Indian J Med Res 152, October 2020, pp 393-400
DOI: 10.4103/ijmr.IJMR_640_19

Quick Response Code:

A comparative study on the anti-inflammatory effect of angiotensin-receptor blockers & statins on rheumatoid arthritis disease activity

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Received April 8, 2019

***Background & objectives*: Rheumatoid artherits (RA) is a refractory disease and the imbalance between pro- and anti-inflammatory cytokines in favor of pro-inflammatory cytokines has been implicated in pathogenesis of RA. In this context, the aim of the present study was to compare the anti-inflammatory and antioxidant effects of candesartan, an angiotensin-receptor blocker, and atorvastatin in RA patients.**

***Methods*: In this single-blinded parallel randomized placebo controlled study, the patients recruited between December 2017 and May 2018 were categorized into three groups: group 1 included 15 RA patients who served as control group and received traditional therapy (+ placebo); group 2 included 15 RA patients who received traditional therapy + candesartan (8 mg/day); and group 3 included 15 patients who received traditional therapy + atorvastatin (20 mg/day) for three months. Clinical status in RA patients was evaluated by Disease Activity Score 28 (DAS28), Health Assessment Questionnaire-Disability Index (HAQ-DI) and morning stiffness before and three months after treatment. All groups were subjected to biochemical analysis of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), tumour necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β) and malondialdehyde (MDA) before and three months after treatment.**

***Results*: Both candesartan and atorvastatin treated groups showed significant decrease in serum levels IL-1β and TNF-α, acute-phase reactants (CRP and ESR), number of swollen joint and patient global assessment. This was also associated with improvement in disease activity and quality of life regarding DAS28 and HAQ-DI as compared to baseline data and the control group. Atorvastatin group showed significant decrease in the serum level of oxidative stress marker (MDA).**

***Interpretation & conclusions*: Both candesartan and atorvastatin showed anti-inflammatory effect and immunomodulatory effects leading to improvement in clinical status and disease activity in RA patients. However, atorvastatin was superior to candesartan through its anti-oxidant effect.**

Key words Anti-inflammatory - atorvastatin - candesartan - inflammatory cytokines - MDA - rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, inflammatory, systemic autoimmune disease affecting mostly the joints but often with systemic involvement, characterized by chronic inflammation and the

progressive destruction of joints[1]. An imbalance between pro-inflammatory and anti-inflammatory cytokines in favour of the pro-inflammatory cytokines [interleukin-1beta (IL-1β) or tumour necrosis factor-alpha (TNF-α)] has been implicated in the pathogenesis of RA[2]. The balance between pro- and anti-inflammatory cytokines is a potential therapeutic target in RA. Renin-angiotensin system is known to be involved in inflammation and immune responses of autoimmune disorders, including RA[3]. Angiotensin II activates angiotensin II type 1 receptors (AT1R), resulting in the production of reactive oxygen species and nuclear factor Kappa B (NF-kB) activation leading to the production of various inflammatory cytokines[4,5]. AT1Rs are upregulated in the rheumatoid synovium and thus may be a novel therapeutic target and angiotensin II-receptor blockers (ARBs) may provide anti-inflammatory benefits[6].

Statins are widely used as cholesterol-lowering agents and also have pleiotropic effects[7,8], which encompass modification of endothelial function, plaque stability and thrombus formation. Statins act as immunomodulators and suppress T-cell activation, and decrease inducible major histocompatibility complex-class II (MHC-II) protein expression by interferon-γ on human endothelial cells and macrophages[9]. Statins also have anti-inflammatory properties that regulate leucocyte-endothelial cell adhesion, reduce nitric oxide (NO) production and decrease levels of inflammatory cytokines such as TNF-α, IL-1 and IL-6[10]. Therefore, the present study was aimed to compare the anti-inflammatory effect of candesartan and atorvastatin in RA patients, through evaluating their impact on inflammatory and oxidative stress markers including TNF-α, IL-1β, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and malondialdehyde (MDA). Furthermore, the clinical status and disease activity of RA patients were also assessed by including the number of swollen joints (NSJ), number of tender joints (NTJ) and morning stiffness with subsequent effect on the quality of life.

Material & Methods

All patients attended at the outpatient clinics of the Internal Medicine department (Rheumatology and Immunology Unit) and Physical Medicine, Rheumatology and Rehabilitation department in Menofia University Hospital, Menofia, Egypt, during December 2017 and May 2018, were enrolled in this study. The selection of patients was based on an American College of Rheumatology/European League Against Rheumatism criteria 2010 for diagnosis of RA[11].

Inclusion criteria included patients with moderate-to-high disease activity and their ages ranging from 18 to 65 yr. All patients received non-biological drugs, corticosteroids and non-steroidal anti-inflammatory drugs. Pregnant and lactating females, patients with liver, renal impairment or any other inflammatory diseases were excluded. The patients treated with TNF-α or IL-1β antagonists were also excluded from the study to exclude the effect of these treatments on serum levels of TNF-α and IL-1β.

The study protocol was approved by the Tanta University Research Ethical Committee, Tanta, Egypt, prior to enrolment of the patients and all participants gave their written informed consent (Clinical Trials. gov Identifier: NCT03770702).

Study design: The study design was single blind parallel randomized placebo controlled study to compare anti-inflammatory effects of candesartan and atorvastatin in RA patients. Ninety five RA patients were randomly selected using sealed envelopes method from a total of 200 patients who attended the hospital. Fifty nine of the eligible patients fulfilled the inclusion criteria and sub-classified into three parallel groups according to their associated medical condition. Out of the 59 eligible patients, only 45 patients completed the study. Fourteen patients did not receive treatment and were excluded from the analysis (Figure). Group 1 served as control group and patients received traditional therapy + placebo (n=15), group 2 patients received traditional therapy + candesartan, 8 mg/day (n=15). Group 3 patients received traditional therapy + atorvastatin, 20 mg/day (n=15) for three months. Medical history of the patients was taken, and demographic data were collected at baseline through a questionnaire. All patients were followed up weekly to ensure compliance to the treatment. Venous blood (5 ml) was drawn from each patient (after 10-12 h fasting) between 9 and 11 h before and after the treatment course; serum was separated after centrifugation, coded and stored at −80°C until analysis.

Methods

Physical and clinical examination: All patients were subjected to clinical examination to determine the number of tender and swollen joints. Pain of the joints was evaluated on the basis of the visual analogue

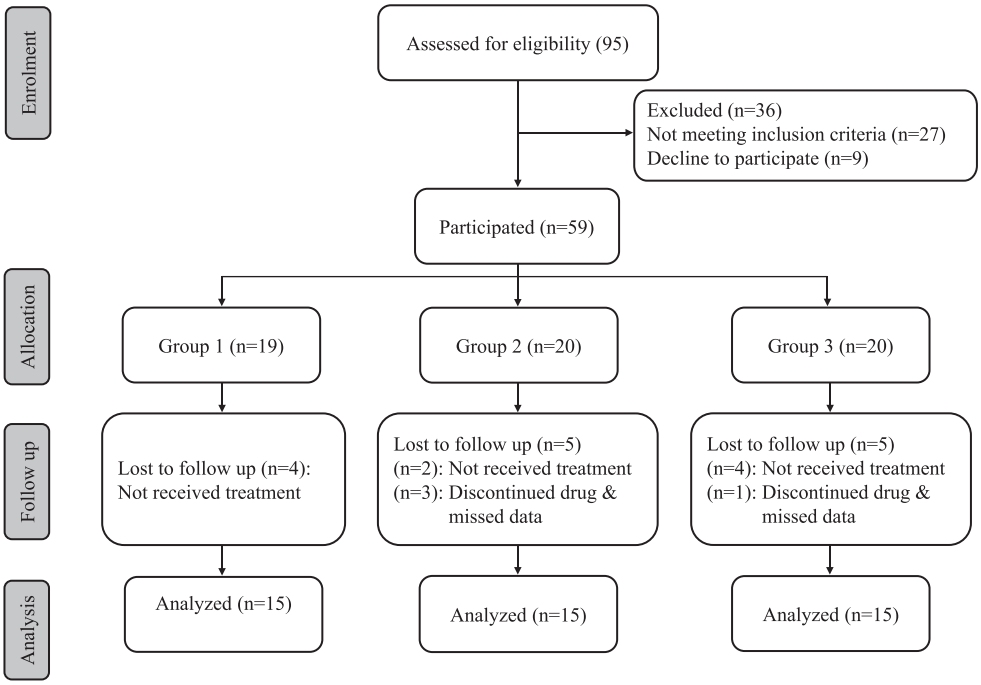

Figure. Flowchart showing study design.

scale. All patients were examined for extra-articular manifestation before and after treatment. The Health Assessment Questionnaire Disability Index (HAQ-DI)[12], was calculated using questionnaire (20 questions), and the patient's responses made on a scale from zero (no disability) to three (completely disabled). Disease Activity Score 28 (DAS28)[13], was calculated using the erythrocyte sedimentation rate (ESR), number of tender and swollen joints and patient global assessment (PGA). Remission was considered achieved if the DAS score was between 0 and <2.6. Low activity corresponded to 2.6 to <3.2. Moderate activity was between 3.2 and ≤5.1, while high activity was strictly >5.1.

Laboratory investigation and biochemical tests: TNF-α, IL-1β and MDA were assayed by ELISA kits (Shanghai Sunred Biological Technology Co., Ltd, China). Complete blood count was assayed by automated Cobas® e411 Haematology analyzer (Roche, Germany). Rheumatoid factor (RF) and CRP were assayed by Heales QR-100™ Protein Analyzer (Heales, China). Alanine aminotransferase (ALT), aspartate transaminase (AST), blood urea nitrogen (BUN), serum creatinine (S.Cr) and lipid profile were assayed by fully automated Beckman Coulter/Olympus AU680 Chemistry Analyzer, Japan.

Statistical analysis: All data were analyzed using IBM SPSS Statistical Package version 24.0 (IBM Corp., Armonk, NY, USA). Fisher's exact test was used for statistical analysis of nominal data. Paired *t* test was used to assess any significant difference between each group at baseline and three months after treatment. The variances among groups are homogenous but different in their associated medical condition; therefore, one-way analysis of variance (ANOVA) test was used to assess any significant difference between three groups at baseline and three months after treatment. All data were presented as mean±standard deviation. The significance level was set at *P* values (*P*) <0.05.

Results

The three groups were matched for age, sex, disease duration and the RA treatment protocols as illustrated in Table I. The ANOVA test was used to compare clinical, laboratory and biochemical parameters between the three groups at baseline and three months after treatment (Table II). At baseline the three groups were significantly different in **s**ystolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), high-density lipoprotein (HDL), triglycerides (TGs), morning stiffness, CRP, and HAQ-DI. At three months after treatment TC, HDL, LDL, morning stiffness, ESR, and HAQ-DI were significantly different among the three groups (Table II).

Table I. Demographic data and baseline treatment of patients of the study groups

Parameters	Groups (n=15)		
	Group 1 (Control)	Group 2 (Candesartan)	Group 3 (Atorvastatin)
Age (yr), mean±SD	49.66±9.57	54.93±7.33	49.06±9.81
Duration of disease (yr), mean±SD	6.06±2.63	5.66±2.89	5.86±2.47
	Groups (n=15), n (%)		
	Group 1 (Control)	Group 2 (Candesartan)	Group 3 (Atorvastatin)
Sex			
Male	2 (13.33)	1 (6.67)	1 (6.67)
Female	13 (86.67)	14 (93.33)	14 (93.33)
Treatment			
Prednisolone	15 (100)	15 (100)	15 (100)
Diclofenac	15 (100)	15 (100)	15 (100)
Methotrexate	10 (66.67)	10 (66.67)	10 (66.67)
Leflunomide	10 (66.67)	10 (66.67)	8 (53.33)
Hydroxychloroquine	10 (66.67)	8 (53.33)	11 (73.33)
Sulphasalazine	2 (13.33)	4 (26.67)	3 (20)

Furthermore, ANOVA was used to compare the percentage of mean changes in clinical and biochemical parameters from baseline to the end of treatment between the three studied groups (Table III). The three groups were significantly different in the percentage of mean changes for CRP, DAS28, HAQ-DI, IL-1β and TNF-α levels from baseline to the end of the treatment.

Both candesartan and atorvastatin treated groups (groups 2 and 3) showed significant decrease in serum levels of IL-1β, TNF-α and acute-phase reactants (CRP and ESR) as compared to baseline values. As compared to the base line, patients on atorvastatin showed significant decrease in RF and MDA levels, while patients on candesartan showed non-significant changes in these parameters (Table II).

The decrease in the serum level of inflammatory cytokines (IL-1β and TNF-α) was accompanied by significant improvement in physical and clinical parameters regarding PGA, number of tender joints (NSJ) and morning stiffness. This was also associated with improvement in the disease activity and the quality of life regarding DAS28 and HAQ-DI for both candesartan and atorvastatin groups as compared to baseline data and as compared to the control group throughout the three months follows up period.

As compared to baseline, group 3 showed significant elevation in liver enzymes which did not exceed the upper limit (ALT level: from 22.40±7.48 to 30.60±7.84 IU/l and AST level: from 23.13±8.45 to 29.40±7.16 IU/l). On the other hand, both group 2 and control group showed non-significant change in liver enzymes as compared to their baseline values. There was no significant change in kidney function (BUN and S.Cr) for all studied groups as compared to their baseline data.

Discussion

In this study, candesartan and atorvastatin were used as anti-inflammatory adjuvant therapy for RA because of their suggested suppressive effects on inflammatory cytokines. The release of inflammatory cytokines, especially IL-1β and TNF-α is attributable to the pathogenesis and activity of RA disease including joint pain, deformity, stiffness, general fatigue and disease progression[14].

Our results are matched with the result reported by Benicky *et al*[15] who stated that, ARBs (candesartan) produced a significant reduction of circulating IL-1β and TNF-α levels in animal models with brain inflammation.

Furthermore, Silveira and Refaat[16,17] reported that ARBS (losartan) and methotrexate combined therapy showed better results than methotrexate alone

Table II. Clinical, laboratory and biochemical parameters among patients of the study groups before and after treatment

Parameters	Group 1 (Control) (n=15)		Group 2 (Candesartan) (n=15)		Group 3 (Atorvastatin) (n=15)		ANOVA (*P*)	
	Baseline	After three months	Baseline	After three months	Baseline	After three months	Baseline	After three months
SBP (mmHg)	122.3±19.4	123.0±17.0	157.6±7.0	133.3±7.9***	125.3±16.3	125.3±15.2	<0.01	NS
DBP (mmHg)	72.00±9.02	72.66±9.42	92.33±2.58	79.00±6.03***	75.33±8.55	73.66±9.53	<0.01	NS
TC (mg/dl)	182.9±12.1	177.4±19.7	173.8±16.7	173.8±19.1	194.8±16.9	133.4±15.0***	<0.01	<0.01
HDL (mg/dl)	49.0±9.9	52.6±10.4	59.2±14.8	60.6±13.1	50.6±8.9	64.2±11.4***	<0.05	<0.05
LDL (mg/dl)	90.9±16.1	89.0±13.1	86.8±13.5	85.5±10.5	98.0±21.9	74.0±12.2***	NS	<0.01
TGs (mg/dl)	111.8±13.9	109.7±17.2	103.1±13.8	105.0±14.5	134.2±22.3	105.6±18.0***	<0.01	NS
Morning stiffness (min)	41.6±16.4	36.7±16.9	65.3±17.2	51.0±15.8***	53.0±18.6	42.0±11.6**	<0.01	<0.05
RF (IU/ml)	53.7±33.5	51.2±33.0	71.4±77.5	62.9±64.6	51.0±32.2	42.9±24.9**	NS	NS
ESR (mm/h)	55.8±15.8	56.0±19.6	49.8±31.4	40.3±20.4*	48.8±19.0	39.8±15.0**	NS	<0.05
CRP (mg/l)	26.3±25.7	28.5±26.5	46.6±29.3	39.9±26.2*	26.6±17.5	21.1±13.5***	<0.05	NS
DAS28	4.71±0.52	4.83±0.56	5.50±1.19	4.95±0.75*	4.97±0.92	4.46±0.79***	NS	NS
HAQ-DI	1.17±0.12	1.20±0.12	1.45±0.24	1.36±0.17*	1.32±0.16	1.22±0.15***	<0.01	<0.01
MDA (nmol/ml)	22.8±11.7	21.7±13.9	17.0±23.0	12.7±17.4	20.7±15.8	12.9±10.9*	NS	NS
IL-1β (pg/ml)	2147.7±591.2	2366.8±544.2	2695.6±1872.4	2033.6±1163.6*	2308.5±1119.4	1861.8±873.8*	NS	NS
TNF-α (ng/ml)	120.5±54.0	140.7±61.2	168.8±139.9	113.2±97.7*	169.0±85.1	120.2±71.5*	NS	NS

Values shown as mean±SD. P^{*}<0.05, **<0.01, ***<0.001 compared to respective baseline. SD, standard deviation; ANOVA, analysis of variance; *P*, *P*-value; NS, not significant; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TGs, triglycerides; PGA, patient global health assessment; RF, rheumatoid factor; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28, disease activity score 28; HAQ-DI, Health Assessment Questionnaire-Disability Index; MDA, malondialdehyde; IL-1β, interleukin one beta; TNF-α, tumour necrosis factor-alpha

Table III. Percentage of mean changes in clinical and biochemical parameters regarding inflammation after three months treatment

Per cent change in variables	Group 1 (n=15)	Group 2 (n=15)	Group 3 (n=15)
Morning stiffness (min)	5.55	−19.04	−15.55
ESR (mm/h)	1.23	−11.99	−15.53
CRP (mg/l)**	10.11	−12.33†	−15.28†
RF (IU/ml)	−4.667	−7.663	−9.599
DAS28*	3.00	−7.67	−9.69†
HAQ-DI*	3.89	−4.77	−7.29†
MDA (nmol/ml)	6.86	17.72	−12.99
IL-1β (pg/ml)*	15.74	−17.67†	−12.52
TNF-α (ng/ml)**	26.93	−25.47†	−23.35†

P<0.05, **<0.01 (ANOVA); †P<0.05 compared to group 1 (*post hoc* test)

in reducing IL-1β and TNF-α levels in experimental models of arthritis.

The current results corroborated with those of Lapteva *et al*[18] who reported that angiotensin II was involved in upregulation of pro-inflammatory cytokines, including TNF-α and IL-1β. So, ARBS provoke downregulation of these cytokines in RA patients. ARBs cause AT1R blockade and stimulation of the angiotensin II type 2 receptors that has an opposite effect to that of AT1R with subsequent anti-inflammatory activity and improvement of local and systemic manifestations of RA disease[19].

Tikiz *et al*[20] reported a significant reduction in IL-1β and TNF-α serum levels in RA patients treated by 20 mg simvastatin in combination with conventional disease-modifying anti-rheumatic drugs (DMARDs) for two months. In another study serum levels of IL-1β and TNF-α were reported to be decreased in arthritic rats treated with atorvastatin (10 mg/kg)[21].

Similar to our results, Zhang *et al*[22] reported that IL-1β, IL-6 and TNF-α were significantly decreased in rat models of Alzheimer's disease treated with atorvastatin. The authors suggested the anti-inflammatory effect of atorvastatin through its inhibitory effects on inflammatory cytokines. Li *et al*[23] in their meta-analysis predicted the ant-inflammatory effect of atorvastatin in RA patients.

Our study showed improvement in clinical status in RA patients treated by candesartan (8 mg daily) regarding the number of tender and swollen joints, PGA and morning stiffness. This improvement could be explained on the basis that the anti-inflammatory activity of ARBs was accompanied by functional improvement. This result was in agreement with Silveira *et al*[16] who reported the anti-inflammatory activity of ARBs through downregulation of inflammatory cytokines including IL-1β and TNF-α with subsequent improvement in local joint inflammation and decrement of the disease activity in experimental models of arthritis.

The effect of atorvastatin was investigated in RA patients and a significant decrease in CRP levels and significant improvement in clinical status as evaluated by DAS28 were demonstrated[24,25]. Our results supported these findings. Our findings were in agreement with previous studies that showed significant improvement in DAS28, HAQ-DI, morning stiffness, CRP and ESR levels in RA patients treated by statins in addition to conventional DMARDs[26,27].

Atorvastatin showed a significant decrease in serum MDA level. In contrast, candesartan showed no significant change in MDA serum level. This result could be explained on the basis that atorvastatin might have anti-oxidant effect and counteracted the oxidative stress in RA patients. Former studies showed the antioxidant activity of atorvastatin in RA patients[28,29]. In contrast to our result, Silveira *et al*[16] reported that ARBs (losartan) decreased the levels of superoxide radical and the expression of NADPH oxidases, an oxidizing stress marker in antigen-induced arthritic mice. Our results were in agreement with Perry *et al*[30] who reported that treatment of RA patients with ARBs (losartan) resulted in a significant decrease in acute phase reactants including CRP and ESR levels.

A direct functional relationship has been reported between the acute phase reactant CRP and angiotensin II[6]. The authors reported that high level of angiotensin II was associated with high CRP level and subsequently ARBs resulted in decline of CRP level.

This current study reported a significant decrement in RF levels in RA patients treated by atorvastatin (20 mg daily), suggesting the immunomodulatory effect of atorvastatin, which seems in agreement with a study by Tascilar *et al*[31] who confirmed the immunomodulatory effects of atorvastatin in RA patients. This study was limited by the relatively small sample size and the short follow up period.

In conclusion, both candesartan and atorvastatin showed anti-inflammatory and immunomodulatory effects that improved the clinical status and disease activity in RA patients through their suppressive effect on inflammatory cytokines including IL-1β and TNF-α. Atorvastatin was superior to candesartan through its antioxidant effect. Atorvastatin and candesartan could represent a useful adjuvant therapy with other conventional therapeutic methods used for the management of RA patients. Large scale and longitudinal studies need to be done on RA patients with the implication of different doses of candesartan and atorvastatin to confirm its anti-inflammatory activity and others beneficial actions in patients with RA.

***Acknowledgment*:** Authors acknowledge all participants for their understanding and help during this work, and thank the physicians at Rheumatology clinics, Menofia University hospitals for their help and recommendations.

***Financial support & sponsorship*:** None.

***Conflicts of Interest*:** None.

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