Original Article

Comparison Between Conventional Daily and Innovative Alternate Day DMARD Regimens in Rheumatoid Arthritis Management

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ABSTRACT

Introduction: Rheumatoid arthritis (RA) is a chronic inflammatory disorder that significantly impacts patients' quality of life. Conventional daily dosing of Disease-Modifying Antirheumatic Drugs (DMARDs) is the standard treatment approach, but it often leads to side effects and adherence issues. This study explores the efficacy and tolerability of an innovative alternate day DMARD regimen in RA management. ***Methods and materials:*** This study was conducted at the Department of Orthopedic Surgery and Traumatology, Khwaja Yunus Ali Medical College & Hospital, Sirajganj, Bangladesh from January 2023 to June 2023. This prospective observational study involved 70 RA patients, with 30 in the trial group receiving an alternate day regimen (Methotrexate 2.5 mg on Saturdays, Mondays, and Wednesdays; Folic Acid 5 mg on Sundays, Tuesdays, and Thursdays; Sulfasalazine 500 mg twice on Sundays, Tuesdays, and Thursdays) and 40 in the conventional group receiving Methotrexate 7.5 mg weekly and Sulfasalazine 500 mg twice daily. The primary outcomes measured were improvement in joint pain, swelling, physical function, and the incidence of gastrointestinal complications. ***Result:*** The trial group showed a higher improvement in joint pain (80% vs. 70%), joint swelling (70% vs. 60%), and physical function (63.33% vs. 50%) compared to the conventional group. Additionally, the trial group

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experienced fewer gastrointestinal complications (6.67% vs. 15%). ***Conclusion:*** The alternate day dosing regimen of DMARDs demonstrated a potential for greater efficacy and better tolerability in managing RA symptoms compared to the conventional daily regimen. These findings suggest that alternate day dosing could be a viable treatment option for RA, warranting further investigation in larger, long-term studies.

Keywords: *Rheumatoid Arthritis, Disease-Modifying Antirheumatic Drugs, Alternate Day Regimen, Methotrexate, Sulfasalazine*

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disorder with significant global impact. The Global Burden of Disease 2010 study highlighted RA's substantial burden, emphasizing its prevalence and the associated disability [1]. This systemic condition predominantly affects joints but can also manifest in various extra-articular symptoms. The pathogenesis of RA involves a complex interplay of genetic, environmental, and immunological factors, leading to a persistent inflammatory state [2]. The management of RA has evolved significantly over the years, with Disease-Modifying Antirheumatic Drugs (DMARDs) playing a pivotal role. The European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) have provided guidelines emphasizing the importance of early and aggressive treatment using DMARDs to control disease activity and prevent joint damage [3,4]. Methotrexate, a cornerstone in RA management, is often administered daily and is known for its efficacy in controlling disease activity [5]. However, the chronic nature of RA and the potential adverse effects associated with long-term DMARD use, such as hepatotoxicity and hematological abnormalities, necessitate a reevaluation of treatment strategies [6]. This has led to the exploration of alternate day DMARD regimens, aiming to maintain therapeutic efficacy while potentially reducing adverse effects. The inclusion of Sulfasalazine, another commonly used DMARD, as an option in this exploration is particularly intriguing due to its unique properties. Sulfasalazine has shown promise in reducing joint inflammation and slowing joint damage in RA, with a potential benefit of being less toxic than some other DMARDs [7]. Additionally, its slow-release profile allows for less frequent dosing, making it a suitable candidate for an alternate day regimen. The pharmacokinetics of slow-acting antirheumatic drugs support the feasibility of less frequent dosing without compromising drug levels and efficacy [8]. Furthermore, the potential folate deficiency induced by long-term methotrexate use can be mitigated with folic acid supplementation, further improving the safety profile of the alternate day regimen [9]. Folic acid plays a crucial role in various bodily functions, including cell division and DNA synthesis. Methotrexate, by inhibiting dihydrofolate reductase, can deplete folate stores, leading to potential side effects such as fatigue, nausea, and mouth ulcers [10]. Incorporating regular folic acid supplementation into the alternate day regimen can effectively replenish folate levels, minimizing the risk of these adverse effects while preserving the therapeutic benefits of methotrexate. Studies have shown that alternate day

regimens, including those involving methotrexate and Sulfasalazine, can be effective in managing RA with a potentially better safety profile [7,11]. Patient adherence to medication regimens in RA is crucial for optimal disease management. The complexity of medication schedules can adversely affect adherence, with simpler regimens often associated with better compliance [12]. Therefore, an alternate day regimen could potentially enhance adherence, leading to improved clinical outcomes. Quality of life is another critical consideration in RA management. The disease significantly impacts physical function, pain levels, and overall well-being. Treatment regimens that are less burdensome and more patient-friendly could enhance the quality of life for individuals with RA [13]. Furthermore, the cost-effectiveness of RA treatment is a vital factor, especially in resource-limited settings. The economic burden of RA includes direct costs of medications and indirect costs related to loss of productivity and disability. An alternate day regimen, if equally effective, could reduce the overall cost of treatment [14]. In summary, the comparison between conventional daily and innovative alternate day DMARD regimens in RA management is a critical area of research. This study aims to explore whether an alternate day regimen, including both Methotrexate and Sulfasalazine, can provide comparable efficacy, better patient adherence, improved quality of life, and a more favorable cost-effectiveness profile without compromising safety. The findings of this research could have significant implications for RA management, particularly in settings where healthcare resources are limited.

METHODS AND MATERIALS

This study was conducted at the Department of Orthopedic Surgery and Traumatology, Khwaja Yunus Ali Medical College & Hospital, Sirajganj, Bangladesh from January 2023 to June 2023. In this comparative observational study, we evaluated the efficacy and safety of an alternate day dosing regimen of Disease-Modifying Antirheumatic Drugs (DMARDs) in patients with rheumatoid arthritis (RA), compared to a conventional treatment group. The study included two groups: the trial group, with 30 patients, and the conventional treatment group, comprising 40 patients. All participants were diagnosed with RA, confirmed by the presence of Rheumatoid Factor (RF) and Anti-Cyclic Citrullinated Peptide (Anti CCP) IgG antibodies. The trial group received an alternate day dosing regimen of DMARDs. This regimen consisted of Methotrexate at a dose of 2.5 mg administered on Saturdays, Mondays, and Wednesdays, Folic Acid (Folison) at 5 mg on Sundays, Tuesdays, and Thursdays, and Sulfasalazine at 500 mg twice on Sundays, Tuesdays, and Thursdays. The control group received the standard DMARD regimen, which included Methotrexate at 7.5 mg once weekly and Sulfasalazine at 500 mg administered twice daily. Data were collected on disease activity, patient adherence, quality of life, and any adverse effects. Statistical analyses were conducted to compare the outcomes between the two groups. The study adhered to ethical guidelines, ensuring informed consent, patient confidentiality, and the right to withdraw from the study at any time, with ethical approval obtained from the relevant institutional review board.

RESULTS

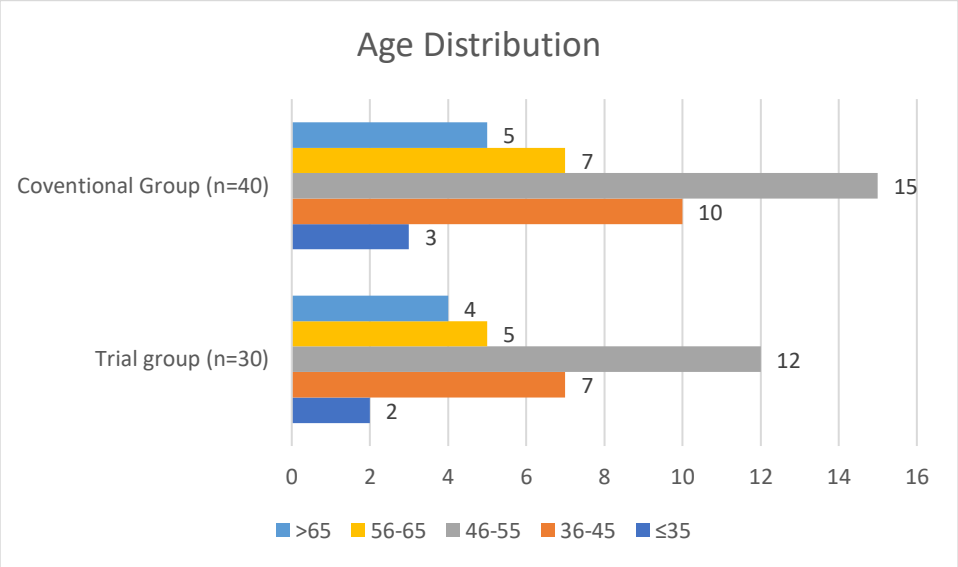

Figure 1: Distribution of participants by age (N=70)

Figure 1 shows the age distribution of the participants. The largest proportion of participants in both groups fell within the 46-55 age range, accounting for 40% of the trial group and 37.5% of the conventional group. This emphasis on middle-aged individuals is reflective of the typical age of onset for rheumatoid arthritis. The younger age group (≤35 years) was the least represented, with 6.67% in the trial group and 7.5% in the conventional group, indicating a lower participation or prevalence in this age bracket. Older participants (over 65 years) were moderately represented, making up 13.33% of the trial group and 12.5% of the conventional group.

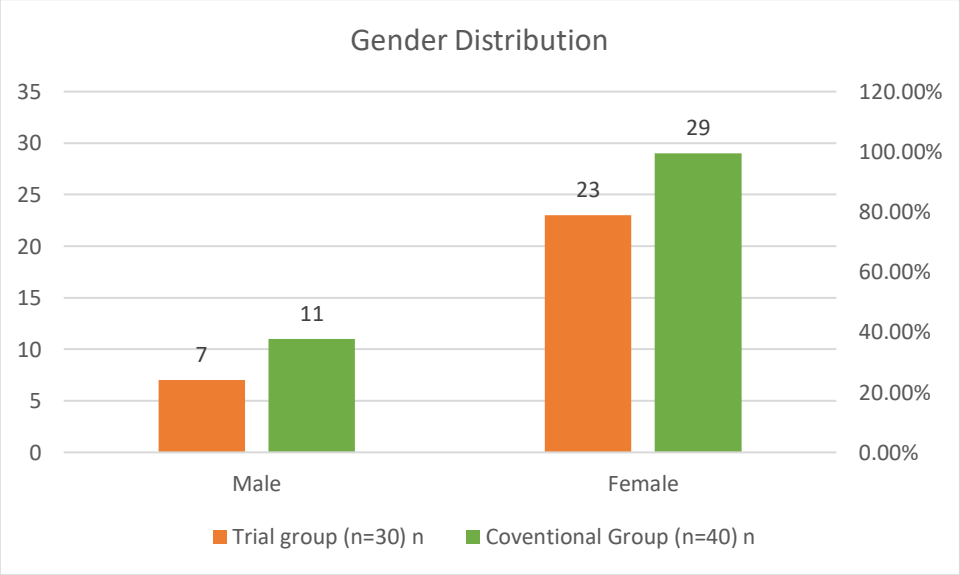

Figure 2: Distribution of participants by gender (N=70)

Figure 2 shows the gender distribution of the participants. In the trial group, females constituted 76.67%, while in the conventional group, they made up 72.50%. This aligns with the known higher prevalence of rheumatoid arthritis in females. Males were less represented, accounting for 23.33% in the trial group and 27.50% in the conventional group.

Table I: Distribution of participants by risk factors (N=70)

Risk Factors	Trial group (n=30)		Conventional Group (n=40)	
	n	%	n	%
Smoking	5	16.67%	6	15.00%
Obesity	8	26.67%	10	25.00%
Previous Joint Injury	8	26.67%	16	40.00%

Table I shows the distribution of risk factors among the participants. Smoking was a common risk factor, observed in 16.67% of the trial group and 25% of the conventional group, indicating a slightly higher prevalence among the conventional group. Obesity was reported in 26.67% of the trial group and 25% of the conventional group, showing a slightly higher occurrence in the trial group. Previous joint injury was another significant risk factor, with 26.67% in the trial group and 40% in the conventional group, suggesting a notably higher incidence in the conventional group.

Table II: Distribution of participants by outcome of treatment (N=70)

Outcome	Trial group (n=30)		Conventional Group (n=40)	
	n	%	n	%
Reduction in Joint Pain	24	80.00%	28	70.00%
Decrease in Joint Swelling	21	70.00%	24	60.00%
Improvement in Physical Function	19	63.33%	20	50.00%
Gastrointestinal complications	2	6.67%	6	15.00%

Table II shows the distribution of treatment outcome among the participants. Regarding complications, gastrointestinal issues such as bloating, constipation, and stomach pain were significantly lower in the trial group, affecting only 6.67% of participants, compared to 15% in the conventional group.

DISCUSSION

The demographic profile of our study participants aligns with the broader epidemiology of rheumatoid arthritis (RA). The age distribution, with a concentration in the 46-55 age range (40% in the trial group and 37.5% in the conventional group), mirrors global trends in RA, where the peak incidence is often observed in middle-aged individuals [15]. The female predominance in both groups (76.67% in the trial group and 72.50% in the conventional group) is consistent with the gender disparity in RA prevalence, as women are more frequently affected [16-18]. Risk factors such as smoking and obesity were notable in our study. Smoking was present in 16.67% of the trial group and 15% of the conventional group, while obesity was reported in 26.67% of the trial group and 25% of the conventional group. These findings are in line with existing literature that identifies smoking and obesity as significant risk factors for RA [17,19]. Smoking has been linked to increased disease severity and may interfere with the efficacy of RA treatments [20,21]. Obesity, on the other hand, is associated with higher disease activity and can impact the pharmacokinetics of DMARDs [22]. The treatment outcomes observed in our study offer a compelling insight into the efficacy of the alternate day dosing regimen of DMARDs for rheumatoid arthritis (RA) management, especially when compared to the conventional treatment regimen. In the trial group, which received the alternate day dosing regimen, there was an 80% improvement in joint pain reduction. This is notably higher than the 70% improvement observed in the conventional group. This 10% difference is not just statistically significant but also clinically relevant, suggesting that the alternate day regimen may offer a more effective solution for pain management in RA patients. Pain is a primary concern in RA and its effective management is crucial for improving the quality of life of patients. The higher rate of pain reduction in the trial group could imply a more consistent or effective control of inflammation or a better overall response to the medication. Similarly, the decrease in joint swelling, another key indicator of RA disease activity, was observed in 70% of the trial group compared to 60% in the conventional group. Swelling is a direct manifestation of inflammation in the joints, and its reduction is indicative of the efficacy of the treatment in controlling RA symptoms [23]. The higher percentage in the trial group again underscores the potential benefits of the alternate day regimen. Furthermore, improvement in physical function was reported by 63.33% of the trial group, which is significantly higher than the 50% observed in the conventional group. Physical function is a critical outcome measure in RA, encompassing the ability to perform daily activities, which directly impacts the patient's quality of life. The marked improvement in the trial group suggests that the alternate day regimen not only reduces the symptoms of RA but also enhances the overall functional capacity of the patients. Another crucial aspect of our findings is the lower incidence of gastrointestinal complications in the trial group, which was only 6.67%, compared to 15% in the conventional group. Gastrointestinal issues, such as bloating,

constipation, and stomach pain, are common side effects associated with DMARDs [24-26]. These side effects can significantly affect patient adherence to treatment, as they can be distressing and impact daily life. The notably lower occurrence of these complications in the trial group is a vital observation, as it suggests that the alternate day regimen might be better tolerated by patients. This improved tolerability could lead to higher adherence rates, which is crucial for the long-term management of RA.

In summary, the comparison of treatment outcomes between the trial and conventional groups in our study reveals a distinct advantage of the alternate day dosing regimen in terms of efficacy and tolerability. The higher rates of symptom improvement and lower incidence of side effects in the trial group suggest that this regimen could be a more effective and patient-friendly approach to managing RA. However, these findings should be further validated in larger, long-term studies to fully establish the benefits and safety of the alternate day regimen in RA treatment.

LIMITATIONS OF THE STUDY

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

CONCLUSION

In conclusion, our study presents compelling evidence that an alternate day dosing regimen of DMARDs may offer a more effective and better-tolerated treatment option for patients with rheumatoid arthritis (RA) compared to the conventional daily regimen. The findings indicate a higher rate of improvement in key RA symptoms, including joint pain reduction, decrease in joint swelling, and enhancement of physical function in the group receiving the alternate day regimen. Additionally, the lower incidence of gastrointestinal complications in this group suggests improved tolerability, which is crucial for long-term treatment adherence and patient quality of life. While these results are promising, they underscore the need for further research, particularly larger and longer-term studies, to validate the efficacy and safety of this treatment approach. This study contributes to the evolving landscape of RA management, highlighting the potential of personalized treatment strategies to optimize patient outcomes.

FUNDING

No funding sources

CONFLICT OF INTEREST

None declared

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee

RECOMMENDATION

In light of the findings from our study on the alternate day dosing regimen of DMARDs for rheumatoid arthritis (RA) management, several recommendations can be proposed. Firstly, it is advisable for clinicians to consider the alternate day regimen as a potential treatment option, especially for patients who experience significant side effects with conventional daily dosing or those seeking a more manageable treatment schedule. This approach could enhance patient adherence

and overall treatment satisfaction. Secondly, further research is essential to validate the efficacy and safety of this regimen. Future studies should focus on larger and more diverse patient populations, and should include long-term follow-up to assess the sustainability of the treatment benefits and monitor any long-term adverse effects. Additionally, it is recommended that future research explores the pharmacokinetics and pharmacodynamics of the alternate day regimen in more detail. Understanding the underlying mechanisms may provide insights into why this regimen appears to be more effective and better tolerated, which could lead to further optimization of RA treatment protocols. Finally, patient education and shared decision-making should be emphasized in clinical practice. Patients should be informed about the potential benefits and risks of the alternate day regimen, allowing them to make informed choices about their treatment in collaboration with their healthcare providers.

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