Medical Journal of Babylon
Vol. 14- No. 2 : 280 - 289, 2017
http://www.medicaljb.com
ISSN 2312-6760©2017 University of Babylon

Original Research Article

Determination of Immune Markers in Renal Disorders Throughout Biological Therapy of Rheumatoid Arthritis

Manal Azzet Aziz[1*] Abdul Kareem Shehab Diab[2] Neama Yassir Habil[3]
[1]Institute of Medical Technology, Baghdad, IRAQ
[2]College of Health and Medical Technology, Baghdad, IRAQ
[3]Medical Technical Institute, Baghdad, IRAQ

[*]E-mail:manalbazaz@yahoo.com

Accepted 28 May, 2017

Abstract

This study was conducted to investigate the serum level of C-reactive protein, erythrocyte sedimentation rate, creatinine, glomular filtration rate, tumor necrosis factor-α (TNF-α) and interlukin-6 (IL6) in rheumatoid arthritis patients associated with renal impairment treated with antiTNF-α. This study included two groups; 54 patients with rheumatoid arthritis treated with Etanercept (Enbrel) 50mg and 58 patients with rheumatoid arthritis on treatment other than Anti TNF-α as a comparative group. The results showed that renal function tests of rheumatoid arthritis patients who received Anti TNF-α were different, before and after treatment. A "significant decrease in the value of creatinine and in the level of GFR after 6 months of treatment was observed ($P \leq 0.0001$). The erythrocyte sedimentation rate, C-reactive protein, interlukin-6 and TNF-α increased in rheumatoid arthritis patients with renal disorders before biologic therapy compared with the comparison group who were on treatment other than Anti TNF-α. Following the administration of Anti TNF-α therapy. These inflammatory parameters were significantly diminished in the rheumatoid arthritis patients after the therapy. The treatment with Anti TNF-α seems to be a factor in restoring the levels of the inflammatory immune markers.

Key Words: Rheumatoid Arthritis, renal disorder, cytokines, CRP, ESR

الخلاصة

صممت هذه الدراسة على مرضى التهاب المفاصل الرثوي لقياس مستوى بعض المؤشرات الالتهابية (البروتين المُتَفاعِلُ C ، معدل ترسب الدم ,انترلوكين ٦ ,عامل تنخّر الأورام- ألفا, ولاظهار العلاقة بين وضيفة الكلى (معدل الترشيح الكبيبي ومستوى الكرياتينين في المصل) ،عند استخدام العلاج البايولوجي (ايتانرسبت) في مصل ٥٤ مريضا مقارنة مع ٥٨ مريضا لم يستخدموا العلاج البايولوجي كمجموعة مقارنة . اظهرت نتائج هذه الدراسة انخفاض ملحوظ في مستوى الكرياتينين وزيادة ملحوظة في مستوى (معدل الترشيح الكبيبي) في مرضى البحث بعد استخدام العلاج لمدة ٦ اشهر مقارنة بمجموعة المقارنة ($P<0.0001$). بينما اظهرت النتائج زيادة ملحوظة في المؤشرات الالتهابية البروتين المُتَفاعِلُ C، معدل ترسب الدم ,انترلوكين ٦ ,عامل تنخّر الأورام- ألفا في المرضى المشاركين بالبحث مقارنة مجموعة المقارنة ($P<0.0001$) . بينما ظهرت زيادة ملحوظة في مستوى وظيفة الكلى مقارنة بمجموعة السيطرة ($p<0.0001$). وتبين بعد ستة اشهر من اعطاء جرعات من العلاج البايولوجي لهؤلاء المرضى تحسن ملحوظ في مستوى وظيفة الكلى والمؤشرات الالتهابية بالمقارنة مع مجموعة الاخرى ($P<0.0001$).

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that targets articular and extra-articular organs, which may leads to substantial morbidity and mortality [1] In addition, uncontrolled RA can cause progressive renal disorders, high medical and social costs, and decreases life expectancy [2].

Reports revealed that in industrialized country the incidence of RA disease affects 0.5-1% of older adults' population and higher in women than men [2-3].

Few studies have specifically examined the association of renal diseases in patients with RA treated with biological therapy (Anti TNF -α). A significant rate of renal damage in RA was found in some researches, that can be expressed by both a reduced glomerular filtration rate (GFR) and tubular function. This complication may range from 5% to 50%.[4-5] The complications in RA patients are clinically common, because it is not only limits the management of primary disease *per see*, but also increases the rate of death.[1] In fact, end stage renal diseases are the common cause of death in RA patients [6].

Over the last decades, a close association between inflammation and renal disease has been recognized in several studies [7-9]. It is not easy to define the main cause of impaired renal function in patients with long standing RA because of the coexistence of multiple possible causes. Diseases modifying anti-rheumatic drugs (DMARD) such as D-penicillamine, cyclosporin and methotrexate that are currently used to treat rheumatic diseases have an impact on renal function due to their side effects, inflammatory mediators, and renal paranchymal toxicity [5,10].

The treatment of autoimmune rheumatic diseases has gradually developed by the introduction of biological therapy that is targeting inflammatory mediators to treat autoimmune disease such as RA. This type of treatment, the biological therapy, is a tumor necrosis factor alpha inhibitor (anti TNF-α). These medications act by inhibiting the proinflammatory cytokine TNF-α such as infliximab and the IL-6 receptor inhibitor (tocilizumab) in which it targets a protein called IL -6.[5] It is prescribed for RA and other groups of inflammatory arthritis to reduce inflammation, decrease joint damage, and may extract effects on renal function.[5,11,12] Etanercept (Enbrel), another anti TNF-α is also indicated and prescribed for Iraqi patients with RA to control disease progression, inhibiting large number of clinical responses; decreases joint damage, and enhancing physical function, therefore, improves QoL in patients with active RA. Etanercept can be started with or without other DMARD such as methotrexate [13].

TNFα is a significant pro-inflammatory cytokine which can cause renal damage and shows various effects on different cell types, and plays an important role in the pathogenesis of chronic inflammatory diseases such as RA [14,15]. According to the Dutch Rheumatoid Arthritis Monitoring register (DREAM), anti-TNF agents are commonly utilized in 60% of the RA patients for the last five years.[16] Interleukin-6 cytokine is produced by several types of immune cells generally in response to physiologic stimuli, such as TNF-α .[14] In RA patients the IL-6 is the most abundantly expressed cytokine [17].

In patients with RA, a precise estimation of renal diseases is particularly important. The incidence of renal diseases in patients with RA is not clearly identified, though patients with RA often show markers of renal function disorders [10] such as blood urea and serum creatinine, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), in addition to the general inflammatory markers such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). To date, according to new National Kidney Foundation classification, there are no data in the literature on the prevalence of renal diseases in RA patients [18-19].

The purpose of this study is to evaluate the incidence of certain abnormal

laboratory and inflammatory markers associated with renal impairment in RA patients. The study appraise the renal function during treatment with anti TNF-α agents, one of the biological DMARD medications that are recently introduced in Iraq for treating RA.

Materials and Methods

This study included 54 RA patients (16 female, 38 male, median age 60 years, range 34-82 years) who attended the outpatients' clinic of the Department of Rheumatology, Al- Yarmook Teaching Hospital and private clinics in Baghdad City. RA was diagnosed according to the classification criteria of the American College of Rheumatology [19]. All patients used different types of non-steroidal anti-inflammatory drugs (NSAID) and pain killers. They received" Anti TNF-α in particular Etanercept (Enbrel) 50mg subcutaneously every 2 weeks for 6 months. A comparison group consisted of 58 of RA subjects (19 female, 39 male, median age 51 years, range 39-72 years) on treatment other than Anti TNF-α was enrolled.

The study included participants with normal blood picture and liver function tests.

Demographic parameters were registered for each patient which included age, gender and body mass index (BMI) which was calculated from the equation: BMI= weight (kg)/height^2 (m).

An exclusion criteria was set for patients with Diabetes Mellitus, patients with long standing urinary tract infections and any other disease that may have effects on the expected results, hence decrease the presence of confounders.

The study procedure was approved by the Ethics Committees of the local hospital. All participants had given written informed consent prior to starting the study.

Biochemical Analyses

Blood was sampled in the morning after overnight fasting. After clotting and separation by centrifuge; the serum was immediately frozen at –20 ^{o}C until analyzed.

Serum concentrations of CRP, TNF-α (BioSystem, Costa Brava, Barcelona, Spain), and IL-6 (R&D® Systems, Minneapolis, MN) levels were measured *via* enzymatic immune-sorbent assay (ELISA). Serum creatinine was estimated by a colorimetric coupled enzymatic reaction at 570 nm. Blood ESR was determined by a modified Westergren method.[20]

Statistical Analysis

"For"all the utilized parameters, results have been expressed as mean values with standard deviations. Statistical analysis was performed using one-way analysis of variance"(ANOVA) followed by a Tukey's" multiple" comparison." Significant differences were set at $^{**}P < 0.01$, $^{***}P < 0.001$, and $^{****}P < 0.0001$. Graphics were generated by Prism version 7 (GraphPad Software,"Inc."CA, USA) for all assays. Correlations between GFR and creatinine (continuous variable) and other variables were analyzed by Pearson test as"appropriate.

Results

"Demographic characteristics for the 54 RA patients under treatment with biological therapy and 58 RA patients as a comparison group are listed in Table1."There were no significant differences between the two groups with regard to parameters such as age, gender, or body weight.

Table 1: Demographic data of the RA patients and comparison group (mean ± SD)"

Characteristic group	**RA group**	**comparison group**	**p value**
"Number (M/F) "	54 (38/16)	58 (19/39)	ns
"Age (yr)"	56.7 ± 9.5	54.9 ± 8.8	ns
"Body weight (kg)"	66.1 ± 7.3	67.3 ± 8.3	ns
"BMI (Kg/m^2)	24.7±4.7	20.9±8.9	ns
Disease duration (yr)"	10.8 ± 4.4	9.8± 7.3	ns

ns:"not a statistically significant difference"

Table 2: Renal function tests for RA patients before and after treatment and comparison group (mean ± SD)

Renal function tests	"Before treatment" n= 54	"After treatment" n= 54	comparison group n= 58
Serum creatinine mg/dL	0.92±0.3	0.8±0.1****	0.61±0.1
GFR("mL/min/1.73 m^2")	88.5±12.3	91.7±15.1****	119±10.2

GFR, Glomerular filtration rate; **** $p < 0.0001$vs the comparison group
"

The results of renal function tests were different in the patients before and after treatment. Even more, in the" biologically treated patients receiving Anti TNF"-α presented a significant decrease in the value of creatinine and significant increase in the level of"GFR after 6 months of treatment compared to the comparison group *(P*≤0.0001)" (Table 2).

"Figure 1"shows the levels of"CRP, ESR, TNF-α IL-6, GFR and serum creatinine of RA patients before and after" biologic therapy compared to the" comparison"group. The "levels of ESR and IL-6 were significantly higher in RA patients after treatment than in comparison group (*P* ≤ 0.0001*)*."RA patients before treatment showed a significant elevation in"ESR, IL-6 and CRP concentration compared to the comparison group (*P* ≤ 0.0001 and *P* ≤ 0.01"respectively*)*. The concentrations of ESR, IL-6 and CRP were lower in RA patients after treatment than that before treatment. As"can be seen from" Figure 1, Etanercept significantly suppressed TNF-α level in the treated RA" patients compared to the comparison's group*"(P* ≤ 0.0001).

Pearson's correlation analysis showed a positive correlation between serum creatinine of RA patients before biologic therapy and with each of the following parameters, CRP"(*r* = 0.812, *P* ≤ 0.0001), "TNF-α (*r* = 0.387, *P* = 0.006), ESR (*r* = 0.462, *P* ≤ 0.001), and IL-6 (*r* = *0.*297, *P* = 0.040) (data not shown). While after treatment, the parameters were CRP (*r* = 0.327, *P* = 0.022), TNF-α (*r* = 0.291, *P* = 0.044), ESR (*r* = 0.128, *P* = 0.399), and IL-6 (*r* = *0.*183, *P* = 0.212) (Figure"2)."On the other hand, GFR levels before treatment were negatively correlated with CRP (*r*= -0.895, *P* ≤ 0.0001), TNF- α (*r* = -0.637, *P* ≤ 0.0001), ESR (*r* = -0.426, *P* = 0.003) and IL-6 (*r* =-0.775, *P* ≤

0.0001) (data not shown)." While after treatment, the parameters were CRP (r = - 0.874, P = 0.0001), TNF- α (r = -0.314, P = 0.035), ESR (r = -0.667, P = 0.0001) and IL-6 (r = -0.899, P = 0.0001) (Figure"3).

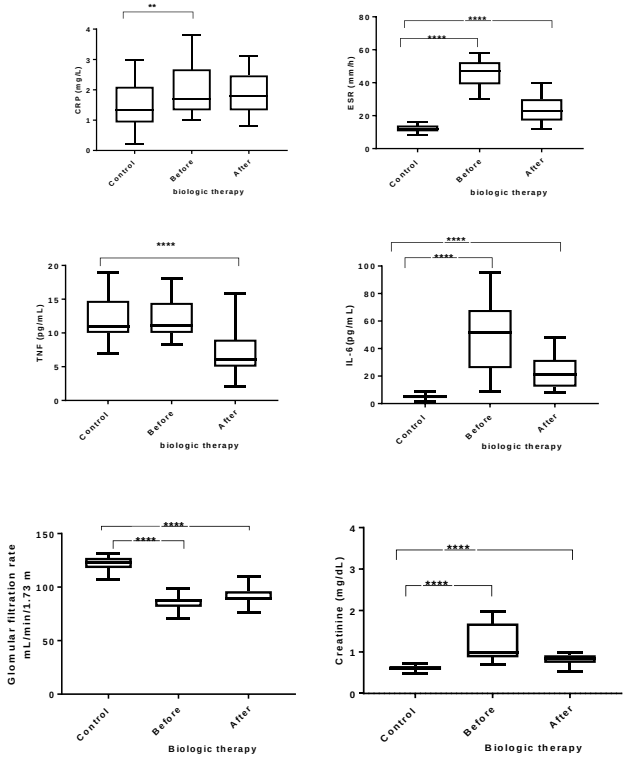

Figure 1:"Changes in C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), Tumor necrosis factor-alpha (TNF-α), interlukine-6 (IL-6), glomular filtration rate (GFRs) and serum creatinine levels before and after biologic therapy of RA (rheumatoid arthritis)"patients."Significant differences in disease activity are indicated by the P"values. ** P < 0.01, and **** P < 0.0001"

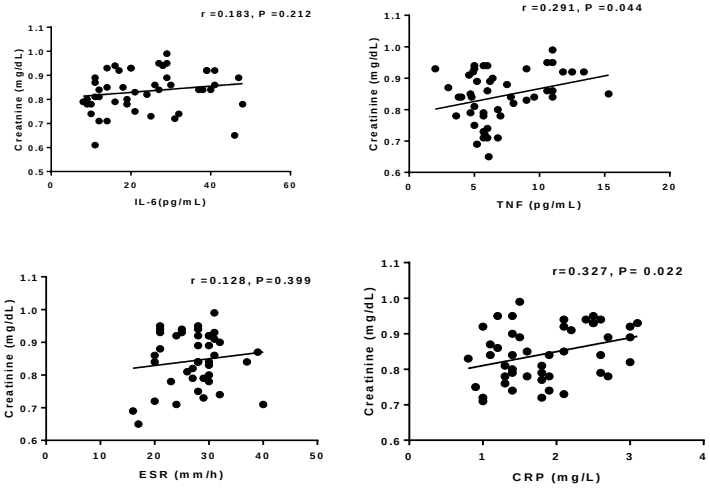

Figure 2:"Correlation between serum creatinine levels and serum IL-6, TNF-α, ESR and CRP r = 0.183 P= 0.212, r = 0.291 P = 0.044, r = 0.128 P = 0.399, r = 0.327 P = 0.022 after biologic therapy"respectively.

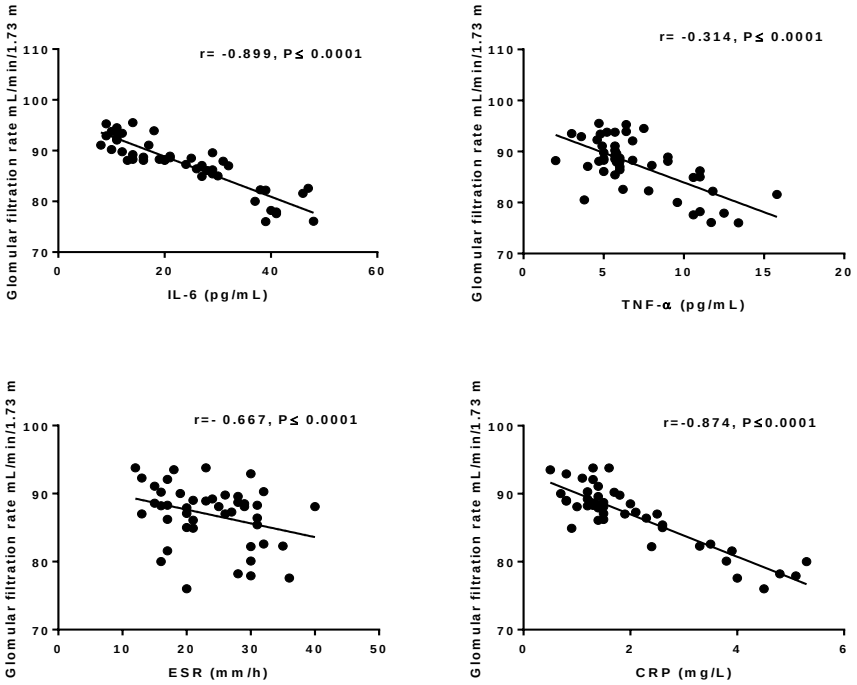

Figure 3:"Correlation between serum glomular filtration rate mL/min/1.73m levels and serum IL-6, TNF-α, ESR and CRP r = - 0.899 $P \leq 0.0001$, r = -0.314 $P \leq 0.0001$, r = -0.667 $P \leq 0.0001$, = -0.874 $P \leq 0.0001$ after biologic therapy "respectively.

Discussion

"RA patients are more likely to"develop renal complications than"people without RA. Although the"occurrence for reduced renal function in patients with RA"is described in few"studies,[21] it is clear"that the cause of the renal involvement in RA patients is debatable, and may be due to secondary renal disease caused by glomerulonephritis or amyloidosis, and associated" co-morbidities [5,22,23]. In" addition, a number of studies are underlying the etiologic role of"chronic inflammation in"renal"involvement.[24-25]."Systemic inflammation may contribute to development of renal disorder and anti-inflammatory"biologic drugs, such as anti TNF-α, that possess therapeutic potential"in preventing renal disorder progression in RA" patients [26-28].

In"general, biological agents had been extremely effective in the treatment of"RA."Nevertheless, cases"with serious adverse events have also been" observed [29]. This study show that successful treatment with the biological agents is associated with the control of renal function expressed by lower serum creatinine and higher"GFRs than in the patients before" treatment," although "GFR and creatinine did not return completely to baseline. Earlier studied had utilized serum creatinine to determine renal disorder, while" recently studies have used GFR to estimate renal disorder, although the relationship between serum creatinine and GFRs is" reciprocal [30]. The" higher results of GFR in the biologic" therapy patients, is effectively" underlying suggestion of bring down an ongoing process" of chronic infla-mmation" which may contribute to lowering the developing" renal" failure."Hanzu-Pazara *et al*. [5] described" a"similar link between the higher GFR in users of Rituximab" (Rituxan), the Anti TNF-α, compared with the non-Anti TNF-α users (100.36 ± 16.76 mL/min/1.73 m2 vs. 63.49 ± 21.60 mL/min/1.73 m2, $P < 0.0001$). This"may be due to the protective role of Anti TNF-α"treatment in the decreasing the probability of

renal"complications. While"Daoussis *et al*. [22] described a correlation between "cardiovascular manifestations and renal disorders, while no association with"other RA-related"factors.

A"number of increased serum levels of"cytokines that associate with the disease activity of RA had been explained. For instance, level of IL-6 was elevated considerably in patients with RA, and it was diminished after administration of anti RA"therapy.[31] These"findings suggest a possible role of IL-6 family cytokines in the pathogenesis of RA." In addition, a favorable clinical response subsequent the administration of anti TNF-α was revealed to be accompanied through the decreased serum levels of these inflammatory"mediators.[32]

So"far, much attention has been paid to the inflammatory cytokines role in RA pathogenesis, especially"TNF-α and IL-6 and their importance in clinical"monitoring of the disease"development.[33]"Numerous studies reported that"TNF-α and IL-6 are known to be raised in serum of RA"patients, and can be used as indicators of disease activity and the use of" biologic therapies in RA"" patients [34-35]. Our"study revealed that the serum"TNF-α level is elevated in RA patients prior to biologic therapy"compared to the"comparison group. While the"TNF-α concentration is significantly decreased in the biologic treated patients on the contrary to a previous study by Charles et"al., who"found a dose dependent increase in serum"TNF-*α* in RA"patients being treated with biological"agents.[36] The"reason for reduced"TNF-α level after treatment in RA" patients that found in this study and few other studies may be due to that "biologic therapy is a recombinant fusion protein composed of receptors and human IgG1"that binds to"both soluble and cell-bound TNF-α"[29].

"Haworth et al. showed that TNF-α plays an influential role in RA, blocking of TNF-α via antibodies significantly decreased the production of IL-6"[37]. In"the current study we found that IL-6 concentration in serum of RA patients before treatment was nine-fold higher than in comparison group. These"results are in agreement with the findings of Madhok et al., and Leeuwen et al. [38-39]. Following"treatment with the biological therapy, RA patients recorded significant decrease"IL-6 level to be four-fold higher than""control. This result"is concordant with Sato et al and Mori"et al. [29,40] who showed remarkable decrease in IL-6 concentration during the course of" treatment.

"In"the "RA patients group, the administration of the biologic therapy led to a reduction of the inflammatory activity as seen by a significant drop of the CRP and ESR"concentration after the reliable period of treatment ($P < 0.001$ and $P < 0.0001$ respectively). Several"studies have been analyzed the synthesis and secretion mechanism of CRP during the acute phase" response."Nonetheless, there is little information about a possible role of renal clearance or catabolism in estimating serum CRP."Panichi et al. [41] reported that"CRP is significantly associated to residual renal function"indicating that a decreased clearance of this molecule may partially explain the increased levels reported in renal disorder" patients."Another explanation of elevated"CRP levels may be due to the long standing of hepatic stimuli as a consequence of increased of cytokine IL-6"in renal" patients.[33-42-43]

"In"addition to age and sex, inflammation can also cause ESR level to be"increased. Whereas"the ESR is not a diagnostic test, it can be utilized as disease activity monitor, response to treatment and the presence of"inflammation. For"instance, in RA patients, the ESR associates well with disease activity, successful treatment can settle inflammatory state and normalize ESR" level. [44,45]. This"

study showed a positive correlation between"CRP and ESR with serum"creatinine in RA patients, which proves the link between renal damage in RA and inflammation."Hanzu-Pazara *et al*. [5]. reported that the effective biologic therapy response can be noticeable by analyzing the inflammatory indicators such as"ESR and CRP"which are correlating with a superior renal"function.

Conclusion

"Renal damage in RA patients appears to be more as a consequence of long standing inflammatory"processes. The study found a significant increase in levels of ESR, CRP, IL-6 and TNF in srea of RA patients with renal disorders before biologic therapy. These inflammatory parameters diminished significantly in the RA patients following the administration of Anti TNF-α therapy. After a reliable period of biologic therapy, significant positive and negative correlation was observed in serum creatinine and GFR with ESR, CRP, IL-6 and TNF-α respectively. We conclude that the inhibition of"IL-6 and TNF-α activity may be the main mechanisms of inflammation modulation explained for the treatment of RA. Further studies are suggested such as a Randomized Controlled Trials to explore other mechanisms, as well as to generalize the results in the features of renal involvement and rheumatoid arthritis will be necessary.

Acknowledgments

The authors thank all the staff at the Al-Yarmouk Teaching Hospital/ Dept. of Rheumatology.

References

1- Chiu HY, et al. Increased Risk of Chronic Kidney Disease in Rheumatoid Arthritis Associated with Cardiovascular Complications –A National Population-Based Cohort Study. *PLoS One*. 2015; 10 (9): 1-13.

2- Scott DL. Biologics-Based Therapy for the Treatment of Rheumatoid Arthritis. *Clinical pharmacology & Therapeutics*.2012; 91(1):30-43.

3- Symmons DP. Rheumatoid arthritis: assessing disease activity and outcome. *Clinical Medicine*. 2010; 10: 248-251.

4- Dieppe PA., Doyle DV., Burry HC., Tucker SM. Renal disease in rheumatoid arthritis. *British Medical Journal*.1976;1:611-612

5- Hanzu-Pazara L., Muflic L., Dusa D., Pana C., Tudorache M., Suta M., Tuta L. Renal disease in patients with rheumatoid arthritis treated with biological therapy. *ARS Medica Tomitana*.2016; 1(22):50-55.

6- Koseki Y., Terai C., MoriguchiM., Uesato M., Kamatani N. A prospective study of renal disease in patients with early rheumatoid arthritis *Annual Rheumatology Dis* 2001; 60: 327–331

7- Tonelli M., Sacks F., Pfeffer M., Jhangri GS., Curhan G. Biomarkers of inflammation and progression of chronic kidney disease. *Kidney International.*2005*;*68:237-245.

8- Akchurin OM., Kaskel F. Update on Inflammation in Chronic Kidney Disease. Blood purification. 2015; 39:84–92

9- Ting-yan Xu., Yi Zhang., Yan Li1., Ding-liang Zhu., Ping-jin Gao. The association of serum inflammatory biomarkers with chronic kidney disease in hypertensive patients. *Renal Failure*.2014; 36(5):666–672.

10- Gandjbakhch KF., Janus N., Launay-Vacher1 V., Rozenberg S., Mai Ba1 CU., Bourgeois P. Deray G. Kidney disease in RA patients: prevalence and implication on RA-related drugs management: the MATRIX study. *Rheumato* 2008; 47:350–354.

11- Keyser FD. Choice of Biologic Therapy for Patients with Rheumatoid Arthritis: The Infection Perspective. *Current Rheumatol Rev*, 2011, *7,* 77-87.

12- Henrique LM. Safe use of biological therapies for the treatment of rheumatoid arthritis and spondyloarthritides *Revista Brasileira de Reumatologia*. 2015; 55(3):281–309

13- Roth AR. And Finckh A. Treatment options in patients with rheumatoid arthritis failing initial TNF inhibitor therapy: a critical review. *Arthritis Research Therapy*. 2009; 11(1):1-11.

14- Taraz M., Taraz S., Khavidaki SD. Association between depression and inflammatory/anti-infla-mmatory cytokines in chronic kidney disease and end- stage renal disease patients: A review of literature. *Hemodialysis Int* 2015; 19:11–22.

15- Madhok R., Crilly A., Watson J., Capell HA. Serum interleukin 6 levels in rheumatoid arthritis: correlations with clinical and laboratory indices of disease activity. *Annals of the Rheumatic Diseases*.1993; 52: 232-234.

16- Punder YM, et al. The prevalence of clinical remission in RA patients treated with anti-TNF: results from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry. *Rheumatol.*2012;51(9):1610-1617.

17- Schulz M., Dotzlaw H., Neeck G. Ankylosing Spondylitis and Rheumatoid Arthritis: Serum Levels of TNF-α and Its Soluble Receptors during the Course of Therapy with Etanercept and Infliximab. *BioMed Res Int*. 2014;2014:1-7.

18- Wang W, et al. Effects of serum creatinine calibration on estimated renal function in african americans: the Jackson heart study. *American J Medical Sciences*. 2015; 349 (5):379-384.

19- Aletaha D. 2010 Rheumatoid arthritis classifi cation criteria: an American College of Rheumatol/ European League Against Rheumatism collaborative initiative. *Annual Rheumatiod Disease*. 2010; 69: 1580-1588.

20- Vennapusa B , De La Cruz L, Shah H, Michalski V, Zhang QY. Erythrocyte sedimentation rate (ESR) measured by the Streck ESR-Auto Plus is higher than with the Sediplast Westergren method: a validation study. *Amer J Clin Pathol*. 2011; 135(3):386-90.

21- Hickson LJ., Crowson CS., Gabriel SE., McCarthy JT., Matteson EL. Development of Reduced Kidney Function in Rheumatoid Arthritis. *Amrican J Kidney Disease*. 2014; 63(2):206-213.

22- Daoussis D, Panoulas VF, Antonopoulos I, John H, Toms TE, Wong P, et al.Cardiovascular risk actors and not disease activity, severity or therapy associate with renal dysfunction in patients with rheumatoid arthritis. Annual Rheumatology Disease.2010; 69: 517–521.

23- Fried L, Solomon C, Shlipak M, Seliger S, Stehman-Breen C, Bleyer AJ, et al. Inflammatory and Prothrombot. c markers and the progression of renal disease in elderly individuals. *Journal of American Society Nephrology*. 2004; 15: 3184–3191.

24- Tonelli M, Sacks F, Pfeffer M, Jhangri GS, Curhan G. Biomarkers of inflammation and progression of chronic kidney disease. *Kidney International*.2005; 68: 237–245

25- Stuveling EM, Hillege HL, Bakker SJ, Gans RO, De Jong PE, De Zeeuw D. C-reactive protein is associated with renal function abnormalities in a non-diabetic population. *Kidney Int*. 2003; 63: 654–661.

26- Chiu H-Y, Cheng Y-P, Tsai T-F. T helper type 17 in psoriasis: From basic immunology to clinical practice. *Dermatologica Sinica*. 2012; 30:136–141.

27- Kim HW, Lee CK, Cha HS, Choe JY, Park EJ, Kim J. Effect of anti-tumor necrosis factor alpha treatment of rheumatoid arthritis and chronic kidney disease. *Rheumatol Int*. 2015;35:727–34.

28- Goicoechea M, Garcia de Vinuesa S, Quiroga B, Verdalles U, Barraca D, Yuste C, et al. (2012) Effects of pentoxifylline on inflammatory parameters in chronic kidney disease patients: a randomized trial. Journal of Nephrology 25: 969–975.
29- Sato M., Takemura M., Shinohe R., Shimizu K**.** Serum Cytokin Concentrations in a Patient with Rheumatoid Arthritis on Etanercept Therapy Who Subsequently Developed Pneumocystis Pneumonia: A Case Report. *Case Reports in Rheumatology*. 2011; 2011:1-4.
30- Kassirer JP. Clinical evaluation of kidney function-tubular function. *NEJM*.1971;285:499-502.
31- Yonsei Med J. The correlation between increased serum concentrations of interleukin-6 family cytokines and disease activity in rheumatoid arthritis patients. 2011;52(1):113-20.
32- Hyrich KL., Watson KD., Silman AJ., Symmons DP. "Predictors of response to anti-TNF-*α* therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register," *Rheumatology*. 2006; 45(12): 1558–1565.
33- Ivashkiv B. Cytokine expression and cell activation in inflammatory arthritis. *Advanced Immunology.* 1996; 63: 337–376.
34- Koch AE., Kunke SL., Striater RM. Cytokine s in rheumatoid arthritis. *Journal Investigative Medicine.* 1995; 43: 28–38
35- Matsuno H., The role of TNF-α in the pathogenesis of inflammation and joint destruction in rheumatoid arithritis (RA): a study using a human RA/SCID mouse chimera. *Rheumatology*.2002;41:329-337.
36- Charles P, et al. "Regulation of cytokines, cytokine inhibitors, and acute-phase proteins following anti-TNF-therapy in rheumatoid arthritis," *J Immunol.,* 1999; 163(3): 1521–1528.
37- Shi Y. Granulocyte-macrophage colony-stimulating factor (GM-CSF) and T-cell responses: what we do and don't know. *Cell Research*. 2006;16:126-133.
38- Beyazal MS, et al. Serum Levels of IL-17, IL-6, TNF-α and Disease Activity in Patients with Rheumatoid Arthritis. Aktuelle Rheumatologie. DOI: 10.1055/s-0035-1564141
39- Van Leeuwen MA, Westra J, Limburg PC, van Rie l PL, van Rijsw ijk MH.Clinical significance of interleukin-6 measurement in early rheumatoid arthritis : relation with laboratory and clinical year prospective study. Ann Rheumatol Dis. 1995; 54: 674-677.
40- M. Mori, et al. Pharmacoknetics, efficacy, and safety of short-term (12 weeks) etanercept for methotrexate-refractory polyarticular juvenile idiopathic arthritis in Japan," *Modern Rheumato*l. 2005;15(6):397–404.
41- Panichi V.et al. C reactive protein in patients with chronic renal diseases. Renal Failure. 2001;23 (3 & 4): 551–562.
42- Nakahama H et al. Plasma interleukin-6 levels in continuous ambulatory peritoneal dialysis and hemodialysis patients. *Nephron*. 1992;61:132–134.
43- Cavaillon JM, Poignet JL, Fitting C, Delons S: Serum interleukin-6 in long term hemodialyzed patients. *Nephron*.1992;60:307–313.
44- Hickson LJ, et al. Development of Reduced Kidney Function in Rheumatoid Arthritis. *American J Kidney Disease*. 2015;63(2):206-213.
45- Castro C., Gourley M. Diagnostic Testing and Interpretation of Tests for Autoimmunity. *Journal Allergy Clinical Immunol*ogy. 2010;125(2): S238–S247.