

Anti TNF- α Therapy in Rheumatoid Arthritis: A New Insight

¹Parsha Shanzana, ²Tanjia Afrin Chowdhury, ³Marufatuzzahan

^{1,2,3}Lecturer

¹Department of Molecular Biology & Genetic Engineering, ²Department of Microbial Biotechnology,

³Department of Animal & Fish Biotechnology

^{1,2,3}Sylhet Agricultural University, Sylhet, Bangladesh

Abstract- The development of anti Tumor necrosis factor alpha (TNF- α) therapies is an alternative to the existing treatments of rheumatoid arthritis (RA). These anti TNF- α therapeutics aim to inhibit the inflammatory activities of TNF- α , which is the major cytokine causing the disease RA. Biologic agents are the newest forms of drugs to treat RA among the disease modifying anti rheumatic drugs (DMARDs). Though, these biologics do not cure the disease, but certainly slow down the progression of the disease with less risk. There are several monoclonal antibody based drugs and fusion proteins which are found to be remarkably successful in this regard. However, comparing the safety concern and immunogenic reactions of these therapeutics this review highlights on further improvements and efficacy of these drugs by subsiding the side effects.

Keywords- Tumor necrosis factor alpha (TNF- α), anti TNF- α , rheumatoid arthritis (RA), disease modifying anti rheumatic antibody drugs (DMARDs), biologics.

I. INTRODUCTION

Rheumatoid arthritis (RA) is one of the most common autoimmune diseases. The most common form of inflammatory arthritis affecting the synovial joints [1] has a worldwide prevalence of about 1% and an annual incidence of 3 per 10,000 adults; it is more common in women than in men [2][3]. RA is accompanied by significant morbidity and mortality. Depending on the severity of the disease at onset, the risk of disability can be as high as 33%, and mortality can be increased by as much as 52%, frequently as a result of infection [4]. It is a multifactorial disorder in which both genetic and non-genetic factors are involved not only in disease susceptibility, but also in the chronicity, severity, and a patient's response to therapy. It has been seen that tumor necrosis factor- α (TNF- α) and interleukin-1 (IL-1) are the major macrophage-derived cytokines present in the rheumatoid joints and both induce the synthesis and secretion from synovial fibroblasts of matrix-degrading proteases, prostanooids, interleukin-6 (IL-6), interleukin-8 (IL-8) and granulocyte-macrophage colony stimulating factor (GM-CSF). Several studies have revealed that the production of IL-1 is TNF- α dependent. So, the inhibition of TNF α can block the activation of IL-1 consequently reducing the severity of RA [5].

The two strategies for inhibiting TNF that have been most extensively studied to date consist of monoclonal anti-TNF antibodies and soluble TNF receptors (TNF-R). Both constructs will theoretically bind to circulating TNF- α , thus limiting its ability to engage cell membrane-bound TNF receptors and activate inflammatory pathways [6]. This review focuses on how TNF- α is intensely associated with rheumatoid arthritis and the interaction between TNF- α and its receptors. Also, the current status of anti TNF- α based therapeutics and their safety issues have been discussed in brief.

II. ASSOCIATION OF TNF-ALPHA IN RA

In rheumatoid arthritis, the inflammation begins in the synovium, a thin membrane that lines the joints causing inflammatory reaction. As a result, joint cells produce harmful substances that attack the joints themselves. Synovial cells also proliferate, forming a rough, grainy tissue that grows into the joint cavity and deteriorates the cartilage. Tumor necrosis factor alpha (TNF- α) is an inflammatory cytokine which mediates antitumor activity. It is primarily produced by monocytes and macrophages, but also by B-cells, T-cells and fibroblasts [7].

From several studies it is evident that, there are elevated levels of TNF- α found in the synovial fluid of patients with RA. Here, TNF- α acts as the key mediator of immune regulation generating autoimmune response and plays significant role in both pathogenic inflammation and joint destruction. The elevated levels of TNF- α stimulates dendritic cells, T cells and B cells, which in turns activates the T-cell and initiates functional differentiation of it. Moreover, the stimulated macrophages then activate NF- κ B-dependent signaling to induce pro-inflammatory cytokines accumulation resulting in an enhanced local inflammation of the synovial membrane (synovitis). This inflammation and then leads to the damage of cartilage and bones [8]. TNF- α affects different cell in different ways during RA inflammation (Table 1).

- TNF and TNF Receptors

TNF- α is found to be overproduced by the macrophages in rheumatoid arthritis joints [9]. It was named after its ability to trigger the necrosis of transplanted tumor cells in mice. The purification and cloning of a molecule called “cachectin”, which causes wasting in chronic diseases, was subsequently found to be identical to TNF- α . TNF is produced primarily by macrophages and, to a lesser extent, by lymphocytes [10]. It is one of 17 known members of a family of poly peptides that bind to a corresponding family of receptors. The polypeptide ligands are characterized by a common core sequence predicted to contain 10 β -sheet forming sequences, and include TNF- α , lymphotoxin-a and -b, Fas ligand, CD40 ligand and others (Table I). TNF-alpha is initially synthesized and expressed as a transmembrane molecule, the extracellular portion of which is subsequently cleaved by TNF- α converting enzyme (TACE) to release the soluble 17 kDa molecule [11]. Soluble TNF- α circulates as a homotrimer and engages its cognate receptors on cell surfaces [12].

In contrast to the relatively restricted synthesis of TNF- α by macrophages and T cells, TNF receptors (TNF-R) are expressed by nearly every mammalian cell. This ubiquitous expression, in conjunction with cell-specific effectors molecules that are triggered by the TNF-R, may explain the variety of effects of TNF which include apoptosis, the synthesis of protein and lipid inflammatory molecules, and transcription factors. Unlike other ligands of the TNF-R family that bind to a single receptor, TNF and lymphotoxin- α are capable of binding to each of the two TNF-R designated as TNF-RI (or p55) and TNF-RII (or p75). Interaction of TNF with its receptor triggers a conformational change and dimerization or clustering of receptors which, in turns, triggers the cellular response. TNF-R, like their ligand, can be cleaved from the cell surface by TACE but soluble TNF-R are believed to be present only in small amounts relative to membrane-bound TNF-R [11][13].

- **Mechanism of anti TNF- α agents**

The goals in treating RA are to prevent or control joint damage, prevent loss of function and reduce pain. Joint damage begins early in the course of the disease. To prevent permanent damage, the disease is often treated aggressively from the start. Anti-TNF agents are among a newer generation of drugs. They can dramatically improve the symptoms of rheumatoid arthritis and slow the progressive damage to the joints that often occurs [14].

Anti-TNF agents may act by reduction of proinflammatory cytokine levels, elimination or clearance of active inflammatory cells from inflamed tissue. These could be achieved by a number of mechanisms including apoptosis induction, antibody and complement mediated cytotoxicity, and by the inhibition of cell migration into the intestinal tissue. Regulatory events both in the cellular and intracellular levels probably play a role as well. Efficacy of anti TNF alpha agents vary according to their physical contact with TNF. It brings consequences like; binding avidities variation, changes of conformation and variable downstream effects.

Anti-TNF drugs are potent and expensive, and they can have serious side effects. But they appear to do what other drugs have failed to do: stop the rate of joint deterioration. In fact, in a number of people with RA, these drugs have induced something close to remission.

III. ANTI TNF ALPHA THERAPIES FOR RA

- **Approved anti TNF α based drugs in use**

Different available and approved drugs for RA treatment are classified in five broad classes. Some of these are glucocorticoids while others act as non-steroidal or analgesic. Besides these approved drugs the TNF antagonists are the biologic alternative to non-biologic disease modifying antirheumatic drugs (DMARDs) [15][16].

There are four approved anti TNF monoclonal antibodies available for RA treatment now; Infliximab, Adalimumab, Golimumab and Certolizumab. These mAbs can lyses the TNF expressing cells by directing apoptosis with the help of complement where certolizumab is an exception [17]. Certolizumab is a pegylated humanized antibody Fab' fragment (F_c free) with an increased half life. Lacking of F_c region has made it unable to exhibit complement dependent cytotoxicity or antibody-dependent cell mediated cytotoxicity. The unique polyethylene glycol (PEG) moiety has increased its half life. Studies showed that administration of certolizumab with MTX (methotrexate) reduces the severity of RA significantly [18]. Unlike certolizumab, infliximab is a chimeric IgG1 mAb composed of human constant and murine variable region. This cell culture product of CHO (Chinese hamster ovary) cells [19] was approved by FDA/EMA for the moderate to severe RA patients in combination with MTX (methotrexate). On the other side, adalimumab is a human recombinant IgG1 mAb (no murine region) that is produced using phage display technology [20]. Presence of 100% human peptide sequences in adalimumab has given it the same structure and function as the natural human IgG1 [21]. It is available in subcutaneous form to treat the adult RA patients of moderate to severe range. Infliximab, adalimumab and certolizumab act almost in a similar way against the RA inflammation. The immune dysregulation in RA patients actually leads to the over expression of TNF- α from macrophages, monocytes and T-cells. The mAbs (infliximab, adalimumab and certolizumab) act against this dysregulatory immune activity. They induce the production of immunosuppressive regulatory macrophages which ultimately blocks the activated T cells proliferation. The production of anti-inflammatory cytokines remains the very next step [22]. Golimumab is a fully human anti-TNF mAb and, it can act on both membrane bound

and soluble TNF [23]. It is available in subcutaneous form to use in 50 mg/month dose. An intravenous formulation of golimumab was evaluated too during a trial named GO-FURTHER [24]. The mode of action of golimumab is similar to infliximab and adalimumab with a weaker apoptotic effect on TNF- α [25]. In addition to IgG1 mAbs there is another type of anti TNF drug available in the market. Etanercept is an Fc fusion protein dimer that is linked to the extracellular ligand binding portion of the human 75kDa (p75) TNF receptor (TNFR). Etanercept does not lyse the TNF expressing cells hence reduces the biologic activity of TNF acting as a competitive inhibitor of TNF and prevents binding of TNF to the cell-surface TNFR [26]. These drugs have their unique characteristics and are approved to use in different dosage based on their trials. Table 2 has summarized characteristics of some approved anti TNF alpha drugs available in the market.

IV. SAFETY & IMMUNOGENICITY

TNF shows an important role in host defense mechanism. It mainly kills intracellular microorganisms such as *Listeria* and mycobacteria, and induces apoptosis of some tumor cells. But long-term inhibition of TNF could lead to an increased incidence of infection and of malignancy. In addition, genetically engineered proteins which will be given repeatedly over long periods of chronic diseases treatment, matter of immunogenicity and injection reactions require careful examination [27].

- **Injection Site Reactions**

Injection reactions represent the most frequent and consistent side effect with both etanercept and infliximab, although rarely limiting administration of the drugs. Reactions occur early after initiation of treatment, are generally resolve completely with repeated dosing [17].

- **Infections**

With the use of all biologics, infections are the most common. Patients with previous infections, significant comorbidities such as, but not limited to, diabetes mellitus and chronic lung disease, the risk of infection is increased in RA. It has been seen that the risk of infection with the TNF inhibitors stabilize after the initial 6 months of use. Most commonly reported infection is respiratory tract infection. RA patients treated with biologics need care with a high index of suspicion and the use of aggressive diagnostic procedures and prompt treatment.

Using monoclonal antibody TNF inhibitors in patients, the risk of granulomatous infections, such as tuberculosis, is also increased. With infliximab, tuberculosis reactivation was often noted after the third or fourth infusion, with two-thirds of reactivation occurring in less than 6 months, with 40% of cases being extrapulmonary. Pretreatment screening in all biologic treatment guidelines has dramatically reduced, but not completely eliminated, the risk. Other opportunistic infections, such as histoplasmosis, coccidiomycosis, listeriosis and *Pneumocystis jirovecii* have also been reported.

Any increased postoperative infectious risk is uncertain. Generally biologics are held for several half-lives before elective surgery. They may be restarted when wound healing has begun 1–2 weeks postoperative [27].

- **Malignancy**

The immune system has an important role in surveillance for malignancy, and the role of TNF, in particular, in triggering apoptosis of some tumor cell types has already been noted. So, an increased risk of malignancy with chronic long-term TNF inhibition is of theoretical concern. Patients with RA have not been associated with an increased risk of solid cancers, with the exception of cutaneous malignancies after using of TNF inhibitors [17].

Rather than the biologic, increasing of lymphoma risk may be related to the level of RA disease activity. Young patients with inflammatory bowel disease treated with infliximab and also other concomitant immunosuppressives, an unusual hepatosplenic lymphoma was reported. TNF inhibitors may be associated with a small increased risk of melanoma and are clearly associated with nonmelanomatous skin cancers. Longer-term follow-up is required to more clearly understand the risk of malignancies with these drugs [28].

- **Demyelinating diseases**

Symptoms of demyelinating neurologic dysfunction have been associated with TNF inhibitors. With drug withdrawal, resolve of these symptoms is common. Peripheral neuropathic symptoms have also been described. If neurologic symptoms occur with use TNF inhibitors, then it should be withdrawn immediately, and probably should be avoided in patients with pre-existing demylelinating symptoms [29][30].

- **Congestive heart failure & other cardiovascular events**

At high doses (in non-RA patients), infliximab was associated with an increased mortality when it was studied as a potential treatment in heart failure. As a consequence the entire class of TNF inhibitors has been considered contraindicated in patients with unstable and late-stage congestive heart failure. RA patients with heart failure should be carried out cautiously on an individual patient basis, if at all, with careful follow-up in case of using any of these drugs. RA patients taking TNF inhibitors do not appear to be increased in Myocardial infarction. In fact, patients responsive to these drugs have recently been shown to decrease in cardiovascular events [31][32][33].

- **Autoimmune syndromes**

TNF inhibitors have been related with increased production of some autoantibodies, including antinuclear and antidouble-stranded DNA antibodies. Clinical manifestations, however, are rare, although mild lupus has been reported. With the use TNF inhibitors in RA, worsening of psoriasis or the onset of new psoriatic lesions have been described. Uveitis has very rarely been reported with etanercept use [34].

- **Immunogenicity**

Antidrug antibodies which have been discussed may be associated with decreased drug effect or survival and both primary and secondary response failure with all TNF inhibitors [17]. At the binding site for TNF, infliximab which is a chimeric monoclonal antibody contains 25% mouse sequence. The potential of the mouse sequence which elicit an anti-infliximab or human anti-chimeric antibody response that would limit the therapeutic efficacy is a matter of concern. Such antibodies have indeed been found but they can be suppressed by the use of associated methotrexate. The effect of these antibodies remains unclear on therapeutic efficacy [27].

Neoepitopes might be generated at the joining regions of the TNF receptor and the immunoglobulin, although etanercept is composed entirely of human sequence. Anti-etanercept antibody response could be elicited by Fc region. This does not appear to be relevant. Patients treated with infliximab and etanercept develops low titers of anti-double stranded DNA (anti-ds-DNA) antibodies.. Anti-ds-DNA antibodies are considered to be specific for systemic lupus erythematosus. However, in general, patients treated with infliximab or etanercept who developed these antibodies do not exhibit lupus like illnesses [17]. The measurement of antidrug antibodies to the TNF-inhibitors in practice is not yet readily available. Although such measurements could be clinically relevant, as diminishing responses in patients with antibodies might require higher doses of drug, whereas in patients without antibodies, a change of drug might be indicated.

V. FUTURE PERSPECTIVES OF ANTI TNF A

TNF- α plays a significant role in the pathogenesis of rheumatoid arthritis, so blocking it efficiently by subsiding the side effects of it offers an excellent pathway to reduce the severity of the disease. Although traditional treatments have some efficacy in the symptoms of RA do not modify the pathogenic process. In contrast, monoclonal antibody based anti TNF- α therapy is found to be remarkably successful against it. However there are still some problems regarding the use of this protein therapeutics. Anti TNF α agents are more often found to interfere with the immune system and there is a concern that infections with intracellular organisms such as *Mycobacterium tuberculosis* are increased in anti-TNF- α treated patients. Though the number is not too high, still some advances should made to reduce the risk of further infections. Also, there was concern that the incidence of malignancies might be increased by administration of injectable protein based therapies to inhibit or block TNF- α , but early fears have been allayed by larger trials and follow-up studies. There have been a few cases of drug-induced lupus, but, overall, safety is good till date [14].

There are a number of monoclonal antibody based drugs seem to elicit more immunogenicity than other types of biologics. The long term data for the newer small oral molecule biologics such as tofacitinib, is not yet available and hence could be used only as a last resort [35]. Almost all preliminary studies indicate that repeated administration of anti-TNF- α neutralizing monoclonal antibodies is feasible [17]. But the long term safety and efficacy of such a strategy needs to be further evaluated [36]. Therefore, further studies should focus on developing oral anti TNF- α drugs of long term persistence in the body with minimal risk

VI. CONCLUSION

The whole phenomenon of RA is a complex scenario. This review is just a highlight on the pivotal role of TNF- α in the RA disease although the actual mechanism is obscure still now. So accepting the undeniable fact of further research present focus should be on the best use of known and useful target like TNF- α . As biologic drugs using anti TNF- α agents for RA has made an impressive success, betterment of the currently available anti TNF- α drugs should be the highest priority.

Tables:

Table 1 Auto-immunogenic effects of TNF- α on various cells in RA

Target sites	Effects of TNF- α on various cells
Macrophage cells	Enhances cytokine production & cell proliferation
Activated T-cells	Increases IL-2 receptor & enhances cell proliferation
B-cells	Increased cell proliferation & differentiation
Synovial lining cell	Stimulates the synthesis of IL-1, granulocyte monocyte colony stimulating factor (GM-CSM), storemelysin, collagenase, Prostaglandins
Endothelial cells	Stimulates the expression of intracellular adhesion molecule-1,vascular cell adhesion molecule-1,endothelial adhesion molecule-1(ELAM 1), IL-8

Table 2 Characteristics of approved anti TNF- α drugs for RA

anti TNF agent	Monoclonal antibodies				Non mAb
	Infliximab	Adalimumab	Golimumab	Certolizumab	Etanercept
Trade/brand name	Remicade	Humira	Simponi	Cimzia	Enbrel
Structure	Chimeric (human-murine) IgG1	Recombinant human IgG1	Fully human IgG1	Fc free PEGylated humanized Fab IgG4	Recombinant human fusion protein; (Human IgG1 Fc + extracellular domain of TNFR)
Half life	8-9 days	10-12 days	around 2 weeks	14 days	3-5 days
Dosage	3mg/kg every 8 weeks after	40mg every other week	50 mg/month	400 mg every 4 weeks	50 mg/week
Route of	i.v.	s.c.	s.c.	s.c.	s.c.

** i.v. =intravenous; s.c. =subcutaneous

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