



CLINICAL SIGNIFICANCE OF HEMOSTASIS AND LABORATORY-IMMUNOLOGICAL INDICATOR DYNAMICS IN THE TREATMENT OF RHEUMATOID ARTHRITIS PATIENTS WHO HAD COVID-19

Abduazizova N.Kh.

Sharapov Z.A.

Tashkent State Medical University, Tashkent, Uzbekistan

<https://doi.org/10.5281/zenodo.22685963>

Introduction

Rheumatoid arthritis (RA) is a chronic, immune-mediated inflammatory disease in which sustained systemic inflammatory activity is frequently accompanied by disturbances of the hemostatic system and a consequently elevated risk of thromboembolic complications. The COVID-19 pandemic introduced an additional pathogenetic dimension to this problem: by virtue of its pronounced prothrombotic and proinflammatory potential, SARS-CoV-2 infection is capable of aggravating the pre-existing thromboinflammatory milieu characteristic of RA, thereby complicating both the clinical course of the disease and the choice of therapeutic strategy. Against this background, a systematic evaluation of the dynamics of hemostatic and laboratory-immunological parameters over the course of treatment in RA patients who have recovered from COVID-19, together with a comparative analysis of the influence exerted by different therapeutic regimens on these parameters, acquires considerable practical and clinical significance.

Keywords: rheumatoid arthritis, COVID-19, hemostasis, D-dimer, fibrinogen, platelets, tocilizumab, thromboinflammatory activity

Aim of the Study

The present study was undertaken to evaluate the clinical significance of the dynamics of hemostatic parameters (D-dimer, fibrinogen, and platelet count) and laboratory-immunological indicators in patients with rheumatoid arthritis who had undergone COVID-19 infection, under conditions of tocilizumab-based combination therapy as compared with standard methotrexate-based basic therapy.

Materials and Methods

The study comprised 60 patients with rheumatoid arthritis who had previously undergone COVID-19 infection; the cohort was stratified into two therapeutic subgroups. **Group IA** (n=26) consisted of patients receiving combination therapy in which tocilizumab was incorporated into the basic treatment regimen, whereas **Group IB** (n=34) comprised patients treated with standard methotrexate-based basic therapy. Hemostatic parameters — D-dimer, fibrinogen, and platelet count — were determined at three time points: at baseline, prior to the initiation of treatment, and after 3 and 6 months of therapy.

Statistical analysis was performed as follows: within-group dynamic changes were evaluated by means of the paired Student's t-test or the Wilcoxon signed-rank test, as appropriate, while between-group differences were assessed using the independent-samples Student's t-test or the Mann-Whitney U test. A probability value of $p < 0.05$ was regarded as statistically significant.

Results

In both therapeutic subgroups, D-dimer, fibrinogen, and platelet count exhibited a consistent downward trend over the course of treatment; nevertheless, the reduction in D-dimer and fibrinogen concentrations was considerably more pronounced in Group IA than in Group IB (Table 1).

In Group IA, the D-dimer concentration, initially 0.96 ± 0.35 mg/L FEU, declined to 0.62 ± 0.24 mg/L FEU by the third month and to 0.46 ± 0.18 mg/L FEU by the sixth month of treatment. In Group IB, the corresponding values decreased from 0.88 ± 0.33 mg/L FEU to 0.74 ± 0.29 mg/L FEU at 3 months and to 0.62 ± 0.25 mg/L FEU at 6 months. By the end of the sixth month, the difference between Groups IA and IB had attained statistical significance ($p=0.008$), a finding that points to a comparatively more active attenuation of thromboinflammatory activity under tocilizumab-based combination therapy.

A similarly more marked reduction in fibrinogen concentration was observed in Group IA, which declined from 4.7 ± 0.8 g/L to 3.9 ± 0.6 g/L at 3 months and to 3.4 ± 0.5 g/L at 6 months ($p=0.002$). In Group IB, fibrinogen decreased from 4.5 ± 0.7 g/L to 4.2 ± 0.6 g/L at 3 months and to 3.9 ± 0.6 g/L at 6 months. The more substantial decline in fibrinogen observed in Group IA paralleled the concomitant reduction in CRP and DAS28 values, thereby reflecting an overall attenuation of systemic inflammatory activity.

Platelet count decreased from $348 \pm 70 \times 10^9$ /L to $282 \pm 51 \times 10^9$ /L in Group IA and from $338 \pm 66 \times 10^9$ /L to $304 \pm 56 \times 10^9$ /L in Group IB. Although a favorable trend was documented in both subgroups, the intergroup difference at the sixth month did not reach statistical significance ($p=0.10$); this parameter was accordingly interpreted as reflecting a general positive tendency associated with the overall decline in inflammatory activity, rather than as a discriminating marker between the two treatment regimens.

Indicator	Group	Before treatment	After 3 months	After 6 months	p1	p2	p3
D-dimer, mg/L FEU	IA (n=26)	0.96 ± 0.35	0.62 ± 0.24	0.46 ± 0.18	<0.001	<0.001	0.008
	IB (n=34)	0.88 ± 0.33	0.74 ± 0.29	0.62 ± 0.25	<0.05	<0.01	—
Fibrinogen, g/L	IA (n=26)	4.7 ± 0.8	3.9 ± 0.6	3.4 ± 0.5	<0.001	<0.001	0.002
	IB (n=34)	4.5 ± 0.7	4.2 ± 0.6	3.9 ± 0.6	<0.05	<0.01	—
Platelets, $\times 10^9$ /L	IA (n=26)	348 ± 70	309 ± 58	282 ± 51	<0.001	<0.001	0.10
	IB (n=34)	338 ± 66	321 ± 60	304 ± 56	<0.05	<0.05	—

Table 1. Six-month dynamics of hemostatic parameters during treatment in Groups IA and IB. Data are presented as $M \pm SD$; p1 — difference between baseline and 3 months within the same group; p2 — difference between baseline and 6 months within the same group; p3 — difference between Groups IA and IB at the sixth month.

Conclusion

In patients with rheumatoid arthritis who had undergone COVID-19 infection, both therapeutic approaches were accompanied by a favorable dynamic of hemostatic parameters,

namely D-dimer, fibrinogen, and platelet count. Nonetheless, the decline in D-dimer and fibrinogen concentrations proved to be statistically significantly more pronounced under tocilizumab-based combination therapy than under standard methotrexate-based basic therapy, indicating a comparatively more active resolution of systemic inflammatory and thromboinflammatory activity in Group IA. Platelet count, for its part, was interpreted as an auxiliary hemostatic marker of secondary diagnostic weight.

These findings should not be construed as evidence of the absolute superiority of tocilizumab; rather, they underscore the clinical importance of comprehensive monitoring of hemostatic and laboratory-immunological parameters, and of an individualized therapeutic strategy, in patients presenting with high clinical-inflammatory activity and a persistent post-COVID thromboinflammatory background.

References:

1. Abduazizova N.Kh., Sagatova D.R., Sharapov Z.A., et al. COVID-19 in cases of rheumatoid arthritis. *Infektsiya, immunitet i farmakologiya*. 2022;(5):8–13.
2. Sharapov Z.A. Modern views on the etiology and pathogenesis of rheumatoid arthritis. *Eurasian Journal of Medical and Natural Sciences*. 2022;2(2):103–107.
3. Landewe R.B.M., Machado P.M., Kroon F., et al. EULAR provisional recommendations for the management of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2. *Ann Rheum Dis*. 2020;79(7):851–858.
4. Alunno A., Najm A., Machado P.M., et al. 2021 update of the EULAR points to consider on the use of immunomodulatory therapies in COVID-19. *Ann Rheum Dis*. 2022;81(1):34–40. doi:10.1136/annrheumdis-2021-221366.
5. Jin L., Gan J., Li X., et al. Rheumatoid arthritis and COVID-19 outcomes: a systematic review and meta-analysis. *BMC Rheumatology*. 2024;8(1):61. doi:10.1186/s41927-024-00431-5.
6. Levi M., Thachil J., Iba T., Levy J.H. Coagulation abnormalities and thrombosis in patients with COVID-19. *Lancet Haematol*. 2020;7(6):e438–e440. doi:10.1016/S2352-3026(20)30145-9.
7. Connors J.M., Levy J.H. COVID-19 and its implications for thrombosis and anticoagulation. *Blood*. 2020;135(23):2033–2040. doi:10.1182/blood.2020006000.
8. Zinellu A., et al. A systematic review and meta-analysis of the association between the D-dimer and rheumatic diseases. *Immun Inflamm Dis*. 2024;12(7):e1349. doi:10.1002/iid3.1349.