WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 8, 2411-2425. Review Article ISSN 2277– 7105

AN OVERVIEW OF TREATMENTS FOR RHEUMATOID ARTHRITIS

Bhavna V. Bohra[1], Diptesh T. Patil*[1], Dr. Vanita Kanase[2], Dr. Pramila Yadav[3]

[1]Oriental College of Pharmacy, Sector 2, Behind Sanpada Railway Station, Sanpada West, Navi Mumbai, Maharashtra 400705

[2]HOD Pharmacology, [1]Oriental College of Pharmacy, Sector 2, Behind Sanpada Railway Station, Sanpada West, Navi Mumbai, Maharashtra 400705

[3]Professor in Pharmacology, Dr. D. Y. Patil Medical College, Belapur, Navi Mumbai, Maharashtra 400614.

Article Received on
16 June 2015,

Revised on 07 July 2015,
Accepted on 29 July 2015

***Correspondence for Author**
Diptesh T. Patil
Oriental College of Pharmacy, Sector 2, Behind Sanpada Railway Station, Sanpada West, Navi Mumbai, Maharashtra 400705

ABSTRACT

Rheumatoid arthritis is a common autoimmune disease that can lead to serious functional limitations, joint destruction, extra-articular disease, poor quality of life, and premature death. Even mild inflammation may result in irreversible damage and permanent disability. To overcome it various medical (pharmacological) and non-pharmacological measures-the goal being to control joint inflammation and prevent joint damage and disability.Pharmacological method includes multiple infusion of a chimeric monoclonal, non-steroidal anti-inflammatory drug, DMARDs and other drugs which is given alone or in a combination. Non-pharmacological treatment includes acupuncture, physiotherapy, yoga etc. which is useful for patients.

KEYWORDS: Methotrexate, Sulfasalazine, Leflunomide, Andrographolide, Janus Kinase Inhibitor, DMARDs, NSAIDs.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown cause. An external trigger (e.g., cigarette smoking, infection, or trauma) that triggers an autoimmune reaction, leading to synovial hypertrophy and chronic joint inflammation along with the potential for extra-articular manifestations, is theorized to occur in genetically susceptible individuals.[1]

India has a high prevalence of arthritis, with about 15% people i.e. over 180 million people affected by it.[2]

The risk of arthritis increases with the increasing age.[3]Individuals are usually diagnosed between the third and fifth decade of life .[3] Women are more prone to acquiring this disease in comparison to men.[1] Therefore, individuals with RA may experience a lower quality of life and amass a large amount of direct and indirect costs due to the managementof the disease, hospitalizations, and physician visits.

Signs and symptoms of rheumatoid arthritis may include the following[4]

- Persistent symmetric polyarthritis (synovitis) of hands and feet (hallmark feature)
- Progressive articular deterioration
- Extra-articular involvement
- Difficulty performing activities of daily living (ADLs)
- Constitutional symptoms

RA can occur at any age, but in men onset before age 45 years is uncommon.[3] The disease can develop rapidly within weeks to months.[3] Commonly affected areas include the hands, wrists, elbows, knee, metatarsophalangeal joint, shoulder, and cervical spine.[5] The area of joint involvement is symmetric and results in pain, morning stiffness lasting more than 1 hour, gelling (or locking with inactivity), tenderness, warmth, redness, and inflammation.[6] This article will deal with newer drugs which are already in use, ones which are in various phases of development, identifying potential targets, the development of new vaccines.

Already In Use

1. Nonsteroidal Anti-Inflammatory Drug: (NSAIDs)

Drugs like Ibuprofen, Diclofenac Sodium, and Celecoxib etc., help in reducing the joint pain and swelling. They do not have any role in suppressing the arthritis. Its pharmacological effects are due to inhibition of cyclooxygenase-2 (COX-2) which decreases the synthesis of prostaglandins involved in mediating inflammation, pain, fever, and swelling.

Ibuprofen and Celecoxib are the nonselective inhibitor of cyclooxygenase, an enzyme involved in prostaglandin synthesis via the arachidonic acid pathway. Ibuprofen is a nonselective inhibitor of cyclooxygenase, an enzyme involved in prostaglandin synthesis via the arachidonic acid pathway. [7] Celecoxib is a highly selective inhibitor of the COX-2 [8]

Diclofenac Sodium acts by inhibition of the lipoxygenase pathways thus reducing formation of the leukotrienes (also pro-inflammatory autacoids). It also may inhibit phospholipase A_2 as part of its mechanism of action. These additional actions may explain its high potency it is the most potent NSAID on a broad basis.[9]

2. Opioids

Opioid are often very effective against pain, they also carry a greater risk of side effects, such as dizziness or drowsiness, than acetaminophen.[10]

3. Disease-Modifying Anti-Rheumatic Drugs:(DMARDs)

I. Methotrexate

Widely used DMARD. Used in combinations to Increase spectrum of activity.

Methotrexate anti-tumor activity is a result of the inhibition of folic acid reductase, leading to inhibition of DNA synthesis and inhibition of cellular replication. [11]

II. Azathioprine

Its mechanism of action is due to incorporation of thiopurine analogues into the DNA structure, causing chain termination and cytotoxicity.[12]

III. Hydroxychloroquine

The mechanism of action of antimalarials in the treatment of patients with rheumatoid arthritis is unknown but is thought to involve changes in antigen presentation or effects on the innate immune system. For prolonged treatment of arthritis, adverse effects include the acute symptoms, plus altered eye pigmentation, acne, anemia, bleaching of hair, blisters in mouth and eyes, blood disorders, convulsions, vision difficulties. [13]

IV. Cyclophosphamide

It is an Alkylating agent.

Alkylating agents work by three different mechanisms: 1) attachment of alkyl groups to DNA bases, resulting in the DNA being fragmented by repair enzymes in their attempts to replace the alkylated bases, preventing DNA synthesis and RNA transcription from the affected DNA, 2) DNA damage via the formation of cross-links (bonds between atoms in the DNA) which prevents DNA from being separated for synthesis or transcription, and 3) the induction of mispairing of the nucleotides leading to mutations.[14]

V.Cyclosporine

Cyclosporine binds to cyclophilin. The complex then inhibits calcineurin which is normally responsible for activating transcription of interleukin 2. Cyclosporine also inhibits lymphokine production and interleukin release.[15]

VI. Minocycline

Minocycline passes directly through the lipid bilayer or passively diffuses through porin channels in the bacterial membrane. Tetracyclines like minocycline bind to the 30S ribosomal subunit, preventing the binding of tRNA to the mRNA-ribosome complex and interfering with protein synthesis.[16]

VII. Mycophenolate Mofetil

Mycophenolate is hydrolyzed to form mycophenolic acid (MPA), which is the active metabolite. MPA is a potent, selective, uncompetitive, and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), and therefore inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA. Because T- and B-lymphocytes are critically dependent for their proliferation on de novo synthesis of purines, whereas other cell types can utilize salvage pathways, MPA has potent cytostatic effects on lymphocytes. MPA inhibits proliferative responses of T- and B-lymphocytes to both mitogenic and allospecific stimulation. Addition of guanosine or deoxyguanosine reverses the cytostatic effects of MPA on lymphocytes. MPA also suppresses antibody formation by B-lymphocytes. MPA prevents the glycosylation of lymphocyte and monocyte glycoproteins that are involved in intercellular adhesion to endothelial cells and may inhibit recruitment of leukocytes into sites of inflammation and graft rejection. Mycophenolate did not inhibit early events in the activation of human peripheral blood mononuclear cells, such as the production of interleukin-1 (IL-1) and interleukin-2 (IL-2), but did block the coupling of these events to DNA synthesis and proliferation.[17]

VIII. Penicillamine

Penicillamine is a chelating agent recommended for the removal of excess copper in patients with Wilson's disease.It works by reducing numbers of T-lymphocytes, inhibiting macrophage function, decreasing IL-1, decreasing rheumatoid factor, and preventing collagen from cross-linking. [18]

4. Corticosteroids

Prednisone is a glucocorticoid receptor agonist. It is first metabolized in the liver to its active form, prednisolone and binds with high affinity to specific cytoplasmic receptors. The result includes inhibition of leukocyte infiltration at the site of inflammation, interference in the function of mediators of inflammatory response, suppression of humoral immune responses, and reduction in edema or scar tissue.[19]

- **NSAIDs are often combined with DMARDs because they complement each other;**
- **But one NSAID should not be combined with another NSAID because it increases the likelihood of their side effects;**
- **On the other hand, "DMARDs are often combined with one another for greater effect."**

COMBINATION THERAPY OF DMARDs:

Sr. No.	DRUG COMBINATION	Result
1.	Methotrexate And Sulfasalazine	Modest benefit which was not statistically significant. Greater improvement in 1 year, No additional toxicity.
2.	Methotrexate and Hydroxychloroquine	Increased bioavailability, increased efficacy, and increased risk of toxicity.
3.	Methotrexate and Ciclosporin	No additional adverse effect (exception: hypertrichosis and increased in level of serum creatinine)
4.	Methotrexate and Leflunomide	Greater improvement, mild leucopenias and neutropenias, elevated level of aminotransferase
5.	Methotrexate And Azathioprine	After 24 week greater improvement. Better results than monotherapy.
6.	Sulfasalazine and Leflunomide	Better improvement and response than Leflunomide monotherapy.
7.	Hydrochloroquine- Methotrexate-Sulfasalazine	Better action, quick response, more efficient. Adverse effect is swollen joints.

New Drugs

1. Leflunomide

Leflunomide is an immunomodulatory drug that achieves its effects by inhibiting the mitochondrial enzyme dihydroorotate dehydrogenase (an enzyme involved in de novo pyrimidine synthesis) (abbreviation DHODH), which plays a key role in the de novo (from scratch) synthesis of the uridine monophosphate (rUMP), which is required for the synthesis of DNA and RNA, hence leflunomide inhibits the reproduction of rapidly dividing cells, especially lymphocytes. The inhibition of human DHODH by teriflunomide, the active

metabolite of leflunomide, occurs at levels (approximately 600 nM) that are achieved during treatment of rheumatoid arthritis (RA). [20,21]

2. Etanercept

There are two distinct receptors for TNF (TNFRs), a 55 kilo Dalton protein (p55) and a 75 kilo Dalton protein (p75). The biological activity of TNF is dependent upon binding to either cell surface receptor (p75 or p55). Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind to two TNF molecules, thereby effectively removing them from circulation.[22]

3. Adalimumab

Adalimumab has been shown to reduce the signs and symptoms of moderate-to-severe rheumatoid arthritis (RA) in adults. It has also been shown to have efficacy in moderate to severe polyarticular juvenile idiopathic arthritis (JIA) in children 4 years of age and older, and is approved for use in the treatment of that condition. In RA it can be used alone or with methotrexate or similar medicines.[23]

4. Infliximab

Infliximab neutralizes the biological activity of TNFa by binding with high affinity to the soluble and transmembrane forms of TNFa and inhibits binding of TNFa with its receptors. Infliximab does not neutralize TNFb (lymphotoxin a), a related cytokine that utilizes the same receptors as TNFa. TNFa activation normally induces the release of proinflammatory cytokines, the enhancement of leukocyte migration and activation of neutrophils among others. Neutralization of the biological activity of TNFa leads to an overall reduction ininflammation.[24]

5. Anakinra

Anakinra binds competitively to the Interleukin-1 type I receptor (IL-1RI), thereby inhibiting the action of elevated levels IL-1 which normally can lead to cartilage degradation and bone resorption.[25]

NEW POTENTIAL DRUGS

1. **Nonsteroidal Anti-Inflammatory Drug: (NSAIDs)**

I. COX-II Inhibitor

i. **Etoricoxib:** Etoricoxib selectively inhibits isoform 2 of cyclooxygenase enzyme (COX-2). This reduces prostaglandins (PGs) generation from arachidonic acid.[26]

ii. **Calcitriol :** Calcitriol (vitamin D) significantly inhibits the expression of the COX-2 gene.[27]

2. **Andrographolide**

Andrographolide is a bicyclic diterpenoid lactone derived from extracts of Andrographis paniculata, a plant indigenous to South Asian countries that shows anti-inflammatory properties. The molecular and cellular bases for this immunomodulatory capacity remain unknown.

In vitro, this molecule was able to interfere with T cell proliferation and cytokine release in response to allogenic stimulation. These results were consistent with the observation that T cell activation by dendritic cells (DCs) was completely abolished by exposing DCs to andrographolide during antigen pulse. This molecule was able to interfere with maturation of DCs and with their ability to present antigens to T cells. Furthermore, in vivo immune responses such as antibody response to a thymus-dependent antigen and delayed-type hypersensitivity were drastically diminished in mice by andrographolide treatment. Finally, the ability of andrographolide to inhibit T cell activation was applied to interfere with the onset of experimental autoimmune encephalomyelitis (EAE), an inflammatory demyelinating disease of the central nervous system that is primarily mediated by CD4 (+) T cells and serves as an animal model for human multiple sclerosis. Treatment with andrographolide was able to significantly reduce EAE symptoms in mice by inhibiting T cell and antibody responses directed to myelin antigens.[28]

3. **Janus kinase inhibitors**

Cytokines play key roles in controlling cell growth and the immune response. Many cytokines function by binding to and activating type I and type II cytokine receptors. These receptors in turn rely on the Janus kinase (JAK) family of enzymes for signal transduction. Hence drugs that inhibit the activity of these Janus kinases block cytokine signaling.

More specifically, Janus kinases phosphorylate activated cytokine receptors. These phosphorylated receptor in turn recruit STAT transcription factors which modulate gene transcription.[29]

I. Filgotinib

Filgotinib is a Janus kinase inhibitor with selectivity for subtype JAK1 of this enzyme. They show long-term efficacy in the treatment of various inflammatory diseases. However, their lack of selectivity leads to dose-limiting side effects. The signal transmission of large numbers of proinflammatory cytokines is dependent on JAK1. Inhibition of JAK2 may also contribute to the efficacy against RA. Nonetheless it is thought that JAK2 inhibition might lead to anemia and thrombopenia by interferencewith erythropoietin and thrombopoietin andgranulocyte- macrophage colony-stimulating factor. Therefore one might prefer to choose a more selective JAK1 inhibitor as a primary therapeutic option. Filgotinib exerts a 30-fold selectivity for JAK1 compared to JAK2. It is however still to be seen to what extent JAK2 inhibition should be avoided. [30]

Time line[31]

June 2011: results of first phase 2 trials

1. November 2014: initiation of DARWIN 1 and 2 trials
2. April 2015: expected date of DARWIN 1 trial results
3. June 2015: expected date of DARWIN 2 trial results

4. Tacrolimus

Tacrolimus is an immunosuppressant that is presently used in organ transplant patients. Like abatacept, tacrolimus acts on T cells by preventing their activation and has been tested in RA patients that have not responded to DMARDs.[32] [33]

NEW TECHNIQUES

1. Acupuncture

One benefit to acupuncture is that it is a drug-free way to minimize pain. With drugs, people often develop a tolerance, or the need for an increased dosage to achieve the same required effect. However, this does not happen with acupuncture. In addition, acupuncture allows the doctor to immediately examine a person's response to the treatment and make adjustments if necessary.

Usually, at least two sessions a week for four to five weeks is a normal course of treatment. It may take several treatments before noticing any benefit. At least 5 or 10 treatments should be tried before giving up.

A recent study from China shows that both traditional acupuncture and electroacupuncture – a type in which pulsating electrical currents are sent through the needles to stimulate target areas – may reduce tenderness. All 36 participants had a standardized treatment, whether they received traditional acupuncture or electroacupuncture. During a total of 20 sessions throughout a 10-week period, needles were placed at a depth of about 10 to 20 millimeters and left in place for 30 minutes.[34]

2. Acupressure: Acupressure relieves arthritic pain in 3 ways.

I. When an acupressure point is held it should increased energy to move through the body and this energy that can heal the joints and relieve pain.

II. Release of endorphins: When acupressure points were held neurochemicals are released called endorphins that doctors know relieve pain. These are natural chemicals that the body manufactures, and acupressure allows them to circulate through the body.

III. Relieving pain is by releasing stress and tension. This increases circulation and enables the person to be relaxed instead of stressing against their arthritic pain. By being more relaxed you can cope better with it, breathe easier, and have more energy in your daily life.[35]

3. Physiotherapy

Physiotherapy treatment is important in helping patients with RA manage their disease. In conjunction with occupational therapists, physiotherapists educate patients in joint protection strategies, use of assistive devices, and performance of therapeutic exercises.[36]

I. Cold/Hot Applications
II. Electrical Stimulation
III. Hydrotherapy
IV. Joint Protection Strategies
V. Therapeutic Exercise
VI. Massage Therapy

4. YOGA

It's important to keep muscles strong to support the joints, and movement is important to reduce stiffness.[37]

AYURVEDIC TREATMENT

RA is known as AMAVATA in Ayurveda, Ama means Toxins are combined with Vata dosha localized in the joints and produces pain, swelling and stiffness**.**

In the initial stage, ayurvedic medications that metabolize the Ama (toxins) and eliminate them out of the body are prescribed. Later, medications that pacify the aggravated Vata dosha are prescribed by assessing the changes in patient's condition**.**

To be followed

Use garlic in regular diet. Buttermilk with garlic is an excellent remedy of rheumatoid arthritis. Use whole grains that are rich in fibre such as wheat, millet, barley, horse gram, brown rice. Consume honey mixed with water. (Older the honey, the greater its benefit) Milk boiled with dry ginger can be taken in the morning and evening instead of tea and coffee. Consume milk mixed with 3 Gms of turmeric powder. Turmeric is very effective to control inflammation of the joints.

To be avoided

Unhealthy and irregular dietary habits can trigger the abnormal immune response and increase the pain in the joints. Curd, Black gram, fermented food items; deep fried oily foods should be avoided. Avoid common foods that cause allergies such as dairy products, peanuts, beets, soy, red meat, processed foods, artificial additives and preservatives, white flour and white sugar. Alcohol, tobacco, tea, coffee, soft drinks and ice creams should not be consumed. Avoid food items that cause indigestion and flatulence. Try to avoid keeping awake at nights and sleeping during daytime. Consume fruits in their whole form and avoid them in the form of juices. Whole fruits with their fibre content aids in proper digestion and regulates the bowel movements.[38]

Role of Surgery

Rheumatoid arthritis surgery may involve one or more of the following procedures:

- Total joint replacement
- Tendon repair
- Joint fusion
- Synovectomy

- **Arthroscopy**

Arthroscopy is performed to clean out bone and cartilage fragments (a process called debridement) that cause pain and inflammation.[39]

VACCINATIONS

People with RA have an increased risk of infections and mortality and recommended vaccinations can reduce these risks. The killed influenza vaccine should be received annually. The pneumococcal vaccine should be administered twice for patients under the age 65 and once for those over 65.Lastly, the live-attenuated zoster vaccine should be administered once after the age 60, but is not recommended in patients on a tumor necrosis factor alpha blocker.[40,41,42,43]

CONCLUSION

RA is a disorder of joint stiffness. There are many drug classes of NSAID,DMARDS,which are used. But this individual drug couldn't give desired effect. Thus new drugs which provide moderate effect with less adverse effects are formulated. Combination of drugs with regular exercise is recommended as it is useful to maintain muscles strength and overall physical function effective in the treatment.

REFERENCE

1. Shah, Ankur. Harrison's Principle of Internal Medicine (18th ed.). United States: McGraw Hill. p. 2738.
2. http://www.arthritis-india.com/
3. Alamanos Y, Voulgari PV, Drosos AA; Voulgari; Drosos. "Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review". Semin. Arthritis Rheum. 2006; 36(3): 182–8.
4. Majithia V, Geraci SA. "Rheumatoid arthritis: diagnosis and management". Am. J. Med. 2007; 120(11): 936–9.
5. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD, Combe B, Costenbader KH, Dougados M, Emery P, Ferraccioli G, Hazes JM, Hobbs K, Huizinga TW, Kavanaugh A, Kay J, Kvien TK, Laing T, MeaseP, Ménard HA, Moreland LW, Naden RL, Pincus T, Smolen JS, Stanislawska-Biernat E, Symmons D, Tak PP, Upchurch KS, Vencovsky J, Wolfe F, Hawker G (2010). "2010 rheumatoid arthritis classification criteria: an American College

of Rheumatology/European League Against Rheumatism collaborative initiative" (PDF). Ann. Rheum. Dis. 2010; 69(9): 1580–8.

6. Linos A, Worthington JW, O'Fallon WM, Kurland LT. The epidemiology of rheumatoid arthritis in Rochester, Minnesota: A study of incidence, prevalence, and mortality. Am J Epidemiol. 1980; 111: 87-98.
7. Gallego-Sandin S, Novalbos J, Rosado A, Gisbert JP, Galvez-Mugica MA, Garcia AG, Pajares JM, and Abad-Santos F: Effect of ibuprofen on cyclooxygenase and nitric oxide synthase of gastric mucosa: correlation with endoscopic lesions and adverse reactions. Dig Dis Sci. 2004 Sep; 49(9):1538-44.
8. Katzung, edited by Bertram G. Basic & clinical pharmacology (10th ed. Ed.). New York: McGraw-Hill Medical. 2007; 579.
9. Scholer. Pharmacology of Diclofenac Sodium. Am J of Medicine Volume 80 April 28, 1986
10. McNicol E, Strassels SA, Goudas L, Lau J, Carr DB (2005). "NSAIDS or paracetamol, alone or combined with opioids, for cancer pain".
11. Rajagopalan, P. T. Ravi; Zhang, Zhiquan; McCourt, Lynn; Dwyer, Mary; Benkovic, Stephen J.; Hammes, Gordon G. "Interaction of dihydrofolate reductase with methotrexate: Ensemble and single-molecule kinetics".Proceedings of the National Academy of Sciences, 2002; 99(21): 13481–6.
12. Cara, C. J.; Pena, A. S.; Sans, M.; Rodrigo, L.; Guerrero-Esteo, M.; Hinojosa, J.; García-Paredes, J.; Guijarro, L. G. (2004). "Reviewing the mechanism of action of thiopurine drugs: Towards a new paradigm in clinical practice". Medical science monitor : international medical journal of experimental and clinical research
13. Colin R. Martin, Victor R. Preedy"Scientific Basis of Healthcare: Arthritis" page no. 16
14. Sistigu A, Viaud S, Chaput N, Bracci L, Proietti E, Zitvogel L. "Immunomodulatory effects of cyclophosphamide and implementations for vaccine design".Seminars in Immunopathology, July 2011; 33(4): 369–83.
15. William F. Ganong. Review of medical physiology, 22nd edition, Lange medical books, chapter 27, and page 530.
16. Amin, AR; Attur, MG; Thakker, GD; Patel, PD; Vyas, PR; Patel, RN; Patel, IR; Abramson, SB. "A novel mechanism of action of tetracyclines: Effects on nitric oxide synthases". Proceedings of the National Academy of Sciences of the United States of America, November 1996; 93(24): 14014–14019.

17. Ransom JT. "Mechanism of action of mycophenolatemofetil". Therapeutic Drug Monitoring, December 1995; 17(6): 681–4.
18. Camp, A. V. "Penicillamine in the treatment of rheumatoid arthritis". Proceedings of the Royal Society of Medicine, 1977; 70 (2): 67–69.
19. Prednisolone. Australian Medicines Handbook. Adelaide: Australian Medicines handbook Pty Ltd. 2010; 497: 598.
20. Teschner, S; Burst, V. "Leflunomide: a drug with a potential beyond rheumatology.". Immunotherapy, September 2010; 2(5): 637–50.
21. Fox, RI; Herrmann, ML; Frangou, CG; Wahl, GM; Morris, RE; Strand, V; Kirschbaum, BJ. "Mechanism of action for leflunomide in rheumatoid arthritis.". Clinical Immunology, December 1999; 93(3): 198–208.
22. Madhusudan S, Muthuramalingam SR, Braybrooke JP et al. "Study of etanercept, a tumor necrosis factor-alpha inhibitor, in recurrent ovarian cancer". J. Clin. Oncol. 2005; 23(25): 5950–9.
23. Siegel, Jay P., M.D., FACP. "Therapeutic Biologic Applications (BLA) - Humira Approval Letter 12/31/02".Center for Drug Evaluation and Research. Retrieved, 2014-02-04.
24. Choy EH, Panayi GS. "Cytokine pathways and joint inflammation in rheumatoid arthritis". The New England Journal of Medicine, March 2001; 344(12): 907–16.
25. Fleischmann RM, Tesser J, Schiff MH et al. "Safety of extended treatment with anakinra in patients with rheumatoid arthritis". Annals of the rheumatic diseases, August 2006; 65(8): 1006–12.
26. Cannon, Christopher P; Curtis, Sean P; Fitzgerald, Garret A; Krum, Henry; Kaur, Amarjot; Bolognese, James A; Reicin, Alise S; Bombardier, Claire; Weinblatt, Michael E; Van Der Heijde, Désirée; Erdmann, Erland; Laine, Loren. "Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: A randomised comparison". The Lancet, 2006; 368(9549): 1771.
27. Michael F. Holick" Vitamin D: Physiology, Molecular Biology, and Clinical Applications" page no. 1094.
28. Wang, J; Tan, X. F.; Nguyen, V. S.; Yang, P; Zhou, J; Gao, M; Li, Z; Lim, T. K.; He, Y; Ong, C. S.; Lay, Y; Zhang, J; Zhu, G; Lai, S. L.; Ghosh, D; Mok, Y. K.; Shen, H. M.; Lin, Q. "A quantitative chemical proteomics approach to profile the specific cellular

targets of andrographolide, a promising anticancer agent that suppresses tumor metastasis". Molecular & Cellular Proteomics, 2014; 13(3): 876–86.

29. Kontzias A, Kotlyar A, Laurence A, Changelian P, O'Shea JJ. "Jakinibs: a new class of kinase inhibitors in cancer and autoimmune disease". Current Opinion in Pharmacology, Aug 2012; 12(4): 464–70.
30. Namour, Florence; Diderichsen, Paul Matthias; Cox, Eugène; Vayssière, Béatrice; Van der Aa, Annegret; Tasset, Chantal; Van'tKlooster, Gerben (2015-02-14). "Pharmacokinetics and Pharmacokinetic/Pharmacodynamic Modeling of Filgotinib (GLPG0634), a Selective JAK1 Inhibitor, in Support of Phase IIB Dose Selection". ClinPharmacokinet. Epub ahead of print.
31. http://en.wikipedia.org/wiki/Filgotinib.
32. Mayo Clinic Rheumatoid arthritis drugs in development. 2006. Available at: «http://www.mayoclinic.com/health/rheumatoid-arthritis-drugs/AR00041». Accessed March 3, 2006.
33. Yocum DE, Furst DE, Bensen WG, Burch FX. Safety of tacrolimus in patients with rheumatoid arthritis: long-term experience.Rheumatol. 2004; 43: 992–999.
34. Casimiro, L; Barnsley, L; Brosseau, L; Milne, S et al. (2005). Casimiro, Lynn, ed. "Acupuncture and electroacupuncture for the treatment of rheumatoid arthritis". Cochrane Database of Systematic Reviews 2005
35. Deborah Cooper ” Acupressure and Arthritis: Ancient Healing to Relieve Pain” http://www.prohealth.com/fibromyalgia/library/showArticle.cfm?libid=518
36. VuralKavuncu, DenizEvcik,” Physiotherapy in Rheumatoid Arthritis” http://www.medscape.com/viewarticle/474880_3
37. Susan Bernstein “Yoga Benefits for Arthritis” http://www.arthritis.org/living-with-arthritis/exercise/workouts/yoga/yoga-benefits.php
38. http://www.gandhijinaturecure.com/rheum_arthritis.html
39. Brian P. McKeon, James V. Bono, John C. Richmond “Knee Arthroscopy” page-1
40. Perry, Lisa M.; Winthrop, Kevin L.; Curtis, Jeffrey R. "Vaccinations for Rheumatoid Arthritis".Current Rheumatology Reports, 13 June 2014; 16(8).
41. Grohskopf, LA; Olsen, SJ; Sokolow, LZ; Bresee, JS; Cox, NJ; Broder, KR; Karron, RA; Walter, EB; Centers for Disease Control and, Prevention. "Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP) -- United States, 2014-15 influenza season". MMWR. Morbidity and mortality weekly report, 15 August 2014; 63(32): 691–7.

42. Black, CL; Yue, X; Ball, SW; Donahue, SM; Izrael, D; de Perio, MA; Laney, AS; Lindley, MC; Graitcer, SB; Lu, PJ; Williams, WW; Bridges, CB; DiSogra, C; Sokolowski, J; Walker, DK; Greby, SM. "Influenza vaccination coverage among health care personnel - United States, 2013-14 influenza season.". MMWR. Morbidity and mortality weekly report, 19 September 2014; 63(37): 805–11.
43. Hales, CM; Harpaz, R; Ortega-Sanchez, I; Bialek, SR; Centers for Disease Control and Prevention, (CDC). "Update on recommendations for use of herpes zoster vaccine. "MMWR. Morbidity and mortality weekly report, 22 August 2014; 63(33): 729–31.