ORIGINAL ARTICLE

Comparative Evaluation of Pitavastatin and Lovastatin on the Incidence and Progression of Rheumatoid Arthritis in Type II Collagen-induced Rat Model

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disorder marked by persistent joint inflammation, cartilage degradation and disability. Statins commonly prescribed for hyperlipidemia have demonstrated potential immunomodulatory activity; however, their role in RA pathogenesis remains uncertain. **Objective:** The present study examined the impact of pitavastatin and lovastatin on RA onset and progression using type II collagen-induced arthritis (CIA) experimental model. **Methods:** CIA was induced in rats, which then received pitavastatin or lovastatin for a period of 42 days. Clinical evaluation included measurement of paw volume, monitoring of body weight and calculation of the arthritic index at regular intervals. On day 42, retro orbital blood samples were collected to determine rheumatoid factor (RF), white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and red blood cell (RBC) count. **Results:** Significant decline in body weight was observed in lovastatin-treated animals from day 35 post-immunization compared with other groups. Both statin-treated groups demonstrated increased paw swelling and higher arthritic index values relative to controls. Hematological findings indicated elevated RF, WBC count, ESR and CRP levels, accompanied by a reduction in RBC count in all statin treated animals. These changes were more marked with lovastatin, which appeared to accelerate arthritis progression and symptom manifestation compared with pitavastatin. **Conclusion:** Statin administration, particularly with lovastatin, may predispose to RA development and intensify disease severity. These results underscore the importance of cautious statin use in individuals at risk of autoimmune joint disorders.

Key words: Arthritic index, autoimmunity, hematology, inflammation, statins

INTRODUCTION

Rheumatoid arthritis (RA) is a protracted inflammatory process primarily characterized by persistent synovitis and the presence of autoantibodies. While it predominantly affects the joints, RA also impacts muscles, tendons, connective tissues, and other fibrous structures, often leading to joint immobility and significant functional impairment.[1] As an immune-mediated inflammatory disease, its progression is driven by dysregulated immune responses and inflammatory pathway.[2] Globally, RA affects approximately 1–2% of the population, with its onset being unpredictable. Although RA can develop at any age, its incidence increases with advancing age, peaking during the seventh decade of

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life.[3] Women are disproportionately affected, with a female-to-male prevalence ratio of approximately 3:1 overall and a striking ratio of 6:1 in women aged 15–45 years. However, this gender disparity diminishes in younger children (<10 years) and the elderly (>60 years).[4]

The clinical manifestation of RA typically progresses through distinct stages. Early symptoms include joint pain and swelling, most commonly in the ankles, accompanied by inflammation of the synovial membrane, causing redness, swelling, and warmth in the affected joints.[5] Over time, synovial cell hyperplasia leads to the formation of pannus, a pathological tissue that secretes enzymes that degrade cartilage and bone.[6] This results in joint deformities, misalignment, pain, and restricted mobility.[7]

Statins, or HMG-CoA reductase inhibitors, are widely prescribed for their lipid-lowering effects and their ability to reduce cardiovascular morbidity and mortality, particularly in individuals with type II diabetes, hyperlipidemia, or hypertension.[8] Beyond their lipid-lowering properties, emerging evidence suggests that statins possess immunomodulatory effects, raising interest in their potential application in autoimmune conditions like RA.[9] However, concerns have been raised about the possibility of statins accelerating RA onset in genetically predisposed individuals by influencing immune pathways. These immunomodulatory effects may inadvertently trigger or amplify autoimmune responses, potentially heightening the risk of RA development.[10]

A widely used experimental model to study the pathophysiology of RA is collagen-induced arthritis (CIA), which closely replicates the immune mechanisms underlying human RA. This model involves the immunization of genetically susceptible rats with collagen type II (CII) emulsified in an adjuvant, eliciting an immune response that leads to severe erosive arthritis.[11] In the CIA model, the interplay between innate and adaptive immune systems drives the production of pro-inflammatory cytokines, activating osteoclasts, fibroblasts, and macrophages, ultimately resulting in progressive joint damage.[12]

The present study explores the possible role of statins in modulating the development and progression of RA, focusing on their dual effects on lipid metabolism and immune regulation. Using the CIA rat model, this research evaluates the effects of two statins, lovastatin and pitavastatin. Following the initial immunization with CII emulsified in Freund's incomplete adjuvant, the animals were challenged with CII 3 weeks later.[13] Disease progression and severity were monitored through arthritic symptom scoring over the study period. This study aims to explain the potential influence of statins on RA pathogenesis, providing insights into their role in modulating autoimmune disease pathways.[14]

MATERIALS AND METHODS

Animal selection and maintenance

Female albino Wistar rats (8–10 weeks old, 150–200 g) were obtained from the Small Animals Breeding Station, Mannuthy, Kerala. After a 2-week acclimatization under controlled conditions (12-h light/dark cycle, 25 ± 2°C, 35–60% humidity), they had unrestricted access to standard feed and water. The study followed IAEC guidelines (IAEC/M.Pharm/DPS/2018-09).

Experimental design and grouping

The rats were divided into six groups (n = 6/group) and subjected to an overnight fast before the commencement of the study. Arthritis was induced in all groups, except the normal control group (Group I), on day 0 by administering a sub-plantar injection of 100 µL of bovine type II collagen (CII) emulsified in Freund's incomplete adjuvant into the left hind paw. On day 21, an additional intraperitoneal injection of CII was administered to all groups except Group I. Group I served as the normal control and received phosphate-buffered saline (PBS) throughout the study. Group II served as the arthritic control and did not receive any treatment.

Groups III and V were pre-treated with pitavastatin (2 mg/kg) and lovastatin (10 mg/kg), respectively, for 28 days before arthritis induction. Groups IV and VI were post-treated with pitavastatin (2 mg/kg) and lovastatin (10 mg/kg), respectively, from day 21 to day 42. PBS (0.2 mL) was used as the vehicle for the statin-naive group. All treatments were administered intraperitoneally.[15,16]

Parameters measured

Body weight

The animals were challenged on day 21 after being immunized on day 0 and monitored until the study endpoint on day 42. Body weight was captured 3 times/week and specifically measured on days 21, 23, 26, 28, 30, 33, 35, 37, and 41.[17]

Arthritic index

The arthritis index was assessed by visually monitoring the severity of inflammation in the left hind paw, focusing on edema and redness. Arthritis scores were recorded on the same days as body weight measurements to evaluate the progression of arthritic symptoms.[18]

Assessment of paw swelling and inflammation

Paw volume was measured on days 21 and 41 using a plethysmometer to evaluate swelling and inflammation in the injured paw. This method provided a quantitative assessment of the inflammatory response and progression of arthritis.[19]

Hematological parameters

On day 42, hematological parameters, including rheumatoid factor (RF), white blood cell (WBC), red blood cell (RBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) values, were evaluated using standard laboratory procedures.[20]

Statistical analysis

Data were analyzed using one-way analysis of variance followed by Tukey's *post hoc* test for multiple comparisons. Statistical analysis was performed using GraphPad Prism software (version 8.00). Results were expressed as mean ± SEM (n = 6/group). Statistical significance was considered at thresholds of $P < 0.05$, $P < 0.01$, and $P < 0.001$.

RESULTS

Assessment of body weight

Body weight was assessed on days 21, 23, 26, 30, 33, 35, 37, and 41. After inducing CIA, a reduction in body weight was evident, with a significant decrease observed in the lovastatin pre-treatment group compared to the CIA control group from day 35 onward ($P < 0.01$). However, the groups treated with pitavastatin, either before or after CIA induction, and the lovastatin post-treatment group did not show significant changes in body weight throughout the study. Between days 21 and 33, no notable differences in body weight were found across any groups [Table 1].

On day 35, the arthritic control group had a significantly higher body weight (167.6 ± 0.6634 g) than the lovastatin pre-treatment group (147 ± 0.8944 g) ($P < 0.001$). Similar trends were observed on day 37 (166.3 ± 0.6634 g vs. 145.7 ± 1.647 g) and day 41 (164.8 ± 0.7491 g vs. 146.8 ± 1.400 g) ($P < 0.001$). No significant body weight changes occurred in other statin-treated groups [Figure 1].

Evaluation of arthritic index

The arthritic index was assessed on days 21, 23, 26, 28, 30, 33, 35, 37, and 41. Both lovastatin and pitavastatin resulted in 100% arthritis incidence by the time of euthanasia, regardless of whether they were administered before or after the induction of CIA, similar to the arthritic control group. Except for pitavastatin pre-treatment, the arthritic index significantly increased in all treatment groups starting from day 33 ($P < 0.05$). Lovastatin led to a faster onset and higher arthritic scores compared to pitavastatin, particularly when administered after CIA induction. Notably, pitavastatin pre-treatment significantly reduced the arthritic index compared to the other statin-treated groups ($P < 0.001$), with this effect becoming apparent as early as day 33 [Table 2].

Evaluation of paw volume

Paw volume measurements on days 21 and 41 revealed significant differences across the study groups. The

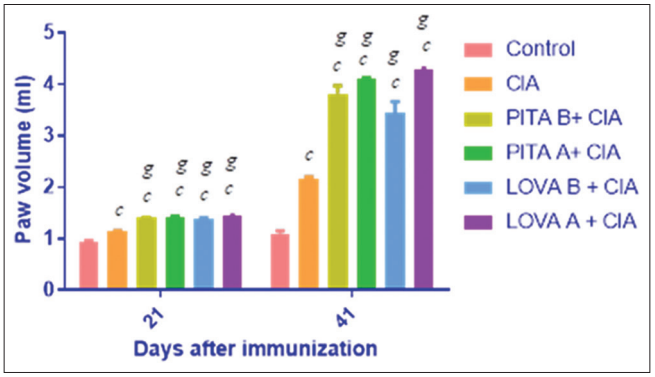

Figure 1: Pitavastatin and lovastatin's effects on the paw volume of a rat model of collagen-induced arthritis (CIA). Values are expressed as mean ± standard error of the mean (n = 6). Data were analyzed by one-way analysis of variance followed by multiple comparison Tukey's *post hoc* test. Test level significance: $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$ when compared with normal, $^{e}P < 0.05$, $^{f}P < 0.01$, $^{g}P < 0.001$ when compared with CIA, $^{p}P < 0.05$, $^{q}P < 0.01$, $^{r}P < 0.001$ when compared with lovastatin before CIA induction

Table 1: Effect of pitavastatin and lovastatin on body weight of collagen induced model

	Body weight (g)					
Days	**Normal control**	**CIA**	**PITAB+CIA**	**PITA A+CIA**	**LOVA B+CIA**	**LOVA A+CIA**
21	183±1.033	175.6±1.04	173.3±0.881	174.5±0.763	171.5±0.9220	173.3±1.065
23	184.8±0.792	174.3±1.08^{c}	173.1±0.93^{c}	173.3±0.881^{c}	171.3±0.843^{c}	172.6±1.174^{c}
26	186.6±0.494	172.8±0.945^{c}	171±1.033^{c}	171.6±0.843^{c}	168.8±0.792^{c}	170.5±1.232^{c}
28	187.3±0.665	171.3±0.792^{c}	170.1±0.980^{c}	170.6±0.802^{c}	168±0.574^{c}	171.3±1.116^{c}
30	188.5±0.619	170.5±0.670^{c}	168.8±1.071^{c}	169.3±0.802^{c}	166.6±0.574^{c}	168.3±1.116^{c}
33	190±0.774	169.3±0.614^{c}	167±1.095^{cr}	167.6±1.089^{cr}	164.6±1.302^{cg}	166.6±0.76^{cr}
35	191±0.7303	167.6±0.667^{c}	165±1.095^{cr}	165.8±1.046^{cr}	147±0.894^{cg}	165.3±0.71^{cr}
37	192.3±0.820	166.3±0.66^{c}	162.8±1.10^{cr}	163.5±0.922^{cr}	145.7±1.64^{cg}	162.8±0.70 ^{cr}
41	193.8±0.542	164.8±0.74^{c}	162±1.39^{cr}	161.8±0.980^{cr}	146.8±1.400^{cg}	161.5±0.56^{cr}

arthritic control group exhibited a significantly higher paw volume compared to the normal control group ($P < 0.001$), confirming the progression of inflammation and edema. Statin administration further exacerbated paw edema, as reflected by significant increases in paw volume ($P < 0.001$) on both days 21 and 41 in the groups treated with pitavastatin (2 mg/kg) and lovastatin (10 mg/kg) compared to the arthritic control group. Among the statin-treated groups, lovastatin administration after CIA induction caused the most pronounced edema, with paw volumes of 1.45 ± 0.0057 on day 21 and 4.29 ± 0.0249 on day 41, exceeding the effects observed in the pitavastatin-treated groups. These results indicate that lovastatin significantly exacerbates paw edema compared to pitavastatin under the experimental conditions [Figure 1].

Hematological profile

Significant alterations in hematological parameters were observed in the test groups compared to both the arthritic control and normal control groups. The arthritic control group showed a reduced RBC count (6.05 ± 0.128 × 10^6 cells/mm^3) and an elevated WBC count (10.4 ± 0.254 × 10^3 cells/mm^3) in comparison to the normal control group (RBC: 7.66 ± 0.091 × 10^6 cells/mm^3; WBC: 8.26 ± 0.047 × 10^3 cells/mm^3). The test groups treated with pitavastatin and lovastatin, both pre- and post-CIA induction, exhibited a significant reduction in RBC counts ($P < 0.001$), ranging from 3.32 ± 0.044 to 4.68 ± 0.128 × 10^6 cells/mm^3. Conversely, all test groups showed a marked increase in WBC counts compared to the arthritic control group ($P < 0.001$), indicating immunomodulatory effects. ESR was significantly elevated in all test groups relative to the arthritic control group ($P < 0.001$). Before CIA induction, ESR values for pitavastatin and lovastatin were recorded as 12.28 ± 0.135 mm/h, which increased to 17.3 ± 0.194 mm/h and 16.3 ± 0.207 mm/h, respectively, following induction. In addition, the test groups exhibited significantly increased levels of CRP and RF ($P < 0.001$), further confirming the pro-inflammatory changes induced by CIA and the effects of the test medications [Table 3].

DISCUSSION

The CIA model in rats mimics human RA, featuring bone loss, cartilage erosion, and joint inflammation.[21] By day 35 post-immunization, CIA induction led to significant body weight loss compared to controls. Lovastatin pre-treatment worsened this weight loss, exceeding that of the CIA control group. Notably, 100% of rats treated with either pitavastatin or lovastatin (pre- or post-induction) developed arthritis by

Table 2 : Evaluation of arthritic index in collagen induced arthritic rat model.

	Arthritic index				
Days	**CIA**	**PITAB+CIA**	**PITAA+CIA**	**LOVAB+CIA**	**LOVAA+CIA**
21	0.0	0.0	0.0	0.0	0.0
23	5.3±0.667	6.6±0.980	7.3±0.987	7±1.125	7.1±0.5578
26	5.3±0.741	6.3±0.909	7.3±0.930	7.66±0.7149	8.6±0.9804
28	7.6±0.650	8.3±0.909	9.2±0.930	9.16±0.7149	10.6±0.9804
30	8.2±0.919	9.6±0.792	10.4±0.609	9.83±0.5426	10.5±0.9804
33	9.3±1.308	10.6±1.23	11.3±0.7491^{ag}	10.5±0.8819^{ag}	12.6±0.4216^{bg}
35	10±0.442	10.4±1.358	12±0.4216^{cf}	11.6±0.4773^{bf}	12.5±0.333 ^{cg}
37	11.4±1.15	11.2±1.193	12.2±0.361^{bf}	11.5±0.493^{af}	13.6±0.3416^{cg}
41	12.6±1.17	11.9±0.447	12.7±0.4216^{cg}	12±0.4773^{bg}	13.3±0.1667^{cg}

Table 3: Effect of pitavastatin and lovastatin on hematological parameters in collagen-induced arthritic rat model

Parameters	Control	CIA	Lovastatin before CIA induction	Lovastatin after CIA induction	Pitavastatin before CIA induction	Pitavastatin after CIA induction
RBC	7.66±0.091	6.05±0.128^{c}	4.10±0.044^{cg}	3.23±0.557^{cgr}	4.68±0.107^{cgqu}	3.68±0.124^{cgu}
WBC	8.26±0.047	10.4±0.254^{cg}	13.1±0.252^{cg}	15.9±0.076 ^{car}	13.1±0.271^{cgu}	15.5±0.160^{cg}
ESR	7.66±0.421	10.1±0.088^{cg}	12.2±0.13^{cg}	17.3±0.194^{cgr}	12.2±0.135^{cg}	16.3±0.203^{cgru}
C-RP	1.23±0.042	6.93±0.154^{cg}	9.73±0.049^{cg}	12.2±0.252^{cgr}	8.95±0.166^{cgpu}	11.9±0.221^{cgr}
RF	6.33±0.332	9.11±0.244^{cg}	13.0±0.110^{cg}	15.7±0.12^{cgr}	12.2±0.172^{cgu}	15±0.2540^{cgr}

CIA: Collagen-induced arthritis, RBC: Red blood cell, WBC: White blood cell, ESR: Erythrocyte sedimentation rate, C-RP: C-reactive protein, RF: Rheumatoid factor. Values were expressed as mean± standard error of the mean (n=6). Data were analyzed by one-way analysis of variance followed by multiple comparison Tukey's *post hoc* test. $^{a}P<0.05$, $^{b}P<0.01$, $^{c}P<0.001$ when compared with normal; $^{e}P<0.05$, $^{f}P<0.01$, $^{g}P<0.001$ when compared with positive control; $^{p}P<0.05$, $^{q}P<0.01$, $^{r}P<0.001$ when compared with lovastatin before CIA induction; $^{s}P<0.05$, $^{t}P<0.01$, $^{u}P<0.001$ when compared with lovastatin after CIA induction

euthanasia. While pitavastatin reduced the arthritic index when given before CIA induction, suggesting potential therapeutic effects, lovastatin post-induction accelerated arthritis onset. Pitavastatin, though, expedited disease progression, increasing the number of affected animals. Paw swelling, a key arthritic marker, was significantly higher in statin-treated groups, likely due to secondary joint lesions. Hematological analysis revealed decreased RBC count, likely from RBC destruction and reduced erythropoietin production, while WBC count rose, indicating immunomodulatory effects. Elevated ESR and RF levels further confirmed systemic inflammation and joint damage. These findings highlight the complex effects of statins in the CIA model.[22,23]

CONCLUSION

The present study utilized the CIA rat model to assess the effects of pitavastatin and lovastatin on type II CIA. The results indicate that the administration of either statin, both before and after CIA induction, accelerated the progression of arthritis. This observation suggests that statin use may lead to immune system dysregulation, potentially contributing to the onset of autoimmunity. Notably, lovastatin exhibited a more pronounced effect in accelerating arthritis development when administered after CIA induction, compared to its pre-induction administration. Furthermore, lovastatin was found to have a stronger overall impact on the disease progression than pitavastatin. These findings highlight the potential risk associated with statin therapy in relation to the development of RA, underscoring the need for further investigation into the immunological consequences of statin use.

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