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A retrospective evaluation of the effects of dimethyl fumarate on hematological parameters in patients with multiple sclerosis

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MAIN POINTS

- Dimethyl fumarate significantly modulates peripheral blood cell profiles in relapsing–remitting multiple sclerosis.
- Treatment-related lymphocyte suppression substantially influences composite systemic inflammation indices.
- Elevated inflammatory indices during dimethyl fumarate therapy do not necessarily indicate increased disease activity.
- Standard inflammatory markers remain largely unchanged despite hematological shifts.
- Interpretation of immune–inflammation indices in treated patients requires integration with clinical and radiological findings.

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ABSTRACT

Aim: Multiple Sclerosis (MS) is a chronic, inflammatory, and demyelinating disease of the central nervous system. Typically seen in young adults, MS progressively leads to neurological impairments and significantly affects the quality of life. The lack of a definitive cure necessitates long-term monitoring and disease-modifying treatments. Dimethyl fumarate (DMF), a disease-modifying agent used in MS treatment, is notable for its antioxidant and anti-inflammatory effects.

Materials and Methods: In the present study, hematological, biochemical, and systemic inflammation parameters in MS patients were retrospectively analyzed before and after DMF treatment. The study aimed to investigate the effects of DMF on peripheral blood parameters and immune indices in MS patients.

Results: DMF treatment resulted in statistically significant decreases in leukocyte, neutrophil, lymphocyte, and platelet counts. Although a significant reduction was detected in creatinine levels, no significant changes were observed in BUN, ALT, AST, sedimentation rate, CRP, eosinophils, basophils, hemoglobin, and monocytes. After DMF treatment, statistically significant increases were observed in PIV, PLR, NLR, MLR, and SIRI. However, these increases likely reflect a mathematical artifact driven by DMF-induced lymphopenia (i.e., reduced lymphocytes in the denominator), rather than true systemic inflammatory activation. Therefore, these indices should be interpreted in the context of absolute cell counts and clinical and radiological findings.

Conclusion: The present study demonstrates that DMF treatment significantly affects peripheral hematological parameters and inflammatory indices. These parameters may serve as practical, low-cost biomarkers for monitoring treatment response in MS patients.

Keywords: Dimethyl fumarate, Hematology, Immune indices, Multiple sclerosis
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INTRODUCTION

Multiple sclerosis (MS) is a chronic, immune-mediated, demyelinating, and neurodegenerative disease of the central nervous system (CNS), predominantly affecting young adults and causing substantial long-term disability [1,2]. Among its clinical phenotypes, relapsing–remitting MS (RRMS) is the most prevalent, characterized by episodes of neurological dysfunction followed by partial or complete remission. Pathogenesis involves the activation of autoreactive T and B lymphocytes in the periphery, disruption of the blood–brain barrier, and infiltration of inflammatory cells into the CNS, leading to demyelination, axonal loss, and progressive neurodegeneration [3-5]. Globally, the prevalence of MS is rising, thereby contributing to an increasing burden on health systems and society [6].

The etiology of MS is multifactorial. Genetic susceptibility, particularly HLA-DRB1*15:01, significantly increases disease risk [7-9]. Among environmental triggers, Epstein–

Barr virus (EBV) infection is the strongest, with prospective studies demonstrating a marked rise in MS risk following EBV seroconversion [10]. Vitamin D deficiency, adolescent obesity, smoking, and low sunlight exposure further modulate disease susceptibility [4,11]. Immunopathologically, Th1/Th17-polarized T cells, B-cell-mediated antigen presentation, and intrathecal IgG production establish the inflammatory milieu observed in MS lesions [12,13]. The revised McDonald criteria integrate dissemination in space and time, supported by cerebrospinal fluid oligoclonal bands, to provide a standardized diagnostic framework [14,15].

Disease-modifying therapies (DMTs) represent the cornerstone of treatment, aiming to reduce relapse frequency, delay progression, and mitigate long-term disability. Among them, dimethyl fumarate (DMF) has emerged as a widely used oral DMT with both immunomodulatory and antioxidant properties [16,17]. DMF exerts its effects by activating the nuclear factor erythroid 2 2-related factor 2(Nrf2)antioxidant pathway while simultaneously inhibiting nuclear factor kappa B (NF-κB)–mediated proinflammatory signaling [18-20]. Pivotal phase III trials demonstrated that DMF significantly reduced annualized relapse rates and the number of new T2 lesions [21,22]. However, treatment requires hematological monitoring due to the risk of lymphopenia, which is frequently observed during therapy [23,24].

Increasing evidence indicates that MS is not solely a CNS-restricted disease; it also involves measurable systemic immune alterations. Hematological indices derived from complete blood counts (CBCs), such as the Systemic Immune-Inflammation Index (SII) and Systemic Inflammation Response Index (SIRI), have been investigated as surrogate markers of systemic immune activation. These indices integrate neutrophil, lymphocyte, monocyte, and platelet dynamics into composite measures that reflect the inflammatory burden. Initially validated in oncology and cardiovascular disease, SII and SIRI have shown potential prognostic value in autoimmune and neuroinflammatory disorders, including MS [25-27]. A related metric, the Pan-Immune-Inflammation Value (PIV), expands this approach by combining neutrophils, monocytes, and platelets relative to lymphocytes, though its role in MS remains to be established [28-30]. Therefore, this study aimed to comprehensively evaluate the effects of dimethyl fumarate therapy on peripheral hematological parameters and systemic immune–inflammatory indices in patients with relapsing–remitting multiple sclerosis.

MATERIALS AND METHODS

Study design

The study protocol was approved by the Uludağ University Clinical Research Ethics Committee (Approval no: 2024-6/15, Date: 13.05.2024), and all procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki. The aim was to evaluate hematological changes in patients with multiple sclerosis (MS) receiving dimethyl fumarate (DMF) therapy by comparing pre- and post-treatment values after at least 6 months of continuous therapy. No direct patient contact or clinical intervention was performed. All data were obtained from the hospital information system, MIA (Medical Information Archive). In this respect, the study provides real-world evidence of the hematological effects of a commonly used disease-modifying therapy.

Patient selection and inclusion criteria

A total of 100 patients diagnosed with MS according to the McDonald criteria and who were initiated on DMF therapy at Bursa Uludağ University Health Application and Research Center between 2020 and 2024 were included. Eligible participants were ≥18 years of age, had been continuously treated with dimethyl fumarate (DMF) for at least 6 months, and had complete hematological data available both before treatment and at follow-up; post-treatment laboratory values corresponded to the last available follow-up visit after initiation of DMF therapy. Patients who switched to another immunomodulatory treatment during follow-up were excluded (Table 1). The mean age of the study cohort was 36.5 years, and the mean duration of DMF treatment was 2.94 years. Of the participants, 52% were male, and 48% were female. Detailed inclusion and exclusion criteria, along with the baseline demographic and clinical characteristics of the study population, are presented in Table 2.

Data collection

The dataset was obtained retrospectively from the MIA electronic medical records system. Collected variables included demographic characteristics, date of MS diagnosis, initiation date and duration of DMF therapy, comorbidities, concomitant medications, and results of hematological tests before treatment initiation and at least six months thereafter. All data were anonymized, and no personal identifiers were recorded at any stage.

Evaluated parameters

Pre- and post-treatment complete blood count results were compared. The following hematological and biochemical parameters were analyzed: hemoglobin (Hb), red blood cells (RBC), white blood cells (WBC), neutrophils, lymphocytes, monocytes, platelets, hematocrit (Hct), mean corpuscular volume (MCV), and mean platelet volume (MPV). In addition, derived systemic inflammation indices were calculated, including the Systemic Immune-Inflammation Index (SII), Pan-Immune-Inflammation Value (PIV), Platelet-to-Lymphocyte Ratio (PLR), Neutrophil-to-Lymphocyte Ratio (NLR), Monocyte-to-Lymphocyte Ratio (MLR), and Systemic Inflammation Response Index (SIRI).

Index formulas were defined as follows: NLR = neutrophils/lymphocytes; PLR = platelets/lymphocytes; MLR =

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monocytes/lymphocytes; SII = (platelets × neutrophils)/lymphocytes; SIRI = (neutrophils × monocytes)/lymphocytes; PIV = (neutrophils × monocytes × platelets)/lymphocytes.

Data quality and control

To ensure data quality, electronic patient records were reviewed independently by two researchers. Extracted data were double-checked, and any missing, inconsistent, or suspicious entries were re-evaluated. Outliers were identified and excluded from the statistical analysis. This rigorous control process enhanced the methodological reliability of the study and strengthened the validity of the findings.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Normality of the data distribution was assessed using the Shapiro–Wilk test. For continuous variables with normal distributions, paired-sample t-tests were used; non-normally distributed data were analyzed using the Wilcoxon signed-rank test. Descriptive statistics were expressed as mean ± standard deviation (SD), median (minimum–maximum), and percentage (%). Values exceeding ±3 standard deviations from the mean were considered potential outliers and excluded from the analysis (A total of 5 observations were excluded based on these criteria). A p-value of <0.05 was considered statistically significant.

RESULTS

Biochemical parameters

No significant difference was observed in blood urea nitrogen (BUN) levels following DMF treatment (baseline: 25.73 ± 9.09 mg/dL; post-treatment: 25.40 ± 8.58 mg/dL; p = 0.788), suggesting no adverse effect on renal function. However, serum creatinine levels decreased slightly but significantly (baseline: 0.715 mg/dL; post-treatment: 0.670 mg/dL; p = 0.008), suggesting a possible indirect effect of DMF on renal excretion. Liver enzymes did not show significant changes. Both AST (p = 0.163) and ALT (p = 0.780) remained stable, indicating no hepatotoxic effect in this patient cohort (Table 3).

Complete blood count and leukocyte subpopulations

A statistically significant decrease was observed in total leukocyte counts after DMF treatment (baseline: 7703 ± 3103/μL; post-treatment: 6400 ± 2465/μL; p = 0.0012). This decline was primarily attributable to a pronounced reduction in lymphocyte counts (baseline: 2145 ± 890.5/μL; post-treatment: 1613 ± 786.1/μL; p<0.0001), consistent with the well-recognized lymphopenic effect of DMF. Neutrophil counts also decreased significantly (baseline: median 5060; post-treatment: 4030; p<0.0001), suggesting that DMF exerts suppressive effects not only on lymphocytes but also on other leukocyte subsets. In contrast, eosinophils (p = 0.060), monocytes (p = 0.541), and basophils (p = 0.372) did not differ significantly. Platelet counts demonstrated a mild but statistically significant reduction (baseline: 267.6 ± 79.2 $\times 10^3$/μL; post-treatment: 251.2 ± 8.1 $\times 10^3$/μL; p = 0.022), though values remained within normal limits. Hemoglobin levels were unaffected (p = 0.297) (Table 4).

Inflammatory markers

No significant differences in erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels were observed after DMF treatment (ESR: p = 0.205; CRP: p = 0.066). However, CRP exhibited a slight upward trend, which might indicate persistent low-grade inflammation and warrant further monitoring (Table 3).

Systemic inflammation indices

Composite systemic inflammation indices showed notable changes following DMF therapy: the Pan-Immune-Inflammation Value (PIV) increased significantly from a median of 288,689 to 340,077 (p = 0.043) and the platelet-to-lymphocyte ratio (PLR) rose from 127.7 to 170.3 (p<0.0001). Despite an absolute decrease in neutrophil counts, the neutrophil-to-lymphocyte ratio (NLR) increased (p = 0.035) owing to a more pronounced reduction in lymphocytes; the monocyte-to-lymphocyte ratio (MLR) also increased (p<0.0001). The systemic inflammation response index (SIRI) exhibited a statistically significant increase (p = 0.001), whereas the systemic immune-inflammation index (SII) did not change significantly (p = 0.415) (Table 5).

Clinical and radiological findings: EDSS Score and MRI lesions

The Expanded Disability Status Scale (EDSS) scores improved significantly after DMF treatment (baseline: 2.8 ± 0.9; post-treatment: 2.3 ± 0.7; p = 0.014), reflecting a slowing of disease progression. This clinical improvement was paralleled by a significant reduction in annual relapse rate (baseline: median 1 [0–5]; post-treatment: median 0 [0–1]; p<0.0001). MRI findings demonstrated a significant reduction in T2 lesion counts, decreasing from 7.4 ± 2.2 at baseline to 5.6 ± 1.9 after treatment (p = 0.009) (Table 6). These findings confirm that DMF reduces both clinical and radiological disease activity (Table 5). Correlation analyses did not reveal any significant association between systemic inflammatory indices and clinical disease activity parameters, including EDSS scores and MRI findings.

DISCUSSION

This study investigated the effects of dimethyl fumarate (DMF) therapy on peripheral blood parameters and systemic inflammation indices in patients with relapsing–remitting multiple sclerosis (RRMS). It evaluated their relationship

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Table 1. Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
Age ≥ 18 years	History of heart failure
Definite MS diagnosis according to McDonald criteria	Coronary artery disease
DMF therapy ≥ 6 months	Renal failure (GFR <60 ml/min)
Complete hematological data available (pre- and post-treatment)	Abnormal liver function tests (ALT/AST >3× ULN)
No switch to another immunomodulatory treatment during follow-up	Known autoimmune disease
Absence of chronic or acute systemic diseases	Rheumatologic diseases
	Malignancy
	Hematological disorders (e.g., leukopenia)
	Active infection
	Pregnancy or breastfeeding
	Missing or inaccessible data

GFR: glomerular filtration rate.

Table 2. Baseline demographic and clinical characteristics of the study population.

Variable	Value
Number of patients	100
Age (years)	36.5 ± 10.4
Female	48 (48%)
Male	52 (52%)
Disease duration (years)	4.9 ± 3.6
Baseline EDSS score	2.8 ± 0.9
Duration of DMF treatment (years)	2.94 ± 1.9

with clinical and radiological findings. The results demonstrated that DMF significantly suppresses not only lymphocytes but also total leukocytes and neutrophils. Furthermore, the observed increases in systemic inflammation indices likely represent mathematical artifacts driven by DMF-induced lymphopenia and related hematological alterations, rather than reflecting true systemic inflammatory activation or increased disease activity. In this context, our study contributes novel insights to the existing literature and proposes a new interpretative framework for the clinical evaluation of inflammation indices.

The approximately 25% reduction in lymphocyte counts clearly reflects the immunosuppressive effect of DMF. This finding aligns with pivotal studies, such as those by Gold et al. [21] and Wright et al. [31], which reported that DMF can reduce lymphocyte counts by up to 30% after one year of treatment. The literature reports that this effect may cause severe lymphopenia (<500 cells/μL) in approximately 5% of patients, thereby increasing the risk of infection. Gold et al. [32] further highlighted that DMF selectively suppresses $CD8^+$ T cells, underscoring the need for careful monitoring of immune balance and infection risk. The lymphocyte reduction observed in our study reflects this biological mechanism at the peripheral blood level.

In addition to a decrease in lymphocytes, our findings revealed a statistically significant decrease in total leukocyte and neutrophil counts. Although neutropenia under DMF therapy has been less frequently reported, studies by Longbrake et al. [33] and Goldman et al. [34] have raised awareness of this potential risk. In our cohort, neutrophil levels remained within the physiological range, but showed a statistically significant decline, suggesting that DMF may exert broader immunomodulatory effects beyond lymphocytes. This observation is clinically relevant to treatment safety and monitoring strategies. Notably, neutrophil decline may have clinical relevance independent of lymphopenia, as reduced innate immune reserve can predispose susceptible patients to bacterial and fungal infections. Accordingly, comprehensive CBC follow-up should include monitoring absolute neutrophil count trajectories as well as lymphocyte counts, particularly in patients with recurrent infections or other risk factors.

The mild reduction in platelet count was statistically significant but not clinically meaningful. This is consistent with phase III trial data reported by Fox et al. [35], which indicated that DMF does not significantly alter platelet counts. Thus, our results reaffirm DMF's favorable safety profile regarding thrombocytopenia. Moreover, given that rare cases of thrombocytopenia are typically associated with other predisposing factors, the changes observed here are unlikely to represent a clinically significant risk.

With respect to systemic inflammation indices, we observed a statistically significant after treatment increase composite parameters (PIV, PLR, NLR, MLR, and SIRI), whereas levels of SII and CRP remained unchanged. Since many of these indices are calculated using lymphocyte count as the denominator, the treatment-induced reduction in lymphocyte count mathematically increases them. For example, despite the observed decrease in neutrophils, NLR increased because the decline in lymphocytes was more pronounced. Therefore, the observed increases in these indices are more likely a reflection of treatment-related hematological changes rather than evidence of heightened systemic inflammation. This interpretation diverges from previous studies, such as those by Gökçe et al. [36] and Fathy et al. [37], which associated such indices with disease activity; however, they did not clearly account for treatment regimens. By focusing exclusively on DMF-treated patients, our study provides stronger causal evidence support-

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Table 3. Biochemical parameters and inflammatory markers.

Parameter	Baseline	Post-treatment	p-value
BUN (mg/dL) (mean ± SD)	25.73 ± 9.09	25.40 ± 8.58	0.788
Creatinine (mg/dL) (median [max--min])	0.715 (1.59--0.43)	0.670 (1.04--0.47)	0.008*
AST (U/L) (median [max--min])	17 (60--8)	18 (50--8)	0.163
ALT (U/L) (median [max--min])	16 (128--6)	17.5 (108--6)	0.780
ESR (mm/h) (mean ± SD)	7.11 ± 5.47	8.11 ± 7.02	0.205
CRP (mg/L)	1.99 (8.40--0.04)	2.10 (57.8--0.20)	0.066

* p<0.05.

Table 4. Complete blood count and leukocyte subsets.

Parameter	Baseline	Post-treatment	p-value
Leukocyte count (/μL) (mean ± SD)	7703 ± 3103	6400 ± 2465	0.0012*
Lymphocytes (/μL) (mean ± SD)	2145 ± 890.5	1613 ± 786.1	<0.0001*
Neutrophils (/μL) (median [max--min])	5060 (17600--1890)	4030 (12460--1600)	0.0001*
Eosinophils (/μL)	110 (623--0)	128 (770--1)	0.060
Monocytes (/μL)	540 (1205--71)	529 (1190--68)	0.541
Basophils (/μL) (mean ± SD)	55.0 ± 47.0	59.6 ± 39.9	0.372
Hemoglobin (g/dL)	13.8 (24.5--9.0)	13.4 (16.2--9.8)	0.297
Platelets (10^3/μL) (mean ± SD)	267.6 ± 79.2	251.2 ± 81.1	0.022*

* p<0.05.

Table 5. Systemic inflammation indices.

Parameter	Baseline	Post-treatment	p-value
SII	682 (4387--137)	671 (5908--154)	0.415
PIV	288,689 (1,740,026--35,861)	340,077 (6,823,630--62,867)	0.043*
PLR	127.7 (483.3--25.9)	170.3 (719.2--46.9)	<0.0001*
NLR	2.38 (18.0--0.18)	2.86 (20.5--0.59)	0.035*
MLR	0.244 (0.714--0.039)	0.356 (1.821--0.057)	<0.0001*
SIRI	1112 (7598--127.6)	1397 (15,130--284.5)	0.001*

* p<0.05.

Table 6. Clinical and radiological findings.

Parameter	Baseline	Post-treatment	p-value
Annual relapse rate	1 (5--0)	0 (1--0)	<0.0001*
EDSS score (mean ± SD)	2.8 ± 0.9	2.3 ± 0.7	0.014
T2 lesion count on MRI (mean ± SD)	7.4 ± 2.2	5.6 ± 1.9	0.009

* p<0.05.

ing interpretation of these changes.

The absence of significant changes in monocyte counts supports the notion that increases in PIV and SIRI primarily result from lymphocyte decline. Similarly, the lack of significant changes in CRP further supports the conclusion that the observed shifts in indices do not reflect a genuine inflammatory response. Radiological outcomes demonstrated that gadolinium-enhancing active lesions were present in 52% of patients at baseline versus 24% post-treatment, alongside a significant reduction in mean T2 lesion number (7.4 ± 2.2 to 5.6 ± 1.9) and an improvement in mean EDSS (2.8 ± 0.9 to 2.3 ± 0.7). These findings confirm the clinical and radiological efficacy of DMF while supporting the interpretation that increases in systemic indices reflect hematological variation rather than disease progression. Although Zivadinov et al. [38] suggested correlations between MRI lesion burden and inflammatory biomarkers, such analyses did not account for treatment effects, limiting their interpretation.

Thus, our study provides both substantive and methodological contributions to the field. The existing literature has proposed systemic inflammation indices as prognostic markers in MS; however, limited data exist on how these indices behave under specific treatments. Our results show that increases in such indices under DMF therapy do not indicate worsening disease. Accordingly, the treatment regimen must be carefully considered when interpreting these markers, and hematological changes must be recognized as potential confounders. Moreover, our findings emphasize that indices such as NLR and PLR should not be interpreted in isolation but must be integrated with clinical and radiological outcomes.

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From a clinical perspective, one of the most important implications of the present study is that indices of systemic inflammation in DMF-treated patients might reflect treatment effects rather than true inflammatory activity. Clinicians should therefore exercise caution in interpreting these parameters. Furthermore, our data suggest that lymphocytes, neutrophils, and platelets should also be monitored in patients on DMF therapy to ensure patient safety and optimize therapeutic follow-up. These findings provide a methodological basis for future studies exploring the integration of hematological biomarkers into clinical decision-making.

Limitations

This study has several limitations. Due to its retrospective design, detailed data on prior disease-modifying therapies and corticosteroid exposure were not available, which may represent a potential source of confounding. In addition, lymphopenia severity grading could not be assessed due to dataset constraints. These limitations should be taken into account when interpreting the results.

CONCLUSION

Dimethyl fumarate therapy in RRMS is associated with significant alterations in peripheral hematological parameters, leading to apparent increases in several systemic inflammation indices. These changes appear to reflect a treatment-related reduction in lymphocyte counts rather than true inflammatory disease activity. Therefore, hematological inflammation indices should be interpreted cautiously in DMF-treated patients, particularly when clinical and radiological outcomes indicate disease stability.

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Ethics Committee Approval: This retrospective study was approved by the Clinical Research Ethics Committee of Bursa Uludağ University Faculty of Medicine (Approval no: 2024-6/15, Date: 13.05.2024).

Informed Consent: Due to the retrospective design of the study and the use of anonymized patient data, the requirement for informed consent was waived by the ethics committee.

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