Chapter

Interleukin 6 in Patients with Rheumatoid Arthritis

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Abstract

Rheumatoid Arthritis is a widespread disease causing varying degrees of disability. It is characterised by flares and remissions and since ancient times, every culture has tried to get the better of it. Even now, research is aimed at finding novel serum biomarkers as surrogates for disease activity and newer targets to sharpen therapy. One such target is IL-6.It mediates neutrophil migration, osteoclast maturation and pannus formation through vascular endothelial growth factor (VEGF) stimulation causing synovitis and joint destruction.IL-6 leads to various systemic manifestations like hepcidin production causing anemia hypothalamo-pituitary–adrenal (HPA) axis activation causing fatigue and mood changes and osteoclast activation causes osteoporosis while increase in acute phase reactants (ESR and CRP). The literature we reviewed and our research, enrolling 40 patients of RA as well describes the role of IL-6 in pathogenesis and various manifestations of RA including articular, extra-articular and other comorbid states. It supports that Serum IL-6 levels correlate with disease activity (DAS-28ESR and BRAF-MDQ) and that IL-6 remains a viable target for drug therapy.

Keywords: rheumatoid arthritis, pathophysiology IL-6, HPA axis, fatigue, DAS-28, BRAF-MDQ

1. Introduction

Rheumatoid arthritis (RA), the most common rheumatological disorder seen in clinical practice, has an estimated prevalence in the Indian community of 0.75%. It afflicts near about 1% of the world's population. Like many other connective tissue disorders, RA affects women more than men (female:male = 2:1 to 4:1) [1]. It is characterized by persistent synovial inflammation, bony erosions and progressive articular destruction, leading to varying degrees of physical disability [2]. The disease is known to produce periods of flares and remissions, therefore, it needs regular monitoring and continuous research to improve the quality of life of sufferers [3].

2. Pathogenesis of rheumatoid arthritis

RA primarily affects the musculoskeletal system which includes the synovial tissue, underlying bone and cartilage. However, being a systemic disease, it also produces a variety of extra-articular manifestations, such as subcutaneous nodules, lung involvement, peripheral neuropathy, vasculitis, pericarditis, hematological abnormalities and fatigue [4].

The macrophages are the key cells that are responsible for the tissue damage in RA. These cells are the source of pro-inflammatory cytokines involved in the pathogenesis.IL-6 is one of the main cytokine which is the cause of inflammation and immune dysregulation [4]. However, the exact pathogenic mechanism remains a complex interplay of genetic, environmental, and immunological factors that produce dysregulation of the immune system and a breakdown in self-tolerance a involvement of IL-6 and the HPA axis in the pathogenesis of fatigue has been shown in RA [5].

3. Interleukin 6 in RA

In RA, numerous cytokines, as we have already seen, are present both in the blood and in synovial joints. Hence, the cytokine network is complex and drives most of the clinical features consequently [6].

Elevation in pro-inflammatory cytokine levels leads to higher levels of fatigue in RA [7]. A significant role is being played by interleukin 6 (IL-6) in the pathogenesis of RA and promotion of fatigue [8].

4. Biology of IL-6

IL-6 is a pleiotropic cytokine. It is known to have substantial effects on non-immunological tissues [9]. It stimulates the production of acute-phase proteins, induces anemia and impairs the HPA axis [10].

Besides the immune system, this cytokine being proinflammatory causes various effects on multiple extraaticular tissues in the body which includes cardiovascular system, glucose metabolism through alteration of the insulin sensitivity, neurohormonal axis causing various psychological behavioural and haematological abnormalities [11]. Role of IL-6 is being considered in maintaining balance between immune and non immune systems of the body both in the healthy and disease states [9].

5. Molecular structure of IL-6

From a structural standpoint, IL-6 is a tetrahelix protein containing 184 amino acids [12]. It acts on various cells including leucocytes, megakaryotes and hepatocytes to name a few [11]. The receptor for IL-6 (IL-6R) are formed of an α chain, CD126, and two chains of glycoprotein 130 (gp130) [13, 14]. The signal transduction can occur through classical and trans signalling mechanisms.

In classical signalling, when IL-6 binds its membrane bound receptors and forms an IL-6/Mil-6Rα pair that leads to downstream signalling [12, 15, 18].

In trans signalling, IL-6 binds to its soluble receptor sIL-6-6Rα which further forms a complex with gp130.This IL-6/sIL-6Rα/gp130 then dimerises and leads to signal transduction [12, 15–19].

As neuronal cells prominently express gp130 and can therefore be activated via IL-6 trans-signalling, IL-6 is purported to have a direct effect on the CNS-related RA symptoms and co-morbidities, particularly, pain, fatigue, and mood [20–23].

6. IL-6 and fatigue in RA

It is well established that the cause of RA-associated fatigue is multidimensional, involving inflammation, pain, anemia, poor sleep, and psychosocial factors. There is also substantial evidence implicating the involvement of IL-6 and the HPA axis in the pathogenesis of fatigue [5].

The positive effects of IL-6 inhibition on symptoms of fatigue by Tocilizumab, Sarilumab, and Sirukumab in patients with moderate to severe RA, as assessed by FACIT-F, have been demonstrated in several clinical studies [8]. Alleviation of fatigue appears to be one of the first beneficial effects that patients with RA may experience when using biologic therapies that block IL-6 signaling [9].

This makes the precise measurement of the subjective feeling of fatigue as important and necessary as the disease activity, to evaluate the potential treatment effects [24].

Classically, the Bristol RA Fatigue Multi-Dimensional Questionnaire (BRAF-MDQ) [25] has been used for measuring fatigue in patients of RA. It was developed from the patient's perspective and evaluated in a British RA population. It was published in 2010 [25].

Nicklin et al. showed that the BRAF-MDQ global score correlated strongly with the MAF, POMS, and FACIT-F while the correlation with the SF-36 vitality subscale was weak [26].

7. Disease activity in RA

In rheumatoid arthritis, the presentation and course of the disease over time, are highly variable. The symptoms and signs of RA vary from joint complaints like pain, stiffness, swelling, and functional impairment, to more constitutional complaints like fatigue and loss of general health [4].

In the past decades a large number of variables have been tried to assess the status and course of disease activity in RA.

In daily clinical practice as well as in clinical trials on a group as well as individual level, the Disease Activity Score (DAS) and the DAS28 have been developed to measure disease activity in RA. These scores are a measure of RA disease activity that have been developed by compiling the information about swollen joints, tender joints, acute phase response, and general health. The variables required for calculation of DAS28 score include a 28-Tender joint Count (28-TJC), a 28-Swollen Joint Count (28-SJC), erythrocyte sedimentation rate (ESR), and a patient global assessment (PGA) of disease activity on a visual analog scale (VAS). C-reactive protein (CRP) may be used as an alternative to ESR in the calculation of the DAS or DAS28 [27].

Previous studies have shown that IL-6 levels were raised in the synovial membrane and synovial fluid of patients with RA [4]. However, the exact correlation of disease activity with serum IL-6 levels is still debatable in patients of RA. We did a study to measure the serum levels of IL-6 and disease activity in patients with RA and aimed to correlate the two statistically.

8. A research

Our study was conducted in the Department of Medicine between November 2016 to March 2018 in a tertiary care hospital of New Delhi. We studied 40 patients of RA (**Table 1**) who were diagnosed according to the ACR/EULAR 2010 Criteria [28].

Demographic data and disease history regarding onset, duration, course and progression, received were obtained from the patients (**Table 1**).

S.no	Character	RA patients(n = 40)
1.	Age (yrs)	38.45 ± 7.51
2.	Gender (female/male)	31/9
3.	Duration of disease	2.31 ± 1.71
4.	ESR(mm in 1st hour)	33.45 ± 20.16
5.	CRP(positive/negative)	23/17
6.	IL-6(pg/ml)	37.92 ± 75.29
7.	Rheumatoid factor(positive/negative)	29/11
8.	Anti CCP(IU/ml)	117.18 ± 107.96

Table 1.
Clinical characteristics of study population.

A general physical and thorough clinical examination of the musculoskeletal system was carried out.

DAS 28-ESR [29] was calculated for each patient as follows:

- **DAS 28 score** = 0.56 x $\sqrt{\text{tender joint count}}$ +0.28 x $\sqrt{\text{swollen joint count}}$ +0.70 x ln [ESR] +1.14 x (patient's global assessment on a scale of 1–100, measured using Visual analog scale).

The **cut-off values of DAS 28 for disease activity** are:

> 5.1	High disease activity,
>3.2 –≤ 5.1	Moderate disease activity
≤ 3.2-2.6	Low disease activity,
< 2.6	Remission.

Fatigue was measured using BRAF-MDQ score [25]

The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0 (IBM, Chicago/USA). The normality of data was tested by the Kolmogorov–Smirnov test. Quantitative variables were compared using the Independent T-test/Mann–Whitney Test (when the data sets were not normally distributed) between the two groups and ANOVA/Kruskal Wallis test between more than two groups. Qualitative variables were correlated using the Chi-Square test. Pearson correlation coefficient/Spearman rank correlation coefficient was used to assess the association of various parameters with each other. A p-value of <0.05 was considered statistically significant.

DAS 28 score ranged from 0.51 to 6.1 with a mean of 3.21 and a standard deviation of 1.26. The distribution of the patients by DAS28 is shown below in **Table 2.**

Total fatigue score ranged from 25 to 65 with a mean of 44.1 and ranged from minimum score of 25 to maximum score of 65.

IL-6 levels correlated with DAS28 with statistical significance, a p-value of 0.0011 and correlation coefficient of 0.497.

Chi-Square test was used to assess the correlation of DAS28 with sex and RF in the study population. But the p values of 0.240 and 0.384 respectively showed that there was no difference in disease activity between male and female patients.

According to DAS28 scores as above, patients were divided into subgroups of remission, low disease activity, moderate disease activity, and high disease activity. We studied the effect of various parameters on DAS28.

Higher concentrations of serum IL-6 were associated with higher disease activity (p = 0.0011, correlation coefficient = 0.497) as shown in **Figure 1**, however age

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DAS-28		
	Frequency	**Percentage**
1) Remission(DAS28 < 2.6)	16	40.00%
2) Low disease activity(DAS28: 2.6 - ≤ 3.2)	5	12.50%
3) Moderate disease activity(Activity (DAS28: >3.2 - ≤ 5.1)	16	40.00%
4) High disease activity((DAS28 > 5.1)	3	7.50%
Total	40	100.00%

Table 2.
Distribution of disease activity by DAS28.

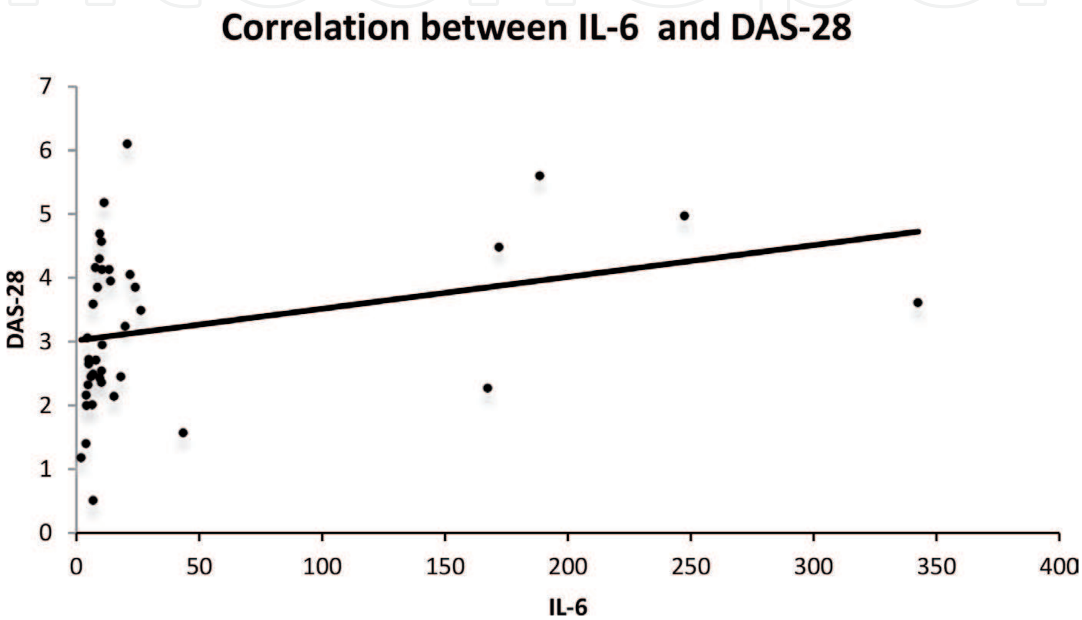

Figure 1.
Scattered plot showing correlation between IL-6 and DAS28.

(p-value = 0.1262), gender(p = 0.240), Anti CCP (p = 0.4296) and RF (p = 0.384) did not correlate with disease activity as measured by DAS28.

Levels of serum IL-6 were found to be very strongly correlating with BRAF-MDQ score, with a p-value of <0.0001 and a correlation coefficient of 0.821 as shown in **Figure 2**.

In our study, the levels of serum interleukin-6(IL-6) in the patients were high with a mean of 37.92 ± 75.29 pg/ml and ranged from 1.95 to 342.5 pg/ml. This finding was consistent with the results of other studies done previously. In the study done by Helal et al. [30] serum IL-6 concentration was significantly elevated in patients with RA ranging between 5 and 130 pg/ml, with a mean of 35.0 ± 21.2.

In a study done by Chung et al. [31] on the correlation between increased serum concentration of IL-6 family cytokines and disease activity in rheumatoid arthritis, the serum concentrations of IL-6 were 41.76 ± 20.28 pg/ml (range:18.0 to 109.1 pg/ml).

IL-6 is one of the cytokines which play a significant role in the pathogenesis of RA and the promotion of fatigue [6, 10, 32–34].Analytical statistics were also done to assess the correlation between BRAF-MDQ score and serum IL-6. Levels of serum IL-6 were found to be very strongly correlated with the BRAF-MDQ score with a p-value of 0.0001 and a correlation coefficient of 0.821. Our results were comparable to those of. Helal et al. [30] They too, found a strong correlation between BRAF-MDQ score and serum IL-6 concentration with r = 0.947, p < 0.001.

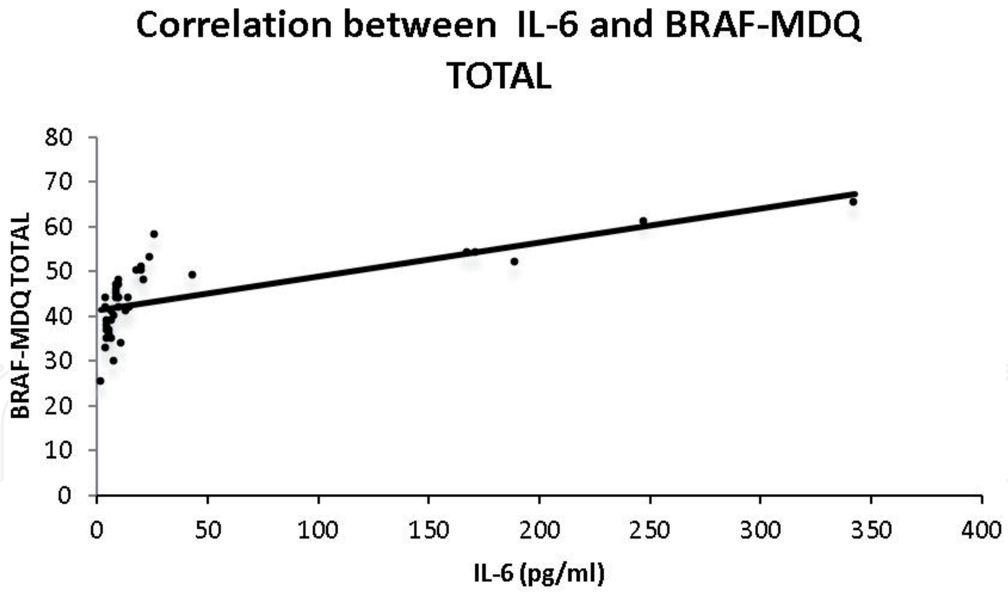

Figure 2.
Correlation between IL-6 and BRAF-MDQ score.

9. IL-6 in various diseases

Environmental stress factors such as infections and tissue injuries trigger immediate and transient rise in the levels of IL-6 which activates host defense mechanisms. As this stress is removed from the host the signal transduction and inflammatory cascade are terminated [35].

Dysregulated IL-6 production leads to the development of various immune and non-immune mediated diseases [35]. This was first demonstrated in a case of cardiac myxoma and remains true till date as seen in the COVID-19 pandemic.

A study done by Hirano et al. [36] in 1988 showed that dysregulation of IL-6 production occurs in the synovial cells of RA. Various gene knockout studies and IL-6 blockade by administration of anti-IL-6 or anti-IL-6R Ab have shown to be promising in the prevention and alleviation of disease symptoms [6, 8]. Mitigation of disease symptoms by this strategy has been shown by Alonzi et al. [37] Ohshima et al. [38] Fujimoto et al. [39] in patients with rheumatoid arthritis.

10. IL-6 and its systemic effects in SRA

In inflammatory arthritis, Osteoclasts play a major role in causing bony erosions [40]. Osteoclasts are recruited by IL-6 that acts on hematopoietic stem cells from the granulocyte-macrophage lineage (**Figure 3**) [41–43].

IL-6 has also been recognized to play a major role in extracellular matrix turnover and levels of IL-6 and CRP correlate with proMMP-3 in patients with early RA [44] which shows a link between IL-6 and proteinase activity. It stimulates hepatocytes to increase the production of acute-phase reactants. The correlation of IL-6 with CRP is seen in RA patients [10].

The anemia of chronic inflammations is seen in RA patients. The iron transport and release of iron from macrophages are inhibited by protein hepcidin which is produced by hepatocytes [10, 45].

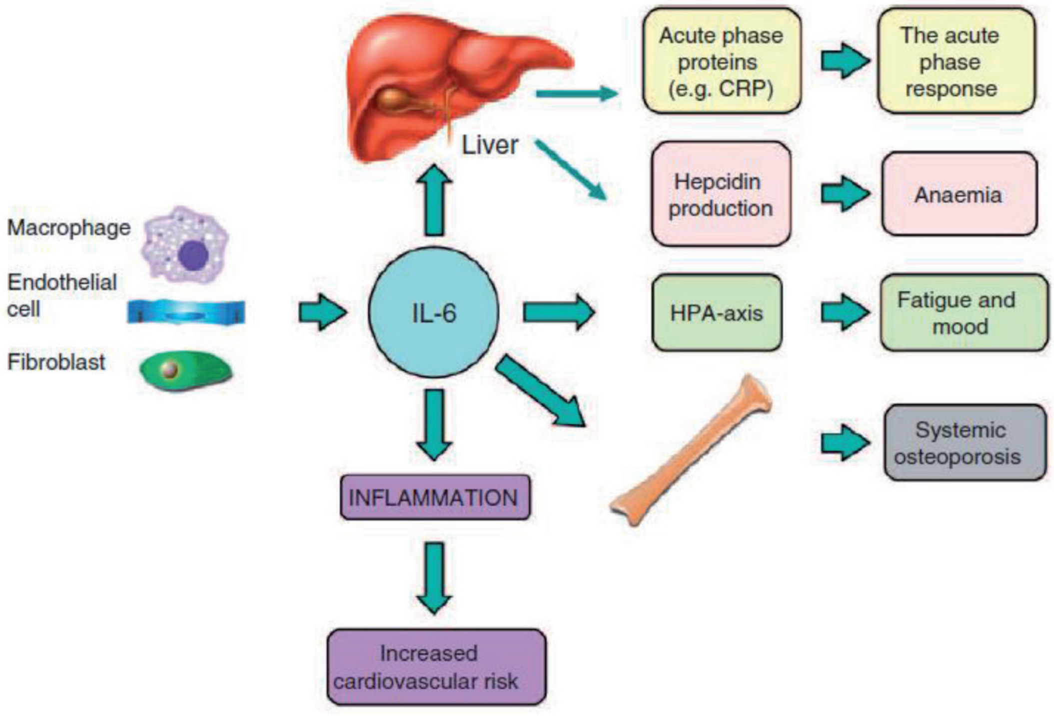

Figure 3.
Systemic effects of IL-6.

The hepcidin regulates iron metabolism by preventing iron transport and the release of iron from macrophage [45].

One of the common systemic manifestations of RA is osteoporosis. IL-6 overexpression results in osteopenia due to osteoclast and osteoblast dysregulation. This was shown in in-vivo studies with IL-6 transgenic mice resulting in increased osteoclastogenesis that leads to accelerated bone resorption, reduced bone formation, and defective ossification [46].

Cardiovascular mortality is predominant in patients with RA. In RA, endothelial dysfunction and dyslipidemia lead to an increased risk of atherogenesis because of systemic inflammation [47–49]. The widespread systemic inflamation is proportionate to elevated CRP levels which leads to increased risk of cardiovascular disease [50].

11. IL-6 blockade as a therapeutic target in RA

As IL-6 has been shown to have an array of biological roles and pathological efsfects in immune diseases, IL-6 targetting would constitute a novel therapeutic option in RA as well. This has been shown in the OPTION study [8] where Tocilizumab has been shown to reduce diseases activity and led to improvement in all ACR core set variables when compared with patients who received placebo(less than 1% on placebo—achieved DAS28 remission). The physical disability was substantially reduced by Tocilizumab more as compared to placebo, suggesting considerable functional benefits for the patients. Also Tocilizumab lead to more improvements in health-related quality of life than with placebo. Sustained improvements in the acute phase response markers including ESR, CRP and, and hemoglobin, were seen, especially with tocilizumab 8 mg/kg. In TAMARA study s, Tocilizumab was highly effective in a setting close to real-life medical care with a rapid and sustained improvement in signs and symptoms of RA [51].

12. Conclusion

It is well established that synovial cytokines, particularly IL-6 are responsible for much of the destruction in RA. The review also suggests that IL-6 is involved in the pathogenesis of various extra-articular manifestations of rheumatoid arthritis including increased risk of cardiovascular diseases, deranged glucose and lipid metabolism and various neurohormonal and psychological behavioural changes in patients with RA. Even, high levels of *serum* IL-6 are associated with a high disease activity, as indicated by various studies, including ours ($p = 0.0011$, correlation coefficient = 0.497). Also, we found that the levels of serum IL-6 very strongly correlated with fatigue, as measured by the BRAF-MDQ score.

It is thus, evident that blocking the IL-6 pathway as a therapeutic target in patients with rheumatoid arthritis, may help in better control of the disease symptoms and prevent flares. The extra-articular manifestations can also be controlled by antagonising IL-6 activity.

So, in conclusion, serum IL-6 is one of the main cytokine that has been involved in the pathophysiology of RA through its complex signalling pathways and as its levels correlate with disease activity, it has emerged as a better test for measuring disease remission and flares. It is simple, convenient and gives a lucid, objective value to a largely subjective and complicated issue in the course of RA-disease activity. And therefore, IL-6 can also prove to be a novel therapeutic target in control of articular as well as extra-articular manifestations of Rheumatoid arthritis.

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References

[1] Alam SM, Kidwai AA, Jafri SR. Jour Pak med assoc. Epidemiology of rheumatoid arthritis in a tertiary care unit. Karachi, Pak. J Pak Med Assoc. 2011; 61(2):123-126.

[2] Sousa EV, Danielle M, Gerlag DM, Paul P. Synovial Tissue Response to Treatment in Rheumatoid Arthritis. Open Rheumatol J. 2011; 5:115-122.

[3] Saleem B, Brown AK, Quinn M, Karim Z, Hensor EM, Conaghan P, et al. Can flare be predicted in DMARD treated RA patients in remission, and is it important? A cohort study. Ann Rheum Dis.2012; 71:1316-1321.

[4] .AnkoorShah,William St. Clair E.Rheumatoid Arthritis. In: Kasper D. Harrison's Principles of Internal Medicine. Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, editors. Volume 2,19th edition. McGraw-Hill Medical Publishing Division; 2016 May 22;2136-2149

[5] ChrousosGP.The hypothalamic–pituitary–adrenal axis and immune-mediated inflammation. N Engl J Med 1995;332:1351-1362.

[6] Garnero P, Thompson E, Woodworth T, Smolen JS. Rapid and sustained improvement in bone and cartilage turnover markers with the anti-interleukin-6 receptor inhibitor tocilizumab plus methotrexate in rheumatoid arthritis patients with an inadequate response to methotrexate: results from a substudy of the multicesnter double-blind, placebo-controlled trial of tocilizumab in inadequate responders to methotrexate alone. Arthritis Rheum 2010;62:33-43.

[7] Dayer E, Dayer J.M, Roux-Lombard Primer P: the practical use of biological markers of rheumatic and systemic inflammatory diseases Nat ClinPractRheumatol 2007; 3:512-520.

[8] Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, Woodworth T, Alten R, OPTION Investigators. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. The Lancet. 2008 Mar 22;371(9617):987-997.

[9] Rohleder N, Aringer M, BoentertM. Role of interleukin-6 in stress, sleep, and fatigue. Ann N Y AcadSci 2012;1261:88-96

[10] S. Srirangan, E.H. Choy. The role of Interleukin 6 in the pathophysiology of rheumatoid arthritis. TherAdvMusculoskel Dis 2010; 2:247-256.

[11] Hunter CA, Jones SA.IL-6 as a keystone cytokine in health and disease Nat Immunol 2015;16:448-457.

[12] Rose-John S.IL-6 trans-signaling via the soluble IL-6 receptor: importance for the pro-inflammatory activities of IL-6. *Int J Biol Sci*2012;8:1237-1247.

[13] Yin T, Taga T, Tsang ML et al. Involvement of IL-6 signal transducer gp130 in IL-11-mediated signal transduction. J Immunol 1993;151:2555-2561.

[14] Yamasaki K, Taga T, Hirata Y et al. Cloning and expression of the human interleukin-6 (BSF-2/IFN beta 2) receptor. Science 1988;241:825-828

[15] Narazaki M, Witthuhn BA, Yoshida K et al. Activation of JAK2 kinase mediated by the interleukin 6 signal transducer gp130. Proc Natl AcadSci USA 1994;91:2285-2289.

[16] Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S.The pro- and anti-inflammatory properties

of the cytokine interleukin-6. BiochimBiophysActa 2011;1813:878-888.

[17] Zhong Z, Wen Z, Darnell JE Jr. Stat3: a STAT family member activated by tyrosine phosphorylation in response to epidermal growth factor and interleukin. Science1994;264:95-8.

[18] Scheller J, Garbers C, Rose-John S.Interleukin-6: from basic biology to selective blockade of pro-inflammatory activities. SeminImmunol 2014;26:2-12.

[19] O'Shea JJ, Gadina M, Schreiber RD.Cytokinesignaling in 2002: new surprises in the Jak/Stat pathway. Cell 2002;109(Suppl):S121–S131.

[20] Jostock T, Müllberg JG, Özbek S et al. Soluble gp130 is the natural inhibitor of soluble interleukin-6 receptor transsignaling responses. Eur J Biochem 2001;268:160-167.

[21] Mihara M, Hashizume M, Yoshida H, Suzuki M, Shiina M.IL-6/IL-6 receptor system and its role in physiological and pathological conditions. ClinSci 2012;122:143-159.

[22] Eijsbouts AM, van den Hoogen FH, LaanRFet al. Hypothalamic-pituitary-adrenal axis activity in patients with rheumatoid arthritis.*ClinExpRheumatol* 2005;23:658-64.

[23] Schaible H-G.Nociceptive neurons detect cytokines in arthritis. Arthritis Res Ther 2014;16:470.

[24] Hewlett S, Dures E, Almeida C. Measures of Fatigue. Arthritis Care Res 2011; 63(S11):S263-S286

[25] Nicklin J, Cramp F, Kirwan J, Greenwood R, Urban M, Hewlett S.Measuring fatigue in RA: a cross-sectional study to evaluate the Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire,Visual Analog Scales, and Numerical Rating Scales. Arthritis Care Res 2010;62:1559-68.

[26] Nicklin J, Cramp F, Kirwan J, Urban M, Hewlett S. Collaboration with patients in the design of patient-reported outcome measures: capturing the experience of fatigue in rheumatoid arthritis. Arthritis Care Res 2010;62:1552-8.

[27] Fransen J, Welsing PMJ, De Keijzer RMH et al. Development and validation of the DAS28 using CRP. Ann Rheum Dis 2003;62 (Suppl. 1):10.

[28] Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010; 62:2569-2581.

[29] Prevoo ML, van't Hof MA, Kuper HH, et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995; 38:44-48.

[30] Abdel Moneim H. Helala, Enas M. Shahinea, Marwa M. Hassana, Doaa I. Hashadb, Riham Abdel Moneima. Fatigue in rheumatoid arthritis and its relation to interleukin-6 serum level. The Egyptian Rheumatologist 2012; 34(4):153-157.

[31] Chung SJ, Kwon YJ, Park MC, Park YB, Lee SK. The correlation between increased serum concentrations of interleukin-6 family cytokines and disease activity in rheumatoid arthritis patients. Yonsei Med J 2011;52:113-120.

[32] M.Bax, J. van Heemst, T.W. Huizinga, R.E. Toes Genetics of rheumatoid arthritis: what have we learned? Immunogenetics 2011; 63:459-466

[33] Emonts, M.J. Hazes, J.J. Houwing-Duistermaat, C.E. De Jongh, L. De Vogel, H.K. Han, *et al.* Polymorphisms in genes controlling inflammation and tissue repair in rheumatoid arthritis: a case control study BMC Med Genet 2011; 12: 36

[34] Milman N, Karsh J, Booth RA. Correlation of a multi-cytokine panel with clinical disease activity in patients with rheumatoid arthritis. ClinBiochem 2010;43:1309-1314.

[35] Naka T, Narazaki M, HirataM, Matsumoto T, Minamoto S, Aono A, Nishimoto N, Kajita T, Taga T, Yoshizaki K, et al.1997. Structure and function of a new STAT-inducedSTAT inhibitor. Nature 387: 924-929.

[36] Hirano T, Matsuda T, Turner M, Miyasaka N, Buchan G,Tang B, Sato K, Shimizu M, Maini R, Feldmann M, et al.1988. Excessive production of interleukin 6/B cell stimulatoryfactor-2 in rheumatoid arthritis. Eur J Immunol18: 1797-1801.

[37] Alonzi T, Fattori E, Lazzaro D, Costa P, Probert L, Kollias G, De Benedetti F, Poli V, Ciliberto G. 1998. Interleukin 6 isrequired for the development of collagen-induced arthritis. J Exp Med 187: 461-468.

[38] Ohshima S, Saeki Y, Mima T, Sasai M, Nishioka K, Nomura S, Kopf M, Katada Y, Tanaka T, Suemura M, et al. 1998.Interleukin 6 plays a key role in the development of antigen-induced arthritis. Proc Natl AcadSci 95: 8222-8226.

[39] Fujimoto M, Serada S, Mihara M, Uchiyama Y, Yoshida H, KoikeN, Ohsugi Y, Nishikawa T, Ripley B, Kimura A, et al.2008. Interleukin-6 blockadesuppressesautoimmunearthritis in mice by the inhibition of inflammatoryTh17 responses. Arthritis Rheum 58: 3710-3719.

[40] Walsh, N.C., Crotti, T.N., Goldring, S.R. and Gravallese, E.M. (2005) Rheumatic diseases: theeffects of inflammation on bone. Immunol Rev208: 228_251.

[41] Yoshitake, F., Itoh, S., Narita, H., Ishihara, K. and Ebisu, S. (2008) Interleukin-6 directly inhibits osteoclastdifferentiation by suppressing receptor activatorof NF-kappaBsignaling pathways. J BiolChem283: 11535_11540.

[42] Liu, X.H., Kirschenbaum, A., Yao, S. and Levine, A.C. (2005) Cross-talk between the interleukin-6 andprostaglandin E(2) signalling systems results inenhancement of osteoclastogenesis through effects onthe osteoprotegerin/receptor activator of nuclearfactor-{kappa}B (RANK) ligand/RANK system.Endocrinology 146: 1991_1998

[43] Otsuka, T., Thacker, J.D. and Hogge, D.E. (1991) The effects of interleukin 6 and interleukin 3 on early hematopoietic events in long-term cultures of human marrow. ExpHematol 19: 1042_1048

[44] Roux-Lombard, P., Eberhardt, K., Saxne, T., Dayer,J.M. and Wollheim, F.A. (2001) Cytokines, metalloproteinases,their inhibitors and cartilage oligomericmatrix protein: relationship to radiological progressionand inflammation in early rheumatoid arthritis. A prospective 5-year study. Rheumatology 40: 544_551.

[45] Ganz, T. (2003) Hepcidin, a key regulator of ironmetabolism and mediator of anemia of inflammation. Blood 102: 783_788.

[46] De Benedetti, F., Rucci, N., Del, F.A., Peruzzi, B.,Paro, R., Longo, M. et al. (2006) Impaired skeletaldevelopment in interleukin-6-transgenic mice: amodel for the impact of chronic inflammation onthe growing skeletal system. Arthritis Rheum54: 3551_3563.

[47] van Leuven, S.I., Franssen, R., Kastelein, J.J., Levi, M., Stroes, E.S. and Tak, P.P. (2008) Systemicinflammation as a risk factor for atherothrombosis. Rheumatology (Oxford) 47: 3_7.

[48] Dessein, P.H., Norton, G.R., Woodiwiss, A.J., Joffe, B.I. and Wolfe, F. (2007) Influence of nonclassical cardiovascular risk factors on the accuracy of predictingsubclinical atherosclerosis in rheumatoid arthritis. JRheumatol 34: 943_951.

[49] Niessner, A., Goronzy, J.J. and Weyand, C.M. (2007) Immune-mediated mechanisms in atherosclerosis:prevention and treatment of clinical manifestations. Curr Pharm Des 13: 3701_3710.

[50] Yeh, E.T. (2004) CRP as a mediator of disease.Circulation 109: 1111_1114.

[51] BurmesterGR, Feist E, Keller H. *et al.* Effectiveness and safety of the interleukin 6- receptor antagonist tocilizumab after 4 and 24 weeks in patients with active rheumatoid arthritis:the first phase IIIb real-life study (TAMARA0)Ann Rheum Dis.2011; 70:755-759.