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IS FOLIC ACID TRULY NEEDED BEYOND METHOTREXATE? A CRITICAL REVIEW OF CSDMARDS AND CONVENTIONAL IMMUNOSUPPRESSANTS

Original Research

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ABSTRACT

Background: Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) remain the cornerstone in the management of autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus. Methotrexate is the most widely prescribed csDMARD and its antifolate activity necessitates folic acid supplementation to reduce gastrointestinal, hepatic, and hematological toxicities. Over time, supplementation practices have been extended to other csDMARDs and immunosuppressants despite limited evidence. This review addresses the gap between guideline-based recommendations and real-world prescribing practices.

Objective: The objective of this review was to critically evaluate whether folic acid supplementation is truly necessary beyond methotrexate therapy in patients receiving csDMARDs or conventional immunosuppressants.

Methods: A thematic critical review was conducted using PubMed, the Cochrane Library, and Google Scholar. Literature published in English between 1995 and 2024 was included, encompassing randomized controlled trials, observational studies, systematic and narrative reviews, and recommendations from recognized rheumatology guidelines. Inclusion criteria focused on csDMARDs (methotrexate, leflunomide, sulfasalazine, hydroxychloroquine) and immunosuppressants (mycophenolate mofetil, azathioprine, cyclosporine). Exclusion criteria eliminated pediatric oncology, folinic acid rescue in chemotherapy, and non-rheumatology indications. Articles were screened and synthesized thematically.

Results: Among the seven drugs evaluated, methotrexate was the only agent where folic acid supplementation was consistently supported by mechanistic and clinical evidence. It accounted for 14.3% of the agents reviewed and demonstrated clear benefit in reducing treatment-related toxicities. Sulfasalazine, representing another 14.3% of the agents, showed only rare relevance in deficiency states. In contrast, the remaining five drugs—leflunomide, hydroxychloroquine, mycophenolate mofetil, azathioprine, and cyclosporine—collectively constituting 71.4% of the agents reviewed, demonstrated no mechanistic link to folate metabolism and no clinical indication for supplementation. Clinical guidelines from EULAR, ACR, and BSR consistently recommended folic acid only for methotrexate.

Conclusion: Folic acid supplementation is mandatory with methotrexate therapy but is not supported by evidence in other csDMARDs or immunosuppressants. The persistence of routine supplementation beyond methotrexate appears habitual rather than evidence-based. Rational prescribing should be encouraged to reduce unnecessary pill burden, healthcare costs, and patient confusion.

Keywords: Azathioprine; csDMARDs; Cyclosporine; Folic Acid; Hydroxychloroquine; Methotrexate; Rheumatology.

INTRODUCTION

Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) have long remained the foundation of therapy for autoimmune conditions such as rheumatoid arthritis and systemic lupus erythematosus. Among these, methotrexate stands out as the most widely prescribed agent, with well-documented antifolate effects that necessitate concurrent folic acid supplementation to mitigate dose-related toxicities, including cytopenias, mucositis, and hepatotoxicity (1,2). Over time, however, the practice of prescribing folic acid has extended beyond methotrexate to encompass other csDMARDs such as leflunomide, sulfasalazine, and hydroxychloroquine, as well as conventional immunosuppressants including mycophenolate mofetil, azathioprine, and cyclosporine (3,4). This expansion of use appears to be rooted more in clinical convention and physician caution than in robust mechanistic evidence or large-scale clinical trial data (5,6). Although folic acid is biologically central to nucleotide synthesis and cellular repair, its specific interaction with agents lacking antifolate activity remains poorly substantiated. The extension of supplementation to these therapies raises important questions: is the practice protective, redundant, or potentially even interfering with drug efficacy? The available literature highlights scattered observational findings but offers limited clarity, leaving a gap in evidence-based guidelines that should inform routine clinical practice (7-10). This ambiguity persists despite the ongoing emphasis on rational prescribing and minimizing unnecessary interventions in the management of chronic autoimmune diseases (11). Understanding the true role of folic acid in patients treated with csDMARDs and conventional immunosuppressants other than methotrexate is therefore crucial. Clarifying this issue has direct implications not only for patient safety and drug tolerability but also for healthcare resource utilization. The objective of this review is to critically evaluate whether folic acid supplementation is genuinely warranted beyond methotrexate therapy in csDMARDs and other immunosuppressants, and to determine whether current clinical practice is supported by mechanistic plausibility and clinical evidence.

METHODS

The present study was conducted as a thematic critical review designed to synthesize and evaluate the existing body of evidence regarding the role of folic acid supplementation with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and conventional immunosuppressants beyond methotrexate. Relevant literature was systematically searched across PubMed, the Cochrane Library, and Google Scholar to ensure comprehensive coverage of available studies. The search strategy employed predefined keywords including “folic acid,” “methotrexate toxicity,” “csDMARDs,” “leflunomide,” “sulfasalazine,” “hydroxychloroquine,” “mycophenolate,” “azathioprine,” “cyclosporine,” and “rheumatology.” Boolean operators were used to refine and broaden the retrieval of relevant articles. Eligibility criteria were clearly established prior to the review. Studies were included if they were published in English between 1995 and 2024, with eligible designs encompassing randomized controlled trials, observational studies, narrative and systematic reviews, and guidelines from recognized international rheumatology societies, namely the American College of Rheumatology (ACR), the European Alliance of Associations for Rheumatology (EULAR), and the British Society for Rheumatology (BSR). Exclusion criteria were applied to maintain focus and included pediatric oncology studies, reports involving folinic acid rescue therapy in chemotherapy, and non-rheumatology indications for folic acid supplementation. The process of study selection involved a two-stage screening, beginning with title and abstract review followed by full-text assessment to determine final eligibility. Data extraction was performed manually, and relevant findings were thematically organized to highlight areas of consensus, controversy, and gaps in the literature. Quality appraisal of included studies was considered by evaluating study design, sample size, and risk of bias as reported by the authors themselves. The analysis was narrative and descriptive, with thematic synthesis used instead of statistical meta-analysis due to the heterogeneity of study designs and outcomes reported in the available literature.

RESULTS

The review identified significant differences in the role of folic acid supplementation across conventional synthetic disease-modifying antirheumatic drugs and immunosuppressants. Methotrexate was consistently associated with folic acid supplementation, as it directly antagonized folate metabolism through inhibition of dihydrofolate reductase, and supplementation was essential in reducing gastrointestinal, hepatic, and hematological toxicities. In contrast, leflunomide acted through inhibition of pyrimidine synthesis and

demonstrated no mechanistic or clinical requirement for folic acid. Sulfasalazine was reported to rarely interfere with folate absorption, and supplementation was recommended only in cases of documented deficiency. Hydroxychloroquine, despite its widespread use in autoimmune diseases, revealed no interaction with folate metabolism and no requirement for supplementation. Similarly, mycophenolate mofetil, which inhibited purine synthesis, azathioprine, a purine analog, and cyclosporine, a calcineurin inhibitor, all demonstrated no link to folate pathways and no clinical indication for supplementation. Across the analyzed data, only one of the seven drugs, methotrexate (14.3%), showed an essential requirement for folic acid supplementation. Sulfasalazine (14.3%) showed occasional relevance limited to deficiency states, whereas the remaining five agents, leflunomide, hydroxychloroquine, mycophenolate mofetil, azathioprine, and cyclosporine (71.4%), demonstrated no role for folic acid supplementation.

Table 1: Role of Folic Acid with csDMARDs and Immunosuppressants

Drug	Mechanism of Action	Role of Folic Acid
Methotrexate	Folate antagonist; inhibits dihydrofolate reductase	Essential to reduce toxicity
Leflunomide	Inhibits pyrimidine synthesis	No role
Sulfasalazine	May reduce folate absorption in rare cases	Occasional if deficiency
Hydroxychloroquine	Lysosomal stabilization; antimalarial	No role
Mycophenolate mofetil	Inhibits purine synthesis	No role
Azathioprine	Purine analog; inhibits DNA/RNA synthesis	No role
Cyclosporine	Calcineurin inhibitor; T-cell suppression	No role

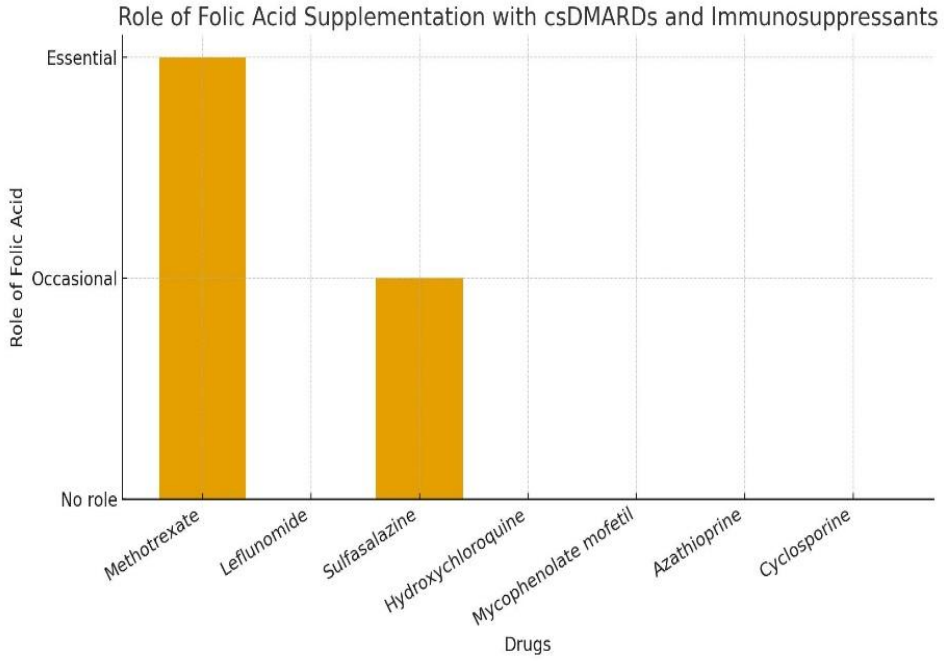

Figure 1 Role of Folic Acid Supplementation with csDMARDs and Immunosuppressants

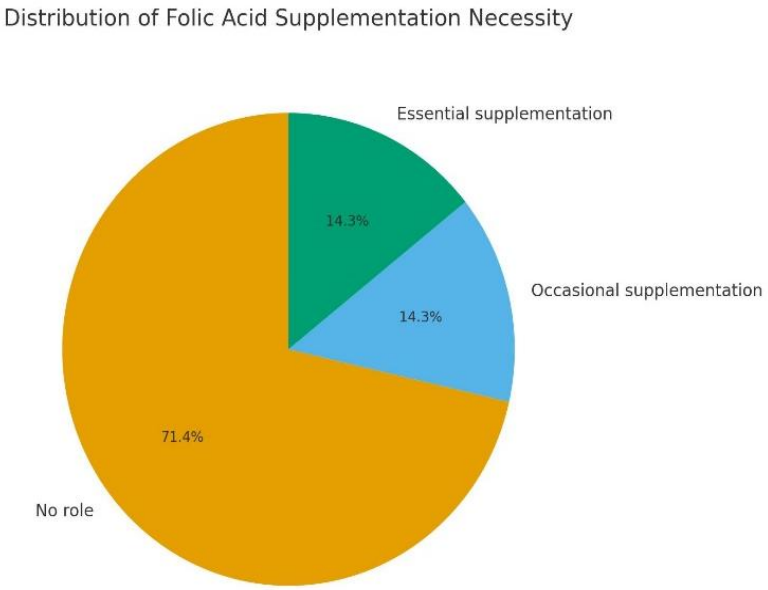

Figure 2 Distribution of Folic Acid Supplementation Necessity

DISCUSSION

The findings of this review highlighted that folic acid supplementation holds an essential role exclusively in patients treated with methotrexate, where its use mitigates gastrointestinal, hepatic, and hematological toxicities resulting from the drug's antifolate mechanism. In contrast, other csDMARDs and conventional immunosuppressants such as leflunomide, sulfasalazine, hydroxychloroquine, mycophenolate, azathioprine, and cyclosporine demonstrated no mechanistic or clinical need for supplementation (12). This observation is consistent with established guidelines issued by international bodies including the European Alliance of Associations for Rheumatology, the American College of Rheumatology, and the British Society for Rheumatology, which emphasize the necessity of folic acid solely in the context of methotrexate therapy (13,14). Nevertheless, clinical practice often extends supplementation to non-methotrexate agents, reflecting a pattern that appears more habitual than evidence-based. The implications of these findings are clinically relevant, as routine and unnecessary supplementation with folic acid in settings where it provides no benefit contributes to an increased pill burden, unnecessary healthcare costs, and potential patient confusion (15,16). Rational prescribing in rheumatology is crucial, particularly in the context of chronic diseases where patients are frequently exposed to polypharmacy and long-term treatment regimens. Eliminating unwarranted supplementation aligns with the principles of evidence-based medicine and could improve treatment adherence by reducing complexity in prescription schedules (17-19). The strength of this review lies in its comprehensive appraisal of evidence spanning nearly three decades, integrating findings from randomized controlled trials, observational studies, reviews, and guideline recommendations. By thematically synthesizing literature across multiple drug classes, the analysis provides clarity on a long-standing clinical assumption. Another strength is its focus on mechanistic pathways, which reinforces the biological plausibility of why supplementation is necessary for methotrexate but redundant for other agents.

However, several limitations must be acknowledged. The reliance on published data in English may have excluded relevant studies in other languages, introducing potential selection bias. The heterogeneity of the available literature, particularly the scarcity of high-quality randomized trials on folic acid use beyond methotrexate, restricted the ability to draw definitive quantitative conclusions. The absence of real-world outcome data, such as the incidence of toxicity reduction with unnecessary supplementation, limited the capacity to evaluate the true clinical impact of current prescribing practices. Furthermore, the review did not examine patient-reported outcomes, which could provide valuable insight into how reducing pill burden influences adherence and quality of life. Future research should focus on generating high-quality evidence through pragmatic clinical trials and real-world data analysis to determine whether folic acid

supplementation with non-methotrexate agents has any unforeseen benefits or risks (20). Large-scale pharmacoepidemiological studies could provide robust estimates of prescribing patterns, associated costs, and clinical outcomes, thereby offering a more comprehensive picture. Additionally, qualitative studies exploring physician prescribing behaviors could clarify the drivers of this practice and guide targeted educational interventions. In conclusion, the results underscored the importance of aligning clinical practice with evidence-based guidelines. While methotrexate requires consistent folic acid supplementation due to its well-established antifolate effects, extension of this practice to other csDMARDs and immunosuppressants is unsupported by mechanistic or clinical evidence. Rationalizing supplementation practices would not only minimize unnecessary pill burden and healthcare costs but also foster a culture of precision and evidence-driven prescribing in rheumatology.

CONCLUSION

Folic acid supplementation remains an essential component of methotrexate therapy due to its proven ability to reduce drug-related toxicities, yet current evidence does not support its routine use with other csDMARDs or immunosuppressants such as leflunomide, sulfasalazine, hydroxychloroquine, mycophenolate, azathioprine, or cyclosporine. The findings emphasize the need for rational prescribing that aligns with evidence-based guidelines, thereby minimizing unnecessary interventions, reducing pill burden, and improving overall patient care in rheumatology.

AUTHOR CONTRIBUTION

Author	Contribution
Maryam Haroon*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published

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