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Research article

Advancing Personalized Care in Rheumatoid Arthritis: A Novel Framework Using NNT, ARR, and Quality of Life Metrics

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Abstract: This study evaluates the efficacy of monotherapy versus combination therapy in rheumatoid ar-thritis (RA) using advanced quantitative metrics such as Number Needed to Treat (NNT), Absolute Risk Reduction (ARR), Relative Risk Reduction (RRR), and Control and Experimental Event Rates (CER and EER). The goal is to provide a structured, clinically relevant framework for op-timizing RA management and bridging the gap between clinical research and real-world appli-cation. A prospective cohort study included 160 RA patients, stratified by age, gender, and dis-ease activity. Patients received either monotherapy (MTX or LEF) or combination therapy (MTX/SSZ/HCQ). Outcomes were assessed over 24 months using statistical significance measures such as confidence intervals, t-tests, ANOVA, and non-parametric alternatives. The findings provide a direct clinical application, guiding treatment selection based on quantifiable response metrics. NNT, ARR, RRR, CER, and EER were calculated to evaluate treatment effectiveness. Combination therapy (MTX/SSZ/HCQ) demonstrated superior efficacy with an NNT of 3, compared to 25 for monotherapy. ARR and RRR were 71% and 90%, respectively, for combination therapy versus MTX/HCQ. Quality of life scores significantly improved in the combination therapy group, correlating with sustained remission over 24 months. This study presents a practical tool for clinicians by integrating longitudinal metrics and patient-specific NNT to personalize RA treatment decisions. By integrating longitudinal metrics and patient-specific NNT, it provides a novel, evidence-based approach to improving treatment outcomes in RA.

Keywords: rheumatoid arthritis, treatment strategies, csDMARD, NNT

1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic disease with an autoimmune origin, primarily affecting small joints and causing local inflammation as well as systemic manifestations [1]. Despite being a well-known condition, RA, like many other complex diseases [2-7], remains partly enigmatic in its etiology and pathogenesis [8,9]. It is characterized by chronic inflammation that leads to joint deformities, destruction of synovial tissue, severe disability, and, in some cases, premature mortality [10]. Beyond its health impact, RA imposes a significant socioeconomic burden due to its associated morbidity, long-term care requirements, and healthcare costs [11].

The clinical variability of RA stems from a complex interaction between genetic predisposition and environmental factors [12]. The disease involves three key pathogenic processes: chronic inflammation, an aberrant immune response (both cellular and humoral), and synovial hyperplasia. Together, these mechanisms contribute to joint damage and destruction [13]. At the joint level, RA is characterized by the proliferation and activation of synovial tissue, forming a pannus infiltrated predominantly with CD4+/T-helper lymphocytes. Leukocyte infiltration is mediated by cytokines, adhesion molecules, and chemo attractants, all of which perpetuate joint inflammation and damage [14,15]. Moreover, synovial macrophage-like and fibroblast-like cells invade adjacent cartilage and bone in a manner similar to tumour invasion, further contributing to joint destruction [16].

A significant breakthrough in RA diagnosis occurred in 1998 with the identification of anti-cyclic citrullinated peptide antibodies (anti-CCP). These antibodies, detected using enzyme-linked immunosorbent assay (ELISA), have superior specificity and sensitivity compared to rheumatoid factor (RF) [17,18]. Anti-CCP antibodies help differentiate RA from other inflammatory arthritis and collagen diseases, especially in seronegative cases [19,20]. Although several other specific and non-specific antibodies have since been identified [20], RF and anti-CCP remain the most clinically useful markers for diagnosing RA. However, traditional treatment evaluation methods focus primarily on clinical response criteria such as Disease Activity Score 28-joint count (DAS28), which do not fully capture the individualized risk-benefit balance of different therapies.

The diagnosis of RA is primarily clinical, characterized by a progressive course of acute or subacute joint inflammation that leads to irreversible joint deformities and significant functional impairments. These features profoundly impact the patient's quality of life. The diagnostic process is supported by tools like joint assessments, manual muscle testing, and measures of disease activity. However, early-stage disease can be challenging to diagnose due to the subtlety of clinical signs and the lack of highly specific biomarkers [21]. Current assessments fail to incorporate longitudinal treatment impact and individualized response probabilities, which are critical for optimizing treatment selection.

Routine assessments include: duration of morning stiffness (in minutes), tender joint count (TJC), swollen joint count (SJC), patient-reported disease severity using a 10-cm visual analog scale (VAS). Laboratory investigations, while non-specific, remain essential in confirming chronic inflammation. Acute-phase reactants like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are commonly used markers. However, the periodic re-evaluation of clinical and laboratory findings is crucial for monitoring disease progression and treatment response [22]. Combining clinical and biological assessments into composite indices, such as DAS28 [23], further aids in tracking disease activity and optimizing treatment decisions. Advancements in imaging techniques have become indispensable in RA management, complementing clinical and laboratory evaluations. X-rays remain a cornerstone for diagnosing RA by confirming the presence of osteoarticular and periarticular lesions. They are particularly useful in detecting erosions and monitoring structural damage progression over time [24,25]. However, newer imaging modalities, including ultrasonography and magnetic resonance imaging (MRI), offer greater sensitivity for detecting early joint inflammation, synovitis, and subclinical damage. These tools are vital for both early diagnosis and the "treat-to-target" strategy [26].

Effective RA management hinges on achieving disease remission or low disease activity to prevent long-term joint damage and preserve the quality of life. For accuracy, in Euope treatment strategies are guided by the European League Against Rheumatism (EULAR) recommendations, which emphasize a treat-to-target approach [27,28]. Treatment regimens include:

- Conventional synthetic Disease-modifying antirheumatic drugs (DMARDs) (csDMARDs): The first-line treatment, with methotrexate being the cornerstone due to its proven efficacy and safety profile;
- Targeted synthetic DMARDs (tsDMARDs): These newer agents include Janus kinase (JAK) inhibitors, which directly target key pathways in the inflammatory cascade;
- Biologic DMARDs (bDMARDs): These therapies, such as tumor necrosis factor (TNF) inhibitors, interleukin (IL) inhibitors, CD-20 monoclonal antibodies and the co-stimulatory molecule inhibitors, have revolutionized RA treatment by providing highly specific immune modulation.

Each treatment strategy aims to reduce inflammation, slow disease progression, and minimize joint damage. Combining these pharmacologic therapies with physical therapy, rehabilitation, and lifestyle interventions further enhances patient outcomes. Non-pharmacological approaches, such as thermotherapy, physical modalities, and range-of-motion exercises, are critical for managing pain and preserving functional capacity, particularly for activities requiring fine motor skills (e.g., grasping) [29].

Over the years, various assessment tools have been developed to evaluate the efficacy of RA treatments. While indicators such as Number Needed to Treat (NNT), Absolute Risk Reduction (ARR), and Relative Risk Reduction (RRR) are well-established in assessing drug efficacy in cardiovascular and oncology research, their application in RA remains relatively limited, particularly for differentiating between monotherapy and combination therapy. This study aims to provide a comprehensive risk-benefit profile for RA therapies by integrating quantitative indicators such as RRR, ARR, and NNT. The study proposes an innovative framework that integrates statistical outcome measures with patient-specific risk assessment to refine treatment selection in RA. By utilizing these advanced evaluation tools, this research aims to bridge the gap between clinical trials and real-world applications, ultimately enhancing personalized care strategies.

2. Materials and Methods

2.1. Study design

We conducted a prospective cohort study over a 6-year period (March 2016–February 2023) to monitor patients with moderate to severe RA using a structured research protocol implemented in hospitals affiliated with the University of Medicine and Pharmacy Craiova, Romania. Patients were evaluated periodically over 24 months, with assessments conducted at baseline (T0) and at six-month intervals (T1, T2, T3, T4). These evaluations included comprehensive clinical, and functional parameters to assess therapeutic efficacy and disease progression.

The study followed a treat-to-target strategy, aiming for disease remission, defined as a DAS28 score <2.6, in line with the guidelines of EULAR [26]. A total of 160 patients were enrolled in the study and divided into three treatment groups based on the therapeutic regimen:

- Methotrexate monotherapy (MTX; n=50);
- Leflunomide monotherapy (LEF; n=49);
- Combination therapy (CT; n=61).

The combination therapy group was slightly larger than the others to enable detailed statistical analysis of the various combination medication subgroups. Treatment groups were balanced in terms of demographic and clinical characteristics, including gender, age, occupation, background, education, disease onset age, and comparable disease severity.

The study maintained an acceptable rate of patient retention, with fewer than 20% of participants discontinuing prematurely due to ineffective therapy, adverse events, or dropout. This ensured the validity and reliability of the study outcomes.

It was deemed necessary, compared to other studies evaluating remission-inducing therapies for RA, to assess efficacy and provide additional useful information for selecting a specific therapy by identifying:

- The most effective therapy that leads to a reduction in the risk of non-response.
- The maximum number of patients that need to be treated over two years to achieve remission in at least one patient. In other words, this study aimed to determine the likelihood that a patient with RA, treated with one of the therapies included in the study, would achieve remission or at least experience a reduction in disease activity.

To achieve these objectives, the following indicators were calculated:

- CER (Control Event Rate): The rate of non-response to remission-inducing therapy in the control group (C): number of non-responders in control group/total control group patients
- EER (Experimental Event Rate): The rate of non-response to remission-inducing therapy in the experimental group (E), which received a specific remission-inducing medication: number of non-responders in experimental group/total experimental group patients
- ARR (Absolute Risk Reduction): CER−EER
- RRR (Relative Risk Reduction): ARR/CER×100%
- NNT (Number Needed to Treat): 1/ARR

Based on the results observed during the monitoring period and the hierarchy established among therapies, the groups were classified as either "control" or "experimental" for comparisons. The experimental group was consistently associated with better outcomes.

2.2. Participants

The study included patients diagnosed with RA according to the American College of Rheumatology (ACR)/EULAR 2010 criteria [27]. A rigorous protocol for eligibility ensured the inclusion of patients who met the following criteria: (1) Provided written informed consent for participation; (2) Age >18 years; (3) DAS28 ≥3.2, regardless of disease duration; (4) No DMARD therapy at the time of inclusion (previous csDMARD use was permitted if discontinued at least three months prior; no history of bDMARD use); (5) Stable non-steroidal anti-inflammatory drug (NSAID) regimen for at least one month; (6) No indication for bDMARD therapy; (7) Adequate language proficiency to understand study instructions.

Exclusion criteria: (1) RA in remission or low activity (DAS28 <3.2); (2) Severe comorbidities such as organ failure, viral hepatitis B or C, immunodeficiencies, or active tuberculosis; (3) Pregnancy or breastfeeding; (4) Conditions that could confound RA symptoms; (5) Severe mental illness; (6) Alcohol dependence, or (7) Uncooperative behavior.

2.3. Study treatments

The study population was divided into three treatment groups:

- Methotrexate monotherapy (MTX; n=50): Weekly doses of 15 mg.
- Leflunomide monotherapy (LEF; n=49): Daily doses of 20 mg.
- Combination therapy (CT; n=61): Step-down regimens involving:
- Methotrexate/Leflunomide (MTX/LEF; n=20),
- Methotrexate/Sulfasalazine (MTX/SSZ; n=21),
- Methotrexate/Hydroxychloroquine (MTX/HCQ; n=20),

The dosing regimen included 10 mg/week of Methotrexate, 10 mg/day of Leflunomide, 2 g/day of Sulfasalazine, and/or 400 mg/day of Hydroxychloroquine.

2.4. Parameters and Measurements

Eligible participants were thoroughly informed about the study objectives, procedures, and their roles in the research. Written informed consent was obtained from all participants prior to enrollment.

Before inclusion in the study, a comprehensive clinical and functional assessment was conducted for each participant. This evaluation included a detailed examination of:

- Joint Assessment: Evaluating the condition of affected joints, including the hands, wrists, elbows, shoulders, hips, knees, ankles, and feet, with a focus on swelling, tenderness, and range of motion;
- Disease Activity: Measuring disease activity using composite indices such as DAS28, CDAI (Clinical Disease Activity Index), and SDAI (Simplified Disease Activity Index), along with patient and physician global health assessments;
- Functional Status: Assessing physical function using validated tools such as the Health Assessment Questionnaire (HAQ) and 36-item Short-Form Health Survey (SF-36), which evaluate daily activity limitations and the overall quality of life;
- Pain and Stiffness: Recording pain levels on a 10-cm Visual Analog Scale (VAS) and assessing morning stiffness duration in minutes to understand the degree of functional impairment;
- Therapeutic Response: Objective measures: evolution of TJC/SJC (0–28), patient/physician global health assessment, and joint pain scores (VAS); EULAR response criteria.

This evaluation was performed in accordance with established clinical practice guidelines for the management of RA in adults [27,28].

The rigorous assessment process ensured that all participants met the eligibility criteria and provided a comprehensive baseline for monitoring therapeutic responses and disease progression in subsequent analyses.

For the analysis of the therapeutic effect, we calculated the following indicators: CER, EER, ARR, RRR, and NNT. Given that the probability of false-negative effects is presumed to be lower than that of false-positive responses, these indicators were calculated based on recommendations from specialized studies, taking into account the lack of response to treatment. These indicators represent:

- CER: The rate of non-response to remission-inducing treatment in the control group;
- EER: The rate of non-response to remission-inducing treatment in the experimental group, compared to the control group. Depending on the purpose of the analysis and the therapeutic regimens being compared, we designated the groups either as control or experimental;
- ARR (Absolute Risk Reduction): Indicates by how much the risk of non-response decreases in the experimental group compared to the control group;
- RRR: Demonstrates the benefit of the studied medication as a percentage compared to the control group;
- NNT (Number Needed to Treat): The most important indicator provided by a trial. It is an integer representing the number of patients who need to undergo the studied therapy for a specified period (in this case, 2 years) to prevent one unfavorable event, such as disease stagnation or progression.

The clinical significance of these indicators is primarily reflected in ARR and NNT.

2.5. Ethics approval

This study prioritized the safety of all participants, emphasizing adherence to ethical standards in research involving adult patients with RA. Participants were informed of their right to withdraw from the study at any time without providing a reason and without facing any negative consequences. Written informed consent was obtained from all participants after a thorough and clear explanation of the study objectives and procedures. The study strictly adhered to the principles outlined in the Declaration of Helsinki and Good Clinical Practice guidelines. Ethical approval was granted by the Ethics Committee of the Craiova University of Medicine and Pharmacy under approval no. 26/01 March 2016.

2.6. Statistical Analysis

The methodological protocol for this randomized controlled trial included: Stratified Analysis (to control for confounding variables) and Group Comparability (Groups were similar in terms of age, gender, disease activity, and clinical parameters, differing only in the type of therapy applied).

The methodological protocol included:

- Stratified Analysis: Applied to control for potential confounding variables related to demographic and disease-related factors.
- Comparative Analysis: Student's t-test was used for comparing continuous variables between two groups when data followed a normal distribution. ANOVA was applied for multiple group comparisons when assumptions of normality and homogeneity of variance were met. Mann-Whitney or Kruskal-Wallis tests were used for non-normally distributed data. Chi-square or Fisher's exact test was employed for categorical data.
- To understand the potential risk reduction for the entire population of patients with RA similar to the study sample, we relied on the confidence interval (CI). The confidence interval provides a range in which we can be 95% confident that the parameter of interest lies at the population level.

Criteria for Statistical Significance: We considered two treatments to be statistically different (statistical significance) if the confidence intervals for the differences in RRR and ARR did not include the value "0". Additionally, the NNT was evaluated, and treatments were considered ineffective if the NNT tended toward infinity. A higher NNT value indicated lower treatment efficacy, as it would require treating a larger number of patients to prevent one adverse event in a single individual.

Practical Application of NNT: Using the calculated NNT from the study, we could estimate the likelihood of an effective therapeutic response for a patient with characteristics similar to those in the study sample. This estimation involves dividing the NNT by a value representing how much higher the patient's risk is compared to the "control" group. We also explored using the NNT to estimate the disadvantages of not applying treatment. However, this method was found to be less practical and difficult to implement, even for patients resembling those in the study

Calculation of Patient-Specific NNT: The patient-specific NNT was calculated assuming PEER= CER, $NNT_{patient} = 1/(PEER \times RRR)$. A nomogram adapted from Chatellier et al. [30] was used to facilitate the calculation of NNT.

Evaluation of Therapeutic Response: To evaluate therapeutic response, we calculated the difference between baseline and final values of the composite DAS28 index, which we denoted as DAS15. This indicator was selected due to its validation in specialized studies as a reliable tool for identifying remission in RA. Based on the DAS15 values, the treatment response was categorized as:

- Favorable Response: Defined as achieving remission;
- Moderate Response: Includes remission as well as achieving a low level of disease activity;

- No Response: Defined as the inability to achieve remission or significant improvement.

Quality of Life as an External Variable: to assess the real-world effects of therapies, we included quality of life as an external variable. This allowed us to account for patient-centered outcomes beyond clinical indices.

Stratified Analysis: using stratified analysis, we dynamically evaluated combinations of treatment regimens and key parameters. This approach helped identify the patient profile for which the therapeutic response was most favorable, optimizing treatment strategies.

Statistical Tools and Software: data were processed using the EpiInfo 2002 software package (CDC Atlanta), which is specifically designed for epidemiological studies [31]. Stratified and dynamic analyses were conducted to ensure robust and reliable interpretations of the results.

3. Results

3.1. Baseline Characteristics of Study Groups

3.1.1. Demographic and Anthropometric Parameters

The initial evaluation of the study population revealed a predominance of female patients across all treatment groups: 84.0% in the Methotrexate (MTX) group, 79.6% in the Leflunomide (LEF) group, and 83.6% in the Combination Therapy (CT) group. The average age of patients (p=0.422) ranged from the early to mid-40s, with mean ages of 41.2 ± 8.6 years for the MTX group, 44.0 ± 9.9 years for the LEF group, and 41.8 ± 7.9 years for the CT group. The mean age of disease onset was also comparable, with values of 37.6 ± 8.4 years in the MTX group, 40.1 ± 9.5 years in the LEF group, and 38.1 ± 7.4 years in the CT group.

Slightly more patients resided in urban areas than rural areas, with urban patients comprising 56.0% in the MTX group, 51.0% in the LEF group, and 59.0% in the CT group. Educational levels were similarly distributed (p=0.853), with approximately half of the participants having secondary or higher education in all groups. Professionally active patients constituted 50.0% of the MTX group, 36.7% of the LEF group, and 42.6% of the CT group, with the remainder being either unemployed or retired. However, the p value for this parrameter suggests that there are no significant differences in these parameters across the MTX, LEF, and CT groups.

The mean Body Mass Index (BMI) was 23.88 ± 3.56 in the MTX group, 24.16 ± 3.31 in the LEF group, and 25.17 ± 3.59 in the CT group (p=0.182). These demographic and anthropometric findings demonstrate the overall homogeneity of the study population at baseline, as shown in Table I.

Table 1. Demographic and anthropometric parameters at T0 moment.

PARAMETER	GROUPS ACCORDING TO MEDICATION			p value
	MTX (n=50)	LEF (n=49)	CT (n=61)	
Gender (n, %)				
F-female,	42 (84.0%)	39 (79.6%)	51 (83.6%)	NA
M-male	8 (16.0%)	10 (20.4%)	10 (16.4%)	
Age (years) (M, SD)	41.200±8.626	44.000±9.916	41.803±7.941	0.422
Age of the patient at disease onset (M, SD)	37.600±8.379	40.102±9.544	38.131±7.395	0.192
Profession (n, %)				
- not working/retired,	25 (50.0%)	31 (63.3%)	35 (57.4%)	0.357
- professionally active	25 (50.0%)	18 (36.7%)	26 (42.6%)	
Residence area (n, %)				

- rural,	22 (44.0%)	24 (49.0%)	25 (41.0%)	0.744
- urban	28 (56.0%)	25 (51.0%)	36 (59.0%)	
Education (n, %)				
- unschooled	24 (48.0%)	26 (53.1%)	32 (52.5%)	0.853
-secondary/higher education	26 (52.0%)	23 (46.9%)	29 (47.5%)	
BMI (M, SD)	23.882±3.555	24.158±3.307	25.174±3.590	0.182

Variables are reported as absolute frequencies = n, relative frequencies = %, M= mean and SD=standard deviation; BMI = body mass index; MTX=Methotrexate, LEF=Leflunomide, CT=Combination Therapy; p= the t-test for independent samples

3.1.2. Baseline Disease Characteristics

As it is presented in Table 2, biological parameters related to disease activity, including (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies, were measured at baseline and demonstrated comparable values across the treatment groups ($p>0.05$). The mean RF levels were 14.58 ± 3.24 UI/mL in the MTX group, 15.39 ± 5.44 UI/mL in the LEF group, and 14.82 ± 4.25 UI/mL in the CT group. Similarly, anti-CCP antibody levels were 21.66 ± 16.12 U/mL in the MTX group, 24.22 ± 13.64 U/mL in the LEF group, and 19.74 ± 12.83 U/mL in the CT group.

The disease duration was consistent across groups ($p=0.726$), with mean values of 3.74 ± 2.80 years in the MTX group, 3.90 ± 2.95 years in the LEF group, and 3.62 ± 2.60 years in the CT group. Most patients reported comorbidities, with 74.0%, 71.4%, and 77.0% of patients in the MTX, LEF, and CT groups, respectively, reporting associated conditions. NSAID or corticosteroid use was prevalent, with only a small minority of patients reporting no concomitant medication use at baseline (12.0% in the MTX group, 12.2% in the LEF group, and 16.4% in the CT group) ($p=0.931$).

Table 2. Disease Characteristics at T0 moment.

PARAMETER	GROUPS ACCORDING TO MEDICATION			p value
	MTX (n=50)	LEF (n=49)	CT (n=61)	
Rheumatoid factor (M, SD)	14.580±3.239	15.388±5.442	14.820±4.245	0.378
Anti-CCP antibodies (M, SD)	21.660±16.123	24.224±13.639	19.738±12.830	0.541
Disease duration (M, SD)	3.740±2.798	3.898±2.946	3.623±2.602	0.726
Comorbidities (n, %)				
-absent,	13 (26.0%)	14 (28.6%)	14 (23.0%)	0.899
-present	37 (74.0%)	35 (1.4%)	47 (77.0%)	
Concomitant medication (NSAIDs, corticosteroids)				
- without medication,	6 (12.0%)	6 (12.2%)	10 (16.4%)	0.931
- with medication	44 (88.0%)	43 (87.8%)	51 (83.6%)	

Variables are reported as absolute frequencies = n, relative frequencies = %, M= mean and SD=standard deviation; BMI = body mass index; MTX=Methotrexate, LEF=Leflunomide, CT=Combination Therapy; p= the t-test for independent samples.

3.1.3. Baseline Disease Activity

All three indices (SDAI, CDAI, DAS28) confirmed that patients were in the moderate to high disease activity range at study inclusion. The SDAI scores were 25.57 ± 3.95 for the MTX group, 26.94 ± 2.35 for the LEF group, and 25.91 ± 2.68 for the CT

group. The CDAI scores were 25.01 ± 1.73, 24.81 ± 2.30, and 24.73 ± 2.23 for the MTX, LEF, and CT groups, respectively. The DAS28 scores showed similar consistency, with values of 5.88 ± 0.77, 5.98 ± 0.70, and 5.98 ± 0.70, respectively.

Table 3. Disease Activity at T0 moment

COMPOSITE INDEX	GROUPS ACCORDING TO MEDICATION			p value
	MTX (n=50)	LEF (n=49)	CT (n=61)	
SDAI (M, SD)	25.574±3.949	26.937±2.348	25.907±2.680	0.000
CDAI (M, SD)	25.014±1.726	24.812±2.300	24.734 ±2.227	0.886
DAS28 (M, SD)	5.876±0.770	5.977±0.704	5.978±0.704	0.887

Variables are reported as M= mean and SD=standard deviation; MTX=Methotrexate, LEF=Leflunomide, CT=Combination Therapy; p= the t-test for independent samples.

3.2. Frequency of Non-Response to Treatment in the Compared Groups

The analysis of non-response rates in the experimental and control groups revealed several significant findings, as illustrated in Table 4 and Figure 1. When the target was remission or low disease activity (Variant I), the triple therapy (MTX/SSZ/HCQ) demonstrated the greatest reduction in the risk of non-response compared to dual therapies or monotherapy. Specifically, a reduction of up to 70% was observed when compared to dual therapy with MTX/HCQ, which consistently ranked lowest in efficacy across all combinations monitored. This is evident in the lower EER for triple therapy compared to other groups. When the target was strictly remission (Variant II), the risk of failing to achieve this outcome decreased by 20% with combination therapy compared to monotherapy, which showed only a modest risk reduction of 2%. As shown in the bar chart, the triple therapy (MTX/SSZ/HCQ) was the most effective, producing reductions in disease activity risk of 33% to 38% (ARR) and facilitating remission with reductions of 21% to 23% (RRR). The visual comparison of CER and EER highlights the superior performance of triple therapy across both variants.

Table 4. Comparison of Treatment Groups: Experimental vs. Control.

Treatment groups (Experimental vs. Control)	Variant I (Target: Remission/Low Disease Activity)		Variant II (Target: Remission)	
	CER	EER	CER	EER
MTX vs. LEF	61%	57%	89%	87%
TC vs. MTX	57%	38%	87%	69%
TC vs. LEF	61%	38%	89%	69%
MTX/SSZ/HCQ vs. MTX/LEF	23%	8%	62%	54%
MTX/SSZ/HCQ vs. MTX/SSZ	40%	8%	73%	54%
MTX/SSZ/HCQ vs. MTX/HCQ	79%	8%	86%	54%
MTX/LEF vs. MTX/SSZ	40%	23%	73%	62%
MTX/LEF vs. MTX/HCQ	79%	23%	86%	62%
MTX/SSZ vs. MTX/HCQ	79%	40%	86%	73%

CER=Control Event Rate; EER=Experimental Event Rate; MTX=Methotrexate; LEF=Leflunomide; TC=Triple Combination Therapy; SSZ=Sulfasalazine; HCQ=Hydroxychloroquine

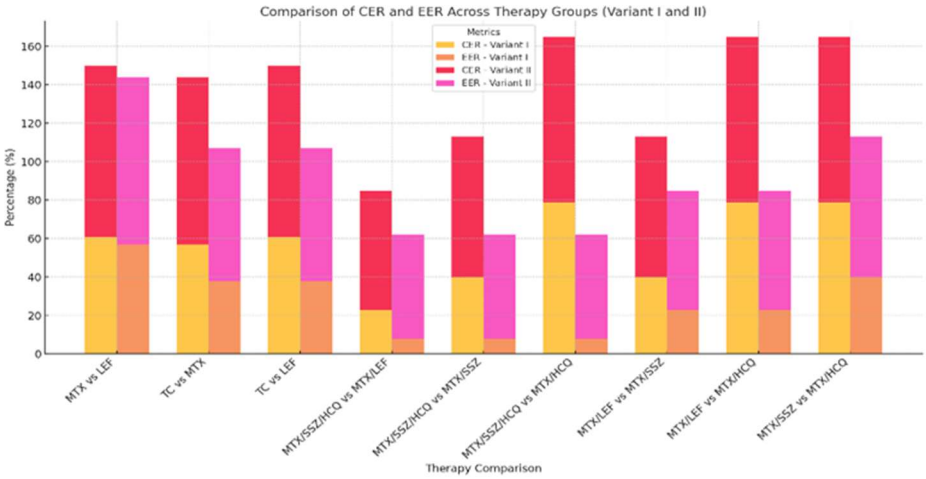

Figure 1. Bar chart comparing the CER and EER across different therapy groups for both Variant I (remission or low disease activity) and Variant II (strict remission).

3.3. Confidence Intervals for Risk Estimates

Table 5 presents the 95% Confidence Intervals for the ARR and RRR metrics associated with the compared therapies.

Table 5. Confidence Intervals (95% CI) for Risk Differences

Therapies Compared	(CI 95%) Variant I		(CI 95%) Variant II	
	ARR	RRR	ARR	RRR
MTX vs. LEF	0.2 - 8	5 – 9	-0.7-5	-0.7-5
TC vs. MTX	12 - 21	24 - 42	15 - 20	14 - 28
TC versus LEF	20 - 27	27 - 50	11 - 29	14 - 32
MTX/SSZ/HCQ vs. MTX/LEF	3 - 27	48 - 72	5 - 31	13 - 45
MTX/SSZ/HCQ vs. MTX/SSZ	27 - 37	66 - 94	5 - 33	19 - 35
MTX/SSZ/HCQ vs. MTX/HCQ	39 - 99	75 - 99	15 - 49	20 - 46
MTX/LEF vs. MTX/SSZ	4 - 30	26 - 60	0 - 22	3 - 27
MTX/LEF/ vs. MTX/HCQ	38 - 73	55 - 87	9 - 39	12 - 44
MTX/SSZ vs. MTX/HCQ	22 - 56	31 - 67	1 - 24	2 - 28

ARR=absolute risk reduction; RRR=relative risk reduction; MTX=Methotrexate; LEF=Leflunomide; TC=Triple Combination Therapy; SSZ=Sulfasalazine; HCQ=Hydroxychloroquine

Confidence intervals for ARR and RRR confirmed the statistical significance of the observed differences. For triple therapy versus MTX/HCQ, the 95% CI for ARR ranged from 39% to 99%, while for RRR, it ranged from 75% to 99%.

3.4. NNT over a period of two years

An indicator considered particularly important, yet underexplored in the current literature, is the NNT over a period of two years to achieve disease remission in at least one patient. The NNT provides valuable insights into the effectiveness of different therapeutic strategies and highlights the comparative benefit of combination therapies over monotherapy.

The analysis revealed that the NNT is higher when the primary objective is remission rather than low disease activity (Table 6).

The NNT for achieving remission in one patient was as follows: Monotherapy (MTX vs. LEF): 25–50 patients; Dual therapy (MTX/LEF vs. MTX/SSZ): 6–9 patients; Triple therapy (MTX/SSZ/HCQ vs. MTX/HCQ): 2–3 patients

This is explained by the stringent criteria that must be met for remission to be achieved, as defined by the American College of Rheumatology (ACR) criteria.

Table 6. Number Needed to Treat Over Two Years to Achieve Remission in One Patient.

Treatment Comparisons	Variant I (Target: Remission or Low Disease Activity)	Variant II (Target: Remission)
	NNT	NNT
MTX vs. LEF	25	50
TC vs. MTX	5	6
TC vs. LEF	4	5
MTX/SSZ/HCQ vs. MTX/LEF	7	6
MTX/SSZ/HCQ vs. MTX/SSZ	3	5
MTX/SSZ/HCQ vs. MTX/HCQ	2	3
MTX/LEF vs. MTX/SSZ	6	9
MTX/LEF/ vs. MTX/HCQ	2	4
MTX/SSZ vs. MTX/HCQ	3	8

MTX=Methotrexate; LEF=Leflunomide; TC=Triple Combination Therapy; SSZ=Sulfasalazine; HCQ=Hydroxychloroquine; NNT= Number Needed to Treat.

For monotherapy, the NNT is nearly double compared to combination therapy (50 patients vs. 25 patients), underscoring the need to transition from initial monotherapy to combination therapy in patients without contraindications. In other words, while monotherapy can offer favorable short-term results, only 1 in 25 patients achieves sustained low disease activity after two years of treatment. This high number of patients potentially not achieving sustained therapeutic response is difficult to justify, given the availability of more effective combination therapies.

The findings reveal a consistent hierarchy in the efficacy of therapies, as assessed by the NNT required to achieve at least one reduction in disease activity over 24 months. Combination therapies consistently outperform monotherapy, regardless of whether the treatment involves LEF or MTX.

The maximum efficacy is observed with triple therapy (MTX/SSZ/HCQ), which achieves the lowest NNT values (2–3 patients) for remission or low disease activity, followed by the dual therapy of MTX/LEF. For patients who cannot tolerate triple therapy, MTX/LEF represents a superior alternative to other dual therapies, such as MTX/HCQ or MTX/SSZ (Figure 2).

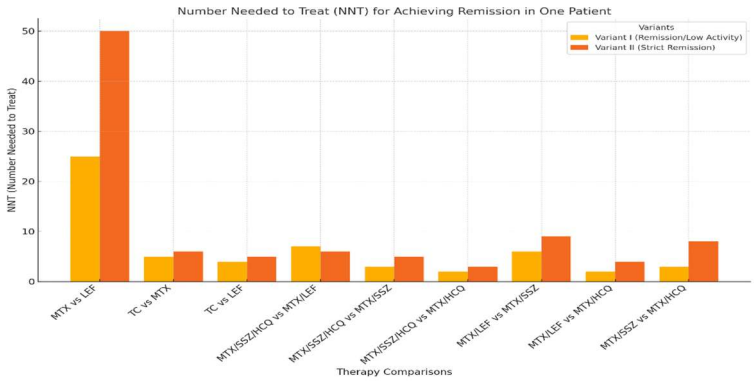

Figure 2. Bar chart illustrating the NNT for achieving remission in one patient across various therapy comparisons for both Variant I (Remission or Low Activity) and Variant II (Strict Remission).

Among the combination therapies evaluated, the triple therapy (MTX/SSZ/HCQ) demonstrated the highest efficacy (Table 7). This regimen is preferred over the initial use of dual conventional disease-modifying antirheumatic drugs (DMARDs). If triple therapy cannot be utilized due to patient-specific contraindications or limitations, the results support the use of MTX/LEF, which is superior to both MTX/HCQ (requiring treatment of 4 patients to achieve remission in one) and MTX/SSZ (requiring treatment of 9 patients).

Table 7. Therapeutic Strategy Hierarchy Based on NNT (Ascending Order).

Variant I (Target: Remission or Low Disease Activity)		**Variant II (Target: Remission)**	
Treatment Comparisons	**NNT**	**Treatment Comparisons**	**NNT**
MTX vs. LEF	25	MTX vs. LEF	50
TC vs. MTX	5	TC vs. MTX	6
TC vs. LEF	4	TC vs. LEF	5
COMBINATION THERAPY			
MTX/SSZ/HCQ vs. MTX/LEF	7	MTX/LEF vs. MTX/SSZ	9
MTX/LEF vs. MTX/SSZ	6	MTX/SSZ vs. MTX/HCQ	8
MTX/LEF/HCQ vs. MTX/SSZ	3	MTX/SSZ/HCQ vs.MTX/LEF	6
MTX/SSZ vs. MTX/HCQ	3	MTX/SSZ/HCQ vs. MTX/SSZ	5
MTX/LEF/HCQ vs. MTX/HCQ	2	MTX/LEF vs. MTX/HCQ	4
MTX/LEF vs. MTX/HCQ	2	MTX/SSZ/HCQ vs. MTX/HCQ	3

MTX=Methotrexate; LEF=Leflunomide; TC=Triple Combination Therapy; SSZ=Sulfasalazine; HCQ=Hydroxychloroquine; NNT= Number Needed to Treat.

The results strongly favor the selection of combination therapies, particularly MTX/SSZ/HCQ or, alternatively, the dual therapy MTX/LEF. These regimens offer a 1 in 2 chance of achieving a favorable therapeutic outcome after two years of treatment.

For remission specifically: 1 in 3 patients treated with triple therapy achieved remission and 1 in 4 patients treated with MTX/LEF achieved remission.

4. Discussion

RA is a chronic disease characterized by heterogeneous outcomes, resulting from a complex interplay between genetic predisposition and environmental triggers [32-34]. These interactions activate multiple independent mechanisms responsible for initiating and perpetuating the disease. Similar to existing literature [35-37], the study group in this research predominantly consisted of female patients with a mean age in the 4th decade of life and disease onset around 40 years.

The progressive nature of RA necessitates an early and accurate diagnosis to mitigate the destructive lesions and functional disabilities associated with disease progression [38,39]. Advances in RA management, including highly effective medications and a treat-to-target strategy, have significantly improved long-term prognosis. Remission remains the ultimate goal, monitored using established criteria such as the American College of Rheumatology (ACR) and the EULAR response criteria [40-42]. However, a subset of patients classified as being in remission continues to exhibit joint progression detectable on radiographs, suggesting gaps in current remission definitions and monitoring tools.

In chronic disease management, predicting long-term outcomes remains challenging due to the variability in clinical manifestations and subjective interpretations [43-47]. Traditional combined parameters for assessing RA treatment efficacy often lack the ability to comprehensively compare monotherapy and combination therapy. This study introduces quantitative indicators: NNT, CER, EER, ARR, and RRR, to provide a multidimensional framework for evaluating short- and long-term therapeutic outcomes. The findings highlight the superior efficacy of combination therapy,

particularly triple therapy (MTX/SSZ/HCQ), in achieving remission and improving quality of life in RA.

In the present study, combination therapy (MTX/SSZ/HCQ) demonstrated a remarkably low NNT of 3, compared to 25 for monotherapy, to achieve remission over a two-year period. This stark difference underscores the superior efficacy and practical impact of combination therapy in RA management. These findings align with those of Kristensen et al. [48], who reported similarly low NNT values for biologic therapies such as Adalimumab and Etanercept in achieving ACR50 responses, ranging between 3 and 7. Such low NNT values indicate the exceptional efficiency of combination regimens in reducing disease activity. Conversely, Deng et al. [49] observed no significant differences in NNT between monotherapy and a combination therapy with Leflunomide over a shorter follow-up period. This divergence may highlight the importance of therapy-specific outcomes and patient selection criteria. Notably, our study's focus on a longer-term follow-up period of two years allowed for a more robust assessment of sustained remission, which may explain the more pronounced differences observed. In a meta-analysis by Alonso-Ruiz et al. [50], NNT values for TNF-α inhibitors in combination with methotrexate were reported to be around 5, supporting the use of combination regimens for moderate to severe RA. Compared to these biologic regimens, our study demonstrates that triple therapy with MTX/SSZ/HCQ can achieve comparable or better efficacy at potentially lower costs, a critical consideration in resource-limited settings.

The comparative analysis of CER and EER in our study further highlights the superiority of combination therapy. For instance, MTX/SSZ/HCQ demonstrated a CER of 79% and an EER of 8% when compared to MTX/HCQ, resulting in an ARR of 71%. Similarly, Kristensen et al. [48] and Harigane et al. [51] emphasized ARR as a critical metric, particularly in identifying cost-effective therapeutic regimens. These findings highlight how combination therapies yield substantial absolute benefits in reducing non-response rates compared to monotherapy.

The RRR observed in our study for MTX/SSZ/HCQ versus MTX/HCQ was an impressive 90%, echoing the findings of Ma et al. [52], who reported significant relative reductions in disease activity for combination DMARD therapy compared to TNF inhibitors. This further reinforces the role of combination therapy as a cornerstone of RA management, particularly for patients with moderate to severe disease activity.

CER and EER provide granular insights into the proportion of patients achieving remission in control and experimental groups, respectively. These metrics are essential for understanding therapeutic efficacy across different regimens. The analysis of CER and EER further validates the findings on the efficacy of combination therapy. For instance, the CER of 61% and EER of 57% observed for MTX vs. LEF reflect the comparable efficacy of these monotherapies. In contrast, the CER of 79% and EER of 8% for MTX/SSZ/HCQ vs. MTX/HCQ illustrates the striking superiority of the combination therapy. Kristensen et al. [48] reported CER values for monotherapy with MTX to be approximately 60%, closely aligning with the CER of 61% observed in this study. This alignment highlights the consistency of findings across multiple studies and underscores the limitations of monotherapy in achieving remission. Moreover, Harigane et al. [51] highlighted the significance of low EER values in evaluating the effectiveness of combination therapies. The EER of 8% observed for MTX/SSZ/HCQ in this study reflects a strong therapeutic effect, further validating the superiority of combination regimens over monotherapy.

Regarding Absolute and Relative Risk Reduction, this study demonstrates that the combination therapy of MTX/SSZ/HCQ provides substantial therapeutic benefits, as evidenced by an ARR of 71% and an RRR of 90% when compared to MTX/HCQ. Ma et al. [52] reported ARR values for combination DMARD therapies ranged be-

tween 50% and 60%, closely aligning with the ARR in this study. This similarity reinforces the significant absolute benefit that combination therapies provide over monotherapies.

These metrics highlight the profound reduction in non-response rates and underline the superiority of combination therapy in achieving remission in RA. It has been emphasized that RRR values above 80% typically signify a notable benefit of combination therapies, which aligns with the RRR of 90% observed in this study. This considerable relative risk reduction highlights the profound effectiveness of combination therapy in altering the trajectory of disease progression [53].

Implications for Clinical Practice:

The integration of quantitative indicators such as NNT, ARR, and RRR into RA treatment decision-making provides clinicians with a more structured approach to selecting the most effective therapy.

- Personalized Treatment Adjustments: By using patient-specific NNT calculations, clinicians can better tailor treatments to individual risk profiles, maximizing treatment efficacy while minimizing unnecessary drug exposure.
- Resource Optimization: Given the substantial differences in NNT between monotherapy and combination therapy, healthcare systems could benefit from prioritizing combination therapy in eligible patients, reducing the burden of prolonged ineffective treatment.
- Treatment Guidelines: These findings support the increasing emphasis in EULAR and ACR guidelines on early combination therapy to improve remission rates and long-term outcomes.

Limitations and Future Directions:

While this study highlights the superiority of combination therapy, certain limitations must be addressed. For instance, the exclusion of biomarkers such as MBDA scores, which have been shown by Curtis et al. [53] to predict aggressive disease progression more effectively than clinical metrics alone, may limit the ability to generalize these findings. Additionally, as Daihua Deng et al. [49] noted, contextual factors such as demographic differences and comorbidities could influence treatment outcomes, warranting further research in diverse patient populations. Acknowledging the limitations of the study—such as small subgroup sizes, lack of biomarker integration, and patient homogeneity—strengthens the credibility of the findings. While the internal validity is robust due to the use of well-defined metrics (ARR, RRR, NNT), external validity could be improved through larger, more diverse patient cohorts and cost-effectiveness analyses:

- Study Population: The study was conducted in a specific geographic and demographic cohort, which may limit generalizability to broader populations.
- Lack of Biomarker Integration: Future studies should incorporate biomarker analysis (e.g., MBDA scores) to enhance predictive modeling of treatment response.
- Longer Follow-Up Needed: While a 24-month follow-up provides valuable insights, extended studies would better assess the long-term sustainability of combination therapy benefits.
- Cost-Effectiveness Analysis: Future research should explore the economic impact of prioritizing combination therapy over monotherapy to optimize healthcare resource allocation.

Future studies should aim to validate these findings across broader cohorts and integrate advanced biomarkers into treatment assessments. Furthermore, comparative cost-effectiveness analyses, as performed by Batticciotto et al. [54], could provide additional insights into optimizing RA management strategies in different healthcare settings.

5. Conclusions

This study introduces an innovative framework for evaluating RA treatment efficacy by incorporating patient-specific NNT calculations and longitudinal analysis

of ARR and RRR. The findings provide compelling evidence supporting the superiority of combination therapy over monotherapy, reinforcing its role in achieving remission and improving quality of life.

By quantifying treatment impact beyond traditional clinical indices, the study results offers clinicians an evidence-based, personalized approach to optimizing RA management. Future research should build upon these findings by incorporating advanced biomarker analysis and cost-effectiveness evaluations to refine treatment strategies further.

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