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# Comparative Analysis of Approaches and Treatment Results of Patients with Early and Nonearly Rheumatoid Arthritis

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## Abstract

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The article presents the results of a comparative analysis of different therapy regimens impact on the effectiveness of treatment of patients with early and late rheumatoid arthritis in steady-state. Data on ongoing basis anti-inflammatory therapy of rheumatoid arthritis and the treatment of associated conditions were obtained by continuous copying from case histories of hospital department patients. The observations lasted 12 months. The activity of rheumatoid arthritis before and after the treatment was determined by the DAS 28 (Disease Activity Score) index. The treatment results were evaluated as per the laboratory research and the DAS 28 index, including the counting of painful and swollen joints, erythrocyte sedimentation rate, and health assessment of the patient on a visual analogue scale.

## Introduction

Rheumatoid arthritis (RA) is one of the most severe and frequent inflammatory rheumatic diseases, which is associated with progression of joint destruction, decreased functional capacity and quality of life of patients, and the socio-economic hardship is occurring in this context [1].

Rheumatic diseases occur in people of any age, starting with children, but have a clear tendency to a significant accumulation with increasing age of patients. In the Russian Federation, up to 700 thousand new cases of inflammatory and degenerative diseases of the joints and systemic diseases of the connective tissue are diagnosed for the first time every year [2], [3]. The peak of the RA debut falls mainly on the working age. The loss of functional activity due to the development of erosive and destructive changes in the joints leads to disability

and incapacitation of patients. Ten years after the onset of the disease, 67% of patients have high (II – III) functional insufficiency of the joints and 44.5% have I and II disability groups [4]. The medical community considers rheumatic diseases as risk factors for the development of severe associated chronic diseases [3], [5]. The accelerated development of cardiovascular and other diseases in RA leads to reduced life expectancy and increased levels of mortality by 50 – 60% as compared to the general population. These are the rheumatic diseases that make the greatest contribution to the reduction of efficiency, deterioration of the general health of the population. All this causes a heavy socio-economic burden of this disease both for the patients, significantly reducing the quality of their life, and for the state health system as a whole due to the required considerable financial expenses for the provision of medical and pharmaceutical care to patients [5], [6], [7].

## Literature Review

Currently, the concept of managing patients with RA includes early diagnosis of the disease, timely active treatment commenced with the implementation of a therapeutic window of opportunity, careful monitoring for RA and response to therapy, the maximum suppression of disease activity in the short term in order to achieve and maintain a state of remission that is aimed at preventing the decline of patients' quality of life (program of "Treatment to reach the target") [8], [9], [10].

The primary method of achieving and increasing the duration of the RA remission stages is long-term use of the disease-modifying anti-rheumatic drugs (DMARD) and genetically engineered biologic drugs (GEBD), which reduce the activity of the inflammatory and autoimmune process. A large number of publications of domestic and foreign authors devoted to various approaches to the RA treatment confirm that the application of this approach in the RA treatment has resulted in tremendous progress [11], [12], [13], [14], [15], [16], [17], [18], [19], [20].

However, as noted by rheumatologists, the disease is the most important socio-economic problem because of its high incidence, poor prognosis (at untimely and inadequate treatment), as well as the need for long-term, and sometimes permanent, administration of different combinations of drugs. Moreover, a significant proportion of patients' needs orthopaedic surgery. The modern approaches to RA treatment are associated with significant financial costs. The above explains the significant socio-economic losses associated with RA that were similar to those seen in ischemic heart disease [4], [15], [16].

According to the data of Sh.F. Erdos, D.V. Goryacheva, O.A. Grigoriev et al., as a result of a clinical and economic study, it was revealed that the failure to obtain a social product due to the temporary disability of patients with RA was, on average, EUR 1 million/year in Russia. The support of one disabled person from the moment of disability until death costs the state EUR 20.4 thousand. The total state expenditures for disabled people with RA are EUR 18 billion. At the same time, the state does not receive a profit for EUR 160.5 thousand to EUR 214.0 thousand per each disabled person [21], [22].

The evaluation of the economic impact of two diseases of the musculoskeletal system and connective tissue, namely the RA and ankylosing spondylitis, showed that the value of direct medical costs was equal to EUR 6,454 per year (medical costs – EUR 4,170 per year, nonmedical costs – EUR 2,284 per year). The indirect costs due to disability constitute EUR 6,447 per year [22].

The cost of treatment and examination of the patient for the state is only 1/3 of the costs associated with RA. The remaining costs are determined by a

decrease in the quality of life of patients, the termination of their contribution to the creation of the common national product, and a decrease in the labour activity of relatives to provide care for the patient [22], [23], [24], [25].

The financial situation is an important factor that affects the performance associated with quality of life, including the functional activity of the patient [25], [26], [27].

Since RA is a chronic disease, and in fact, patients need expensive drugs for the life term, strategic approach to treatment is required.

## Methods

The content analysis of publications of domestic and foreign authors, the methods of mathematical statistics, structural, correlation, the nonparametric analysis were used in the process of work.

Statistica 6.0 (Statsoft, USA) was used for statistical data processing. The results are presented in the form of a median and interquartile interval (Me [25th; 75th percentile]). To compare the frequencies of qualitative traits in groups, the  $\chi^2$  criterion was used. When comparing the groups, the Mann-Whitney U test was used, and the correlation analysis was performed using the Spearman's Rank-Order Correlation. Differences were considered significant at  $p < 0.05$ . RA activity was determined from the DAS 28 value recommended by the European League Against Rheumatism (EULAR) as follows: DAS 28  $> 5.1$  – first class of activity, DAS 28 [3,2;5,1] – second class of activity, DAS 28 [2,6;3,2] – third class of activity, and DAS 28  $< 2.6$  – remission [28], [29].

## Results

The study included data on the results of treatment in 200 patients with a definite diagnosis of RA (165 women and 35 men) aged 19 to 73 years who had been treated in a special hospital.

**Table 1: The structure of the cohort of patients included in the study (n = 200)**

Indicator	Value
Gender, female/male, of them:	165/35 or 4.7:1
Women from 19 to 55 years old, n (%)	79 (47.9)
Women over 55 years old, n (%)	86 (52.1)
Men from 26 to 60 years old, n (%)	27 (77.1)
Men over 60 years old, n (%)	8 (22.9)

As can be seen from Table 1, almost half (47.9%) of the women and the majority (77.1%) of the

men suffering from RA were in working age.

One hundred and forty four patients (72.0%) had concomitant diseases, with arterial hypertension most commonly occurring – 60.0%, dyslipidemia – 45.0%, fractures of various localization – 29.5%, coronary heart disease – 21.0%, and also myocardial infarction (1.5%), stroke (1.0%), diabetes mellitus (7.5%), osteoporosis (15.5%), and ulcerative lesions of the upper gastrointestinal tract (14.9%).

Using continuous copying from the case histories, information on the medical prescription of drugs to the population of patients under study was obtained. Methotrexate was administered as the main DMARD; 139 (69.5%) patients received it. Leflunomide (9.0%) and sulfasalazine (1.5%) were also used. The GEBD therapy was used in 21.5% of cases and was represented by TNF-alpha inhibitors (9.0%), rituximab (6.5%), abatacept (4.5%), and tocilizumab (1.0%). Nineteen patients (9.5%) received nonsteroidal anti-inflammatory drugs (diclofenac, nimesulide, and meloxicam), 95 (47.5%) patients – selective COX-2 inhibitors (etoricoxib), and 86 (43%) patients – glucocorticoids (methylprednisolone, prednisone).

Additional therapy was assigned for the treatment of associated diseases. Ninety-eight (81.7%) of 120 patients received antihypertensive drugs; 27 (22.5%) patients – statins; 12 (10%) patients – hypoglycemic therapy; and 27% of the total number of patients received low doses of aspirin.

For a comparative analysis of the approaches and results of treatment of patients with early and nonearly RA, the patients were divided into two groups as follows (Table 2): the first one – with early RA (eRA) with a disease duration of up to two years (n = 60), the second included the patients with nonearly RA (more than two years) (nRA) (n = 140). The patient groups were matched by age, sex, and RA activity.

**Table 2: Characteristics of patient groups prior to observation**

Indicator	eRA value	nRA value
Gender, female/male (%), of them:	49/11 (82)	116/24 (83)
Women from 19 to 55 years old, n (%)	22 (36.7)	42 (30)
Women over 55 years old, n (%)	27 (45)	74 (52.9)
Men from 26 to 60 years old, n (%)	10 (16.7)	17 (12.1)
Men over 60 years old, n (%)	1 (1.6)	7 (5)
Disease duration, years	0.7 [0.3; 1.2]	8 [4; 14]
Me [25th; 75th percentile]		
Activity, n (%): I/II/III	28/39/33	31/54/15
DAS 28, Me [25th; 75th percentile]	4.23 [3.1; 5.7]	3.8 [3.1; 4.7]

Methotrexate was prescribed to most patients as basic therapy: in the first group – to 49 patients (81.7%) at a dose of 20 [15; 25] mg/week, in the second group – to 90 (64.3%) patients at a dose of 15 [10; 20] mg/week. All patients treated with methotrexate also received folic acid at a dose of 4.5 [3.3; 10.0] mg/week. Two (3.3%) patients of the first group and 16 (11.4%) patients of the second group received leflunomide; one patient (1.6%) of the first group and two (1.4%) patients of the second group

received sulfasalazine. Twelve (20%) patients with eRA and 31 (22%) patients with nRA received GEBD.

The frequency of assigning various GEBD is presented in Table 3. More than half of the patients were additionally administered NSAIDs, of which two (3.3%) patients of the first group and 17 (12%) patients of the second group received nonselective NSAIDs, 32 (53.3%) patients of the first group and 63 (45.0%) patients of the second group received selective NSAIDs.

**Table 3: The frequency of use of drugs for the RA treatment in patients with eRA (n = 60) and with nRA (n = 140)**

Name of the drug	Assignment frequency, n (%)	
	eRA	nRA
Methotrexate	49 (81.7)	90 (64.3)
Leflunomide	2 (3.3)	16 (11.4)
Sulfasalazine	1 (1.6)	2 (1.4)
GEBD:	12 (20)	31 (22)
Adadimumab	8(13.3)	5 (3.6)
Certolizumab	2 (3.3)	1 (0.7)
Infliximab	-	3 (2.1)
Tocilizumab	-	2 (1.4)
Rituximab	-	13 (9.3)
Abatacept	2 (3.3)	7 (5)
NSAID, of them:	34 (56.6)	80 (57.0)
- nonselective	2 (3.3)	17 (12.0)
- selective	32 (53.3)	63 (45.0)

The patients had been monitored for 12 months. By the end of the study, 26 patients were selected of which three had died, 13 had refused further research, and eight had not taken drugs for various reasons (pregnancy, high cost, and patient reluctance).

The results of the therapy were evaluated after 12 months in 56 patients with eRA and 128 patients with nRA. The characteristics of the patients are presented in Table 4. No differences have been found between weight and disease activity in groups of patients with eRA and nRA after 12 months.

**Table 4: Characteristics of patients after 12 months of treatment**

Indicator	eRA (n = 56)	nRA (n = 128)
DAS 28, points	3.0 [2.3; 4.4]	3.5 [2.6; 4.5]
Activity, remission/I/II/III, n	13/15/22/6	14/36/61/17

In general, in the eRA group, after 12 months, a decrease in the disease activity was observed as evidenced by the dynamics of the DAS 28 level from 4.23 to 3.0 points (p = 0.01), as well as a decrease in the number of patients with a third (III) degree of activity (from 33 to 6 people), and identification of the stage of drug remission in 13 patients (p < 0.01). In the nRA group, there was a tendency to a decrease in the level of DAS 28 from 3.8 to 3.5 points (p = 0.06).

As a result of analyzing the effect of drug combinations on the DAS 28 index, it was found that only the patients receiving combinations with GEBD had shown a significant decrease in DAS 28. Rituximab in the first group significantly reduced DAS 28 (n = 15, p = 0.04) from 4.5 [3.5; 5.3] to 3.8 [3.0; 4.4]. In the second group of patients (n = 14), the reliability of the results decreased (p = 0.06).

To verify the data obtained, a parallel study was conducted. It included data on the treatment of 64 patients with RA (54 women and 10 men) aged 55 [48; 60] years, with a prolonged course of the disease (5 [1 – 10] years), with moderate and high clinical disease activity (DAS 28 = 4.5 [3.5 – 5.3]). All patients received GEBD: tumor necrosis factor- $\alpha$  inhibitors (TNF- $\alpha$ ) were used in 27/64 (42%) patients, rituximab – in 15/64 (23%) patients, abatacept – in 12/64 (19%) patients, and tocilizumab – in 10/64 (16%) patients. Therapy with DMARDs was carried out in all patients. The patients were monitored for 12 months, and the disease activity was assessed by DAS 28.

As a result of the analysis of the GEBD influence on the DAS 28 index, a significant decrease in the index from 4.5 [3.5 – 5.3] to 3.7 [2.5; 4.6],  $p < 0.01$  was revealed. The most significant decrease in the DAS 28 index was observed during therapy with rituximab (4.5 [3.5; 5.3] and 3.8 [3.0; 4.4],  $p = 0.04$ ). The results are consistent with the research of R.M. Balabanova, V.N. Amirjanova, E.L. Nasonova, D.V. Goryacheva [13], [30].

According to the results of the clinical studies, a decrease in the level of C-reactive protein and rheumatoid factor by 73% and 59%, respectively, was observed in the studied group of patients. It was found that the most significant reduction in the average values of these indicators was typical for the patients whom rituximab was administered.

## Discussion

As noted above, the indicator of the quality of life is largely determined by the financial situation of the RA patient. For treatment, each patient with RA must be hospitalised once a year for 10 – 21 days (the average cost of hospitalisation is RUB 50,000 (EUR 687.54), and make blood tests once a month (RUB 500/month; RUB 6,000/year); the cost of each injection of the drug is about RUB 1,000. Direct medical expenses of the patient for the treatment will amount to RUB 58,000 – 128,000 (EUR 798 – 1,760) per year, excluding the cost of drugs.

The total direct costs for RA therapy using methotrexate and leflunomide regimens will be RUB 58,714 – 209,265 (EUR 807 – 2,878), respectively. However, these regimens do not have a significant effect on reducing RA activity.

GEBD therapy is 3 – 5 times more expensive due to the high cost of the GEBD (EUR 2,550 – 15,365). These therapy regimens reliably reduce the DAS 28 index, increase the frequency of remissions almost two times, compared to traditional therapy; therefore, improve the quality of life of patients. The frequency of deaths with strategies with the use of GEBD decreases by more than 10% in ten years [26].

In conclusion, the comparative analysis of different approaches to the treatment of RA has revealed a significant decrease of DAS 28 using rituximab (4.5→3.8). At the same time, the total direct cost of the RA therapy with rituximab is significantly lower than that in the treatment of RA using other GEBD. The GEBD treatment is especially important for patients with the nRA, more than half of whom are pensioners. Even the minimum direct cost of the RA therapy is 1.4 times higher than the average old-age retirement pension in Russia. For working people, the total direct costs for the GEBD therapy are 53.4 – 82.0% of the average wage.

It is obvious that the average citizen of Russia cannot afford the GEBD treatment; therefore, the main burden of using biological products must be taken by the state budget, which has significant limitations for carrying out expensive therapies. For the sustainable use of limited budgetary funds in medical organizations of the state healthcare system in Moscow, a commission has been set up to monitor the treatment using GEBD.

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