Innovative Uses of Tumor Necrosis Factor α Inhibitors

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KEYWORDS

• Biologic • Etanrcept • Infliximab • Adalimumab • Skin • Off-label

Tumor necrosis factor α (TNF-α) is an inflammatory cytokine that is released by a variety of cell types, including immune effector cells, such as macrophages, monocytes, lymphocytes, and neutrophils, as well as tissue-specific cells, including keratinocytes and dendritic cells. TNF-α has been shown to promote inflammation via the activation and induction of cytokines interleukin 1 (IL-1), IL-6, and IL-8 and by the upregulation of adhesion molecules on endothelial cells leading to increased leukocyte extravasation.[1–4] Theoretically, the blockade of TNF should have widespread potential in the treatment of numerous inflammatory diseases. Currently, 3 TNF-α inhibitors available in the United States are approved for psoriasis and psoriatic arthritis: infliximab, etanercept, and adalimumab. Numerous case reports and case series have been published in recent years reporting the off-label uses of these drugs in various inflammatory skin diseases. This review summarizes the most recent reports on 20 such conditions.

INFLIXIMAB (REMICADE)

Inflizimab is a chimeric IgG_1 monoclonal antibody against TNF-α that is comprised of the human constant (Fc) region of human IgG and the murine variable (Fab) region that binds to soluble and membrane-bound TNF-α, therefore preventing binding of TNF-α to its receptor. In addition, it also fixes complement and causes apoptosis of cells with cell surface TNF.[5] It is currently approved by the US Food and Drug Administration for the treatment of psoriasis, psoriatic arthritis, Crohn disease and associated fistulas, rheumatoid arthritis (RA), ulcerative colitis, and ankylosing spondylitis. It is contraindicated in patients with a murine protein sensitivity and should be avoided in patients with known or recent malignancies as well as congestive heart failure and multiple sclerosis.[6] The most common side effect is infusion-related reactions, which occur in 16% of patients and have been linked to the presence of antichimeric antibodies. Symptoms include fever, chills, urticaria, chest pain, hypotension, hypertension, and shortness of breath. This infusion reaction risk can be decreased through the concomitant use of methotrexate, azathioprine, or corticosteroids, preventing the formation of antichimeric antibodies.[7] Infections such as pneumonia and sepsis as well as opportunistic infections such as histoplasmosis have been reported, and because of the ability of the drug to inhibit granuloma

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formation, mycobacterial infection or reactivation is of concern. Therefore a baseline purified protein derivative (PPD) is necessary, and many physicians opt to obtain a chest radiograph before imitation of treatment.[8] There has been a proven increased risk of lymphoproliferative diseases and malignancies as well as onset or flares of multiple sclerosis.[9] Clinical systemic lupus erythematosus (SLE)-like syndromes have been reported with the formation of antinuclear and antinuclear-DNA antibodies. This process has been shown to be reversible on cessation of the agent. Dermatologic conditions such as the paradoxic new onset of psoriasis, cutaneous small vessel vasculitis, and interstitial granulomatous dermatitis have all been reported.[10] Infliximab is pregnancy category B.

ETANERCEPT (ENBREL)

Etanercept is a receptor fusion protein consisting of the extracellular domain of the TNF-α receptor fused with the Fc portion of human IgG, which binds to and inhibits soluble and, to a lesser degree, cell membrane-bound TNF-α. It has 2 p75-binding sites, which confers it a higher affinity for TNF-α compared with the natural receptor.[11] It does not fix complement, cause antibody-dependent cytotoxicity, or trigger T-cell apoptosis compared with infliximab.[12] Etanercept is given as a self-administered subcutaneous injection at a dosage of 25 mg twice weekly for RA, ankylosing spondylitis, and psoriatic arthritis or 50 mg twice weekly for 3 months with a subsequent decrease to 50 mg weekly for psoriasis.[13,14] Entanercept is contraindicated in patients with sepsis or with known hypersensitivity to the medication and should be avoided in patients with a history of an active infection, malignancy, multiple sclerosis, and unstable cardiac disease. Injection site reactions were the most common adverse events in initial clinical trials and occurred in up to 40% of patients. In trials there was an increased rate of upper respiratory infections. Also, there is a debate on the oncogenic potential of etanercept with regard to lymphoma occurrence; some reports show a 3-fold increase. There is an increase in antinuclear antibody formation, with a small series of patients developing signs and symptoms of SLE; this is readily reversible.[15] The rate of development of antietanercept antibodies has been less than 10% and has not been observed to lead to decreased efficacy. Etanercept is pregnancy category B, with no evidence of harm to the fetus in animal studies. However, the drug has not been specifically studied in pregnant women nor is it known if it is secreted in breast milk. Salmon and Alpert[16] have suggested that etanerept and other TNF antagonists be avoided in the first trimester.

ADALIMUMAB (HUMIRA)

Adalimumab is a human recombinant IgG_1 monoclonal antibody against human TNF-α. It binds to soluble and membrane-bound TNF-α, with apoptosis of cells with membrane-bound TNF occurring.[17] Like infliximab, it fixes complement and causes lysis of cells expressing membrane-bound TNF-α. It was initially approved for the treatment of RA and then for psoriatic arthritis, ankylosing spondylitis, and Crohn disease, and is administered as a 40-mg dose subcutaneously or intravenously every other week or weekly. An initial loading dose of 80 mg is used to increase rapidity of response onset. It is contraindicated in patients with known sensitivity reactions and should be avoided in patients with active infections or malignancies as well as multiple sclerosis or congestive heart failure.[18] Live vaccines should be avoided. Mycobacterial infections are a concern and therefore all patients need a baseline PPD. Injection site reactions are the most common adverse event and occur in 20% of patients in clinical trials. In clinical trials for RA, antiadalimumab antibodies were seen in 12% of patients receiving adalimumab as monotherapy and 1% of patients receiving concomitant methotrexate. Antinuclear antibodies seem to be increased in patients being treated with adalimumab, with some patients experiencing SLE-like symptoms. New onset psoriasis as well as cutaneous small vessel vasculitis have been known to complicate therapy.[19] Adalimumab is pregnancy category B and its lactation profile is unknown.[20]

OFF-LABEL USES OF TNF-α ANTAGONISTS

Sarcoidosis

Sarcoidosis is a multiorgan system idiopathic granulomatous disease that affects the lungs, skin, bone, and other organs. TNF-α is believed to play a key role in the pathogenesis of sarcoidosis. In pulmonary sarcoidosis, increased production of TNF-α by alveolar macrophages is seen and TNF-α plays an essential role in the process of granuloma formation. Genetic polymorphisms in the TNF-α promoter are also associated with specific clinical subtypes of sarcoidosis. More than 35 cases of sarcoidosis, including cutaneous, pulmonary, hepatic, and gastrointestinal types, have been reported to be treated with infliximab.[21] Meyerle and Shorr[22] reported the use of infliximab for sarcoidosis. A typical dosing regimen was intravenous infliximab at a dose of 3 to 5 mg/kg