RESEARCH ARTICLE

Pharmacological Approaches in Rheumatoid Arthritis- An In-depth Analysis of Prescribed Medications

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ABSTRACT

Inflammation, pain, swelling, and stability of the joints are some of the symptoms associated with rheumatoid arthritis (RA). A variety of treatment options are available to manage symptoms and slow the progression of RA, despite the fact that there is no cure. This cross-sectional study, which was conducted in a tertiary care hospital in Kerala, India, aimed to evaluate medication prescribing practices and therapeutic strategies in RA patients. The study included 280 RA patients and data on demographics, medications prescribed, dosage, and mode of administration were collected. The findings revealed that disease-modifying anti-rheumatic drugs (DMARDs) were the cornerstone of RA treatment, with hydroxychloroquine (HCQ), methotrexate (MTX), and sulfasalazine (SAAZ) being the most frequently prescribed DMARDs. Combination DMARD therapy, particularly the triple combination of HCQ + Folitrax + SAAZ, was prevalent among patients. Furthermore, the study highlighted the use of biologic DMARDs, such as rituximab and tofacitinib, albeit at a relatively lower rate due to the outpatient population's milder disease severity. Supplement therapy, including vitamin D3 and folic acid, was commonly prescribed to address deficiencies and mitigate the side effects of medications like MTX. The prescription patterns also encompassed analgesics, anti-anxiety, and antidepressant medications to manage pain and psychological symptoms associated with RA. Steroids were administered initially to control inflammation, with a focus on minimizing long-term usage. The study underscores the complexity of RA management and the importance of individualized treatment approaches. It highlights the evolving landscape of RA therapeutics, emphasizing the need for clinicians to stay updated on emerging evidence and guidelines. Future research should focus on evaluating the long-term efficacy, safety, and cost-effectiveness of different treatment regimens to optimize patient outcomes in RA management.

Keywords: Rheumatoid arthritis, Medication usage, DMARDs, Combination therapy, Biologics, Therapeutic strategies, Indian population.

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INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune condition characterized by the immune system targeting healthy cells, leading to inflammation and painful swelling in affected areas.[1,2] Common symptoms include swelling, stiffness, and pain. Achieving remission in RA may not always be feasible; however, there exist several treatment alternatives to effectively manage the disease and alleviate its symptoms. These interventions usually involve using medications to mitigate inflammation, halt disease progression, engage in physical therapy to preserve joint function and adopt lifestyle modifications to enhance overall well-being.[3,4]

To investigate and analyze prescription patterns in RA with a specific focus on the combination of drugs disease-modifying anti-rheumatic drugs (DMARDs), emphasizing dosage and administration frequency, thereby contributing to a more comprehensive understanding of prescribing practices in the clinical setting.

MATERIAL AND METHODS

This cross-sectional study was carried out at the rheumatology outpatient clinic at Dr Shenoy's CARE, Kochi, Kerala.

The ethical clearance for the study was obtained prior to the study from VIT Ethical Committee for studies on human subjects as well as ethical committee at Sree Sucheendra Hospital Ethical Committee, Kochi. About 280 patients, after fulfilling the inclusion-exclusion criteria, were included in the study.

The study included 280 consecutive patients who attended the RA clinic or RA OP at CARE, Kochi, Kerala, India, from September 2020 to August 2021. In this cross-sectional study, information regarding medications such as analgesics,

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anti-inflammatory drugs, steroids, DMARDs, biologicals for RA, vitamin supplements, anti-anxiety and antidepressants, etc and DMARD combinations were studied. Data collection involved the collection of patient demographics and meticulous examination of medication details, with a specific focus on discerning patterns in drug combinations, dosages, and administration frequencies. The study aimed to provide insights into prescribing practices related to the combination of drugs, shedding light on dosage preferences and administration frequencies. The medications were classified according to pharmacological class; dose and mode of administration were noted. The prescription pattern was analyzed by calculating the percentage (%) of drugs prescribed, the subcategorization of each pharmacological class according to prescribing frequency, and the frequency of prescription of each subcategory.

RESULT AND DISCUSSION

The demographic analysis of the patient population was as given in Table 1. The majority of the patients were female. The patients were also categorised based on age, level of education, duration of illness and employment status of the patients.

Drug analysis encompassed the examination of 280 patient prescriptions, revealing a comprehensive total of 2,220 medications. The treatment regimens comprised of DMARDs, DMARD in combination therapy, biological medicines, vitamin supplements, analgesics, antidepressants, steroids, and potassium pump inhibitors, as outlined in Table 2. Within this dataset, notable categories included 793 instances of disease-modifying anti-rheumatic drugs (DMARDs), 667 vitamin supplements, 284 DMARDs prescribed as combinations and 194 proton pump inhibitors.

Table:1 Frequency and percentage distribution of demographic variables (N = 280)

S No	*Variable*	*Frequency*	*Percentage*
1.	Gender		
	Male	27	9.5
	Female	253	90.5
	Age		
	< 40	45	16.0
	41–50	98	35
	51–60	80	28.5
	> 60	57	20.3
2.	Education		
	<SSLC	27	9.6
	SSLC	86	30.7
	HSSC	57	20.3
	Degree	89	31.7
	PG and above	21	7.5
3.	Employment status		
	Employed	105	37.5
	Unemployed	150	53.5
	Discontinued due to illness	25	9
4.	Duration of illness (years)		
	< 5	80	28.5
	5–10	110	39.2
	10–20	75	26.7
	>20	15	5.3

The study revealed that 35.7% of the total 2220 drugs prescribed were DMARDs, with hydroxychloroquine (HCQ) at 200 mg emerging as the most prevalent choice 33.8% (Table 2). Methotrexate (MTX) was administered in various dosages, with 7.5 mg, 12.5 mg, and 20/30 mg, constituting 14.3, 10.7, and 9.46%, respectively. Sulfasalazine (SAAZ) was also a frequently prescribed DMARD at 25.7%. Other single DMARD drugs included leflunomide 5 mg/10 mg at 3.9%, followed by iguratimod (MIMOD) at 1.5%. Hydroxychloroquine at 300 mg was a rarely prescribed dose (0.76% of population). This prescription pattern aligns with contemporary recommendations, emphasizing hydroxychloroquine/methotrexate/sulfasalazine as the preferred first-choice DMARDs for RA therapy. The administration of methotrexate occurred on a weekly basis, reflecting adherence to current therapeutic guidelines.

On analysis of combination DMARDs (Figure 1), the triple combination HCQ + Folitrax + SAAZ shows the highest prescribed drug for 58.8%. The other triple combination DMARDs are very minimally prescribed; HCQ + Leflunomide + SAAZ – 3.8%, Rituximab + SAAZ + Leflunomide -0.7%, Iguratimod + HCQ + Folitrax – 4.2%, and Folitrax + Leflunomide + SAAZ – 2.8%. The double combinations fall under the following percentages: HCQ + Folitrax – 18.3%, HCQ + SAAZ – 7.7%, and Leflunomide + Folitrax – 3.5%.

The specifics of the biological treatment that the research patients underwent are presented in Figure 2. Rituximab was given to 9.6% of participants and tofacitinib to about 3.5% of subjects. However, since the patient population was an atypical outpatient subpopulation having relatively milder disease severity than one can expect in-patient settings, the number of biologics prescribed in our study was relatively low.

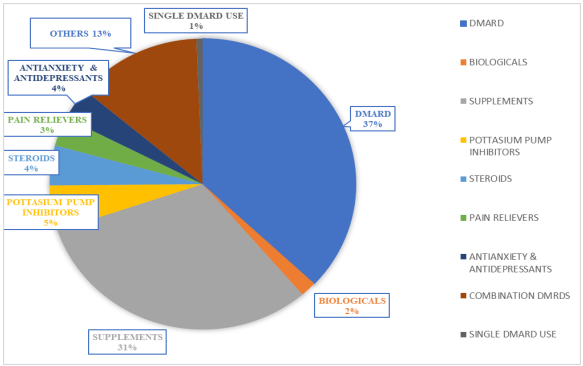

Figure 1: Percentage of drugs prescribed categorized by class

Table 2. : Percentage of prescribed medicine in each class

S No	*Medications*	*Frequency of prescription*	*% Prescribed in each class*
1	DMARDS (doses prescribed alone or in combination)		
	Methotrexate 7.5 mg (alone + combination)	114	14.38
	Methotrexate 12.5 mg	85	10.72
	Methotrexate 20/30 mg	75	09.46
	Hydroxychloroquine (HCQs) 200 mg	268	33.80
	Hydroxychloroquine (HCQs) 300 mg	6	00.76
	Sulfasalazine (SAAZ)	202	25.47
	Leflunomide 5 mg/10 mg	31	03.91
	Iguratimod (MIMOD)	12	01.51
		793	
2	Biologicals		
	Tofacitinib	10	03.57
	Rituximab	27	09.67
		37	
3	Supplements/vitamins		
	Ferrous sulphate	42	06.30
	Calcium (OSTEOCAL) 500 mg	57	08.55
	Vit D3	245	36.73
	Folic Acid 5 mg	275	41.23
	Theloxin (Nutraceuticals)	18	02.70
	Neurobion	21	03.15
	Evion	6	00.90
	Keraboost (supplement for hair fall)	3	00.45
		667	
4	Steroids		
	Deflazacort	30	10.71
	Methylprednisolone (Medrol) 2 mg/4 mg	65	23.21
		95	
5	Pain relievers		
	Zylcolchicine	21	30.43
	Ultracet	20	28.99
	Etericoxib (Nucoshine)60 mg	18	26.09
	Etoricoxib (Retoz 60 mg) + Thiocolchicoside	4	05.80
	Celecoxib (Bixo) 200 mg	6	08.70
		69	
6	Anti anxiety and antidepressants		
	Tolydol	11	14.29
	Amitryptylline (HP TRIP) 10 mg	5	06.49
	Nortriptyline (Sensival)	8	10.39
	Duloxetine (Symbal)	25	32.47
	Flupentixol and Melitracen. (antidepressant)	6	07.79

		77	
7	Dmard combinations		
	HCQ + Mtx (Folitrax) + SAAZ	167	58.80
	HCQ + Leflunomide + SAAZ	11	03.87
	HCQ + Mtx (Folitrax)	52	18.31
	HCQ + SAAZ	22	07.75
	Leflunomide +Mtx (Folitrax)	10	03.52
	Rituximab + SAAZ + Leflunomide	2	00.70
	Iguratimod + HCQ + Mtx (Folitrax)	12	04.23
	Mtx(Folitrax) + Leflunomide+ SAAZ	8	02.82
		284	
8.	Hcq alone	9	
	Methotrexate (folitrax) alone	5	
9.	Potassium pump inhibitors		
	Omeprazole 20/40 mg	198	70.71
10.	Others (Antidiabetic, Drugs for BP, Hypercholesterolemia, Thyroid disorders, etc)	288	
10.	Total no of drugs	2220	
	Total no of prescriptions	280	

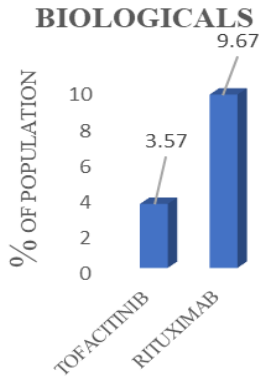

Figure 2: Percentage of biological drugs

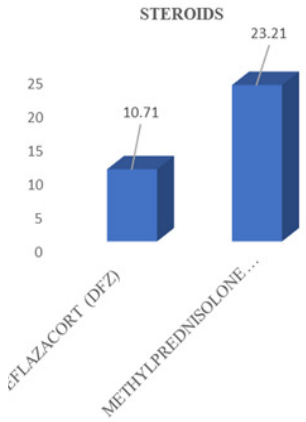

Figure 3: Percentage of steroids

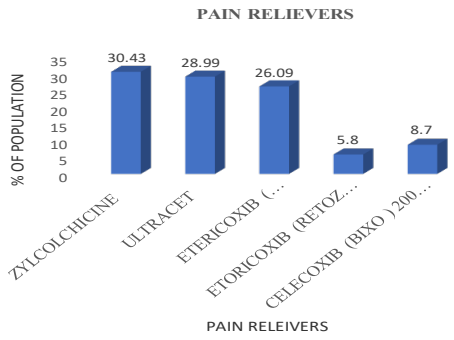

Figure 4: Percentage of pain relievers

About 23.2% of patients also received methylprednisolone at doses of 2 and 4 mg and 10.7% received deflazacort (DFZ) in addition to DMARDs (Figure 3). Among the analgesics (Figure 4), zylcolchicine – 30.4%, ultracet – 28.9%, and 60 mg etericoxib – 26% are the commonest choice of prescription to the patients. Etoricoxib -5.8% and celecoxib – 8.7% were the least prescribed as pain relievers for patients suffering from RA.

The average quantity (0–10%) of supplement therapy received by the patient is 6.3%. Ferrous sulfate, 8.5%, 500 mg calcium, 3.1% of neurobion, and 2.7% theloxin. The minimal quantity of supplements received is 0.9% evion and 0.4% keraboost (supplement for hair fall). Folic acid of 5 mg (41.2%) and vitamin D3 (36.7%) were the highest percentage of supplements received by the patients (Figure 5). In this study, vitamin D3 supplements were given to 36.7% of the patients.

Duloxetine – 32.4%, and tolydol -14.2% followed by nortriptyline -10.3%, are the favourite drugs of choice in

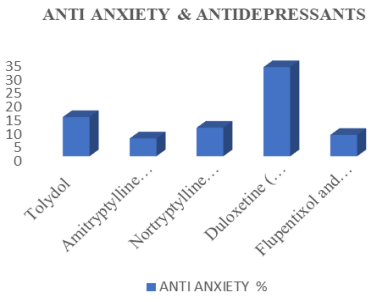

Figure 5: Percentage of antidepressant/anti-anxiety drugs

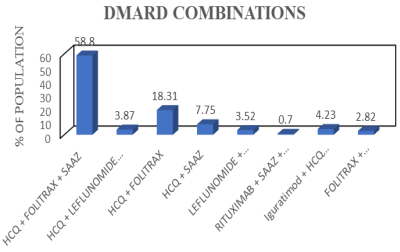

Figure 6: Percentage of DMARD combinations

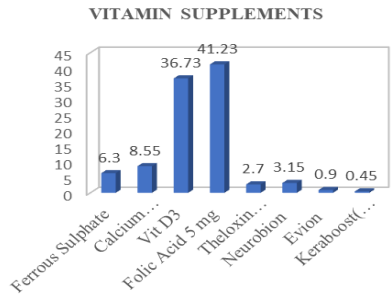

Figure 7: Percentage of vitamins

prescription by rheumatologists as the anti-anxiety and antidepressant drugs. The flupentixol and melitracen. (antidepressant) – 7.8% and 10 mg amitriptyline -6.5% were the less popular prescription choice.

DISCUSSION

In recent decades, there has been notable progress in rheumatoid arthritis (RA) treatment, driven by an enhanced understanding of the disease's pathophysiology.[5-8] The therapy armament for RA has been greatly enhanced with the development of DMARDs, focused medicines such as monoclonal antibodies that fight cytokines and their receptors, and small molecule inhibitors that target intracellular cytokine pathways. To help in the treatment of RA, the American College of Rheumatology (ACR) published recommendations in 2015.[9] Glucocorticoids (GCs), biologics (bDMARDs), targeted synthetic DMARDs (tsDMARDs), and conventional synthetic disease-modifying anti-rheumatic medicines (csDMARDs) were all part of the treatment protocol that covered both the early and late phases of the illness.

The main medications currently used in the management of RA worldwide are traditional conventional synthetic DMARDs like methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), and leflunomide. This is especially true in developing nations like India, where most people cannot afford biologics and there is no federal health insurance policy in place. Three separate dosages of methotrexate–7.5, 12.5, and 20/30 mg–were administered once a week in this study. In the study, methotrexate dosage variation could be due to the varying disease severity and individualized treatment regimens. Furthermore, in actual practice, the maintenance dose of MTX might range from 7.5 to 30 mg weekly, suggesting that individuals need a personalized dosage for optimal disease management.[10]

The highest recommended dosage of MTX is 20 to 30 mg weekly. However, there are no recommendations for titration from the European League Against Rheumatism (EULAR). Spanish standards have recommended a starting dose of 10 mg weekly. The dosage for an adult weighing 70 kg is 15 mg per week or 0.2 mg per kg. This corresponds to a starting dose of 10 to 15 mg of oral MTX per week, with a dosage increase of 5 mg every 2 to 4 weeks up to a maximum of 20 to 30 mg. The American College of Rheumatology (ACR) recommendations do not specify a dosage range for MTX; nonetheless, it is believed that 25 to 30 mg/week is the highest tolerable dose for RA (Feng X *et al.* 2013 and Bello AE *et al.* 2017). In around 9.46% of the cases, the recommended maximum dose was actually administered. Oral tablets containing two dosages of HCQ – 200 mg and 300 mg – were taken once a day at night. A single daily dose of 200 to 400 mg of HCQ, or two separate doses, is advised for RA. Patients who take higher dosages of HCQ medication run the risk of developing retinal toxicity.

On analysis of combination DMARDs (Figure 6), the triple combination HCQ + Folitrax + SAAZ shows the highest prescribed drug for 58.8%. The other triple combination DMARDs are very minimally prescribed; HCQ + Leflunomide + SAAZ – 3.8%, rituximab + SAAZ + Leflunomide -0.7%, Iguratimod + HCQ +Folitrax – 4.2%, and Folitrax + Leflunomide+ SAAZ – 2.8%. The double combinations fall under the following percentages: HCQ + Folitrax – 18.3%, HCQ + SAAZ – 7.7%, and leflunomide + Folitrax – 3.5%. Although methotrexate (MTX) is the main medication used to treat RA, if there are no contraindications and if the disease activity scores (DAS28) show that the treatment response is insufficient following a sufficient trial, then two or three DMARDs are tried as supplementary therapy. When triple therapy proves ineffective, the recommendation is to turn to biologic disease-modifying anti-rheumatic drugs (bDMARDs). For certain patients with severe illness and high-risk characteristics, it is recommended to start a combination of DMARD medications right away. Tobacco use, being a woman, having an abnormally high number of painful and swollen joints, a high disease activity score, small erosions on first X-rays, and high levels of rheumatoid factor are all potential contributors. Furthermore, several trials have shown that combined DMARD medication is effective in treating rheumatoid arthritis (RA). Notably, for

patients responding only partially to DMARD monotherapy, combinations such as MTX + anti-TNF and/or SSZ/HCQ have demonstrated the highest efficacy (Kavanaugh A, 2007). Contrary to two earlier Indian studies where MTX and HCQ combination treatment was administered in more than 50% of RA patients, HCQ together with Leflunomide and SAAZ was the most commonly recommended DMARD combination in this research.[11]

Most RA patients in our study context received MTX as a single DMARD monotherapy; when the illness was out of control, other combinations of DMARDs were administered. In line with other studies that also identify MTX and HCQ as the most desired drugs, these two DMARDs were the most preferred in our research, whether used alone or in combination (Dahiya A. *et al*., 2016; Syngle A. *et al*., 2017). The ACR 2020 guidelines suggest that for patients with low, moderate, or high disease activity who have DMARD-naïve RA, MTX monotherapy should be the first line of treatment. According to several research, the most popular regimen consists of three traditional synthetic DMARDs together. The differing degrees of illness seen in various hospital settings may be the cause of the difference in the quantity of DMARDs administered.

As a result, in this context, monotherapy was most common, followed by double and triple DMARD treatment. These results are in accordance with the latest ACR 2020 recommendations, which rank the three most preferred combinations of conventional synthetic medicine-assisted recovery (csDMARD) monotherapy, double combination treatment, and triple combination therapy.[3]

Figure 3 displays the details of the biological therapy that the study participants received. About 3.5% of individuals were administered tofacitinib and 9.6% were given rituximab. According to Rai AK *et al*. (2016), biologic DMARDs such as etanercept, infliximab, adalimumab, and golimumab, as well as rituximab, tocilizumab, and abatacept, which are anti-IL-6 and co-stimulation blocking, are given in India. However, since the patient population was a a typical outpatient subpopulation having relatively milder disease severity than one can expect in in-patient settings the number of biologics prescribed in our study is relatively lower.

The average quantity (0–10%) of supplement therapy received by the patient is 6.3% ferrous sulfate, 8.5% of 500 mg calcium, 3.1% of neurobion, and 2.7% of theloxin. 0.9% evion and 0.4% keraboost (supplement for hair fall) were among the minimally prescribed supplements. Folic acid of 5 mg (41.2%) and vitamin D3 (36.7%) were the highest percentage of supplements prescribed to patients (Figure 7). In this study, vitamin D3 supplements were given to 36.7% of the patients. Vitamin D insufficiency was shown to be significantly frequent in individuals with RA and was revealed to be associated with the severity of the illness in 2012 research. There is a connection between generalized musculoskeletal discomfort and vitamin D insufficiency. Patients with RA may be offered vitamin D supplements to help prevent osteoporosis and provide some pain relief (Kostoglou-Athanassiou I, *et al*., 2012). In another study research, vitamin D was linked to both increasing an anti-inflammatory response and delaying the onset and pathogenesis of RA (Feng X, *et al*., 2013). Adjuvant treatment included calcium on a daily basis since RA causes bone loss (Heidari B *et al*., 2012). Five mg of folic acid, which lessens the side effects of the MTX folate antagonist, was administered to each patient on methotrexate. The risk of gastrointestinal side effects and hepatic impairment is reduced, and patients are less likely to discontinue taking MTX, when supplemented with folic or folinic acid. If this interaction were to occur, the therapeutic efficacy of MTX would be diminished since folate and MTX competes for absorption, but this is prevented when folic acid is given the day after MTX. Citation: Bello AE *et al*., 2017. About 198 prescriptions for omeprazole (20–40 mg) were accounted which can counter the hyperacidity induced by DMARDS and other drugs. Similar findings were seen in one research, which also noted that folic acid, calcium supplements, and proton pump inhibitors (PPIs) were recommended in addition to DMARDs. (Syngle A, *et al*., 2017). About 57 individuals in this study received calcium supplements, whereas 198 patients received 20 to 40 mg of omeprazole. This was consistent with prior research that found that a sizable portion of prescriptions also contained gastroprotective drugs and calcium supplements.[12] These medications are most likely used to avoid adverse drug reactions (ADRs) such as gastrointestinal discomfort and osteoporosis brought on by RA or glucocorticoids.

Steroids are powerful anti-inflammatory drugs that are administered until the initial DMARD's activity begins. Similar to other research where the majority of patients took oral/intramuscular glucocorticoids, in our study too, patients (23.2%) received methylprednisolone at 2 and 4 mg and 10.7% received DFZ. (Figure 3). Additionally, new guidelines support treating RA with glucocorticoids at the lowest dose for the shortest amount of time. (Buttgereit F, *et al*., 2020). According to EULAR, chronic glucocorticoid usage up to 15 mg/day improves disease activity and the addition of low-dose glucocorticoids (<7.5 mg/day) to DMARDs in early RA significantly reduces radiographic progression. Pain reduction is the primary goal of intra-articular GCs in RA patients.

Among the analgesics (Figure 4), zylcolchicine – 30.4%, ultracet – 28.9%, and 60 mg etericoxib – 26% are the commonest choice of prescription to the patients. Etoricoxib -5.8% and celecoxib - 8.7% were the least prescribed as pain relievers for patients suffering from RA. Duloxetine – 32.4%, 25 mg and tolydol -14.2% followed by nortriptyline -10.3% are the favorite drugs of choice in prescription by rheumatologists as the anti-anxiety and antidepressant drugs. The flupentixol and melitracen. (antidepressant) – 7.8% and 10 mg amitriptyline -6.5% were the least choice for the prescription (Figure 5).

CONCLUSION

In conclusion, this study provides valuable insights into the prescription patterns and therapeutic strategies employed in the management of RA. Through comprehensive analysis, we have delineated the various categories of drugs utilized in RA treatment and their combinations, shedding light on

current clinical practices. In order to get the best possible results in managing RA, a personalized strategy that includes biologics, targeted treatments, disease-modifying anti-rheumatic medications (DMARDs), and other components is essential, as our research shows. Furthermore, the adjunctive use of vitamins, pain relievers, as well as anti-anxiety and antidepressant medications emphasizes the holistic approach adopted in addressing the diverse symptomatology and comorbidities associated with RA. Our study shows that the landscape of RA therapeutics is continually evolving, with ongoing advancements in drug development and treatment paradigms. As such, clinicians must remain vigilant in staying abreast of emerging evidence and guidelines to provide patients with the most effective and personalized care.

Future research endeavors should aim to elucidate the long-term efficacy, safety profiles, and cost-effectiveness of different treatment regimens, facilitating informed decision-making and optimizing patient outcomes in the management of RA. Overall, this study contributes to the body of literature surrounding RA management, offering valuable insights that can inform clinical practice and enhance the quality of care for individuals living with this chronic autoimmune condition.

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