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DYNAMICS OF BLOOD LIPID INDICATORS AND INFLAMMATORY MARKERS DURING BASIC THERAPY WITH ROSUVASTATIN IN EARLY RHEUMATOID ARTHRITIS

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Abstract

Objective: To evaluate blood lipid metabolism disorders, systemic inflammatory markers, and clinical outcomes in patients with early rheumatoid arthritis (RA) receiving basic disease-modifying antirheumatic therapy combined with rosuvastatin over a 12-month follow-up period. Materials and Methods: A prospective, open-label comparative clinical study was conducted enrolling 80 adult patients aged 18–60 years with confirmed early RA (2010 ACR/EULAR classification criteria). Patients were randomized into two parallel groups (n = 40 each). Group I received basic disease-modifying monotherapy with oral leflunomide (20 mg/day). Group II received oral leflunomide (20 mg/day) combined with rosuvastatin (20 mg/day). Clinical disease activity (DAS-28-ESR), pain severity (VAS 0–100 mm), functional disability (HAQ-DI), serum acute-phase reactants (CRP, ESR), immunological markers (RF, anti-CCP), and full lipid profiles—total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)—were assessed at baseline, 6 months, and 12 months. Results: At 6 and 12 months, patients in Group II demonstrated statistically significant reductions in atherogenic lipids and inflammatory biomarkers compared to Group I ($P < 0.001$). In Group II, TC decreased by 24.0% at 6 months and 27.0% at 12 months, TG by 47.0% and 52.0%, and LDL-C by 50.0% and 55.0%, respectively, accompanied by a significant elevation in antiatherogenic HDL-C. Simultaneously, serum CRP declined by 54.0% at 6 months and 69.0% at 12 months in Group II, outperforming leflunomide monotherapy. Greater reductions in ESR, tender/swollen joint counts, morning stiffness, DAS-28-ESR, and HAQ-DI scores were observed in the combined therapy cohort without clinically significant hepatotoxicity or myopathy. Conclusion: Adding rosuvastatin (20 mg/day) to standard leflunomide therapy in patients with early RA effectively corrects atherogenic dyslipidemia, enhances systemic anti-inflammatory control, and accelerates functional recovery, thereby reducing long-term cardiovascular risk.

Keywords: early rheumatoid arthritis, atherosclerosis, basic therapy, leflunomide, rosuvastatin, atherogenic dyslipidemia, inflammatory markers.

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory disorder characterized by persistent synovitis, progressive articular cartilage degradation, juxta-articular bone erosion, and extra-articular systemic manifestations that substantially impair quality of life and shorten life expectancy [1, 2]. Although modern therapeutic paradigms aim to achieve sustained remission or low disease activity through early administration of synthetic and biological disease-modifying antirheumatic drugs (DMARDs), complete drug-free remission is attained in only 20% to 40% of patients [3, 4]. Epidemiologically, RA affects 0.5% to 1.8% of the general adult population (rising up to 5.0% in elderly cohorts), with an annual incidence of 5 to 50 cases per 100,000 individuals and a pronounced female predominance (female-to-male ratio up to 5:1) [2, 5]. Notably, alterations in serum lipid metabolism can be detected even during the earliest clinical stages of RA [1, 6].

Cardiovascular disease (CVD), driven primarily by accelerated atherosclerosis and its thromboembolic complications, represents the leading cause of premature mortality in patients with RA [6, 7]. Extensive immunopathological evidence confirms shared pathogenic mechanisms between rheumatoid synovitis and atherosclerotic plaque progression, as both conditions are governed by chronic immune-mediated vascular inflammation, endothelial dysfunction, and pro-inflammatory cytokine cascades [7, 8]. Active systemic inflammation disrupts lipid homeostasis, elevating atherogenic lipoprotein fractions and increasing the atherogenic index. Conversely, targeted anti-inflammatory therapy not only suppresses articular disease activity but also favorably modulates lipid atherogenicity [4, 8].

Seropositivity for Rheumatoid Factor (RF) and anti-citrullinated protein antibodies (ACPA/anti-CCP), alongside persistently elevated C-reactive protein (CRP), independently predicts accelerated carotid atherosclerosis and adverse cardiovascular outcomes in RA [9, 10]. Key determinants of heightened vascular risk in this population include the clustering of traditional cardiovascular risk factors, potential metabolic side effects of antirheumatic agents, and insufficient implementation of primary cardiovascular prevention strategies in routine rheumatological practice [9, 11]. Furthermore, qualitative and subfractional alterations in modified serum lipoproteins remain underexplored in early autoimmune arthritis [12, 13].

Defining and intervening within the 'window of opportunity' - typically encompassing the first 3 to 12 months from symptom onset—is critical for halting irreversible joint damage and vascular remodeling [5]. Beyond their lipid-lowering properties, HMG-CoA reductase inhibitors (statins) exert pleiotropic anti-inflammatory, immunomodulatory, and endothelial-protective effects. Preclinical studies in collagen-induced arthritis models first demonstrated that simvastatin markedly suppresses synovial inflammation [14]. Subsequently, the landmark randomized placebo-controlled TARA trial established that adjunctive atorvastatin (40 mg/day) significantly reduces CRP levels, erythrocyte sedimentation rate (ESR), and swollen joint counts in RA patients [15]. Accordingly, early screening for dyslipidemia and integration of potent statins such as rosuvastatin into basic DMARD regimens represent a promising dual-target strategy. This study aimed to investigate the dynamics of lipid metabolism indicators and systemic inflammatory activity during combined leflunomide and rosuvastatin therapy in patients with early RA.

Materials and methods

A prospective, open-label comparative clinical study was conducted enrolling 80 adult patients aged 18 to 60 years diagnosed with early rheumatoid arthritis (disease duration ≤ 12 months) in accordance with the 2010 ACR/EULAR classification criteria. Exclusion criteria comprised pre-existing coronary artery disease, prior myocardial infarction or stroke, uncontrolled arterial hypertension, chronic hepatic or renal insufficiency (transaminases > 2× upper limit of normal), baseline statin or fibrate therapy, and pregnancy or lactation.

All patients underwent comprehensive clinical and laboratory evaluations at baseline, 6 months, and 12 months. Clinical assessment included detailed medical history, morning stiffness duration (minutes), 28-joint counts for tenderness (TJC) and swelling (SJC), patient global pain assessment via a 100-mm Visual Analog Scale (VAS), composite disease activity scoring using DAS-28-ESR, and functional disability evaluation via the Health Assessment Questionnaire Disability Index (HAQ-DI).

Fasting venous blood samples were analyzed for complete blood count, ESR (Westergren method), quantitative serum CRP (immunoturbidimetric assay), RF, and anti-CCP antibodies (ELISA). Serum lipid profiles—total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)—were measured enzymatically, and the

atherogenic index (AI = [TC − HDL-C] / HDL-C) was calculated. Hepatic transaminases (ALT, AST) and creatine phosphokinase (CPK) were monitored at baseline and every 3 months to ensure treatment safety.

Patients were randomized into two parallel treatment cohorts (n = 40 per group): Group I (Control / Basic DMARD Monotherapy): Received oral leflunomide at a standard maintenance dose of 20 mg/day as basic disease-modifying therapy. Group II (Combined Therapy): Received oral leflunomide (20 mg/day) combined with oral rosuvastatin (20 mg/day) throughout the 12-month observation period.

Statistical processing was performed using SPSS version 26.0. Data distribution normality was verified using the Shapiro-Wilk test. Continuous variables are presented as mean ± standard deviation (M ± SD) or percentage changes from baseline, while categorical variables are expressed as frequencies and percentages (%). Intra-group longitudinal changes were evaluated using paired Student's t-tests (or Wilcoxon signed-rank tests), and inter-group differences were compared using independent t-tests (or Mann-Whitney U tests). Statistical significance was defined as $P < 0.05$.

Table 1. Baseline demographic and immunological characteristics of the early RA cohort (n = 80)

Clinical / Demographic Parameter	Total Early RA Cohort (n = 80)
Gender: Female / Male, % (ratio)	84.0% / 16.0% (~5:1)
Age range (years)	18–60
Age distribution: 20–30 / 30–40 / 40–50 yrs, %	27.0% / 38.0% / 22.0%
Very early RA duration (≤ 3 months), %	31.0%
Overall seropositivity (RF and/or anti-CCP), %	79.0%
Rheumatoid Factor (RF) positivity (≤ 6 months), %	48.0%
Anti-CCP (ACPA) positivity, %	78.0%

Results and discussion

Demographic analysis confirmed a marked female predominance among the 80 examined patients (84.0% women vs. 16.0% men; ratio ~5:1). Age stratification across both cohorts revealed that early RA predominantly affected working-age adults, with 38.0% aged 30–40 years, 27.0% aged 20–30 years, and 22.0% aged 40–50 years (the remaining 13.0% distributed across the 18–20 and 50–60 age brackets). Immunological profiling demonstrated overall seropositivity in 79.0% of patients; specifically, anti-CCP antibodies were detected in 78.0% of the cohort, while RF positivity was documented in 48.0% of patients with disease duration up to 6 months. Furthermore, 31.0% of seropositive individuals presented within the very early stage of disease (≤ 3 months). Baseline clinical and lipid parameters showed no statistically significant differences between Group I and Group II ($P > 0.05$).

Longitudinal evaluation demonstrated that incorporating rosuvastatin (20 mg/day) alongside basic leflunomide therapy (Group II) yielded substantial, statistically significant improvements in serum lipid profiles compared to leflunomide monotherapy (Group I) at both 6 and 12 months ($P < 0.001$). Specifically, in Group II, total cholesterol (TC) levels decreased by 24.0% at 6 months and by 27.0% at 12 months relative to baseline. Atherogenic lipoprotein fractions exhibited even more pronounced reductions: triglycerides (TG) fell by 47.0% at 6 months and 52.0% at 12 months, while

low-density lipoprotein cholesterol (LDL-C) decreased by 50.0% at 6 months and 55.0% at 12 months ($P < 0.001$). Concurrently, antiatherogenic high-density lipoprotein cholesterol (HDL-C) concentrations rose significantly at both 6 and 12 months, markedly lowering the atherogenic index and mitigating long-term cardiovascular risk.

Importantly, lipid-lowering therapy exerted a synergistic anti-inflammatory effect. In Group II, serum C-reactive protein (CRP) levels declined by 54.0% after 6 months and by 69.0% after 12 months of combined treatment ($P < 0.001$), significantly surpassing the reductions observed in Group I. Parallel decreases in ESR were documented in the rosuvastatin-treated cohort. These findings align with experimental and clinical literature demonstrating that statins attenuate pro-inflammatory cytokine expression (such as TNF-α, IL-6, and IL-1β), inhibit endothelial adhesion molecules, and suppress synovial vascular proliferation [13–15].

Clinically, while both treatment regimens improved articular status over 12 months, patients in Group II achieved superior reductions in tender and swollen joint counts, VAS pain scores, and morning stiffness duration. Functional assessment via the HAQ-DI confirmed that patients receiving combined leflunomide and rosuvastatin therapy experienced significantly greater ease in performing daily physical activities and self-care tasks compared to those receiving leflunomide alone ($P < 0.001$). Both regimens demonstrated favorable safety profiles; routine biochemical monitoring revealed no clinically relevant elevations in hepatic transaminases (> 3× ULN) or CPK, and no cases of statin-induced myopathy were observed.

Table 2. Percentage reduction in atherogenic lipid parameters and C-reactive protein in Group II (Leflunomide + Rosuvastatin, n = 40) compared to baseline

Biochemical / Inflammatory Parameter	6 Months (% Change vs. Baseline)	12 Months (% Change vs. Baseline)	Statistical Significance (vs. Group I)
Total Cholesterol (TC)	−24.0%	−27.0%	P < 0.001
Triglycerides (TG)	−47.0%	−52.0%	P < 0.001
Low-Density Lipoproteins (LDL-C)	−50.0%	−55.0%	P < 0.001
High-Density Lipoproteins (HDL-C)	Significant increase	Significant increase	P < 0.001
C-Reactive Protein (CRP)	−54.0%	−69.0%	P < 0.001

Conclusion

Patients with early rheumatoid arthritis exhibit pronounced atherogenic lipid disturbances alongside systemic immune-mediated inflammation from disease onset. Integrating rosuvastatin (20 mg/day) into basic leflunomide (20 mg/day) therapy effectively normalizes total cholesterol, triglycerides, and LDL-C levels while increasing protective HDL-C over 6 to 12 months. Beyond lipid correction, rosuvastatin amplifies the suppression of systemic acute-phase reactants (CRP and ESR), reduces articular inflammation, and accelerates functional rehabilitation (HAQ-DI), providing an effective dual strategy for controlling RA activity and preventing premature cardiovascular complications.

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