Chin J Integr Med 2024 Sep;30(9):842-851

Chinese Journal of Integrative Medicine

Available online at link.springer.com/journal/11655
Journal homepage: www.cjim.cn/zxyjhen/zxyjhen/ch/index.aspx
E-mail: cjim_en@cjim.cn

Review

Targeting Therapeutic Windows for Rheumatoid Arthritis Prevention*

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ABSTRACT Rheumatoid arthritis (RA) is a worldwide public health problem. Interventions to delay or prevent the onset of RA have attracted much attention in recent years, and researchers are now exploring various prevention strategies. At present, there is still no unified consensus for RA prevention, but targeting therapeutic windows and implementing interventions for at-risk individuals are extremely important. Due to the limited number of clinical trials on pharmacologic interventions, further studies are needed to explore and establish optimal intervention regimens and effective measures to prevent progression to RA. In this review, we introduce the RA disease process and risk factors, and present research on the use of both Western and Chinese medicine from clinical perspectives regarding RA prevention. Furthermore, we describe several complete and ongoing clinical studies on the use of Chinese herbal formulae for the prevention of RA.

KEYWORDS rheumatoid arthritis, prevention, Chinese medicine, review

Rheumatoid arthritis (RA) is one of the most common chronic autoimmune diseases in the world and can lead to severe joint damage by causing inflammation of the cartilage, bone and synovium, which ultimately leads to joint deformities and disability. Extra-articular manifestations also occur frequently, and overall, the disease causes a high social and economic burden.[1] Although awareness, early diagnosis and therapy, the implementation of treat-to-target strategies, and recent biologic agents and other Western drugs have led us into a new era of RA treatment, the ultimate goal of prevention remains unmet. Therefore, researchers have proposed the use of terminologies for the preclinical stage of RA (pre-RA)[2] and the criteria for clinically suspected arthralgia[3] to help us identify individuals at risk of RA development, a stage at which a therapeutic window appears, and to provide us with the opportunity to stop RA onset. However, finding the most appropriate therapies for at-risk individuals is not an easy task because the causes of the disease are multiple and complex,[4] and the concepts and descriptions of the at-risk stage of RA are still being developed and refined. This review aims to summarize recent research on RA prevention and its developmental landscape while exploring potential future strategies.

Epideminlogy

Despite all the achievements in RA treatment in recent years, the prevalence and incidence rates of RA have remained constant and even continue to

*Supported by the National Natural Science Foundation of China (No. 82274421), the Research Project of Guangdong Provincial Hospital of Chinese Medicine (Nos. 2023KT14118, YN2023RD01, YN2021RD01, MY2022KF08), the Specific Fund of State Key Laboratory of Dampness Syndrome of Chinese Medicine (Nos. SZ2021ZZ0202, SZ2021ZZ35), the Guangdong Provincial Key Laboratory of Chinese Medicine for Prevention and Treatment of Refractory Chronic Diseases (2018): 2018B030322012 (No. YN2023MB15), the Science and Technology Planning Project of Guangdong Province (Nos. 2023B1212060063, YN2023ZH22), and the Project of Administration of Traditional Chinese Medicine of Guangdong Province of China (No. 20231112)

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DOI: https://doi.org/10.1007/s11655-024-3760-2

rise,[5] with nearly 0.46% of the global population,[6] approximately 0.63% of the American population,[7] 0.65% of the Canadian population[8] and 0.75% of the Japanese population[9] being affected. In China, there are more than 5 million people suffering from RA, and the number continues to increase.[10] The overall prevalence of RA is as high as 4.86% in adults over 40 years of age, especially in Naqu City, Tibet.[11] Regarding geographical disparities, the prevalence and incidence of RA vary based on income level and environment, and low-income regions (e.g., Southeast Asia, sub-Saharan Africa) and rural settings generally exhibit lower age-related prevalence and incidence.[12] Considering racial and ethnic nationality distribution, American Indians exhibit the highest prevalence of RA, followed by Caucasians and Hispanics; conversely, Asians and individuals of other unknown races have the lowest prevalence of RA.[13,14] In addition, a notable sex disparity exists, with the number of women with RA being 2 to 4 times the number of men with RA, and the prevalence of RA in women tends to increase with age.[15]

RA Progression

The development of RA is complex, and it is a disease with a continuous progression.[16] RA begins with a high-risk or susceptibility stage. In this stage, no symptoms or signs of autoimmunity are detectable, but several risk factors are known to be involved, primarily genetic factors, which account for 60% of the risk factors and include susceptibility genes and epigenetic modifications. The other 40% of risk factors are the proposed environmental risk factors such as smoking, changes in the microbiota, infections, vitamin D deficiency, diet and obesity, sex, and ethnicity.

Then, the developmental process proceeds through the preclinical stage, the stage before articular inflammation develops. The preclinical stage is the time when autoimmunity initially occurs in the body. For example, peptides can undergo citrullination, acetylation, or carbamylation. This stage is the point of the activation and presence of autoantibodies, including anti-citrullinated peptide antibodies (ACPAs) and rheumatoid factor (RF), and increasing levels of cytokines and chemokines can also be detected. The preclinical stage can last for up to 10 years before clinical disease onset. Some individuals in this stage may experience symptoms such as joint stiffness, arthralgia, fatigue, or insomnia but not arthritis or synovitis.

When patients are found to have undifferentiated arthritis, the disease has progressed to the early stage of RA. As autoimmunity continues to propagate during this period, early treatments are strongly recommended. The next stage is established RA, which can be diagnosed according to the classification criteria. However, the disease continues to progress, leading to bone destruction and even other severe comorbidities.

Why Focus on RA Prevention?

Once RA with typical manifestations is diagnosed, most patients do not return to the preclinical state even after receiving strong anti-rheumatic treatments—it becomes a lifelong battle. Although an increasing number of RA patients have received an early diagnosis over time, with the average time from symptom onset to diagnosis confirmation being 2.5 years, the best treatment window of opportunity is within 6–12 months after symptom onset.[10] As a result of delayed diagnosis, more patients have had moderate to high disease activity when they first sought medical care; therefore, more refractory cases have occurred in China, and only 28.65% of the patients achieve remission.[10] Moreover, when patients achieve clinical remission and theircs DMARDs or TNF inhibitors doses are tapered, approximately 60% of patients experience a disease flare.[17] Joint diseases are a major cause of physical disability, with RA at the top of the list; 20% of affected individuals develop joint deformity and disability after 1 year, and this percentage increases to 61.25% if the disease duration is longer than 15 years.[10] Moreover, RA-related financial burden was ranked first among rheumatic diseases and was much greater in China than in other countries, with the cost of chronic care being US$12 million each year.[10] Therefore, the pre-RA phase before the actual onset of RA provides chances for us to perform clinical therapy of both Western medicine and Chinese medicine.[18]

Targeting Therapeutic Windows

Identifying Risk Factors for RA Development

Genetic Factors

Family heritability

Significant genetic characteristics of RA, as well as familial aggregation among patients, have been suggested. Individuals with a family history of RA have a 3–5-fold increased risk of disease onset.[19] The heritability of RA in twins is 53%–66%, and that in twins positive for ACPAs increases to 68%.[20,21]

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HLA and non-HLA loci

With the rapid development of high-throughput genotyping technology, large sample candidate gene studies and genome-wide association studies have identified more than 100 genetic regions associated with genetic susceptibility to RA, but the findings of these studies remain insufficient to fully explain the heritability of RA.[22] Major histocompatibility complex genes, including HLA class Ⅰ (HLA-A, B, C), class Ⅱ (HLA-DR, DP, DQ) and class Ⅲ genes, are the most relevant genes.[23] Among them, HLA-DRB1 is recognized as the gene most strongly related to RA.

In addition to HLA loci, single nucleotide polymorphisms at non-HLA loci are also involved in regulating RA progression, including the regulation of immune cells and proinflammatory cytokines.[24] The genes INFG-1616 G and INFG-1616 GG, as well as TNF-α-308A, are associated with disease susceptibility and severity.[25,26] Many gene mutations, such as the rs26232 allele located in the C5orf30 intron, may increase RA susceptibility and severity by affecting fibroblast-like synoviocytes activity.[27] Many potential novel risk loci for RA have been revealed through both domestic and international investigations, including genes such as SLAMF6, CXCL13, SWAP70, IL12RB2, BOLL-PLCL1, and CCR2.[28,29]

Epigenetics

As the understanding of epigenetics has improved, changes in DNA methylation, the acetylation of histones, microRNAs, and lncRNAs have been found. The expression of other noncoding RNAs also plays a nonnegligible role in the pathogenesis of RA.

Nongenetic Factors

Environmental factors are important triggers of the autoimmune system, and the mechanism may involve a systemic stimulus that acts on genetically susceptible individuals, causing a series of changes that lead to the development of RA.

Smoking status and air pollutants

Smoking is one of the most serious environmental risk factors for RA. Twenty-five percent of RA cases and 35% of seropositive RA cases are attributable to smoking.[30] The prevalence of RA in long-term moderate-intensity smokers is approximately twice that in nonsmokers,[31] especially for heavy smokers and men positive for RF.[32] A longer smoking duration is associated with a greater RA risk. Compared with people who smoke for less than 10 years, the risk in people who smoke for more than 40 years increases by at least 1.5 times and does not decrease even after quitting smoking.[33] Additionally, smoking is associated with more severe joint symptoms and greater disease activity.[34] Although the biological mechanism of RA development caused by smoking has not been fully clarified, nicotine, carbon monoxide, and other components in tobacco can affect the normal immune response, including the innate and adaptive immune responses, after entering the human body from the respiratory mucosa.[35] Moreover, there is a very strong interaction between smoking and genetic factors, especially the HLA-DRB1 allele,[36,37] which can further induce autoimmune reactions and affect the production of ACPAs and RF in the body,[38] thus leading to the occurrence of diseases.

Overweight

Obesity increases the risk of RA. Compared with those with a BMI below 30 kg/m^2, the risk of RA in obese individuals is 1.25 times greater.[39] The risk increases by 13% for every 5 units of BMI.[40] For every 10 cm increase in waist circumference, the risk increases by 1.13 times.[41] Obesity is also associated with high disease activity and a low remission rate, which are more pronounced in women.[42,43] In addition, BMI can change the immunohistochemical characteristics of RA by affecting synovial inflammatory cells. Compared with patients with a normal body weight, patients with a BMI greater than 25 kg/m^2 have a greater incidence of synovial inflammation and more active inflammatory cells.[44] However, most studies on the correlation between obesity and RA risk have been conducted in Europe and the United States, and more exploration is needed in other geographical regions.

Microbes and infections

Exposure to bacterial and viral infections increases the risk of developing RA. In mouse models, microbial species and their metabolic pathways can induce RA-like immune responses, providing preliminary evidence for specific mechanisms by which the microbiome is associated with RA development.[45] For example, periodontal disease is likely a predisposing factor that increases symptom severity in pre-RA patients.[46] *Porphyromonas gingivalis* infection may be related to the loss of early

tolerance to autoantigens[47] and can increase the risk of seropositive RA.[48] The rate of ACPA positivity is greater in RA patients infected with actinomycetes.[49] Bone loss and arthritis might be accelerated by oral inoculation of *Fusobacterium nucleatum* and *Aggregatibacter actinomycetemcomitans*.[50]

Parainfluenza virus, coronavirus, and metapneumovirus infection are all associated with an increased incidence of RA, especially in women and elderly patients, suggesting that respiratory virus infection may also be a new environmental risk factor for RA pathogenesis.[51] Changes in the oral and intestinal microbiota induced by antibiotic drugs, diet, aging, etc., lead to dysbiosis, which may be associated with the pathogenesis of RA.[52]

Weather influences

Cold and humidity may contribute to the development of RA, and temperature and wind speed affect the appearance of joint symptoms.[53] This finding is consistent with the induction factors of RA in Chinese medicine (CM) theory. *The Inner Canon of Huangdi* (Huang Di Nei Jing) points out that wind, coldness and dampness are the pathogens of articular diseases (Bi syndrome).

Other factors

Dietary habits, such as higher intakes of higher intakes of red meat,[54] protein,[54,55] iron,[55] sugar,[56] sodium,[57] and antioxidants,[58] increase the risk of developing RA.[59] Vitamin D intake is negatively associated with the development of RA.[60] A low education level, high birth weight and not having children may also increase the risk of developing RA.[41] The number of women with RA is 2 to 4 times greater than the number of men with RA.[15] Lactating women, especially those lactating after the birth of their first child, are at increased risk of RA, which may be associated with the substantial increase in prolactin during lactation.[15] Ethnic factors also contribute to the incidence of RA.[13]

Identifying "At-Risk" Individuals

Individuals at the pre-RA stage, including those with genetic/environmental risk factors for RA, systemic autoimmunity associated with RA, symptoms without clinical arthritis and unclassified arthritis, are considered at risk for a future diagnosis of RA. However, the exact probability of developing RA is unknown. Exploration of this uncharted research area is awaited, as there is still no consensus to help define these "at-risk" cohorts. For clinical practice, these "therapeutic windows" need to be described more specifically to guide treatment strategies. Despite the risk factors mentioned above, particular characteristics of individuals, including physical symptoms, laboratory tests and imaging features, should also comprehensively be considered in target cohort selection.

One important thing we must pay attention to is autoantibodies, among which a variety of immunoglobulin isotypes can be detected years before the onset of RA. ACPAs are frequently found,[61] and the positive predictive values (PPVs) are usually 80%.[62] The PPVs of ACPA positivity in individuals who develop RA within 2 to 5 years are approximately 20%–70%.[63-67] When ACPA positivity is accompanied by other risk factors, such as high-titer RF, joint pain, tenderness, persistent smoking, obesity, and other genetic factors, the risk of developing RA is even greater. These individuals can be targeted for risk intervention. Although there is no consistency in the duration of the at-risk stage, relevant studies have estimated that for individuals with two or more first-degree relatives suffering from RA, for those who were only RF-positive and only ACPA-positive, the PPVs of RA onset within 5 years were 37.7% and 69.4%, respectively, and 100% of individuals positive for both RF and ACPAs developed RA within 5 years.[68]

Musculoskeletal manifestations such as arthralgia and fatigue are also important.[3,69] Moreover, Doppler ultrasound can increase the accuracy of RA prediction.[64] Magnetic resonance imaging helps to sensitively distinguish structural inflammation that generally does not exist in healthy individuals without RA.[70]

Recent Interventions for RA Prevention

Clinical studies on RA prevention are still in progress. To date, many published studies have provided a valuable and effective clinical basis for therapeutic intervention in "at-risk" cohorts. Most of them target individuals who are ACPA positive but without synovial inflammation or arthritis. Several clinical studies in recent decades have used MTX, dexamethasone, etanercept, rituximab, and other means for drug intervention, and the results suggest that these drugs might reduce the risk factors for RA if administered within a certain period, but there is no

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evidence indicating that they can significantly block the development of RA. The incidence of RA development was approximately 0–32%, and the observation duration ranged from 4 months to 3 years (Table 1).[71-77] As shown in Table 1, the rates of RA development and arthritis development were even greater in some of the intervention groups than in the placebo group. The findings of a systematic literature review and meta-analysis published in 2019 indicated that early treatment with DMARDs may markedly reduce the risk of RA onset in patients with arthritis but not in symptomatic patients without arthritis; however, the beneficial effect could differ between csDMARDs and biologics.[78] At present, a study focused on finding the optimal therapeutic window for RA prevention is still in progress and are expected to be completed in the next decade.[79]

Thus, at present, there is no consensus intervention strategy for at-risk individuals receiving Western medicine. Furthermore, which drugs are optimal for these intervention strategies remains a matter of controversy, and there is also the possibility of adverse drug reactions and overtreatment. However, if therapeutic means are not applied in this at-risk stage, the optimal intervention window may be missed, eventually resulting in the occurrence and development of RA.

Possibility of RA Prevention Through CM

Effects of CMs on RA

Therapeutic Characteristics and Advantages of CM

Previous studies have shown that CM can decrease the levels of autoantibodies,[80] reduce bone damage[81] and achieve a strong therapeutic effect;[82] CM formulae contain multiple components and targets multiple pathways.[83] Additionally, the synergies among different herbs in one formula give CM great potential in RA treatment. All these factors make CM a treasure trove and resource for new drug development, attracting more scientists to explore its latent energy.[84,85]

Many CM formulae and their monomers exhibit anti-rheumatic effects mainly by inhibiting the production of inflammatory cytokines, blocking signaling pathways, inducing apoptosis, decreasing the proliferation of immune cells and angiogenesis, etc. Among them, the most effective ingredients include alkaloids, flavonoids, terpenoids, phenols and quinines.[83,86] Compared to DMARDs or other antirheumatic drugs, one of the highlighted advantages of CM is that they can be widely used at any stage during RA development. Even in healthy people, CM can be used for physical conditioning and as health products. This means that, under the guidance of CM theory, CM formulae can be widely used for disease prevention, whereas DMARDs cannot.

Commonly Used CM Formulae and Products

Most CM formulae for RA treatment are classic ones commonly used in clinical practice, mainly Guizhi Shaoyao Zhimu Decoction (桂枝芍药知母汤, GSZD), Juanbi Decoction (蠲痹汤), Wutou Decoction (乌头汤), Duhuo Jisheng Decoction (独活寄生汤), Danggui Niantong Decoction (当归拈痛汤), and Huangqi Guizhi Wuwu Decoction (黄芪桂枝五物汤). For example, in early RA patients with damp-heat syndrome, GSZD combined with leflunomide is more effective than leflunomide alone in resolving inflammation, joint pain, swelling, and other laboratory parameters.[87] Additionally, GSZD inhibits RA osteoclastogenesis by regulating NF-κB signaling.[88] GSZD is a favorable choice in terms of efficacy and safety and is considered one of the alternatives to Western medicine.[89]

Among modern innovative CM compounds, Huayu Qiangshen Tongbi Formula (化瘀强肾通痹方,

Table 1. Clinical Trials in At-Risk Individuals in Recent Decades

Researcher	Year	Patients	Patients selected	Intervention	Placebo	Observation period	RA development	Arthritis development
Boss[71]	2010	83	ACPA/RF(+)	Dexamethasone	√	≥12 months	7.14% *vs.* 7.32%	21.43% *vs.* 19.51%
Wevers[77]	2012	122	ACPA/RF(+)	MTX	×	4 months	/	/
Nam[72]	2014	82	ACPA&RF(+)	MTX+ETN	√	18 months	/	/
Stamm[74]	2018	90	ACPA/RF(+)	MTX+IFX	√	1 year	/	/
Gerlag[73]	2019	81	ACPA(+)	RTX	√	29 months	31.71% *vs.* 27.50%	34.15% *vs.* 40.00%
Li[76]	2019	97	ACPA/RF(+)	Vit D2	√	18 months	0	1.96% *vs.* 6.52%
Laurette[75]	2021	62	ACPA/RF(+)	Atorvastatin	√	3 years	26% *vs.* 19%	29% *vs.* 19%

Notes: ACPA: anti-cyclic citrullinated peptide antibody; RF: rheumatoid factor; MTX: methotrexate; ETN: etanercept; IFX: infliximab; RTX: rituximab; Vit D2: vitamin D2; *vs.*: *versus*, the medicine group compared to the placebo group.

HQT), which is also a well-studied formula, is an effective therapeutic regimen for treating RA.[90,91] HQT could cause a decrease in several cytokine pathways, such as the TNF-α, IL-1β, IL-6, and IL-17A pathways, by normalizing the levels of the lncRNA uc.477, which are increased in the serum of RA patients, by targeting miR-19b in fibroblast-like synoviocytes.[92] Moreover, HQT has anti-inflammatory effects by regulating various signaling pathways, especially the toll-like receptor, phosphoinositide-3-kinase-Akt, mitogen-activated protein kinase, and activator protein 1 signaling pathways.[93] Moreover, HQT helps alter gut microbial species to affect RA-related clinical indicators.[83]

Moreover, proprietary CM products provide more options for RA treatment. *Tripterygium wilfordii* preparations, such as *Tripterygium wilfordii Hook* F tablets and Kunxian Capsules (昆仙胶囊), which are often used in combination with other DMARDs, are commonly used and effective. The efficacy of *Tripterygium wilfordii* preparations in treating active RA is suggested to be comparable to that of MTX, and the combination of these two agents is more effective than MTX alone.[94] Another CM product is *Sinomenium Acuturn* preparations, such as Zhengqing Fengtongning (正青风痛宁), which has outstanding analgesic and anti-inflammatory effects. Their combination with MTX is also very effective, resulting in fewer adverse reactions.[95]

Challenges of CM in RA Prevention

Like any other drugs, any CM formula or product has certain side effects or health risks. For instance, when prescribing *Tripterygium wilfordii*,[96] clinicians need to pay attention to the digestive system and reproductive system.[97] For some CM formulae, gastrointestinal discomfort is one of the most common adverse reactions. However, the synergistic effect helps us reduce the toxicity of CM formulae, and combining CM with DMARD therapy also reduces the likelihood of other adverse events during RA treatment.[98] The hope for disease treatment is that the benefits of medications outweigh the risks for patients, and the same is true for disease prevention. Obviously, products such as *Tripterygium wilfordii*, which is associated with toxic side effects, may not be suitable for preventing RA. Softer, milder and more effective remedies are needed. Which formulae are more appropriate for prevention remains unknown, but this is a key focus to explore.

Another challenge is that although CM formulae can be used at any stage during RA progression, their use is based on the theory of CM syndrome differentiation and individualized treatment, which requires clinicians to have sufficient medical experience.

RA Prevention through CM: the First Attempt

To investigate this topic in the field, we conducted a single-arm prospective clinical trial with an optimized HQT.[99] First, we analyzed the 24-week clinical information of 19 individuals to determine the proportion of patients who met the 2010 ACR/ACR/EULAR classification criteria for RA during observation. However, due to the small sample size in this trial, which limited the generalizability and statistical power of the findings, it is still difficult to determine whether HQT could prevent RA onset. Moreover, before a diagnosis of RA can be established, long-term progression can occur, and 24 weeks of follow-up is not long enough to accurately evaluate the treatment effect and potential side effects. Overall, this trial still provides some insights for future works.

RA Prevention through CM: Ongoing Trials

Decoction A

In this multi-center, double-blind, placebo-controlled, randomized clinical trial, 72 individuals aged 18–75 years positive for anti-CCP but without synovitis and not meeting the 2010 ACR/EULAR RA criteria will be randomly assigned to receive 52 weeks of Decoction A (DA) or placebo, and another 52-week follow-up will be conducted.[100] The primary outcome is the time to the first clinical synovitis occurrence, referring to the time interval from baseline to diagnosis. Based on CM theory, which has been used in clinical practice in China for thousands of years, DA has been developed, optimized, and subjected to animal studies and a pilot clinical observation study, both of which indicated that DA may have the potential to reduce the progression of RA. DA is a Chinese herbal formula containing 8 different herbs (The trial was registered in the Chinese Clinical Trial Registry on October 1, 2021. Registration No. ChiCTR2100051741. URL: http://www.chictr.org.cn/showproj.aspx?proj=133579.)

Yunpi Qufeng Chushi Formula

In this multicenter, double-blind, placebo-controlled clinical trial, 390 participants positive for anti-CCP antibodies and at least one swollen or tender joint, as well as a CM syndrome of Spleen (Pi) deficiency

and wind-damp blockade syndrome, will be recruited to take Yunpi Qufeng Chushi Formula (运脾祛风除湿方) or placebo for 48 weeks to compare the RA transition rate during the follow-ups. CRP, ESR, RF, anti-CCP, Doppler ultrasound semiquantitative score, and other disease assessments will be assessed.[101]

Total Glucosides of Paeony

In a non-randomized control trial, a total of 200 ACPA-positive participants were divided into 2 groups and treated with 600 mg total gluvosdes of paeony twice a day or no medicinal intervention. Additionally, in this study, intestinal samples were collected to identify the characteristics of the intestinal flora of ACPA-positive participants, the changes and relationships of the intestinal flora as the disease progresses, and the clinical effect of TGP intervention and its influence on the intestinal flora and underlying mechanism. (The trial was registered in the Chinese Clinical Trial Registry on April 18, 2019. Registration No. ChiCTR1900022605. URL: https://www.chictr.org.cn/showproj.html?proj=29196.)

Conclusion

RA induces chronic synovitis in patients, which subsequently leads to the erosion of joint cartilage and bone, eventually resulting in deformity and even functional impairment of the affected joints. RA patient inability to work has become a key factor affecting social progress. Therefore, the prevention of RA has become the subject of extensive discussion.

Can the onset of RA eventually be stopped? We cannot provide a definite answer at this time, but scientists in this field are trying hard to investigate this topic. The optimal drugs to prevent RA need to be safe, cost-effective, and globally available. Since the mechanisms of RA pathology involve multiple immune cells, effector cells, stromal cells, and many different intracellular signaling pathways, a drug or combination of active compounds with a wide window of action might be preferable. Ongoing studies will increase our knowledge and understanding of this phase, leading to better and more refined criteria for at-risk individuals, tailored treatment regimens, and ultimately the overall goal of RA prevention.

Conflict of Interest

The authors declare that they have no competing interests.

Author Contributions

Gao KX and Yang YH contributed equally to this work. Huang RY and Gao KX contributed to the conception and design of the study. Gao KX and Yang YH wrote the first draft of the manuscript, and the other authors contributed to the revision of the manuscript. All the authors have read and approved the final manuscript for publication.

Abbreviations

csDMARD: conventional synthetic disease modifying antirheumatic drugs; HLA: human leucocyte antigen; INFG: interferon gamma; LAMF6: signaling lymphocytic activation molecule family member 6; CXCL13: C-X-C motif chemokine ligand 13; SWAP70: switch-associated protein 70; IL12RB2: interleukin-12 receptor subunit beta-2; BOLL-PLCL1: boule homolog-phospholipase c-like 1; CCR2: C-C motif chemokine receptor 2; HLA-DRB1*04: human leukocyte antigen-DRB1*04; BMI: body mass index; MTX: methotrexate; DMARDs: disease-modifying antirheumatic drugs; NF-κB: nuclear factor-kappa B; IL: interleukin; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ACR/EULAR: American College of Rheumatology/European League Against Rheumatism; anti-CCP: anti-cyclic citrullinated peptide.

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(Accepted March 15, 2024; First Online May 16, 2024)
Edited by WANG Wei-xia