

# Rheumatoid Arthritis: Risks & Management

Deeksha Kaloni<sup>1,2</sup>, Debolina Chakraborty<sup>1</sup>, Archana Tiwari<sup>2</sup>, Sagarika Biswas<sup>1</sup>

<sup>1</sup>Department of Genomics & Molecular Medicine, CSIR- Institute of Genomics & Integrative Biology, Mall Road, Delhi-110007, India

<sup>2</sup>School of Bio Technology, Rajiv Gandhi Technological University, Bhopal

\*\*\*

**Abstract** - Rheumatoid arthritis is a chronic inflammatory autoimmune disease distinctive by inflamed joints resulting in articular tissue damage. The physiologic factors associated are genetic, epigenetic and certain environmental. Inflammation of the synovium is the major mediator in the progression of RA. The disease is not limited to joints but affects other internal organs as well. This causes disability, high mortality rates and socio-economic burden. The current treatment suppresses the symptoms associated with RA but possess certain adverse effects. Therefore, therapeutic advancement is needed to manage the disease better. In this review we provide an account of the factors associated with RA and the present & advanced pharmacological therapy.

**Key Words:** Rheumatoid arthritis, Genetics, Environment, Epigenetics, Inflammation, Pathology, Treatment

## 1. INTRODUCTION

Rheumatoid arthritis is a chronic autoimmune disease which is systemic in nature. Genetic, Epigenetic and Environmental are the major risk factors although age and gender also contribute to it. [1]. Characteristics of RA include swelling, redness, stiffness, pain and inflammation of joints, weakening of tendons and ligaments, cartilage and bone destruction by production of auto-antibodies.

RA particularly affects the joints (primarily hand, wrist and knee) resulting in obstructed movement due to damage of articular cartilage [2].

In RA the immune system target's the own body by producing antibodies known as "rheumatoid factor" causing inflammation and tissue destruction. Various modulators of the immune system like cytokines immune cells and signaling pathway are the key players in the pathogenesis of RA. The clinical manifestations of RA includes multi-joint symmetry, invasive arthritis, and involvement of extra-articular organ [3]. Fever, fatigue, pleuritis, depressive disorder, subcutaneous nodules, peripheral neuropathy, and other physical and mental diseases are also displayed by some patients [4]. Blood test of rheumatoid arthritis patients has shown the presence of "rheumatoid factor" in 80% of the cases. Genetic history, smoking habits, silica inhalation, periodontal disease, and microbes in the bowels (gut bacteria) are the risks associated with the development and progression of rheumatoid arthritis.

Cytokines and chemokines are secreted at the site which induces hypoxic condition and further angiogenesis occur [5]. These micro-environmental changes results in the buildup of synovial inflammatory tissues in rheumatoid arthritis. These are related with various complications including pain, swelling, stiffness, loss of function of joint. The dysregulated immune system leading to inflammation is associated with various risks and complications targeting multiple organs and various other areas of the body apart from the joints like lungs, skin, heart, and kidney [6]. As there is no cure for RA but the present treatments aims to lower the disease state. The treatment for rheumatoid arthritis involves medication in coalition with proper rest, exercise, adequate knowledge and in severe cases surgery. Currently available treatment includes NSAID's, DMARD's Anti-TNF biologics (which is a class of DMARDs) and few new medications which are under clinical phase. Therefore, the review outlines the causes of RA, pathology involved and the treatment for its management.

## 2. CAUSES OF RA

### 2.1 ENVIRONMENTAL ASPECT

Many environmental factors are associated with the pre disposition of RA; this includes cigarette smoking, atmospheric agents, infections, dietary factors, pollutants and birth weights. Recent evidences indicate the relation of atmospheric and occupational agents with RA. Silica exposure in people leads to ACPA-positive rheumatoid factor positive RA [7,8]. Silica exposure can be encountered in mining, quarrying, drilling and some electronic industries [7]. Cigarette smoking is the well-studied factor correlated with RA. Smokers have approximately 2-fold higher risk of RA than nonsmokers and the risk is not because of nicotine but due to some other inhaled compound [9, 10]. The correlation found to be restricted to the anti-citrullinated protein/peptide antibody (ACPA)-positive RA [11]. Increased prevalence of RA is also associated with urbanization [12]. High weight at the time of birth is also related with RA (OR, 3.3) (birth weight > 4.5 kg corresponds to 2-fold increased risk of RA compared to birth weight in the 3.2-3.85 kg range [12], whereas breast feeding seems to impose a protective effect. Microchimerism is another aspect that may influence the probability of RA occurrence. Microchimerism is persistence in the body of the cells and/or DNA that make its journey from the foetus to the mother during the period of pregnancy. These cells remain in the mother's body for several decades and may give rise to the development of autoimmune disorders [12].

Infectious agents like *Human parvovirus B19*, *Hepatitis A virus*, *Epstein-Barr virus*, *Rubella virus*, *Porphyromonas gingivalis*, *cytomegalovirus (CMV)*, *Human retrovirus 5*, *Proteus mirabilis*, *Chlamydia pneumonia*, *Mycoplasma*, *Alphaviruses*, *Borrelia burgdorferi*, *Herpes simplex virus I and II*, *Porphyromonas Gingivalis* [13] and *Helicobacter pylori* links to the development of RA as they results in increased production of pro-inflammatory factor IL-6 and C-reactive protein [14]. This further leads to synovial inflammation and secretion of citrullinated proteins [14].

### 2.2 GENETIC ASPECT

RA is also found to be linked with certain alterations at the genetic level, around 37-65% is estimated heritability [14]. According to the genomic study the HLA-DRB1 locus is the dominant genetic risk factors for RA [15]. HLA-DRB1 is a class II histocompatibility complex located at chromosome 6. It encodes for an amino acid motif, located in the  $\beta$ -chain of the MHC molecule involved in antigen presentation and recognition between self and non-self. The mutation occurs at the antigen recognizing binding groove

Apart from the alteration in HLA, mutations in the protein tyrosine phosphatase non-receptor 22 (PTPN22) gene [16, 17] is also linked with multiple autoimmune diseases including RA. PTPN22 gene encodes for lymphoid tyrosine phosphatase, is a negative regulator of signal transduction from the TCR [18]. Polymorphisms of TRAF1-C5 and TNFAIP3 have also been associated with RA. Other non-HLA genetic risk factors includes mutation in STAT4 [19] and CTLA- 4, IL2/IL21, polymorphisms of PADI4 (which encodes an enzyme that converts the arginine residues of proteins into citrullines, which can then be recognized by ACPAs in the sera of RA patients [12].

Also, the probability of occurrence of RA is far more in women as compared to men, the female-to-male proportion being 3:1. The peak age at RA onset is the fifth decade, period when hormonal changes occur in women. Although, recent studies have suggested a slide to an older age. The dominance of RA in women's also suggests the role of hormonal factors. In addition, estrogens stimulate the immune system while low levels of testosterone have been reported in men with RA [12].

### 2.3 EPIGENETIC ASPECT

Epigenetics are a heritable change that focus on DNA methylation and Histone modifications, and is the interconnection between the genetic and environmental factors associated with RA. Studies have demonstrated that hypomethylation patterns of synovial fibroblasts DNA in RA, including hypomethylation of CXCL12 gene at promoter site [20] and the LINE1 retrotransposons [21]. LINE1 retrotransposons are repetitive elements usually oppressed by DNA methylation. The loss of this oppressive DNA methylation process, the expression level of gene gets upregulated. Different hypo and hyper methylated patterns in the genomic regions were found in RA synovial fibroblasts

[22]. It was also found that the HAT to HDAC activity proportion in case of arthritic joints was slided towards HAT, leading to acetylation of histone [23], thereby increasing in gene transcription.

### 3. PATHOGENESIS OF RHEUMATOID ARTHRITIS

The initiation of pathology occurs with the infiltration of leukocytes in the synovial compartment resulting in synovitis formation. These infiltrated cells then migrate in synovial microvessels enabled by the endothelial activation, which further up-regulates the expression of adhesion molecules and coordinates production of chemokines and pro-inflammatory cytokines. This causes chronic inflammation at the site and activation of fibroblast [1]. The environmental factors also contribute towards it by modifying our own antigens such as IgG antibodies, Type II collagen and Vimentin,  $\alpha$ -1-antitrypsin (A1AT), keratin type II, dynein heavy-chain 3, fibrinogen $\text{\textcircled{R}}$  chain, cuticular Hb4 (KRT84), lumican, and tubulin  $\text{\textcircled{R}}$ -chain (TUBB). These proteins get modified by a process known as citrullination in which the amino acid arginine is converted to citrulline that act as a self altered antigen. These self antigens are recognized by the APC's and are carried to the lymph nodes. CD4 T<sub>H</sub> cells are activated and stimulate B- lymphocyte cells which proliferate, differentiate into antibody producing plasma cells. These antibodies along with the TH cell enter the circulation and reaches to the joints. Cytokines (interferon gamma and interleukin 17) are secreted at the site and macrophages are recruited which further produce TNF- $\alpha$ , Interleukin-1, Interleukin-6 and induces the proliferation of the synovial cells (synovitis), this creates pannus at the site. Pannus is thick, swollen synovial membrane with granulation tissue which results in pain, joint swelling and joint damage. Over the time, the pannus can damage the cartilage, other soft tissue and can erode bones. The proliferated synovial cells secrete proteases that causes breakdown of proteins in articular cartilage and the underline bone gets exposed. Meanwhile, auto-antibodies (IgM and anti-CCP) enter the joint, bind the altered Ag and form an immune complex activating the complement system resulting in joint inflammation and injury [24].

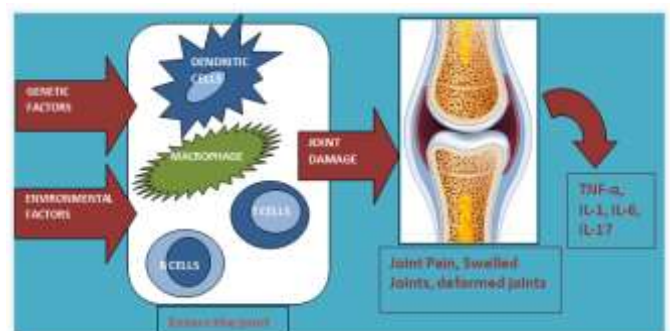
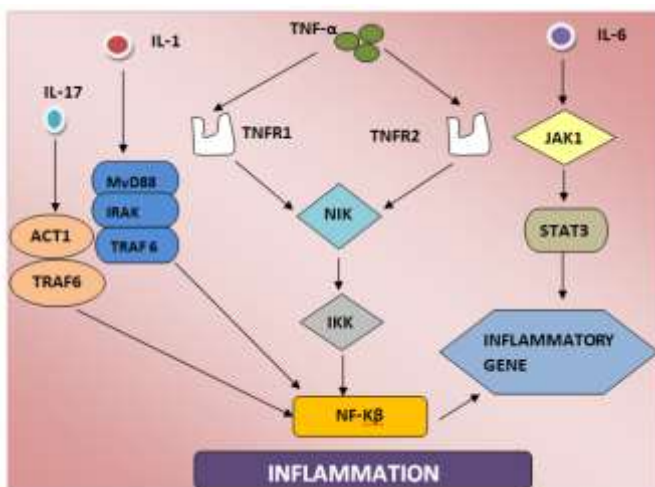


Fig-1: Pathogenesis that occurs during Rheumatoid arthritis.

#### 4. INFLAMMATION

Inflammation is a localized condition that is associated with various diseases. It is the defense mechanism of the host body during infection or injury and maintains tissue homeostasis in noxious conditions. It is one of the hallmarks of rheumatoid arthritis. There are many pro-inflammatory agents involved in inflammation, few prominent ones are tumor necrosis factor (TNF), interleukin IL-6, IL-1, IL-17. TNF- $\alpha$  secreted by the macrophages involved in tissue destruction and remodeling associated with the inflammatory disease. It is considered as a master regulator of cytokine production. Excessive secretion of these cytokines is triggered in RA which further results in its binding to specific receptors and stimulation of the signaling pathways. Two receptors of TNF that mediates the signaling pathway and results in the effects of TNF are TNFR1 (P55) and TNFR2 (P75). Except erythrocyte all the cell types expresses TNFR1 whereas TNFR2 is strictly expressed by the immune cells [25]. In case of rheumatoid arthritis the secretion of TNF- $\alpha$  is dysregulated resulting in induction and maintenance of synovitis. The cytokines TNF- $\alpha$ , IL-6, IL-1 are released in the synovial microenvironment and leads to various systemic manifestations. It also affects the bone marrow, causing anemia in patients with rheumatoid arthritis [26, 27].



**Fig-2:** Mechanism of activation of inflammation facilitated by different pro-inflammatory cytokines TNF- $\alpha$ , IL-1, IL-6, IL-17.

#### 5. TREATMENT

Treatment of rheumatoid arthritis is the conjunction of both the pharmacologic and non-pharmacologic therapies. The non-pharmacological therapy includes the physio-therapy, balanced diet, adequate exercise, stress reduction and surgery which include synovectomy, replacement of joint and tendon repair. Earlier aspirin and colloidal gold were administered to a RA patient. These drugs provides symptomatic relieves but does no slow down the progression of the disease.

The pharmacologic therapy is drug based constituting of various classes of agents, Non-steroidal anti-inflammatory drugs (NSAID's) and Disease-modifying anti-rheumatic drugs (DMARD's) being the major ones. The DMARDs are further classified as cs-DMARDs, b-DMARDs and ts-DMARDs. The b-DMARDs also known as the anti-biologics are specific against the inflammatory cytokines. DMARDs have been the central focus for managing rheumatoid arthritis combined with physical therapy and aspirin (acetylsalicylic acid) or NSAID's. DMARDs include Methoteroxate (MTX), Sulfasalazine (SSZ), Hydroxychloroquine (HCQ), Cyclosporine, Gold salts, Penicillamine, and Azathioprine which retard the progression of the disease. Methoteroxate (MTX) is the cornerstone in the treatment of RA. It can be combined with other DMARDs in different dosage. It modifies the cytokine profile and downregulates the MMPs that damages the bone and cartilage. The anti-inflammatory mechanism of NSAIDs is through the inhibition of the enzyme cyclooxygenase (COX) [28]. COX enzymes exist in two forms, e.g., COX-1 and COX-2. The COX-1 is expressed constitutively by most of the tissues and is associated with the formation of prostaglandins and thromboxane A2, while the expression of COX-2 is mediated by the inflammatory mediators [29]. Although they are effective against COX-1 and COX-2 but also inhibit platelet aggregation and leads to significant gastrointestinal disorders such as bleeding, ulcers, and perforation [30]. COX-2 inhibitors have adverse effect on the cardiovascular system [31]. NSAID's improves the physical function of joints by decreasing pain, swelling and stiffness but does not prevent the joint damage. A more potent anti-inflammatory than NSAIDs drug is Corticosteroids. They prevent the release of phospholipids and decreasing the actions of eosinophils, thereby further decreasing inflammation.

The anti-TNF biologics inhibits the expression of pro-inflammatory cytokines (IL-1, IL-6, and GM-CSF) in the synovial culture [32]. Anti-TNF biologics Infliximab and Adalimumab suppress antigen-induced IFN- $\gamma$  production in blood [33] whereas Tocilizumab and Sarikumab target the cytokine IL-6. But these anti-biologics are not equally effective in all patients. Up to 40% of patients are non-responsive to anti-TNF treatment [34] and are associated with certain risks which need to be taken into account [35]. While the synthetic DMARD's targets the Janus kinase [JAK] enzyme.

Further genetically modified chimeric monoclonal antibody Rituximab have been developed that targets CD20-positive B lymphocytes [36]. The population of B lymphocytes which contributes to the inflammation cascade is depleted by this drug. Drugs like BCD-020, Maball, and MabTas are analogs of Rituximab which have been approved in some countries [37]. Although there are associated side effects reported include hypogammaglobulinemia, infection, late-onset neutropenia, and mucocutaneous reactions. Another monoclonal antibody is Belimumab that targets the stimulator of B lymphocyte thereby inhibiting its activity.

However, it does not come up as an effective drug during the phase II clinical trials [36].

T-cell medications are also being investigated at the clinical phases for their efficiencies. Some of them are ALX-0061, Sirukumab, Clazakizumab, Olokizumab [36].

Denosumab (DMab) is a human monoclonal antibody inhibits bone resorption by binding the receptor activator of the NF- $\kappa$ B ligand (RANKL) which is crucial for osteoclastogenesis and bone resorption [36]. Despite the increasing new therapeutic regimes, complete long-term disease remission is not achieved in many cases and therefore much advancements are still required.

## 6. CONCLUSION

In order to develop new and effective therapeutics for RA, much insight knowledge of the pathophysiology is needed. However the adverse effects associated with them should also be well measured and analyzed. Gene array analysis is also being used to determine the risk of developing RA as it provides rapid and early diagnosis. It can be integrated with other classical and novel pharmacological therapies to achieve better results in diagnosing and treating RA. It is foreseen that treatment methods will face tremendous improvements in the management of RA. Therefore, with the aim to prevent remission of the disease and with no adverse effects various permutation and combination of the existing therapies and development of novel therapies is required.

## REFERENCES

- [1] Pnina Fishman and Sara Bar-Yehuda Rheumatoid Arthritis: History, Molecular Mechanisms and Therapeutic Applications. A 291 3 Adenosine Receptors from Cell Biology to Pharmacology and Therapeutics, 2010. [https://doi.org/10.1007/978-90-481-3144-0\\_15](https://doi.org/10.1007/978-90-481-3144-0_15).
- [2] L. Haywood and D.A. Walsh, "Vasculature of the normal and arthritic synovial joint," *Histol Histopathol.* Vol. 16, 2001, pp. 277-284.
- [3] Abhishek A, Doherty M, Kuo CF, Mallen CD, Zhang W, Grainge MJ, "Rheumatoid arthritis is getting less frequent results of a nationwide population-based cohort study," *Rheumatol.* 2017.
- [4] Puchner R, Hochreiter R, Pieringer H, Vavrovsky A, "Improving patient flow of people with rheumatoid arthritis has the potential to simultaneously improve health outcomes and reduce direct costs," *Bmc Musculoskel Dis.* Vol. 18, Issue. 7, 2017.
- [5] Polzer K, Baeten D, Soleiman A, Distler J, Gerlag DM, Tak PP, Schett G, and Zwerina J, "Tumour necrosis factor blockade increases lymphangiogenesis in murine and human arthritic joints," *Ann Rheum Dis.* Vol. 67, 2008, pp. 1610-1616.
- [6] J. Michelle Kahlenberg, David A. Fox, "Advances in the Medical Treatment of Rheumatoid Arthritis," *Hand Clin.* Vol. 27, Issue 1, 2011, pp. 11-20.
- [7] Stolt P. et al., "Silica exposure is associated with increased risk of developing rheumatoid arthritis: results from the Swedish EIRA study," *Annals of the rheumatic diseases* Vol. 64, 2005, pp. 582-586. <https://doi.org/10.1136/ard.2004.022053>
- [8] Stolt P. et al., "Silica exposure among male current smokers is associated with a high risk of developing ACPA-positive rheumatoid arthritis," *Annals of the rheumatic diseases* Vol. 69, 2010, pp. 1072-1076. <https://doi.org/10.1136/ard.2009.114694>.
- [9] Costenbader K H, Feskanich D, Mandl L A, & Karlson E W, "Smoking intensity, duration, and cessation, and the risk of rheumatoid arthritis in women," *The American journal of medicine* Vol. 119, 2006, pp. e501-509.
- [10] Jiang X, Alfredsson L, Klareskog L, & Bengtsson C, "Smokeless tobacco (moist snuff) use and the risk of developing rheumatoid arthritis: Results from the Swedish Epidemiological Investigation of Rheumatoid Arthritis (EIRA) case-control study," *Arthritis Care Res (Hoboken)*, 2014. <https://doi.org/10.1002/acr.22325>.
- [11] Kallberg H. et al., "Smoking is a major preventable risk factor for rheumatoid arthritis: estimations of risks after various exposures to cigarette smoke," *Annals of the rheumatic diseases* Vol. 70, 2011, pp. 508-511. <https://doi.org/10.1136/ard.2009.120899>.
- [12] Gabriel J. Tobón, Pierre Youinou, Alain Saraux, "The environment, geo-epidemiology, and autoimmune disease: Rheumatoid arthritis," *Autoimmunity Reviews*, Vol. 9, Issue 5, 2010, pp. A288-A292.
- [13] Schmickler J, Rupprecht A, Patschan S et al., "Cross-sectional evaluation of periodontal status and microbiologic and rheumatoid parameters in a large cohort of patients with rheumatoid Arthritis," *J Periodontol.* Vol. 88, 2017, pp. 368-79
- [14] Zhu J, Quyyumi AA, Norman JE, et al., "Effects of total pathogen burden on coronary artery disease risk and C-reactive protein levels," *Am J Cardiol.* Vol. 85, 2000, pp. 140-6.
- [15] Okada Y. et al., "Genetics of rheumatoid arthritis contributes to biology and drug discovery," *Nature* Vol. 506, 2014, pp. 376-381. <https://doi.org/10.1038/nature12873>.
- [16] Begovich AB, Carlton VE, Honigberg LA et al., "A missense single-nucleotide polymorphism in a gene encoding a protein tyrosine phosphatase (PTPN22) is associated with rheumatoid arthritis," *Am J Hum Genet.* Vol. 75, 2004, pp. 3307.
- [17] Viken MK, Amundsen SS, Kvien TK et al., "Association analysis of the 1858C>T polymorphism in the PTPN22 gene in juvenile idiopathic arthritis and other autoimmune diseases," *Genes Immun.* Vol. 6, 2005, pp. 2713.
- [18] Bottini N, Musumeci L, Alonso A et al., "A functional variant of lymphoid tyrosine phosphatase is associated with type I diabetes," *Nat Genet.* Vol. 36, 2004, pp. 3378.
- [19] Remmers EF, Plenge RM, Lee AT, Graham RR, Hom G, Behrens TW, et al., "STAT4 and the risk of rheumatoid arthritis and systemic lupus erythematosus" *N Engl J Med.* Vol. 357, 2007, pp. 977-86.

- [20] Karouzakis E, Rengel Y, Jungel A, Kolling C, Gay RE, Michel BA, Tak PP, Gay S, Neidhart M, Ospelt C, "DNA methylation regulates the expression of CXCL12 in rheumatoid arthritis synovial fibroblasts," *Genes Immun.* Vol. 12, 2011, pp. 643–652.
- [21] Neidhart M, Rethage J, Kuchen S, Kunzler P, Crowl RM, Billingham ME, Gay RE, Gay S, "Retrotransposable L1 elements expressed in rheumatoid arthritis synovial tissue: association with genomic DNA hypomethylation and influence on gene expression," *Arthritis Rheum.* Vol. 43, 2000, pp. 2634–2647.
- [22] Nakano K, Whitaker JW, Boyle DL, Wang W, Firestein GS, "DNA methylome signature in rheumatoid arthritis," *Ann Rheum Dis.* Vol. 72, 2013, pp.110–117.
- [23] Huber LC, Brock M, Hemmatazad H, Giger OT, Moritz F, Trenkmann M, Distler JH, Gay RE, Kolling C, Moch H, Michel BA, Gay S, Distler O, Jungel A, "Histone deacetylase/acetylase activity in total synovial tissue derived from rheumatoid arthritis and osteoarthritis patients," *Arthritis Rheum.* Vol. 56, 2007, pp.1087–1093.
- [24] Gary S. Firestein, Iain B. McInnes, "Immunopathogenesis of Rheumatoid Arthritis," *Immunity* Vol. 46, Issue 2, 2017, pp. 183-196.
- [25] Faustman D, and Davis M, "TNF receptor 2 pathway: drug target for autoimmune diseases," *Nat. Rev. Drug Discov.* Vol. 9, 2010, pp. 482–493.
- [26] Gortz B, Hayer S, Tuerck B, Zwerina J, Smolen JS, Schett G, "Tumour necrosis factor activates the mitogen-activated protein kinases p38alpha and ERK in the synovial membrane in vivo" *Arthritis Res Ther.* Vol. 7, Issue 5, 2005, pp. R1140–R1147.
- [27] Voulgari PV, Kolios G, Papadopoulos GK, Katsaraki A, Seferiadis K, Drosos AA, "Role of cytokines in the pathogenesis of anemia of chronic disease in rheumatoid arthritis," *Clin Immunol.* Vol. 92, Issue 2, 1999, pp.153–160.
- [28] Simmons DL, Botting RM, and Hla T, "Cyclooxygenase isozymes: the biology of prostaglandin synthesis and inhibition," *Pharmacol. Rev.* Vol. 56, 2004, pp. 387–437.
- [29] Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, and Taubert KA, "Use of nonsteroidal Antiinflammatory drugs an update for clinicians - A scientific statement from the American Heart Association," *Circulation* Vol. 115, 2007, pp. 1634–1642.
- [30] Fujita T, Kutsumi H, Sanuki T, Hayakumo T, and Azuma T, "Adherence to the preventive strategies for nonsteroidal anti-inflammatory drug-orlow-doseaspirin-induced gastrointestinal injuries," *J. Gastroenterol.* Vol. 48, 2013, pp. 559–573. <https://doi:10.1007/s00535-013-0771-8>
- [31] Hermann M, and Ruschitzka F, "Coxibs, non-steroidal anti-inflammatory drugs and cardiovascular risk," *Intern. Med. J.* Vol. 36, 2006, pp. 308-319.
- [32] Feldmann M, Brennan F M, and Maini R N, "Role of cytokines in rheumatoid arthritis" *Annu. Rev. Immunol.* Vol. 14, 1996, pp. 397–440.
- [33] Wallis RS, "Reactivation of latent tuberculosis by TNF blockade: the role of interferon gamma," *J. Invest. Dermatol. Symp. Proc.* Vol. 12, 2007, pp. 16–21.
- [34] Roda G, Jharap B, Neeraj N, and Colombel JF, "Loss of response to anti TNFs: definition, epidemiology, and management," *Clin. Transl. Gastroenterol.* Vol. 7, 2016, pp. 135. <https://doi:10.1038/ctg.2015.63>
- [35] Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, and Montori V, "Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies :systematic review and meta-analysis of rare harmful effects in randomized controlled trials," *JAMA* Vol. 295, 2006, 2275–2285.
- [36] Qiang Guo, Yuxiang Wang, Dan Xu, Johannes Nossent, Nathan J. Pavlos & Jiake Xu, "Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies," *Bone Res.* Vol. 6, 2018.
- [37] Braun J, & Kay J, "The safety of emerging biosimilar drugs for the treatment of rheumatoid arthritis," *Expert. Opin. Drug. Saf.* Vol. 16, 2017, pp. 289–302.