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RESEARCH ARTICLE

Immune and mathematical procedures in early diagnosis of psoriatic and seronegative rheumatoid arthritis

Alesea Nistor[1,2*], Eugeniu Russu[1], Liliana Groppa[1,2], Lia Chișlari[1], Lucia Dutca[1], Liudmila Gonța[1]
[1]Discipline of Internal Medicine, Department of rheumatology and nephrology, Nicolae Testemitanu State University of Medicine and Pharmacy, Chișinău, Republic of Moldova
[2]Rheumatology laboratory, Timofei Moșneaga Republican Clinical Hospital, Chișinău, Republic of Moldova.

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Corresponding author:
Alesea Nistor, MD, university assistant
Discipline of Internal Medicine, Department of rheumatology and nephrology, Nicolae Testemitanu State University of Medicine and Pharmacy, Republic of Moldova.
29 N. Testemițanu, MD-2025, Chisinau, Republic of Moldova
e-mail: alesea.nistor@usmf.md

What is not yet known on the issue addressed in the submitted manuscript

It is of particular interest to determine the early diagnosis of psoriatic arthritis (PsA) and rheumatoid arthritis (RA) based on clinical data, immunological and mathematical research methods.

The research hypothesis

The difficulties in the early diagnosis of PsA and RA especially when RA is seronegative drive clinicians to search for different methods to establish the diagnosis – these may include clinical, immunological, and mathematical methods.

The novelty added by manuscript to the already published scientific literature

Immune disorders in the early stages of RA and PsA are nonspecific and are characterized by an increase in CD16+ and CD29+ in RA, which is significantly higher than in PsA, that is why mathematical model of RA and PsA has been developed and may serve as an additional way in diagnosing seronegative RA and early PsA.

Abstract

Objectives. Improvement of early diagnosis of psoriatic arthritis based on clinical data, immunological and mathematical research methods.

Material and methods. The study was carried out between 2019 and 2022 at the Rheumatology and Nephrology Discipline, in the arthrology and rheumatology departments of the *Timofei Moșneaga* Republican Clinical Hospital. To accomplish the tasks set out in the study, 110 patients were examined, including 55 patients with psoriatic arthritis (group I) and 55 patients with rheumatoid arthritis (group II).

Results. The range with the highest probability of psoriatic arthritis for the instrumental index is between 0.54 and 1.86. Of the 55 patients with psoriatic arthritis in 95% of patients clinical, laboratory, immunological and instrumental indices were within the range of the highest probability of the disease, which indicates a fairly high reliability of the mathematical model.

Conclusions. Immune disorders in the early stages of rheumatoid arthritis and psoriatic arthritis are nonspecific and are characterized by an increase in CD16+ (26.2±1.5) and CD29+ (24.8±2.1) in rheumatoid arthritis, which is significantly higher than in psoriatic arthritis CD16+ (22.0±1.3) and CD29+ (17.4±3.2) ($p < 0.05$). A mathematical model of rheumatoid arthritis and psoriatic arthritis has been developed, which serves as an additional way of diagnosing rheumatoid arthritis and early psoriatic arthritis.

Keywords: rheumatoid, psoriatic arthritis, mathematical, immune diagnosis.

Introduction

Psoriatic arthritis (PsA), as well as rheumatoid arthritis (RA) refer to diseases of great medical and social importance, due to the significant prevalence and progressive character of the disease, leading to early disability in individuals [1-3]. Lately, revisions have appeared dedicated to the description of new clinical forms of PsA and RA [4-6]. This creates difficulties in diagnosing the early stages of the diseases. At the same time, many joint lesions at the initial stage do not have sufficiently characteristic clinical and radiological signs that can be used as diagnostic criteria. In some cases, the recognition of joint conditions is extremely difficult in atypical natural history of diseases, especially with mono- or oligoarthritis [2, 4].

At the same time, it became known that the early years of the evolution of PsA and RA are crucial in the development and progression of the pathological process [1, 4, 7, 8]. It has

been established that the early stage of PsA and RA differs significantly from the later stages of the disease from a morphological point of view [3, 5, 9]. Therefore, remissions of the diseases are much more frequently observed in the initial period of PsA and RA [5, 6, 10]. This is fundamental for the initiation of appropriate pathogenetic treatment, when it is possible to suppress the active immuno-inflammatory process faster and more firmly and therefore prevent irreversible destruction of the joints [2, 5, 7].

However, such an approach to therapy is possible only under the conditions of early diagnosis of PsA and RA. Nevertheless, the problem of early diagnosis, especially PsA, remains an unresolved problem and of the most urgent in modern rheumatology.

PsA and RA are considered diseases where the pathogenesis are of great importance to immunological disorders [1, 3, 11, 12]. However, quantitative data and qualitative characteristics of individual indicators of the immune system and their significance in the development of PsA and RA are contradictory [2, 8, 9]. Therefore, the question of the importance of immunological disorders in the diagnosis of these pathologies remains relevant.

Thus, the polymorphism of clinical forms of PsA and RA, the lack of reliable early diagnostic criteria and methods create difficulties in recognizing the early stages of PsA and RA.

The purpose of the study was to improve the early diagnosis of psoriatic arthritis based on clinical data, immunological and mathematical research methods.

Material and methods

The study was carried out between 2019 and 2022 at the Rheumatology and Nephrology Discipline, in the arthrology and rheumatology departments of the *Timofei Moşneaga* Republican Clinical Hospital - Favorable opinion of the Research Ethics Committee at minutes No.21 from 21.12.2019. To accomplish the objectives, 110 patients were examined, including 55 patients with PsA (group I) and 55 patients with RA (group II). The diagnosis of RA was established according to the EULAR criteria (2010), PsA was established using the CASPAR classification criteria [1-3].

The age of patients at enrollment in the study ranged from 18 to 64 years (average 42.69±1.09 years), of them women – 82 patients (74.5%) and men – 28 patients (25.5%). The duration of the disease at the time of observation was the following – less than one-year (on average 5.91±0.38 months) – 85 (77.3%) patients, from 1.1 years to 3 years (on average 26.33±2.84 months) – 3 patients (2.7%) and with a course of the disease over 3 years (on average 157.5±18.43 months) – 22 patients (20%). Statistical analysis of the results was carried out through Statistics Software Package 9.0.

Results

Arthralgias were the most common symptom that persistently precedes joint syndrome in PsA and RA, however, joint pain was significantly more common in the group of patients with RA than in the group with PsA ($p < 0.05$). At the same time, in the group of patients with RA, the pain was more often localized in the joints of the upper extremities and most often in the shoulder (38.2%). In the group of patients with PsA, the joints of the lower extremities were the most common affected, while the knee joints were in first place in terms of frequency of occurrence (25.5%). Pain in the lumbo-sacral region was found only in the 2nd group of patients, being one of the causes of inflammatory low back pain (in 9.5% of patients). Talalgia was isolated as a separate element and was significantly more common ($p <0.05$) in the group of patients with PsA (25.5%) than in patients with RA (5.5%).

The onset of RA in most of the cases in our study had a classical course, in patients with RA joint damage was predominated arthritis – 76.4%, which was more often detected in women (61.8%). The disease began with lesions of the joints of the hands – radiocarpal joints (41.8%), proximal interphalangeal (47.3%) and metacarpophalangeal (58.2%); the lesions were symmetrical. The joints of the knee (34.5%) and ankles (25.5%) were often involved in the process, and the injury was asymmetrical in 24.2% of patients. However, in 23.6% of RA patients, the disease started atypically with mono-oligoarthritis, and these cases showed the greatest difficulties in establishing the diagnosis, but this form was not stable and turned into polyarthritis during the first year of the disease.

In the first year of the disease in the group of patients with RA, the indicators of the number of inflamed joints (10.4±0.8), the Ritchie articular index (11.05±0.69) and the Lee functional test (11.8±0.82) were significantly higher ($p <0.05$) than in the group of patients with PsA (2.88±0.36, 6.71±0.82, and 7.16±0.86 correspondingly). Especially they differ by the number of inflamed joints. In any case, over time and as PsA progress, these indicators become similar to the characteristics of RA.

Statistically significant differences in the groups of patients with early RA and PsA were detected by hemoglobin (113.6±1.8 g/l, 120.6±2.5 g/l), ESR (34.9±2.1 mm/h, 22.0±2.4 mm/h) RF (2.46±0.07 and 1.56±0.09) and CIC (88.6±5.2 and 68.3±6.1). In the group of patients with PsA with a duration of the disease of more than 3 years, the indicators of ESR, RF and CIC increase and correspond to the group of patients with RA.

The statistical analysis of the immunological parameters revealed significant differences ($p <0.05$) in the IgG content (20.09±0.09 and 14.35±1.2) in patients with early RA versus patients with early PsA, which correlate with the increase in RF content and the frequency of its detection in patients with RA. In the group of patients with early RA, the content of CD16+ cells at IgG Fc fragment were significantly higher, which correlates with an increased IgG content in this group compared to the group of patients with early PsA. This increase is natural, because in the group of patients with early RA, RF is detected more frequently. However, in the group of patients with PsA with a duration of the disease of more than 3 years, this difference disappears, which is because in these patients the frequency of RF detection increases over time.

The level of CD29+ (Th2) cells in early RA was also significantly higher than in early PsA ($p <0.05$), which can be

explained by the higher activity and systemic autoimmune reactions, with more implications of humoral immunity. The rate of CD38+, CD45+ and CD11+ in patients with RA and PsA was higher than normal, although their absolute values were normal, which is possible due to the increased level of leukocytes and lymphocytes (Table 1).

Table 1. Quantitative indicators of T lymphocyte subpopulations involved in autoimmune reactions in patients with PsA and RA at different stages of the disease.

Normal indexes and values	Duration of the disease			
	<1 year (I)		≥3 years (II)	
	RA (n = 55)	PsA (n = 30)	PsA (n = 25)	
CD38+	23±6	31.3±1.0	29.8±2.1	39.6±2.7
	Absolute values (300-600)	544.1±34.3	444.0±43.7	545.3±60.2
CD45+	25±5	31.3±1.8	34.4±2.9	34.4±3.9
	Absolute values (500 - 700)	483.0±45.4	504.3±63.2	487.2±79.8
CD29+	24±6	24.8±2.1	17.4±3.2*	25.7±5.6
	Absolute values (400-600)	391.8±39.6	239.6±52.1	336.6±67.1
CD16+	12±6	26.2±1.5	22.0±1.3*	29.5±1.8
	Absolute values (200-300)	447.2±37.7	358,1±42.0	416.4±36.2
CD11+	21±6	30.2±1.7	29.9±1.9	33.9±3.4
	Absolute values (300-600)	475.0±38.7	404.3±41.2	515.5±77.8

***Note:** * - p <0,05; group ≥3 years consist of: 1.1 to 3 years – 3 and over 3 years 22 patients. CD – clonal determinant; PsA - psoriatic arthritis; RA - rheumatoid arthritis.*

To form a mathematical model of PsA and RA the results of the study were accumulated in 2 groups of patients with PsA and RA. Clinical, laboratory, immunological and instrumental studies were evaluated on the three-point scale depending on the severity of symptoms. Indexes of immunoglobulins and lymphocyte populations on a two-point scale were evaluated. Next, the diagnostic value of each characteristic was evaluated, and the highest informative value was achieved (Table 2).

Table 2. Mathematical expectations and X^2 deviation of indexes in the group of patients with RA.

Indexes	M	I	Indicators	M	I
Clinical indexes			**Immunological indexes**		
Decrease in body mass	0.78	1.13	RF (latex test)	1.92	1.04
Arthralgia	2.26	0.56	ICC	1.60	0.91
Morning stiffness	1.68	0.73	IgA	0.39	0.78
Articular index, points	1.54	0.64	IgM	1.43	0.90
NSJ	2.34	0.59	IgG	1.14	0.95
Lee test, points	1.56	0.70	CD3+	1.14	0.40
Laboratory indexes			CD19+	1.13	0.67
ESR (mm\hour)	2.02	0.93	CD4+	1.29	0.49
α_2-globulins	0.90	0.61	CD8+	1.31	0.46
γ- globulins	1.24	0.88	CD4+/CD8+	0.88	0.77
CRP	0.90	1.15	CD16+	1.76	0.42

***Note:** M – median; I – informative value of index; ESR – erythrocyte sedimentation rate; CRP – C-reactive protein.*

The most informative of the clinical indexes in early RA were – joint pain, the nature of joint damage and the number of inflamed joints. All laboratory indicators were of low informative value due to low average indices and significant data dispersion. Among the immunological data, the indicators RF, CIC, CD4+, CD8+ were the most informative. Then the laboratory (φL), clinical (φC) and immunological (φI) indexes were calculated according to the following formulas:

$\varphi C = a1S1 + a2S2 + a3S3 + \ldots + a11S11;$

$\varphi L = b1C1 + b2C2 + \ldots + b6C6;$

$\varphi I = c1D1 + c2D2 + \ldots + c12D12;$

where a, b, c is the informative coefficient of indicators, S – clinical indicators, C – laboratory indicators, D – Immunological indicators.

As a result, the clinical index corresponded to the range from 1.26 to 2.60; laboratory – from 0.11 to 2.24; immunological – from 0.85 to 1.68. Provided that the patient is clinical, laboratory and immunologically framed in the above intervals, then it can be stated with a high degree of probability that he has RA. In our group of 55 patients with RA in 89% of patients by clinical, laboratory and immunological indices calculated according to the proposed formulas, in the elaborated model they were within the range with the highest probability of the disease, which demonstrates a fairly high reliability of the model. The three previously introduced indices were complemented by another instrumental one, which was determined as a weighted average of 60 instrumental indicators, each of which was detected in 30 patients out of 55. The introduction of the instrumental index is a development of the previously developed RA mo-

del. The instrumental index was calculated by the formula: $\varphi In = 0{,}02\sum_{p=1}^{60} DS(Ap)$, where Ap – Instrumental indicator with the number p, SD (Ap) – the standard deviation of the indicator, if SD = 0, then the indicator is insignificant and was not taken into account.

The range with the highest probability of RA for the instrumental index is between 0.82 and 2.21, which corresponds to the mathematical expectation of 1.52, increased and decreased by 0.69. Distribution histograms were constructed for all four indices. The PsA model was developed according to the regressive methodology. The formulas for clinical, laboratory and immunological indices were determined by the method of the lowest X^2 based on the evaluation of the severity of the disease by the doctor on a scale of three points similar to RA. The mathematical model can be expressed by the formulas: $\varphi C = \sum_{1=1}^{12} a1S1$, $\varphi L = \sum_{1=1}^{6} b1C1$, $\varphi In = \sum_{1=1}^{12} c1D1$, where a1, b1, c1 unknown coefficients, to be determined, S1 – clinical indicators, C1 – laboratory indicators, D1 – immunological indicators.

The coefficients a1, b1, c1 were found from the best state (in the sense of standard deviation) the coincidence of the subjective assessment of the severity of the disease φC, determined by the doctor with a combination of indicators from the above formulas. For example, the coefficients a, were in the state $\sum_{k=1} a1\,(-\sum_{k=1}^{12} a1S1(k))$. In the result, the following formulas were obtained:

φC = 0.367S1- 0.130S2 + 0.073S3 + 0.121S4 + 0.038S5 + 0.155S6 + 0.014S7 + 0.122S8 + 0.327S9 + 0.266S10 – 0.026S11 – 0.151S12

φL = 0.409C1 + 0.211C2 + 0.162C3 + 0.142C4 – 0.012C5 + 0.246C6

φI = 0.498D1 + 0.405D2 + 0.106D3 + 0.183D4 + 0.293D5 – 0.166D6 – 0.096D7 – 0.013D8 + 0.148D9 + 0.043D10 – 0.106D11 + 0.099D12

The values of the indecency determined by these formulas in most cases coincided with the subjective evaluation of the doctor. The range of values for the clinical index corresponded from 0.58 to 1.84, for the laboratory – 0.63 - 1.93, immunological – 0.63 - 1.66, which corresponds to the increased and low mathematical expectation of SD.

The instrumental index for PsA was determined by the same method as for RA, as a weighted average: $\varphi In = 0{,}015\sum_{p=1}^{60} DS(Ap)$.

Discussions

In our study, the most common symptoms in the prenosological period, that is, the previous stage chronologically the development of persistent joint syndrome in both groups, were arthralgia (RA – 69.1%, PsA – 38.2%), an increase in body temperature (RA – 36.4%, PsA – 29.1%), a decrease in body weight (RA – 25.5%, PsA – 5.5%). Weight loss was significantly more common in patients with RA ($p < 0.05$), which may indirectly indicate a more systemic nature of the inflammatory process in RA [7-9].

However, the picture of immunopathological indicators between RA and early PsA shows more similarities than differences. In all groups, there was a decrease in the level of CD3+ cells (RA – 58.3±1.3% and 57.3%±1.9% PsA). CD8+ levels in patients with RA and PsA were determined at the upper limit of the norm (23.9±1.7% and 26.4±1.9%). The rate of CD19+ cells (RA 21.6±1.5%, 20.8±1.2% PsA) and CD4+ (50.9±1.8% RA, 48.3±2.2% PsA) in both diseases were increased compared to the norm. In any case, the absolute values of CD19+ (355.0±32.8 RA, 311.4±26.4 PsA) and CD4+ (833.5±53.7 RA, 695.2±64.7 PsA) are close to normal. With an increase in the duration of PsA, inflammatory and immunological indicators in absolute and percentage values approach those in RA.

Based on the results obtained from clinical, laboratory and instrumental studies using multidimensional methods of statistical analysis, we have developed mathematical models of PsA and RA.

The range with the highest probability of PsA for the instrumental index is between 0.54 and 1.86. Of the 55 patients with PsA in 95% of patients, clinical, laboratory, immunological and instrumental indices were within the range of the highest probability of the disease, which indicates a fairly high reliability of the model [4, 9, 11]. In order to test the effectiveness of the mathematical models created for PsA and RA, we converted the results of studies on patients with RA (clinics, laboratory, immunological and instrumental) into a mathematical model of PsA and vice versa, then the results of patients with PsA into a mathematical model of RA. Results are presented in Table 3.

Table 3. Correlation of index values in batches of patients with PsA and RA, converted into a mathematical model of RA and PsA, respectively.

Group of patients		φL	φC	φI	φL, φC, φI	φIn
Convert RA to PsA	%	62	64	16	8	95
	Absolute values	31	32	8	4	28
Convert PsA to RA	%	60	12	58	5	77
	Absolute values	33		32		23

Note: *laboratory (φL), clinical (φC) and immunological (φI) indexes. PsA – psoriatic arthritis; RA – rheumatoid arthritis.*

As can be seen from Table 3, there were fewer coincidences in laboratory and immunological indices (12% and 16%, respectively). Several values coincided with the clinical index of 62% and 60%. The instrumental index rate was the highest 95% and 77%. However, the associated index is a combination of clinical, laboratory and immunological indices, which demonstrated the lowest error result of 8% and 5%. This indicates a fairly marked reliability of PsA and RA models.

Thus, according to the mathematical model, persistent arthralgia for more than 4 months can be a manifestation from

the early stage of chronic arthritis, especially RA and PsA, which require clinical and laboratory examination and monitoring of patients with persistent arthralgia syndrome, and in case of detection of low back pain syndrome, the early manifestation of psoriatic sacroiliitis should be assumed, which is determined in 9.5% of patients with skin psoriasis. Significant disorders of the immune status of patients were observed from the early stages of RA and PsA. These data indicate a large contribution of immunopathological disorders already at the beginning of RA and PsA, which confirms the appropriateness of timely prescribing the medication DMARD [2, 3, 7, 11]. The mathematical model of early RA and PsA is easy to handle and can be used in a wide medical practice, as an auxiliary method that allows optimizing the diagnosis of these diseases.

Conclusions

1. Arthralgias were the most common early symptoms of RA and PsA, which occurred even in the prenosological period of the disease in 69.1% and 38.2% of patients, respectively. The arthralgia stage of PsA was significantly longer than in RA, amounting to 4.62±0.03 months in RA and 10.91±2.21 months in PsA ($p < 0.05$).
2. The number of inflamed joints in the first year in early RA (10.4±0.8), Ritchie articular index (11.05±0.69) and functional Lee test (11.8±0.82) were significantly higher ($p < 0.05$) than in the group of patients with PsA (2.88±0.36, 6.71±0.82, 7.16±0.86, respectively). Over time, as PsA progress, these indicators become close in value and the clinical picture acquiring RA characteristics.
3. Immune disorders in the early stages of RA and PsA are nonspecific and are characterized by an increase in CD16+ (26.2±1.5) and CD29+ (24.8±2.1) in RA, which is significantly higher than in PsA CD16+ (22.0±1.3) and CD29+ (17.4±3.2) ($p < 0.05$).
4. A mathematical model of RA and PsA has been developed, which serves as an additional way of diagnosing RA and early PsA.

Abbreviations

CD – Cluster of Differentation; CIC – Circulating Immune Complexes; CRP – C-reactive protein; DMARD – Disease-Modifying Antirheumatic Drugs; ESR – Erythrocyte Sedimentation Rate; NSJ – Number of Swollen Joints; PsA - Psoriatic Arthritis; RA – Rheumatoid Arthritis; RF – Rheumatoid Factor.

Declaration of conflict of interest

Nothing to declare

Authors' contribution

Study conception and design: ER, LG. Data acquisition: ER, LC, LD, AN, LGo. Analysis and interpretation of data: ER, LC, AN. Drafting of the manuscript: ER, LGo. Significant manuscript review with significant intellectual involvement: ER, LD, AN. All authors approved the „ready for print" version of the manuscript**.**

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Authors's ORCID ID:

Alesea Nistor, https://orcid.org/ 0000-0003-2077-8744
Eugeniu Russu, https://orcid.org/ 0000-0001-8957-8471
Liliana Groppa, https://orcid.org/ 0000-0002-3097-6181
Lia Chişlari, https://orcid.org/ 0000-0002-7088-568X
Lucia Dutca, https://orcid.org/ 0000-0002-1815-2294
Liudmila Gonța, https://orcid.org/ 0000-0001-7688-0145