

2018 Chinese guidelines for the diagnosis and treatment of rheumatoid arthritis

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Abstract

A multidisciplinary guideline development group was established to formulate this evidence-based diagnosis and treatment guidelines for rheumatoid arthritis (RA) in China. The grading of recommendations, assessment, development, and evaluation (GRADE) system was used to rate the quality of the evidence and the strength of recommendations, which were derived from research articles and guided by the analysis of the benefits and harms as well as patients' values and preferences. A total of 10 recommendations for the diagnosis and treatment of RA were developed. This new guideline covered the classification criteria, disease activity assessment and monitoring, and the role of disease modifying antirheumatic drugs (DMARDs), biologics, small molecule synthetic targeting drugs, and glucocorticoids in the treat-to-target approach of RA. This guideline is intended to serve as a tool for clinicians and patients to implement decision-making strategies and improve the practices of RA management in China.

Keywords

arthritis • diagnosis • guideline • rheumatoid • therapy

Rheumatoid arthritis (RA) is an autoimmune disease with destructive arthritis as its main clinical manifestation and can occur at any age.^[1, 2] Although the pathogenesis is unclear, synovitis, pannus formation, joint cartilage, and bone damage gradually occur, resulting in joint malformations and loss of function.^[3, 4] RA can also present with lung and cardiovascular damage; in some patients RA may have complications such as malignancy and depression.^[4–10] Epidemiological surveys have shown that the incidence rate of RA is 0.5–1% globally^[1] and 0.42% in mainland China. Based on this epidemiological data, it is estimated that the total number of RA patients in mainland China is 5 million.^[11] The ratio of men to women with RA is approximately 1:4.^[12, 13]

The disability rate of Chinese RA patients increases along with disease duration. For patients with 1–5 years of disease, the disability rate is 18.6%, for patients with 5–10 years of disease, the disability rate is 43.5%, for patients with 10–15 years of disease, the mortality rate is 48.1%, for patients with the disease for more than 15 years, the disability rate is 61.3%.^[12] The rate of disability and functional restriction also increases with disease progression. Importantly, RA impacts physical fitness, quality of life, social participation of patients, and creates a huge financial burden on both families and society.^[11, 14, 15]

In recent years, the American College of Rheumatology

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(ACR), the European League Against Rheumatism (EULAR), the Asia-Pacific League of Associations for Rheumatology (APLAR), and other international academic organizations in rheumatology developed or revised their RA management guideline.^[16–18] Chinese Rheumatology Association published China practice guidelines for the diagnosis and treatment of RA in 2010.^[19] Despite the growing number of guidelines released internationally, the diagnosis and treatment of RA still faces many challenges in China because of the limitations of applying these guidelines in real-world clinical practice. One reason is that the quality of the international recommendations for RA is incomparable and some recommendations are inconsistent.^[20] Another reason is that most of the international guidelines did not include the epidemiological and clinical research on Chinese RA patients. Furthermore, the focus of the diagnostic, treatment, and prescription practices in China is somewhat different from other countries^[13, 20, 21] due to the differences in rheumatologists' training programs, specialty settings, and behavior patterns of Chinese patients. Surveys have shown that about 60% of hospitals in China do not have a standalone rheumatology department, and more than 80% of the existing 7200 rheumatologists work in tertiary hospitals,^[22] leading to limited access to rheumatologists for treatment and diagnosis of patients who live in small cities and rural area. Surveys have revealed that only 23% of RA patients visit rheumatologists when they had the first symptom suggesting the diagnosis of RA.^[23]

Therefore, the formulation and implementation of practical RA guideline that conform to local situation will play a vital role in improving the management capability of physicians (e.g., rheumatologists, orthopedists, and internists), especially those working at county-level and primary care institutions, to make correct diagnosis and treatment for RA, to emphasize patient education, and to improve the quality of diagnosis and treatment of RA in China. Thus, based on new evidences and experiences from domestic rheumatologists and studies, taking the preferences and values of Chinese patients into consideration and balancing the benefits and risks of each recommended intervention, the Chinese Rheumatology Association developed the "2018 Chinese Guidelines for the Diagnosis and Treatment of RA".

Recommendation 1: Early diagnosis has a significant impact on the treatment and prognosis of RA, so clinicians need to make the diagnosis promptly based on patient's clinical presentations, laboratory tests, and imaging examinations (1A). The 1987 ACR and 2010 ACR/EULAR classification criteria (2B) for RA are recommended as the reference for RA diagnosis.

Surveys have shown that the median time from the onset

of typical symptoms of RA such as multiple joint swelling and morning stiffness to the diagnosis of RA may take up to 6 months in China. It takes more than 1 year to be diagnosed in as many as 25% of patients.^[23] The timing of diagnosis will directly affect the treatment effectiveness and prognosis of RA. Therefore, early diagnosis shall be based on patient's clinical presentations, laboratory tests, and imaging examinations results. Currently, there are 2 international classification criteria used to help diagnosing RA: one is "The 1987 ACR classification criteria," which has the sensitivity of 39.1% and the specificity of 92.4%,^[24, 25] and the other one is "The 2010 ACR/EULAR classification criteria," which has a sensitivity of 72.3% and a specificity of 83.2%.^[25, 26] Given the specific advantages of each criteria in terms of sensitivity and specificity, clinicians can refer to both as references to make accurate diagnosis of RA based on specific characteristics of Chinese RA patients.^[25]

Recommendation 2: We recommend that clinicians choose the most suitable imaging modalities such as X-rays, ultrasound, (computerized tomography (CT), and magnetic resonance imaging (MRI) (2B) based on the specific signs and symptoms of the patient (2B).

Imaging examinations are effective tools to assist clinicians to make the diagnosis of RA. The value for diagnosis and disease monitoring as well as the advantages of various imaging modalities are listed in Table 1.^[19, 27–32] EULAR issued an evidence-based recommendation for selecting imaging modalities for RA diagnosis in 2013. This recommendation greatly aids clinicians to choose appropriate image modalities to make correct diagnosis.^[28] It should be noted that Chinese RA patients may go to various levels of medical institutes seeking care, which is very different from that of foreign countries. In addition, there are considerable differences in the availability of imaging equipment and technology in different regions of the country; therefore, clinicians should choose the most suitable diagnostic imaging modalities available locally to assist in making the diagnosis.

Recommendation 3: The principles of management of RA are early, standardized treatment, regular monitoring, and follow up (1A). The goal of RA treatment is to achieve disease remission or lower disease activity, that is, to treat the disease to the target. The overall goal of treatment is to control the disease activity, reduce disability, and improve patients' quality of life (1B).

The joint lesions of RA are caused by inflammatory cell infiltration and release of inflammatory factors.^[1] To inhibit the production of cytokines and their effects as early as possible can effectively prevent or minimize the destructions in joint

Table 1. The value of imaging modalities in the diagnostics, follow up, and monitoring of RA

Image modalities	Applied situations	Advantages ^[27]	Disadvantages ^[27]
Regular radiologic examination	Regular radiologic examinations are the most commonly used imaging tools for assessing structural damage of RA joints. ^[27] X-rays of hands, wrists, and other affected joints are important for the diagnosis of RA. Early X-rays showed swelling of soft tissue around the joint and osteoporosis near the joint. As the disease progresses, it will show joint surface damage, stenosis of joint gaps, joint fusion, or dislocation. ^[19] Joint injuries could be regularly assessed by hand and foot X-rays. However, routine X-rays in patients with RA whose disease course is less than half year may be normal. ^[28]	(1) Low cost. (2) Accessibility is very high.	(1) 3D lesion shown in 2D image. (2) Exposure to radiation. (3) Low sensitivity to early bone damage.
Ultrasound	Ultrasound detects joint structural damage with higher sensitivity than conventional radiological examinations. ^[27] Doppler ultrasound can be used to confirm the presence of synovitis, monitor disease activity and progression, and assess inflammation. ^[28–29] Ultrasound can clearly show synovium, synovial bursa, joint fluid, joint cartilage thickness, morphology, etc. Color Doppler blood flow imaging (CDFI) and color Doppler energy (CDE) can directly detect the distribution of blood flow in joint tissues, reflecting inflammation of synovium with high sensitivity. Ultrasound can also dynamically determine the amount of joint fluid and the distance from the body surface to guide joint aspiration and treatment. ^[19]	(1) Medium cost. (2) No radiation. (3) Can assess multiple joints. (4) Offers guidance to diagnosis and therapy. (5) Detects early damage to bone and cartilage. (6) Energy Doppler can detect severity of inflammation.	(1) Operator-dependent. (2) Less sensitive to changes in large joints (buttocks, shoulder joint, and hip joint).
CT	CT can detect bone erosion more accurately than other modalities. It is valuable particularly in large joint lesions and lung disease, but CT cannot detect active inflammation in synovitis, tenosynovitis, for example. ^[19] Thus when intend to detect large joints involvement or lung lesions, CT can be used to monitor the disease.	(1) Detects bone Erosion. (2) Detects complicated lung disease. (3) Detects large joint disease.	(1) High radiation exposure. (2) Cannot detect active inflammation. (3) Relatively high cost.
MRI	MRI is the most sensitive tool to detect early RA lesions. ^[27] MRI is superior to X-rays in showing joint lesions because it can detect thickening of synovium, bone marrow edema, and early mild articular surface erosions, and thus helps in early diagnosis of RA. ^[19] MRI can detect joint changes much earlier than conventional radiological modalities such as synovitis, joints narrowing, and bone erosion. ^[31] MRI can detect inflammation even earlier than physical examination, so it can be used to identify subclinical inflammation and predict whether the current undifferentiated arthritis may progress to RA. MRI can also be used to predict future joint damage in clinically remission patients. Bone marrow edema has been shown to be one of the powerful independent predictive factors for early RA imaging progression and can be used as one of the prognostic indicators. ^[28, 32]	(1) Sensitivity in detecting early inflammation is high. (2) No radiation exposure. (3) Can be used to detect bone marrow edema, early bone and cartilage injury.	(1) The cost is high. (2) Not widely accessible. (3) Time duration for examination is long. (1) Only one site can be visualized per examination (knee, hand).

CT, computerized tomography; MRI, magnetic resonance imaging.

synovium and cartilage.^[1] Therefore, timely treatment should be carried out as soon as the diagnosis is made. Indeed, studies have shown that irregular use of disease-modifying antirheumatic drugs (DMARDs) is one of the independent risk factors for joint function limitation in RA patients.^[12]

Although RA is not curable, the treat-to-target strategy is effective in alleviating symptoms and controlling the disease progression.^[33] Treat-to-target is referred to treat to achieve clinical remission, i.e., 28 joint disease activity (DAS28) \leq 2.6, or clinical disease activity index (CDAI) \leq 2.8, or simplified disease activity index (SDAI) \leq 3.3. When the above criteria cannot be met, low disease activity can be the alternative treatment target, i.e., DAS28 \leq 3.2, CDAI \leq 10 or SDAI \leq 11. However, it should be noted that there are limitations in the disease activity evaluation tools and studies have shown that RA patients with swollen joints can still suffer further joint

damage even when their DAS28 score is less than 2.6.^[34] In 2011, the ACR and EULAR proposed new remission criteria, which included tender joint count, swollen joint count, C-reactive protein (CRP) level, and patient global assessment were all \leq 1.^[35] Due to its high specificity and the ease of use and implementation, the criteria has been gradually adopted in clinical practice. Nevertheless, remission rate based on this new criterion is low,^[36] so clinicians should choose the appropriate evaluation criteria according to their real practice situation.

Recommendation 4: For patients who do not achieve the treatment target, we recommend to monitor their disease activity once every 1–3 months (2B). For patients who are treatment naïve and patients with moderate/high disease activity, we recommend to monitor their disease once every month (2B). For patients who have reached

the treatment target, we recommend to monitor their disease once every 3–6 months (2B).

For treatment naïve patients, we recommend to monitor their disease once every month due to the slow onset of action of DMARDs and the frequency of adverse reactions. For patients who encounter difficulties with the schedule, monitoring can be done every 3 months. However, randomized controlled trials have shown that monitoring and adjusting the medication regimen monthly can further decrease disease activity, delay radiological progression, and improve the function and quality of life compared to the regimen done once every 3 months.^[37] Other randomized controlled studies have revealed that significant progression of joint damage can happen within 3 months in patients with moderate/high disease activity. For these patients, we recommend the frequency of monitoring as once per month. The monitoring frequency for patients who have reached the therapeutic target can be adjusted to be once every 3–6 months.^[29, 38, 39]

A systematic review comprehensively analyzed the existing 63 RA disease monitoring and evaluation tools, including comparison for credibility, effectiveness, and responsiveness of DAS28, SDAI, and CDAI. The results showed that DAS28 was better in all 3 aspects.^[33] For laboratory tests, CRP was shown to have several advantages when compared to ESR, including more sensitive to inflammation and less susceptible to other factors such as age, sex, and rheumatoid factor (RF).^[40] Furthermore, the SDAI and CDAI do not need complicated calculations and their formulas are easy to remember.

Recommendation 5: The number of affected joints, ESR, CRP, RF, ACPA, and other indicators should take into consideration when selecting treatment regimens (1B). Meanwhile, extra-articular lesions should also be considered. Common complications, including cardiovascular disease, osteoporosis, and malignancy should be monitored as well (1B).

Evaluation of poor prognostic factors is crucial to RA management, and evaluation can provide important clues to clinicians to adjust treatment plans and select appropriate medications. Several predictive models have shown that joint pain, swollen joint counts, and elevated ESR, CRP, RF, and ACPA levels are predictive factors for joint damage.^[41–44] Thus, poor prognostic factors can help physicians to determine the best treatment strategy.

Data from a Chinese registry for rheumatic diseases shows that the common complications and risk factors are cardiovascular diseases (2.2%), fragile fractures (1.7%), and malignancy (0.6%). Aging and long-term disease have a positive relationship with these complications.^[13] Furthermore,

these complications have been found to influence prognosis and increase mortality rate.^[45, 46] RA patients will also experience extra-articular organ involvement. Studies have shown that the incidence of extra-articular manifestation is between 17.8% and 47.5%, and the affected tissues and organs include skin, lungs, heart, nervous system, eyes, blood, and kidneys. Patients with complications have higher mortality rate when compared with patients with no complications.^[47, 48] Therefore, clinicians should evaluate every patient's condition comprehensively to develop the most appropriate treatment regimen and adjust the treatment plans accordingly.

Recommendation 6: Once RA is diagnosed, conventional synthetic DMARDs treatment should be initiated as early as possible. We recommend methotrexate (MTX) monotherapy as the first-line therapy (1A). In patients who are contraindicated to MTX, leflunomide or sulfasalazine monotherapy should be considered (1B).

Conventional synthetic DMARDs are the cornerstone of RA treatment and are recommended as the first-line therapy by domestic and international guidelines.^[16–19] A cohort study showed that the higher cumulative doses of conventional synthetic DMARDs in RA patients within the first year of diagnosis the later the time for joint replacement. The risk for surgical procedure was reduced by 2–3% if treatment was initiated 1 month earlier.^[49] MTX is the “anchor drug” for RA treatment.^[50] In general, two-thirds of patients with RA can achieve treatment goals using MTX alone or in combination with other conventional synthetic DMARDs.^[21, 50] In terms of safety, studies based on the Chinese population revealed that adverse reactions from small doses of MTX (≤ 10 mg/week) are typically mild and have better long-term tolerability. In addition, a systematic review showed that folic acid supplementation during MTX therapy (at a dose of approximately 5 mg per week) can reduce the risk of adverse reactions such as gastrointestinal side effects and liver damage.^[51]

Surveys conducted in 15 European countries and the United States showed that 83% patients were treated with MTX in average, much higher than that of other DMARDs;^[21] however, only 55.9% RA patients had ever being treated with MTX^[13] in China. In view of the current situation of China's health economy, the role of MTX as the core drug in RA treatment in China should be further strengthened. Studies have shown that for patients who are contraindicated to MTX, the efficacy and safety of leflunomide or sulfasalazine monotherapy are comparable to MTX.^[52–55] Internationally, 21% of RA patients were treated with leflunomide, which is much lower than MTX, sulfasalazine, and hydroxychloroquine usage.^[21] However, in

China, 45.9% of RA patients were treated with leflunomide in average, ranked to the second most commonly prescribed medications, just less than MTX,^[13] and its usage rate was even higher than MTX in some regions. This phenomenon has raised concerns from the rheumatology professions in the country.^[56] The safety profile of sulfasalazine in Chinese RA patients is good, but only 4.4% has ever been treated with it, which is far lower than the 43% utilization rate in foreign countries. The vast majority patients were treated with sulfasalazine combined with other conventional synthetic DMARDs.^[57] Compared with MTX, sulfasalazine is more cost-effective monotherapy compatible to China's national economic conditions. The utilization rate of hydroxychloroquine in China and internationally are 30.4%^[13] and 41%,^[21] respectively. Cross-sectional studies showed that hydroxychloroquine was most frequently, in 95% case, prescribed in combination with other DMARDs.^[58] Based on systematic reviews, hydroxychloroquine may be beneficial to the metabolism of RA patients and may reduce the occurrence of cardiovascular events; therefore, it is generally recommended in combination with other DMARDs.^[59]

Recommendation 7: When a single conventional synthetic DMARD treatment can't reach the treatment target, we recommend to combine one DAMRD with another 1 or 2 DMARDs (2B) or combine one DMARD with one of the biological DMARDs (2B), or combine one DMARD with one of the small molecule targeted synthetic DMARDs for the treatment (2B).

After being treated with MTX or leflunomide or sulfasalazine monotherapy, if the patients can't reach the treatment target, we recommend to combine medications for treatment. Studies reported that conventional synthetic DMRDs combination therapy could improve clinical symptoms and reduce joint damage in early RA patients with high disease activity.^[52, 60] In patients who did not respond well to MTX, a meta-analysis showed that the combination of 3 conventional synthetic DMARDs (MTX, sulfasalazine, and hydroxychloroquine) could control the disease activity. This regimen was no less effective than that of MTX combined with a biological DMARD or a small molecule targeted synthetic DMARD.^[61]

When the conventional synthetic DMARD combination therapy still could not reach the treatment target, treating for extended time and careful monitoring of the efficacy may be considered. A multicenter randomized controlled trial revealed that in patients who were unable to reach the target by intensive conventional synthetic DMARDs for 3–6 months, treatment for an extended time was able to improve the clinical remission rate with good tolerability.^[62]

For patients who do not reach the treatment target with conventional synthetic DMARDs, we recommend to combine one DMARD with a biological DMARD or a small molecule targeted synthetic DMARD.

Tumor necrosis factor-alpha (TNF- α) inhibitors are the most widely used biological DMARDs in treating RA with abundant evidence. In North America, 50.7% patients were treated with biological DMARDs.^[63] However, the data from the Chinese registry for rheumatic diseases showed that only 8.3% were treated with biological DMARDs in China.^[13] We recommend to use biologic DMARDs in a standardized way in patients who satisfied the indications for biological DMARDs therapy. Tocilizumab is a recombinant humanized IgG1 monoclonal antibody that targeted interleukin-6 (IL-6) receptors. For RA patients who have an insufficient response to conventional synthetic DMARDs, we recommend to combine conventional synthetic DMARDs with tocilizumab.^[64–67]

Small molecule targeted synthetic DMARDs, referred to Janus kinase (JAK) inhibitors only so far, are a class of anti-rheumatic drugs with novel mechanisms of action. For patients who do not respond well to conventional synthetic DMARDs, we recommend combining JAK inhibitors (tofacitinib) with conventional synthetic DMARDs.^[68–71]

No precedence over each other for TNF- α inhibitors, tocilizumab and tofacitinib in the treatment of RA. If the treatment target could not be achieved with conventional synthetic DMARDs combined with one of the 3 categories of medications, treatment with 1 of the other 2 categories of drugs should be the alternatives.^[17]

Iguratimod, an anti-rheumatic drug approved by China's Food and Drug Administration in 2011, is currently used mainly in China and Japan. However, its mechanism of action needs further investigation. Studies have shown that iguratimod and MTX combination therapy can improve clinical symptoms in active RA patients.^[72, 73] The 2015 APLAR guidelines recommended that patients with active RA could be treated with iguratimod.^[18] Tripterygium wilfordii Hook II is an herbal medicine, which has been used to treat RA since 1969 in China, but its use is limited due to insufficient data on safety and effectiveness. Studies published in the past 2 years had shown that Tripterygium wilfordii Hook II alone or in combination with MTX was effective in patients with no fertility requirements. The adverse reactions besides genital toxicity of Tripterygium wilfordii Hook II were not significantly different from those of MTX. Nevertheless, its toxicity needs to be closely monitored and evaluated.^[74–76] In addition, herbal preparations such as total glucosides of paeony and sinomenine offer alternatives for RA treatment,

but high-quality clinical trials are needed to further document their effectiveness and safety.^[77]

Recommendation 8: For patients with moderate/high disease activity, we recommend conventional synthetic DMARDs in combination with glucocorticoid therapy to quickly control the symptoms (2B). Adverse events should be closely monitored during treatment. Monotherapy or long-term, high-dose glucocorticoid use is strongly not recommended (1A).

Glucocorticoids, first used to treat RA in 1948, has strong anti-inflammatory and immunosuppressive effects.^[78] Due to the concerns of serious side effects caused by glucocorticoids, clinicians rarely used glucocorticoids for RA management for a long time in the past.^[79, 80] However, systematic reviews showed that for patients with moderate/high disease activity, combining low-dose glucocorticoids (prednisone \leq 10 mg/day or equivalent) with conventional synthetic DMARDs could quickly control symptoms and synergize the action of conventional synthetic DMARDs.^[81–83]

Data from the China registry for rheumatic diseases had shown that 40.6% of patients with RA had ever been treated with glucocorticoid.^[13] According to a cross-sectional study, misuse of glucocorticoids is very common in China: 70% of patients with RA received long-term treatment of glucocorticoid (e.g., longer than 6 months) and 11.3% of patients were treated with glucocorticoid alone. Therefore, the use of glucocorticoids in RA treatment needs to be standardized, especially in primary healthcare institutions.^[84]

Recommendation 9: If the patient reached disease remission after being treated with a biological DMARD or small molecule targeted synthetic DMARD, tapering of the biological DMARD or the small molecule targeted synthetic DMARD could be considered. Close monitoring of disease activity during tapering is warranted given the potential for disease flare (2C). Clinicians may discuss with the patient about discontinuation of biological DMARDs or small molecule targeted synthetic DMARDs if the patient has been in sustained remission for more than 1 year (2C).

Based on the safety of long-term use of biological DMARDs or small molecule targeted synthetic DMARDs, as well as from the economic considerations, gradual reduction of the dosage when the treatment target has been reached is of great importance in China. A systematic review showed that biological DMARDs or small molecule targeted synthetic DMARDs can help patients to reach the treatment target within 6 months. The flare rate among those patients with reduction in doses was lower than those patients who stopped these medications completely and was comparable to those who did not reduce the dosage. As many as one-third to one-half of patients with RA showed clinical remission or low disease activity 1 year following biological DMARDs or small molecule targeted synthetic DMARDs discontinuation.^[85, 86] Disease activity in patients who stopped small molecule targeted synthetic DMARD therapy was generally higher than in those who continued the treatment, while 37% of patients did not relapse within 1 year after drug discontinuation. Therefore, if a patient has been in sustained remission for over 1 year, the clinician may discuss the possibility of discontinuation of the biological DMARDs or small molecule target synthetic DMARDs with the patient based on his or her medication status and financial affordability.

Recommendation 10: Patients with RA should be advised to lifestyle modification, including smoking cessation, weight control, healthy diet, and exercise (2C).

Patient education is essential for disease management, because it helps to improve the effectiveness of RA treatment.^[87, 88] Clinicians should help patients to fully understand the nature and prognosis of RA, help them to set up the confidence to receive standard treatment, and remind them to be monitored and followed-up regularly. In addition, patients should be encouraged to change their unhealthy life style. Obesity and smoking not only increase the incidence of RA,^[89–90] but also worsen the disease.^[91–92] Studies have shown that a balanced diet can help control the disease.^[93–94] Adherence to aerobic exercise (rather than high-intensity exercise) 1–2 times per week helps to not only improve joint function and quality of life but also reduce fatigue.^[95–98]

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Conflict of Interest

None Declared.

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Appendix 1. Algorithm for the diagnosis and treatment of RA (Figure 1)

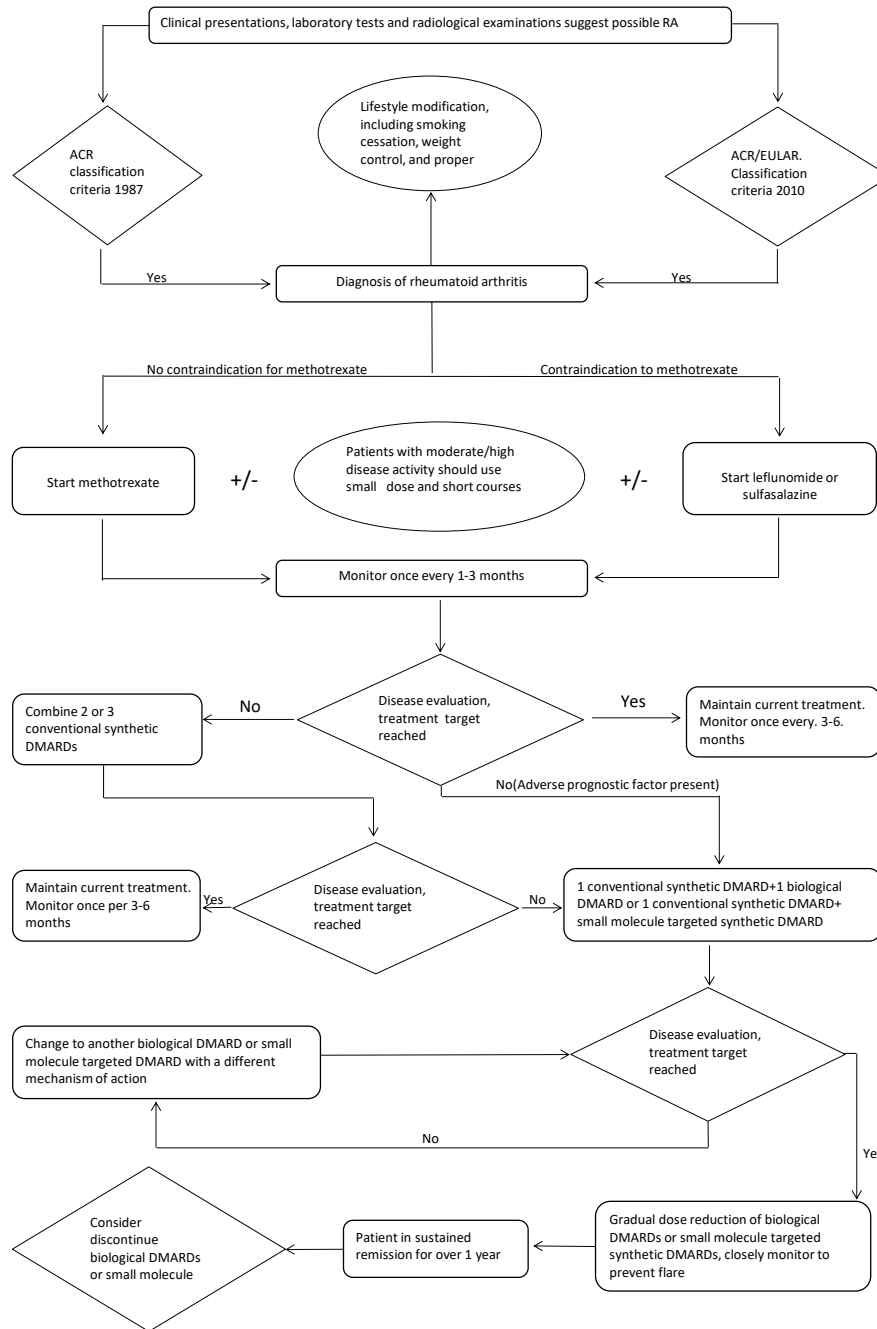


Figure 1. Procedure for the diagnosis and treatment of RA. Note: ACR, American Rheumatology Society; EULAR, European League Against Rheumatism; NSAIDs, nonsteroidal anti-inflammatory drugs; DMARDs, disease-modifying anti-rheumatic drugs; RA, rheumatoid arthritis. ^aPatients with RA need to change lifestyle after diagnosis. ^bShort-term use or non-use of glucocorticoids or NSAIDs depending on patients' symptoms and condition. ^cEvaluation as to whether treatment has significant effects. "No" indicates the effect is not significant, i.e., no significant improvement in RA disease activity within 3 months or cannot reach treatment target within 6 months. "Yes" indicates the effect is significant, disease activity is improved within 3 months and the treatment target is reached within 6 months. ^dPhysicians and patients jointly make decisions on whether or not to discontinue biological DMARDs or small molecule targeted synthetic DMARDs

Appendix 2. Process of guideline development

This guideline was initiated and developed by the Chinese Rheumatology Association. Chinese Grading of recommendations, assessment, development, and evaluation (GRADE) Center, Evidence-Based Medicine Center, Lanzhou University, contributed in methodology and evidence support. The kickoff meeting of the guideline development team was held on May 13, 2017, in Zhengzhou, Henan Province, during the 22nd Annual Meeting of the Chinese Rheumatology Association. The draft was finalized on January 1, 2018. The development of the recommendations of this guideline complies with the WHO Guidelines Development Manual^[99] issued by the World Health Organization in 2014 and the Basic Methods and Procedures for the Development/Revision of the “clinical practice guideline” published by the Chinese Medical Association in 2016,^[100] with reference to Appraisal of Guidelines for Research and Evaluation II (AGREE II)^[101] and Reporting Items for Practice Guidelines in Healthcare (RIGHT), <http://www.right-statement.org> ^[102, 103].

1. Registration and guideline development proposal: This guideline was registered on the International Practice Guide Registry Platform, IPGRP, <http://www.guides-registry.org> (registration number IPGRP-2017CN027), from which readers can contact and request a guideline proposal.
2. Guideline users and the target population: This guideline is intended to be used by rheumatologists, endocrinologists, orthopedic surgeons, clinical pharmacists, diagnostic imaging physicians, and professionals who may deal with RA diagnosis and management. The target population is RA patients.
3. Guidelines Working Group: The Guideline development group is composed of a multidisciplinary expert group, including experts in rheumatology, endocrinology, imaging, evidence-based medicine, etc. The Working Group was divided into consensus expert group and evidence evaluation group.
4. Conflict of Interest Statement: Members of the Guideline Working Group are required to sign the Statement of Interest form and declare that there is no interest conflict directly related to this Guideline.
5. Selection and identification of clinical scenario: The Guidelines Working Group selected clinical scenario by questionnaire survey. By systematically reviewing the published guidelines and systematic reviews of RA, the working group developed 40 clinical scenario and then investigated their clinical importance and practical relevance. The first round of survey collected 66 questionnaires from the rheumatologists, with a total of 68 clinical questions and 90 outcome indicators. After merging and removing duplicates, the second round of surveys was proceeded to determine the top 10 outcome indicators for the 47 clinical questions. The survey collected 196 questionnaires from 107 medical institutions in 20 provinces, municipalities, and autonomous regions. Based on the findings of the survey and the discussions of the Working Group, the relevant clinical questions were selected and included into this guideline.
6. Evidence searching: For clinical questions and outcome indicators that were eventually included, the questions were decomposed according to population, intervention, comparison, and outcome (PICO) principles and retrieved according to the decomposed questions: (1) Medline, The Cochrane Library, Epistemonikos, Chinese Biomedical Literature Database, Wanfang Database, and CNKI Database, the majority of the included evidence were systematic evaluation, meta-analysis, and mesh meta-analysis. The searching timeframe is the time from database establishment to January 25, 2018; (2) Up-to-date, DynaMed, Medline, China Biomedical Literature Database, Wanfang Database, and CNKI Database were retrieved. The mostly included were original studies (including randomized controlled trials, cohort studies, case-control studies, case series, epidemiological investigations, etc.). The searching timeframe is the time when these studies are available to January 25, 2018; (3) The National Institute of Health and Care Excellence, National Guideline Clearinghouse, Scottish Intercollegiate Guidelines Network, ACR, EULAR, APLAR, and other official websites, and Medline, CNKI database, medical network database, mainly to search the RA field of relevant guidelines; (4) Other websites, such as Google scholar, were also included.
7. Evidence evaluation: Assessment of the Methodological quality of Systematic Review (AMSTAR) scale was used to assess the quality of the included systematic review. ROB (Bias Risk Assessment) was used to assess the risk of bias for randomized controlled trials. QUADAS-2 (for diagnostic trials) was used to assess the quality of diagnostic studies. The Newcastle-Ottawa Scale (NOS)^[104] were used to evaluate the quality of methodology of the original studies and observational studies, respectively. The evaluation process was carried out independently by 2 individuals, and if there was a disagreement, discussion or consultation with a third one was the way to reach consensus. The body of evidence and recommendations were graded using the GRADE method.^[105–109]
8. Recommendations: Based on a summary of the domestic and foreign evidence provided by the evidence evaluation team, taking patients' preferences and values, the cost, and the pros and cons of interventions into consideration,

the Working Group developed 10 recommendations, which were formulated on August 25, 2017. Four face-to-face consensus meetings were held in Beijing, Fuzhou, October 14, 2017, December 14, 2017, respectively, and in Beijing, February 1, 2018, to collect 299 feedbacks. All recommendations and the quality of evidence were discussed and reviewed by the Working Group.

Dissemination and implementation: After the publication of the guideline, the Chinese Rheumatology Association will work with the World Health Organization Guidelines Implementation and Knowledge Transformation Cooperation Center to disseminate and promote the guideline by the following approaches: (1) Interpretation in academic conferences; (2) Organizing guideline promotion meetings around the whole country to ensure that rheumatologists, clinicians, pharmacists, imaging diagnosticians, and professionals related to RA diagnosis and management of RA could fully understand and could implement the guidelines correctly; (3) Publication in academic journals; (4) Promotion through public media such as WeChat.

The Working Group on Updated Guidelines plans to update the Guidelines over the next 3–5 years. The update method will comply with the update process of the international guidelines.^[110]

Working Group of 2018 Chinese Guidelines for the Diagnosis and Treatment of RA

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