ORGINAL ARTICLE UDC: 616.72-002.77:547.781::[616.72-008.8:616.15

Histamine index and clinical expression of rheumatoid arthritis activity

Histaminski indeks i stepen aktivnosti reumatoidnog artritisa

Aleksandra P. Tomić-Lučić*, Suzana B. Pantović†, Gvozden L. Rosić†, Zdravko M. Obradović†, Mirko A. Rosić*

***University of Kragujevac,** School of Medicine, Department of Physiology, **Kragujevac, Serbia; †Clinical Center Kragujevac,** Internal Clinic, Department of Rheumatology, **Kragujevac, Serbia**

Abstract

Background/Aim. Many arguments prove the pathophysiologic role of histamine in the process of remodeling and joint destruction in rheumatoid arthritis. The aim of our study was to find out if there was a relation between histamine concentration in synovial fluid and blood with clinical expression of disease activity. **Methods.** Histamine concentration in synovial fluid and blood was determinated in 19 patients with rheumatoid arthritis. Histamine concentration measurement was based on the Shore's fluorometric method. Histamine index (HI) was evaluated as a ratio between histamine concentration in synovial fluid and blood. Disease activity score, DAS 28 (3), with three variables (erythrocyte sedimentation rate, the number of swelled joints and the number of tender joints) was also evaluated. **Results.** Our results showed that there was no significant difference in concentration of histamine in synovial fluid and blood related to disease activity. However, there was a significiant difference in the histamine index which was increased proportionally with disease activity. **Conclusion.** Our study indicates that histamine index could be useful in estimation of rheumatoid arthritis activity.

Key words:
arthritis, rheumatoid; histamine; blood; synovial fluid; disease progression.

Apstrakt

Uvod/Cilj. Mnogobrojni dokazi idu u prilog patofiziološkoj ulozi histamina u procesu remodelovanja i oštećenja zgloba kod reumatoidnog artritisa. Cilj načeg istraživanja bio je da utvrdimo da li postoji uzajamna povezanost nivoa koncentracije histamina u sinovijalnoj tečnosti i krvi sa klinički ispoljenom aktivnošću reumatoidnog artritisa. **Metode.** Praćena je koncentracija histamina u sinovijalnoj tečnosti i krvi 19 bolesnika koji boluju od reumatoidnog artritisa. Određivanje koncentracije histamina bilo je bazirano na Shoreovoj fluorimetrijskoj metodi. Histaminski indeks određen je kao odnos koncentracije histamina u sinovijalnoj tečnosti i krvi bolesnika. Određena je aktivnost bolesti prema skoru DAS-28 (3) sa tri varijable (sedimentaija eritrocita, broj bolno osetljivih zglobova, broj otečenih zglobova). **Rezultati.** Nije nađena statistički značajna razlika u koncentraciji histamina u krvi i sinovijalnoj tečnosti u zavisnosti od aktivnosti bolesti. Međutim, postojala je značajna razlika u histaminskom indeksu koji se povećavao proporcionalno sa povećavanjem aktivnosti reumatoidnog artritisa. **Zaključak.** Naša studija pokazuje da bi histaminski indeks mogao biti koristan parametar u proceni aktivnosti reumatoidnog artritisa.

Ključne reči:
artritis, reumatoidni; histamin; krv; sinovijalna tečnost; bolest, progresija.

Introduction

Many arguments prove the pathophysiologic role of histamine in the process of remodeling and joint destruction in rheumathoid arthritis (RA). Histamine modifies behaviour of many cells *in vitro* including chondrocytes, fibroblasts, osteoclasts, macrophages, T lymphocytes, endothelial cells. Histamine also modifies cytokine production and receptor expression [1, 2]. There are evidences of an increased production of chondrocytes matrix metalloproteinases (MMP3, MMP 13) induced by histamine, as well as chondrocytes stimulation and proliferation *via* H1 receptors [3, 4]. Histamine stimulates synovial fibroblast proliferation and that effect is mediated by H1 receptors [5]. Interaction between histamine from mast cells and macrophages and synovial fibroblasts H1 receptors has important role in the process of remodeling and joint destruction in RA [5]. Osteoclasts differentiation is induced by histamine and mediated by H2 receptors [1].

Mast cells express histidine decarboxilase, an enzyme that is essential for histamine production. Human chondrocytes also produces histidine decarboxilase. It indicates that histamine originates from chondrocytes, as well as from mast

Correspondence to: Mirko Rosić, University of Kragujevac, School of Medicine, Kragujevac, Department of Physiology, Svetozara Markovića 69, 34 000 Kragujevac, Serbia. E-mail: mrosic@medf.kg.ac.yu

cells and takes place in inflammatory events in RA [6–8]. There was an evidence of decreased expression of H2 receptors on lymphocytes, bone marrow mononuclear cells and synovial fibroblasts, as well as decreased expression of H1 receptors on RA chondrocytes [9, 10]. It means that beneficial effects of histamine could be decreased due to H2 receptors hypofunction. Abnormality in the function of histamine receptors could play a significant role in maintaining the inflammation process in RA [10]. It has been suggested that histamine supress TNFα gene expression, as well as its secretion from peripheral blood mononuclear cells. This effect was mediated by H2 receptors [11]. As far as it is concerned, it could indicate that histamine released from mast cells could paradoxically limit the stage of inflammation and immune reaction by supressing cytokine secretion in the H2 bearing cells [11]. However, this effect is suppressed because of a decreased function of H2 receptors in RA patients [9, 10].

There is an increased number of mast cells in synovial tissue of RA patients, predominantly on the places with cartilage erosion. Mast cells contain potent mediators such as histamine, leukotrienes, proteinases, heparin and many cytokines. Therefore, their role in inflammation process and destruction of matrix in RA becomes evident [12]. Le et al. [13] reported that mice that lack mast cells are resistant to inflammatory and erosive arthritis induced by arthritogenic serum. It was proposed that mast cells play an important role as the cellular link among autoantibodies, the complement network, and inflammatory mediators. Therefore, the activation of mast cells makes a pivotal contribution to inflammatory arthritis [13].

It is likely that direct migration of mast cells within tissues is a very important mechanism of increasing the number of mast cells in synovial tissue in RA. There was an evidence that several factors in the synovial fluid can act as mast cell chemoattractants, such as the stem cell factor (SCF), transforming growth factor (TGF β), C5a, and platelet activation factor (PAF) [14–16]. Stem cell factor regulates growth, differentiation, adhesion and activation of the mast cells [17]. Besides that, histamine influences chemotaxis of mast cells by the H4 receptors, their activation leads to mobilisation of intracellular Ca^{++}, and includes Gαi/o protein mechanism and phospholipase C [18]. The expression of H4 receptors was reported on the two populations of cells from synovial tissue (fibroblast-like cells and macrophage-like cells) in RA patients [19–21]. It is lickely that there is a difference in H4 receptors expression in the different stages of RA activity [21].

Recent investigations indicate that the histamine releasing factor (HRF) signifficantly influences the releasing of histamine. Histamine relasing factor is an intracellular protein (as cytokine) that modulates the secretion of cytokines from human basophills, eosinophills, T and B lymphocytes [22]. The expression of HRF and its mRNA is evidented on the pannus (fibroblasts, macrophages) which destroyed cartilage in RA patients, but not in the healthy population. That confirms the role of histamine in pathogenesis of RA and other autoimmune diseases [22].

As far as histamine concentration in synovial fluid of RA patients is concerned there are many contradictory results [23–28].

The aim of our investigation was to detect histamine concentration in synovial fluid and blood in RA patients and to explore its relation with clinical expression of disease activity.

Methods

The investigated patients suffered from RA that was diagnosed in accordance with American College of Rhemumathology (ACR) criteria [29, 30]. The mean age of patients was 57.45 ± 3.56 years, (min 30 max 79, years). There were 15 female patients, and 4 male patients. All patients underwent routine clinical and laboratory investigations. Laboratory data including erythrocyte sedimentation rate, C-reactive protein, rheumatoid factors (latex test and hemaglutination test), blood count, blood urea, blood creatinine, aspartat aminotransferasis, alanin aminotransferasis, were obtained. In clinical assessment radiography of hands and clinical activity of the disease were registred. Clinical activity was determined according to the Disease Activity Score – DAS-28 (3) with three variables (erythrocyte sedimentation rate, the number of swelled joints and number of tender joins) [31, 32]. All patients were classified in three groups according to the disease activity: very active (VA) with DAS-28 (3) score more than 5.1, moderate activity (MA) with DAS-28 (3) score between 3.2 and 5.1, and inactive with DAS-28 (3) score below 3.2. The control group comprised age- and sex-matched healthy persons.

Synovial fluid was obtained from the knee under sterile procedure during therapeutic arthrocentesis, collected in heparinized tubes and centrifuged. Histamine concentration in the synovial fluid and blood of the RA patients was detected. Concentration of histamine in the blood of the 19 healthy individuals were taken as control, too. Histamine index was evaluated as a relation between synovial fluid histamine concentration and blood histamine concentration multiplied by 100.

$$\text{Histamin index} = \frac{\text{Synovial fluid histamine conc. (ng/mL)}}{\text{Blood histamine conc. (ng/mL)}} \times 100$$

Detection of histamine was based on the Shore′s fluorometric method [33].

The mean values of biological parameters were compared using the Student′s *t*-test, where p value of < 0.05 was considered as a statistically significant difference. The data in tables are presented as mean ± standard error of the mean.

Results

Our results showed histamine concentration in synovial fluid in all RA patients about 1.548 ± 0.10 ng/mL. Histamine level in blood of the same group of the patients was 48.84 ± 3.05 ng/mL, while histamine index was 3.155 ± 0.035. Histamine concentration in blood of healthy subjects in the control group was 51.35± 3.75 ng/mL. There was no significant difference in histamine concentration in blood between healthy population and RA patients.

Among the investigated patients, 73.6% (14 patients) had positive rheumatoid factors, and 26.3% (5 patients) had negative. There was no significant difference between the seropositive and seronegative patients in histamine concentration in synovial fluid and blood, as well as in histamine index (Table1).

All patients were clasiffied into three groups according to the disease activity (Table 2): very active (VA) with DAS-28 (3) score more than 5.1, moderately active (MA) disease with DAS-28 (3) score between 3.2 and 5.1, and inactive (IA) with DAS-28 (3) score below 3.2. Histamine levels in synovial fluid and blood, and histamine index, as well as a number of tender and swelled joints and erythrocyte sedimentation rate are presented in Table 2.

The mean number of tender joints in all patients suffering from RA was 6.57 ± 1.07 (median = 6, minimum = 2, maximum = 16). The mean number of swelled joints was 4.42 ± 0.54 (median = 4, minimum = 1, maximum = 9). The mean erythrocyte sedimentation rate was 25.89 ± 3.51 (median = 25, minimum = 6, maximum = 60). The mean value of DAS 28 (3) score was 4.48 ± 0.26 (median = 4.61, minimum = 2.79, maximum = 6.52).

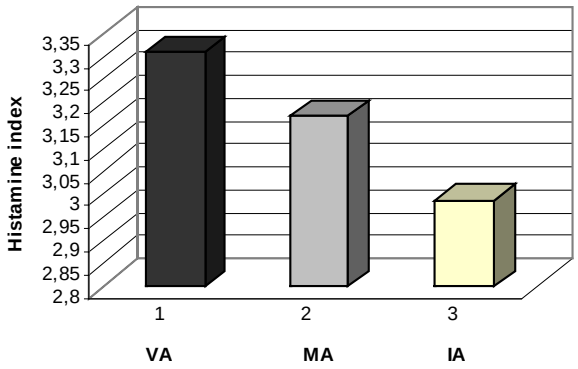

Fig. 1 – Histamine index and rheumatoid arthritis activity according to DAS 28 (3) score: very active (VA) with DAS-28 (3) score more than 5.1; moderate activity (MA) with DAS-28 (3) score between 3.2 and 5.1, and inactive (IA) with DAS-28 (3) score below 3.2. (Student's *t*-test, *$p < 0.05$)

Table 1

Histamine concentration and histamine index in dependence on rheumatoid factor presence

Rheumatoid factor	Synovial fluid (ng/ml) $\bar{x} \pm SD$	Blood (ng/ml) $\bar{x} \pm SD$	Histamine index $\bar{x} \pm SD$
Positive	1.54 ± 0.13	48.33 ± 4.05	3.170 ± 0.043
Negative	1.56 ± 0.16	49.71 ± 4.93	3.131 ± 0.064

Table 2

Dependance of DAS 28(3) score, histamine concentration in synovial fluid and blood, histamine index, number of tender and swelled joints, and erythrocyte sedimentation on rheumatoid arthritis activity

Parameters*	Disease activity		
	very active	moderately active	inactive
DAS 28 (3)score	6.056 ± 0.23	4.52± 0.12	3.07± 0.05
Histamine concentrations (ng/mL)			
sinovial fluid	1.68 ± 0.13	1.57 ± 0.14	1.4 ± 0.24
blood	50.36 ± 3.88	49.61 ± 4.35	46.56 ± 7.71
Histamine index	3.331 ± 0.041†	3.171 ± 0.023†	2.988 ± 0.038
Number of tender joints	13.4 ± 1.2	5.12 ± 0.58	2.16 ± 0.16
Number of swelle joints	7.4 ± 0.67	4.0 ± 0.37	1.66 ± 0.33
Sedimentation rate	46 ± 5.33	24.5 ± 1.42	9.0 ± 0.87

***values of all parameters are given as $\bar{x} \pm SD$; †$p < 0.05$ *vs* inactive**

Histamine concentration in synovial fluid tended to increase in relation to RA activity. Besides, there was no statisticaly significant difference in histamine levels in synovial fluid and blood related to disease activity. However, there was a significant difference in histamine index and it was increased proportionaly to the disease activity (Figure 1).

Discussion

Histamine level in synovial fluid of all the patients with RA was in accordance with the previous literature data [24, 25] that are related to determination of histamine concentration using the fluorometric assay method of Shore [33]. These authors reported increased histamine levels in synovial fluid of patients with ostheoarthritis in comparison with RA. On the other hand, there is data that shows very low (almost undetectable) amounts of histamine in synovial fluid in RA, using the radioimmunoassay method for histamine detection [26]. The authors, who used ELISA method for histamine detection reported decreased plasma histamine levels in RA patients compared to healthy population, while synovial fluid levels were even lower [27]. Other authors detected higher plasma histamine levels in RA patients compared to population without inflammatory arthritis [28]. They notified higher histamine levels in synovial fluid than in correspondent plasma samples. Radioenzyme assay for histamine detection was used in their investigations [28]. Results of various investigations indicate that histamine levels in synovial fluid and plasma depend on the method for histamine detection that is used.

Our results indicate that there are no significant differences in histamine blood concentration between the RA patients and the healthy population. Histamine levels in blood are within the previous reported values in the literature [34, 35].

Rheumatoid arthritis activity was determined in accordance with DAS 28 (3) score observing the erythrocyte sedimentation rate, the number of swelled joints and the number of tender joints [31, 32]. We registrated the lowest synovial fluid histamine levels in the patients with inactive disease (DAS-28 < 3.2). On the other hand, the patients with very active disease (DAS-28 > 5.1) had the highest levels of histamine in synovial fluid. However, these diferences in histamine concentration were not statistically significant because of the large individual variabilities. Although it could be expected that there is a relationship between histamine level in the synovial fluid and desease activity, this "hypothesis" is shown to be incorrect. The definition of the previously mentioned "hypothesis" has been confirmed by many literature data: increased histidine decarboxylase (HDC) activity influenced by cytokines IL-1 and TNF-α which are producted in larger amounts in evolutive forms of RA [36, 37]; increased number of synovial tissue mast cells in patients with active and evolutive form of RA, compared to patients with inactive form and the end stage of the disease [38]; possible different H4 receptor expression in dependance of RA activity [21]; increased histamine levels in bronchoalveolar lavat (BAL) as a useful marker for pulmonal disease activity in RA [39].

Considering the increased histamine concentration in synovial fluid of RA patients with very active disease, it can be suggested that there is a different expression of histamine releasing factor and/or different chemoattractant (SCF, TGF-β, C5a, PAF) concentration that influences mast cells migration according to the disease activity. It was also suggested that histamine could play an important role in autocrine regulation of cytokine secretion from mast cells. That indicates a possible pathway of inflamatory response modulation in certain diseases (asthma) [40].

Although histamine level in synovial fluid tends to elevate according to increased RA activity, there was no significant difference between the patients with a distinct disease activity. There was no difference in blood histamine concentration, as well. That was the reason to involve "histamine index" in our investigation as a more sensitive tool in determination of histamine role in RA.

The patients were treated in accordance with therapeutic strategies for RA, with disease modifying antirheumatic drugs (DMARD) methotrexate and/or chloroquine, nonsteroid antiinflammatory drugs (NSAID), and some of them with low doses of prednisone (≤ 10 mg per day) [41]. There has been literature data that suggests decrease of histamine release influenced by methotrexate and prednisolone [42–44]. On the other hand, a decrease of histamine catabolism by chloroquine inhibition of histamine N-methyltransferase may lead to the increase of histamine concentration [45]. Our results showed no difference in histamine index in relation to the mentioned therapeutic protocols. The reason for this may be the fact that patients were in the various phases of illness activity at the moment of our investigation. There were no difference in DAS 28 score in relation to various therapeutic protocols applied before our investigation. To investigate the effects of various therapeutic protocols on histamine index we have to measure histamine blood and synovial fluid concentrations before and after the applied therapeutic protocol. That will be the subject of our further investigations.

Our results obviously suggest that histamine index is significantly increased in patients with high disease activity. This new parameter is increased proportionally with disease activity expressed by DAS-28 score. Values of histamine index (HI) below 3.02 represent inactive disease, values of HI between 3.02 and 3.29 moderate activity of the RA and HI more than 3.29 very active disease. According to this, histamine index could be a new, additional parameter in the evaluation of disease activity.

Conclusion

It can be concluded that, although there is no difference in histamine concentration in blood and synovial fluid related to RA activity, histamine index is increased proportionally with the disease activity. According to this, histamine index can be considered as a useful parameter in the evaluation of RA activity.

R E F E R E N C E S

1. *Yamaura K, Yonekawa T, Nakamura T, Yano S, Ueno K.* The histamine H2 receptor antagonist cimetidine inhibits the articular osteopenia in rats with adjuvant inducet arthritis by suppressing ihe osteoclast diferentiation induced by histamine. J Pharmacol Sci 2003; 92(1): pp. 43–9.
2. *Falus A, Meretey K.* Histamine: an early messenger in inflammatory and immune reactions. Imunol Today 1992; 13(5): 154–6.
3. *Tetlow LC, Woolley DE.* Histamine stimulates matrix metalloproteinase-3 and 13 production by human articular chondrocytes in vitro. Ann Rheum Dis 2002; 54: 737–40.
4. *Tetlow LC, Woolley DE.* Histamine stimulates the proliferation of human articular chondrocytes in vitro and is expressed by chondrocytes in osteoarthritic cartilage. Ann Rheum Dis 2003; 62: 991–4.
5. *Zenmyo M, Hiraoka K, Komiya S, Morimatsu M, Sasaguri Y.* Histamine stimulated production of matrix metalloproteinase 1 by human rheumathoid synovial fibroblasts is mediated by histamine H1 receptors. Virchows Arch 1995; 427(4): 437–44.
6. *Taylor J, Yoffe R, Brown M, Wolley D.* Histamine stimulates prostaglandin E production by rheumathoid synovial cells and human articular chondrocytes in culture. Arthritis Rheum 1986; 29: 160–6.
7. *Tetlow LC, Woolley DE.* Immunolocalisation of histamine and histidine decarboxylase in chondrocytes of arthritic cartilage. Inflam Res 2004; 53(Suppl 1): S21–2.

8. *Maslinska D, Gujski M, Laure-Kamionkowska M, Szukiewicz D, Wojtecka-Lukasik E.* Subcellular localisation of histamine in articular cartilage chondrocytes of rheumathoid arthritis patients. Inflam Res 2004; 53(Suppl): S35–6.
9. *Tanaka S, Sohen S, Fukada K.* Histamine receptors in arthritis. Nippon Rinsho 1992; 50(3): 455–62.
10. *Tanaka S, Sohen S, Fukada K.* Role for histamine receptors in rheumathoid arthritis. Semin Arthritis Rheum 1997; 26(6): 824–33.
11. *Vannier E, Miller L, Dinarello C.* Histamine suppres gene expression and synthesis of tumor necrosis factor alpha via histamine H2 receptors. J Exp Med 1991; 174: 281–4.
12. *Woolley DE.* The mast cell in inflammatory arthritis. N Eng J Med 2003; 348(17): 1709–11.
13. *Lee DM, Friend DS, Gurish MF, Benoist C, Mathis D, Brenner MB.* Mast cells: a cellular link between autoantibodies and inflammatory arthritis. Science 2002; 297:1689–92.
14. *Olsson N, Ulfgren AK, Nilsson G.* Demonstration of mast cell chemotactic activity in synovial fluid from rheumatoid patients. Ann Rheum Dis 2001; 60(3): 187–93.
15. *Jose PJ, Moss IK, Maini RN, Williams TJ.* Measurement of the chemotactic complement fragment C5a in rheumatoid synovial fluids by radioimmunoassay: role of. C5a in the acute inflammatory phase. Ann Rheum Dis 1990; 49: 747–52.
16. *Nilsson G, Metcalfe DD, Taub DD.* Demonstration that platelet-activating factor is capable of activating mast cells and inducing a chemotactic response. Immunology 2000; 99: 314–9
17. *Galli SJ, Zsebo KM, Geissler EN.* The kit ligand, stem cell factor. Adv Immunol 1994; 55: 1–96.
18. *Hofstra CL, Desai PJ, Thurmond RL, Fung-Leung WP.* Histamine H4 receptor mediates chemotaxis and calcium mobilization of mast cells. J Pharmacol Exp Ther 2003; 305: 1212–21.
19. *Ikawa Y, Suzuki M, Shiono S, Ohki E, Moriya H, Negishi E*, et al. Histamine H4 receptor expression in human synovial cells. Obtained from patients suffering from rheumatoid arthritis. Biol Pharm Bull 2005; 28(10): 2016–8.
20. *Ohki E, Suzuki M, Aoe T, Ikawa Y, Negishi E, Ueno K.* Expression of histamine H4 receptor in sinovial cell from rheumathoid arthritis patients. Biol Pharm Bull 2007; 30(11): 2217–20.
21. *Grzybowska-Kowalczyk A, Wojtecka-Lukasik E, Maslinska D,. Gujski* M, *Maslinski S*. Distribution pattern of histamine H4 receptor in human synovial tissue from patients with rheumatoid arthritis. Inflamm Res 2007; 56(Suppl -): S59–S60.
22. *Maslinska D, Opertowska J, Chabros W, Maslinska M, Grzybowska-Kowalczyk A, Paradowska A,* et al. Histamine releasing factor (HRF) in pannus of joints affected by rheumatoid arthritis. Inflamm Res 2008; 57 (Suppl 1): S61–2.
23. *Buckley MG, Walters C, Wong WM, Cawley MI, Ren S, Schwartz LB,* et al. Mast cell activation in arthritis: detection of alpha- and beta-tryptase, histamine and eosinophil cationic protein in synovial fluid. Clin Sci 1997; 93(4): 363–70.
24. *Renoux M, Hiliquin P, Galoppin L, Florentin I, Menkes CJ.* Release of mast cell mediators and nitrites into knee joint fluid in osteoarthritis – comparison with articular chondrocalcinosis and rheumatoid arthritis. Osteoarthritis Cartilage 1996; 4:175–9.
25. *Partsch G, Schwagerl W, Eberl R.* Histamine in rheumatoid diseases. Z Rheumatol 1982; 41: 19–22.
26. *Rovensky J, Imrich R, Radikova Z, Simorova E, Greguska O, Vigas M*, et al. Peptide hormones and histamine in plasma and synovial fluid of patients with rheumatoid arthritis and osteoarthritis. Endocrine Regulations 2005; 39: 1–6.
27. *Adlesic M, Verdrengh M, Bokarewa M, Dahlberg L, Foster SJ, Tarkowski A.* Histamine in rheumatoid arthritis. Scand J Immunol 2007; 65: 530–7.
28. *Frewin DB, Cleland LG, Jonsson JR, Robertson PW.* Histamine levels in human synovial fluid. J Rheumatol 1986; 13: p. 13–4.
29. *Arnett F, Edworthy S, Bloch D.* The American rheumatism association 1987 revised criteria for the classification of rheumadoid arthritis. Arthritis Rheum 1988; 31: 315–24.
30. *Ranganath VK, Khanna D, Paulus HE.* ACR remission criteria and response criteria. Clin Exp Rheumatol 2006; 24(suppl 43): S14–S21.
31. *van der Heijde DM, van 't Hof M, van Riel PL, van de Putte LB.* Development of a disease activity score based on judgment in clinical practice by rheumatologists. J Rheumatol 1993; 20: 579–81.
32. *van Gestel AM, Prevoo ML, van Hof MA, van Rijswijk MH, de van Putte LB, van Riel PL.* Development and validation of the european league against rheumatism response criteria for rheumatoid arthritis: comparison with the preliminary american college of rheumatology and the world health organization/international league against rheumatis. Arthritis Rheum 1996; 39: p. 34–40.
33. *Shore PA, Burkhalter A, Cohn VH.* A method for the fluorometric assay of histamine in tissues. J Pharmacol. Exp Ther 1959; 127: 182–6.
34. *Bruce C, Taylor WH, Westwood A.* An improved radioenzymatic whole blood, urine, and gastric juice. Ann Clin Biochem 1979; 16(5): 259–64.
35. *Nielsen H, Edvardsen L, Vangsgaard K, Dybkjaer E, Skov P.* Time-dependent histamine release from stored human blood and products. Brithis J Surg 1996; 83(2): 259–62.
36. *Endo Y.* Induction of histidine decarboxylase in inflamation and immune responses. Folia Pharmacologica Japonica 2001; 118(1): 5–14.
37. *Endo Y, Tabata T, Kuroda H, Tadano T, Matsushima K, Watanabe M.* Induction of histidine decarboxilase in sceletal muscle in mice by electrical stimulation, produced by interleukin-1. Journal of Phisiology 2008; 52: 587–97.
38. *Godfrev D, Hardi C, Fugber W, Graziato F.* Quantitation of human synovial mast cells in rheumathoid arthritis and other rheumatic diseases. Arthritis Rheum 1984; 27(8): 752–6.
39. *Casale TB, Little MM, Furst D, Wood D, Hunninghake GW.* Elevated BAL fluid histamine levels and parenchymal pulmonary disease in rheumatoid arthritis.Chest 1989; 96: 1016–21.
40. *Bissonnette E, Hirsh A, Befus C.* Stem cell factor potentiates histamine secretion by muliple mechanisms, but does not affect tumor necrosis factor-alfa release from rat mast cells. Immunology 1996; 89(2): 301–7.
41. *O'Dell JR.*. Therapeutic strategies for rheumatoid arthritis. N Engl J Med 2004; 350(25): 2591–602.
42. *Cronstein BN.* Methotrexate and its mechanism of action. Arthritis Rheum 1996; 39: 1951–60.
43. *Cole ZA, Clough GF, Church MK.* Inhibition by glucocorticoids of the mast cell-dependent weal and flare response in human skin in vivo. British J Pharm 2001; 132: 286–92.
44. *Madlone D, Wilder R, Saavedra-Delgado A, Metcalfe D.* Mast cell numbers in rehumatoid synovial tissues. Correlations with quantitative measures of lymphocytic infiltration and modulation by antiinflammatory therapy. Arthritis Rheum 1987; 30: 130–7.
45. *Horton J, Sawada K, Nishibori M, Xiaodong C.* Structural basis for inhibition of histamine N methyltransferase by diverse drugs. J Mol Biol 2005; 353: 334–44.

Received on February 17, 2009.
Revised on April 23, 2009.
Accepted on July 9, 2009.