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Cytokines Approach: Treatment of Rheumatoid Arthritis, One of the serious cause physical disability in North zone of India

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Abstract

Introduction: Cytokine expression and regulation may yield effective therapeutic targets in rheumatoid arthritis. Pathogenesis reveals (arguably) the most inclusive study of pathologic cytokine function in a chronic inflammatory disease in recent years. Presence of IL-1, IL-6, TNF alpha, chemokines (e.g., IL-8) and GM-CSF has been reported in patients with rheumatoid arthritis irrespective of curative therapy. They must be produced *de novo* in response to an immune stimulus. Generally act over short distances and short time spans and at very low concentration. India does not have a national rheumatoid arthritis surveillance system creation, it is very difficult to methodically access and determine burden of hospital-acquired rheumatoid arthritis. This review reports cytokine approach for the treatment of rheumatoid arthritis in north zone of India.

Methods: Methodical review of the peer-reviewed works reporting the incidence of cytokine expression and regulation may yield effective therapeutic targets in rheumatoid arthritis and approach of cytokines for the treatment of RA in North Indian hospitals was identified using MEDLINE and CINAHL records.

Results: Data of the 934 research papers recognized in the search, 30 articles were included in this review, these studies suggest that cytokines act by binding to specific membrane receptors, which then signal the cell via second messengers, often tyrosine kinases, to alter its behavior (gene expression).Subsequently, other proinflammatory cytokines were also suppressed if TNF alpha was neutralized, paving way for the novel idea that the proinflammatory cytokines were linked in a network with TNF alpha at its apex. It shows that TNF alpha was of major importance in rheumatoid arthritis and was a therapeutic target. Numerous clinical trials using a chimeric anti-TNF alpha antibody have revealed marked clinical advantage, verifying the hypothesis that TNF alpha is of major importance in rheumatoid arthritis. Retreatment studies have also shown benefit in repeated relapses, indicating that the disease remains TNF alpha dependent.

Conclusion: Overall, these studies demonstrate that analysis of cytokine expression and regulation may yield effective therapeutic targets in Rheumatoid arthritis.

Keywords: Rheumatoid arthritis, Cytokines, Chemokines.

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease with 1% prevalence in the industrialized world specially in north zone of India, China and Asia due to improper lifestyle Fig-1 [1]. It comprises a syndrome of pain, stiffness, and symmetrical synovitis (inflammation of the synovial membrane) of diarthrodial joints (freely moveable joints such as the knee) that leads to functional decline, substantial comorbidity, and articular destruction in the metabolic systems, neurologic, and cardiovascular. Therapeutic approaches used previously relied on disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and sulfasalazine that had only partial clinical benefit and were associated with significant toxicity [2]. Extensive genetic and pathogenetic studies point to dysregulation of both innate and adaptive immune compartments. These lead to an elaboration of autoantibody responses and dyslipidemia, which might

predate clinical disease onset by up to a decade [3]. After this particular localization onsets via mechanisms still unknown, which further leads to chronic synovitis. RA synovial membrane contains activated B and T cells, sometimes organized into germinal center–like structures, plasma cells, mast cells, and particularly activated macrophages, all recruited via an intense neovascularization process with associated lymphangiogenesis [4][5]. It is also recognized that host tissue cells (activated synovial fibroblasts, chondrocytes, and osteoclasts) are involved, mediating cartilage and bone destruction as well as feeding back to promote perpetuation of inflammation. A system of cytokines guide the employment, activation, and effector function of each of the contributor lineages [6].

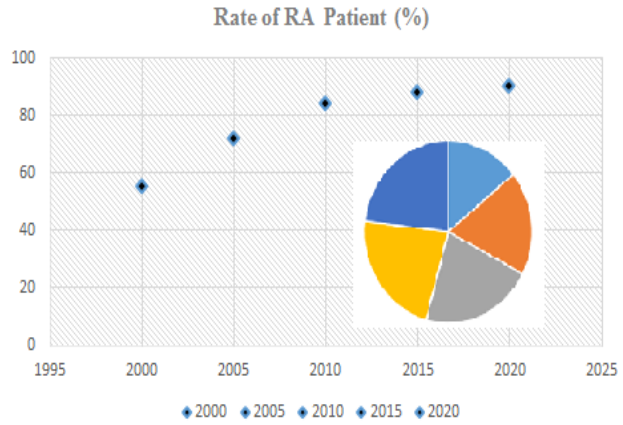

Figure 1: Percentage of Rheumatoid arthritis patients in north zone of India form 2000 to 2020

mRNA and protein analysis of cytokines in tissue with RA exposed that many proinflammatory cytokines such as tumor necrosis factor–α (TNF-α), GM-CSF, interleukin (IL-1, IL-6), and chemokine's such as IL-8 are copious in all patients despite of therapy [2][7]. This is balanced to some extent by the amplified manufacture of anti-inflammatory cytokines such as IL-10 and TGF-β and cytokine inhibitors such as IL-1ra and soluble TNF-R. However, this enhancement in homeostatic regulatory mechanisms is not sufficient as these are unable to neutralize all the TNF-α and IL-1 produces [7].

The cell cultures from rheumatoid joints that spontaneously produce IL-1, TNF-α was found to be the key regulator of IL-1. TNF--α was found to be the main culprit since its neutralization subsequently inhibited, other proinflammatory cytokines. Gave rise to the new concept that TNF-α is at apex of the proin-flammatory cytokines network. This led to hypothesize that TNF-α was of key significance in rheumatoid arthritis and was a therapeutic target. This hypothesis has been positively tested in *in-vivo* models for example, collagen-induced arthritis, and these studies have provided the rationale for clinical trials of anti-TNF-α therapy in patients with long-standing rheumatoid arthritis [8]. Several clinical trials using a chimeric anti-TNF-α antibody have shown marked clinical benefit, verifying the hypothesis that TNF-α is of major importance in rheumatoid arthritis. Repeated treatments have also shown benefit in recurring relapses, signifying that the disease remains TNF-α dependent. Overall these studies demonstrate that analysis of cytokine expression and regulation may yield effective therapeutic targets in inflammatory disease [9].

2. Signs and symptoms

Sluggish advancement of signs and symptoms over weeks to months. First notices stiffness in one or more joints Pain on movement and by tenderness in the joint Rheumatoid arthritis is additive poly arthritis, involving five or more joints [10]. The joints involved most often are the proximal inter phalangeal (PIP): metacarpophalangeal (MCP) hands, wrists, shoulders, elbows, knees, and ankle: metatarsophalangeal (MTP) joints. Stiffness in morning that persists for more than one hour but often lasting several hours. Nonspecific systemic symptoms primarily fatigue, malaise, and depression, May commonly precede other symptoms of the disease by weeks to months [11][12]. A range of chemical mediators including neurotransmitters, contribute towards pathogenesis of RA. Histamine is a classical mediator of inflammation and three types of receptors are known Histamine is involved in the pathogenesis of RA [13]. It is a chronic, autoimmune, inflammatory systemic disease of unknown etiology. Intense episodic synovitis in RA cause severe injury to the bone and cartilage. This episodic synovitis can be attributed to various potent pro- inflammatory mediators known as cytokines that include IL–1, TNF–α, as well as several other cytokines [14]. IL–1 and TNF-α particularly abundant in the cytokine profile of the synovial lining of the joint. As a result of its potential effects on mediating joint damage, IL–1 is of particular interest in the pathogenesis of rheumatoid arthritis [15][16].

3. Cytokines

Hematopoiesis, management of immunity & inflammation are the basic functions of cytokines, which are a group of proteins which intervene & control immunity. They must be produced *de novo* in response to an immune stimulus. Commonly act over short distances and small time spans and at very low concentration[17][18]. They function by binding to their receptors on the cell surface, which signal the cell via second messengers, often tyrosine kinases, to alter its behavior (gene expression). Responses to cytokines include increasing or decreasing

expression of membrane proteins (including cytokine receptors), proliferation, and secretion of effecter molecules[19]. Cytokine is a general name; other names are:

- Cytokines from lymphocytes - lymphokine
- cytokines from monocytes - monokine
- cytokines with chemo tactic activities - chemokine
- cytokines made by one leukocyte and acting on other leukocytes - interleukin

Cytokines possess autocrine action, paracrine action, and in some instances endocrine action. It is a regular phenomenon for different cell types to produce the same cytokine or for a single cytokine to act on several different cell types pleiotropy [20]. They are outmoded in their activity i.e., resembling functions can be stimulated by other cytokines also, usually produced in a cascade, as one cytokine stimulates its cellular targets to make supplementary cytokines [21]. Also be synergistic in their action (two or more cytokines acting mutually) or antagonistic (cytokines possessing opposite activities). Their small half-life, pleiotropic, redundancy, and low plasma concentrations all complicated the isolation and characterization of cytokines. Searches for new cytokines are now often conducted at the DNA level, identifying genes similar to known cytokine genes [19].

3.1 Cytokine receptors

Cytokine receptors have been classified based on their 3-D structure. These provide several unique perspectives for attractive pharmacotherapeutic targets [22].

- Immunoglobulin (Ig) super group, which are universally present maximum several cells and tissues of the vertebrate body, and it shares structural homology with immunoglobulins (antibodies), cell adhesion molecules, with some cytokines. Examples: IL-1 receptor types [23][24].
- Haemopoietic Growth Factor (type 1) group, whose members have certain conserved motifs in their extracellular amino-acid domain. The IL-2 receptor belongs to this sequence, which when deficient in γ-chain (common to many other cytokines), is directly accountable for the x-linked form of Severe Combined Immunodeficiency (X-SCID)[25].
- Interferon (type 2) group, whose members are receptors for IFN β and γ [26].
- Tumor necrosis factors (TNF) (type 3) group, whose effective members share a cysteine-rich mutual extracellular compulsory domain, and includes several other non-cytokine ligands like CD40, CD27 and CD30, besides the ligands on which the group is named (TNF) [27].

Seven Trans membrane helix family, the ubiquitous receptor type of the animal kingdom. All G protein-coupled receptors (for hormones and neurotransmitters) belong to this family. Chemokine receptors, two of which act as binding proteins for HIV (CXCR4 and CCR5), also belong to this family [28].

Types of cytokines

The Member cytokines of four-α-helix bundle family, have three-dimensional structures with four bundles of α-helices [29][30].

Table 1: Types of cytokines

Cytokine	Producing Cell	Target Cell	Function
GM-CSF	T h cells	Progenitor cells	Growth and differentiation of Monocytes and DC [31]
IL-1	Monocytes macrophages B cells DC	T h cells B cells NK cells Various	Co-stimulation Maturation and proliferation Activation Inflammation, acute phase response, fever [32]
IL-2	T h1 cells	Activated T and B cells, NK cells	Growth, proliferation, activation [33]
IL-3	T h cells NK cells	Stem cells ,Mast cells	Growth and differentiation Growth and histamine release [34][35]
IL-4	T h2 cells	Activated B cells Macrophages T cells	Proliferation and differentiation IgG1 and Ig E synthesis MHC Class II Proliferation [35]
IL-5	T h2 cells	Activated B cells	Proliferation and differentiation IgA synthesis [34]
IL-6	Monocytes macrophages T h2 cells stromal cells	Activated B cells Plasma cells Stem cells Various	Differentiation into plasma cells Antibody secretion Differentiation Acute phase response [36]
IL-7	Marrow stroma thymus stroma	Stem cells	Differentiation into progenitor B and T cells [37]
IL-8	Macrophages endothelial cells	Neutrophils	Chemo taxis [38]

Table 1 Continue.....			
IL-10	T h2 cells	Macrophages B cells	*Cytokine production* Activation [39]
IL-12	Macrophages B cells	Activated Tc cells NK cells	Differentiation into CTL (with IL-2)Activation [40]
IFN-α	Leukocytes	Activate NK cells and to augment their cytotoxic activity	Innate immune response against viral infection [41]
IFN-β	Fibroblasts	Various	*Viral replication* MHC I expression [42]
TGF-β	T cells, Monocytes	Monocytes, macrophages Activated macrophages Activated B cells Various	Chemotaxis IL-1 synthesis IgA synthesis *Proliferation* [43]
TNF	Macrophages, mast cells, NK cells	Macrophages Tumor cells	CAM and cytokine expression Cell death [44]
TNF-α	T h1 and Tc cells	Phagocytes Tumor cells	Phagocytosis, NO production Cell death [45]

3.2 Role of cytokines in RA

The appreciation of the role played by cytokines in RA pathogenesis reflects (arguably) the most comprehensive analysis of pathologic cytokine function in a chronic inflammatory disease in recent years [46].The ease of procurement of diseased tissue from the infrected site (synovial joint) has facilitated both the investigation and recognition of the key molecules involved in the pathogenesis of the disease [47]. In this Review, we are providing a historical standpoint outlining those studies that recognized the pivotal role of TNF-α in the pathogenesis of RA, which covered the method to the principal clinical trials of a biological therapeutic in this disease. Thereafter, this article would address other cytokines too which might play a role in the disease, including those found in the IL-1, IL-6, and IL-23 superfamilies [48][38]. Later this review will also cover some selected cytokines that bind a receptor containing the common γ-chain (γ_c) [49]. Notably, the nature of rheumatoid disease has changed since authors have started their studies around more than 20 years back. This resulted in part from more aggressive intervention initiated earlier and is reflected in improved functional outcomes and reduced erosive progression manifest in fewer arthroplasties (joint replacements) [50]. Presently, RA synovial tissue is acquired for ex-vivo analysis is usually less cellular and inflammatory than previously analyzed tissues (authors' unpublished observations). Furthermore, because it is obtained from joint replacement surgery from "end-stage" disease [51], it might not be useful for identifying factors important in the early phases of disease. These facts have implications for identifying novel targets in this disease and might also contribute to the differences recently observed between results of studies in vitro and in mouse models and those on human diseased tissue [52]. Nevertheless, we propose that novel therapeutic targets and further improvement in outcomes might be offered by continued elucidation of the effector biology of cytokines. TNF inhibitors embody the first rational treatment. TNF-α and IL-1 induce both, synthesis and secretion of matrix-degrading proteases [51], prostanoids, IL-6, IL-8 and granulocyte-macrophage colony stimulating factor (GM-CSF) from synovial fibroblasts. These are the chief macrophage-derived cytokines present in the rheumatoid joint.Consequently, attention has focused on inhibition of TNF-a as a way to treat RA [53][54].

3.3 Treatment

Till the 1950s, Aspirin (an anti-inflammatory agent) was the core of RA therapy. Disease-modifying anti-rheumatic drugs (DMARDs), corticosteroids like methotrexate (MTX), sulphasalazine, and leflunomide [55]. Conventional DMARDs, however, have several limitations, like slow onset of action, Induction of partial remission and modest 5-year retention rates. The quest for an ideal DMARD thus continues [56] Biological response modifiers are therapeutic agents that have potential to inhibit the RA.

Table 2: Drug used in treatment of RA

Drug	Dose	Mechanism	Interaction	Adverse effect
Etanercept	50 mg self-administered once per week by subcutaneous injection.	Etanercept binds TNF in the circulation and in the joint, preventing interaction with cell surface TNF receptors thereby reducing TNF activity[57][58]	Anakinra[59][60], cyclophosphamide[60]	Upper respiratory infection, Transient neutropenia, blood dyscrasias [61][62][63][64].
Infliximab.	3 mg/kg for RA given as an intravenous infusion	Infliximab binds TNF in the joint and in the circulation, preventing its interaction with TNF receptors on the surface of inflammatory cells,Thus Infliximab inhibits the activity of TNF.	Methotrexate [64].	Sepsis, disseminated tuberculosis, fever, chills, body aches, and headache Cancer Risk, Congestive Heart Failure and Multiple Sclerosis [64][65].
Adalimumab.	40 mg dose is given by self-administered subcutaneous (SC) injection every other week.	Adalimumab binds specifically to TNF and blocks its interaction with the p55 and p75 cell surface TNF receptors, thereby interfering with endogenous TNF activity	Methotrexate or other non-biologic drugs.	Upper respiratory tract infections, bronchitis and urinary tract infection[61]
Tocilizumab [66] .	4 milligrams of tocilizumab per kilogram of body weight	Works by blocking a cytokine known as interleukin 6, or IL-6[2].	_	Fever and chills, tuberculosis
Anakinr [15]	100 mg/day administered daily by subcutaneous injection.	Anakinra blocks the biologic activity of IL-1 by binding to IL-1R type I with the same affinity as IL-1 beta.	Taking etanercept with an akinra can increase your risk of getting an infection.[67]	Injection site reactions, erythema, itching, and discomfort[14].
Rituximab [68]	375 mg intravenously weekly infusions	Stops the activation of a type of white blood cell called B cells.	enalapril, metoprolol, vera pamil azathioprine, cyclosporine, prednisone, [68]	Heart attack, low blood pressure[69], Itching, chest pain,cancer,
Abatacept [70]	500 mg IV	Blocks a particular chemical that triggers the overproduction of white blood cells called T cells that play a role in rheumatoid arthritis inflammation[71].	Combining etanercept with abatacept can increase your risk of getting an infection.	Diarrhea, headache, dizziness, swelling, bruising, mild pain, or redness at the injection site, mild sore throat, nausea, stomach pain or upset, stuffy nose[72].
Golimumab	**50 mg injected subcutaneously once monthly**.	Reduce inflammation by blocking tumor necrosis factor (TNF)[73].	Combining anakinra (Kineret), abatacept (Orencia),rituximab (Rituxan) with golimumab may result in a reduction of white blood cells in the blood(neutropenia)[74].	Respiratory tract infections liver tests, tuberculosis, sepsis , congestive heart failure. Cancer, hepatitis virus ,psoriasis[75].

The first two biological developed for the treatment of RA were the TNF-α inhibiting agents, namely etanercept and infliximab. The first two biological developed for the treatment of RA were the TNF-α inhibiting agents, namely etanercept and infliximab [76].

There after newer agents were developed, including anakinra, a recombinant form of the naturally occurring IL-1 receptor antagonist, and adalimumab, a fully human monoclonal antibody against TNF-α. These biological represent a major advance in the treatment of RA.

4. Conclusion

RA remains a formidable clinical problem despite the remarkable advances of recent years. Progressive articular damage (radiographic progression), functional decline, and risk of comorbidities remain for a substantial proportion of patients. Crucially, there is as yet little evidence that we can reestablish immunologic tolerance and hence aim for drug-free remission on a regular basis. Drug responses and toxicities remain idiosyncratic, with few reliable biomarkers for prognostic or therapeutic purposes yet available.

In recent years the most inclusive investigation of pathologic cytokine function in a chronic inflammatory disease, is their role in pathogenesis of RA.

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Conflicts of interest: No other conflicts to declare.

Reference

[1] J. S. Smolen, D. Aletaha, and I. B. McInnes, "Rheumatoid arthritis," *The Lancet*, 2016; 388(10055) : 2023–2038.

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

[3] J. A. Singh *et al.*, "2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis.," *Arthritis Care Res. (Hoboken).* 2016; 68(1): 1–25.

[4] I. B. McInnes and G. Schett, "The Pathogenesis of Rheumatoid Arthritis," *N. Engl. J. Med.*, 2011; 365 (23): 2205–2219.

[5] P. C. Taylor and R. O. Williams, "Editorial: Combination cytokine blockade: The way forward in therapy for rheumatoid arthritis?," *Arthritis and Rheumatology*, 2015; 67 (1): 14–16.

[6] I. B. McInnes and G. Schett, "Cytokines in the pathogenesis of rheumatoid arthritis," *Nat. Rev. Immunol.* 2007; 7(6): 429–442.

[7] L. Yeo *et al.*, "Cytokine mRNA profiling identifies B cells as a major source of RANKL in rheumatoid arthritis.," *Ann. Rheum. Dis.*, 2011; 70 (11): 2022–8.

[8] F. M. Brennan and I. B. McInnes, "Evidence that cytokines play a role in rheumatoid arthritis," *Journal of Clinical Investigation*, 2008; 118(11): 3537–3545.

[9] M.-M. Hu *et al.*, "TRIM38 inhibits TNF - and IL-1 - triggered NF- B activation by mediating lysosome-dependent degradation of TAB2/3," *Proc. Natl. Acad. Sci.* 2014; 111(4): 1509–1514.

[10] T. N. Kung and V. P. Bykerk, "Detecting the earliest signs of rheumatoid arthritis: Symptoms and examination," *Rheumatic Disease Clinics of North America*, 2014; 40(4): 669–683.

[11] K. A. Beattie, N. J. MacIntyre, and A. Cividino, "Screening for signs and symptoms of rheumatoid arthritis by family physicians and nurse practitioners using the gait, arms, legs, and spine musculoskeletal examination," *Arthritis Care Res.*, 2012; 64(12): 1923–1927.

[12] A.-L. Cedströmer, A. Andlin-Sobocki, L. Berntson, B. Hedenberg-Magnusson, and L. Dahlström, "Temporomandibular signs, symptoms, joint alterations and disease activity in juvenile idiopathic arthritis - an observational study.," *Pediatr. Rheumatol. Online J.* 2013,; 11(1): 37.

[13] M. Trenkmann, M. Brock, C. Ospelt, and S. Gay, "Epigenetics in rheumatoid arthritis," *Clin. Rev. Allergy Immunol.*, 2010; 38(2–3): 10–19.

[14] T. Hughes *et al.*, "Interleukin-1beta selectively expands and sustains interleukin-22+ immature human natural killer cells in secondary lymphoid tissue.," *Immunity*, 2010; 32(6): 803–14.

[15] W. P. Arend, M. Malyak, C. J. Guthridge, and C. Gabay, "Interleukin-1 receptor antagonist: Role in Biology," *Annu. Rev. Immunol*, 1998; 16): 27–55.

[16] W. P. Arend, G. Palmer, and C. Gabay, "IL-1, IL-18, and IL-33 families of cytokines," *Immunological Reviews*, 2008; 223(1): 20–38.

[17] H. Schulze-Koops and J. R. Kalden, "The balance of Th1/Th2 cytokines in rheumatoid arthritis," *Best Practice and Research: Clinical Rheumatology*, 2001; 15(5. pp. 677–691.

[18] B. Bartok and G. S. Firestein, "Fibroblast-like synovioctyes: key effector cells in rheumatoid arthritis," *Immunol Rev.*, 2011; 233(1): 233–255.

[19] K. Yoshida, T. Hashimoto, Y. Sakai, and A. Hashiramoto, "Involvement of the circadian rhythm and inflammatory cytokines in the pathogenesis of rheumatoid arthritis," *Journal of Immunology Research*, 2014; 2014..

[20] L. Wang, X. Chang, L. She, D. Xu, W. Huang, and M. -m. Poo, "Autocrine Action of BDNF on Dendrite Development of Adult-Born Hippocampal Neurons," *J. Neurosci.*, 2015; 35(22): 8384–8393.

[21] J.-M. Zhang and J. An, "Cytokines, Inflammation, and Pain," *Int. Anesthesiol. Clin.*, 2007; 45(2): 27–37.

[22] G. Trinchieri, "Cytokines and cytokine receptors,"

Immunological Reviews, 2004; 202: 5–7.

[23] L. Robb, "Cytokine receptors and hematopoietic differentiation," *Oncogene*, 2007; 26(47): 6715–6723.

[24] G. Buchan, K. Barrett, T. Fujita, T. Taniguchi, R. Maini, and M. Feldmann, "Detection of activated T cell products in the rheumatoid joint using cDNA probes to Interleukin-2 (IL-2) IL-2 receptor and IFN-gamma.," *Clin. Exp. Immunol.*, 1988; 71(2): 295–301.

[25] P. Palange *et al.*, "Circulating haemopoietic and endothelial progenitor cells are decreased in COPD," *Eur. Respir. J.*, 2006; 27(3): 529–541.

[26] C. T. Ng, J. L. Mendoza, K. C. Garcia, and M. B. A. Oldstone, "Alpha and Beta Type 1 Interferon Signaling: Passage for Diverse Biologic Outcomes," *Cell*, 2016; 164(3): 349–352.

[27] A. Caminero, M. Comabella, and X. Montalban, "Tumor necrosis factor alpha (TNF-??), anti-TNF-?? and demyelination revisited: An ongoing story," *Journal of Neuroimmunology*, 2011; 234(1–2). pp. 1–6.

[28] L. Martinez-Munoz *et al.*, "CCR5/CD4/CXCR4 oligomerization prevents HIV-1 gp120IIIB binding to the cell surface," *Proc. Natl. Acad. Sci.*, 2014; 111(19): E1960–E1969.

[29] H. Zhang, L. M. Wu, and J. Wu, "Cross-talk between apolipoprotein e and cytokines," *Mediators of Inflammation*, 2011; 2011..

[30] J. Hiscott and C. Ware, "Cytokines," *Current Opinion in Immunology*, 2011; 23(5): 561–563.

[31] H. M. Mehta, M. Malandra, and S. J. Corey, "G-CSF and GM-CSF in Neutropenia," *J. Immunol.*, 2015; 195(4): 1341–1349.

[32] M. G. Netea, A. Simon, F. Van De Veerdonk, B. J. Kullberg, J. W. M. Van Der Meer, and L. A. B. Joosten, "IL-1?? processing in host defense: Beyond the inflammasomes," *PLoS Pathogens*, 2010; 6(2..

[33] A. M. Ring *et al.*, "Mechanistic and structural insight into the functional dichotomy between IL-2 and IL-15," *Nat. Immunol.*, 2012; 13(12): 1187–1195.

[34] M. A. Guthridge *et al.*, "Mechanism of activation of the GM-CSF, IL-3, and IL-5 family of receptors.," *Stem Cells*, 1998; 16): 301–313.

[35] W. H. Zhao and Z. Q. Hu, "Up-regulation of IL-33 expression in various types of murine cells by IL-3 and IL-4," *Cytokine*, 2012; 58(2): 267–273.

[36] M. Mihara, M. Hashizume, H. Yoshida, M. Suzuki, and M. Shiina, "IL-6/IL-6 receptor system and its role in physiological and pathological conditions.," *Clin. Sci. (Lond).*, 2012; 122(4): 143–59.

[37] W. Lundstrom *et al.*, "Soluble IL7R potentiates IL-7 bioactivity and promotes autoimmunity," *Proc. Natl. Acad. Sci.*, 2013; 110(19): E1761–E1770.

[38] S.-Y. Hwang *et al.*, "IL-17 induces production of IL-6 and IL-8 in rheumatoid arthritis synovial fibroblasts via NF-kappaB- and PI3-kinase/Akt-dependent pathways.," *Arthritis Res. Ther.*, 2004; 6(2): R120-8.

[39] T. Alanärä, K. Karstila, T. Moilanen, O. Silvennoinen, and P. Isomäki, "Expression of IL-10 family cytokines in rheumatoid arthritis: elevated levels of IL-19 in the joints.," *Scand. J. Rheumatol.*, 2010; 39(2): 118–26.

[40] R. M. Pope and S. Shahrara, "Possible roles of IL-12-family cytokines in rheumatoid arthritis," *Nat. Rev. Rheumatol.*, 2012; 9(4): 252–256.

[41] H. Nie *et al.*, "Phosphorylation of FOXP3 controls regulatory T cell function and is inhibited by TNF-α in rheumatoid arthritis," *Nat. Med.*, 2013; 19(3): 322–328.

[42] R. Zhao *et al.*, "Exogenous IFN-beta regulates the RANKL-c-Fos-IFN-beta signaling pathway in the collagen antibody-induced arthritis model," *J. Transl. Med.*, 2014; 12(1) 330.

[43] E. Gonzalo-Gil and M. Galindo-Izquierdo, "Role of transforming growth factor-beta (TGF) beta in the physiopathology of rheumatoid arthritis.," *Reumatol. Clin.*, 2014; 10(3): 174–9.

[44] K. Chaabo and B. Kirkham, "Rheumatoid Arthritis - Anti-TNF," *Int. Immunopharmacol.*, 2015; 27(2): 180–184.

[45] R. De Stefano *et al.*, "Comparison of combination therapies in the treatment of rheumatoid arthritis: Leflunomide-anti-TNF-alpha versus methotrexate-anti-TNF-alpha," *Clin. Rheumatol.*, 2010; 29(5): 517–524.

[46] J. J. O'shea, A. Kontzias, K. Yamaoka, Y. Tanaka, and A. Laurence, "Janus kinase Inhibitors in autoimmune diseases Role of Type I/II cytokines in RA and related diseases," *Ann. Rheum. Dis.*, 2013; 72(2): 1–11.

[47] S. Mateen, A. Zafar, S. Moin, A. Q. Khan, and S. Zubair, "Understanding the role of cytokines in the pathogenesis of rheumatoid arthritis," *Clinica Chimica Acta*, 2016; 455. pp. 161–171.

[48] P. Libby, "Role of Inflammation in Atherosclerosis Associated with Rheumatoid Arthritis," *Am. J. Med.*, 2008; 121(10): S21–S31.

[49] G. M. Deng and M. Lenardo, "The role of immune cells and cytokines in the pathogenesis of rheumatoid arthritis," *Drug Discov. Today Dis. Mech.*, 2006; 3(2): 163–168.

[50] E. Brzustewicz and E. Bryl, "The role of cytokines in the pathogenesis of rheumatoid arthritis--Practical and potential application of cytokines as biomarkers and targets of personalized therapy.," *Cytokine*, 2015;

76(2): 527–536.

[51] H. E. Barksby, S. R. Lea, P. M. Preshaw, and J. J. Taylor, "The expanding family of interleukin-1 cytokines and their role in destructive inflammatory disorders," *Clinical and Experimental Immunology*, 2007; 149(2. pp. 217–225.

[52] R. Badolato and J. J. Oppenheim, "Role of cytokines, acute-phase proteins, and chemokines in the progression of rheumatoid arthritis," *Seminars in Arthritis and Rheumatism*, 1996; 26(2. pp. 526–538.

[53] T. Griseri *et al.*, "Granulocyte Macrophage Colony-Stimulating Factor-Activated Eosinophils Promote Interleukin-23 Driven Chronic Colitis," *Immunity*, 2015; 43(1): 187–200.

[54] G. Gorny, A. Shaw, and M. J. Oursler, "IL-6, LIF, and TNF-?? regulation of GM-CSF inhibition of osteoclastogenesis in vitro," *Exp. Cell Res.*, 2004; 294(1): 149–158.

[55] J. M. Kahlenberg and D. A. Fox, "Advances in the medical treatment of rheumatoid arthritis," *Hand Clinics*, 2011; 27(1. pp. 11–20.

[56] A. K. Shrivastava and A. Pandey, "Inflammation and rheumatoid arthritis," *Journal of Physiology and Biochemistry*, 2013; 69(2) 335–347.

[57] K. Peppel, D. Crawford, and B. Beutler, "A tumor necrosis factor (TNF) receptor-IgG heavy chain chimeric protein as a bivalent antagonist of TNF activity.," *J. Exp. Med.*, 1991; 174: 1483–1489.

[58] S. Madhusudan *et al.*, "Study of etanercept, a tumor necrosis factor-alpha inhibitor, in recurrent ovarian cancer," *J. Clin. Oncol.*, 2005; 23(25): 5950–5959.

[59] P. Vassalli, "The pathophysiology of tumor necrosis factors.," *Annu. Rev. Immunol.*, 1992; 10): 411–452.

[60] C. A. Dinarello, "Biologic basis for interleukin-1 in disease.," *Blood*, 1996; 87(6): 2095–147.

[61] M. E. Weinblatt *et al.*, "A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate.," *N. Engl. J. Med.* 1999; 340(4): 253–9.

[62] J. M. Bathon *et al.*, "A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis.," *N. Engl. J. Med.*, 2000; 343(22): 1586–93.

[63] D. J. Lovell *et al.*, "Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group.," *N. Engl. J. Med.*, 2000; 342(11): 763–9.

[64] M. J. Elliott *et al.*, "Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis," *Lancet*, 1994; 344(8930): 1105–1110.

[65] R. N. Maini *et al.*, "Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis.," *Arthritis Rheum.*, 1998; 41(9): 1552–63.

[66] T. Gout, A. J. K. Östör, and M. K. Nisar, "Lower gastrointestinal perforation in rheumatoid arthritis patients treated with conventional DMARDs or tocilizumab: A systematic literature review," *Clin. Rheumatol.*, 2011; 30(11): 1471–1474.

[67] W. P. Arend and J. M. Dayer, "Inhibition of the production and effects of interleukin-1 and tumor necrosis factor alpha in rheumatoid arthritis.," *Arthritis Rheum.*, 1995; 38(2): 151–60.

[68] G. J. Weiner, "Rituximab: Mechanism of action," *Semin. Hematol.*, 2010; 47(2): 115–123.

[69] C. Bezombes, J.-J. Fournié, and G. Laurent, "Direct effect of rituximab in B-cell-derived lymphoid neoplasias: mechanism, regulation, and perspectives.," *Mol. Cancer Res.*, 2011; 9(11): 1435–1442.

[70] G. M. Keating, "Abatacept: A review of its use in the management of rheumatoid arthritis," *Drugs*, 2013; 73(10): 1095–1119.

[71] E. M. Vital and P. Emery, "Abatacept in the treatment of rheumatoid arthritis," *Therapeutics and Clinical Risk Management*, 2006; 2(4): 365–375.

[72] E. Martín Mola *et al.*, "Abatacept use in rheumatoid arthritis: evidence review and recommendations.," *Reumatol. Clin.*, 2013; 9(1): 5–17.

[73] J. A. Singh, S. Noorbaloochi, and G. Singh, "Golimumab for rheumatoid arthritis," in *Cochrane Database of Systematic Reviews*, 2010.

[74] E. Cummins, C. Asseburg, M. Prasad, J. Buchanan, and Y. S. Punekar, "Cost effectiveness of golimumab for the treatment of active psoriatic arthritis," *Eur. J. Heal. Econ.*, 2012; 13(6): 801–809.

[75] D. A. Pappas, J. M. Bathon, D. Hanicq, U. Yasothan, and P. Kirkpatrick, "Golimumab," *Nat. Rev. Drug Discov.*, 2009; 8(9): 695–696.

[76] J. S. Smolen, D. Aletaha, and I. B. McInnes, "Rheumatoid arthritis.," *Lancet (London, England)*, 2016; 6736(16): 1–16.