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Review Article

Saga of the Rheumatoid Arthritis Activity Criteria

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Received: February 17, 2020; **Published:** April 29, 2020

Abstract

The analysis of ideas about the rheumatoid arthritis activity criteria demonstrated not only the evolution of the its severity assessment, but also the advantages of domestic criteria, facilitating their use in routine clinical practice on the one hand, and the possible reasons making it difficult to use them on the other hand. The foreign colleagues have developed the complex indices that are inferior to the domestic criteria for diagnosing the rheumatoid arthritis activity in the number of objective indicators and ease of determination for a targeted assessment of the inflammatory process activity. In addition, a comparative study of the activity, widely determined by DAS28 and domestic criteria, showed a high level of statistical correlation, which allows us to discuss not only the appropriateness of using the latter in clinical practice, but to recommend it in the clinical studies as well.

Keywords: *Rheumatoid Arthritis; Activity Criteria; DAS28*

Introduction

In the 30's of the last century, the medical community recognized the need to create unified criteria for assessing the rheumatoid arthritis (RA) treatment effectiveness, since the relevant messages abounded in diverse, often misleading, terminology [1-3]. Therefore, the New York Association of Rheumatologists specifically organized the Committee on Therapeutic Criteria [4]. One of the main difficulties faced by its members is a wide palette of definitions of the therapeutic effect, which does not contribute to accurate assessment. For example, when presenting their findings, authors of articles on the treatment of RA used terms such as excellent, good, improvement, significant improvement, moderate improvement, objective improvement, etc. Even having specially studied treatment methods, the various investigators informed of the results in the form of not quite comparable conclusions. It became apparent that it was impossible for the reader not only to understand the meaning of many of them, but even to establish the usefulness of the data being reported.

An important problem in evaluating the results of treatment carried out by both the investigator and the patient was the enormous influence of subjective factors. Particularly confusing were the attempts to evaluate the effect of the received treatment on pain, since any new method could and did have a psychogenic effect. Therefore, it was decided to use only terms that objectively reflect the patient's condition during the treatment period. No less important was the exclusion of patients with a dubious diagnosis of RA, so a descriptive definition of RA was given: it is a systemic disease of unknown etiology that occurs at any age, reversible, especially at an early stage; generally progressive, involving joints (the main manifestation), usually multiple and usually symmetrical; with the spindle-shaped swelling being typical; the affected joints are characterized by pain, swelling, stiffness and other signs of inflammation, subcutaneous nodules and muscle atrophy often occur, the progression of the process is manifested by deformation, subluxation and/or ankylosis; osteoporosis, destruction of cartilage and subchondral bone are determined radiologically, the increased ESR, leukocytosis, anemia, and weight loss are sometimes noted. The course is usually progressive with exacerbations, but spontaneous remissions may occur.

Another problem that the members of the Committee on Therapeutic Criteria faced was the lack of understanding among many investigators about the natural course of the disease, which at some period can lead to spontaneous remission that is not related to treatment, or (more often) to exacerbation, since the disease usually progresses. Therefore, to assess the effectiveness of treatment, a sufficiently

long observation period is important, which allows taking this into account. It was assumed that the duration of such a period should be at least a year. A gradation of response to treatment has been developed. Complete remission - the most significant indicator (degree I response to treatment) meant: the absence of systemic manifestations and symptoms of joint inflammation; the absence of extra-articular symptoms; violation of joint mobility only as a result of irreversible changes; deformation of joints only as a result of irreversible changes; ESR within normal limits; lack of progression of radiological changes. Significant improvement (grade II response to treatment) included only: minimal (residual) swelling of the joints (without involving new joints); minimal extra-articular symptoms (without the appearance of new ones); limited mobility of the joints due to only minimal activity; joint deformation associated only with irreversible changes; ESR can be expedited; lack of progression of radiological changes. To eliminate possible errors in the interpretation of the natural course of the disease, the Committee recommended that the minimum improvement (grade III response to treatment) not be considered significant, which avoids false overstatement of successful results. The degree of IV response to treatment (without improvement) included the absence of changes. In the report on the therapeutic effect, it was recommended to consider the degree of changes in each case before treatment. To facilitate this task, it was proposed to classify patients according to the stage of the disease before treatment, as it allowed: to evaluate the progression of the disease; to note any differences in the response of each group of patients depending on the stage, to compare the results of different investigators. In addition, the patient's functional ability was also determined, since there is a relationship between structural changes and joint function, although not always proportional. According to the New York Association of Rheumatologists, treatment rarely leads to an improvement in the stage of the disease, while disease activity and/or functional ability may improve [4]. Therefore, it was initially necessary to establish a diagnosis of RA, the presence or absence of activity (the degree of activity was not yet determined at that time), the stage and functional class, and subsequently establish the severity of the response to treatment, evaluating the dynamics of changes in objective symptoms of activity.

The Institute of Rheumatism of the AMS [Academy of Medical Sciences] of the USSR also developed degrees of activity (their initial assessment was descriptive) of the disease (inactive, minimal, moderate, high activity), which in the future should have been important for the choice of treatment [5]. In the future, the assessment of the activity of the disease became more objective and it became possible to determine it in points: lack of activity - 0; minimal - 1 - 6; moderate - 7 - 12; high -13 - 18 points (Table 1), having developed standard basic indicators - three clinical (morning stiffness, hyperthermia and exudative phenomena in the joints) and three laboratory (increased levels of α_2-globulins, erythrocyte sedimentation rate (ESR), C-reactive protein - CRP) [6], such a unique complex set of markers of inflammation is not included in any of the modern activity indices. To calculate the activity, computer technology was not required, and the degree of activity could be established only by clinical criteria, designating it as "clinical activity". The obtained values could be compared during repeated studies, that is, in essence, these were indicators "for assessing the dynamics of the course of the disease".

Morning stiffness
No - 0; up to 30 min - 1; up to 12:00 p.m.- 2; over 12 hours -3.
Hyperthermia (joint hyperthermia)
No - 0; insignificant - 1; moderate - 2; expressed - 3.
Exudative phenomena in the joints
No - 0; insignificant - 1; moderate - 2; expressed -3.
Increased α2-globulin level (rel. %)
Up to 10.0 - 0; Up to 12.0 -1; Up to 15.0 -2; Over 15.0 -3.
ESR mm/hr (acc. to Panchenkov)
Normal (up to 12) - 0; Up to 20 - 1; Up to 40 - 2; Over 40 -3.
CRP (C -reactive protein)
Negative - 0; + 1; ++ 2; +++ 3.
Activity (A)
A 0 0; A1 - 1-6;A2 - 7-12;A3 - 13-18.

Table 1: *Criteria for diagnosing process activity in RA (points).*

Errors in the "Clinical Rheumatology" and "Rheumatic Diseases" national guidelines issued in circulation of 73,000 and 5,000, respectively [7,8] and the lesser-known monograph "Rheumatoid Arthritis", in which Russian authors did not describe the method for scoring RA activity [9], hindered its practical application. Only a few years later, the American College of Rheumatology (ACR) developed preliminary criteria for remission [10]: complete remission implied the absence of all articular and extra-articular signs of inflammation and immunological activity associated with RA. In practice, these criteria were used very limited, since very few patients corresponded to those criteria.

After another thirteen years, the World Health Organization (WHO), together with the International Association of Rheumatologists, finally suggested the baseline indicators for assessing the effectiveness of basic anti-inflammatory drugs in patients with RA (pain, patient's global assessment (PGA), functional failure, and the swollen joints count (SJC), tender joints count (TJC), acute phase indicators, Physician's Global Assessment (PhGA) and X-ray examination of joints with prolonged (not less than a year) treatment [11]. Finally, the disease activity score (DAS) was developed, which is a combination of individual activity indicators [12]. The original DAS includes the Richie index (0 - 78); SJC (0 - 44); ESR - 0 - 200 mm/hour according to Westergren; patient's global assessment (PGA) on VAS (visual analog scale) - 0 - 100 mm. Later, a simplified version of the DAS - DAS28 was proposed, which is calculated according to the results of the study of 28 joints. At the same time, SJC, TJC, patient's global assessment (PGA) and ESR are used as initial components. DAS as well as DAS28 can be calculated using CRP in mg/L [13,14] instead of ESR. 8 versions of these indicators are available. It is used only for RA, for other rheumatic diseases it is not formally validated. DAS and DAS28 indicators range from 0 to 10 and from 0 to 9.4, respectively. Moreover, in long-term observations up to 6 years, it was found that DAS28 is not inferior to DAS in sensitivity. To calculate DAS, computer technology is required, since this is a complex and cumbersome procedure, which proved to be of little use for everyday clinical practice, therefore, Russian rheumatologists in practical healthcare assessed the activity of RA randomly, based on personal experience. In addition, the DAS and DAS28 index have a number of limitations due to their components. In particular, since the ESR parameter is affected by the age of patients, the calculation of DAS and DAS28 will not allow to accurately assess remission in the elderly, i.e. patients over 60 years of age [15,16]. Moreover, DAS is very sensitive to changes in almost normal ESR parameters, that is, it is subject to significant fluctuations [17]. In addition to the presence and severity of the inflammatory process, ESR is influenced by a number of other factors [18]. Possible reasons for the increase in ESR are: anemia with a normal erythrocyte morphology, which is explained by a change in the ratio of red blood cells and plasma, which contributes to the formation of red blood cell columns regardless of fibrinogen concentration; an increase in plasma concentration of all proteins except fibrinogen; renal failure; hypercholesterolemia; extremely high obesity, accompanied by obesity fibrinogen level; female; elderly. According to rough estimates, in men, the upper level of normal ESR is the figure obtained by dividing the age by 2, for women - the age of plus 10, and divided by 2; technical errors. Deviation of the tube from the vertical position to the sides by 3° from the vertical line can lead to an increase in ESR up to 30 units. Factors that contribute to the decrease in ESR: morphological changes in red blood cells; polycythemia; significant increase in white blood cell count; DIC-syndrome (due to hypofibrinogenemia); dysfibrinogenemia and afibrinogenemia; cachexia; technical errors (ambient temperature, the period before determination over 2 hours).

Having spent effort and time (5 - 8 minutes to evaluate joint counts, as well as the waiting time for ESR results for 1 hour [19], when determining the DAS index, it is often possible to erroneously establish a higher degree of disease activity due to such a component as patient's global assessment (PGA) on VAS (visual analog scale), subjective and largely dependent on the concomitant pathology of the indicator and to carry out the appropriate correction (essentially unnecessary) of the drug treatment, which cannot always be neglected due to the possible adverse reactions. According to DAS28, up to 8 swollen joints are recorded in patients with remission, but there may be more, since the joints of the feet are not taken into account when calculating this index. In addition, the use of DAS28 in daily clinical practice is hampered by the need to directly obtain the actual results of ESR determination. Thus, the 2.6 DAS28 criteria are considered to be insufficiently reliable [20-25]. It is even proposed to consider a more rigorous definition of remission: < 2.4 according to DAS28 [26]. As an alternative, the definition of CRP as a marker of inflammation is discussed, because [27]: the content of CRP in plasma is determined only by the level of its synthesis, which, in turn, depends solely on the severity of the inflammatory process; CRP belongs to acute phase proteins, the content of which during the period of inflammation can increase by 100 or even 1000 times. A special study of the compara-

bility of DAS28-SOE and DAS28-CRP with early (n = 520) and unfolded (n = 364) RA showed them a significant difference in moderate and high activity, especially in women [27]. DAS28-CRP gives a higher assessment of efficiency according to the EULAR criteria than DAS28-ESR [28]. When comparing the indicators DAS28-CRP and DAS28-ESR, the difference in the frequency of detection of remission reached 11.2% [29]. The use of CRP for calculating DAS28 is a reasonable alternative to ESR for several reasons: CRP, like ESR, is well correlated with dynamic changes in inflammation activity, radiological progression, and functional impairment [30]. At the same time, unlike ESR, its level does not depend on such factors as gender, age, and plasma protein levels; CRP is determined by laboratory tests faster than ESR and can be standardized; and the progression of joint damage and functional status can be determined according to the level of CRP as well [30,31].

The RA activity criteria developed at the Institute of Rheumatism of the Academy of Medical Sciences of the USSR [6] do not have the abovementioned shortcomings, having no pain indicator (being a very subjective one), and the calculation process not requiring the PC like it is for the corresponding calculation of the DAS index (programmable calculator or computer, or computer with Internet connection) which is very important in our time. Domestic authors comparing the domestic criteria for RA activity with the DAS and DAS28 indicators have made some errors in the calculations, so the results are doubtful [33].

We, in turn, carried out a comparative analysis of the assessment of RA activity according to DAS 28 and according to domestic criteria [6], modifying the results of CRP in them in accordance with the proposals adopted at the round table "Classification of Rheumatoid Arthritis" at the III Congress of Russian Rheumatologists (Table 2).

Parameters	Activity degrees*			
	0	1	2	3
VAS pain* (cm)	0	Up to 3	4-6	> 6
Morning stiffness (min)	No	30 - 60	Up to 12 hours	During the day
ESR (mm/hour)	5 - 15	16 - 30	31 - 45	> 45
C-reactive protein, upper limit	≤ 1	≤ 2	≤ 3	> 3

Table 2: *Determining the rheumatoid arthritis activity degree.*
*Note: *0: Remission; 1: Minimum; 2: Medium; 3: Maximum.*

The study included patients with 31 RA in the number that meet the classification criteria of ACR (American College of Rheumatology)/EULAR (European League Against Rheumatism), 2010 [10], the average age of the patients was 54 ± 9 years, the median disease duration was 5.5 years with an interquantile range (1.75 - 10). The activity of RA was determined according to domestic criteria [6] - table 3 and according to the activity index DAS28 [13] - table 4.

Parameters	Activity degrees			
	0	1	2	3
Activity (A), points	0	1 - 6	7 - 12	13 - 18
% (n)	0	32,3 (10)	35,6 (11)	32,3 (10)
Morning stiffness (min)	No	30 - 60	Up to 12 hours	During the day
% (n)	0	32,3 (10)	35,6 (11)	32,3 (10)
Hyperthermia (joints) at palpation	No	Insignificant	Moderate	Expressed
% (n)	29 (9)	19,4 (6)	41,9 (13)	9,7 (3)
Exudative phenomena in the joints at palpation	No	Insignificant	Moderate	Expressed
% (n)	3,2 (1)	16,1 (5)	51,6 (16)	29 (9)
Increased a^2-globulin level (rel. %)	Up to 10	Up to 12	Up to 15	> 15
% (n)	42,1 (8)	26,3 (5)	26,3 (5)	5,2 (1)
ESR according to Panchenkov (mm/hour)*	Up to 12	Up to 20	Up to 40	> 40
% (n)	22,6 (7)	29 (9)	22,6 (7)	25,8 (8)
CRP, upper limit	≤ 1	≤ 2	≤ 3	> 3
% (n)	22,6 (7)	22,6 (7)	6,5 (2)	48,4 (1)

Table 3: *Rheumatoid arthritis activity parameters according to the domestic criteria, n = 31.*

The average activity value is 8.9 ± 4.2 points.

Parameters	(M ±)
DAS28	5,2 ± 1,0
TJC	6,4 ± 5,0
SJC	4,9 ± 3,8
PGA	67,8 ± 15,4
ESR acc. to Westergren (mm/hour)	31 ± 27

Table 4: *Activity criteria according to DAS28, n = 31.*

A comparison of RA activity, determined by domestic criteria and DAS28, showed a pronounced level of statistical correlation of two scales, r = 0.69 (Figure).

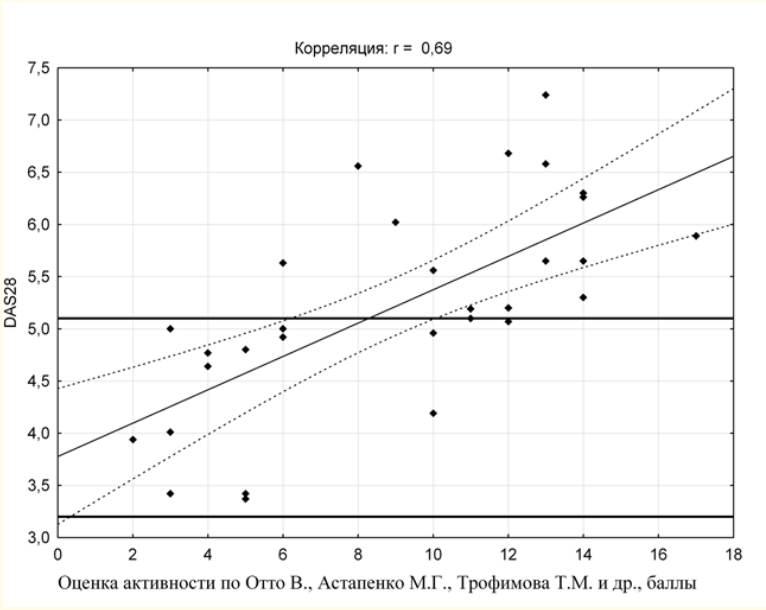

Figure: *Correlation analysis. scatter plot.*

Correlation; activity assessment according to Отто В., Астапенко М.Г., Трофимова Т.М. and others, points [6].

The strict control strategy discussed since the beginning of this century [24], which is essentially a renaissance of domestic dispensary observation, can significantly increase the effectiveness of treatment of RA [34-36]. According to the order of the Ministry of Health of the USSR No. 648 dated 15.07.1975 (i.e., almost half a century ago), all patients with RA were subject to follow-up, the tasks of which were: 1) to maintain the process at the level of minimal activity; 2) to prevent exacerbations; 3) to restore and maintain functions of the musculoskeletal system; 4) to determine the indications for re-hospitalization of patients or their referral for health resort treatment. Clinical examinations, including rheumatological profile, dedicated to the Resolution of the July (1983) Plenum of the Central Committee of the CPSU [37].

Now, according to the foreign experts, the remission should be considered the main goal of RA therapy [38-40]. The low disease activity may be the suitable alternative [41]. However, among rheumatologists there are still significant differences in understanding RA remission [10]. Obviously, therefore, in the first decade of the 21st century, the medical community finally realized the need to create unified criteria for RA remission, which led to the organization of a committee to review the definition of remission in RA under the auspices of ACR and EULAR, which prepared an appropriate systematic review [42], as well as a plan for such a review and ways of its implementation. In the future, a decision was made regarding the revision of the definition of remission and a consensus was reached that any definition should include at least the TJC, SJC and the level of acute phase indicators, but exclude treatment, duration of remission, indicators of physical function and radiological progression. It seems that the above exceptions are not just a simplification, but a step backward compared with the understanding of RA remission in the middle of the last century [4], in addition, it contradicts the 7th recommendation of the modern treat to target strategy, according to which the structural and functional changes must be taken into consideration along with the assessment of activity indices (therefore, joint radiography should be performed annually and in cases where progression occurs despite the achievement of the desired goal, intensification of treatment is necessary) [41] and finally, almost excludes the drug-free remission. Nevertheless, the ACR/EULAR proposed two definitions of remission (though for research purposes), including the estimation of CRP and not requiring special computing techniques to calculate [43]: logical (Bulevo): TJC, SJC, CRP (in mg/dl) and PGA ≤ 1, (when assessing TJC and SJC for 28 joints, it is also advisable to take into account the joints of the feet and ankles) [44]; the SDAI index (simplified diseases activity index) ≤ 3.3 [42]. In clinical practice, a condition in which TJC, SJC and PGA is ≤ 1 is recommended to be considered as a remission [45]. However, almost half a century ago, the Institute of Rheumatism of the Academy of Medical Sciences of the USSR already developed criteria for the lack of activity of the RA, i.e. remission (in points: morning stiffness -0; hyperthermia of the joints - 0; exudative effects in the joints - 0, normal values of three acute phase indicators), and the clinical activity of the disease, using these criteria, could be calculated within a few seconds right at the patient's bedside [6].

Conclusion

Thus, the generally accepted basis of the criteria for the effectiveness of treatment of RA is the activity of the inflammatory process, for the purpose of which our foreign colleagues have developed complex indices that are inferior to the criteria for diagnosing RA activity developed by domestic scientists in terms of the number of objective indicators and the ease of determination. In addition, a comparison of RA activity, determined by DAS28 and domestic criteria, showed a pronounced level of statistical correlation, which allows not only to discuss the advisability of using the latter in clinical trials, but also to recommend it in clinical practice.

B	**P**	**B**	**P**	**B**	**P**	**B**	**P**
1	1	31	27	61	48	91	66
2	2	32	27	62	49	92	67
3	3	33	28	63	49	93	67
4	4	34	29	64	50	94	68
5	5	35	30	65	50	95	68
6	6	36	30	66	51	96	69
7	7	37	31	67	52	97	69
8	8	38	32	68	52	98	70
9	9	39	33	69	53	99	70
10	10	40	33	70	54	100	71
11	11	41	34	71	54	101	71
12	12	42	35	72	55	102	72

13	13	43	36	73	55	103	72
14	14	44	36	74	56	104	73
15	14	45	37	75	57	105	73
16	15	46	38	76	57	106	74
17	16	47	38	77	58	107	74
18	17	48	39	78	59	108	75
19	17	49	40	79	59	109	75
20	18	50	40	80	60	110	76
21	19	51	41	81	60	111	76
22	20	52	42	82	61	112	77
23	21	53	43	83	61	113	77
24	21	54	43	84	62	114	78
25	22	55	44	85	63	115	78
26	23	56	45	86	63	116	79
27	24	57	45	87	64	117	79
28	24	58	46	88	64	118	80
29	25	59	47	89	65	119	80
30	26	60	47	90	65	120	81

Supplement Table: **Correspondence of ESR results (obtained by the methods of Westergren and Panchenkov).*

Note: ESR results are presented in mm/hour; B: Westergren method; P: Panchenkov's method.

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