

Summaries

Patricia Malerich and Dirk M. Elston
Introduction to TNF/Pathophysiology of TNF

Summary
Seth R. Stevens and Ting H. Chang
History of development of TNF inhibitors

Tumor necrosis factor- α (TNF α) plays an important role in the early and primary orchestration of the inflammatory response. One of the first clues that TNF α might be a good therapeutic target for inflammatory diseases, such as rheumatoid arthritis, came from observations that elevated TNF α production was a major driver of chronic inflammation characterizing autoimmune diseases. Therefore, inhibition of TNF α could be therapeutically useful. Rodent arthritic models provided strong evidence of the potential therapeutic benefits of anti-TNF therapy, and led to the development of two classes of TNF inhibitors—soluble TNF α receptors such as etanercept and monoclonal antibodies to TNF α such as infliximab and adalimumab.

Key Words: TNF α inhibitor, etanercept, infliximab, adalimumab, anti-cytokine

Summary
Rahul Shukla and Ronald B. Vender
Pharmacology of TNF Inhibitors

TNF alpha (TNFa) and lymphotoxin (previously termed TNF beta), are members of the TNF family which are particularly important in T cell effector function. Although TNFa plays a critical role in the activation of the innate and acquired immune responses, evidence that elevated levels of TNFa play a major role in the development and maintenance of inflammatory diseases such as CD, psoriasis, psoriatic arthritis and RA provides a rationale for the use of anti-TNFa therapies. Currently, there are 2 classes of drugs that reduce TNF bioavailability: soluble TNF receptors (etanercept) and TNF-binding monoclonal antibodies (infliximab and adalimumab). By eliminating surplus TNFa in the blood and from sites of inflammation, adalimumab, etanercept and infliximab have an ameliorable effect when managing diseases where TNFa is inappropriately elevated. The pharmacology of these drugs will be reviewed in the following section.

Key words: Tumor necrosis factor alpha, lymphotoxin, adalimumab, etanercept, infliximab, structure, binding characteristics, immunogenicity, pharmacokinetics, pharmacodynamics

Jeffrey D. Greenberg and Mitsumasa Kishimoto
Etanercept in rheumatology

Noah Gratch and Andrew F. Alexis
Etanercept in dermatology and off-label use

Summary
Mihaela B. Taylor and Dahlia T. Lainer
Infliximab in rheumatology

This book chapter summarizes the current rheumatologic indications for infliximab: rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis, and includes a review of the studies and trials that lead to FDA approval of the drug for these diseases. There is also a discussion of the potential uses of infliximab in other rheumatic diseases, including systemic lupus erythematosus and vasculitis.

Key words: Infliximab, rheumatoid arthritis, spondyloarthropathy, ankylosing spondylitis, psoriatic arthritis, ATTRACT, ASPIRE, ASSERT, IMPACT

Noah Scheinfeld
Infliximab in dermatology, gastroenterology and off-label use

Harry D. Fischer
Adalimumab in rheumatology

Jennifer Clay Cather and Melody Young
Adalimumab in dermatology

Summary
Jeffrey M. Weinberg
A review of the safety of the tumor necrosis inhibitors infliximab, etanercept, and adalimumab

The TNF-inhibitors infliximab, etanercept, and adalimumab share a number of common safety issues and concerns. There is an increased risk of reactivation of granulomatous diseases, especially tuberculosis, with all three agents and appropriate steps should be taken for detection and treatment of latent infections. In terms of malignancy, an association between non-Hodgkin's lymphoma and treatment with TNF-antagonists has been reported, although patients with active, long-standing rheumatoid arthritis (RA) and psoriasis have been reported to have an increased incidence this condition. The biological plausibility of lymphomas associated with immunomodulatory agents raises concern and vigilance is recommended until the relationship is fully characterized. Large phase II and III trials have shown a negative effect of TNF-inhibitors in advanced heart failure and these agents should be avoided in this population. Rare case reports of drug-induced lupus, seizure disorder, pancytopenia, and demyelinating diseases have been noted after use of these agents and continued vigilance is warranted in patients on TNF-antagonists for the development of these

diseases. Currently there is no evidence implicating TNF-inhibitors with embryotoxicity, teratogenicity, or increased pregnancy loss.

TNF-alpha Inhibitors

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