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# The yin and yang of tumor necrosis factor inhibitors

## ABSTRACT

Tumor necrosis factor (TNF) inhibitors have proven highly effective against a number of autoimmune diseases but have been disappointing in treating others. An increase in the risk of *Mycobacterium tuberculosis* and other opportunistic infections has been noted in patients treated with these agents. If we use these drugs, we need to weigh their beneficial and adverse effects.

## KEY POINTS

TNF blockers have proven highly effective against rheumatoid arthritis, Crohn disease, psoriasis, and ankylosing spondylitis.

Despite hopes based on theoretical considerations, TNF blockers are not effective against multiple sclerosis, sarcoidosis, Sjögren disease, and congestive heart failure.

Patients using TNF blockers have increased rates of *M tuberculosis* infection and other uncommon opportunistic infections.

TNF blockers are expensive, yet they are highly effective, and they can greatly improve quality of life and perhaps allow patients to avoid future joint replacement and reconstructive surgery.

As most experienced physicians know, there are two sides to almost any treatment. The most potent and effective therapies are sometimes accompanied by the most profound and dangerous side effects.

The tumor necrosis factor (TNF) inhibitors are a case in point. Since their introduction less than a decade ago, they have revolutionized our approach to a variety of autoimmune disorders, such as rheumatoid arthritis, Crohn disease, ankylosing spondylitis, and psoriasis. The exuberance over these drugs has led researchers to examine TNF inhibitors in areas such as heart failure and endometriosis.

But as the yin and yang of taoist philosophy tell us, the universe is composed of opposites, all contained within a whole. And so it is with TNF inhibitors. Despite their efficacy, rare but formidable toxicities such as lymphoma and infections have occurred. Autoimmune diseases that researchers thought would respond to these drugs have not responded, and in some cases the disease got worse. And the high cost of these genetically engineered drugs can stretch the budget of patients, insurers, and the health system as a whole.

This presentation provides an introduction to the immune system and the role of cytokines, discusses drug design of TNF-blocking agents to target autoimmune diseases, and describes the successes, limitations, and adverse effects of the new therapeutics thus far.

## TNF: THE MODEL CYTOKINE

Cytokines are small, nonantibody protein molecules that act as chemical messengers between cells to regulate diverse physiologic processes, including cell growth, differentia-

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tion, inflammation, repair, and immunity. More than 150 have now been identified, most of them glycoproteins.

Cytokines were previously referred to by their presumed source, eg, lymphokines from lymphocytes and monokines from monocytes, but since many cytokines, particularly TNF, are produced by a wide range of somatic cells, the more general term cytokine is now used.

## Discovery and development of TNF

In the 1970s, Carswell and colleagues[1] were the first to isolate a factor from mouse macrophages that caused experimental tumor death (necrosis). Soon after, the cytokine TNF was identified, sequenced, and cloned.

Other researchers independently "discovered" TNF as they searched for different substances in their field of interest. In 1985, Beutler et al[2] studied a factor, which turned out to be TNF, that caused widespread wasting by acting on lipoprotein lipase and other metabolic pathways. Simultaneously, Dayer et al,[3] searching for a factor that mediated shock, isolated TNF from cells of monocytic lineage.

## Shared immunologic pathways

**TNF acts on blood-vessel endothelial cells, synovial cells, nervous system pathways, and bone**

Effector cells, mast cells, neutrophils, and monocytes engage in an integrated but very redundant immune response. An antigen-presenting cell presents an antigen to certain T cells, which generate a cell-mediated immune response. The T-cell response can be characterized by two important pathways: T helper (Th)1, responsible for granuloma formation and cellular immunity; and Th2, which facilitates humoral immunity and atopy.

Dysregulation of the Th1 responses is involved in rheumatoid arthritis, inflammatory bowel disease, sarcoidosis, psoriasis, and others. The Th2 type responses are responsible for asthmatic allergic diseases, bronchopulmonary aspergillosis, and parasitic diseases. It is a particular challenge to develop specific therapies for these seemingly disparate diseases that share pathways. The goal is to have specific targeted pathway inhibition.

The inflammatory response involves a plethora of cytokines with opposing actions. Some are inflammatory (especially the Th1 cytokines, which include interferon gamma, IL-1, and TNF), and others are anti-inflammatory.

## TNF features and effects

TNF is only one of a family of structurally defined molecules. Within the TNF family, more than 20 peptides have been identified. Some, such as CD-40 ligand, lymphotoxin, and FAS-ligand, mediate T and B lymphocyte activation and control apoptosis. Some are starting to be used as therapeutic targets. Their structural similarities have added to the impetus to design specific drugs.

TNF affects many organs. Normally, it is present in nanomolar concentrations and is believed to be essential for tumor surveillance, the regulation of inflammatory response, and perhaps local tissue repair.

Large amounts of TNF are released in response to a lipopolysaccharide challenge. A few hours after a mouse is sensitized with just a few micrograms of lipopolysaccharide, it develops a fever, a disrupted sleep cycle, and an acute response-phase leukocytosis. With moderate concentrations of lipopolysaccharide, inflammatory cytokines can be detected. A large lipopolysaccharide challenge stimulates an out-of-control inflammatory response, leading to multiple organ dysfunction, septic shock, and death.

TNF has a variety of actions. In blood vessels and smooth muscle cells, it promotes proliferation and influences endothelial cells to go from an anticoagulant state to a procoagulant state. In synovium, it promotes proliferation and upregulates adhesion molecules, causing an influx of inflammatory cells. In the central nervous system it disregulates pathways, causing fever and sleep disruption. In bone, it is involved in destruction and repair. TNF affects repair and scar formation by its action on fibroblasts. It also causes direct lysis of tumor cells.

## TNF expression

TNF is expressed by a variety of immune cells but is also rapidly induced in many nonimune cells by a variety of stimuli.

TNF is expressed within cell membranes as a homotrimer, with aggregated monomers. These are cleaved by TNF-alpha converting enzyme (a metalloproteinase), allowing TNF molecules to circulate freely and to bind to receptors for TNF on a variety of target cells. These soluble receptors may be cleaved off of

**TABLE 1**

**Indications for TNF blockers**

| DISEASE | ETANERCEPT | INFLIXIMAB | ADALIMUMAB |
|---|---|---|---|
| Rheumatoid arthritis | Yes | Yes | Yes |
| Psoriatic arthritis | Yes | Yes | Yes |
| Ankylosing spondylitis | Yes | Yes | Under investigation |
| Juvenile rheumatoid arthritis | Yes | Under investigation | Under investigation |
| Crohn disease | No | Yes | Under investigation |
| Ulcerative colitis | No | Yes | Under investigation |

cell surfaces and decrease the circulating levels of TNF, a process that helps keep the potent TNF system in check.

## DRUGS DESIGNED TO ALLEVIATE INFLAMMATION

TNF's effects are mediated by two distinct types of TNF receptors, both of which are involved in inflammation and the induction of cell death. TNF and other cytokines interact with their specific receptors, thereby initiating an inflammatory signal.

One drug-design strategy is to neutralize cytokines by developing TNF-specific monoclonal antibodies. Another specific strategy is to use solubilized receptors to bind the circulating cytokine.

Three drugs that inhibit TNF have been approved by the US Food and Drug Administration. Their structural differences confer distinct properties[4]:

- **Etanercept** (Enbrel) is a construct of the Fc portion of immunoglobulin G (IgG) bound to a TNF receptor. It is given by subcutaneous injection and has a half-life of 4.8 days.
- **Infliximab** (Remicade) is a chimeric monoclonal antibody with a human IgG Fc region and murine antigen-binding regions that are highly specific for TNF. It is given by intravenous infusion and has a half-life of 9.5 days.
- **Adalimumab** (Humira) is similar to infliximab, but is wholly of human construct. However, under certain circumstances it still may be perceived by the body as foreign. It is given by subcutaneous injection and has a half-life of 12 to 14 days.

TNF inhibitors can be viewed as a model for biologic therapy for autoimmune inflammatory diseases. More agents with different targets are being investigated, including drugs that modulate IL-2, IL-4, or IL-10.

## RHEUMATOID ARTHRITIS AS A MODEL

Rheumatoid arthritis is a multisystem inflammatory disease, targeting joints, that occurs in genetically susceptible people. It involves a variety of cells, including T cells, B cells, and accessory cells. Judging by the success of new cytokine-blocking agents, cytokines appear to drive the rheumatoid process. Patients today no longer suffer the highly destructive and deforming effects of the disease common just 25 years ago, and we are now able to set our sights on achieving remission and even disease regression.

Most drugs used to treat rheumatoid arthritis were originally intended for other diseases, such as tuberculosis and malaria. In the 1990s, Ravinder Maini (who was knighted for his work), Marc Feldmann, and others recognized that cultured synovial tissue contained a "soup" of inflammatory cytokines. They eventually focused their research on two of them: interleukin 1 and TNF.

Although methotrexate is still considered to be the gold standard treatment of rheumatoid arthritis, adding etanercept leads to significantly more gains than are achieved by treating with either medication alone. In the Anti-TNF Trial in Rheumatoid Arthritis With Concomitant Therapy (ATTRACT), Smolen et al[5] found that patients treated with a combination of methotrexate and infliximab had a dramatic slowing of joint damage

**In rheumatoid arthritis, methotrexate plus a TNF blocker is better than methotrexate alone**

as seen by radiography vs patients on methotrexate alone, with healing seen at the highest doses studied (infliximab 10 mg/kg every 4 weeks).[5]

With nearly 7 years of experience with TNF inhibitors, we now know that long-term therapy is feasible. Therapy maintains long-term suppression of disease activity, particularly in rheumatoid arthritis, and there is no evidence of mounting toxicity as is seen with glucocorticoids.

## OTHER USES FOR TNF BLOCKERS

### Crohn disease

Biologic therapy, including TNF inhibitors, is revolutionizing the treatment of Crohn disease and possibly ulcerative colitis as well. Like rheumatoid arthritis, Crohn disease occurs in genetically susceptible people. The disease involves nonspecific granulomatous inflammation, leading to tissue injury and repair.[6–8] Van Dullemen et al[9] showed that a single infusion of infliximab leads to profound healing of the mucosa of patients with active Crohn disease as seen by colonoscopy. Long-term regimens have been approved and are increasingly used.

**TNF inhibitors do not work in all diseases in which, in theory, they should**

### Psoriasis

Biologic treatments including etanercept and infliximab have been used to treat psoriasis. Adalimumab is expected to be approved soon.

All TNF inhibitors appear to be highly effective in treating both psoriasis and psoriatic arthritis and represent major advances in the treatment of these disorders.[10]

### Ankylosing spondylitis

Drug manufacturers have traditionally regarded ankylosing spondylitis as a low priority, since the disease is uncommon and causes such severe damage and joint ankylosis that substantial improvement appeared unlikely. However, the effects of TNF inhibitors on the disease have been even more dramatic than for rheumatoid arthritis.[11]

## THE DOWNSIDE TO TNF INHIBITION

Despite the success of TNF inhibitors, much of the early exuberance is giving way to a more measured view of these drugs. They continue to transform our care of many patients with autoimmune disease, but as you can see from the discussion below, researchers are finding that these drugs do not work in all diseases in which, theoretically, they should. And as experience with these drugs grows, we are seeing some predictable and unexpected side effects. Also, as with all genetically engineered drugs, there is the issue of cost.

## UNSUCCESSFUL USES OF TNF INHIBITORS

### Wegener granulomatosis

TNF blockers showed great promise in the treatment of Wegener granulomatosis in a 6-month open-label study of etanercept in 20 patients.[12] The mean vasculitis activity score for the disease improved dramatically in treated patients, and there were no apparent adverse effects. However, a subsequent multicenter, randomized, placebo-controlled trial[13] in 180 patients followed for a mean of 27 months did not show that etanercept was effective for maintaining remission. Also, the rate of treatment-related complications was high and included a possibly increased rate of solid cancers in the treatment group, who also received cyclophosphamide.

### Multiple sclerosis

Multiple sclerosis would appear to be an ideal target for TNF inhibitors: TNF kills oligodendrocytes and injures myelin and is found in plaques and cerebrospinal fluid, correlating with multiple sclerosis activity. Furthermore, animal models of multiple sclerosis showed that disease worsens when TNF activity is enhanced and improves when TNF is downregulated. However, in two small trials, TNF inhibitors were not successful for the treatment of multiple sclerosis, and some treated patients actually had a worsening of their condition. Another disturbing finding is a rare illness resembling multiple sclerosis that has been increasingly reported in patients treated with TNF inhibitors for other conditions.[14]

### Other conditions

Etanercept, the first and mostly widely tested TNF blocker, has been unsuccessful for treating Crohn disease, sarcoidosis, Sjögren disease, and congestive heart failure.

## EVIDENCE OF INFECTION RISKS

TNF serves a homeostatic role. Although high levels of TNF contribute to chronic local or systemic inflammation and joint destruction, low levels increase the risk of infection. The goal of therapy with TNF blockers is not to eliminate TNF completely, but rather to restore a balance of TNF.

The lack of evidence of excess infections in patients treated with TNF blockers during phase III clinical trials reassured the medical community that these drugs were relatively safe in this regard. However, evidence of disturbing trends of increased infections and other diseases is starting to emerge as the use of TNF blockers increases. For example, I had one patient with severe rheumatoid disease uncontrolled with methotrexate and prednisone. We treated her with a 6-week course of infliximab infusions, and 2 weeks later she developed staphylococcal bacteremia and meningitis. She recovered, then developed skin lesions due to *Mycobacterium chelonae*.

### Tuberculosis and TNF

TNF is a macrophage activator and appears to be critical in helping the body form granulomas. The granuloma response is critical to protect against disseminated *M tuberculosis* infection. Excessive and prolonged inhibition of TNF signaling leads to exacerbation of tuberculosis. "TNF-knockout" mice develop uncontrolled mycobacterial infections that lead to death.[15,16] *Mycobacterium* also proliferates in wild-type mice treated with anti-TNF antibody.

Gomez-Reino et al[17] analyzed a database of patients in Spain who were treated with infliximab or etanercept and found more than 20 times the incidence of tuberculosis over the background rate, though the risk was markedly greater for infliximab than for etanercept. In the United States, no increase in the incidence of tuberculosis has been detected in patients taking TNF inhibitors, but this may be due to a much lower background rate and less opportunity for disease spread than exists in Spain. Infections from other intracellular pathogens, however, are being reported in patients taking etanercept and especially infliximab, including *Listeria monocytogenes*, *Histoplasma capsulatum*, and others.[18–20]

**Test for tuberculosis before starting anti-TNF drugs.** All patients being considered for anti-TNF therapy should be screened for tuberculosis exposure . This should include questioning to determine risk factors, testing with purified protein derivative (PPD), and chest radiography. The PPD testing sensitivity varies with the cutoff value used: use a lower cutoff for patients deemed to be at higher risk of tuberculosis infection. Treatment with isoniazid for 9 months is recommended for patients with a PPD test result greater than 5 mm. Anti-TNF therapy should be delayed until isoniazid therapy is completed.

### Other potential major adverse effects of TNF inhibition

- An increased risk of non-Hodgkin lymphoma has also been observed in patients taking TNF inhibitors, but patients with moderate to high rheumatoid disease activity have an up to 26 times greater risk of lymphoma,[21–27] making it difficult to determine whether treatment with TNF constitutes an independent risk factor.
- TNF inhibition may increase the risk of atypical neurologic damage, eg, demyelination.
- Recently, TNF inhibitors have been linked to activation of latent viruses, including hepatitis B, which has led to some deaths.
- TNF inhibitors have been linked to vasculitic syndromes.

**Disturbing trends of increased infections with TNF blockers are emerging**

## THERAPY COSTLY, BUT BENEFICIAL

Most TNF inhibitors cost about $1,000 per month, which means they are a luxury treatment for many patients. Still, they are an important option for patients with rheumatoid arthritis, Crohn disease, psoriasis, and ankylosing spondylitis. Although expensive, TNF inhibitors often allow patients to return to work, have fewer hospitalizations, and avoid joint replacements and reconstructive surgery.

TNF inhibitors are not yet uniformly accessible, even within the United States. Outside of western countries, they are not available at all.

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