EJMO

DOI: 10.14744/ejmo.2017.47955
EJMO 2017;1(2):69–75

Research Article

Relationship Between Disease Activation, Serum Erythrocyte Sediment Level and C-reactive Protein Level in Rheumatoid Arthritis Patients Receiving Anti-Tumor Necrosis Factor Alpha Treatment

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Abstract

Objectives: Rheumatoid arthritis (RA) is a progressive, multisystemic disease with a course of chronic inflammation, and which is thought to be immune-originated, though the etiopathogenesis is not fully understood. Elimination of pain with adequate treatment is important in terms of preventing damage and systemic complications. As such, it is important to determine prognostic markers in the evaluation of disease activation. The goal of this study was to explore the relationship between the Disease Activity Score 28 (DAS 28), one of the disease activation indices, erythrocyte sedi-ment rate (ESR) and C-reactive protein (CRP) level.

Methods: A total of 93 patients who presented at the rheumatology polyclinic of Dr. Lütfi Kırdar Kartal Training and Research Hospital were included in the study. Of those, 46 were included in the study group (receiving anti-tumor necrosis factor alpha [TNF-α] treatment), and 47 were included in the control group (not receiving anti-TNF-α treatment). The patients enrolled did not have any malignancy or other inflammatory disease. Patients included in the study were also screened for findings of anemia, polycythemia leukocytosis, or lymphocytosis. The DAS 28 score of the study pa-tients was obtained from medical records. Biochemical analyses, as well as CRP and ESR measurements taken after 1 year, were recorded retrospectively.

Results: A statistically significant relationship was observed between the DAS 28 score and ESR in patients who received anti-TNF-α treatment, while a statistically significant relationship was not found between the DAS 28 score and CRP level. There was no statistically significant relationship in RA patients between the DAS 28 score and ESR or CRP in those who did not receive anti-TNF-α treatment.

Conclusion: According to these results, RA patients receiving anti-TNF- α treatment demonstrated a better ESR marker of disease activity in long-term follow-up.

Keywords: Anti-tumor necrosis factor-alpha, C-reactive protein, erythrocyte sediment rate, rheumatoid arthritis

Cite This Article: Gungor Olcum G, Celik Yagan F, Cekin R, Ataman Tasan D, Erdogan M, Aliustaoglu M. Relationship Between Disease Activation, Serum Erythrocyte Sediment Level and C-reactive Protein Level in Rheumatoid Arthritis Patients Receiving Anti-Tumor Necrosis Factor Alpha Treatment. EJMO. 2017; 1(2): 69-75

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Submitted Date: June 07, 2017 **Accepted Date:** August 09, 2017 **Available Online Date:** August 26, 2017

Rheumatoid arthritis (RA) is a chronic systemic disease generally with a course of inflammation in more than one joint. There are also other findings outside joints such as rheumatoid nodules, vasculitis, heart or lung disease, anemia and peripheral neuropathy. Much as the exact cause is unknown the general opinion is that it is an autoimmune disease.[1] Although complex autoimmune etiopathogenesis of Rheumatoid Arthritis is not fully understood, it has been revealed in studies that some cytokines such as TNF-alpha, IL-6, and mediators have an important role in the development of the disease in the inflammatory process.[2]

Anti-TNF drugs have been found to be effective in suppressing clinical signs and symptoms of Rheumatoid arthritis (RA), prevention of disability, enhancement of the life quality and prevention of joint destruction. To this end, there are anti-TNF drugs which are used in the world and our country and one of them is Etanercept which is a TNF receptor fusion protein that is connected to TNF-alpha and which blocks TNF-alpha's connecting to receptors; and Infliximab which is a 75% human, 25% rat chimeric anti TNF-alpha monoclonal antibody; and Adalimumab is 100% human monoclonal antibodies. These three anti-TNF medicines generally show their anti-inflammatory effects by antagonizing TNF-α. However due the difference in their chemical structure and physiological characteristics they have different effects on the immunity system and inflammation.[3]

Erythrocyte sediment rate (ESR) and C-reactive protein (CRP) are non-specific acute phase reactants. CRP is one of the best indicators of inflammation. It is synthesized in hepatocytes and its level increases in cases of infection, inflammation, malignancy and tissue damage.[1] ESR is an indirect marker of inflammation and is affected by conditions such as age, gender and anemia.[4]

Although they are not specific, it was shown in the laboratory studies that ESR and CRP levels correlate with disease activation and radiographic findings in RA patients.[5] In addition to studies in literature revealing the fact that CRP is the most useful indicator in evaluation of disease activity,[6] there are also publications stating that there is strong correlation between disease and severity, and ESR. [7] The objective of this study is to assess the correlation between disease activation, and serum ESR and CRP levels in patients receiving anti-TNF-α therapy.

Materials and Methods

The study was approved by the Local Ethics Committee. 93 female patients who applied to the Rheumatology Polyclinic of Dr. Lutfi Kirdar Kartal Training and Research Hospital were included in the study and 46 of them were included in the study group (receiving Anti TNF-α-treatment) while 47 of them were included in the control group (not receiving Anti TNF-α-treatment).

The ages of patients changed between 25 and 64 with an average age of 48.52±9.96. Disease diagnosis was made according to diagnosis criteria of the American Rheumatism Association's RA diagnosis criteria reviewed in 1987. Accordingly patients with at least 4 positive criteria were accepted as RA patients. Patients with liver disease, renal insufficiency, malignancy and additional inflammatory disease were not included in the study. Patients detected with anemia, polycythemia, leukocytosis, lymphocytosis and with compliant findings with infection in concurrent blood count tests were excluded from the study in patients.

Information as to disease-related symptoms, presence of systemic disease, drug use and family history as well as general physical examination and examination of the locomotor system of RA patients were received from the medical records thereof. Biochemical analyzes as well as CRP and ESR measurements and initially viewed RF measurements of patients were recorded. Disease severity of patients included in the study and control groups were determined according to disease activity score (DAS 28).

Determination of the Disease Activity

DAS 28 scores assessing rheumatoid arthritis activity were calculated.[8] DAS 28 scores were considered to be inactive, moderate and very low if they were ≤3,2,>3,2≤5,1 and >5,1 respectively.

Parameters Used in DAS 28 Calculations

1. Number of sensitive joints: sensitivity in hands, PIF (proximal interphalangeal), MKF (metacarpophalangeal), wrist, elbow, knee and shoulder joints.
2. Number of swelled joints: swelling and arthritis findings in hands, PIF (proximal interphalangeal), MKF (metacarpophalangeal), wrist, elbow, knee and shoulder joints.
3. Overall well-being: to what extent the patient's rheumatoid arthritis was active in last seven days; overall well-being by requiring patients to give a value between 0 and 100: proximity to zero indicated lack of activity while proximity to 100 indicated high amount of activity.
4. Sediment value.

All these parameters were calculated by using calculators specially prepared for DAS 28 with a fixed formula.

DAS 28=(0.56 x √ HES) + (0.28 x √ SES) + (0.70 x Ln (ESR)) + (0.014 x GHA)

Table 1. Evaluation of general characteristics by groups

	Study group(n=46) Mean±SD		Control group (n=47) Mean±SD		[+]p
Age	47.60±10.15		49.42±9.78		**.386**
Duration of illness (months)	89.92±27.93		85.70±14.54		**0.414**
CRP	18.35±20 11		14.11±27.77		**.402**
ESR	43.02±19.36		35.17±24.63		**0.092**
HDL	55.95±1.68		58.63±14.61		**0.195**
LDL	108.62±26.03		110.27±21.78		**.798**
Triglycerides	116.71±41.21		124.21±55.05		**.764**
Total cholesterol	86.32±42.42		191.31±25.43		**.515**
DAS 28	5.29±0.83		4.86±1.17		**0.073**
History	**n**	**%**	**n**	**%**	**[++]p**
Cigarette	2	4.3	8	17	**0.091**
HT	19	41.3	22	46.8	**.593**
DM	0	0	0	0	–
Statin or fenofibrate	0	0	0	0	–
HBs Ag	0	0	0	0	–
RF					
Positive	25	54.3	23	48.9	**.602**
Negative	21	45.7	24	51.1	

SD: Standard deviation; CRP: C-reactive protein; ESR: Erythrocyte sediment rate.

Table 2. Use of anti-TNF in study group

Using anti-TNF	n	%
Adalimumab	18	39.1
Etanercept	18	39.1
Infliximab	10	21.7

TNF: Tumor necrosis factor.

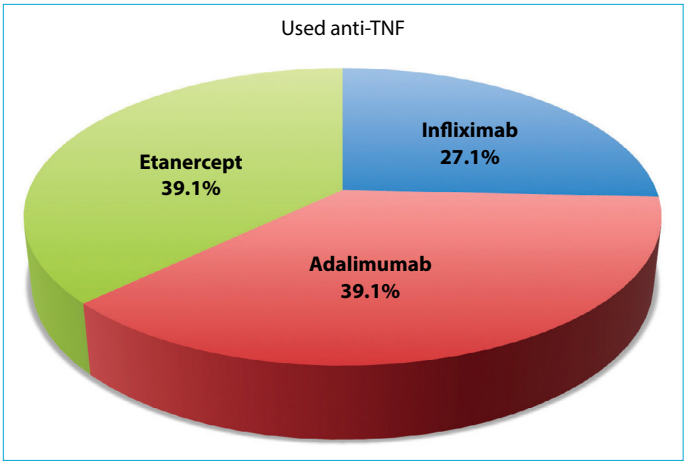

Figure 1. Distribution of Anti TNF used.

General Health Assessment (GHA): GHA by requiring patients to put a line corresponding to their current pain on the point on a 10 cm line: 0 was evaluated as no pain, 10 cm was evaluated as irresistible pain. The point marked by the patient was used as GHA.[8]

It was paid attention that the blood of the patient was taken after 12 hours of fasting between 08: 30–09:00 from the front arm vein and laboratory values received in our hospital were taken into consideration in his biochemical measurement. CRP measurement values of 0–5 mg/L was accepted as normal CRP level while CRP measurement values of 5 mg/L and above was accepted as high CRP level. Because sediment value was accepted as <ESR 20 mm/h for men and <30 mm/h for woman determined by the American Rheumatism Association's (AC) RA remission criteria and because the study and control groups in our work was composed of female patients 30 and over was accepted as high.[9]

Rheumatoid factor (RF): between 0 and 15 IU/ml was accepted as normal (negative) value and 15 IU/ml and over was accepted as high value (positive).

Statistical Method

While the findings obtained in the study were evaluated, NCSS (Number Cruncher Statistical System) 2007 & PASS 2008 Statistical Software (Utah, USA) program was used. Student t test was used while the study data were evaluated in comparison of parameters with normal distribution between two groups in comparison of descriptive statistical methods (Mean, Standard deviation) in addition to comparison of quantitative data and Paired Samples t test

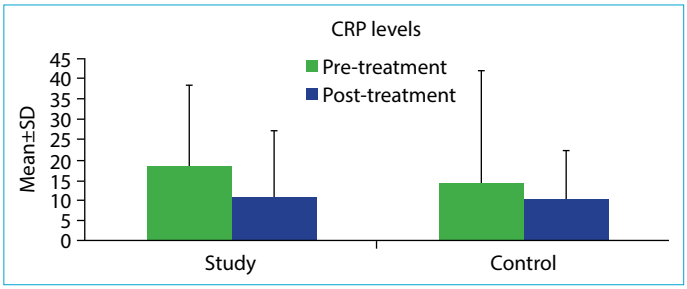

Figure 2. Distribution of CRP levels.

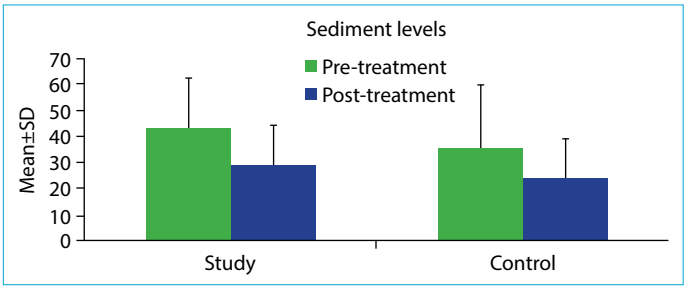

Figure 3. Distribution of ESR levels.

Table 3. CRP evaluation

CRP	Study group Mean±SD	Control group Mean±SD	p
Start	18.35±20.11	14.11±27.77	**.402**
After 12 months	10.79±16.42	10.35±11.79	**.883**
Differences in CRP level at start and after 12 months	**0.001****	**0.272**	

SD: Standard deviation; Student t test; Paired Samples t test; *p<0.05; **p<0.01.

Table 4. Sediment evaluation

Sediment	Study group Mean±SD	Control group Mean±SD	p
Start	43.02±19.36	35.17±24.63	**0.092**
After 12 months	28.50±16.13	24.27±14.99	**.186**
Difference in ESR level observed at start and after 12 months	**0.001****	**0.001****	

SD: Standard deviation; Student t test; Paired Samples t tes; **p<0.01.

was used for analysis of changes before treatment to after treatment change. The Chi-square test was used for comparison of qualitative data. The significance was evaluated at p<0.05 level. Correlation analysis was made by using Pearson's correlation coefficient.

Results

93 female patients were included in the study and 46 of them were included in the study group (RA diagnosed patients receiving Anti TNF-α-treatment) while 47 of them were included in the control group (RA diagnosed patients not receiving Anti TNF-α-treatment). The ages of patients changed between 25 and 64 with an average age of 48.52±9.96.

There was no statistically significant difference between groups in terms of age, duration of illness, CRP, ESR, HDL, LDL, triglyceride, total cholesterol and DAS 28 scores (p>0.05).

Table 5. Relation between DAS 28 scores and CRP

	DAS 28	
	r	p
Study group		
CRP	.256	**0.085**
ESR	.451	**0.002****
Control group		
CRP	-0.114	**.445**
ESR	0,035	**.817**

R: Pearson correlation coefficient; **p<0.01; DAS: Disease activity score CRP: C-reactive protein.

There was no statistically significant difference between groups in terms of smoking status, HT, DM, statin or fenofibrate and HbsAg status (p>0,05). There was no statistically significant difference between the rheumatoid factor status according to the groups (p>0,05).

18, 18 and 10 of the study group patients used Adalimumab, Etanercept and Infliximab respectively.

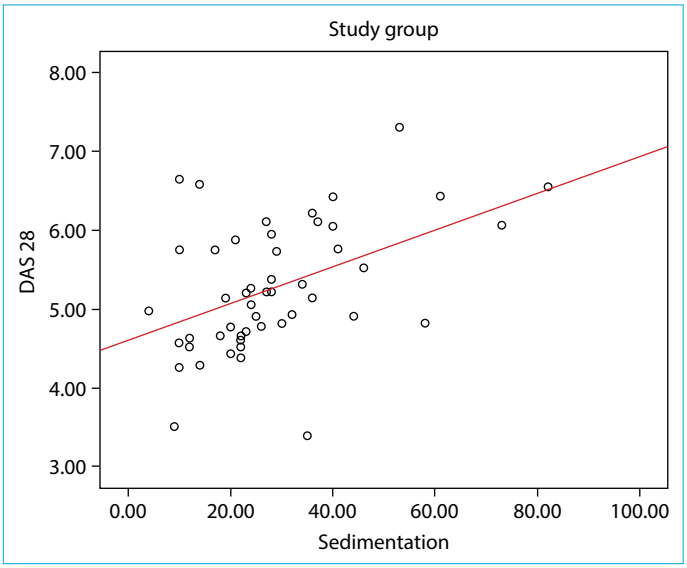

Figure 4. Relation between sediment level and DAS 28 scores in the study group.

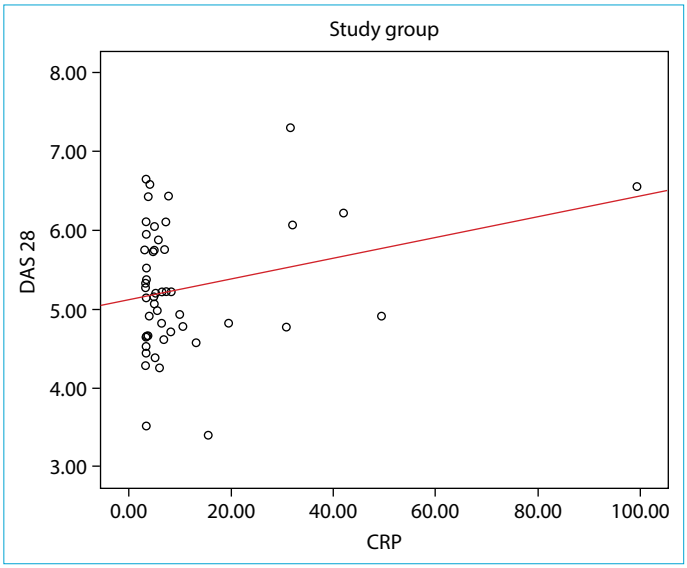

Figure 5. Relation between CRP level and DAS 28 scores in the study group.

Start CRP levels of the study group was not statistically different in a significant way compared to start CRP levels of the control group (p>0.05). There was no statistically significant difference between groups in post-treatment CRP levels (p>0,05). In the study group, there was a statistically significant decrease in CRP levels after 12 months compared to start CRP levels (p<0.01). In the control group, there was a statistically significant change in CRP levels after 12 months compared to baseline start CRP levels (p>0.05).

There was no statistically significant difference between start sediment levels of the study group and start sediment levels of the control group (p<0.05). There was no statistically significant difference between the sediment levels observed after 12 months in two groups (p>0,05). In the study group, there were statistically significant decreases in sediment levels after 12 months compared to start CRP levels (p<0.01). In the control group, there were statistically significant decreases in sediment levels after 12 months compared to start CRP levels (p<0.01).

In the study group, there was no statistically significant relation between DAS 28 scores and CRP (p>0,05) while there was statistically significant relation between the scores of DAS 28 and Sediment positively at the level of 45.9% (p<0,01). In the control group, there was no statistically significant relation between DAS 28 scores and CRP and Sediment (p>0.05).

Discussion

RA is a disease seen with inflammation in multiple joints, characterized by symmetrical and erosive synovitis which can develops severe disability and deformities, etiology of which is not known, with a chronic course and inflammatory character and which is systemic and autoimmune. It is seen in the whole world and in all races and ethnic groups.[1] The target in RA treatment is relief of pain, taking the disease under control, and prevention of joint erosions and systemic complications. Erosions which are radiological indicators of joint damages in patients with RA emerge to a large extent in the first two years of the disease and it is thought that joint erosions accelerate after this period. Patients who do not receive appropriate treatment may become unable to work within 10 years. Failure to choose appropriate treatment approaches may lead to reactivation and progression of the disease. As such, the selection of appropriate treatment combinations is very important. Recently developed biological agents have begun to be used in combination therapy. In the studies conducted it was found that combinations of methotrexate-anti-TNF-α and methotrexate-leflunomide are more effective performed than application of only MTX.[10, 11]

In the study conducted by E Lindqvist et al., in order to investigate the relation between joint damage and prognostic laboratory it was expressed that evaluation of anti-CCP,IgA, RF, anti-IL-1α, ESR, CRP, joint oligomeric matrix protein (COMP) combinations in early RA will be useful in terms of evaluating the prognosis.[12]

The evaluation of the activation of the disease in RA and determination of treatment protocols accordingly is very important in prevention of morbidity and achievement of remission. Therefore indices covering clinical, laboratory and radiological evaluations have been developed to evaluate disease activity.

CRP is one of the best indicators of inflammation. It is synthesized in hepatocytes and its level increase in cases of infection, inflammation, malignancy and tissue damage.[1, 13] CRP reflects short term change in disease activity in RA.[14] ESR is an indirect indicator of inflammation and its level is affected by conditions such as age, gender, anemia, fibrinogen level hipergamaglobune and RF.[4] ESR reflects the past few weeks of disease activity in RA.[14] Despite their not being specific, it was shown in laboratory studies that ESR and CRP levels correlate with disease activity and radiographic findings in RA patients.[5, 15]

In a study conducted by Mallya et al. in patients with RA, they examined the relation between ESR and CRP values, and objective, semi-objective and objective criteria of RA and they revealed the fact that there is a strong correlation between both ESR and CRP values and CRP showed a stronger relation compared to ESR with subjective and semi-objective criteria, including the morning arrest.[15]

K. Yildirim et al., in their study consisting of 97 patients comprising patients with RA receiving only MTX, and a combined therapy of MTX and SAZ (not receiving glucocorticoid and other immunosuppressive treatment) and healthy individuals have aimed to determine the relation between DAS 28 score, ESR, Hp, ferritin, fibrinogen and DAS 28/ESR levels. They have reported that ESR and CRP were higher in the study group compared to healthy subjects and that there was a strong correlation between DAS 28 score and CRP levels compared to other acute phase proteins (eg, Hp, Ferritin, fibrinogen).[6, 16]

In the study condcuted by JS. Dixon et al. with 105 RA patients, in which study group received hydroxychloroquine, sulfosalazine, gold preparations and azathioprine treatment, in which the control group received only aspirin therapy, it was shown, when acute phase proteins seen after 6 months of treatment were compared with CRP and ESR, that CRP is a better disease index of activation than haptoglobulin, fibrinogen or ESR.[17]

In the study conducted by F. Wolfe to develop an easy follow-up form for follow-up and evaluation of RA patients following 7 Clinical variables were examined: 1- Demography (age, gender, race, BMI, disaese period) 2- Clinical variables (AIMS, VAS, Grip Strength, Number of affected joints; VAS, HAQ), 3- Hematological parameters (Hemoglobin, HCT, RBC,MCV), 4-Acute phase proteins (Thrombocyte, CRP, ESR, alpha-1 antitrypsin, Haptoglobulin), 5-Immunoglobulin (GAM), 6-Various proteins (Albumin, Prealbumin; C4), 7-Rheumatoidfactor). Although in the study, CRP is thought to be the better test in relation to measurement of acute phase it has been mentioned that ESR may be better than CRP in general measurement even in cases when inflammation is very low because it is sensitive to immunoglobulins and RF. As a result, it has been expressed that combined use of ESR and CRP may provide more useful information than use of single test.[18]

In a study conducted by MM. Ward et al. in RA patients using DMARD, they have reported that in the 12th and 24th week of the treatment, ESR is more sensitive to change compared to CRP. It was stated that changes before 12th week were evaluated in very few studies.[19]

In the study carried out by NG Arvidson et al. on daily life activities and acute phase reactors of RA patients using Infliximab, the TNF alpha antagonist, ESR, CRP, Fibrinogen, Granulocyte, Lymphocyte, Platelet and HAQ scores were evaluated on start day, 4th day and 14th day and it was expressed that CRP decreased in a fast way while decrease of ESR was slower. It was expressed that Infliximab was effective on CRP, fibrinogen and ESR in treated patients in the early period.[20] As is seen in literature, there are few studies showing the relation between CRP changes and disease activation in RA patients who use DMARD or Anti TNF. In particular, studies showing this relation in RA patients who use Anti TNF are both few and limited in terms of short-term results. Arvidson et al. have focused on short-term consequences of the correlation between CRPESRand disease activation in RA patients who use Infliximab.[20] Furthermore, there are also studies in literature with RA patients using a single type of anti-TNF.[20]

Our study group consisted of RA patients who use one of the 3 anti TNF (Etanercept, Infliximab, Adalimumab) In contrast, the control group consisted of RA patients who did not use anti-TNF. We determined our monitoring period as 1 year and thus targeted long-term results.

In this study, there was significant decrease in ESR values in the study and control group, ESR after 1 year compared to start. In contrast, CRP values decreased significantly only in the study group. However, when the change in ESR and CRP parameters were evaluated according to disease activation, it was seen that ESR had better correlation with disease activation in anti TNF activity group. In contrast, there was no relation between CRP and disease activity in the control group. In the same way there was no relation between ESR and disease activation in the control group. As a result of this study, we can say that there is a better correlation between disease activation and ESR in long-term in RA patients receiving anti-TNF. We think that new studies to be conducted with laboratory tests with a wider population in patients treated anti-TNF which show the activation in early and late periods of the disease will be effective in determination of appropriate treatment protocols and decreasing the number of disability and deaths arising from the disease.

However, it was observed that ESR showed better correlation in study group which used anti TNF with disease activation when the change in ESR and CRP parameters were evaluated according to disease activation. In contrast, there was no relation between CRP and disease activity in the study and control groups. In the same way there was no relation between ESR and disease activation in the control group.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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