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Review article

Use of drug Methotrexate with Biological Drugs for treatment of RA

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Abstract

Several inflammatory diseases have been treated with methotrexate alone or with biological drugs. Medicines slow the damage process.in rheumatoid arthritis RA inflammation occur in joints, tissues of heart, lungs, kidneys, and pleura. Some biological and environmental factors are responsible for that. Steroidal and non-steroidal anti-inflammatory drugs are used for the treatment of these. Disease modifying anti rheumatic drugs have been used. Monoclonal antibodies (MAbs) focused against chemical mediators of inflammation. Biological therapy termed as biological DMARDs are more beneficial to patients for RA. Biological drugs as abatacept is soluble fusion protein, adalimumab is human MAbs, Anakinra is a recombinant antagonist , Etanercept is a human amino acid , Infliximab is first biological anti rheumatic drug . Rituximab is used in treatment of neoplastic diseases. For minimizing cardiovascular risk, it is better to limit exposure to non-steroidal anti-inflammatory drugs

Rheumatoid arthritis

(RA) is a prolonged systemic inflammatory illness. It is related with substantial disease and increased mortality. It leads to irreparable joint damage and systemic complications. Numerous inflammatory diseases, containing some of autoimmune aetiology, are either being cured with biological drugs or under medical investigation with these drugs. A list of some of these illnesses is given below:

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- Ulcerative colitis
- Alzheimer's disease
- Asthma
- Atherosclerosis
- Crohn's disease
- Irritable bowel syndrome (IBS)
- Dermatitis
- Hepatitis
- Diverticulitis
- Colitis
- Systemic lupus erythematosus (SLE)
- Nephritis
- Arthritis
- Parkinson's disease
- Psoriasis

Irreversible joint damage happens very early. Additionally, initial treatment with disease modifying anti-rheumatic drug therapy (DMARD) enhances both short and long-term radiological, clinical, and functional results. Indicators of rheumatoid arthritis (RA) Symptom of rheumatoid arthritis (RA) is soreness of the joints. Inflammation may also arise in other tissues, involving heart, lungs, kidneys, and pleura. The cause is currently unspecified, but may include working conditions, climate, and gender, it is more prevailing in women. RA may strike at different times, at several diverse joints, irreparable damage is done to the joint due to tenderness of the synovial membrane, which makes the lining of the joints and tendon sheaths. As the disease proceeds, it damages the joint tissues and joint mobility through erosion and tethering of the tendons. This suggests that the tendon becomes attached to adjacent tissues, which confines its movement.

RA should be doubted in someone who has had continuing polyarthritis, specifically altering minute joints of hands and feet, for no less than 12 weeks providing that other reasons for similar presentation for example osteoarthritis, reactive arthritis, rheumatic fever or systemic lupus erythematosus and tuberculous arthritis.

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Environmental and biological aspects related with RA -

- Tumour necrosis factor (TNF)-a activity.
- Cigarette smoking.
- Discovery of circulating autoantibodies called 'rheumatoid factor', and they occupied in the inappropriate presentation of antigens to T cells by B cells.
- Uncharacteristic and improper B-lymphocyte activity, i.e. Unusual antibody production. * Irregular movement in synovial tissue, e.g. immersed in embryonic development and cell renewal. In patients with RA synovial cells have unusually great activity of the Wnt gene.

Any four of the conditions listed beneath must be recognised for positive diagnosis of RA:

- Arthritis in joints for 6 weeks or more.
- Rheumatoid nodules
- Discovery of serum RF.
- Morning stiffness for 60 minutes or longer for more than 6 weeks
- Continuation for 6 weeks or more of symmetrical arthritis.
- Erosion or unequivocal bony decalcification.
- Arthritis for 6 weeks or more in hand joints.

All patients with continuing inflammatory arthritis (symptom duration > 12 weeks) would gain from DMARD therapy. Ordinary DMARDs used with initial RA comprise methotrexate, sulphasalazine and leflunomide. Methotrexate is also as efficient as anti-TNF monotherapy in early RA. Methotrexate has better retention rate than other DMARDs. Hydroxychloroquine is a possibility for patients who reject blood monitoring. It could take about 2-4 months for the DMARDs to give result. DMARDs are not symptom reducing medicines. All patients should be advised on side effects of DMARD therapy.

Precautions

Chest X-ray notice past or existing sign of tuberculosis. Complete blood counts (CBC), liver and renal function tests should be examined before beginning a DMARD. For patients beginning hydroxychloroquine, inspection for visual acuity is obligatory. For patients starting methotrexate, excess alcohol ingestion should be dissuaded for fear of hepatotoxicity.

Women in their reproductive years, should follow a dependable technique of contraception before beginning teratogenic drugs like methotrexate or leflunomide.

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Biological DMARDs

Usually, RA was cured with non-steroidal and steroidal anti-inflammatory drugs. The grave consequences of steroidal drugs were water retention and relocation of body fat. The harsh results of nonsteroidal drugs such as aspirin on the stomach and Paracetamol has a comparatively little therapeutic index. These medications do not reduce the movement of tissue damage and loss of hand use and flexibility. Numerous drugs, e.g. Methotrexate, gold and azathioprine, penicillamine, normally known as DMARDs, or disease-modifying anti-rheumatic drugs, have been consumed for quite a lot of years. These may slow the development of the illness and deliver respite but are related with grave unpleasant consequences. The biological DMARDs have been developed. These are monoclonal antibodies (MAbs) particularly TNF-a, and interleukins IL-1 and IL-6. These MAbs contest with the endogenous ligands at their receptor sites on cells, e.g. CD20 and CD22 the biological drugs, also called 'biological DMARDs'. Biological Therapeutics have serious adverse effects due to the dropping of resistance to infection through their influential inhibition of the immune system.

The benefits of biological DMARDs comprise:

- Restoration of joint function and decrease in joint stiffness, swelling and pain
- lengthening of usable joint life
- decrease of early morning stiffness of joints
- decrease of the rate of joint damage.
- MAbs overpower the immune response and enable infections e.g. Respiratory infection.

Shortcomings-

MAbs are contraindicated in patients with heart failure, active tuberculosis, recognized hypersensitivity to murine (mouse)- derivative products (many biological DMARDs have murine-derived macromolecular components) .

Administration of biological drugs

Infliximab

Infliximab (Remicade) was the first biological anti-rheumatic medication effectively made for clinical usage. It is a monoclonal antibody composed of a chimeric human hgi–murine Fv1 gene complex, which connects both soluble TNF-a and membrane-bound with solid affinity. Following infliximab administration, there are significant falls in the blood concentrations of

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some cytokines, remarkably IL1-RA (an IL-1 receptor antagonist), and of solvable TNF-a receptors, both of which add to the inflammatory response. Infliximab is still greatly recommended in view of its high efficacy. Infliximab may also decrease the angiogenesis linked with the inflammatory response.

Infliximab and Rituximab

These are administered by intravenous infusion approaches. Unfavourable effects may be contemplated in terms of infusion-related results e.g. Headache, dyspnoea, and urticaria. TNF-a inhibitors comprises central nervous system (CNS) demyelination, opportunistic malignancies, e.g. Lymphomas and optic neuritis. Harmful neurological reactions registered thereby stopping the endogenous inflammatory agents from activating the immune response.

Rituximab

Rituximab (mabthera), collectively with methotrexate, is accepted for the treatment of neoplastic illnesses, e.g. Follicular lymphoma and severe RA. Rituximab was genetically engineered as a mouse/human chimeric monoclonal igg1 k antibody focused against the CD20 receptor. It contains flexible heavy and light chain murine antibody sequences related to steady human sequences. CD20 arises as a transmembrane receptor on the surface of B cells and rituximab fixes to it with very high affinity Rituximab is administered by measured intravenous infusion. In RA, T cells may then distinguish this complex through their T-cell receptor.

The synovial cell B cells may discharge substantial quantities of inflammatory cytokines comprising TNF-a. Besides, B cells may also function as apcs, which show the foreign antigen complex with the MHC on its surface.

Abatacept

Abatacept (Orencia) is a solvable fusion protein, formulated by combining the extracellular domain of the human cytotoxic T-lymphocyte-associated antigen (hctla-4) to an adapted human G1 immunoglobulin. When abatacept attaches to its focused receptors, namely CD80 and CD86 on the T cell, blocks the inflammatory cascade, it stops endogenous ligands from attachment and Generally, two procedures trigger T cells, specifically the connecting of the T cell's CD28 receptor to receptor proteins on the surface of the APC, the binding of the T-cell receptor to the antigen–MHC complex on the antigen-presenting cell (APC) and Abatacept binds to the B7 protein receptor with high affinity and thus blocks binding of B7 protein, thereby hindering the inflammatory reaction. Abatacept is suggested together with

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methotrexate, alternative DMARD. Methotrexate is a moderately small molecule that controls the immune for response

Anakinra

Anakinra is a recombinant antagonist at the IL-1 receptor. It is founded on the structure of the IL-1RA receptor. It impedes the inflammatory actions of IL-1 by binding to it, thus delaying the cartilage degradation and inflammation caused by IL-1.

Adalimumab

Adalimumab (Humira) is a totally human Mab that displays high affinity TNF-a, preventing binding to its receptors. Adalimumab is given as a prefilled syringe holding 40 mg adalimumab .It has been proposed stimulation of the T cell INFLAMMATION TISSUE DESTRUCTION Activated T cell Activated B cell Autoantibodies Activated macrophage Rituximab blocks initiation of B cells and may provoke B-cell apoptosis (complex set of actions)

. It has been discovered to be operational not only for Crohn's diseases but also for RA psoriatic arthritis, ankylosing spondylitis. Patients typically feel the gains in about 1–4 weeks after beginning treatment. The unpleasant effects of adalimumab, block TNF-a, comprise infections, counting upper respiratory tract and urinary tract infections. Patients with dormant TB may experience reactivation throughout or after a course of adalimumab or with other biological DMARDs. Mouth ulcers, Skin rashes and gastrointestinal disorders have been registered. Blood tests have exposed antinuclear antibodies (anas) in many patients with symptoms of SLE.

Etanercept

Etanercept (Enbrel) contains of a fully human amino acid sequence p75 TNFR11 dimer connected to the Fc of human igg. It acts by stopping the binding of TNF-a to its receptor. It is a dimer that can bind with very high affinity to two TNF-a receptors whether it is cell bound or free.

Etanercept is often suggested together with methotrexate. The most severe consequence is a slight injection site reaction, which usually vanishes with multiple use. The hostile results that happen when Etanercept is used in patients who are also on immunosuppressant treatment, who are immunocompromised or who have current infections such as sepsis.

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Monitoring of DMARD therapy

Liver enzymes and CBC should be checked frequently whenever dosage of DMARD is increased. Abnormal trends should be monitored (e.g. Moderate rise in ALT or moderate drop in white cell count). Treatment should be stopped if patient stars to suffer from leukopenia (< 4 X109/L), thrombocytopenia (< 150 X109/L), neutropenia (< 1.5 X109/L), or increase of liver enzymes many times the upper limit of normal. If the patient develops allergic skin rash or pruritis (more common with sulfasalazine), treatment should be dropped permanently. Patients on methotrexate complaining of panting and persistent cough should have a chest X-ray + pulmonary function studies. If methotrexate pneumonitis is detected, methotrexate should not be used in treatment.If patients show gastrointestinal side effects. Those patients on methotrexate could try to increase the dose of folic acid up to 3- 6 times/week. Patients taking hydroxychloroquine should withdraw treatment if visual symptoms such as blurring or if the patients find it hard to focus than seek advice from optician. All patients with RA have common signs including pain, inflexibility and swelling affecting multiple joints, tiredness, poor sleep, anaemia, depression, fibromyalgia.

Non-steroidal anti-inflammatory drugs (NSAID)

NSAID treatment of active inflammatory arthritis. Increased myocardial infarction, incidence of thrombotic events and stroke by taking selective cyclo-oxygenase-2 inhibitors (coxibs)

Advices

- Any NSAID should be taken in the lowest possible amount for the shortest possible period.
- All coxibs are contraindicated in patients with ischemic heart illness or stroke.
- In patients with both cardiovascular risk factors, gastrointestinal and it is preferable to use non-selective NSAID with proton pump inhibitor than a coxib. Patients must be cautious if they have cardiovascular risk factors such as diabetes mellitus, hypertension, smoking history, hyperlipidaemia.
- NSAID are also not ideal for senior citizens (> 65 years). Concomitant anticoagulant therapy, renal impairment, congestive heart failure, peptic ulcer disease, hypertension, pregnancy, breast-feeding and asthma.

- The usage of methotrexate alone or mutually with biological dmards Methotrexate is given

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alone as a DMARD for RA. It does decreases tissue swelling and lessens pain and will slow the rate of progress of joint damage and deterioration. It is given together with the biological dmards. The drug needs to be taken with caution since it is a folic acid antagonist and it is preferred that a dose of 5 mg folic acid should be ingested with each weekly dose of methotrexate (usually 7.5–20 mg weekly). Regular blood cell counts are strongly preferred for patients who are using methotrexate.

Systemic corticosteroids

Corticosteroids are very useful in rapidly controlling inflammatory joint indications and recovering mobility and function. Both low doses (7.5 mg of prednisolone/day) as well as high doses (initial dose of 60 mg of prednisolone/day) retard radiographic progression. Corticosteroids are also useful in patients with extraarticular manifestations. Corticosteroids are not good for long-term use because of their ill effect If long-term use is inevitable than all patients should be given adequate prophylaxis against steroid induced osteoporosis. Corticosteroids should always be taken with a DMARD for alcoholic patients with liver disease or severe renal failure and pregnant patients (use < 10 mg/day).

Corticosteroids can be handed out as: Methylprednisolone in a dosage of 80-120 mg, intramuscularly, every 4 weeks for the first 2-4 months. Intravenous methylprednisolone pulses, especially if impassive to oral or intramuscular corticosteroids. Up to 1000 mg is handed out with each pulse, delivered on alternate days up to three pulses.

Measures to reduce cardiovascular risk

Accelerated atherosclerosis is a prominent cause of death among patients with RA and occurs due to multiple mechanisms including therapy with corticosteroids and NSAID, uninhibited active inflammatory disease, and traditional risk factors such as hypertension, smoking, dyslipidaemia ,diabetes mellitus and obesity. The following measures should be taken to lessen cardiovascular morbidity and mortality:

- Inflammatory disease should be adequately regulated with DMARD therapy. Methotrexate is defensive against cardiovascular mortality. Patients should stop smoking. Patients are recommended to exercise, take a healthy diet, and use fish oil supplements.
- Contact to corticosteroids and NSAID should be curtailed.

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- Diabetes mellitus, Hypertension and dyslipidaemia should be managed. Statins have positive effect on inflammatory process in decreasing cardiovascular risk.

Conclusion

Current goals of treatment of RA are -

- Decelerate the rate of disease progression.
- Curb inflammation and pain.
- Design the appropriate medication regimen for each patient.
- Regular meetings with the clinic and the rheumatologist.
- Regular patient observing for adverse effects of treatments.
- Routine blood tests.
- Oversee patient compliance.

The aim of medical science is total prevention or cure of disability in RA. The goal can be achieved by patient and physician awareness. There are limited numbers of specialist in rheumatology, lack of infrastructure, general negligence, practical difficulties, and very high cost of biological therapy, we have to take care of RA patients.

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