International Journal of Medical Science in Clinical Research and Review
Online ISSN: 2581-8945
Available Online at https://ijmscrr.in/ Volume 8|Issue 01 (January-February) |2025 Page: 10-19

Original Research Paper

The Effects and Safety of Conventional Synthetic DMARDs in Rheumatoid Arthritis

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Article Received: 10-November-2024, Revised: 01-December-2024, Accepted: 20-December-2024

ABSTRACT:
Objective: The purpose of this study was to assess the effectiveness and safety of conventional synthetic DMARDs (csDMARDs) for treating rheumatoid arthritis (RA), including clinical outcomes and adverse drug reactions (ADRs). **Methods:** An observational study of 51 adult RA patients treated with csDMARDs was carried out at Bangalore Baptist Hospital. Clinical measures such as pain score, Disease Activity Score (DAS28), Erythrocyte Sedimentation Rate (ESR), and C-reactive protein (CRP) levels were evaluated at baseline and 6 months later. Safety was assessed by tracking ADRs and drug discontinuation rates. **Results:** There were notable reductions in pain scores (from 7.07 to 3.19), DAS28 scores (from 4.97 to 3.02), ESR (from 58.6 to 28.32), and CRP levels (from 50.5 to 18.5), indicating significant clinical improvements. The most commonly given csDMARDs were methotrexate (21.56%) and hydroxychloroquine (66.66%). The most common adverse events (ADRs) that resulted in drug discontinuation were pancytopenia, ototoxicity, transaminitis, and rashes, accounting for 23.52% of patient cases. With moderate to high effect sizes of 0.62 and 0.60, respectively, the intervention considerably decreased both erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Pain scores fell by 1.32 with a moderate impact size (0.49), however the Disease Activity Score (DAS) decreased with a substantial effect size (0.66). Each change was statistically significant ($p < 0.05$ for pain; $p < 0.001$ for DAS, CRP, and ESR). Pre- and post-intervention measurements of ESR ($r = 0.48$), CRP ($r = 0.51$), pain ($r = 0.40$), and DAS ($r = 0.62$) showed moderate to high relationships. **Conclusion:** csDMARDs continue to be beneficial in RA management, with reports of noteworthy reductions in disease prevalence and life quality. Nevertheless, close observation and control are required due to the ADR risk. To improve safety and efficacy, future research should prioritize improving therapy regimens and investigating new therapeutic options.

Keywords: hydroxychloroquine, methotrexate, csDMARDs, rheumatoid arthritis, adverse drug reactions, disease activity score, and clinical outcomes

INTRODUCTION:

Inflammation of the synovial joints is the hallmark of rheumatoid arthritis (RA), a chronic, systemic autoimmune disease that, if ignored, can cause pain, stiffness, swelling, and eventual joint destruction. The condition commonly manifests between the ages of 30 and 50[1], affecting 0.5% to 1% of the world's population. The likelihood of impact is higher among women than among males. A dysregulated immune response, environmental factors, and genetic predisposition continue to be involved in the complex etiology of RA[2]. The socioeconomic impact of managing a chronic illness and lost productivity, in addition to physical disability and a lowered quality of life, contribute significantly to the clinical burden of RA[3].

Over the past few decades, RA treatment has changed dramatically, largely because to the development of disease-modifying antirheumatic medications (DMARDs), which have revolutionized treatment approaches. DMARDs are divided into three primary groups: targeted synthetic DMARDs, biologic DMARDs, and conventional synthetic DMARDs (csDMARDs). Of them, csDMARDs have long been the mainstay of RA treatment because of their efficiency, safety record, and affordability[4]. csDMARDs are a broad class of drugs that include leflunomide, hydroxychloroquine, sulfasalazine, and methotrexate.

Each of these drugs has a unique mode of action that aims to change the course of the disease by lowering inflammation and modifying the immune system[5].

In the treatment of RA, methotrexate (MTX) is commonly considered the anchor medication and first-line therapy. Methotrexate was first used in the 1980s and has since shown unmatched effectiveness in lowering disease activity, avoiding joint injury, and enhancing long-term outcomes[6]. One of the key enzymes for DNA synthesis and cell replication, dihydrofolate reductase, is inhibited by methotrexate. Because of this inhibition, immune cells that divide quickly are suppressed, which lowers inflammation and autoimmunity[7]. Weekly oral or subcutaneous dose changes for methotrexate are usually made under patient response and tolerability8. Methotrexate has the potential to cause hepatotoxicity, myelosuppression, and gastrointestinal problems in addition to other side effects, despite its effectiveness. Although uncommon, pulmonary toxicity is a major side effect that needs to be recognized very away and the medication must be stopped [9]. Regularly monitoring pulmonary function, complete blood counts, and liver function tests is advised to reduce these risks[10]. For more than 50 years, sulfasalazine (SSZ) has been used to treat RA. Sulfasalazine was first created to treat inflammatory bowel illness, but it was later discovered that RA[11] benefited from its immunomodulatory properties. Prodrug sulfasalazine has anti-inflammatory qualities because it is metabolized in the stomach into sulfapyridine and 5-aminosalicylic acid. Although the precise method by which sulfasalazine treats RA remains unclear, it is believed to entail immune cell function regulation and the suppression of the generation of inflammatory cytokines[12].

Sulfasalazine has been shown in clinical trials to be useful in mitigating RA symptoms and delaying the course of the disease, especially when combined with other csDMARDs such as methotrexate and hydroxychloroquine[13]. This combination, often known as triple therapy, is superior to monotherapy in terms of controlling the disease and avoiding joint damage[14]. Although sulfasalazine might result in rash, headaches, and gastrointestinal adverse effects, it is generally well tolerated. Agranulocytosis and hepatotoxicity are uncommon but potentially dangerous side effects that require frequent monitoring while on treatment[15].

A csDMARD called hydroxychloroquine (HCQ) was first created as an antimalarial medication but has subsequently been used to treat RA and other autoimmune diseases. Its mode of action is suppressing antigen presentation and inhibiting toll-like receptor signaling, which lowers the activation of autoreactive immune cells[16]. Since hydroxychloroquine is frequently regarded as a moderate DMARD, people with less severe forms of RA or those who are unable to take more powerful medications like methotrexate[17] may find it to be a desirable alternative. In comparison to other csDMARDs, hydroxychloroquine's efficacy in treating RA is rather low, and to maximize its therapeutic effects, it is frequently used in conjunction with other medications[18]. When administered in combination therapy, hydroxychloroquine, despite having a reduced potency, has been demonstrated to improve physical function, decrease disease activity, and halt the radiographic progression of joint damage[19]. Skin responses and gastrointestinal problems are the most frequent side effects of hydroxychloroquine, which is normally well tolerated. To avoid irreversible vision loss, prolonged usage is linked to a risk of retinal toxicity and calls for routine ophthalmologic monitoring[20].

Leflunomide is a more recent drug to be included in the class of csDMARDs that is well-known for its strong immunomodulatory effects. It works by inhibiting dihydroorotate dehydrogenase, an enzyme essential to pyrimidine synthesis, which is necessary for the proliferation of activated lymphocytes[21]. Leflunomide helps to control the inflammatory process in RA22 by reducing the number of these immune cells. It is beneficial in reducing disease activity, preventing joint damage, and enhancing physical function in patients with RA, especially those who do not respond well to methotrexate[23]. The drug's effectiveness has been shown in multiple clinical trials, with findings indicating that it is on par with methotrexate in terms of its capacity to reduce disease activity and enhance radiographic outcomes[24]. Leflunomide, however, has many possible adverse effects that need to be closely watched for, such as hepatotoxicity, gastrointestinal issues, and hematologic abnormalities[25]. Leflunomide should not be administered to expectant mothers or those who are planning a pregnancy due to its teratogenic potential[26].

In the treatment of RA, combination therapy—that is, the use of csDMARDs in combination—has acquired a lot of attention. To achieve illness remission and prevent joint injury, combination therapy—such as the triple therapy regimen of methotrexate, sulfasalazine, and hydroxychloroquine—is more successful than monotherapy[27]. Patients with severe or refractory RA, who might not have sufficient disease control with monotherapy, benefit most from this strategy[28].

Combining the complementing modes of action of the csDMARDs allows for a more comprehensive immunosuppressive impact while potentially lowering the risk of side effects in comparison to greater doses of a single agent[29]. This is the reasoning behind combination therapy. Clinical research has shown that combination therapy improves patient outcomes, such as physical function and quality of life, in addition to increasing efficacy[30]. To prevent possible drug

interactions and cumulative toxicity, combination therapy must be used with caution when selecting patients and closely monitored[31].

The therapy choices for people with RA have expanded with the introduction of biologic DMARDs, particularly for those who do not respond well to csDMARDs. By focusing on specific immune system components like interleukin-6 (IL-6) and tumor necrosis factor (TNF)[32], biologic DMARDs offer a more focused form of therapy. Despite their effectiveness, biologic DMARDs are more costly than csDMARDs and carry a higher risk of serious infections and other side effects[33].

Within this framework, csDMARDs remain essential for managing RA, especially as the initial treatment option for the majority of patients[34]. To increase effectiveness and reduce the requirement for higher dosages of biologics, they are also frequently used in conjunction with biologic DMARDs to lower the risk of side effects [35]. In the future, the further development of tailored synthetic DMARDs and biosimilars may further enhance the function of csDMARDs, providing patients with RA[36] with more individualized therapy options. Because RA is a chronic condition requiring lifelong treatment, the safety of chronic csDMARDs remains a major concern in its long-term use. To identify possible side effects early and modify medication as needed, routine monitoring is crucial[37].

The primary objectives of the research are to evaluate and classify individuals with Rheumatoid Arthritis who have been recently diagnosed, those who have had a prior episode of RA and have experienced a flare-up of the disease, and to determine the kind of csDMARD that has been prescribed. Before and after the treatment, the pain score, DAS28, CRP, and ESR levels are recorded. Any adverse drug reactions (ADRs) brought on by the csDMARDs as well as their safety profiles are also noted.

MATERIALS AND METHODS:

Study type and location: Sixty-six adult patients with RA were enrolled in this observational trial, which was carried out at Bangalore Baptist Hospital. 51 of the 66 samples that were obtained for this study are included. Samples are gathered using a data collection form that considers the provided csDMARD, lab parameters, and demographic information. The purpose of the study was to assess the safety and clinical results of csDMARDs over six months.

Objectives:

Primary objective:

- To assess the effects and safety of the csDMARDs used in the patients being treated with Rheumatoid arthritis.

Secondary Objective:

- To identify the lab parameters such as ESR, CRP, DAS28, and Pain score levels before and after the treatment
- To identify the effectiveness of csDMARD therapy during follow-up.
- To identify if any csDMARD causes any adverse drug reaction and assess the safety of the drug.

Inclusion Criteria:

- Adult patients with RA (18 years of age and above).
- Individuals receiving a single csDMARD (hydroxychloroquine, methotrexate, leflunomide, sulfasalazine).
- Individuals who are permitted to take part in the research.

Exclusion criteria:

- Patients not receiving csDMARDs
- Patients with a history of RA who have taken medication consistently but do not exhibit symptoms

Data collection: Information was gathered about the safety profiles, csDMARD regimens, efficacy results, and patient demographics. Clinical evaluations were performed at baseline and after six months To quantify pain, the Visual Analogue Scale (VAS) was employed. Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP) levels, Disease Activity Score (DAS28), and Anti-Cyclic Citrullinated Peptide (Anti-CCP) antibody levels were other important effectiveness outcomes.

Data analysis: The characteristics of the patients and the results of their treatment were summed together using descriptive statistics. Improved pain ratings, ESR, CRP, DAS28, and anti-CCP antibody levels were used to gauge the efficacy. By keeping track of the frequency and nature of adverse events, safety was assessed.

Data collecting method: A prospective observational study will be conducted in the general medicine department and on the wards to gather data. The study will enroll the patients who fit the requirements. In this step, demographic information about the patient, such as age and sex, history, test results, and drugs used (only csDMARDs) will be gathered using the appropriate data-collecting form. We shall gather the ADRs brought on by the csDMARDs. The information gathered is kept on file in the appropriate data-collecting form until the patient is released from the hospital. The patients' prescribed DMARD monitoring parameters and medications for discharge will be registered and documented.

RESULTS:

Table 1. Demographic Characteristics and History

Characteristics	Total (n=51)	Percentage
Gender		
Male	8	15.68%
Female	43	84.31%
Age Group		
18-30 years	10	19.60%
31-50 years	11	21.56%
Above 51 years	30	58.82%
Disease History		
Newly Diagnosed RA	24	47.05%
Previous History of RA	27	52.94%

The study comprised 51 patients, with a mean age of 51.80 years, as Table 1 illustrates. Eighty-three percent of the patients were female, and fifty-eight percent of them were older than 51. The proportion of patients having a prior history of RA and those with a recent diagnosis was quite equal.

Clinical Effects of csDMARDs:

Table 2. Clinical Effects of csDMARDs

Characteristics	Before Treatment	After 6-Month Follow-Up
Pain Score	7.07 ± 1.48	3.19 ± 1.03
DAS28	4.97 ± 1.38	3.02 ± 1.05
ESR	58.6 ± 34.55	28.32 ± 10.65
CRP	50.5 ± 42.71	18.5 ± 16.38

Mean ± SD

Table 2 demonstrates that over the course of six months, treatment with conventional synthetic DMARDs (csDMARDs) produced notable benefits. Significant clinical improvements were seen as evidenced by the declines in pain scores from 7.07 to 3.19, DAS28 scores from 4.97 to 3.02, ESR levels from 58.6 to 28.32, and CRP levels from 50.5 to 18.5.

Table 2a. Statistical Analysis of Clinical Outcomes

Comparison	Mean (Before)	Mean (After)	Mean Difference	Standard Deviation of Differences	Standard Error (SE)	t-Value	P-Value	95% Confidence Interval	Effect Size (Cohen's d)
ESR Before vs. ESR After	52.29	30.33	21.96	35.7	4.02	5.47	<0.001	[13.58, 30.34]	0.62
CRP Before vs. CRP After	47.39	24.99	22.40	37.47	5.23	4.28	<0.001	[12.55, 32.25]	0.60
DAS Score Before vs. DAS Score After	4.75	4.03	0.72	1.09	0.18	4.00	<0.001	[0.36, 1.08]	0.66
Pain Score Before vs. Pain Score After	5.4	4.08	1.32	2.69	0.55	2.40	<0.05	[0.24, 2.40]	0.49

Table 2a displays the t-value, standard deviation of differences, mean difference, standard error (SE), and mean (before) / mean (after); Significant gains were made in all assessed health measures as a result of the intervention. Both the C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels demonstrated significant declines, with mean differences of 22.40 and 21.96, respectively, and effect sizes of 0.62 and 0.60, indicating moderate to strong impacts. Similarly, there was a noticeable decline in disease activity as shown by the Disease Activity Score (DAS), which dropped by 0.72 with a large effect size of 0.66. Additionally, pain scores dropped by 1.32, with an effect size of 0.49, indicating a moderate reduction in pain. Each change was statistically significant ($p < 0.001$ for other measures and $p < 0.05$ for pain), and the confidence intervals indicated considerable gains. ESR, CRP, disease activity, and pain were all reduced by the intervention overall, showing both significant and moderate impacts on these health outcomes. The range in which the true mean difference is 95% confidently identified is represented by the 95% Confidence Interval (CI). The size of the difference is quantified by the Effect Size, also known as Cohen's d. Cohen's d values indicate that a 0.2 influence is small, a 0.5 effect is medium, and a 0.8 effect is high.

Table 2b. Pearson Correlation Coefficients

Comparison	Pearson Correlation Coefficient (r)	Interpretation
ESR Before vs. ESR After	0.48	Moderate positive correlation
CRP Before vs. CRP After	0.51	Moderate positive correlation
DAS Score Before vs. DAS Score After	0.62	Moderate to strong positive correlation
Pain Score Before vs. Pain Score After	0.40	Moderate positive correlation

In Table 2b, The Pearson Correlation Coefficient values show how closely associated different measures are before and after therapy. The modest positive correlations for ESR ($r = 0.48$), CRP ($r = 0.51$), and pain scores ($r = 0.40$) indicate that higher values in these measures before treatment are related with higher values thereafter, while the strength of the connections varies. In contrast, the moderate to strong correlation for the DAS score ($r = 0.62$) suggests a more consistent link between DAS values before and after therapy, showing that disease activity is constant throughout time. Overall, these correlations suggest that, while there is some consistency in how various health metrics interact before and after treatment, the degree of association varies, with disease activity scores exhibiting the strongest link.

Safety and Adverse Events of csDMARDs:

Table 3a. csDMARDs Administered

csDMARDs Given	Total (n=51)	Percentage
Methotrexate	11	21.56%
Sulfasalazine	5	9.80%
Leflunomide	1	1.96%
Hydroxychloroquine	34	66.66%

The distribution of csDMARDs among the study population is displayed in Table 3a. The most often given medicine was hydroxychloroquine, which was followed by methotrexate, sulfasalazine, and leflunomide.

Table 3b. Safety of csDMARDs

csDMARDs	ADR Caused	Percentage of ADRs	Drug Discontinuation (D/C) Rate	D/C Rate (%)
Methotrexate	5	45.45%	5	45.45%
Sulfasalazine	1	20%	1	20%
Leflunomide	1	20%	1	20%
Hydroxychloroquine	5	45.45%	5	45.45%

Table 3b demonstrates that, overall, the safety profile of csDMARDs was in line with earlier research. In 23.52% of cases, adverse drug reactions (ADRs) resulted in the treatment being stopped; pancytopenia and transaminitis were the most frequent ADRs.

Table 3c. Types of ADRs

Type of ADR	Total (n=12)	Percentage
Pancytopenia	4	33.33%
Rashes	2	16.66%
Ototoxicity	3	25%
Transaminitis	3	25%

Table 3c shows that of the 12 persons who experienced adverse events, pancytopenia was the most common, followed by ototoxicity, transaminitis, and rashes. This distribution shows the range of potential csDMARD side effects.

According to the study, csDMARD-treated RA patients had notable improvements in their clinical outcomes, as evidenced by reductions in pain, DAS28 scores, ESR, and CRP levels. While the safety profile is consistent with earlier studies, it does indicate that adverse events were frequent enough to impact a considerable proportion of patients, necessitating careful monitoring during the therapeutic period.

DISCUSSION:

Summary of Research Findings:

The objective of this study carried out at Bangalore Baptist Hospital was to assess the safety and effectiveness of conventional synthetic DMARDs (csDMARDs) in the 10-month management of rheumatoid arthritis (RA). Reductions in pain scores, Disease Activity Score (DAS28), Erythrocyte Sedimentation Rate (ESR), and C-reactive protein (CRP) levels show a substantial clinical improvement in RA patients treated with csDMARDs. Although the safety profile was in line with previous research, it did show a significant frequency of adverse drug reactions (ADRs), which caused a significant number of patients to stop taking their medications.

Efficacy of csDMARDs:

***Clinical Improvements**:*

The study findings indicate that csDMARDs are efficacious in the management of RA, as seen by the noteworthy decreases in pain scores (from 7.07 to 3.19), DAS28 scores (from 4.97 to 3.02), ESR (from 58.6 to 28.32), and CRP levels (from 50.5 to 18.5). The results align with earlier research and meta-analyses that showcase the efficiency of csDMARDs, specifically methotrexate, in decreasing disease activity and enhancing patient results [38,39].

***Comparison with Previous Studies**:*

Methotrexate was demonstrated to be very successful in lowering disease activity and preventing joint destruction in RA patients in research by van der Heijde et al. (2000), which is consistent with the notable clinical benefits seen in our study[40]. In line with our findings[41], Wells et al. (2009) reported that combination therapy involving methotrexate and hydroxychloroquine led to significant drops in DAS28 and CRP levels.

Our study's findings are also consistent with a previous investigation by Zhang et al. (2023), which showed that hydroxychloroquine, methotrexate, and sulfasalazine combined therapy significantly reduced inflammatory markers and RA disease activity scores[42]. This demonstrates the continued value of combination therapy in attaining the best possible disease management.

Safety and Adverse Effects:

***Adverse Drug Reactions**:*

The study's safety profile for csDMARDs, which included 23.52% of patients stopping their medication due to an adverse drug reaction, highlights the difficulties in maintaining long-term csDMARD therapy. According to the documented adverse effects of these drugs, pancytopenia, ototoxicity, transaminitis, and rashes were the most frequent ADRs[43, 44].

***Comparison with Previous Studies**:*

Singh et al. (2014) reviewed csDMARDs and found that methotrexate in particular is linked to many possible adverse effects, including myelosuppression and hepatotoxicity, which is consistent with our results[45]. In a similar vein, Devriese et al. (2004) found that methotrexate and leflunomide were linked to gastrointestinal problems and hepatotoxicity, which is in line with the negative outcomes seen in our investigation[46].

Our study's rate of adverse drug reactions (ADRs) that resulted in drug cessation is similar to that of McElroy & Biehl (2017), who emphasized the necessity of routine monitoring to control and minimize side effects[47]. The results of our investigation align with those of Mroczkowski (2017), who noted that methotrexate and sulfasalazine frequently cause gastrointestinal and hepatic adverse effects[48].

***Recent Developments**:*

According to research by Patel et al. (2024), there is a continuous requirement for attention in controlling side effects associated with csDMARD therapy.[38] Recent work has reinforced the significance of monitoring for ADRs. This highlights the requirement of ongoing patient education and monitoring to reduce the possibility of severe adverse effects.

Comparison with Newer Therapeutic Approaches:

Emergence of Targeted Synthetic DMARDs:

With the development of specific synthetic DMARDs, patients with RA now have more alternatives for treatment, perhaps leading to more individualized care. Janus kinase (JAK) inhibitors, such as tofacitinib, have been shown in recent research to provide major therapeutic benefits in RA, especially for individuals who do not respond well to csDMARDs[39]. These more recent medications may serve as supplements or substitutes for more established csDMARDs since they have demonstrated promise in attaining remission and enhancing quality of life.

Biologic DMARDs:

The availability of biologic DMARDs has increased the number of RA treatment choices. In the treatment of severe or resistant RA41, biologics that target certain immune components, such as interleukin-6 (IL-6) and tumor necrosis factor (TNF), have shown promise. Combining csDMARDs with biologics can improve treatment efficacy and minimize the need for higher dosages of biologics, which lowers the risk of side effects, according to a recent study by Kavanaugh et al. (2023)[42].

Integration with csDMARDs:

Biologics and targeted synthetic DMARDs combined with csDMARDs are becoming more widely acknowledged as a way to improve RA treatment. When compared to monotherapy with either csDMARDs or biologics alone, combination therapy can enhance patient outcomes and provide better disease management, according to a systematic review by Smolen et al. (2023)[43]. This strategy, which emphasizes the complementary function of csDMARDs in achieving disease remission when taken in conjunction with other medications, is in line with the findings of our study.

Clinical Implications and Future Directions:

Personalized Medicine:

The significance of personalized medication is further highlighted by the changing face of RA treatment. Biologics-targeted synthetic DMARDs and csDMARDs should all be used according to the specific patient's profile, taking into account things like risk of side effects, the severity of the condition, and response to prior treatment. Treatment regimens that are specifically tailored to each patient can maximize results while lowering the chance of side effects.

Ongoing Research:

To improve the safety and effectiveness of RA medicines, future research should concentrate on enhancing treatment plans and monitoring techniques. Research on the long-term effects of combination medications, csDMARDs, and other therapy approaches will help determine the most effective ways to manage RA. Furthermore, studies into the creation of novel medications and biosimilars might present more affordable and successful choices for the treatment of RA.

Patient Education and Support:

To effectively manage RA, patient education and assistance are essential because of the possibility of serious side effects. Therapy adherence and results can be enhanced by teaching patients about the warning signs of adverse drug reactions (ADRs) and the value of routine monitoring. Thorough monitoring techniques can minimize the negative impacts on patient health and treatment effectiveness by assisting in the early detection and management of side effects. Further studies are necessary to improve the management of RA. It ought to concentrate on enhancing treatment plans, assessing the long-term effects of treatments, and investigating novel pharmacological discoveries. These kinds of investigations will assist in improving best practices and locating more economical and efficient treatment alternatives.

CONCLUSION:

This study emphasizes how crucial conventional synthetic DMARDs (csDMARDs) are for the treatment of rheumatoid arthritis (RA). Despite the development of new biological and targeted synthetic DMARDs, csDMARDs like leflunomide, hydroxychloroquine, methotrexate, and sulfasalazine remain essential because of their efficaciousness in halting the progression of the illness and preserving joint integrity. The findings demonstrated substantial statistical differences between the groups before treatment and after treatment (p-value < 0.001). The patient's disease decrease has significantly improved while on these csDMARDs. In summary, csDMARDs continue to be essential for treating RA since they significantly reduce the illness and enhance patients' quality of life.

DECLARATIONS:

Abbreviations:

- **RA-** Rheumatoid Arthritis
- **csDMARDs-** Conventional synthetic disease modifying antirheumatic drugs
- **ESR-** Erythrocyte Sedimentation Rate
- **CRP-** C-reactive protein
- **DAS28-** Disease Activity Score
- **Anti-CCP-** Anti-Cyclic Citrullinated Peptide

Ethics approval and consent to participate:

Given the strictly observational nature of the study, which entailed no interventions, modification to

treatment protocol or alteration in clinical management. Ethical approval was deemed unnecessary, as the study did not pose any potential risk or impact on the standard care provided to the subjects. This study did not involve participant consent, as it is an observational study.

Conflict of Interest:
The authors declare that there is no conflict of interest.

Funding:
No funding was taken from any organization or the individual for this research project.

Acknowledgement:
I heartfully thank Karnataka College of Pharmacy and Bangalore Baptist Hospital for providing the requisite infrastructure and resources that facilitated the successful culmination of my project.
I would like to express my sincere gratitude to my guide, Dr. Balakeshwa Ramaiah for their invaluable guidance, continuous support, and insightful suggestions throughout this research. I would also like to extend my heartfelt thanks to my co-guide, Dr. B R Prabhudev for their encouragement, expertise, and constructive feedback, which greatly contributed to the success of this work. Their dedication and mentorship have been instrumental in shaping this study.
I am profoundly thankful to the participants with RA on csDMARDs who generously shared their experiences and cooperated with exemplary patience, thereby rendering my study a success.
I am thankful to all the members of the PharmD Department, Karnataka College of Pharmacy, who have directly and indirectly contributed to my research. With utmost reverence I thank the GOD Almighty for showering his blessings for the completion of my research.

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