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Feature Article

On Research Progress of Western and Chinese Medicine Treatment on Pre-Rheumatoid Arthritis*

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ABSTRACT Pre-rheumatoid arthritis is the inevitable phase before the actual onset of rheumatoid arthritis and has the crucial clinical significance of early controlling and preventing disease progression. Full understanding, from both Western medicine (WM) and Chinese medicine (CM), could offer new ideas for decision making in clinical and mechanism research. This paper reviews the novel studies of WM and CM to discuss the advantages and potential mechanisms working behind.

KEYWORDS pre-rheumatoid arthritis, Western medicine, Chinese medicine

Rheumatoid arthritis (RA) is a common systematic autoimmune disorder, characterized as inflammatory response, chronic synovitis and bone destruction, with high disability rate and diverse clinical manifestations. Uncontrolled RA with poor prognosis also affects lung, kidney, and heart. However, the pre-clinical symptoms related to RA are inconspicuous, which makes it easy to miss the diagnosis and therefore, enhance the difficulty on remission and treatment. Pre-RA patients, with distinct genetic background, are proved to have abnormal serological features and dysfunctional microbiome in the pre-clinical phase before the actual onset of polyarthritis RA. Moreover, emerging researches are gradually turning to focus on such phase, in the pursuit of achieving the early control upon RA development and drawing the attention of rheumatologists of both Western medicine (WM) and Chinese medicine (CM). How to prevent RA onset or how to prevent the progression from seropositive pre-RA towards RA remains the critical clinical issue.

Definition of Pre-RA

WM Definition of Pre-RA

Pre-RA is the classification for individuals at risk for RA. European League Against Rheumatism (EULAR) made the detailed definition for Pre-RA,[1] including preclinical RA, inflammatory arthralgia, autoantibody-positive arthralgia, and undifferentiated arthritis, which partly shares the same character with RA while fails meeting the criteria according to either EULAR or American College of Rheumatology.[2] Besides, genetic risk factors, environmental risk factors, associated systemic autoimmunity, symptoms without clinical arthritis, unclassified arthritis have been involved the terminology, and the combinatorial manner is used to describe the heterogeneity of pre-RA. It is well widely acknowledged that early diagnosis and intervention lead to better RA remission and prognosis. However, there still lacks recognized treatment for pre-RA.

Systemic autoimmunity, or the presence of autoantibody, can be found prior to the onset of RA based on several retrospective studies,[3] and relevant biomarkers like anti-cyclic citrullinated peptide (ACCP), rheumatoid factor (RF) and especially the anti-citrullinated protein antibodies (ACPA) are used to describe pre-RA. Although not all the seropositive individuals show RA development, research showed that more than 50% of individuals at risk of RA with CCP-positive progressed to RA within 12 months.[4]

Studies focused on the etiology revealed that RA is the result of the combined effect of environmental,

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genetic, and epigenetic factors. It is worth noting that, pre-RA, as the distinctive phases of RA, has a distinct transcriptional signature compared to healthy individuals at risk or RA patients.[5] Also, the microbiome plays a crucial role, as the environmental factor, in the development of RA by mediating mucosal autoimmune response.[6] *Porphyromonas gingivalis*, whose product could lead to internal citrullination, is reported as the leading cause of RA-related autoimmune periodontitis.[7] Moreover, relatively abundant *Prevotella copri* can be found in pre-RA patients.[8] However, it still needs more work on the underlyingmechanisms.

CM Definition of Pre-RA

There is no corresponding terminology for pre-RA in CM, while it could be classified as "Bi" for the shared symptom of arthralgia. It is first recorded in the *Plain Questions of the Yellow Emperor's Classic of Medicine* (Huang Di Nei Jing) 2000 years ago that wind, cold and dampness evil invade together and make Bi. In addition, other factors like damaged congenital qi and dystrophic acquired qi also contribute to the progression of its development.

Pi (Spleen), or the foundation of acquired constitution, plays a vital role both in the development and prevention for pre-RA. If lacking sufficient nourishment, deficient Pi would lose the capacity of producing qi and blood, and whole human body would be vulnerable to all kinds of exogenous evils. Therefore, the syndrome differentiation of pre-RA in CM is widely considered as dampness abundance due to the deficient Pi and wind-cold-dampness causing arthralgia. The manifestations are swelling and pain in the single small joint, fatigue, subcutaneous nodule, and short-time morning stiffness.

WM Treatment for Pre-RA

Hitherto it remains unclear in clinical how pre-RA should be treated. Given the consensus that early diagnosis and medicine interventions in the newly diagnosed RA, even in the individuals at risk, could significantly prevent pre-RA from progressing to RA and increase the remission rate of RA. Rheumatologists are looking for reliable treatment, mostly referring to the routine treatment of RA, namely disease-modifying antirheumatic drugs (DMARDs) including synthetic chemical compounds (sDMARDs) and biological agents (bDMARDs).

Glucocorticoid

Glucocorticoid (GC) is not the first choice for pre-treatment, but updated EULAR's recommendations for the management of RA had illustrated that low-dose GC could be the initial treatment strategy,[9] in combination with other DMARDs, for up to 6 months. Klaus' Stop Arthritis Very Early (SAVE) research found that GC,[10] or methylprednisolone, could not help the remission of very early RA either the delay for the RA development.[9] Also, GC treatment failed to influence the need to start DMARDs. Although GC showed quick relieving efficacy on the related clinical manifestations, the long-run immunomodulatory effect was observed compared with placebo control in this study.

sDMARDs

Methotrexate (MTX) is the preferred sDMARDs for RA treatment. Clinical trial found that MTX has a potential preventive effect for RA progression in individuals at risk for RA and undifferentiated arthritis patients,[11] besides the delay of injury of joints. However, MTX showed similar spontaneous remission rate as the placebo control,[12] which indicated that for quite a portion of pre-RA patients, MTX treatment could be considered as the unnecessary treatment. The combined use of MTX and GC, based on the induction therapy with MTX and Prednisone in Rheumatoid Or Very Early arthritic Disease (IMPROVED) study,[13] could dramatically increase the remission rate of pre-RA while such formula could limitedly prevent the RA development for individuals with ACPA negative. The possible explanation is that this subpopulation, with ACPA negative, may represent a different disease.

bDMARDs

Novel bDMARDs, with relatively precise therapeutic mechanisms, have a higher specificity and biological activity. The wide use of bDMARDs on RA treatment offers new ideas about making decisions on pre-RA.[14]

Lymphocytes, like T cells and B cells, are the regulator in autoimmune RA. As the indispensable antigen-presenting cells, B cells could differentiate and produce representative autoantibodies like RF and ACPA. Moreover, T cells participate in the initiation of immunology and breakdown of immunological surveillance can be found in the infiltrating T cells on active synovial joints.[15] B cells targeted anti-CD20 antibody, namely rituximab, significantly delays the development of arthritis in the prearthritis stage of autoantibody-positive

RA.[16] Abatacept, functions as modulating the T cell costimulation, showed robust efficacy in combination with MTX in pre-RA, with an excellent safety profile.[17] Another clinical trial also demonstrated the abatacept plus MTX has the long-term benefit.[18]

Besides, elevated tumor necrosis factor alpha (TNF α) is the hallmark of RA, and TNF α blockage showed remarkable clinical efficacy on the RA. For the early RA patients who failed to achieve the spontaneous remission, adalimumab combined with MTX showed significantly more remission during the IMPROVED trial.[19] Infliximab, working as eliminating the autoimmune inflammatory responses, showed moderate influence on relieving the symptoms related pre-RA while did little on the prevention of progression toward RA.[20]

Prevention

Except for medication, WM also gives much advise upon the individuals at risk of RA and first-degree relatives of RA patients in the pursuit of early diagnosis and prevention of progression.[21]

First, regular screening and follow-up of people at risk of developing RA are necessary to prevent the clinical events, and by treating within a very early, 'Window of opportunity,' the natural history of RA could also be altered. However, low prevalence of autoantibodies requires comprehensive routine screening at large scale, and it will be costly to identify the at-risk individuals among communities. In response to such a problem, an appropriate screen targeting on the first-degree relative seems to be the optimal strategy.

Next, clinical symptoms like pain and swelling on single joints, which does not meet current criteria, should be paid with more attention in clinical practice. Individuals who are symptomatic need preventative treatment. Palindromic rheumatism and undifferentiated arthritis patients, who have a high chance of progression towards RA, often respond to disease-modifying agents, like methotrexate. However, more randomized controlled clinical trials with longer-term of follow-up are needed to discuss which treatment could provide the best outcome or alter RA course.

Primary Strategies of CM Treatment on Pre-RA

The primary strategies of CM on the treatment on pre-RA are preventive treatment and symptomatic treatment according to the differentiation of syndrome.

Preventive Treatment

Pre-RA needs both prevention before disease onset and controlling on emerged disorder in the perspective of CM. Pre-RA, as the particular clinical phase of RA, has already definitive pathological changes as subcutaneous nodules and bone erosion, in the presence of the influence of genetic factor. All those features indicate the significance of preventive treatment, and pre-RA should be treated as a separated disorder from RA for the unique CM pathogenesis and syndrome differentiation. The transform of pre-RA to RA onset does not accomplish in an action, the long-run affection of evils and hidden pathogen, which is made of evils, will turn to a vicious circle and accelerate the progression.

The preventative medication of moderate efficacy without harm for the human body is the top principle and reaches an agreement with the WM, which is aiming at the early intervention as possible to preventing bone destruction. No established prescription for pre-RA treatment for that pre-RA is heterogeneous and shows diverse clinical manifestations. The pathogenesis of pre-RA is complicated; damaged congenital qi and dystrophic acquired qi, hidden pathogen and exogenous evils all together contribute to the development of pre-RA and help make the vicious circle. While it is widely accepted that Pi, the foundation of acquired constitution, plays a significant regulatory role in the translation of pre-RA. Therefore, the treatment for pre-RA should be emphasized at the Pi meanwhile prevent the generation of dampness caused by the deficient Pi. Besides, the build-up of defensive qi should also be involved in the decision-making.

Symptomatic Treatment Based on Syndrome Differentiation

Pre-RA is characterized as the deficient Pi, the overabundance of dampness, and multilevel pain among skin, tendons, and joints. Emerging evidence revealing the role of microbiome give news ideas for WM that dysfunction inside the intestinal. However, such phenotype, according to the holistic view of CM, is caused by abnormal function of the Pi, which failed in controlling dampness. Under such condition, overabundant dampness would accumulate in the Pi and harm the small intestine, which is separating clear and excreting turbid, and conducting large intestine, Following the long-term losing of probiotics, by loose stool, intestine would lose the function of biological barrier. Ultimate damaged mucosal immunity may

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directly or indirectly promote the development of pre-RA. All discussed above describes the cause and effect of how Pi affects the distant microbiome.

The basic idea of treatment for pre-RA is to correct the dysfunction of the Pi by tonifying and transportation and transforming the dampness. According to the actual symptoms of cold and heat, tonifying can be divided as warm-tonifying and cool-nourishing. Moreover, transportation and transformation could also be accompanied by the medicine of resolving and draining dampness to expand the comprehensive ability of prescription.

Besides, relieving the acute symptoms of the sudden progression of pre-RA is critical, and heat-clearing drugs of immunosuppressive, *Tripterygium Wilfordli*, for instance, can be used. As a chronic disease, patients with pre-RA often have over-consumption of qi and blood, so that appropriate application of tonifying drugs can also show a good efficacy.

CM Treatment on Pre-RA and Novel Ideas for Therapy

Various CMs have been used for the treatment of pre-RA to prevent the progression or to alleviate the RA activity. Guzhi Shaoyao Zhimu Decoction (桂枝芍药知母汤, GSZD), firstly recorded in the *Synopsis of Prescriptions of the Golden Chamber* (Jin Gui Yao Lue) by ZHANG Zhong-jing, showed remarkable efficacy in the last 2,000 years. Moreover, a recent meta-analysis of 13 randomized controlled etrials (RCTs) demonstrated that GSZD has equal even superior effectiveness and safety in treating RA compared to non-steroidal anti-inflammatory drugs (NSAIDs) or DMARDs, while the only minimal adverse effect was detected in GSZD treatment.[22] As well related working mechanisms are investigated in the presence of emerging analytical approach such as bioinformatics.[23] Jiedu Tongluo Lishi Decoction (解毒通络利湿汤, JTLD), is also widely used in clinical and proven to function via suppressing the inflammatory responses.[24] And further research about the detailed compatibility of JTLD revealed that appropriate treatment according to the different stages of RA could obtain better outcomes.[25]

Various CM herbs, like *Paeoniae Radix Alba, Tripterygium Wilfordii* and *Sinomenii Caulis*, are widely used in treating RA for their outstanding capacity of anti-inflammatory and analgesia. The extract of *Tripterygium Wilfordii* is proven not inferior to DMARD treatment, and combined use of both *Tripterygium Wilfordii* and MTX shows better efficacy by significantly reducing the ESR.[26] Meta-analysis indicates the potential adjuvant role of total glucosides of paeony (TGP), from *Paeoniae Radix Alba*, for RA treatment while fewer adverse effects, hepatotoxicity especially, are the advantage of TGP treatment.[27] Also, Liu's work of systematic review of multiple RCTs indicates that sinomenine and related synthetic drugs has better clinical efficacy compared to DMARDs like MTX, with relatively fewer adverse events.[28] Although not all discussed above are focused on pre-RA, new ideas and novel therapy can be established based on numerous trials for CM herbs. However, more studies aiming to investigate the mechanisms should be carried out for uncovering how CM herb work without harming the human body.

Discussion and Expectation

CM and WM share the same idea of early control for pre-RA and can be complementary for each other in clinical practice. WM, with a long history of attention on pre-RA research, has already established a relatively applicable understanding for pre-RA. Also, serval feasible treatment showed good efficacy in clinical. However, all those treatments are based on RA treatment, and some are not ideally suitable for distinct pre-RA features.

Although there are few CM researches focusing on pre-RA, the idea of prevention before disease onset and controlling on the emerged disorder can help make strategy and ultimately reduce the rate of mortality and disability. WM treatment seeks for the way out by combining multiple DMARDs, while the adverse reaction and side effect remains the limitation for a better outcome. For some newly diagnosis pre-RA patients, short-term GC is the initiative therapy, which is hard to withdrawal. CM has moderate long-term efficacy and shows the remarkable capacity of helping to deal with the side effect and adverse reactions which WM brings. The comibined effect of integrated CM and WM is how CM reach its full potentials and WM could breakthrough its limitation like unwanted effects.

For better intervention of pre-RA, more active ingredients, extracted from CM, of distinctive function like immunoregulation, anti-inflammation and regulations upon microbiome, should be used, in company with DMARDs. Also, novel tools, such as

Traditional Chinese Medicine Integrated Database (TCMID, http://www.megabionet. org/tcmid/),[29] systems pharmacology and other databases provide great assistance for the research on mechanisms how CM herbs and active ingredients work.

REFERENCES

1. Gerlag DM, Raza K, Van Baarsen LGM, Brouwer E, Buckley CD, Burmester GR, et al. EULAR recommendations for terminology and research in individuals at risk of rheumatoid arthritis: Report from the Study Group for Risk Factors for Rheumatoid Arthritis. Ann Rheum Dis 2012;71:638-641.
2. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569-2581.
3. Bizzaro N, Bartoloni E, Morozzi G, Manganelli S, Riccieri V, Sabatini P, et al. Anti-cyclic citrullinated peptide antibody titer predicts time to rheumatoid arthritis onset in patients with undifferentiated arthritis: results from a 2-year prospective study. Arthritis Res Ther. 2013;15(R16):1-9.
4. Rakieh C, L Nam J, Hunt L, Hensor EMA, Das S, Bissell LA, et al. Predicting the development of clinical arthritis in anti-CCP positive individuals with non-specific musculoskeletal symptoms: a prospective observational cohort study. Ann Rheum Dis 2015;74:1659-1666.
5. Macías-Segura N, Castañeda-Delgado JE, Bastian Y, Santiago-Algarra D, Castillo-Ortiz JD, Alemán-Navarro AL, et al. Transcriptional signature associated with early rheumatoid arthritis and healthy individuals at high risk to develop the disease. PLoS One 2018;13:1-19.
6. Okamoto Y, Parish M, Kongpachith S, Lauren J, Kinslow J. IgA Plasmablasts are elevated in subjects at risk for future rheumatoid arthritis. Arthritis Rheumatol 2016;68:2372-2383.
7. Manley G, Conn JR, Catchpoole EM, Runnegar N, Mapp SJ, Markey KA. Peptidylarginine deiminase from *Porphyromonas gingivalis* citrullinates human fibrinogen and α-enolase: implications for autoimmunity in rheumatoid arthritis. PLoS One 2017;32:736-740.
8. Alpizar-Rodriguez D, Lesker TR, Gronow A, Gilbert B, Raemy E, Lamacchia C, et al. *Prevotella copri* in individuals at risk for rheumatoid arthritis. Ann Rheum Dis 2019;78:590-593.
9. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960-977.
10. Machold KP, Landewé R, Smolen JS, Stamm TA, Van Der Heijde DM, Verpoort KN, et al. The Stop Arthritis Very Early (SAVE) trial, an international multicentre, randomised, double-blind, placebo-controlled trial on glucocorticoids in very early arthritis. Ann Rheum Dis 2010;69:495-502.
11. Eriko KT, Takashi S, Takuro N, Satoru T, Maiko Y, Akane W, et al. Early therapeutic intervention with methotrexate prevents the development of rheumatoid arthritis in patients with recent-onset undifferentiated arthritis: a prospective cohort study. Mod Rheumatol 2015;25:831-836.
12. Van Aken J, Heimans L, Gillet-Van Dongen H, Visser K, Karel Ronday H, Speyer I, et al. Five-year outcomes of probable rheumatoid arthritis treated with methotrexate or placebo during the first year (the PROMPT study). Ann Rheum Dis 2014;73:396-400.
13. Wevers-De Boer K, Visser K, Heimans L, Ronday HK, Molenaar E, Groenendael JHLM, et al. Extended report: Remission induction therapy with methotrexate and prednisone in patients with early rheumatoid and undifferentiated arthritis (the IMPROVED study). Ann Rheum Dis 2012;71:1472-1477.
14. Weinblatt ME, McInnes IB, Kremer JM, Miranda P, Vencovsky J, Guo X, et al. A randomized phase Ⅱb study of mavrilimumab and golimumab in rheumatoid arthritis. Arthritis Rheumatol 2018;70:49-59.
15. Luo Q, Jiangqing Y, Lulu Z, Zhongqin L, Zhen D, Xue L, et al. Elevated expression of PD-1 on T cells correlates with disease activity in rheumatoid arthritis. Mol Med Rep 2018;17:3297-3305.
16. Gerlag DM, Safy M, Maijer KI, Tang MW, Tas SW, Starmans-Kool MJF, et al. Effects of B-cell directed therapy on the preclinical stage of rheumatoid arthritis: The PRAIRI study. Ann Rheum Dis 2019;78:179-185.
17. Emery P, Burmester GR, Bykerk VP, Combe BG, Furst DE, Barré E, et al. Evaluating drug-free remission with abatacept in early rheumatoid arthritis: results from the phase 3b, multicentre, randomised, active-controlled AVERT study of 24 months, with a 12-month, double-blind treatment period. Ann Rheum Dis 2015;74:19-26.
18. Smolen JS, Wollenhaupt J, Gomez-Reino JJ, Grassi W, Gaillez C, Poncet C, et al. Attainment and characteristics of clinical remission according to the new ACR-EULAR criteria in abatacept-treated patients with early rheumatoid arthritis: new analyses from the Abatacept study to Gauge Remission and joint damage progression in methotrexate. Arthritis Res Ther 2015;17:1-12.
19. Heimans L, Wevers-de Boer KVC, Visser K, Goekoop RJ, Van Oosterhout M, Harbers JB, et al. A two-step treatment strategy trial in patients with early arthritis aimed at achieving remission: the improved study. Ann Rheum Dis 2014;73:1356-1361.
20. Saleem B, Mackie S, Quinn M, Nizam S, Hensor E, Jarrett S, et al. Does the use of tumour necrosis factor antagonist therapy in poor prognosis, undifferentiated arthritis prevent progression to rheumatoid arthritis? Ann Rheum Dis 2008;67:1178-1180.
21. Xie ZJ, Wen CP, Wang XC, Cao LY, Fan YS. The clinical research of the Jiedu Tongluo Qushi principle on treating the rheumatoid arthritis in active stage. Chin J Basic Med Tradit Chin Med (Chin) 2008;14:865-867.
22. Hunt L, Emery P. Defining populations at risk of rheumatoid arthritis: the first steps to prevention. Nat Rev Rheumatol 2014;10:521-530.
23. Daily JW, Zhang T, Cao S, Park S. Efficacy and safety of Guizhi-Shaoyao-Zhimu Decoction for treating rheumatoid arthritis: a systematic review and meta-analysis of randomized clinical trials. J Altern Complement Med 2017;10:756-770.
24. Huang L, Lv Q, Xie D, Shi T, Wen C. Deciphering the potential pharmaceutical mechanism of Chinese traditional medicine (Gui-Zhi-Shao-Yao-Zhi-Mu) on rheumatoid arthritis. Sci Rep 2016;6:22602.
25. Wen CP, Jin CY, Xu ZL, Cao LY. Clinical observation of Jiedu Tongluo Lishi Decoction on treating reactive rheumatoid arthritis. China J Chin Mater Med (Chin) 2007;13;1306-1310.
26. Lv QW, Zhang W, Shi Q, Zheng WJ, Li X, Chen H, et al. Comparison of *Tripterygium wilfordii* Hook F with methotrexate in the treatment of active rheumatoid arthritis (TRIFRA): a randomised, controlled clinical trial. Ann Rheum Dis 2015; 74:1078-1086.
27. Luo J, Jin DE, Yang GY, Zhang YZ, Wang JM, Kong WP, et al. Total glucosides of paeony for rheumatoid arthritis: a systematic review of randomized controlled trials. Complement Ther Med 2017;34:46-56.
28. Liu WW, Qian X, Ji W, Lu Y, Wei G, Wang Y. Effects and safety of sinomenine in treatment of rheumatoid arthritis contrast to methotrexate: a systematic review and Meta-analysis. J Tradit Chin Med 2016;36:564-577.
29. Huang L, Xie D, Yu Y, Liu H, Shi Y, Shi T. TCMID 2.0: a comprehensive resource for TCM. Nucleic Acids Res 2018;46:D1117-D1120.

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