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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease requiring early and sustained remission to prevent joint damage and disability. Gut microbiota plays a role in systemic immune regulation. Emerging data suggest probiotics may support immune modulation and treatment response in RA.

AIMS

- To evaluate the effects of the probiotic formulation on disease activity, quality of life, fatigue, and inflammatory markers in newly diagnosed RA patients treated with conventional Disease-Modifying Antirheumatic Drugs (DMARDs) over 12 months.
- To assess the impact of probiotic supplementation on the tolerability and safety profile of methotrexate.

METHODS

Design: 12-month single center, double-blinded, placebo-controlled randomized clinical trial (RCT)

Population: 100 newly diagnosed RA patients

Groups:

Group A: cDMARDs + probiotics (n=50)

Group B: cDMARDs alone

Probiotics used:

Lactobacillus casei BLn2401

Lactobacillus salivarius BL2201

Bifidobacterium breve BL3406

Assessments: At 0, 3, 6, 9, and 12 months

Outcomes: DAS28, ESR, CRP, VAS, HAQ, RAQoL, MTX tolerability

Statistical Analyses: Repeated measures ANOVA, Kaplan-Meier, Cox regression

RESULTS

Baseline Characteristics

- Age:** 57 ± 14 years
- Sex:** 84% female
- Hypertension:** 65%
- Smokers (current/former):** 49%
- No significant differences between groups in demographics or RA serology (RF, anti-CCP)**
- MTX was better tolerated in Group A (0% switch vs. 20% in Group B, $p = 0.03$)

Longitudinal Outcomes (Table 1)

Key Clinical Results:

- DAS28:** Greater reduction in Group A (2.3 ± 0.4 vs. 4.8 ± 0.7 at 12 months)
- Pain (VAS):** Group A improved from 9.3 to 0.2; Group B relapsed to 7.8
- ESR, CRP:** Significant decline in Group A; rebound in Group B
- HAQ & RAQoL:** Improved in Group A; worsened/stagnant in Group B
- Steroid Use:** 40% (Group A) vs. 80% (Group B) at 12 months ($p < 0.05$)

Kaplan-Meier Analysis (Figure 1)

- Faster and higher rate of remission/LDA in Group A ($p < 0.05$)
- “Survival” (i.e., not in remission) at 12 months:
 - Group A:** ~0%
 - Group B:** 45%

Predictors of Remission (Cox Regression)

- Only **treatment group** significantly predicted remission (HR = 2.703, 95% CI: 1.59–4.60, $p < 0.001$)
- Other variables (sex, age, smoking, RF/anti-CCP, ESR, CRP) were not significant

CONCLUSIONS

Adjunctive use of *L. casei* BLn2401, *L. salivarius* BL2201, and *B. breve* BL3406 with cDMARDs:

- Accelerated and sustained remission
- Reduced inflammation, pain, and disability
- Improved MTX tolerability
- Lower corticosteroid use

Larger, multi-center studies incorporating microbiome analyses are warranted to confirm these results and elucidate underlying mechanisms.

Table 1. Longitudinal changes in clinical parameters over 12 months in patients with RA treated with cDMARDs + probiotics (Group A) versus cDMARDs alone (Group B)

| Parameter | Group | Baseline | 3M | 6M | 9M | 12M | p (time) | η^2 (time) | p (Group × Time) | η^2 (Group × Time) |
|------------|-------|-----------|------------|-----------|-----------|------------|----------|-----------------|------------------|-------------------------|
| ESR (mm/h) | A | 40 ± 22 | 20 ± 14 | 16 ± 11 | 16 ± 10 | 14 ± 9 | <0.05 | 0.414 | <0.05 | 0.078 |
| | B | 47 ± 23 | 26 ± 19 | 28 ± 12 | 28 ± 12 | 35 ± 15 | | | | |
| CRP (mg/L) | A | 28 ± 3.3 | 8 ± 11 | 7 ± 8 | 5 ± 5.5 | 4.1 ± 4 | <0.05 | 0.198 | 0.026 | 0.038 |
| | B | 32 ± 4.1 | 13 ± 1.9 | 8.5 ± 8 | 11 ± 10 | 25 ± 3 | | | | |
| DAS28 | A | 4.9 ± 0.8 | 2.8 ± 0.7 | 2.4 ± 0.7 | 2.6 ± 0.6 | 2.3 ± 0.4 | <0.05 | 0.665 | 0.01 | 0.344 |
| | B | 5.2 ± 0.6 | 3.4 ± 0.9 | 3.4 ± 0.7 | 4 ± 0.8 | 4.8 ± 0.7 | | | | |
| VAS (0-10) | A | 9.3 ± 0.7 | 1.8 ± 1.3 | 0.6 ± 1 | 0.3 ± 0.6 | 0.2 ± 0.4 | <0.05 | 0.851 | 0.001 | 0.602 |
| | B | 9.5 ± 0.5 | 4.7 ± 2 | 4.7 ± 1.8 | 6 ± 1.6 | 7.8 ± 1.6 | | | | |
| HAQ | A | 1.0 ± 0.4 | 0.86 ± 0.4 | 0.8 ± 0.4 | 0.8 ± 0.4 | 0.77 ± 0.5 | 0.016 | 0.04 | 0.035 | 0.33 |
| | B | 1.1 ± 0.5 | 0.9 ± 0.4 | 1 ± 0.6 | 1 ± 0.53 | 1.2 ± 0.5 | | | | |
| RAQoL | A | 12 ± 7 | 8.7 ± 6.5 | 8.16 ± 6 | 7.8 ± 6.2 | 7.59 ± 6 | <0.05 | 0.125 | 0.01 | 0.056 |
| | B | 14 ± 7 | 10 ± 7 | 11 ± 6.7 | 12.7 ± 7 | 14 ± 6.7 | | | | |

RA – rheumatoid arthritis, Gr – group, M – month, ESR – erythrocyte sedimentation rate, CRP – C reactive protein, DAS28 – Disease Activity Score, VAS – Visual analogue scale, RAQoL – Rheumatoid arthritis quality of life questionnaire, HAQ – Health Assessment Questionnaire. Values are presented as mean ± standard deviation. p (time): significance of time effect in repeated measures ANOVA. η^2 (time): effect size for time ($\eta^2 \geq 0.14 =$ large). p (Group × Time): significance of interaction between group and time. η^2 (Group × Time): effect size for interaction. Significant Group × Time interaction indicates that the change over time differed between the two groups.

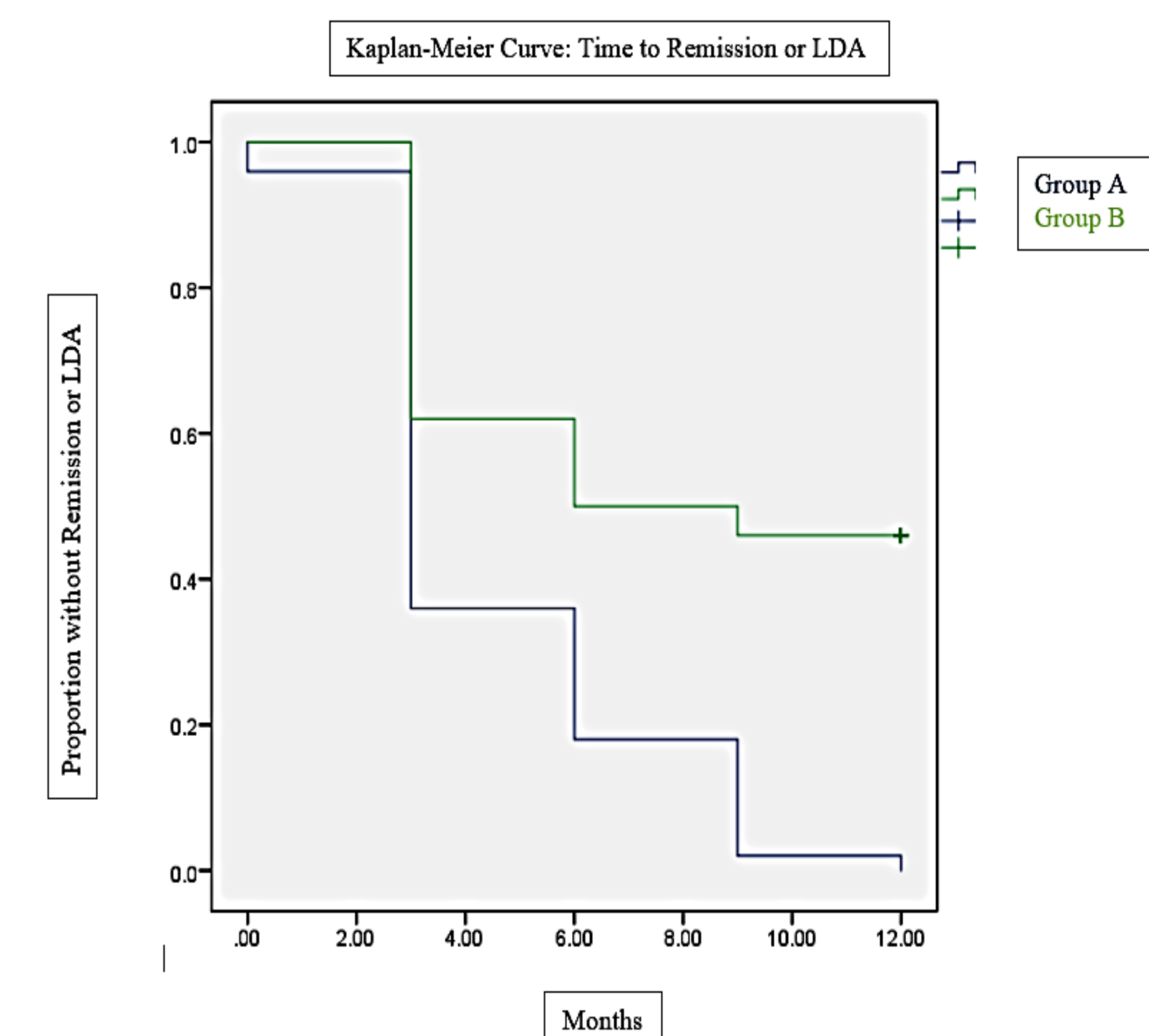


Figure 1. Kaplan-Meier survival curve for time to achieving remission or low disease activity (DAS28 ≤ 3.2) in patients treated with immunobiotics + cDMARDs (Group A) vs. cDMARDs alone (Group B) over 12 months. Survival in this context represents not yet achieving remission/low disease activity.

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