EFFECTIVENESS OF SPIRONOLACTON IN COMPLEX THERAPY OF RHEUMATOID ARTHRITIS

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ABSTRACT

Aldosterone blocker – Spironolactone has anti-inflammatory, anti-proliferative and anti-oxidative effects, that is why pathogenetically it is expedient to use it in complex therapy of rheumatoid arthritis.

Material and methods: 46 patients with RA took 25-50 mg/day of Spironolactone during 12 months as an addition to standard therapy, the comparison group consisted of 47 patients that got only standard therapy, all the patients were fully examined prior and post the treatment.

Results: complex RA therapy leads to improved VAS, HAQ, the antioxidative potential index F; decreased blood concentrations of TNF-α, ICAM-1, FGF and VEGF in contrast to standard therapy. Complex therapy made reduced the DAS 28 more > 0.6.

Conclusions: applying of Spironolactone in complex therapy of rheumatoid arthritis contributes to more pronounced improvement in indices of articular syndrome and patient's life quality, reduce of anti-inflammatory, anti-proliferative and angiogenic cytokines, and more effectively reduces the activity of the disease comparing to standard therapy.

UDC CODE & KEYWORDS

■ UDC: 616-002 ■ Rheumatoid arthritis ■ Aldosterone ■ Spironolactone ■ Activity of disease

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease which is characterized by erosive and destruction process in joints and leads to early disability of patients, decrease of life quality and low incidence of remission obtaining under applying the methods of standard base therapy (Kalden, 2003). Study of new links of RA pathogenesis and development of correction of the disturbances found is a topical problem of modern rheumatology.

It is known that aldosterone (ALD) possesses pro-inflammatory and pro-fibrotic properties, stimulating the production of pro-inflammatory cytokines, molecules of adhesion and different growth factors. Experimental researches showed that ALD stimulates the activity of nuclear transcription factor kappa B, expression of intracellular adhesion molecules (ICAM-1), as well as fibroblast growth factor (FGF) (Delcayre, Swynghedauw 2002, Sugiyama et al. 2005). Increase of ALD level in synovial fluid leads to persistent synovial hypoxia, which in its turn can induce genotoxic agents, lead to DNA disturbance and synovial cells' mutations, exaggerates fibroblasts proliferation and reduces the opportunity of these cells' apoptosis, which is one of the most important phases of pannus mass progressive growing and cartilage erosion in RA.

Aldosterone blocker – Spironolactone (SPIR) possesses early suppressing effect on some immunoactive and pro-inflammatory cytokines and stimulates effects of apoptosis of different cells (Sønder et al. 2006). Experimental models showed that SPIR reduced oxidative stress, normalized hypertrophic reconstruction reducing collagen and fibronectin, reduced ICAM-1 expression in vessel wall (Klimiuk et al. 2002, Rombouts et al. 2001). K. Bendtzen et al. demonstrated that taking SPIR suppresses production of TNF-α и -β, IFN-γ, IL–6 and macrophage granulocytes colony stimulation factor and reduces inflammatory signs in patients with RA and juvenile RA (Bendtzen, Hansen, Rieneck, 2003).

The results of the analysis of foregoing data allow suggesting as a prospective aim applying aldosterone blockers in complex RA therapy.

The aim of present research was to study the effectiveness of SPIR in complex therapy of RA.

Materials and methods

In the rheumatologic department of Lugansk Regional Clinical Hospital 93 patients with RA (diagnosis verification according ACR/EULAR, 2010 criteria), without accompanying pathologies were examined. In all the patients the characteristics of joint syndrome were studied: duration of morning stiffness, health assessment according to visual analogous scale (VAS) and life quality estimation according HAQ; markers of inflammation process were studied: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), disease activity score DAS28, tumour necrosis factor-α (TNFα); antioxidative system activity – integrative index F = catalase (CAT) x superoxide dismutase (SOD) / malonic dialdehyde (MDA); cytokine profile was studied: aldosterone (ALD), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), intracellular adhesion molecules (ICAM-1). Cytokine concentration in blood was measured by immune-enzyme analysis with the help of research kits: TNF-α and VEGF (Vector-Best, Russia), ICAM-1 (Diaclone, France), FGF and ALD (Diagnostic, Canada).

Among the patients there were 11 males and 81 females with average age 42.82 ± 10.2 years, average duration of the disease is 3.82 ± 3.43 years.

All the patients examined were divided into two groups with the technique of random sampling: I – 47 patients got standard RA therapy according the protocols of rheumatoid diseases treatment (Guidelines for the Management of Rheumatoid

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Arthritis, 2002), II – 46 patients got complex treatment during 12 months which included standard therapy with adding aldosterone blocker – Spironolactone in 25 - 50 mg per day. Initial dose was 50 mg/day during 2 weeks, and then the dose was corrected depending on the potassium content in blood serum. The patients of both group I and group II statistically did not different in all the characteristics studied before the treatment.

Statistical analysis was carried out in system Statistica, version 8.0 (StatSoft, USA). Nonparametric methods were also used: median (Me), Lower and Upper quartile (LQ; UQ), Mann-Whitney test (U), Wilcoxon test (W). The result with $p < 0.05$ level considered reliable.

Results and discussion

Dynamics of joint syndrome indices in the groups studied is shown in Table 1. As we can see from the Table 1, positive dynamics can be noted in both groups after the treatment, accept health assessment according VAS in group I, but grade of gain was different. Thus, VAS ($p < 0.05$) and HAQ ($p < 0.01$) indices improved reliably more significantly in group II after the treatment.

Table 1 : Dynamics of joint syndrome indices post treatment in the studied groups, Me (LQ; UQ)

Indices	I group (n = 47)			II group (n = 46)			U	p
	Prior treatment	Post treatment	Gain (%)	Prior treatment	Post treatment	Gain (%)		
VAS	60 (50; 80)	60 (50; 70)	0	70 (50; 80)	50 * (40; 60)	-29	1361	0.048
Morning stiffness, min.	120 (60; 180)	90 * (60; 120)	-25	120 (60; 180)	90 * (45; 120)	-25	1153	0.713
HAQ	1.6 (1.15; 1.9)	1.5 * (1.12; 1.8)	-6	1.45 (1.1; 1.67)	1.2 * (0.9; 1.4)	-17	1481	0.004
* - differences are reliable after the treatment within one group, $p < 0.05$								

Source: Authors

Analysis of inflammation markers dynamics prior and post treatment in studied groups (Table 2) revealed that reduce of inflammation markers TNF-α ($p < 0.01$) and DAS28 ($p < 0.05$) was statistically more significant in group II comparing to the results of treatment in group I. Tendency for pronounced reduce of CRP after treatment should be noted but statistical reliability was not ascertained.

Table 2 : Dynamics of inflammation markers post treatment in the studied groups, Me (LQ; UQ)

Indices	I group (n = 47)			II group (n = 46)			U	p
	Prior treatment	Post treatment	Gain (%)	Prior treatment	Post treatment	Gain (%)		
ESR, mm/hr	28 (18; 35.5)	20 * (13.5; 28)	-29	25 (15; 33)	18 * (12; 20.5)	-28	1342.5	0.071
CRP, mg/ml	18.1 (10; 36.3)	13.9 * (6; 25.65)	-23	18,1 (12.9; 24.3)	11.3 * (8.15; 14)	-38	1332.5	0.085
TNF-α, pg/ml	2.1 (1.75; 2.8)	2 (1.55; 2.5)	-3	1.9 (1.3; 2.3)	1.5 * (1.05; 1.95)	-17	1558	0.001
DAS28	4.9 (4.22; 5.59)	4.72 (4.08; 5.26)	-3	4.87 (4.2; 5.78)	4.26 * (3.32; 4.97)	-10	1364	0.048
* - differences are reliable after the treatment within one group, $p < 0.05$								

Source: Authors

Analysis of antioxidative system post treatment showed that in group I CAT, mcat/l (prior treatment: 13.82 (13.3; 14.05), post treatment: 13.99 (13.65; 14.36)) and SOD, standard unit (prior treatment: 31.48 (31; 31.59), post treatment: 32.15 (31.8; 32.81)) ($W = 1593$, $p < 0.05$) improved reliably, but integral index F didn't change reliably ($W = 685$, $p = 0.204$), in group II all the indices improved with reliable prevailing over corresponding indices of group I: MDA, nmol/ml ($U = 1103.5$, $p = 0.047$), CAT, mcat/l ($U = 541$, $p = 0.002$), SOD, standard unit ($U = 375$, $p < 0.001$), F, standard unit ($U = 557$, $p = 0.004$).

Analysis of changes in cytokines concentration post treatment (Table 3) showed that patients of group I didn't have statistically significant changes, moreover there was a tendency to ALD and VEGF growing, in group II ALD, VEGF, FGF and ICAM-1 ($p < 0.001$) reduced considerably.

Thus, including of SPIR into complex RA therapy leads to improvement of joint syndrome indices: health assessment according to VAS by 29% and life quality HAQ by 17% comparing to standard therapy; contributes to reduce TNF-α by 17% of in blood; increase of blood antioxidative potential integrative index F by 9% (due to MDA reducing and CAT, SOD increasing); influences positively on reducing of ICAM-1 and FGF 1.5 times, VEGF 2 times in contrast to standard therapy. Complex therapy made reduce DAS28 more than > 0.6, that according to treatment efficacy estimation EULAR is considered satisfactory.

Including of aldosterone blockers into complex therapy leads to reduce of ALD producing which possesses pro-inflammatory and proliferative effects (Rombouts et al. 2001, Sugiyama et al. 2005). This in its turn leads to reduce of pro-inflammatory cytokine expression TNF-α initiating the cascade of autoimmune inflammation reactions and contributing to chronicity of

Table 3 : Dynamics of cytokines post treatment in the studied groups, Me (LQ; UQ)

Indices	I group (n = 47)			II group (n = 46)			U	p
	Prior treatment	Post treatment	Gain (%)	Prior treatment	Post treatment	Gain (%)		
ALD, pg/ml	189.1 (159.63; 233.76)	194 (167.8; 239.7)	3	189.25 (160.63; 235.88)	157.4 * (132.65; 197.82)	-17	1589	< 0.001
ICAM-1, pg/ml	8.2 (7.2; 10)	8.2 (6.9; 9.89)	0	7.66 (6.14; 8.85)	6.34 * (5.37; 7.21)	-17	1727.5	< 0.001
VEGF, pg/ml	467.5 (289.3; 621.8)	478.3 (283; 612.5)	2	455.1 (269; 518.55)	245.6 * (200.05; 355.85)	-31	1596.5	< 0.001
FGF, pg/ml	24.3 (20.23; 28.7)	23.6 (20.8; 27.55)	-3	23.2 (20.28; 27.47)	19.7 * (17.85; 23.4)	-15	1559.5	0.001
* - differences are reliable after the treatment within one group, $p < 0.05$								

Source: Authors

the disease (Romas, Gillespie, Martin, 2002; Bendtzen, Hansen, Rieneck, 2003). Increase of antioxidative blood potential due to complex therapy reduces the processes of hypoxia and lipid peroxidation which are trigger factors of RA pathogenesis (Giatromanolaki et al. 2003, Paleolog 2004). ALD production blocking contributes to pronounced reduce of VEGF and ICAM-1 concentration in blood which are markers of angiogenesis and endothelial dysfunction which are important links of pathological changes in synovial membrane and developing of visceral complications in RA (Klimiuk et al. 2002, Malemud 2007). Reducing of FGF contributes to fibroblast proliferation reducing and normalizes synovial fibroblasts apoptosis reactions, which in its turn may brake pannus growth and joint tissue destruction in RA (Huber et al. 2006, Malemud 2007). Applying of aldosterone blockers will never substitute base therapy of RA (methotrexate, biological anti-cytokine therapy) but can be recommended as effective addition to therapy and control of disease activity in patients with RA and prevention of visceral complications development.

Conclusion

Applying of Spironolactone in complex therapy of rheumatoid arthritis during a year contributes to more pronounced improvement in indices of articular syndrome and patient's life quality, reduce of pro-inflammatory, proliferative and angiogenic cytokines, and more effectively reduces the activity of the disease comparing to standard base therapy.

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