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Diagnostic Markers and Cytokine Profile in Rheumatoid Arthritis During Basic Therapy

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Annotation: The aim of this study was to evaluate the diagnostic and prognostic significance of anti-mutated citrullinated vimentin (anti-MCV) antibodies, anti-keratin antibodies (AKA), and interleukin-6 (IL-6) in patients with rheumatoid arthritis (RA) undergoing methotrexate-based therapy. A 12-month prospective observational study was conducted involving 76 patients with both early and established RA. A comprehensive assessment was performed, including clinical disease activity evaluation, serum levels of anti-MCV, AKA, rheumatoid factor (RF), and IL-6, as well as dynamic radiographic monitoring. Elevated levels of anti-MCV and IL-6 were found to be associated with high inflammatory activity and rapid progression of joint erosions. Notably, anti-MCV showed particular diagnostic value in patients with seronegative RA. A reduction in anti-MCV and IL-6 levels correlated with the achievement of clinical remission during therapy. The novelty of this study lies in demonstrating the prognostic value of anti-MCV and IL-6 as biomarkers for monitoring the long-term effectiveness of RA treatment.

Keywords: rheumatoid arthritis, anti-MCV, interleukin-6, anti-keratin antibodies, biomarkers, methotrexate, inflammation, joint destruction, disease activity.

INTRODUCTION

Rheumatoid arthritis (RA) is one of the most complex and socially significant chronic inflammatory joint diseases, characterized by its autoimmune nature, persistent progression, and the development of severe destructive changes in the musculoskeletal system. Despite significant progress in understanding the pathogenesis of RA and the introduction of novel diagnostic approaches, early disease detection, monitoring of inflammatory activity, and predicting the effectiveness of basic therapy remain pressing challenges in modern rheumatology.

Traditionally, the diagnosis of RA has been based on the detection of rheumatoid factor (RF), but its limited specificity has hindered early diagnosis. The introduction of antibodies to cyclic citrullinated peptides (anti-CCP) into clinical practice marked a significant breakthrough, increasing the specificity of serological tests to 95–98%. However, as noted by Gavrilă, Ciofu, and Stoica (2016), approximately 20–30% of patients with a typical clinical presentation of RA remain seronegative for both RF and CCP, complicating timely diagnosis and delaying treatment initiation. In this subgroup, anti-mutated citrullinated vimentin (anti-MCV) antibodies gain particular diagnostic value, as they allow for early detection of RA, even in its seronegative form, according to the authors.

In parallel, the role of the cytokine profile as a marker of inflammatory activity in RA has been extensively investigated in recent years. Interleukin-6 (IL-6), a key mediator of chronic inflammation, contributes to the stimulation of C-reactive protein (CRP) synthesis, elevated erythrocyte sedimentation rate (ESR), enhanced angiogenesis, and the promotion of osteoclastogenesis. The study by Ali, Al-Anee, and Al-Anee (2024) demonstrated that IL-6 levels strongly correlate with clinical activity indicators (e.g., DAS28) and the rate of radiological progression in patients with RA. These findings support the inclusion of IL-6 in comprehensive assessments of inflammatory activity, particularly when planning modifications to basic therapy.

However, despite the established significance of anti-MCV and IL-6, their diagnostic and prognostic value remains a topic of scientific debate. For example, the study by López-Romero, Martinez-Gamboa, and Bang (2020) found that anti-MCV antibodies did not demonstrate high prognostic value

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in predicting radiological progression during the first year of therapy, whereas antibodies to carbamylated proteins (anti-CarbV) showed stronger predictive utility.

These data raise questions about the heterogeneity of RA patient groups, differences in laboratory methods for determining antibodies, and the influence of various factors such as disease duration, initial inflammation activity, and individual response to therapy.

Thus, an analysis of published works reveals several contradictory aspects that require further investigation. Although the high diagnostic value of anti-MCV antibodies has been demonstrated, it remains uncertain whether they are superior to CCP antibodies in terms of sensitivity and specificity, particularly in patients with seronegative rheumatoid arthritis. Moreover, the role of anti-MCV as a prognostic marker is still under debate. While some studies report an association between elevated anti-MCV levels and the development of erosive arthritis, others fail to establish a correlation with radiological progression.

Similarly, IL-6 is widely recognized as a marker of systemic inflammation; however, its utility as an independent prognostic indicator for long-term structural joint damage has not been confirmed through prospective studies. In addition, there is a lack of comprehensive data on how the dynamic changes in anti-MCV and IL-6 levels during the course of basic therapy could serve to predict therapeutic effectiveness and the achievement of remission.

Based on these identified gaps in current scientific understanding, the following hypothesis was proposed: The serum levels of anti-MCV, anti-keratin antibodies (AKA), and interleukin-6 (IL-6) are closely associated with inflammatory activity and the extent of joint destruction, and may serve as valuable prognostic markers for assessing the effectiveness of basic therapy in patients with rheumatoid arthritis.

The objective of this research is to investigate the diagnostic and prognostic significance of anti-MCV, AKA, and IL-6 in patients with early and established RA undergoing methotrexate-based treatment. **To accomplish this objective, the study pursues the following aims:** First, to perform a comprehensive analysis of clinical, laboratory, and instrumental data in RA patients, including the measurement of anti-MCV, AKA, RF, and IL-6 levels.

Second, to determine the frequency and diagnostic relevance of anti-MCV and AKA in both seropositive and seronegative forms of RA.

Third, to examine the relationship between anti-MCV, AKA, RF, and IL-6 levels and clinical indicators of disease activity, joint destruction, and systemic manifestations. Fourth, to evaluate the changes in titers of anti-MCV, AKA, RF, and IL-6 over a 12-month period of methotrexate therapy, and to assess their predictive value in determining treatment response. Finally, to propose improved criteria for early diagnosis, disease monitoring, and prognosis in RA based on the study's findings.

The subsequent sections of the manuscript consistently reflect the progression of the study. The materials and methods section provides a comprehensive description of the clinical and laboratory examination protocols, criteria for assessing RA activity, imaging techniques for joint evaluation, and statistical methods employed for data analysis.

The results section presents empirical findings demonstrating the association between anti-MCV, AKA, and IL-6 levels and disease activity, radiographic progression of erosions, as well as the changes in these markers during methotrexate therapy.

The discussion section offers a critical interpretation of the results in the context of current knowledge on the role of immunological and cytokine markers in RA, integrating findings from Gavrilă, Ciofu, and Stoica (2016), Ali, Al-Anee, and Al-Anee (2024), and López-Romero, Martinez-Gamboa, and Bang (2020).

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Based on the comprehensive analysis, conclusions are drawn regarding the diagnostic and prognostic relevance of the studied biomarkers, and practical recommendations are proposed for their integration into routine monitoring protocols for RA patients.

This study aims to address existing gaps in the understanding of immunological and cytokine markers in RA and to provide clinicians with novel tools for personalized assessment of disease activity and prediction of therapeutic response.

MATERIALS AND METHODS

The methodological foundation of this study was developed in alignment with the formulated objective—to assess the diagnostic and prognostic significance of anti-citrullinated vimentin antibodies (anti-MCV), anti-keratin antibodies (AKA), and interleukin-6 (IL-6) in patients with early and established rheumatoid arthritis (RA) receiving methotrexate-based therapy. To address the research objectives, a comprehensive approach was applied, incorporating clinical observation, detailed laboratory analysis of immunological markers, instrumental joint assessment, and modern statistical methods for data processing. This multi-level design enabled an objective evaluation of the relationships between inflammatory activity, structural joint damage, and the dynamics of serological and cytokine markers.

In the initial stage, a cohort of patients meeting the 2010 ACR/EULAR classification criteria for RA was identified. Patients were recruited from the rheumatology department between January 2022 and December 2023. The inclusion criteria encompassed individuals aged 25 to 70 years with either early RA (symptom duration less than 12 months) or established disease (duration over five years). Exclusion criteria included the presence of other systemic connective tissue diseases, infectious arthritis, malignancies, and prior treatment with TNF-α inhibitors or other targeted biological therapies.

A total of 76 patients were enrolled, comprising 58 women and 18 men, with a mean age of 49.2 ± 11.4 years. Among them, 44 were diagnosed with seropositive RA and 32 with seronegative RA. All participants received methotrexate therapy at an average dose of 15 mg per week. For those intolerant to methotrexate, leflunomide was administered at 20 mg per day (12 patients). In cases of severe pain, non-steroidal anti-inflammatory drugs (NSAIDs), primarily meloxicam at 15 mg per day, were prescribed in short courses. Low-dose glucocorticoids (prednisolone 5–7.5 mg/day) were used in 24 patients.

Clinical activity of RA was assessed using the DAS28 scale, which includes the number of tender and swollen joints, erythrocyte sedimentation rate (ESR), and the patient's self-reported pain score on a visual analog scale (VAS). Joint condition was evaluated by radiographic imaging of the hands and feet, with assessment of erosive changes and joint space narrowing according to the Sharp score, modified by Van der Heijde.

Laboratory methods included measurement of anti-MCV levels using enzyme-linked immunosorbent assay (ELISA) with a commercial kit (ORGENTEC Diagnostika, Germany), with titers above 20 U/ml considered positive. AKA were determined via indirect immunofluorescence on cryostat sections of rat esophagus (BIOSYSTEMS S.A., Spain). IL-6 levels were measured using solid-phase ELISA kits from ROSTA-Diagnostika, with values above 10 pg/ml considered elevated.

Additional serological markers included rheumatoid factor (RF), measured by latex agglutination (positive if >20 IU/ml), and anti-cyclic citrullinated peptide (anti-CCP) antibodies, determined by ELISA (positive if >5 U/ml).

Statistical analysis was conducted using SPSS Statistics version 26.0 (IBM, USA). The Kolmogorov-Smirnov test was applied to assess the normality of data distribution. Quantitative data were expressed as means and standard deviations (M ± SD). Comparisons between groups were made using the Student's t-test for normally distributed data and the Mann-Whitney U test for non-normally

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distributed data. Correlations were analyzed using Spearman's rank correlation coefficient. A p-value of less than 0.05 was considered statistically significant.

Patients were followed over a 12-month period, with clinical assessments and laboratory measurements (anti-MCV, AKA, IL-6, RF, and CCP) conducted at three-month intervals. Radiographic imaging of hands and feet was performed at baseline and after 12 months to monitor the progression of joint damage.

Several methodological limitations should be acknowledged. The relatively small sample size (n = 76) may limit the generalizability of the findings. Additionally, the exclusive focus on methotrexate therapy restricts the assessment of marker dynamics under alternative treatment regimens, such as biologic agents. Nonetheless, given methotrexate's status as the standard of care in RA management, the findings remain clinically relevant.

Another potential limitation is the absence of a healthy control group, which may affect the assessment of marker specificity in distinguishing RA from other inflammatory or autoimmune diseases. However, since the primary aim was to evaluate the dynamics of markers within the RA population under treatment, this study design remains justified.

This methodology enabled sequential clinical and laboratory monitoring of RA patients, capturing the dynamic changes in disease activity and biomarker levels under standard therapy. The comprehensive approach ensured data integrity, revealed significant correlations between immunological markers and clinical outcomes, and provided insight into their prognostic value during long-term observation.

RESULTS

Serum levels of anti-MCV, AKA, and IL-6 showed significant variability among RA patients. These levels were found to correlate with disease duration, serological status, and response to methotrexate therapy.

In patients with early RA (disease duration less than 12 months), anti-MCV concentrations ranged from 22 to 76 U/ml. Levels exceeding 65 U/ml were frequently associated with pronounced morning stiffness (over 150 minutes), intense pain (VAS score >70 mm), elevated ESR (≥55 mm/h), and high CRP levels (≥35 mg/l).

For instance, a 43-year-old woman with newly diagnosed polyarthritis affecting the hands and feet exhibited an anti-MCV level of 71 U/ml. She presented with 180 minutes of morning stiffness, a DAS28 score of 5.9, ESR of 60 mm/h, and CRP of 42 mg/l. In contrast, a 50-year-old man with early polyarthritis had an anti-MCV level of 28 U/ml, morning stiffness of less than 45 minutes, DAS28 score of 3.4, and ESR of 18 mm/h.

In patients with longer disease duration (over 5 years), a different pattern emerged. Those in remission or with low disease activity typically showed anti-MCV levels between 20–45 U/ml. Conversely, patients with high disease activity exhibited titers exceeding 85 U/ml, often accompanied by radiographic progression of joint damage.

A 58-year-old woman receiving methotrexate for six years had an anti-MCV level of 92 U/ml. She reported 120 minutes of morning stiffness, a DAS28 score of 5.8, and an 8-point increase in the Sharp score over the past year. In contrast, a 62-year-old man with nine years of disease duration and an anti-MCV level of only 33 U/ml was in stable remission. He reported no joint pain, morning stiffness lasting less than 15 minutes, a DAS28 score of 2.6, and no new erosions over the past two years.

A significant correlation was also observed between IL-6 levels and the extent of joint erosive changes. Patients with IL-6 concentrations above 60 pg/ml experienced Sharp score increases exceeding five points per year. In contrast, patients with IL-6 levels below 20 pg/ml showed no evidence of structural progression.

For example, a 61-year-old male patient with an IL-6 level of 88 pg/ml showed a 7-point increase in joint erosions over the past year, a DAS28 score of 6.0, and ESR of 65 mm/h. Meanwhile, a 54-year-

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old female patient with an IL-6 level of 14 pg/ml exhibited no erosion progression, a DAS28 score of 2.8, and ESR of 12 mm/h.

Table-1. IL-6 Levels and Sharp Score Erosion Progression

IL-6 Level (pg/ml)	Number of Patients	Erosion Increase (points)	DAS28
<20	24	0	2.5–3.2
21–60	31	1–4	3.5–4.8
>60	21	5–10	5.5–6.5

Positive AKA titers were detected in 53% of patients, predominantly in those with seropositive RA. Patients with high AKA levels (2+ and 3+) more frequently presented with systemic manifestations such as rheumatoid vasculitis, sicca syndrome, and fibrosing alveolitis.

For example, a 56-year-old male with vasculopathy, high RA activity (DAS28 6.1), and an AKA level of 3+ had an IL-6 concentration of 82 pg/ml and a 9-point increase in Sharp erosion score over the past year. In contrast, a 48-year-old woman without detectable AKA, with low disease activity (DAS28 3.2), had an IL-6 level of 10 pg/ml and no erosions.

Table-2. Correlation of AKA titers with IL-6 levels

AKA Presence	Number of Patients	IL-6 Level (pg/ml)	Mean Sharp Score Increase
Positive	39	30–87	4.8
Negative	37	10–34	1.3

Monitoring of anti-MCV and IL-6 levels during 12 months of methotrexate therapy showed that in 72% of patients who achieved remission, anti-MCV levels decreased by more than 40% from baseline. For example, a patient with anti-MCV of 88 U/ml before treatment showed a level of 35 U/ml after one year of therapy, with DAS28 decreasing from 5.8 to 2.7. In the group of patients with persistent activity, a decrease in anti-MCV was noted in only 18%; in 9 patients, titers remained consistently high – above 80 U/ml.

Table-3. Marker dynamics during methotrexate therapy

Indicator	Before Treatment	After 6 Months	After 12 Months	DAS28 after 12 Months
Anti-MCV (U/ml)	70 ± 22	48 ± 19	35 ± 16	2.8 ± 0.9
IL-6 (pg/ml)	52 ± 24	31 ± 17	18 ± 10	2.6 ± 0.8

Correlation analysis revealed statistically significant positive correlations between anti-MCV and IL-6 levels, RA activity (DAS28), Sharp score erosion increase, and CRP concentration. Correlation coefficients ranged from 0.55 to 0.74, indicating the high prognostic value of these markers.

These results suggest that anti-MCV and IL-6 can be used as independent indicators of inflammatory activity, the degree of destructive changes, and the effectiveness of basic RA therapy.

DISCUSSIONS

The results of this study provide a new perspective on the diagnostic and prognostic significance of anti-MCV, AKA, and IL-6 levels in patients with rheumatoid arthritis (RA), both in the early stages of the disease and during its long-term course under basic methotrexate therapy. Comparison of our data with findings from recent publications reveals both consistencies and discrepancies, underscoring the complexity of RA pathogenesis and the multifactorial influence of immunological markers on inflammatory activity and structural joint damage.

The association between elevated anti-MCV levels and pronounced clinical disease activity, reflected in high DAS28 scores, prolonged morning stiffness, and accelerated radiographic progression, is

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largely in agreement with earlier reports [9]. These authors indicated that anti-MCV concentrations above 50–70 U/ml in early RA predict erosive changes within the first two years of disease. Our findings extend this by demonstrating that persistently high anti-MCV levels over five years or more are also associated with continued erosion progression and inadequate response to standard therapy.

Furthermore, earlier work [2,8] demonstrated a correlation between anti-MCV levels and systemic manifestations of RA, including rheumatoid vasculitis and internal organ involvement. Our study similarly identified a higher frequency of extra-articular manifestations in patients with elevated anti-MCV and AKA titers, particularly among those with disease duration exceeding five years and persistently high inflammatory activity.

IL-6 levels in our cohort were closely associated with clinical activity markers (DAS28, ESR, CRP) and with the progression of erosive joint damage, supporting previous findings [13]. Specifically, we showed that patients with IL-6 levels above 60 pg/ml had more than a fourfold increased risk of Sharp score erosion progression within one year, compared to those with IL-6 below 20 pg/ml. This finding reinforces the importance of regular IL-6 monitoring, especially in patients with suboptimal response to methotrexate.

Notably, we observed significant declines in anti-MCV and IL-6 levels over the 12-month methotrexate therapy course in patients achieving remission or low disease activity. These reductions (exceeding 40% of baseline values) are consistent with previous data [12]. However, approximately 28% of patients maintained persistently high anti-MCV and IL-6 levels, in line with prior observations [4], suggesting a link between elevated IL-6 and methotrexate resistance.

Our study also supports earlier claims [2] about the diagnostic utility of anti-MCV in seronegative RA. In our cohort, 63% of seronegative patients had positive anti-MCV levels (>50 U/ml), allowing for earlier diagnosis and timely initiation of therapy, preventing joint damage.

The combined dynamic assessment of anti-MCV, AKA, and IL-6 showed greater prognostic value than traditional serological markers such as RF or CCP, aligning with findings from other studies [10]. The correlation between AKA levels and systemic manifestations—especially vasculitis and interstitial lung disease—was also evident in our cohort and echoes prior findings [6]. Additionally, our study observed a link between the presence of AKA and elevated IL-6 levels, suggesting a potential synergistic effect of these markers in driving systemic inflammation.

Despite the overall consistency with previous studies, some discrepancies emerged. Voronina and Vinogradov [12] reported that anti-MCV levels decrease in almost all patients undergoing methotrexate therapy. However, our data showed that 28% of patients retained high anti-MCV levels, possibly due to individual immunopathologic characteristics or persistent seronegative inflammation.

In conclusion, our findings not only confirm but also expand the understanding of the diagnostic and prognostic roles of anti-MCV, AKA, and IL-6 in RA. Their integrated assessment appears useful for early diagnosis and for tracking treatment response. IL-6, in particular, shows promise as a predictor of erosion progression and methotrexate resistance, supporting earlier conclusions [1,3]. Incorporating anti-MCV and IL-6 into standard monitoring protocols seems clinically justified, especially in patients with high disease activity, systemic involvement, or poor response to therapy. Long-term prospective studies are warranted to refine these markers' prognostic value and guide therapeutic strategies in methotrexate-resistant RA.

CONCLUSIONS

Based on the results of this study, several important conclusions can be drawn that refine existing understanding of the diagnostic and prognostic significance of the immunological markers anti-MCV, anti-keratin antibodies (AKA), and interleukin-6 (IL-6) in rheumatoid arthritis (RA) patients undergoing basic methotrexate therapy. The data show that these markers independently contribute to assessing inflammatory activity, the rate of joint destruction progression, and treatment efficacy. Their

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combined use enhances diagnostic capabilities, especially in patients with seronegative RA, and allows for personalized patient management.

First, the strong correlation between anti-MCV levels and clinical markers of disease activity, such as DAS28, morning stiffness, ESR, and CRP, confirms the rationale for including this marker in standard laboratory test panels when evaluating patients suspected of having RA. The diagnostic value of anti-MCV is particularly significant in patients lacking classical serological markers of the disease, such as RF and CCP. In such cases, as this study shows, the detection of high anti-MCV titers allows for early confirmation of RA and timely initiation of therapy, thereby preventing the development of severe joint deformities.

Anti-MCV is most clinically significant in seronegative RA, where standard diagnostic methods often lack sufficient information. This study found that more than half of seronegative patients exhibited high anti-MCV levels, which correlated with inflammatory activity and structural joint damage. This suggests anti-MCV can be considered an independent, highly specific marker, overcoming diagnostic challenges in seronegative disease.

Furthermore, the results confirmed the importance of assessing IL-6 levels as a universal marker of systemic inflammation and destructive processes in RA. IL-6 concentration clearly reflected clinical disease activity and was associated with the rate of joint erosion progression according to the Sharp method. This underlines the value of regular IL-6 monitoring in patients with aggressive RA, which can be particularly useful when basic therapy provides an inadequate clinical effect.

A rising IL-6 level over time should be considered a signal for timely treatment adjustments, including the potential for early transition to combination or biologic therapy.

The dynamic changes in anti-MCV and IL-6 observed over 12 months of methotrexate therapy in this study are particularly important. Patients who achieved clinical remission or low RA activity showed a significant decrease in anti-MCV levels by more than 40% and a 2.5-fold reduction in IL-6 concentration from baseline values. Conversely, patients with persistent high disease activity maintained consistently high anti-MCV titers, and IL-6 levels remained virtually unchanged. This suggests that the dynamics of these markers can serve as an additional tool for assessing the effectiveness of basic therapy. If anti-MCV and IL-6 levels do not decrease after 6 months of treatment, a change in therapeutic strategy should be considered.

Therefore, the practical significance of this study is as follows:

1. The high diagnostic value of anti-MCV, especially in seronegative RA, is confirmed, suggesting its inclusion in the early diagnosis algorithm.

2. The prognostic significance of IL-6 as a marker of inflammatory activity and the rate of joint destruction is established, justifying its use for patient monitoring and timely therapy adjustments.

3. The informativeness of the dynamic assessment of anti-MCV and IL-6 against the background of basic methotrexate therapy for predicting treatment efficacy is demonstrated, which can be implemented in clinical practice as an additional criterion for therapy monitoring.

Moreover, the results allow for a novel perspective on personalized approaches to managing RA patients. Specifically, the combined assessment of anti-MCV, IL-6, and classical markers (RF, CCP) could form the basis for developing improved diagnostic and monitoring schemes aimed at identifying patients with a potentially unfavorable prognosis and timely administration of aggressive therapy.

Despite the significant results, the study has limitations that necessitate further research. The sample included a limited number of patients, predominantly receiving methotrexate therapy. Therefore, a promising avenue for future research is evaluating the dynamics of anti-MCV and IL-6 in patients receiving various treatment regimens, including TNF-α inhibitors, Janus kinase inhibitors, and other targeted therapies. This would refine the prognostic value of these markers for different patient categories.

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Furthermore, multicenter studies with long-term follow-up are warranted to determine the long-term consequences of persistent elevation of anti-MCV and IL-6, and to clarify their association with the development of extra-articular systemic complications of RA.

Of particular interest is the study of cytokine and autoantibody gene polymorphisms that regulate the synthesis of anti-MCV and IL-6, which could be the next step in creating personalized management strategies for RA patients.

The results of this study conclude that anti-MCV and IL-6 should be considered not only as additional laboratory indicators but also as independent prognostic markers. Their use in the dynamic monitoring of RA patients will improve treatment efficacy, prevent the development of erosive joint changes, and improve the long-term prognosis of the disease.

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