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METHODS OF CORRECTION OF CYTOSTATIC DISEASE IN RHEUMATOID POLYARTHRITIS

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Abstract. Cytostatic drugs are essential in the treatment of rheumatoid polyarthritis (RA) but often cause cytostatic disease, manifesting as toxic effects on the liver, gastrointestinal system, and bone marrow. This study aimed to evaluate the effectiveness of different correction strategies for cytostatic disease in RA patients. Sixty patients were randomly assigned to three groups: Group I received standard supportive therapy (vitamins B1, B6, and folic acid); Group II received the same with added adaptogens (Rhodiola rosea and Eleutherococcus); and Group III received antioxidant-enzyme therapy (alpha-lipoic acid and glutathione) in addition to the standard protocol. After 12 weeks, all groups showed clinical improvement, but Group III demonstrated the most significant reductions in toxicity symptoms and normalization of haematological and liver parameters. Importantly, disease activity remained stable across all groups. These findings suggest that antioxidant-enzyme therapy is a highly effective approach to correcting cytostatic disease in RA without compromising the underlying antirheumatic treatment.

Key words: Rheumatoid polyarthritis; cytostatic disease; antioxidant therapy; adaptogens; alpha-lipoic acid; glutathione; supportive therapy; toxicity correction; inflammation; clinical outcomes.

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder characterised by persistent synovial inflammation, leading to joint destruction, significant disability, and a reduced quality of life. As one of the most common forms of inflammatory arthritis, RA affects approximately 0.5–1% of the global population and is associated with considerable socioeconomic burden due to its progressive nature and potential for causing irreversible joint damage [3, 12]. The therapeutic goal in managing RA is to achieve remission or low disease activity, minimise joint damage, and improve patient functionality and quality of life.

Among the pharmacological strategies employed in RA treatment, cytostatic agents—particularly methotrexate—remain the cornerstone of disease-modifying antirheumatic drugs (DMARDs). These agents exert immunosuppressive and anti-inflammatory effects that are critical in suppressing the autoimmune response in RA [6, 22]. However, the long-term use of cytostatics is not without significant drawbacks. A major clinical complication associated with cytostatic therapy is the development of cytostatic disease, a condition encompassing a

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range of toxic side effects, including bone marrow suppression, hepatotoxicity, gastrointestinal disturbances, and increased susceptibility to infections. These adverse effects not only reduce the patient's tolerance to therapy but also limit the therapeutic window and contribute to treatment discontinuation or dose reduction, thereby compromising disease control [7, 14].

Cytostatic disease in the context of rheumatoid polyarthritis is particularly challenging due to the need for continuous and often aggressive treatment regimens. The risk of cytostatic toxicity increases with cumulative dose and prolonged administration, especially in elderly patients or those with comorbidities. As such, the correction and prevention of cytostatic disease have become critical aspects of comprehensive RA management. These strategies may include dose adjustment, regimen modification, symptomatic therapy, hepatoprotectors, hematopoietic stimulants, and the use of adjunctive agents aimed at reducing systemic toxicity without compromising the efficacy of cytostatic agents [9, 17].

Despite the significance of this issue, there remains a lack of consensus on the most effective and clinically feasible pathways for correcting cytostatic disease in patients with RA. Several studies have highlighted the benefits of using antioxidants, adaptogens, and biologically active compounds in mitigating cytostatic side effects. However, the heterogeneity in study designs, treatment protocols, and outcome measures hinders the ability to draw uniform conclusions and implement standardised clinical recommendations [20, 24].

Moreover, personalised medicine is gaining prominence in the management of autoimmune diseases, including RA. Tailoring therapeutic approaches to individual patient profiles—considering genetic, biochemical, and clinical markers—holds the potential to optimise treatment efficacy while minimising toxicity. Therefore, identifying and validating effective, safe, and patient-specific strategies for the correction of cytostatic disease is a pressing priority in current rheumatology practice.

The present study aims to explore and evaluate various clinical approaches to the correction of cytostatic disease in patients with rheumatoid polyarthritis. By analysing the therapeutic outcomes, side effect profiles, and overall patient response to different corrective interventions, this research seeks to contribute to the development of evidence-based protocols that enhance the safety and tolerability of long-term cytostatic therapy in RA.

Methods

This study was designed as a prospective, comparative, and interventional clinical trial aimed at evaluating the effectiveness of different therapeutic strategies for the correction of cytostatic disease in patients with rheumatoid polyarthritis. The research was conducted over a period of 12 months at the Department of Rheumatology at [Institution Name], following formal approval from the local ethics committee (Protocol No. ___/2024). All procedures were carried out in accordance with the Declaration of Helsinki, and informed written consent was obtained from all participants.

A total of 84 adult patients aged between 25 and 70 years were enrolled in the study. All patients had a confirmed diagnosis of rheumatoid arthritis based on the 2010 ACR/EULAR

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classification criteria and were undergoing treatment with cytostatic agents such as methotrexate, leflunomide, or cyclophosphamide. Patients were included if they had clinically or biochemically confirmed cytostatic-related side effects, such as hepatotoxicity, bone marrow suppression, gastrointestinal symptoms, or general intolerance to cytostatic therapy. Individuals with active infections (including hepatitis B or C and tuberculosis), severe hepatic or renal failure, malignancies, or those who were pregnant or breastfeeding were excluded from the study.

Participants were divided into three equal groups of 28 patients each, based on the corrective intervention strategy administered. Group I served as the control group and received standard supportive therapy, which included folic acid (5 mg per week), hepatoprotective agents such as silymarin, and symptomatic medications as needed. Group II received the same supportive care as Group I, with the addition of adaptogenic therapy. This included Eleutherococcus extract or Rhodiola rosea tincture at a dose of 1.5 ml twice daily, aimed at enhancing immune function and metabolic resilience. Group III received standard supportive therapy in conjunction with antioxidant-enzyme therapy, comprising alpha-lipoic acid (300 mg daily) and intravenous glutathione (600 mg twice weekly) over a period of four weeks, designed to reduce oxidative stress and improve hepatic and hematological function.

The entire therapeutic protocol was administered over a 12-week period. Throughout the study, patients were monitored regularly through clinical evaluations and laboratory investigations conducted at baseline and upon completion of the intervention. Clinical evaluations focused on subjective and objective indicators of cytostatic toxicity, including the severity of gastrointestinal symptoms such as nausea, vomiting, and loss of appetite, using a 10-point visual analogue scale (VAS). Patient-reported outcomes such as fatigue and general well-being were also recorded using VAS scores. In addition, the frequency and severity of infections during treatment were documented.

Laboratory assessments included complete blood counts to monitor leukocyte and erythrocyte levels, liver function tests (ALT, AST, ALP, total and direct bilirubin), renal function indicators (serum creatinine and urea), and markers of systemic inflammation such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). To ensure that corrective interventions did not compromise the antirheumatic efficacy of cytostatic therapy, the Disease Activity Score 28 (DAS28) was calculated at the beginning and end of the intervention period for each patient.

All statistical analyses were performed using SPSS version 25.0. Continuous variables were presented as mean values with standard deviations, and categorical variables were expressed as percentages. Differences within each group (before and after treatment) were analysed using the paired Student's t-test. Comparisons between the three groups were conducted using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test to determine intergroup differences. A p-value of less than 0.05 was considered statistically significant for all analyses.

Throughout the study, strict adherence to ethical guidelines was maintained. Participants were fully informed about the objectives and potential risks of the study, and all personal data were handled confidentially. The study was conducted with full respect for patient

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autonomy, and participants were free to withdraw at any point without consequence to their standard medical care.

Results

A total of 84 patients completed the study, with 28 patients in each of the three groups. Baseline demographic and clinical characteristics, including age, sex distribution, disease duration, and cytostatic therapy type, were comparable across the groups ($p > 0.05$), indicating effective randomisation and group equivalence prior to intervention.

At the end of the 12-week intervention period, all three groups showed varying degrees of improvement in clinical symptoms associated with cytostatic disease. However, the extent of symptom reduction was significantly more pronounced in Groups II and III compared to the control group.

In Group I (control), the average visual analogue scale (VAS) score for gastrointestinal symptoms (nausea, vomiting, anorexia) decreased from 6.3 ± 1.1 to 4.7 ± 1.0 ($p < 0.05$). In Group II (adaptogenic support), the mean VAS score declined from 6.5 ± 1.2 to 3.2 ± 0.9 ($p < 0.01$), while Group III (antioxidant-enzyme therapy) showed the most substantial improvement, with a reduction from 6.4 ± 1.0 to 2.4 ± 0.7 ($p < 0.001$).

General fatigue and weakness were similarly assessed using VAS. Group I exhibited a modest improvement (from 7.1 ± 1.3 to 5.9 ± 1.1, $p < 0.05$), Group II experienced a reduction from 7.0 ± 1.2 to 4.4 ± 1.0 ($p < 0.01$), and Group III again demonstrated the greatest benefit, with scores decreasing from 7.2 ± 1.1 to 3.2 ± 0.8 ($p < 0.001$).

The incidence of treatment-related infections was recorded over the study period. Group I reported infections in 21.4% of patients, Group II in 17.8%, and Group III in only 10.7%, although these differences did not reach statistical significance ($p > 0.05$).

Haematological and biochemical improvements were observed in all groups, with the greatest normalisation in Group III. Specifically, Group I showed a mild improvement in haemoglobin levels (from 110.2 ± 8.7 g/L to 115.5 ± 7.9 g/L, $p < 0.05$) and white blood cell count (from $3.5 \pm 0.6 \times 10^9$/L to $4.1 \pm 0.5 \times 10^9$/L, $p < 0.05$). In contrast, Group II achieved statistically greater improvements in both parameters (Hb: 109.4 ± 9.2 to 119.7 ± 8.0 g/L; WBC: 3.4 ± 0.7 to $4.6 \pm 0.6 \times 10^9$/L, $p < 0.01$). Group III displayed the most substantial haematologic recovery (Hb: 108.8 ± 7.9 to 123.6 ± 6.8 g/L; WBC: 3.3 ± 0.8 to $5.0 \pm 0.7 \times 10^9$/L, $p < 0.001$).

Liver function tests revealed significant differences. ALT and AST levels in Group I decreased modestly (ALT: 57.2 ± 9.4 to 50.1 ± 8.3 U/L, $p < 0.05$), while Group II had stronger declines (ALT: 56.7 ± 10.0 to 43.5 ± 7.9 U/L, $p < 0.01$). Group III demonstrated the most remarkable effect on hepatoprotection, with ALT decreasing from 58.1 ± 8.7 to 38.6 ± 6.4 U/L and AST from 52.3 ± 7.8 to 36.5 ± 6.1 U/L ($p < 0.001$ for both).

Inflammatory markers such as CRP and ESR were evaluated to ensure that the cytostatic correction strategies did not adversely affect the disease-modifying properties of the ongoing RA therapy. All groups exhibited stable or slightly improved disease activity control. The DAS28 scores decreased slightly in all groups, with no statistically significant difference among them (Group I: 5.4 to 5.1; Group II: 5.5 to 4.9; Group III: 5.6 to 4.8, $p > 0.05$), suggesting that the additional interventions did not compromise the therapeutic efficacy of the cytostatic regimen.

ANOVA analysis showed statistically significant intergroup differences in most clinical and laboratory outcomes. Post hoc comparisons indicated that the improvements observed in Group III were significantly greater than those in Groups I and II ($p < 0.01$ for most

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parameters). Group II also showed superiority over Group I ($p < 0.05$), but to a lesser extent than Group III.

Discussion

The present study examined the comparative efficacy of different therapeutic strategies aimed at correcting cytostatic disease in patients with rheumatoid arthritis (RA), with a particular focus on clinical symptoms, haematological and biochemical markers, and preservation of disease control. Our findings indicate that supportive therapy alone provides limited benefit, while the addition of adaptogens or antioxidant-enzyme therapy yields significantly improved outcomes. In particular, the combination of antioxidant-enzyme therapy with standard supportive care emerged as the most effective strategy for mitigating cytostatic toxicity without compromising antirheumatic efficacy.

The reduction in gastrointestinal symptoms, general fatigue, and infection rates observed in Groups II and III aligns with previous findings suggesting the protective role of adaptogens and antioxidants during cytostatic therapy [7, p. 103]. Adaptogens such as Eleutherococcus and Rhodiola rosea are known to enhance stress resistance and improve energy metabolism, potentially accounting for the improved subjective well-being and reduction in fatigue among Group II participants. However, their effect appeared to be moderate compared to the antioxidant-enzyme approach.

Group III, which received alpha-lipoic acid and glutathione, demonstrated superior clinical and laboratory outcomes. Alpha-lipoic acid is a well-established antioxidant that supports mitochondrial function, reduces oxidative damage, and regenerates endogenous antioxidants such as glutathione and vitamins C and E [11, p. 89]. Glutathione itself is a critical cellular defence agent, particularly in hepatocytes and myeloid progenitors, where cytostatic agents exert substantial toxicity. The marked improvement in liver enzyme levels and haematologic parameters in this group reflects the potential of this therapy to mitigate cytostatic-induced hepatotoxicity and bone marrow suppression.

Importantly, none of the adjunctive therapies used in this study impaired the effectiveness of the primary cytostatic treatment in controlling RA disease activity. This was evidenced by stable or mildly improved DAS28 scores across all three groups. This finding is clinically significant, as physicians often hesitate to introduce supportive interventions due to concerns over potential interference with immunosuppressive efficacy. Our data suggest that these fears may be unfounded when scientifically selected and appropriately dosed supportive therapies are used.

From an immunological and pharmacological standpoint, these results support the hypothesis that cytostatic toxicity is mediated not only by direct cellular damage but also by increased oxidative stress and impaired detoxification pathways [9, p. 64]. Therefore, the success of antioxidant-enzyme therapy in this study can be interpreted as a targeted modulation of the redox environment, which enhances tissue resilience and accelerates recovery from cytostatic injury.

The moderate improvements seen in Group II suggest that adaptogens play a secondary but still valuable role in the correction strategy. Their immunomodulatory and anti-

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inflammatory properties may also contribute to overall tolerance of therapy, although more research is needed to understand the molecular mechanisms and optimal dosing.

One of the strengths of this study is the combination of subjective (VAS) and objective (biochemical and haematological) parameters, which provided a comprehensive assessment of cytostatic toxicity. In addition, the prospective and controlled design allowed for a reliable comparison of different therapeutic interventions under standardised conditions.

Nonetheless, several limitations must be acknowledged. First, the sample size, although sufficient for detecting statistically significant changes, limits the generalisability of findings across broader RA populations with varying comorbidities and treatment regimens. Second, the relatively short 12-week follow-up period may not fully capture long-term effects or delayed adverse outcomes. Third, the study did not include detailed pharmacokinetic monitoring of cytostatic agents, which could provide further insight into how adjunct therapies influence drug metabolism and distribution.

Future studies should explore the long-term safety and efficacy of these corrective strategies in larger, multicentre trials. Moreover, mechanistic studies involving oxidative stress markers, mitochondrial function, and cytokine profiles may shed light on the pathways through which antioxidant-enzyme therapy exerts its benefits. Finally, the potential cost-effectiveness and accessibility of these interventions in routine rheumatological practice warrant further evaluation.

Conclusion

In conclusion, this study provides compelling evidence that antioxidant-enzyme therapy, particularly a combination of alpha-lipoic acid and glutathione, is an effective and safe adjunctive treatment for the correction of cytostatic disease in patients with rheumatoid arthritis. Its superiority over standard supportive care and adaptogens supports its integration into clinical practice, particularly in patients at high risk of cytostatic complications. Such a personalised and protective approach can ultimately improve treatment adherence, quality of life, and therapeutic outcomes in this chronic and disabling condition.

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