Original Research Article

Individualized treatment strategy for patients with rheumatoid arthritis based on imaging evaluation

Fan Xiaoli[1], Fan Yanhua[2]*, Wang Juan[2], Bu Shunlin[1], Chen Rong[3], Pang Xiaoli[4], Chen Mingliang[1], Wang Longxiang[1]

[1]Department of Radiology, Nanjing Jiangbei Hospital, [2]Department of Ultrasound, The Second Affiliated Hospital of Nanjing Medical University, [3]Department of Rheumatology and Immunology, The Second Affiliated Hospital of Nanjing Medical University, [4]Department of Rheumatology, Nanjing Jiangbei Hospital, Nanjing, China

*For correspondence: **Email:** fanyanhua102053@163.com

Abstract

Purpose: To study the effect of individualized treatment strategy based on imaging evaluation in patients with rheumatoid arthritis (RA).

Methods: Eighty patients with RA of the wrist treated in the Second Affiliated Hospital of Nanjing Medical University, China from January 2018 to December 2022 were assigned to control and study groups. Conventional methods were used for treating control subjects, based on RA laboratory index results, while the study group received individualized treatment based on RA laboratory index results and results of imaging evaluation. Before and after treatment, serum levels of rheumatoid factor (RF) and C-reactive protein (CRP) were assayed using immunoturbidimetry. Erythrocyte sedimentation rate (ESR) was determined by Wei method. Imaging examination - ultrasound or magnetic resonance imaging (MRI) - was carried out in study group before and after treatment. Disease activity score 28 (DAS28) and score on the visual analogue scale (VAS) were evaluated before and after treatment, and the curative effect in the two groups was compared based on curative effect evaluation.

Results: In both groups, post-treatment values of RF, CRP and ESR were lower than the corresponding pre-treatment levels, but were significantly smaller in study group ($p < 0.05$). The DAS28 and VAS scores of the two groups after treatment were significantly lower ($p < 0.05$) than the pre-treatment levels, but the DAS28 and VAS scores were significantly lower in study group ($p < 0.05$). Treatment efficacy in study group (95.0 %) was significantly higher than in control patients (77.5 %, $p = 0.0476$). The results of imaging indicators showed significantly reduced post-treatment synovial thickness and joint effusion in study group patients when compared with control patients ($p < 0.01$).

Conclusion: Individualized treatment strategy for RA patients based on imaging results enhances curative effectiveness, reduces disease activity, relieves pain, and improves the quality of life of patients.

Keywords: Rheumatoid arthritis (RA), Imaging examination, Individualized treatment strategy

INTRODUCTION

Rheumatoid arthritis (RA) is a common chronic inflammatory joint disease which manifests mainly as joint pain, swelling and dysfunction. The pathogenesis of RA is complex due to the involvement of several factors such as immune system abnormalities, genetic factors and

environmental factors [1,2]. In the clinics, the comprehensive detection of RA is mainly on the basis of the symptoms, signs, laboratory examination and imaging findings in patients [3]. At present, the treatment of RA depends mostly on drug therapy involving non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and disease-modifying anti-rheumatic drugs (DMARDs). Non-steroidal anti-inflammatory drugs such as ibuprofen naproxen, and glucocorticoids (e.g. prednisone) are used for quick relief of joint pain and inflammation. However, glucocorticoids are reserved in cases of acute attack or when other treatments are ineffective, because long-term use of glucocorticoids may cause side effects such as infection and immune disorder [4]. These DMARDs are a class of drugs used for treating joint inflammation and structural damage. They comprise traditional synthetic DMARDs such as methotrexate, azathioprine and chloroquine; biological agent DMARDs i.e., tumor necrosis factor inhibitors such as infliximab and adalimumab; interleukin-6 inhibitors, e.g. dozumab, and targeted synthetic DMARDs, e.g. tofatib. Close monitoring of the safety of drugs during treatment with DMARDs is crucial [5]. Due to the large individual differences in the clinical manifestations and progression of RA, traditional treatment strategies are often ineffective in meeting the needs of all patients. Therefore, individualized treatment strategy has attracted much research interest in the field of RA treatment. Individualized treatment strategy is aimed at selecting the most suitable drugs for individual needs in line with the specific situations of patients, and at predicting and improving the treatment effectiveness so as to reduce adverse reactions.

Imaging examination is an important approach that assists physicians in evaluating the condition of RA, in addition to laboratory markers and disease activity scores, and it is vital in individualized treatment strategies. The use of imaging techniques such as Computed Tomography (CT), ultrasound and magnetic resonance imaging (MRI), enhances the evaluation of joint structure and degree of inflammation in patients with RA. Imaging indicators provide information on disease activity, degree of joint injury, and prognosis [6,7]. This information is helpful in drug selection and prediction of treatment effect.

The present research was done to investigate the influence of application of individualized treatment strategy based on imaging evaluation in patients with RA. Specifically, the progression and severity of arthritis were assessed with either ultrasound or MRI, in order to guide drug selection and adjust the treatment plan, and the effect of treatment was monitored using imaging.

METHODS

General information on patients

A total of 80 patients with rheumatoid arthritis of the wrist who were treated at the Second Affiliated Hospital of Nanjing Medical University, China from January 2018 to December 2022 were included in this study. The subjects were assigned to control and study groups, depending on whether or not an imaging examination was performed prior to treatment. There were 40 patients in each group. This study received approval from the ethics committee of the Shanghai Sixth People's Hospital, Shanghai, China (approval no. 2021-021-(1)) and was performed using the Chinese guidelines for the diagnosis and treatment of rheumatoid arthritis [8].

Inclusion criteria

All patients who met the Chinese guidelines for the diagnosis and treatment of rheumatoid arthritis [8]; those in normal spirits and with healthy cognition, and those who cooperated fully in the completion of basic investigation and research, were included in the study. Moreover, patients who volunteered to participate in the study and signed informed consent after knowing the purpose of the research, and those with complete clinical data, were included.

Exclusion criteria

The excluded patients were those with advanced and multiple bone erosion, patients who took anti-rheumatism drugs in the previous 1 month, patients with severe organ dysfunction affecting key organs (liver, heart and kidneys); patients who had systemic infections, and patients who were pregnant or lactating. In addition, patients with malignant tumors were excluded.

In study group, the determination of RA laboratory index and imaging examination (ultrasound or MRI) were done at the same time before treatment.

Determination of laboratory RA index

The laboratory RA index was determined in the two groups before and after treatment. After a 12-h fast, 4 mL of blood sample drawn from peripheral vein was centrifuged at 3,500 rpm for 10 min at 4 °C, and the serum was collected. The

serum levels of RF and CRP were measured using immunoturbidimetry, while ESR was determined with infrared barrier technique of the Sistat device (Sistat Ltd., Ankara, Turkey) [9].

Imaging examination

Procedure used for MRI examination: The back of the patient's hand was placed facing upwards and rotated 15 – 20º outward. The conditions of the conventional MRI scan were: sagittal plane, transverse plane fast spin echo (FSE) T1WI and T2WI, stir sequence of Tr: 6.8ms and te: 2.7ms; layer thickness of 3.0 mm, spacing of 0.30 mm, and for 300 mm x 300 mm. The scanning time was 0.32 sec, and scanning was done twice. A radiologist with a 5-year experience completed all the above examinations. After scanning, the image was transferred to the workstation. The characteristics of the MRI image of the wrist joint were quantitatively evaluated using ramiis scoring system [10].

Ultrasonic examination

The patient stretched out the wrist joint, with the back of the hand straight and flat. A color Doppler ultrasound diagnostic equipment with a high-frequency probe was used to scan the palmar, dorsal, radial and ulnar sides of the wrist joint that had swelling and tenderness. The intensity of pressure from the ultrasonic probe was kept moderate in order to avoid synovial deformation while ensuring good quality of the image obtained. Ultrasound scoring was performed according to Szkudlarek standard Sitting positionGe logiqe9 E11 and Philips iu22 IU elite [11].

Drug selection

The patients in the control group received only traditional treatment based on the results of laboratory indicators and clinical symptoms. Individualized drug treatments were developed for patients in study group based on data on laboratory indicators, imaging evaluation and clinical symptoms. Commonly used drugs were NSAIDs, DMARDs and biological agents. Common medications included the NSAIDs, i.e., ibuprofen sustained-release capsules (orally, 600 mg twice a day); diclofenac sodium sustained-release tablets (orally, 50 mg twice a day); celecoxib (orally, 100 mg twice a day), and meloxicam tablets (orally, 7.5 mg twice a day); disease-modifying antirheumatic drugs (DMARDs), i.e., methotrexate tablets (orally, 10 mg once a week) and sulfasalazine (orally, 1 g three times a day), and corticosteroids, i.e., prednisolone tablets (orally, 5 – 10 mg once a day) and dexamethasone (orally, 2.5 – 5 mg three times a day).

Scoring indices

DAS28 for RA

The DAS28 scores of patients before and after 1 month of treatment were obtained using the RA disease activity score system recommended by the European Union for the prevention and treatment of rheumatism (EULAR). Eq 1 was used for calculation of the score [12].

DAS28 = (0.56 x Sqrt of no. of tender joints) + (0.28 x Sqrt of no. of swollen joints) + (0.70 x ln ESR) + (0.014 x phsc) ………… (1)

where *ESR* = erythrocyte sedimentation rate, and *phsc* = patients' health score. The lower the score, the lower the disease activity.

Visual analogue scale (VAS)

Patients were asked to use a ruler or line segment to mark their degree of pain on a scale with scores ranging from 0 to 10, where 0 represents *no pain,* and 10 represents *very severe pain.* The lower the score, the less severe the pain [13].

Evaluation of treatment effectiveness

Treatment effectiveness was ranked into four categories: significantly effective, progressed, effective, and ineffective. If the levels of laboratory indicators were close to normal or significantly improved, and the overall reduction in signs and main symptoms was ≥ 75 %, the treatment was significantly effective. If the levels of laboratory indicators were improved significantly, with 50 – 75 % overall reduction in signs and main symptoms, the treatment outcome was deemed progressed. Treatment was deemed effective if the levels of laboratory indicators were improved, with 30 - 50 % overall reduction in signs and main symptoms of the disease. However, if the levels of laboratory indicators did not improve, and the overall reduction in signs and main symptoms was less than 30 %, treatment ineffectiveness was inferred. Total effectiveness of treatment was taken as the sum of the number of subjects whose treatment outcomes were significantly effective, progressed and effective.

Statistical analysis

The SPSS 23.0 software package was used for data processing. Data from measurements are

presented as mean ± standard deviation (SD), and *t*-test was used to compare two groups. Counted results are expressed as (n (%)), and chi-squared (χ^2) test was applied to compare two groups. Statistical significance was assumed at *p* < 0.05.

RESULTS

General biodata

Study group comprised 18 males and 22 females aged 29 - 71 years (mean age = 51.33 ± 10.91 years) and with a disease course of 1-8 years (mean disease course = 3.83 ± 2.25 years).

In control group, there were 16 men and 24 women in the age range of 31-75 years (average age = 53.56 ± 10.71 years), and the course of disease was 1-7 years (mean course = 3.57 ± 1.86 years). There were no significant differences in general data between the two groups (*p* > 0.05).

Laboratory pre- and post-treatment RA index values

Pre-treatment values of RF, CRP and ESR were comparable in the two groups. However, post-treatment values of RF, CRP and ESR were significantly reduced in both groups, relative to the corresponding pre-treatment levels, but after treatment, they were significantly lower in study group (*p* < 0.05; Table 1).

Pre-and post-treatment DAS28 and VAS scores

The DAS28 and VAS scores were comparable in the two groups before treatment (*p* > 0.05). However, after treatment, the DAS28 and VAS scores of the two groups were significantly reduced, relative to the corresponding scores before treatment (*p* < 0.05), but with significantly lower DAS28 and VAS scores in study group (Table 2).

Treatment effectiveness

The results of evaluation of curative effect showed that treatment efficacy was significantly higher in study group (95.00 %) than in the control group (77.50 %, *p* = 0.0476; Table 3).

Synovial thickness and joint effusion

As shown in Table 4, in study group, results of imaging index before and after treatment showed that after the individualized treatment strategy, the synovial thickness and joint effusion were significantly reduced, relative to the corresponding pre-therapy values.

Table 1: Levels of RF, CRP and ESR in the two groups before and after treatment

Group	RF (IU/mL)		CRP (mg/L)		ESR (mm/h)	
	Pre treatment	*Post treatment*	*Pre treatment*	*Post treatment*	*Pre treatment*	*Post treatment*
Control	44.77±9.51	29.51±6.73*	40.74±6.18	26.50±2.90*	68.30±8.60	51.95±6.38*
Study	43.85±7.20	23.39±4.70*	39.02±5.75	21.68±4.85*	70.94±9.17	47.36±8.33*
t	0.4878	4.715	1.289	5.395	1.328	2.425
P-value	0.6271	<0.0001	0.2013	<0.0001	0.1880	0.0176

Note: *P < 0.05, vs corresponding pre-treatment value (n=40). Values are presented as mean ± SD

Table 2: Pre- and post-treatment DAS28 and VAS scores in both groups (mean ± SD, n = 40)

Group	DAS28 score		VAS score	
	Before treatment	*After treatment*	*Before treatment*	*After treatment*
Control	5.92±1.64	3.26±1.11*	6.58±1.66	4.48±1.33*
Study	6.34±2.08	2.70±0.97*	6.16±1.93	3.48±1.01*
T	1.003	2.403	1.043	3.787
P-value	0.3190	0.0187	0.3000	0.0003

*P < 0.05, vs corresponding pre-treatment value (n=40). Values are presented as mean ± SD

Table 3: Treatment efficacy in both groups (n=40; (%))

Group	Significantly effective	Progressed	Effective	Not effective	Total effectiveness
Control	10 (25.00)	13 (32.50)	8 (20.00)	9 (22.50)	31 (77.50)
Study	16 (40.00)	15 (37.50)	7 (17.50)	2 (5.00)	38 (95.00)
P-value					0.0476

Table 4: Imaging index values in study group before and after treatment

Imaging indicator	Study group
Synovial thickness	
Before treatment	6.29±1.88
After treatment	4.00±1.32
t	6.305
p-value	<0.0001
Joint effusion	
Before treatment	7.05±1.41
After treatment	4.12±1.28
t	9.731
p-value	<0.0001

Note: Values are presented as mean ± SD

Typical pre- and post-treatment cases in study group subjects, as seen using MRI and ultrasound imaging

MRI Imaging examination

Case 1 was a 59-year-old woman. The MRI before treatment (Figure 1 A and B) showed bones of the left wrist (no. 1 - 5) with massive bone marrow edema at the base of the metacarpal bone and distal radius and ulna. Coronal Stir sequence signal was increased and the boundary was unclear. The synovium of the wrist joint was significantly thickened, and an effusion signal was seen in the joint space. Axial position Stir Sequence showed no obvious abnormalities in the tendons; the surrounding synovium was thickened and the signal was increased. There was no obvious abnormal signal shadow in carpal tunnel. The soft tissue around the joint was swollen. The MRI of the same bones of the left wrist after treatment is shown in Figure 1 C and D (bone no. 1 - 5). There was focal bone marrow edema at the base of the metacarpal bone distal radius and ulna. Coronal Stir sequence signal was increased; the boundary was relatively clear, and cystic bone erosion was seen in the local joint bone. The synovium of the left wrist joint was thickened, and the degree of synovium thickening was reduced. There was a small amount of effusion signal in the joint space. Axial position Stir Sequence showed no obvious abnormalities in the tendons, and the surrounding synovium was slightly thickened. The soft tissue around the joint was slightly swollen, but the degree of swelling was significantly reduced when compared with the degree of swelling before treatment.

Ultrasonic imaging features

Case 2 was a 66-year-old woman. The synovium of the wrist joint was significantly thickened before treatment (Figure 2 A). However, after treatment, the thickness of the wrist joint synovium was visibly reduced (Figure 2 B).

Figure 1: MRI findings in a typical case (case 1) before treatment (A and B) and after treatment (C and D)
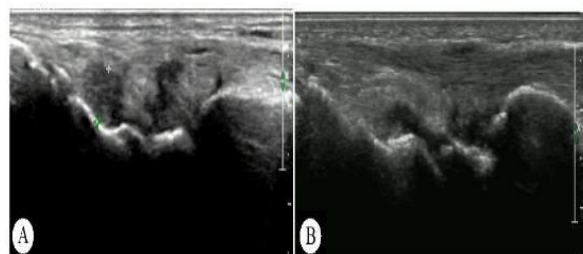

Figure 2: Ultrasonic imaging results in a typical case (case 2) before treatment (A) and after treatment (B)

DISCUSSION

Magnetic resonance imaging and ultrasound imaging techniques have been used to evaluate arthritis lesions in patients with RA in study group. Magnetic resonance imaging (MRI) provides detailed information on joint structure, including information on soft tissue, bone and articular cartilage. Moreover, MRI is used to examine injury in articular cartilage, inflammatory reactions in joint capsule and synovium, and swelling and edema of soft tissue around the joint, thereby enhancing understanding of inflammatory reactions in the joint, as well as the degree of damage in the joint.

Ultrasound is helpful in real-time examination of soft tissue lesions in the joint, including synovial thickening, joint effusion and joint capsule thickening. Ultrasound is also used for evaluating

articular cartilage injury and inflammatory reactions in tendons around the joint, which are indices that reflect the degree of inflammatory activity and extent of damage in the joint [14,15]. Through evaluation of imaging of patients, a more accurate understanding is obtained of the degree and type of lesions, which, in combination with clinical manifestations and laboratory examination results, aids the formulation of individualized treatment plans for patients.

The values of laboratory RA indices (RF, CRP and ESR) were significantly reduced in study group after treatment. Clinically, RF and ESR are used for evaluating the condition of patients with RA, while CRP level is used to evaluate inflammatory reactions [16]. The levels of the above three indicators were significantly lowered in study group, relative to control levels, indicating that following individualized treatment, the condition and inflammatory reaction of patients in study group had better improvement than those in the control subjects. The DAS28 and VAS scores in both groups pre-and post-treatment were also compared.

The DAS28 rating is employed for evaluating disease status in RA subjects [17], while VAS score is usually used to determine the magnitude of pain. The results of the present study showed that relative to control, there were significantly lower post-treatment DAS28 and VAS scores in the study subjects, indicating that the disease activity reduction and joint pain relief effects in study group were significantly better than those in the control group. The results of evaluation of curative effect revealed that the total treatment effectiveness was significantly better in study group. Moreover, the results of analysis of changes in imaging indicator levels showed significantly lower post-treatment synovial thickness and joint effusion in study patients, thereby reflecting obvious curative effect on the patients. The above results suggest that the efficacy of individualized treatment strategy based on imaging results for RA subjects is better than that of traditional therapy. Individualized treatment strategies based on imaging results have the following advantages for RA patients:

 (a) Accurate diagnosis: imaging results provide accurate diagnostic information which helps doctors confirm the existence and degree of RA, thereby preventing misdiagnosis and missed diagnosis, and it ensures that patients receive correct treatment.

(b) Good guide in treatment decision-making: Imaging results assist doctors in understanding the involvement of the joint, the degree of damage to the joint structure and other related lesions, all of which are crucial in the development of individualized treatment strategies such as selection of appropriate drug treatment, physical therapy, or surgical intervention.

(c) Monitoring of therapeutic effect: Through regular imaging examination, therapeutic effect and changes in joint structure may be effectively monitored. These are useful guides for making timely adjustments in the treatment plan so as to achieve the best therapeutic effect.

(d) Improvement of patient satisfaction: Individualized treatment strategies are better than general treatment in meeting the needs and expectations of patients and in improving patient satisfaction [18,19]. At the same time, pain may be reduced; joint function may be improved, and the quality of life of patients may be enhanced through timely adjustment of the treatment plan.

Limitations of this study

This study has some limitations. The small sample size limits the generalizability and statistical applicability of the findings. There was no long-term follow-up on the RA subjects. Therefore, it may not be possible to fully understand the long-term curative effect of personalized treatment. Moreover, this research was done in only one hospital. There is therefore the need for larger-sample, multi-center studies involving long-term follow-up data collection so as to verify the effectiveness and long-term effects of individualized treatment strategies.

CONCLUSION

Imaging has potential benefits in the formulation of individualized treatment strategies for patients with RA. By accurately evaluating the degree and type of lesions through imaging, doctors may be able to formulate individualized treatment plans, effectively improve the curative effect on patients, reduce disease activity, and relieve pain in patients, all of which will result in improved quality of life of patients.

DECLARATIONS

Funding

This study was supported by the Scientific Research Foundation of Shanghai Sixth People's Hospital (Project No. ynhg202105).

Ethical approval

This study was approved by the ethics committee of the Shanghai Sixth People's Hospital, Shanghai, China (approval no. 2021-021-(1))..

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

Open Access

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0) and the Budapest Open Access Initiative (http://www.budapestopenaccessinitiative.org/read), which permit unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

REFERENCES

1. Scherer HU, Häupl T, Burmester GR. The etiology of rheumatoid arthritis. J Autoimmun 2020; 110: 102400.
2. Chien LH, Deng JS, Jiang WP, Chou YN, Lin JG, Huang GJ. Evaluation of lung protection of Sanghuangporus sanghuang through TLR4/NF-κB/MAPK, keap1/Nrf2/HO-1, CaMKK/AMPK/Sirt1, and TGF-β/SMAD3 signaling pathways mediating apoptosis and autophagy. Biomed Pharmacother 2023; 165: 115080
3. Cush JJ. Rheumatoid arthritis: Early diagnosis and treatment. Med Clin North Am 2021; 105(2): 355-365.
4. Ben Mrid R, Bouchmaa N, Ainani H, El Fatimy R, Malka G, Mazini L. Anti-rheumatoid drugs advancements: New insights into the molecular treatment of rheumatoid arthritis. Biomed Pharmacother 2022; 151: 113126.
5. Huang J, Fu X, Chen X, Li Z, Huang Y, Liang C. Promising therapeutic targets for treatment of rheumatoid arthritis. Front Immunol 2021; 12: 686155.
6. Baker JF, Conaghan PG, Gandjbakhch F. Update on magnetic resonance imaging and ultrasound in rheumatoid arthritis. Clin Exp Rheumatol 2018; 36(5): 16-23.
7. Carstensen SMD, Terslev L, Jensen MP, Østergaard M. Future use of musculoskeletal ultrasonography and magnetic resonance imaging in rheumatoid arthritis. Curr Opin Rheumatol 2020; 32(3): 264-272.
8. Tian X, Wang Q, Li M, Zhao Y, Zhang Z, Huang C, Liu Y, Xu H, Chen Y, Wu L, et al. 2018 Chinese guidelines for the diagnosis and treatment of rheumatoid arthritis. Rheumatol Immunol Res 2021; 2(1): 1-14.
9. Sunar İ, Ataman Ş. Serum C-reactive protein/albumin ratio in rheumatoid arthritis and its relationship with disease activity, physical function, and quality of life. Arch Rheumatol 2020; 35(2): 247-253.
10. Just SA, Nielsen C, Werlinrud JC, Larsen PV, Klinkby CS, Schrøder HD, Humby F, Torfing T, Lindegaard H. Six-month prospective trial in early and long-standing rheumatoid arthritis: evaluating disease activity in the wrist through sequential synovial histopathological analysis, RAMRIS magnetic resonance score and EULAR-OMERACT ultrasound score. RMD Open 2019; 5(2): e000951.
11. Ohrndorf S, Boer AC, Boeters DM, Ten Brinck RM, Burmester GR, Kortekaas MC, van der Helm-van Mil AHM. Do musculoskeletal ultrasound and magnetic resonance imaging identify synovitis and tenosynovitis at the same joints and tendons? A comparative study in early inflammatory arthritis and clinically suspect arthralgia. Arthritis Res Ther 2019; 21(1): 50-59.
12. Vadell AKE, Bärebring L, Hulander E, Gjertsson I, Lindqvist HM, Winkvist A. Anti-inflammatory diet in rheumatoid arthritis (ADIRA)-a randomized, controlled crossover trial indicating effects on disease activity. Am J Clin Nutr 2020; 111(6): 1203-1213.
13. Guagnano MT, D'Angelo C, Caniglia D, Di Giovanni P, Celletti E, Sabatini E, Speranza L, Bucci M, Cipollone F, Paganelli R. Improvement of inflammation and pain after three months' exclusion diet in rheumatoid arthritis patients. Nutrients 2021; 13(10): 3535.
14. Ranganath VK, Hammer HB, McQueen FM. Contemporary imaging of rheumatoid arthritis: Clinical role of ultrasound and MRI. Best Pract Res Clin Rheumatol 2020; 34(6): 101593.
15. Rubin DA. MRI and ultrasound of the hands and wrists in rheumatoid arthritis. I. Imaging findings. Skeletal Radiol 2019; 48(5): 677-695.
16. Liu W, Zhang Y, Zhu W, Ma C, Ruan J, Long H, Wang Y. Sinomenine Inhibits the Progression of Rheumatoid Arthritis by Regulating the Secretion of Inflammatory Cytokines and Monocyte/Macrophage Subsets. Front Immunol 2018; 9: 2228.
17. Jamali F, Ahmadzadeh A, Sahraei Z, Salamzadeh J. Study of the Effects of N-acetylcysteine on Inflammatory

Biomarkers and Disease Activity Score in Patients with Rheumatoid Arthritis. Iran J Allergy Asthma Immunol 2021; 20(5): 574-583.

18. *Harnden K, Di Matteo A, Mankia K. When and how should we use imaging in individuals at risk of rheumatoid arthritis? Front Med (Lausanne) 2022; 9: 1058510.*

19. *Akram M, Daniyal M, Sultana S, Owais A, Akhtar N, Zahid R, Said F, Bouyahya A, Ponomarev E, Ali Shariat M, Thiruvengadam M. Traditional and modern management strategies for rheumatoid arthritis. Clin Chim Acta 2021; 512: 142-155.*