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The role of circulating miR-146a in patients with rheumatoid arthritis treated by *Tripterygium wilfordii* Hook F

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Abstract

Rheumatoid arthritis (RA) is polygenic autoimmune disease with unclear etiology. MicroRNAs (miRNAs) play a critical role in the pathogenesis of RA. The objective of this study was to evaluate the role of miR-146a in patients with RA receiving *Tripterygium wilfordii* Hook F (TwHF) treatment.

In total, 69 patients with RA and 69 healthy controls (HC) were included in the study, and patients with RA received TwHF treatment for 24 weeks. Blood samples were collected from RA patients and HC, and peripheral blood mononuclear cells (PBMCs) were isolated. Expression of miR-146a was analyzed in RA patients (baseline, 12 weeks and 24 weeks) and HC.

Circulating miR-146a expression was markedly increased in patients with RA compared with healthy controls ($P < .001$), *ROC* analysis of miR-146a for diagnosis for RA showed that the *AUC* was 0.908 (95% CI: 0.862–0.955) with a sensitivity of 87.0% and a specificity of 82.6% at best cutoff. And miR-146a expression was positively associated with the DAS28 score and CRP level ($P = .002$ and $P = .019$). Moreover, miR-146a expression was markedly reduced after TwHF therapy ($P < .001$), and baseline miR-146a level was observed to present an increased tendency in responders compared with non-responders at 24 weeks ($P = .066$).

Our study presented that circulating miR-146a level was correlated with risk and disease activity of RA patients by TwHF treatment, which could strikingly decrease expression of miR-146a in RA patients, and miR-146a may have a value in predicting clinical response of TwHF treatment. It indicates that circulating miR-146a plays a prominent role in RA patients treated by TwHF.

Abbreviations: cDNA = complementary DNA, CI = confidence interval, CRP = C-reactive protein, CT = threshold cycle, ESR = erythrocyte sedimentation rate, HAQ-DI = health assessment questionnaire-damage index, HC = healthy controls, miRNAs = MicroRNAs, PBMC = peripheral blood mononuclear cells, PBMCs = peripheral blood mononuclear cells, PBS = phosphatebuffered saline, PCR = polymerase chain reaction, PGA = patients global assessment, RA = rheumatoid arthritis, ROC = receiver operating characteristic, TwHF = *Tripterygium wilfordii* Hook F.

Keywords: circulating, disease activity, miR-146a, rheumatoid arthritis, *Tripterygium wilfordii* Hook F

1. Introduction

Rheumatoid arthritis (RA) is a chronically inflammatory autoimmune disease, characterized by of the damage of articular cartilage and bone.[1,2] The pathogenesis of RA is still not very clear. Substantial data have demonstrated that RA is the result of interaction among genetics, abnormal immune responses, and environmental triggers.[3,4] Pathological characteristics are inflammation, synovium hyperplasia, and cartilage damage, which result in the irreversible joint damage with severe functional deterioration and high mortality, the typical clinical features of RA.[5] Therefore, RA creates an increasing health concern and significant social and economical load, which states that acute diagnosis and reliable treatment for RA are a pressing need.[5]

MicroRNAs (miRNAs) are small, non-coding RNAs, which is reported to mediate mRNA cleavage, translational repression or mRNA destabilization. miRNAs are involved the process of cellular proliferation, apoptosis, and differentiation, and dysregulation of miRNAs has been observed in several autoimmune disease.[6] MiRNAs presents in the peripheral blood and body fluids as complex with proteins in a very high stability, which makes it possible that miRNAs can be used as good candidates for the diagnosis, evaluation, and prognosis of some disease.[7] Previous studies have shown that level of miR-16 in synovial fluid from patients with RA was markedly low compared with that in plasma, and miR-16 expression is correlated disease activity in RA.[8] Moreover, miR-21 expression is found to be decreased in RA and involved the modulation of Th17 and Treg imbalance in RA.[9,10]

MiR-146a is one of miRNAs that participate in the pathogenesis of RA. MiR-146a is found to be expressed in T cells, B cells, macrpphages, and monocytes.[11–13] Data have shown that miR-146a inhibits Th1-mediated cell response and promotes activity of Treg cells in RA, which are the main mechanisms of RA.[14] Expression of miR-146a is observed to be

Editor: Samantha Martin.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2017) 96:20(e6775)

Received: 2 September 2016 / Received in final form: 12 March 2017 / Accepted: 7 April 2017

http://dx.doi.org/10.1097/MD.0000000000006775

correlated with CRP, ESR, and plasm TNF concentration.[15]-*Tripterygium wilfordii* Hook F (TwHF), a traditional Chinese medicine, has been used for several decades to treat RA, and the effectiveness of TwHF has been proved well.[16,17] However, the roles of circulating miR-146a in TwHF treatment in patients with RA are still obscure.

In our current study, peripheral blood was collected to examine miR-146a expression and aimed to investigate the role of circulating miR-146a in the treatment of TwHF in patients with RA.

2. Materials and methods

2.1. Participants

In total, 69 subjects (15 males and 54 females, aged 51 ± 16 years), who were diagnosed as RA with moderate to severe activity in Dongzhimen Hospital of Beijing University of Chinese Medicine from April 2014 to January 2016, were enrolled in this study. Patients with RA received TwHF treatment (20 mg, tid) for 24 weeks, and the previous treatment remained the same during entire observation period. The inclusion criteria were as follows subjects aged 18–65 years; diagnosed with RA according to the 2010 ACR/EULAR classification criteria; simultaneously meeting the following A, B, and one of C, D, E: A, ≥ 4 swelling joints, B, 6 tender joints; C, morning stiffness duration ≥ 45 minutes; D, erythrocyte sedimentation rate (ESR) > 28 mm/h, E, C-reactive protein (CRP) > 10 mg/L; with lack of efficacy by previous treatment of methotrexate (MTX) or leflunomide (LEF) alone. Patients were excluded if they had a history of severe deformation of joint, receiving TwHF, biological agent, or combination of DMARDs treatment within 3 months before included in the study. Pregnant or lactating women were also excluded. In addition, 69 healthy donors (20 males and 49 females, aged 54 ± 19 years) were also included in this study as controls. The study was approved by the Institutional Review Board for Clinical Research of Dongzhimen Hospital of Beijing University of Chinese Medicine. Written informed consents were also obtained from all subjects before initiating the study protocol.

2.2. Evaluation of the disease

ESR, CRP, disease activity score in 28 joints (DAS28), patients global assessment (PGA), and health assessment questionnaire-damage index (HAQ-DI) were examined in patients with RA at each visits (0 week, 12 weeks, and 24 weeks). When the decreased degree of DAS28 was above 1.2, the treatment was considered as respond according to EULAR response criteria.

2.3. Isolation of PBMCs and RNA

Blood samples (10 mL) were collected from RA patients at each visit (baseline, 12 weeks and 24 weeks) and healthy controls in EDTA plasma tubes. Peripheral blood mononuclear cells (PBMC) were isolated by standard Ficoll density-gradient centrifugation, and washed twice in sterile phosphatebuffered saline (PBS). Total RNA was isolated from PBMCs using the miRNA Isolation kit (Ambion, Austin, TX) according to manufacturer's protocol, and then reversedly transcribed to complementary DNA (cDNA).

2.4. Real-time PCR analysis

For the examination of miR-146a, the real-time PCR assay was performed using a TaqMan PCR kit according to the manufacturer's instructions (95°C for 5 minutes, followed by 40 cycles of 95°C for 15 seconds and 60°C for 60 seconds). Relative expression of miR-146a was calculated based on the threshold cycle (CT) and was normalized to U6. Data were analyzed by the $2^{-\Delta Ct\Delta Ct}$ method. The Primer of miR-146a and U6 were as follows: miR-146a, forward: ACACTCCAGCTGGGTGAGAACTGAATTCCATG, reverse: TGTCGTGGAGTCGGCAATTC; U6, forward: CTCGCTTCG GCAGCACA, reverse: AACGCTTCACGAATTTGCGT.

Table 1

Characteristics of patients with rheumatoid arthritis (RA) at baseline and health controls.

Characteristics	RA patients (n = 69)	Health controls (n = 69)	*P*
Age, y	51 ± 16	54 ± 19	.331
Female, %	54 (78%)	49 (70%)	.328
Disease duration, mo	98 (65–143)	–	–
ESR, mm/h	39.1 (31.6–47.4)	11.6 (8.7–13.9)	<.001
CRP, mg/L	24.5 (17.8–34.9)	5.6 (4.3–6.5)	<.001
DAS28	5.9 ± 2.1	–	–
PGA Score, 0–100 mm	63 ± 27	–	–
HAQ-DI	1.8 ± 0.7	–	–
MTX	30 (43%)	–	–
LEF	39 (57%)	–	–

Data are presented as mean values ± SD, median and 25th–75th or counts (percentage). A *P* value < .05 was considered statistically significant. Significance of the comparison was determined by the Student *t* test, the Mann–Whitney test, and the χ^2 test.
CRP = C-reactive protein, DAS28 = disease activity score in 28 joints, ESR = erythrocyte sedimentation rate, HAQ-DI = health assessment questionnaire-damage index, LEF = leflunomide, MTX = methotrexate, PGA = patients global assessment.

2.5. Statistical analysis

Statistical analysis was performed using SPSS V.20.0 (SPSS, Chicago, Illinois). Data are presented as mean values ± SD, median and 25th–75th or counts (percentage). Significance of the comparison was determined by the Student *t* test, the paired *t* test, the χ^2 test, Wilcoxon rank sum test, or the Wilcoxon signed-rank sum test. Significance of the correlations was determined by the Spearman test. The susceptibility and sensitivity of miR-146a for diagnosis of RA and baseline miR-146a expression for clinical response at 24 weeks were determined using the area under the receiver operating characteristic (*ROC*) curve. A *P*-value < .05 was considered statistically significant.

3. Results

3.1. Characteristics of patients with RA at baseline and health controls

The baseline characteristics of all the subjects included in this study are listed in Table 1. No significant difference was observed in age and gender between RA patients and healthy controls. The averaged levels of ESR and CRP in RA patients were 39.1 (31.6–47.4) mm/h and 24.5 (17.8–34.9) mg/L. The mean DAS28 and PGA were 5.9 ± 2.1 and 63 ± 27 mm, respectively. Among 69 RA patients, 30 patients meanwhile received MTX treatment, and 39 received LEF treatment at the same time.

3.2. Expression of miR-146a was extremely increased in patients with RA, and correlated with disease activity

To determine the role of miR-146a in RA, real-time PCR analysis was performed to examine miR-146a expression in PBMCs from patients with RA. Interestingly, the level of miR-146a was observed to be markedly increased in PBMCs from patients with RA compared with healthy controls when matched with age and

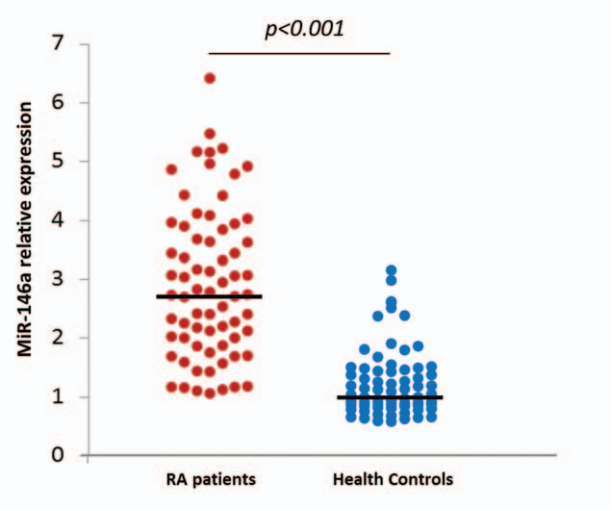

Figure 1. The expression of miR-146a in rheumatoid arthritis (RA) patients and healthy controls. RA = rheumatoid arthritis.

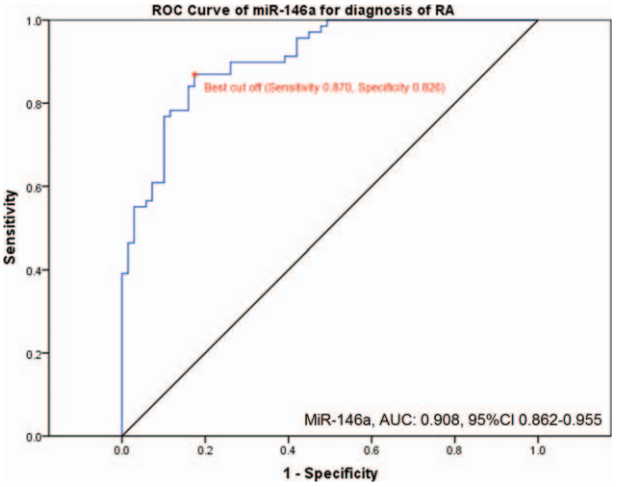

Figure 2. ROC curve for miR-146a for diagnosis of RA. ROC = receiver operating characteristic, RA = rheumatoid arthritis.

gender (2.754 (1.940–3.887) vs. 1.024 (0.820–1.447), $P < .001$, Fig. 1). To further investigate whether expression of miR-146a could be used a potential diagnosis biomarker of RA, *ROC* analysis was performed. We found that the *AUC* was 0.908 for miRNA-146a (95% CI: 0.862–0.955), with a sensitivity of 87.0% and specificity of 82.6% at best cutoff (Fig. 2), which indicates that the miR-146a level was a strong diagnosis biomarker of RA. Moreover, miR-146a expression was correlated with DAS28 ($P = .002$) and CRP ($P = .019$) (Table 2), suggesting that miR-146a expression was correlated with disease activity.

3.3. MiR-146a level was decreased after TwHF treatment in RA patients

As shown in Table 3, the disease severity was markedly ameliorated at 12 or 24 weeks after TwHF treatment in RA patients compared with the baseline, characterized by the reduced DAS28, PGA Score, ESR, CRP, and HAQ-DI ($P < .001$).

We then analyzed miR-146a expression at 12 or 24 weeks after TwHF treatment. We observed that the miR-146a level significantly decreased at 12 weeks after TwHF treatment compared with baseline (2.218 [1.653–2.700] vs 2.754 [1.940–3.887], $P < .001$, Fig. 3). At 24 weeks after TwHF treatment, miR-146a expression also deceased when compared with baseline (1.683 [1.465–2.270] vs 2.754 [1.940–3.887], $P < .001$, Fig. 3). Furthermore, when compared with the miR-146a level at 24 weeks after TwHF treatment at 12 weeks, we observed that expression also decreased (1.683 [1.465–2.270] vs 2.218 [1.653–2.700], $P < .001$, Fig. 3). These data suggest that TwHF treatment can markedly reduce expression of miR-146a in patients with RA.

3.4. Expression of miR-146a might predict the response of TwHF treatment

Whether miR-146a can be used a marker in predicting response of TwHF treatment, we divided 69 RA patients into 2 groups (responders and non-responder) according to the decreased

Table 2

Correlation of MiR-146a expression with disease activity, ESR, CRP, HAQ, and PGA assessment.

	DAS28	ESR	CRP	HAQ	PGA
MiR-146a level					
rs	0.382	0.256	0.331	0.318	0.229
P value	.002	.156	.019	.075	.287

P value < .05 was considered statistically significant. Significance of the correlations was determined by the Spearman test. DAS28 = disease activity score in 28 joints, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, HAQ = health assessment questionnaire, PGA = patients global assessment.

Table 3

Clinical and laboratory measures of RA patients treated by TwHF at each visit.

Variables	Baseline	12 weeks	24 weeks	*P* value (24 weeks vs 0 week)
DAS28	5.9 ± 2.1	3.8 ± 1.4	2.9 ± 1.3	<.001
PGA score, 0–100 mm	63 ± 27	43 ± 21	31 ± 14	<.001
ESR, mm/h	39.1 (31.6–47.4)	28.8 (23.7–36.2)	21.6 (17.8–26.1)	<.001
CRP, mg/L	24.5 (17.8–34.9)	20.1 (17.5–30.8)	16.3 (12.7–21.6)	<.001
HAQ-DI	1.8 ± 0.7	0.9 ± 0.4	0.5 ± 0.2	<.001

Data are presented as mean values ± SD, median and 25th–75th. A *P* value < .05 was considered statistically significant. Significance of the comparison was determined by the paired *t* test or the Wilcoxon signed-rank sum test.

CRP = C-reactive protein, DAS28 = disease activity score in 28 joints, ESR = erythrocyte sedimentation rate, HAQ-DI = health assessment questionnaire-damage index, PGA = patients global assessment, RA = rheumatoid arthritis, TwHF = Tripterygium wilfordii Hook F.

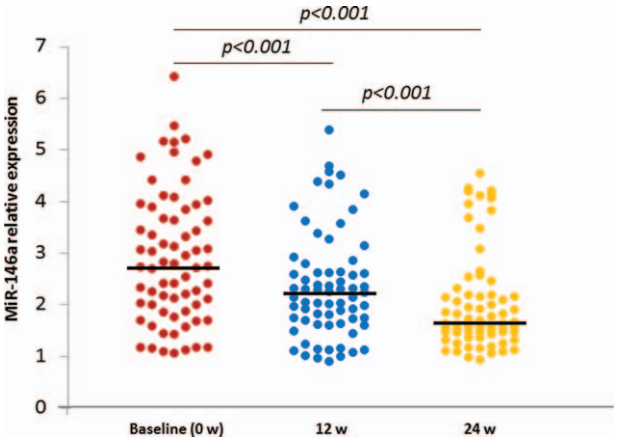

Figure 3. The expression of miR-146a in RA patients receiving TwHF therapy at 0, 12, 24 weeks. RA = rheumatoid arthritis, TwHF = Tripterygium wilfordii Hook F.

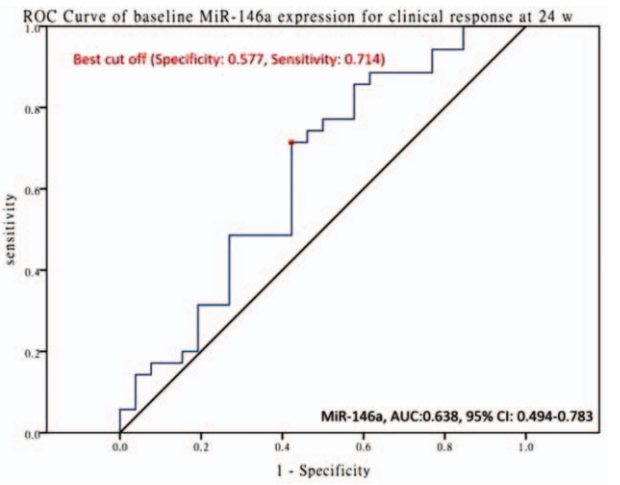

Figure 5. ROC curve for baseline miRNA-146a expression for clinical response at 24 weeks. ROC = receiver operating characteristic.

degree of DAS28. At 12 weeks after TwHF treatment, 6 subjects dropped out of study, the reason of 2 subjects were bad effects, another 2 were side effects, 1 was losing of follow up, and another 1 was other reasons. Therefore, at 12 weeks after TwHF treatment, 25 subjects were included in the responder group, and 40 subjects were non-responder group. Baseline miR-146a expression was compared between responders and non-responder, and no significantly differences was observed (3.083 [2.000–4.274] vs 2.775 [1.743–3.649], $P = .275$, Fig. 4).

At 24 weeks after TwHF treatment, there were 11 subjects who dropped out of the study. Among them, 2 subjects withdrawn for bad effects, another 2 for side effects, 1 for losing of follow up, and another 1 for other reasons. At last, 35 subjects were included in the responders group, and 26 in the non-responders group. No significantly difference of baseline miR-146a expression was found between responders group and non-responders group; however, there was an increased tendency in responders compared with non-responders (3.064 [2.254–4.041] vs 2.310 [1.662–3.874] $P = .066$, Fig. 4).

Then, we analyzed baseline miR-146a expression for clinical response at 24 weeks using *ROC* curve. We observed that the *AUC* was 0.638 for baseline miRNA-146a for clinical response at 24 weeks (95% CI: 0.494–0.783), with a sensitivity of 71.4% and a specificity of 57.7% at best cutoff (Fig. 5). These data demonstrated that miR-146a expression may have a value in predicting clinical response of TwHF treatment.

4. Discussion

RA is a common inflammatory disease with a heterogeneous clinical presentation affecting approximately 1% of population.[13] MiRNAs have been reported to emerge as key regulators of innate and adaptive immune responses.[18] In our current study, we observed that miR-146a expression was associated with susceptibility of RA and disease activity, and miR-146a may predict clinical response of TwHF treatment, which could markedly reduce miR-146a level in RA patients.

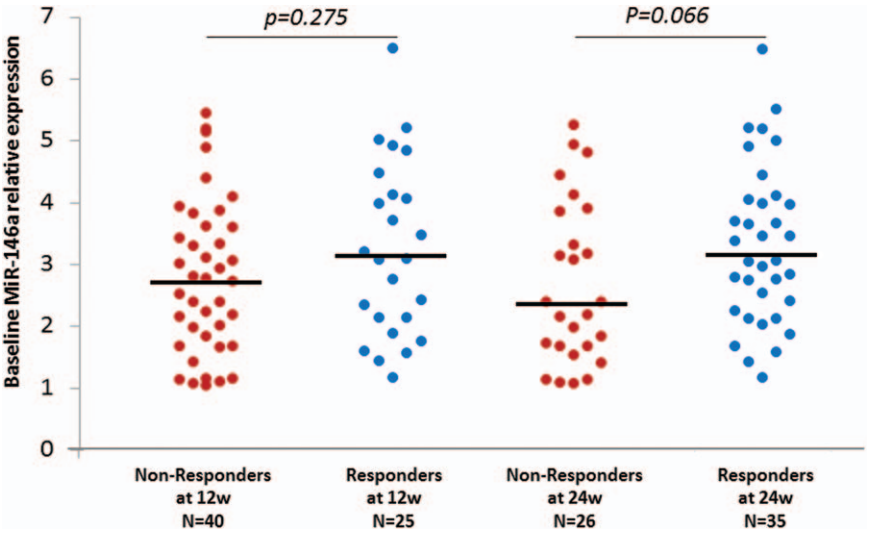

Figure 4. The expression of miR-146a in responders and non-responders at 12 and 24 weeks.

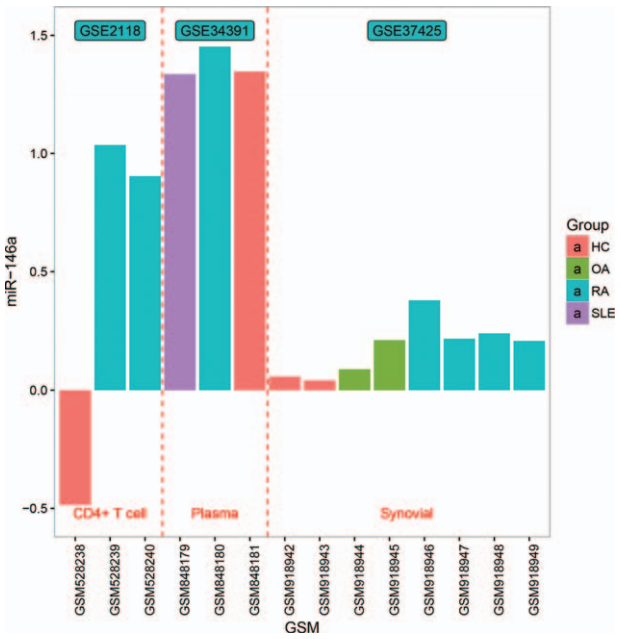

Figure 6. miR-146a expression in RA by GEO database analysis. RA = rheumatoid arthritis. GEO = gene expression omnibus.

Substantial study have proved that miR-146a is one of several miRNAs participates in pathogenesis of inflammatory disease. In human monocytic cell line THP-1, after the stimulation with LPS and other inflammatory stimuli, miR-146a expression is markedly enhanced, and miR-146a plays a critical role in negatively regulating NF-kB activity through targeting TNF receptor associated factor 6 and IL-1 receptor-associated kinase.[19,20] On the other hand, miRNA- 146a is also able to regulate gene such FAF1, IRAK2, FADD, IRF-5, Stat-1, and PTC-1.[21] In arthritis mouse model, intravenous administration of double stranded miR-146a suppresses of cartilage and bone destruction.[20] These demonstrated that miR-146a may be involved in inflammatory responses in RA. In our study, we found that expression of miR-146a was highly enhanced in PBMCs from RA patients, and associated with disease activity, which were consistent with previous research.[13] Furthermore, *ROC c*urve demonstrated miR-146a level was a strong diagnosis biomarker of RA. This result was in accordance with previous studies which elevated expression of miR-146a was detected in synovial fluid, synovial tissue and whole blood in RA patients.[15] Furthermore, we searched miRNA profiles of RA patients in GEO dataset, and got profiles of miR-146a by GEO2R for 3 selected datasets by the methods described previously (Fig. 6).[22] GSE2118 compared the miRNA expression in CD4+ T cell between healthy control and 2 RA patients (from left to right). GSE34191 compared the miRNA profiles in plasma among healthy control, RA and SLE (from left to right). GSE37425 compared miRNA levels in synovial tissues among 2 healthy control, 2 OR, and 4 RA patients (from left to right). According to barplots of miR-146a, all these 3 datasets agreed that miR-146a was unregulated in RA patients.

The effect of treatment on miR-146a level in RA patients has not been widely studied. One study had reported no difference was found in miR-146a expression between patients with RA receiving anti-TNF drugs and no medications.[23] In another study, Abou-Zeid et al[13] considered the possible reason might be the unfinished anti-TNF therapeutic course, or the small proportion of patients treated with anti-TNF. In our study, after RA patients receiving TwHF treatment, the disease activity was markedly reduced, and we found that TwHF treatment could strikingly decrease expression of miR-146a in patients with RA, which suggested that miR-146a might play a critical role of TwHF treatment in patients with RA.

Triptolide, as a critical ingredient of TwHF, is disclosed to decline immune function or host defense related genes expressions, such as pro-inflammatory cytokines and chemokines including TNF-α, IL-1β, CCL-1,2 and so on. Besides, accumulating studies also indicate that expressions of several adhesion molecules (such as laminin gammal, intercellular cell adhesion molecule-1 (ICAM-1)) as well as transcription factors (such as activating transcription factor 3 (ATF3), nuclear factor kB (NF-kB) and signal transducer and activator of transcription 5 (STAT5)) are suppressed by triptolide as well. Thus, it's hypothesized that triptolide affects the precursor of miR-146a through these transcription factors indirectly.[17]

It is widely accepted that the pathogenesis of RA is characterized by systemic inflammation and autoimmunity with multiple joint lesion, or even joint deformity, which not only affects the life quality of patients, but also results in social burden.[24] Therefore, early and reliable treatment for patients with RA is of great importance. Pursuing biomarkers that can guide therapy and predict clinical response of treatment is an urgent task. In our study, baseline miR-146a level was observed to present an increased tendency in responders compared with non-responders at 24 weeks, and *ROC* curve showed that miR-146a may have a value in predicting clinical response of TwHF treatment. However, the significant difference was not very clear, and this study needed to be studied in a larger population.

Some limitations existed in this study: (1) it was a single armed study that RA patients were treated by TwHF, and MTX or LEF was used as combination which was a confounding factor. However, our study recruited RA patients who lack efficacy by previous treatment of MTX or LEF alone, and at the screen period, all RA patients were moderate to severe active. So the bias was reduced by the inclusion criteria, and the previous treatment remained the same during the entire observation period. (2) The sample size was relatively small, so some significance might not be discovered, such as the predictive value of miR-146a for clinical response.

In summary, in our current study, miR146a level was enhanced in patients with RA, and correlated with risk and disease activity. TwHF treatment could strikingly decrease expression of miR-146a in RA patients, and miR-146a may have a value in predicting clinical response of TwHF treatment. Our present study provides the first insights into the interaction between miR-146a expression and TwHF treatment in RA patients. Therefore, miR-146a could be used as a diagnostic, therapeutic and predictive biomarker in TwHF treatment for RA in the future.

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