Serum galectin-3/galectin-9 ratio is a novel marker of the disease activity in the rheumatoid arthritis

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Hee-Jin Park

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ABSTRACT

Serum galectin-9 and galectin-3/galectin-9 ratio can be used as the disease activity marker of rheumatoid arthritis

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Objective. To investigate the utility of serum galectin-9 and ratio of galectin-3/galectin-9 in the evaluation of the disease activity of rheumatoid arthritis (RA).

Method. The serum concentration of galectin-3 and galectin-9 from RA patients and controls was estimated using enzyme-linked immunosorbent assays (ELISAs). We compared serum concentration of galectin-3 and -9 and ratio of galectin-3/galectin-9 according to disease activity in RA. We followed-up active RA patients and measured serum concentration of galectin-3 and -9 and disease activity after treatment after mean 14 months with disease modifying anti-rheumatic drugs (DMARDs) and tumor necrosis factor (TNF)-α inhibitors. The follow-up serum concentration of galectin-3 and -9 and ratio of galectin-3/galectin-9 were compared with those of initial visits. Next, we measured serum level of cytokines including TNF-α, interleukin (IL)-1β, IL-10 and interferon gamma (IFN-γ), and analyzed association with not only RA activity but also serum concentration of galectin-3 and -9 and their ratio.

Result. Serum concentration of galectin-9 from RA patients was higher than that from controls as well as galectin-3. After treatment active RA mean serum concentration of galectin-9 was significantly elevated than initial concentration, while follow-up mean serum concentration of galectin-3 and galectin-3/ galectin-9 ratio was significantly lower than initial value. Serum concentration of galectin-3

and ratio of galectin-3/galectin-9 in RA patients were positively correlated with DAS 28. Serum level of IFN-γ showed strong association with disease activity, and significantly correlated with serum ratio of galectin-3/galectin-9 as well as concentration of galectin-3.

Conclusion. We firstly showed that serum concentration of galectin-9 had negative correlation with disease activity in RA. And the serum ratio of galectin-3/galectin-9 was more significantly correlated with RA activity than only serum concentration of galectin-3, so it might be a useful complementary serologic marker for assessing disease activity in RA.

Key words :Galectin-9; Galectin-3; Rheumatoid arthritis; Interferon-γ; DAS 28

Serum galectin-3/galectin-9 ratio can predict the disease activity of rheumatoid arthritis

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I. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disorder affecting multiple synovial joints. Inflammation is mainly driven by the overproduction of pivotal pro-inflammatory cytokines that are important in the pathophysiology of RA: tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β, IL-10 and interferon gamma (IFN-γ)[1,2,3]. These cytokines mediate long-term cartilage degradation and bone erosion, resulting in joint pain and dysfunction[4].

Galectin is one of the endogenous lectin-family and its eleven subtypes were found in human. Galectin has been reported to have controversial immune-modulatory entities in the inflammatory diseases; pro-inflammatory and anti-inflammatory actions[5,6]. Until now, three galectin subtypes including galectin-1, galectin-3 and galectin-9 have been mainly studied in rheumatoid arthritis[7-9]. Galectin-3 is known as a pro-inflammatory mediator, which can produce reactive oxygen species in neutrophil, promote chemotaxis of monocytes and inhibit apoptosis of T cells, resulting in accelerating and prolonging the inflammatory processes in rheumatoid arthritis[8,10]. While, galectin-9 might have anti-inflammatory effects; it binds to T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) on the surface of activated $CD4^+$ T cell, leading to apoptosis of activated $CD4^+$ T cell through the $Ca2^+$-calpain-caspase-1 pathway and subsequent apoptosis of fibroblast-like synovial cells [9,11,12]. In the

previous study, galectin-9 concentration in synovial fluid was inversely correlated to the extent of inflammation of synovial tissues in RA patients[9]. Thus, it can be reasonably speculated that galectin-9 concentration in serum can reflect RA activity similar to that in synovial fluid. However, to our best knowledge, there was no report on the link between RA activity and serum concentration of galectin-9, although there have been several reports on the role of serum galectin-3 in RA[13,14]. Further, the ratio of two contrary parameters, galectin-3/galectin-9, might also reflect RA activity, but there was no report regarding their serum ratio in RA patients.

To address these issues, we measured serum concentration of galectin-3 and galectin-9, calculated the ratio of galentin-3/galectin-9 and compared them among healthy subjects and patients with active or inactive RA. Also we investigated the correlation of serum concentration of galectin-3 or galectin-9 and their ratio with RA activity. Further we examined whether their serum concentration or ratio could have significant relation to serum levels of several cytokines involved in pathophysiology of RA.

II. MATERIALS AND METHODS

1. Patients

We prospectively investigated clinical and laboratory results in 70 RA patients. All patients were diagnosed with RA at Severance Hospital, Yonsei University Medical Center, Seoul, Korea, between July 2008 and May 2011. They fulfilled the American College of Rheumatology classification criteria for RA. We assessed the number of tender and swollen joints and health assessment questionnaire (HAQ), visual analogue scale (VAS) scores of physician, patient and global in subjects. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were measured. The disease activity score 28 (DAS28) was used to evaluate RA activity. Patients were divided into two subgroups according to the score 3.2 of DAS 28; the active group (DAS28 > 3.2, N = 35) vs the inactive group (DAS28≤ 3.2, N = 35). Thirty

healthy persons, who visited at Yonsei University health Center for a medical checkup and had no diseases, were distributed to sex- and age-matched control group.

2. *Enzyme-linked immunosorbent assays (ELISAs) of galectin-3 and galectin-9*

Blood samples were obtained in 70 RA patients and 30 controls. Collected samples were centrifuged at 1,000g for 15 min for isolating of serum, aliquoted, and stored frozen at -80°C until use. Serum concentration of galectin-3 and galectin-9 was measured using ELISA kits (Uscn, Life Science Inc., Wuhan, China) according to the manufacturer's protocol. Standard and serum samples incubated for overnight at 37°C. The optical density was read at 450 nm. All samples were analyzed in duplicate.

3. *Measurement of cytokines*

We also measured serum levels of cytokines, TNF-α, IL-1β, IL-10 and IFN-γ, in patients with RA by the MILLIPLEX^{TM} Human cytokine/chemokine panel based on the Luminex xMAP technology. All cytokines were analyzed in duplicate

4. *Followed-up assessment*

Serum samples were also obtains in 35 patients with active RA, when their disease was controlled to the most extent during the follow-up period, and serum concentration of galectin-3 and galectin-9, cytokines and inflammatory serologic markers were measured. Mean interval between the two samples collected was 14months (range; 4-30 months).

5. *Statistical analysis*

Mean differences between continuous variables were evaluated using the Student's *t*-test, and one way ANOVA. Mean differences between mean initial

and follow-up serum in active RA group were evaluated using Wilcoxon signed rank test. Correlations were evaluated using Pearson's correlation coefficients. Sensitivity and specificity of a cut-off value related to serum galectin-3/galectin-9 ratio was set using Receiver operating characteristic (ROC) curve. Determined values were presented as means ± standard deviation. *P* values of less than 0.05 were considered significant. All statistical analyses were performed using SPSS for Windows (version 18.0).

III. RESULTS

7. Patients' characteristics

Seventy patients (male 18, female 52) were evenly divided to the active and inactive groups (N=35 for each). Mean age of patients was 46.9 ± 14.5 years old. Age and sex ratio were not different between two groups. Mean symptom duration in the inactive group is longer than that in the active group (23.3 ± 10.6 months vs 5.4 ± 3.2 months, respectively). Tender and swollen joint counts and HAQ or VAS score were elevated and the time of morning stiffness was extended in patients with active RA compared to those with inactive RA. Patients in the active group had higher level of ESR, CRP, and DAS 28 than those in the inactive group (Table 1).

Table 1. Demographics, clinical characteristics of patients with rheumatoid arthritis according to disease activity

	Inactive RA group (n=35)	Active RA group (n=35)	Control (n=30)	P value
Age (year)	44.94 ± 16.22	48.8 ± 12.67	45.83 ± 15.76	0.532
Sex (M/F)	8/27	10/25	8/22	0.885
Disease duration (months)	23.34±10.58	5.43±3.20		<0.001
Tender joint count	0.97 ± 2.24	13.74 ± 11.57		<0.001
Swollen joint count	0.17 ± 0.857	5.31 ± 4.12		<0.001
HAQ	0.11 ± 0.19	1.12 ± 0.57		<0.001
Pain VAS	0.78 ± 1.12	5.14 ± 2.65		<0.001
Global VAS	0.78 ± 1.00	5.57 ± 2.23		<0.001
Physician VAS	1.05 ± 0.65	5.74 ± 1.26		<0.001
MS time (min)	5.00 ± 14.35	115.0 ± 102.45		<0.001
ESR (mm/hr)	10.69 ± 8.39	64.31 ± 26.67		<0.001
CRP (mg/L)	1.39 ± 1.87	23.45 ± 29.49		<0.001
DAS 28	1.64 ± 0.56	5.65 ± 0.91		<0.001

HAQ: health assessment questionnaire; VAS: visual analogue scale (VAS) scores; pain VAS and global VAS were assessed by patients themselves; physician VAS was checked by doctor; MS time: duration of morning stiffness of hands; ESR= erythrocyte sedimentation rate; CRP=C-reactive protein; DAS 28= disease activity score 28

8. *Serum concentrations of galectin-3 and galectin-9 in healthy controls and RA patients*

Serum concentration of galectin-3 was significantly elevated in RA patients compared to healthy controls (10.0 ± 6.9 vs 6.5 ± 2.4 ng/mL, p=0.001, respectively) (Figure 1A). RA patients had higher serum concentration of galectin-9 than controls (134.4 ± 123.3 vs 100.7 ± 54.4 pg/mL, p=0.002, respectively) (Figure 1B). Thus, we found that serum concentrations of galectin-3 and galectin-9 were associated with the presence of RA.

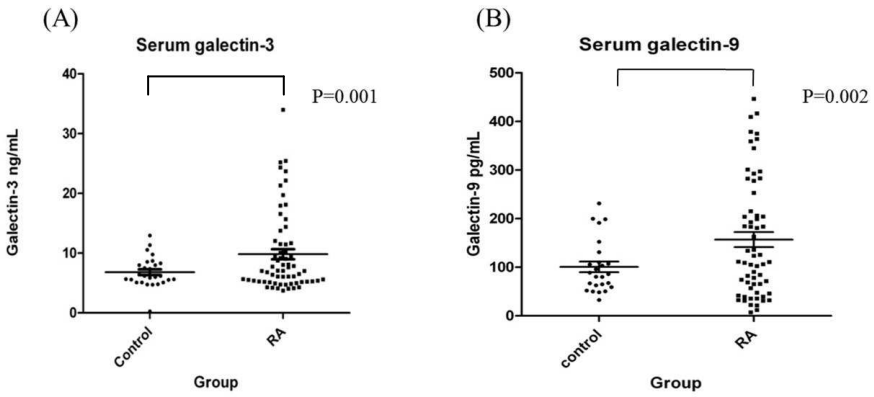

Figure1. Serum concentrations of galectin-3 and galectin-9 in RA patients and controls

Both (A) galectin-3 and (B) galectin-9 concentrations were significantly elevated in the serum of RA patients compared to that of controls (p= 0.001 and 0.002, respectively).

9. *Differences in serum concentrations of galectin-3 and galectin-9 and ratio of glaectin-3/galectin-9 according to disease activity*

To investigate the association of serum concentrations of galectin-3 and galectin-9 with disease activity in RA, we compared their mean serum concentrations and the ratio of galectin-3/galectin-9 between the two RA groups. Mean serum concentration of galectin-3 in the active RA group was significantly higher than that in the inactive RA group (13.4 ± 8.1 vs 6.7 ± 2.5 ng/mL, $p<0.001$, respectively). Mean serum concentration of galectin-9 in active RA group was lower than that in inactive RA group (142.6 ± 122.8 vs 170.7 ± 120.6 pg/mL, respectively), but it was not statically significant. While, mean ratio of galectin-3/galectin-9 in active RA group was significantly higher than that in inactive RA group (258.3 ± 364.1 vs 65.8 ± 58.0, $p=0.002$, respectively) (Figure 2). Although serum concentration of galectin-9 had only a tendency of decreasing according to disease activity of RA, serum ratio of galectin-3/galectin-9 was significantly in positive correlation with disease activity as well as serum concentration of galectin-3.

To elucidate the relation continuously distributed serum concentrations of galectins and their ratio with RA activity, we analyzed their correlation with DAS 28 by Pearson's correlation coefficients and proved that serum ratio of galectin-3/galectin-9 was significantly correlated with DAS 28 (r=0.329, $p=0.013$), comparable to serum galectin-3 level (Figure 3).

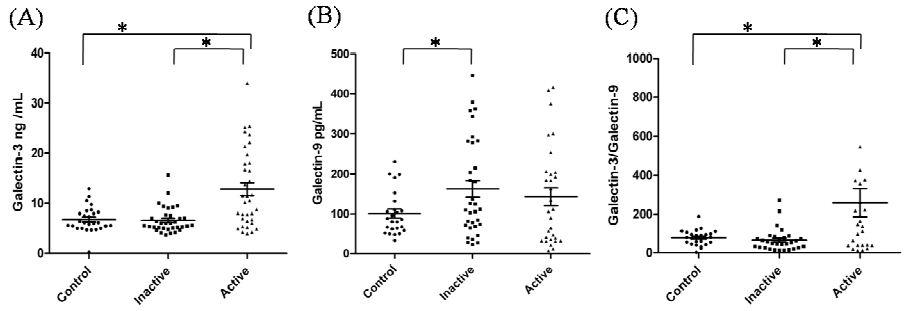

Figure2. Differences of serum concentration of galectin-3 and galectin-9 and glaectin-3/galectin-9 ratio between groups

(A) Serum concentration of galectin-3 and (C) serum ratio of galectin-3 /galectin-9 in the active RA group is higher than those of the inactive group (p=0.001 and 0.002, respectively). (B) The mean concentration of galectin-9 in serum from patients with active RA is lower than that from patients with inactive RA, but is not statically significant (p>0.05), * = p<0.05

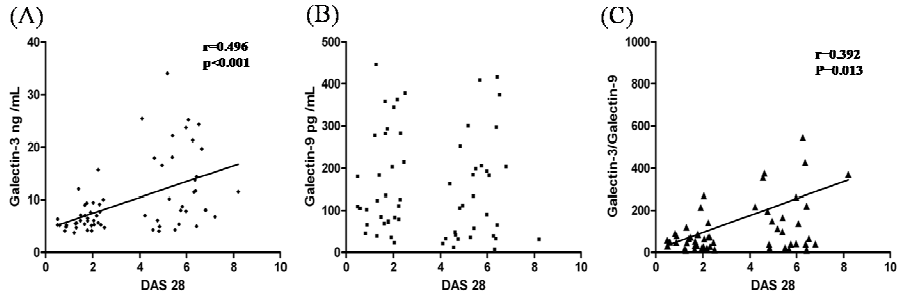

Figure3. Correlations between disease severity and serum concentration of galectin-3 and galectin-9 and galectin-3/galectin-9 ratio in RA patients

(A) Serum concentration of galectin-3 is positively correlated with DAS 28(r=0.496, p<0.001). But (B) serum concentration of galectin-9 is not correlated with DAS 28. (C) Serum ratio of galectin-3/galectin-9 is also positively correlated with DAS 28 comparable to galectin-3(r=0.329, p=0.013).

10. ***Differences of serum concentrations of galectin-3 and galectin-9 and serum ratio of galectin-3/galectin-9 in active RA patients between initial and follow-up visits***

We followed-up 35 patients in active RA group after the diagnosis of RA. When patients had the lowest DAS 28 score during follow-up period, we compared RA activity and serum concentrations of galectin-3 and glaectin-9 and serum ratio of galectin-3/galectin-9 with those at initial visit. The follow-up ESR and DAS 28 were significantly decreased to 14.2 ± 11.6 mm/hr and 1.8 ± 0.8. The follow-up mean serum concentration of galectin-3 and galectins-3/galectins-9 ratio were significantly lower than initial mean value (p=0.002 vs p=0.001, respectively) (Figure 4A, C), whereas the follow-up mean serum concentration of galectin-9 was significantly higher than initial mean value (p=0.023) (Figure 4B). Thus serum ratio of galectin-3/galectin-9 showed alterations between initial and follow-up comparable to serum concentration of galectin-3.

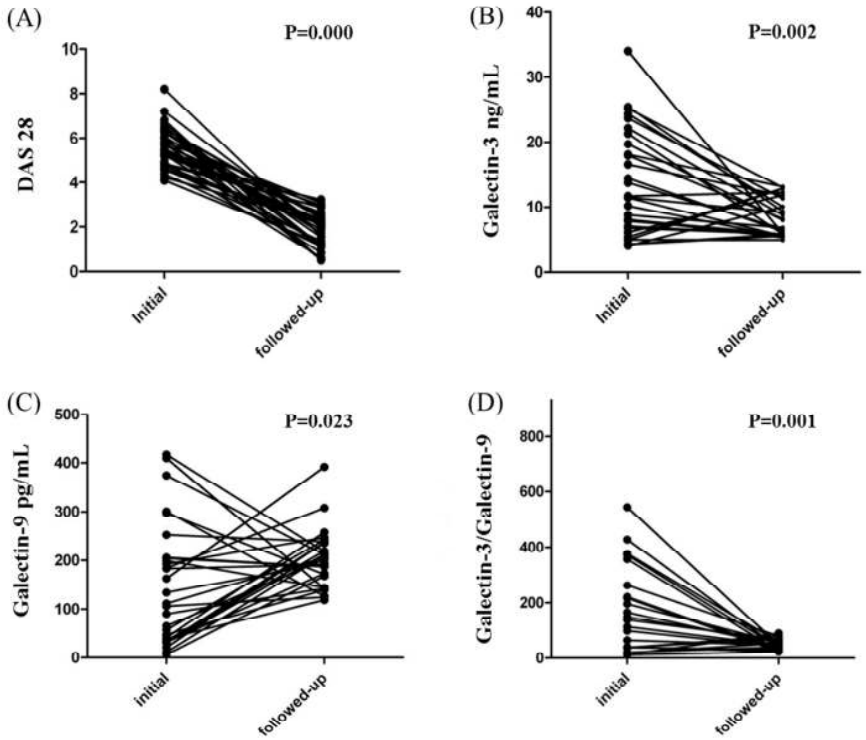

Figure4. Differences of serum concentrations of galectin-3 and galectin-9 and ratio of galectin-3/galectin-9 in active RA patients between initial and follow-up visits

(A) DAS 28 is markedly decreased after treatment of RA at the follow-up time (p<0.001) and (B) serum concentration of galectin-3 and (D) ratio of galectin-3/galectin-9 at the follow-up visit are significantly lower than those at the initial visit (p=0.002 and 0.001, respectively), while (D) the follow-up serum concentration of galectin-9 is higher than that of initial visit (p=0.023).

11. ***Diagnostic accuracy of serum ratio of galectin-3/galectin-9 as a parameter of disease activity in the rheumatoid arthritis***

Since we found that serum ratio of galectin-3/galectin-9 showed the significantly correlation with the disease activity in RA patients, we considered its ratio as another factor to assess the disease activity of RA and assumed its cut-off value using ROC curve (Area under curve=0.700). When a cut-off value of serum galectin-3/galectin-9 ratio was set at 90, the sensitivity was 61.5% and the specificity was 86.7% to predict the active RA (positive predictive value= 80% and accuracy= 75%). Because mean serum ratio of galectin-3/galectin-9 from healthy controls was 78, we assumed a cut-off value at 80 and found that the sensitivity was 61.5% and the specificity was 76.7%. We compared ESR, DAS 28 and HAQ between newly divided active group and inactive group according to a cut-off value of 80, and all of them from active group were definitely higher than inactive group.

12. ***Serum levels of cytokines according to RA activity***

We measured serum concentrations of cytokines in RA patients. Active RA group showed significantly higher level of IFN-γ than those in the inactive RA group ($p= 0.03$) and in paired samples, IFN-γ levels decreased after control of RA activity ($p=0.019$). By contrast, TNF-α, IL-1β and IL-10 level showed no significant differences (Table 2,Table3). When we analyzed the correlation of cytokine-levels in RA patients with ESR, CRP and DAS28, we found that IFN-γ level was positively correlated with all of them ($r= 0.281$, $r=0.463$, $r= 0.256$, $p <0.05$, respectively). Further we investigated the association between levels of cytokines and serum concentration of galectins and their ratio. Galectin-3 exhibited significant correlation with IFN-γ level, while galectin-9 showed inverse correlation with those cytokines, but there was no statistical significance. Serum ratio of galectin-3/galetin-9 had higher correlation coefficients with IFN-γ than serum concentration of galectin-3($r=0.383$, $p=0.014$) (Table 4).

Table 2. Serum levels of cytokine according to disease activity in patients with RA

	Inactive RA group	Active RA group	p value
IFN-γ (pg/mL)	0.84 ± 1.15	2.69 ± 4.19	0.030*
TNF-α (pg/mL)	8.43 ± 4.22	13.50 ± 14.97	0.091
IL-1β (pg/mL)	8.85 ± 29.72	6.31 ± 10.58	0.673
IL-10 (pg/mL)	5.23 ± 1.67	5.45 ± 1.51	0.608

Serum level of IFN-γ was significantly higher in the active RA group than the inactive RA group (p=0.031). The other cytokine show no differences according to activity with significance. *=p<0.05

Table 3. **Serum levels of cytokine according to disease activity in paired patients with active RA**

	Initial	Follow-up	p value
IFN-γ (pg/mL)	2.30 ± 4.01	0.52 ± 0.68	0.019*
TNF-α (pg/mL)	12.91 ± 14.10	9.92 ± 9.03	0.277
IL-1β (pg/mL)	7.00 ± 10.69	5.40 ± 18.53	0.629
IL-10 (pg/mL)	6.35 ± 3.95	5.86 ± 8.19	0.740

Serum level of IFN- γ was remarkably deceased after treatment of RA in the active group (2.30±4.01 pg/mL vs 0.52±0.68 pg/mL, p=0.019, respectively). *=p<0.05

Table 4. Correlation between serum level of cytokines and serologic markers or serum concentrations of galectin-3 and -9 and their ratio

	IFN-γ	TNF-α
	Pearson`s correlation coefficient (r)	**Pearson`s correlation coefficient (r)**
ESR	.281*	0.117
CRP	.463**	.325**
DAS28	.256*	0.154
Galectin-3	.309*	.265*
Galectin-9	-0.133	-0.149
Galectin-3/Galectin-9	.393**	0.185

Serum level of IFN- γ is correlated with ESR(r=0.281, p=0.02), CRP(r=0.463, p<001) and DAS 28(r=0.256,p=0.035) and TNF- α correlated with only CRP(r=0.325, p=0.009). Serum level of IFN- γ is correlated with concentration of galectin-3(r=0.309, p=0.014) and more significantly associated with serum ratio of galectin-3/galectin-9(r=0.393, p=0.003). *= p<0.05, **=p<0.01

IV. DISCUSSION

In the present study, we first demonstrated that serum concentration of galectin-9 was significantly elevated in RA patients compared to controls, and it exhibited a tendency of inverse correlation with disease activity in RA patients. Galectin-9, which has an anti-inflammatory property, is produced and secreted by various cells such endothelial cells and fibroblasts[5]. Especially, galectin-9 is over-expressed in fibroblast-like synovial cells and its mRNA expression is increased in synovial fluid mononuclear cells and tissues in RA patients compared to osteoarthritis patients[9]. Galectin-9 is not produced in physiologic condition (inflammation-free state), but it starts to be expressed by the stimulation of the pro-inflammatory cytokine, interferon (IFN)-γ[15]. Therefore, galectin-9 is thought to be expressed in synovial cells of inflamed joints in RA patients to quench the local inflammation[9,12]. These previous reports might support our finding that serum concentration of galectin-9 increased in RA patients rather than controls.

Moreover, when exogenous galectin-9 was intravenously injected to collagen-induced arthritis (CIA) mice, it improved the severity of arthritis in CIA mice compared to galectin-1, -3 or -8[9]. Also the extent of the susceptibility to arthritis was markedly higher in galectin-9 deficient mice than wild-type ones[16]. Thus, galectin-9 can give a negative feedback to vicious cycle of inflammation in RA affected joints and it can provide consent to our finding that its concentration was elevated in patients with inactive group compared those with active group despite no statistical significance.

To precisely analyze the correlation between serum concentration of galectin-9 and RA activity, we prospectively measured its concentrations with the proper interval based on the improvement of disease activity during follow-up period in patients with active RA. Finally, we confirmed that mean serum concentration of galectin-9 showed the significantly inverse correlation with disease activity of RA.

In this study, galectin-3 exhibited the significantly positive correlation with DAS28 and furthermore, it showed the parallel alteration in its concentration to

DAS28 during follow-up period. The findings of this study were similar to those in the previous studies[13,14], but our study has strength that we enrolled more patients and we compared galectin-3 level in paired samples in comparison with the previous studies. Thus galectin-3 can also help to predict the disease activity in RA patients. Additionally prescribed medications during follow-up period included methotrexate (N=35), hydroxycholoroquine (N=23), leflulonomide (N=15), sulfasalazine (N=17), cyclosporine (N=6) and tacrolimus (N=4). And nineteen patients had received TNF-α inhibitor such as etanercept and adalimumab. Duration that they reached the lowest DAS 28 and change of serum concentrations of galectins had no difference between16 patients who received TNF- α inhibitor and 19 patients who did not (data not shown).

Since galectin-3 or galectin-9 represented one-sided pro-inflammatory or anti-inflammatory property, although each could well reflect RA activity, we first introduced a novel parameter, galectin-3/galectin-9 ratio possessing two opposite properties both to predict and to draw the changes in RA activity. Galectin-3/galectin-9 ratio showed the significant correlation with DAS28 comparable to galectin-3, but the ratio reflected the alteration in RA activity in paired samples better than only galectin-3. Therefore, we propose that galectin-3/galectin-9 might be useful to evaluate the response to treatment.

In addition, we proposed the cut-off value of galectin-3/galectin-9 to assess RA activity, but its sensitivity or specificity was not satisfactory compared to DAS28. From the clinical point view, to complete the equation of DAS28, the item of patient VAS score should be filled up, but patient VAS score is not such a relatively objective parameter. Thus, we need more objective parameter which evaluates the activity of RA in the clinic. With these respects, galectin-3/ galectin-9 ratio might be used as a complementary parameter to DAS28 to assess RA activity and another study with large number of patients will be needed to validate its accuracy.

Here, we introduced a novel parameter, serum ratio of galectin-3/galectin-9, and confirmed that it could reflect RA activity. In the previous studies, TNF-α and

IFN-γ are considered to be correlated with RA activity[17,18], despite their debating accuracy. We showed that serum level of IFN- γ markedly reflected the disease activity, including ESR, CRP and DAS 28. To validate the extent of serum ratio of galectin-3/galectin-9 to assess cross-sectional contribution to disease activity of RA, we analyzed its correlation with TNF-α and IFN-γ and found that serum ratio of galetin-3/galectin-9 was significantly in positive correlated with IFN-γ. Thus, we concluded that serum ratio of galectin-3/ galectin-9 plays a comparable role to current serologic markers as well as serum concentration of cytokines to reflect RA activity.

Our study has several limitations; first, the number of patients with RA was small to search statistical significance for serum galectin-9. Second, we did not measure other kinds of galectin subtypes. Third, there was a significant difference in symptom-duration between patients in active and inactive groups. Last, the levels of cytokines involved in pathophysiology of RA were not measured and their relevancies of galectin-3 or galectin-9 were not analyzed.

V. CONCLUSION

In conclusion, serum concentration of galectin-9 was higher in patients with RA and galectin-9 was higher in the inactive RA than those with active RA and galectin-3/galectin-9 ratio represented the disease activity of RA comparable to galectin-3. Thus, we suggest that galectin-3/galectin-9 ratio possessing both pro-inflammatory and anti-inflammatory properties might be useful to assess RA activity as well as its changes along with follow-up.

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ABSTRACT(IN KOREAN)

류마티스 관절염 환자에서 질병의 활성도에 따른 혈장 내 galectin-9의 농도 및 galectin-3/galectin-9 비의 변화에 대한 전향적 연구

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박희진

목 적: 류마티스 관절염 환자에서 혈장 내 galectin-9의 농도 및 galectin-3/galectin-9의 농도비가 질병의 활성도를 반영할 수 있는 새로운 지표가 될 수 있는지 알아보고자 한다.

방 법: 류마티스 관절염 환자 70명과 건강 대조군 30명을 대상으로 혈장 내 galectin-3와 galectin-9 의 농도를 측정하고 이 농도의 비를 계산하여 산출하였다. 관절염 환자는 DAS 28 기준으로 3.2 이하인 경우 비활성군(환자수 =35 명), 3.2이상인 경우 활성군(환자수 =35명)으로 나누어 연구대상자를 선출하였으며, 활성군 35명은 류마티스 관절염 치료를 시작하고 질병이 조절 되었을 때 galectin-3와 galectin-9의 농도를 재측정하였다. 이를 통해 질병의 활성도에 따라 혈장 내 galectin-9의 농도 및 galectin-3/galectin-9의 농도비가 변화하는지 비교하였으며 치료 이후 변화에 대해서도 분석하였다. 또한 혈장 내 싸이토카인의 농도를 함께 측정하여 galectin-3와 galectin-9의 농도가 싸이토카인의 혈장 내 농도 변화와 연관성이 있는지 분석하였다.

결 과: 대조군에 비해 류마티스 관절염 환자군에서 혈장 내 galectin-9과 galectin-3의 농도가 높았다. 그리고 질병의 활성도가 높을수록 galectin-3

의 농도는 증가하였으며 galectin-3/galectin-9의 비도 증가하였다. 그러나 galectin-9은 활성군이 비활성군에 비해 혈장 농도가 낮았으며, 활성군 환자에서 치료 이후 galectin-9의 농도가 의미 있게 감소하여 질병의 활성도와 반비례하는 것을 확인하였다. 또한 류마티스 환자에서 DAS 28은 galectin-3뿐 만 아니라 galectin-3/galectin-9의 농도비가 의미 있게 상관성을 보였다. 혈장 내 싸이토카인 중에서는 인터페론-감마(IFN-γ) 가 질병의 활성도를 반영하였으며 적혈구 침강속도 및 C-반응성 단백질, DAS 28 모두 상관성을 보였다. 그리고 galectin-3/galectin-9의 농도비는 혈장 내 인터페론-감마의 농도와 가장 유의한 상관성을 보였다. 따라서 혈장 내 galectin-3/galectin-9 농도비는 류마티스 관절염에서 질병의 활성도를 반영한다고 볼 수 있었다.

결 론: 염증억제작용을 하는 것으로 알려진 galectin-9 은 류마티스관절염의 활성도가 낮을 수록 혈장 내 농도가 증가하는 것을 처음으로 밝혔다. 또한 질병의 활성도와 상관성이 있다고 밝혀진 galectin-3을 단독으로 측정하는 것보다 galectin-3/galectin-9의 농도비가 류마티스 관절염 활성도를 더 의미있게 반영하였다. 그러므로 혈장 내 galectin-3/galectin-9의 농도비는 임상적으로 질병의 활성도를 평가하는데 쉽게 사용할 수 있는 보조적인 혈청학적 지표가 될수 있을 것이다.

핵심되는 말: 류마티스 관절염; galectin-3; galectin-9; 질병활성도