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Problems of treatment adherence in patients with rheumatoid arthritis and comorbidity

Abstract

Aim of the study. Evaluation of treatment adherence in patients with rheumatoid arthritis (RA) and comorbidity. **Materials and methods.** One hundred thirty-two women (mean age: 55.5 ± 10.5 years) with proven RA (mean duration of disease: 10.2 [4; 14] years) were included in this study. Patients with moderate and high disease activity were prevalent (average DAS28: 5.0 [4.3; 5.8]). All patients had comorbidities. All patients underwent clinical examination, laboratory evaluation and imaging. Functional capacity was assessed using the Steinbroker classification (functional class — FC) and Stanford Health Assessment Questionnaire (HAQ). Pain severity was evaluated using visual analog scale (VAS). Patients' social status was assessed. Baseline adherence to treatment was evaluated using two questionnaires. Morisky-Green questionnaire was used to evaluate general adherence to treatment among 132 (100%) patients. Quantitative evaluation of treatment adherence was performed in 82 (62.1%) patients using N.A. Nikolaev questionnaire. **Results**. Analysis of adherence to treatment as assessed by Morisky-Green questionnaire has established that 68 (52.3%) of patients are non-adherent to treatment. Low treatment adherence as assessed by Nikolaev questionnaire was found in 33 (40.3%) of patients. Lifestyle modification was characterized by lowest adherence. Young age, lower duration of disease and lower income were predictive of higher adherence to treatment. Non-adherent patients had higher RA activity index and lower functional capacity. **Conclusion**. Simultaneous use of several methods to assess treatment adherence is a reasonable way to get more information about the patient and to implement therapy as planned. Evaluation of baseline adherence to treatment among patients with rheumatoid arthritis allows to develop an optimal plan for follow-up and treatment control.

Key words: *Rheumatoid arthritis, comorbidity, adherence to treatment*

Conflict of interests

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DMARDs — disease-modifying anti-rheumatic drugs, QEA — quantitative evaluation of adherence, RA — rheumatoid arthritis, VAS — visual analogue scale

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Rheumatic diseases are currently of great social importance. The prevalence of rheumatoid arthritis (RA) in the population is 0.61%, ankylosing spondylitis — 0.1%, psoriatic arthritis — 0.37%, reactive arthritis — 0.42%, gout — 0.3%, systemic diseases of connective tissue and blood vessels — 0.11% [1].

Comorbidity is a combination of two or more chronic diseases in one patient. Said diseases are ethiopathogenetically interconnected or coexist regardless of the activity of each of them [2]. With age, the number of comorbidities in one patient increases. Thirty-six percent of patients aged 50–59 years have two or three diseases; 40.2% of patients aged 60–69 years have four or five diseases; 65.9% of patients aged 75 years and over have more than five diseases [3].

According to Damjanov N. et al. (2014) [4], the most common comorbidities in patients with rheumatic diseases are cardiovascular disorders, infections, lung diseases, depression, neoplasms, and diseases of the gastrointestinal tract.

The presence of RA increases the risk of comorbidities and premature death. At the same time, comorbidity has an effect on the course of RA, reduces treatment efficacy, and increases the frequency of hospitalizations. According to a study of patients with RA (n = 328) performed in our clinic, comorbidities were found in 86.6% of patients. At the same time, 163 episodes of the withdrawal of synthetic disease-modifying anti-rheumatic drugs (DMARDs) were observed; these were associated with the worsening of the course of a comorbid disease [5].

F. I. Belyalov (2009) articulated and substantiated 12 principles of comorbidity [6]. According to the 9th principle, comorbid diseases reduce patients' adherence to treatment. Adherence is the degree to which patients follow the physician's recommendations on time, frequency, and dosage of drug administration, as well as compliance with recommendations on lifestyle changes [7]. The term "adherence" implies conscious cooperation between the physician and the patient and members of his/her family. The present-day concept of the management of rheumatoid arthritis, "Treat to Target" (i.e., treatment to achieve the goal), considers the interaction between the physician and patient as the key to successful treatment [8].

In most of works on adherence to treatment, adherence to drug therapy is studied based on the amount of drugs taken and actual implementation of medical recommendations [9].

There are few works on the evaluation of initial adherence in patients with RA, especially in those with comorbidity [10].

Goal of the Study: studying adherence to treatment in comorbid patients with RA.

Materials and Methods

This study included 132 women with proven RA according to ACR/EULAR (American College of Rheumatology / European League Against Rheumatism) criteria 2010. They were treated at the Rheumatology Department of the Regional Clinical Hospital (Saratov) from 2017 to 2019.

The mean age of the patients was 55.5 ± 10.5 years, the mean duration of RA was 10.2 [4; 14] years. Disease activity was assessed by DAS28 (disease activity score): low for DAS28 ≤ 3.2; moderate for 3.2 < DAS28 ≤ 5.1; high for DAS28 > 5.1. Most of the patients had moderate and high activity of RA: mean DAS28 was 5.0 [4.3; 5.8].

Criteria for the inclusion of patients in this study were: proven diagnosis of RA according to ACR/EULAR criteria (2010); female gender; age over 18 years; steady intake of disease-modifying anti-rheumatic drugs (DMARDs) for at least 4 weeks; intake of glucocorticoids less than 7.5 mg equivalent to prednisolone; at least one comorbid disease not in exacerbation.

Exclusion criteria for this study: other inflammatory joint diseases except for RA, pregnancy, lactation, comorbid diseases in exacerbation.

All participants signed an informed consent to the collection and processing of personal information. The study was approved by the Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education "Razumovsky Saratov State Medical University" of the Ministry of Health of Russia.

All patients underwent clinical examination, laboratory tests and X-ray. The functional capacity of patients was determined by Steinbroker functional classification and Stanford Health Assessment Questionnaire (HAQ). Functional

disorders (HAQ) were considered minimal with 0.5–1 HAQ points, moderate with 1–2 points, and severe with 2–3 points.

Pain intensity was defined according to the 100-mm visual analogue scale (VAS): 0 mm — no pain, 100 mm — maximum pain intensity.

Table 1 presents the clinical profile of patients with RA (Tab. 1). The social status of patients was assessed, including marital status, education, employment and financial opportunities.

Table 1. *Clinical characteristics of patients with rheumatoid arthritis (n=132) (M±SD, Me [Q25; Q75]), n (%)*

Index	Patients with RA
Average age, years	55,5±10,5
Average duration of rheumatoid arthritis, years	10,2 [4;14]
Activity (DAS28):	
low (≤3,1), n (%)	6 (4,5%)
moderate (3,2-5,1), n (%)	56 (42,5%)
high (≥5,2), n (%)	70 (53%)
Positive RF, n (%)	94 (71,2%)
X-ray stage:	
I-II, n (%)	62 (47%)
III-IV, n (%)	70 (53%)
Extraarticular manifestations of RA, n (%)	42 (31,8%)
Stage of RA:	
early, n (%)	5 (3,7%)
expanded, n (%)	76 (57,6%)
late, n (%)	51 (38,7%)
Pain on VAS:	
Slight, n (%)	20 (15,2%)
Mild, n (%)	65 (49,2%)
Severe, n (%)	47 (35,6%)
Functional disorders on a HAQ:	
absent, n (%)	12 (9,1%)
minimal, n (%)	25 (18,9%)
mild, n (%)	69 (52,3%)
severe, n (%)	26 (19,7%)
The average number of comorbid states	6 [4;9]

Note: DAS — disease activity score, HAQ — Health Assessment Questionnaire, VAS — visual analog scale, RA — rheumatoid arthritis, RF — rheumatoid factor

Initial adherence of patients with RA to treatment was assessed using two questionnaires. The Morisky—Green questionnaire (MMAS-4) was used for assessing overall adherence to treatment in 132 (100%) patients [11]. Quantitative evaluation of adherence (QEA) to treatment was carried out in 82 (62.1%) patients based on the N. A. Nikolaev questionnaire (KOP-25) [12].

According to the Morisky—Green questionnaire, patients with 4 points were considered adherent to treatment; patients with 1–2 points — non-adherent to treatment; patients with 3 points — not sufficiently adherent, with the risk of transfer to the group of non-adherent patients [11].

Quantitative evaluation of adherence included adherence to drug therapy, medical support, lifestyle changes, and the integral parameter. For all parameters of KOP-25, values under 50% were interpreted as "low" ("non-adherent to treatment"), 51–75% as "medium"; more than 75% as "high" ("adherent to treatment").

Statistical processing of the information obtained was carried out using Microsoft Office Excel 2007 and Statistica 10.0 (Statsoft, USA) software packages.

The Kolmogorov—Smirnov test was used to check the normality of distribution. For describing normally distributed quantitative parameters, the mean value of the parameter and standard deviation (M ± SD) were used; for describing the selective distribution of parameters different from the standard, median, upper and lower quartiles were defined — Me [Q25; Q75]. Correlation analysis was performed using Spearman's correlation coefficient. Statistical significance of differences (p) was assessed using the Mann—Whitney test (U) for quantitative parameters; for nominal variables with two categories, Fisher's exact test was used. Differences in parameters were considered significant at $p < 0.05$.

Results

The combination of two or more comorbidities was found in 118 (90.7%) patients with RA. Table 2 presents the structure of comorbidity in the examined patients.

Osteoarthritis was most frequently found in patients with RA — it was detected in 103 (79.2%) patients.

Table 2. *The structure of comorbid pathology in patients with RA (n=132)*

Index	Number of patients	
	n	%
The number of patients with two or more comorbid conditions	118	90,8%
Cardiovascular pathology:	80	61,5%
Cardiac ischemia disease	9	6,9%
including		
Myocardial infarction	4	3,0%
Chronic heart failure (I-II FC)	4	3,0%
Arterial hypertension	78	60%
incuding:		
I stage	8	6,2%
II stage	46	35,4%
III stage	24	18,5%
Chronic cerebral ischemia	13	0,1%
Digestive system pathology	94	72,3%
including:		
Diseases of the stomach and duodenum	76	58,5%
Chronic cholecystitits	44	33,8%
Chronic pancreatitits	21	16,2%
Esophageal hernia of the diaphragm	17	13,1%
Chronic colitis	8	6,2%
Chronic viral hepatitis	5	3,8%
Other diseases of the joints of them:	103	79,2%
Ostheoarthritis	103	79,2%
Gout	2	1,5%
Urinary tract diseases (chronic pyelonephritis, chronic cystitis)	26	20%
Endocrine pathology:	47	36,2%
including:		
Diabetes 2 type	16	12,3%
Autoimmune thyroiditis	37	28,5%
Respiratory diseases:	22	16,9%
including:		
Chronic rhinopharyngitis	18	13,8%
COPD	1	0,7%
Bronchial asthma	4	3,0%
Varicose veins disease	28	21,5%
Oncopathology (in history)	6	4,6%
Anemia	56	43%
Cataract	17	13,1%
Hemorrhoids	8	6,2%

Note: COPD — chronic obstructive pulmonary disease, FC — functional class

Chronic disorder of gastrointestinal tract (GIT) was observed in 94 (72.3%) patients, cardiovascular diasease was found in 80 (61.5%) patients with RA. High incidence of anemia should also be noted; it was found in 56 (43%) patients.

Among the 132 examined patients, 74 (56%) were married, 24 (18.2%) were widowed, 34 (25.8%) were divorced or never had a family. Patients with secondary education were predominant — there were 75 of them (56.8%); there were 10 (7.6%) patients with incomplete higher education, and 42 (31.8%) patients with higher education; 5 (3.8%) patients had primary education. A third of the patients worked full-time, 14 (10.6%) patients — part-time, 2 (1.5%) had casual earnings, and 75 (56.8%) patients were unemployed. Fifty-nine (44.7%) patients were disabled. Fifty-one (38.6%) patients with RA had sufficient financial resources, and 81 (61.4%) patients had limited financial means.

Analysis of adherence to treatment using the Morisky—Green questionnaire revealed that only 34 (26.1%) patients were adherent to treatment, and 68 (52.3%) patients were non-adherent (1–2 points) (Table 3).

Table 3. *Assessment of adherence to treatment according to the questionnaire Morisky-Green in women with rheumatoid arthritis and comorbidity (n=132)*

Index, points	Number of patients (%)
1-2 points	68 (52,3%)
3 points	30 (21,6%)
4 points	34 (26,1%)

Results of quantitative evaluation demonstrated that adherence to medical support was 60.7 [46.7; 72] %; adherence to lifestyle changes — 42.1 [34; 53.8] %; adherence to drug therapy — 56.4 [45.3; 72] %. Overall adherence to treatment was 54.3 [42.3; 64.1] %, which corresponds to the lower limit of medium adherence.

Table 4 shows the results of patients distributed according to the quantitative evaluation of adherence to treatment according to the N. A. Nikolaev questionnaire (KOP-25).

Patients demonstrated the lowest adherence to recommendations for lifestyle changes. Negative correlations were found between age and adherence

to lifestyle changes (r = –0.24, ρ = 0.039), adherence to drug therapy (r = –0.23, ρ = 0.037), and overall adherence to treatment (according to KOP-25) (r = –0.25, ρ = 0.041). There was a tendency to higher adherence to treatment in patients with RA onset before the age of 39 years.

Negative correlation was found between the financial situation of patients and adherence to lifestyle changes (r = –0.32, ρ = 0.038). There was no relationship between adherence to drug treatment (according to the Morisky—Green questionnaire), duration of RA, and the number of comorbid diseases.

For the quantitative analysis of adherence to treatment, patients with RA were divided into two groups depending on disease duration: up to 12 years inclusively (n = 46) and over 12 years (n = 36). In patients of both groups, there was an established relationship between adherence to medical support according to the KOP-25 questionnaire and the number of comorbid diseases (r = –0.3 and r = –0.29, respectively, ρ = 0.032). In patients with disease duration of over 12 years, there were correlations between disease duration and overall adherence to treatment (r = –0.26, ρ = 0.039), as well as adherence to medical support (r = –0.28, ρ = 0.041).

Non-adherent patients demonstrated significantly higher RA activity (erythrocyte sedimentation rate (ESR)), number of swollen joints, DAS28, pain intensity according to VAS), and lower functional capacity than patients adherent to treatment (Table 5).

The groups were comparable in terms of the number of married patients (Table 6).

Among non-adherent patients, there were three times more widows than single patients — 11 (33%) and 7 (14%), (ρ = 0.041).

Table 4. *Quantitative evaluation of treatment adherence to women with rheumatoid arthritis and comorbidity (n=82)*

	Adherence to medical support (Cm), n (%)	Adherence to lifestyle modification (Cc), n (%)	Adherence to drug therapy (Cd), n (%)	General adherence to treatment (C), n (%)
Low (before 50%)	26 (31,7%)	54 (65,9%)	30 (36,6%)	33 (40,3%)
Medium (51%-74%)	39 (47,6%)	26 (31,7%)	36 (43,9%)	43 (52,4%)
High (over 75%)	17 (20,7%)	2 (2,4%)	16 (19,5%)	6 (7,3%)

Table 5. *Clinical and laboratory characteristics of patients with rheumatoid arthritis depending on general adherence to therapy (M±SD, Me [Q25; Q75]) (n=82)*

Index	Adherence to treatment, (n=49)	Not adherence to treatment, (n=33)	Value ρ
Age, years	51,04±10,3	56,7±9,11	ρ=0,002
Disease duration, years	10,07±5,6	11,8±7,7	ρ=0,582
Debut age, years	40,76±11,73	44,76±12,6	ρ=0,102
ESR mm/h	15,84±9,73	20,2±10,33	ρ=0,069
CRP, mg/ml	10,72±12,81	12,25±11,39	ρ=0,431
RF, e/l	65[18,9;95,2]	56,9[15,7;86]	ρ=0,636
NPJ	14[8;16]	14[9;20]	ρ=0,202
NSJ	5[2;8]	8[6;12]	ρ=0,006
VAS, mm	66[48;77]	74[61;81]	ρ=0,034
DAS28	4,86[4,2;5,57]	5,43[49;6,0]	ρ=0,025
Scale Morisky-Green, points	3[2;4]	2[1;3]	ρ=0,048
HAQ, баллы	1,13[0,75;1,63]	1,37[1,0;1,75]	ρ=0,035

Note: DAS — disease activity score, HAQ — Health Assessment Questionnaire, VAS — visual analog scale, CRP — c-reactive protein, RF — rheumatoid factor, ESR — erythrocyte sedimentation rate, NPJ — number of painful joints, NSJ — number of swollen joints

Table 6. *Marital status of patients with rheumatoid arthritis (n=82)*

Marital status	Adherence to treatment, n=49	Not adherence to treatment, n=33	Значение p Value p
Not married, n (%)	13(27%)	4 (12%)	p=0,049
Married, n (%)	29 (59%)	18 (55%)	p=0,072
Widows, n (%)	7 (14%)	11 (33%)	p=0,041

Discussion

In recent years, much attention has been paid to the communication between the physician and the patient. This is because the patient's understanding of his/her illness and medical recommendations and compliance with all of the physician's recommendations is the key to successful treatment of any chronic disease, including RA. The set of established facts and results obtained in large-scale studies, and the identified relationships and patterns indicate the current challenges in monitoring adherence to long-term treatment of patients with RA [13].

The comparison of the level of adherence to treatment of patients in different countries is a complex process. The differences can be explained by race, national peculiarities, various data collection tools, definitions and metrics of adherence to treatment, differences in healthcare systems, in particular, accessibility of medical services and rules for dispensing drugs.

At present, there is no standard method for assessing adherence to treatment. Therefore, the choice is left to the researcher to determine the method based on the expected result and personal preferences [14]. The simultaneous use of several assessment methods can yield a more accurate measurement of the patient's adherence to treatment, since the methods allow the collection of different information using different approaches, thereby complementing each other. In the study, where four methods were used to evaluate adherence to treatment among patients taking methotrexate, the greatest correlation was found between the Medication Event Monitoring System (MEMS), which is an objective method and the Visual Analogue Scale for adherence (VAS), which is a subjective method [15]. The results of this study showed that VAS could be used in everyday practice as a quick and easy method for assessing adherence to treatment.

The article by L.A. Anghel et al. (2018), cites data on the adherence to treatment among patients with rheumatic diseases [16]. Parameters of adherence to treatment varied widely, from 9.3% to 94%. The results depended on the specific rheumatic disease, the method used to assess adherence, and dividing patients into "adherent" and "non-adherent" groups. Different sources describe adherence of patients with RA to treatment as varying from 30% to 80% [13].

According to the recommendations of the Russian Scientific Medical Society of Therapists (RSMST), adherence to treatment is an integral parameter that includes three components: adherence to drug therapy, medical support, and lifestyle changes [17]. There are two approaches to evaluating adherence to treatment: evaluation of actual and initial adherence to treatment.

In general clinical practice, the Morisky—Green test is the most common for evaluating initial adherence to treatment due to its simplicity and repeatability [11]. During a visit, the attending physician asks the patient four questions and draws a conclusion on the patient's adherence to treatment depending on the number of positive answers.

Analysis of adherence to treatment using the Morisky—Green questionnaire revealed that only 34 (26.1%) patients with RA that we examined adhered to treatment.

Quantitative evaluation of adherence (KOP-25 questionnaire) showed the overall adherence to treatment of 54.3 [42.3; 64.1] %, and the lowest adherence — to lifestyle changes — of 42.1 [34; 53.8] %.

The relationship between RA duration and adherence to treatment was revealed. In patients with disease duration of over 12 years, there was

a tendency to decreased adherence to medical support and overall adherence to treatment.

According to the World Health Organization (WHO) report (2003) on patient adherence to treatment, all factors that have an effect on adherence to treatment can be divided into five groups: socioeconomic factors; factors related to medical personnel and healthcare system; factors associated with the therapy conducted; factors associated with the patient; factors associated with the current state of the patient [7]. Experts emphasize that none of these factors is the most important and determining factor for patient's behavior — they are all interconnected. N.Yu. Kuvshinova (2015) identifies the following reasons for low adherence of patients to treatment in different fields of medicine: cognitive impairment, asymptomatic disease, low treatment efficacy, lack of patient faith in treatment, lack of patient awareness of the disease, lack of mutual understanding between physician and patient, psychological problems, depression, inconvenient dosage frequency, complicated treatment regimen, need for long-term treatment [18].

Some studies showed that age, gender, comorbidity and disease activity had no effect on adherence to treatment using disease-modifying drugs for RA. In other studies, authors concluded that adherence is influenced by age, level of education, psychological status, disease severity, and administration of glucocorticoids [19]. There were no correlations between gender, age, level of education, social status, family, and material status of patients with RA and their adherence to treatment with DMARDs. However, non-adherent patients with RA had more significant pain intensity according to VAS and a worse functional status (HAQ) [20], which is consistent with our data.

Several studies showed that elderly patients with RA tend to have higher adherence to treatment [21, 22, 23]. According to our data, on the contrary, younger patients with RA demonstrated higher adherence to treatment, consistent with the results of other studies [24].

A study by Machado M.A. et al. (2016) revealed that low-income patients with RA tend to have higher adherence during the first and second years of follow-up than high-income patients [25]. According to our study, patients with the least material means have higher adherence to lifestyle recommendations, which is one of the components of adherence to treatment.

Several studies showed that increased family support was associated with higher adherence to therapy, and loneliness had a negative effect on adherence [23]. According to our data, both groups were comparable in the number of married patients, although widows dominated in the group of non-adherent patients.

A wide range of factors related to the disease, such as the variant of the disease and its duration, activity, and degree of functional limitations, and comorbidities, can impact adherence to treatment. Several studies revealed that a longer duration of the disease is associated with a lower level of pain [23, 24], and RA activity affects adherence to treatment [20, 21]. According to our study, significantly higher RA activity and low functional activity were observed in the group of patients non-adherent to drug therapy.

The patient's knowledge of his/her disease, motivated and willful use of drugs in the prescribed regimen and dose and the possibility of actual assessment of treatment efficacy by the patient are important factors that affect adherence to treatment. According to the literature, a positive attitude to taking medications and significant awareness of drug treatment were associated with higher adherence to treatment [23, 24].

Comorbidity is common in patients with RA [5]. The combination of various diseases generates additional challenges for management and contributes to reduced treatment efficacy [5]. According to researchers, comorbidities (coronary heart disease, hypertension, COPD, chronic kidney disease and liver diseases) can have both a negative [21, 22] and a positive effect on adherence to treatment [15]. In our opinion, the positive effect of comorbidity on adherence to treatment can be explained by the fact that a patient with many chronic diseases is more likely to follow all the physician's recommendations to maintain the quality of life. At the same time, one cannot disagree with the fact that comorbidities can reduce patients' adherence to treatment [6]. During a Brazilian retrospective crossover study, the relationship between adherence to therapy and chronic comorbid diseases (≥6 nosologies)

was established in the form of increased adherence with an increase in the number of diseases, the duration of treatment in hospitals (more than 15 years) and distance from a central medical institution [26]. According to our data, patients with more diseases are less adherent to medical support, which may be due to their need to visit physicians of various specialties, as well as intake of multiple medications.

Patients who are willfully adherent to treatment are three times more likely to improve their quality of life and increase their functional capabilities than patients not undergoing treatment [27]. In our study, quantitative evaluation of adherence to treatment according to the KOP-25 questionnaire revealed that non-adherent patients had worse HAQ values (functional status).-

Adherence to treatment is a dynamic process. Therefore, it can be described more accurately only when evaluated repeatedly (initially and during treatment). A physician should know about the patient's initial adherence to treatment to build the right dialog with said patient and develop an individual approach to the patient's treatment. These issues require special attention today when personal contact between patient and physician is not always possible. It is important to speak with the patient in a language that he/she understands when discussing issues relating to his/her treatment. An evaluation of the initial level of the patient's "willingness" to accept information about his/her disease from the physician will allow us to develop an optimal plan for monitoring and controlling treatment.

Conclusions

1. Most patients with rheumatoid arthritis have multiple comorbidity. Osteoarthritis, GIT, and cardiovascular diseases dominate the structure of comorbidity in patients with rheumatoid arthritis.
2. An evaluation of the initial overall adherence to treatment using the Morisky—Green questionnaire showed that 68 (52.3%) patients were non-adherent to treatment. Quantitative assessment (according to KOP-25 questionnaire) revealed the lowest adherence to recommendations on lifestyle changes.
3. Predictors of high adherence to treatment are the young age of patients, shorter disease duration, and poor financial situation.
4. Non-adherent patients have higher RA activity and lower functional status.
5. Simultaneous use of several methods to assess adherence to treatment is advisable to obtain more complete information about a patient. Evaluation of initial adherence to treatment in patients with rheumatoid arthritis will allow developing an optimal procedure for patient follow-up and treatment monitoring.

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication.

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