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REVIEW

Advances in the Diagnosis and Treatment of Rheumatoid Arthritis: From Pathological Mechanisms to Integrated Chinese and Western Medicine Therapeutic Strategies

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Abstract: Rheumatoid arthritis (RA) is an autoimmune disease whose exact cause remains unclear and is likely the result of multiple factors such as genetics and environmental influences. This disease primarily affects the joints and subsequently presents with extra-articular manifestations.The pathogenesis of RA is complex, and current research is yet to fully elucidate the underlying mechanisms. Consequently, investigations into the pathophysiological processes of RA remain in its early stages. Recent advancements in diagnostic methodologies and pharmacological interventions have significantly improved RA management. A growing number of novel therapeutic agents have been introduced, with methotrexate (MTX) remaining the cornerstone of first-line treatment. Furthermore, contemporary drug development efforts have increasingly focused on molecular medicine to enhance the therapeutic efficacy and safety profiles. Traditional Chinese medicine (TCM), with its unique theoretical system and therapeutic approaches, demonstrates promising potential in the treatment of RA and is increasingly attracting global attention. Clinical studies on Tripterygium wilfordii (thunder god vine) and preparations of Paeonia lactiflora (white peony) in rheumatoid arthritis and related conditions have also demonstrated certain efficacy and safety of Chinese herbal medicine. Currently, the integration of traditional Chinese and Western medical approaches for RA treatment is gaining wider acceptance. Therefore, this review will focus on exploring the potential of traditional Chinese medicine in improving RA outcomes, based on the diagnosis, epidemiology, and pathophysiological mechanisms of rheumatoid arthritis.

Keywords: rheumatoid arthritis, autoimmunity, traditional Chinese medicine, combination of Chinese and Western medicine

Introduction

Rheumatoid arthritis (RA) is an autoimmune disorder characterized by progressive and symmetrical inflammation of the joints, which ultimately results in cartilage degradation, bone erosion, and functional disability as the disease advances.[1] Extra-articular manifestations are frequently observed in affected individuals.[1] The onset and progression of RA typically occurs insidiously. In the early stages, joint involvement tends to be predominantly asymmetric, with the hallmark presentation of symmetrical polyarthritis emerging only in the later phases of the disease.[2] Prompt referral, preferably to a specialized early arthritis treatment center, is critical to facilitate the timely evaluation of patients exhibiting initial signs and symptoms of inflammatory arthritis.[3] Clinically, the symptomatology of RA differs markedly between early and late stages. Early RA is primarily characterized by fatigue, flu-like symptoms, joint swelling, tenderness, morning stiffness, elevated C-reactive protein (CRP) level, and increased erythrocyte sedimentation rate (ESR).[4] Inadequately managed RA is associated with severe systemic manifestations, including pleural effusion, pulmonary nodules, interstitial pneumonia, progressive bone

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erosion, and cartilage destruction.[5] Despite considerable advancements in RA research, the understanding of the underlying pathogenic mechanisms remains limited, as evidenced by the frequent lack of efficacy of novel molecular therapeutics. Traditional Chinese medicine demonstrates promising potential in the treatment of RA with its unique theoretical system and therapeutic approaches.

According to TCM theory, RA is attributed to the invasion of damp-heat pathogens, which obstruct the bones, muscles, and meridians. Therefore, treatment should be guided by syndrome differentiation, focusing on principles such as regulating qi and blood circulation, dispelling wind and alleviating pain, and clearing heat and dampness. Compared to the limitations of Western medicine in areas such as treatment target achievement rates, early intervention, management of refractory RA, and medication tapering during the maintenance phase, TCM, through its syndrome-based therapeutic approach, can significantly improve disease activity in RA patients, alleviate symptoms such as joint pain, swelling, and stiffness, and enhance their quality of life.[6–9] Recent studies have provided evidence for the clinical efficacy and safety of Chinese herbal medicine, suggesting its potential as a beneficial complementary and alternative therapy for patients with rheumatoid arthritis.[10–12] While the EULAR guidelines[13] do not directly recommend TCM as a complementary therapy for RA, they note that "certain herbal medicines (eg, Tripterygium wilfordii) possess anti-inflammatory potential, though more clinical evidence is needed to support their use". The 2021 safety profile of Chinese herbal medicine in RA treatment also indicated a low incidence of severe adverse events, although standardized application is necessary to avoid liver and kidney function impairment.[14] Therefore, this review will focus on exploring the potential of comprehensive traditional Chinese medicine treatment in improving RA outcomes, based on the diagnosis, epidemiology, and pathophysiological mechanisms of rheumatoid arthritis.

Epidemiology

RA imposes a substantial burden on both affected individuals and society.[3,15] The individual burden primarily arises from musculoskeletal impairments, which are accompanied by a decline in quality of life and an increased likelihood of comorbid conditions.[16] Global Burden of Disease data reveal that the number of rheumatoid arthritis cases worldwide reached approximately 17.6 million in 2020, reflecting a 14.1% increase compared to 1990. It is projected that the global patient count may rise to 31.7 million by 2050. The disease caused around 38,300 deaths in 2020, a 23.8% decline from 1990, with an overall disease burden of about 3.06 million disability-adjusted life years (DALYs). Smoking is a significant risk factor, contributing to approximately 7.1% of the disease burden.[17] The global incidence of RA ranges between 0.5% and 1%, exhibiting a decreasing trend from urban to rural settings and from developed to developing countries.[18,19] Established risk factors associated with the onset and severity of RA include smoking and lower socioeconomic status,[20,21] which may partially account for these epidemiological patterns alongside genetic variability. A positive family history elevates the risk of RA by three–five times, and increased concordance rates among twins further suggests a genetic component in disease pathogenesis.[22] The heritability of RA remains a subject of debate, currently estimated at 40–65% for seropositive RA and approximately 50% for seronegative RA.[23] This has stimulated extensive genetic research aimed at identifying the pathogenic mechanisms, clinical subtypes, and prognostic biomarkers. The integration of advanced genetic methodologies with large, well-characterized clinical cohorts has significantly enhanced our understanding. Genome-wide association studies (GWAS), immunochip analyses, and next-generation sequencing have identified over 100 loci linked to RA susceptibility, predominantly involving immune-related pathways. These loci are largely conserved across diverse populations and some overlap with other chronic inflammatory diseases.[24] The human leukocyte antigen (HLA) region remains the most influential genetic factor,[25,26] with disease-associated alleles sharing a common amino acid motif in the peptide-binding groove, termed the "shared epitope".[27] Certain HLA genotypes correlate with more severe erosive disease and increased all-cause mortality, indicating that peptide binding exerts a critical and quantitatively significant functional effect.[28,29] Moreover, HLA genotypes mediate gene-environment interactions, particularly between smoking and RA risk, although these associations have not been consistently replicated and warrant further investigation.[30] Additional genetic loci may exert smaller cumulative effects through mechanisms such as altered costimulatory signaling, cytokine pathways, lymphocyte receptor activation thresholds, and innate immune responses.[31] Notably, family aggregation studies have revealed that known genetic and environmental factors explain only a fraction of familial clustering, suggesting that additional determinants remain to be elucidated.The increased risk associated with HLA-DRB1 shared epitopes is also linked to the presence of anti-citrullinated protein antibodies

(ACPA) and immunoglobulin G rheumatoid factor (RF), which characterize approximately 80% of patients with established RA and approximately 50% of those with early disease. This immunological association further implicates a shared epitope in the progression of joint damage, whereas patients negative for ACPA and/or RF exhibit a weaker association.[32] Epigenetic mechanisms are also believed to contribute to RA pathogenesis, potentially by integrating genetic and environmental influences.[33] At the population level, a recent epigenome-wide association study identified 70 differentially methylated sites that may enhance genetic susceptibility to RA.[34] Ongoing research continues to explore these epigenetic mechanisms.

Diagnosis of RA

As a chronic disease, RA imposes an exponentially increasing burden over time; in turn, efforts to establish early diagnosis and design novel therapeutic strategies are critically important. The diagnosis of RA was based on the established criteria. The most recent diagnostic framework was developed collaboratively by the American College of Rheumatology (ACR) and EULAR in 2010.[35] This system assigns a cumulative score ranging from 0 to 10, with a threshold score exceeding 6 indicating a definitive diagnosis of RA.Clinically, individuals with RA typically present with symptoms such as recent onset of joint tenderness and swelling, morning stiffness of the joints, systemic manifestations, and abnormal laboratory findings.[18] Early identification of RA is critical because it can mitigate or decelerate disease progression and reduce the risk of subsequent disability.[5] The diagnosis of RA necessitates an integrative approach that considers clinical symptoms, laboratory test results, family history, and imaging modalities including ultrasound and laboratory biomarkers.[5,36] Ultrasound and magnetic resonance imaging (MRI) are recommended for diagnosing RA and monitoring disease activity.[37] Ultrasound enables the visualization of synovial proliferation through grayscale imaging and detection of active inflammation and neovascularization via power Doppler techniques.[38] It can also identify subclinical synovitis, which may contribute to radiographic disease progression, even in patients in clinical remission.[3] Owing to these diagnostic capabilities, ultrasound is extensively used in both clinical practice and research settings for RA diagnosis and disease monitoring.[39] Ultrasound offers several advantages, including relatively low cost, broad accessibility, absence of contraindications, and the ability to provide noninvasive, real-time imaging. However, its effectiveness is limited by operator dependency as it requires substantial training for accurate measurement and quality assessment.[39] Although MRI is highly sensitive for detecting early pathological changes, such as synovial hypertrophy or pannus formation prior to bone erosion, its routine use in RA diagnosis is constrained by high costs and limited capacity to image multiple joints simultaneously.[40] In terms of clinical biomarkers, CRP and ESR are routinely used to assess the systemic inflammatory status of patients with RA. CRP is an acute-phase protein composed of five 23-kDa subunits belonging to the pentraxin family. Its serum concentration can increase by several orders of magnitude in response to infection, inflammation, or tissue injury.[41,42] CRP synthesis is primarily induced in hepatocytes following stimulation with pro-inflammatory cytokines, including interleukin-6 (IL-6), interleukin-1 (IL-1), and tumor necrosis factor-alpha (TNF-α).[43]

Pathophysiological Mechanisms

Synovitis is the characteristic manifestation of autoimmune-mediated tissue damage in RA.[18] Joint inflammation arises from a complex interplay between various dendritic cell (DC) subsets and other cellular components. The persistence of chronic inflammation and synovial hypertrophy within the joint[18] results from the inadequate clearance of specific autoantigens. This sustained inflammatory milieu ultimately contributes to bone erosion and cartilage degradation.[5]

The Role of Dendritic Cells in the Establishment and Maintenance of Inflammation in RA

Research has demonstrated that RA, along with other autoimmune disorders, plays a significant role in the pathogenesis of autoimmune inflammation.[44] A reduction in the frequency of both conventional dendritic cells (DCs) and plasmacytoid dendritic cells has been observed in the peripheral blood of individuals with RA.[45] This decrease is potentially attributable to the augmented migration of DCs into inflamed joint tissues.[44] It is postulated that this recruitment of DCs is facilitated by the upregulated expression of CCR6, a chemokine receptor for CCL20, which is abundantly expressed in the synovial tissue.[46] Upon migration to the joints, mature DCs secrete IL-12 and IL-23, which drive antigen-specific T helper 17 (Th17) cell responses. This activity contributes to a dysregulated balance among Th1, Th2, and Th17 immune responses.[47] Notably, Th17 cells have been identified as key mediators in the pathophysiology and clinical severity of RA.[47]

Arthritis in RA Is Mediated by T Cells, B Cells, Macrophages, and Fibroblasts

Epithelial and antigen-presenting cells within the synovium initiate autoantigen-specific responses involving both T and B cells.[5] Activated T cells that migrate to the synovial membrane engage locally with resident macrophages, dendritic cells, synovial fibroblasts, and osteoclasts, thereby facilitating the onset and progression of RA.[48] Th1 cells play a critical role by providing effective support to other immune cells, thereby triggering inflammatory responses within the synovium.[48] Notably, CD4+ CD28- T cells co-express perforin and granzymes, molecules that have recently been found to be elevated in a subset of peripheral blood samples from RA patients.[49] The detection of perforin-expressing cells in synovial fluid and tissue further implicates these cells in the pathogenesis of RA.[50] The equilibrium between effector T cells and regulatory T (Treg) cell subsets appears to be a key factor influencing both disease initiation and progression. It has been proposed that the inflammatory milieu characteristic of patients with RA may contribute to dysfunction in Treg cells that normally control autoreactive T cells, as well as promote the differentiation of Tregs into pathogenic T cell phenotypes. Supporting this notion, CD4+ CD25+ Foxp3+ Tregs with the capacity to convert into pathogenic Th17 cells have been observed to accumulate in inflamed synovial tissues.[50] Moreover, Tregs isolated from the synovial fluid of patients with RA exhibit a loss of suppressive function, in contrast to Tregs from peripheral blood, which maintain their inhibitory capabilities.[51] Finally, a distinct subset of Tregs possessing transforming growth factor-beta (TGF-β)-dependent suppressive activity can be induced through inhibition of TNF-α.[52]

Effect of Cytokines on RA Inflammation

Cytokines function as critical signaling molecules that facilitate communication between immune cells and between immune and tissue cells, thereby playing a pivotal role in the initiation and maintenance of inflammation in RA. The principal effector cytokines secreted by infiltrating T cells include TNF-α, IL-17A, interferon-gamma (IFN-γ), and receptor activator of nuclear factor-κB ligand (RANK-L).[19] TNF-α is ubiquitously detected in most arthritic tissue biopsies. Experimental evidence from various rodent models of arthritis has demonstrated that overexpression of TNF-α induces spontaneous inflammatory responses.[53] This cytokine contributes to cartilage degradation[54] and enhances bone resorption processes.[55] Furthermore, TNF-α has been shown to upregulates RANK-L secretion by bone cells, thereby facilitating osteoclastogenesis.[56] Another significant function of TNF-α is its capacity to stimulate the production of additional proinflammatory cytokines, which collectively foster the establishment of a proinflammatory milieu within the synovium.[57] IL-17A, predominantly produced by Th17 cells, promotes the synthesis of proinflammatory cytokines such as IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor (GM-CSF) by epithelial cells, endothelial cells, and fibroblasts.[58] IL-17A also facilitates neutrophil recruitment.[59] Through these mechanisms, IL-17A contributes to bone erosion, cartilage destruction, and neovascularization in patients.[60] It also induces the differentiation of osteoclast progenitors into mature osteoclasts, resulting in diminished bone formation and increased bone resorption.[61,62] Moreover, IL-17A has been implicated in the upregulation of matrix metalloproteinase-1 (MMP-1) production by synovial cells, which further exacerbates cartilage degradation.[62] Angiogenesis is a critical pathological feature of RA, and IL-17A has been demonstrated to enhance endothelial cell migration[63] and stimulate vascular endothelial growth factor (VEGF) production by synovial fibroblasts,[64] thereby promoting neovascularization within the inflamed synovium.

The Role of B Cells and Autoantibodies in the Pathogenesis of RA

Autoantibodies generated through aberrant activation of autoreactive B cells play a critical role in the pathogenesis of RA by facilitating immune complex formation and subsequent complement system activation.[65] The principal autoantibodies implicated in RA include rheumatoid factor (RF) and ACPA. Although RA exhibits pathological heterogeneity, the presence of RF and ACPA is correlated with heightened disease severity, increased joint destruction, and elevated mortality rates.[21] Rheumatoid factors are detected in approximately 69% of RA patients, with a specificity ranging from 60% to 85%.[66,67] However, it is important to note that RF may also be present in other diseases as well as in healthy individuals.[18] Similarly, ACPA is identified in 60%–80% of patients with RA, exhibiting a higher disease specificity between 85% and 99%.[68] Patients positive for both RF and ACPA face an estimated 40% risk of morbidity.[69] ACPA serves as a valuable diagnostic biomarker, as it can be detected in the circulation of patients with RA up to a decade prior to the onset of clinical symptoms. During disease progression, both the concentration of ACPA and the diversity of its epitopes increase concomitantly with elevated levels of proinflammatory cytokines. ACPA contributes to RA

pathogenesis by activating macrophages, promoting osteoclast activation through immune complex formation, and directly inducing bone loss by binding to citrullinated vimentin localized in the periosteum.[65] The pathophysiology of RA is summarized in Figure 1. And summarize the key cytokines involved in the pathogenesis of RA and their roles in Table 1.

Treatment of RA

Over time, various therapeutic approaches have been employed to manage RA and enhance patients' quality of life. The ACR established the "Treat to Target" principle, which emphasizes selecting an optimal treatment strategy to achieve either disease remission or, alternatively, a significant reduction in disease activity. Therapeutic interventions must be both aggressive and prompt, given that existing joint erosion is irreversible.[35] The standard treatment paradigm commences with a precise diagnosis and encompasses preventive measures as well as both non-pharmacological and pharmacological therapies to facilitate rapid clinical improvement. The 2021 ACR guidelines for RA treatment provide an updated framework for medication management, comprising seven strong recommendations and 37 conditional recommendations.[70]

Non-Drug Interventions for RA

Identification and characterization of risk factors are valuable tools for the prevention of RA. Emphasizing preventive strategies is critical for the comprehensive management of RA. Four distinct levels of prevention were delineated: primary, secondary, tertiary, and clinical. Primary prevention aims to inhibit the initiation of pathological processes, secondary prevention focuses on the management and early detection of risk factors to mitigate their impact, and tertiary

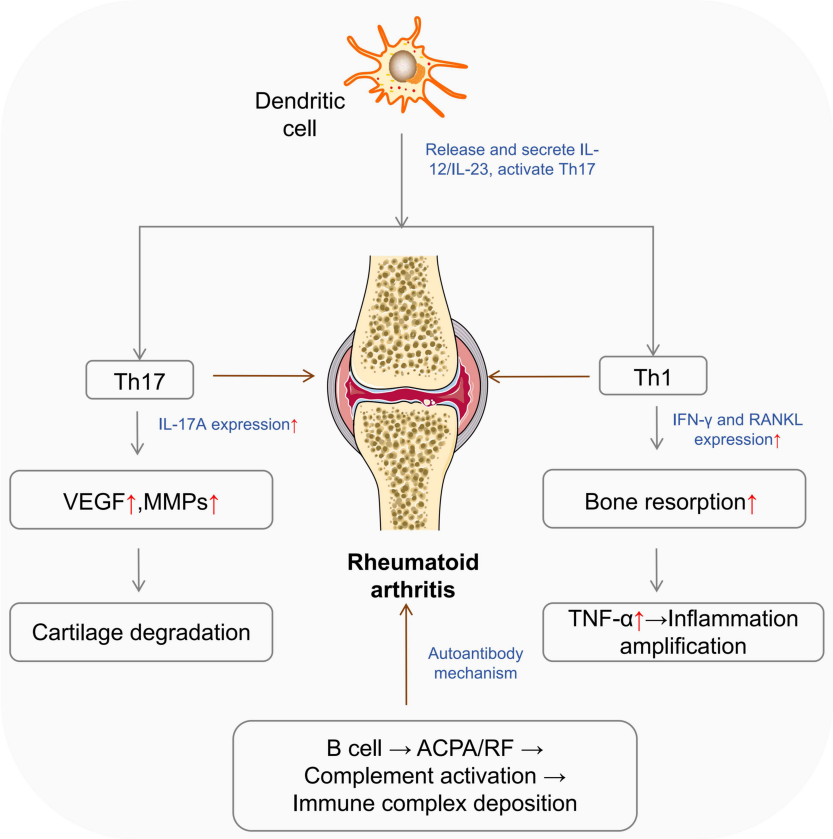

Figure 1 Pathophysiological Mechanisms in Rheumatoid Arthritis (RA). This figure demonstrates the key immunological processes involved in the pathophysiology of Rheumatoid Arthritis. Dendritic cells release IL-12 and IL-23, which activate Th17 cells. Th17 cells produce IL-17A, leading to increased expression of VEGF and MMPs, promoting cartilage degradation and rheumatoid arthritis development. Additionally, Th1 cells produce IFN-γ and RANKL, contributing to bone resorption. The autoantibody mechanisms, including ACPA/RF and complement activation, further amplify inflammation in RA. The red arrow indicates a promoting effect.

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Table 1 Key Cytokines in the RA Synovial Microenvironment and Their Major Pathological Roles

Cytokine	Target Cells/Molecules	Pathological Effects
TNF-α	Synovial cells, Osteoclasts, Chondrocytes	↑MMP, ↑RANKL, ↑IL-1/6; Cartilage degradation, Bone erosion
IL-17A	Osteoprogenitor cells, Synovial fibroblasts, Endothelial cells	↑MMP-1/3, ↑VEGF, ↑Osteoclast differentiation; Bone erosion, Pannus formation
IL-6	Hepatocytes, Osteoclasts, Treg cells	↑CRP, ↑Anemia, ↑Osteoclastogenesis; Treg function↓
IL-1β	Chondrocytes, Synovial cells	↑MMP, ↑NO, ↑PGE_2; Degradation of cartilage matrix
RANK-L	RANK+ Osteoclast precursors	↑Osteoclast differentiation, ↓Bone formation
GM-CSF	Macrophages, Neutrophils	↑Myeloid cell survival, ↑Inflammation amplification
IFN-γ	Macrophages, Synovial cells	↑Antigen presentation; Induces iNOS, MHC-II
VEGF	Vascular endothelium	↑Angiogenesis; Sustained infiltration of inflammatory cells

Note: ↑ indicates promotion or increase; ↓ indicates inhibition or decrease.

prevention addresses mechanisms to limit existing damage. Clinical prevention encompasses efforts to reduce complications and prevent disease recurrence.[22] Screening individuals at elevated risk for RA, such as blood relatives, twins, and seropositive individuals associated with RA patients, may contribute to lowering the incidence and prevalence of the disease.[71] The objectives of nonpharmacological interventions include alleviating anxiety and depression, diminishing pain, and enhancing mobility. Polyunsaturated fatty acids (PUFAs), particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) from the omega-3 fatty acid family, have garnered increasing attention because of their involvement in various neuropsychiatric conditions including anxiety and depression.[72] Current medical evidence indicates that PUFAs may influence several neural mechanisms that are involved in anxiety. Despite the heterogeneity of diagnoses, the predominant finding is that omega-3 PUFA supplementation is associated with a significant reduction in anxiety symptoms compared with the control groups.[73] Surgical intervention is reserved for patients with advanced stages of RA. Various surgical techniques can be used to alleviate pain and restore joint function. Recent advancements in surgical methods have expanded the available options, including synovectomy, radial synovectomy, arthroscopy, osteotomy, arthrodesis, phalangeal head resection arthroplasty, and total joint replacement.[74] The mechanism of non-drug therapy for RA is summarized in Figure 2.

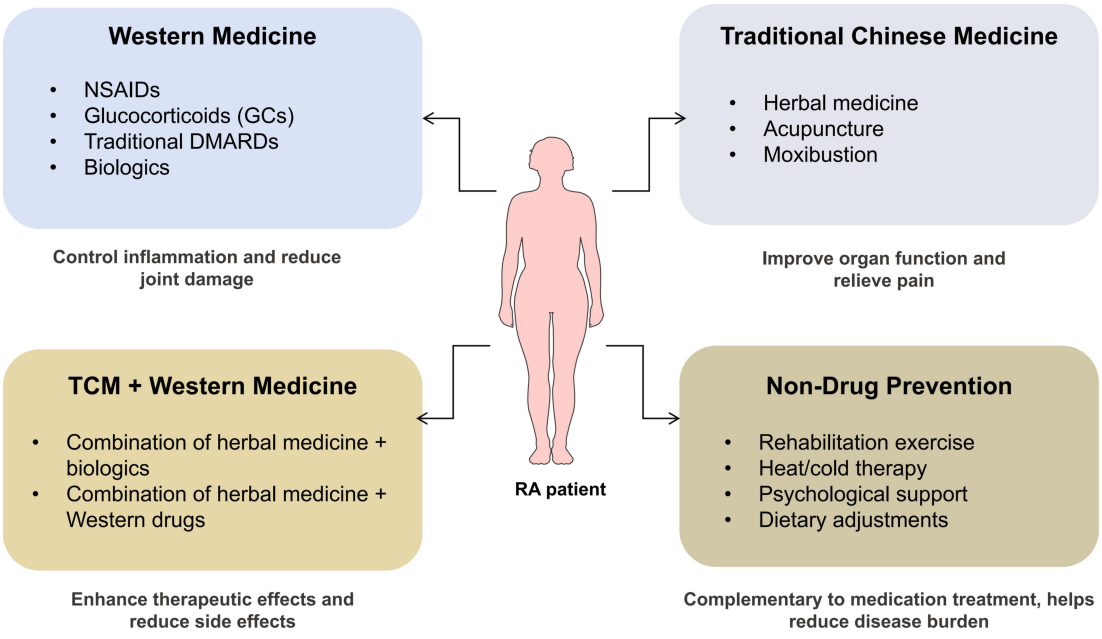

Figure 2 Treatment Approaches for Rheumatoid Arthritis (RA). This figure summarizes the therapeutic approaches for managing RA, incorporating Western Medicine, Traditional Chinese Medicine (TCM), Integrative Medicine (TCM + Western Medicine), and Non-Drug Prevention. Western Medicine includes NSAIDs, glucocorticoids, DMARDs, and biologics to control inflammation and reduce joint damage. TCM focuses on herbal medicine, acupuncture, and moxibustion to improve organ function and relieve pain. Integrative Medicine combines TCM with biologics or Western drugs to enhance therapeutic effects and reduce side effects. Non-Drug Prevention includes rehabilitation, psychological support, and dietary adjustments to complement drug treatment.

Drug Therapy for RA

Advancements in drug design methodologies have significantly enhanced the pharmacological strategies for the treatment of RA. These novel therapeutic approaches have proven to be effective in alleviating symptoms, decelerating disease progression, and preventing associated complications. Current management of RA adheres to treatment protocols established by the ACR and the EULAR, focusing on two primary objectives: symptomatic relief and disease remission.[75] The symptomatic management of RA predominantly involves the administration of nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GCs). Additionally, short-term use of weak opioid analgesics may be considered for pain control.[75,76] NSAIDs, including naproxen, ibuprofen, and coxibs, mitigate pain primarily through their anti-inflammatory effects, achieved via cyclooxygenase (COX) inhibition. The efficacy of NSAIDs in RA treatment has been extensively validated through randomized controlled trials (RCTs).[77,78] Glucocorticoids exhibit greater potency and therapeutic efficacy than NSAIDs, although NSAIDs are generally associated with a more favorable safety profile.[79] Long-term glucocorticoid therapy is linked to adverse effects such as weight gain, fluid retention, muscle weakness, diabetes mellitus, and osteoporosis; consequently, GCs are typically prescribed for short durations.[80] Disease-modifying antirheumatic drugs (DMARDs) constitute the cornerstone of disease-modifying therapies for RA. These pharmacological agents induce remission by suppressing autoimmune activity and preventing or delaying joint destruction. Given their delayed onset of action, ranging from six weeks to six months, early initiation of DMARD therapy is recommended.[81] Conventional synthetic DMARDs (csDMARDs) represent a heterogeneous group of drugs that includes methotrexate (MTX), leflunomide (LEF), and salicylazosulfapyridine (SASP). Currently, csDMARDs are widely employed as first-line treatment in patients newly diagnosed with RA.[82] The 2021 ACR treatment guidelines designate methotrexate as the preferred initial therapy for RA, either as monotherapy or in combination with other agents.[83] These guidelines strongly favor MTX monotherapy over leflunomide and salicylazosulfapyridine monotherapy. A recent systematic review encompassing 73 studies assessing the efficacy and safety of MTX concluded that it is the safest among csDMARDs and demonstrates significant therapeutic benefit.[84] Etanercept, the first anti-cytokine biologic agent approved by the US Food and Drug Administration (FDA) for RA treatment, is distinctive among TNF-α inhibitors because it is a dimeric fusion protein rather than an antibody.[85] Long-term studies have demonstrated that etanercept maintains sustained efficacy and a favorable safety profile over a 36-month treatment period.[86]

Treatment of RA with TCM

Traditional Chinese medicine (TCM) has a long history of treating RA and has rich clinical experience and practice. In recent years, under the guidance of TCM theory and modern molecular mechanism, research has been deepened, especially reflected in the systematic association and mutual interpretation between TCM pathogenesis and Western medicine pathology. For example, the syndrome of "dampness-heat obstruction" is associated with the activation of inflammatory signaling pathways such as NF-κB and MAPK, and "qi and blood blockage" is associated with vascular endothelial dysfunction, microcirculatory disturbance and hemorheological abnormalities. These studies not only reveal the disease nature of RA from two dimensions: the overall and microscopic mechanisms of the system, but also elucidate the action characteristics of multiple components, multiple targets, and multiple pathways of TCM compound at the molecular, cellular, and animal model levels, deepening the understanding of the mechanism of action of TCM in the treatment of RA. Among these, Tripterygium wilfordii stands out as a classical example, and its therapeutic efficacy in RA is widely acknowledged on an international scale.[87] The 2020 head-to-head trial demonstrated that tripterygium glycosides, as monotherapy for active RA, achieved non-inferior ACR20 response rates compared to methotrexate, while combination therapy yielded even better outcomes.[88] A 2021 international multicenter study found that the combination of total glucosides of paeony with DMARDs effectively reduced inflammatory markers with a favorable safety profile.[89] Additionally, research by Luoyang et al[90] demonstrated that TCM may exert protective effects against RA via modulation of the NLRP3 inflammasome.It is important to note, however, that TCM primarily employs compound formulations rather than monotherapies, and thus, research focusing solely on individual monomers may not represent the principal direction of TCM investigation. The prescription of traditional Chinese herbal formulas remains central to TCM practice. For instance, Yang Fang et al[91] reported that Gulao Yukang Pill can inhibit RA progression by regulating the balance between Th17 and Treg cells. Furthermore, the combination of *Rhodiola rosea* and *Euonymus alatus*,[92] a classical drug pair, is utilized to tonify qi and blood, expel pathogenic factors, promote blood circulation, alleviate collateral

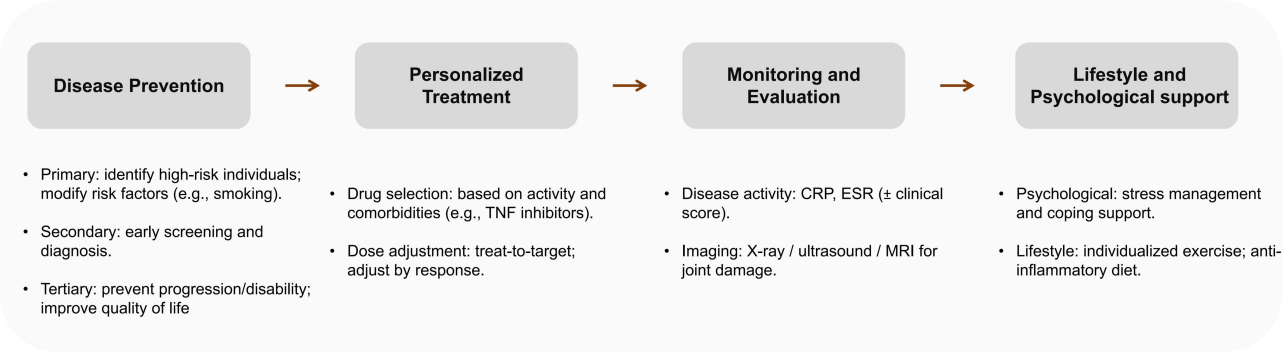

Figure 3 Comprehensive Management Strategies and Prevention for Rheumatoid Arthritis (RA). This figure illustrates the comprehensive management and prevention strategies for Rheumatoid Arthritis (RA). It includes four major components: disease prevention, personalized treatment, monitoring and evaluation, and lifestyle and psychological prevention. Primary prevention involves avoiding high-risk groups, secondary prevention emphasizes early diagnosis, and tertiary prevention focuses on reducing disease progression and improving quality of life. Personalized treatment includes drug selection and dosage adjustment based on disease status. Monitoring involves regular disease activity assessments, including tests like CRP, ESR, and imaging evaluations like X-rays and MRIs. Lifestyle interventions include psychological support and dietary adjustments to help manage RA symptoms.

obstruction, and relieve arthralgia during RA treatment.Moreover, patented Chinese medicines have been shown to play a significant role in RA therapy. For example, Huangqin Qingre Chubi Capsule[93] has been shown to clear heat, promote diuresis, and alleviate arthralgia, thereby effectively contributing to the treatment of RA characterized by damp-heat obstruction syndrome.Currently, integrated treatment approaches that combine traditional Chinese and Western medicine constitute the mainstream clinical strategy for RA. Xu et al[94] found that the combination of adalimumab with Guizhi Shaoyao Zhimu Decoction enhances qi, dispels wind, clears heat, and promotes diuresis, effectively reducing inflammation in RA patients and exerting therapeutic benefits. Similarly, Huiping et al[95] demonstrated that LEF combined with Guiqi Bufei Decoction effectively treated RA complicated by interstitial pneumonia, primarily through modulation of the Wnt/β-catenin signaling pathway to achieve therapeutic outcomes.The mechanism of integrated Chinese and Western medicine treatment of RA is summarized as follows, as shown in Figure 3.

Beyond China, multiple clinical trials in India have confirmed that traditional medicinal compounds such as curcumin exhibit anti-inflammatory effects comparable to NSAIDs, with superior safety profiles (eg, reduced gastrointestinal reactions).[96] In addition, it should be pointed out that there are still some limitations in the treatment of RA with traditional Chinese medicine therapy: the compound components are complex and the targets of action are multiple, resulting in that its efficacy mechanism is difficult to be completely explained with modern pharmacology, and there is a lack of large-scale, multicenter, randomized controlled evidence-based medical evidence. Furthermore, although individualized syndrome differentiation and treatment is an advantage, it also brings challenges such as non-uniform efficacy evaluation criteria and poor reproducibility. Integrative medicine provides a feasible framework for bridging these gaps. Through the research mode of "combining disease and syndrome", TCM syndrome classification can be introduced on the basis of clarifying the diagnosis and staging of western medicine diseases, and then a prospective study of stratified design can be carried out. With the help of systems biology, artificial intelligence and real world data platform, the network map of the action of traditional Chinese medicine compound can be constructed to realize the leapfrogging of mechanism interpretation from "punctate breakthrough" to "network analysis". In the future, deepening the integration and innovation of Chinese and Western medicine at the theoretical, methodological and technical levels not only helps to promote the modernization of Chinese medicine, but also provides a new paradigm reference for the individualized and comprehensive management of RA worldwide.

Summary

RA has now become a chronic autoimmune disease that is "controllable but not curable". With the advancement of modern diagnostic and therapeutic techniques, the clinical remission rate of RA has increased significantly. Modern drugs (such as methotrexate, biologics) can effectively control inflammation and delay joint injury, but there are still some patients with insufficient efficacy, significant side effects, easy to relapse of the disease and other problems. TCM has

shown unique value in the treatment of RA. TCM can not only play an important role at the non-drug level (such as diet regulation, emotional counseling, traditional exercises) by constructing an integrated diagnosis and treatment path of "Western medicine evaluation framework + TCM intervention strategy" (as shown in Figures 2 and 3), but also form synergy with conventional DMARDs and biologics and show unique value in enhancing efficacy, attenuation and synergism, improving quality of life and delaying joint structural damage. In order to promote the standardization and internationalization of traditional Chinese medicine in the treatment of RA, future research should build an evidence-based platform integrating "disease-syndrome-target", promote the quality traceability of traditional Chinese medicine, real world data and AI auxiliary syndrome differentiation, and achieve reproducible efficacy, analyzable mechanism, and early warning of risks; at the same time, large-scale, prospective, double-blind RCTs should be designed and implemented to directly compare the long-term efficacy and safety of integrated traditional Chinese and western medicine regimens with standard western medicine treatment. To provide a high level of evidence for individualized, precise, affordable integrated treatment of RA worldwide.

Disclosure

The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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