Anti-cyclic citrullinated peptide antibody predicts the development of rheumatoid arthritis in patients with undifferentiated arthritis

Chun Li[1], Yan Zhang[2], Hui Song[2], Jie Gao[3], Dong-Bao Zhao[3], Qi Zhu[4], Dong-Yi He[4], Li Wang[5], Xiang-Pei Li[5], Xu-Dong Liu[6], Wei-Guo Xiao[6], Xin-Yu Wu[7], Hua-Xiang Wu[7], Wei Tu[8], Shao-Xian Hu[8], Xin Wang[9], Zhi-Jun Li[9], Zhi-Min Lu[10], Zhan-Yun Da[10], Bo Liang[11], Xiao-Min Liu[11], Jin-Wei Zhao[12], Ling Li[12], Feng Han[13], Wu-Fang Qi[13], Wei Wei[14], Xu Ma[15], Zhen-Bin Li[15], Gui-Min Zheng[16], Feng-Xiao Zhang[16], Yi Li[17], You-Lian Wang[17], Guang-Hui Ling[18], Jin-Wei Chen[18], Xiao-Qiang Hou[19], Jing Zhang[20], Qing-Ping Chen[20], Chang-Lian Liu[21], Yan Zhang[22], Jia-Shun Zeng[22], Qing-Hua Zou[23], Yong-Fei Fang[23], Yin Su[1], Zhan-Guo Li[1]

[1]Department of Rheumatology and Immunology, Peking University People's Hospital, Beijing 100044, China;

[2]Department of Rheumatology and Immunology, Beijing Jishuitan Hospital, Beijing 100035, China;

[3]Department of Rheumatology and Immunology, Changhai Hospital, Shanghai 200433, China;

[4]Department of Rheumatology, Shanghai Guanghua Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai 200052, China;

[5]Department of Rheumatology and Immunology, Anhui Provincial Hospital, Hefei, Anhui 230001, China;

[6]Department of Rheumatology and Immunology, The First Hospital of China Medical University, Shenyang, Liaoning 110001, China;

[7]Department of Rheumatology, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang 310009, China;

[8]Department of Rheumatology and Immunology, Tongji Hospital, Wuhan, Hubei 430030, China;

[9]Department of Rheumatology, The First Affiliated Hospital of Bengbu Medical College, Bengbu, Anhui 233004, China;

[10]Department of Rheumatology and Immunology, Affiliated Hospital of Nantong University, Nantong, Jiangsu 226001, China;

[11]Department of Rheumatology and Immunology, The Hospital of Shunyi District Beijing, Beijing 101300, China;

[12]Department of Infection and Immunology, Tianjin Union Medical Center, Tianjin 300121, China;

[13]Department of Rheumatology and Immunology, Tianjin First Central Hospital, Tianjin 300192, China;

[14]Department of Rheumatology and Immunology, Tianjin Medical University General Hospital, Tianjin 300052, China;

[15]Department of Rheumatology and Immunology, Peace Hospital, Shijiazhuang, Hebei 050000, China;

[16]Department of Rheumatology and Immunology, Hebei General Hospital, Shijiazhuang, Hebei 050051, China;

[17]Department of Rheumatology, Jiangxi Provincial People's Hospital, Nanchang, Jiangxi 330006, China;

[18]Division of Rheumatology and Immunology, The Second Xiangya Hospital of Central South University, Changsha, Hunan 410011, China;

[19]Department of Rheumatology and Immunology, The First College of Clinical Medical Science of China Three Gorges University & Yichang Central People's Hospital, Yichang, Hubei 443003, China;

[20]Department of Rheumatology and Immunology I Wald, Xi'an No. 5 Hospital, Xi'an, Shaanxi 710082, China;

[21]Department of Rheumatology and Immunology V Wald, Xi'an No. 5 Hospital, Xi'an, Shaanxi 710082, China;

[22]Department of Nephrology and Rheumatology, The Affiliated Hospital of Guizhou Medical University, Guiyang, Guizhou 550004, China;

[23]Department of Rheumatology, The First Hospital Affiliated to AMU (Southwest Hospital), Chongqing 400038, China.

Abstract

Background: Clinical outcomes of undifferentiated arthritis (UA) are diverse, and only 40% of patients with UA develop rheumatoid arthritis (RA) after 3 years. Discovering predictive markers at disease onset for further intervention is critical. Therefore, our objective was to analyze the clinical outcomes of UA and ascertain the predictors for RA development.

Methods: We performed a prospective, multi-center study from January 2013 to October 2016 among Chinese patients diagnosed with UA in 22 tertiary-care hospitals. Clinical and serological parameters were obtained at recruitment. Follow-up was undertaken in all patients every 12 weeks for 2 years. Predictive factors of disease progression were identified using multivariate Cox proportional hazards regression.

Results: A total of 234 patients were recruited in this study, and 17 (7.3%) patients failed to follow up during the study. Among the 217 patients who completed the study, 83 (38.2%) patients went into remission. UA patients who developed RA had a higher rheumatoid factor (RF)-positivity (42.9% *vs.* 16.8%, $\chi^2 = 8.228$, $P = 0.008$), anti-cyclic citrullinated peptide (CCP) antibody-

positivity (66.7% *vs.* 10.7%, $\chi^2 = 43.897$, $P < 0.001$), and double-positivity rate of RF and anti-CCP antibody (38.1% *vs.* 4.1%, $\chi^2 = 32.131$, $P < 0.001$) than those who did not. Anti-CCP antibody but not RF was an independent predictor for RA development (hazard ratio 18.017, 95% confidence interval: 5.803–55.938; $P < 0.001$).

Conclusion: As an independent predictor of RA, anti-CCP antibody should be tested at disease onset in all patients with UA.

Keywords: Anti-cyclic citrullinated peptide antibody; Arthritis, Rheumatoid; Rheumatoid factor; Undifferentiated arthritis

Introduction

Undifferentiated arthritis (UA) is an common type of inflammatory arthritis that cannot be diagnosed as a specific rheumatic disease.[1] Nearly half of UA patients achieve remission without treatment,[2] and less than half of them eventually develop rheumatoid arthritis (RA). Patients with a high likelihood of disease progression to RA can benefit from early intervention, whereas those with a lower likelihood of progression could also benefit from avoiding unnecessary treatment.

Several prediction models exist that evaluate people at a high risk of developing RA. The Leiden score is used widely and has been validated in many studies to have high sensitivity and specificity.[3,4] However, its utility is challenging.[5] It assesses nine parameters, on a scale of 0.5 to 2.0 points; therefore, it is not very feasible for daily clinical use. Thus, discovering baseline markers that can predict UA progression is very important.

Previous epidemiological studies on UA have reported that the incidence varies from 41 to 149 per 100,000 adults.[6-8] There are nearly 1 million UA patients in China, whereas there are only 6000 rheumatologists. It is, thus, of great value to determine reliable and feasible baseline parameters that can easily predict disease development.

Accurate prediction of RA among UA patients utilizing simple clinically relevant parameters is a key clinical advancement. Clinically actionable biomarkers for RA among UA patients remain debatable and there is yet a multi-center study to investigate novel predictors of RA among Chinese UA patients. This study aimed to identify clinically significant predictor for RA among UA patients and evaluated their respective clinical outcomes.

Methods

Ethical approval

This study protocol was approved by the Ethics Committee of Peking University People's Hospital (Beijing, China; No. FWA00001384). All individuals provided written informed consent for participation before enrollment.

Study design

We performed an observational, prospective, multi-center study. All patients were recruited between January 2013 and October 2016 to analyze the progression of UA and to determine the predictors of RA development in UA patients.

Patients

The inclusion criteria were patients aged >18 years with persistent arthritis ≥6 weeks and ≤24 weeks. None of the patients received treatment with glucocorticoids, disease-modifying anti-rheumatic drugs (DMARDs), or biologic agents.

The exclusion criteria were patients who were pregnant; those with evidence of uncontrolled hypertension, abnormal heart, liver, or renal function (≥1.5-times of the upper limit); and patients suffering from alcohol addiction.

Patients with UA were recruited from 22 tertiary-care hospitals in China [Supplementary Table 1, http://links.lww.com/CM9/A135]. All patients were evaluated by a rheumatologist upon study inclusion and were followed up every 12 weeks. Follow-up was stopped if patients developed a specific connective tissue disease (such as RA, spondyloarthritis [SpA], and reactive arthritis [ReA], etc) or if 2 years of follow-up had been completed.

The classification criteria for psoriatic arthritis (PsA) was used for the diagnosis of PsA[9]; the diagnosis of RA was made according to the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism classification criteria[10]; the ACR criteria of the hand,[11] hip,[12] and knee[13] was used for the diagnosis of osteoarthritis (OA); the 2012 Systemic Lupus International Collaborating Clinics criteria was used for the diagnosis of systemic lupus erythematosus (SLE)[14]; Bohan and Peter criteria was used for the diagnosis of dermatomyositis[15]; and the Spondyloarthritis International Society criteria was used to assess SpA.[16] "Rhupus syndrome" was defined as patients who could be diagnosed both RA and SLE. Patients with clinical manifestation and exclusion of other diseases were defined as having ReA.[17] The definition of "remission" was that patients had no clinical manifestations of arthritis (soft-tissue swelling) and did not receive treatment for 3 months.

Demographic characteristics, clinical manifestations, and laboratory parameters were entered into the database by well-trained investigators in each center. We extracted the data from the electronic system for analyses.

Statistical analysis

The age of the patients followed a normal distribution and is presented as the mean ± standard deviation. The diease duration, the numbers of tender joints and swollen joints showed skewed distributions and are presented as medians and interquartile ranges. The remaining data, which are normally distributed, are presented as absolute numbers with percentages of the total.

The Student's *t* test was used to compare the age at arthritis onset between the two groups. The Mann-Whitney *U* test was used to compare the disease duration, the numbers of

tender joints and swollen joints between the groups. A multivariate model, using Cox proportional hazards regression, was used to identify independent predictors of RA development. Statistical significance was set as $P < 0.05$. SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA) was used for all analyses.

Table 1: Baseline characteristics of 217 patients with undifferentiated arthritis.

Characteristics	Values
Age (years), mean ± SD	44.2 ± 11.7
Female, n (%)	162 (74.7)
Underlying disease, n (%)	
Thyrotoxicosis	9 (4.1)
Diabetes mellitus	3 (1.4)
Hypertension	15 (6.9)
Family history of RA, n (%)	15 (6.9)
Risk factors, n (%)	
Smoking	15 (6.9)
Periodontitis	11 (5.1)
Infection	19 (8.8)
TJC, median (IQR)	2 (1–4)
SJC, median (IQR)	1 (0–2)
Morning stiffness, n (%)	129 (59.4)
CRP-positive, n (%)	32 (14.7)
ESR increased, n (%)	51 (23.5)
RF-positive, n (%)	42 (19.4)
Anti-CCP antibody-positive, n (%)	35 (16.1)
RF and anti-CCP antibody double-positivity, n (%)	16 (7.4)

SD: Standard deviation; RA: Rheumatoid arthritis; TJC: Tender-joint count; IQR: Interquartile range; SJC: Swollen-joint count; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; RF: Rheumatoid factor; CCP: Cyclic citrullinated peptide.

Results

Baseline characteristics of patients with UA

A total number of 234 patients were recruited in our study. Among these patients, 17 (7.3%) failed to follow-up during the study period, and 217 (92.7%) participants completed the study. Table 1 showed the baseline characteristics of the UA patients.

Among these patients, 59.4% had morning stiffness. The median number of tender and swollen joints were 2 (1–4) and 1 (0–2), respectively. The most implicated joint was the proximal interphalangeal, followed by wrist. The positivity rates for anti-citrullinated peptide (CCP) antibody and RF were 16.1% and 19.4%, respectively.

Hypertension (6.9%) was the most common underlying disease. Fifteen (6.9%) patients had a family history of RA. Tobacco smoking and periodontitis were documented in 15 (6.9%) and 11 (5.1%) patients, respectively. Furthermore, 19 (8.8%) patients had a history of infection.

Diagnosis after follow-up

Most patients had persistent UA and 83 (38.2%) patients went into remission after 2-years of follow-up. Among the latter, 50 (60.2%) were treated with total glucosides of paeony, 30 (36.1%) patients underwent symptomatic treatment, and 2 (2.4%) patients went into remission without treatment. Twenty (9.2%), 10 (4.6%), and 2 (0.9%) patients developed RA, OA, and PsA, respectively. SLE, dermatomyositis, Rhupus syndrome, and ReA developed in 1 (0.5%) patient each [Figure 1].

Predictive factors of RA

UA patients who developed RA had a significantly higher prevalence of positivity for anti-CCP antibody (66.7% vs.

Table 2: Predictive factors for UA developing into RA.

Parameters	Developed RA (including Rhupus syndrome) ($n = 21$)	Did not develop RA ($n = 196$)	Statistics	P
Females, n (%)	17 (81.0)	145 (74.0)	0.487[*]	0.485
Age at arthritis onset (years), mean ± SD	40.5 ± 15.7	44.6 ± 11.2	−1.527[†]	0.128
Disease duration (months), median (IQR)	3.0 (2.0–4.5)	3.0 (2.0–5.0)	−0.108[†]	0.914
Family history, n (%)	3 (14.3)	12 (6.1)	1.964[*]	0.166
Periodontitis, n (%)	2 (9.5)	9 (4.6)	0.959[*]	0.289
Smoking, n (%)	1 (4.8)	14 (7.1)	0.167[*]	1.000
Morning stiffness, n (%)	16 (76.2)	113 (57.7)	2.704[*]	1.000
Infection, n (%)	4 (19.0)	15 (7.7)	3.083[*]	0.095
SJC, median (IQR)	2 (1–4)	2 (1–4)	−0.515[‡]	0.607
TJC, median (IQR)	1 (0–2)	1 (0–2)	−1.917[‡]	0.055
RF-positive, n (%)	9 (42.9)	33 (16.8)	8.228[*]	0.008
Anti-CCP antibody positive, n (%)	14 (66.7)	21 (10.7)	43.897[*]	<0.001
RF and anti-CCP antibody double-positivity, n (%)	8 (38.1)	8 (4.1)	32.131[*]	<0.001
ESR increased, n (%)	5 (23.8)	46 (23.5)	0.001[*]	1.000
CRP-positive, n (%)	4 (19.0)	28 (14.3)	0.324[*]	0.524

[*] χ^2 value; [†] t value; [‡] Z value. UA: Undifferentiated arthritis; RA: Rheumatoid arthritis; SD: Standard deviation; IQR: Interquartile range; SJC: Swollen joint count; TJC: Tender joint count; RF: Rheumatoid factor; CCP: Cyclic citrullinated peptide; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein.
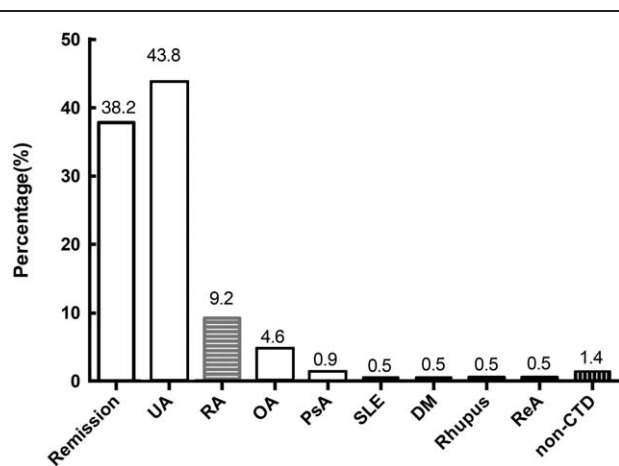
Figure 1: Clinical diagnosis of 217 patients with UA after 2-year follow-up. CTD: Connective tissue disease; DM: Dermatomyositis; OA: Osteoarthritis; PsA: Psoriatic arthritis; RA: Rheumatoid arthritis; ReA: Reactive arthritis; Rhupus: Rheumatoid arthritis-systemic lupus erythematosus syndrome; SLE: Systemic lupus erythematosus; UA: Undifferentiated arthritis.

10.7%, $\chi^2 = 43.897$, $P < 0.001$), RF (42.9% *vs.* 16.8%, $\chi^2 = 8.228$, $P = 0.008$), and a double-positivity rate of anti-CCP antibody and RF (38.1% *vs.* 4.1%, $\chi^2 = 32.131$, $P < 0.001$) [Table 2]. Anti-CCP antibody (hazard ratio 18.017, 95% confidence interval: 5.803–55.938, $P < 0.001$) but not RF was an independent predictive factor for RA progression.

Discussion

This study showed that nearly half of the patients with UA achieved spontaneous remission without DMARDs, and only a few UA patients developed RA. UA can also develop into various rheumatic diseases. Instead of using a complicated algorithm, anti-CCP antibody can be used as a good and accurate predictor for RA development.

RF positivity was a risk factor of RA development according to Jansen *et al*.[18] However, RF was not related to RA development in another study.[19] RF is a traditional serologic marker for inflammatory arthritis. The sensitivity of using RF positivity is the same as that using anti-CCP antibody positivity for RA diagnosis, but the specificity of using RF positivity is lower for RA diagnosis. Whether we should "abandon" the use of RF as a marker remains controversial.[20] Conversely, the positivity of RF and anti-CCP antibody positivity are independent observed in UA.[21,22] This study showed that RF was not a predictor of RA. However, it is necessary to test for RF in clinics to increase the sensitivity of UA diagnosis.

The importance of anti-CCP antibody is also controversial. Studies have shown that a high titer of anti-CCP antibody is a risk factor for radiographic progression and worsening disease activity in RA patients.[23-25] However, the titer of anti-CCP antibody is not related to the outcome in patients with early arthritis.[26] In the prediction model using the Leiden score, the titer of anti-CCP antibody is a key item

for diagnosing UA. In clinical practice, it is easy to test for anti-CCP antibody. In patients with UA or arthralgia, anti-CCP antibody could predict RA development and is the strongest predictor for poor outcome.[3,27,28] Thus, all patients with UA should have their anti-CCP antibody tested to predict the development of RA.

Patients with RF and anti-CCP antibody double-positivity are likely to show to radiographic progression.[29] Although the double-positivity rate was significantly higher in patients who developed RA, but it was not an independent predictor for UA development.

Smoking is related to disease activity and RF titer in RA. Harrison *et al*[30] showed that in patients with inflammatory polyarthritis, smokers had a higher RF titer. The prevalence of smoking in our group was 6.9%, and we did not observe this association. The results might have been because the smoking prevalence in our study cohort was relatively low. Periodontitis is clinically associated with RA.[31]*Porpyromonas gingivalis* can citrullinate antigens using the peptidyl arginine deiminase enzyme. However, in patients with arthralgia, having antibodies against *P. gingivalis* is not a predictor for anti-CCP antibody seropositivity or RA development. There was no correlation between periodontitis and RA development.

There were two major limitations in our study. First, the number of participants was relatively small. Second, we did not include the early treatment of DMARDs in UA patients. Studies have shown that early methotrexate treatment could prevent UA development.[32,33] Initial triple-DMARD therapy can decrease disease activity and reduce the use of biologics by 50% after 3 months.[34] Biological DMARDs can slow the progression of UA, and abatacept can suppress the radiological progression.[35-37]

In conclusion, only a small proportion of UA patients progressed to RA. As a predictor for RA, anti-CCP antibody should be tested in all patients with early arthritis. UA patients who are anti-CCP antibody positive should be treated with DMARDs to prevent the onset of RA.

Conflicts of interest

None.

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