Effectiveness of Combined DMARD and NSAID Therapy Versus NSAID alone in Rheumatoid Arthritis：A Multi-center Study

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1. Abstract

This study aimed to compare the effectiveness of combined Disease-Modifying Anti-Rheumatic Drugs (DMARDs) and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) therapy versus NSAID alone in the management of Rheumatoid Arthritis (RA). Utilizing a comprehensive statistical approach, including the Cochran-Mantel-Haenszel test and Analysis of Covariance (ANCOVA), we found that patients receiving the combined therapy were 2.5 times more likely to achieve an ACR20 response than those on NSAID, with a significant improvement in several clinical outcomes. Despite the short-term clinical benefits of the treatment, Kaplan-Meier survival analysis showed no significant difference in the duration until treatment discontinuation due to lack of efficacy between the two treatments, highlighting the importance of considering patient preference and other factors in long-term RA management. These findings suggest the superiority of combined DMARD and NSAID therapy in improving key aspects of RA, while also emphasizing the need for personalized treatment strategies to optimize long-term outcomes.

2. Introduction

This report presents an analysis of a six-month study on the effectiveness of combined DMARD and NSAID treatment versus NSAID in RA. The study hinges on the American College of Rheumatology 20 (ACR20) response rate as the primary indicator of treatment efficacy, marked by at least a 20% improvement across specific measurements. This investigation enriches its analysis through seven secondary endpoints, including physician and patient assessments of disease activity, counts of painful and swollen joints, a visual analog pain scale, levels of C-reactive protein, and health assessment questionnaire scores.

A primary analysis of ACR20 responses without adjusting for study center variations is conducted, followed by a secondary analysis that includes center adjustments. Further, the report employs ANCOVA to analyze the secondary endpoints, considering treatment, center, and baseline measurements, while exploring interactions between treatment with center and baseline. Additionally, the report assesses the time to discontinuation due to lack of efficacy through survival analysis, utilizing the Last Observation Carried Forward (LOCF) approach for handling missing data. The report aims to offer a comprehensive evaluation of the treatments' impact on RA management and patient outcomes.

3. Data Summary

This dataset encompasses information from 181 patients across 27 centers, recording their visits, days, treatment types (a combination of DMARDs and NSAIDs as treatment 2, NSAID as treatment 1), seven specific measurements related to disease activity, and final status. Measurements include physician and patient assessments of disease activity (rated on a scale from 1 for 'no symptom' to 5 for 'very severe'), the number of painful joints (0-68), the number of swollen joints (0-66), visual analog

pain scale scores (0-31), C-reactive protein levels, and health assessment questionnaire scores, with lower scores indicating improvement in condition. Final status is recorded into four outcomes: 1 for complete study, 2 for discontinuation due to lack of efficacy, 3 for discontinuation due to safety reasons, and 4 for discontinuation due to other reasons.

The dataset's primary endpoint, the response rate of ACR20, is determined based on a 20% improvement in the number of painful and swollen joints, plus a 20% improvement in at least three out of the five other measurements. For the assessments of disease activity by physicians and patients, an improvement means at least one level up on their respective scales. The secondary endpoints are the seven measurements.

To ensure the integrity of the analysis in the face of missing data, the Last Observation Carried Forward (LOCF) method is employed, using the most recent available data point for each patient. This approach allows for a continuous and comprehensive evaluation of the treatment's effectiveness and patient outcomes throughout the study period.

Table 1. Summary Statistics of ACR20 Response and Proportions

	ACR20 Response			
Treatment	**1**	**0**	**Total**	**Proportion**
NSAID	24	64	88	48.62%
NSAID+DMARD	45	48	93	51.38%
Total	69	112	181	100.00%

4. Methods

In this section, we detail the statistical analysis methods utilized, including the CMH test, ANCOVA, and time to event analysis. Across all statistical tests conducted, the significance threshold is set at 0.05.

4.1. CMH Tests

In our primary analysis, we aimed to assess the comparative effectiveness of treatment 1 and treatment 2 in achieving an ACR20 response in patients with RA. To analyze the categorical data, we employed the CMH test to evaluate the association between treatment types and response rates across patients.

In our secondary analysis, we conducted a exploration of the treatment effectiveness in achieving an ACR20 response, meticulously adjusting for center variability. We also employed the CMH test to mitigate center-related confounding effects, thereby offering a precise evaluation of treatment impacts within a multi-center framework.

4.2. ANCOVA Analysis

To evaluate the efficacy of two treatments across seven secondary endpoints, the report employed ANCOVA, integrating variables including treatment, center, and baseline as covariates in a model that deliberately excluded interaction terms.

We expanded our analysis to investigate interactions, particularly between treatment and center, and treatment and baseline, through a new model. This aimed to reveal complex dynamics, enhancing our insight into how treatment effectiveness might vary by center context and patient starting conditions.

4.3. Time to event analysis

In this study, we compared the duration until treatment discontinuation due to lack of efficacy between Treatment 1 and Treatment 2 in RA utilizing the Kaplan-Meier estimator.

5. Results

5.1. CMH Tests

The primary analysis was to assess the statistical significance of the difference in effectiveness between two treatments in inducing an ACR20 response in RA patients. The analysis was designed to test the null hypothesis that the odds ratio (OR) of achieving an ACR20 response with Treatment 2 relative to Treatment 1 is equal to 1, against the alternative hypothesis that the OR differs from 1.

Utilizing the CMH test, a significant difference in treatment effectiveness was detected. The calculated odds ratio was 2.50, with a 95% confidence interval (CI) ranging from 1.34 to 4.65 and a p-value of 0.0003. This suggests that patients receiving Treatment 2 are 2.5 times more likely to achieve an ACR20 response compared to those receiving Treatment 1.

In the exploratory analysis, which adjusted for variability across treatment centers, the null hypothesis tested was that the odds ratio of achieving an ACR20 response with Treatment 2 versus Treatment 1 is equal to 1, after accounting for center effects. The alternative hypothesis proposed that the adjusted OR is not equal to 1 after accounting for center effects. The result confirmed a significant association between treatment type and ACR20 response rate after adjusting for center variability.

Table 2. summary of CMH Test Results for Treatment Effectiveness

Test Group	**X^2**	**DF**	**Pr > X^2**	**OR (95%CI)** [a]
Treatment 2 vs treatment 1	8.50	1	0.0036	2.50 (1.34, 4.65)
Treatment 2 vs treatment 1, adjusted	8.27	1	0.0040	2.50 (1.29, 4.85)

[a] OR denotes the odds ratio, 95% CI refers to the 95% confidence interval.

5.2. ANCOVA

In the assessment of two treatments across seven secondary endpoints using ANCOVA, for each secondary endpoint, the analysis was framed around testing the

null hypothesis that there is no difference in the effect of two treatment for each secondary endpoint against the alternative hypothesis that a significant difference exists between the treatment effects.

The findings revealed significant differences in treatment effects for six endpoints, including physician assessment of disease activity (p=0.0045), patient assessment of disease activity (p=0.0137), number of swollen joints (p=0.0023), visual analog pain scale (p=0.0469), health assessment questionnaire (p=0.0329), and C-reactive protein (p=0.0191), indicating a clear advantage of treatment 2 in these areas. However, for number of painful joints, the analysis did not indicate a significant difference between the treatments (p=0.0829), suggesting similar efficacy for this specific outcome.

Table 3. Treatment Effects on Endpoints: ANCOVA Model Summary

Endpoint	SS	df	MS	F Value	p - value
physician assessment of disease activity	4.34	1	4.34	8.33	0.0045
patient assessment of disease activity	4.20	1	4.20	6.22	0.0137
number of swollen joints	425.62	1	425.62	3.05	0.0829
number of painful joints	639.10	1	639.10	9.65	0.0023
visual analog pain scale	232.13	1	232.13	4.02	0.0469
health assessment questionnaire	1.03	1	1.03	4.64	0.0329
C-reactive protein	16.52	1	16.52	5.61	0.0191

Our analysis targeted interaction effects among treatment, center, and baseline conditions across seven secondary endpoints, with the goal of understanding their influence on treatment outcomes. We tested two sets of hypotheses: one regarding the consistency of treatment efficacy across different study centers, and another concerning the effect of initial patient conditions on treatments. Our findings showed no significant interaction between treatment and study center ($p > 0.05$), confirming our null hypothesis that treatment efficacy does not vary significantly by center. However, we found significant interactions between treatment and baseline conditions in the context of physician assessments of disease activity and C-reactive protein levels ($p < 0.05$), affirming our alternative hypothesis. These results highlight the critical role of initial patient conditions in influencing the efficacy of treatment on these specific outcomes.

Table 4. Interaction of Treatment and Center on Endpoints: Model Summary

Endpoint	SS	df	MS	F Value	p - value
physician assessment of disease activity	10.61	25	0.42	0.82	0.7150
patient assessment of disease activity	16.36	25	0.65	0.97	0.5103
number of swollen joints	4607.14	25	184.29	1.40	0.1158
number of painful joints	2279.31	25	91.17	1.48	0.0827
visual analog pain scale	1130.66	25	45.23	0.75	0.8011
health assessment questionnaire	5.34	25	0.21	0.98	0.5037
C-reactive protein	46.08	25	1.84	0.61	0.9213

Table 5. Interaction of Treatment and Baseline on Endpoints: Model Summary

Endpoint	SS	df	MS	F Value	p - value
physician assessment of disease activity	3.36	1	3.36	6.46	0.0122
patient assessment of disease activity	2.26	1	2.26	3.35	0.0697
number of swollen joints	180.96	1	180.96	1.38	0.2429
number of painful joints	67.68	1	67.68	1.10	0.2964
visual analog pain scale	36.84	1	36.84	0.61	0.4374
health assessment questionnaire	0.65	1	0.65	2.96	0.0876
C-reactive protein	25.53	1	25.53	8.51	0.0042

5.3. Time to event analysis

Our time-to-event analysis compared the duration until treatment discontinuation due to lack of efficacy between Treatment 1 and Treatment 2 in RA. We tested the null hypothesis that there is no difference in the discontinuation times due to efficacy between two treatments. The alternative hypothesis posited that there is a difference in the discontinuation times. Kaplan-Meier survival curves and subsequent statistical tests yielded p-values of 0.9774, 0.8360, and 0.9834, respectively, indicating that the evidence did not support the alternative hypothesis, leading to the conclusion that the two treatments are equivalent regarding the time patients remain on treatment before discontinuation due to lack of efficacy.

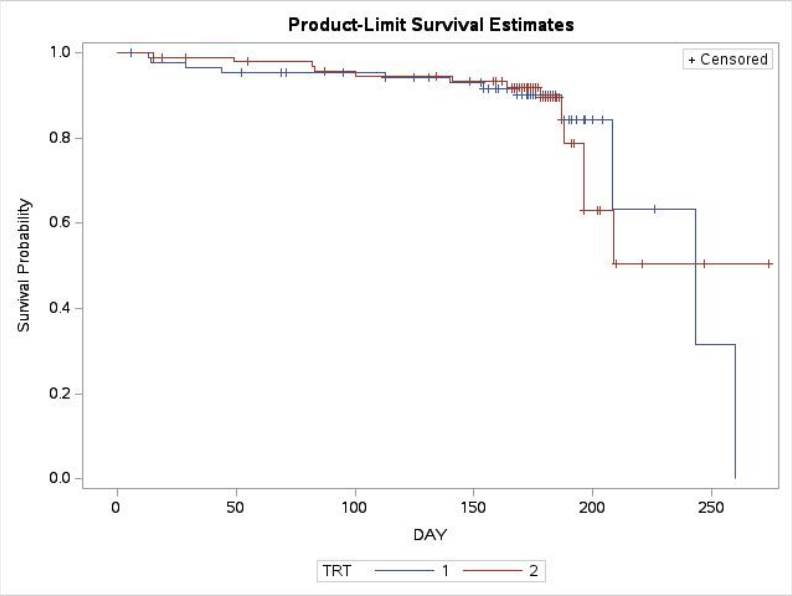

Figure5.3. Comparison of Time to Discontinuation Due to Lack of Efficacy

Table 6. Analysis of Treatment Discontinuation Due to Lack of Efficacy in RA

Test	**X^2**	**df**	**Pr > X^2**
Log-Rank	0.0008	1	0.9774
Wilcoxon	0.0429	1	0.8360
-2Log(LR)	0.0004	1	0.9834

6. Discussion and Conclusion

This study aimed to assess the effectiveness of combined DMARD and NSAID Therapy Versus NSAID in Rheumatoid Arthritis. The primary analysis using the CMH test revealed a significant difference in treatment effectiveness, with patients receiving combined treatment 2.5 times more likely to achieve an ACR20 response compared to those on NSAID alone. This effect remained significant after adjusting for center, indicating a robust association between treatment type and effectiveness.

Analysis via ANCOVA confirmed the superiority of combined treatment over the NSAID across several endpoints, including physician and patient assessments of disease activity, number of swollen joints, pain scale, health assessment questionnaire scores, and C-reactive protein levels. This analysis reinforces the CMH test's findings, suggesting a clear advantage for Treatment 2 in improving key aspects of RA. Despite these positive findings, the lack of a significant difference in the number of painful joints between treatments suggests that both treatments might offer comparable relief in this specific area. The interaction between treatment and center showed no significance, indicating that treatment efficacy remains consistent across centers. Conversely, significant interactions were observed between treatment and baseline, specifically in physician assessments of disease activity and C-reactive protein levels, highlighting the influence of baseline conditions on treatment effectiveness.

In contrast to the significant differences observed in treatment effectiveness, time to event analysis suggested no significant difference between the two treatments in terms of the duration patients remained on treatment before discontinuation due to lack of efficacy. This indicates that, despite combined treatment’s superior effectiveness in achieving clinical responses, both treatments are equivalent concerning patients' long-term commitment to treatment for efficacy, potentially due to factors not directly related to the treatments' clinical efficacy.

In all, the study evaluated the effectiveness of combined DMARD and NSAID therapy versus NSAID alone in Rheumatoid Arthritis, revealing a superiority of combined DMARD and NSAID in inducing an ACR response and improving other key indicators of disease activity.These results highlight the potential of combined DMARD and NSAID to offer more comprehensive benefits in RA. However, the equivalence in treatment discontinuation times suggests that factors beyond clinical efficacy, such as patient preference or side effects, may play a crucial role in long-term treatment adherence. This underscores the necessity for personalized treatment strategies that account for individual patient preferences, ensuring optimal long-term management of RA.

7. Appendix

7.1. SAS Code

```
data dta01;
input CENTER PATIENT DAY VISIT VAPS CRP FINAL TRT PHYASMT
```

```
PATASMT PAINJT SWELLJT HAQ ;
cards ;
1       55        -6     -1     22     7.10     1     1     5     4     38     31       .
1       55        -1      0     27     7.16     1     1     5     4     38     29    2.31530
......
;

data dta11; set dta01; by center patient day ; retain b1-b7 e1-e7 ;
        array b b1-b7 ; array e e1-e7 ; array d d1-d7 ;
        array v phyasmt patasmt painjt swelljt vaps haq crp ;
        if first.patient then do i=1 to 7; b{i}=.; e{i}=.; d{i}=.; end ;
        if day<2 then do i=1 to 7; if v{i} ne . then b{i}=v{i}; end ;
        if day>1 then do i=1 to 7; if v{i} ne . then e{i}=v{i}; end ;
        do i=1 to 7; d{i}=e{i}-b{i}; end ;
        a1=0; a2=0; a3=0; a4=0; a5=0; a6=0; a7=0; acr=0 ;
        if .<d1<0 then a1=1; if .<d2<0 then a2=1 ;
        if .<d3/b3<=-.2 then a3=1; if .<d4/b4<=-.2 then a4=1 ;
        if .<d5/b5<=-.2 then a5=1; if .<d6/b6<=-.2 then a6=1; if .<d7/b7<=-.2 then
a7=1 ;
        a8=a1+a2+a5+a6+a7; if a3=1 and a4=1 and a8>2 then acr=1 ;
        if d1=. or d2=. or d3=. or d4=. or d5=. or d6=. or d7=. then delete ;
        if last.patient then output ;

proc means data=dta11 noprint; var b1-b7; output out=dta12 mean=bas1-bas7 ;
data dta13; merge dta11 dta12 (in=g) ;
        retain bx1-bx7; array bas bas1-bas7; array bx bx1-bx7; array b b1-b7; array nb
nb1-nb7 ;
                if g then do i=1 to 7; bx{i}=bas{i}; end ;
                do i=1 to 7; nb{i}=b{i}-bx{i}; end ;
        dcloe=0; if final=2 then dcloe=1 ;

proc means data=dta13 n mean std; class trt; var b1-b7 d1-d7 ;


/* CMH */

proc freq data=dta13;
tables trt*acr/cmh;
run ;

proc freq data=dta13;
tables center*trt*acr/cmh;
run ;
```

```
/* ANCOVA */

%ancova_analysis;

%macro ancova_analysis;
	%do i = 1 %to 7;
		proc glm data=dta13;
			class trt center;
			model d&i = trt center b&i;
		run;
	%end;
%mend;

%ancova_analysis;

%macro ancova_analysis_inter;
	%do i = 1 %to 7;
		proc glm data=dta13;
			class trt center;
			model d&i = trt center nb&i trt*center trt*nb&i;
		run;
	%end;
%mend;

%ancova_analysis_inter;

/* Time to event analysis*/

title "Analysis of time to discontinuation for lack of efficacy" ;
proc lifetest data=dta13 ;* outsurv=test notable ;
	time day*dcloe(0); id patient ;    strata trt ;
```