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PATHOGENETICALLY ORIENTED CORRECTION OF PLATELET ACTIVITY, COAGULATION IMBALANCE AND ENDOTHELIAL DYSFUNCTION IN RHEUMATOID ARTHRITIS

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ABSTRACT

Rheumatoid arthritis is frequently accompanied by platelet activation, coagulation imbalance, and endothelial dysfunction, which may persist despite standard anti-inflammatory treatment. This study evaluated the effects of standard therapy and pathogenetically oriented combined therapy on platelet function, coagulation parameters, and endothelial dysfunction markers in patients with rheumatoid arthritis. Patients without adverse thrombophilia-related genotypes received either standard treatment alone or standard treatment supplemented with endothelial, antiplatelet, and anticoagulant correction, whereas patients with adverse genotypes received genotype-oriented therapy that additionally included folate correction. Platelet count, adhesion, aggregation, activated partial thromboplastin time, prothrombin index, fibrinogen, D-dimer, endothelin-1, and soluble intercellular adhesion molecule were assessed before and after treatment. Platelet count decreased after therapy but did not normalize consistently. In contrast, platelet adhesion and aggregation improved more markedly with combined therapy than with standard treatment. Among patients without adverse genotypes, adhesion decreased from 46–52 to 28–30, while aggregation decreased from 49–52 to 31–33. Activated partial thromboplastin time increased from 19.5–24.2 seconds to 30.5–38.5 seconds, fibrinogen decreased from 3.55–4.66 g/L to 2.44–3.13 g/L, and D-dimer declined from 380–460 ng/mL to 291–332 ng/mL. Endothelin-1 and soluble intercellular adhesion molecule levels also decreased more substantially after combined therapy. These findings indicate that pathogenetically oriented combined treatment provides more pronounced correction of platelet hyperactivity, hypercoagulability, and endothelial dysfunction than standard therapy alone.

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Keywords: *rheumatoid arthritis, combined therapy, platelet aggregation, hypercoagulation, endothelial dysfunction, D-dimer, fibrinogen, endothelin-1, sICAM.*

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Introduction

Rheumatoid arthritis is a systemic autoimmune inflammatory disease in which persistent immune activation affects not only the joints but also the vascular and hemostatic systems [1-3]. Platelet activation, coagulation imbalance and endothelial dysfunction contribute to the development of a prothrombotic state [3-7,15].

Traditional treatment of rheumatoid arthritis is primarily directed toward suppression of inflammation and control of joint damage [1]. However, clinical improvement may not always be accompanied by complete normalization of hemostatic and endothelial markers. Persistent hypercoagulation and endothelial dysfunction may maintain vascular risk even during anti-inflammatory therapy [4-7,15].

The pathogenesis of hemovascular disturbances in rheumatoid arthritis includes several interconnected mechanisms: platelet activation, increased fibrinogen and D-dimer, shortening of coagulation times, increased prothrombin index and elevation of endothelial dysfunction markers [3-7,15].

Folate cycle gene polymorphisms may influence homocysteine metabolism and endothelial function. Hyperhomocysteinemia can aggravate endothelial injury, platelet activation and procoagulant balance; therefore, genotype-oriented correction and prolonged laboratory monitoring may be important in selected patients [8-14].

The present study evaluates the dynamics of platelet, coagulation and endothelial markers under standard and combined therapeutic approaches in patients with rheumatoid arthritis.

Materials and Methods

The study included patients with rheumatoid arthritis who were evaluated before and after therapy. Laboratory assessment included platelet count, platelet adhesion, platelet aggregation, activated partial thromboplastin time, prothrombin index, fibrinogen, D-dimer, endothelin-1 and sICAM.

Patients without adverse thrombophilia-related genotypes received standard therapy alone or standard therapy combined with pathogenetically oriented correction aimed at endothelial protection, platelet inhibition and anticoagulant support. The combined protocol included L-arginine, rivaroxaban and clopidogrel for 10 days under physician supervision.

Patients with adverse thrombophilia-related genotypes received standard therapy combined with folate correction, endothelial support, low-molecular-weight heparin according to body weight and antiplatelet correction under physician supervision.

Patients were analyzed according to disease duration and genotype status. Quantitative values are presented according to the available study dataset. Statistical significance was accepted at $p<0.05$.

Results

Effect of therapy on platelet count

Platelet count decreased after both standard and combined therapy, but the changes were not statistically reliable. In patients without adverse genotypes, platelet count decreased from 332 to 296 after standard therapy and to 267 after combined therapy in group 1. In group 2, platelet count decreased from 450 to 418 after standard therapy and to 385 after combined therapy. In group 3, it decreased from 278 to 254 after standard therapy and to 266 after combined therapy.

In patients with adverse genotypes, platelet count also decreased after combined therapy: from 556 to 509 in group 2 heterozygous carriers, from 412 to 388 in group 3 heterozygous carriers and from 687 to 612 in group 3 homozygous carriers.

Table 1. Platelet count dynamics after therapy

Patient category	Before therapy	Standard therapy	Combined therapy
Group 1, without adverse genotype	332	296	267
Group 2, without adverse genotype	450	418	385
Group 3, without adverse genotype	278	254	266
Group 2, heterozygous genotype	556	NA	509

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Group 3, heterozygous genotype	412	NA	388
Group 3, homozygous genotype	687	NA	612

Note: NA - not available / not applicable in the summarized dataset.

Effect of therapy on platelet adhesion and aggregation

Platelet adhesion and aggregation improved more clearly than platelet count. In patients without adverse genotypes, platelet adhesion decreased from 46 to 31 after standard therapy and to 28 after combined therapy in group 1. In group 2, adhesion decreased from 52 to 37 after standard therapy and to 30 after combined therapy.

Platelet aggregation showed similar dynamics. In group 1, aggregation decreased from 49 to 35 after standard therapy and to 31 after combined therapy. In group 2, aggregation decreased from 52 to 38 after standard therapy and to 33 after combined therapy.

In patients with adverse genotypes, combined therapy also reduced platelet functional activity. Adhesion decreased from 70 to 45 in group 2 heterozygous carriers, from 66 to 48 in group 3 heterozygous carriers and from 79 to 54 in homozygous carriers. Aggregation decreased from 66 to 44, from 70 to 48 and from 85 to 59, respectively.

Table 2. Platelet adhesion and aggregation after therapy

Parameter / category	Before therapy	Standard therapy	Combined therapy
Adhesion, group 1 without adverse genotype	46	31*	28**
Adhesion, group 2 without adverse genotype	52	37*	30**
Aggregation, group 1 without adverse genotype	49	35*	31**
Aggregation, group 2 without adverse genotype	52	38*	33**
Adhesion, group 2 heterozygous genotype	70	NA	45**
Adhesion, group 3 heterozygous genotype	66	NA	48**
Adhesion, group 3 homozygous genotype	79	NA	54**
Aggregation, group 2 heterozygous genotype	66	NA	44**
Aggregation, group 3 heterozygous genotype	70	NA	48**
Aggregation, group 3 homozygous genotype	85	NA	59**

*Note: *p<0.05; **p<0.01 compared with pre-treatment values.*

Effect of therapy on coagulation parameters

APTT increased more markedly after combined therapy than after standard therapy. In patients without adverse genotypes, group 1 APTT increased from 24.2 s to 28.2 s after standard therapy and to 38.5 s after combined therapy. In group 2, APTT increased from 21.6 s to 25.8 s after standard therapy and to 32.3 s after combined therapy. In group 3, it increased from 19.5 s to 24.6 s after standard therapy and to 30.5 s after combined therapy.

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Prothrombin index also improved. In group 1, it decreased from 105% to 80% after standard therapy and to 74% after combined therapy. In group 2, it decreased from 128% to 96% and 88%, respectively. In group 3, it decreased from 136% to 105% and 99%.

In patients with adverse genotypes, combined therapy improved but did not fully normalize coagulation parameters. APTT increased from 16.6 to 22.6 s in group 2 heterozygous carriers, from 17.8 to 23.5 s in group 3 heterozygous carriers and from 15.2 to 20.6 s in homozygous carriers. Prothrombin index decreased from 140% to 106%, from 168% to 112% and from 181% to 138%, respectively.

Table 3. APTT and prothrombin index after therapy

Parameter / category	Before therapy	Standard therapy	Combined therapy
APTT, group 1 without adverse genotype, s	24.2	28.2	38.5**
APTT, group 2 without adverse genotype, s	21.6	25.8*	32.3**
APTT, group 3 without adverse genotype, s	19.5	24.6	30.5**
APTT, group 2 heterozygous genotype, s	16.6	NA	22.6*
APTT, group 3 heterozygous genotype, s	17.8	NA	23.5*
APTT, group 3 homozygous genotype, s	15.2	NA	20.6*
Prothrombin index, group 1 without adverse genotype, %	105	80*	74**
Prothrombin index, group 2 without adverse genotype, %	128	96*	88**
Prothrombin index, group 3 without adverse genotype, %	136	105*	99*
Prothrombin index, group 2 heterozygous genotype, %	140	NA	106*
Prothrombin index, group 3 heterozygous genotype, %	168	NA	112**
Prothrombin index, group 3 homozygous genotype, %	181	NA	138*

*Note: *p<0.05; **p<0.01 compared with pre-treatment values.*

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Effect of therapy on fibrinogen and D-dimer

Fibrinogen and D-dimer decreased after therapy, with stronger improvement after combined treatment. In patients without adverse genotypes, fibrinogen decreased from 3.55 to 2.75 g/L after standard therapy and to 2.44 g/L after combined therapy in group 1. In group 2, fibrinogen decreased from 4.46 to 3.25 g/L and 3.01 g/L, respectively. In group 3, it decreased from 4.66 to 3.64 g/L and 3.13 g/L.

D-dimer decreased from 380 to 320 and 312 ng/ml in group 1, from 460 to 349 and 332 ng/ml in group 2, and from 450 to 324 and 291 ng/ml in group 3.

In patients with adverse genotypes, combined therapy also reduced fibrinogen and D-dimer, although residual elevation remained. Fibrinogen decreased from 5.90 to 4.51 g/L, from 6.30 to 4.74 g/L and from 7.12 to 5.68 g/L in the corresponding genotype subgroups. D-dimer decreased from 820 to 652 ng/ml, from 780 to 608 ng/ml and from 1284 to 846 ng/ml.

Table 4. Fibrinogen after therapy

Patient category	Before therapy, g/L	Standard therapy, g/L	Combined therapy, g/L
Group 1, without adverse genotype	3.55	2.75*	2.44**
Group 2, without adverse genotype	4.46	3.25*	3.01**
Group 3, without adverse genotype	4.66	3.64*	3.13**
Group 2, heterozygous genotype	5.90	NA	4.51**
Group 3, heterozygous genotype	6.30	NA	4.74*
Group 3, homozygous genotype	7.12	NA	5.68*

*Note: *p<0.05; **p<0.01 compared with pre-treatment values.*

Table 5. D-dimer after therapy

Patient category	Before therapy, ng/ml	Standard therapy, ng/ml	Combined therapy, ng/ml
Group 1, without adverse genotype	380	320	312
Group 2, without adverse genotype	460	349*	332*
Group 3, without adverse genotype	450	324*	291**
Group 2, heterozygous genotype	820	NA	652*
Group 3, heterozygous genotype	780	NA	608*
Group 3, homozygous genotype	1284	NA	846**

*Note: *p<0.05; **p<0.01 compared with pre-treatment values.*

Effect of therapy on endothelial dysfunction

Endothelial dysfunction markers decreased after therapy. In patients without adverse genotypes, endothelin-1 decreased from 2.9 to 2.1 pg/ml after standard therapy and to 1.8 pg/ml after combined

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therapy in group 1. In group 2, endothelin-1 decreased from 3.5 to 2.4 and 2.0 pg/ml, respectively. In group 3, it decreased from 4.1 to 3.0 and 2.6 pg/ml.

sICAM also decreased after therapy. In group 1, it decreased from 298 to 234 and 226 ng/ml. In group 2, it decreased from 324 to 246 and 221 ng/ml. In group 3, it decreased from 360 to 271 and 255 ng/ml.

In patients with adverse genotypes, combined therapy reduced endothelin-1 from 4.5 to 3.2 pg/ml, from 4.8 to 3.6 pg/ml and from 5.2 to 4.1 pg/ml. sICAM decreased from 418 to 316 ng/ml, from 425 to 331 ng/ml and from 451 to 344 ng/ml.

Table 6. Endothelial dysfunction markers after therapy

Parameter / category	Before therapy	Standard therapy	Combined therapy
Endothelin-1, group 1 without adverse genotype, pg/ml	2.9	2.1*	1.8**
Endothelin-1, group 2 without adverse genotype, pg/ml	3.5	2.4*	2.0**
Endothelin-1, group 3 without adverse genotype, pg/ml	4.1	3.0*	2.6**
Endothelin-1, group 2 heterozygous genotype, pg/ml	4.5	NA	3.2*
Endothelin-1, group 3 heterozygous genotype, pg/ml	4.8	NA	3.6*
Endothelin-1, group 3 homozygous genotype, pg/ml	5.2	NA	4.1*
sICAM, group 1 without adverse genotype, ng/ml	298	234*	226*
sICAM, group 2 without adverse genotype, ng/ml	324	246*	221**
sICAM, group 3 without adverse genotype, ng/ml	360	271*	255*
sICAM, group 2 heterozygous genotype, ng/ml	418	NA	316*
sICAM, group 3 heterozygous genotype, ng/ml	425	NA	331*
sICAM, group 3 homozygous genotype, ng/ml	451	NA	344*

*Note: *p<0.05; **p<0.01 compared with pre-treatment values.*

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Figure 1 is provided below to visually summarize the central quantitative findings described in the Results section.

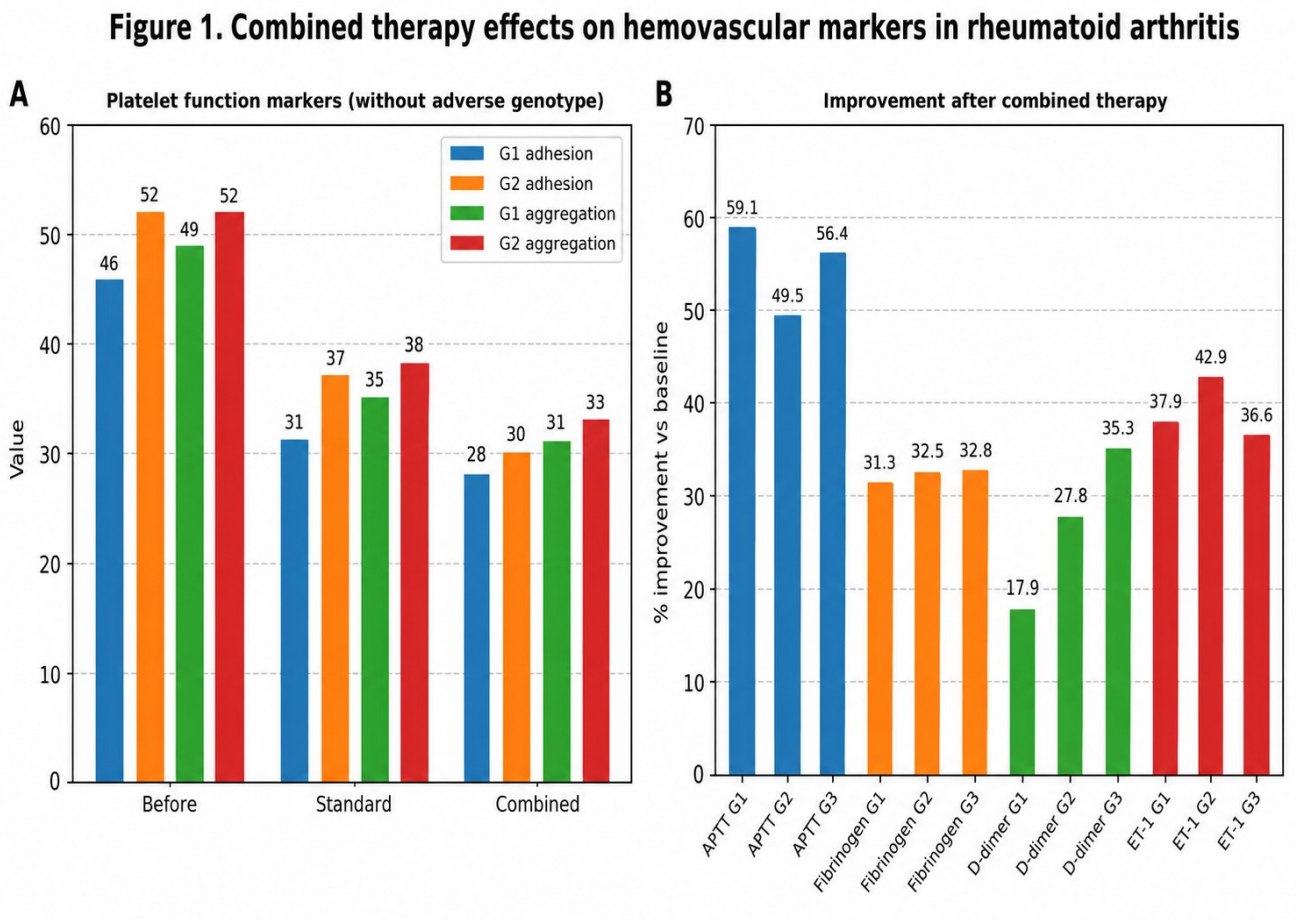


Figure 1. Visual summary of combined therapy effects on platelet function, coagulation markers, and endothelial dysfunction in rheumatoid arthritis.

Note. Panel A compares platelet adhesion and aggregation before treatment, after standard therapy, and after combined therapy in patients without adverse thrombophilia-related genotypes. Panel B presents percentage improvement from baseline after combined therapy for APTT, fibrinogen, D-dimer, and endothelin-1 across the summarized study groups. The figure was constructed from the numerical values reported in Tables 2–6.

Discussion

The results of this study show that combined pathogenetically oriented therapy has a more pronounced corrective effect on hemovascular disturbances in rheumatoid arthritis than standard therapy alone. The most evident improvements were observed in platelet adhesion and aggregation, APTT, prothrombin index, fibrinogen, D-dimer, endothelin-1 and sICAM.

Platelet count decreased after treatment, but these changes were not reliable. In contrast, platelet functional activity improved significantly. This suggests that platelet function may be a more sensitive marker of therapeutic response than platelet count alone.

The increase in APTT and decrease in prothrombin index after combined therapy indicate reduction of hypercoagulability. The decrease in fibrinogen and D-dimer further supports improvement of coagulation balance and reduction of fibrin formation and degradation activity [4-7,15].

Endothelial dysfunction markers also responded better to combined therapy. Reduction of endothelin-1 suggests improvement of endothelial vasoregulatory function, while reduction of sICAM indicates decreased inflammatory endothelial activation [3,9,15].

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Patients with adverse thrombophilia-related genotypes improved after combined therapy, but their parameters did not fully normalize. This indicates that genetic predisposition may reduce the completeness of hemovascular correction and may require longer monitoring [8-14].

Overall, the findings support a personalized therapeutic model in rheumatoid arthritis. In patients with endothelial dysfunction and hypercoagulation, treatment assessment should include not only inflammatory and articular markers but also platelet, coagulation and endothelial parameters.

Conclusions

1. Standard therapy improves some hemostatic parameters in rheumatoid arthritis, but combined therapy has a stronger corrective effect.

2. Platelet adhesion and aggregation decreased more significantly after combined therapy than after standard therapy.

3. Combined therapy increased APTT, reduced prothrombin index and improved coagulation balance.

4. Fibrinogen and D-dimer decreased more markedly after combined therapy, indicating reduction of hypercoagulability.

5. Endothelin-1 and sICAM decreased after combined therapy, confirming improvement of endothelial dysfunction.

6. Patients with adverse thrombophilia-related genotypes improved after therapy but retained residual abnormalities.

7. Pathogenetically oriented therapy may be considered a promising adjunctive approach for correction of hemovascular disturbances in rheumatoid arthritis.

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