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COMPARATIVE ASSESSMENT OF THE STATINS AND ANGIOTENSIN-RECEPTOR BLOCKERS FOR THEIR ANTI-INFLAMMATORY EFFECTS ON THE DISEASE ACTIVITY OF RHEUMATOID ARTHRITIS: A CLINICAL STUDY

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ABSTRACT

Background: RA (Rheumatoid Arthritis) is a refractory disease affecting a large population globally. Pathogenesis of rheumatoid arthritis is attributed to an imbalance between anti-inflammatory cytokines and pro-inflammatory cytokines where this cytokine rush is in favour of pro-inflammatory cytokines.

Aims: The present study was conducted to compare and assess an angiotensin-receptor blocker, Candesartan, and atorvastatin for their antioxidant and anti-inflammatory effects in subjects with rheumatoid arthritis.

Methods: The present randomized study included 36 subjects divided into 3 groups of 12 subjects each where Group I subject were treated traditionally with placebo and served as controls, Group II subjects were treated with traditional therapy and candesartan of 8mg/day, and Group III subjects with traditional therapy and atorvastatin of 20mg/day for duration of 3 months. Health Assessment Questionnaire- Disability Index (HAQ-DI) and Disease Activity Score 28 (DAS28) were used to evaluate the study subjects clinically. Also, morning stiffness was assessed for the study subjects before the treatment and 3 months following treatment. Laboratory parameters assessed were malondialdehyde (MDA), interleukin-1beta (IL-1β),

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tumor necrosis factor-alpha (TNF-α), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) for all the study subjects.

Results: The study results showed that both atorvastatin and candesartan showed a significant reduction of patient global assessment, number of swollen joints, and serum levels of acute-phase reactants (CRP and ESR), TNF-α, and IL-1β in the study subjects. These drug therapies also showed improvement in quality of life with HAQ-DI and DAS28 and disease activity. A more significant reduction was seen in oxidative stress marker (MDA) serum levels for the atorvastatin group.

Conclusions: The present study concludes that both atorvastatin and candesartan showed immunomodulatory and anti-inflammatory effects showing improvements in disease activity and clinical status in subjects with rheumatoid arthritis. However, superior results were seen with atorvastatin compared to the candesartan owing to its anti-oxidant effect.

Keywords: Anti-inflammatory, atorvastatin, candesartan, proinflammatory cytokines, anti-inflammatory cytokines, rheumatoid arthritis

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INTRODUCTION

RA (Rheumatoid arthritis) is a systemic, refractory, and chronic inflammatory disease affecting the joints with common association with systemic involvement and chronic inflammation which progressively leads to joint destruction. Pathogenesis of rheumatoid arthritis is attributed to an imbalance between anti-inflammatory cytokines and pro-inflammatory cytokines where this cytokine rush is in favor of pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α) or interleukin-1beta (IL-1β). The potential therapeutics for rheumatoid arthritis aim at maintaining the balance between anti-inflammatory and pro-inflammatory cytokines.[1]

Immune responses and inflammation in autoimmune disorders including rheumatoid arthritis usually had an impact on the renin-angiotensin system. Angiotensin II type 1 receptors (AT1R) are activated by Angiotensin II leading to reactive oxygen species production and activation of nuclear factor Kappa B (NF-kB) which produces various inflammatory cytokines. Angiotensin II type 1 receptors are upregulated in subjects with RA in the synovium, and hence, they may be a novel target in therapeutics and anti-inflammatory benefits can be achieved with ARBs (angiotensin II-receptor blockers).[2]

Statins are the agents used as agents for lowering cholesterol levels and show pleiotropic effects encompassing thrombus formation, plaque stability, and endothelial functions. Statins also work as suppressors of T-cell activation and as immunomodulators decreasing MHC-II (major histocompatibility complex class II) protein expression in macrophages and human endothelial cells by the interferon-γ. Statins also show the anti-inflammatory effect decreasing the production of NO (Nitric Oxide) and regulating leukocyte-endothelial cell adhesion along with the reduction of inflammatory cytokines including IL-6, IL-1, and TNF-α.[3]

Hence, the present study was conducted to compare and assess an angiotensin-receptor blocker, Candesartan, and atorvastatin for their antioxidant and anti-inflammatory effects in subjects with rheumatoid arthritis. These markers included malondialdehyde (MDA),

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erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), IL-1β, and TNF-α. Also, disease activity and clinical status were assessed in subjects with rheumatoid arthritis by assessing the quality of life, morning stiffness, number of tender joints (NTJ), and number of swollen joints (NSJ).

MATERIAL AND METHODS

The present randomized clinical study was conducted to compare and assess an angiotensin-receptor blocker, Candesartan, and atorvastatin for their antioxidant and anti-inflammatory effects in subjects with rheumatoid arthritis.

The study was conducted at Department of Biochemistry, Sri Venkateswara Medical College, Tirupati, Andhra Pradesh. The study population was comprised of the subjects visiting the Outpatient Department of the same Institute with rheumatoid arthritis. The subjects were selected based on the criteria of the American College of Rheumatology/European League Against Rheumatism of 2010 for diagnosing rheumatoid arthritis.

The inclusion criteria for the study were subjects within the age range of 18-66 years, having moderate to high disease activity, and subjects who were willing to participate in the study. The exclusion criteria for the study were subjects with a history of other inflammatory diseases and drugs, corticosteroid therapy, non-biologic drugs, renal diseases, liver impairment, pregnant females, lactating females, and not fulfilling the inclusion criteria. The exclusion criteria for the study were also subjects who received IL-1β and TNF-α as these may affect the serum levels of IL-1β and TNF-α. After explaining the detailed study design, informed consent was taken from all the study subjects.

The study initially assessed and screened 86 subjects with rheumatoid arthritis visiting the Outpatient Department of the Institute. Inclusion criteria were fulfilled by 45 subjects that were divided into three groups of subjects where only 36 subjects completed the study and were finally included in the study. Based on their clinical conditions, these subjects were divided into 3 groups of 13 subjects each where Group I subject were treated traditionally with placebo and served as controls, Group II subjects were treated with traditional therapy and candesartan of 8mg/day, and Group III subjects with traditional therapy and atorvastatin of 20mg/day for duration of 3 months.

After final inclusion, detailed history was taken from all the subjects followed by general examination and collection of the sociodemographic data at baseline before the start of the therapy using a structured questionnaire. All the subjects were recalled at an interval of 1 week to assess the treatment compliance. For assessing the laboratory parameters, venous blood was collected from all the subjects under strict sterile and aseptic conditions at the fasting of 10 hours prior to and following the treatment. For separation of the serum, centrifugation was done for the collected blood and the samples were stored at -80^{o} C till the assessment.

A general physical examination was done to assess the number of swollen and tender joints. A visual analog scale (VAS) was used to assess the pain. Extra-articular manifestations were assessed for all the subjects prior to and following the therapy for rheumatoid arthritis. Disease Activity Score 28 (DAS28)[4] was assessed using patient global assessment (PGA), the number of tenders and swollen joints, and erythrocyte sedimentation rate (ESR). Also, The

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Health Assessment Questionnaire Disability Index (HAQ-DI)[5] used a questionnaire comprising of 20 questions where the response of the study subjects was calculated from zero to three where zero denoted no disability and 3 completely disabled. High disease activity was denoted by the score of >5.1, moderate disease activity by 3.2 and ≤5.1, low by 2.6 to <3.2, and remission with a score of 0 and <2.6.

The laboratory parameters assessed were MDA, IL-1β, and TNF-α using ELISA, CBC (Complete blood count), CRP, rheumatoid factor, lipid profile, serum creatinine, BUN (blood urea nitrogen), AST (aspartate transaminase), and ALT (alanine aminotransferase). The collected data were subjected to the statistical evaluation using SPSS software version 21 (Chicago, IL, USA) for results formulation. The data were expressed in percentage and number. The level of significance was kept at $p<0.05$.

RESULTS

The present randomized clinical study was conducted to compare and assess an angiotensin-receptor blocker, Candesartan, and atorvastatin for their antioxidant and anti-inflammatory effects in subjects with rheumatoid arthritis. 45 subjects were divided into three groups of subjects where only 36 subjects completed the study and were finally included in the study. Based on their clinical conditions, these subjects were divided into 3 groups of 13 subjects each where Group I subject were treated traditionally with placebo and served as controls, Group II subjects were treated with traditional therapy and candesartan of 8mg/day, and Group III subjects with traditional therapy and atorvastatin of 20mg/day for a duration of 3 months. The demographic characteristics of the study subjects are listed in Table 1. The mean age of the study subjects was 49.64±9.55, 54.91±7.31, and 49.04±9.83 years for Group I, II, and III subjects respectively. The disease duration was 6.04±2.61, 5.64±2.87, and 5.84±2.45 years respectively for Group I, II, and III subjects respectively. There were 16.66% (n=2) males and 83.33% (n=10) females in Group I, 8.33% (n=1) male and 91.66% (n=11) females in group II group III. Sulphasalazine was given to 16.66% (n=2), 25% (n=3), and 25% (n=3) subjects of groups I, II, and III respectively. Hydroxychloroquine, Leflunomide, methotrexate, diclofenac, and prednisolone was given to 83.33% (n=10), 75% (n=9), 83.33% (n=10), 91.66% (n=11), and 91.66% (n=11) subjects of Group I, 66.66% (n=8), 83.33% (n=10), 75% (n=9), 91.66% (n=11), and 100% (n=12) subjects respectively from Group II, and in 83.33% (n=10), 66.66% (n=8), 75% (n=9), 91.66% (n=11), and 100% (n=12) subjects respectively from Group III (Table 1).

The study results showed that both atorvastatin and candesartan used in Group II and III were associated with a statistically significant reduction in serum levels of acute-phase reactants as ESR and CRP, TNF-α, and IL-1β after 3 months of therapy as compared to the baseline pre-treatment values. In comparison to the baseline pre-treatment, a significant reduction in MDA and RF levels was seen in subjects taking atorvastatin compared to the subjects taking candesartan were changes in these parameters were non-significant. In the atorvastatin group (Group III), TNF- α levels changed from 169.2±85.3 to 120.4±71.3ng/ml which was significant, IL-1β from 2308.43±1119.2 to 1861.6±873. pg/ml, CRP from 26.4±17.3 to 21.3±13.7mg/l, and ESR from 48.6±19.2 to 39.6±15.2. These parameters were statistically significant in atorvastatin as shown in Table 2. Reduction in the levels of inflammatory

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cytokines IL-1β and TNF- α was associated with a significant reduction in morning stiffness, PGA, and the number of tender joints. This also showed improved quality of life and disease activity based on HAQ-DI and DAS-28 compared to Group I control.

On assessing the Percentage changes in Biochemical, laboratory, and clinical parameters in the study subjects at 3 months, TNF- α was 26.91, -25.45, and -25.33 respectively for Group I, II, and III where Group II and II had statistically significant change. IL-1β was -17.65 for Group II which was statistically significant, MDA, RF, ESR, morning stiffness showed no significant change, HAQ-DI was significant for Group III with -7.27, DAS-28 for Group III with the value of -9.67, and CRP was statistically significant for Group II and III with respective values of -12.31 and -15.26 as summarized in Table 3.

DISCUSSION

The present randomized clinical study was conducted to compare and assess an angiotensin-receptor blocker, Candesartan, and atorvastatin for their antioxidant and anti-inflammatory effects in subjects with rheumatoid arthritis. 45 subjects were divided into three groups of subjects where only 36 subjects completed the study and were finally included in the study. Based on their clinical conditions, these subjects were divided into 3 groups of 13 subjects each where Group I subject were treated traditionally with placebo and served as controls, Group II subjects were treated with traditional therapy and candesartan of 8mg/day, and Group III subjects with traditional therapy and atorvastatin of 20mg/day for a duration of 3 months. The mean age of the study subjects was 49.64±9.55, 54.91±7.31, and 49.04±9.83 years for Group I, II, and III subjects respectively. The disease duration was 6.04±2.61, 5.64±2.87, and 5.84±2.45 years respectively for Group I, II, and III subjects respectively. There were 16.66% (n=2) males and 83.33% (n=10) females in Group I, 8.33% (n=1) male and 91.66% (n=11) females in group II group III. Sulphasalazine was given to 16.66% (n=2), 25% (n=3), and 25% (n=3) subjects of groups I, II, and III respectively. Hydroxychloroquine, Leflunomide, methotrexate, diclofenac, and prednisolone was given to 83.33% (n=10), 75% (n=9), 83.33% (n=10), 91.66% (n=11), and 91.66% (n=11) subjects of Group I, 66.66% (n=8), 83.33% (n=10), 75% (n=9), 91.66% (n=11), and 100% (n=12) subjects respectively from Group II, and in 83.33% (n=10), 66.66% (n=8), 75% (n=9), 91.66% (n=11), and 100% (n=12) subjects respectively from Group III. These sociodemographic characteristics were comparable to the results of Tascilar K et al[6] in 2016 and Li GM et al[7] in 2018 where authors assessed subjects with similar demographic and disease characteristics as in the present study. The study results showed that both atorvastatin and candesartan used in Group II and III were associated with a statistically significant reduction in serum levels of acute-phase reactants as ESR and CRP, TNF-α, and IL-1β after 3 months of therapy as compared to the baseline pre-treatment values. In comparison to the baseline pre-treatment, a significant reduction in MDA and RF levels was seen in subjects taking atorvastatin compared to the subjects taking candesartan were changes in these parameters were non-significant. In the atorvastatin group (Group III), TNF- α levels changed from 169.2±85.3 to 120.4±71.3ng/ml which was significant, IL-1β from 2308.43±1119.2 to 1861.6±873. pg/ml, CRP from 26.4±17.3 to 21.3±13.7mg/l, and ESR from 48.6±19.2 to 39.6±15.2. These parameters were statistically significant in atorvastatin. Reduction in the levels of inflammatory cytokines IL-1β and TNF-

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α was associated with a significant reduction in morning stiffness, PGA, and the number of tender joints. This also showed improved quality of life and disease activity based on HAQ-DI and DAS-28 compared to Group I controls. These results were consistent with the results of the studies by Zhang YY et al[8] in 2013 and Chang Y et al[9] in 2015 where authors showed better results with the use of candesartan and atorvastatin where atorvastatin showed better results compared to candesartan.

Concerning the percentage changes in Biochemical, laboratory, and clinical parameters in the study subjects at 3 months, TNF- α was 26.91, -25.45, and -25.33 respectively for Group I, II, and III where Group II and II had statistically significant change. IL-1β was -17.65 for Group II which was statistically significant, MDA, RF, ESR, morning stiffness showed no significant change, HAQ-DI was significant for Group III with -7.27, DAS-28 for Group III with the value of -9.67, and CRP was statistically significant for Group II and III with respective values of -12.31 and -15.26. These results were in agreement with the studies of Banfi C et al[10] in 2017 and Arvikar Sl et al[11] in 2017 where authors reported comparable percentage changes in Biochemical, laboratory, and clinical parameters following treatment of rheumatoid arthritis.

CONCLUSION

Within its limitations, the present study concludes that both atorvastatin and candesartan showed immunomodulatory and anti-inflammatory effects showing improvements in disease activity and clinical status in subjects with rheumatoid arthritis. However, superior results were seen with atorvastatin compared to the candesartan owing to its anti-oxidant effect. However, the present study had a few limitations including a smaller sample size, geographical area biases, recall bias, and single-institution nature. Hence, more longitudinal and prospective studies with larger sample sizes, and longer monitoring periods are needed to reach a definitive conclusion.

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TABLES

Characteristics	Group I (n=12)	Group II (n=12)	Group III (n=12)
Mean age (years)	49.64±9.55	54.91±7.31	49.04±9.83
Gender n (%)			
Males	2 (16.66)	1 (8.33)	1 (8.33)
Females	10 (83.33)	11 (91.66)	11 (91.66)
Disease duration (years)	6.04±2.61	5.64±2.87	5.84±2.45
Treatment given			
Sulphasalazine	2 (16.66)	3 (25)	3 (25)
Hydroxychloroquine	10 (83.33)	8 (66.66)	10 (83.33)
Leflunomide	9 (75)	10 (83.33)	8 (66.66)
Methotrexate	10 (83.33)	9 (75)	9 (75)
Diclofenac	11 (91.66)	11 (91.66)	11 (91.66)
Prednisolone	11 (91.66)	12 (100)	12 (100)

Table 1: Demographic and Treatment characteristics of the study subjects

Parameter	Group I		Group II		Group III		p-value	
	Baseline	3 months	Baseline	3 months	Baseline	3 months	Baseline	3 months
TNF-α (ng/ml)	120.3± 54.2	140.5± 61.4	168.6± 139.7	113.4± 97.5	169.2± 85.3	120.4±71.3	NS	NS
IL-1β	2147.5±	2366.6±	2695.4±	2033.4±	2308.43±	1861.6±873.6	NS	NS

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(pg/ml)	591.4	544.4	1872.2	1163.4	1119.2			
MDA (nmol/ml)	22.6± 11.5	21.5± 13.7	17.2± 23.2	12.5± 17.2	20.5±15.6	12.7±10.7	NS	NS
HAQ-DI	1.15± 0.12	1.18± 0.12	1.43± 0.22	1.34± 0.15	1.30± 0.14	1.20±0.13	<0.01	<0.01
DAS-28	4.69± 0.54	4.81± 0.54	5.52± 1.17	4.93± 0.73	4.95± 0.94	4.44±0.77	NS	NS
CRP (mg/l)	26.1± 25.5	28.3± 26.3	46.4± 29.1	39.7± 26.0	26.4± 17.3	21.3±13.7	<0.05	NS
ESR (mm/h)	55.6± 15.6	56.2± 19.4	49.6± 31.2	40.1± 20.2	48.6± 19.2	39.6±15.2	NS	<0.05
RF (IU/ml)	53.5± 33.3	51.0± 33.2	71.2± 77.3	62.7± 64.4	51.2± 32.4	42.7±24.7	NS	NS
Morning stiffness (min)	41.4± 16.2	36.5± 16.7	65.1± 17.4	51.2± 15.6	53.2± 18.4	42.2±11.4	<0.001	<0.05
TGs (mg/dl)	111.6± 13.7	109.5± 17.4	103.3± 13.6	105.2± 14.3	134.4± 22.1	105.4±18.2	<0.01	NS
LDL (mg/dl)	90.7± 16.3	89.2± 13.3	86.6± 13.3	85.3± 10.3	98.2± 21.7	74.2±12.4	NS	<0.01
HDL (mg/dl)	49.2± 9.7	52.4± 10.2	59.4± 14.6	60.4± 13.3	50.4± 8.7	64.4±11.6	<0.05	<0.05
TC (mg/dl)	182.7± 12.3	177.2± 19.5	173.6± 16.5	173.6± 19.3	194.6± 16.7	133.2±15.2	<0.01	<0.01
Diastolic BP (mmHg)	72.02± 9.04	72.64± 9.44	92.31± 2.56	79.02± 6.01	75.31± 8.53	73.64±9.51	<0.01	NS
Systolic BP (mmHg)	122.1± 19.2	123.2± 17.2	157.4± 7.2	133.1± 7.7	125.1± 16.1	125.1±15.4	<0.01	NS

Table 2: Biochemical, laboratory, and clinical parameters in the study subjects before and following treatment

Percentage variable changes	Group I (n=12)	Group II (n=12)	Group III (n=12)
TNF-α (ng/ml)	26.91	**-25.45**	**-25.33**
IL-1β (pg/ml)	15.72	**-17.65**	-12.50
MDA (nmol/ml)	6.84	17.74	-12.97
HAQ-DI	3.87	-4.75	**-7.27**
DAS-28	3.02	-7.65	**-9.67**
RF (IU/ml)	-4.665	-7.661	-9.597
CRP (mg/l)	10.13	**-12.31**	**-15.26**
ESR (mm/h)	1.21	-11.97	-15.51

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Morning stiffness (min)	5.53	-19.02	-15.53

Table 3: Percentage changes in Biochemical, laboratory, and clinical parameters in the study subjects at 3 months