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RESEARCH ARTICLE

Spironoctone in Psoriatic Arthritis; Safety, Efficacy and Effect on Disease Activity

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Abstract

Background: Therapeutic approaches used previously reliedon disease-modifying antirheumatic drugs (DMARDs) that had only partial clinical benefitand were associated with significant toxicity.Spironolactone, an oral aldosterone antagonist, suppresses inflammatory mediators. Clinical efficacy of spironolactone compared with placebo inpatients with active psoriatic arthritis despite treatment with priortraditional DMARDs.

Methods: In the 24-week, open label, placebo-controlled, prospective study, patients (n=38) were randomized to placebo and spironolactone (2m/kg/day). Patients on background concurrent DMARDs continued stable doses (methotrexate, leflunomide and/or sulfasalazine). Primary outcome measures were the assessment of disease activity measures i.e. 28-joint disease activity score (DAS28) and diseases activity in psoriatic arthritis (DAPSA) at week 24. The key secondary endpoint was change from baseline in Health Assessment Questionnaire–Disability Index (HAQ-DI) at week 24. Additional efficacy outcome measures at week 24 included improvements in the markers of inflammation (ESR and CRP) and pro-inflammatory cytokines TNF-α, IL-6 and IL-1.

Results: At week 24, spironolactone significantly reduced disease activity measure DAS-28 ($p<0.001$) and DAPSA ($p=0.001$) compared with placebo. Significant improvements in key secondary measures HAQ-DI (disability index) were evident with spironolactone ($p=0.02$) versus placebo. After week 24, there was significant reduction in pro-inflammatory cytokines level TNF-α, IL-6 ($p<0.01$) as compared with placebo group. However, there was no significant improvement in IL-1 in both treatment and placebo groups. No change in any biochemical profile was noted after spironolactone treatment.

Conclusions: Spironolactone was effective in the treatment of PsA, improving disease activity, physical function and suppressing the level of proinflammatory cytokines. Spironolactone demonstrated an acceptable safety profile and was well tolerated.

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory spondyloarthropathy of the peripheral joints and axial skeleton [1]. Patients with PsA have erosive disease, physical limitations, and negatively affect quality of life [2]. Apart from inflammation, psoriatic arthritis patients have greater cardiovascular risk due to endothelial dysfunction and accelerated atherosclerosis [3]. Therapeutic approaches used previously relied on disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and sulfasalazine that had only partial clinical benefit and were associated

with significant toxicity. Thus, a need exists for additional safe, efficacious and preferably cheap oral treatment option for management of PsA.

Spironolactone is a safe and generic oral drug in clinical use for more than five decades. The suppressive and immunomodulatory effect of spironolactone on the production of proinflammatory cytokines have previously been demonstrated in various autoimmune diseases [4-6]. Spironolactone also appears to improve the endothelial dysfunction associated with the chronic inflammation of RA and AS [7-8]. So aim of the present study was to evaluate the safety and efficacy of spironolactone in PsA patients.

Material and Method

Patients and study design

Thirty eight PsA patients (aged >18 years) who fulfilled the CASPAR criteria (Classification criteria for Psoriatic Arthritis) criteria were enrolled in the study from a rheumatology outpatient clinic [9]. In this 24 weeks, open label, placebo controlled, prospective study in which patients with active PsA were randomized to receive spironolactone (2 mg/kg/day) or matched placebo as an adjunct to existing stable synthetic DMARDs. The allocation ratio of active to placebo treatment was 1:1. Patients with diabetes mellitus, hepatic and renal failure, peripheral artery disease, stroke, coronary artery disease, hypertension, pregnant women and smokers were excluded from the study. Patients with previous exposure of biologic DMARDs were also excluded from the study. Patients had to be taking stable doses of DMARDs for at least 3 months before entering the study. The study protocol was approved by the regional ethical research committee and was performed in accordance with the declaration of Helsinki and the code of Good Clinical Practice. All patients provided written informed consent to participate after a full explanation of the study.

Outcome measures

The primary efficacy endpoint was the improvement in disease activity measures i.e. 28-joint disease activity score (DAS28) and diseases activity in psoriatic arthritis (DAPSA) [10]. The key secondary endpoint was change from baseline in Health Assessment Questionnaire–Disability Index (HAQ-DI) at week 24. Additional efficacy outcome measures at week 24 included improvements in the biomarkers of inflammation (ESR and CRP) and pro-inflammatory cytokines tumor necrosis factor (TNF)-α, interleukin (IL)-6 and IL-1.

Safety measures

All patients who were randomized and received study drug and placebo were evaluated for safety, including adverse events and premature discontinuations from the study. Standard laboratory tests, including hematology, serum chemistry and urinalysis, were performed at all scheduled clinic visits at screening, week 12 and week 24. Serum samples were obtained at baseline and week 24 to be tested for inflammatory cytokines.

Statistical analysis

Continuous data are expressed as the mean ± standard deviation (SD). Spironolactone and placebo patients were compared using unpaired Student's *t*-test for continuous variables and paired Student's t test for compared within group difference. Two-sided *P*-values of less than 0.05 were considered statistically significant. The statistical analysis was carried out using Sigmastat 5.5 for Windows 7.

Results

Patient profile

A total of 38 adult PsA patients recruited for the study gave informed consent to participate in the research study. The treatment group had 19 patients with mean age 44.2 ± 13.9 (8 females and 11 males) compared with 19 in the placebo group with mean age 48.7 ± 13.1 (7 females and 12 males). Seven patients were excluded (three from spironolactone and four patients from placebo group) from the study due to lost to follow-up. The baseline demographic and clinical characteristics of the spironolactone and placebo controls patients are presented in Table 1. We found that there was no statically significant difference in the demographic and laboratory parameters of spironolactone group and placebo group.

Outcome

The post-treatment changes in the inflammatory markers and disease variables are shown in Table 2. After 24 weeks treatment, DAS28 score was significantly lower in the spironolactone group ($p< 0.001$) compared with the placebo group ($p=0.08$) (Table 2). After treatment with Spironolactone, DAPSA score improved significantly ($p=0.001$) while there was no significant improvement in DAPSA score in placebo group ($P=0.09$). ESR and CRP level also decreased significantly, after treatment with spironolactone as compared to placebo group (Table 2). The levels of pro-inflammatory cytokines TNF-α, IL-6, and IL-1 were higher in both treatment and placebo groups (Table I). After treatment with spironolactone there was a significant decrease in TNF-α and IL-6 ($p<0.01$) as compared with placebo group. However, there was no significant improvement in IL-1 in both treatment and placebo groups (Table

2). There were minor side effects which did not mandate stopping of spironolactone. However, one patient in spironolactone group discontinued spironolactone because of oligomenorrhea. No change in any biochemical profile was noted after spironolactone treatment.

Table 1 Demographic characteristics and disease activity measures at baseline.

Variable	Spironolactone	Placebo Controls	*P* value
n	19	19	-
Age (years)	44.2 ± 13.9	48.7 ± 13.1	0.36
Sex (men:women)	9:7	9:6	-
Duration of PsA (years)	8.3 ± 4.7	7.2 ± 6.2	0.59
BMI (kg/m^2)	25.0 ± 2.0	26.4 ± 3.6	0.20
Systolic BP (mm Hg)	127.6 ± 9.5	123.8 ± 8.1	0.26
Diastolic BP (mm Hg)	80.9 ± 8.8	77.4 ±7.2	0.25
HbA1c (%)	5.31 ± 0.6	5.65 ± 0.4	0.11
Fasting serum glucose (mg/dl)	100.4 ± 9.3	102.8 ± 4.8	0.39
S. Na+, mEq/L	139.2 ± 0.9	136.0 ±1.2	0.62
S. K+, mEq/L	4.25 ± 0.08	3.96 ± 0.02	0.36
ESR(mm 1st hr)	30.46 ±7.76	27.06 ±12.43	0.33
CRP(mg/dl)	13.28 ± 5.68	11.47 ± 4.56	0.34
DAS-28	4.08 ± 0.56	4.00 ± 0.66	0.71
DAPSA	23.08 ± 8.76	19.89 ± 7.47	0.29
Serum creatinine (mg/dl)	0.91 ± 0.07	0.90 ± 0.06	0.69

Values are mean ± SD; BMI: body mass index, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, DAS-28: disease activity score in 28 joints, DAPSA: disease activity in psoriatic arthritis. *P*-value *<0.05* was considered significantly.

Table 2 Effect of spironolactone and placebo after 24 weeks of treatment with spironolactone and placebo on outcome measures

	Psoriatic Arthritis					
	Spironolactone			Placebo		
	(n=19)	(n=16)		(n=19)	(n=15)	
	Week 0	**Week 24**	**p**	**Week 0**	**Week 24**	**p**
ESR	30.46 ± 7.76	21.13 ± 5.02	p<0.001	27.06 ±12.43	24.80 ± 10.77	p=0.09
CRP	13.28 ± 5.68	9.18 ± 6.74	P=0.007	11.47 ± 4.56	10.93 ± 4.28	P=0.06
DAS-28	4.08 ± 0.56	2.95 ± 0.45	p<0.001	4.00 ± 0.66	3.89 ± 0.64	P=0.08
DAPSA	23.08 ± 8.76	15.27 ± 6.27	p=0.001	19.89 ± 7.47	18.72 ± 6.89	P=0.09
TNF-α	5.27 ± 2.48	4.22 ± 1.67	p=0.001	5.74 ± 3.81	5.44 ± 3.45	p=0.09
IL-6	10.04 ± 4.10	7.37 ± 2.99	p<0.001	9.70 ± 4.155	9.40 ± 4.13	P=0.08
IL-1	164.4 ± 69.8	155.0 ± 68.87	P=0.09	166.4 ± 74.98	161.6 ± 75.33	P=0.10
HAQ-DI	1.01 ± 0.28	0.78 ± 0.21	P=0.02	0.96 ± 0.32	0.89 ± 0.32	P=0.54

Values are mean±SD; ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, DAS-28: disease activity score in 28 joints, DAPSA: disease activity in psoriatic arthritis, TNF: tumor necrosis factor, IL: interleukin, HAQ-DI: Health Assessment Questionnaire–Disability Index. *P*-value *<0.05* was considered significantly.

Discussion

The present study demonstrated that oral administration of spironolactone (2mg/kg/day) for 24 weeks significantly reduced disease activity and proinflammatory cytokines in PsA on synthetic DMARDs. The impact of spironolactone in PsA has not been previously investigated while previous clinical studies and laboratory evidence supports its potential role in treatment of rheumatic and other autoimmune diseases.

PsA is a chronic inflammatory autoimmune disease associated with significant morbidity. The effect of antirheumatic treatment, i.e. steroidal and non-steroidal anti-inflammatory drugs and synthetic DMARDs have demonstrated variable efficacy in psoriasis and PsA [11]. Kingsley et al., 2012 conclude that the evidence that either MTX or SSZ has DMARD like effects in PsA is inconclusive [12]. More recently, expensive parenteral biologic

DMARDs that inhibit the pro-inflammatory cytokines– tumor necrosis factor (TNF), interleukin (IL) 6 and IL-1 – are increasingly being used in rheumatic patients who have failed traditional DMARD therapy [13]. But modern biologic DMARDs suffer from several major limitations like parenteral administration, development of neutralizing antibodies with prolonged therapy, risk of serious infections and huge costs. Thus, there is need a safe, efficacious and economical novel therapeutic agents that address the varied clinical manifestations of PsA.

In the current prospective, open label, placebo controlled study with active and long lasting disease and history of treatment experience, spironolactone (2 mg/kg/day) significantly reduced the inflammation of PsA at week 24. Spironolactone demonstrated statically significant improvement in disease activity measures DAS28 and DAPSA. It also significantly improved the physical function, as measured by HAQ-DI at week 24. Biomarkers of inflammation (ESR and CRP) were significantly reduced with spironolactone as compared with placebo. The study results are consistent with previous results which have shown spironolactone reduces ESR, CRP and disease activity measures in rheumatic diseases and heart failure patients [7-8, 14]. In PsA arthritis, the over-expression of pro-inflammatory cytokine has been documented extensively in preclinical and clinical investigations [15]. In our study we demonstrated spironolactone significantly reduced TNF-α and IL-6 compared with placebo whereas the level of IL-1 was not significantly reduced in spironolactone treated patients suggesting that the anti-inflammatory and immunomodulatory effects of spironolactone in PsA result from inhibition of TNF-α and IL-6. A previous study has demonstrated that SPIR inhibits the stimulated production of TNF-alpha, IL-6, and interferon-gamma in various rheumatic patients with RA, AS, systemic lupus erythematosus and juvenile idiopathic arthritis [4].

Spironolactone was first known to possess anti-inflammatory properties as early as 1961 [16].The observed suppressive effect of spironolactone on inflammatory markers and disease activity is probably be due to inhibition of CRP and inflammatory cytokines i.e TNF-α and IL-6. Spironolactone suppresses upregulation of nuclear factor kappa B (NF-κB), transcription factor which regulates a battery of proinflammatory genes [6]. NF-κB is one of the most important regulators of proinflammatory gene expressions. Synthesis of cytokines TNF-alpha, IL-6, Il-1β and IL-8 is mediated by NF-κB. The increased level of NF-κB has been demonstrated in collagen induced arthritis animal model and it gradually increases during the evolution of disease [17-18]. NF-kB has been demonstrated as a potential therapeutic target in osteoarthritis RA and PsA [19-20].

Spironolactone at dose of 2mg/kg/day orally was generally well tolerated over 24 weeks. The most common adverse event was lightheadedness and gastritis and did not lead to discontinuation of spironolactone. One patient discontinued spironolactone because of oligomenorrhea and 4 patients in placebo and 3 patients in spironolactone group were lost to follow-up. Spironolactone use did not result in clinically meaningful laboratory abnormalities, suggesting that routine laboratory monitoring may not be required when using spironolactone.

Conclusion:

These findings demonstrate that spironolactone is effective for the treatment of active PsA across a diverse group of patients with prior treatment experience, in combination with traditional synthetic DMARDs. Furthermore, spironolactone was well tolerated in the majority of patients and demonstrated an acceptable safety profile. These results confirm the therapeutic potential of spironolactone for treatment of patients with PsA.

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Disclosures None

Conflict of interest None

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