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RESEARCH ARTICLE

ROLE OF INTERLEUKIN-1 ALPHA (IL-1A) AND INTERLEUKIN-1 RECEPTOR ANTAGONIST (IL-1RA) IN PATHOGENESIS OF JUVENILE IDIOPATHIC ARTHRITIS AND ADULT ONSET RHEUMATOID ARTHRITIS OF IRAQI PATIENTS

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ABSTRACT

Introduction: Arthritis diseases in particular juvenile idiopathic arthritis (JIA) and rheumatoid arthritis (RA) are considered as autoimmune disorders, in which cytokines play a role in their pathogenesis.
Methods: Serum levels of IL-1α and IL-1RA were assessed in 49 JIA and 43 and RA Iraqi patients, as well as 20 JIA controls and 17 RA controls.
Results: Serum level of IL-1α was significantly ($P \leq 0.05$) decreased in JIA patients compared to their controls (28.7 ± 1.7 *vs*. 52.5 ± 3.1) pg/ml, as well as in RA patients compared to their control (44.1 ± 2.5 *vs*. 51.2 ± 2.5) pg/ml. For IL-1RA, the serum level showed no significant difference between patients (JIA or RA) and their controls. Some significant variations were also observed when both groups of patients were distributed by disease severity scale, disease activity score and type of therapy and JIA patients by clinical subtypes.
Conclusions: It was concluded that IL-1α was down-regulated in JIA and RA.

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INTRODUCTION

Arthritis is the most common cause of joint pain and physical disability worldwide; including Iraq, but juvenile idiopathic arthritis (JIA) and rheumatoid arthritis (RA) are the two major groups of arthritis that are characterized by chronic joint inflammation (Sanmart *et al*., 2013; Albers, 2015). For JIA, the criteria of International League of Associations for Rheumatology (ILAR) defined the disease as arthritis in one or more joints that begins before the age of 16 years, persists for at least six weeks, and excludes all other known conditions that cause similar symptoms (Albers, 2015). Based on such criteria, the JIA patients are distributed into six main subgroups; oligoarthritis (OLI), polyarthritis (POL), systemic arthritis (SA), enthesitis-related arthritis (ERA), psoriasis arthritis and undifferentiated arthritis. Oligoarthritis patients are further classified into persistent (POLI) and extended (EOLI), and polyarthritis into RF positive (RF+ve POL) and RF negative (RF-ve POL) (Anink, 2015).

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Rheumatoid arthritis is a further type of arthritis, which is characterized by an inflammation of the synovium and a destruction of cartilage and bone (Scott *et al*., 2010; Chopra, 2012). However, details of RA pathogenesis are also not well-characterized, although there is strong evidence that immune components; especially T and B lymphocytes or their products (i.e. cytokines and antibodies) are involved in disease progression and pathogenesis, and it is suggested that RA is a cytokine-mediated disease (Remy *et al*., 2011; Shi *et al*., 2015). Cytokines play a prominent role in the etiopathogenic mechanism of JIA and RA; therefore this study came to deeply inspect the role of IL-1α and IL-1RA in both diseases with special reference to JIA, because the two cytokines have not been determined in Iraqi JIA patients. Interleukin-1 is an important pro-inflammatory cytokine that has multiple properties and almost all types of cells are affected by it. It is a powerful cytokine that mediates acute local and systemic inflammatory, as well as IL-1 is involved the induction of adhesion molecules expression on endothelial cells, which are necessary for infiltration of affected tissue by inflammatory and immune-competent cells (Paul and Zhu, 2010; van Herwaarden *et al*., 2014).

This cytokine is strongly expressed by monocytes, tissue macrophages and dendritic cells, but B, NK and epithelial cells are also producer of IL-1 (Dinarello, 2011). Both types of IL-1 (IL-1α and IL-1β) exert their activity by binding and signalling through IL-1RI (IL-1 receptor type I), which is expressed by almost all types of cells. The cytoplasmic part of such receptor carries a toll/IL-1 receptor domain, which is also present in toll-like receptors (TLR); an observation that points to an important role of IL-1 in inflammation and innate immunity (Weber *et al*., 2010). The agonists for IL-1RI are IL-1α and IL-1β, while binding of IL-1 receptor antagonist (IL-1RA) to IL-1RI prevents IL-1α and IL-1β binding to it and consequently leads to blockade the initiation of IL-1RI signalling, and an administration of recombinant IL-1RA has been successfully used and approved for the treatment of RA (Contassot *et al*., 2012). Blood monocytes from systemic JIA patients have also been demonstrated to secrete more IL-1β than do cells from healthy controls, and treatment with IL-1β blockers was found to be highly effective in ameliorating the symptoms of disease (Jesus and Goldbach-Mansky, 2014).

MATERIALS AND METHODS

Subjects

A total sample of 129 Iraqi Arab subjects was enrolled in the study. They were distributed as 49 JIA patients (25 females and 24 males; age range: 2.5 – 16 years), 20 JIA controls (control I; 12 females and 8 males; age range: 3 – 16 years), 43 RA patients (23 females and 20 males; age range: 23 – 60 years) and 17 RA controls (control II; 9 females and 8 males; age range: 18 – 50 years). The patients were referred to the Rheumatology Units at Baghdad Teaching Hospital and Imamein Kadhimein Medical City in Baghdad for diagnosis and treatment during the period July 2013 – April 2014. The diagnosis was made by the consultant medical staff at the two hospitals, and it was based on a clinical examination, X-ray findings and laboratory tests. For JIA and its subtypes, inclusion and exclusion criteria are those defined by the International League of Associations for Rheumatology (ILAR) for active JIA (Anink, 2015). Rheumatoid arthritis patients were diagnosed according to the revised diagnostic criteria established by the American College of Rheumatology. The 2010 criteria included tender and swollen joint counts, C-reactive protein (CRP), anti-cyclic citrullinated peptide (anti-CCP) antibodies or rheumatoid factor (RF), and symptom duration (Funovits *et al*., 2010; Tamai *et al*., 2014).

Both JIA and RA patients were under therapy, but different protocols were followed. The patients were either treated with methotrexate (MTX: single oral weekly dose of 5 – 15 mg), Enbrel (etanercept: single weekly subcutaneous dose of 25 mg), corticosteroids (oral methylprednisolone: single daily dose of 50 mg) or disease-modifying anti-rheumatic drugs (DMARDs), which included leflunomide (daily oral dose of 5 mg), sulfasalazine (daily oral dose of 500 – 1000 mg), imuran (azathioprine; daily oral dose of 50 mg), or hydroxyl-chloroquine (daily oral dose of 200 – 500 mg). In a further group of patients, the therapy included a combination of the four protocols (combined group). Normally, blood samples were taken from patients seven days-post last dose. It is also worth to mention that there was a group of patients in which the therapy was discontinued for a period of at least the last six month. Based on the aforementioned data, the patients were distributed into groups on the basis of some principles. In the first, the ACR functional classification (ACRFC) of disease severity was adopted (Horneff and Becker, 2014; Nagano *et al*., 2015). The second principle is disease activity score (DAS). In JIA patients, DAS-27 was estimated, which yields a score ranging from 0 to 57, or can be simplified as low (0 – 3), moderate (4 – 10) and high (11 – 57) (Consolaro *et al*., 2014). For RA patients, DAS-28 was estimated.

A DAS-28 value > 5.1 corresponds to a high disease activity, 3.2 – 5.1 corresponds to a moderate disease activity and < 3.2 corresponds to a low disease activity (Wells *et al*., 2009; Capela *et al*., 2015). The calculations of DAS-28 were carried out online using the DAS-28 calculator, which is available online (http://www.das-score.nl). The patients were also distributed into groups according to the type of administrated therapy, and for the necessity of analysis, the patients were distributed into four main groups, which were group I that received all types of therapies with the exception of Enbrel and corticosteroids; groups II and III were treated with Enbrel and corticosteroids, respectively and group IV, in which the therapy was discontinued or has not received any therapy. Finally JIA patients were classified into four clinical subtypes; oligoarthritis (OLI), polyarthritis (POL), systemic arthritis (SA) and enthesitis-related arthritis (ERA). Oligoarthritis patients were further classified into persistent (POLI) and extended (EOLI), and polyarthritis into RF positive (RF+ve POL) and RF negative (RF-ve POL), as suggested by ILAR (Huang, 2012).

Laboratory Methods

Sera of patients (JIA and RA) and both controls (I and II) were also assessed for the level of IL-1α and IL-1β by means of an ELISA method that was based on similar principles, in which ELISA kits were employed in such assessments (PeproTech Company; UK).

Statistical Analyses

The results of present study were tabulated in a DATA sheet of SPSS (statistical package for social sciences) version 13.0, which was used to achieve the statistical analyses. The data were presented as mean ± standard error (S.E.), significant differences between means were assessed by ANOVA (analysis of variance), followed by Duncan test.

RESULTS

Interleukin-1α

Serum level of IL-1α was significantly ($P \leq 0.05$) decreased in JIA patients compared to their controls (28.7 ± 1.7 *vs*. 52.5 ± 3.1) pg/ml, as well as in RA patients compared to their controls (44.1 ± 2.5 *vs*. 51.2 ± 2.5) pg/ml. However, the level of IL-1α was significantly increased in RA patients compared to JIA patients, while their controls demonstrated no significant difference between their means Table 1.

Table 1. Serum level of IL-1α in total juvenile idiopathic arthritis and rheumatoid arthritis patients and their controls

Groups		No.	IL-1α Level Mean ± S.E. (pg/ml)	Percentage of Total Sum
Juvenile Idiopathic Arthritis	Patients	49	28.7 ± 1.7^{C}	35.3
	Control I	20	52.5 ± 3.1^{A}	64.7
Rheumatoid Arthritis	Patients	43	44.1 ± 2.5^{B}	46.3
	Control II	17	51.2 ± 2.5^{A}	53.7

Different superscript letters: Significant difference (P ≤ 0.05) between means.

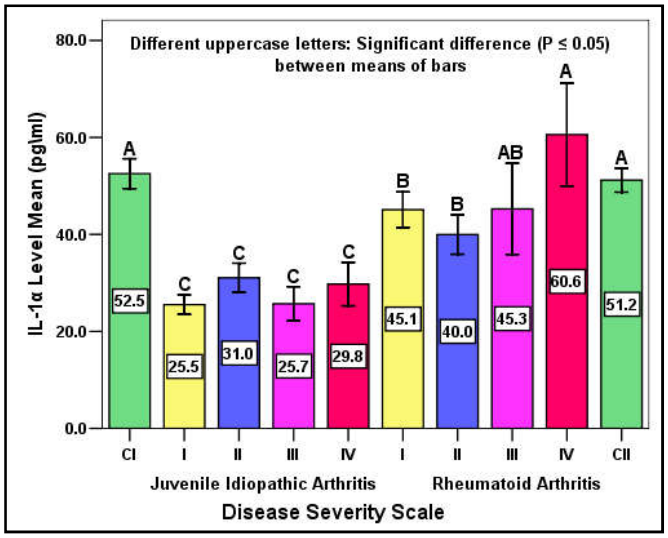

Figure 1.Serum level of IL-1α in juvenile idiopathic arthritis and rheumatoid arthritis patientsdistributed by disease severity scale (C: controls)

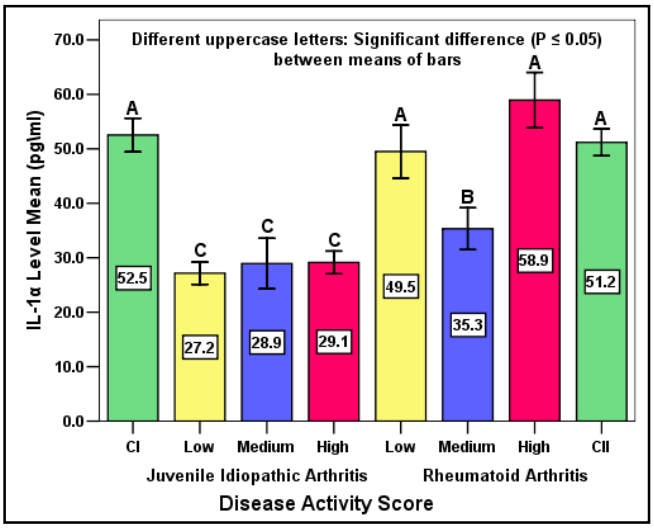

Figure 2. Serum level of IL-1α in juvenile idiopathic arthritis and rheumatoid arthritis patients distributed by disease activity score

Table 2. Serum level of IL-1α in juvenile idiopathic arthritis patients distributed by clinical subtypes and controls

JIA Clinical Subtypes		No.	IL-1α Mean Level ± S.E. (pg/ml)	Percentage of Total Sum
Oligoarthritis	Persistent	16	27.5 ± 2.4^{B}	12.0
	Extended	12	29.4 ± 4.3^{B}	12.8
Polyarthritis	RF Positive	5	30.4 ± 6.1^{B}	13.3
	RF Negative	11	29.9 ± 3.7^{B}	13.1
Systemic Arthritis		3	24.4 ± 8.2^{B}	10.7
Enthesitis-Related Arthritis		2	34.6 ± 4.3^{B}	15.1
Controls		20	52.5 ± 3.0^{A}	23.0

Different superscript letters: Significant difference (P ≤ 0.05) between means.

Disease severity scale had no effect on IL-1α serum level in JIA patients, but scale IV RA patients showed a significant increased level compared to RA patients in scales I and II (60.6 ± 10.6 *vs*. 45.1 ± 3.7 and 40.0 ± 4.1) pg/ml, respectively. There were no DAS-associated variations in the means of IL-1α among JIA patients, while RA patients with Medium DAS showed a significant decreased level compared to RA patients with Low or High DAS (35.3 ± 3.8 *vs*. 49.5 ± 4.9 and 58.9 ± 5.1) pg/ml, respectively (Figure II). Type of therapy had no effect on serum level of IL-1α in JIA patients, while in RA patients some variations were observed, but the differences were not significant (Figures 1, 2 and 3). The clinical subtypes of JIA showed no significant differences between the means of IL-1α Table 2.

Interleukin-1 Receptor Antagonist (IL-1RA)

Serum level of IL-1RA showed no significant difference between patients (JIA or RA) compared to their controls (Table 3). In addition, patients distributed by diseases severity scale, DAS or types of therapy also demonstrated no variations in the means of IL-1RA between their groups (Data not shown). However, distributing JIA patients by their clinical subtypes revealed some differences. Patients with EJIA subtype recorded a significant decreased level of IL-1RA (40.5 ± 3.0) pg/ml compared to other clinical subtypes (except RF+ve PJIA) or controls (55.6 ± 1.4 pg/ml) Table 4.

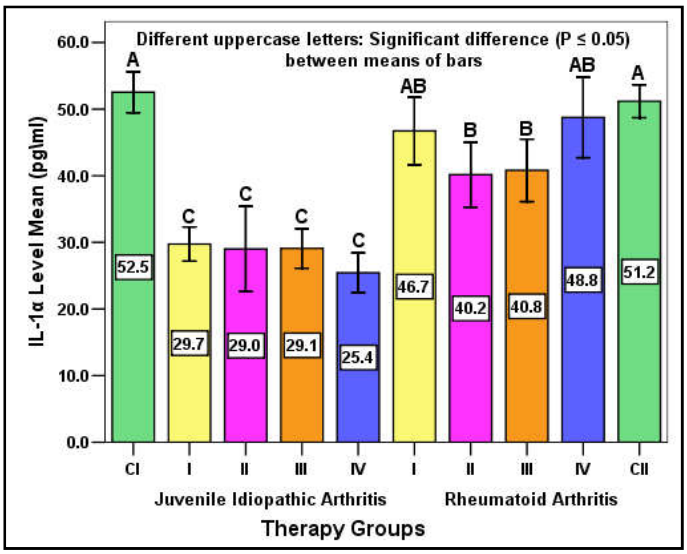

Figure 3. Serum level of IL-1α in juvenile idiopathic arthritis and rheumatoid arthritis patients distributed by type of therapy (C: controls)

Table 3. Serum level of IL-1RA in total juvenile idiopathic arthritis and rheumatoid arthritis patients and their controls

Groups		No.	IL-1RA Level Mean ± S.E. (pg/ml)	Percentage of Total Sum
Juvenile Idiopathic Arthritis	Patients	49	55.7 ± 2.0^{A}	50.1
	Control I	20	55.6 ± 1.4^{A}	49.9
Rheumatoid Arthritis	Patients	43	57.0 ± 1.4^{A}	49.9
	Control II	17	57.2 ± 1.4^{A}	50.1

Similar superscript letters: No significant difference (P > 0.05) between means.

Table 4. Serum level of IL-1RA in juvenile idiopathic arthritis patients distributed by clinical subtypes and controls

JIA Clinical Subtypes		No.	IL-1RA Mean Level ± S.E. (pg/ml)	Percentage of Total Sum
Oligoarthritis	Persistent	16	57.3 ± 3.2^{A}	15.4
	Extended	12	53.4 ± 4.6^{A}	14.4
Polyarthritis	RF Positive	5	50.6 ± 8.4^{AB}	13.6
	RF Negative	11	59.6 ± 3.4^{A}	16.1
Systemic Arthritis		3	53.9 ± 4.0^{A}	14.5
Enthesitis-Related Arthritis		2	40.5 ± 3.0^{B}	10.9
Controls		20	55.6 ± 1.4^{A}	15.0

Different superscript letters: Significant difference (P ≤ 0.05) between means

DISCUSSION

The role of IL-1α in the pathogenesis of JIA was not well-defined in the present study, especially if we notice that its serum level in patients represented about 50% of IL-1α level in controls; therefore this cytokine is down-regulated in the present JIA patients. Such observation contradicted the findings of Pascual *et al*. (2005) and Lopalco *et al*. (2015) that highlighted the up-regulation of IL-1α in a clinical subtype of JIA, which was sJIA. However, the latter findings were not replicated in two further studies (Ogilvie *et al*., 2007; Barnes *et al*., 2009). Based on these contradicted findings, one cannot reach a firm conclusion about the role of in IL-1α etiology and progression JIA or its profile as biomarker for the disease. In addition, the level of IL-1α was also not correlated with the disease activity as suggested by the observation made on patients with different DASs. This was also in agreement with Spîrchez *et al*. (2012) who found no correlation between serum IL-1α level and disease activity in JIA patients during clinical remission after Etanercept therapy (Spîrchez *et al*., 2012). It was also not possible to discriminate between the clinical subtypes of JIA patients on the basis of IL-1α serum level; an observation that has also been noticed by Militaru and Sabau (2011).

The same argument can also be hold for RA, in which the patients showed a significant decreased level of IL-1α, but the difference was in a less magnitude of that in JIA patients, because the difference between RA patients and controls was below 10%, but still other studies might have introduced a different concept, in which several members of the IL-1 family have been implicated in RA pathogenesis. IL-1α and IL-1β, as well as, the natural IL-1RA are expressed abundantly in the synovial membrane of RA patients (Dayer, 2003), and targeting IL-1 and IL-1 receptor components in various animal models of arthritis was found to be effective in reducing the degree of inflammation, in particular articular damage, and IL-1 blockade was suggested to be advantageous in reducing articular damage in RA patients (Zwerina *et al*., 2007).

However, clinical evaluations have been disappointing, and although Anakinra (a recombinant, nonglycosylated version of human IL-1ra) reduced inflammation and suppressed bone erosion in RA patients, it has not reduced the RA magnitude compared with agents that blocked TNF-α (Nordström *et al*., 2012). The serum level of IL-1RA (a naturally occurring receptor antagonist for IL-1) showed no significant variation between JIA or RA patients and controls, and distributing the patients according to disease activity or severity did not change such profile.

The level was also not affected by the type of administrated therapy. Such IL-1 family cytokine is produced locally in response to infection or inflammation by various tissues, and is observed with high levels in the circulation secondary to hepatic production as an acute-phase protein. The physiological role of IL-1RA is to inhibit competitively local and systemic inflammatory effects of IL-1α and IL-1β (Arend and Gabay, 2000). In this context, studies have reported that maintenance of a balance between IL-1 and IL-1RA may be important in preventing the development of inflammatory diseases in IL-1RA knockout mice. Spontaneous development of inflammatory arthritis in IL-1RA knockout mice with many features resembling human RA has also been described (Kay and Calabrese, 2004). Therefore, questions can be posed about the possible pathophysiologic consequences of an imbalance between IL-1 and IL-1RA in inflammatory disease of joints in JIA and RA patients.

The present study results might not in favor of such presentation, because no significant difference was observed between patients and controls in the level of IL-1RA; however, when the results of IL-1α and IL-1RA are considered together in term of IL-1α/IL-1RA ratio, the picture may be different. Such ratio was 0.52 and 0.77 in JIA and RA patients respectively; while in their controls was almost approximated to 1.0 (0.94 and 0.90, respectively).

The latter presentation of results declared that the balance between IL-1α and IL-1RA was des-regulated in JIA and RA patients, but not in controls, and such des-regulation might contributed to arthritis in both groups of patients. In agreement with such conclusion, imbalance between production of IL-1α and IL-1RA was demonstrated in rheumatoid synovitis (Arend, 2001).

An auto-inflammatory syndrome of bone and skin caused by recessive mutations in *IL1RN* (encoding gene for IL-1RA) may further highlight the importance of IL-RA in pathophysiology of JIA and RA (Lukens and Kanneganti, 2014). Therefore, Anakinra, which is an analogue to the naturally occurring ILRA that blocks IL-1, and other IL-1 blockers have been suggested to be a promising therapy for JIA, especially SJIA, and RA (Stoll and Cron, 2014; Pasi *et al*., 2015).

REFRENCESES

Albers, H. M. 2015. Genetics in juvenile idiopathic arthritis. Leiden University. Rotterdam, the Netherlands. a dissertation.

Anink, J. 2015. Advances in the Management of Juvenile Idiopathic Arthritis the coming of age of biologic treatment. The Erasmus University Rotterdam. Pfizer, Dutch. a dissertation.

Arend, W.P. 2001. Cytokine imbalance in the pathogenesis of rheumatoid arthritis: the role of interleukin-1 receptor antagonist. *Semin Arthritis Rheum*., 30(5 Suppl 2):1-6.

Arend, W.P. and Gabay, C. 2000. Physiologic role of interleukin-1 receptor antagonist. *Arthritis Res*., 2(4):245-248.

Barnes, M.G., Grom, A.A., Thompson, S.D., Griffin, T. A., Pavlidis, P., Itert L., Fall, N., Sowders, D.P., Hinze, C.H., Aronow, B.J., Luyrink, L.K.; Srivastava, S., Ilowite, N.T., Gottlieb, B.S., Olson, J.C., Sherry, D.D., Glass, D.N. and Colbert, R.A. 2009. Subtype-specific peripheral blood gene expression profiles in recent-onset juvenile idiopathic arthritis. *Arthritis Rheum.*, 60(7):2102-2112.

Capela, R.C., Corrente, J.E. and Magalhães, C.S. 2015. Comparison of the Disease Activity Score-28 and Juvenile Arthritis Disease Activity Score in the juvenile idiopathic arthritis Rev Bras Reumatol. 55(1):31-36.

Chopra, A. 2012. The WHO ILAR COPCORD Latin America: consistent with the world and setting a new perspective. *Journal of Clinical Rheumatology*, 18(4):167–169.

Consolaro, A., Negro, G., Gallo C.M., Bracciolini, G., Ferrari, C., Schiappapietra, B., Pistorio, A., Bovis, F., Ruperto, N., Martini, A. and Ravelli, A. 2014. Defining criteria for disease activity states in nonsystemic juvenile idiopathic arthritis based on a three-variable juvenile arthritis disease activity score. *Arthritis Care Res*., (Hoboken), 66(11):1703-1709.

Contassot, E., Beer, H.D. and French, L.E. 2012. Interleukin-1, inflammasomes, autoinflammation and the skin. Swiss Med Wkly., 142:w13590.

Dayer, J.M. 2003. The pivotal role of interleukin-1 in the clinical manifestations of rheumatoid arthritis. Rheumatology (Oxford). 42 Suppl 2:ii3-ii10.

Dinarello, C.A. 2011. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases Blood, 117(14):3720-3732.

Funovits, J., Aletaha, D., Bykerk V., Combe, B., Dougados, M., Emery, P., Felson, D., Hawker, G., Hazes, J.M., Huizinga, T., Kay, J., Kvien, T.K., Smolen, J.S., Symmons, D., Tak, P.P. and Silman, A. 2010. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: methodological report phase I. *Ann Rheum Dis*., 69(9): 1589-1595.

Horneff, G. and Becker, I. 2014. Definition of improvement in juvenile idiopathic arthritis using the juvenile arthritis disease activity score. Rheumatology (Oxford). 53(7):1229-1234.

Huang, J.L. 2012. New Advances in juvenile idiopathic arthritis. *Chang Gung Med J.,* 35(1): 1-14.

Jesus, A.A. and Goldbach-Mansky, R. 2014. IL-1 blockade in autoinflammatory syndromes *Annu Rev. Med*., 65:223-244.

Kay, J. and Calabrese, L. 2004. The role of interleukin-1 in the pathogenesis of rheumatoid arthritis. Rheumatology (Oxford). 43 Suppl 3:iii2-iii9.

Lopalco, G., Cantarini, L., Vitale, A., Iannone, F., Anelli, M.G., Andreozzi, L., Lapadula, G., Galeazzi, M. and Rigante, D. 2015. Interleukin-1 as a common denominator from autoinflammatory to autoimmune disorders: premises, perils, and perspectives. *Mediators of Inflammation*, 2015:194864-194885.

Lukens, J.R. and Kanneganti, T.D. 2014. Beyond canonical inflammasomes: emerging pathways in IL-1-mediated autoinflammatory disease. *Semin Immunopathol*., 36(5):595-609.

Militaru, A.S. and Sabau, I. 2011. Correlations Between Clinical Forms and Biomarkers in Juvenile Idiopathic Arthritis. TMJ., 61 (3 – 4):204-209

Nagano, J., Sudo, N., Nagaoka, S., Yukioka, M. and Kondo, M. 2015. Life events, emotional responsiveness, and the functional prognosis of patients with rheumatoid arthritis. *Biopsychosoc Med*., 23; 9:15.

Nordström, D., Knight, A., Luukkainen, R., van Vollenhoven, R., Rantalaiho, V., Kajalainen, A., Brun, J.G., Proven, A., Ljung, L., Kautiainen, H. and Pettersson, T. 2012. Beneficial effect of interleukin 1 inhibition with anakinra in adult-onset Still's disease. An open, randomized, multicenter study. *J Rheumatol*., 39(10):2008-2011.

Ogilvie, E.M., Khan, A., Hubank, M., Kellam, P. and Woo, P. 2007. Specific gene expression profiles in systemic juvenile idiopathic arthritis. Arthritis Rheum., 56(6):1954-1965.

Pascual, V., Allantaz, F., Arce, E., Punaro, M. and Banchereau ,J. 2005. Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. *J. Exp. Med.,* 201(9):1479-1486.

Pasi, S., Kant, R., Gupta, S., and Surolia, A. 2015. Novel multimeric IL-1 receptor antagonist for the treatment of rheumatoid arthritis. *Biomaterials*, 42:121-133.

Paul, W.E. and Zhu J. 2010. How are T(H)2-type immune responses initiated and amplified? Nat Rev Immunol. 10(4):225-35.

Remy, A., Avouac, J., Gossec, B.L. and Combe, B. 2011. Clinical relevance of switching to a second tumour necrosis factor-alpha inhibitor after discontinuation of a first tumour necrosis factor-alpha inhibitor in rheumatoid arthritis: A systematic literature review and meta-analysis. *Clinical and Experimental Rheumatology*, 29(1): 96-103.

Sanmart, R., Ruiz-Esquide, V. and Hern´andez, M. V. 2013 "Rheumatoid arthritis: a clinical overview of new diagnostic and treatment approaches," *Current Topics in Medicinal Chemistry*, 13(6): 698–704.

Scott, D. L., Wolfe, F. and Huizinga, T. W. J. 2010. "Rheumatoid arthritis," *The Lancet*, 376 (9746): 1094–1108.

Shi, G., Zhang, J., Zhang, Z.J. and Zhang, X. 2015. Systemic Autoimmune Diseases 2014. *J Immunol Res*., 2015:183591-183592.

Spîrchez, M., Samaşca, G., Iancu, M., Bolba, C. and Miu, N. 2012. Relation of interleukin-6, TNF-alpha and interleukin-1alpha with disease activity and severity in juvenile idiopathic arthritis patients. *Clin Lab.,* 58(3-4):253-260.

Stoll, M.L. and Cron, R.Q. 2014. Treatment of juvenile idiopathic arthritis: a revolution in care. *Pediatr Rheumatol*., 12:13.

Tamai, M., Kita, J., Nakashima, Y. Suzuki, T., Horai, Y., Okada, A., Koga, T., Kawashiri, S.Y., Iwamoto, N., Ichinose, K., Arima, K., Yamasaki, S., Nakamura, H., Origuchi, T., Uetani, M., Fukushima, A., Aoyagi, K., Eguchi, K .and Kawakami, A. 2014. Combination of MRI-detected bone marrow oedema with 2010 rheumatoid arthritis classification criteria improves the diagnostic probability of early rheumatoid arthritis. Ann Rheum Dis., 73(12):2219-2220.

van Herwaarden, N., den Broeder, A.A., Jacobs, W., van der Maas, A., Bijlsma, J.W., van Vollenhoven, R.F. and van den Bemt, B.J. 2014. Down-titration and discontinuation strategies of tumor necrosis factor blocking agents for rheumatoid arthritis in patients with low disease activity. SO: Cochrane Database of Systematic Reviews. 29;9:CD010455.

Weber, A., Wasiliew, P. and Kracht, M. 2010. Interleukin-1beta (IL-1beta) processing pathway. Sci Signal. 3(105):cm2.

Wells, G., Becker, J.C., Teng, J., Dougados, M., Schiff, M., Smolen, J., Aletaha, D. and van Riel, P.L. 2009.Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria

based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. *Ann Rheum Dis*., 68(6):954-60.

Zwerina, J., Redlich, K., Polzer, K., Joosten, L., Krönke, G., Distler, J., Hess, A., Pundt, N., Pap, T., Hoffmann, O., Gasser, J., Scheinecker, C., Smolen, J.S., van den Berg, W. and Schett G. 2007. TNF-induced structural joint damage is mediated by IL-1. Proc Natl Acad Sci U S A. 104(28):11742-1177.

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