THE ROLE OF INTERLEUKIN-1 RECEPTOR ANTAGONIST IN THE PATHOGENESIS OF ARTHRITIS

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ABSTRACT

Objective: *The objectives from this study was to compare serum levels of interleukin-1 receptor antagonist (IL-1Ra) with synovial fluid levels in patients with rheumatoid arthritis (RA) and osteoarthritis (OA), and to correlate the level of the naturally occurring IL-1 inhibitor with indices of disease activity and severity in RA patients. A correlation was also done between IL-1Ra and tumor necrosis factor α (TNF-α) with knee radiographs in OA patients as a parameter of disease severity.*

Methods: *IL-1Ra and TNF-α were assessed by Enzyme Linked Immunosorbent Assay (ELISA) in serum and synovial fluids in 20 female patients with RA, 20 female patients with OA and in the serum of 15 controls.*

Results: *We found that IL-1Ra and TNF-α concentrations were increased in both RA and OA sera compared with the control group. Although there was no significant difference between the concentration of serum IL-1Ra in RA patients when compared to those with OA, we observed that its mean level were higher in patients with RA. Moreover, IL-1Ra levels were correlated significantly with the levels of ESR, CRP as well as all the clinical parameters of disease activity measured in RA patients. We also found significant correlation between the synovial levels of both IL-1Ra and TNF-α in RA when compared to OA patients. The mean*

level of synovial IL-1Ra in RA patients is about twice that was found in OA patients.

Conclusion: *Our data reveal a consistent association between IL-1Ra production and disease activity and severity in RA patients. It also reveals a high serum and synovial IL-1Ra and TNF-α in OA patients that make us suggest that OA should be considered a disease with a systemic and local inflammatory response. Further studies are needed to determine the association of cytokines and its inhibitors in OA.*

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic inflammation of the synovium that often leads to destruction of articular cartilage and juxtaarticular bone *(Malyak et al., 1993).* However, joint erosion is a prevalent feature of RA, which is not of many other chronic arthritides. Of these chronic arthritides is osteoarthritis (OA) that is characterized by focal cartilage loss and osteophyte formation. In healthy states, chondrocytes maintain cartilage integrity by regulating the balance between cytokines mediated protein synthesis and degradation. Disruption of this equilibrium in favor of matrix degradation results in the pathologic changes typical of destructive arthritis *(Fraenkel et al., 1998).*

Tumor necrosis factor a (TNF-α) and interleukin-1 (IL-1) are considered as master cytokines which play important role in pathogenesis of arthritis. They produce inflammatory cells and help in secretion of destructive enzymes, which lead to proteoglycan degradation, cartilage destruction and bone erosion *(Van de Loo et al., 1995 and Jiang et al., 2000).*

Interleukin-1 receptor antagonist (IL-1Ra) functions as a major natural anti-inflammatory cytokine. It selectively inhibits the effect of IL-1 by competing for IL-1R *(Schiff, 2000).* IL-1Ra includes one secreted isoform (sIL-1Ra) and three intracellular isoforms (icIL-1Ra) sIL-1Ra is secreted from monocytes, macrophages, neutrophils, hepatocytes and other cells. Both secreted and intracellular IL-1Ra contributes to maintenance of balance between IL-1 and IL-1Ra and homeostasis of immune system *(Arend and Guthridge, 2000).* Disturbance of this balance with IL-1Ra deficiency relative to IL-1 predisposes to the development of destructive arthritis *(Jiang et al., 2000).*

IL-Ra is implicated in metalloproteinase down regulation as feed back mechanisms that are used by chondrocytes to regulate the level of proinflammatory cytokines and collagenases, this influence the clinical stage of remission or active osteoarthritis *(Shlopov et al., 2000).* Now IL-1Ra is considered as a one of biological agent in the treatment of RA *(Bresnikan et al., 1998).* It reduces radiological progression of RA, suppresses joint erosion and inhibits osteopenia *(Jiang et al., 2000 and Van de Berg, 2001).* Treatment with IL-1Ra has shown no evidence of immunosuppression or increased risk of infection or malignancy. It is a safe and well tolerated drug can be used in treatment of RA *(Schiff, 2000).*

The objectives from this study were to compare serum levels of IL-1Ra with synovial fluid levels in patients with RA and OA, and to correlate the level of the naturally occurring IL-1 inhibitor with indices of disease activity and severity in RA patients. A correlation was also done between IL-1Ra and TNF-α with knee radiograph in OA patients, as a parameter of disease severity.

MATERIALS &METHODS

This study was carried out at the Rheumatology and Rehabilitation Outpatient Clinic of Ain Shams University Hospitals. It included 55 individuals who were divided into 3 groups:

RA patients

Twenty-female patients with RA who fulfilled the criteria of the American College of Rheumatology *(Arnett et al., 1988).* The clinical data included data about sex, age, pain scale, and disease severity, duration of morning stiffness, number of joints affected, and activity of daily living.

Clinical assessment for patients was done in the morning by the same investigator. Disease activity was assessed using the multivariate analysis done by *(Mallya & Mace, 1981).* Disease severity was assessed using the classification of progression of RA reprinted from the classification of progression of RA reprinted from Steinbrocker and colleagues *(Steinbrocker et al., 1979).* Severity of pain was assessed using the horizontal 10cm visual analogue scale (VAS). Activity of daily living was assessed using the American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis *(Hochbery et al., 1992).*

For comparative studies the patient population were divided into 3 groups (grade I, II, and III) according to the grading of their disease activity,

severity and activity of daily living (no patients with grade IV were included). Another classification was based upon the patient's medical treatment. in which patients were divided into 3 groups. Group I comprised of 10 patients who were receiving methotrexate (MTX) and non-steroidal anti-inflammatory (NSAIDs) drugs. Group II comprised of 8 patients who were receiving NSAIDs only. Group III comprised of 2 patients who were receiving NSAIDs and steroids.

OA patients

Twenty- female patients with knee OA who fulfilled the criteria of the American college of Rheumatology *(Altman et al., 1986),* each patient had a bilateral weight bearing anterior-posterior knee radiographs. All radiographs were scored by a radiologist interested in musculoskeletal radiology. The scoring was done using Kellgren-Lawrence Scale *(Kellgren & Lawrence, 1957)* for OA knees. According to the grading of the x-ray the patients were divided into 3 groups (grade IV patients were not included). All patients were on non-steroidal anti-inflammatory drugs (NSAIDs) except 3.

Control group

Fifteen age-matched apparently healthy females.

Sample collection

Synovial fluid samples

Synovial fluid (SF) samples were aspirated from knees of all patients (RA and OA) under the most aseptic conditions. For ethical reasons, no samples were collected from controls. The medial side approach, around the midpoint of the patella was used. Following arthrocentesis, aliquots of SF were immediately placed into glass tubes containing EDTA. The samples were incubated at 37°c for 20 minutes to remove cells. The cell- free SF samples were then stored at-20°c until used.

Serum samples

From each individual enrolled in the study 4 ml of venous blood was collected. It was allowed to clot at room temperature for about 30 minutes, after which centrifugation was done for 10 minutes. The serum was divided into aliquots and stored at -20°c until used.

Analytical methods

Routine laboratory investigations: This included complete blood picture on Coulter S Plus Cell Counter (Coultronics, FI, USA) and differential blood count, ESR by Westergren method ,C-reactive protein (CRP) and Rheumatoid factor (RF) by agglutination method.

Serum IL-1Ra and TNF-alpha assay: They were determined using Quantikine ELISA kits *(Elsasser et al., 1993 and Jouvenne et al., 1999)* supplied by R&D systems Inc. (Mckinley Place, N.E., Minneapolis, MN.USA) the values were expressed in pg/ml.

Statistical analysis

In the statistical comparison between the control group and the two studied groups (OA and RA) the nonparametric Mann-Whitney rank sum test was used. The significance (p-value) was computed and the decision to accept the no-difference hypothesis was based on a *P*-value greater than 0.05. Correlation between the clinical parameters was done using Wilcoxon signed ranks test and the one way ANOVA test.

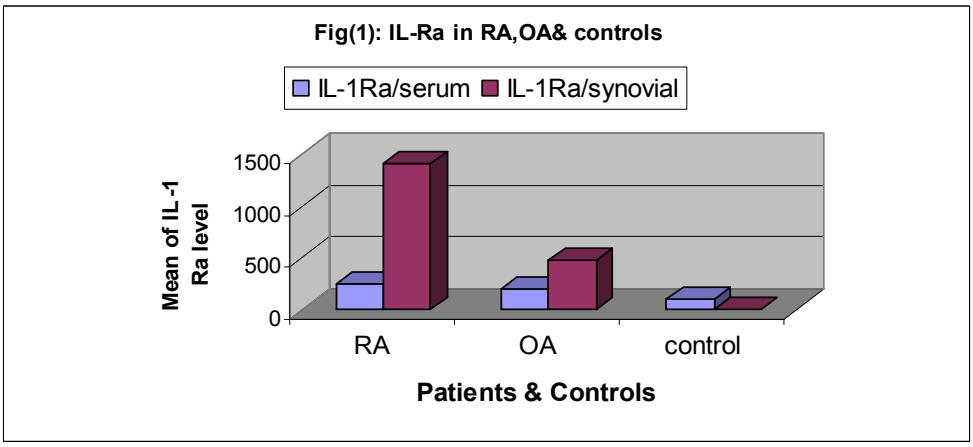
RESULTS

The results are illustrated in Tables 1 and 2 and figures 1&2. The clinical parameters of patients and controls are summarized in table (1).

Table (1): Characteristics of patients and control groups.

Variable	Minimum	Maximum	Mean
RA/Age	35 years	72 years	41.85 years
OA/Age	45 years	63 years	53.7 years
Control/Age	45 years	55 years	47.4 years
RA/duration	1 year	10 years	6 years
OA/Duration	1 year	10 years	5 years
RA/pain severity	2.5 cm	8.0 cm	5.38 cm

Analysis of serum and synovial IL-1Ra in RA and OA patients (Fig. 1):



The serum levels of IL-1Ra in RA and OA patients were significantly different than the control (p= 0.002 in both cases), while there were no significant differences between the serum levels of IL-1Ra in RA patients when compared to OA patients (p= 0.664).

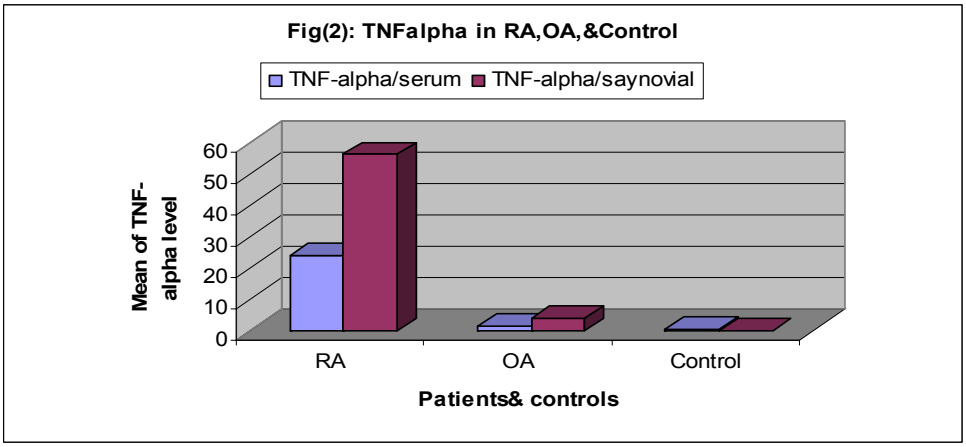
The mean serum levels of IL-1Ra in RA and OA patients were 243.25±50 pg/ml and 200.8±40 pg/ml respectively. The mean levels of IL-1Ra in controls were 99.4±11 pg/ml.

There were a highly significant difference between the IL-1Ra synovial levels in RA patients when compared with those of OA (*P*=0.000).

The mean synovial levels of IL-1Ra in RA and OA patients were 1411.5±70and 480.6±55 pg/ml respectively.

Analysis of serum and synovial TNF-α in both RA and OA patients (Fig. 2):

A highly significant difference was observed between the serum level of TNF-α in RA patients (mean=24.0±3 pg/ml) and the control (mean =0.24±0.2 pg/ml) were p= 0.000. A second significant difference was observed between serum TNF-α levels in OA patients (mean=1.18±0.1pg/ml) when compared to the control were p=0.001. A third significant difference was observed between TNF-α serum levels in RA patients when compared to those of OA patients (p=0.000). The fourth significant difference was observed between the synovial TNF-α levels in RA patients (mean=56.45±6.0 pg/ml) and synovial TNF-α (mean=3.9±2 pg/ml) in OA (p=0.000).



Correlation between the clinical parameters and each of Il-1Ra and TNF-α in the serum and synovial fluid of RA patients (Table 2):

Using Wilcoxon signed ranks test, the clinical parameters (pain scale, morning stiffness, disease duration and number of joint affected), hemoglobin level (HB), ESR, and CRP were found to be positively correlated with the levels of IL-1Ra in both serum and synovial fluid (*P*= 0.000 for all) also, these parameters, were found to be positively correlated with the levels of TNF-α in both serum and synovial fluid with exception of ESR in synovial fluid the activity of daily living (ADL) parameter correlated positively with the level of IL-1Ra in serum but not with its levels in the synovial fluid.

Table (2): IL-1Ra and TNF-α in RA patients.

	Disease activity	Disease severity	ADL
IL-1Ra/serum	0.009 (S)	0.012 (S)	0.040 (S)
Il-1Ra/synovial	0.044 (S)	0.029 (S)	0.262 (NS)
TNF-α/serum	0.003 (S)	0.004 (S)	0.132 (NS)
TNF-α/synovial	0.004 (S)	0.007 (S)	0.177 (NS)

S=Significant, NS=Non significant

For inter-group correlation with the levels of serum and synovial IL-1Ra, the RA patients' clinical parameters disease activity, disease severity, and ADL were further divided into three groups (I, II, & III). We found a

significant correlation between groups of disease activity and severity and levels of serum and synovial IL-1Ra and TNFα. As regard to groups of ADL, there was a significant correlation only to serum IL-1Ra and TNF-α but a non significant correlation to synovial IL-1Ra and TNFα.

When we divided the patients of RA into three groups according to their medical treatment received and compared each group to the level of IL-1Ra and TNF-α in both serum and synovial no significant differences (P>0.05) were found (using *Kruskall-Wallis U test*).

Correlation between the levels of IL1-Ra and TNF-α in both synovial fluid and serum and the x-ray grading of OA patients

Using one-way ANOVA test a significant difference was found (P=0.01) between the level of synovial IL-1Ra and x-ray grading of OA patients. On the other hand no significant differences were found between the levels of serum IL-1Ra, serum TNF-α, or synovial TNF-α and the x-ray grading of OA patients.

DISCUSSION

It is now generally accepted that a network of cytokines participated in the breakdown of cartilage and induction of chronic destructive arthritis.

Along with TNF-α and other proinflammatory cytokines, IL-1 plays a pivotal role in the pathogenesis of RA. Thus, in a disease characterized by increased IL-1 production, detection of specific IL-1 inhibitor is essential. And because of the accumulating data implicating cytokines in the pathogenesis of OA, and the recent evidence for mild systemic inflammation of this disease *(Spector et al., 1997),* we questioned whether IL-1Ra and TNF-α might be associated with OA or not, we also established a correlation between those cytokines and the clinical parameters of RA patients.

In this study we measured the levels of TNF-α and IL-1Ra in both the serum and synovial fluids of female patients with both RA and knee OA. We found that IL-1Ra and TNF-α concentrations were increased in both RA and OA sera compared with control. Although there was no significant difference between the concentrations of serum IL-1Ra of RA patients when compared to those with OA, we observed that its mean levels were higher in patients with RA. Our results are confirmed by many studies, *Hrycaj et al. (1995) and Shlopov et al. (2000)* detected a high level of TNFα in serum

and synovial fluid of OA patients. *Horai et al. (2001)* found a high level of TNFα in RA joint. *Gabay et al. (2001)* reported that production of IL-1Ra increased in joints during induced arthritis. Moreover, IL-1Ra levels were correlated significantly with the levels of ESR, CRP, as well as all the clinical parameters of disease activity measured in RA patients which in consistence with *Buchs et al. (2001)* study, These results indicate that IL-1Ra, although an acute phase protein with anti-inflammatory properties *(Gabay et al., 1997),* can also be used as a new biologic marker of disease activity in RA. Because of the significant correlation between IL-1Ra and TNF-α and the number of joints affected this demonstrates a link between those markers and the kinetics of joint destruction in RA. These results are consistent with results found by *(Jouvenne et al., 1999).*

An important finding in our study is the significant correlation between the synovial levels of both IL-1Ra and TNF-α in RA when compared to OA patients. Another interesting finding is that the mean levels of synovial IL-1Ra in RA patients is about twice that was found in OA patients. This high increase in RA patients was explained by *(Seitz et al., 1995)* as an indicator of an effective drug treatment. They observed those high levels in patients entering the inactive state of the disease. However, in this work our patients had a high pain scale, morning stiffness that lasts more than 30 minutes and a high ESR and CRP levels that we would have an opposite explanation to what they had claimed. We suggest that this increase reflects an imbalance between the levels of cytokine and cytokine inhibitors. In other words the produced cytokine is not sufficient to put the patient into a state of remission, which also means that a careful drug monitoring should be done either to increase the dose or to add another regime of treatment.

Keeping in mind that IL-1 is a key mediator of RA, the positive correlation between IL-1Ra levels and indices of disease activity in patients with active synovitis may simply reflect insufficient production of IL-1Ra in relation to the excessive amounts of IL-1 produced locally (Jouvenne et al., 1999). We agree with others *(Arend, 2001 and Buchs et al., 2001)* that are an imbalance between pro-inflammatory cytokines and cytokine inhibitors or antagonists may be one factor predisposing to initiation or perpetuation of rheumatoid synovitis. Results confirmed the important role of IL-1 and TNF-α in the mediation of tissue damage in the rheumatoid joint. They also reported that deficiency of IL-1Ra relative to IL-1 led to more severe disease and even to the spontaneous development of RA.

Since the extra cellular stimuli such as the proinflammatory cytokines IL-1 and TNF-α are over expressed in rheumatoid synovium, clinical trials with cytokine inhibiting molecules such IL-1Ra may be promising. Distler and his colleagues *(Distler et al., 1999)* were the first to use this method. They found it promising, however their clinical safety and usefulness was not proven. On the other hand, many studies reported that IL-1Ra is a specific selective inhibitor of IL-1 pathway, offers an important new and safe treatment for RA. Furthermore, IL-1Ra therapy (by gene therapy intra-articular or subcutaneous injection) significantly reduced joint inflammation and prevent radiographic progression both in RA and OA animal models *(Fernandes 1999; Arend & Guthridge Jiang et al., 2000 and Van de Berg, 2000, 2001).* Another study which was published early this year *(Bresnihan, 2001)* concluded that targeted interleukin inhibition significantly reduce both the clinical manifestations and the rate of progressive joint damage in patients with RA. In our study we didn't find any correlation between the serum and synovial IL-1Ra levels and the type of treatment received. We think a study with a larger number of patients is needed.

Another interesting finding in our study is the high mean synovial level of TNF-α in RA patients when compared to those of OA. This may explain the destructive nature of RA compared to the less erosive and destructive nature of OA. In our study we observed high mean levels of synovial TNF-α and IL-1Ra in OA patients when compared to serum levels of the same patients. This agreed with others *(Shlopov et al., 2000).* They explained this result by the fact that many cell types in the synovium could produce this cytokine, such as macrophages synovial fibroblast or chondrocytes themselves. A second interesting finding is that these high levels are present in patients with mean disease duration of 5 years, so the presence of cytokines in OA does not have to be in the early stages of the disease only. This may explain the perpetuating nature of OA. In other words once OA is initiated the process continue unchecked. Moreover, we found no relation between TNF-α and severity of OA shown by radiological studies. *Kammermann et al., (1996).* Disagreed with us on their study on animal models, they found a relation to disease severity.

As in early OA the chondrocytes exhibit a transient proliferative response. Chondrocytes also produce increased quantities of cytokines such as IL-1, TNF-α, and other growth factors and enzymes. IL-1 and TNF-α promote cartilage degradation by inducing enzymes that degrade collagen

and proteoglycans and block the synthesis of cartilage matrix proteins *(Woo et al., 1992).* In theory, an imbalance between the production of cytokines and its inhibitors tips the scales in favor of increased proteolysis of extra cellular matrix could promote and maintain osteoarthritis changes

Although OA is not considered a disease with systemic inflammatory response *(Loose et al., 1993).* We observed a high serum TNF-α and IL-1Ra in our knee OA patients compared to controls. This finding may suggest that a low-grade inflammatory process may play a significant role in this disease. Our results are supported by some studies that found elevated serum C-reactive protein in subjects with OA compared to controls *(Wolfe, 1997);* they also had suggested that a low grade of inflammation is going on. Our data is also consistent with results of Fraenkel and his colleagues *(Fraenkel et al., 1998).* who observed an increase of serum IL-Ra production in knee OA patients compared to hand OA.

In conclusion, our data reveal a consistent association of IL-1Ra an IL-1 inhibitor, production and disease activity and severity in RA patients. It also reveal a high serum and synovial IL-1Ra and TNF-α in OA patients that make us suggest that OA should be considered a disease with a systemic and local inflammatory response. Further studies are needed to determine the association of cytokines and its inhibitors in OA.

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دور مضاد مستقبل إنترلوكين-1 في حدوث التهاب المفاصل

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قسمي الطب الطبيعي و التأهيل و الباثولوجيا الإكلينيكية* كلية الطب - جامعة عين شمس

يهدف هذا البحث إلى مقارنة مستوي مضاد مستقبل إنترلوكين 1 في المصل و في سائل المفاصل الزلالي في مرضى الرثيان المفصلي و الالتهاب العظمى المفصلي و أيضا علاقة هذه العوامل بنشاط المرض و حدته في مرضى الرثيان المفصلي و أيضا علاقتهم بالتغيرات الظاهرة في مفصل الكبة بواسطة التصوير بالأشعة في مرضى الالتهاب العظمى المفصلي. و قد تم قياس هذه العوامل في المصل و السائل المفصلي الزلالي في 20 سيدة يعانون من الرثيان المفصلي و 02 يعانون من الالتهاب العظمى المفصلي و تم مقارنتهم ب15 سيدة طبيعية كمجموعة ضابطة. و قد وجد زيادة ذو دلالة إحصائية عند مقارنة مضاد مستقبل إنترلوكين1 و عامل ضمور الورم بالمجموعة الضابطة في كل من مرضى الرثيان المفصلي و مرضى الالتهاب العظمى المفصلي بينما لم يوجد أي اختلاف ذو دلالة إحصائية بين تركيز هذين العاملين في المصل في كل من مرضى الرثيان المفصلي و مرضى الالتهاب العظمى المفصلي. و كذلك وجد أن مضاد مستقبل إنترلوكين 1 له علاقة ذو دلالة إحصائية بمستوى سرعة الترسيب و مستوى البروتين التفاعلي ج و العوامل الإكلينيكية لنشاط المرض في مرضى الرثيان المفصلي.

و قد وجد أيضا علاقة ذو دلالة إحصائية بين مستوى مضاد مستقبل إنترلوكين1 و عامل ضمور الورم في السائل المفصلي في مرضى الرثيان المفصلي عند مقارنته بمرضى الالتهاب العظمي المفصلي. و أيضا وجد أن مستوى مضاد مستقبل إنترلوكين 1 في السائل المفصلي لمرضى الرثيان المفصلي ضعف الموجود في السائل المفصلي لمرضى الالتهاب العظمى المفصلي. و من هذه النتائج نستنتج أنة يوجد علاقة وثيقة بين مضاد مستقبل إنترلوكين1 و نشاط المرض و حدته في مرضى الرثيان المفصلي .و أيضا يوجد مستوى عالي لكل من مضاد مستقبل إنترلوكين1 و عامل ضمور الورم في المصل و السائل المفصلي الزلالي في مرضى الالتهاب العظمى المفصلي و هذا جعلنا نقترح أن مرض الالتهاب العظمى المفصلي له ردود فعل للالتهابات موضعية و عامة في الجسم و نحن في حاجة إلى مزيد من الدراسات لتحديد علاقة هذه العوامل بمرض الالتهاب العظمى المفصلي .