, immunoglobulin and complement will be tested once every 3 months. The CCP and anti-keratin antibody (AKA) 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 (SDAI), Clinical Disease Activity Index (CDAI) and Routine Assessment of Patient Index Data (RAPID-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), health care resource utilization (HCRU), the patient global impression change (PGIC) 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) pre- 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 (e.g., traditional DMARDs or biological agents), haematology indexes (e.g., CCP and RF) and radiographic progression.

Statistical analyses

All statistics will be calculated independently with Statistical Product and Service Solutions (SPSS) (V.20, SPSS Inc., Chicago, IL, USA). Continuous variables will be described by the mean, standard deviation, 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 nonparametric 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 (e.g., traditional

DMARDs or biological agents), haematology indexes (e.g., CCP and RF) and radiographic progression. To investigate the effect of duration of treatment target on RA patients, the study will classify RA patients 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 odds ratios (ORs) and their 95% confidence intervals (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 odds ratios (AORs) 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 Chinese Yuan (CNY) 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 early RA patients 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 RA patients.

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 aging. Approximately 5 million RA patients have been diagnosed, although China has no more than 8000 rheumatologists. Influenced by traditional culture, most RA patients 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 RA patients 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 early RA patients 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 authorized individuals can access the patients' health information. All researchers handling data must follow specific training to address adverse events. The study has been approved by the Nanfang Hospital Ethics Committee (identification number NFEC-2017-192). The results will be published in international peer-reviewed journals.

ACKNOWLEDGEMENTS

All authors acknowledge all of the contributors to this study, especially the nurses in the Departments of Rheumatology of Nanfang Hospital and Zhujiang Hospital. We are also grateful for the patients' support and the patients' advisers.

CONTRIBUTORS

Min Yang and Jinjun Zhao are responsible for all phases from setup to the end of this study, including data collection, analysis and interpretation of the manuscript. Min Yang, Jinjun Zhao and Taihe Zhan participated in the drafting of the protocol and applied for ethics committee approval. Min Yang, Jinjun Zhao, Taihe Zhan and Junqing Zhu participated in revising the manuscript. Min Yang, Jinjun Zhao, Taihe Zhan, Junqing Zhu, Meida Fan, Qin Huang, Hao Ren, Qinghong Yu, Jing Wu, Jingli Lin, Qingqing Ouyang and Shengli An all participated in the study design. All authors have checked and approved the protocol to be published.

FUNDING

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COMPETING INTERESTS

None.

ETHICS APPROVAL

The study has been approved by the Nanfang Hospital ethics committee.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

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FIGURE LEGENDS

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 anti-rheumatic drugs (DMARDs) and in patients with DMARD failure or biologic 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.

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	√	√	√	√	√	√

Note: DAS, disease activity score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; HAQ-DI, Health Assessment Questionnaire Disability Index; SF-36, Short Form 36 Health Survey Questionnaire; EQ-5D, European Quality of Life-5 Dimensions; WPAI, Work Productivity and Activity Impairment Questionnaire; HCRU, Health Care Resource Utilization; PGIC, Patient Global Impression Change; SAS, self-rating anxiety scale; SDS, self-rating depression scale.

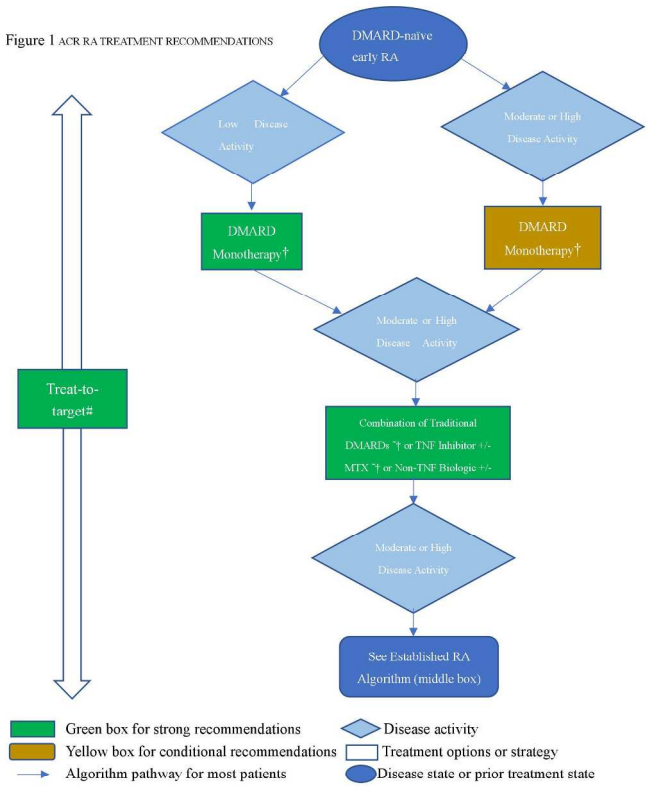

Figure 1. 2015 ACR RA Treatment Recommendations

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 anti-rheumatic drugs (DMARDs) and in patients with DMARD failure or biologic 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.

210x297mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	**Title**: a multicentre prospective observational study
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	This study will focus on the real-world rates of remission and low disease activity (LDA) of early RA patients 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. Two hundred early RA patients will be enrolled, treated and followed up once every 3 months for 48 months. Those patients should fulfil the 2010 RA classification criteria of the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR), with a disease course of no more than 6 months and 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

				DAS28 and HAQ-DI. The secondary outcome variables are SDAI, CDAI and RAPID-3 results, imaging data and personal medical costs. The data will be analysed using appropriate statistical analyses.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5	lines 56-98 of the manuscript.
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6	To investigate the real-world rates of remission and LDA of early RA patients 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	4	Present key elements of study design early in the paper	6	lines 105-110 of the manuscript.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8	This multicentre prospective observational study will be conducted in full compliance with the articles of the Declaration of Helsinki. It will be conducted in Nanfang Hospital and Zhujiang Hospital of Southern Medical University and will recruit 200 early RA patients treated according to the 2015 ACR Guideline. 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.

Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6-7	The participants must meet the following criteria: 1. ≥18 years of age, 2. fulfil the ACR/EULAR 2010 Rheumatoid arthritis classification criteria, 3. disease course of less than 6 months, 4. demonstrate complete understanding of the survey and have the ability to complete the questionnaires independently and 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 and 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 and 2. the participants refuse to answer the questionnaires or do not follow the follow-up time schedule included in the research

				protocol.
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8,9	Paragraph under section heading, **Outcomes**.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9	Paragraph under section heading, **Clinical examinations and blood samples** and **Outcomes**.
Bias	9	Describe any efforts to address potential sources of bias	6,11	All analyses will be conducted by a statistician, according to the prespecified statistical analysis plan. statistical analysis and confounder adjustment are taken. All researchers handling data must follow specific training to address adverse events.
Study size	10	Explain how the study size was arrived at	7,8	Paragraph under section heading, **Sample size calculation**

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8,9,10	Paragraphs in the **Sample size calculation** and **statistical analyses**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9,10	Paragraphs in the **Statistical analyses**
		(*b*) Describe any methods used to examine subgroups and interactions	9,10	Paragraphs in the **Statistical analyses**
		(*c*) Explain how missing data were addressed	None	The patients missing data will not be included in the analysis
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	None	The patients missing data will not be included in the analysis
		(*e*) Describe any sensitivity analyses	9,10	Paragraphs in the **Statistical analyses**
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A	N/A
		(b) Give reasons for non-participation at each stage	N/A	N/A
		(c) Consider use of a flow diagram	N/A	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A	N/A
		(b) Indicate number of participants with missing data for each variable of interest	N/A	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A	N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A	N/A
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A	N/A
		(*b*) Report category boundaries when continuous variables were categorized	N/A	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time	N/A	N/A

	period

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Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A	N/A
Discussion				
Key results	18	Summarise key results with reference to study objectives	10	the real-world rates of remission and LDA of early RA patients
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11	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
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10,11	**DISCUSSION** (paragraphs 1,2,4).
Generalisability	21	Discuss the generalisability (external validity) of the study results	11	**DISCUSSION** (paragraph 3).
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12	Provided. Southern Medical University

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.