A Review Study of Infliximab and Methotrexate Use In Management of Rheumatoid Arthritis

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ABSTRACT

The present study is designed to review whether the combination therapy of Infliximab and Methotrexate is better than Methotrexate monotherapy. We have reviewed that combination therapy of TNF-α inhibitors and Methotrexate in RA. How TNF-alpha inhibitors (Infliximab) and Methotrexate performed in randomized controlled trials when compared to Methotrexate in Methotrexate naive Rheumatoid Arthritis patients.

Keywords: Cytokines and inflammatory mediators, Immunology, Rheumatic diseases, Rheumatoid Arthritis (RA), Tissues.

INTRODUCTION

Rheumatoid arthritis is a common disease, and it produces substantial morbidity as well as an increase in mortality. Although the exact cause of RA remains unknown recent findings, laboratory data and clinical evidence suggests that pro-inflammatory cytokines, particularly Tumor Necrosis Factor (TNF) have an important role in its pathogenesis.[1] More than 80% of patients carry the epitope of the HLA-DRB1*04 cluster, and patients expressing two HLA-DRB1*04 alleles are at elevated risk for nodular disease, major organ involvement and surgery related to joint destruction.[2] Single-nucleotide polymorphism genotyping across the MHC has been identified and additional alleles found to RA risk, including those found on the conserved A1-B8-DR3 haplotype and those near the HLA-DPB1 gene . Other RA-associated loci are PTPN22, PADI4, STAT4, TRAF1-C5 and TNFAIP3, although non-MHC risk alleles may represent only 3.5% of the genetic burden of RA.[3] Environmental factors, such as smoking and infection, may also influence the development, rate of progression and severity of RA Various immune modulators (cytokines and effector cells) and signaling pathways are also involved in the pathophysiology of RA. The complex interaction of immune modulators is responsible for the joint damage that begins at the synovial membrane and covers most IA structures. Synovitis is caused by the influx or local activation, or both, of mononuclear cells (including T cells, B cells, plasma cells, dendritic cells, macrophages and mast cells) and by angiogenesis.[4] The synovial lining then becomes hyperplasic, and the synovial membrane expands and forms villi. The osteoclast-richportion of the synovial membrane, or pannus, destroys bone, here as enzymes secreted by neutrophils, synoviocytes and chondrocytes degrade cartilage.[5]

In addition to joint symptoms, many patients experience extra-articular or systemic manifestations or both .According to a US pharmacy claims data analysis with a mean follow-up of 3.9 years, 47.5% of 16,752 patients with RA experienced at least one extra-articular or systemic manifestation. Extra-articular manifestations include rheumatoid nodules, vasculitis, pericarditis, keratoconjunctivitis, sicca, uveitis and rheumatoid lung .Systemic manifestations include acute-phase protein production, anemia, cardiovascular disease (CVD), osteoporosis, fatigue and depression.[6]

Rheumatoid Arthritis (RA) is a common, frequently severe, chronic inflammatory disease. Although the cause of RA remains unknown, recent advances in understanding its pathogenesis have been substantial. Despite the use of a variety of medications, particularly Methotrexate, treatment of RA is not fully effective in most patients. This gap now will likely be bridged in the

form of a new strategy for treating RA-cytokine blockade. Although a variety of cytokines are important in the pathogenesis of RA, tumor necrosis factor (TNF) seems to play a pivotal role. Anti-TNF monoclonal antibodies, has proven to be a powerful means of controlling disease activity. Some Studies are proved that combination of TNF alpha blockers and Methotrexate is effective for Rheumatoid Arthritis.[7]

Infliximab

Infliximab, a chimeric (mouse Fv1, human IgG1) monoclonal antibody, specifically binds to both soluble and membrane-bound TNF-α with high affinity ($Ka = 10^{10}\,M^{-1}$), forming stable non-disassociating immune complexes. The binding of Infliximab to TNF-α prevents the binding of TNF-α to its receptors and blocks the initiation of the intracellular signaling that leads to gene transcription and subsequent biologic activity. From the early stages of disease, rheumatoid synovial inflammation is accompanied by a marked increase in angiogenesis. The increase in blood vessel density provides a conduct for the increased trafficking of blood-borne immune and inflammatory cells into joints. This increase in trafficking leads to the formation of vascular pannus tissue that invades and destroys cartilage and bone in the "bare area" of the attachment of synovium to subchondral bone.[8]

The cytokine vascular endothelial growth factor (VEGF) is implicated in new blood vessel formation and is increased in the joints and blood of RA patients. Infliximab therapy reduces circulating VEGF levels and the density of neovasculature in the synovium. A reduction in angiogenesis may be relevant to our understanding of the anti-inflammatory and anti-destructive properties of Infliximab. In addition, although unproven, the exudative leakage of plasma mediated by VEGF may also be ameliorated by Infliximab. IL-1 appears to play a critical role in cartilage destruction; it has been proposed that IL-1 may be a better therapeutic target in RA and that the joint protective effect of anti-TNF-α therapy involves regulation of IL-1 production. The activation and function of osteoclasts appear to involve not only IL-1 and TNF-α, but also the receptor activator of NFκB ligand (RANKL), also known as TNF-related activation-induced cytokine (TRANCE).[9]

MTX Mechanism of Action

Methotrexate (4-amino-N10-methylpteroyl glutamic acid) is an analogue of folic acid and of aminopterin (4-amino-pteroyl glutamic acid) that is also a folic acid antagonist. It was first introduced in 1948 to treat acute leukemia. Many pharmacological mechanisms of MTX action have been suggested,

- including inhibition of purine synthesis,

- promotion of adenosine release,
- inhibition of production of pro-inflammatory cytokines,
- suppression of lymphocyte proliferation,
- Neutrophil, chemo taxis and adherence, and
- Reduction of serum immunoglobulin. [10]

However, the mechanism by which MTX at a low dose modulates inflammation in RA is still unknown. Studies to date indicate that the most important actions of low-dose MTX are its effects in increasing adenosine level and reducing the pro-inflammatory while increasing the anti-inflammatory cytokine levels.[11]

Effects on Dihydrofolate Reductase

MTX with high affinity binds and inactivates the Dihydrofolate Reductase (DHFR), resulting in the depletion of metabolically active intracellular folates with subsequent inhibition of the synthesis of Thymidylate and Inosinic acid. Inhibition of DHFR causes cessation of the synthesis of purine metabolites which are important for cell proliferation. In RA patients, this is rather not the main element of action because the doses required for MTX's anti proliferative effect are Considerably higher.[12]

Effects on Adenosine

The intracellular 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) formylotransferase also plays an important role in the purine metabolism of the cell. Its inhibition by low-dose MTX decreases the conversion of AICAR to formyl-AICAR. Accumulation AICAR inhibits the degradation of adenosine 5-P and adenosine by Adenosine 5-monophosphate (AMP) deaminase and Adenosine deaminase (ADA). As concentrations of adenosine and adenosine-5-P rise intracellularly, they are more likely to appear in the extracellular milieu.

In the extracellular space, adenosine 5-P is converted to adenosine, which binds predominantly to A2_receptors.After binding to the A2 receptor, the intracellular Cyclic Adenosine monophosphate (cAMP) level increases. Higher levels of cAMP produce a range of anti-inflammatory effects, such as decreased secretion of Tumor Necrosis Factor (TNF), interferon (IFN)-_ interleukin (IL)-12, IL-6, and inhibition of phagocytosis . Thus adenosine-mediated anti-inflammatory effects may play a central role in producing the anti-inflammatory actions of MTX.[13]

Effects on Cytokines

MTX reduces the production of pro-inflammatory cytokines, decreases the gene expressions of TH1cytokines, and increases those of anti-inflammatory TH2 cytokines. The inhibition of the

monocytic and lymphocytic pro-inflammatory cytokines involved in rheumatoid Synovitis seems to play an important role in the anti-inflammatory action of low-dose MTX.[14]

MTX effects on Immunoglobulin

Variable effects of MTX treatment on immunoglobulin M (IgM) rheumatoid factor production were shown. MTX's influence on B-cell function in RA is probably not a major target of its action, and it is difficult to conclude that the effects of MTX therapy on RF levels are related to the beneficial effects of this drug in the therapy of RA.[15]

Effect on T Cells

The effect of MTX on T cells is likely to be minor at the doses used in RA. The immunosuppressive effect with low-dose MTX is controversial (12 weeks of therapy diminished the number of circulating T and B cells, while long-term MTX therapy led to an increase in the percentage of CD3 and CD4 cells in the peripheral blood) .[16]

MTX effects on Cyclo and Lipooxygenase

An anti-inflammatory effect of MTX has been suggested by its rapid onset of action (4–6 weeks after therapy begin) and the equally rapid flare after drug discontinuation. Its effect on the generation of Leucotriene remains somewhat controversial and is unlikely to contribute on its own in a major way to the efficacy of MTX therapy. MTX applied to RA synoviocytes cultures *in vitro* inhibited the IL-1 -stimulated production of prostaglandin E2, whereas neither Cyclooxygenase (COX)-1 nor COX-2 mRNA expression was affected. This suggested that MTX could have an anti-inflammatory action by decreasing prostaglandin E2 release [112]. COX-2 activity was found to be reduced in the plasma of RA patients treated with MTX compared with healthy controls. However, a specific COX-2 inhibitor, celecoxib, had no significant effect on MTX pharmacokinetics in patients with RA. In conclusion, the effect on Cyclo and Lipooxygenase seems to be indirect.[17]

MTX effects on apoptosis

Apoptosis is important in the down-regulation of the immune responses after the activation and proliferation of T and B cells. In recent years, an association between apoptosis and autoimmune diseases, including RA, has been reported. It has been considered that the process of apoptosis may play an important role in RA by limiting synovial tissue hyperplasia.

- MTX could induce *in vitro* apoptosis of mitogen activated CD4+ and CD8+ lymphocytes, but not resting T cells.
- Peripheral blood lymphocytes (PBLs) from MTX treated RA patients underwent apoptosis upon *ex vivo* activation.

- MTX-induced apoptosis of mitogen-activated cells occurred through a CD95-independent pathway.

- Good response of RA patients to MTX treatment is not always accompanied by a peripheral blood mononuclear cell (PBMC) response to MTX *in vitro.* It seems that either apoptosis of the cells in the tissue directly involved in the inflammatory process is more important than that observed in peripheral blood lymphocytes or another mechanism of the MTX action may be responsible for the clinical improvement in patients treated with low doses of MTX.[18,19]

Other effects of MTX

Low-dose MTX in RA treatment seems to exert its anti-inflammatory effects by acting at different levels of the pathophysiological cascade. It decreases the recruitment of inflammatory cells in joints, it has a significant suppressive effect on Neutrophil, chemo taxis, it reduces the numbers of macrophages and inflammatory cells in synovial tissue, it reduces intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1(VCAM-1) in synovial tissue, it decreases metalloproteinase-1 production, which is probably caused by direct cytokine regulation by MTX (down-regulation of IL-1), it suppresses TNF induced expression of ICAM-1 and VCAM-1 by vascular endothelial cells . Its inhibition of angiogenesis does not significantly contribute to the anti-arthritic effect of MTX seen in patients and animal models for RA.[20]

DISCUSSION

At doses of 7.5 mg to 25 mg per week, Methotrexate relieves pain, reduces the number of affected joints, and provides a functional improvement. It has the adverse effects common to all immunosuppressants, particularly gastrointestinal and hematological disorders. Treatment withdrawals due to adverse effects are infrequent at the doses used in rheumatoid arthritis. Other synthetic antirheumatic drugs such as azathioprine, chloroquine and its derivatives, cyclosporine, cyclophosphamide, D-penicillamine, leflunomide, gold salts and sulfasalazine are no more effective than Methotrexate.

Infliximab works by binding to TNF-α. TNF-α is a chemical messenger (cytokine) and a key part of the autoimmune reaction in rheumatoid arthritis. In rheumatoid arthritis, Infliximab seems to work by preventing TNF-α from binding to its receptor in the cell. Infliximab is an artificial antibody. It was originally developed in mice as a mouse antibody. Because humans have immune reactions to mouse proteins, the mouse common domains were replaced with similar human antibody domains. They are monoclonal antibodies and have identical structures and

affinities to the target. Because they are a combination of mouse and human antibody amino acid sequences, they are called a "chimeric monoclonal antibody". It cannot be administered orally because the digestive system would destroy the drug.

However, Infliximab has been found to have a relatively acceptable toxicity profile. Characteristics of Infliximab that may influence patient persistence include a preferred administration method and less frequent needle sticks compared with subcutaneous agents.

Infliximab improves HDL-cholesterol anti-oxidative capacity in RA patients. Research indicates that smoking has a negative effect in RA patients treated with infliximab.[20]

Analysis of whole blood gene expression profiles of RA patients can be used to build a robust predictor of the response to Infliximab therapy, in which an eight-gene blood expression profile predicts the response to Infliximab in RA patients. For example, a significantly higher number of CD4+CD25+ cells were found in the responder group compared to the non-responder group at baseline[16]. Apo lipoprotein A-1 was predictive of a good response to Infliximab, whereas platelet factor 4 was associated with non-responders.

According to the, Jeffry A Katz MD, et.al. Proved that No increased risk of adverse outcome was detected, in a larger numbers of pregnant women exposed to Infliximab will be necessary to definitively exclude any fetal risk.[21]

There is no firm evidence that other combinations of antirheumatic drugs are more effective than TNF-alpha antagonist-Methotrexate combinations. There is no firm evidence that Tocilizumab (an interleukin inhibitor) or Abatacept drug acting on T lymphocytes) has a better risk-benefit balance than TNF-α blockers such as Infliximab and Rituximab. The symptomatic efficacy of long-term corticosteroid therapy lasts at least three months but usually less than a year. [22,23]

CONCLUSION

Although the causes of rheumatoid arthritis are not fully understood, laboratory and clinical evidence suggests that proinflammatory cytokines, particularly tumor necrosis factor (TNF), have an important role in its pathogenesis TNF induces the release of matrix metalloproteases from neutrophils, fibroblasts, and chondrocytes; induces the expression of endothelial adhesion molecules involved in the migration of leukocytes to extra vascular sites of inflammation; and stimulates the release of other proinflammatory cytokines[1]TNF concentrations are increased in the synovial fluid of persons with active rheumatoid arthritis, and increased plasma levels of TNF are associated with joint pain. Administration of TNF antagonists to patients with rheumatoid arthritis has been shown to reduce symptoms.

Using MTX+IFX as initial treatment for patients with recent onset RA is more effective than reserving MTX+IFX for patients who failed on traditional DMARDS for patients with active RA in its early stages, combination therapy with MTX and Infliximab provides greater clinical, radiographic, and functional benefits than treatment with MTX alone. Early intervention with Infliximab in patients with active RA despite MTX therapy may provide long term benefits by preventing radiographic progression and preserving joint integrity. Infliximab is effective in pregnant women and also effective in CAD patients.

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