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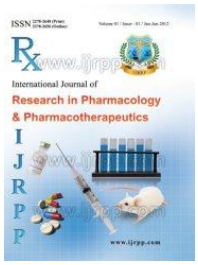

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Review of various treatment strategy for rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis is a chronic systemic inflammatory disorder affecting joints leading to limited range of motion affecting daily activities. Various drug therapies were used to preserve range of motion; joint function and to prevent systemic complications.

But due to serious adverse effects of the drugs and limited improvement a 'Novel drug free implant' is introduced to improve quality of life and reduce adverse effects of the drugs. This drug free implant works through electric stimulation of peripheral nerve as a treatment for immune disease.

This article is a review on assessing various drugs used to treat Rheumatoid arthritis comparing it's efficacy and advantages of 'Drug free implant' over other drug therapy. It is assessment of various anti-rheumatic drugs related adverse effects and safety profile.

Keywords: Rheumatoid arthritis, Drug Free Implant, Triple therapy, Dual Therapy, Tofacitinib, PRT-318.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder that primarily affects joints. It may result in deformed and painful joints, which can lead to loss of function. It is characterized by synovial inflammation and hyperplasia ("swelling") autoantibody production rheumatoid factor and anti-citrullinated protein antibody and cartilage and bone destruction deformity systemic features including cardiovascular, pulmonary, psychological and skeletal disorders.[1]

The process involves an inflammatory response of the capsule around the joints (synovium) secondary to swelling (turgescence) of synovial cells, excess synovial fluid, and the development of fibrous tissue (pannus) in the synovium. It also affects the underlying bone (focal erosions) and cartilage (thinning and destruction).[1]

Current pharmacotherapies include four main classes of drugs are currently used:

Biologic disease-modifying antirheumatic drugs **(DMARD)** and Anti TNF agents: Methotrexate, sulfasalazine, leflunomide hydroxyl chloroquine and etanercept.[2]

Combination therapy

Triple therapy: (Methotrexate+ sulfasalazine+ hydroxychlorquine)

Methotrexate

For the treatment of rheumatoid arthritis, inhibition of DHFR is not thought to be the main mechanism, but rather multiple mechanisms appear to be involved

including: the inhibition of enzymes involved in purine metabolism, leading to accumulation of adenosine; inhibition of T cell activation and suppression of intercellular adhesion molecule expression by T cells; selective down-regulation of B cells; increasing CD95 sensitivity of activated T cells; inhibition of methyl transferase activity, leading to (de)-activation of enzyme activity relevant to immune system function. Another mechanism of MTX is the inhibition of the binding of Interleukin 1 beta to its cell surface receptor. [2]

Sulfasalazine

It does this via a number of mechanisms such as reducing the synthesis of inflammatory mediators known as eicosanoids and inflammatory cytokines. Sulfasalazine is only a mild immunosuppressant.[2]

Hydroxychlorquine

It is believed that hydroxyl chloroquine interferes with communication of cells in the immune system. The innate immune system in humans senses the invasion of microorganisms using the family of Toll receptors, stimulation of which initiates a range of host defense mechanisms. In humans antimicrobial responses rely on two signaling pathways: the Toll pathway and the IMD pathway. In humans there are at least 10 members of the Toll-like receptor (TLR) family that recognize specific components conserved among microorganisms. Activation of the TLRs leads not only to the induction of inflammatory responses but also to the development of antigen-specific adaptive immunity. The TLR-induced inflammatory response is dependent on a common signaling pathway that is mediated by the adaptor molecule MyD88. However, there is evidence for additional pathways that mediate TLR ligand-specific biological responses.[5]

The efficacy and benefit of combination therapy with MTX + HC + SSZ compared

to MTX alone (still considered to be the optimal DMARD for RA) for long term treatment (2 years). Use of this combination may be efficacious in the earliest phase of the disease to slow RA progression and reduce the risk of joint damage. [4]

Dual therapy: (etanercept+ Methtrexate)

Etanercept

It reduces the effect of naturally present TNF, and hence is a TNF inhibitor, functioning as a decoy receptor that binds to TNF. Etanercept mimics the inhibitory effects of naturally occurring soluble TNF receptors, the difference being that etanercept, because it is a fusion protein rather than a simple TNF receptor, has a greatly extended half-life in the bloodstream, and therefore a more profound and long-lasting biologic effect than a naturally occurring soluble TNF receptor

Inhibition of its action by etanercept reduces the inflammatory response which is especially useful for treating autoimmune diseases.[6]

Tofacitinib (JAK kinase inhibitor)

Tofacitinib is a novel oral Janus kinase inhibitor that is being opted for the treatment of rheumatoid arthritis.

Tofacitinib is an inhibitor of the enzyme janus kinase 3(JAK3), which means that it interferes with the JAK-STAT signaling pathway, which transmits extracellular information into the cell nucleus, influencing DNA transcription. [3]

Recently it has been shown in a murine model of established arthritis that tofacitinib rapidly improved disease by inhibiting the production of inflammatory mediators and suppressing STAT1-dependent genes in joint tissue. This efficacy in this disease model correlated with the inhibition of both JAK1 and 3 signaling pathways, suggesting that tofacitinib may exert therapeutic benefit via pathways that are not exclusive to inhibition of JAK3.

Tofacitinib was rapidly absorbed, with plasma concentrations and total radioactivity peaking at around 1 hour after oral administration. Half life was approximately 3.2 hours.

Hepatic clearance made up around 70% of total clearance, while renal clearance made up the remaining 30%. Cytochrome P450 (P450) profiling indicated that tofacitinib was mainly metabolized by CYP3A4, with a smaller contribution from CYP2C19.

Patients receiving tofacitinib must be monitored by their physician for such events.

There were two cases of pulmonary tuberculosis; Changes in laboratory values that were observed with tofacitinib, as compared with placebo, included small

increases in serum creatinine levels and increases in mean levels of LDL and HDL cholesterol.[3]

Notable adverse events included cytopenia, which may be attributable to the inhibition of JAK2; infections (especially respiratory and urinary tract infections); upper respiratory tract infections, headache, diarrhea and inflammation of the nasal passage (nasopharyngitis).The recommended dose of tofacitinib is 5 mg twice daily. [3]

PRT-318: SPLEEN TYROSINE KINASE (SYK)

Spleen tyrosine kinase (Syk) is an intracellular cytoplasmic tyrosine kinase that

is an important mediator of immuno receptor signaling in macrophages, neutrophils, mast cells, and B cells. Syk is present in the synovium of patients with rheumatoid arthritis, and activation of Syk is important for cytokine and metalloproteinase production induced by tumor necrosis factor α in fibroblast-like synoviocytes from patients with rheumatoid arthritis. Adverse events included diarrhea, hypertension, and neutropenia.[7]

TABLE 1:

S no	Types of drugs	Dose	Pharmacological action	Adverse effects
1	Tofacitinib JAK kinase inhibitor	5 mg twice daily	Inhibits enzyme janus kinase 3(JAK3), which means that it interferes with the JAK-STAT signaling pathway	respiratory and urinary tract infections gastrointestinal infections and cytopenia
2	SYK Spleen tyrosine kinase inhibitor	100 mg twice daily	Mediator of immunoreceptor signaling in macrophages, neutrophils, mast cells, and B cells	Gastrointestinal and urinary tract infections weight gain.
3	Triple therapy: methotrexate + sulfasalazine + hydroxychlorquine	20mg + 200mg + 200mg	Use of this combination may be efficacious in the earliest phase of the disease to slow RA progression and reduce the risk of joint	Gastrointestinal disorders infections and skin and subcutaneous disorders
4	Dual therapy: methotrexate + etanercept	20mg + 50mg	decoy receptor that binds to TNF inhibitor	

Drug free implant: (Novel therapy)

Drug free Implant device" works on a simple concept that nerves, which affect nearly every cell in your body, can be controlled with electrical signals.

In rheumatoid arthritis the neural control exerted by the vagus nerve fails and the production of TNF goes out of control.

In healthy people, the nervous system provides a precise mechanism of checks and balances that maintains the levels of TNF within a safe range. But in rheumatoid arthritis, its like like brake failure in a car barreling down a mountain[8]. The arthritis-regulating device is implanted in the patient's neck and wraps around the vagus nerve, a bundle of nerve fibers that communicates sensory information from internal organs and controls involuntary body functions such as heart rate and digestion. The device stimulates the nerve at regular intervals in a particular pattern that regulates the immune system, which is overactive in rheumatoid arthritis.[9]

A nerve-stimulating electrical is covering new ground by testing peripheral-nerve stimulation as a treatment for immune disease. A nerve-stimulating electrical implant could give people a drug-free alternative to current treatments. An electronic stimulator device with electrical leads that are placed over the affected area and held in place with a lightweight, flexible wrap and velcro fasteners. The

battery-powered device delivers small electrical currents of 0.0 to 12.0 volt output. It is recommended that the device be worn for at least 6 hours per day. Patients are reported to often wear the device while sleeping. Electro-stimulation can be much more selective; The targets are neural circuits that are not behaving as they should."

Neuro stimulator, usually referred to as an implantable pulse generator (IPG). The IPG is a battery-powered micro-electronic device, implanted in the body, which delivers electrical stimulation to the nervous system. An essential part of surgically implanted systems designed to treat a wide array of conditions, the IPG delivers very small pulses of electricity to block or stimulate nerve signals (or impulses), and depending upon the condition[10] .Implanted device can be used alone or in combination with medicine.

- Implantable devices allow for sustained release of a therapeutic agent .
- The last and perhaps most important advantage is patient compliance, as the treatment regimen associated with an drug free implant device is generally less burdensome than pills or injection.
- The advantage of implanted device over drugs is that it causes no side effects provided the impulses are properly regulated.

Figure 1:

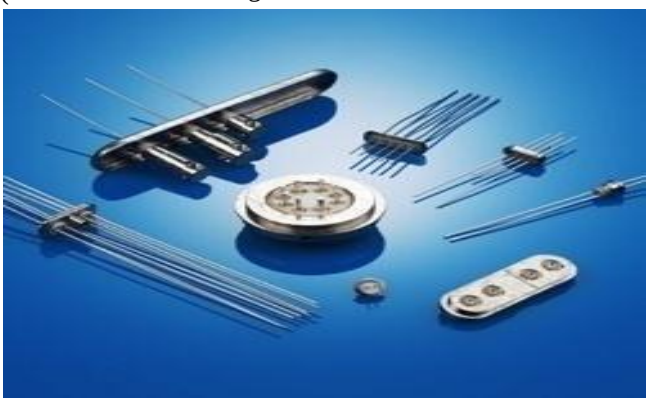

Figure 2:

Review of various results

The study of combination therapy conducted by Department of Veterans Affairs Office of Research and Development. With respect to clinical benefit, triple therapy, with sulfasalazine and hydroxyl chloroquine added to methotrexate, was non inferior to etanercept plus methotrexate in patients with rheumatoid arthritis who had active disease despite methotrexate therapy. Two published trials, the Swedish Pharmacotherapy (Swefot) study and the Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) study ,have compared conventional therapy with TNF inhibitors in patients with active disease despite treatment with methotrexate. The Swefot study, which was not blinded and allowed frequent switches, showed no significant difference between infliximab therapy and therapy with sulfasalazine and hydroxyl chloroquine at 6 months but did show a benefit with infliximab at 12 months. The TEAR study, which involved patients with very early rheumatoid arthritis, included a subgroup of patients who had not had an adequate response to methotrexate and then received either etanercept or sulfasalazine and hydroxyl chloroquine; there was no significant difference in outcome between these two regimens[11].

In randomized trial involving patients with rheumatoid arthritis who were receiving methotrexate therapy, inhibition of Syk with R788 at a dose of 100 mg twice a day was superior to placebo[12].

In randomized, phase 3 trial involving patients with rheumatoid arthritis who had an incomplete response to methotrexate, the efficacy of 5 mg or 10 mg of tofacitinib given twice daily was significantly superior to that of placebo. The safety of tofacitinib should be evaluated in a larger number of patients who have received treatment for longer durations.[13]

A New Approach to Rheumatoid Arthritis: Treating Inflammation with Computerized Nerve Stimulation (Drug free implant)

Kevin Tracey surgically implanted nerve stimulator to treat disabling rheumatoid arthritis. The patient underwent a minor surgical procedure during which a neurosurgeon implanted a small pacemaker-like device and attached the electrode to a nerve in neck. This vagus nerve, which runs from the brain, across the chest and thorax, and into the abdomen, sends branches into all of the major organs of the body. The implanted computer began delivering electrical signals that instructed his immune system to stop attacking his joints. As a result, after years of incapacitating pain in hands, wrists, elbows, and legs. This remarkable, suggesting for the first time that it may be possible to replace powerful immune system–suppressing drugs with a computerized device to treat crippling inflammatory diseases[14]

The basic problem in rheumatoid arthritis, and other autoimmune diseases, is that immune system cells begin to attack the body's own tissues. Current therapies suppress the attacking action of the immune cells with an armamentarium of drugs that includes aspirin-like substances, corticosteroids, and other so-called disease-modifying anti-rheumatic drugs. While such drugs can be effective, toxicity significantly limits their use in some cases, and treatment failure limits them in others. Another mainstay of therapy is drugs that target cytokines, molecules produced by white blood cells during inflammation. In rheumatoid arthritis, high cytokine levels accumulate in the cartilage and other inflamed joint tissues to produce pain and destroy tissues. Treatments that specifically block the action of cytokines have shown major promise in alleviating the disease in some autoimmune patients. These advanced drugs have now been administered to millions of individuals, providing insight into the important role that cytokines play in the development of the disease. The downside, however, is that these drugs are powerful immune system–suppressing agents that impair defenses, which can leave the patient susceptible to major infection. Some of these therapies even carry a black box warning, a notice mandated by the FDA that immunosuppressive side effects can be extremely dangerous, or even fatal. Even if patients undertake these risks and costs, 50 percent fail to achieve significant clinical benefit. So there obviously remains a major unmet medical need for the development of new treatment options for rheumatoid arthritis and other autoimmune diseases.[15]

CONCLUSION

After studying various drug profiles and their relative clinical trials we conclude that "Computerized nerve stimulation" is much more efficacious , safer, compliant and superior to all other Anti-rheumatic drugs including 'Tofacitinib'; 'SYK'; and 'combination therapy'. Drug free implant can be the ultimately appropriate treatment for "rheumatoid arthritis' in future. Implant can be 'Ray of hope' to various patient who had been suffered from deteriorative adverse effects of various drugs.

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