Spironolactone (an adjuvant therapy) in rheumatoid arthritis: a case control study

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Abstract

Objectives: Disease-modifying anti-rheumatic drugs (DMARDs) are conventionally used in rheumatoid arthritis (RA). The role of spironolactone as add on therapy to DMARDs in RA patients was evaluated.

Material and methods: A total of 100 patients with rheumatoid arthritis diagnosed as per 1987 criteria having evidence of active disease despite ongoing DMARD therapy were enrolled in this study. Patients were assigned randomly to two groups. Group I (n = 50) patients were treated with 50 mg/day of spironolactone along with their maintenance DMARD and NSAID therapy. Group II (n = 50) patients continued their maintenance DMARD therapy without spironolactone. Disease activity was assessed using the Disease Activity Score-28 (DAS28) and the Clinical Disease Activity Index (CDAI) in each patient of each group was evaluated monthly for the next three months.

Results: All patients completed the study. Mean age of group I was 46.44 ±11.67 and of group II 44.52 ±11.82. DAS28 assessed in time according to the schedule was for group I 6.78 ±0.74, 5.34 ±0.74, 3.98 ±0.7, 3.00 ±0.75, while in group II it was 6.61 ±0.82, 5.49 ±0.90, 4.58 ±0.81, 3.55 ±0.93 at baseline, 4, 8, and 12 weeks respectively. CDAI in group I was 41.68 ±11.14, 24.36 ±8.13, 12.34 ±5.73, 6.42 ±4.4 and in group II 37.84 ±11.12, 24.54 ±9.4, 16.38 ±6.81, 9.62 ±6.1 at baseline, 4, 8, and 12 weeks respectively. Group I showed significant improvement in disease activity in the form of tender joint count (p = 0.001), swollen joint count (p = 0.023), patient global assessment (p = 0.001), physician global health (p = 0.001), DAS28 (p < 0.001) and CDAI (p = 0.001) but other parameters showed non-significant improvement compared to group II. No serious adverse events were observed in either group during the course of the study.

Conclusions: Spironolactone as an adjuvant therapy can improve the effect of conventional DMARD treatment of patients with RA.

Key words: rheumatoid arthritis, spironolactone, adjuvant therapy.

Introduction

Several developments during the past two decades have changed the therapeutic landscape in rheumatoid arthritis (RA). They include the emergence of methotrexate as a disease-modifying anti-rheumatic drug (DMARD) of first choice for treatment of early RA; the development of novel highly efficacious biologics that can be used alone or in combination with methotrexate; and the proven superiority of combination DMARD regimens over methotrexate alone [1, 2].

Presently treatment of RA has evolved into a new strategy that focuses on: a) early aggressive therapy (to prevent damage and disability) [3], b) frequent modification of therapy with utilization of combination therapy [4, 5], c) individualization (personalized medicine for maximum response and minimum side effects), d) achieving whenever possible remission of clinical disease activity [6]. Disease-modifying anti-rheumatic drugs, whether conventional (non-biological) or biological, single or in combination, are the fundamental treatment of inflammatory arthritis, and nonsteroidal anti-inflammatory...
drugs (NSAIDs) and glucocorticoids (GK) have been used mainly for symptomatic relief. Besides these conventional drugs, recently certain adjuvant therapies to DMARDs in RA have been used. Androgen therapy, high dose of vitamin E, omega 3 fatty acid infusion, statins, and spironolactone have been used as adjuvant therapies in RA [7–13].

Spironolactone is a steroid that blocks mainly the effects of the hormone aldosterone but also its anti-inflammatory anti-proliferative and anti-oxidant effects are described. However, few studies have shown the effectiveness of spironolactone in therapy of rheumatoid arthritis [11, 13]. This is because it blocks aldosterone, which possesses proinflammatory and profibrotic properties, due to its stimulating action on cytokines, molecules of adhesion and different growth factors [14, 15].

Increase of aldosterone levels in synovial fluid leads to persistent hypoxia, which may induce genotoxic agents, leads to DNA disturbance and synovial cell mutation, exaggerates fibroblast proliferation and reduces the opportunity of cell apoptosis, which contributes to pannus mass progressive growth and cartilage erosion in RA [15]. Only limited studies are available regarding the role of spironolactone as adjuvant therapy with DMARDs in RA [11–13].

Material and methods

A total of 100 RA patients diagnosed as per American College of Rheumatology (ACR) 1987 criteria [16] who had active (moderate to severe) disease, directed to the Out Patient Department of Rheumatology Clinic of Pt. Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, were included in the study. Informed consent was obtained from all the patients. Patients with pre-existing hepatic disease, renal disease, heart failure, endocrinological disorders, haematological disorders, uncontrolled hypertension, coronary heart disease and hyperkalemia were excluded from the study. Pregnant or lactating mothers and patients not willing to practice contraception were also excluded. The patients included in the study were maintained on their previous dose of DMARDs along with use of NSAIDs.

In all patients the DAS28 score using 28 joint counts (tenderness/swelling), erythrocyte sedimentation rate (ESR) and global health assessment using the Visual Analogue Scale (VAS in 0 to 100 mm) were evaluated [16]. With the use of above measurements the DAS28 score was calculated using the following formula:

\[
DAS28 = 0.56 \sqrt{TJC} + 0.28 \sqrt{SJC} + 0.70 \log \text{ESR} + 0.014 \text{GH}
\]

All subjects were also scored for the Clinical Disease Activity Index (CDAI) using 28 joint count (tenderness/swelling), patient’s global assessment of disease activity (PaGA) as per the VAS (0 to 100 mm) and the care provider (physician) global health assessment of disease activity using the VAS (0 to 100 mm) (PhGA). The VAS used in the study for scoring DAS28 and CDAI was based on evaluator/patient assessment of his/her feeling about his general health on that day in which 0 (left hand point) indicated “feeling completely alright” (in the words of the patient) and “feeling very bad” scored 100 (right hand point) [17].

The Clinical Disease Activity Index of the same patients at the same visit was calculated by the following formula:

\[
\text{CDAI} = \text{TJC} + \text{SJC} + \text{PhGA} + \text{PaGA}
\]

Disease activity was assessed using the DAS28 and the Clinical Disease Activity Index in each patient of each group was evaluated monthly for the next three months.

After basal evaluation patients selected for the study were assigned randomly to two groups. Both groups (I and II) received their maintenance dose of DMARDs and NSAIDs as per need. Group I (n = 50) patients were treated with 50 mg per day of spironolactone along with their maintenance DMARDs and NSAIDs therapy as per need. Group II (n = 50) patients continued their maintenance DMARD therapy without spironolactone treatment.

The study was approved by the bioethical committee. All adverse events also were noted. All data collected in the study were analyzed statistically at the end of the study using the independent t-test, paired t-test, χ² test, and repeated measures ANOVA.

Results

The mean age in group I (n = 50) was 46.44 ±11.67 years and in group II (n = 50) was 44.52 ±11.82 years. 82% of subjects were female in group I and 78% in group II. Comparison of baseline parameters between the two groups did not show any significant difference (Table I).

The comparison of CDAI between the groups was insignificant at baseline (p = 0.088) and 4 weeks (p = 0.919) but significant at 8 weeks and 12 weeks with a p-value of 0.002 and 0.003 respectively (Table II).

On comparing the disease activity using the DAS28 score, group I had numerically higher disease activity as compared to group II at baseline (p = 0.268). The comparison of DAS28 score between groups revealed a p-value of 0.365, < 0.001 and 0.002 at 4 weeks, 8 weeks and 12 weeks respectively (i.e. a non-significant p-value at 4 weeks but significant at 8 and 12 weeks) (Table II). In both groups not only disease activity was decreased

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Table I. Comparative assessment of baseline parameters between two groups

|                | Group I          | Group II         | *p-value |
|----------------|------------------|------------------|----------|
| Age            | 46.44 ±11.67     | 44.52 ±11.82     | 0.416    |
| % female       | 82%              | 78%              | 0.617    |
| TJC (0–28)     | 20.66 ±5.74      | 18.90 ±6.33      | 0.149    |
| SJC (0–28)     | 7.52 ±5.57       | 5.44 ±4.46       | 0.042    |
| PGA (0–10 cm)  | 7.24 ±1.15       | 7.38 ±1.41       | 0.588    |
| EGA (0–10 cm)  | 6.06 ±1.23       | 6.10 ±1.60       | 0.889    |
| GH (0–100 mm)  | 72.40 ±11.52     | 73.80 ±14.12     | 0.588    |
| ESR (mm 1st hour) | 38.00 ±9.75    | 41.24 ±8.07      | 0.075    |
| DAS28          | 6.78 ±0.743      | 6.64 ±0.853      | 0.393    |
| CDAI           | 41.68 ±11.14     | 37.84 ±11.12     | 0.088    |

*Paired t-test

TJC – tender joint count; SJC – swollen joint count; PGA – patient global assessment; EGA – evaluator global assessment; GH – global health; ESR – erythrocyte sedimentation rate; DAS28 – Disease Activity Score-28; CDAI – Clinical Disease Activity Index

Table II. Comparative assessment of CDAI (Clinical Disease Activity Index) and DAS28 (Disease Activity Score-28) between two groups

|                | CDAI          | DAS28         |
|----------------|--------------|---------------|
|                | Group I      | Group II      | p-value* | Group I      | Group II      | p-value* |
| Baseline       | 41.68 ±11.14 | 37.84 ±11.12  | 0.088    | 6.78 ±0.74   | 6.61 ±0.82    | 0.268    |
| 4 weeks        | 24.36 ±8.13  | 24.54 ±9.40   | 0.919    | 5.34 ±0.74   | 5.49 ±0.90    | 0.365    |
| 8 weeks        | 12.34 ±5.73  | 16.38 ±6.81   | 0.002    | 3.98 ±0.70   | 4.58 ±0.81    | < 0.001  |
| 12 weeks       | 6.42 ±4.40   | 9.62 ±6.10    | 0.003    | 3.00 ±0.75   | 3.55 ±0.93    | 0.002    |

*Paired t-test

Table III. Comparative assessment of parameters at 12 weeks between two groups

|                | Group I      | Group II      | p-value |
|----------------|--------------|---------------|---------|
| TJC (0–28)     | 2.56 ±2.06   | 4.30 ±3.31    | 0.002   |
| SJC (0–28)     | 0.64 ±0.964  | 0.624         | > 0.05  |
| PGA (0–10 cm)  | 1.76 ±1.04   | 2.86 ±1.41    | < 0.001 |
| EGA (0–10 cm)  | 1.46 ±0.930  | 1.90 ±1.16    | 0.040   |
| GH (0–100 mm)  | 17.60 ±10.41 | 28.60 ±1.14   | < 0.001 |
| ESR (mm 1st hour) | 14.12 ±5.19 | 18.10 ±6.25 | 0.001   |
| DAS28          | 3.00 ±0.752  | 3.55 ±0.934   | 0.002   |
| CDAI           | 6.42 ±4.40   | 9.62 ±6.10    | 0.003   |

TJC – tender joint count; SJC – swollen joint count; PGA – patient global assessment; EGA – evaluator global assessment; GH – global health; ESR – erythrocyte sedimentation rate; DAS28 – Disease Activity Score-28; CDAI – Clinical Disease Activity Index.

At 12 weeks, all parameters of disease activity except SJC showed statistically significant differences between the two groups.

but also various parameters such as TJC (tender joint count), SJC (swollen joint count), PGA (patient global assessment), GH (global health), DAS28, and CDAI were reduced (Table III).

Further, in group I the improvement in disease activity score as well as various parameters of disease activity were numerically significant in all patients but statistically significant only for TJC, SJC, PGA, GH, DAS28 and CDAI f (Table IV, Fig. 1).

Discussion

The role of spironolactone as a therapeutic option in RA has come to light recently. Experimental models...
showed that spironolactone reduced oxidative stress, normalized hypertrophic reconstruction reducing collagen and fibronectin and reduced ICAM-1 expression in the vessel wall [18, 19]. Spironolactone suppresses production of TNF-α, IFN-γ, IL-6 and macrophage granulocyte colony stimulating factor and reduces inflammatory signs in patients with RA and juvenile RA [12].

Inhibition of aldosterone production contributes to pronounced reduction in VEGF and ICAM-1 concentration in blood, which are markers of angiogenesis and endothelial dysfunction. There are important links of pathological changes in synovial membrane and developing visceral complications in RA [18, 19]. Reduction of FGF contributes to fibroblast proliferation reduction and normalization of synovial fibroblast apoptosis reactions, which in turn may brake pannus growth and joint tissue destruction in RA [20, 21].

In the present study the group treated with DMARDs and spironolactone had a significantly (p < 0.05) lower disease activity score (DAS 28 and CDAI) (Tables II and III) at 12 weeks. Of the variables for disease activity, the decrease in TJC, SJC, PGA, ESR and GH in the spironolactone group was significant (p-value < 0.05) for all above-cited parameters.

A study was conducted by Bendtzen et al. [12] to evaluate spironolactone therapy in patients suffering from immuno-inflammatory disorder. They tested the effects of spironolactone on ex vivo activated human blood leucocytes using gene expression analyses and enzyme immunoassay for quantitating secreted pro- and anti-inflammatory cytokines. Furthermore, to evaluate the safety and efficacy of spironolactone as an anti-inflammatory drug, 21 patients with RA, juvenile idiopathic arthritis or other arthritis were treated for up to 22 months with 1–3 mg/kg/day. Spironolactone, at in vivo attainable doses, markedly suppressed transcription of several proinflammatory cytokines and, accordingly, inhibited release of tumor necrosis factor, lymphotoxin, interferon gamma, granulocyte–macrophage colony stimulating factor and interleukin 6 (70–90% inhibition). Release of these cytokines was also suppressed when testing whole blood from RA patients receiving 50 mg of spironolactone twice daily, indicating that pharmaceutical use of the drug may suppress the release of inflammatory cytokines. Spironolactone therapy was generally well tolerated. Sixteen of 21 arthritis patients (i.e. 76%) responded favorably to spironolactone in this study. In the study group 67% of RA patients showed a favorable response according to American College of Rheumatology (ACR) criteria [12].

Komarova and Rebrov [11] followed patients with RA for 12 months while they were on additional therapy of 25–50 mg/day of spironolactone and observed a significant reduction in DAS28 value (p-value = 0.048) and also found improvement in the VAS and HAQ (Health Assessment Questionnaire), suggesting improvement in patients’ quality of life. It concluded that spironolactone contributes to more pronounced improvement in indices along with reduction of anti-inflammatory, anti-proliferative and angiogenic cytokines and more effectively reduces disease activity. Syngle et al. [13] (Indian study in patients of RA) found a significant reduction in DAS28 and HAQ-DI (p-value < 0.05 for both).

Spironolactone was well tolerated in most of the patients (only 3 patients had dizziness and 2 patients developed hyperkalemia). None of the side effects required discontinuation of the therapy or hospitalization. Similar observations were also made in other studies [12, 13].

| Table IV. Improvement in disease activity and individual variables over 12 weeks from baseline |
|---------------------------------|-----------------|-----------------|
|                                | Group I | Group II | p-value |
| TJC | 18.10 | 14.60 | 0.001 |
| SJC | 6.88 | 4.80 | 0.023 |
| PGA | 5.48 | 4.52 | 0.001 |
| EGA | 4.60 | 4.20 | 0.145 |
| GH  | 54.80 | 45.20 | 0.001 |
| ESR | 23.12 | 23.14 | 0.991 |
| DAS28 | 3.77 | 3.06 | < 0.001 |
| CDAI | 35.26 | 28.22 | 0.001 |

TJC – tender joint count; SJC – swollen joint count; PGA – patient global assessment; EGA – evaluator global assessment; GH – global health; ESR – erythrocyte sedimentation rate; DAS28 – Disease Activity Score-28; CDAI – Clinical Disease Activity Index.

Fig. 1. Graph showing improvement in disease activity and individual variables over 12 weeks from baseline.
As there is a paucity of literature regarding use of spironolactone in RA patients, our study has shown promising results, the drug opening a new hope for the patients. However, there is minor concern regarding causation of autoimmune disorders with use of spironolactone as per FDA reports. Long-term multicenter randomized controlled studies are required to determine the effective role of spironolactone in treatment of RA [22].

Conclusions

The present study shows that the spironolactone acted synergistically with conventional DMARD therapy. The reduction in disease activity was greater in RA patients in combination therapy (group I). These results may provide a window of opportunity in RA to modify the treatment of chronic inflammatory disease. Spironolactone due to its pleiotropic effect as an anti-inflammatory and immunomodulatory agent may brings a benefit as additional therapy.

The authors declare no conflict of interest.

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