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RESEARCH ARTICLE

Comparative Study on Treatment of Rheumatoid Arthritis

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ABSTRACT:

Rheumatoid arthritis is an autoimmune inflammatory disease which has affected almost 0.5-1% of total population in the world. It is the disease which causes inflammation in the joints due the attack of various inflammatory agent resulting in formation of antibody against body's own self antigen. Various inflammatory mediators are activated during this immune response. Rheumatoid factor, tumor necrosis factor, peptidylargininedeiminase, Jak-STAT kinase are some of the major causes of rheumatoid arthritis. The main purpose of this work is to comparatively study various anti-arthritic drugs for their therapeutic dose, potency and their side effects, so that it will help in correct choice of medication to treat it. It will also provide most of the data related to treatment in a collaborated form. Different classes of drugs have been compared such as NSAIDS, Biologic and Non-biologic DMARDS, including adjuvants drugs. Nowadays combination therapy is also used which is also compared in this review article. All data related to combinations have been compiled by studying various articles and information from the books. Article also involves comparison of newer drugs and suggestion for which combination can be tried for better treatment of RA, based on study of drugs for their chemistry and compatibility.

KEYWORDS: Rheumatoid arthritis, Antirheumatoid drugs, Combination therapy, Mechanism of action, Adverse reactions.

INTRODUCTION:

Rheumatoid arthritis is a long term, progressive and disabling autoimmune disease which causes inflammation, swelling and pain in and around the joints and other body organs. There are three types of rheumatoid arthritis like seropositive RA, seronegative RA, and juvenile idiopathic arthritis.

Pain, swelling, stiffness in more than one joint, symmetrical joint involvement, joint deformity unsteadiness when walking, general feeling of being unwell, fever, loss of function and mobility, weight loss, weakness are the symptoms of rheumatoid arthritis.

The main objective of this article is to promote the welfare and research education, by studying preventive measures, diagnosis, causes and treatment of RA. Study aims to ensure dissemination of existing knowledge and to provide pertinent information for primary care provider. Additionally its objective is to identify the new drug target for the treatment of rheumatoid arthritis.

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Many treatment therapies are available for treatment of RA which only gives symptomatic relief and can be overcome by using new drug combination. Many combination therapies are available in market which is not specific or the drugs used just increase the efficacy or potency of other drug. In this review article, combination therapies of some drugs are proposed for the treatment RA. Also the causes of RA on which the drugs are under research have been also studied.

Pathophysiology and causes of RA:

The synovitis, swelling, and joint damage that characterize active RA are the end results of complex autoimmune and inflammatory processes that involve components of both the innate and adaptive immune systems. Self-proteins that contain a citrulline residue are generated via post translational modification of arginine residues to citrulline residues by the enzyme peptidylargininedeiminase (PAD). Synovitis occurs due to the infiltration of leukocyte into the synovium. This accumulation of the leukocyte at the synovium is due to the expression of adhesion molecule and chemokines by activated endothelial cells of synovial micro vessels. All of the various cytokines, chemokine, antibodies, and antigens that contribute to inflammation bind to receptors on the cell surface of specific target cells. Various causes of rheumatoid arthritis like Rheumatoid factor, Tumor necrosis factor-alpha, peptidylargininedeaminase, Jak kinase are mainly responsible and are also targeted for the treatment of rheumatoid arthritis[1.]

Rheumatoid factor is the first autoantibody which causes rheumatoid arthritis. RF binds to aggregated IgG or immune complex with a greater affinity than to monomeric IgG[2]. RFs are generally polyclonal IgM of low affinity which are produced during the secondary immune response[3]. The RF genes are differentiated in normal and diseased persons by Nucleotide Sequences Analysis. The RFs of normal individuals are encoded by limited sets of IgV genes whereas the coding of RFs found in synovial of RA patients consists of a wider range of IgV genes. In RA, IgM RFs are the major RFs species and are detected in 60 to 80 % of patients[4,5,6,7].

Tumor necrosis factor is also the cause of rheumatoid arthritis. It is an autocrine stimulator as well as a potent paracrine inducer of other inflammatory cytokines, including interleukin-1 (IL-1), IL-6, IL-8 and granulocyte monocyte-colony stimulating factor (GM-CSF)[8,9,10,11]. Studies have indicated that the residues involved in receptor binding occur on both sides of each cleft between the subunits.(Two distinct membrane receptors that have been identified and cloned are tumor necrosis factor-receptor 1 (TNF-R1) and tumor necrosis factor-receptor 2 (TNF-R2).TNF-R1 is responsible for triggering inflammatory response whereas TNF-R2 is responsible for proliferation of T-cells and also suppressing TNF alpha mediated inflammation[12,13]. Also TNF- alpha activates osteoblast which in turn activates RANKL which convert pre osteoclast into osteoclast which is responsible for the erosion of the bones[14,15,16,17]. Experimental data on mice with induced arthritis showed that erosive damage is mainly related to the activity of osteoclast[18,19,20,21].Various cytokines causes inflammatory response through jak kinase signal transducer and activators of transcription pathway. There are four types of JAK – JAK1, JAK2, JAK3 and TKY2 and 7 types of STAT- STAT1, 2, 3, 4, 5a, 5b, and 6[22,23,24]. They act by mechanism which constitute STAT 3a DNA binding in synovial fluid mononuclear cells and soluble factors in synovial fluids gets effectively activates STAT 3[21]. This STAT 3 is responsible for the suppression of synovial fibroblast apoptosis, promoting T cells survival and antibody formation[26,27,28]. Peptidylargininedeiminase is responsible for formation of peptidylcitrulline which cause inflammation in joints. It also cause erosion of bone and production of peptidylcitrulline antibodies. When there is any inflammation in the joints it leads to activation of human PAD enzymes which cause citrullination of host protein e.g., Enolase, vimentin, fibrin and collagen type II[29,30].

Classification of Antirheumatoid Drugs[31]:

NSAIDS and Corticosteroids:

Many drugs used in rheumatoid arthritis treatment gives symptomatic relief against inflammation, pain etc. NSAIDS like paracetamol, ibuprofen, celecoxib, diclofenac, reduce inflammation by inhibiting COX-1 enzyme which is responsible for activating various inflammatory responses. These inhibit PG production in the body. But this medication also has some side effects like gastric disturbance, bleeding, peptic ulcer etc. Because of this reason they are least used in the treatment of rheumatoid arthritis or used for symptomatic relief. The next category of drugs is corticosteroids like hydrocortisone, prednisolone, prednisone, etc. can be used. Again these drugs are also used for symptomatic relief against pain and inflammation.

NON-BIOLOGIC DMARDS:

Recent advancement in the antirheumatoid drugs is the introduction of DMARDS (Disease Modifying Antirheumatic drug) as the first line drug treatment for rheumatoid arthritis. In the DMARDS, there are various class like biologic and non- biologic DMARDS. Of this non-biologic DMARDS methotrexate is the mostly used drug for treatment of rheumatoid arthritis.

Table no. 1 - Examples of NSAIDs and Cortcosteroids:

Name	Mechanism of action	Precautions	Pregnancy	Potential Side Effects	Dose
Celecoxib	Selective COX-2 inhibitors Inhibit prostaglandin synthesis Relieves pain and inflammation.	• Tell your doctor if you have had a heart attack, stroke, angina, blood clot, or high blood pressure or if you have sensitivity to NSAIDS or sulfa drugs.	X	• Increased risk of heart attack and stroke, Indigestion, diarrhea, and stomach pain • Serious skin reactions	100-200mg bid
Diclofenac sodium	Preferential COX-2 inhibitors Inhibit prostaglandin synthesis Relieves pain and inflammation.	Tell your doctor if you: • Drink alcohol • Use blood thinners • Take ACE inhibitors, lithium, warfarin, or furosemide	X	• Abdominal cramps, diarrhea • Dizziness or drowsiness • Heartburn, indigestion, nausea, vomiting, ulcer, or bleeding	50mg 3-4 times a day
Ibuprofen	Non- Selective COX inhibitors Relieves pain and inflammation.	Tell your doctor if you: • Drink alcohol • Use blood thinners • Take ACE inhibitors, lithium, warfarin, or furosemide	X	• increased risk of heart attack and stroke Abdominal cramps, diarrhea • Dizziness or drowsiness • Increased risk of blood clots, heart attacks, and stroke	1200mg / day
Acetamino-phen	Non selective COX inhibitors	• Tell your doctor if you have 3 or more drinks of alcohol daily. • Avoid taking more than one product with acetaminophen.	No risk factor	Side effects uncommon if taken as directed.	4mg/ day
Betameth-asone Injectable	Long acting glucocorticoids Negative regulation of COX-2 Decrease production of ELAM-1 and ICAM-1 in endothelial cells	Tell your doctor if you have: • Fungal infection • History of TB • Underactive thyroid • Diabetes • Stomach ulcer • High blood pressure	X	• Increased cholesterol •Atherosclerosis • Increased appetite or indigestion • Muscle weakness • Osteoporosis • Infections	30mg/ 5ml 1-2 ml Accordi ng to target
Predniso-lone	Intermediate acting glucocorticoids Negative regulation of COX-2 Decrease production of ELAM-1 and ICAM-1 in endothelial cells	Tell your doctor if you have: • Fungal infection • History of TB • Underactive thyroid	X	• Bruising • Cataracts •Atherosclerosis • High blood pressure • Increased appetite or indigestion • Muscle weakness • Osteoporosis • Infections	5-60 mg / Day

Methotrexate has direct inhibitory effects on proliferation and stimulates apoptosis in immune-inflammatory cells and also inhibits proinflammatory cytokines linked to rheumatoid synovitis leading to decreased inflammation seen with rheumatoid arthritis. Many other non-biologic agents used are cyclosporine, azathioprine, sulphasalazine, leflunomide, etc. These non-biologic agents are mostly immunosuppressant which suppresses the hyperactivity of certain immune response.

Table no. 2 - Examples of Non-biologic DMARDS[32,33,34,35,36,37,38]:

Name	Mechanism of action	Precautions	Pregnancy	Potential side effects	Dose
Hydroxyc-hloroquine sulphate	Inhibits antigen presentation of the cell, Reduces the inflammatory response	Concern with doctor if there is vision problems. Vision may be damaged with high doses or long term use.	X	• Blurry vision or increased light sensitivity • Abdominal cramps or pain • Itching or rashes and redness to the skin	400 mg-800 mg/ day
Lefluno-mide	Immunomodulatory drug Inhibiting the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH), Inhibit de novo synthesis of uridine monophosphate (rUMP)	Tell doctor if: • Active infection • Liver or kidney disease • Cancer Stop taking leflunomide before trying to conceive.	X	High blood pressure • Gastrointestinal or liver problems • Low blood cell count • Neuropathy • Skin rash	10mg-20mg/ day
Methotre-xate	Inhibits dihydrofolate reductase Inhibit inflammatory response.	Tell doctor if: • Abnormal blood counts • Liver or lung disease• Alcoholism• Active infection or hepatitis • Active plans to conceive	X	Liver problems • Low blood counts Rare, but serious: Dry cough, fever, or trouble breathing, which may result from lung inflammation	2mg-4mg /day

Sulphasa-lazine	Immunosuppressive Anti-inflammatory effects	Tell your doctor: -Prescription and nonprescription medications you are taking, especially digoxin (Lanoxin), folic acid, and vitamins. Asthma, kidney or liver disease, blood problems, blockage in your intestine or urinary tract.	X	• Decreased appetite. • Headache. • Nausea. • Vomiting. • Stomach upset and pain. • Rash. • Itching. • decreased sperm count	30 mg/kg/day
Upadacit-inib		Rinvoq increases the risk of serious infections, cancers, lymphoma, and skin cancers • May cause blood clots • Tears in the stomach and intestines are possible	X	• Upper respiratory infections • Cough • Fever • Nausea	15mg/day

BIOLOGIC DMARDS:

Biologic DMARDS are the drugs which act on the specific target like TNF-alpha inhibitors, etc. This drugs are of more used because of their specific activity and also has least side effects. Biologic DMARDS include the drugs like abatacept, enteracept, adalimumab, infliximab, toclizumab, etc. Most of their side effects are redness, pain, itching, chill, fever, headache, severe skin reaction.

Table no. 3 - Examples of biologic DMARDS[39,40,41,42,43]: -

Name	Mechanism of action	Precautions	Pregnancy	Potential Side Effects	Dose
Abatacept	inhibition of autoimmune T-Cell activation	• Tell your doctor if you have a serious infection, such as pneumonia or COPD. • Do not take live vaccines.	X	• Infusion reaction • Serious infections, like TB, and infections from bacteria, viruses, or fungi	10mg/ kg
Adalimu-mab	Tumor necrosis factor-alpha inhibitors alters biological responses ELAM-1, ICAM-1, VCAM-1	• Tell your doctor if you have a serious infection, such as pneumonia. • Do not take live vaccines. Get tested for TB and hepatitis before starting treatment.	No risk factors	• Redness, pain, itching, or bruising at injection site • Upper respiratory infection • Serious infections, like TB, and infections from bacteria, viruses, or fungi	40mg/ every other week
Anakinra	blocks the biologic activity of IL-1 alpha Inhibit cartilage deterioration and bone sorption	• Tell your doctor if you have a serious infection or a history of it. • Do not take live vaccines.	No risk factor	• Redness, swelling, pain, or bruising at injection site • Low white blood cell count • Upper respiratory infection	100mg/ day
Etanerc-ept	Tumor necrosis factor (TNF) inhibitor	Do not take if you have congestive heart failure, and tell your doctor if you have: • Diabetes, HIV, or a weakened immune system	X	Redness, pain, itching, swelling, or bruising at injection site Rare complications: • Increased risk of malignancy Neurological events	50mg/ week
Rituxi-mab	Monoclonal antibody Inhibit B cell activation responsible for various inflammatory responses	• Tell your doctor if you have a serious infection, or heart or lung disease. • Do not take live vaccines.	X	• Abdominal pain • Chills or fever • Headache Serious side effects: • Infusion reactions • Tumor lysis syndrome • Severe skin reactions	1g on 0, 2 and 24th week iv
Inflixi-mab	IgG1κ monoclonal antibody Reduction of lymphocyte and leukocyte migration to sites of inflammation	• Do not take this medicine if you have moderate to severe heart failure. Tell your doctor if you have had tuberculosis or hepatitis.	No risk Factor	• Diarrhea • Headache • Fatigue • Nausea • Rash at site of infusion • Upper respiratory infections	3mg/ kg on 0, 2, 6 weeks and then every 8 weeks
Golim-umab	Inhibits soluble and transmembrane human TNFα Prevents leukocyte infiltration Prevent pro-inflammatory cytokine secretion	•Tell your doctor if you have any infections or health conditions, like heart disease, MS, or diabetes• Get tested for TB before starting treatment.	X	• Redness at the injection site • Upper respiratory infections Rare complications: • Serious infections, like TB, fungal infections, and reactivation of a previous hepatitis B infection	50mg/mon th
Certolizu-mab pegol	Inhibition of TNF-alpha Inhibit inflammatory response.	• Tell your doctor if you have an infection or are being treated for an infection, or if you have diabetes, HIV, hepatitis B, cancer, or TB.	No risk factor	• Nerve problems such as MS • Allergic reactions • Autoimmune problems like lupus • Reactivation of hepatitis B	400 mg on 0, 2, 4 weeks then 200 mg weekly

Tociliz-umab	Inhibit IL-6-mediated signaling	• Tell your doctor if you have a serious infection, history of gastrointestinal perforation, or if you are pregnant or plan on becoming pregnant. • Do not take live vaccines.	X	• Upper respiratory tract infection • Inflammation of the nose or throat • High blood pressure • Headache • Abnormal liver enzyme level	4 mg/kg or 8 gm. /kg once every 4 weeks
Sarilu-mab	interleukin-6 (IL-6) receptor antagonist	• Tell your doctor if you have had TB, if your immune system is weakened by deconditions such as diabetes, hepatitis or HIV	X	• Upper respiratory tract infection • Urinary tract infection • Sore throat • Runny nose • Redness at the injection site	200 mg every 2 weeks

JANUS KINASE INHIBITORS:

Newly introduced jak inhibitors are having more importance for the treatment of RA because of their efficacy and potency to bond to jak kinase and inhibit its action. Baricitinib selectively and reversibly inhibits JAK1 and JAK2 to modulate their signalling pathways, thereby reducing the phosphorylation and activation of STATs. The JAK-STAT signaling pathway is involved in the transcription of cells involved in hematopoiesis, and immune cell function. Tofacitinib works therapeutically by inhibiting the JAK-STAT pathway to decrease the inflammatory response.

Table no. 4 - Examples of Janus Kinase inhibitors:

Name	Mechanism of action	Precaution	Pregnancy	Potential side effects	Dose
Tofaci-tinib	Janus kinase (JAK) inhibitor. Prevents the phosphorylation and activation of STATs.	• Xeljanz adds to risk of serious infections, cancers, and lymphoma. • May increase cholesterol levels and liver enzymes. • May lower blood count.	X	Inflammation of the nasal passage and the upper part of the throat blood clots and tears in the intestine	5mg-10mg/day
Barici-tinib	Inhibit the activity of selective JAK1 and JAK2 enzymes	• Olumiant increases the risk of serious infections, cancers, and lymphoma. • May raise cholesterol levels and liver enzymes. • May lower blood count.	X	• Upper respiratory tract infection • Headache • Diarrhea • Inflammation of the nasal passage and the upper part of the throat blood clots and tears in the intestine	2 mg / day

COMBINATION THERAPY FOR RHEUMATOID ARTHRITIS:

Most of the monotherapy are not much efficacious because of some of the side effect or some pharmacokinetic problems they faced when administered. Also these monotherapies do not give the complete relief in rheumatoid arthritis. Because of this reason and many more, combination therapies are been included in the treatment of rheumatoid arthritis. Most of the combination available are with methotrexate, as it is more efficacious and more potent drug for treatment. Most of the combination used in the rheumatoid arthritis are either increasing the efficacy of other/increasing potency/increasing pharmacokinetic property of drug. E.g. methotrexate when given alone it show less effect or has inadequate response in some patient, but when given in combination with enteracept its efficacy is increased. Many other combination are also available such as methotrexate and adalimumab, methotrexate and sulphasalzine, etc[44,45].

Table no. 5 - Examples of some combination drugs

Sr No.	Combination Drugs With	Mechanism of Action Individually	Efficacy of Drug After Combination	ADR	
				Individually	In Combination
(A)	METHOTHREXATE	Dihydrofolate reductase inhibitor	__	__	__
1	TOFACITINIB	JAK 3 and JAK 1 kinase inhibitor.	Efficacy of tofacitinib was increased.	1.Cirrhosis, nausea 2.Anemia, diarrhea	__
2	BARCITINIB	JAK inhibitor	More efficacious than alone methotrexate	__	Increase in the toxicity
3	ETANERCEPT	TNF inhibitor	More efficacious	1.Nausea 2.Pain, Redness	__
4	INFLIXIMAB	TNF inhibitor	Improves response and decreases antibody formation against Infliximab	2.Respiratory infection	__
5	ADALIMUMAB	TNF inhibitor	Improves response and decreases antibody formation against Adalimumab	2.Respiratory infection	__

6	GOLIMUMAB	TNF inhibitor	Improves response and decreases antibody formation against Golimumab	—	—
7	ABATACEPT	TNF inhibitor	Increases response of methotrexate	—	—
8	RITUXIMAB	Monoclonal antibody	Increases response of methotrexate	Chills, urticarial rashes, pruritus	—
9	SULFASALAZINE	Generation of superoxide radical and cytokine elaboration	Second-line treatment for milder cases	Neutropenia, thrombocytopenia	—
(B)	ABATACEPT + ANAKINRA	1.TNF inhibitor 2.Blocks IL -1 receptors	Single drug is more efficacious than in combination	Increase in the adverse effects	—
(C)	RITUXIMAB + TOCILIZUMAB	1.Monoclonal Antibodies 2. Inhibit IL-6	—	—	—

Combination of CSA and LFE gives improved effects than given as monotherapy and combined treatment shows less adverse effects. The alleviation of steroid dose was important in the group of patients under combined therapy, which also shows the effectiveness of the combination. No serious short term toxicity was reported both drugs affect blood pressure but when given in combination, severe deterioration of preexisting hypertension was not observed (except in only one case hypertension noted). The case of one withdrawn Patient. This study shows that when CSA administered along with DMARDs gives improved effects. Additionally, when patients gives incomplete response to MTX, the addition of CSA, etanercept or LEF gives comparable ratio of ACR response[46].

CONCLUSION:

From the above study regarding causes, treatment methods and combination therapy of RA we come to the conclusion that, the treatment methods and drugs available in the market, most of them gives symptomatic relief or are effective towards only one of the cause of RA which fails in treating RA. The combination therapies are used nowadays for treating rheumatoid arthritis, but if this combination are multitargeted treating multiple causes then it might be useful for chronic RA treatment. If the combination of JAK inhibitor and TNF-alpha inhibitor is formulated as sustained released tablet it can give better relief to arthritis patient giving relief from inflammation due to various inflammatory mediators and also due to JAK inhibitors the bone erosion can be reduced which will contribute for the treatment of RA. Peptidylargininedeiminase enzyme can be the new target for treating RA. Cl-amidine moiety which is PAD inhibitor is under study which can contribute towards the treatment method for rheumatoid arthritis.

LIST OF ABBREVIATIONS:

Sr. No.	Abbreviations	Full form
1	**CCP**	Cyclic citrullinated peptide.
2	**COX-1**	Cyclooxygenase enzymes 1
3	**COX-2**	Cyclooxygenase enzymes 2
4	**DKK-1**	Dickkopf WNT Signaling Pathway Inhibitor 1
5	**DMARDS**	Disease modifying anti- rheumatic drugs
6	**DNA**	Deoxyribonucleic Acid
7	**dsDNA**	Double-stranded Deoxyribonucleic acid
8	**GM-CSF**	Granulocyte monocyte-colony stimulating factor
9	**ELAM-1**	Endothelial leukocyte adhesion molecule
10	**ICAM-1**	Intracellular adhesion molecule 1
11	**Ig G**	Immunoglobulin G
12	**Ig M**	Immunoglobulin M
13	**Ig V**	Immunoglobulin V
14	**IL**	Interleukin
15	CSA	Cyclosporin
16	**IR**	Immediate release
17	**IV**	Intravenous
18	**JAK**	Janus Kinase
19	**JIA**	Juvenile Rheumatoid Arthritis
20	rUMP	Uridine monophosphate
21	**MAPK**	Mitogen- activated protein kinase
22	**MR**	Modified-release
23	ACR	American College of Rheumatology
24	DHODH	Dehyroorotate dehydrogenase
25	**NF-κB**	Nuclear factor kappa-light-chain-enhancer of activated B cells)
26	**NSAIDS**	Non-Steroidal anti-inflammatory drugs
27	**OTC**	Over the counter
28	**PAD**	Peptidylargininedeiminase
29	**PEG**	Polyethelene glycol
30	**RA**	Rheumatoid arthritis
31	**RANKL**	Receptor activator of the NF kappa B ligand
32	**RF**	Rheumatoid Factor
33	**RNA**	Ribonucleic acid
34	**SOCS**	Suppressor of cytokine signaling
35	VCAM-1	Vascular cell adhesion molecule 1
36	**STAT**	Signal transducer and activator of transcription
37	**TB**	Tuberculosis
38	**TGF**	Tissue growth factor
39	**TNF**	Tumor necrosis Factor
40	**TYK2**	Tyrosine kinase 2
41	**LEF**	Leflunomide
42	**MTX**	Methotrexate
43	**COPD**	Chronic obstructive pulmonary disorder
44	**HIV**	Human immunodeficiency virus

REFERENCE:

1. Mohan Harsh, (2018), Textbook of Pathophysiology, Jaypee Brothers Medical Publishers, New Delhi.
2. Pike RM, Sulkin SE, Coggeshall HC, (1949); "Serological reactons in rheumatoid arthritis; factors affecting the agglutination of sensitized sheep erythrocytes in rheumatoid- arthritis serum"; J. Immunol; 63(4); 441-446.
3. Hardy RR, Hayakawa K, Shimizu M, Yamasaki K, Kishimoto T, (1987); "Rheumatoid factor secretion from human Leu-1+ B cells"; Science; 236(4797); 81-83.
4. Moynier M, Abderrazik M, Didry C, Sany J, Brochier J, (1992); "The B cell repertoire in rheumatoid arthritis. III. Preferential homing of rheumatoid factor-producing B cell precursor in the synovial fluid"; Arthritis Rheum; 35(1); 49-54.
5. Mageed RA, Borretzen M, Moyes SP, Thompson KM, Natvig JB, (1997); "Rheumatoid factor autoantibodies in health and disease"; Ann. NY Acad. Sci.; (815); 296-311.
6. Van Snick JL, Van Roost E, Markowetz B, Cambiaso CL, Masson PL, (1978); "Enhancement by IgM rheumatoid factor of in vitro ingestion by macrophages and in vivo clearance of aggregated IgG or antigen-antibody complexes"; Eur. J. Immunol; 8(4); 279-285.
7. Brown PB, Nardella FA, MAnnik M, (1982); "Human complement activation by self- associated IgG rheumatoid factors"; Arthritis Rheum; 25(9); 1101-1107.
8. Grell M, Scheurich P, (2001); "Tumor Necrosis Factors. Encyclopedia of Life Sciences"; Nature Publishing Group, Chennai.
9. Choy EHS, Panayi GS, (2001); "Cytokine pathways and joint inflammation in rheumatoid arthritis"; NEJM; (344), 907–16.
10. Butler DM, Maini RN, Feldmann M, Brennan FM, (1995); "Modulation of proinflflammatory cytokine release in rheumatoid synovial membrane cell cultures: comparison of monoclonal anti TNF-α antibody with interleukin-1 receptor antagonist; Eur Cytokine Netw; (6), 225–30.
11. Haworth C, Brennan FM, Chantry D, Turner M, Maini RN, Feldmann M, (1991); "Expression of granulocyte-macrophage colony-stimulating factor in rheumatoid arthritis: regulation by tumor necrosis factor-α"; Eur J Immunol; (21), 2575–9.
12. Halliwell B, (1995); "Oxygen radicals, nitric oxide and human inflammatory joint disease"; Ann Rheum Dis; (54), 505–10.
13. Deon D, Ahmed S, Tai K, et al., (2001); "Cross-Talk between IL-1 and IL-6 signaling pathways in Rheumatoid Arthritis synovial fibroblasts"; J Immunol; (167); 5395–403.
14. Jimenez-Boj E, Nobauer-Huhmann I, Hanslik-Schnabel B, et al, (2007); "Bone erosions and bone marrow edema as defined by magnetic resonance imaging reflect true bone marrow inflammation in rheumatoid arthritis"; Arthritis Rheum; (56); 1118–24.
15. McQueen FM, Benton N, Perry D, et al., (2003); "Bone edema scored on magnetic resonance imaging scans of the dominant carpus at presentation predicts radiographic joint damage of the hands and feet six years later in patients with rheumatoid arthritis"; Arthritis Rheum; (48); 1814–27.
16. Gravallese EM, Harada Y, Wang JT, et al., (1998); "Identification of cell types responsible for bone resorption in rheumatoid arthritis and juvenile rheumatoid arthritis"; Am J Pathol; (152); 943–51.
17. Komine M, Kukita A, Kukita T, et al., (2001); "Tumor necrosis factor-alpha cooperates with receptor activator of nuclear factor kappaB ligand in generation of osteoclasts in stromal cell-depleted rat bone marrow cell culture"; Bone; (28); 474–83.
18. Kotake S, Udagawa N, Hakoda M, et al., (2001); "Activated human T cells directly induce osteoclastogenesis from human monocytes: possible role of T cells in bone destruction in rheumatoid arthritis patients"; Arthritis Rheum; (44); 1003–12.
19. Bartok B, Firestein GS., (2010); "Fibroblast-like synoviocytes: key effector cells in rheumatoid arthritis"; Immunol Rev; (233); 233–55.
20. Pettit AR, Ji H, von Stechow D, et al., (2001); "TRANCE/RANKL knockout mice are protected from bone erosion in a serum transfer model of arthritis"; Am J Pathol; (159); 1689–99.
21. Diarra D, Stolina M, Polzer K, et al., (2007); "Dickkopf-1 is a master regulator of joint remodeling"; Nat Med; (13); 156–63.
22. Kisseleva T, Bhattacharya S, Braunstein J, Schindler CW, (2002); "Signaling through the JAK/STAT pathway, recent advances and future challenges"; Gene; 285; 1-24.
23. Schindler CW, (2002); "JAK-STAT signaling in human disease"; J Clin Invest; (109); 1133-7.
24. Gadina M, Hilton D, Johnston JA, et al., (2001); "Signaling by type I and II cytokine receptors: ten years after"; Curr Opin Immunol; (13); 363-73.
25. Ivashkiv LB, Hu X, (2004); "Signaling by STATs"; Arthritis Res; (6); 159-68.
26. Chen W, Daines MO, Hershey GKK, (2004); "Turning off signal transducer and activator of transcription (STAT): the negative regulation of STAT signaling"; J Allergy Clin Immunol; (114); 476-89.
27. Ernst M, Inglese M, Waring P, et al., (2001); "Defective gp130-mediated signal transducer and activator of transcription (STAT) signaling results in degenerative joint disease, gastrointestinal ulceration, and failure of uterine implantation"; J Exp Med; (194); 189-203.
28. Wang F, Sengupta TK, Zhong Z, Ivashkiv LB; (1995); "Regulation of the balance of cytokine production and the signal transducer and activator of transcription (STAT) transcription factor activity by cytokines and inflammatory synovial fluids"; J Exp Med; (182); 1825-31.
29. Pamela Mangat, Natalia Wegner, Patrick J Venables and Jan Potempa, (2010); "Arthritis Research and Therapy"; (volume 12).
30. Wegner N, Lundberg K, Kinloch A, Fisher B, Malmström V, Feldmann M, and Venables PJ, (2010); "Autoimmunity to specific citrullinated proteins gives the first clues to the etiology of rheumatoid arthritis"; Immunol Rev; (233); 34-54. 10.
31. Tripathi KD, (2019), Essential of Medical Pharmacology, Jaypee Brothers Medical Publisher, New Delhi
32. Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum. 2008 Jun 15; 59(6):762–784.
33. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, (2008); "American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis"; Arthritis Rheum; 59(6); 762-84.
34. Rajendra B. Pawade, Pramod P. Bhalerao, Rahul R. Kunkulol, Nilam S. Kute; "Disease-Modifying Anti-Rheumatic Drugs (DMARDs) used for Rheumatoid Arthritis- P"; 272-288.
35. Verstappen SM, Albada-Kuipers GA, Bijlsma JW, et al., (2005); "A good response to early DMARD treatment of patients with rheumatoid arthritis in the first year predicts remission during follow up"; Ann Rheum Dis; (64); 38-43.
36. Bruce N. Cronstein; (2005); "Low-Dose Methotrexate: A Mainstay in the Treatment of Rheumatoid Arthritis"; The American Society for Pharmacology and Experimental Therapeutics; (57)
37. Smolen JS, Landewé R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017 Jun; 76(6):960–977.
38. Smolen JS, Landewé R, Breedveld FC, et al. EULAR recommendation for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis. 2014 Mar; 73(3):492–509.
39. Keystone EC, Kavanaugh A, Weinblatt ME, Patra K, Pangan AL, (2011); "Clinical consequences of delayed addition of adalimumab to methotrexate therapy over 5 years in patients with rheumatoid arthritis"; J Rheumatol; 38(5); 855-62.
40. Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, (2004); "Efficacy of Bcell-targeted therapy with rituximab in patients with rheumatoid arthritis"; N Engl J Med; 350(25); 2572-81.

41. Fleischmann R, Vencovsky J, van Vollenhoven RF, Borenstein D, Box J, Coteur G., (2009); "Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study"; Ann Rheum Dis; 68(6); 805-11.
42. Singh JA, Saag, KG, Bridges SL Jr., et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2016 Jan; 68(1):1–25.
43. Singh JA, Furst DE, Bharat A, et al. 2012 Update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012 May; 64(5):625–639.
44. Whittle S.L. and Hughes R.A.; (2004); "Folate supplementation and methotrexate treatment in rheumatoid arthritis: a review"; Rheumatology; (43); 267–271.
45. Haire and Ana Fernandez James R O'Dell, Kara Petersen, Robert Leff, William Palmer, Eric Schned, Kent Blakely, Claire; (2006); "Treatment of rheumatoid arthritis. Etanercept in combination with sulfasalazine, hydroxychloroquine, or gold"; The Journal of Rheumatology; (33); 213-218.
46. Christos; (2006); "Combination of cyclosporine and leflunomide versus single therapy in severe rheumatoid arthritis"; The Journal of Rheumatology; (33); 486-489.